N-cadherin-based adherens junction regulates the maintenance, proliferation, and differentiation of neural progenitor cells during development

Yasunori Miyamoto*, Fumi Sakane, and Kei Hashimoto

The Graduate School of Humanities and Sciences; Ochanomizu University; Tokyo, Japan

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Abbreviations: AJ, adherens junction; aPKC, atypical protein kinase C; EC, extracellular; Fox, forkhead box; Frz, frizzled; GFAP, glial fibrillary acidic protein; GSK3β, glycogen synthase kinase 3β; Hes, hairy/enhancer of split; Hh, hedgehog; IP, intermediate progenitor; iPSC, induced pluripotent stem cell; KO, knockout; LEF, lymphocyte enhancer factor; ngn2, neurogenin 2; NPC, neural progenitor cell; Par, partition defective complex protein; Ptc, Pached; shRNA, short hairpin RNA; Smo, smoothened; Sox2, sry (sex determining region Y)-box containing gene 2; TCF, T-cell factor; TA cell, transient amplifying cell; ZO-1, Zonula Occludens-1.

This review addresses our current understanding of the regulatory mechanism by which N-cadherin, a classical cadherin, affects neural progenitor cells (NPCs) during development. N-cadherin is responsible for the integrity of adherens junctions (AJs), which develop in the sub-apical region of NPCs in the neural tube and brain cortex. The apical domain, which contains the sub-apical region, is involved in the switching from symmetric proliferative division to asymmetric neurogenic division of NPCs. In addition, N-cadherin-based AJ is deeply involved in the apico-basal polarity of NPCs and the regulation of Wnt-β-catenin, hedgehog (Hh), and Notch signaling. In this review, we discuss the roles of N-cadherin in the maintenance, proliferation, and differentiation of NPCs through components of AJ, β-catenin and αE-catenin.

Introduction

N-cadherin is a classical cadherin which is prominently expressed in the neural system.1,2 Based on sequence comparison, the classical cadherins are divided into 2 subfamilies: type I and type II. N-cadherin is included in the type I classical cadherins.3-5 The type I classical cadherins are defined by 5 extracellular (EC) domains (EC1-5), followed by a single-pass transmembrane domain and 2 well-conserved catenin-binding domains in the cytoplasmic portion.1,2 In general, type I classical cadherins participate in Ca2+-dependent homophilic interactions with the EC1 domains.1,6 During the development of the nervous system, N-cadherin mainly contributes to cell-cell adhesion in neural progenitor cells (NPCs) and neurons, and develops junctional complexes together with α-catenin, β-catenin, and actin fibers, called adherens junctions (AJs).1,7 N-cadherin-based AJs are involved in various processes of neural development. There are several excellent reviews and papers detailing the roles of N-cadherin in neurulation, migration of neurons, axon elongation and guidance, and synaptogenesis.1,2,8-12

N-cadherin-based AJs are also known to be related to the transition from symmetric proliferative division to asymmetric neurogenic division of NPCs. The proliferative division is responsible for the self-renewal of NPCs, and the neurogenic division generates nascent neurons and intermediate progenitors (IPs), which commit to become neurons in the ventricular zone of neural tube and brain cortex.13-15 The balance between self-renewal and differentiation is tightly controlled to produce the organ of predetermined size.16-18 In this review, we will concentrate on roles of N-cadherin in the mechanism underlying the maintenance of NPCs and the balance between the proliferation and differentiation of NPCs.

