Review Article

Axoglial Interaction via the Notch Receptor in Oligodendrocyte Differentiation

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Abstract

Introduction: Increasing evidence has revealed that the Notch signalling pathway is one of the pivotal systems that mediate oligodendrocyte development. The Notch receptor is a type I transmembrane molecule that represents a novel cellular signalling paradigm, namely, regulated intramembrane proteolysis (RIP). Method: The typical Notch ligands, such as Delta, Serrate/ Jagged and Lag2 (DSL), promote the formation of oligodendocyte precursor cells (OPCs) and maintain them in an uncommitted stage, thus retarding oligodendrocyte appearance in the central nervous system (CNS). Results: In contrast, our recent studies have revealed that F3/ contactin, a GPI-linked neural adhesion molecule, interacts with Notch and speeds up the generation and maturation of oligodendrocytes. Conclusions: Considering the distinct, albeit somewhat overlapping expression patterns of F3 and DSL in the CNS, the Notch receptor appears to function ligand-dependently during oligodendrocyte development. This multipotentiality may well designate the Notch receptor as one of the therapeutic targets that one can manoeuvre to treat demyelinating diseases, such as multiple sclerosis, that is characterised by chronic myelin degeneration.

Ann Acad Med Singapore 2004;33:581-8

Key words: Development, F3/contactin, Multipotency, Promote

Introduction

Oligodendrocytes (OLs) derived from the common neural progenitor cells in the central nervous system (CNS) ensheathe the nude axon to form the myelin that not only effects saltatory conduction but also protects and maintains the axonal structure. It is the last type of cells that appear in the CNS.[1] The other 2 earlier types are neurons and astrocytes. Recent studies have shown that the Notch signalling pathway plays a crucial role in OL development.[2]

Notch is a type I transmembrane molecule which presents itself on the cell surface as a heterodimer.[3] The Notch receptor responds to the ligand binding to its extracellular epidermal growth factor (EGF)-like repeats[4] and releases the intracellular domain (NICD) into the nucleus,[5] where NICD acts as a second messenger to modulate target gene expression, such as Hes1 and Hes5,[6,7] which in turn inhibit NeuroD and Mash1 expression.[8] This signalling pathway is widely adopted during the development of many organs and systems, such as the neural system and the pancreas.[9,10] In particular, in the CNS, the Notch signalling pathway plays both inhibiting and instructive roles in cell fate selection, dependent of temporal and spatial context.[11]

In the CNS, typical ligands of Notch include Delta, Serrate/Jagged and Lag2 (DSL). Delta-Notch signalling has been shown to specify glial fate rather than neuronal fate and to favourably direct a ventral population of precursors to oligodendrocyte precursor cells (OPCs) rather than motoneurons.[12] In the rat optic nerve, Jagged1-Notch interaction inhibits further differentiation of OPCs.[13] However, one curious point is that even after Jagged1 expression diminishes after postnatal day 6 (P6), the Notch expression persists.[13] The selective ablation of Notch in the OPCs in the spinal cord result in abnormal prematuration of OLs ectopically which undergo massive apoptosis soon

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after.[14] These studies suggest that there should be other molecules that signal to the remaining Notch to instruct the later stage of OPC differentiation to young OLs and OL maturation.

Our recent work designates F3/contactin as a functional ligand of Notch.[15] F3 is a glycosyl-phosphatidylinositol (GPI)-linked neural adhesion molecule belonging to the immunoglobulin superfamily.[16] Previous studies have demonstrated that F3 is heavily involved in myelination together with other molecules, such as Tenascine-R,[17] PTPα,[18] Caspr,[19] Fyn[20] and NogoA.[21] We have found that F3 binds to Notch1 and F3-Notch1 interaction leads to the nuclear translocation of NICD and recruitment of Deltex1 (DTX1) to accentuate OPC differentiation to OLs and promotes the expressions of 2 hallmarks of OL maturation, myelin-associated glycoprotein (MAG) and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) in OLs. Since F3 clusters from P4 at the paranode, a critical site of axo-glial dialogue for myelination,[22] a signal switch model may well depict the whole scenario of OL development. That is, the switch of extracellular ligands results in the shift of Notch intracellular signalling properties to coordinate OL differentiation.

