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Neurotrophin Signaling and Stem Cells—Implications for Neurodegenerative Diseases and Stem Cell Therapy

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Abstract Neurotrophins (NTs) are members of a neuronal growth factor protein family whose action is mediated by the tropomyosin receptor kinase (TRK) receptor family receptors and the p75 NT receptor (p75NTR), a member of the tumor necrosis factor (TNF) receptor family. Although NTs were first discovered in neurons, recent studies have suggested that NTs and their receptors are expressed in various types of stem cells mediating pivotal signaling events in stem cell biology. The concept of stem cell therapy has already attracted much attention as a potential strategy for the treatment of neurodegenerative diseases (NDs). Strikingly, NTs, proNTs, and their receptors are gaining interest as key regulators of stem cells differentiation, survival, self-renewal, plasticity, and migration. In this review, we elaborate the recent progress in understanding of NTs and their action on various stem cells. First, we provide current knowledge of NTs, proNTs, and their receptor isoforms and signaling pathways. Subsequently, we describe recent advances in the understanding of NT activities in various stem cells and their role in NDs, particularly Alzheimer's disease (AD) and Parkinson's disease (PD). Finally, we compile the implications of NTs and stem cells from a clinical perspective and discuss the challenges with regard to transplantation therapy for treatment of AD and PD.

Keywords Neurotrophin · BDNF · NGF · TRK · Stem cell · Alzheimer's disease · Parkinson's disease

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Introduction

Neurotrophins (NTs) are a family of trophic factor proteins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT3, and NT4 [1, 2]. Active research over the past decades has shown that NTs regulate various aspects of neural function, including cell proliferation and differentiation, axon and dendrite growth, apoptosis, myelination, synaptogenesis, and synaptic plasticity [2–7]. Signaling of NTs and their precursors is mediated by their binding to cell membrane-integrated tropomyosin receptor kinase receptors A, B, C (TRKA, TRKB, TRKC, respectively) and to the common p75 NT receptor (p75NTR) [6, 8]. The immature forms of NTs (proNTs) preferentially bind to a p75NTR/sortilin receptor complex to initiate cell death [9–11]. Additional members of the NT family, such as NT6 [12] and NT7 [13, 14], have been identified in other non-mammalian species; however, these are considered pseudogenes in human [15] and will not be further discussed here.

In 1981, pluripotent embryonic stem cells (ESCs) were first isolated from the inner cell mass of mouse blastocysts [16, 17]. The ability of ESCs to differentiate into three germ layers (ectoderm, mesoderm, and endoderm) [18] and then into fully specialized cells [19] has advanced the expectations that stem cells might be a useful resource to understand disease mechanisms, to effectively and safely screen for drugs, and to treat patients with various diseases and injuries [20–23]. In adult life, different tissues contain stem cells called adult stem cells. These adult stem cells usually exist in specific niches, are multipotent, and can undergo asymmetrical division; one cell can remain as a self-renewing stem cell for a long period, while others differentiate into specialized cells with specific functions [24, 25]. The plasticity of differentiation in these cells is associated with transcription accessibility for genes

expressed in different normal tissues [25]. Reprogramming of adult somatic cells into a pluripotent embryonic-like state, induced pluripotent stem cells (iPSCs), represents a major scientific breakthrough in advancing the fields of disease modeling, drug development, and regenerative medicine [26, 27].

Due to the pivotal role of growth factors in stem cell biology, NTs and their receptors are arising as key regulators of stem cell differentiation, self-renewal, plasticity, homeostasis, survival, and regeneration [28–30]. The aim of this review is to decipher the functions of NTs and their receptors in ESCs, neural stem cells (NSCs), mesenchymal stem cells (MSCs), and hematopoietic stem cells (HSCs), with a focus on the potential implementation of this knowledge for therapeutic applications. In the first part, we provide current knowledge of NTs, proNTs, and their receptor isoforms and signaling pathways. Subsequently, we describe recent advances in the understanding of NT activities in various stem cells and their role in neurodegenerative diseases (NDs), particularly Alzheimer's disease (AD) and Parkinson's disease (PD). Finally, we compile the implications of NTs and stem cells from a clinical perspective and discuss the challenges with regard to transplantation therapy for treatment of AD and PD.

NTs and proNTs

NGF

In the early 1950s, Rita Levi-Montalcini and Viktor Hamburger discovered that implantation of a piece of mouse sarcoma tissue close to the spinal cords of developing chicken embryos produced a soluble factor that promoted the growth of nearby sensory and sympathetic ganglia [31]. Soon after, this soluble factor was isolated, characterized, and named NGF [5, 7, 32]. Subsequent studies have revealed that NGF plays an essential role in the survival, differentiation, development, and maintenance of neurons [33–35]. Changes in the levels and activities of NGF have been observed in a number of neurological diseases, including AD and PD [36, 37]. NGF is also a mediator of pain, itch, inflammation, allergy, bronchial asthma, and other diseases [38–42]. For instance, several types of immune cells, including B cells, produce, store, and release NGF [39, 43], where it has important functional roles in lymphocyte proliferation and differentiation, as well as regulating the production of immunoglobulins [38, 39].

Biosynthesis, Processing, and Secretion of NGF

NGF is encoded by the NGF gene, which is located on chromosome (chr) 1p13 [44]. The mRNA and protein sequences of NGF indicate a highly conserved molecule that shares considerable homology across different species [45]. NGF is encoded by two exons that are distributed over 45 kilobases (kb) [46, 47]. The precursor protein of NGF is initially synthesized in the endoplasmic reticulum (ER) as pre-proNGF, which is then converted to proNGF species of 32 or 25 kDa by the removal of the signal peptide [6, 47]. ProNGF is further cleaved by furin, a proprotein convertase, in the *trans*-Golgi network (TGN) to generate mature NGF (13.2 kDa) [48, 49]. ProNGF can be processed intracellularly in both constitutive and regulated pathways [50]. ProNGF (32–34 kDa) is also biologically active and can be released intact from cells [51, 52]. Upon secretion, both the amino- and carboxyl-terminal ends of proNGF are cleaved extracellularly by plasmin, a serine protease derived from a zymogen called plasminogen and activated by tissue plasminogen activator (tPA), to generate mature NGF (13.2 kDa) [53, 54]. The proNGF maturation process is regulated by neuroserpin, the main inhibitor of tPA in the central nervous system (CNS) [54, 55].

3D Structure of NGF

The NGF crystal structure was initially discovered for the 7S-NGF mouse-derived NGF as a high-molecular weight complex that is composed of α, β, and γ subunits [56–58]. The mature form of NGF is a symmetrical dimer composed of two 13.2-kDa monomers of β subunits that associate via hydrophobic interactions [59]. However, heterodimers involving βNGF are relatively unstable and slowly rearrange into their parent homodimers [60]. Similarly, the crystal structure at 3.75-Å resolution shows proNGF complexed with p75NTR in a symmetric (2:2, proNGF:p75NTR) binding mode [61]. The structure of proNGF in the proNGF-p75NTR complex also shows mostly disordered pro-regions of proNGF. In contrast, crystal structures of mature NGF (and also NT3) were bound to p75NTR in an asymmetric (2:1) fashion. Binding characteristics of proNGF to sortilin using surface plasmon resonance and cell-based assays have revealed that Ca^{2+} ions promote the formation of a stable heterotrimeric complex of proNGF-sortilin-p75NTR [61].

BDNF

During the 1980s, Barde et al. isolated an NT from pig brain and named it BDNF [62]. BDNF has since emerged as a major regulator of neural development, synaptic plasticity, neural survival, and differentiation in both developing and adult brains, in particular in hippocampal neurons, cerebellar granule neurons, and cerebral cortical neurons [63–67]. Changes in the levels and activities of BDNF have been observed in a number of NDs, including AD, PD, and Huntington's disease (HD) [66, 68], schizophrenia and depression [69], neuropathic pain and inflammation [70], and neonatal and adult asthma, sinusitis, influenza, and lung cancer [71]. BDNF is also

expressed in immune cells and can exert neuroprotective effects against autoimmune demyelination [72].

Biosynthesis, Processing, and Secretion of BDNF

BDNF is encoded by the BDNF gene, which is located on chr 11p13. The BDNF gene locus is very complex; multiple promoters determine the expression of BDNF transcripts and mature BDNF proteins [73]. Similar to NGF, the precursor protein of BDNF is initially synthesized in the ER as a pre-proBDNF, which is then converted to proBDNF (32 kDa) by removal of the signal peptide (Fig. 1). ProBDNF is cleaved to generate BDNF (13.5 kDa, 119 amino acids (AAs)); however, the exact location of this cleavage and the protease(s) involved remain to be determined [3, 74]. However, some studies have argued that the processing of proBDNF into mature BDNF takes place both intracellularly and extracellularly [3, 75]. Intracellular cleavage of proBDNF to mature BDNF occurs after cleavage next to arginine residue 125 or 128 either by furin or by other proprotein convertases in the TGN [6, 76, 77]. Intracellular cleavage of proBDNF also generates a truncated form of BDNF (28 kDa). Truncated BDNF is generated by a cleavage of proBDNF at threonine 57 by the specific Ca^{2+}-dependent serine proteinase membrane-bound transcription factor site-1 protease (MBTFS-1), also known as subtilisin/kexin-isozyme 1 (SKI-1) [77, 78]. During the extracellular processes, proteases such as matrix metalloproteinase 7 (MMP7) or tPA/plasmin system can also cleave proBDNF to generate mature BDNF [51, 79, 80]. Mature BDNF is naturally found as a dimer of two 13.5 kDa subunits. The BDNF-dimer (27 kDa) can be distinguished from the 28-kDa truncated BDNF monomer based on molecular mass [51, 78].

3D Structure of BDNF

The 3D structure of the BDNF subunit (119 AAs, 13.5 kDa) in the BDNF/NT3 heterodimer contains eight anti-parallel β-pleated strands, two short helixes, and four distinct loop regions [60]. BDNF also forms a heterodimer with NT4, and a comparison of the surface of a model of a BDNF homodimer with the crystallography structures of NT3 and NT4 homodimers, respectively, reveals common topological features that might be important for binding with their respective TRK receptors. Biocomputational modeling analyses have revealed that the protomer structures of BDNF (BDNF/NT3, BDNF/NT4) showed no significant variations compared with the 3D homodimer structures of NGF, NT3, and NT4, respectively, displaying different crystal forms [81].

NT3

NT3 is the third member of the NT family [82–84] and plays various roles during the development of the CNS and peripheral nervous systems (PNS), including the enteric nervous system [83, 85] and the cerebellum [86]. Despite being crucial for neuronal survival, development, and differentiation, elevated NT3 protein level has been observed under pathological conditions associated with inflammatory disorders, asthma, and various types of cancer [87–89].

Biosynthesis, Processing, and Secretion of NT3

NT3 is encoded by the NT3 gene, which is located on chr 12p13 [82, 84]. The NT3 precursor protein is initially synthesized in the ER as pre-proNT3, which is then converted by a furin/proconvertase to proNT3 (available as 33.5 and 35 kDa isoforms, where the 33.5 kDa appears as the major isoform) and mature NT3 (14.5 kDa) (Fig. 1) [50, 90, 91]. The perturbation of post-translational modification leads to proNT3 secretion instead of the production of mature NT3 [50, 90, 91].

3D Structure of NT3

Structurally, NT3 resembles NGF and BDNF [92] and forms a twisted four-stranded β-sheet, with three intertwined disulfide bonds. Mature NT3 is naturally found as a homodimer of two 14.5-kDa subunits [92] and as a heterodimer with BDNF [60]. A comparison of the dimer interface between the NT3 homodimer and the BDNF/NT3 heterodimer reveals similar patterns of hydrogen bonds and nonpolar contacts, which reinforces the notion that the conserved NT interface resulted from the need for receptor dimerization in signal initiation [60, 92].

NT4

The fourth NT identified was variously named NT4 or NT5 [93, 94]. As a compromise between the alternative nomenclatures, the fourth mammalian NT is usually referred to as NT4/5. It is possible that NT4 has a role in the control of survival and differentiation of vertebrate neurons, such as hippocampal neurons, cerebellar neurons, striatal central neurons, spiral ganglion neurons, retinal ganglion neurons, and cranial sensory neurons [93, 95–97]. Despite being a neural survival and differentiation factor, altered NT4 level has been associated with breast cancer [98], asthma severity in children [99], allergic airway inflammation [100], and atopic dermatitis [101]. Importantly, keratinocyte-derived NT4 acts as a possible link between the immune and nerve systems of human skin [102]. It is the most divergent NT and, in contrast to the other NTs, its expression is ubiquitous and appears to be less influenced by environmental signals [93]. NT4 seems to have a unique requirement for binding to p75NTR in order to assert efficient signaling and retrograde transport in neurons [93].

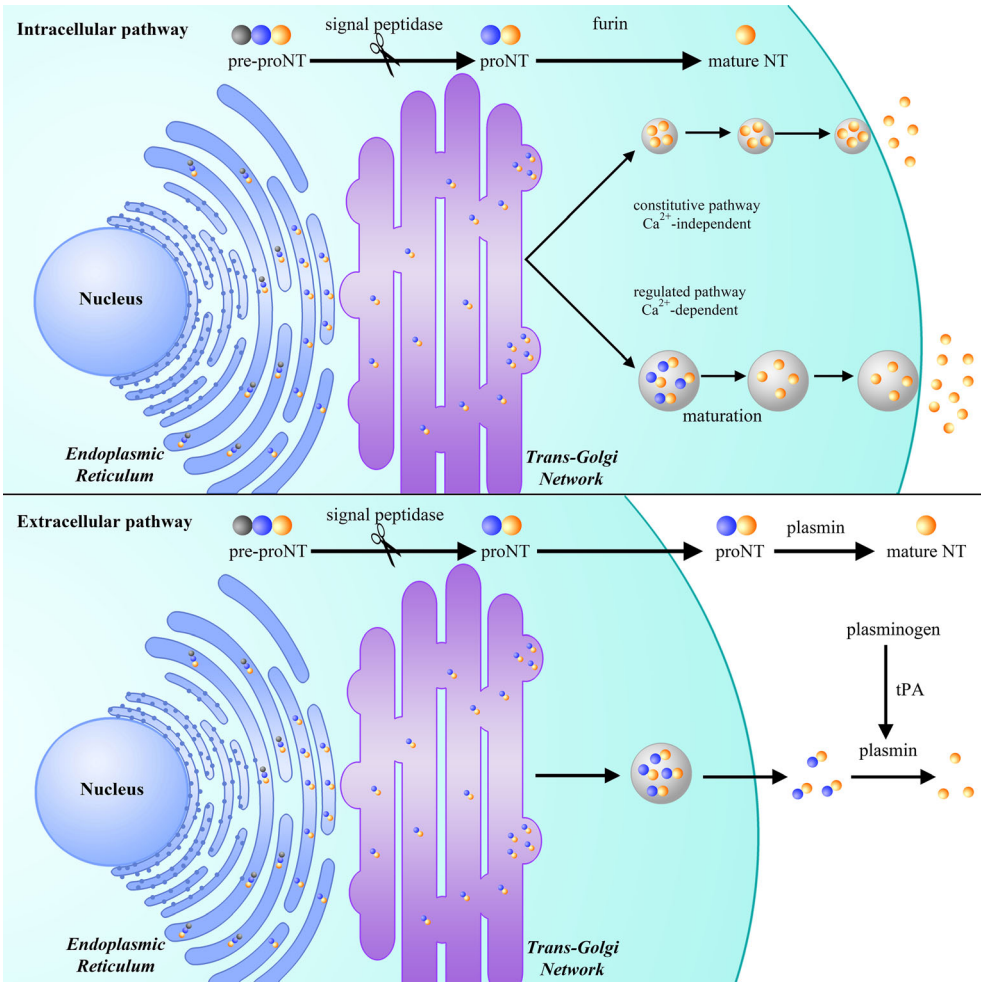

Fig. 1 Biosynthesis of NTs. NT mRNAs are initially synthesized by ribosomes attached to the rough ER as nascent pre-proNTs, which are cleaved by a signal peptidase to generate proNTs. The proNTs are transported to the Golgi system and then to the TGN, where they are released to the cytosol by the constitutive and regulated pathways. ProNTs can be processed intracellularly or extracellularly to generate mature NTs. Intracellularly, proNTs undergo post-translational processing by furin to generate mature, biologically active NTs. Extracellularly, proNTs are further cleaved at both amino- and carboxyl-terminal ends to generate NTs by reaction with plasmin, a serine protease derived from a zymogen called plasminogen and activated by tPA

Biosynthesis, Processing, and Secretion of NT4

NT4 is encoded by the NT4 gene, which is located on chr 19q13.3 [15]. Similar to other NTs, the precursor protein of NT4 is initially synthesized in the ER as pre-proNT4, and removal of the signal peptide produces proNT4 [6]. Post-translational modifications convert proNT4 into mature NT4 (14 kDa) [103]. Mature NT4 is further processed until it is eventually secreted into the extracellular space as a mature dimeric protein complex. However, there is no specific report regarding the functional activity of proNT4, and further study is needed on this NT.

3D Structure of NT4

Mature NT4 is naturally found as a homodimer or heterodimer with BDNF [81]. The common 3D structures of the BDNF, NT3, NT4, and NGF protomers comprise eight β-strands that contribute to four antiparallel pairs of twisted β-strands. A comparison of the 3D protein structures of the BDNF/NT4 heterodimer, BDNF/NT3 heterodimer, NT3 homodimer, and NT4 homodimer showed strong structural similarity of the NTs protomers, particularly at the dimer interfaces, showing no significant variation compared with the structures of the homodimers of NGF, NT3, and NT4 in different crystal forms [81, 104].

Different Isoforms of the NT Receptors

TRKA

TRKA is the specific receptor for NGF [2] and is encoded by the NTRK1 gene, which is located on chr 1q21-q22 [105]. Alternative splicing of NTRK1 encodes different TRKA isoforms, including TRKA-I, TRKA-II, TRKA-III, TRKA-Kin14, TRKA-L1, and TRKA-L0 (Fig. 2). TRKA-I and TRKA-II are biologically active, full-length (FL) receptors. An additional six-AA insertion has been observed in TRKA-II, between the second immunoglobulin-like domain (Ig2) and the transmembrane region of the extracellular domain [106]. TRKA-III lacks the functional extracellular Ig1 domain [107]. TRKA-Kin14 is a full-length isoform, having an insertion of 14 AAs in the tyrosine kinase domain [108]. A deletion of two

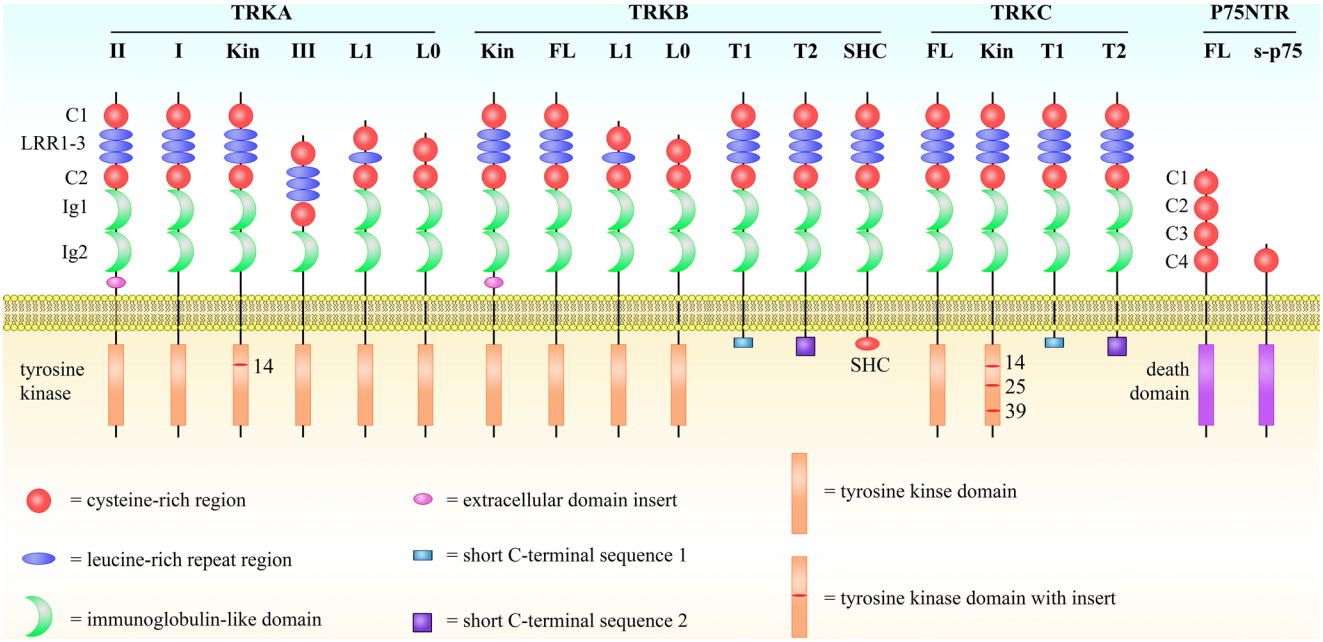

Fig. 2 Schematic representation shows the different full-length (FL) and truncated (T) isoforms of TRKA (I, II, III, Kin14, L1, and L0), TRKB (Kin, FL, L0, T1, and T2), TRKC (FL, Kin14, Kin25, Kin39, T1, and T2), and p75NTR (FL and s-p75). The extracellular domains of the full-length TRK receptors (TRKA, TRKB, and TRKC) contain three LRRs flanked by two cysteine repeats (C1 and C2, respectively) and the Ig1 and Ig2 domains proximal to the transmembrane region. The full-length TRK receptors possess a tyrosine kinase domain in the cytoplasmic part. The truncated TRKB and TRKC proteins contain a similar extracellular domain to the full-length TRKs but missing a tyrosine kinase domain in the cytoplasmic part. The full-length p75NTR receptor contains four cysteine-rich regions (C1-C4) in the extracellular region and a death domain in its cytoplasmic part. The short isoform (s-p75) contains only one C domain in the extracellular part but still has a death domain in the cytoplasmic part

leucine-rich repeats (LRRs) in the extracellular domain has been observed in TRKA-L1, whereas a deletion of three LRRs has been observed in TRKA-L0 [109] (Fig. 2). The synthesis of TRKA takes place in the ER, with the N-terminus facing the ER lumen, and the C-terminus facing the cytoplasm. After the cleavage of the signal peptide, TRKA is transported from the ER to the Golgi complex and then to the cell surface. TRKA undergoes post-translational N-glycosylation and matures from a 110-kDa precursor to a 140-kDa mature form [110–112]. The crystal structures of the ligand-binding domains of TRKA, TRKB, and TRKC show strand-swapped protein dimers. A basic scheme of the structures of TRKs is shown in Fig. 2. The ligand binding domains of TRKA, TRKB, and TRKC fold into an Ig-like domain comprising two β-sheets in a β-sandwich arrangement and share 41 to 44 % pairwise sequence identity [81, 104, 113–115]. A recent work has demonstrated that TRKA and TRKC are ligand-dependent receptors that promote cell death in their unbound states (with NGF and NT3 as their respective ligands), whereas TRKB does not trigger neuronal death if unbound to its ligand BDNF [116].

