Notch Signaling: From Neurogenesis to Neurodegeneration

Nalani Sachan, Mousumi Mutsuddi, and Ashim Mukherjee

Abstract

Notch signaling pathway plays a pivotal role during development of an organism. The Notch pathway is an evolutionarily conserved signaling system which has been shown to play a major role in cell fate determination, differentiation, proliferation and apoptotic events, as well as self-renewal processes of different tissues. The same pathway can be deployed in numerous cellular contexts to play varied and critical roles for the development of an organism. In *Drosophila* embryo, loss of Notch function produces remarkable excess of neurons at the expense of the epidermis, and hence Notch was identified as a "neurogenic gene". Several studies have revealed the importance of Notch in the nervous system, including in the maintenance of immature neurons and the control of neurite outgrowth of differentiated neurons. Notch signaling also contributes to the regulation of synaptic plasticity and olfactory functions in the adult brain. Notch signaling has been known to play a crucial role in neural stem cell maintenance and neurogenesis in embryonic as well as adult brain. Thus, it is not surprising that aberrant Notch function can lead to various neurodegenerative diseases. The wealth of genetic resources available for flies offers a unique opportunity to dissect involvement of Notch signaling in neurodegeneration. Understanding the different spatiotemporal regulatory mechanisms of Notch signaling and involvement of Notch signaling pathway in neurodegeneration will help to comprehend various underlying causes of human neurodegenerative diseases at the molecular level.

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Notch Signaling

Notch mutation was first discovered more than a century ago by Morgan and colleagues as a dominant X-linked mutation that exhibits a notched wing phenotype in *Drosophila melanogaster*, and hence the name *Notch* was given for this gene (Mohr 1919). Decades later loss of *Notch* function studies in *Drosophila* embryo revealed *Notch* as a "neurogenic gene" because it produces remarkable excess of neurons at the expense of the epidermis (Lehmann et al. 1983; Poulson 1945). The Notch pathway is an evolutionarily conserved signaling system that operates to influence an astonishing array of cell fate decisions in different developmental contexts. Notch signaling is highly pleiotropic in nature since it regulates different developmental processes such as cell fate determination, differentiation, proliferation, apoptosis, and stem cell maintenance (Andersson et al. 2011; Artavanis-Tsakonas et al. 1999; Baron et al. 2002; Fortini 2009; Liu et al. 2010). Notch is exceptionally sensitive to gene dosage that is both haplo-insufficiency and presence of extra copies of *Notch* results aberrant phenotypes. Notch signaling pathway affects cell fate determination not only across the wide spectrum of metazoan species, but also across a broad range of cell types in a single organism and at different steps during cell lineage progression (Guruharsha et al. 2012; Lai 2004). Thus, aberrant Notch function leads to many diseases in humans including neurodegenerative diseases. Notch signaling has been known to play a crucial role in neural stem cell maintenance and neurogenesis in embryonic as well as adult brain (Alberi et al. 2011; Artavanis-Tsakonas et al. 1999; Borggrefe and Oswald 2009; Lugert et al. 2010). Neuronal atrophy and eventual neuronal loss are the prevalent characteristics of several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, etc.

The Core Notch Pathway

Notch is a single-pass transmembrane receptor that regulates diverse cellular processes during the development of an organism. Almost all core components in Notch signaling pathway are well conserved from *Drosophila* to humans, such as Notch receptors, ligands, negative and positive modifiers, and transcription factors (Gazave et al. 2009). A simple schematic of Notch signaling pathway is shown in Fig. 1. The prototype Notch receptor is synthesized as a 300 kDa polypeptide. During maturation in *trans*-Golgi network, Notch receptor is proteolytically cleaved by furin-like convertases (S1 cleavage), which give rise to a 180 kDa N-terminal extracellular subunit (Notch-ECD) and a 120 kDa C-terminal transmembrane intracellular subunit (NTM) (Blaumueller et al. 1997). These two subunits are held

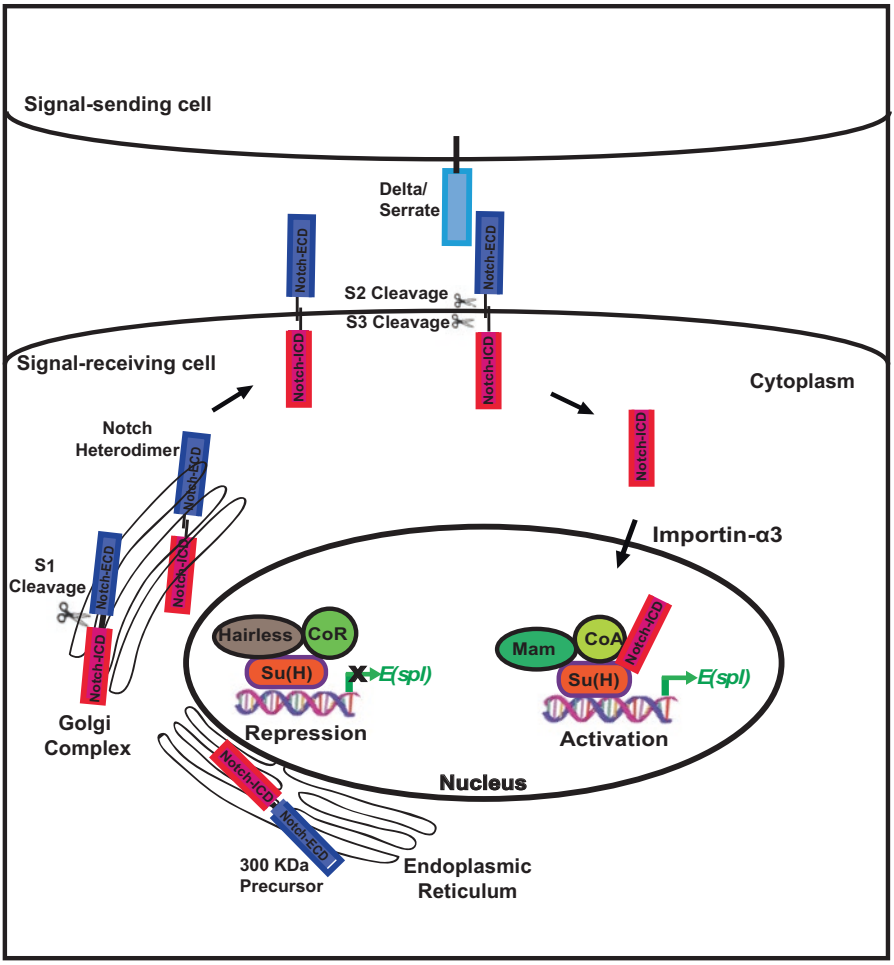

Fig. 1 Notch signaling pathway
Notch receptor (Notch1–4 in mammals) is synthesized as a 300 KDa polypeptide in the endoplasmic reticulum. During post-translational processing in the *trans*-Golgi network, Notch receptors are cleaved by furin-like convertases at site 1 (S1 Cleavage) to create Notch heterodimer (Notch-ICD and Notch-ECD). N- and C-terminal halves of the Notch heterodimers are held together by non-covalent interaction. Heterodimer of Notch receptor translocates to the cell membrane. *Trans*-activation of Notch heterodimer is mediated by the Notch ligands, Delta/Serrate (DLL1, DLL3, DLL4, Jagged1, Jagged2 in mammals) present in the neighboring cell. Ligand binding to the Notch receptor leads to the second cleavage by ADAM metalloprotease(s) at site S2 (S2 cleavage) and γ-secretase at site S3 (S3 cleavage), releasing the Notch-ICD in the cytoplasm. Notch-ICD is translocated to the nucleus with the help of Importin-α3. In the nucleus, Notch-ICD initially interacts with Su(H) DNA-binding protein (CBF1 or RBP-Jk in mammals) and then helps in the recruitment of activator, Mastermind, and other co-activators. This association turns on the transcription of Notch target genes such as *E(spl)* family genes such as *Hey* and *Hes*, whereas in the absence of Notch-ICD, Su(H) recruits repressor (Hairless) and corepressors, which turn off the transcription of Notch target genes

