The role of adherens junctions in the developing neocortex

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Abbreviations: VZ, ventricular zone; SNP, short neural precursor; CBD, catenin binding domain; JMD, juxtamembrane domain; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; GSK3β, glycogen synthase kinase 3β; PCP, planar cell polarity; SHH, sonic hedgehog; Hh, Hedgehog; CK1, Casein kinase 1; APC, Adenomatous polyposis coli.

The disproportional enlargement of the neocortex through evolution has been instrumental in the success of vertebrates, in particular mammals. The neocortex is a multilayered sheet of neurons generated from a simple proliferative neuroepithelium through a myriad of mechanisms with substantial evolutionary conservation. This developing neuroepithelium is populated by progenitors that can generate additional progenitors as well as post-mitotic neurons. Subtle alterations in the production of progenitors vs. differentiated cells during development can result in dramatic differences in neocortical size. This review article will examine how cadherin cell-cell adhesion proteins, in particular α-catenin and N-cadherin, function in regulating the neural progenitor microenvironment, cell proliferation, and differentiation in cortical development.

Cortical neural progenitors are polarized neuroepithelial cells

The generation of neocortical neurons, or neurogenesis, in rodents begins shortly after the neural tube is closed and continues until just before birth.9 Cortical projection neurons are generated from neural progenitors that develop from the pseudostratified neuroepithelium of the developing neocortex adjacent to the lateral ventricles termed the Ventricular Zone (VZ). Radial glial cells are highly polarized neural progenitors that possess a process attached to the apical (luminal) surface and a long process attached to the basal (cortical) surface that provides a physical structure to facilitate neuronal migration (Fig. 1).10 Radial glial cells translocate their cell bodies to divide at the apical surface and can self-renew,11-13 generate neurons,14,15 as well as produce transient amplifying cells (termed basal or intermediate progenitors) that serve to produce later-generated neurons (Fig. 1).16-18 There is another progenitor type that resides in the VZ of developing mouse brains, the short neural precursor (SNP). These apical progenitors also divide at the apical surface, can self-renew, and generate neurons (Fig. 1).19 Unlike radial glia, they do not possess a long basal process and typically do not generate transient-amplifying basal progenitors.

Through the course of neural development, a balance between self-sustaining proliferative divisions and neurogenic differentiation divisions must be appropriately maintained, and modest alterations in the fraction of daughter cells that exit or re-enter the cell cycle can result in dramatic changes in cortical size.1,2 Dividing precursor cells in the VZ can yield daughter cells with the same fate (symmetric) or with differing fates (asymmetric).20-22 The control of cell fate choices, cell proliferation and differentiation, is regulated by both cell-intrinsic and environmental influences on radial glial cells in the VZ.23-25 Environmental influences have received less attention than cell intrinsic mechanisms, however recent evidence has demonstrated that cerebrospinal fluid can promote proliferation of radial glia.26

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Proliferative fate decisions are also regulated by a myriad of different intrinsic processes. The orientation of cell division and asymmetric inheritance of cellular components can predict the behavior of daughter cells. As in other tissues, in the neuroepithelium the daughter cell that inherits the older (mother) centrosome is preferentially retained in the VZ as a progenitor. Inheritance of another component of the primary cilium, the apical ciliary membrane, has also been shown to help retain the recipient daughter cell in the VZ.

Asymmetric inheritance of adhesion machinery and polarity protein complexes can also influence cell fate decisions. Daughter cells with higher levels of Par3, a key component of the Par protein complex that regulates polarity, are preferentially retained as progenitors. Cadherin adhesion also plays a critical role in establishing and maintaining apical-basal polarity in epithelia. Evidence that adherens junctions could regulate asymmetric division in Drosophila neuroblasts further supported the possibility that cadherin adhesion could impact cell behaviors in the developing cortical neuroepithelium. However, the critical role that cadherin adhesion served in maintaining epithelial architecture in cortical development complicated the interpretation of broad genetic loss-of-function methods with regard to the role of adhesion in neural cell fate determination.