Tissue Architecture Mediated by N-cadherin-based AJ in Nervous System

One important role of N-cadherin on NPCs is to connect the NPCs tightly to each other for the tissue architecture of the nervous system.19-23 Several investigations have observed that a loss of function of N-cadherin in the NPCs of the neural tube, brain cortex, and retina destroys the tissue architecture.11,22-27 In this chapter, we describe the distribution of N-cadherin, the structure of N-cadherin-based AJ, and the AJ’s maintenance of tissue architecture and apico-basal polarity of NPC.
Expression of N-cadherin in neuroepithelial cells and radial glia cells

Embryonic ectoderm first expresses E-cadherin, but this E-cadherin is replaced by N-cadherin during neurulation.19,28 The neural tube wall constitutes a monolayer of neuroepithelial cells. At the onset of neurogenesis, neuroepithelial cells transform to radial glia cells.29,30 With this transformation, the cells lose expression of occluding and functional tight junction.31 However, the expression of Zonula Occludens-1 (ZO-1), a peripheral membrane protein of tight junction, remains in the sub-apical region of radial glia cells (Fig. 1). Radial glia cells directly or indirectly generate all neurons and, later in development, glia cells as NPCs.32 Radial glia cells are polarized when the apical membrane is exposed to the ventricle and the basal side contacts the pial basal membrane (Fig. 1).

N-cadherin is broadly expressed in neuroepithelial cells and radial glia cells as NPCs, although this protein is most highly concentrated at the sub-apical region of these cells, where the AJs develop (Fig. 1).20,33,34 We recently reported that N-cadherin is localized at the sub-apical region of the ventral midbrain at embryonic day 11.5 (E11.5) (Fig. 2).34,35 These N-cadherin-based AJs contribute to the strong adhesion between the NPCs to maintain the tissue architecture.

The expression of N-cadherin in the developing neural tube and brain is regulated by sex-determining region Y (sry)-box containing gene 2 (Sox2), known as one of the early proneural transcription factors, forkhead box protein transcription factors Foxp2/4, and miR379-410 cluster microRNA (miRNA).36-39 Sox2 is observed to be expressed prior to N-cadherin in the neural plate, and has been shown to activate N-cadherin expression in the regions.28,38 Meanwhile, Foxp2 and Foxp4 repress the expression of N-cadherin during neurogenesis from NPCs in the development of the nervous system.37 After neurogenic cell division of NPCs in a developing chick’s spinal cord, the elevated expression of either of the Foxp transcription factors, promoted by a proneural gene neurogenin 2 (ngn2), represses the expression of N-cadherin, and thereby promotes the detachment of nascent neurons or IPs from the apical region of neuroepithelium.37,40 This detachment is crucial for further neurogenesis and neuronal migration from the ventricular zone.40,41 The expression of ngn2 in NPCs is regulated by Delta-Notch signaling during neurogenesis.42,43 Delta activates the Notch receptor on directly adjacent NPCs to release the Notch intracellular domain that mediates the transcription of hairy/enhancer of split 1 (Hes1) gene.43 Up-regulation of Hes1 expression in turn represses the expression of ngn2 in NPCs and keeps NPCs in a proliferative state.42 In the developing mouse cerebral cortex, it has been reported that inhibition of Notch leads to down-regulation of Hes1 and sustained upregulation of ngn2.42 After asymmetric neurogenic division in the developing mouse cortex, Delta-Notch signaling components are divided asymmetrically into daughter cells, and therefore Notch signaling in the nascent neuron or IP is lower than in the cell, which maintains the identity of NPCs.44,46 These facts suggest the downregulation of Notch signaling may be important for the down-regulation of N-cadherin expression.

The expression of N-cadherin is also regulated by miRNAs of the miR379–410 cluster in NPCs during the development of the mouse cerebral cortex.49 Overexpression of the miRNAs in NPCs represses the expression of N-cadherin and increases the neuronal differentiation, suggesting that the miRNA regulate neurogenesis in the developing mouse cerebral cortex.39

