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## Restraining Stem Cell Niche Plasticity: A New Talent of Eph Receptors

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Multiple Eph receptor tyrosine kinases and ephrin ligands are expressed in stem cells and their niches, where their complex roles are under intense investigation. Nomura *et al.* (2010) reveal an unexpected function of Eph signaling in suppressing cell fate plasticity of niche cells in the adult brain.

Harnessing the power of stem cells to repair or replace damaged tissues is one of the great hopes of regenerative medicine. Use of stem cells as a therapy necessitates a thorough understanding of intrinsic programs and extrinsic factors that govern their maintenance, expansion and differentiation. Resident stem cells in the adult brain also play an integral role in tissue homeostasis, regeneration and brain plasticity. However, the ability of these cells to divide and maintain their multipotency is highly dependent on intimately associated niche cells in the microenvironment (Fig. 1A) (Zhao *et al.*, 2008). Thus, preservation of stem and niche cells alike, is essential for the regulation and function of adult neurogenic zones. In this issue of *Cell Stem Cell*, Nomura *et al.* show that two niche cell lineages – ependymal cells and non-proliferating subventricular zone astrocytes – retain an important level of cell fate plasticity in the adult mouse brain that contributes to the natural resilience of the system. Unexpectedly, the work reveals that a portion of ependymal cells that line the lateral ventricular wall and astrocytes in the subventricular zone are capable of mutually replacing one another following an injury. In the normal brain, the ability of these cell types to interconvert is suppressed by signaling events downstream of Notch and EphB receptor tyrosine kinases. However, these pathways are overridden following injury (Fig. 1B).

Using genetic fate mapping techniques, Nomura *et al.* find that normally quiescent ependymal cells and non-proliferating astrocytes acquire the ability to interconvert their cellular properties and location when the niche is perturbed, for example by a mild injury due to intraventricular injection of neuraminidase (Del Carmen Gomez-Roldan *et al.*, 2008) or by disrupting Notch and Eph signaling. A small fraction of converted cells in each lineage (approximately 1% of astrocytes and 5% of ependymal cells monitored) appear to change their phenotype following neuraminidase-mediated damage. Most of the astrocytes that transform lose expression of the protein glial fibrillary acidic protein (GFAP) and gain the

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characteristics of ependymal cells, including becoming multiciliated and interposed in the ependymal cell layer. Conversely, lineage-labeled ependymal cells begin to express the astrocytic markers GFAP and glutamine synthetase but remain in the ependymal layer and retain features of ependymal cells, such as S100 $\beta$  expression. However, some ependymal cells that acquire astrocytic properties relocate to the subventricular zone, downregulate S100 $\beta$ , and take on morphological features of astrocytes in this region. Thus, cues derived from the new environment following a change in niche location may help drive full commitment to the new cell fate. Importantly, the mutual interconversion of ependymal cell and astrocyte populations occurs in the absence of cell proliferation, indicating that these are purely cell fate changes. This form of niche plasticity likely serves to balance these two niche cell populations when cells from each lineage are damaged or lost.

At the core of these cellular interconversion events is signaling through Notch and EphB receptors. Both of these receptor systems rely on membrane-tethered ligands on adjacent cells to trigger their activation. Canonical Notch signaling is critical for maintaining cell fate and quiescence of ependymal cells near the subventricular zone (Carlen et al., 2009), while EphB signaling regulates stem cell proliferation and survival as well as neuroblast migration (Conover et al., 2000; Furne et al., 2009; Genander and Frisen, 2010; Theus et al., 2010). Interestingly, Nomura *et al.* reveal that EphB2 expression in ependymal cells is positively regulated by Notch signaling in the normal brain. Following injury to the lateral ventricles, however, EphB2 levels are significantly reduced. Surprisingly, Notch signaling remains intact, indicating that another mechanism governs EphB2 expression in ependymal cells following injury. Inflammatory cytokines that are released as a result of brain injury may be among the factors that downregulate the levels of EphB receptors (including EphB2 and EphB3) in the niche to promote cellular conversion and stem/progenitor cell proliferation (Del Carmen Gomez-Roldan et al., 2008; Theus et al., 2010). It still remains to be determined if EphB receptor downregulation also plays a role in the astrocyte transformation to ependymal cells observed by Nomura and co-workers. Importantly, restoring EphB2 levels after injury or following inhibition of Notch signaling prevents conversion of ependymal cells to astrocytes, indicating that the loss of EphB signaling is directly involved in the transformative process of ependymal cells.

