Cell. Mol. Life Sci. 64 (2007) 522 – 532
1420-682X/07/050522-11
DOI 10.1007/s00018-006-6328-8

Cellular and Molecular Life Sciences

Review

Transcriptional regulation of Trk family neurotrophin receptors

L. Lei[a,] * and L. F. Parada[b]

[a] School of Life Sciences, Arizona State University, Tempe, Arizona 85287-4501 (USA), Fax: +1480 965 6899, e-mail: Lei.Lei.2@asu.edu
[b] Center for Developmental Biology and Kent Waldrep Center for Nerve Growth and Regeneration, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9133 (USA)

Received 13 July 2006; received after revision 9 October 2006; accepted 24 November 2006
Online First 27 December 2006

Abstract. The Trk family of neurotrophin receptors plays essential roles in cell fate specification, survival, growth, and differentiation. Their expression patterns are complex and dynamically regulated under many physiological and pathological conditions. However, the molecular mechanisms that control their tissue-specific expression are largely unknown. In this report, we review current knowledge about the transcriptional regulation of Trk receptors.

Keywords. Transcription, neurotrophin, TrkA, TrkB, TrkC, Klf7, Brn3a, Runx1, Runx3, Wt1, HF-1b, CREB, NeuroD, Ngn1, Ngn2, C-Jun, T3R.

Introduction

The nerve growth factor (NGF) family of neurotrophins and their receptor tyrosine kinases (Trks) play important roles in cell fate specification, neuronal survival, growth, and differentiation [1–3]. There are four NGF-related neurotrophins and three corresponding Trk receptors: NGF binds TrkA; brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT4) bind TrkB; and NT3 binds TrkC. NT3 can also signal through TrkA and TrkB. All four neurotrophins also bind with a lower affinity to a noncatalytic receptor known as p75(NTR), a member of the tumor necrosis factor receptor (TNFR) superfamily [4]. Neurotrophins are largely derived from target tissues innervated by Trk-expressing neurons, while Trk receptors are transmembrane proteins and function in a cell-autonomous fashion. Trk receptors have dynamic expression patterns in developing embryos and in adults. The proper expression of Trk receptors plays a paramount role in the development and function of the vertebrate nervous system. Moreover, altered expression of Trk receptors has been associated with many human diseases. Therefore, the study of Trk receptor expression is important to our understanding of transcriptional regulation in development and disease.

Trk receptor expression and function

In the peripheral nervous system (PNS), TrkA is expressed in the small-diameter nociceptive sensory neurons in dorsal root ganglia (DRG) and trigeminal ganglia (TG), and also in sympathetic neurons [5, 6]. In the central nervous system (CNS), TrkA is found in basal forebrain cholinergic neurons (BFCNs) [6–8]. These neurons provide the major cholinergic input to the cerebral cortex and hippocampus and are severely affected in many neurodegenerative diseases including Alzheimer's disease (AD) and Down syndrome

* Corresponding author.

[9]. TrkB is broadly expressed in the nervous system, including the medium-sized mechanoreceptive neurons in DRG and TG, and in some nonneural tissues [10, 11]. TrkC is also broadly expressed in the nervous system, including the large-diameter proprioceptive neurons in DRG and TG, and also in some nonneural tissues [12]. Within the DRG and TG, Trk receptors are expressed in a largely nonoverlapping pattern.

Different subclasses of sensory neurons require different neurotrophins and Trk receptors for survival. For example, mice carrying null mutations in NGF or TrkA show a specific loss of virtually all nociceptors, while mice carrying null mutations in NT3 or TrkC lack proprioceptive neurons [13–21]. The sensory neuron loss is more severe in NT3-null mice than in TrkC-null mice, suggesting that NT3 can signal through TrkA and TrkB in addition to TrkC [22]. Trk receptors also play important roles in the development and function of the CNS. For example, BFCNs respond to NGF/TrkA signaling in vitro [7]. In TrkA null mice, BFCNs do not mature fully and begin to die by the time of target innervation [23]. TrkB is known to be upregulated in hippocampus and cortex in an activity-dependent manner [24]. In TrkB conditional knockout mice in which TrkB is ablated in the brain using a CamKII-Cre transgenic line, specific populations of CNS neurons are lost and synapse formation and synaptic plasticity are abnormal [25, 26]. Further analysis indicates that TrkB is required at both the presynaptic and postsynaptic sites for the formation of Schaffer collateral synapses [27]. When TrkB is deleted in cerebellar precursors using a Wnt1-Cre transgenic line, the establishment of GABAergic synapses in the cerebellum is greatly inhibited [28]. TrkC is broadly expressed in the CNS, including strong expression in several thalamic nuclei. In NT3 conditional knockout mice in which TrkC activation from cortex-derived NT3 is specifically abolished using a BF1-Cre transgenic line, thalamocortical axon projections and collateral branching are affected, leading to 'cortical blindness' [29]. TrkB and TrkC also cooperate to promote the survival of hippocampal and cerebellar granule neurons [30]. In TrkB−/−TrkC−/− double-knockout mice, there is massive cell death of postnatal hippocampal and cerebellar granule neurons. Moreover, cerebellar Purkinje cells were found to be poorly differentiated in TrkB−/−TrkC−/− mice [30]. Therefore, neurotrophins and Trk receptors regulate the survival and differentiation of both peripheral and central neurons.

By crossing the NGF and TrkA mutant alleles into the Bax-null background, in which apoptosis in the PNS is completely abolished, it was elegantly demonstrated that NGF/TrkA signaling is not only required for the survival of nociceptive neurons, but also for the full phenotypic maturation of these neurons, including the expression of neuropeptides and ion channels, axonal growth, and target innervation in vivo [31]. Similar results were obtained by crossing the NT3 mutant allele into the Bax-null background [32]. Moreover, in mice that express TrkC from the endogenous TrkA locus, some presumptive TrkA(+) neurons adopted a proprioceptive phenotype, demonstrating that neurotrophin signaling has an instructive role in sensory subclass specification and differentiation [33].

The expression of Trk receptors is altered under many physiological and pathological conditions. For example, TrkA expression is a prognostic marker for neuroblastoma, the most frequent solid tumor in children [34, 35]. Neuroblastomas that express TrkA at high levels tend to regress, while tumors that do not express TrkA tend to become aggressive and malignant. This suggests that TrkA may actively promote growth arrest and differentiation of neuroblastoma tumor cells. TrkA expression also induces the apoptosis of neuroblastoma cells, at least in part through p53 [36]. These results suggest that TrkA may be a novel target for treatment of this disease. Indeed, ectopic expression of TrkA was shown to be able to reduce the tumorigenecity of aggressive neuroblastoma cell lines in a mouse xenograft model [37]. Interestingly, the expression of TrkB is often associated with malignant neuroblastomas while TrkC is associated with favorable neuroblastomas [34, 38–41]. This suggests that the downstream signaling pathways in neuroblastoma cells may be different for these three Trk receptors. The mutation or downregulation of TrkA is also at the root of a rare human genetic disease, congenital insensitivity to pain with anhydrosis (CIPA), also known as the hereditary autonomous neuropathy IV [42, 43]. These patients do not feel pain, lose thermal regulation, often self-mutilate, and some are mentally retarded. The downregulation of TrkA in BFCNs has been found in AD patients and in aged rodents, which leads to the dysfunction of the cholinergic system that is essential for attention, learning, and memory [44].