The Segmental Structure of the Axon and Neural Adhesion Molecules

In vertebrates, the axon in the CNS is characterised by its segmental structure. That is, the nude axon is tightly wrapped and insulated by the myelin sheath formed by OLs in tandem, leaving the intervals exposed to the extracellular environment. In this way, OLs define the axon into several domains: node of Ranvier (the nude intervals unwrapped by OLs on either side), paranode (the region just beside the node of Ranvier and where myelin loops land), juxtaparanode (a small region beside the paranode and where potassium channels cluster) and internode (the remaining large portion of the axon wrapped by compact myelin sheath).[23] In particular, the paranodal region resembles the septate junction in invertebrates and is a critical site of active axo-glial dialogue for myelination. This is maintained by the network interactions between various molecules, including neural adhesion molecules belonged to the immunoglobulin superfamily (IgSF).[24]

Of particular importance among these adhesion molecules is the F3/contactin family. F3/contactin is a GPI-linked neural cell adhesion molecule.[16] It has 6 Ig domains followed by 4 fibronectin type III repeats and is widely expressed in various regions of the brain. In the rat brain stem, F3 is expressed from birth and reached a plateau from postnatal day 14 (unpublished data). A study in the rat hippocampus reveals that the expression of F3 decreases after 30 months,[25] revealing its possible role in age-related memory deficiency. As an axonal molecule, F3 promotes neurite outgrowth and participates in axonal guidance during the early development.[26,27] On the other hand, F3 is actively involved in myelination. First, F3 co-localises and forms co-receptor with contactin-associated protein (Caspr) at the paranode which flanks the node of Ranvier.[19] The paranodal region is a critical site where the myelin loops land and wrap the axon. F3 null mice exhibit partially disrupted paranodal structure and dispersed distribution of shaker-type Kv1.1 and Kv1.2 potassium channels. The mutant also shows reduced nerve conduction velocity by 3-fold and death by P18,[28] suggesting that F3 may be critical for development of the paranode and its proper physiological functions. Second, OLs also express F3 which interacts with protein kinase phosphatase α (PTPα) in a *cis* manner and this interaction transduces signals to intracellular *Scr* family tyrosine kinase, such as Fyn,[18] which is specifically required for the initiation of myelination.[29]

F3 is also present in the node of Ranvier in the CNS.[30] It associates with the beta subunit of the sodium channels and this interaction promotes the surface expression of sodium channels.[31] The beta subunit associates with another 2 cell adhesion molecules neurfascin 186 (NF186) and NrCAM, both belonging to the L1 subfamily.[32,33] Thus, this network of protein interactions may stabilise the nodal structure and ensure the physiological function of sodium channels.

Other members of the F3/contactin family include NB-3,[34] TAG-1,[35] Big-1,[36] and Big-2.[37] Our recent study locates NB-3 in the paranodal region in the rat brain stem from postnatal day 5 (unpublished data), suggesting that NB-3 may also be involved in myelination. TAG-1, however, is located and enriched in the juxtaparanode and is expressed by both OLs and neurons.[38] In the juxtaparanodal region, TAG-1 interacts with Caspr2, a molecule resembling Caspr and associating with potassium channels Kv1.1 and Kv1.2.[23,39]

The Notch Signalling Pathway

The Notch signalling pathway is 1 of the 5 signalling systems that are repeatedly used throughout development. The core element is the Notch receptor which has 4 homologs in vertebrates.[40] The whole molecule crosses the membrane once with its N-terminal in the extracellular space and C-terminal in the intracellular compartment. The N-terminal contains multiple tandemly-arranged EGF-repeats, usually 36 repeats, which is necessary for ligand binding.[4] The intracellular domain (NICD) includes 4 distinct regions: (1) The RAM domain, which is the site for direct binding of Notch downstream transcriptional complex CSL/RBP-J;[41] (2) The 6 ankyrin-like repeats which mediates interaction between NICD and CSL/RBP-J.[6,42] These 6 repeats are flanked by 2 nuclear localisation signals (NLS);[43] (3) the OPA region that acts as a transcriptional activation domain;[44] and (4) the PEST region, that mediates ubiquitination and

degradation of NICD.[45]