TRKB

TRKB is the specific receptor for BDNF and NT4, owing to its wide pattern of expression and a higher binding affinity for BDNF and NT4 compared to p75NTR [66, 117]. TRKB is encoded by the NTRK2 gene, which is located on chr 9q22.1 [118]. Alternative splicing of NTRK2 encodes different full-length and truncated (T) TRKB isoforms, including TRKB-FL, TRKB-Kin, TRKB-L1, TRKB-L0, TRKB-T1, TRKB-T2, and TRKB-SHC (Fig. 2). TRKB-FL and TRKB-Kin have a full-length kinase domain, while TRKB-Kin contains an additional six-AA insertion between the Ig2 of the extracellular part and the transmembrane region [119]. Deletion of two LRRs at the extracellular domain was observed in TRKB-L1, whereas a deletion of three LRRs was described for TRKB-L0 [120]. TRKB-T1 and TRKB-T2 are truncated isoforms lacking a tyrosine kinase domain and containing only short C-terminal sequences of 23 and 21 AAs, respectively, in the cytoplasmic part [121]. Another truncated isoform, TRKB-T-SHC, also lacks a tyrosine kinase domain and contains a short C-terminal sequence [122], a putative internalization sequence [123], and a SHC-binding site at its cytoplasmic end [122].

TRKC

TRKC is the specific receptor for NT3 [124] and is encoded by the NTRK3 gene, which is located on chr 15q25 [125]. Similar to TRKB, alternative splicing of the NTRK3 gene encodes both full-length and truncated isoforms, including

TRKC-FL, TRKC-Kin14, TRKC-Kin25, TRKC-Kin39, TRKC-T1, and TRKC-T2 (Fig. 2). TRKC-FL [126], TRKC-Kin14, TRKC-Kin25 [127], and TRKC-Kin39 [128] have full-length tyrosine kinase domains, whereas TRKC-Kin14, TRKC-Kin25, and TRKC-Kin39 contain different lengths of insertions of 14, 25, and 39 AAs, respectively, within their intracellular domains. TRKC-T1 and TRKC-T2 are truncated isoforms that lack a tyrosine kinase domain but contain short C-terminal sequences within their intracellular domains [128, 129].

P75NTR

P75NTR is a common receptor for both NTs and proNTs [130, 131]. The NGFR gene encodes P75NTR, which is located on chr 17q21-q22 [131]. Alternative splicing of the NGFR mRNA encodes both full-length (p75NTR) and short isoforms (s-p75NTR) (Fig. 2). The extracellular portion of p75NTR contains four cysteine-rich repeats, and the intracellular part contains a death domain [132]. P75NTR regulates a wide range of cellular functions, including programmed cell death, axonal growth and regeneration, cell proliferation, myelination, synaptic plasticity, migration, and differentiation depending on the cell type, proNT binding, interacting transmembrane co-receptor expression, intracellular adaptor molecule availability, and post-translational modifications, such as regulated proteolytic processing [28, 133, 134]. The s-p75NTR transcribed by alternative splicing of exon III of the NGFR locus was detected by RT-PCR in wild-type adult mice [135]. This s-p75NTR was also present in p75NTR partial knockout mice ($p75NTR^{exonIII-/-}$) [136] lacking exon III (encoding the cysteine-rich domains 2, 3, and 4, essential for extracellular ligand-binding) but containing all other exons (I, II, IV–VI). Both isoforms p75NTR and s-p75NTR were eliminated after targeting of the NGFR genomic locus in exon IV ($p75NTR^{exonIV-/-}$) [135]. Western blot analysis showed a discrete 62-kDa band in the $p75NTR^{exonIII-/-}$ mice, corresponding to the size of the s-p75NTR protein; no band was observed in $p75NTR^{exonIV-/-}$ mice [135]. However, the same report by von-Schack et al. did not clearly show the protein band corresponding to the presumed 62-kDa s-p75NTR in their Western blot analysis of wild-type mice. Thus, it remains a crucial question to detect the endogenous existence of s-p75NTR at protein level, and further study is needed for the detection of s-p75NTR [135, 137, 138].

The s-p75NTR form has limited functional homology to full-length p75NTR. The short form does not bind to any NT as it contains only one cysteine-rich domain, which is necessary for the binding of the rabies virus glycoprotein [139, 140]. The initial crystallography structural analysis of the extracellular domain of p75NTR bound to NGF indicated that the receptor monomer binds NGF in an asymmetrical fashion, resulting in a 1:2 ratio (p75NTR: NGF) [141]. However, other biochemical data have indicated that p75NTR associates with NTs in a 2:2 ratio [61, 133, 142, 143]. The crystal structure of proNGF–p75NTR also demonstrated a proNGF dimer bound to two p75NTR ectodomains with symmetric complexes formation (2:2) [61]. Functional studies, together with cross-linking analysis, indicate that proNGF simultaneously binds with p75NTR and sortilin, a receptor complex that activates neuronal apoptosis. The pro and mature domains of proNGF bind to sortilin and p75NTR, respectively [10, 61, 141].

Signaling Pathways Activated by TRK and p75NTR Receptors

TRK receptors activate signaling pathways, namely those of phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK), and phospholipase C (PLC)-γ, all of which have a high impact on many diverse neuronal functions, including cell survival, differentiation, cytoskeletal rearrangement, synapse formation, and synaptic plasticity. In the following sections, we briefly review the mechanisms of signal initiation, propagation to the functional destination, and signaling pathway stimulation by each NT-TRK interaction in the different types of neurons. Subsequently, the signaling pathways stimulated by TRK receptor transactivation, truncated TRK receptors, and p75NTR are comprehensively discussed.

PI3K/AKT Signaling

Upon NT binding with TRK receptors, dimerization and autophosphorylation of the TRKs at their tyrosine residues within the tyrosine kinase domain (e.g., Y490 in TRKA and its corresponding residues in TRKB and TRKC) cause the recruitment and phosphorylation of the Src homology domain-containing (SHC) and fibroblast growth factor receptor substrate 2 (FRS2) adaptor protein molecules [144]. This subsequently activates the PI3K pathways via GRB2 and GAB1 [145, 146], and the phosphorylation of phosphatidylinositol (4,5)-bisphosphate (PIP2) at the 3′ position produces phosphatidylinositol (3,4,5)-trisphosphate (PIP3). Importantly, hydrolysis of PIP2 by PLCγ leads to production of inositol trisphosphate (IP_3) and diacylglycerol (DAG) (as will be discussed further, see "PLCγ signaling" section). Consequently, PIP3 activates AKT that translocates to the plasma membrane and is eventually activated by the colocalized pleckstrin homology domains of 3-phosphoinositide-dependent protein kinase-1 (PDK1) (Fig. 3). AKT activation results in increased protein translation via the mammalian target of rapamycin (MTOR)-p70S6 kinase and 4E binding protein 1 (4E-BP1) pathways and eventually enhances axonal growth through phosphorylation and inactivation of glycogen synthase kinase 3β (GSK3β)

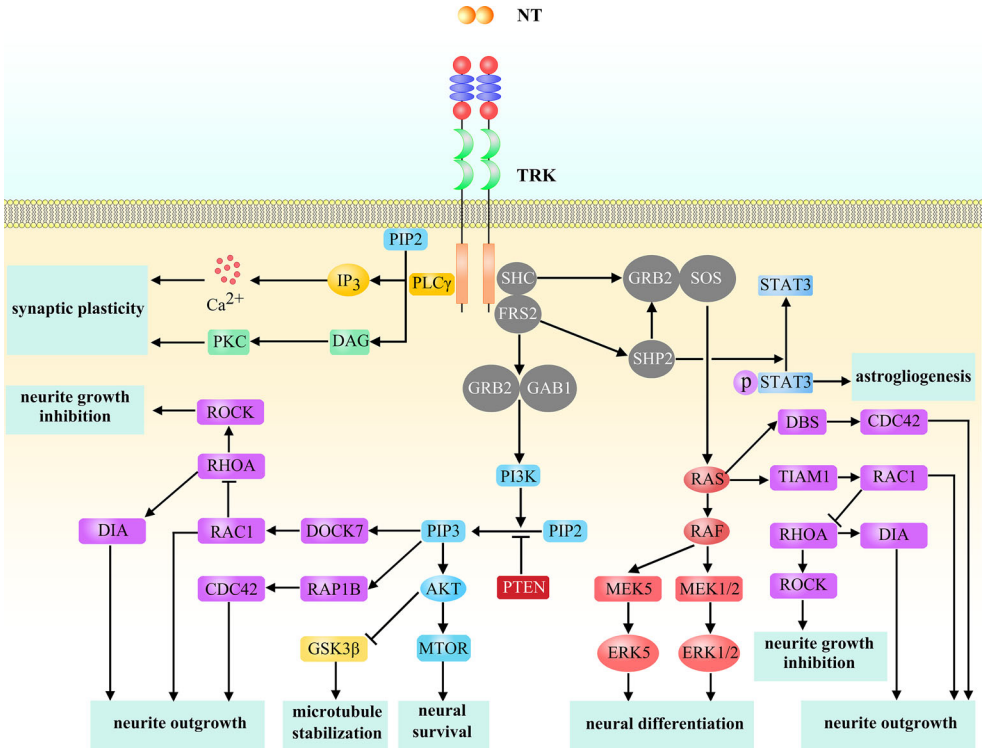

Fig. 3 General NT-TRK signaling pathways. Upon respective ligand binding, TRK receptors form homodimers (e.g., TRKA, TRKB, and TRKC homodimers) that transduce various signaling pathways mediated by RAS/MEK/ERK, PLCγ, PI3K/AKT, and STAT3. Activation of RAS results in transduction of several signaling pathways, including those of MEK/ERK, RAC1, and CDC42. Activation of PI3K through RAS or GAB1 leads to phosphorylation of PIP2 and generation of PIP3, which in turn activates multiple signaling pathways, including those of AKT, RAC1, and CDC42. Generation of PIP3 from PIP2 can be inhibited by phosphatase and tensin homolog (PTEN), which inhibits the activity of PI3K. Activation of AKT also protects neurons from apoptosis through inhibition of GSK3β signaling via phosphorylation at Ser9. Activated RAC1 can also inhibit RHOA signaling, which either promotes or inhibits neurite outgrowth depending on the type of effector (DIA or ROCK, respectively). Activation of PLCγ leads to hydrolysis of PIP2 into IP_3 and DAG, which results in Ca^{2+}-release and PKC activation, respectively. Additionally, NTs activate SHP2, which results in the dephosphorylation and inhibition of STAT3, which promotes astrogliogenesis

(Fig. 3). It is understood that the apoptotic activity of GSK3β is inhibited by its phosphorylation at Ser9 via AKT (Fig. 3) [147], whereas proapoptotic activity of GSK3β is stimulated by its phosphorylation at Tyr216 via proline-rich tyrosine kinase 2 (Pyk-2) [148]. Furthermore, GSK3β inhibited by phosphorylation at Ser9 can be re-activated by protein phosphatase 2A (PP2A) [149].

Activation of PI3K is also mediated through RAS signaling. RAS-mediated activation of PI3K also leads to the production of the PIP3, which in turn activates also survival signals and cellular morphogenesis signals [150–152]. In addition to survival signaling through the AKT pathway, PIP3 signaling is a central signal for the regulation of cytoskeletal RHO-family proteins (small GTPase protein), including RAS-homolog family member A (RHOA), RAS-related C3 botulinum toxin substrate 1 (RAC1), and cell division cycle 42 (CDC42), which are linked to morphological neuroplasticity (Fig. 3) [152–155]. Importantly, PIP3 leads to further activation of RAS-related protein RAP1B, which in turn activates CDC42 [156]. CDC42 is an effector of a number of downstream molecules, e.g., IQ motif-containing GTPase activating protein 3 (IQGAP3), p21-activated kinase (PAK), partitioning defective-6 (PAR6), and neural Wiskott–Aldrich syndrome protein (N-WASP), which control a variety of activities, including cytoskeletal rearrangement such as microtubule stabilization and actin polymerization during axon growth [157–159]. CDC42 can also activate RAC through an interaction between PAR3 (complexed with PAR6 and atypical PKC) and T lymphoma invasion and metastasis 1 (TIAM1) or TIAM2, which is critical for cell morphology, adhesion, migration, and polarity [160, 161]. PIP3, produced by PI3K, also activates RAC1 via dedicator of cytokinesis 7 (DOCK7), a guanine nucleotide exchange factor (GEF), and thereby regulates microtubule stability through inhibition of the microtubule destabilizing protein stathmin/OP18 [162]. RAC1 and CDC42 induce actin polymerization by activating PAK, which can inhibit the actin-depolymerizing factor cofilin through LIM kinase (LIMK) [163]. Cross-talk analysis in PC12 cells showed that RAC1 and RHOA antagonize the activity of one other [164, 165]. RHOA can promote axon

growth through the downstream effector, mammalian diaphanous protein (DIA), which promotes microtubule stability [159, 166], or inhibit axon growth through the downstream effector, RHO-associated kinase (ROCK), which can inhibit the actin-depolymerizing factor cofilin through LIMK [153, 154]. Thus, PI3K-modulated regulation of the RHO-GTPase effectors RHOA, RAC1, and CDC42 allows them to function as key regulators of neuronal morphology and morphological neuroplasticity [152, 153, 157]. In addition, NT-induced activation of RHO-GTPases effectors, RAC1, and CDC42 is also possible through PI3K-independent pathways via direct RAS signaling (as will be discussed further, see "RAS/RAF/MEK/ERK signaling" section) [167–169].

NGF/TRKA-Mediated PI3K/AKT Signaling in Different Neurons

Since its first description as a growth promoter, NGF has received much attention with regard to the signaling pathways that it stimulates [31]. Kuruvilla et al. reported that NGF-TRKA regulates the activation of PI3K/AKT both locally within distal axons and in a retrograde fashion from proximal axons to cell bodies of sympathetic neurons obtained from newborn rat superior cervical ganglia [170]. The authors demonstrated that PI3K signaling within the cell body is an important factor for mediating cell survival because it propagates AKT activation and other downstream pro-survival signals. They found that PI3K signaling in distal axons promotes neuronal survival because it is critical for the initiation of NGF-mediated retrograde transport in distal axons to the cell bodies. They observed that NGF acting exclusively on distal axons of sympathetic neurons depends more on PI3K for mediating neuronal survival compared to neurons supported by NGF acting directly on cell bodies [170]. NGF also promotes the survival and functioning of basal forebrain cholinergic neurons (BFCN) in a retrograde manner. Synthesized and secreted by neurons in the cortex and hippocampus, NGF binds to TRKA produced within BFCN neurons and transmits neuronal pro-survival signals via phosphorylation of AKT, GSK3, and the transcription factor cyclic AMP (cAMP) response element binding protein (CREB) to activate these respective pathways in a retrograde manner [171, 172]. Likewise, NGF-TRKA-mediated PI3K/AKT signaling is important for the survival, proper development, and functioning of cholinergic neurons in the septal area [173]. Specifically, data have indicated that expression of both choline transporter and cholinergic gene was mediated through an NGF-stimulated PI3K/AKT pathway in primary septal neurons [173]. Another study investigated the axon growth effect via an NGF-mediated RAS pathway in embryonic sensory neurons obtained from dorsal root ganglia [174]. This study demonstrated that the activation of the TRK-RAS pathway mediated an increase in axon caliber and branching via the AKT signaling cascade, while the RAF/MEK/ERK pathway was more responsible for axon lengthening [174]. The same research team also determined that AKT was more strongly activated by NT3-TRKC than NGF-TRKA [171–177]. The NT-mediated PI3K/AKT pathway activation is vital for the survival of motor neurons [178]. Specifically, activated AKT showed a dual function in supporting neuronal survival and axonal regeneration of hypoglossal motor neurons in vivo, and the PI3K/AKT pathway is more important for motor neuron survival than is the RAS/ERK pathway [178]. Similarly, NGF-induced TRKA phosphorylation provides neuroprotection and hippocampal neuron survival involving PI3K/AKT activation, whereas the MEK/ERK is not highly involved [179].

Furthermore, NGF-induced activation of the TRKA-PI3K/AKT signaling pathway phosphorylates Ser9 and inhibits GSK3β, the protein kinase that phosphorylates the Ca^{2+}/calcineurin-dependent transcription factor nuclear factor of activated T cells (NFAT) and thus promotes its inactivation and export from the nucleus [180, 181], thereby prolonging retention of dephosphorylated and activated NFAT in the nucleus. Since NFAT is usually activated by action potential firing or neuronal depolarization that leads to Ca^{2+}/calcineurin-dependent dephosphorylation of NFAT and its translocation to the nucleus, it was suggested that NFAT acts as an integrator of depolarization-driven Ca^{2+}-signaling, while NGF-TRKA-PI3K/AKT facilitatory effects stimulate NFAT-dependent gene expression by concurrently inducing the nuclear import of NFAT and inhibition of GSK3β-mediated NFAT phosphorylation [181].

NGF/TRKA-induced activation of CDC42 and RAC1 through PI3K was preliminarily observed in PC12 cells and PNS neurons such as the superior cervical ganglionic neuron and dorsal root ganglionic neurons [165, 182, 183]. NGF-activated CDC42 and RAC1 pathways are not thoroughly characterized in CNS neurons, though there is a strong possibility that NGF/TRKA also activates CDC42 and RAC1 pathways in CNS neurons, such as those of the hippocampus and cerebellum [183]. Hippocampal neurons treated with NGF have shown numerous long neurite outgrowths through RHOA/ROCK cascade inactivation [184].

BDNF- and NT4/TRKB-Mediated PI3K/AKT Signaling in Different Neurons

It is well documented that BDNF-TRKB activates PI3K/AKT pathways to mediate survival signals in a wide range of neuronal cell types [185]. In cerebellar granule neurons, BDNF activates both the PI3K/AKT and MEK cascades to promote cell survival [186]. Activated AKT phosphorylates BAD (BCL-2-associated death promoter) at Ser136. Importantly, BAD is a proapoptotic member of the BCL2 family, and phosphorylation of BAD at two critical sites, Ser112 and Ser136, leads to dissociation of BAD from the pro-survival BCL2

protein [186]. A recent study elucidated that PI3K/AKT is one of the primary pathways through which BDNF promotes its neuronal survival and neurite extension effects on cochlear spiral ganglion neurons [187]. Furthermore, regulation of soma size, dendritic branching pattern, and spine morphology was induced by BDNF-mediated PI3K/AKT/MTOR pathways in hippocampal neurons [188, 189]. For the survival of retinal ganglion cells, BDNF-mediated signaling involves the activation of both MEK and AKT [190].

Accumulating data indicates that GSK3β has a key role as a "gatekeeper" over a broad array of transcription factors, many of which are activated when GSK3β is inhibited and consequently contribute to cell proliferation and survival [149]. Hetman et al. showed that inhibition of GSK3β via phosphorylation at Ser9 is one of the mechanisms through which BDNF-induced PI3K/AKT activation protects cortical neurons from apoptosis [149, 191]. Although GSK3β phosphorylates four serine residues at the N-terminal region of β-catenin and causes β-catenin degradation, thereby mediating neuronal apoptosis [192], Hetman et al. suggested that β-catenin is not the critical substrate by which GSK3β induces neuron death [191]. A later study by the same group indicated that both the PI3K/AKT and the ERK1/2 pathways are required for BDNF suppression of GSK3β activity, as the inhibition of ERK1/2 also increased the basal activity of GSK3β in the cortical neurons [193]. However, they suggested that the relative contributions of the ERK1/2 and PI3K/AKT pathways to neuronal survival depend on the neuronal subtype and specific cellular injury [191, 193, 194]. Interestingly, microtubule-associated protein tau (MAPT) phosphorylation by GSK3β can cause axonal dysfunction and trigger neuronal apoptosis in AD, and inhibition of GSK3β by PI3K/AKT is an important mechanism for preventing neuronal degeneration [195].

NT4 mediates neuronal survival via TRKB in various types of neurons, including cultured spiral ganglion neurons [96], retinal ganglion neurons [97], and cranial sensory neurons [196]. Like BDNF, NT4 seems to induce cell survival effects via either the PI3K/AKT or MEK/ERK pathway or both [132]. The specific modified pathways containing mutations in the SHC-binding site of TRKB that lead to loss of NT4-dependent neurons (e.g., sensory neurons, saphenous nerve) but showed only modest effects on BDNF-dependent neurons (e.g., vestibular ganglion neuron) remain unknown [197].

BDNF/TRKB-induced activation of RAC1 and CDC42 signaling through PI3K was observed in migration of cerebellar granule cell precursor cells [168]. Hippocampal neurons treated with BDNF also showed increased neurite outgrowth through inactivation of the RHOA/ROCK cascade [184]. Recently, another study showed that BDNF/TRKB-mediated activation of RAC1 and CDC42 had distinct functions during adult hippocampal neurogenesis [198]. Importantly, CDC42 activity has been shown to be associated with early dendritic growth and dendritic spine maturation in adult hippocampal neurogenesis. In contrast, RAC1 activity was associated with the early stages of neuronal development and is required for the late stages of dendritic growth and spine maturation [198, 199].

NT3/TRKC-Mediated PI3K/AKT Signaling in Different Neurons

Although NT3 activates both neuroprotective MEK/ERK and PI3K/AKT pathways in cortical neurons, specific inhibition of the AKT pathway prevented the anti-apoptotic effect of NT3, whereas inhibition of the ERK pathway did not. That study concluded that the anti-apoptotic activity of NT3 is mainly a PI3K/AKT-dependent mechanism [200]. NT3-TRKC strongly activates the AKT pathway, which increases both axon caliber and distal branching in embryonic dorsal root ganglion neurons [174]. Moreover, a study of NT3 and glial cell-derived neurotrophic factor (GDNF) showed that NT3 enhanced GDNF-induced tyrosine-phosphorylation of RET (rearranged during transfection) receptor to increase the survival of the developing sympathetic neurons through activation of the PI3K/AKT pathway to a greater extent than did GDNF alone [201]. GDNF binds to GFRα1 receptor (GDNF family receptor α 1), which subsequently stimulates the tyrosine kinase domain of the RET receptor [202]. The mechanism of enhancement of GDNF-induced tyrosine-phosphorylation of RET by NT3, however, remains to be demonstrated.

In addition, NT3 treatment of hippocampal neurons showed increased neurite outgrowth through inactivation of the RHOA/ROCK cascade [184]. NT3-induced activation of RAC1 and CDC42 is presumably required for morphology regulation of CNS neurons [203].

