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Postnatal neuronal migration in health and disease

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Postnatal neuronal migration modulates neuronal circuit formation and function throughout life and is conserved among species. Pathological conditions activate the generation of neuroblasts in the ventricular-subventricular zone (V-SVZ) and promote their migration towards a lesion. However, the neuroblasts generally terminate their migration before reaching the lesion site unless their intrinsic capacity is modified or the environment is improved. It is important to understand which factors impede neuronal migration for functional recovery of the brain. We highlight similarities and differences in the mechanisms of neuroblast migration under physiological and pathological conditions to provide novel insights into endogenous neuronal regeneration.

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Introduction

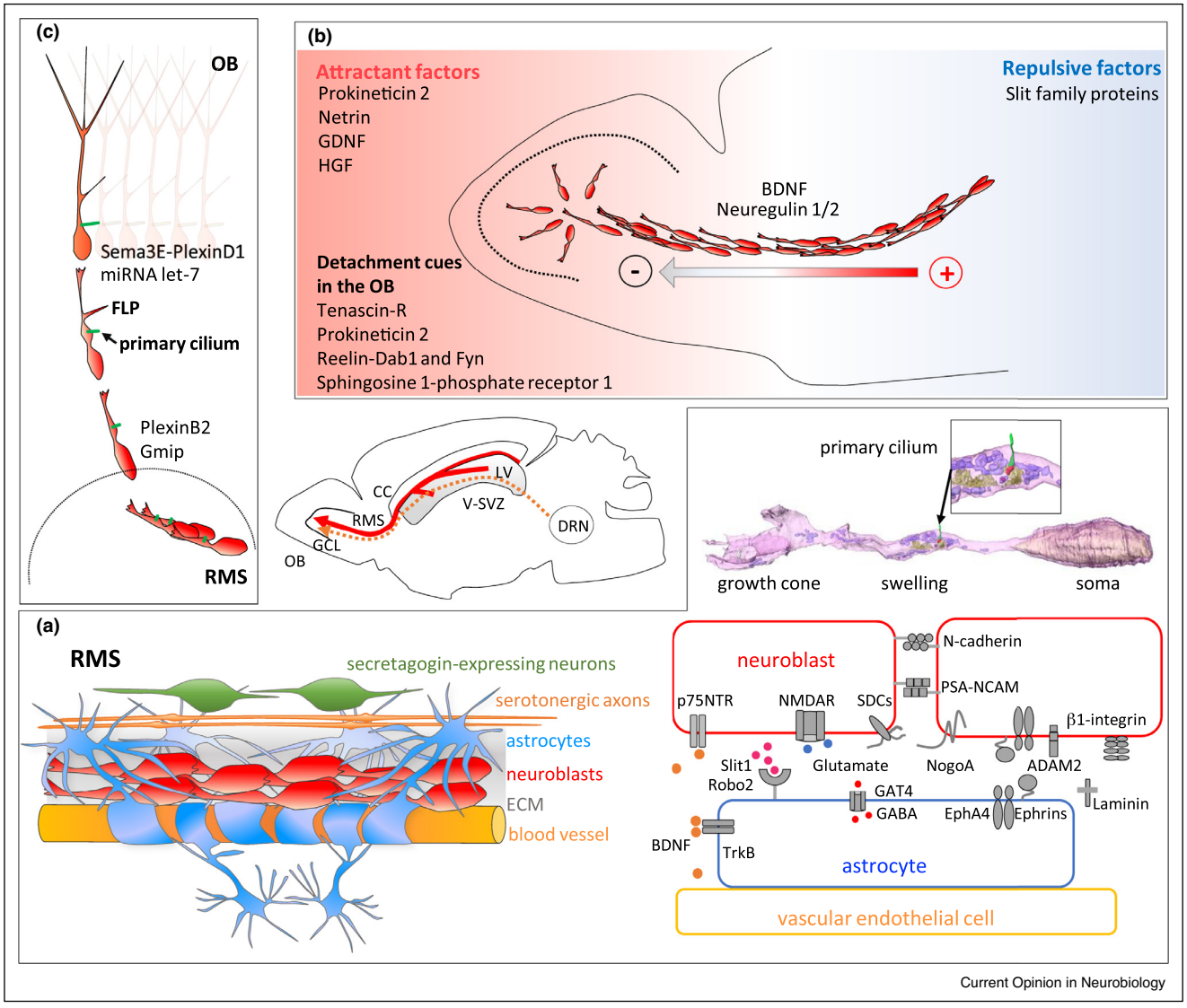
Neurogenesis and neuronal migration are fundamental processes in the organization and function of the central nervous system (CNS). During development, newly generated immature neurons (neuroblasts) migrate from germinal zones toward their final destinations. Efficient neuroblast migration is supported by surrounding scaffold cells, extracellular stimuli, intrinsic transcription and polarized morphology of the neuroblasts. The appropriate spatiotemporal positioning of neurons leads to neuronal circuit formation and, in turn, brain function. After initial neuronal circuits are established, extensive neuronal migration ceases but migration continues postnatally in specific niches to fine tune the network in response to external stimuli.