The Notch signalling is characterised by regulated intramembrane proteolysis (RIP), which also applies to a few other proteins, such as APP and ErbB4.[46] After synthesis, the Notch protein experiences glycosylation by Fringe[47] and the first enzymatic cleavage by furin in the Golgi body.[3] Thus, Notch appears on the cell surface as a heterodimer. At the cell surface, upon the ligand binding, Notch is first cleaved by metalloprotease just outside the membrane[48] and then processed in the intramembrane region (site 3, S3) by presenilin-dependent gamma-secretase.[49]

The consequence of these ligand-induced programmed proteolyses is the release from the membrane NICD, which translocates into the nucleus. In the nucleus, NICD assumes 2 pathways depending on the recruitment of distinct factors and cofactors. First, NICD binds to co-repressor complex containing CSL/RBP-J, SMRT, Skip, CIR and KyoT2[50-54] and converts it from transcription repressor to activator. Surprisingly, few immediate target genes have been identified for this ubiquitous Notch signalling pathway. One group is the *hairy* and *enhancer* of *split* (E(spl)) (HES in mammals). Another group is HEY genes, which are related to HES.[55] HES represses the expression of another group of basic helix-loop-helix (bHLH) genes, referred to as proneural genes, such as NeuroD, Mash, Math and Neurogenins.[56,57] Second, cytosolic NICD recruits Deltex1 through the ankyrin repeats and moves into the nucleus where, by binding to transcriptional activator p300, NICD-Deltex1 inhibits transcriptional activation by Mash1.[58]

The Delta/Jagged1-Notch Signalling Inhibits Neurogenesis and Promotes Glial Fate Selection

The specification of oligodendroglial fate involves 2 steps. First, the common neural progenitor cell assumes either the neuronal or glial fate. Second, those following the glial fate give rise to either astrocytes or OLs. Recent studies have implied a central role of Notch in these 2 cell fate selections (Fig. 1).

Upon activation by Delta, released NICD binds to CSL/RBP-J and starts up HES expression. As a result, proneural genes, such as Mash1 and NeuroD, are inhibited.[57] Proneural genes are those that are required in neurogenesis and only neural progenitor cells that express these genes can become neuroblasts that may further differentiate into neurons. Indeed, in transgenic mouse models, such as HES1 null, Notch1 null and CSL/RBP-J null embryos, Mash1 is significantly upregulated.[59] Thus, the activation of Delta/Notch signalling pathway inhibits the differentiation of recipient cells to neurons. In other words, only signalling cells have the potential to become neurons. This mode of suppression is referred to as lateral inhibition, the purpose of which is to generate asymmetric differentiation patterns among 1 group of initially identical cells and also maintain a pool of progenitor cells. When HES1 is ectopically expressed in the transgenic mouse brain, most HES1 expressing cells remain in the ventricular zone undifferentiated.[60]

On the other hand, recent studies have implied an instructive role for Notch in differentiation of many types of glial cells, including radial glia,[61] Schwann cells,[62] Muller cells in the retina[63] and astrocytes.[64,65]

In the spinal cord, OPCs arise from a ventral population of progenitor cells that also give rise to motoneurons.[59] Thus, some signalling mechanisms must exist to ensure the correct specification of oligodendroglial and motoneuronal fates. One study using transgenic mice that express constitutive-active Notch shows the increased number of OPCs at the expense of motoneurons.[59] Conversely, in a zebrafish model mutant for the Notch ligand, Delta, the spinal cord possesses excess motoneurons while lacking proliferative cells as revealed by BrdU incorporation. And the promotion of OPC formation by constitutive NICD requires the co-expression of a bHLH transcription factor Olig2 as well as Nkx2.2.[66] Cells that express Olig2 can differentiate into OLs while those that express both Olig2 and Neurogenins (Ngns) only develop as motoneurons.[67] Studies show that the Delta/Notch signalling pathway differentially regulates Olig2 and Ngns expressions.[59] In zebrafish null for Delta or mind bomb (Mib), an ubiquitin ligase necessary for normal Notch signalling, the expression of Olig2 diminishes after 12 hours post-fertilisation while the wide type embryos maintain Olig2 expression. In contrast, at a comparable stage, mutant embryos express higher levels of Ngns than their wide type littermates.[59] Collectively, these studies show that Delta/Notch signalling promotes the generation of OPCs from a progenitor cell pool.