together non-covalently by a calcium-dependent interaction (Rand et al. 2000). This processed heterodimeric Notch receptor is then transferred to the cell membrane and it interacts with ligands of the DSL family (*Drosophila* Delta and Serrate (Jagged in mammals) and *C. elegans* LAG-2). Binding of ligands expressed in adjacent cell to Notch-ECD leads to second proteolytic cleavage (S2) by ADAM family of metalloproteases in the extracellular portion of NTM (Brou et al. 2000). This is followed by an intramembranous cleavage (S3) by γ-secretase complex (Presenilin, nicastrin, PEN-2 and APH-1) and results in the release of Notch intracellular domain (Notch-ICD) from the membrane (Brou et al. 2000; De Strooper et al. 1999; Struhl and Greenwald 1999). Then the released Notch-ICD translocates to the nucleus with the help of importin-α3/importin-β transport pathway, where it transduces Notch signals by regulating the transcription of downstream target genes (Kopan et al. 1994; Sachan et al. 2013; Struhl and Adachi 1998, 2000). This Notch-ICD is a transcriptional co-activator, and exceedingly small, histochemically invisible amount of Notch-ICD is sufficient to activate target genes. This Notch-ICD directly participates in a transcriptional complex involving CSL transcription factor (CBF1 or RBP-Jk of mammals/*Drosophila* suppressor of hairless [Su(H)]/*C. elegans* LAG-1) and transcriptional co-activators like Mastermind (Mam) in *Drosophila*/Mastermind-Like (MAML) in mammals. This ternary complex also recruits histone acetylase CBP/p300 and SKIP leading to activation of Notch target genes (Aster et al. 1997; Leong et al. 2002; Mishra et al. 2014; Oswald et al. 2001; Petcherski and Kimble 2000; Sachan et al. 2015; Singh et al. 2019; Tamura et al. 1995; Vasquez-Del Carpio et al. 2011; Wu et al. 2000). This association converts CSL transcriptional repressor to transcriptional activator, and it activates the most classical target genes, belonging to basic helix-loop-helix (bHLH) families of transcription factor, e*nhancer of split* [*E(spl)*] in *Drosophila*, *hairy/enhancer of split* (HES), and *Hrt* (Hes-related) or *hairy/enhancer of split-related with YRPW motif* (Hey, also called HESR) in mammals. These bHLH transcription factors in turn repress *achaete-scute complex* (As-C) proneural genes (Campos-Ortega 1993; Fortini and Artavanis-Tsakonas 1994; Wu et al. 2000). Thus, these factors repress the transcription of genes involved in differentiation. While in the absence of Notch-ICD, CSL recruits corepressor factors such as NCoR (nuclear receptor corepressor)/SMRT (silencing mediator of retinoid and thyroid hormone receptors), histone deacetylase (HDAC), SHARP (SMRT and HDAC-associated repressor protein)/MINT (Msx2-interacting nuclear target), CIR (CBF1 interacting corepressor), SKIP (Ski-interacting protein), and histone demethylases KDM5A/Lid (Borggrefe and Oswald 2009; Engel et al. 2010; Lai 2002; Liefke et al. 2010; Moshkin et al. 2009; Oswald et al. 2005; VanderWielen et al. 2011). Various components of Notch signaling pathway have been mentioned in Table 1. Depending upon the cellular context *wg*, *cut*, *string, c-myc, cyclin D,* etc., are also Notch target genes (reviewed in Bray and Bernard 2010). Apart from these factors, there are also specific corepressors that antagonize the gene expression engaging the Notch signaling pathway at different cellular contexts. For example, *Drosophila insensitive*, which is homolog of mammalian BEND6, has been identified as a neural-specific CSL corepressor for peripheral

Table 1 Components of Notch signaling pathway

Components	*Drosophila*	Mammals	*Caenorhabditis elegans*
Receptor	Notch	NOTCH1 NOTCH2 NOTCH3 NOTCH4	LIN-12 GLP-1
Canonical ligands	Delta	Delta-like 1 (Dll1) Delta-like 3 (Dll3) Delta-like 4 (Dll4)	APX-1 (Soluble) LAG-2 (Soluble) ARG-1 DSL1-7
	Serrate	Jagged1 Jagged2	
Non-canonical ligands	Weary (Wry) (reported in cardiomyopathy)	DLK1 (in angiogenesis) DLK2 (in preadipocytes) DNER (in cerebellar development) EGFL7 (in neurogenesis)	DOS OSM-11
Transcription factor	Su(H)	RBPjk/CBF-1	LAG-1
Transcriptional co-activators	Mastermind Chip Hat-trick	Mastermind like1 (MAML1) Mastermind like2 (MAML2) Mastermind like3 (MAML3)	LAG-3
Transcriptional corepressors	Hairless, SMRTR CtBP, CtIP, Groucho, HDAC, Sin3A, LSD1, CoREST1, Insensitive, LID	SHARP, CIR1, NCoR/ SMRT (NCoR2), HDAC, BEND6, KDM5A, Bcl-6, CtBP1, NKAP, SAP30	
S1 cleavage (furin convertase)	Furin	Furin, PC5/6	
S2 cleavage (metalloprotease)	Kuzbanian, kuzbanian-like, TACE	ADAM10, ADAM17/TACE	SUP-17/ kuzbanian, ADM4/TACE
S3 cleavage (γ-secretase)	Presenilin Nicastrin APH-1 PEN-2	Presenilin 1 Presenilin 2 Nicastrin APH1a-c PEN-2	SEL-12/ Presenilin APH-2/nicastrin APH-1 PEN-2
HECT-type E3 ubiquitin ligase (for lysosomal degradation)	dNedd4 Su(dx)	Nedd4 Itch	WWP-1
Ring finger-type E3 ubiquitin ligase (Promotes Notch towards Rab 11 vesicles)	Deltex	Deltex 1–4	

(continued)

Table 1 (continued)

Components	*Drosophila*	Mammals	*Caenorhabditis elegans*
F-box protein E3 ubiquitin ligase (Promotes degradation of Notch-ICD by phosphorylation)	Archipelago	Fbw7	SEL-10
E3 ubiquitin ligase (Targets Notch ligands Delta and Jagged/Serrate during endocytosis)	Mind bomb 1–2 Neuralized	Mind bomb, Skeletrophin, Neuralized 1–2	Y47D3A.22
DUB (Deubiquitinating enzyme)	USP12 eIF3-S5	USP12 eIF3f	
Cytoplasmic Notch inhibitor	Numb	Numb, Numb-like	
Numb-associated kinase	Numb-associated kinase	AP2-associated kinase	SEL-5
Notch target genes	*E(Spl)*-complex genes, *myc, wg, cut* etc.	*HES/HEY/ESR, Myc, p21, Bcl-2, cyclin D1*	*REF-1*
Notch nuclear transport pathway component	Importin-*α3 or* Karyopherin-*α3*	Importin subunit alpha-3 or Karyopherin subunit alpha-4	
Negative cytoplasmic regulators of Notch	DTRAF6 Deltex	TRAF6 Deltex-1 NRARP	

neurogenesis, which promotes neural differentiation and inhibits neural stem cell renewal (Dai et al. 2013).

Notch activity is regulated at multiple levels, including patterns of receptor and ligand expression, Notch-ligand interactions, trafficking of the receptor and ligands, and covalent modifications including glycosylation, phosphorylation, and ubiquitination of the receptor (reviewed in Andersson et al. 2011). In addition, Notch signaling is also modified by various cytoplasmic factors such as Deltex, a positive as well as negative modulator of Notch signaling depending on the cellular context (Matsuno et al. 1995; Mukherjee et al. 2005), Numb, negatively regulates Notch (Frise et al. 1996), and SEL10, an F-box protein that promotes Notch-ICD turnover (Gupta-Rossi et al. 2001).

Modes of Notch Action

The core Notch signaling pathway is conserved in most of the Notch-dependent processes. The Notch pathway functions in diverse developmental and physiological processes, which are broadly subdivided into three classes: lateral inhibition, cell lineage decision, and boundary formation. The first report that Notch is involved

in all the above-mentioned functions came from studies involving neurogenesis in *Drosophila* (reviewed in Artavanis-Tsakonas et al. 1999). From these studies it became evident that Notch is involved in the development of various stages of a particular tissue. For example, during the first stage of neurogenesis, Notch regulates the number of cells, which will adopt neuronal fate (through lateral inhibition); subsequently it determines whether progeny will acquire neural or glial fates (through lineage decision) (reviewed in Bray 2006).