Since the first report of adult mammalian neurogenesis by Joseph Altman in the 1960s [1] the brain has been perceived as an organ with plasticity and regenerative capacity in various species. In mammals, neurogenesis in the V-SVZ of the lateral ventricles persists into the adult stage by retaining neural stem cells (NSCs) and producing neuroblasts [2]. These neuroblasts form chain-like homophilic associations and tangentially migrate through a meshwork of astrocytic glial tubes along the rostral migratory stream (RMS) toward the olfactory bulb (OB). Neuroblasts detach from the chains after reaching the OB core and migrate radially into the granule cell layer and glomerular layer, where they differentiate into mature olfactory interneurons and acquire functional properties [3–5]. The postnatal neurogenesis and neuroblast migration toward the OB is limited to a specific time window in primates but not in rodents [6]. Importantly, neurogenesis and neuroblast migration are enhanced by brain damage. Upon lesion, V-SVZ NSCs are activated [7] and produce neuroblast chains migrating toward injured sites [8–10]. The understanding of the mechanisms that underlie migration, final positioning, and circuit integration of neuroblasts after injury is still in its infancy. Here we focus on postnatal V-SVZ-derived neuroblast migration under physiological and pathological conditions and discuss the latest advances in the field. We further propose that elucidating the underlying mechanisms of endogenous neurogenesis will facilitate the generation of novel therapeutic approaches for neuronal regeneration and functional recovery.

Migratory mechanisms in normal postnatal brain

In the RMS, neuroblasts directly contact neighboring neuroblasts and astrocytes, and utilize these cells as their migratory scaffolds. Neuroblasts adhere to each other via adherent junction (AJ)-like structures during chain migration. Although the molecular components of AJ-like structures have not been identified, homophilic cell adhesion molecules, such as N-cadherin and PSA-NCAM, have been shown to regulate chain migration of neuroblasts [11,12]. Neuroblast-extracellular matrix (ECM) interaction also affects chain migration. β1-integrin and Nogo-A-Δ20, expressed in neuroblasts, associate with laminin and heparan sulfate proteoglycans, respectively, to promote chain migration [13–15]. The ECM