The Jagged1/Notch Signalling Inhibits Oligodendrocyte Development

However, once the cell is committed to oligodendroglial fate, the Jagged1/Notch signalling pathway appears to inhibit further OPC differentiation into mature, myelinating OLs. One study revealed that the rat optic nerve axon expresses Jagged1, while OPCs express Notch1.[13] In the rat optic nerve, the first OPC appears at around embryonic day 16,[68] the first OL does not appear until birth[69] and the rapid generation of OLs starts even later, from about postnatal day 6.[70] These time delays reflect that there may exist some signalling mechanism preventing the immediate differentiation of OPCs. Interestingly, the sharp decrease of Jagged1 expression parallels the onset of rapid myelination. Purified OPCs from P8 rat optic nerve exposed

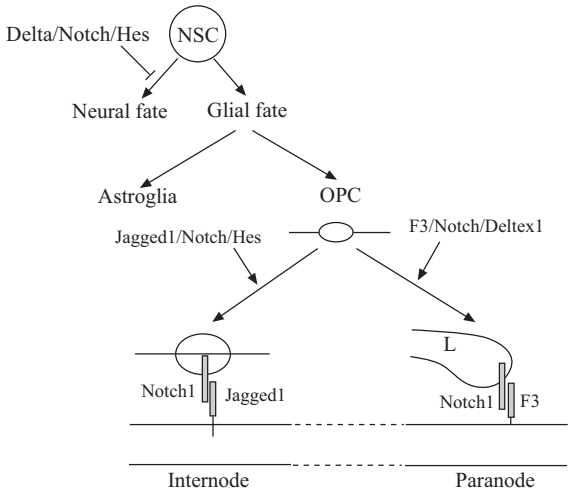

Fig. 1. Delta/Notch signalling pathway via Hes inhibits neural fate specification from neural stem cells (NSCs), while favouring glial fate selection. In the central nervous system (CNS), the glial fates include astrocytes, oligodendrocyte precursor cells (OPCs), as well as radial glia cells and Muller cells. However, once the cell is committed to the oligodendroglial lineage, axonal Jagged1 along the internode signals to OPC Notch to prevent further differentiation of OPCs, keeping them proliferative and migratory. On the other hand, when OPCs contact axonal F3/contactin clustering at the paranodal region, they start to differentiate into young OLs that mature to form spiral loops (L) around the axon.

to monolayer of Jagged1-expressing cells or soluble Jagged1 protein remained undifferentiated after 3 days in in vitro culture when most of the control cells started to express myelin-related proteins, such as Gal-C and proteolipid protein (PLP).[13]

The inhibitory effect of Jagged1/Notch on OPC differentiation is corroborated by another study on multiple sclerosis (MS).[71] MS is an inflammatory demyelinating disease which is characterised by vast and chronic demyelination and poor remyelination in MS lesions.[72] The study shows that the inflammation-induced cytokine transforming growth factor (TGF-β) specifically starts the re-expression of Jagged1 on astrocytes. And upon the contact between the vast amount of astrocytes and OPCs which express Notch1 on the cell surface, Jagged1/Notch/Hes5 signalling pathway is activated, preventing the differentiation of these OPCs and subsequent remyelination.

However, other studies suggest that the Notch receptor may play multiple roles in modulating OL development. When Notch1 is selectively eliminated on the OPCs in the spinal cord, these cells differentiate precociously and ectopic immature OLs appear in the grey matter at embryonic day 17.5. Immature OLs are even observed in the cerebellum. And upon birth, these young OLs undergo a large scale of apoptosis.[73] This indicates that the Notch receptor is needed to ensure correct temporal and spatial differentiation of OPCs, and this complex machinery is underestimated or inadequately depicted as merely a differentiation inhibitor. It is thus conceivable that Notch may have other ligands to act as a multipurpose receptor in the whole process of OL development.