TrkB and its ligand BDNF are regulated in an activity-dependent manner [24, 45]. For example, depolarization of cultured mouse cortical neurons increased the expression of TrkB [24]. Moreover, stress, seizure, exercise, antidepressants, and antipsychotic agents were shown to affect TrkB expression in vivo. TrkB expression is also found to be essential for the proper development of the heart [46]. Interestingly, NT3/TrkC signaling also plays an important role in heart development [20, 47–49]. Therefore, understanding the transcriptional regulation of Trk receptors is not only important to the study of developmental biology, it also has important therapeutic implications. We

Table 1. Transcriptional regulation of Trk receptors.

T/S Factors	TrkA	TrkB	TrkC	References
Klf7	↑	X	X	6,58
Brn3a	↑	↑	↑	66–70
Runx1	?			75–80
Runx3		↓	↑	75, 76, 81, 111
Wt1		↑		46
HF1-b			↑	113
CREB		↑		24,85
NeuroD		↑	↑	87
Ngn1	↑			71, 72, 82
Ngn2		↑	↑	71, 72, 82
C-Jun	↓			53
T3R	↓	↑	↓	86
T3R + ligand		↓		86

↑ activation; ↓ repression; X no effect; ? unclear

divide the following review into three sections, covering the transcriptional regulation of TrkA, TrkB, and TrkC. Table 1 summarizes the known transcription factors that have been implicated in regulating the expression of Trk receptors.

TrkA transcriptional regulation

Among all three Trk receptors, the transcriptional regulation of TrkA has been most intensively studied. The human TrkA gene spans at least 23 kilobases (kb) and contains 17 exons [50]. Exon sizes range from 18 to 394 base pairs (bp) and intron sizes range from 170 bp to 3.3 kb. Many putative transcription-factor-binding sites have been found within the 5′-flanking region of the human TrkA gene. The 5′ region of the mouse TrkA gene was characterized by reporter assays in PC12 and N2a neuroblastoma cells which normally express TrkA [51]. The mouse TrkA promoter sequence is GC -rich and is contained within a CpG island that extends over the entire first coding exon. The TrkA promoter lacks a genuine TATA box and the transcription start site is located 70 bp upstream of the ATG translation initiation codon. A 150-bp DNA fragment, immediately upstream of the transcription start site, was shown to be able to drive transcription in N2a and PC12 cells. Furthermore, a 13-bp cis element within this fragment was shown to be important for both promoter activity and cell-type-specific expression. Multiple proteins bind this region in TrkA-expressing cells and the transcription factor Sp1 was implicated as one potential regulator of this promoter activity. Similarly, a 138-bp region located just upstream of the transcription initiation site of the human TrkA gene was also shown to be important for transcription of TrkA in neuroblastoma cell lines [52]. Aberrant or increased TrkA expression has also been reported in human nonneural tumors including prostate, breast, lung, and pancreatic cancers [53]. A negative cis-acting AP1-like sequence, TGAGCGA, was found in the 5′-untranslated region of the human TrkA gene [53]. This AP1-like site was bound mainly by c-Jun homodimers and the binding was directly blocked by methylation. Steady-state TrkA expression correlated positively with the accumulation of methylated CpG around the AP1-like sequence. The activation of TrkA expression in various pancreatic cell lines was considered to be caused by the direct interference with c-Jun binding to this negative AP1-like sequence. Therefore, unlike global methylation at CpG islands that typically leads to gene silencing, specific methylation at this negative AP1-like site plays a crucial epigenetic role in activating TrkA expression during pancreatic cancer progression.

The AML1-ETO fusion protein, generated by the t(8; 21) chromosomal translocation in acute myeloid leukemia (AML), upregulates the level of TrkA mRNA and protein in human CD34+ hematopoietic stem/progenitor cells [54]. This renders the CD34+ hematopoietic cells responsive to NGF. This could provide important proliferative or survival signals to AML1-ETO-expressing leukemic or preleukemic cells, and the NGF/TrkA signaling pathway may be a suitable target for therapeutic approaches to AML.

Aging is accompanied by a marked change in the expression level of TrkA and p75(NTR) in the brain [55]. TrkA predominates in younger animals while p75(NTR) predominates in older animals. This TrkA to p75(NTR) switch is under the control of the insulin-

like growth factor-1 receptor (IGF1-R), the common regulator of lifespan and aging in many organisms. The signaling pathway that regulates the expression of TrkA and p75(NTR) downstream of IGF1-R requires IRS2, Akt, PTEN, and the short isoform of p53. The hyperactivation of IGF1-R leads to an accelerated form of aging and an early switch from TrkA to p75(NTR).

It has been reported that in the parietal cortex of postmortem brains of AD patients, the TrkA mRNA level is more than twofold lower than in controls, while the expression of TrkB and TrkC does not change [56]. The reduced expression of TrkA may contribute to impaired NGF signaling and reduced retrograde transport of NGF in cholinergic neurons. This study suggests a specific role for TrkA during neurodegeneration in AD.

The mouse TrkA minimal enhancer and sensory neuron expression

Despite the accumulating evidence that TrkA is regulated by many physiological and pathological conditions, relatively little is known about the underlying mechanisms at the molecular level. Because TrkA is specifically expressed in neural-crest-derived sensory and sympathetic neurons, therefore, the molecular mechanisms that regulate TrkA expression can be studied in vivo. Using a transgenic approach, a mouse TrkA minimal enhancer was identified that is necessary and sufficient to drive the expression of a β-galactosidase reporter gene in embryonic mouse DRG and TG neurons in vivo [57]. The expression of β-galactosidase appears to be restricted in TrkA(+) neurons within the DRG. This 457-bp enhancer is highly conserved in mouse, chick, and human. Within this minimal enhancer, many consensus DNA-binding sites were found, nine of which were shown to be important for the enhancer function in transgenic mice. When these cis elements were individually mutated by site-directed mutagenesis, the enhancer activity in vivo was either lost or greatly reduced. This implies that multiple transcription factors are involved in regulating TrkA expression in vivo.

A molecular screen of a mouse DRG cDNA expression library using the above-mentioned nine cis elements as probes led to the identification of transcription factors that bind to these cis elements [6]. One of these transcription factors is Klf7, a novel zinc finger protein of the kruppel-like factor family. Experiments using gel mobility shift assays and chromatin immunoprecipitation (ChIP) assays showed that Klf7 indeed binds its cognate site within the TrkA enhancer in vitro and in vivo [6, 58]. Klf7 is coexpressed with TrkA in sensory and sympathetic neurons and its expression precedes that of TrkA [6]. Functional studies in PC12 cells show that Klf7 binding to its cognate site is sufficient to activate the TrkA minimal enhancer [58]. Analysis of Klf7 knockout mice demonstrated that Klf7 is required for TrkA expression in vivo [58, 59]. The ablation of Klf7 leads to the loss of a subset of TrkA(+) neurons through apoptosis [58]. On the other hand, the expression of TrkB and TrkC is normal in Klf7-null DRG. Similarly, the innervation of dorsal spinal cord by TrkA(+) DRG neurons is largely reduced, while the Ia afferent from the TrkC(+) DRG neurons is normal. As a result, Klf7 null mice have a specific defect in nociception, the sensation of pain and noxious stimuli, while they have normal mechanoreception, the sensation of innocuous mechanical stimuli, and proprioception, the sensation of body position and limb placement. By crossing the Klf7-null allele into the Bax−/− background to circumvent neurotrophin dependence for survival, it was demonstrated that the downregulation of TrkA expression is a direct effect of Klf7 gene ablation, rather than a secondary effect of cell death [58]. Thus Klf7 represents the first transcription factor identified that specifically binds the TrkA enhancer and regulates TrkA expression in sensory neurons in vivo.