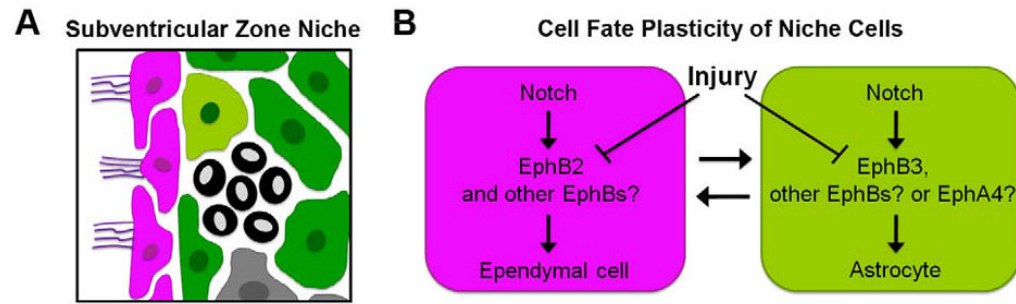
Multiple Eph receptors and ephrin ligands are expressed in combinatorial patterns in both ependymal cells and astrocyte-type cells of the subventricular zone (Conover et al., 2000; Furne et al., 2009; Genander and Frisen, 2010; Nomura et al., 2010; Theus et al., 2010). Nomura *et al.* found that global loss of EphB signaling causes a similar restructuring of the niche as mild injury, and promotes the conversion of ependymal cells to astrocytes and vice versa. Directly interfering with the ability of EphB receptors to transduce signals within ependymal cells (known as forward signaling) also triggers the cellular conversion event. In contrast, blocking the ability of the transmembrane ephrin-B ligands to convey their own signals within the cells through their cytoplasmic domain (known as reverse signaling) fails to convert ependymal cells to astrocytes. Thus, only signaling events downstream of EphB receptors are needed to preserve ependymal cell and astrocyte identity in the niche. The exact nature of these EphB signaling events still remains to be identified. Perhaps, EphB2 promotes the function or expression of genes involved in maintaining ependymal wall integrity, such as Numb and Numb-like (Kuo et al., 2006), or of Sox2, a stem cell transcription factor also expressed in ependymal cells and that has been recently linked to EphB2 signaling (Parrinello et al., 2010). Interestingly, EphB receptors as well as both Numb and Sox2 are known to promote cadherin-dependent intercellular adhesion, which may become disrupted following neuraminidase treatment of the ependymal layer (Del Carmen Gomez-Roldan et al., 2008). Thus, EphB signaling may be part of an active feedback loop that constitutively stabilizes the stem cell niche.

The full repertoire of Eph receptors and ephrins that participate in these processes still remains unclear. Is there molecular redundancy in the system or do different members of the large Eph receptor and ephrin families have distinct roles? It also is uncertain how the cell fate changes mediated by the ephrin-B/EphB system in ependymal cells and astrocytes interface with the previously reported roles of these proteins in decreasing Akt activation, promoting p53 expression, inhibiting proliferation of subventricular zone progenitors and regulating neuroblast migration (Conover et al., 2000; Furne et al., 2009; Theus et al., 2010). Furthermore, the impact of perturbation of EphB signaling on other niche cell types, such as microglia and vascular cells, requires further investigation.

The work by Nomura *et al.* confronts several unresolved aspects of niche homeostasis, and importantly uncovers some of the major signaling pathways involved. Whether or not these mechanisms play a role in niche plasticity following other brain injuries or during processes such as aging remains to be determined. However, the present findings along with other recent studies highlight the tremendous self-preservation capacity of adult neurogenic centers in the brain.

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**Figure 1. Unleashing niche cell plasticity in the adult brain**

(A) Schematic showing the basic organization of the subventricular zone niche in the adult mouse brain. Ependymal cells (magenta) line the wall of the lateral ventricles as a single cell layer. Non-proliferating (light green) and proliferating (green and grey) astrocyte-like cells, as well as neuroblasts (black), are positioned within the niche. (B) Mild injury interferes with normal signaling downstream of Notch and EphB receptors and promotes intercellular conversion of ependymal cells (left) and non-proliferating astrocyte-like cells (right). Multiple EphB receptors (and possibly EphA4), each expressed in different subsets of cell types, are likely involved in these processes.