Lateral Inhibition

In *Drosophila*, during patterning of neuroectoderm, groups of 4–7 cells termed as "proneural clusters" are defined by the expression of patterning genes. Although all these cells in a proneural cluster have equivalent potential to give rise to neural cell type, one cell will be destined to become either neuroblast for generation of neuron in central nervous system (CNS) or sensory organ precursor (SOP) cell in the peripheral nervous system (PNS) (reviewed in Furukawa et al. 2000; Gaiano and Fishell 2002; Gaiano et al. 2000). Among equivalent groups of cells, one specific cell is preferred for progenitor of CNS or PNS by lateral inhibition (Fig. 2). Constitutively in this process two kinds of genes are involved, proneural and neurogenic genes. Proneural genes of *achaete-scute* complex (*achaete*, *scute*, *asense*, *lethal of scute*), *atonal*, *Bearded,* and *SoxNeuro*, which encodes for basic helix-loop-helix transcription factors, direct the cell to acquire neural fate. In contrast, neurogenic genes such as *Notch*, *Delta*, *Serrate*, *mastermind*, *neuralized*, and *enhancer of split complex* mediate the cell to adopt epidermal fate (reviewed in Iso et al. 2003). Balance between proneural and neurogenic genes determines the fate of a specific cell in a proneural cluster to become a neuroblast or a SOP. The cell that becomes neuroblast or SOP, expresses highest levels of Notch ligand Delta, thus activating Notch in the surrounding cells, inhibiting their differentiation into neuroblasts or the SOP. Neighboring cells, which are now deprived of proneural genes due to Notch expression, convincingly adopt epidermal fate due to lateral inhibition. In Notch mutants due to deficiency of *Notch*, all cells start expressing proneural genes at the expense of epidermis resulting in the overproduction of neurons (reviewed in Gaiano and Fishell 2002).

Cell Lineage Decision

In addition to lateral inhibition, Notch also plays another vital role for cell fate diversification when cells choose between two alternative fates and this process is known as a binary fate decision. During the development of CNS, cells can opt for neuroblast fate where with each asymmetric division, it recapitulates itself and at the same time gives rise to secondary precursor cell known as ganglion mother cell (GMC). After the SOP cell of PNS is chosen, first division of SOP generates two cells, pIIa (Notch on) and pIIb (Notch off) (Fig. 2). Each of these two cells further divides and generates hair and socket from pIIa and pIIb undergoes division to form pIIIb and glial precursor cell (GP), which moves away and gives rise to many glial or adult mechanosensory bristles. The next division of pIIIb generates neuron and sheath. During PNS development, Notch plays an opposite role in glial cell

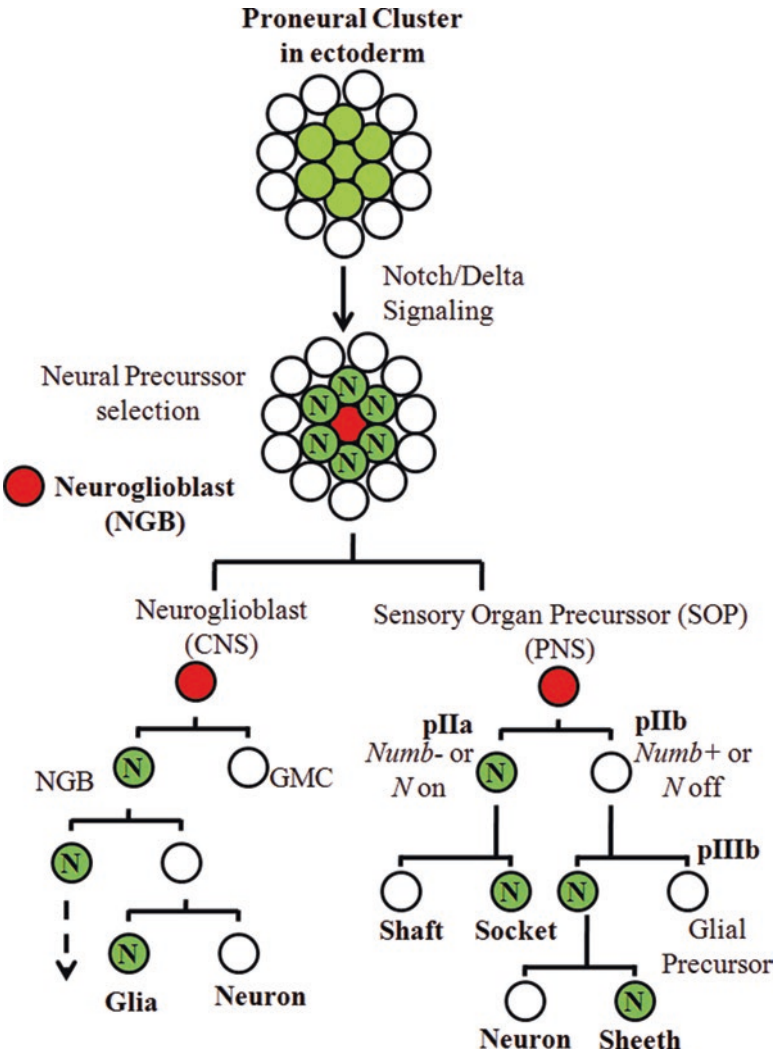

Fig. 2 Lateral inhibition mediated by Notch signaling
Schematic representation showing Notch-mediated lateral inhibition during cell-fate specification in the central nervous system (CNS) and peripheral nervous system (PNS) in *Drosophila*. A single cell within a proneural cluster will become neuroblast for CNS or SOP for PNS and inhibits other neighboring cells from acquiring a neuronal fate

development compared to CNS. At the same time, there is also some evidence where during SOP lineage a few glial cells require Notch. In these Glial cells, Numb protein accumulates, which acts as an antagonist of Notch, and physically interacts with Notch-ICD in association with α-Adaptin. α-Adaptin is a member of AP-2 complex, which acts like an adaptor molecule and binds with the Numb, which in turn is accountable for receptor-mediated endocytosis of Notch for differentiation into pIIb cells (Berdnik et al. 2002).

The role of Notch in the maintenance of stem cells is another example of binary cell fate choices. Notch plays a major role in the decision of which cell will become a stem cell to maintain the stem cell pool and which cell will differentiate (Chiba 2006). It has been reported that Notch1 regulates neural stem cell (NSC) number during development, and Notch1 signaling maintains the reservoir of undifferentiated cells in adult mice during hippocampal neurogenesis (Ables et al. 2010).

Boundary Formation

In *Drosophila*, Notch and Wingless (Wg) signaling pathways are key controllers for dorsoventral (DV) boundary formation in both developing eye, and wing imaginal discs. *apterous* (*ap*) expression in the early wing primordium induces expression of the Notch ligand Serrate in dorsal (D) cells and restricts the expression of another Notch ligand Delta to ventral (V) cells (Diaz-Benjumea and Cohen 1995). Serrate (dorsal) and Delta (Ventral) cells activate the Notch symmetrically in cells on both sides of the DV compartment boundary (de Celis et al. 1996; Doherty et al. 1996). Expression of the glycosyltransferase Fringe makes dorsal cells more sensitive to Delta and less sensitive to Serrate (Fleming et al. 1997; Moloney et al. 2000; Munro and Freeman 2000). Consequently, activated Notch induces Wg expression in cells along the DV boundary. Wg further induces the expression of Serrate and Delta in nearby dorsal and ventral cells and Serrate and Delta signal back to activate Notch, thereby maintaining Cut and Wg expression along the DV boundary (Milan and Cohen 2000, 2003) (Fig. 3).

In the vertebrate central nervous system, neural plate acts as a signaling hub for planar signals. The cells along the neural plate separate into cell population for forebrain, midbrain, hindbrain, and spinal cord (Fraser et al. 1990; Kiecker and Lumsden 2005).

Midbrain-hindbrain boundary (MHB) is the best characterized place to study the boundary formation. In a similar manner to DV boundary of *Drosophila* wing

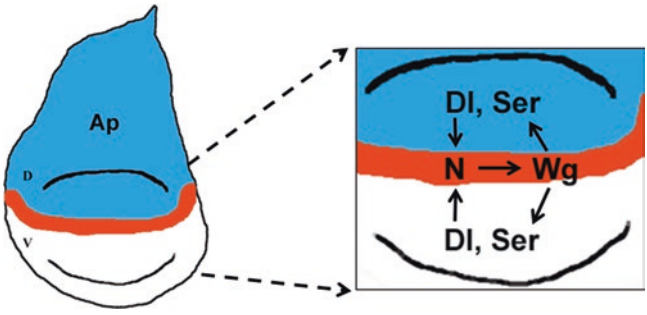

Fig. 3 Schematic representation of role of Notch in the dorsoventral (DV) boundary formation in late third instar larval wing imaginal disc
Notch is activated in DV boundary by its ligands, Dl and Ser, expressed in neighboring cells. Activated Notch turns on Wingless (Wg) expression in DV boundary cells. A positive-feedback loop between Wg expressing cells along the DV boundary and Ser- and Dl-expressing cells in adjacent cells maintain the signaling center along the DV boundary

imaginal disc, Notch is active in the narrow boundary of MHB. Blocking the Notch signaling either by inhibitor of γ-secretase activity or with truncated ligand in the MHB of neural tube in chick embryo leads to the morphologically absence of MHB in the embryos. It has been reported that differential Notch signaling stabilizes the MHB through regulating cell sorting and specifying boundary cell fate (Tossell et al. 2011). Notch also plays an important role in boundary formation in other places as well during development. For example, Notch has a profound role in boundary formation between the prospective somites during somitogenesis in vertebrates.