Brn3a is a homeobox transcription factor that is strongly expressed in sensory neurons [60–65]. In Brn3a-null mice, the expression of TrkA is greatly reduced while the expression of TrkB and TrkC is abolished [66–69]. Crossing the Brn3a-null allele into a Bax−/− background demonstrated that the downregulation of TrkA is a direct effect of Brn3a gene ablation rather than a secondary effect of apoptosis [70]. Through DNA footprinting and gel mobility shift assays, two Brn3a-binding sites were identified within the mouse TrkA minimal enhancer. Mutation of both sites leads to a great reduction of the enhancer activity in transgenic embryos [70]. This suggests that TrkA might be a direct transcriptional target of Brn3a in vivo.

Although Klf7 and Brn3a are coexpressed in the majority of sensory neurons, epistasis analysis indicates that the expressions of Klf7 and Brn3a are independently regulated [our unpublished results]. Although Brn3a is unable to activate the TrkA minimal enhancer in PC12 cells, the addition of both Brn3a and Klf7 synergistically activate the TrkA minimal enhancer. The analysis of TrkA expression in Brn3a and Klf7 mutant embryos revealed that at E11.5, TrkA expression is normal in Brn3a−/−Klf7−/− trigeminal ganglia. This is supported by the fact that the precursor cells that are destined to become TrkA(+) neurons are present in Brn3a−/−Klf7−/−

trigeminal ganglia as marked by normal Ngn1 expression [71, 72]. Therefore, both Brn3a and Klf7 are dispensable for the initiation of TrkA expression in sensory neurons. One day later, at E12.5, while TrkA expression is unaffected in Brn3a−/− trigeminal ganglia and only slightly reduced in Klf7−/− trigeminal ganglia, TrkA expression is severely reduced in the double-knockout mice [our unpublished results]. By E15.5, TrkA expression is completely abolished in the double-knockout trigeminal ganglia [our unpublished results]. This suggests that Klf7 and Brn3a are independent and yet partially redundant in regulating TrkA expression in vivo.

The Runt domain transcription factors interact with a common transcriptional cofactor CBFβ to control a variety of developmental processes [73, 74]. Both Runx1 and Runx3 are expressed in sensory neurons of DRG and trigeminal ganglia [75–77]. During embryonic development, Runx1 is coexpressed with TrkA in nociceptive neurons while Runx3 is coexpressed with TrkC in proprioceptive neurons [75–77]. After birth, a subset of TrkA(+) neurons cease to express TrkA but instead express Ret, the receptor for glia-derived neurotrophic factor (GDNF) [78]. These neurons continue to express Runx1 [79]. By using a conditional knockout approach to ablate Runx1 in premigratory neural crest cells including the progenitors of DRG neurons, it was shown that the developmental transition from TrkA to Ret is impaired and the number of TrkA(+) neurons in DRG increases significantly in the mutants [79]. Interestingly, a large cohort of nociceptive ion channels and sensory receptors are also affected in Runx1 mutant DRG, suggesting that Runx1 coordinates the phenotypes of a large set of nociceptors. As a consequence, Runx1-deficient mice demonstrate specific deficits in thermal and neuropathic pain, but not in mechanical pain [79]. This study suggests that Runx1 controls the segregation of TrkA(+) and Ret(+) nociceptive neurons by suppressing TrkA and activating Ret. However, it is unclear whether Runx1 directly inhibits TrkA transcription in DRG neurons.

In a separate study using chick embryos and in ovo electroporation, it was shown that the Runt activity is required for TrkA expression and the survival of nociceptive sensory neurons [80]. It was further shown that Runx1 is sufficient to induce ectopic TrkA expression in chick embryos after electroporation. A putative Runx-binding site was found in the mouse TrkA minimal enhancer and Runx1 can activate this enhancer in transfected PC12 cells. This suggests that Runx1 can activate TrkA expression in vivo and in vitro, although a direct binding of Runx1 to the TrkA minimal enhancer has not yet been demonstrated. However, it was shown in mice that overexpression of Runx1 from the tau locus through homologous recombination does not affect the level of TrkA expression in DRG neurons, although it significantly suppresses CGRP expression [81]. It is possible that the expression level of exogenous Runx1 is much higher in the electroporated chick embryos than in mice, which may explain the different results using these different systems. It is also possible that some necessary cofactors are present in the chick embryos but are missing in mouse DRG neurons.

Ngn1 and Ngn2 are neural-specific basic helix-loop-helix (bHLH) transcription factors that control neurogenesis in the developing sensory ganglia in the PNS [71, 82]. Gene knockout studies demonstrate that TrkA(+) neurons in the developing DRG require Ngn1, while Ngn2 is transiently required only for TrkB(+) and TrkC(+) neurons [72]. The initial requirement for Ngn2 is subsequently compensated in an Ngn1-dependent manner. The development of DRG is completely abolished in Ngn1−/−Ngn2−/− double knockouts while the development of the sympathetic ganglion is unaffected [72]. However, it is unclear whether Ngn1 and Ngn2 directly regulate the expression of the Trk receptors in the sensory neurons.

As mentioned earlier, nine cis elements within the mouse TrkA minimal enhancer are important for TrkA expression in sensory neurons in vivo [57]. This implies that other TrkA enhancer-binding proteins participate in regulating TrkA expression. It also remains a challenge to identify and characterize transcription factors that regulate TrkA expression in BFCNs. A complete understanding of TrkA regulation in BFCNs may lead to the identification of novel therapeutic targets for neurological diseases including AD and Down syndrome.

TrkB transcriptional regulation

The human TrkB gene spans 590 kb and contains 24 exons [83]. Due to different promoters, alternative splicing, and different polyadenylation sites, the human TrkB gene can create at least 100 different transcripts that encode 10 proteins. However, Northern blot and RT-PCR analysis reveal that only three major protein isoforms are generated: the full-length receptor, a truncated receptor lacking the kinase domain, and a truncated receptor lacking the kinase domain but containing an Shc-binding site. Both truncated isoforms are potential negative regulators of TrkB signaling [83].

The mouse TrkB gene is transcribed from two different promoters named P1 and P2 [84]. By RNase protection assays, P1 has been located at 1.8 kb

upstream of the TrkB translation start codon. P2 has been located at 0.5 kb upstream of the TrkB translation start codon. In addition, transcription of the mouse TrkB locus results in two different TrkB isoforms (full-length and truncated receptors) due to alternative splicing of the mRNA. There is no correlation between promoter usage and alternative splicing, as transcripts originating from both promoters encode both full-length and truncated receptors [84].

Like its ligand BDNF, TrkB expression is upregulated in an activity-dependent manner [24, 45]. Depolarization of mouse cortical neurons in culture increases the expression of the full-length TrkB transcript without affecting the expression of the truncated isoform [24]. Depolarization also regulates the transcription of TrkB via the entry of Ca^{2+} through voltage-gated Ca^{2+} channels and subsequent activation of Ca^{2+}-responsive elements in the two TrkB promoters. Reporter assays in which luciferase expression is driven by the TrkB promoter demonstrate that Ca2+ inhibits the upstream promoter P1 but activates the downstream promoter P2. Two adjacent but nonidentical Ca^{2+}-responsive elements located within P2 are required for the Ca^{2+}-dependent stimulation of TrkB expression in cortical neurons in vitro. Therefore, the coordinated regulation of BDNF and TrkB by Ca^{2+} may play a role in activity-dependent survival and synaptic plasticity by enhancing BDNF/TrkB signaling [24].