By comparing the phenotypes between Notch mutant and CSL/RBP-J mutant in Drosophila, one can observe that the Notch mutant phenotype is slightly stronger than the CSL/RBP-J littermates, indicating that the CSL/RBP-J signalling mode does not account for all functions of Notch.[74,75] Molecular and genetic analyses have revealed that Deltex1 is another Notch downstream signalling component that may well bypass CSL/RBP-J.[76,77] Deltex1 consists of 3 domains: the N-terminal, a proline-rich motif and a Ring-H2 finger motif. It binds via its N-terminal to the ankyrin repeats on NICD. The interaction represses Mash1 transcriptional activity and the JNK signalling pathway. It also cooperates with Wingless signalling pathway to time the differentiation of related cells.[77] However, the putative ligand for Notch/Deltex1 signalling has not yet been identified.

The F3/contactin-Notch-Deltex1 Signalling Promotes Oligodendrocyte Differentiation

Our recent study shows that F3/contactin functions as a novel Notch ligand via Deltex1 to promote OPC differentiation and subsequent OL maturation.[15] The fact that F3 binds to the EGF-like repeats on extracellular matrix molecule Tenascin-R[17] suggests that F3 may also interact with Notch to mediate myelination.

In our study, OLN-93 cell line resembling young OLs is utilised to explore whether F3 is the novel binding partner of Notch. This cell line expresses both Notch1 and Notch2 on the cell surface. In cell adhesion assays, OLN-93 cells adhere preferentially to F3 protein coated on dishes, compared with other control proteins, such as BSA and CHL1.[78] Interestingly, pretreatment of the cells with antibody against Notch1, Notch2 or F3 blocks the cell adhesion. This raises the possibility that F3 and Notch may directly or indirectly participate in this adhesion event. We also show that F3 and Notch1 or Notch2 can immunoprecipitate each other from the adult rat brain, providing the in vivo evidence that F3 binds to Notch under physiological conditions. In addition, the binding sites on Notch1 for F3 are mapped to 2 regions, 1 containing EGF-like repeats 1-13 and the other EGF-like repeats 22-34. This is different from DSL binding in that these ligands bind to EGF-like repeats 11-12.[4]

However, similar to DSL, F3 triggers the most prominent event of Notch signalling – NICD nuclear translocation – and this event occurs in a concentration-dependent manner. Strikingly, the increase of F3 leads to the similar increase in nuclear NICD to Jagged1 stimulation, indicating that the

Notch ligands share some common properties in the whole signalling pathway. On the other hand, when the Notch molecule is mutated at S3, it can no longer respond to F3 stimulation and the molecule remains intact and tethered on the cell membrane, which mimicks the action of gamma-secretase inhibitor on F3 stimulation. These studies indicate that F3 induces NICD nuclear transportation in a gamma-secretase dependent and S3-directed manner, which is exactly the initial phase of the typical Notch signalling pathway.

To study the physiological role of F3/Notch interaction in OL development we plated OLN-93 cells together with F3-transfected, TAG-1-transfected, TAX-transfected CHO or parental CHO cells. TAG-1 and TAX are 2 members of the F3/contactin subfamily.[79] As a result, we observed that OLN-93 cell processes halted and flattened upon contact with F3-expressing CHO cells, while in other cases the processes just passed through the CHO cell bodies. This means that there must be some signals transduced from F3 to the opposing OLN-93 cells, maybe though the Notch receptor, to effect the morphological alteration. And the flattened cytoplasmic structure is reminiscent of myelination.

Thus, we measured the expression of myelin-related protein MAG in the above co-culture systems and in primary OLs purified from P7 rat cerebella. As expected, MAG expression soared upon F3 stimulation and another OL marker, CNPase, also increased. However, when OLN-93 cells were first transfected with dominant-negative Notch1 or Notch2, which disables the endogenous wild type Notch, the upregulation of MAG by F3 stimulation was completely blocked. This clearly indicates that F3/Notch signalling pathway antagonises the Jagged1/Notch pair and promotes OL maturation. Since previous experiments have established that F3 starts the Notch signalling pathway in a seemingly similar way to Jagged1, this distinction in ultimate physiological function reflects the specialty of F3 induction, or more generally inferred, the ligand specificity in the Notch signalling pathway. This notion was confirmed by introducing constitive-active NICD into OLN-93 cells. Then these cells are ligand-independent while maintaining a high level of NICD activity. No matter what stimulation was given to the cells, MAG expression remained undetectable in these transfected cells.