Notch Signaling in Neurodegeneration

Conservation of human disease genes, powerful genetic tools, and short life cycle of *Drosophila* make it an invaluable model of choice to study human diseases. Here we review the involvement of Notch signaling in the neurodegeneration process by focusing specifically on the information obtained using *Drosophila* as a model system. Notch signaling plays a critical role in brain development. Notch signaling pathway also has a profound role in adult synaptic plasticity and memory formation. Thus, it is not surprising that aberrant Notch function leads to neurodegenerative diseases in humans. Although there is plethora of information on the role of Notch signaling in neurodegeneration using different model systems, here we will restrict our discussion mainly on the information gathered about the involvement of Notch signaling in different neurodegenerative diseases using *Drosophila*.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a widespread age-related neurodegenerative disorder that mainly affects the central nervous system of elderly population (Ferri et al. 2005). Clinically, AD is characterized by progressive memory loss and cognitive impairment because synaptic contacts are lost in the neocortex as well as in the hippocampus, which results in dementia and impaired intellectual and linguistic skills (O'Brien and Wong 2011; Scheff et al. 2006). The hallmark pathognomonic features such as senile plaques and neurofibrillary tangles (NFTs) are observed during post-mortem examination for the diagnosis of AD. In 1907, Physician Alois Alzheimer first identified these two pathological alterations in the brain of a female patient suffering from dementia (LaFerla et al. 2007). Senile plaques are formed due to the accumulation of misfolded protein that is a pathogenic form of amyloid-ß, which is derived from amyloid protein precursor (APP). In the specific regions of brain, extracellular deposition of aggregates of small peptide amyloid-ß (Aß), such as $A\beta_{40}$ and $A\beta_{42}$, generates pathogenic amyloid plaques (Hardy and Higgins 1992; Karran et al. 2011). NFTs are intraneuronal aggregation of hyperphosphorylated forms of tau, which is a microtubule-associated protein (Goedert et al. 1988; Grundke-Iqbal et al. 1986; Ihara et al. 1986; Kosik et al. 1986). According to the

data from the National Center for Health Statistics 2014, AD was the leading cause of death after heart disease in the United States (Xu 2016). Majority of known AD cases fall under sporadic category, while about 5% cases are of familial AD (FAD) (Rogaeva 2002). Due to insufficient knowledge of the cause of Alzheimer's disease, its effective treatment is unavailable.

AD state is generated due to improper cleavage of APP in the brain (Fig. 4). APP has very short half-life of ~30–60 mins and undergoes post-translational modifications (Storey et al. 1999). Mutations in either gene encoding for APP or APP processing catalytic component, Presenilin (PS), have been directly linked to AD (Goate et al. 1991; Levy-Lahad et al. 1995; Sherrington et al. 1995). In normal conditions, APP undergoes a series of proteolytic processing by α-secretase (*Drosophila* Kuzbanian) and γ-secretase. While in Alzheimer's disease state, APP undergoes sequential proteolytic processing by β and γ-secretase. β-Secretase activity is delivered by β-site APP-cleaving enzyme (BACE), while γ-secretase activity is provided by PS. These consequent cleavages lead to elevated levels of longer and pathogenic form $A\beta_{42}$ peptides compared to more benign 40-amino-acid-long amyloid ß-peptide ($A\beta_{40}$) (Selkoe 2004; Wolfe and Haass 2001).

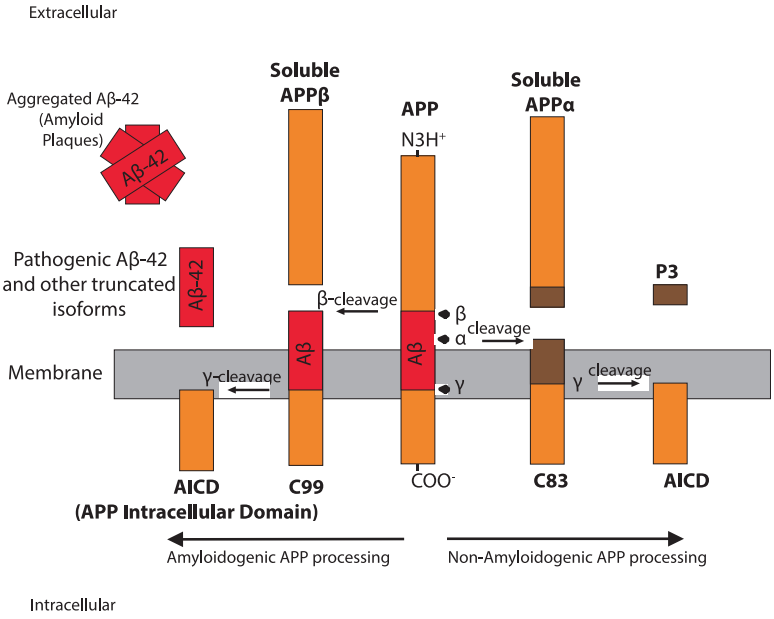

Fig. 4 APP processing by α, β and γ secretase
Cleavage of APP by α-secretase releases a soluble fragment of APPα extracellularly and a membrane-bound fragment, C83. γ-Secretase cleaves C83 to produce the P3 and APP intracellular domain (AICD) during non-amyloidogenic pathway. However, during amyloidogenic processing in Alzheimer's state, mutations in PS subtly modify the cleavage pattern. Associated mutations cause cleavage of APP by β-secretase that generates the soluble APPβ fragment extracellularly and C99 transmembrane fragment. Cleavage of C99 by γ-secretase produces longer and pathogenic form $A\beta_{42}$ peptides and AICD

Table 2 *Drosophila* models for human Alzheimer's disease

AD-associated genes	Fly models	References
APP (Alzheimer's Disease)	Overexpression APP transgenic lines (*pUAST-APP, UAS-APP695II*, *UAS-APP695III*, *UAS-APP-Swedish* (K670 N/M671 L)), *Appl* and *Aβ* mutants	Chakraborty et al. (2011), Fossgreen et al. (1998), Furotani et al. (2018), Greeve et al. (2004), Merdes et al. (2004), Mhatre et al. (2014), Muhammad et al. (2008), Rieche et al. (2018), Stokin et al. (2008) and Wentzell et al. (2012)
APP-Like (Alzheimer's disease)	*Appl* $^{-/-}$ *Appl*-42,673 RNAi line *Appl*-G3 RNAi w	Goguel et al. (2011), Luo et al. (1992)
AB Peptide (Alzheimer's disease)	Overexpression model of full length *Appl* and *dAβ*	Carmine-Simmen et al. (2009), Feng et al. (2018), Finelli et al. (2004) and Iijima et al. (2004)
	Human $A\beta_{40}$ or $A\beta_{42}$ peptide was expressed in the *Drosophila* CNS	
PSEN (Alzheimer's disease)	Overexpression of full-length *Drosophila Psn*	Seidner et al. (2006)
	14 different mutations at conserved residues in *Drosophila* Presenilin has been created corresponding to identified mammalian *Psn1*mutations	
Tau (Alzheimer's disease)	Isolation of *Tau* cDNA and generation of Tau antibodies	Heidary and Fortini (2001), Jackson et al. (2002), Passarella and Goedert (2018), Sealey et al. (2017) and Wittmann et al. (2001)
	Wild-type, mutant forms of human tau (such as Δ306-311 human Tau-383), as well as two isoforms of human Tau, 0N3R and 0N4R were expressed in *Drosophila*	
	Overexpression of *Drosophila Tau*	
Autophagy-related genes in *Drosophila*, neurodegenerative phenotypes	Studies of *ATG1*, *ATG5, ATG7*, *ATG8a* and *ATG18* genes in *Drosophila* Human $A\beta_{1\text{-}40}$ or $A\beta_{1\text{-}42}$ protein expression in *Drosophila* neurons	Juhasz et al. (2007), Kim et al. (2016), Ling et al. (2014), Omata et al. (2014) and Simonsen et al. (2008)