Cadherins and catenins mediate adhesion and signaling

There are 4 different classes of cadherins: classical types 1 and 2, protocadherins, desmosomal, and atypical. Classical cadherins interact with cadherin molecules in other cells (trans-interactions) as well as those nearby in the same cell (cis-interactions). Once initial contact is made between adjacent cells expressing cadherin, the cadherins cluster into puncta along the point of contact, then strengthen to form concentrated plaques of cadherin complexes. The intracellular domain of classic cadherins consists of a juxtamembrane domain (JMD) and catenin binding domain (CBD). The JMD binds p120-catenin while the CBD binds β-catenin. Additionally, the cadherin intracellular domain also binds a number of other proteins that regulate normal housekeeping and trafficking functions such as endocytosis and degradation. β-catenin contains 12 characteristic imperfect sequence armadillo repeats that form a triple α-helix. This portion of β-catenin contains the cadherin binding site, while the N-terminal portion contains the α-catenin binding site. β-catenin also serves as the defining downstream mediator of the canonical Wnt signaling pathway. When Wnt signaling is activated, β-catenin degradation by an APC-containing “destruction complex” is inhibited, allowing for β-catenin to accumulate.

Figure 1. Organization of the developing mouse neocortex. The two classes of neural precursor, radial glia and short neural precursors, both reside in the Ventricular Zone (VZ) with a process attached to the apical (luminal) surface adjacent to the developing lateral ventricle. The overt structural distinction between the 2 neural precursors is that radial glia possess a process attached to the basal (cortical) surface while short neural precursors do not. During mitosis the cell body migrates to the apical surface where it will divide to generate 2 daughter cells. In the case of radial glia, the daughter cells can be new radial glia cells, basal progenitors, or post-mitotic neurons. Basal progenitors are a transient type of progenitor that resides basal to the VZ in the Subventricular Zone (SVZ), and can also self-renew as well as generate post-mitotic neurons. Post-mitotic neurons migrate away from the VZ and/or SVZ along radial glia processes through the Intermediate Zone (IZ) to populate the developing Cortical Plate (CP) in an inside-out fashion, where the deepest cortical layers are generated first. The other apical precursor type, short neural precursors, can also self-renew or generate post-mitotic neurons, however they do not produce basal progenitors.
α-catenin serves as the link between the cadherin/catenin complex and the actin cytoskeleton, as it can bind both β-catenin and filamentous actin. When sufficient physical tension is present within the cell, a strong bond is formed between F-actin and the ternary α-catenin/β-catenin/cadherin structure. This linkage is not static, but rather dynamic as F-actin rapidly dissociates from the ternary complex when the tension is substantially reduced. The ternary structure is incredibly stable, which provides further support for this 2-state bond model linking the cytoskeleton and the ternary complex. Thus α-catenin serves as the dynamic link between cadherin adhesion and the cytoskeleton.

δ-catenin/p120-catenin plays a role in maintaining synaptic contacts as well as dendritic spines. However, while present in neural precursors no specific function has been identified during neocortical development. No function of any kind has been described in neural tissue for γ-catenin/plakoglobin. As such, the other members of the catenin family, γ- and δ-catenin, will not be discussed in detail in this review.

β-Catenin signaling regulates cortical progenitor proliferation and differentiation

As the downstream mediator of canonical Wnt signaling and an essential component of the cadherin adherens complex, β-catenin is positioned at the intersection of cell-cell adhesion and signaling. In the developing cerebral cortex, transgenic overexpression of a degradation-resistant β-catenin caused massive enlargement of the cortical progenitor pool and expansion of cortical surface area. Complementary studies provided evidence that the signaling function of β-catenin was critical in regulating cell proliferation in cortical development. While these and many other studies pointed to the importance of β-catenin signaling in development, how adhesion and signaling might interact remained difficult to dissect experimentally.

Regulation of proliferation by cadherins in cortical development depends on context

As in other epithelia, cadherin adhesion in the developing nervous system regulates tissue integrity. Following closure of the neural tube N-cadherin is expressed in all portions of the tube except for the neural crest. Injection of an N-cadherin function blocking antibody into the developing diencephalon of chick embryos caused a profound disruption in epithelial structure and the formation of neuroepithelial rosettes. These findings were recapitulated in the developing cortex of mice where conditional deletion of N-cadherin resulted in disruption of the normal laminar organization of the cortex and a complete loss of apically concentrated adherens junction component expression. Similarly, conditional deletion of β-catenin, or αE-catenin from neural precursors caused profound disruption of cortical layering and loss of the apically-located adherens junctions.

The striking architectural disorganization of the developing cortex following adherens junction disruption was accompanied by the mis-regulation of cell proliferation. When N-cadherin transport and localization were altered by conditional deletion of a subunit of the KIF3 molecular motor, KAP3 (kinesin-associated protein 3), hyperproliferation of neural progenitors and enlargement of the cortex resulted. Similarly, conditional deletion of αE-catenin caused hyperproliferation of cortical progenitors and overgrowth of the cerebral cortex. While Lien et al. observed upregulation of the hedgehog signaling pathway in the cortices of the conditional αE-catenin knockout mice, the specific mechanisms underlying the control of proliferation by cell adhesion remain poorly understood. The regulation of cell polarity and cell growth are intimately linked, and the maintenance of distinct cellular domains by adherens junction adhesion likely plays a critical role in the proper balance of pro- and anti-proliferative signals.