Since F3/Notch signalling acts in an opposite manner to Jagged1/Notch with regard to OL maturation, it is conceivable that F3-induced NICD may go through other downstream pathways besides binding to CSL/RBP-J co-repressor complex. Indeed, when Hes1 expression is blocked in OLN-93 cells by either Hes1 antisense oligonucleotides or dominant-negative RBP-J, the cells still respond to F3 stimuation and show MAG upregulation. On the other hand, another Notch downstream element, Deltex1 has been found to participate in MAG upregulation based on the observation that the introduction Deltex1 deletion mutants completely abolish F3-induced MAG upregulation in OLN-93 cells. These deletion mutants lack the Ring-H2 finger motif that is required for the formation of homodimer of Deltex1.[58,80] And previous studies show that Deltex1 can only function as a homodimer, but not as a monomer or heterodimer.[81] When these deletion mutants enter OLN-93 cells, they form heterodimers with endogenous Deltex1, thus dysfunctioning the Deltex1 activity. Collectively, these data clearly indicate that the F3/Notch signalling requires Deltex1 to increase MAG expression.

Similarly, when purified OPCs from P7 rat optic nerve are exposed to F3, most cells differentiate into CNPase-expressing young OLs in 2 days while those exposed to Jagged1 remained uniformly undifferentiated at a comparable time point. This suggests that F3 can even start its own Notch signalling pathway in OPCs to speed up their differentiation into young OLs. In other words, F3/Notch signalling can at least play an instructive role in 2 stages of OL development: from OPCs to immature OLs and from newly born OLs to mature, myelinating cells.

The Switch Model of the Notch Signalling Pathway

Collectively, Notch appears to function throughout the 3 phases of OL development. First, Delta/Notch signalling favours OPC formation from the ventral progenitor cell pool and second, neuronal Jagged1 signals to OPC Notch to block OPC differentiation. Third, OPC Notch interacts with axonal F3 to facilitate OL generation and maturation. Thus, we propose a switch model to summon the multipotency of Notch, i.e., the specificity of extracellular ligands determines Notch downstream signalling properties and consequences.

This model is supported by both spatial and temporal evidence. Our experiments using rat brain stems show that Jagged1 is evenly distributed in the juxtaparanode and internode (unpublished data). On the other hand, F3 is clustered at the paranode and is also expressed at the node of Ranvier.[30] Thus, the proliferative and migratory OPCs have the opportunity of contacting different Notch ligands along the axon during development. In addition, the expression of Jagged1 decreases sharply after postnatal day 6[13] while F3 expression reaches the plateau and maintains the level just from P7 (unpublished data).

The switch model of Notch signalling is bound to have significant therapeutic value. If further in vivo evidence of the F3/Notch signalling pathway can be obtained, one could, hopefully, manipulate Notch signalling in demyelinating diseases, such as MS, by handling the balance

between different ligands like F3 and Jagged1. This can be achieved either by activating endogenous expression of relevant ligands, by transplanting exogenous stem cells that are pre-treated by F3 into the lesion sites or even by directly injecting F3 protein or F3 expression vector into the proper sites to promote remyelination.

F3/Notch Signalling and Other Factors Dictating Oligodendroglial Fate

Recently, some bHLH factors have been identified to be involved in OL development. Among these are Olig1 and Olig2, which are expressed in OPCs of the spinal cord and cortex, preceding the appearance of any of the OPC markers, for example, PDGFRα.[82,83] The expression of Olig1 and Olig2 persists even in mature OLs and in particular, Olig1 has some roles in OL maturation.[66,84] And these genes are the downstream component of Sonic Hedgehog (Shh) signalling.[82] However, a recent study shows that Olig2 expression is also mediated by Delta/Notch signalling and contributes to OL specification from a common pregenitor pool that is destined to either OLs or motor neurons.[59] Thus, it is conceivable that the F3/Notch/Deltex1 signalling pathway may be related to downstream Olig genes to time and promote oligodendroglial specification and subsequent OL maturation.

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