Similar to Notch pathway components, most of the AD-linked genes are evolutionarily conserved in *Drosophila.* Most importantly fruit flies can recapitulate the phenotypes observed in AD patients. Different *Drosophila* models generated for human AD have been mentioned in Table 2. During the process of understanding the molecular basis of this disease, Presenilin (PS) gene that encodes eight-pass transmembrane protein was identified. PS is the catalytic component of γ-secretase complex. PSs are frequently present in the endoplasmic reticulum, Golgi body, and

Table 3 Association of Notch signaling and AD

Associated AD mutants	Effect on Notch signaling
PS mutation	Impaired proteolytic release and nuclear translocation of Notch (Song et al. 1999)
PS deletion	Defective expression of Dll1 and hes5 and failure of normal embryogenesis with several neuronal defects (Donoviel et al. 1999; Saura et al. 2004)
APP interaction with Numb	Decreases Notch signaling (Kyriazis et al. 2008)

the plasma membrane and cleave the amyloid precursor protein (APP) for further processing. Mutations in this gene have been associated with early onset of AD (Table 3) (De Strooper and Woodgett 2003; Levy-Lahad et al. 1995; Mahoney et al. 2006; Ray et al. 1999; Selkoe 1998; Sherrington et al. 1995). In mammals, both Presenilins, PS1 and PS2, are also expressed throughout the development in most of the cell types, whereas compared to PS2, PS1 is mostly expressed during early development. Half of all FAD cases are associated with mutations in three known genes, APP, PS1, and PS2, which cause majority of early-onset Alzheimer's disease in humans (Berezovska et al. 1997; Lee et al. 1996). Majority of these mutations belong to missense substitutions in Presenilins (Fraser et al. 2000; Rogaeva 2002). There are a large number of known substrates of PS/γ-secretase (reviewed by Haapasalo and Kovacs 2011), but little is known about their regulation and activity due to their complex structure (Haapasalo and Kovacs 2011). For most of the substrates, the mechanism of action has not been identified. In those cases, it might act as a catalytic enzyme, which simply eliminates the transmembrane stubs of protein after extracellular membrane shedding (Mahoney et al. 2006; Struhl and Adachi 2000; Wolfe and Kopan 2004). Due to the complex nature of PSs, their full mechanism of action is not very well understood, but they have been well implicated in three processes: Notch signaling, β-amyloid deposition, and apoptosis. Mutation in PS results in the generation of neurotoxic form of β-amyloid ($A\beta_{42}$) compared to $A\beta_{40}$ (Haass 1997). However, in the case of the Notch family receptors, γ-secretase/PS controls the signaling process. Its requirement in Notch signaling cascade has been confirmed in various organisms including *Drosophila* and Human (Wolfe and Kopan 2004).

Notch signaling plays an essential role in neural stem cells (NSCs), in neural development, and in learning and memory formation (Fortini and Artavanis-Tsakonas 1994; Ge et al. 2004; Louvi and Artavanis-Tsakonas 2006; Yoon and Gaiano 2005). Loss of function of Notch in *Drosophila* generates defective long-term memory resulting in the regulatory role in neuronal plasticity (Presente et al. 2004). However, it has also been seen that enhanced Notch signaling suppresses the long-term memory formation in adult *Drosophila* (Zhang et al. 2015). Studies in mice supports the hypothesis that impaired Jagged1-Notch signaling is associated with defective spatial memory in adult mice (Sargin et al. 2013). In the context of age-related human diseases like Alzheimer's disease, various aspects of Notch signaling have been explored since PS-dependent γ-secretase cleavage is common in

processing of Notch and APP (Berezovska et al. 1998; Fraser et al. 2000). To understand the broad role of PS1, targeted null mutation has been created in PS1 locus to generate the knockout mice, but these mice are embryonically lethal and show various abnormalities including excessive neuronal loss, severe hemorrhages in the CNS, and defective skeletal formation. This finding supports the role of PS1 in neural progenitor cell and axial skeletal formation (Shen et al. 1997; Wong et al. 1997). These mice show reduced expression of Notch1 and Dll1in the presomatic mesoderm. FK506-binding proteins (FKBPs) are well-known modifiers of PS in *Drosophila*. FKBPs play an essential role in protein folding and trafficking. FKBP14 mutants genetically interact with components of Notch signaling and show reduced expression of Notch target genes, Presenilin protein levels, and gamma-secretase activity (van de Hoef et al. 2013). Studies have shown that microRNA-124 (miR-124) is highly expressed in CNS and potentially regulates the Notch ligand Delta. miR-124 mutant flies have defects in the climbing ability as well as have reduced life span. RNAi of *Delta* can also rescue the learning defect and enhance the life span of AD flies (Kong et al. 2015). Thus, it was concluded that miR-124 plays a neuroprotective role in AD *Drosophila* model by targeting Notch ligand Delta (Kong et al. 2015).

Dysregulation of microtubule stability causes impairment of axonal transport, degeneration of synaptic contact, and impairment of neuronal function, which ultimately leads to neuronal loss. Among several signaling pathways, Notch pathway also plays a major role in assembly-disassembly of microtubules. It has been demonstrated that Notch activation results in increased microtubule stability and it was proposed that Notch can be a potential target for microtubule stabilization and thus it may have therapeutic potential for the treatment of neurodegenerative diseases including Alzheimer's disease (Bonini et al. 2013). It has been demonstrated that Notch1 is significantly accumulated in the brain parenchyma of sporadic AD patients and consistent reduction of Notch1 signaling in neurons in AD patients suggests that Notch1 may potentially be considered a novel hallmark of AD (Brai et al. 2016).

Parkinson's Disease (PD)

Parkinson's disease (PD) is a very common late-onset neurodegenerative disease that affects the motor neurons and leads to progressive impairment in motor functions (Alexander et al. 1986; Konczak et al. 2009; Lang and Lozano 1998). It is characterized by two main pathological features: premature selective loss of dopamine neurons and accumulation of misfolded α-synuclein protein, known as Lewy bodies in multiple systems of the patients. Major symptoms of Parkinson patients include dementia, bradykinesia, impaired balance, sleep and mood dysfunction, loss of coordination between voluntary and reflexive motors commands, etc. (Braak et al. 2003; Rizek et al. 2016).

Leucine-rich-repeat-kinase2 (LRRK2) has been identified as a causative gene for autosomal-dominant familial and idiopathic PD. Genome-wide-association-studies

(GWAS) identified LRRK2 and SNCA/ α-synuclein as two strong risk loci for sporadic PD (Satake et al. 2009). A single LRRK gene, dLRRK, is present in *Drosophila* and dLRRK is localized in endosomes in which it regulates the function of Rab7 in the late endosomal-lysosomal pathway (Dodson et al. 2012). It has been shown that two LRRK2-binding proteins, NEURL4 [Bluestreak (Blue) in *Drosophila*] and HERC2 (dHERC2 in *Drosophila*), genetically and physically interact with Notch ligand Delta-like 1 (Dll1)/Delta (Dl). LRRK2, along with NEUR4 and HERC2, promotes the recycling of Dll1/Dl through endosomal trafficking of Dll1/Dl, and consequently levels of Dll1/Dl are increased in the plasma membrane. Higher concentration of Dll1/Dl negatively regulates Notch signaling through cis-inhibition. This effect was seen to be enhanced by PD-associated mutation of LRRK2 gene (R1441G ROC domain mutant). As a result, inhibition of Notch signaling accelerates neural stem cell differentiation and affects the function and survival of adult dopaminergic neurons (Imai et al. 2015). The alteration of Notch signaling in adult dopaminergic neurons in *Drosophila* modulates the function and survival of these cells, which may be associated with the neurodegeneration caused by LRRK2 mutations. These findings clearly show that there is a possible link between Notch signaling pathway and Parkinson's disease.

Polyglutamine Diseases (PolyQ Diseases)

A group of neurodegenerative disorders caused by abnormal trinucleotide repeat expansions of CAG that encode long chain of glutamine (Q) amino acid in the coding region of respective gene is known as polyglutamine (PolyQ) diseases. The expansion in the repeat length is directly proportional to disease severity (Table 4) (David et al. 1997; Imbert et al. 1996; La Spada and Taylor 2003; Orr and Zoghbi 2007; Ross et al. 1999). Although each disease falling under this category leads to neurodegeneration, each disease is diagnosed by a specific symptom and a specific pattern of neuronal death (Seidel et al. 2012). The pathogenesis of these set of diseases is not very well understood, and no effective treatment is available (Margulis et al. 2013). Among the PolyQ diseases, Huntington's disease and SCA3 account for the highest prevalence worldwide and Huntington's disease is the most well-studied PolyQ disease (Bauer and Nukina 2009).