Structure of AJ

N-cadherin and related molecules are composed of an adhesive complex, AJ which is responsible for strong cell-cell adhesion between NPCs to maintain the tissue architecture (Fig. 3).7,47 First, N-cadherin constitutes a cluster on the cell surface, and its extracellular domains on adjacent cells are bound to each other. The intracellular domain of N-cadherin is connected to β-catenin and p120-catenin. The β-catenin, in turn, is connected to α-catenin. The α-catenin was thought to bind to a cytoskeleton, actin fiber directly. Recently, it has been reported that a monomer of α-catenin bound to β-catenin does not interact with F-actin, and that only α-catenin dimers, isolated from the cadherin-β-catenin complex, bind actin bundles.48-51 This finding suggests that some actin binding molecules mediate between α-catenin and actin fiber. The candidate of the molecule which mediates α-catenin and actin fiber is reported to be vinculin and EPLIN.52,53 Moreover, p120 catenin also combines with the intracellular domain of N-cadherin.7,54 These factors, α-catenin, β-catenin, and p120-catenin, are not only components of AJ,
but also are responsible for the integrity of AJ. Various reports have observed that loss of α-catenin, β-catenin, or p120-catenin perturbs the integrity of AJ and destroys the adhesion.\textsuperscript{55-58} Three subtypes of α-catenin, αE, αN, and αT, are known.\textsuperscript{59-62} The expression of αE-catenin disappears with the differentiation of NPCs, and instead, αN-catenin is expressed in the differentiated neuron.\textsuperscript{60,61}

Integrity of apico-basal polarity in NPCs by N-cadherin

N-cadherin–based AJ is important for maintaining the apico-basal polarity in NPCs. Radial glia cells as NPCs exhibit a characteristic bipolar radial morphology with apical and basal processes.\textsuperscript{32,63,64} The apical and basal processes are responsible for 2 points of adhesion at the sub-apical region of N-cadherin-based AJ, and integrin-laminin interaction at their basal laminae, respectively (Fig. 1).\textsuperscript{32} The basal processes are attached to the sub-pial extracellular matrix through integrin-laminin interactions.\textsuperscript{65,66} The destruction of apico-basal polarity is closely related to downregulation of N-cadherin in nascent neurons and IPs after asymmetric neurogenic division.\textsuperscript{37,40,41} Nascent neurons often first adopt bipolar radial morphology, then quickly detach their process from the apical surface by down-regulation of N-cadherin.\textsuperscript{37,40,41} Abnormal persistence of N-cadherin inhibits the detachment of the apical process.\textsuperscript{40} Thus, N-cadherin regulates the detachment of the apical process, which results in the loss of AJ integrity and the apico-basal polarity of NPC.\textsuperscript{37,40,41} Recently, it has been reported that Slit1b-Robo3 signaling and N-cadherin regulate apical process retraction in developing retinal ganglion cells.\textsuperscript{41}

Localization of AJ in the apical domain of NPCs

AJ is formed in the sub-apical region of NPCs in the ventricular zone of neural tube, cerebral cortex, and midbrain as shown in Figure 3.\textsuperscript{21,34,67,68} The locus determination of AJ is deeply involved in cell polarization. In various cells, cell polarization is known to be required for the cell polarity complex partition defective complex protein 3 (Par3)-atypical protein kinase C (aPKC)-Par6.\textsuperscript{69,70} Par3 and aPKC are observed to be localized at the apical domain of radial glia cells in the mouse neocortex and of NPCs in the chick neural tube (Fig. 1).\textsuperscript{71,72} In addition, mislocalization of aPKC results in the aberrant distribution of cell adhesion molecules ZO-1 and N-cadherin, and disrupts AJ and neural progenitor polarity in the developing chick neural tube. Besides the cell polarity complex, in NPCs, Numb plays a critical role in the mechanism in which AJ is formed in the apical domain.\textsuperscript{67,73-76} Numb is an endocytic adaptor involved in the formation of apico-basal polarity.\textsuperscript{77} The reported relationship between Numb and the cell polarity complex is that Numb interacts with a component of the cell polarity complex, Par3.\textsuperscript{74} In NPCs during the development of the mouse cerebral cortex, Numb is localized in the apical domain of NPCs prior to N-cadherin localization (Fig. 3).\textsuperscript{67,73} According to the site of Numb, N-cadherin-based AJ is formed in the sub-apical region.\textsuperscript{67,73} Numb is known to interact with p120-catenin,\textsuperscript{58,77} so p120-catenin may be involved in the localization of N-cadherin-based AJ by Numb.
Role of N-cadherin on the Fate of NPCs

N-cadherin contributes not only to the integrity of AJ and the apico-basal polarity of NPCs, but also to the maintenance, proliferation, and differentiation of NPCs.