RAS/RAF/MEK/ERK Signaling

In addition to PI3K/AKT signaling, NT binding and autophosphorylation of the TRK receptors lead to activation of the MEK/ERK pathway through a common mediator, the SRC homology 2 domain containing (SHC)-growth factor receptor bound protein 2 (SHC-GRB2) adaptor protein complex, which is modulated by fibroblast growth factor receptor substrate 2 (FRS2)-SH2 domain-containing protein tyrosine phosphatase (FRS2-SHP2) [144–146]. In this regard, a number of studies have demonstrated that SHP2 is an essential associated molecule located downstream of FRS2, critically involved in modulating the RAS/MEK/ERK signaling cascade [204–206]. Both FRS2 and SHP2 bind to GRB2, which constitutively associates with the RAS activator son of sevenless (SOS) for GRB2/SOS recruitment in RAS signaling [205, 207, 208]. Recruitment of a complex of GRB2 and SOS stimulates the activation of the small G-protein RAS and leads to transient activation of the RAF/MEK/ERK kinases cascade

further downstream (Fig. 3). SOS is a nucleotide exchange factor that activates RAS by replacing GDP with GTP. Activated RAS then interacts directly with the serine-threonine kinase RAF, followed by MEK-ERK activation. Prolonged ERK activation is also initiated at the phosphorylated site of TRK receptors but requires the kinase D-interacting substrate of 220 kDa (Kidins220, also known as ankyrin repeat-rich membrane spanning (ARMS)), which recruits CT10 (chicken tumor virus number 10) regulator of kinase (CRK), another adaptor protein [146]. Binding of Kidins220/ARMS to CRK activates the exchange factor CRK SH3-domain-binding guanine-nucleotide-releasing factor (C3G) and thus initiates RAF-dependent MEK/ERK signaling [209]. Ultimately, ERK signaling leads to local axonal growth and initiation of CREB-mediated transcriptional events [146]. Additionally, NTs can also inhibit signal transducer and activator of transcription 3 (STAT3) signaling via SHP2-mediated dephosphorylation of STAT3 [208, 210–212]. The dephosphorylation of STAT3 by SHP2 has also already been reported in leukemia inhibitory factor (LIF) signaling [210].

Activated RAS also directly binds to PI3K, initiating the major pathways and activating survival signals and cellular morphogenesis signals (see "PI3K/AKT signaling" section) [150–152]. NT-induced activation of RAS signaling also regulates RHO-GTPases effectors and RAC1 and CDC42 pathways in a PI3K-independent fashion [167–169]. Activated RAS interacts with TIAM1, which activates RAC1 [169]. A similar type of mechanism in which activated RAS interacts with Dbl's big sister (DBS) in a GTP-dependent manner to promote activation of CDC42 has been suggested [169, 213, 214]. Although it remains unclear whether RAS-mediated direct activation of RAC1/CDC42 antagonizes RHOA activity, it is possible that RHOA activity is regulated in an opposing manner to RAC1 by GEF and GTPase-activating proteins (GAPs) (reviewed in [159, 215, 216]) in the signal transduction cascades of neurons [217].

NGF/TRKA-Mediated RAS/MEK/ERK Pathway Signaling in Different Neurons

NGF-mediated MEK1/2/ERK1/2 appears to be particularly involved in neuronal survival and development of the PNS [218]. Specifically, NGF-induced ERK1/2 signaling is required for cutaneous sensory neuron innervation at late embryonic and early postnatal stages [218]. In addition to ERK1/2, ERK5 has been established as a retrograde survival signal for NGF-dependent sensory neurons of the dorsal root ganglia and sympathetic ganglia neurons [218–220]. Morphologically, NGF-induced axon elongation in sensory neurons of the dorsal root ganglia is also mediated via the MEK1/2/ERK1/2 pathway [174]. In the CNS, NGF-TRKA also regulates cholinergic neuron differentiation in the developing basal forebrain, possibly through the MEK1/2/ERK1/2 pathway [221–223].

NGF-mediated RAS is also involved in neurite growth regulation in a PI3K-independent fashion. Neurite outgrowth analysis of superior cervical ganglion and dorsal root ganglion neurons in response to NGF suggests that activated RAS mediates RAC1 activation through interaction with TIAM1 [167]. Although concomitant with RAC1 activation, CDC42 and RHOA activation has been demonstrated in the regulation of morphology of sensory neurons [152, 153]; the cellular determinants favoring NGF-induced activation of these effectors through RAS interaction in a PI3K-independent manner remain to be elucidated for CNS neurons.

BDNF- and NT4/TRKB-Mediated RAS/MEK/ERK Pathway Signaling in Different Neurons

BDNF and its receptor TRKB play key roles in neural development and plasticity [119, 224, 225]. In addition to the PI3K/AKT pathway, the ERK1/2 is a major pathway through which BDNF inhibits apoptosis and supports cortical neuron survival [194]. Likewise, BDNF-TRKB makes use of the MEK1/2/ERK1/2 pathway to regulate the survival of newly generated cerebellar granule neurons [186]. BDNF-induced MEK promotes this neural survival effect through a dual mechanism. Firstly, it phosphorylates endogenous BAD at Ser112 within minutes of TRKB activation by BDNF. Secondly, it increases the transcription of pro-survival genes, such as BCL2 [186]. Similarly, during the development of the cerebral cortex, BDNF/NT4-TRKB induces bone morphogenetic protein 7 (BMP7) in embryonic neurons through the activation of MAPK/ERK1/2 signaling and the negative regulation of p53/p73 function. Activated BMP7 in these neurons locally instructs competent precursors to generate astrocytes [226]. BDNF-dependent BMP7 expression possibly requires the activation of a TRKB-FL-mediated MAPK/ERK pathway, as the TRK inhibitor K252a and the ERK1/2 and ERK5 inhibitor U0126 have been shown to block BMP7 induction by BDNF [226]. Although Ortega and colleagues have reported that BDNF-activated TRKB-FL promotes astrogenesis via activation of the BMP7 pathway [226], other data suggest that BDNF-activated TRKB-T1 leads to astrogenesis accompanied with inhibition of neurogenesis [227] (see "Truncated TRKB-mediated differentiation of NSCs—astrogenesis versus neurogenesis" section). Remarkably, BDNF/TRKB-stimulated MEK1/2/ERK1/2 signaling frequently increases dendritic spine density and synaptic plasticity in hippocampal CA1 pyramidal neurons via the transcription factor CREB [228]. Similarly, BDNF-TRKB activates MEK1/2 and PI3K in hippocampal neurons, though the co-activation of these two pathways was not sufficient for the modulation of synaptic plasticity, indicating that an additional (other than PLCγ) signaling pathway is required to explain the findings [229–231].

The MEK5-ERK5 signaling pathway could be such an alternative pathway contributing to BDNF-mediated neurogenesis, synaptic plasticity, and memory formation by stimulating, e.g., myocyte-specific enhancer factor 2C (MEF2C) transcription factor in cortical neurons [232, 233].

With respect to apoptosis inhibition through the counteracting of GSK3β activity, the notion is that PI3K/AKT and MEK1/2/ERK1/2 negatively regulate GSK3β activity in CNS neurons [149, 191, 193]. Although the PI3K and ERK1/2 pathways can independently inhibit GSK3β activity, the combination of the two causes a much more significant decrease in GSK3β activity in cortical neurons, thus promoting cell survival [193]. As described above, PI3K/AKT-mediated GSK3β inhibition occurs through phosphorylation of GSK3β at Ser9; however, neither PI3K/AKT nor ERK1/2 inhibits phosphorylation of GSK3β at Tyr216, whose phosphorylation stimulates GSK3β activity. In fact, ERK1/2-induced inhibition probably does not occur through phosphorylation of GSK3β at Ser9 and seems to be a novel mechanism that is independent of Ser9 and Tyr216 phosphorylation in cortical neurons [193].

Neurite outgrowth experiments suggest that BDNF also induces the activation of CDC42 and RAC1, presumably through RAS signaling in, for example, cerebellar neurons [168]. In spiral ganglion neurons, a BDNF-mediated increase in the number of neurite outgrowths was associated with inhibition of the RAS-promoted RAC1/CDC42 cascades [187]. Whether the intermediate molecules TIAM1 or DBS are involved in the RAS-mediated activation of RAC1 or CDC42 for BDNF in CNS neurons remains unclear and needs to be elucidated.

NT3/TRKC-Mediated RAS/MEK/ERK Pathway Signaling in Different Neurons

NT3 has been shown to facilitate neurogenesis in the developing cerebral cortex, as mediated by phosphorylation of ERK1/2 and ERK5 [234]. NT3 expression was observed in the developing rat cochlea and has been shown to promote the survival and neurite outgrowth of spiral ganglion neurons [235]. The mechanism involved in the survival and neurite outgrowth of spiral ganglion neurons was found to be mediated primarily by the MEK1/2/ERK1/2 signaling pathway but not that of p38MAP kinase [235].

In the PNS, NT3-TRKC stimulates RAC1 and CDC42 signaling through RAS. RAC1-specific TIAM1 acts as a key mediator of TRKC-induced migration of Schwann cells. Particularly, TIAM1 activation of RAC1 requires RAS [213]. Thus, RAS is an important candidate in NT3-TRKC-dependent Schwann cell migration. The same study also suggested that the RAS-induced signaling pathway also requires DBS-promoted CDC42 signaling for Schwann cell migration [213]. Since the essential and distinct roles of NT3/TRKC-induced CDC42 and RAC1 in the regulation of PNS development have been demonstrated, the fundamental role of NT3/TRKC in the regulation of RAS-mediated RHO-GTPases effectors, RHOA, RAC1, and CDC42 in CNS neurons might be important and needs to be determined in future experiments.

PLCγ Signaling

Autophosphorylation of the TRK receptors at the most C-terminal tyrosine residue (e.g., Y785 in TRKA and its corresponding residues in TRKB and TRKC) allows recruitment of PLCγ, which activates the Ca^{2+}/calmodulin-dependent protein kinase (CaMK)/CREB signaling pathway via hydrolysis of PIP2 into DAG and IP_3 (Fig. 3) [144–146]. An elevated level of IP_3 leads to the release of intracellular Ca^{2+}, which in turn activates Ca^{2+}-dependent enzymes such as CaMK and the phosphatase calcineurin. Additionally, the release of Ca^{2+} and the production of DAG activate PKC, which subsequently stimulates ERK1/2 signaling via RAF [146].

NGF/TRKA-Mediated PLCγ Signaling in Neurons

Growth cone guidance is controlled by the co-activation of PLCγ and PI3K mediated by NGF-TRKA, though it does not exclude the involvement of other pathways, such as the SHC-RAS-MEK pathway, in triggering more long-term effects of NGF-TRKA, including an increase in the rate of neurite extension [236–239]. NGF-TRKA-mediated activation of PLCγ leads to an increase in cytoplasmic Ca^{2+}, which regulates growth cone attraction in *Xenopus* spinal neurons [236]. The PI3K pathway might regulate PLCγ-mediated Ca^{2+} signaling and might operate in concert with other inputs to control PKC [236].

BDNF- and NT4/TRKB-Mediated PLCγ Signaling in Neurons

In cultured cerebral cortical neurons, BDNF has been shown to stimulate a much stronger interaction between TRK and PLCγ than between TRK and NT3 [240]. BDNF- and NT3-induced PLCγ stimulates Ca^{2+} release from intracellular storage sites through the production of IP3. Accordingly, Ca^{2+} level was more highly increased in cells exposed to BDNF than in those exposed to NT3 [240]. Consequently, BDNF induced glutamate release via the activation of the PLCγ/Ca^{2+} system [241]. Similarly, BDNF-TRKB activates the PLCγ/Ca^{2+} signal system in hippocampal neurons, which modulates CaMKII-dependent cascades to propagate the signal to CREB, which in turn regulates gene expression for synaptic plasticity [242, 243]. Similarly, Minichiello et al. have revealed that BDNF-TRKB mediates hippocampal long-term potentiation (LTP) and synaptic plasticity via PLCγ and through the subsequent phosphorylation of CaMKIV and CREB [244]. However, others have shown that

both MEK and PI3K are essential for BDNF modulation of synaptic fatigue in the hippocampus [229].

Strikingly, Mizoguchi et al. found that, during the development of the hippocampus, the γ-aminobutyric acid (GABA)-activity shift from de- to hyperpolarization is modulated by BDNF and mediated via PLCγ [245]. More importantly, the change in modulatory role of BDNF on ionotropic $GABA_A$ accompanies a change in TRKB-mediated PLCγ signaling such as changes in CaMKII activity [245]. Interestingly, PLCγ mediates both TRK- and mGluRI-triggered regulation of hippocampal NT secretions [246].

NT3/TRKC-Mediated PLCγ Signaling in Neurons

NT3-induced potentiation of synaptic transmission at the neuromuscular synapses in *Xenopus* spinal neurons requires activation of both PLCγ and PI3K [247]. The same study demonstrated that the effect of NT3 was interrupted by the inhibition of either the PI3K or PLCγ pathway, which suggests that NT3-induced synaptic potentiation requires a concomitant activation of PI3K and PLCγ. In addition, it was demonstrated that NT3 can induce Ca^{2+} release from intracellular stores in spinal neurons but not muscle cells in a PLCγ-dependent but MEK- and PI3K-independent manner.

TRK Receptor Transactivation

Under some circumstances, TRK receptor activation is possible in the absence of NTs via transactivation by G protein-coupled receptors (GPCRs). Adenosine, a small ligand of a GPCR family, can transactivate the TRKA pathway by binding to adenosine receptor 2A, which then mediates the phosphorylation of the TRK tyrosine kinase and the SHC-binding domains via a G-protein pathway [248–252]. TRKA activation by adenosine can eventually result in prolonged activation of the PI3K/AKT pathway [248, 253]. A different study showed that adenosine agonists (e.g., CGS21680) could also transactivate TRKB for survival of motor neurons via the AKT pathway. That same report demonstrated that the adenosine agonist-mediated survival effect was abolished in isolated $TRKB^{-/-}$ motor neurons, indicating that transactivation through TRKB plays an essential role in survival responses of motor neurons [254]. Recent observation indicated that activation of epidermal growth factor receptor (EGFR) by EGF leads to transactivation of TRKB and TRKC in cortical neurons [255]. No significant differences in transactivation of TRKB and TRKC were observed in the $BDNF^{-/-}$, $NT3^{-/-}$, and wild-type mice. Moreover, activation of TRKB and TRKC by EGF was significantly reduced in $EGFR^{-/-}$ mice. Based on these observations, TRK receptor activation occur independent of NT via other receptors like GPCR or EGFR [255].

Truncated TRK Receptor-Mediated Signaling Pathways

In addition to full-length TRK receptor signaling, the truncated forms of TRK receptors are also expressed in the brain but lack the intracellular catalytic tyrosine kinase domain. The signaling pathways and biological functions of truncated TRK receptors are not well understood. Some data have suggested that the truncated versions of TRK receptors act as dominant negative inhibitors of full-length receptors and have own signaling pathway [146]. To date, available data on truncated isoforms of TRK receptors are limited to TRKB and TRKC, and no data are available for truncated TRKA [146, 256].

Truncated TRKB Signaling

There are some contradictions about truncated TRKB receptor signaling [256]. Some studies have reported that TRKB-T1 acts as a negative regulator of kinase signaling, e.g., via dominant negative inhibition of TRKB-FL through formation of nonfunctional heterodimers with TRKB-FL [256–258]. Other studies have demonstrated that truncated TRKB potentially activates kinase activity through its own signaling pathway, a G-protein signaling mechanism involving PKC [121, 227]. Functional studies on truncated TRKB receptors in hippocampal neurons have indicated that the truncated TRKB-T1 and TRKB-T2 receptors become more abundant at later stages of postnatal development [259].

Different roles of TRKB-FL, TRKB-T1, or TRKB-T2 were detected in the *Xenopus* oocyte system [260]. It was found that only TRKB-FL-expressing *Xenopus* oocytes but neither TRKB-T1- nor TRKB-T2-expressing cells were sufficient to elicit Ca^{2+} efflux response, as measured by PLCγ activation after stimulation by BDNF. Further, co-expression of either TRKB-T1 or TRKB-T2 with TRKB-FL did not elicit Ca^{2+} signaling upon stimulation by BDNF. Thus, TRKB-T1 and TRKB-T2 acted as dominant negative receptors, inhibiting the BDNF signal by forming nonfunctional heterodimers TRKB-FL/TRKB-T1 or TRKB-T2 with full-length TRKB receptors [260]. Likewise, a neural differentiation study has indicated that the various TRKB isoforms have different effects on dendritic arborization [261]. In that study, Yacoubian and Lo transfected ferret visual cortical slices with TRKB-FL and TRKB-T1 receptors in order to examine their roles in the regulation of cortical dendrite development [261]. TRKB-FL promotes net proximal dendritic branching and inhibits net distal dendritic elongation, while truncated TRKB isoforms counteract these actions by minimizing net proximal branching and promoting net elongation of dendrites [261]. Truncated TRKB receptors can act as dominant-negative

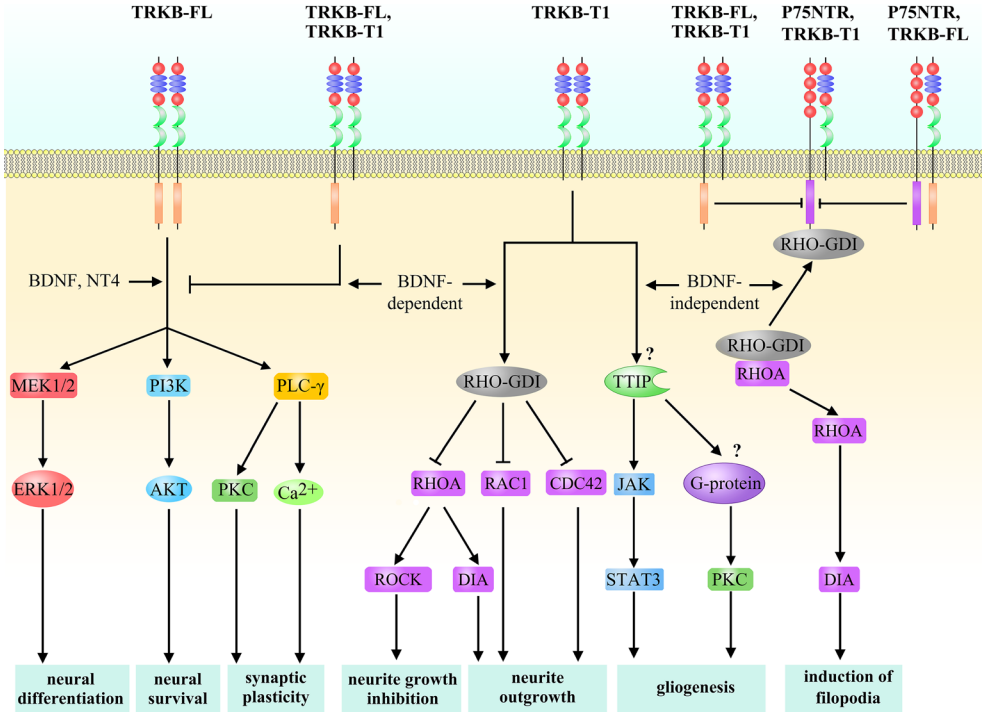

Fig. 4 General signaling cascades of full-length and truncated TRKB receptors. TRKB dimers are present in the brain as full-length (TRKB-FL) homodimers, truncated TRKB (TRKB-T1) homodimers, and heterodimers of TRKB-FL and TRKB-T1. When TRKB-T1 forms a heterodimer with TRKB-FL, it becomes a dominant-negative receptor that inhibits activation of TRKB-FL signaling [260, 261]. TRKB-T1 not only inhibits TRKB-FL in a heterodimer protein complex but also generates its own signaling cascades in BDNF-independent [259, 270, 271] and BDNF-dependent manners [264–266]. In a BDNF-independent pathway, a G-protein and its downstream signaling pathways are activated; this signaling pathway is not fully understood. In a BDNF-dependent pathway, RHO-GDI dissociates from truncated TRKB. Free RHO-GDI is available to inhibit RHO-GTPase, RHOA, RAC1, and CDC42 activity to regulate neuronal morphology (details of the RHO-GTPase and RHOA activity regulation by GEF and GAP are shown in Fig. 5). In addition, TRKB-T1 induces formation of filopodia in a BDNF-independent manner through interacting with p75NTR. Interaction of TRKB-T1 with p75NTR can lead to the activation of RHOA, which promotes filopodia growth via DIA signaling. Additionally, it was suggested that TRKB-FL might inhibit the downstream signaling of the putative TRKB-T1-p75NTR heterodimers by either forming heterodimers with TRKB-T1 or with p75NTR

inhibitors of full-length TRKB kinase activity and subsequent PLCγ, PI3K/AKT, and MEK/ERK signaling because expression of truncated TRKB receptors inhibits BDNF-induced neurite outgrowth (Fig. 4) [256, 262]. It was found that loss of TRKB-T1 (TRKB-T1$^{-/-}$) decreased neurite complexity and dendrite length in the amygdala. In contrast with the amygdala, TRKB-T1$^{-/-}$ does not affect hippocampus neurite morphology [263]. Particularly, the TRKB-T1 receptor is an important regulator of TRKB-FL signaling as it selectively affects dendrite complexity of certain neural populations in the amygdala [263]. Using transfected L cell fibroblasts expressing TRKB-FL, TRKB-T1, or TRKB-T2, Baxter et al. revealed that TRKB-FL transfectants but not transfected cells expressing TRKB-T1 or TRKB-T2 treated with BDNF exhibited induction of c-fos protein expression [121]. In addition, BDNF activation of either TRKB-T1 or TRKB-T2 increases the rate of acidic metabolite release from the cell, a common physiological consequence of many signaling pathways [121].

With respect to cell shape, TRKB-T1 has been reported to be involved in the regulation of astrocyte morphology through the control of RHO-GTPases in a BDNF-dependent manner [264, 265]. Binding of BDNF to TRKB-T1 dissociates RHO-GDI from the C-terminal tail of TRKB-T1, which in turn reduces the activity of RHO-GTPases, RHOA, RAC1, and CDC42 [265]. BDNF-dependent RHO-GDI dissociation from TRKB-T1 also causes a decrease in the activities of RHO-signaling molecules such as RHOA, ROCK, and PAK [266]. The activation of RHOA inhibits neurite outgrowth [267], whereas both RAC1 and CDC42 promote neurite outgrowth [268]. Thus, involvement of BDNF/TRKB-T1 in RHO proteins signaling regulates cytoskeletal rearrangement and thus affects how cells adjust their shapes. Another study on cerebral cortex-derived astrocytes have reported a predominance of truncated isoforms over the TRKB-FL receptor with regard to the influence of BDNF on the activity of glycine transporters, which was demonstrated through application of specific inhibitors of PLCγ, PI3K, and MEK upon BDNF stimulation, indicating that the evoked signaling pathways did not occur through a canonical TRKB-FL pathway. In contrast, BDNF action was lost through knockdown of truncated

TRKB (using the RNAi method) and also in the presence of a RHO family-specific blocker (toxin B), a signaling pathway that has been associated with TRKB-T1 [269].