In a separate report, it was shown that forskolin rapidly stimulates the expression of both the full-length and truncated TrkB isoforms in primary culture of mouse cortical neurons [85]. This activation depends upon protein kinase A (PKA) and cyclic-AMP-responsive-element-binding protein (CREB). It was shown that activated CREB binds the second cAMP-responsive element located within the P2 promoter of the TrkB gene [85]. This study demonstrates that TrkB is a target for CREB regulation and may explain the increase of TrkB expression produced during different adaptive responses of the nervous system in which CREB is involved.

Expression of TrkB is regulated by thyroid hormone (T3) during development of the rat brain [86]. The TrkB transcript level is increased in the cerebral cortex of neonatal experimental hypothyroid rats. An increase in the transcription rate of the TrkB gene accounts for this effect. It was shown that unliganded thyroid hormone receptor (T3R) stimulates the TrkB promoter activity, while the addition of T3 reverses the activity below basal levels. T3-dependent repression of the TrkB promoter requires the binding of the T3R to a specific region located downstream of the transcription start site. This region contains an array of thyroid hormone response half-sites that binds T3R as heterodimers with retinoid X receptor (RXR). The deletion of these half-sites causes the loss of the T3-dependent repression. Therefore, thyroid hormone inhibits the expression of TrkB through the active repression of the thyroid hormone response elements located downstream of the transcription start site. Moreover, unliganded thyroid hormone receptor can also induce TrkB expression in the mouse neuroblastoma N2a cell line while concomitantly reducing the expression of TrkA and TrkC.

Inner ear sensory neurons are dependent on NeuroD, a bHLH transcription factor, for survival [87]. Mice lacking NeuroD are deaf due to the apoptosis of inner ear sensory neurons during development. The affected inner ear sensory neurons fail to express TrkB and TrkC, two receptors important for the survival of inner ear sensory neurons in vivo [87]. This study suggests that the ability of NeuroD to support neuronal survival may be directly mediated through the regulation of responsiveness to the neurotrophins. It remains to be determined whether NeuroD directly regulates the expression of TrkB and TrkC in inner ear sensory neurons.

In Brn3a knockout trigeminal ganglia, TrkB expression was initially upregulated but then gradually disappeared [68]. By P0, no TrkB(+) neurons can be found in the mutant trigeminal ganglia. It is unclear whether Brn3a directly regulates TrkB expression in vivo.

During early embryonic development, coexpression of TrkC, TrkB, and Ret was observed in mouse DRG [81]. These hybrid TrkC(+)/TrkB(+) and TrkC(+)/Ret(+) neurons represent distinct early and transient populations of DRG neurons. By overexpressing Runx3 from the tau locus through homologous recombination, it was elegantly demonstrated that Runx3 promotes the transition from TrkC(+)/TrkB(+) hybrid neurons to a solitary TrkC(+) phenotype by suppressing TrkB expression and promoting TrkC expression [81]. Runx3 also represses TrkB expression and activates TrkC expression in TrkB(+)/Ret(+) neurons. It is unclear whether Runx3 directly inhibits TrkB expression in vivo.

Both BDNF and TrkB are expressed in the developing heart [46, 88, 89]. BDNF−/− and TrkB−/− mice have multiple heart defects [46, 88]. It was recently shown that the Wilms' tumor gene-1, Wt1, is coexpressed with TrkB in coronary vessels of mouse hearts [46]. The ablation of the Wt1 gene leads to the near complete absence of TrkB expression in the epicardium and subepicardial blood vessels. Activation of Wt1 in an inducible cell line significantly stimulated TrkB expression and the TrkB promoter was strongly upregulated by Wt1 in a transient transfection experi-

ment. A consensus Wt1-binding site was located within the TrkB enhancer and this binding site was necessary to direct the expression of a reporter transgene to the epicardium and the developing vasculature of embryonic mouse hearts. This study demonstrates that transcriptional activation of TrkB by Wt1 plays a crucial role for normal vascularization of the developing heart [46].

In addition, the expression of TrkB is altered under many physiological and pathological conditions including, but not limited to, exposure to retinoic acid, ethanol, antidepressants, antipsychotic agents, and stress. TrkB expression is also altered in traumatic brain injury, motoneuron axonomy, Parkinson's disease, AD, seizures, schizophrenia, and aging [90–109]. The underlying mechanisms for the altered TrkB expression in these conditions are unclear.

TrkC transcriptional regulation

TrkC is broadly expressed in the nervous system [12]. It is also expressed in many nonneural tissues. The human TrkC gene consists of 20 exons [110]. Analysis of the 5′ flanking region revealed the absence of a TATA box, a very high GC content, and the presence of putative binding sites for AP1, AP2, GC, ATF, Brn2, AML1, and Nkx2.5 transcription factors.

In Brn3a knockout trigeminal ganglia, TrkC expression was completely abolished from as early as E11.5 [68]. It is possible that TrkC is a direct transcriptional target of Brn3a. However, this needs to be experimentally demonstrated.

Runx3 was found to be coexpressed with TrkC in TG and DRG neurons [75, 76]. One study reported that there are fewer TrkC(+) neurons in Runx3−/− DRG [76]. However, in another study using a separate line of Runx3−/− mice, it was reported that the number of TrkC(+) neurons did not change in Runx3−/− DRG although proprioceptive afferent axons failed to project to their targets [75]. As mentioned earlier, overexpression of Runx3 from the tau locus can activate TrkC expression in TrkC(+)/TrkB(+) and TrkB(+)/Ret(+) DRG neurons, while inhibiting TrkB expression [81]. However, ectopic expression of Runx3 is unable to induce TrkC expression in the TrkA(+) sensory neurons. Therefore, Runx3 can promote TrkC expression in a context-dependent manner. This is consistent with another report demonstrating that ectopic expression of Runx3 in chick DRG by a focal in ovo electroporation does not induce the expression of TrkC or ER81, two proprioceptive markers, although it represses TrkB expression [111]. It remains to be determined whether Runx3 directly regulates TrkC expression. Importantly, the status of Runx3 expression is a major determinant of the dorsal-ventral position of termination of sensory axons within the spinal cord.

NT3 and TrkC are expressed in the developing heart [89, 112]. It was shown that NT-3 was expressed in the ventricular region from E11 to birth in rats. Full-length TrkC was detected in the walls of aorta and pulmonary trunk from E13 to birth and in the cardiac ganglion neurons from E14 to adult age. Both truncated TrkC and TrkB receptors, TrkC.TK− and TrkB.T1, were detected in the outflow tract at E12 and in the walls of developing aorta and pulmonary trunk from E13 to birth. This study suggests a specific role for NT3/TrkC signaling in the innervation of the conducting system and the development of the smooth muscle cells [89]. Indeed, NT3- and TrkC-null mice have multiple cardiac defects, including atrial and ventricular septal defects, and valvular defects including pulmonic stenosis [20, 48]. These defects resemble some of the most common congenital heart malformations in humans. It was shown that these cardiac defects were caused by abnormal development of both cardiac neural crest cells and cardiac myocytes [47, 49]. Moreover, HF-1b is a transcription factor required for the specification of the cardiac conducting system [113]. The absence of HF-1b in the neural crest led to atrial and atrioventricular dysfunction resulting from deficiencies in TrkC expression [113]. It remains to be determined whether HF-1b directly regulates TrkC expression.