In contrast to the hyperproliferation observed when adhesion and cell polarity was globally disrupted, focal inhibition of cadherin adhesion in an intact neuroepithelium appears to reduce, instead of increase, pro-proliferative signaling. In utero electroporation methods enabled the focal loss of adherens proteins while preserving the integrity of the VZ. Instead of the epithelial disorganization and hyperproliferation that resulted from widespread deletion of αE-catenin, focal deletion of αE-catenin resulted in premature cell-cycle exit, neuronal differentiation, and migration from the ventricular zone to the cortical plate. The cells in which αE-catenin was reduced also showed reduction in β-catenin mediated Wnt signaling, and rescuing β-catenin signaling largely restores proliferation. Similarly, cell-autonomous deletion of N-cadherin in neural precursors caused premature cell-cycle exit, neuronal differentiation, migration from the VZ, as well as reduced β-catenin mediated Wnt signaling.

Together these studies suggest that cadherin adhesion in cortic al progenitors in a normal, intact VZ promotes neural progenitor self-renewal via activation of β-catenin signaling. The hyperproliferation observed in tissue-wide knockout of cadherin adhesion might therefore result indirectly from the loss of cell polarity and tissue organization. Pro-proliferative signals or their receptors may be released from their normal subcellular locations and regulation with loss of apical-basal polarity. Taken together, these findings suggest that the regulation of cell proliferation by cadherin adhesion is highly context-dependent in developing tissues and organs.

Cadherin adhesion and the neural progenitor niche

The local microenvironment, or niche, plays an important function in regulating the development of stem and progenitor cells. The physical attachment of stem/progenitor cells to the niche is important for maintaining stem cell identity and function. The structural organization of the developing cortical VZ differs from the typical stem cell niche in that it lacks specific support cells, and is comprised exclusively of proliferating progenitor cells.

We proposed that cadherin adhesion in the cortical VZ functions to sustain a proliferative niche where neural precursors support and maintain themselves. Cell-cell adhesion in the VZ niche likely provides them with optimized exposure to pro-proliferative Wnts expressed by progenitors in the VZ.
migration from the VZ would ensure that pro-proliferative Wnt signaling was reduced, and indeed, Wnt signaling activity is markedly reduced outside of the VZ.69,77 However, the model that cadherin maintenance of β-catenin signaling occurs solely via physical retention of cells in the VZ is no doubt overly simplistic. We observed that electroporated progenitors still located in the VZ showed reduced β-catenin signaling after N-cadherin or αE-catenin reduction, indicating that reductions in β-catenin signaling preceded exit from the VZ.6-8 Therefore, cadherin cell-cell adhesion appears to serve at least 2 related functions to promote Wnt/β-catenin signaling in cortical development: 1) to directly maintain β-catenin signaling in the VZ, and 2) to physically retain cells in the VZ to ensure proximity to pro-proliferative Wnt ligands.

What is the evidence that cadherin adhesion directly positively regulates Wnt/β-catenin signaling? A simple model, where cadherins set a threshold for β-catenin signaling, was suggested by numerous observations that forced overexpression of cadherins antagonized β-catenin transcriptional activation.69-93 In this model, cadherin is able to titrate available β-catenin from its role in Wnt signaling.69-93 Our observations that cadherin adhesion can also positively regulate Wnt/β-catenin signaling support increasing recent evidence that the relationship between cadherin adhesion and β-catenin signaling is context-dependent.94 In the developing cortex, N-cadherin appears to function in Wnt signaling both through phosphorylation of LRP6 and activation of AKT signaling.9 The assembly of functional Wnt signaling receptor complex also requires cadherin.95-97 Moreover, a recent study suggests that only cadherin-associated β-catenin is Wnt-signaling competent, and functionally distinct from β-catenin that has never interacted with cadherin.94 Cadherin also appears to maintain a pool of β-catenin that can be available for signal transduction, supporting studies suggesting that cadherin-bound β-catenin can translocate to the nucleus and activate transcription.94,98,99