In addition, TRKB-T1-induced effects on the formation of filopodia in hippocampal neurons were completely independent of endogenous and exogenous TRKB ligands (e.g., BDNF) and of TRKB-FL kinase signaling and originated from the intracellular domain of TRKB-T1 [259]. This possible mechanism suggests an interaction between TRKB-T1 and p75NTR receptors at extracellular or intramembrane areas, initiating filopodial growth via downstream activation of certain aspects p75NTR intracellular signaling (Fig. 4). Expression of both TRKB-FL and TRKB-T1 in hippocampal neurons resulted in inhibition of the TRKB-T1-induced growth of filopodia by TRKB-FL in a dominant-negative fashion. It is likely that TRKB-FL inhibits the downstream signaling of the putative TRKB-T1-p75NTR heterodimers by either forming heterodimers with TRKB-T1 or with p75NTR (Fig. 4) [259]. Another study, however, showed contradictory results, that TRKB-T1 had an inhibitory effect on p75NTR with regard to morphological alterations in primary hippocampal neurons without involvement of the ligand BDNF [270]. Thus, it remains unclear how TRKB-T1 exactly modulates filopodial growth without involvement of BDNF. BDNF induces TRKB-T1 signaling in cytoskeletal organization to regulate cell shape in astrocytes, while TRKB-T1 signaling in neurons occurs independent of BDNF. The crucial issue that needs to be addressed is whether subcellular expression of TRKB-FL and TRKB-T1 in astrocytes and neurons account for this dissimilar ligand dependency in TRKB-dependent cytoskeletal regulation variation [259, 261, 264]. Subsequently, it remains to be determined whether heterodimers of TRKB-FL and truncated TRKB activated (or inhibit) any downstream signals and whether p75NTR has a role in this regulatory mechanism.

The link between truncated TRKB and intracellular signaling can be explained by the presence of specific adaptor proteins. Kryl and Barker isolated a TRKB-T1 adaptor protein, named truncated TRKB-interacting protein (TTIP), from neuroblastoma cells by coimmunoprecipitation [271]. However, BDNF stimulation cannot modulate the interaction between TRKB-T1 and TTIP, and it is yet unclear whether RHO-GDI and TTIP bind directly to different motifs in TRKB-T1 or compete for the same binding site. Potential signaling cascades of full-length and truncated TRKB receptors are shown in Fig. 4 [256].

Truncated TRKC Signaling

Truncated TRKC receptors are expressed in various types of neurons such as vestibular ganglia neurons, dorsal root ganglion neurons, and cranial neurons [272]. Functional studies overexpressing the truncated TRKC transgene revealed neuronal losses in the PNS such as trigeminal neurons, geniculate neurons, and vestibular neurons, as in the $NT3^{-/-}$ mutant mice. Accordingly, truncated TRKC probably inhibits the TRKC-FL receptor directly by acting as a dominant-negative receptor [272, 273]. Binding of NT3 to truncated TRKC-T1 leads to recruitment of the scaffolding protein tamalin. NT3 initiation of this complex leads to the activation of RAC1 through adenosine diphosphate-ribosylation factor 6 (ARF6), which translocates to the cell membrane, causing membrane ruffling and formation of cellular protrusions [146, 274].

P75NTR-Mediated Signaling Pathways

P75NTR signaling regulates a wide range of cellular functions depending upon co-receptors, adaptor proteins, and specific ligands (Fig. 5). The pro-domain of proNTs interferes in the binding with and activation of TRK receptors, indicating that proNTs are distinctive ligands of p75NTR [275]. Interactions between TRK receptors and p75NTR increase the binding affinity for NTs and support pro-survival and pro-growth signaling via various pathways such as MEK/ERK, PI3K/AKT, and PLCγ [276–278]. At higher concentration, NTs encourage homo-dimerization of p75NTR [275], which subsequently activates JNK and NF-κB pathways depending upon the associations of specialized adaptor molecules such as tumor necrosis factor receptor-associated factor 1-6 (TRAF1-6), NT receptor-interacting factor (NRIF), NT receptor-interacting melanoma-associated antigen (MAGE) homolog (NRAGE), and receptor-interacting protein 2 (RIP2). Interestingly, JNK activation via p75NTR interactions with NRAGE, TRAF6, and NRIF leads to apoptosis. Association of TRAF6 with NRIF promotes JNK activation [279, 280]. NRAGE also acts as direct binding partner of p75NTR and induces caspase activation and cell death through a JNK-dependent mitochondrial apoptotic pathway [281]. However, it is not fully understood whether NRAGE, TRAF6, and NRIF form a complex or function independently to control different stages of the JNK signaling cascade. Another pathway through which p75NTR can activate JNK signaling is the lipid signaling of the molecule ceramide via activation of sphingomyelinases [282, 283].

Survival is promoted through activation of NF-κB by the binding of NTs to p75NTR in the absence of TRK receptors, possibly through the associations of adaptor molecules RIP2 and TRAF6 [284–287]. This p75NTR-adaptor-protein interaction is ligand-dependent, and maximal interaction was observed for NGF-p75NTR activation, while the other NTs promoted a weaker association of TRAF6 with p75NTR [285]. These observations indicate that adaptor molecules act as a bifunctional switch for cell survival or apoptosis mediated by p75NTR. The TRK receptor-independent pro-survival effects of p75NTR are not fully understood; however, one

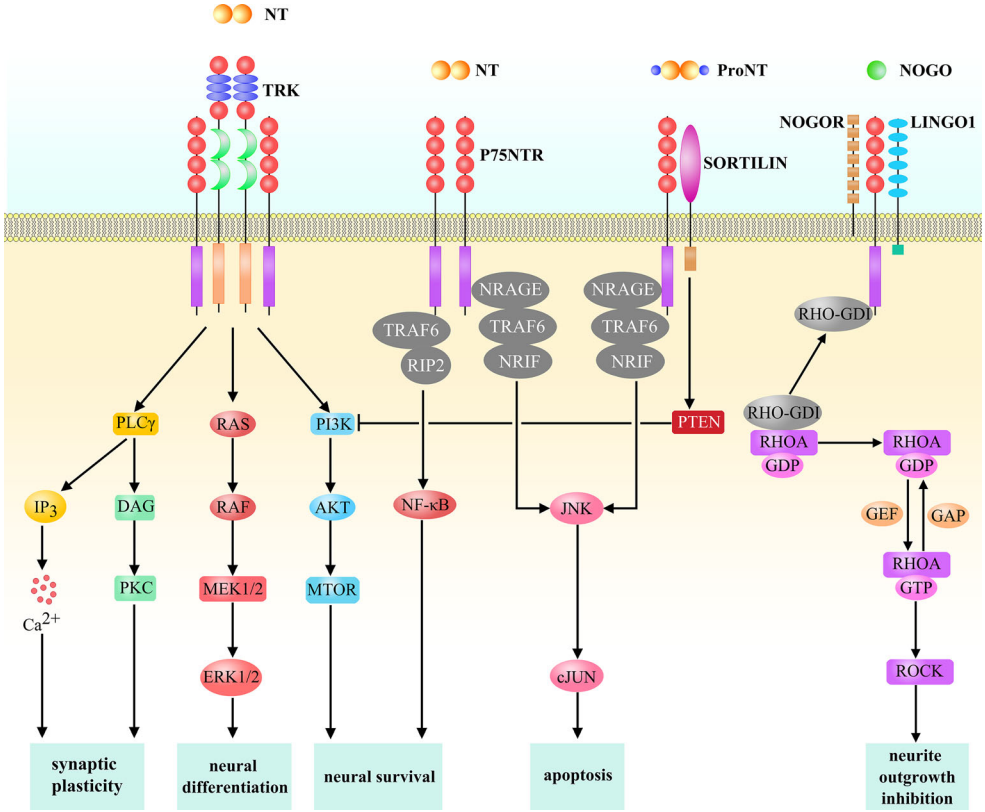

Fig. 5 P75NTR mediates several signaling pathways depending on co-receptors and ligands. Interactions between TRK receptors and p75NTR regulate several pathways including MEK/ERK, PI3K/AKT, and PLCγ through high-affinity binding with mature NTs (see Fig. 3). At higher concentration, NTs encourage homo-dimerization of p75NTR, which subsequently activates JNK upon association of specialized adaptor molecules, presumably TRAF6, NRAGE, and NRIF. The binding of NTs to p75NTR also activates survival signaling of NF-κB, possibly through associations with the adaptor molecules RIP2 and TRAF6. Binding with sortilin allows p75NTR to activate JNK/cJUN and PTEN. Activation of PTEN eventually inhibits the survival-supporting PI3K signaling pathway (see Fig. 3). Binding of NOGO, MAG, or MOG to the receptor complex of p75NTR, NOGOR, and LINGO1 leads to dissociation of RHO-GDI from the RHO-GDI/RHOA complex. Dissociation of RHO-GDI from the RHO-GDI/RHOA complex results in activation of the RHOA that modulates the cellular cytoskeleton system and eventually modulates neuronal axon growth. GEF activates RHOA by promoting the phosphorylation of GDP into GTP, whereas GAP inactivates RHOA by dephosphorylation of GTP into GDP

downstream pathway that has been identified involves the transcription factor NF-κB [133, 286, 287].

ProNT binding to the p75NTR/sortilin protein dimer receptor complex mediates apoptosis via the transcription factor JNK3 and activation of cJUN [10, 133, 278]. The precise signaling cascades elicited by the p75NTR/sortilin complex remain to be elucidated, but available data have indicated that adaptor molecules NRIF, NRAGE, and TRAF6 play key roles in death signaling cascades evoked by p75NTR depending on the type of neurons [288]. In hippocampal neurons, NRIF is required for p75NTR-mediated apoptosis through binding of proBDNF and proNGF. NRIF$^{-/-}$ mice show an increase in p75NTR expression; however, these neurons fail to undergo apoptosis in contrast to those in wild-type mice [289]. Coimmunoprecipation analysis demonstrated that proBDNF and proNGF induced the interaction between NRIF and NRAGE to form a complex for p75NTR-mediated apoptosis in hippocampal neurons [289]. Further data support the supposition that proNGF requires NRAGE for p75NTR/sortilin-mediated apoptosis in retinal ganglion cells [10, 11, 288]. Previous studies have also demonstrated that p75NTR-dependent apoptosis in sympathetic neurons (e.g., super cervical ganglionic neurons) requires the binding of NRIF to TRAF6 [290, 291]. Since TRAF6 is a required adaptor protein for p75NTR-dependent apoptosis in sympathetic neurons, it remains to be determined whether TRAF6 interacts with NRIF in the various CNS neurons [292].

Interactions of p75NTR with the NOGO (reticulon 4, RTN4) receptor (NOGOR, also known as RTN4R or NGR) and LINGO1 (leucine-rich repeat and Ig-domain containing 1) form a tripartite receptor complex of NOGO, MAG (myelin-associated glycoprotein), and MOG (myelin oligodendrocyte glycoprotein) [239, 293]. This receptor complex mediates axonal growth inhibition and plays a role in regulating axonal regeneration and plasticity in the adult CNS, and LINGO1 provides additional mechanisms in the control of growth. Binding of myelin proteins (e.g., NOGO, MAG, or MOG) with the receptor complex of p75NTR with NOGOR and

LINGO1 eventually activates RHOA [237, 238, 293] by displacement of RHO-GDI and concurrently suppresses RAC, leading to a collapse of nerve growth cones, neurite retraction, and decrease in spine density (Fig. 5) [278, 294]. In contrast, NTs binding to p75NTR inactivate RHOA in HN10e cells and cerebellar neurons, abolishing the interactions of p75NTR with RHO-GDI and RHOA [238, 295].

Through the investigation of the ultimate fate of neurons in terms of survival and apoptotic signaling pathways meditated through TRKs and p75NTR, it seems that PTEN phosphatase is a pivotal switch relay [296] (Figs. 3 and 5). Crucially, concurrent proNGF-mediated activation of p75NTR and BDNF-mediated activation of TRKB can induce apoptosis even in the presence of phosphorylated and activated TRKB kinase. P75NTR-induced apoptosis occurs through PTEN, which concurrently suppresses TRKB-induced PI3K pro-survival signaling (Figs. 3 and 5). Moreover, inhibition of PTEN can regenerate the BDNF-induced pro-survival PI3K/AKT pathway and protects basal forebrain neurons from proNGF-induced apoptosis. Thus, PTEN is a pivotal switch relay molecule that decisively mediates the coherence between p75NTR-induced apoptotic signaling and TRK-mediated survival signaling in the brain [296].

NTs and Synaptic Plasticity

Synaptic plasticity is a key architectural feature of several current theories explaining neuronal network abnormalities during NDs, including AD and PD [297–299]. Synaptic plasticity, essentially mediated in the form of LTP and LTD (long-term depression), appears to be a striking feature of the brain, reflecting its ability to encode and retain memories via the activity-dependent functional and morphological restoration of synapses [300].

NGF and Synaptic Plasticity

Exogenous application of NGF to hippocampal neurons could demonstrate its potential role as a modulator of learning and memory processes [301]. NGF is able to convert high-frequency stimulation (HFS)-induced LTP into LTD in visual cortical neurons [302]. The blockade of NGF signaling by anti-TRKA antibody did not change the amplitude of the LTD induced by low-frequency stimulation (LFS) [302]. The NGF-induced LTD shift from LTP, selective for synaptic modification induced by HFS, was mediated by TRKA [302]. Another previous report found that, at 200 ng/ml, NGF had no effect on LTP in the developing visual cortex [303]. Conversely, Conner et al. indicated that increased NGF significantly potentiates cholinergic neuronal markers and facilitates hippocampal LTP [304]. Blockade of endogenous NGF considerably attenuated hippocampal LTP and impaired retention of spatial memory [304]. A critical recent report argued that NGF has a dual effect on LTP, reducing LTP at 200 ng/ml but significantly enhancing LTP at higher concentrations (>350 ng/ml) [305]. It remains unclear how this is mediated, and the exact mechanism needs to be investigated to understand NGF release at synaptic clefts and NGF action and signaling through TRKA or p75NTR receptors, leading to induction of LTD and favoring synaptic weakening over synaptic strengthening. It was suggested that higher concentrations of NGF modulate LTP via p75NTR signaling [305]. It is crucial to understand this exact mechanism because p75NTR can generate a number of different downstream signaling pathways depending on its specific ligand (proNGF or NGF) and co-receptors (Figs. 3 and 5).

BDNF and Synaptic Plasticity

BDNF is the most attractive candidate in the study of activity-dependent refinement of synaptic connections like LTP. Despite numerous queries regarding the effect of endogenous BDNF on LTP at physiological conditions, the detailed mechanism of synaptic BDNF release, and BDNF signaling through TRKB receptors leading to time-dependent (t)-LTP, a number of excellent reviews have addressed and revealed convincing evidence that BDNF promotes LTP [3, 306, 307]. Patterson et al. first observed that expression of BDNF in the hippocampus is induced by HFS, which is often used to induce LTP [308]. Subsequently, Figurov et al. demonstrated LTP regulation by BDNF, as treatment of hippocampal slices (postnatal day 12–13 rats) with BDNF induced early phase LTP (E-LTP) by theta burst stimulation (TBS). In the absence of BDNF, TBS induces only short-term synaptic potentiation (STP) [309]. The same study also showed that inhibition of BDNF activity by the BDNF scavenger TRKB-IgG reduces the magnitude of LTP in the adult hippocampus [309]. Further, hippocampal slices from BDNF-knockout mice showed that a reduction in BDNF expression was associated with a significant reduction in hippocampal LTP [310, 311]. Moreover, Korte et al. confirmed that $BDNF^{+/-}$ and $BDNF^{-/-}$ mice showed significant and similar degrees of reduction in LTP [310]. Thus, it has been suggested that a certain level of BDNF in the hippocampus is essential for LTP induction and/or maintenance [310]. More recently, Edelmann et al. reported that single postsynaptic action potentials paired with presynaptic excitatory stimulation activated a BDNF-independent canonical t-LTP. Conversely, the theta bursts of postsynaptic action potentials preceded by presynaptic excitatory stimulation elicited BDNF-dependent postsynaptic t-LTP that relied on postsynaptic BDNF secretion [4]. Despite improved understanding of the possible role of proBDNF, many questions and major challenges in the regulation of LTP and LTD remain to be resolved. Suggestions of bidirectional regulation of synaptic plasticity by proBDNF and mature BDNF have been made

[80, 312]. Interestingly, treatment of hippocampal neurons with proBDNF enhances LTD through activation of p75NTR [80, 312]. In contrast, it was shown that LTD in hippocampal CA3-CA1 neurons of conditional BDNF-knockout mice is unaffected, suggesting that neither pro- nor mature BDNF is necessary for the induction of LTD [313]. In this context, the exact role of proNTs and NTs in the homeostasis of synaptic plasticity, in particular in the CNS, needs to be explored, which will be also essential for understanding of a variety of neurological conditions, including learning and memory formation, neuropathic pain, epilepsy, and depression [314, 315].

NT3 and Synaptic Plasticity

In terms of synaptic plasticity, it seems that NT3 does not play an essential role in LTP in the hippocampus [316, 317]. However, studies of neuromuscular synapses have demonstrated that BDNF and NT3 are both released in an activity-dependent manner and act on presynaptic terminals to potentiate neurotransmitter release [247, 318]. External Ca^{2+} must enter the nerve terminal for BDNF to be effective, and its potentiating action is facilitated by elevated cAMP level. In contrast, Ca^{2+} entry is not needed for NT3 to be effective; instead, NT3 increases Ca^{2+} concentrations within terminals by releasing it from intracellular stores [247, 318]. Potentiation of presynaptic motor neuron neurotransmitter release induced by NT3 requires PI3K activation. It was suggested that PI3K is necessary but not sufficient to convey the effects of NT3 [247].

Intrahippocampal microinfusion of NT3 induces LTP of synaptic efficacy in the hippocampal dentate gyrus CA3 projection accompanied by a mossy fiber (a pathway that originates from the dentate gyrus granule cells and provides an excitatory synaptic input to neurons in the dentate gyrus hilus and hippocampal CA3 area [319]) synaptic reorganization of the CA3 hippocampal area of adult rats in vivo [320]. Further, intrahippocampal microinfusion of NT3 blocks LTP induction induced by HFS in the hippocampal CA3 area. This modification in synaptic plasticity by NT3 at the CA3 pathway was shown to be blocked by the presence of the TRK receptor inhibitor K252a [320]. It was suggested that NT3 regulates homeostatic structural reorganization of hippocampal mossy fibers.

NT4 and Synaptic Plasticity

With respect to learning and memory, hippocampal slices from $NT4^{-/-}$ mice showed normal basal synaptic transmission, short-term plasticity, and deleterious LTP at the Schaffer collateral-CA1 synapses [321, 322]. Those reports demonstrated that, although hippocampal development was largely unaffected, the long-term memory defects and the long-lasting (L)-LTP at the same synapses were significantly reduced in the mutant mice. Based on impairment of both L-LTP and long-term memory, it was suggested that NT4/TRKB signaling is crucial for long-term information storage. NT4-mediated LTP induction was observed in rat hippocampal slices pre-treated with amyloid beta (Aβ), where Aβ inhibited LTP at hippocampal synapses [323]. Further evidence showed that NT4 has a role in LTP expression and in learning and memory. Blockade of NT4 using anti-NT4 inhibited LTP but had no effect on short-term memory [324].

In general, all aspects of NT functions depend on their diverse biochemistry and specific receptors [2, 3, 6, 119]. Expression, post-translational modification, and subsequent secretion are crucial steps that direct NTs, whether to the pro-form or mature form, to mediate the entire signaling action in the different types of neuronal and non-neuronal cells [2, 3, 6, 38, 119]. NT receptors themselves have many isoforms, which ultimately produce different downstream signaling events depending upon NT or proNT binding. Upon binding of NTs and pro-forms to their receptors, recruitment of an appropriate wide array of signal transducer proteins results in the activation of various downstream signaling pathways, which in turn eventually manifest as cellular events [2, 3]. In the understanding of neuronal network architecture of the brain as a basis of its diseases, synaptic plasticity is an important neurochemical machinery where the role of an NT, proNT, and their receptors are critical factors, a precise understand of which is needed at the molecular level for the regulation of synaptic plasticity [297, 299, 325].

Expression of NTs and Its Receptors in Stem Cells

ESCs and NTs

ESCs

ESCs are stem cells that are derived from a cell population of the inner cell mass of an embryonic trophoblast, which are subsequently isolated and grown in vitro [18]. ESCs are mitotically active and thus have the ability to proliferate indefinitely; as pluripotent cells, they can differentiate into all types of cell in the body. In culture, ESCs require complex signaling regulation to be maintained in an undifferentiated state [326]. Clonal survival of human ESCs in vitro is very low, even in the presence of basic fibroblast growth factor (bFGF) [327].

NT Receptors in Human ESCs Mediate Stem Cell Survival

Pyle et al. have reported that NTs have a positive role in promoting clonal survival of human ESCs [30]. That group observed that human ESCs of the H1 and H9 lines expressed TRKB and TRKC receptors, as determined by qRT-PCR,

immunostaining, and Western blotting [30]. Strikingly, these ESCs did not express TRKA or p75NTR. Another report, however, described that the same H9 ESCs expressed p75NTR, as demonstrated by RT-PCR analysis; however, no other TRK receptors were assessed [328].

Based on receptor expression in the Pyle et al. study, a cocktail of NTs composed of BDNF, NT3, and NT4 was introduced into ESC culture media to study the effect of NTs on human ESCs. They found an improvement in human ESC survival following single-cell passaging, indicated by a 36-fold increase in the resulting alkaline phosphatase-positive colonies. Furthermore, human ESC colonies induced with NTs survived the subsequent passaging, whereas colonies without NTs induction did not. The pro-survival effects of BDNF, NT3, and NT4 were abolished when the NTs were inhibited by blocking antibodies specific to the NTs [30]. That study concludes that the pro-survival effects of NTs are specifically attributed to the anti-apoptotic signaling pathway downstream of TRKB and TRKC receptor phosphorylation. The TRKs were rapidly phosphorylated upon NT addition, and pro-survival effects could be attributed to the activation of the PI3K/AKT pathway since the addition of PI3K-specific inhibitor abolished the pro-survival effect. These findings indicate that BDNF, NT3, and NT4 act together as survival factors of human ESCs and are mediated by the PI3K/AKT signaling pathway.

NTs and Receptor Expression in Mouse ESCs

The BAC7 line of mouse ESCs, a derivation of D3 mouse ESCs that overexpresses a green fluorescence protein (GFP) under the β-actin promoter, releases NGF, BDNF, and NT3 when cultured on feeder cells (mouse embryonic fibroblast (MEF) as feeder cells) [329]. CGR8, a feeder-independent line of mouse ESCs, releases only BDNF and NT3 and at significantly lower level compared to the BAC7 line, even after accounting for the difference that arises from the NTs (NGF, BDNF, and NT3) released by the feeder cells [329]. Moreover, the CGR8 clone does not express NGF. That study further compared the NT expression of these ESCs when treated with tissue extracts derived from healthy brains or a traumatic brain injury model. The study concluded that BDNF level was increased in normal brain and traumatic injury brain after extract treatment, while NGF and NT3 levels were decreased. However, the differences in NT release in the two conditions were not significant.

Contrary to human ESCs, mouse ESCs express TRKA, TRKB, and p75NTR but not TRKC during the late blastocyst stage [330]. However, when these cells are cultured in vitro as ESCs, they express high levels of p75NTR and TRKA, as confirmed by qRT-PCR and immunostaining. The expression level of p75NTR, however, decreases when these ESCs undergo differentiation. By applying specific inhibitors, it was further demonstrated that NGF has a pro-survival and enhancing proliferation effect on ESCs via binding of NGF to TRKA or p75NTR [330].

ESCs and Neural Fate Commitment Mediated by NGF

NGF has been studied with regard to directing mouse ESC differentiation to a neuronal lineage, resulting in the accelerated appearance of neuron-like cells in the differentiating embryoid bodies [331].