Summary

The expression of Trk receptors is complex and dynamically regulated. Although there is a large body of descriptive studies regarding the expression of Trk receptors under various physiological and pathological conditions, the molecular mechanisms that control the tissue-specific expression of Trk receptors are just beginning to be discovered. So far, multiple transcription factors are implicated in regulating the expression of Trk receptors (Table 1). However, most of the data on these transcription factors are from gene knockout studies and the direct involvement of these transcription factors in regulating Trk receptor expression at the molecular level remains to be demonstrated. A detailed study of the transcriptional regulation of Trk receptor expression will greatly improve our understanding of cell fate specification and differentiation. It will also have important therapeutic implications for the treatment of neurodegenerative diseases, cancers, and congenital heart diseases.

1 Huang E.J. and Reichardt L.F. (2001). Neurotrophins: roles in neuronal development and function. Annu. Rev. Neurosci. 24, 677 – 736.
2 Huang E.J. and Reichardt L.F. (2003). Trk receptors: roles in neuronal signal transduction. Annu. Rev. Biochem. 72, 609 – 642.
3 Parada L.F., Tsoulfas P., Tessarollo L., Blair J., Reid S.W. and Soppet D. (1992). The Trk family of tyrosine kinases: receptors for NGF-related neurotrophins. Cold Spring Harb. Symp. Quant. Biol. 57, 43 – 51.
4 Chao M.V. (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat. Rev. Neurosci- 4, 299 – 309.
5 Martin-Zanca D., Barbacid M. and Parada L.F. (1990). Expression of the trk proto-oncogene is restricted to the sensory cranial and spinal ganglia of neural crest origin in mouse development. Genes Dev. 4, 683 – 694.
6 Lei L., Ma L., Nef S., Thai T. and Parada L.F. (2001). mKlf7, a potential transcriptional regulator of TrkA nerve growth factor receptor expression in sensory and sympathetic neurons. Development 128, 1147 – 1158.
7 Holtzman D.M., Li Y., Parada L.F., Kinsman S., Chen C.K., Valletta J.S., Zhou J., Long J.B. and Mobley W.C. (1992). p140trk mRNA marks NGF-responsive forebrain neurons: evidence that trk gene expression is induced by NGF. Neuron 9, 465 – 478.
8 Sobreviela T., Clary D.O., Reichardt L.F., Brandabur M.M., Kordower J.H. and Mufson E.J. (1994). TrkA-immunoreactive profiles in the central nervous system: colocalization with neurons containing p75 nerve growth factor receptor, choline acetyltransferase, and serotonin. J. Comp. Neurol. 350, 587 – 611.
9 Salehi A., Delcroix J.D. and Mobley W.C. (2003). Traffic at the intersection of neurotrophic factor signaling and neurodegeneration. Trends Neurosci. 26, 73 – 80.
10 Klein R., Parada L.F., Coulier F. and Barbacid M. (1989). trkB, a novel tyrosine protein kinase receptor expressed during mouse neural development. EMBO J. 8, 3701 – 3709.
11 Klein R., Martin-Zanca D., Barbacid M. and Parada L.F. (1990). Expression of the tyrosine kinase receptor gene trkB is confined to the murine embryonic and adult nervous system. Development 109, 845 – 850.
12 Tessarollo L., Tsoulfas P., Martin-Zanca D., Gilbert D.J., Jenkins N.A., Copeland N.G. and Parada L.F. (1993). trkC, a receptor for neurotrophin-3, is widely expressed in the developing nervous system and in non-neuronal tissues Development 118, 463 – 475.
13 Crowley C., Spencer S.D., Nishimura M.C., Chen K.S., Pitts-Meek S., Armanini M.P., Ling L.H., McMahon S.B., Shelton D.L., Levinson A.D. and Phillips H.S. (1994). Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell 76, 1001 – 1011.
14 Smeyne R.J., Klein R., Schnapp A., Long L.K., Bryant S., Lewin A., Lira S.A. and Barbacid M. (1994). Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature 368, 246 – 249.
15 Liebl D.J., Tessarollo L., Palko M.E. and Parada L.F. (1997). Absence of sensory neurons before target innervation in brain-derived neurotrophic factor-, neurotrophin 3-, and TrkC-deficient embryonic mice. J. Neurosci. 17, 9113 – 9121.
16 Farinas I., Jones K.R., Backus C., Wang X.Y. and Reichardt L.F. (1994). Severe sensory and sympathetic deficits in mice lacking neurotrophin-3. Nature 369, 658 – 661.
17 Farinas I., Yoshida C.K., Backus C. and Reichardt L.F. (1996). Lack of neurotrophin-3 results in death of spinal sensory neurons and premature differentiation of their precursors. Neuron 17, 1065 – 1078.
18 Klein R., Silos-Santiago I., Smeyne R.J., Lira S.A., Brambilla R., Bryant S., Zhang L., Snider W.D. and Barbacid M. (1994). Disruption of the neurotrophin-3 receptor gene trkC eliminates la muscle afferents and results in abnormal movements. Nature 368, 249 – 251.
19 Tessarollo L., Vogel K.S., Palko M.E., Reid S.W. and Parada L.F. (1994). Targeted mutation in the neurotrophin-3 gene results in loss of muscle sensory neurons. Proc. Natl. Acad. Sci. USA 91, 11844 – 11848.
20 Tessarollo L., Tsoulfas P., Donovan M.J., Palko M.E., Blair-Flynn J., Hempstead B.L. and Parada L.F. (1997). Targeted deletion of all isoforms of the trkC gene suggests the use of alternate receptors by its ligand neurotrophin-3 in neuronal development and implicates trkC in normal cardiogenesis. Proc. Natl. Acad. Sci. USA 94, 14776 – 14781.
21 Wilkinson G.A., Farinas I., Backus C., Yoshida C.K. and Reichardt L.F. (1996). Neurotrophin-3 is a survival factor in vivo for early mouse trigeminal neurons. J. Neurosci. 16, 7661 – 7669.
22 Huang E.J., Wilkinson G.A., Farinas I., Backus C., Zang K., Wong S.L. and Reichardt L.F. (1999). Expression of Trk receptors in the developing mouse trigeminal ganglion: in vivo evidence for NT-3 activation of TrkA and TrkB in addition to TrkC. Development 126, 2191 – 2203.
23 Fagan A.M., Garber M., Barbacid M., Silos-Santiago I. and Holtzman D.M. (1997). A role for TrkA during maturation of striatal and basal forebrain cholinergic neurons in vivo. J. Neurosci. 17, 7644 – 7654.
24 Kingsbury T.J., Murray P.D., Bambrick L.L. and Krueger B.K. (2003). Ca(2+)-dependent regulation of TrkB expression in neurons. J. Biol. Chem. 278, 40744 – 40748.
25 Xu B., Gottschalk W., Chow A., Wilson R.I., Schnell E., Zang K., Wang D., Nicoll R.A., Lu B. and Reichardt L.F. (2000). The role of brain-derived neurotrophic factor receptors in the mature hippocampus: modulation of long-term potentiation through a presynaptic mechanism involving TrkB. J. Neurosci. 20, 6888 – 6897.
26 Xu B., Zang K., Ruff N.L., Zhang Y.A., McConnell S.K., Stryker M.P. and Reichardt L.F. (2000). Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor TrkB. Neuron 26, 233 – 245.
27 Luikart B.W., Nef S., Virmani T., Lush M.E., Liu Y., Kavalali E.T. and Parada L.F. (2005). TrkB has a cell-autonomous role in the establishment of hippocampal Schaffer collateral synapses. J. Neurosci. 25, 3774 – 3786.
28 Rico B., Xu B. and Reichardt L.F. (2002). TrkB receptor signaling is required for establishment of GABAergic synapses in the cerebellum. Nat. Neurosci. 5, 225 – 233.
29 Ma L., Harada T., Harada C., Romero M., Hebert J.M., McConnell S.K. and Parada L.F. (2002). Neurotrophin-3 is required for appropriate establishment of thalamocortical connections. Neuron 36, 623 – 634.
30 Minichiello L. and Klein R. (1996). TrkB and TrkC neurotrophin receptors cooperate in promoting survival of hippocampal and cerebellar granule neurons. Genes Dev. 10, 2849 – 2858.
31 Patel T.D., Jackman A., Rice F.L., Kucera J. and Snider W.D. (2000). Development of sensory neurons in the absence of NGF/TrkA signaling in vivo. Neuron 25, 345 – 357.
32 Patel T.D., Kramer I., Kucera J., Niederkofler V., Jessell T.M., Arber S. and Snider W.D. (2003). Peripheral NT3 signaling is required for ETS protein expression and central patterning of proprioceptive sensory afferents. Neuron 38, 403 – 316.
33 Moqrich A., Earley T.J., Watson J., Andahazy M., Backus C., Martin-Zanca D., Wright D.E., Reichardt L.F. and Patapoutian A. (2004). Expressing TrkC from the TrkA locus causes a subset of dorsal root ganglia neurons to switch fate. Nat. Neurosci. 7, 812 – 818.
34 Brodeur G.M., Nakagawara A., Yamashiro D.J., Ikegaki N., Liu X.G., Azar C.G., Lee C.P. and Evans A.E. (1997). Expression of TrkA, TrkB and TrkC in human neuroblastomas. J. Neurooncol. 31, 49 – 55.
35 Brodeur G.M. (2003). Neuroblastoma: biological insights into a clinical enigma. Nat. Rev. Cancer 3, 203 – 216.