Distinct from its role in Wnt-activation of β-catenin, N-cadherin can also stimulate β-catenin transcriptional activation through AKT. N-cadherin adhesion triggers PI3K-mediated activation of AKT.100-102 In turn, activated AKT signaling can stimulate β-catenin signaling. In intestinal stem cells the loss of a negative regulator of PI3K/AKT, PTEN, leads to β-catenin stabilization and upregulated β-catenin signaling.103 AKT phosphorylates β-catenin at Serine residue 552, priming it for 14-3-3γ binding and stabilization, which in turn allows β-catenin to translocate and accumulate in the nucleus.104 AKT can also phosphorylate and inactivate GSK3β at Serine 9, which leads to stabilization

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**Figure 2.** Hypothetical signaling hub, or extra-nuclear hub, containing both adherens junction and Wnt signaling components at the apical surface. The high density of adherens junction and Wnt signaling components located in the apical end feet of neural precursors located in the VZ, coupled with emerging data suggests that these pathways may physically and functionally interact. In the absence of a Wnt signal, a destruction complex comprised of Axin and APC bind to β-catenin (β) and recruit the kinases GSK3β and CK1, which phosphorylate β-catenin thereby targeting it for ubiquitination and ultimately destruction. In the presence of a Wnt ligand, a Frizzled (Fzd) and LRP5/6 complex is formed and bound by Dishevelled (Dvl), leading to the phosphorylation of the LRP5/6 receptor by several kinases, including GSK3β and CK1. The phosphorylated LRP5/6 receptor recruits axin to the plasma membrane, leading to the decay of the destruction complex, and allowing stabilized β-catenin to be translocated to the nucleus. A growing number of studies suggest that several key components of Wnt signaling may physically interact with members of the adherens junction, in particular N-cadherin (N-cad). N-cadherin binds both p120-catenin (p120) at the JMD domain (juxtamembrane intracellular domain) and β-catenin at the CBD domain (catenin binding domain). β-catenin in turn binds to α-catenin (α), which is dynamically tethered to the actin cytoskeleton. PI3K, which through activation of AKT stabilizes β-catenin allowing it to participate in signaling, has also been shown to interact with N-cadherin. The research detailing additional potential interactions are detailed in the main text.
and nuclear accumulation of β-catenin.105 In cortical progenitors, AKT activation also results in stabilization and activation of β-catenin signaling by direct phosphorylation at Serine 552.7–8

In addition to Wnt/β-catenin and PI3K/β-catenin signaling, appropriate regulation of other signaling pathways important in neural development depend on adherens junctions. A single cilium extends from the apical process of cortical progenitors.96 Recent studies have supported a role for cilia in coordinating critical signaling pathways in neural development such as SHH.107 Although the relationship of adherens junctions and the regulation of cilia-based signaling pathways remains poorly understood, recent evidence that the planar cell polarity (PCP) proteins implicated in ciliogenesis must be first positioned apically107 suggest that adherens junctions, apical-basal polarity, and planar polarity are intimately linked. Indeed, the findings of upregulated hedgehog (Hh) signaling following αE-catenin7 or N-cadherin deletion108 suggest that intact epithelial architecture functions to restrain Hh signaling. The observations that Hh signaling maintains adherens junctions in zebrafish neural tube suggests a potential reciprocal inhibitory relationship between adherens junctions and SHH signaling.108

The signaling machinery critical for polarity, adhesion, and proliferation cluster at the apical foot process of VZ precursors,3,7,30,109,110 where the high density of these pathway components indicates the potential for cross-talk. A growing amount of data indicates that there are physical interactions between various components of these different cellular processes. APC, a component of the destruction complex that phosphorylates β-catenin, is also known to localize to the cellular microdomain or niche, should be fruitful and elucidating. Moreover, understanding which pathways intersect and how/when they intersect will be useful not only to the field of developmental neurobiology but many others (e.g. cancer) where alterations in cell-cell adhesion impact cell behaviors.

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**Summary**

Recent experiments examining the roles of αE-catenin and N-cadherin have demonstrated that proper adhesive function is important in maintaining neural precursors within the proliferative ventricular zone of the developing neocortex, as well as maintaining β-catenin mediated Wnt signaling. Furthermore, adherens junctions help maintain a self supportive proliferative neural stem cell niche. The apical concentration of adhesive and signaling molecules may provide an extra-nuclear hub utilized to sustain the proliferative neuroepithelium during development. Future studies investigating the roles of these apically concentrated signaling molecules play in maintaining a proliferative microdomain or niche, should be fruitful and elucidating. Moreover, understanding which pathways intersect and how/when they intersect will be useful not only to the field of developmental neurobiology but many others (e.g. cancer) where alterations in cell-cell adhesion impact cell behaviors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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