NPC niche during development

Adult neural stem cells have some properties of astrocytes, such as producing glial fibrillary acidic protein (GFAP), and reside in the subventricular zone along the wall of the lateral ventricle.78-80 Adult neural stem cell niches are organized by specialized supporting cells, ependymal cells and endothelial cells of blood vessels.81,82 N-cadherin is co-expressed with MT5-MMP in adult stem cells and ependymal cells. MT5-MMP-mediated cleavage of N-cadherin is dispensable for the regulation of adult neural stem cell generation and identity.81 However, the signals from ependymal cells and endothelial cells to maintain the niche are mostly unknown. The neural stem cells can renew themselves and generate transient amplifying (TA) cells by asymmetric division, and subsequently the TA cells generate neuroblast cells.28,83

However, in the developing neural tube and brain cortex, NPCs reside in a neurogenic niche lacking distinct supporting cells. In the case of radial glia cells as NPCs, the apical and basal processes of radial glia cells are required for the formation of a self-supporting NPC niche (Fig. 1 and 4).37,40,84,85 The nuclei of radial glia cells move within the ventricular zone as the cells progress through the cell cycle (Fig. 4).86,87 During neurogenesis, radial glia cells perform 2 types of division: one

Figure 4. Description of neural progenitor cell niche during development. The nuclei of radial glia cells move within the ventricular zone as the cell progresses through the cell cycle. During neurogenesis, radial glia cells perform 2 types of division: one is symmetric, proliferative division, and the other is asymmetric neurogenic division. The symmetric division provides both processes to the daughter cells; however, the asymmetric division does not provide the basal process to one daughter cell, and that cell loses the identity of NPCs and differentiates into nascent neuron or intermediate progenitor (IP).

is symmetric, proliferative division, and the other is asymmetric neurogenic division (Fig. 4).88 Inheritance of the apical and basal process to the daughter cell is important for the maintenance of NPCs’ identity in mouse NPCs.32,89,90 The symmetric division of NPCs provides both processes to the daughter cells; however, the asymmetric division does not provide the basal process, but only the apical process to one daughter cell, and then the cell loses the identity of NPCs and differentiates into a nascent neuron or IP.32,88 Meanwhile, the other daughter cell inherits both processes and maintains the identity of NPCs.

Contribution of N-cadherin to niche formation

The maintenance of the NPC’s niche is required for N-cadherin-based AJ.39,84,85,91 In the apical domain of NPCs, the AJ exists with high density to form strong adhesions.21,34,92 Moreover, in the case of adult NPCs in zebra fish, it has been shown clearly that adhesion through N-cadherin on NPCs of the subventricular zone where Rostral migration occurs constitutes the niche of NPCs in the brain of an adult zebra fish.85

A high level of N-cadherin protein in the apical domain of NPCs seems to be important to undergo symmetric proliferative division and to maintain the identity of NPCs.37,40 The nascent neurons and IPs derived from NPCs lose the identity of NPC while the expression of N-cadherin is down-regulated.37,40,41 Furthermore, loss of function of N-cadherin by the conditional knockout (KO) and short hairpin RNA (shRNA) in the cerebral cortex, causes premature differentiation of NPCs.84,93 These results demonstrate that N-cadherin plays a critical role in the self-supportive niche to keep the identity of NPCs.