In human ESCs, Schuldiner et al. induced ESC differentiation with eight individual growth factors (i.e., bFGF, transforming growth factor β1 (TGF-β1), activin-A, BMP4, hepatocyte growth factor (HGF), EGF, NGF, and retinoic acid) and assayed the mRNA expression of the resulting tissues using ecto-/meso-/endodermal lineages markers. NGF, as well as retinoic acid and bFGF treatments, strongly promoted the expression of the neural marker neurofilament heavy chain (NF-H) [328]. More importantly, NGF treatment induced the expression of all markers (ecto-/meso-/endodermal) used in the study, which signifies that NGF allows the differentiation of ESCs into all three embryonic layer lineages [328]. The same authors followed this study by comparing the neural differentiation potential of retinoic acid, NGF, and TGF-β1 [332]. The study reported that 100 ng/ml NGF increased the expression of the early and late neural marker neurofilament light chain (NF-L) that is comparable to a low concentration (10^{-7} M) of retinoic acid, whereas TGF-β1 did not increase neural differentiation. Similarly, NGF alone or in combination with retinoic acid has been shown to increase neural differentiation, shown by increases in nestin and βIII-tubulin (TUBB3) in human ESCs that were grown on a 3D synthetic scaffold system [333].

ESCs and Neural Fate Commitment Mediated by BDNF

The role of NTs, particularly BDNF, has been studied in mouse ESCs constitutively over-expressing BDNF from the Gt(ROSA)26Sor locus [334]. Neuronal differentiation via embryoid body formation demonstrated a subcellular location shift of BDNF from the cytosol during the undifferentiated/early stage, presumably in the proBDNF form, and progressing toward the dendrites and axons of mature neurons. Over-expression of BDNF greatly enhanced the neurogenesis capability of ESCs, in particular to GABAergic neurons. Moreover, the same study reported that BDNF increased the number of dendrites in differentiated neurons.

ESCs and Neural Fate Commitment Mediated by NT3

A study using human cells grown on a 3D synthetic scaffold system revealed that NT3 has higher neural differentiation

potential compared to NGF and retinoic acid based on expression of nestin and TUBB3 in 4- and 9-day-old embryoid bodies [333]. The NT3 neurogenic potential also has been demonstrated to be synergistic with retinoic acid.

ESCs and Cardiac Fate Commitment Mediated by NT Signaling

A recent study by Xu et al. explored the pro-cardiomyogenic effect of the BDNF mimetic peptide Betrofin3 on transgenic α-MHC (myosin heavy chain) enhanced-GFP (EGFP) mouse ESCs [335]. Results of this study revealed that Betrofin3 exerted the most striking pro-cardiomyogenic effect on ESCs compared to FGF8 and FGF10 based on mesodermal (brachyury) and cardiac-specific myosin light chain 2 (MLC-2 V) marker expression, as well as EGFP-positive cells. Application of Betrofin3 also increased the beating frequency of embryoid bodies. Specifically, the authors demonstrated that TRKB expression was up-regulated during cardiomyogenic differentiation and that the effect of Betrofin3 was abolished in the presence of the TRKB inhibitor K252a.

NSCs and NTs

NSCs

NSCs are multipotent stem cells that have the ability to self-renew and differentiate into various cell types of the CNS such as neurons, astrocytes, and oligodendrocytes. Adult NSCs exist in the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampus, which function to replace lost or damaged neural cells [336]. NSCs can be derived from primary tissues, including fetal, postmortem, neonatal, and adult brain tissues, as well as ESCs and iPSCs [337, 338].

NSCs, NTs, and Neurogenesis

Mouse embryonic NSCs have been demonstrated to express the NT receptors TRKA, TRKB, TRKC, and p75NTR [339–341]. This finding was partially confirmed by brain slice immunocytochemistry that showed dense TRKB-positive cells in the granular hippocampal area, known to harbor adult NSCs [342]. The data indicate that the truncated isoform of TRKB is abundantly expressed in these NSCs, while it is known that cortical neurons preferentially express the full-length form of TRKB [339, 341]. Mouse NSCs also have been demonstrated to produce NGF, BDNF, and NT3 [29, 343].

Stimulation of embryo-derived rat neural precursor cells (NPCs) by retinoic acid leads to increased expression of TRKB and p75NTR receptors, as well as sustained TRKC expression [344]. These NPCs are responsive to BDNF or NT3 but not NGF, as evidenced by a significant increase in the generation of GABA-, tyrosine hydroxylase (TH)-, and calbindin-positive neurons [344]. Acetylcholinesterase (AChE)-positive neurons, however, are mostly generated from BDNF-stimulated NPCs but not NT3 [344]. The notion that different NTs direct neurogenesis to different paths has been discussed previously [340]. The authors mentioned that NT3 drives the differentiation of embryonic forebrain NSCs into bipolar neural cells and oligodendrocyte, while BDNF leads to multipolar neural cells [340].

Another study using mouse embryonic NSCs showed that BDNF and NT3 promoted survival and differentiation of cultured embryonic NSC into neurons [345]. The authors further deduced that inhibition of NSC endogenous NT signaling by blocking antibodies for BDNF, NT3, or both significantly increased apoptosis and decreased NSC proliferation and neural differentiation.

NTs-Induced Neurogenesis—Activation of Transcription Factors

In addition to BDNF, NT4 has also been demonstrated to promote neurogenesis of mouse embryonic NSCs by inhibition of pro-astrogliogenesis STAT3 signaling [211]. This study showed a rapid reduction in STAT3 phosphorylation upon stimulation with NT4. However, another study reported that BDNF induction of mouse embryonic neurosphere increased STAT3 phosphorylation [339]. Thus, BDNF and NT4 have opposing actions toward STAT3 phosphorylation despite sharing a common TRKB receptor [211, 339]. Numerous other studies support the notion that NTs promote neurogenesis [341, 346, 347].

Another in vitro study used rat embryonic NSCs to illustrate that, in addition to BDNF, NGF also promotes neurogenesis [348]. The study revealed that BDNF has a higher neurogenesis potential than NGF; and a combination of NGF and BDNF induced the highest expression of the neural marker neuron-specific Tubb3. Additionally, the study concluded that the neurogenesis potential of NTs is mainly mediated by the MEK/ERK pathway and basic helix-loop-helix (bHLH) transcription factors, i.e., Achaete-Scute Family BHLH Transcription Factor 1 (ASCL1, also known as MASH1), neurogenin 1 (NEUROG1), and neuronal differentiation 1 (NEUROD1) [348, 349]. Human NSCs display a similar response when stimulated by NTs [347]. In their experiment, Caldwell et al. reported that NTs increase the population of TUBB3-positive cells and decrease glial fibrillary acidic protein (GFAP)-positive (glia) cells. Furthermore, they concluded that NT4 has the highest neurogenic potential compared to NT3 or BDNF [347].

WNT/β-catenin is another possible signaling pathway triggered by BDNF to promote neurogenesis of newborn mouse NSCs [350]. This study reported an increased

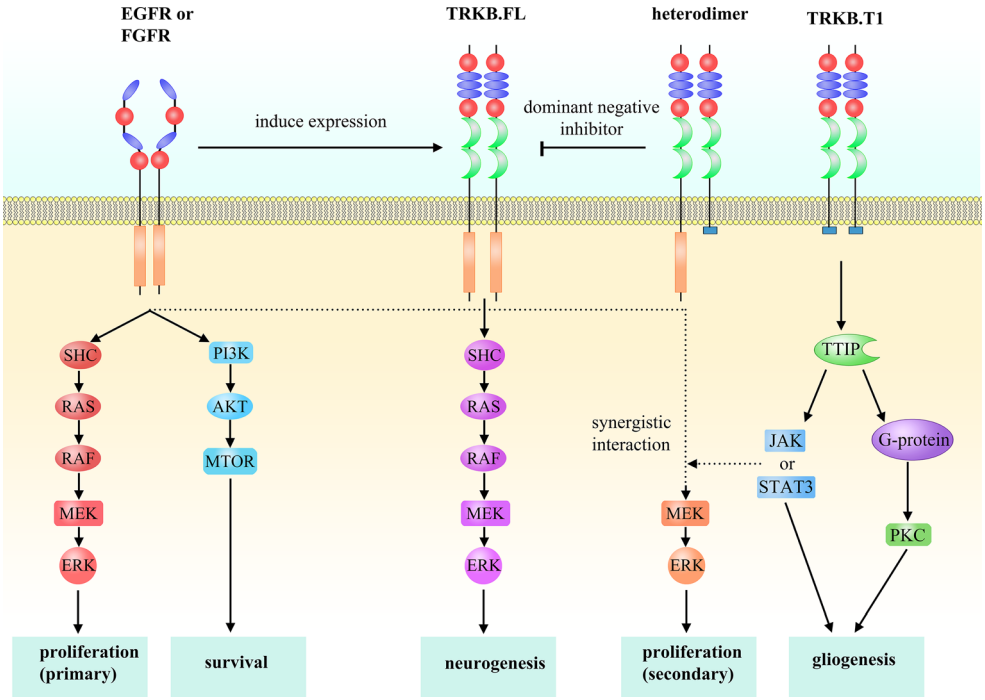

Fig. 6 The possible interplay between FL- and truncated-TRKB activation in NSCs. BDNF promotes NSC proliferation in synergy with mitogen receptor (FGFR or EGFR), possibly through interaction with TRKB-T1 downstream signals. BDNF activation through TRKB-FL induces neurogenesis, while activation of TRKB-T1 in the absence of bFGF induces gliogenesis. TRKB-T1 can also act in a dominant-negative manner by forming nonfunctional heterodimers with TRKB-FL to block BDNF/TRKB-FL-mediated neurogenesis (as explained in 4.5.1)

number of Tubb3-expressing cells when the NSCs were treated with BDNF, and Wnt signaling inhibitor abolished the increase. This study also reported a slight increase in 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (CNPase)-expressing cells in the BDNF-treated group, signifying that BDNF also stimulates differentiation to oligodendrocytes.

Truncated TRKB-Mediated Differentiation of NSCs—Astrogenesis Versus Neurogenesis

Cheng et al. demonstrated that activation of the TRKB-T1 receptor leads to differentiation of mouse embryonic NSCs into astrocytes, accompanied by inhibition of neurogenesis, as confirmed by in vitro and in vivo analyses (Fig. 6) [227]. We described above (see, "Truncated TRKB signaling" section) that truncated TRKB is considered a dominant-negative inhibitor of TRKB-FL in neurons via heterodimer protein complex formation [260, 261]. However, data from Cheng et al. suggest that TRKB-T1 does not act passively as an NT sink to inhibit TRKB-FL in a heterodimer TRKB-T/FL protein complex formation, but rather stimulates its own signaling pathway, since TRKB-T1 activity can be blocked specifically by G-protein and PKC pathway inhibitors [227]. Interestingly, another group reported a significant increase in neurogenesis using TRKB-T1-over-expressing mouse embryonic NSCs, although the specific pathway was not explored [351].

NTs Promote Proliferation of NSCs

NTs promote the proliferation of NSCs. The combination of NGF, BDNF, and bFGF has a significantly higher proliferative effect compared to a combination of bFGF with NGF or BDNF or a combination of NGF and BDNF only [352]. Thus, the data concluded that NGF and BDNF work synergistically with bFGF to promote proliferation of NSCs. Others have also observed proliferative effects of BDNF on NSCs [339, 350]. Islam et al. further elaborated that the BDNF effects on embryonic mouse NSCs are likely to be mediated by the TRKB-T1 receptor as it is highly expressed in NSCs, while the TRKB-FL has a drastically lower expression level [339]. This observation is further supported by a TRKB-T1 over-expression study reported by Tervonen et al. using mouse embryonic NSCs [351] (Fig. 6). While Chen et al. have suggested that the TRKB-T1-mediated proliferation signal is possibly transduced by a Wnt/β-catenin signaling pathway [350], others have discussed the possible involvement of TRKB-T1-modulation of STAT3, PI3K/AKT, and MEK/ERK pathways [339].

The role of NT3 in NSC proliferation is controversial. One study showed that NT3-over-expressing mouse NSCs has an accelerated proliferation as demonstrated by larger neurospheres [353]. However, this notion is rejected by an in vitro study that demonstrated that NT3 inhibits NSCs proliferation via blocking the FGF2-induced phosphorylation of AKT and its downstream target GSK3β [354].

NTs and NSCs—Motility and Quiescence

NTs, in particular BDNF, also have a role in modulation of NSC motility [355]. For instance, BDNF acts as molecular cue for migrating NPCs and is mediated by the PI3K/AKT pathway [356–358].

A recent in vivo study using transgenic mice that express low levels of NTs has demonstrated that NTs are involved in maintaining NSC quiescence [359]. This study suggested that endothelial cell-derived NT3 switches the fate of a specific NSC subtype, so called B1 cells, from an actively proliferating state into a quiescent state. Eventually, early activation of B1 cells leads to premature depletion of this cell type at older age and decreases in neurogenesis and oligodendrogenesis.

BDNF as a Molecular Guide for NSCs Migration—Evidence from In Vivo Studies

It is persistently maintained that BDNF level is elevated in brain regions affected by ischemia or stroke and is produced by endogenous neural cells [360–363], astrocyte, microglia, and ependymal cells [364]. Further, it has been demonstrated that NSCs have the ability to mobilize into damaged areas, even in the event of severe injury [365–371]. It has been concluded that BDNF, produced in the injured region, acts as signaling cue to mediate NSC migration to the pathologic area. These facts are supported by the finding that BDNF guides NSC migration along the vasculature [356, 372]. The migration of human NSCs, however, can be inhibited by pre-differentiation of the NSCs in vitro before transplantation, e.g., by applying NT4, which resulted in higher accumulation of donor cells around the transplantation site [347].

MSCs and NTs

MSCs

MSCs are stem cells capable of forming bone, cartilage, adipocyte, and other mesodermal tissues [373]. MSCs can be isolated from bone marrow, placenta, adipose tissue, lungs, blood, umbilical cord blood, and Wharton's jelly of the umbilical cord [374–376]. Most commonly, MSCs are isolated from adult bone marrow and so are also branded as bone marrow stromal stem cells (BM-MSCs) [377]. Since MSCs can differentiate into a variety of cell types, they have great potential in regenerative medicine, as they are widely used for cell transplantation therapies [378], in particular for the treatment of NDs [379, 380].

MSCs and NTs Production

Over the past few years, various groups have observed that MSCs produce neurotrophic factors (NTFs) including NTs [381–383] (Fig. 7). More specifically, using qRT-PCR and ELISA analyses, it has been determined that human bone marrow-derived MSCs express BDNF and NGF but not NT3 and NT4 [384]. However, it has also been stressed that the ability of MSCs to produce NTs is highly variable among clonal lines [384]. The ability to produce NTs can also vary among individuals. Montzka et al. also concluded from RT-PCR experiments that the basal expression of NTs by human MSCs varies among donors [385]. The study only used a very small number (i.e., three) of samples; thus, the possible variation at the population level is yet to be determined.

MSC Transdifferentiation into Neurons

Conservatively, MSCs are the precursor cells for the mesodermal lineage; however, it has been described numerous times that MSCs are also able to transdifferentiate into ectodermal linages, such as neurons and glia cells [386–389]. Woodbury et al. elaborated that TRKA is rapidly expressed upon the induction of neural transdifferentiation of human and rat MSCs, indicating the involvement of NGF signaling [386]. The neurogenesis potential of human MSC has been tested in vivo for transplantation to treat brain ischemia in rats [390]. This study transplanted human BM-MSCs into the rat cortex near infarction sites. Transplanted BM-MSCs successfully integrated into the neural circuitry and expressed markers of neuron (TUBB3, neurofilaments, neuron specific enolase (NSE)), astrocyte (GFAP), and oligodendrocyte (galactocerebroside (GALC)). Ultimately, the transplanted BM-MSCs also promoted functional recovery [390].

NTs Expression by MSCs—Results from Co-culture and Conditioned Media Studies

Although MSCs can transdifferentiate into neural lineages, other scientists have posited that the positive impact of MSC transplantation is due to its ability to secrete trophic factors that promote neuronal survival and neurogenesis [391]. This hypothesis has been tested using a non-contact co-culture system of MSCs and neural cells or using MSC-conditioned media for culture of NSCs or neurons. Hsieh et al. co-cultured mouse N2a cells with human MSCs from bone marrow or Wharton's jelly, designated as BM-MSCs and WJ-MSCs, respectively [392]. The authors concluded that co-culture with MSCs significantly improved N2a cells neurite outgrowth and survival when the model was induced by stress. Furthermore, the authors confirmed that the WJ-MSCs had higher neuroprotective capability compared to the BM-MSCs. The gene expression analysis determined that WJ-MSCs expressed a higher level of trophic factors, including NT3, EGF, and FGF9. Another study used human BM-MSC-conditioned

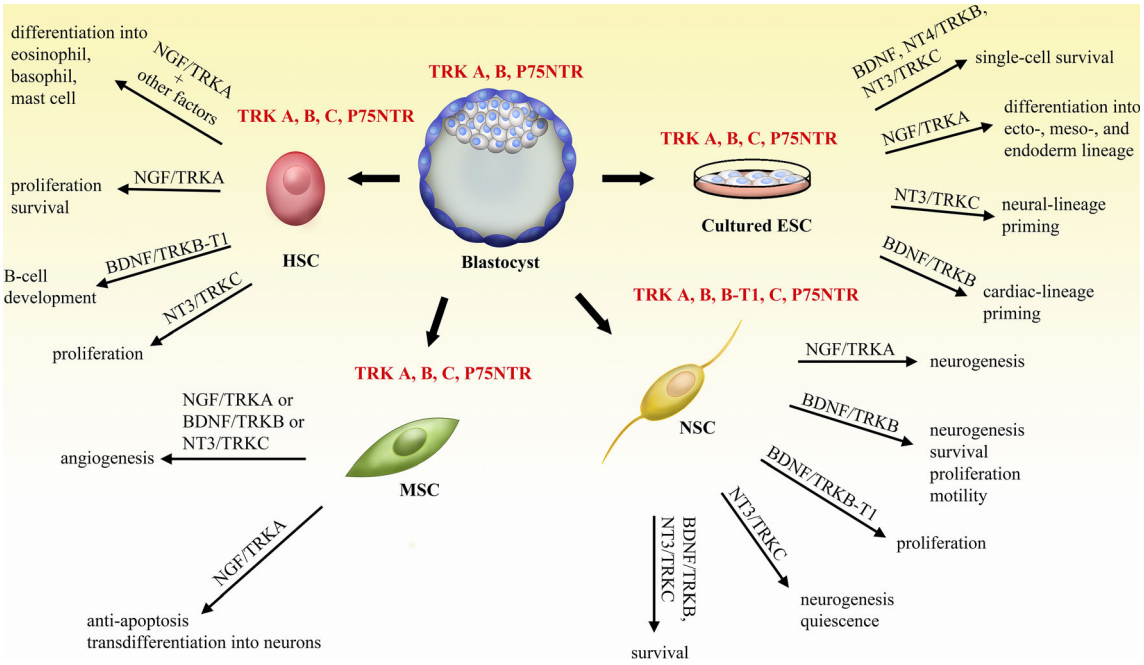

Fig. 7 NT receptor expression in various embryonic and adult stem cells and its cellular functions. NTs support survival following single-cell passaging, proliferation, and differentiation into three-germ layer lineages and stimulate neural and cardiac commitment in ESCs, while also acting as important regulators of neurogenesis, survival, proliferation, astrogliogenesis, motility, and quiescence in NSCs. NTs also promote neural transdifferentiation and angiogenesis in MSCs and their derivatives, while also acting as survival factors. Furthermore, NT receptors are also expressed by HSCs to promote survival, proliferation, and differentiation

media on rat embryonic cortical neurons that were exposed to trophic factor withdrawal and NO exposure, suggesting a similar conclusion that the neuroprotective effect of MSC-conditioned media was achieved through BDNF expression by MSCs, which significantly increased the PI3K/AKT pathway activation and reduced apoptotic p38 signaling in cortical neurons [393].

MSCs, NTs, and Angiogenesis

MSCs can differentiate into an endothelial lineage, which is the main actor in the formation of blood vessels [394]. NTs are strong mediators of angiogenesis by modulating the differentiation of MSC-derived endothelial progenitor cells into endothelial cells [394–396]. BDNF increases angiogenesis, as observed by the formation of capillary-like tubes in vitro [395]. Other NTs, such as NGF and NT3, also have positive effects, though they are not as potent as those of BDNF [395]. The potential mechanism of BDNF-mediated angiogenesis is possibly through the modulation of VEGF (vascular endothelial growth factor) and HIF-1α (hypoxia-inducible factor 1α) signaling [397]. The authors described that stimulation by BDNF led to activation of TRKB receptors and PI3K/AKT and MTOR pathways, which ultimately led to over-activation of VEGF promoter and VEGF stimulation in TRKB-expressing SHSY5Y neuroblastoma cells [397]. This mechanism has also been observed in brain endothelial cells co-cultured with NSCs, where BDNF acts as mediator of NSC-brain endothelial cell cross-talk [398]. This study demonstrated that BDNF released from NSCs can stimulate TRKB of brain endothelial cells to prompt VEGF production [398]. NT3 also improves wound healing in diabetic mice by activating MSCs to produce more NTFs, such as VEGF, NGF, and BDNF, which further promoted endothelial cell proliferation and motility [399].

MSCs, NTs, and Osteogenesis

NTs have been reported to mediate the proliferation of MSC-derived osteoblast precursor cells via activation of p75NTR pathways, suggesting a possible benefit for osteogenesis [400, 401]. MSC-derived osteoblasts are responsible for the development of bone tissues. The mouse osteoblast precursor cell line MC3T3-E1 expresses TRK receptors and innately low levels of p75NTR [401]. Over-expression of p75NTR in these cells significantly increases proliferation and expression of osteogenesis-supporting genes. The authors further determined that the effects are mediated by TRK receptors, since its action is attenuated by a TRK-specific inhibitor, thus concluding the involvement of TRK-dependent signaling, possibly through binding of p75NTR to TRK receptors, rather than NOGOR-dependent signaling [401]. However, the human osteoblast precursor cell line MG63 expresses NOGOR, which was absent in the mouse osteoblast precursor MC3T3-E1 cell line [400]. The author then suggested that the p75NTR-

NOGOR action is contradictory to that of p75NTR-TRK. To test the hypothesis, the authors deleted the GDI domain of the p75NTR receptors, the domain responsible for RHOA binding, which is downstream of the p75NTR-NOGOR pathway. The deletion of the GDI domain from p75NTR resulted in improved proliferation and differentiation of the MG63 cells into osteocytes. Another study also used MC3T3-E1 cells and discovered that NGF, BDNF, and their receptors were expressed by these cells, and their expression levels were all modulated by pro-inflammatory cytokines mixtures of IL-1β (interleukin 1β), TNF-α (tumor necrosis factor α), and IFN-γ (interferon γ) [402]. This study concluded that endogenous NGF protects osteoblasts from apoptosis induced by cytokines.

HSCs and NTs

HSCs

HSCs are the progenitor cells of all blood cells in the vascular system and thus have the ability to self-renew and differentiate into all types of functional blood cells [403]. HSCs can be isolated from umbilical cord blood of newly born infants and from the adult bone marrow, where they co-exist with MSCs [404, 405].