Spinocerebellar Ataxia Type 1 (SCA1)

Spinocerebellar ataxia type 1 (SCA1) is a progressive neurodegenerative disease caused by the expansion of trinucleotide CAG repeat within the coding region of the *ataxin-1* (*ATXN1*) gene (Banfi and Zoghbi 1994; Orr et al. 1993). The characteristic features include progressive loss in the motor co-ordination and speech mutilation. Degeneration of specific neurons of brain stem neurons is also very common (Robitaille et al. 1995).

To explore the molecular mechanism behind SCA1-related neuronal degeneration, full-length human SCA1 gene was expressed in *Drosophila* using UAS/GAL4 system. The transgenic flies generated from the construct that encodes ataxin-1 30Q

Table 4 PolyQ diseases

PolyQ diseases	Locus in human	Affected gene	*Drosophila* homolog	Glutamine repeat size	
				Normal	Pathological
SCA1	6p23	Ataxin-1 (ATXN1)	Ataxin-1 (CG4547)	6–39	41–83
SCA2	12q24	Ataxin-2 (ATXN2)	Ataxin-2 (CG5166)	15–31	34–50
SCA3/MJD	14q24-q31	Ataxin-3 (ATXN3)	NA	12–43	60–87
SCA6	19p13	CACNA1A	α1ACT	4–18	21–30
SCA-7	3p21-p12	Ataxin-7 (ATXN7)	NA	7–18	38–200
SCA-17	6q27	TBP	Tbp (CG9874)	29–42	45–63
Huntington Disease	4p16.3	Huntingtin	Huntingtin	6–35	36–121
Spinal and bulbar muscular atrophy (SBMA)/Kennedy's disease	Xq12	Androgen receptor (AR)	Estrogen-related receptor	9–36	38–62
Dentatorubral-pallidoluysian atrophy	12p13.31	Atrophin 1	Atrophin	7–34	49–88

are known as wild-type human isoform, whereas the flies which were derived from the construct that encodes ataxin-1 82Q are termed as SCA1 expanded isoform. Expression of wild-type and expanded SCA1 with eye-specific *GMR-GAL4* produces degeneration of ommatidia in both cases; however, severity of the phenotype is proportional to the number of PolyQ repeats (Fernandez-Funez et al. 2000). This finding in *Drosophila* is very similar to dendritic arborization study of Purkinje cells in SCA1 mice. Transgenic mice for ataxin-1 82Q undergo neurodegeneration at a very early stage (12 weeks), whereas in the case of ataxin-1 30Q, mice neuronal atrophy is not visible until 59th week (Fernandez-Funez et al. 2000). Ataxin-1 30Q in humans may never reach the critical level required for pathogenesis and that may be the reason ataxin-1 30Q is not toxic in humans (Fernandez-Funez et al. 2000).

Ataxin-1 function is not limited to motor coordination and processing of β-amyloid protein (Crespo-Barreto et al. 2010; Matilla et al. 1998; Zhang et al. 2010). It interacts with members of transcriptional corepressor SMRT (silencing mediator of retinoid and thyroid hormone receptors) in *Drosophila* as well as in mammals (Tsai et al. 2004). Capicua and LANP (leucine-rich acidic nuclear protein) cofactor are other interactors of ataxin-1 involved in transcriptional repression (Cvetanovic et al. 2007; Lam et al. 2006; Riley and Orr 2006). Mizutani and colleagues characterized another protein BOAT1 (brother of ataxin-1), which was very similar to ataxin-1 (Mizutani et al. 2005). Tong and co-workers have further explored the role of ataxin-1 and BOAT1 in the Notch signaling pathway. At this end, when BOAT1 was expressed in the posterior compartment of the wing disc by *hedgehog-GAL4* (*hh-GAL4*) driver, it showed the phenotype that mimics *Notch*-mutant wing phenotype in adult flies such as thick longitudinal vein 5 (LV5) and absence of posterior crossvein. At the

same scenario, *hh-GAL4* induced overexpression of BOAT1 in *Notch* mutant background, expanded LV5 thickening phenotype in adult wing was observed. Notch regulates the wing vein thickening phenotype by lateral inhibition by activating various target genes such as *E(spl)* (De Celis and Diaz-Benjumea 2003). In BOAT1 expressing wing imaginal disc, *E(spl)* expression was fairly reduced. This experiment concludes that BOAT1 is an inhibitor of Notch activity (Tong et al. 2011). Further, *hh-GAL4* induced expression of BOAT1 in *Su(H)* mutant background can rescue the LV5 thickening phenotype because repressive effect of *Su(H)* is alleviated in this background. It has been shown through co-immunoprecipitation experiments that BOAT1 and ataxin-1 directly interact with CBF1 [mammalian homologue of *Drosophila* Su(H), also called RBP-Jk]. It has also been reported that BOAT1 and ataxin-1 compete with each other to bind with CBF1. Interestingly, presence of Notch-ICD demolishes the transcriptional repressor complex of BOAT1 or ataxin-1 along with CBF1 (Tong et al. 2011). These results conclude that BOAT1 and ataxin-1 are the components of Notch signaling pathway; hence they might play an essential role in Notch-dependent developmental processes.

Spinocerebellar Ataxia Type 2 (SCA2)

Spinocerebellar ataxia type 2 (SCA2) is one of the neurodegenerative disorders caused by expansion in the CAG nucleotide repeat in the translated sequence of the *ataxin-2* (*ATXN2*) gene. The characteristic features of the patients who carry this disorder are progressive cerebellar ataxia, oculomotor abnormalities, pyramidal and extrapyramidal features (EPS), dementia and peripheral neuropathy, and dystonia (Geschwind et al. 1997; Jhunjhunwala et al. 2014). The main function of ataxin-2 is unknown, but ataxin-2 interacting proteins provide a direction of the possible functions controlled by ataxin-2. Ataxin-2 interacts with various RNA-binding proteins, suggesting its major role in RNA metabolism. Ataxin-2 has also a wide variety of other interacting partners as shown in Table 5. It clearly demonstrates the broad mode of action of ataxin-2. Ataxin-2-binding protein 1 (A2BP1 or Rbfox1) is a nuclear RNA-binding protein and binds to C-terminus of ataxin-2. Both ataxin-2 and A2BP1 are enriched in Purkinje cells and dentate neurons (Shibata et al. 2000).

Table 5 Various Ataxin-2 interactors

Ataxin-2 interactors	Function	References
A2BP1/ RBFOX1	RNA binding	Shibata et al. (2000)
Endophilin A1 Endophilin A3	Vesicle endocytosis	Ralser et al. (2005)
DDX6 (DEAD/H-box RNA helicase)	RNA binding	Nonhoff et al. (2007)
Parkin	Ubiquitination	Huynh et al. (2007)
CIN85	Vesicle endocytosis	Nonis et al. (2008)
TDP-43	RNA binding	Elden et al. (2010)
RGS8 mRNA	Ca2+ signaling	Dansithong et al. (2015)
PABPC1(poly(A)-binding protein, cytoplasmic 1)	RNA metabolism	Yokoshi et al. (2014)

Mutation associated with A2BP1 leads to complex neuronal disorders (Bhalla et al. 2004; Martin et al. 2007; Sebat et al. 2007). A2BP1 is an important regulator of splicing of various neuronal genes that regulates synaptic activity (Lee et al. 2009; O'Brien et al. 2012; Underwood et al. 2005). RNAi knockdown of A2BP1 in *Drosophila* embryo leads to a reduction in neuronal cell number (Koizumi et al. 2007). Not surprisingly, A2BP1 has a profound role in the development of nervous system.