Regulation of differentiation of NPCs by N-cadherin

It has been reported that downregulation of N-cadherin after asymmetric, neurogenic division is closely related to neuronal differentiation in various NPCs.37,39-41,85,94 Down-regulation of N-cadherin is observed to be associated with the detachment of the apical process from the ventricular zone of the chick embryo spinal cord.37,40 Abnormal persistence of N-cadherin expression inhibits the apical process withdrawal and cell cycle exit in prospective neurons.40 These facts suggest the onset of neuronal differentiation is characterized by downregulation of N-cadherin.37,40,41,94 Furthermore, experiments using N-cadherin gain- and loss-of-function approaches show that these perturb the neuronal differentiation in chick and zebra fish retina, mouse cerebral cortex, zebra fish cerebellum, and mouse ventral midbrain during development.11,27,34,39,95-97 In adult zebra fish, down-regulation of N-cadherin is a trigger of the differentiation of NPCs during Rostral migration.85 In addition, it has been reported that N-cadherin regulates neuronal differentiation from induced pluripotent stem cells (iPSCs).98,99 These findings support the notion that the down-regulation of the N-cadherin level in nascent neurons and IP is required for the onset of neuronal differentiation of NPCs.
Regulation of β-catenin Activity by N-cadherin

β-catenin is not only a component of AJ, but also a component of the canonical Wnt pathway. Wnt allows β-catenin to translocate into the nucleus. In the nucleus, β-catenin combines with the transcription T-cell factor (TCF)/lymphocyte enhancer factor (LEF), and it causes the induction of proliferation-related genes such as cyclin D. Thus, Wnt affects the level of β-catenin in the cytoplasm of NPCs. In addition, it is also known that N-cadherin affects the level of β-catenin signaling. In this chapter, we would like to introduce the regulation of β-catenin signaling level by N-cadherin.

Structure of β-catenin

β-catenin contains a repetitive sequence (armadillo repeat) of 42 amino acids, located in the center of the molecule. The portion of this repetitive sequence combines with the cytoplasmic region of N-cadherin, or APC, and Axin. This N-cadherin binding site and the APC and Axin binding sites overlap, so β-catenin cannot combine with N-cadherin and the APC or Axin simultaneously. It combines with the N-terminal domain of β-catenin with α-catenin and APC and Axin form a complex with glycogen synthase kinase 3β (GSK3β) to degrade β-catenin.

Regulation of β-catenin distribution and degradation by N-cadherin

N-cadherin sequesters β-catenin by the binding of the cytoplasmic domain to β-catenin on the cytoplasmic membrane, and controls the level of β-catenin protein in the cytoplasm. N-cadherin is localized in the apical domain of NPCs in the brain ventricular zone with a high level of β-catenin protein. It seems that N-cadherin can serve as a “pool” of β-catenin protein to control the level of β-catenin protein in the cytoplasm of NPCs. We recently observed that loss of N-cadherin allows β-catenin to diffuse throughout the cytoplasm of NPCs and increase the β-catenin signaling in NPCs of dorsal midbrain during development. The same phenomenon is observed also in E-cadherin. These findings suggest that N-cadherin may be a factor that regulates the distribution of β-catenin.

As described above, GSK3β plays a critical role in the degradation of β-catenin. GSK3β activity is known to be affected by N-cadherin-based AJ. Phosphodestruction complex, GSK3β, Axin, and APC complex are localized at the joint area of the apical domain of NPC in the mouse cerebral ventricular zone. These complexes are activated by maintaining the adhesion between the NPCs results in the decrease of the phosphodestruction complex for β-catenin. On the other hand, N-cadherin is concerned with the stabilization of β-catenin through Akt. The phosphorylation of Ser552 in β-catenin by Akt stabilizes β-catenin and allows β-catenin to translocate into the nucleus. Regulation of Akt activity by N-cadherin is confirmed by the finding that a knockdown by the N-cadherin shRNA in the cerebral cortex causes the reduction of Akt activity.

Control of the Fate of NPCs by β-catenin Signaling

Regulation of niche formation by β-catenin signaling

A high level of β-catenin is involved in the niche formation of NPC in the apical region of the neural tube, brain cortex, and retina, just as N-cadherin. Co-localization of β-catenin with N-cadherin is observed in the apical domain of NPCs in the cerebral cortex and midbrain (Fig. 2). It seems that N-cadherin can serve as a “pool” of β-catenin protein to control the level of β-catenin protein in the cytoplasm of NPCs. We recently observed that loss of N-cadherin allows β-catenin to diffuse throughout the cytoplasm of NPCs and increase the β-catenin signaling in NPCs of dorsal midbrain during development. The same phenomenon is observed also in E-cadherin. These findings suggest that N-cadherin may be a factor that regulates the distribution of β-catenin.