HSCs and NGF-TRKA

Despite poorly understood mechanisms of a possible functional role of NGF in hematopoiesis, available experimental data demonstrate the expression of p75NTR and TRKA in human and rodent HSCs, indicating that NGF has a crucial role in hematopoiesis as a cycling signal that influences development or differentiation of myeloid and erythroid cells [406–408]. Specifically, TRKA is expressed in about 12 to 15 % proliferating HSCs, and stimulation of HSCs with NGF was shown to enhance HSC proliferation [406]. HSCs derived as $CD34^+$ cells from umbilical cord blood cells express NGF and TRKA receptors [409]. Remarkably, TRKA level is higher in cord blood-derived HSCs than in their peripheral blood-derived counterparts, once again suggesting that the NGF-TRKA system is of high significance in HSCs.

NGF binding to TrkA promotes proliferation of human peripheral blood-derived HSCs, as indicated by colony-forming assays in methylcellulose culture, and drives the differentiation of HSCs into eosinophils or basophils, especially in the presence of other growth factors [408, 410] (Fig. 7). NGF alone, however, is inadequate to induce HSC differentiation [410–412]. One study showed that NGF in combination with low-dose IL-3 significantly increased the formation of mast cell colonies of murine BM-derived HSCs compared to treatment with IL-3 alone [412] (Fig. 7). A follow-up study confirmed the role of NGF using blocking antibodies [411]. NGF also interacts with other factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), to drive the differentiation of HSCs from human peripheral blood into basophils [413]. Further, NGF is also involved in the priming and activation of mature eosinophils and basophils [38, 414–420]. HSC requires a complex mixture of cytokines and mitogens for maintaining survival and net expansion. Recently, NGF combined with collagen 1 has been shown to function as an additive that can improve adult mouse BM-derived HSC survival and long-term expansion in a defined serum-free medium [421].

HSCs and Other NTs

Other NTs, such as BDNF, also plays important roles in HSC and blood cell development. For instance, both full-length and truncated TRKB isoforms are expressed in a subset of T cells [422]. BDNF is also an important regulator of B cell development (Fig. 7). $BDNF^{-/-}$ mice have significantly lower B cell number in the blood and spleen compared to wild-type mice, suggesting that BDNF is required for B cell development [423]. However, T cell development has been shown to be unaffected by BDNF deficiency. Fluorescence-activated cell sorting (FACS) analysis using various B cell developmental stages-specific surface markers (CD25, CD45R, CD45, CD117, CD135, and IgM) further showed that BDNF deficiency resulted in arrested development during the Pre BI to Pre BII stages. Interestingly, the authors determined that BDNF triggered Ca^{2+} influx through activation of TRKB-T1 [423].

Co-expression of TRKB and BDNF efficiently transforms HSCs and induces lymphoblastic leukemia in a mouse model [424], and activation of TRKB by BDNF in mouse HSCs efficiently induced a disease with striking similarities to human systemic mastocytosis [425]. The NT3-TRKC system might also regulate the fate of HSCs. Human umbilical cord blood-derived HSCs demonstrate significantly increased proliferation when synergistically cultured in the presence of NT3 and IGFBP-2 (insulin-like growth factor binding protein 2) [426]. That study further determined that NT3 and IGFBP-2 promote the phosphorylation of AKT and ERK1/2 in the HSC.

NTs and NDs

NTs and AD

AD is a brain debilitating condition caused by progressive neural death and synaptic loss in certain areas of the brain. In the advanced stage, this disease manifests as a cognitive dysfunction that also negatively affects memory and learning, language, emotion, and behavior. At the molecular level, AD

is characterized by accumulation of protein aggregates consisting of amyloid precursor protein (APP)-derived misfolded Aβ and the appearance of neurofibrillary tangles (NFTs) composed of wound-up hyperphosphorylated MAPT. The loss of cognitive function strongly correlates with the progression of neurodegeneration and synaptic loss in the frontal cortex and temporal lobe, particularly the hippocampal area, in AD brains, which is potentially caused by these cytotoxic proteins [427–432]. The present theory suggests that various accumulating interactive mechanisms are responsible for the progressive neurodegeneration observed in AD: cytotoxic Aβ induces neural death due to oxidative stress [433], calcium homeostasis imbalance [434, 435], mitochondrial dysfunction [436], impairment of neural plasticity [437], and impairment of the protein degradation system that leads to accumulation of cytotoxic protein aggregates [438–441], while misfolded MAPT causes an impaired axonal transport system [442–444] and proteotoxicity [440, 441, 445]. Recent advances have shown that Aβ and MAPT proteins behave in a prion-like manner to accelerate the assembly of protein aggregates, which spread in a deterministic manner to other brain regions [446].

The earliest hypothesis of AD pathology is the selective loss of BFCN [447, 448]. To date, the precise direct cause of the death of BFCN remains unknown. NTs, in particular NGF and BDNF, are crucial trophic factors for BFCN survival and function [449–454]. NGF also has been demonstrated to increase the activity of choline acetyltransferase (ChAT) in cholinergic neurons [455]. Comparably, BDNF is a well-known pro-survival factor in neurons, including cholinergic neurons [456–458]. Therefore, it is hypothesized that an inadequate supply of NTs in AD is another potential cause of neurodegeneration observed in AD [459, 460].

NTs Expression Changes in AD

In the 1990s, many groups reported an apparent increase in NGF protein level [459, 461–463] but not mRNA [464, 465] in AD-affected brain areas. Another report stated that NGF is increased throughout the brain except the cerebellum (no change) and the nucleus basalis (significantly lower NGF level) [36]. Increased NGF level is specific to AD and is less pronounced in PD. These data revealed impaired retrograde transport of NGF as a major contributor of cholinergic neural death in AD [466–469].

The discovery of proNGF led to a paradigm shift in the NGF story; consequently, the role of NGF in AD was revisited [51]. Ultimately, it was reported that proNGF rather than NGF accumulates in AD brains, with mature NGF not being detected [52]. This finding was confirmed by another group that further reported that elevated proNGF was observable in mild cases of AD and suggested possible impairment of the NGF maturation process as a disease mechanism [470].

It seems that NGF and BDNF are regulated through different mechanisms in AD brains [470]. While the deregulation of NGF is caused by impaired maturation and translocation, BDNF is decreased at the transcriptional level [471, 472]. BDNF mRNA has been found to be reduced in the hippocampus and parietal cortex in AD [471, 472]. Specifically, three of seven transcripts of the human BDNF gene are underexpressed in AD, potentially caused by deregulation of calcium influx [49]. Concurrently, both pro- and mature BDNF protein levels are decreased throughout AD brains, most notably in the hippocampus and parietal cortex [463, 473–477]. Moreover, decreased expression of pro- and mature BDNF is already exhibited at early stages of AD [478]. Reduced BDNF level was also observed in the cerebrospinal fluid of AD patients [479]. NT3 and NT4 have not been the focus of AD studies; however, NT3 level appears to be unchanged in AD [459, 465, 471, 475], while NT4 mRNA is not unaltered [465], but NT4 protein level is slightly reduced [480].

NTs Polymorphisms in AD

In addition to changes in NTs expression in AD, NTs polymorphisms are also associated with the AD pathogenesis. For instance, substitution of valine (V) to methionine (M) in the pro-domain of human BDNF (V66M) caused by G to A single nucleotide polymorphism (SNP) at nucleotide number 196 (G196A) has been reported to disturb the regulated secretion pathway of BDNF but not the constitutive secretion pathway [481, 482]. One study argued that the V66M substitution alters proBDNF binding to sortilin in the secretory granules of neurons [483]. The defect in BDNF secretion is manifested as reduced hippocampal activity, lower episodic memory functions, and a smaller hippocampal volume [481, 484, 485].

Although in vitro and in vivo knock-in transgenic animal model experiments have suggested that BDNF V66M polymorphism may play a role in the AD pathology [481–484], association studies found conflicting conclusions [486–495]. Thus, it might be possible that BDNF V66M polymorphism interferes with other factors to aggravate AD pathology; for example, it may interact with aging to cause a volume reduction of the brain areas that are susceptible to AD [496, 497]. Furthermore, it has been suggested that BDNF V66M polymorphism is associated with an increased risk to AD-related depression and other psychiatric disorders [498–501]. Interestingly, BDNF V66M polymorphism seems to have a stronger association in female AD patients [488, 495, 502].

In addition to the V66M (nucleotide G196A) polymorphism, a C to T mutation at nucleotide position 270 (C270T) [503], which is located in the 5′-non-coding region, has been reported to be associated with late-onset AD [480, 493, 494, 504], while other results concluded no significant association [493, 495]. Despite the controversial association between

BDNF polymorphisms and AD, a considerable amount of evidence suggests that an impaired BDNF regulation may play a significant role in AD [505].

Potential Cause of NGF Imbalance in AD—Implication of Impaired Transport

The disruption of NGF transport by APP was clearly demonstrated in a mouse model of Down syndrome with trisomy in chr 16 (the ortholog of human chr 21, which encodes the APP gene) [506]. Down syndrome is genetically related to AD due to increased APP expression and exhibits a similar neurological pathology to AD [507]. The authors compared APP expression and NGF vesicular transport in normal, Ts1Cje, and Ts65Dn mice [508]. Ts1Cje mice have partial trisomy for chr 16 but with only two copies of the APP gene, while Ts65Dn mice have complete trisomy for chr 16 with three copies of APP. In the experiment, Ts1Cje mice were used as a control for the other genes expressed on chr 16. The authors then injected radiolabeled NGF into the hippocampi of the mutant mice to assess the NGF transport. NGF transport was significantly reduced in Ts65Dn mice (approximately 80 % reduction compared to control) and Ts1Cje (approximately 30 % reduction compared to control). It was also noted that NGF protein level was increased in the hippocampus without an increase in NGF mRNA, consistent with NGF pathology in AD. The authors further reported that APP enlarged the NGF-transporting endosome size that impaired its transport. Decreased NGF transport was also observed in mice expressing human Swedish-mutant APP (APP_{Swe}) and was exacerbated with presenilin-1 (PSEN1) A246E mutation. This last finding is important because AD is not caused by an overexpression of the APP gene (except AD-like pathology in Down syndrome), but rather a mutation in APP in familial AD or, more commonly, a mutation in PSEN1 [509, 510]. These studies showed that APP can cause abnormalities in the endosome system that ultimately impair NGF retrograde transport to the BFCN. That study is in agreement with another describing that Aβ inhibits the kinesin protein Eg5 that consequently impairs the locomotion of vesicles containing NT receptors and potentially NTs themselves, in particular NGF [511]. Moreover, a possible link among APP, NGF, kinesin, an adaptor protein syd (Sunday driver protein in *Drosophila*, orthologous to human mitogen-activated protein kinase 8 interacting protein 3 (MAPK8IP3)), and impaired axonal transport has been proposed previously [512].

Previous APP-associated experiments only studied familial AD but not the sporadic form. Sporadic AD might be comparatively more complicated and involves the hyperphosphorylation of MAPT. Hyperphosphorylation caused MAPT to become detached from the microtubule, destabilizing the cytoskeletal organization, and eventually clogging vesicular transport [513–518]. Very convincing evidence for this hypothesis was reported in a recent study in *Drosophila*. The authors screened 7000 genes that modified MAPT-toxicity using RNAi technology. Silencing of the dynein/dynactin complex aggravated the tauopathy and caused impaired retrograde transport [519]. Using a single-molecule study, Dixit et al. reported that MAPT patches inhibited both dynein (retrograde) and kinesin (anterograde) transport [520]. When encountering MAPT patches, dynein tended to reverse direction, whereas kinesin tended to detach. The failure of axonal transport by disruption of the motor system can explain the abnormal NGF retrograde transport in sporadic AD [467, 468, 518, 521]. NT maturation and secretion are regulated by secretory vesicles [522], and the secretion of TGN vesicles to dendrites of neurons is regulated by kinesin superfamily proteins [523–525]. Therefore, disruption in the dynein and kinesin motor might also impact the maturation and secretion processes of NTs.

Potential Causes of BDNF Imbalance in AD

We already mentioned that the expression of BDNF is reduced throughout the AD brain, including the hippocampus and neocortical areas [463, 473–477]. The AD hippocampus showed 3-fold lower BDNF level compared to healthy control [476]. The reduction of BDNF could be caused by the direct interference of Aβ with CREB signaling, which regulates BDNF transcription [479, 526].

NT Receptors in AD

In accordance with NT reduction, NT receptor expression is also reduced in AD brains. The reduction of TRKA is observed in the nucleus basalis of Meynert (NBM) and cortical areas both at mRNA and protein levels [465, 527–531]. Equally, TRKB mRNA and protein are also reduced in AD frontal cortex and hippocampus [474, 532]. Furthermore, Allen et al. described that only full-length TRKB protein level was decreased in AD, while the level of the truncated isoform was unchanged [532] or even increased [474]. The immunoreactivity of full-length TRKB was decreased in neurons with NFTs. The down-regulation of TRK receptors in AD signifies that reduction of neurotrophic support is not only attributed to lack of NT production but also impaired uptake and signaling.

NTs and PD

PD is a disease characterized by the death of dopaminergic neurons in the substantia nigra (SN) of the midbrain and dopamine depletion in the striatal area, leading to motor function deficits, such as rest tremor, Parkinsonian gait, rigidity, bradykinesia, and postural deformities [533, 534]. In the severe stage, PD also exhibits cognitive deficits such as dementia and depression [535, 536]. At the

cellular and molecular levels, PD is characterized by the appearance of Lewy bodies, which are composed of aggregated α-synuclein proteins and are often associated with other proteins such as ubiquitin and MAPT. The aggressiveness of Lewy bodies is associated with the severity of the disease and loss of neurons [537]. The exact cause of PD is yet to be elucidated; however, there are several genes known to be associated with PD. The most common mutations associated with PD are those of α-synuclein and parkin RBR E3 ubiquitin protein ligase (PARK2) genes, which encode for α-synuclein and parkin E3 ligase, respectively [538]. The α-synuclein functions in regulation of synaptic transmission and neural plasticity; thus, it is enriched in the presynaptic terminal and is associated with synaptic vesicular membranes. Parkin is an E3 ligase, an enzyme that catalyzes the addition of ubiquitin to the substrate targeted for proteolytic degradation by the ubiquitin proteasome system [440]. Other gene mutations are also associated with PD, namely those in leucine-rich repeat kinase 2 (LRRK2), PTEN-induced putative kinase 1 (PINK1), parkinson protein 7 (PARK7, also known as DJ1), and ubiquitin C-terminal hydrolase 1 (UCHL1) (see reviews [538–540]). Based on the genetic component of PD, it was hypothesized that PD neuropathological symptoms and features arise due to deficits in synaptic exocytosis and endocytosis, endosomal trafficking, lysosome-mediated autophagy, and mitochondrial maintenance. Interestingly, there is also genetic and pathological overlap between AD and PD with regard to the pathophysiology of MAPT, suggesting that there is a common impaired axonal transport in the pathology of both diseases [440, 541, 542].

NT Expression and Trafficking Changes in PD

BDNF and GDNF expression has been reported to be decreased in the SN of the PD brain, whereas NGF, NT3, NT4, and CNTF are rather unchanged [543]. In contrast, ELISA analysis of PD brain extracts showed significant reductions in BDNF and NGF in the SN [544]. Similar results were achieved by another group that showed a more than 10-fold reduction in BDNF-positive neurons in the SN and 50 % reduction in the ventral tegmental area of PD patients [545]. In contrast, non-BDNF-expressing neurons were only reduced by about 20 %. The authors concluded that BDNF cannot protect SN neurons from degeneration. Another conclusion, however, can be inferred from the data: lack of BDNF input leads to degradation of BDNF-dependent neurons. The latter hypothesis is supported by a gene expression study showing that the mRNA of BDNF is decreased in the SN of the PD brain [546]. Indeed, BDNF is an important autocrine/paracrine survival factor in dopaminergic neurons in the SN, as demonstrated by midbrain-specific $BDNF^{-/-}$ mice displaying a dramatic reduction in dopaminergic neurons [547]. Moreover, BDNF has been shown to be directly involved in the induction of dopamine D3 receptor [548, 549] and TH [550] expression.

Potential Causes of BDNF Imbalance in PD—Reduced Gene Expression and Impaired Trafficking

The lack of BDNF expression in PD might be caused by inadequate signaling of GDNF or by down-regulation of paired-like homeodomain 3 (PITX3) [551]. BDNF, but not GDNF, can protect dopaminergic neurons from 6-hydroxydopamine (6-OHDA)-induced cell death in the absence of PITX3, which signifies that BDNF is a more proximal cause of dopaminergic neuron degeneration. Expression of BDNF is transcriptionally down-regulated by α-synuclein, possibly by inhibiting the signaling of BDNF regulators, such as NFAT and CREB [552].

Further, BDNF deficits can also be potentially caused by deficits in BDNF trafficking due to impaired cellular transport in neurons, caused by aggregation of α-synuclein or MAPT [553]. It has been speculated that an imbalance of retrograde dynein-dependent and anterograde kinesin-dependent transports is one of the molecular pathologies of PD [554]. Overexpression of α-synuclein in the SN causes a general decrease in anterograde transport motor proteins but an increase in retrograde transport motor proteins [555]. The α-synuclein, especially the pathologic mutant form of α-synuclein, decreases kinesin-dependent microtubule locomotion by disrupting microtubule-kinesin binding and destabilization of the microtubule system [556]. PD brains have revealed reduced kinesin proteins in the earlier stages of PD, whereas dynein is reduced during later stages [553]. Of equal importance, SN neurons of the PD brain that contains α-synuclein inclusions exhibited greater reductions in kinesin level than did neurons without α-synuclein inclusions [553]. In contrast, dynein level is reduced in nigral neurons only in the presence α-synuclein inclusions. Since BDNF has been repeatedly demonstrated to be transported in an anterograde-manner [557–559], the α-synuclein-induced disturbance of anterograde transport might be one of the key pathological events in the development and progression of PD.

Implication of NTs in Stem Cell Therapy for NDs—Evidence from In Vitro and Preclinical Studies

ESC-Derived Progenitors and NTs for the Treatment of AD

Research on and therapeutic application of ESCs face ethical issues because potential human life has to be destroyed to obtain them [560–562]. However, research on ESCs might

lead to the discovery of new medical treatments that would open new avenues of treatment for various diseases. It remains controversial which moral principle should have precedence in this conflicting situation [560–562]. ESCs serve as a potential renewable source of cells in regenerative medicine [21]. Although undifferentiated ESC transplantation causes development of teratomas [563, 564], several studies have suggested that ESC-derived progenitor cells such as NSCs, MSCs, and HSCs can serve as regenerative sources for transplantation therapies [21, 338, 565, 566]. Transplantation of mouse GFP-transfected ESC-derived NSCs into the frontal association cortex and barrel field of the S1 cortex of an AD mouse model; subsequent behavioral tests; and immunostaining of ChAT, serotonin, Aβ, GAD (glutamate decarboxylase), GFAP, and GFP indicated that the NSCs transplanted into the mouse cortex survived and produced many ChAT-positive neurons and a few serotonin-positive neurons in and around the grafts [564]. Further, double staining with ChAT-Aβ, serotonin-Aβ, ChAT-GFP, serotonin-GFP, GAD-GFP, or GFAP-GFP showed that NSC transplantation sites in the frontal and parietal regions give rise to ChAT-positive cells and a few serotonin-positive cells, as recognized by ChAT-GFP and serotonin-GFP double stains, respectively. There were no GAD-GFP or GFAP-GFP double stained cells in or around the grafts, indicating that transplanted NSCs did not produce GABAergic neuron or glia. Transplanted mice also showed functional recovery of working memory [564]. It was demonstrated that the alleviation of AD-related neurological deficits is due to differentiation of the transplanted NSCs into many ChAT-positive neurons and a few serotonin-positive neurons in and around the grafts. Recently, mouse ESCs have been differentiated into mature and functional BFCNs [567]. Transplantation of mouse ESC-derived BFCN progenitors into the NBM of 5XFAD, APP/PS1-mice (a transgenic AD mouse model expressing high levels of mutant APP [KM670/671NL, I716V, V717I] and PSEN1 [M146L, L286V] [568, 569]) resulted in predominant differentiation into mature cholinergic neurons that functionally integrated into the endogenous basal forebrain cholinergic projection system. The AD mice grafted with mouse ESC-derived BFCNs showed improvements in learning and memory performances [567]. Others (than Ref. [564, 567]) have observed that BDNF level was increased after transplantation, and this increase might be involved in the functional recovery of neurological function in AD [338, 570, 571].

ESC-Derived Progenitors and NTs for the Treatment of PD

ESC-derived neural progenitors have been widely studied in PD. Neural progenitors derived from human ESCs were grafted into the striatum of a rat PD model and differentiated into dopaminergic neurons [572]. Transplanted rats showed a significant improvement in stepping adjustments and forelimb placing tests, as well as considerable correction of D-amphetamine and apomorphine-induced rotational behavior, which might be related to trophic effects. Another study showed that transplantation of low doses of undifferentiated mouse ESCs into the rat striatum resulted in differentiation of ESCs into fully mature dopaminergic neurons [573].

BDNF is an essential component of differentiation of mouse ESCs into multiple neural subtypes, including GABAergic, serotonergic, dopaminergic, and cholinergic neurons [574]. Both BDNF and NT4 are required for generation of GABAergic neurons [574]. Monkey ESCs were also utilized with BDNF and NT3 for the generation and transplantation of dopaminergic neurons into a primate PD model, where they successfully attenuated neurological symptoms [575]. Thus, preclinical data indicate that NTs are important trophic factors for regulating terminal differentiation of ESCs to region-specific neuronal subtypes for application in neurological therapies [574, 576].

NSCs and NTs for the Treatment of AD

Transplantation of mouse (C57Bl6 strains)-derived NSCs into the hippocampus rescued cognitive functions in 3xTg-AD mice (a triple-transgenic AD mouse model expressing mutant APP, MAPT, and PSEN1 and exhibiting Aβ and MAPT pathologies of AD [577]) [570]. The cognitive improvement was independent from the clearance of Aβ or MAPT, but by increasing synaptic density and restoring hippocampal-dependent cognition by elevating BDNF levels in the affected areas. A subsequent study by the same group questioned whether the cognitive dysfunction arose due to loss of hippocampal CA1 neurons (CaM/Tet-DTA) or Aβ and MAPT accumulation [571]. The CaM/Tet-DTA is a transgenic mouse model of hippocampal cell loss. This model uses a Tet-Off inducible transgene system by crossing tetracycline responsive element (TRE)-diphtheria toxin A (DTA) mice with CaMKIIa-tTA mice, producing a consistent and non-invasive lesion in CA1 upon withdrawal of doxycycline from the diet, thus causing expression of DTA, which in turn mediates the lesion in the hippocampal CA1 area [578, 579]. Human NSC transplantation improved cognitive function in transgenic 3xTg-AD and CaM/Tet-DTA mice without affecting Aβ or MAPT pathology [571]. Cognitive function improvement by human NSC transplantation in both transgenic mouse AD models was attuned by increased level of BDNF [571, 580]. Still, it remains to be determined whether the other NTs, NGF, NT3, and NT4, have any such specific activity in cognitive function modulation for use in transplantation therapy. A number of studies also indicate that NGF plays a pivotal role in AD and control of NSC proliferation and differentiation [54, 581, 582].