During neurogenesis, A2BP1 acts as a positive regulator of Notch signaling in a context-specific manner. In *Drosophila,* thoracic bristles are a part of peripheral nervous system and follow the lateral inhibition phenomenon (Heitzler and Simpson 1991; Jan and Jan 1994). Each of these thoracic bristles arises from sensory organ precursors (SOPs) that form a complete sensory organ made of shaft, socket, sheath, neuron and glia (Hartenstein and Posakony 1989; Reddy and Rodrigues 1999). A2BP1 is a nuclear protein and is broadly present in developing embryo and imaginal discs with some specificity (Koizumi et al. 2007; Usha and Shashidhara 2010). Overexpression of *Drosophila* A2BP1 in the proneural cluster results in the loss of adult sensory bristles, whereas its downregulation increases bristle number. It has been reported that A2BP1 is part of the Su(H) complex in the presence and absence of Notch and might function as a transcriptional co-factor to regulate the expression of *E(spl)-C* (Shukla et al. 2017). It has been suggested that A2BP1 is a context-specific positive regulator of Notch signaling during neurogenesis in *Drosophila* (Shukla et al. 2017). Similar to ataxin-2, its interactor protein A2BP1 has two PolyQ domains and it is involved in the regulation of Notch signaling pathway (Shukla et al. 2017). Notch protein also contains polyglutamine stretch. Significance of these PolyQ domains and the role of Notch in SCA2 pathology remain to be explored.

Spinocerebellar Ataxia Type 17 (SCA17)

Spinocerebellar ataxia type 17 (SCA17) is a late-onset, progressive neurodegenerative disease caused by an expanded CAG trinucleotide repeat in TATA-binding protein (TBP) gene (Bauer and Nukina 2009; Koide et al. 1999; Nakamura et al. 2001). The characteristic features are ataxia, dementia, seizures, and involuntary movements, including chorea and dystonia (Koide et al. 1999; Rolfs et al. 2003). The expanded PolyQ repeats in TBP modify the interaction with other cellular proteins and influence the gene expression such as downregulation of HSPB1 (heat shock protein and neuroprotective factor) due to boosted interaction between mutant TBP and TFIIB, reduced expression of TrkA (receptor for nerve growth factor) due to enhanced interaction between mutant TBP and Sp1 transcription factor, and reduced expression of Chaperone system-associated factor and MANF (mesencephalic astrocyte-derived neurotrophic factor) due to inefficient binding of mutant TBP and XBP1 transcription factor; also expanded repeats in TBP reduce the association of MyoD with TBP and DNA promoters that cause muscle degeneration (Davidson 2003; Friedman et al. 2007; Huang et al. 2015; Pugh 2000; Shah et al. 2009; Yang et al. 2014).

Notch signaling pathway plays a profound role in various developmental events such as neurogenesis and maintenance of neural stem cells (Hitoshi et al. 2002). Su(H) acts as an essential transcription factor in Notch signaling. In general, Su(H) belongs to the group of proteins that are rich in glutamine (Q) and asparagine (N) (Michelitsch and Weissman 2000). Upon ligand-induced activation, released Notch-ICD translocates to the nucleus and directly interacts with the Su(H) and promotes the transcription of downstream target genes, while in the absence of Notch-ICD, Su(H) acts as a transcriptional repressor and blocks the expression of target genes (Aster et al. 1997; Oswald et al. 2001; Petcherski and Kimble 2000; Tamura et al. 1995; Vasquez-Del Carpio et al. 2011; Wu et al. 2000). Ren and co-workers (2011) explored the importance of Su(H) in SCA17 model in *Drosophila*. TBP is a general transcription factor used by all three nuclear RNA polymerases during transcription process (Nikolov and Burley 1994). Highly conserved C-terminal domain of TBP directly binds to TATA-box (TATAAA), which is present at 25–30 base pairs upstream of transcription start site in all metazoans (Burley and Roeder 1996; Davidson 2003; Gill and Tjian 1991; Lee and Young 2000; Pugh 2000). Not surprisingly, homozygous mutant *dtbp* (*Drosophila* TBP) (piggyback insertion at 5′ of *dTBP*) allele is first instar larval lethal that suggest the importance of TBP in fly (Ren et al. 2011). Overexpression of *dTBP* or wild-type *hTBP* with *Hsp70-GAL4/*UAS system in homozygous mutant flies can partially rescue first instar larval lethality. Interestingly, overexpression of pathogenic form of TBP, such as hTBP54Q (54 glutamines) or hTBP80Q (80 glutamines), with *GMR-GAL4* produces eye-patterning defects (disorganized photoreceptor and progressive retinal degeneration) with severity depending upon Poly-Q length as compared to normal Poly-Q expressing TBP protein (hTBP34Q). Overexpression of normal and pathogenic form of TBP with panneuronal driver (*elav-GAL4*) causes age-onset locomotor impairment including early mortality in pathogenic form of TBP, which is the characteristic feature of SCA17 pathology in humans. Microarray analysis of these flies revealed differential regulation of many known candidate genes such as HSPB1 in the above-mentioned background as well as many novel candidates. Q/N--rich protein-dependent transcription regulators are one of them (Ren et al. 2011). Q/N-rich family proteins play an important role during neurogenesis (Harrison and Gerstein 2003). A genetic modifier screen in *GMR-GAL4* driven hTBP80Q expression for Q/N-rich transcription factors validated the role of Su(H) in the neuropathology of SCA17 disease. Knockdown of Su(H) in hTBP80Q background worsens the photoreceptor defects up to the level of irregular shape of ommatidia with missing bristles, necrosis, and retinal degeneration. Interestingly, overexpression of Su(H) in *GMR-GAL4*-driven hTBP80Q flies can rescue the patterning and retinal degeneration. hTBP80Q contains Su(H)-binding sites, which enhances this particular interaction, that reduces the fraction of available Su(H) for normal cell physiology. Although knockdown of *Su(H)* and *hTBP80Q*, together with *GMR-GAL4*, results in bristle loss, the role of Notch-ICD in this aspect needs to be further explored since this phenomenon can be due to Notch-dependent or Notch-independent function (Ren et al. 2011). Studies in the mammalian system suggest that Notch1 or RBP-J/Su(H) mutant mice result in learning and memory defects

(Costa et al. 2003). Altogether, studies in *Drosophila* and mammalian system suggest that Su(H)/RBP-J plays a functional key role in neuropathology of SCA17.

Huntington's Disease (HD)

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by abnormal trinucleotide repeat of CAG in the exon 1 of *Huntingtin* (*Htt*) gene, which leads to accumulation of Huntingtin protein in the CNS. In contrast to a normal individual where CAG repeat varies from 6 to 34, in HD-affected patients, CAG repeats exceed from 36 to 121 (Andrew et al. 1993). HD begins usually in mid-life with the first sign of chorea (involuntary jerking or twitching movements), progressive selective neuronal loss (preferentially medium-sized, spiny, GABAergic neurons in the striatum), decreased neurogenesis, dementia, and psychological symptoms (DiFiglia 1997; DiFiglia et al. 1997; Martin and Gusella 1986; Moores et al. 2008; Petersen et al. 1999). Despite being an extensively studied disease, very little is known about cellular pathways involved in pathogenic Huntingtin protein expression, which leads to neuronal loss. There is no treatment available to increase the life expectancy of patients with this disorder. Due to limitations of human tissue, significant HD investigation has been established through model systems.

Drosophila homologue of *Htt (DmHtt)* gene shares a similar distribution pattern and sequence conservation with five different regions of human *Htt* (Li et al. 1999). Various transgenic *Drosophila* models have been generated to explore the many aspects of the HD. Table 6 includes the major contribution of *Drosophila* as a model system in solving the puzzle of the HD. In 1997, identification of Huntingtin interacting protein 1 (Hip1) has broadened the mechanistic aspect of HD. Hip1 has been identified as a strong binding partner of Htt, and Hip1 is also involved in the clathrin-mediated endocytosis and intracellular trafficking. This result signifies a functional link in the cellular mechanism underlying the HD. Above the threshold level of polyglutamines, the interaction between Htt and Hip1 diminishes as the number of polyglutamines increases (Gervais et al. 2002; Hackam et al. 2000; Kalchman et al. 1997; Legendre-Guillemin et al. 2002; Legendre-Guillemin et al. 2005; Mishra et al. 2001; Rao et al. 2003; Sun et al. 2005). In *Caenorhabditis elegans*, Hip1 mutant study reveals that during development it has a protective role against polyglutamine pathogenicity and mutants have defective pre-synaptic vesicles (Parker et al. 2007). Dysfunctions of HD-associated genes alter neurogenesis. The role of Notch-mediated neurogenesis in HD has been explored thoroughly. Notch and Hip1 both are known to be involved in endocytosis and intracellular trafficking.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that severely affects the motor neurons (corticospinal or upper motor neuron and spinal or lower motor neurons). Most of the patients die within 3–5 years of symptom onset (Ince et al. 2003). The first gene associated with ALS was *SOD1*, and so far over 100 *SOD1*-associated mutations have been identified (Boillee et al. 2006).