36 Lavoie J.F., Lesauteur L., Kohn J., Wong J., Furtoss O., Thiele C.J., Miller F.D. and Kaplan D.R. (2005). TrkA induces apoptosis of neuroblastoma cells and does so via a p53-dependent mechanism. J. Biol. Chem. 280, 29199 – 29207.
37 Eggert A., Grotzer M.A., Ikegaki N., Liu X.G., Evans A.E. and Brodeur G.M. (2002). Expression of the neurotrophin receptor TrkA down-regulates expression and function of angiogenic stimulators in SH-SY5Y neuroblastoma cells. Cancer Res. 62, 1802 – 1808.
38 Schramm A., Schulte J.H., Astrahantseff K., Apostolov O., Limpt V., Sieverts H., Kuhfittigkulle S., Pfeiffer P., Versteeg R. and Eggert A. (2005). Biological effects of TrkA and TrkB receptor signaling in neuroblastoma. Cancer Lett. 228, 143 – 153.
39 Svensson T., Ryden M., Schilling F.H., Dominici C., Sehgal R., Ibanez C.F. and Kogner P. (1997). Coexpression of mRNA for the full-length neurotrophin receptor trk-C and trk-A in favourable neuroblastoma. Eur. J. Cancer 33, 2058 – 2063.
40 Yamashiro D.J., Liu X.G., Lee C.P., Nakagawara A., Ikegaki N., McGregor L.M., Baylin S.B. and Brodeur G.M. (1997). Expression and function of Trk-C in favourable human neuroblastomas. Eur. J. Cancer 33, 2054 – 2057.
41 Yamashiro D.J., Nakagawara A., Ikegaki N., Liu X.G. and Brodeur G.M. (1996). Expression of TrkC in favorable human neuroblastomas. Oncogene 12, 37 – 41.
42 Indo Y., Tsuruta M., Hayashida Y., Karim M.A., Ohta K., Kawano T., Mitsubuchi H., Tonoki H., Awaya Y. and Matsuda I. (1996). Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat. Genet. 13, 485 – 488.
43 Alberti L., Carniti C., Miranda C., Roccato E. and Pierotti M.A. (2003). RET and NTRK1 proto-oncogenes in human diseases. J. Cell Physiol. 195, 168 – 186.
44 Saragovi H.U. (2005). Progression of age-associated cognitive impairment correlates with quantitative and qualitative loss of TrkA receptor protein in nucleus basalis and cortex. J. Neurochem. 95, 1472 – 1480.
45 West A.E., Griffith E.C. and Greenberg M.E. (2002). Regulation of transcription factors by neuronal activity. Nat. Rev. Neurosci. 3, 921 – 931.
46 Wagner N., Wagner K.D., Theres H., Englert C., Schedl A. and Scholz H. (2005). Coronary vessel development requires activation of the TrkB neurotrophin receptor by the Wilms' tumor transcription factor Wt1. Genes Dev. 19, 2631 – 2642.
47 Youn Y.H., Feng J., Tessarollo L., Ito K. and Sieber-Blum M. (2003). Neural crest stem cell and cardiac endothelium defects in the TrkC null mouse. Mol. Cell Neurosci. 24, 160 – 170.
48 Donovan M.J., Hahn R., Tessarollo L. and Hempstead B.L. (1996). Identification of an essential nonneuronal function of neurotrophin 3 in mammalian cardiac development. Nat. Genet. 14, 210 – 213.
49 Lin M.I., Das I., Schwartz G.M., Tsoulfas P., Mikawa T. and Hempstead B.L. (2000). Trk C receptor signaling regulates cardiac myocyte proliferation during early heart development in vivo. Dev. Biol. 226, 180 – 191.
50 Indo Y., Mardy S., Tsuruta M., Karim M.A. and Matsuda I. (1997). Structure and organization of the human TRKA gene encoding a high affinity receptor for nerve growth factor. Jpn. J. Hum. Genet. 42, 343 – 351.
51 Sacristan M.P., de Diego J.G., Bonilla M. and Martin-Zanca D. (1999). Molecular cloning and characterization of the 5′ region of the mouse trkA proto-oncogene. Oncogene 18, 5836 – 5842.
52 Chang B.B., Persengiev S.P., de Diego J.G., Sacristan M.P., Martin-Zanca D. and Kilpatrick D.L. (1998). Proximal promoter sequences mediate cell-specific and elevated expression of the favorable prognosis marker TrkA in human neuroblastoma cells. J. Biol. Chem. 273, 39 – 44.
53 Fujimoto M., Kitazawa R., Maeda S. and Kitazawa S. (2005). Methylation adjacent to negatively regulating AP-1 site reactivates TrkA gene expression during cancer progression. Oncogene 24, 5108 – 5118.
54 Mulloy J.C., Jankovic V., Wunderlich M., Delwel R., Cammenga J., Krejci O., Zhao H., Valk P.J., Lowenberg B. and Nimer S.D. (2005). AML1-ETO fusion protein up-regulates TRKA mRNA expression in human CD34+ cells, allowing nerve growth factor-induced expansion. Proc. Natl. Acad. Sci. USA 102, 4016 – 4021.
55 Costantini C., Scrable H. and Puglielli L. (2006). An aging pathway controls the TrkA to p75NTR receptor switch and amyloid beta-peptide generation. EMBO J. 25, 1997 – 2006.
56 Hock C., Heese K., Muller-Spahn F., Hulette C., Rosenberg C. and Otten U. (1998). Decreased trkA neurotrophin receptor expression in the parietal cortex of patients with Alzheimer's disease. Neurosci. Lett. 241, 151 – 154.
57 Ma L., Merenmies J. and Parada L.F. (2000). Molecular characterization of the TrkA/NGF receptor minimal enhancer reveals regulation by multiple cis elements to drive embryonic neuron expression. Development 127, 3777 – 3788.
58 Lei L., Laub F., Lush M., Romero M., Zhou J., Luikart B., Klesse L., Ramirez F. and Parada L.F. (2005). The zinc finger transcription factor Klf7 is required for TrkA gene expression and development of nociceptive sensory neurons. Genes Dev. 19, 1354 – 1364.
59 Laub F., Lei L., Sumiyoshi H., Kajimura D., Dragomir C., Smaldone S., Puche A.C., Petros T.J., Mason C., Parada L.F. and Ramirez F. (2005). Transcription factor KLF7 is important for neuronal morphogenesis in selected regions of the nervous system. Mol. Cell Biol. 25, 5699 – 5711.
60 Gerrero M.R., McEvilly R.J., Turner E., Lin C.R., O'Connell S., Jenne K.J., Hobbs M.V. and Rosenfeld M.G. (1993). Brn-3.0: a POU-domain protein expressed in the sensory, immune, and endocrine systems that functions on elements distinct from known octamer motifs. Proc. Natl. Acad. Sci. USA 90, 10841 – 10845.
61 He X., Treacy M.N., Simmons D.M., Ingraham H.A., Swanson L.W. and Rosenfeld M.G. (1989). Expression of a large family of POU-domain regulatory genes in mammalian brain development. Nature 340, 35 – 41.
62 Artinger K.B., Fedtsova N., Rhee J.M., Bronner-Fraser M. and Turner E. (1998). Placodal origin of Brn-3-expressing cranial sensory neurons. J. Neurobiol. 36, 572 – 585.
63 Fedtsova N.G. and Turner E.E. (1995). Brn-3.0 expression identifies early post-mitotic CNS neurons and sensory neural precursors. Mech. Dev. 53, 291 – 304.
64 Ninkina N.N., Stevens G.E., Wood J.N. and Richardson W.D. (1993). A novel Brn3-like POU transcription factor expressed in subsets of rat sensory and spinal cord neurons. Nucleic Acids Res. 21, 3175 – 3182.
65 Xiang M., Zhou L., Macke J.P., Yoshioka T., Hendry S.H., Eddy R.L., Shows T.B. and Nathans J. (1995). The Brn-3 family of POU-domain factors: primary structure, binding specificity, and expression in subsets of retinal ganglion cells and somatosensory neurons. J. Neurosci. 15, 4762 – 4785.
66 Xiang M., Gan L., Zhou L., Klein W.H. and Nathans J. (1996). Targeted deletion of the mouse POU domain gene Brn-3a causes selective loss of neurons in the brainstem and trigeminal ganglion, uncoordinated limb movement, and impaired suckling. Proc. Natl. Acad. Sci. USA 93, 11950 – 11955.
67 Eng S.R., Gratwick K., Rhee J.M., Fedtsova N., Gan L. and Turner, E.E. (2001). Defects in sensory axon growth precede neuronal death in Brn3a-deficient mice. J. Neurosci. 21, 541 – 549.
68 Huang E.J., Zang K., Schmidt A., Saulys A., Xiang M. and Reichardt L.F. (1999). POU domain factor Brn-3a controls the differentiation and survival of trigeminal neurons by regulating Trk receptor expression. Development 126, 2869 – 2882.
69 McEvilly R.J., Erkman L., Luo L., Sawchenko P.E., Ryan A.F. and Rosenfeld M.G. (1996). Requirement for Brn-3.0 in differentiation and survival of sensory and motor neurons. Nature 384, 574 – 577.