Moreover, therapeutic effects of BDNF gene delivery have been observed in multiple animal models of AD, including mutant amyloid mice (APP Indiana (V717F) and Swedish (K670M) mutations (J20 strain) on a C57BL/6 background), cognitive decline aged rats, and adult perforant path lesioned rats, improving their performances during cognitive tasks [583]. The same study also showed amelioration of cell death, enhancement of cell size, and improvement in age-related cognitive decline in response to BDNF in aged monkeys. BDNF gene delivery reverses synapse loss, partially normalizes aberrant gene expression, improves cell signaling, and restores learning and memory through amyloid-independent mechanisms in amyloid-transgenic mice [583]. Moreover, BDNF gene delivery improved synaptophysin immunoreactivity in the entorhinal cortex and, through anterograde BDNF transport, in the hippocampus of the APP transgenic mice [584]. As BDNF application led to an improvement of neuroprotective effects in mutant amyloid models of AD but did not affect amyloid plaque numbers, amyloid reduction might not be necessary to achieve significant neuroprotective benefits in mutant amyloid in rodents and non-human primate models of AD [583, 584].

NSCs and NTs for the Treatment of PD

Transplantation of human fetal brain-derived NSCs into a rat model of PD can survive long-term, migrate, and differentiate into both neurons and astrocytes following intracerebral grafting [585]. Overwhelming evidence strongly supports that established NSCs have a promising potential to be used as an exogenous source for neural transplantation in PD therapy strategies [586]. Regarding PD, generation of dopaminergic neurons is of foremost interest. In that context, human and rodent fetal brain NSC-derived dopaminergic neurons are associated with lower risk of tumor formation and immune rejection than ESCs [587].

Undifferentiated human fetal-derived NSC implantation into 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primate models of PD showed that human NSCs could survive, migrate, and produce a functional outcome as assessed quantitatively by behavioral improvements [588]. The finding indicated that the host brain can generate intrinsic microenvironmental signals that lead to differentiation of uncommitted human NSCs toward a dopaminergic phenotype. It may also be the case that human NSCs have the self-potentiality to respond to dopamine deficiency even in the absence of pre-induction factors or transgenes [588]. The transplanted human NSCs differentiated into a variety of neural cell types, including tyrosine hydroxylase and dopamine transporter-immunopositive cells, in the affected SN of the PD monkey. It was suggested that the microenvironment within and around the damaged adult host SN still permits development of a dopamine phenotype by responsive progenitor cells. The function of human NSC-derived astrocytic progeny cells in the damaged dopamine systems was most likely to promote homeostatic rearrangement of nigral dopamine neurons and their nigrostriatal projections. The underlying mechanism of the differentiation of human NSCs into dopamine phenotype neurons, however, is not clear, and it has been speculated that this differentiation is mediated by trophic factors and GDNF-expression by human NSC-derived astrocytic progeny [588]. Transplantation of rat NSCs expressing NT3 (NT3-NSC) into 6-OHDA-treated PD rats showed that the combined treatment of NT3 and NSCs had a higher functional impact on reversing the main symptoms of PD than did NSCs alone. The NT3-NSCs had the ability to differentiate into dopaminergic neurons in the ventral tegmental area and the medial forebrain bundle and to migrate around the lesion site [589]. In this regard, an ex vivo organotypic model of nigrostriatal degeneration induced by mechanical transection of the medial forebrain bundle made of brain sagittal slices elucidated the survival, differentiation, and neuroprotective mechanisms of human NSCs adhering to NT3-releasing laminin-coated pharmacologically active microcarriers [590, 591]. NT3-loaded microcarrier microspheres were prepared using a solid/oil/water emulsion solvent extraction-evaporation method [592, 593]. Poly lactic-coglycolic acid (PLGA) copolymer with a lactic/glycolic ratio of 37.5:25 (molecular weight of 25 kDa) was used for PLGA microsphere preparation. Microcarriers were prepared with PLGA microspheres that were coated by incubation with a combination of laminin and poly-D-lysine molecules at a final concentration of 9 and 6 mg/ml, respectively [594]. Daviaud et al. specifically illustrated that NSCs had very little neuroprotective effect and differentiated mostly into dopaminergic neurons when adhering to microcarriers and NT3. The same group previously observed repair and functional recovery after treatment with human marrow-isolated adult multi-lineage inducible cells adhered to NT3-releasing microcarriers in hemi-parkinsonian rats [593]. The underlying data on the association of NT with NSC transplantation are limited to NT3 expression, while other NTs and receptor expression have not yet been investigated in detail. Expression of receptors might be the most important unresolved question in understanding NT involvement in PD therapy via stem cell transplantation strategies.

MSCs and NTs for the Treatment of AD

The neural differentiation property of MSCs suggests that they can be used as a potential cell source for therapeutic approaches for the treatment of AD. Firstly, the possible positive roles of MSCs in AD include the generation of neurons to replace the degenerating neurons [595, 596]. Secondly, MSCs have the ability to promote neurogenesis of resident neural progenitors and survival of resident

neural cells by expressing trophic factors, such as BDNF, NGF, and IGF-1 [596, 597]. Thirdly, MSCs interact with and activate endogenous microglia, which can induce rapid clearance of Aβ plaques via phagocytosis both in vitro and in vivo [598–602] and release neurotrophic molecules such as NGF, subsequently promoting repair and regeneration of neural cells [597, 603]. Stimulation of BM-MSCs with Aβ notably enhances migration of microglia in vitro [602]. The chemotactic activity of BM-MSCs is thought to be mediated by the secretion of CCL5 (chemokine (C-C motif) ligand 5). This hypothesis was tested by transfection of these cells with CCL5 siRNA, which led to a decreased effect on microglia migration [602]. However, the functional role of NTs, expression of its receptors, the possibility of using them as signaling mediators in MSC-microglia crosstalk, and their subsequent migration to the pathologic area remain unknown. Specifically, receptor expression is more crucial here as different receptor isoforms decide the fate of differentiation into neurons or glia cells in the affected brain area. Previous experiments have indicated that MSCs transplanted into the AD differentiate into astrocytes [604, 605]. Astrocytes play an essential role in neuron-glial communication, which might be disrupted earlier of neuronal deficits in AD and can therefore contribute to AD onset [606, 607]. Furthermore, transplantation of adult mouse astrocytes supported the degradation of Aβ deposits in an APdE9 AD mouse model (a transgenic mice model created by breeding mice expressing familial AD-linked APP double mutation KM670/671NL (Swedish) and mice that express PSEN1 lacking exon 9 [608]) [609]. A more recent report interestingly showed that BDNF-expressing MSCs (BDNF-MSCs), in which the transgene BDNF was inserted into MSCs using an adeno-viral vector for the generation of BDNF-MSCs [610], exerted a synergistic therapeutic potential on in vitro neurons derived from the 5XFAD mice model [610]. Co-culture of degenerative neurons derived from 5XFAD mice with only MSCs showed only a slightly reversed AD pathology due in part to the BDNF supply from the MSCs [610]. Further, to enhance BDNF supply in the co-culture, Song et al. co-cultured 5XFAD mice-derived neurons with BDNF-MSCs, and protection against neuronal death was significantly increased when co-cultured with BDNF-MSCs compared to normal MSCs [610].

A pilot in vitro study reported that BM-MSCs (derived from 6-week-old rats) and their secretomes are also able to rescue AD-related cell death induced by misfolded truncated MAPT protein [611]. AD-related MAPT-mediated cell death can be counteracted by co-culturing the neurons with MSCs or by supplementing the MAPT-mediated AD cell medium with a conditioned MSC secretome, which contains significant amounts of BDNF, NGF, and NT3 [611]. Further, in vivo studies showed that transplantation of human umbilical cord blood-derived MSCs in APP/PS1 mice (a transgenic AD mouse model expressing mutant APP (KM670/671NL) and PSEN1 (L166P) [612]) significantly inhibited MAPT hyperphosphorylation in the hippocampus and cortex [600]. Immunofluorescence analysis using anti-AT8 antibody showed that MAPT expression was significantly decreased in MSC-treated hippocampus and cortex of APP/PS1 mice compared with those from the control group [600]. The underlying mechanism behind the inhibitory role of MSCs on MAPT phosphorylation remains to be revealed.

MSCs and NTs for the Treatment of PD

Transplantation of MSCs has been reported to improve functional outcome in PD [613, 614]. An intra-striatal transplantation study of human adult BM-MSCs in the experimental 6-OHDA rodent model of PD demonstrated that the trophic factors released by this transplanted MSCs induced neurogenesis, proliferation, and migration of resident NSCs [615]. The cultured human MSCs actively secreted trophic factors like EGF, BDNF, and NT3 in vitro. The human MSCs transplanted into 6-OHDA rats survived 23 days after transplantation and expressed BDNF in vivo [615]. Moreover, a graft of adult rat BM-MSCs ameliorated behavioral deficits induced by 6-OHDA and partially restored the dopaminergic markers and vesicular striatal pool of dopamine in a rat model [616]. Furthermore, in culture conditions, adult rat BM-MSCs express mRNA encoding BDNF, GDNF, FGF2, and FGF8 [616]. Recently, a novel technique for noninvasive intranasal delivery of adult rat BM-MSCs into the brain successful exhibited long-term survival and exhibition of dopaminergic features accompanied by a significant increased expression of BDNF in 6-OHDA mice, though the exact source of BDNF was not described [595, 617]. In line with this, intravenous human BM-MSC administration into a 6-OHDA PD rat model showed MSCs differentiating into dopaminergic neurons [618]. The human BM-MSCs expressed several NTFs, including NGF and BDNF, and elicited endogenous brain repair mechanisms [618]. Ex vivo differentiation of human BM-MSCs into astrocyte-like cells is capable of generating NTFs (GDNF, NGF, and BDNF), suggesting their suitability for transplantation applications in basal ganglia of PD patients. Transplantation of such NT-producing human ex vivo MSC-derived astrocyte-like cells into the striatum of a 6-OHDA-lesioned rat model of PD revealed that the engrafted cells survived and expressed astrocyte markers, which acted to regenerate the damaged dopaminergic nerve terminal system. MSC-derived astrocyte-like cells have the capability to secrete NTs and are a potential autologous transplantation strategy for therapeutic approaches to PD [619]. Similarly, the protection and survival of dopaminergic neurons through the secretion of GDNF, BDNF, and NGF were

also achieved with rat adult adipose-derived MSCs [620–622].

iPSCs and NTs for the Modeling and Treatment of AD

iPSCs for Modeling AD

A major barrier to research on human AD is inaccessibility of diseased brain cells for study. iPSC technology can be used for the modeling of disease-specific neurons and glia from primary somatic cells (e.g., fibroblast) of AD patients [623, 624]. Mutations A246E in PSEN1 and N141I in PSEN2 induced the Aβ42/Aβ40 ratio, which is a causative factor of autosomal-dominant early-onset familial AD [594, 623, 625]. Generation of iPSC from fibroblasts of familial AD patients with the PSEN1 mutation A246E and the PSEN2 mutation N141I and differentiation of these cells into neurons showed a significant increase in Aβ42/Aβ40 ratio compared to that in control iPSC-derived neurons. Secretion of Aβ42 was significantly increased in PSEN1 and PSEN2 mutant iPSC-derived neurons compared with control iPSC-derived neurons; however, the Aβ40 secretion was unclear whether its secretion increased or decreased [623]. Israel et al. generated iPSC-derived neurons from the fibroblasts of familial AD patients with a duplication of the Aβ precursor protein gene, sporadic AD; however, they did not detect a significant increase in Aβ42/Aβ40 ratio in patient samples versus controls [626]. Further studies from the same group generated iPSC-derived neurons from familial AD patient fibroblasts with mutation in PSEN1 (deletion of exon 9) and demonstrated increases in the Aβ42/Aβ40 ratio by increasing Aβ42 and decreasing Aβ40 [627]. Thus, patient-specific disease modeling using iPSC-technology appeared be an essential approach for better understanding disease origin and mechanism in order to find new drugs to treat AD. In vitro human AD cell generation might also succeed where animal models and other types of cells have thus far failed [626–629].

iPSCs for Treatment of AD

Differentiation of patient-derived iPSCs into NSCs might offer an opportunity for cell therapy for AD. Transplantation of patient-specific autologous iPSC-derived NSCs might also overcome limitations associated with allogeneic transplantation for AD, such as immunogenicity [338]. It might be possible that iPSC-derived NSCs transplanted into the brains of AD patients might have potential to migrate into multiple areas of the damaged brain and differentiate into new, healthy neurons and glia that need to be effectively integrated into the brain, making connections to replace the damaged parts of a complex network of AD brain [630–632].

In case of mutation-associated familial AD, correction of the specific gene mutations using genome editing methods in iPSCs or iPSC-derived cells (e.g., NSCs) from AD patients might also be a promising source for cell replacement therapies for AD [631, 633]. Importantly, there are several genome editing methods that have been used to edit the genomes of iPSCs and iPSC-derived cells, including zinc finger nucleases (ZFNs) [634], transcription activator-like effector nucleases (TALENs) [635, 636], and the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) systems [637, 638]. The ZFNs and TALEN use DNA-binding proteins to guide the endonuclease or DNA nickase. Each zinc-finger of ZFNs comprised of ~30 AAs recognize approximately three base pairs of DNA, whereas individual TALE repeats contain 33–35 AAs that recognize a single base pair of DNA (for a recent review see, e.g., [639–641]). CRISPR consists of a Cas9 endonuclease and a guide RNA (gRNA). Cas9 is directed by the gRNA to cleave a target DNA sequence [642–645]. A protospacer-adjacent motif (PAM) sequence is necessary for Cas9 to bind to the target DNA sequence, and the exact PAM sequence is dependent upon the species of Cas9 (e.g., 5′-NGG-3′ for *Streptococcus pyogenes* Cas9) (for a recent review, see, e.g., [642–645]). Thus, patient-specific iPSC-derived NSCs might offer a therapeutic strategy for the treatment of both sporadic and familial AD.

Another possible approach is to use iPSC-derived NSCs for combined therapy with NTs (e.g., NGF) because healthy brain NTs support the growth and survival of neurons [2, 3, 119], while the level of NTs is low in AD [476, 512, 581]. The approach has not yet been tested in AD patients, and further studies are needed to analyze this theory. Thus, it would be interesting to research the combined approach of iPSC-derived NSCs with NTs to promote therapeutic strategies for the treatment of AD.

iPSCs and NTs for the Modeling and Treatment of PD

iPSCs for Modeling PD

PD modeling has the same barrier as AD modeling, which is inaccessibility of diseased brain cells for mechanistic study or clinical testing. iPSC technology can be used to generate disease-specific neurons and glia from primary somatic cells (e.g., fibroblasts) of PD patients [646]. Generation of iPSC-derived midbrain dopaminergic neurons from the fibroblasts of a patient with a triplication in the α-synuclein gene locus showed that iPSCs readily differentiated into functional neurons associated with elevated expression and accumulation of α-synuclein [647, 648]. Furthermore, generation of iPSC from the fibroblasts of PD patients and their differentiation into neurons showed various mutations such as G2019S in LRRK2, allele mutation in PINK1, allele mutation in PARK2, homozygous mutation in GBA (β-glucocerebrosidase), and increased expression of α-

synuclein mRNA and protein [646, 649–652]. Recently, midbrain dopaminergic neurons were generated through iPSCs generated from the fibroblasts of a set of monozygotic twins harboring the heterozygous GBA mutation (N370S), only one of whom had PD [653]. Upon analysis of the iPSC-derived cell models, it was found that the dopamine-producing neurons from both twins had reduced GBA enzymatic activity, elevated α-synuclein protein level, and a reduced capacity to synthesize and release dopamine. Importantly, in comparison to the unaffected twin, the neurons generated from the PD-affected twin produced less dopamine and had a higher level of monoamine oxidase B (MAO-B) [653]. Thus, patient-specific PD cell line generation using iPSC-technology appears to be an essential approach for experimental preclinical models used to study disease mechanisms unique to PD. Furthermore, in vitro generation of PD-relevant neurons and glia from patients might succeed where animal models and other types of cells have thus far failed [654, 655].

iPSCs for Treatment of PD

Patient specific iPSC-derived NSCs might provide an emerging resource for cell therapy for the treatment of PD [586]. Recently, a promising study by Hallett et al. reported that autologous iPSC-derived dopaminergic neurons transplanted into the striatum of a non-human primate (cynomolgus monkey) model of PD survived in large numbers for an extended period (at least 2 years), giving rise to extensive reinnervation and improved motor functions [656]. These results were observed in one of three monkeys. The relatively positive outcome of this rigorous preclinical study on non-human primates provides preclinical support for further translational research of dopaminergic neurons derived through iPSC technology for transplantation in PD [656].

In genetic mutation-associated familial PD, correction of the specific gene mutations in the iPSCs or iPSC-derived cells (e.g., NSCs or neurons) might be essential for therapeutic use in PD. Recently, genome editing by ZFNs was able to correct the PD mutation in patient-derived iPSCs carrying the A53T (G209A) α-synuclein mutation [634]. Similarly, genetic repair of the LRRK2 G2019S mutation in iPSC-derived neural cells and NSCs from patient fibroblasts was also possible using ZFNs [657]. Mutation-corrected iPSCs and iPSC-derived cells from PD patient fibroblasts using genome editing methods such as ZFNs, TALENs, and CRISPR/Cas9 system are also a promising source for cell replacement therapies for PD. Cells in replacement therapy involving transplantation of mutation-corrected iPSC-derived NSCs into the brain of a PD patient have the potential to migrate into multiple areas of the damaged brain to produce the different types of neurons that need to be integrated effectively into the local neural network of the affected brain area, making connections to replace the damaged parts of PD brain [630, 631, 634, 657]. Hence, iPSCs derived from patient somatic cells and their differentiation into NSCs or neurons might offer a therapeutic strategy for the treatment of both sporadic and familial PD.

Likewise, another possibility might be to use iPSC-derived NSCs for combined therapy with NTs (e.g., BDNF) in the brain because healthy brain NTs support the growth and survival of neurons [2, 3, 119], while NT level is low in PD [551, 552]. NTs have a potent ability to protect degenerating dopamine neurons and promote regeneration of the nigrostriatal dopamine system and thus demonstrate therapeutic potential and use as a molecule in combination with iPSC-derived NSCs for treatment of PD [658–660].

Clinical Studies Associated with NTs and Stem Cells in AD and PD

Clinical NGF Infusion in AD

Due to its trophic property in cholinergic neurons, NGF has been used clinically for treating AD. The first human trial of NGF was conducted by intraventricular infusion of mouse NGF into the lateral ventricle of female AD patients. In that study, NGF increased nicotine uptake by the neurons [661]. The second trial using a similar delivery method of NGF, however, ended within 3 months due to constant back pain and weight loss in the patients [662]. This trial prompted exploration of other strategies for delivering NGF to the damaged neurons and provided some insight into the importance of the accuracy of NGF delivery.

Clinical NGF Gene Therapy Trials in AD

Two major pathways for delivering NGF to the brain have cleared phase 1 clinical trials. The first is use of an in vivo gene therapy approach by injecting a genetically engineered adeno-associated serotype-2 viral vector to express pre-proNGF (AAV2-NGF), developed by Ceregene (since acquired by Sangamo Bioscience) [663]. The viral vector was then injected stereotactically into the NBM of AD patients. The 24-month-long trial concluded that the NGF gene therapy procedure was safe with few adverse effects (76 % were deemed mild; 21 % were deemed moderate; and 4 % were deemed severe). However, the efficacy of the treatment could not be determined from the study due to the small number of participants (10) and lack of a treatment control. Importantly, post-mortem (causes of death were unrelated to the NGF therapy) NGF staining showed immunoreactivity adjacent to the injection sites, and the increased NGF expression was linked to a greater number of p75NTR-positive neurons in the neighboring areas. The phase II clinical trial of this method was completed in March 2015; however, the data on the trial has not yet been published. Unfortunately, it has been reported

that the company terminated the CERE-110 program (http://investor.sangamo.com/releasedetail.cfm?ReleaseID=908026).

The second approach for delivering NGF to the brain is using an ex vivo gene therapy approach of NGF delivery by implanting autologous fibroblasts genetically modified to express human NGF into the forebrain [664]. After 22 months of observation, the study did not find any long-term adverse effect of NGF delivery. The study also reported reduced cognitive decline after treatment. Furthermore, as demonstrated by FDG-PET (18 F-fluorodeoxyglucose (18 F-FDG) positron emission tomography) analysis, brain metabolism was increased by NGF treatment. Recently, a follow-up report for both studies (AAV2-NGF and autologous fibroblast-NGF) has been published and describes the autopsied brains of the deceased patients up to 10 years after the treatment [665]. NGF delivery produced a dense population of cholinergic neurons adjacent to the graft sites and an increase in immunostaining for pCREB and c-fos, the downstream signaling molecules of NGF [665]. More importantly, this 10-year follow-up study did not reveal any adverse pathological side-effects related to NGF, including neural toxicity or tumor formation [665].

Stem Cell Transplantation in AD

Clinical stem cell therapy for AD has not been reported yet. Stemgenex is currently performing a clinical trial for human MSC-based therapy on early and late stages of AD. Stemedica has also been granted permission to conduct MSC-based transplantation therapy based on preclinical data (http://www.stemedica.com/info/allogeneic-adult-stem-cells/alzheimer-clinical-trial/2015-06-09-FDA-Grants-IND-Approval-for-Phase-IIa-Clinical-Trial-Using-Stemedica-itMSC-Therapy-to-Treat-Alzheimers.asp) and a good safety profile of MSC transplantation in ALS [666].

Clinical Trials of NTFs in PD

Adrenal medullary autograft combined with intraputaminal delivery of NGF has been used for PD therapy [667]. NGF, however, did not act directly on the recipient brain but was administered to prolong the transient survival of the adrenal graft [668, 669]. The adrenal graft was able to provide support for the degenerating neurons through increased catecholaminergic activity albeit only for 2 months. The conditions of the two patients were similar to those prior to transplantation after a 6-month follow-up period [668, 669].

GDNF was previously thought to be the prime candidate for treatment for PD. Despite positive preclinical data in aged or chemical-induced (MPTP or 6-OHDA) lesions in rodents and non-human primates [670–676], GDNF clinical trials showed mixed results [677–682]. Intraventricular infusion of GDNF showed considerable adverse effects, such as weight loss, nausea, Lhermitte's phenomenon, and asymptomatic hyponatremia [677]. Also, this study found no improvement in motor function in the GDNF-treated patients. However, other studies argued a positive result from intraputamenal GDNF infusion [678, 680]. In the following year, a randomized controlled clinical trial of intraputamenal GDNF infusion concluded that GDNF did not provide any clinical benefits [681]. GDNF-based therapy failed to clear phase II of clinical trials due to technical difficulties in the infusion system [681, 682]. GDNF failed to be distributed evenly in the target area but concentrated in the area adjacent to the catheter tip [683, 684]. Therefore, direct NTFs infusion seems to not be an appropriate method for delivering NTFs [659, 684]. To overcome this issue, ongoing clinical trials are using AAV-mediated delivery of GDNF and an improved infusion technique, with results expected in 2018 and 2020, respectively [684]. Another explanation of the failure of GDNF application to prevent neurodegeneration is the down-regulation of RET receptor by α-synuclein [685]. This has been demonstrated in two studies, which showed that GDNF failed to rescue neurodegeneration of transgenic rats over-expressing wild-type or A30P-mutant α-synuclein [686, 687]. Another study revealed that α-synuclein deregulates the expression of NURR1 (nuclear receptor related 1 protein), which is the up-stream regulator of RET in SN mouse neurons [685]. The study further showed that NURR1 knock-out mice experienced GDNF blockade similar to that in the α-synuclein model.