Table 6 Different Transgenic *Drosophila* models of pathogenic HD using different tissue/neuronal subtype-specific driver lines

Transgenic *Drosophila* models	Effect	Finding	Reference
Amino-terminal fragments of human Htt containing tracts of Q2, Q75 and Q120 with *GMR-GAL4*	Nuclear accumulation of pathogenic Htt, Progressive Neurodegeneration severity increases with number of PolyQ length	Neuron loss phenotype cannot be rescued by co-expression of anti-apoptotic P35 protein	Jackson et al. (1998)
Htt Q20 or Q93 in exon 1with *Elav-Gal4*	Htt-Q93 leads to Progressive loss of rhabdomeres with age; 70% lethality with early adult death (Htt-Q93) compared to Htt-Q20 (Control) expressing flies	Identification of two binding factors of Htt: CREB-binding protein (CBP) and p300/CBP-associated factor (P/CAF); prevent the Progressive neurodegeneration can be reduced by HDAC inhibitors	Steffan et al. (2001)
Htt-Q0 and Htt-Q128 with *GMR-GAL4* and *Elav-GAL4*	Htt-Q128 leads to Reduced life span, Progressive loss of motor coordination, and formation of huntingtin aggregates	Htt-Q128 causes Photoreceptor degeneration, aggregation of pathogenic Htt in the cytoplasm and neurites, but not in the nucleus	Lee et al. (2004)
Htt-Q16 and Htt-Q128 with *GMR-GAL4* and *C164-GAL4*	Htt-Q128 leads to progressive neurodegeneration but not Q16 control	Partial loss of Synaptic Transmission genes (Snap, Syx, Rop) and voltage-gated Ca2+ channel gene (Vha100-1) can suppress the neurodegenerative phenotype in HD	Romero et al. (2008)
Htt exon 1 fused to EGFP with Q18 or Q62	Q62 leads to accumulation of mutant Htt and degeneration of eye	RNAi screening provided new modifiers of pathogenic Htt	Doumanis et al. (2009)
DmHtt knockout	Developmentally normal (Contrast to Htt KO mice)	Larval neurons show delayed transport rate of synaptic vesicles Adults show locomotor defects and reduced viability	Gunawardena et al. (2003), Li et al. (1999) and Zala et al. (2013)

Advancements in ALS genetics have identified several other ALS-associated mutations such as *TDP-43, FUS/TLS* (fused in sarcoma/translocated in liposarcoma), *C9ORF72* (chromosome 9 open reading frame 72), *MATR3 (matrin 3)*, *CCNF (cyclin F),* and *VCP* (valosin-containing protein) (Chia et al. 2018). However, the pathophysiological mechanisms that lead to ALS motor neuron dysfunction are

Table 7 *Drosophila* models of ALS

Gene	Mutation	Effect	Result	References
TDP-43	C-Terminus Gly-rich domain	cytosolic aggregation of TDP-43	Degeneration of neurons; early lethality	Cushman et al. (2010), Johnson et al. (2009), Neumann et al. (2006) and Zhan et al. (2013)
FUS/TLS	C-terminus Nuclear Localization Sequence	Cytosolic aggregation of FUS	Degeneration of Neurons, larval-crawling defect and early lethality	Fushimi et al. (2011), Lanson et al. (2011) and Sun et al. 2011)
C9ORF72	GGGGCC (G4C2) repeat expansion in the non-coding region	Presence of RNA foci and dipeptide repeat (DPR) proteins in the cytoplasm	Degeneration of neurons; reduced life span	Burguete et al. (2015), Freibaum et al. (2015), Mizielinska et al. (2014), Tran et al. (2015) and Xu et al. (2013)
Ter94/ VCP	R152H and A229E	VCP and TDP-43 genetically interact and disease-causing mutations in VCP promote reorganization of TDP-43	Degeneration of neurons; reduced life span	Ritson et al. (2010)
Hrp38 (hnRNP)	Gly-rich tract of Hrp38 (293–365) interacts with TDP-43	Hrp38 interacts with TDP-43	Hrp38 and TBPH genetically interact to prevent locomotor defects and reduce life span	Romano et al. (2014)

poorly understood. Various *Drosophila* models have been generated to explore the pathophysiological mechanisms, as mentioned in Table 7.

TDP-43 plays an important role in the regulation of mRNA splicing by binding to UG repeats in target RNAs. CFTR has been identified as the first RNA substrate for TDP-43. TDP-43 binding with CFTR intron 8 promotes the skipping of exon 9. This kind of important observation leads to a detailed study of the RNA interactome of TDP-43 (Polymenidou et al. 2011; Tollervey et al. 2011). Whole genome microarray in *GMR-GAL4*-driven *TDP-43* overexpressing flies has been performed, and, interestingly, Notch intracellular pathway component *Hey* came up as a direct target of TDP-43. In the TDP-43-associated neurodegeneration, *Hey* was upregulated. Life span of *TDP-43* mutant flies can be enhanced by mutating the Notch pathway components such as Delta and Serrate (Zhan et al. 2013). Loss of *htk* suppresses TDP-43-mediated age-dependent neurodegeneration seen in ALS in *Drosophila* model (Sreedharan et al. 2015). Recently, we have shown that Htk is a component

of Notch-Su(H) activation complex and hence positively regulates Notch signaling (Singh et al. 2019).

Genetic mutation in the *C9ORF72* repeat expansion GGGGCC (G4C2) in the non-coding region generates pathogenic dipeptide repeat proteins (DRP). They are known to be associated with ALS. To understand which nucleotide repeats of *C9ORF72* are toxic to the cells, three different genotypes of the flies were generated: flies that express 80 copies of GGXGCX (GA)80, 80 copies of GGXCGX (GR)80, or 80 copies of CCXCGX (PR)80 where the X can be randomly one out of four nucleotides. Cell type-specific overexpression of these repeats identified that only (GR)80 and (PR)80 repeats are toxic to the cells (neuronal/non-neuronal) (Kwon et al. 2014; Yang et al. 2015). Flies expressing (GR)80 results in notching in the wing margin of the adults implying that (GR)80 can suppress the Notch signaling. iPSC-derived human neurons and brain tissue of C9ORF72 patients also have lower expression of few Notch target genes (Yang et al. 2015). Thus, Notch signaling pathway is the target of Poly(GR) toxicity in C9ORF72-associated ALS (Yang et al. 2015).

Future Perspectives

Notch receptor is the central element of an evolutionarily conserved signaling mechanism which plays a fundamental role in metazoan development (Artavanis-Tsakonas et al. 1999). Notch signaling is known to affect a broad spectrum of cell-fate decisions throughout development. Thus, Notch malfunction has been associated with many diseases including neurodegeneration in humans. To allow the Notch signal to be deployed in numerous contexts, many different mechanisms have evolved to regulate the level, duration, and spatial distribution of Notch activity.

It has been reported that neurogenesis is impaired due to Notch signal suppression in mice that express AD-associated mutant Presenilin 1 (Veeraraghavalu et al. 2010). Parkinson's disease-associated mutation of LRRK2 causes inhibition of Notch signaling in adult dopaminergic neurons, which ultimately impairs their functions and survival (Imai et al. 2015). Recently it has been revealed that loss of *htk* suppresses TDP-43-mediated age-dependent neurodegeneration seen in ALS in *Drosophila* model (Sreedharan et al. 2015). Investigations on gene expression patterns in the TDP-43-associated neurodegeneration in *Drosophila* system have shown strong upregulation of Notch target genes (Zhan et al. 2013). It has also been reported that mutations in Notch pathway components extended the life span of TDP-43 transgenic lines (Zhan et al. 2013). Thus, Notch activation has a deleterious effect in TDP-43 flies. Recently, we have reported that Htk is a component of Notch-Su(H) activation complex and positively regulates Notch signaling (Singh et al. 2019). All these findings indicate a possible link between Notch pathway and the neurodegenerative diseases such as AD, Parkinson's disease, and ALS. Despite the plethora of information about Notch pathway, the involvement of Notch signaling in the neurodegeneration process remains largely uncharacterized. The wealth of genetic resources available for *Drosophila* offers a unique opportunity to dissect

involvement of Notch signaling in different neurodegenerative diseases. Due to the high degree of conservation between *Drosophila* and mammalian Notch signaling pathway, future research to explore intricate molecular mechanism of Notch function in neurodegeneration using *Drosophila* as a model system will advance search for therapies of neurodegenerative diseases targeting Notch pathway.

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