In canonical Wnt signaling, β-catenin as a component of Wnt signaling up-regulates cyclin D1, which is involved in the progress of the cell cycle. As described above, in the developing mouse midbrain. It has been reported that the expression of active β-catenin increases the proliferation of NPC and decreases the neurogenesis.

Contribution of β-catenin to differentiation of NPCs

The signaling of β-catenin is also related to progress not only in proliferation but also differentiation. As it is for N-cadherin, β-catenin is deeply involved in the balance between the self-renewal and differentiation of NPC. The level of β-catenin is regulated by various factors such as N-cadherin, Wnt, Akt and phosphodestruction complex. During the differentiation of NPCs, the downregulation of β-catenin level is observed in nascent neuron and IP from NPCs. In the developing cerebral cortex, loss of function of N-cadherin by the shRNA decreases Akt activity and thereby decreases the level of β-catenin by failure of phosphorylation level of Ser552 in

Figure 5. Structure of β-catenin. Human β-catenin has 781 amino acids and contains 13 repetitive sequences (armadillo repeat) of 42 amino acid is located in the center of the molecule. The N-terminal of β-catenin has 3 phosphorylation sites (33Ser, 37Ser, 41Thr) for GSK3β and the C-terminal of β-catenin has a phosphorylation site (Ser552) for Akt. β-catenin binds to α-catenin and cytoplasmic of N-cadherin to develop AJ. On the other hand, β-catenin binds to APC, and Axin to construct a phosphodestruction complex with GSK3β. The phosphodestruction complex phosphorylates β-catenin for the degradation.
The decrease of the β-catenin level results in the premature differentiation of NPC.\(^{122}\)

**Relationship of Hh and Notch Signaling to N-cadherin-based AJ**

The fate of NPCs is regulated by Notch, Hh, and Wnt signaling during development. As mentioned above, Wnt signaling regulates the fate of NPCs through β-catenin. In this chapter, we discuss the relationship of Notch and Hh signaling to N-cadherin-based AJ in NPCs during development. Furthermore, the Hh signaling has been reported to interact with Wnt signaling, as shown in Figure 6.\(^{35,125}\)

**Relationship of Notch signaling to N-cadherin-based AJ**

Notch signaling plays a critical role in maintenance of NPCs niche and switching from proliferative cell division to neurogenic cell division.\(^{46,126}\) After asymmetric neurogenic division, numerous nascent neurons and/or IPs expressing the ligand of Notch retain apical process transiently at the ventricular zone in the developing mouse cerebral cortex.\(^{127}\) Both Notch1 and its ligand Delta-like 1 (Dll1) are distributed around AJs in the apical process.\(^{127}\) The nascent neurons and IPs inherited lower level of Delta-Notch signaling components than the cell, which maintains the identity of NPC.\(^{44,46}\) The down-regulation of Notch signaling is important for the downregulation of N-cadherin and subsequent apical process detachment.\(^{127}\) As described above, some studies show a functional link between Notch signaling and cadherin-mediated AJ.\(^{128,129}\)

In addition, a crosstalk between Notch and Hh signaling pathway has been reported.\(^{43}\) Hh activity in NPCs up-regulates the expression of Hes1 and brain lipid-binding protein (Blbp), downstream targets of Notch signaling and promotes symmetric proliferative division of NPCs.\(^{43}\) As described in the above chapter, Hes1 suppresses the expression of ngn2 and maintains the expression of N-cadherin.\(^{43}\)