70 Ma L., Lei L., Eng S.R., Turner E. and Parada L.F. (2003). Brn3a regulation of TrkA/NGF receptor expression in developing sensory neurons. Development 130, 3525 – 3534.

71 Ma Q., Chen Z., del Barco Barrantes I., de la Pompa J.L. and Anderson D.J. (1998). Neurogenin1 is essential for the determination of neuronal precursors for proximal cranial sensory ganglia. Neuron 20, 469 – 482.

72 Ma Q., Fode C., Guillemot F. and Anderson D.J. (1999). Neurogenin1 and neurogenin2 control two distinct waves of neurogenesis in developing dorsal root ganglia. Genes Dev. 13, 1717 – 1728.

73 de Bruijn M.F. and Speck N.A. (2004). Core-binding factors in hematopoiesis and immune function. Oncogene 23, 4238 – 4248.

74 Komori T. (2005). Regulation of skeletal development by the Runx family of transcription factors. J. Cell Biochem. 95, 445 – 453.

75 Inoue K., Ozaki S., Shiga T., Ito K., Masuda T., Okado N., Iseda T., Kawaguchi S., Ogawa M., Bae S.C., Yamashita N., Itohara S., Kudo N. and Ito Y. (2002). Runx3 controls the axonal projection of proprioceptive dorsal root ganglion neurons. Nat. Neurosci. 5, 946 – 954.

76 Levanon D., Bettoun D., Harris-Cerruti C., Woolf E., Negreanu V., Eilam R., Bernstein Y., Goldenberg D., Xiao C., Fliegauf M., Kremer E., Otto F., Brenner O., Lev-Tov A. and Groner Y. (2002). The Runx3 transcription factor regulates development and survival of TrkC dorsal root ganglia neurons. EMBO J. 21, 3454 – 3463.

77 Theriault F.M., Roy P. and Stifani S. (2004). AML1/Runx1 is important for the development of hindbrain cholinergic branchiovisceral motor neurons and selected cranial sensory neurons. Proc. Natl. Acad. Sci. USA 101, 10343 – 10348.

78 Molliver D.C., Wright D.E., Leitner M.L., Parsadanian A.S., Doster K., Wen D., Yan Q. and Snider W.D. (1997). IB4-binding DRG neurons switch from NGF to GDNF dependence in early postnatal life. Neuron 19, 849 – 861.

79 Chen C.L., Broom D.C., Liu Y., de Nooij J.C., Li Z., Cen C., Samad O.A., Jessell T.M., Woolf C.J. and Ma Q. (2006). Runx1 determines nociceptive sensory neuron phenotype and is required for thermal and neuropathic pain. Neuron 49, 365 – 377.

80 Marmigere F., Montelius A., Wegner M., Groner Y., Reichardt L.F. and Ernfors P. (2006). The Runx1/AML1 transcription factor selectively regulates development and survival of TrkA nociceptive sensory neurons. Nat. Neurosci. 9, 180 – 187.

81 Kramer I., Sigrist M., de Nooij J.C., Taniuchi I., Jessell T.M. and Arber S. (2006). A role for Runx transcription factor signaling in dorsal root ganglion sensory neuron diversification. Neuron 49, 379 – 393.

82 Fode C., Gradwohl G., Morin X., Dierich A., LeMeur M., Goridis C. and Guillemot F. (1998). The bHLH protein NEUROGENIN 2 is a determination factor for epibranchial placode-derived sensory neurons. Neuron 20, 483 – 494.