In addition, researchers also tested the application of other GDNF-family members for PD clinical trials. Instead of binding to GFRα1 like GDNF, neurturin binds to GFRα2 to activate the common RET tyrosine kinase receptor [202]. Neurturin phase I clinical trials were focused on intraputamenal AAV2-mediated gene delivery rather than infusion. The phase I trials concluded the safety and initial efficacy of neurturin treatment [688, 689]. However, during the phase II study, it was concluded that neurturin treatment showed no significant improvement over sham surgery [690]. Moreover, the treatment was associated with some adverse effects [690]. Further, a subsequent phase II, double-blind trial also failed to show significant benefit of AAV2-mediated neurturin treatment in comparison to a sham-surgery control group [684, 691]. A possible explanation of discrepancy between the positive pre-clinical results, which were achieved in aged or chemical-induced model animals, and the negative results of clinical trials of GDNF and neurturin might be due to the down-regulation of their common RET receptor by overexpressed α-synuclein [685].

Stem Cell Transplantation in PD

In the 1980s, the first clinical transplantation study on PD patients was performed in Lund, Sweden, using autologous transplantation of catecholamine-producing adrenal medulla cells [668, 669, 692]. However, it resulted in a disappointing outcome due to poor graft survival (reviewed in [586, 693]). Due to optimistic preclinical data, transplantation of human fetal ventral mesencephalic (fVM) tissue has been widely conducted in clinical trials over the last three decades. A large number of studies of this transplantation have shown encouraging results in PD patients, along with some major challenges. It has been established that grafts of human fVM tissue rich in dopaminergic neurons survive and become morphologically integrated after transplantation. Increased ^{18}F-DOPA uptake has been detected in this tissue through PET [694]. Histopathological analyses have affirmed survival of transplanted human fVM tissue rich in dopaminergic neurons and re-innervation of the striatum [586].

Open-label trials, a type of clinical trial in which participants are aware of the treatment being applied, showed clinical improvement [694]. Patients in the best cases were able to withdraw L-DOPA treatment after transplantation and exhibited major recovery for several years [694, 695]. The motor improvement was sustained up to 18 years post-transplantation, after withdrawal of dopaminergic therapy for more than 10 years [613, 695]. A number of similar studies in the USA have shown promising outcomes but also faced major challenges [586, 693]. Two specific reports concluded that human fVM transplants did not provide significant improvements in patients with PD and produced unacceptable adverse effects, including dyskinesia [696, 697]. Further, Lewy bodies have been noted in a fraction of grafted dopaminergic neurons that survived for 10 years or longer in PD patients [586, 698, 699]. This observation led to a new hypothesis that PD pathology can be reappeared with time after transplantation, and α-synuclein can act in a prion-like fashion in PD [586, 693]. Conversely, Mendez and colleagues did not detect Lewy body pathology in the grafted human fVM tissue rich in dopaminergic neurons in their PD patients for up to 14 years [700]. Long-term surviving grafted dopaminergic neurons have shown reduced expression of dopamine transporter [698, 701]. Recent findings by Hallett and colleagues, who transplanted human fVM tissue rich in dopaminergic neurons in PD patients, showed a healthy and non-atrophied morphology for at least 14 years [702]. They showed that the vast majority of transplanted neurons remained healthy for the long term in PD patients, consistent with clinical findings that transplanted human fVM tissue rich in dopaminergic neurons maintains function for up to 15–18 years in patients. Moreover, they found that dopamine transporter was robustly expressed in transplanted dopamine neuron terminals in the re-innervated host putamen and caudate long after transplantation [702].

Recently, the European commission-funded TRANSEURO has started a clinical trial using human fVM tissue with the principal objective of developing an efficacious and safe treatment methodology for PD patients [693]. The first graft of the clinical trial conducted by TRANSEURO was completed in May 2015, and the entire trial is expected to be completed in 2018 [693]. The limited availability of human fetal mesencephalic tissue is a major challenge to transplantation in a large number of patients. Thus, stem cell resources including iPSCs could be tried as alternatives to meet the need for dopaminergic neurons.

In addition to clinical works on fVM tissue, other cell sources have been investigated and used in PD clinical trials [693]. In a report published in 2010, an open-labeled trial of unilateral autologous patient-derived BM-MSC transplantation in seven PD patients showed improvement from PD symptoms (e.g., Parkinsonian gait, facial expression) in three patients, two patients were able to significantly reduce the dosages of PD medicine (L-DOPA), and no serious adverse events occurred in any of the seven PD patients. These results confirmed the improvement in symptomology and quality of life after treatment of PD with MSCs [703].

Another report from 2012 describes a clinical investigation conducted on transplantation of adult allogenic human BM-MSCs into the SVZ of eight PD and four PD plus multiple system atrophy and progressive supranuclear palsy patients between 5 and 15 years after diagnosis who were followed-up for 12 months post-transplantation [704]. This study showed that eight PD patients gained speech clarity and reductions in tremors, rigidity, and freezing attacks. It was also observed that patients treated in the early stages of the disease (less than 5 years) showed more improvement in comparison to the late-stage patients (11–15 years). However, no change in symptoms (e.g., clarity in speech, reduced tremors, and rigidity) was observed in the four PD plus multiple system atrophy and progressive supranuclear palsy patients after the BM-MSC transplantation [704]. This study suggests that BM-MSC transplantation in the early stages of PD has the possibility to prevent further progress of the disease.

Challenges and Future Perspectives

NTs and Stem Cells as a Therapeutic Perspective for NDs—AD and PD

Here, we emphasized that characteristic proteins of AD (APP and MAPT) and PD (α-synuclein) are interacting with axonal

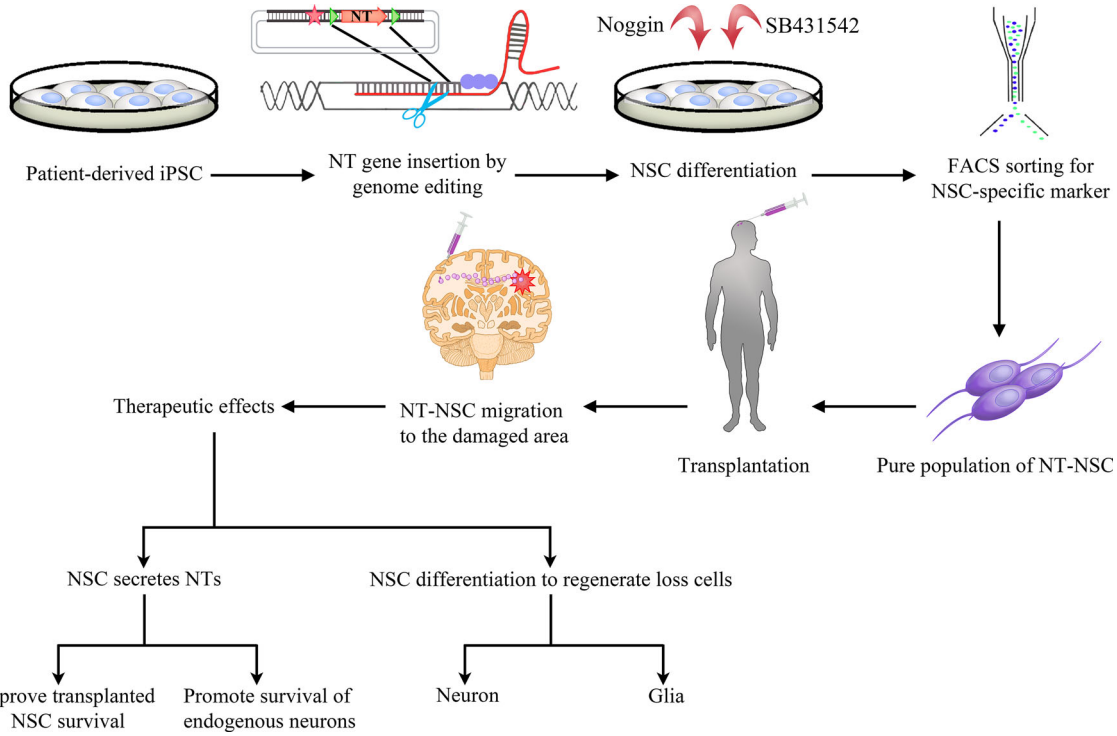

Fig. 8 Proposed therapeutic strategy for the treatment of AD and PD using iPSC-derived NSCs expressing NT (NT-NSCs). Transplantation of NT-NSCs into the brains of AD and PD might have both potentialities, where NSCs would differentiate to generate neurons and glia cells to repair the damaged brain cells, and NTs would support the growth and survival of NSCs and neurons to promote recovery from AD and PD. In addition, transplanted NT-NSCs would have potentiality to migrate to multiple sites of the affected brain and minimize the risk of transplantation

transport proteins, such as dynein and kinesin, respectively, where their oligomeric species, generated due to mutation or faulty proteolytic processing, can disturb the logistic processes of NGF and BDNF (see "Potential Cause of NGF Imbalance in AD—Implication of Impaired Transport" and "NT expression and trafficking changes in PD" sections). The perturbation of NGF and BDNF transport is the direct cause of inadequate innervation and selective degeneration of BFCN in AD and midbrain dopaminergic neuron in PD. Therefore, a strategy to supply exogenous NT might help to rescue the degenerating neurons [66, 583, 584, 665].

This hypothesis is in agreement with the majority of preclinical data, which reflects that NSCs, MSCs, and specific neural subtypes derived from primary tissues, ESCs or iPSCs, can have significant positive effects on NDs, including AD and PD [338, 586, 693]. It has been observed that transplanted stem cells increase the NT level. NT delivery therapy has been shown to produce significant physiological and functional improvements in animal models and ND patients. Thus, transplantation of iPSC-derived NSCs into the brains of AD or PD patients might be a reasonable approach, where NSCs would migrate into various areas of the damaged brain to differentiate into new healthy neurons and other cells and integrate successfully into existing neural networks in the degenerated areas of the brain affected in AD and PD [630, 631, 634, 657]. It might be necessary to apply genetic engineering in these iPSCs to repair mutations (e.g., APP, PSEN1, and PSEN2 for familial AD) using genome editing techniques [630, 633]. Another possible reasonable approach might be to transplant NSCs that carry NTs (introduced into iPSCs by genetic engineering or genome editing) into the brain because NTs support the growth and survival of neurons [2, 3, 119]; these NT levels are low in AD and PD (Fig. 8) [476, 512, 551, 552, 581]. This approach might be therapeutically more effective compared to transplantation of NSC alone because synergistic effects of NSCs and NTs would generate different brain cells in order to repair the damaged brain areas and support the growth and survival of functionally reintegrated neurons to recover cognitive functions in AD or motor functions in PD.

Future Perspective of NTs in AD

To date, the clinical trials of NGF in AD has been limited to in vivo gene delivery using viral vectors and ex vivo gene delivery using autologous fibroblast. Despite the positive results and good safety outcomes achieved in the first phase of

the clinical trial, in vivo virus-mediated gene delivery raises some concerns regarding the safety of the procedure [665, 705]. The gene of interest is inserted into the host genome in a semi-random manner, which can potentially cause dangerous insertional mutagenesis by activating oncogenes or silencing tumor suppressor genes [705–707]. Transplantation of autologous NGF-expressing fibroblasts has shown promising potential for NGF delivery for the treatment of AD [708]. Using autologous cells minimizes the risk of immune rejection and thus increases the probability of success [709, 710]. This approach can be improved by using iPSC technology combined with integrated NT-gene engineering to generate an appropriate cell type carrying NTs such as NGF.

Similar to NGF, BDNF is also neuroprotective for cholinergic neurons [456, 711]. The study also concluded that BDNF and NGF act synergistically to improve ChAT activity but had no additive effect for maintaining neural survival. Preclinical studies in transgenic mice and aged primates have revealed that BDNF restored synaptic integrity, improved cognitive function, and reversed neural atrophy [583, 584]. Therefore, BDNF can be used in conjunction with NGF for the treatment of AD [711–713].

Future Perspective of NTs in PD

An in vivo study using 6-OHDA-lesioned rats suggested that GDNF is a more potent NTF for dopamine neurons than is BDNF [676]. Another in vitro experiment using the conditioned medium from BDNF- or GDNF-transfected fibroblasts concluded that GDNF has higher TH^+-neuron survival-promoting potential [714]. However, a latter study using organotypic cultures suggested that BDNF has a higher promoting function than GDNF [715]. Despite convincing preclinical data from primates, GDNF failed to improve PD patients' conditions during clinical trials [684, 716, 717]. Further investigation showed that AAV-mediated GDNF delivery was not effective in preventing neurodegeneration in the overexpressed α-synuclein PD rat model due to reduced RET expression caused by α-synuclein [685, 686]. If the α-synuclein-associated pathology of PD significantly affects RET expression, then GDNF or neurturin might not be effective for PD treatment unless the expression of RET is also improved through combined gene delivery of RET with GDNF or neurturin [684, 718]. Another possible approach is the use of RET-independent NTs/NTFs, such as BDNF, NGF, NT3, or NT4. These alternative NTs might show better results and need to be explored as a therapeutic strategy of PD [684, 691]. In this regard, it is noteworthy that BDNF infusion has shown positive results on primate models of PD [719, 720]. Therefore, it might be beneficial to revisit the possibility of BDNF treatment for PD with an improved delivery method. Limited preclinical data have also indicated the potential benefits of NT3 for driving differentiation of donor NSCs into dopaminergic neurons and suggest it as a viable alternative as a candidate for NSC-mediated NT-based gene therapy [589, 590, 593].

NSCs and NTs: Migration, Neurogenesis, and Neural Survival

NSC-carrying NGF would probably be an effective combined genetic engineering, cell-based therapy for AD. The justification of using NSCs is that brain cells (neurons, glia, and oligodendrocytes) are natively derived from NSCs; therefore, NSCs are the most natural candidate for cell transplantation-based therapies. Since NSCs can also differentiate into neurons, transplanted NSCs have the potential to be functionally integrated into the local neural circuits in the brain and regenerate the lost neurons [721]. Moreover, NSCs intrinsically secrete various NTs that can promote their own survival and that of surrounding neurons upon transplantation [29, 722]. Alternatively, NSCs can be genetically modified by NTs gene insertion based on genome engineering methods [571, 580, 583, 589] to secrete NTs such as NGF and/or BDNF. More importantly, as discussed in the previous parts of this review, NSCs have the intrinsic ability to migrate to the pathologic area in the brain even over a long distance [660, 721, 723]. This special feature of NSCs is advantageous for therapy since data of clinical trials using direct injections of NGF as, for instance, a virus-based gene delivery system, revealed that only a small area adjacent to the injection site was overexpressing NGF; thus, multiple sites of injection were required [665]. Therefore, NSC-carrying NGF will minimize the number of cell transplantation sites needed to deliver NSCs and might finally offer a wider NGF distribution pattern in comparison to native NGF, virus-mediated, or fibroblast-mediated delivery. It has been echoed numerous times that NSCs are the best candidate for combined therapy with NGF because they have natural potentiality to migrate to different degenerated sites, differentiate into various brain cells, replace degenerated neurons, functionally integrate into existing neuronal circuits, and also stimulate and activate endogenous NSCs and NT secretion at multiple sites in AD brains (Fig. 8) [29, 371, 660, 722–724]. A similar strategy can be applied for NSC-based delivery of BDNF or GDNF for the treatment of PD.

Autologous iPSC-Derived NSCs

The availability of human ESC- and fetal-derived NSCs is limited in number and immunogenicity profile selection. Furthermore, a major barrier to the research and therapeutic application of human ESCs is an ethical issue because

an early embryo, a potential human life, has to be destroyed to procure human ESCs. This problem can be solved by utilizing iPSC technology to produce autologous iPSC-derived NSCs that have a patient-matching immune profile. NSCs can be obtained conveniently from patient-derived iPSCs, and their differentiation can be readily induced from autologous iPSC through exposure to the BMP and activin/nodal inhibitors Noggin and SB431542, respectively [725, 726]. In addition, pure NSC populations can be achieved through FACS based on positive and negative selection of cell surface markers (e.g., CD184+/CD271−/CD44−/CD24+) [727]. Transplanted iPSC-derived NSCs would differentiate into neurons and glia cells to repair the damaged brain cells of AD and PD brains [338, 728].

Challenges Regarding iPSCs, Gene Delivery, and Administration Sites

The first challenge of using (autologous) iPSC-derived NSCs is caused by general concern associated with pluripotent stem cells that can develop malignant teratoma [729]. This risk can be removed by using partially or even terminally differentiated cells, which are comparatively limited in term of proliferation, differentiation potential, and integration into existing neuronal circuits. Moreover, differentiated cells can be purified using FACS to ensure complete removal of pluripotent cells [727, 730]. Another step to further eliminate pluripotent cells from mixed culture is to use small molecules that selectively induce apoptosis of pluripotent cells [731, 732].

The second challenge for using iPSCs is their genomic and genetic instability, which can be associated with cancer [733, 734]. This concern is especially true if the iPSCs were generated using retroviral or lentiviral vectors. Episomal plasmid-derived iPSCs are comparatively more genetically stable. A whole-genome sequencing study of three human iPSC lines revealed that episomal plasmid-derived iPSCs have low incidence of DNA sequence variation [735]. Next-generation, high-throughput, whole-genome sequencing made it possible to achieve robust genomic, genetic, and epigenetic quality control of transplanted cells [736].

The best method for inserting the desired transgene, e.g., NTs, into stem cells also needs to be addressed. Recent advancement of gene editing techniques using site-specific nucleases such as ZFNs, TALENs, and CRISPR/CRISPR-Cas9 enable targeted genetic modifications of the chromosome when combined with homology-directed repair (HDR) mechanisms [737–739]. Using these programmable nucleases, it is possible to safely transform the gene of interest into the specific targetable sites of the cells, especially in comparison to virus-based transformation that carries the risk of insertional mutagenesis [630, 737]. The targeted gene can be accurately inserted into genomic safe harbor sites to minimize dangerous phenotypes that can arise due to the transformation process [740]. Genomic safe harbors are regions of the genome where the transgene can be integrated without disturbing endogenous gene structure and function [741].

Perhaps the biggest challenge that needs to be addressed is the administration site of NT delivery. Intraventricular delivery of NGF and GDNF has been demonstrated to produce serious adverse effects [659, 661, 662, 677]. Moreover, the injection sites that were successful in animal models often poorly replicate in humans, probably due to differences in brain size and neural projections. The key prerequisite to solve this question is a good understanding of the location, regulation, and transportation of NTs in the context of disease pathology. For example, NGF level is decreased in AD due to impaired processing and transport, while BDNF level is decreased transcriptionally. Another example is that NGF is mainly transported in a retrograde manner, while BDNF can be transported both retrogradely and anterogradely [3, 466, 467, 742]. These differences would translate into different approaches (e.g., administration sites) for application of the respective NT for therapy. At least theoretically, the use of NSCs, genetically modified to release NTs, would lower the requirement of NT-delivery accuracy since NSCs are able to home to the pathologic area, where they can then differentiate, integrate functionally into existing neuronal circuits, and the NTs can exert their neuronal survival effects. This hypothesis, however, is yet to be tested in humans, who have a considerably larger brain size in comparison to animal models used thus far.

Future Perspective of iPSC-Derived NSCs and NTs for the Treatment of AD

Despite significant challenges, there is great potential in the use of iPSC-derived NSCs for the treatment of AD. Cell reprogramming technology might solve the problems of patient immunogenicity and ethical issues associated with the use of human NSCs from fetal brain or ESCs [571, 627]. Recent progress in genome editing technology has allowed editing of genetic mutations in human iPSCs and iPSC-derived cells [631, 633]. Thus, combining these two novel technologies might also produce patient-specific healthy NSCs even for familial AD patients who carry genetic mutations (e.g., APP, PSEN1, PSEN2 for familial AD [626] or APOE4 for sporadic AD [743]). Recently, NT (e.g., NGF) gene therapy studies have been showing potential therapeutic activity [713] and required a proper delivery method to affect the multiple sites affected in the AD brain [665, 708]. In this context, combined therapy of iPSC-derived NSCs with

genome engineering for the expression of NTs such as NGF might be a better approach for the treatment of AD compared to conventional NSC transplantation therapy. With these new approaches, future efforts are needed to address the following issues: (i) reprogramming of AD patients' primary somatic cells (e.g., fibroblasts) to produce sufficient high-quality iPSCs and ensure their proper purification and characterization; (ii) genetic repair of any mutation in iPSCs or iPSC-derived cells using genome editing techniques; (iii) appropriate NT (e.g., NGF) transgene insertion into the iPSCs, specifically using genome editing techniques, their appropriate differentiation into NSCs in order to avoid teratoma, and subsequent purification and characterization; and (iv) experimental clinical verification to evaluate the therapeutic benefit in humans (Fig. 8).

Future Perspective of iPSC-Derived NSCs and NTs for the Treatment of PD

Cell replacement therapy has been showing promise for the treatment of PD patients since 1980–1990s [586, 693]. Recent advancements in reprogramming and genome editing demonstrate great potential for new medical applications, including replacement therapies for PD patients using patients' own primary somatic cells [634, 657]. Similarly, NT (e.g., BDNF) gene therapy has been showing potential therapeutic activity, although it requires a suitable delivery method to migrate to multiple degenerated areas of the PD brain [66, 659, 676, 716]. Thus, similar to AD, a combined therapy of iPSC-derived NSCs and genome engineering for the expression of NTs such as BDNF might be a potential approach for the treatment of PD patients (Fig. 8).

However, it is also crucial to be aware that the underlying pathophysiological mechanisms of AD and PD are not yet fully understood. Thus, in addition to trying to develop a therapeutic strategy using iPSC-derived NSCs and NTs, much work needs to be done to investigate and identify the underlying pathophysiological mechanisms of these diseases with the help of reprogramming approaches for the further development of treatment strategies [624, 626, 627].

Conclusions

As we described in this review, increasing evidence indicates that NTs and stem cells, particularly iPSC-derived NSCs, have great therapeutic potential for the treatment of AD and PD [571, 586, 633]. This evidence includes the observation that (i) NTs support the growth and survival of neurons in the healthy brain; (ii) NT level is significantly reduced in AD and PD [66, 476, 581]; (iii) different types of neurons are affected in various areas of the AD and PD brains; (iv) transplanted NSCs have the potential to travel into the affected areas for neuronal differentiation [589, 660, 724]; and (v) new neurons could successfully be functionally integrated into the existing neural circuits in order to form new connections to replace the lost parts of the complex neural network. Thus, for the further development of a useful treatment for AD and PD, a therapy of iPSC-derived NSCs, which have been genetically modified to release NTs, should be tested, using optimal patient selection, meticulous cell preparation, specific transgene insertion, and appropriate transplantation procedures in well-defined clinical studies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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