**Regulation of Hh signal in NPCs by αE-catenin**

αE-catenin has been reported to be able to detect the cell density of NPCs and is responsible for the negative feedback loop of proliferation in the cerebral cortex.\(^{16}\) In a mouse cerebral cortex suffering from the loss of αE-catenin, the up-regulation of Hh signaling is observed and excess proliferation of NPC takes place in the cortex.\(^{16}\) This finding is supported by the notion that Hh signaling is known to be concerned with proliferation of NPCs.\(^{130,131-133}\) Furthermore, this finding proposes a negative feedback loop controlling the size of the developing cerebral cortex.\(^{16,134}\) Recently, it has been reported that tension causes a conformational change of α-catenin, which allows a varied vinculin-binding site in α-catenin protein to expose and interact with β-catenin.\(^{134,135}\) The force-dependent interaction between vinculin and αE-catenin might be involved in chemical response such as Hh signaling in NPC.

**Relationship between apico-basal polarity and Hh signaling**

How does apico-basal polarity in neural tube and brain cortex regulate the fate of NPC? The apico-basal polarity is known to be related to Hh signaling.\(^{16,40,136,137}\) After asymmetric neurogenic division of NPCs, nascent neurons and IPs lose the apico-basal polarity and progress the differentiation in the developing neural tube and cerebral cortex.\(^{40}\) The relation between the polarity and Hh signal is analyzed with mouse and chick neural tubes.\(^{40}\) In prospective neurons in the neural tube, the reduction of N-cadherin expression and loss of polarity is observed.\(^{40}\) As a result of losing polarity, the primary cilium are temporarily lost in the cells.\(^{40}\) The primary cilium has Smo and Gli, which are components of Hh signaling pathway.\(^{138,139}\) Therefore, loss of the primary cilium results in the suppression of Hh signaling.\(^{40}\) In addition, the primary cilium activity is required for maintaining proper apico-basal

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**Figure 6.** Interaction of N-cadherin-based AJ with Wnt signaling and hedgehog (Hh) signaling. N-cadherin regulates not only the integrity of AJ, but also the balance between Wnt signal and Hh signal. About Wnt signal, β-catenin (β) is mediated with N-cadherin-based AJ and canonical Wnt signal. On the other hand, α-catenin (α) is mediated with the junction and Hh signal. Ptc, patched; Smo, smoothened; Frz, frizzled.
polarity as neuroepithelium cells transform radial glia cells. However, in the retina and neural tube of zebra fish, the destruction of the apico-basal polarity of NPC by N-cadherin knockout and mutants, or knockout of αE-catenin, increases the proliferative division and decreases the neurogenesis from the NPCs. This decrease of neurogenesis is related to Hh signaling. These findings reveal that the apico-basal polarity of NPC is deeply involved in Hh signaling.

Relationship between Wnt signaling and Hh signaling

The interaction between Wnt-β-catenin signaling and Hh signaling is observed in the NPCs of the mouse neural tube and midbrain ventral region during development. Upregulation of the Wnt-β-catenin signal in the developing ventral midbrain is observed to suppress Hh signaling. Conversely, the inhibition of Wnt signaling is observed to increase Hh signaling. In addition, in the neural tube of the embryo, Wnt signaling induces expression of the cyclin D1, and affects the G1 phase; on the other hand, Hh signaling affects the G2 phase. These findings suggest that the balance between Wnt signaling and Hh signaling regulates the proliferation and differentiation of NPC.

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Conclusion and Perspective

In this review, we discuss the role of N-cadherin-based AJ in not only the integrity of tissue architecture and apico-basal polarity, but also the integrity of various signaling such as β-catenin and αE-catenin in NPC. N-cadherin regulates the balance between the self-renewal and differentiation of NPC, and thereby controls the size and architecture of the neural system. However, the molecular mechanism underlying the control of NPC fate by N-cadherin remains unclear. Further study is needed to elucidate this mechanism. It has also been shown that N-cadherin is involved in the neuronal differentiation from an iPS cell. If the mechanism underlying the determination of the NPCs by N-cadherin is found, it is expected to lead to a technique of development of efficient neurogenesis. It is further expected that development of this technique will become an effective method in the medical treatment of neurodegenerative diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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