83 Stoilov P., Castren E. and Stamm S. (2002). Analysis of the human TrkB gene genomic organization reveals novel TrkB isoforms, unusual gene length, and splicing mechanism. Biochem. Biophys. Res. Commun. 290, 1054 – 1065.

84 Barettino D., Pombo P.M., Espliguero G. and Rodriguez-Pena A. (1999). The mouse neurotrophin receptor trkB gene is transcribed from two different promoters. Biochim. Biophys. Acta 1446, 24 – 34.

85 Deogracias R., Espliguero G., Iglesias T. and Rodriguez-Pena A. (2004). Expression of the neurotrophin receptor trkB is regulated by the cAMP/CREB pathway in neurons. Mol. Cell Neurosci. 26, 470 – 480.

86 Pombo P.M., Barettino D., Espliguero G., Metsis M., Iglesias T. and Rodriguez-Pena A. (2000). Transcriptional repression of neurotrophin receptor trkB by thyroid hormone in the developing rat brain. J. Biol. Chem. 275, 37510 – 37517.

87 Kim W.Y., Fritzsch B., Serls A., Bakel L.A., Huang E.J., Reichardt L.F., Barth D.S. and Lee J.E. (2001). NeuroD-null mice are deaf due to a severe loss of the inner ear sensory neurons during development. Development 128, 417 – 426.

88 Donovan M.J., Lin M.I., Wiegn P., Ringstedt T., Kraemer R., Hahn R., Wang S., Ibanez C.F., Rafil S. and Hempstead B.L. (2000). Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. Development 127, 4531 – 4540.

89 Hiltunen J.O., Arumae U., Moshnyakov M. and Saarma M. (1996). Expression of mRNAs for neurotrophins and their receptors in developing rat heart. Circ. Res. 79, 930 – 939.

90 Al-Majed A.A., Brushart T.M. and Gordon T. (2000). Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. Eur. J. Neurosci. 12, 4381 – 4390.

91 Angelucci F., Mathe A.A. and Aloe L. (2000). Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered after haloperidol and risperidone administration. J. Neurosci. Res. 60, 783 – 794.

92 Bergman E., Fundin B.T. and Ulfhake B. (1999). Effects of aging and axotomy on the expression of neurotrophin receptors in primary sensory neurons. J. Comp. Neurol. 410, 368 – 386.

93 Croll S.D., Ip N.Y., Lindsay R.M. and Wiegand S.J. (1998). Expression of BDNF and trkB as a function of age and cognitive performance. Brain Res. 812, 200 – 208.

94 Dugich-Djordjevic M.M., Ohsawa F., Okazaki T., Mori N., Day J.R., Beck K.D. and Hefti F. (1995). Differential regulation of catalytic and non-catalytic trkB messenger RNAs in the rat hippocampus following seizures induced by systemic administration of kainate. Neuroscience 66, 861 – 877.

95 Hicks R.R., Zhang L., Dhillon H.S., Prasad M.R. and Seroogy K.B. (1998). Expression of trkB mRNA is altered in rat hippocampus after experimental brain trauma. Brain Res. Mol. Brain Res. 59, 264 – 268.

96 Johnson H., Hokfelt T. and Ulfhake B. (1996). Decreased expression of TrkB and TrkC mRNAs in spinal motoneurons of aged rats. Eur. J. Neurosci. 8, 494 – 499.

97 Kaplan D.R., Matsumoto K., Lucarelli E. and Thiele C.J. (1993). Induction of TrkB by retinoic acid mediates biologic responsiveness to BDNF and differentiation of human neuroblastoma cells. Eukaryotic Signal Transduction Group. Neuron 11, 321 – 331.

98 Kobayashi N.R., Bedard A.M., Hincke M.T. and Tetzlaff W. (1996). Increased expression of BDNF and trkB mRNA in rat facial motoneurons after axotomy. Eur. J. Neurosci. 8, 1018-1029.

99 Light K.E., Brown D.P., Newton B.W., Belcher S.M. and Kane C.J. (2002). Ethanol-induced alterations of neurotrophin receptor expression on Purkinje cells in the neonatal rat cerebellum. Brain Res. 924, 71 – 81.

100 Marvanova M., Lakso M., Pirhonen J., Nawa H., Wong G. and Castren E. (2001). The neuroprotective agent memantine induces brain-derived neurotrophic factor and trkB receptor expression in rat brain. Mol. Cell Neurosci. 18, 247 – 258.

101 Merlio J.P., Ernfors P., Kokaia Z., Middlemas D.S., Bengzon J., Kokaia M., Smith M., Siesjo B.K., Hunter T., Lindvall O. and Persson H. (1993). Increased production of the TrkB protein tyrosine kinase receptor after brain insults. Neuron 10, 151 – 164.

102 Nibuya M., Nestler E.J. and Duman R.S. (1996). Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J. Neurosci. 16, 2365 – 2372.

103 Nibuya M., Takahashi M., Russell D.S. and Duman R.S. (1999). Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci. Lett. 267, 81 – 84.

104 Numan S. and Seroogy K.B. (1997). Increased expression of trkB mRNA in rat caudate–putamen following 6-OHDA lesions of the nigrostriatal pathway. Eur. J. Neurosci. 9, 489 – 495.

105 Olivieri G., Otten U., Meier F., Baysang G., Dimitriades-Schmutz B., Muller-Spahn F. and Savaskan E. (2003). Beta-amyloid modulates tyrosine kinase B receptor expression in SHSY5Y neuroblastoma cells: influence of the antioxidant melatonin. Neuroscience 120, 659 – 665.
106 Ruiz-Leon Y. and Pascual A. (2003). Induction of tyrosine kinase receptor b by retinoic acid allows brain-derived neurotrophic factor-induced amyloid precursor protein gene expression in human SH-SY5Y neuroblastoma cells. Neuroscience 120, 1019 – 1026.
107 Salin T., Mudo G., Jiang X.H., Timmusk T., Metsis M. and Belluardo N. (1995). Up-regulation of trkB mRNA expression in the rat striatum after seizures. Neurosci. Lett. 194, 181 – 184.
108 Takahashi J., Palmer T.D. and Gage F.H. (1999). Retinoic acid and neurotrophins collaborate to regulate neurogenesis in adult-derived neural stem cell cultures. J. Neurobiol. 38, 65 – 81.
109 Takahashi M., Shirakawa O., Toyooka K., Kitamura N., Hashimoto T., Maeda K., Koizumi S., Wakabayashi K., Takahashi H., Someya T. and Nawa H. (2000). Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. Mol. Psychiatry 5, 293 – 300.
110 Ichaso N., Rodriguez R.E., Martin-Zanca D. and Gonzalez-Sarmiento R. (1998). Genomic characterization of the human trkC gene. Oncogene 17, 1871 – 1875.
111 Chen A.I., de Nooij J.C. and Jessell T.M. (2006). Graded activity of transcription factor Runx3 specifies the laminar termination pattern of sensory axons in the developing spinal cord. Neuron 49, 395 – 408.
112 Bernd P., Miles K., Rozenberg I., Borghjid S. and Kirby M.L. (2004). Neurotrophin-3 and TrkC are expressed in the outflow tract of the developing chicken heart. Dev. Dyn. 230, 767 – 772.
113 St Amand T.R., Lu J.T., Zamora M., Gu Y., Stricker J., Hoshijima M., Epstein J.A., Ross J.J., Ruiz-Lozano P. and Chien K.R. (2006). Distinct roles of HF-1b/Sp4 in ventricular and neural crest cells lineages affect cardiac conduction system development. Dev. Biol. 291, 208 – 217.