Figure 1



Mechanisms of postnatal neuroblast migration through the RMS toward the OB in rodents. The diagram in the center shows a sagittal plane of the brain. RMS is shown as red lines. Dorsal raphe nucleus-derived serotonergic axonal projections are shown as an orange dotted line. **((a) Left)** In the RMS, V-SVZ-derived neuroblasts form chains that migrate long distances inside glial tubes. This provides neuroblasts with a critical microenvironment for their oriented migration. Astrocyte endfeet wrap around vasculature to act as a scaffold for chain migration. Serotonergic axons and mature secretagogin neurons also support neuroblast migration in the RMS. Adhesion to ECM molecules modulates cell–cell interaction and motility of neuroblasts. **((a) Right)** During migration, as indicated in the three-dimensional reconstruction image of a neuroblast from serial block-face scanning electron microscopy [27], neuroblasts show unique bipolar morphology. Neuroblasts extend a leading process that forms a growth cone and swelling, assemble a primary cilium, and translocate soma during the migration. **((a) Bottom)** Cellular interactions are facilitated by the combination of molecules shown in the diagram. BDNF is derived from endothelial cells, Slit1 and GABA are from neuroblasts and glutamate is from astrocytes. **(b)** Repulsive factors from the V-SVZ, attractive factors from the OB, and electric currents along the RMS facilitate the directional migration of neuroblasts in the RMS. Secreted factors expressed along the RMS promote neuroblast migration. Upon arrival in the OB, neuroblasts detach from the chains and migrate radially in accordance to the detachment cues in the OB. **(c)** Morphological changes of neuroblasts occur during their radial migration in the OB, from chain detachment until their termination of migration. Molecules recently reported to be involved in this process are indicated. Neuroblasts with an extended primary cilium and an FLP decrease migration speed, terminate migration in the granule cell layer or glomerular layer, and differentiate into interneurons. CC, corpus callosum; DRN, dorsal raphe nucleus; LV, lateral ventricle; V-SVZ, ventricular-subventricular zone; RMS, rostral migratory stream; OB, olfactory bulb; GCL, granule cell layer.

components in the V-SVZ might be affected by choroid plexus-derived OTX2 [16]. In neuroblast-astrocyte interaction, Slit-Robo signaling maintains glial tubes by controlling astrocytic morphology [17]. Moreover, ephrin-EphA4 signaling promotes bundling of neuroblast chains by glial tube-forming astrocytes [18]. Astrocytes in the RMS not only form glial tubes but also their endfeet wrap around vascular endothelial cells and support blood vessel-guided chain migration [19]. Thus, intercellular adhesions and signaling coordinately support long-distance chain migration of neuroblasts in the postnatal RMS (Figure 1a).

For their long journey from the V-SVZ to the OB, the directionality of neuroblast migration in the RMS must be precisely controlled. This is determined by a choroid plexus-derived repulsive Slit [20] and OB-derived attractive factors such as prokineticin 2 [21]. Endogenous electrical currents along the RMS might also be involved in the guidance of neuroblast migration [22]. In addition to these long-range directional cues, brain-derived neurotrophic factor (BDNF) and Neuregulin-1/2, which are expressed in the RMS, also promote neuroblast migration in the RMS. Thus, directionality of migrating neuroblasts in the RMS is determined by a combination of both long-range guidance cues and local factors that promote migration. We will not focus on these molecules, as they have been reviewed previously [23,24] (Figure 1b).

Neuroblast migration is also controlled by mature neurons. Secretagogin-expressing mature neurons produce matrix metalloprotease-2 that remodels the ECM and supports chain migration in the RMS [25]. Serotonergic axonal fibers, originating from the raphe nuclei and extending along the V-SVZ-OB pathway, induce Ca^{2+} influx in neuroblasts and promote their migration [26••]. Serotonergic receptors can be localized to the primary cilium that occasionally makes contact with presynaptic structures [27], raising the possibility that the primary cilium mediates serotonin-controlled neuroblast migration (Figure 1a).

After arriving at the OB, neuroblasts detach from chains and migrate radially as individual cells toward their final destination layers. Reelin promotes neuroblast detachment via Dab1 and Fyn by regulating AJ-like structures, possibly mediated by N-cadherin [28]. Downregulation of sphingosine-1-phosphate receptor 1 also lowers levels of NCAM and β1-integrin in detaching neuroblasts [29]. These findings indicate that extracellular detachment signals decrease intercellular adhesion levels to promote neuroblast detachment. During radial migration in the OB, while PlexinB2 and the RhoGAP protein, Gmip, suppress neuroblast migration [30,31], tenascin-R and Sema3E-PlexinD1 signaling promote radial migration [32,33,34•]. The miRNA, let-7, also promotes radial migration by activating autophagy [35]. Altering migration of neuroblasts affects their final positioning, dendritic patterns, and functions in the OB [31,34•,35], suggesting that precise regulation of the maintenance and termination of neuroblast migration are essential for the formation and functions of postnatal OB circuits (Figure 1c).

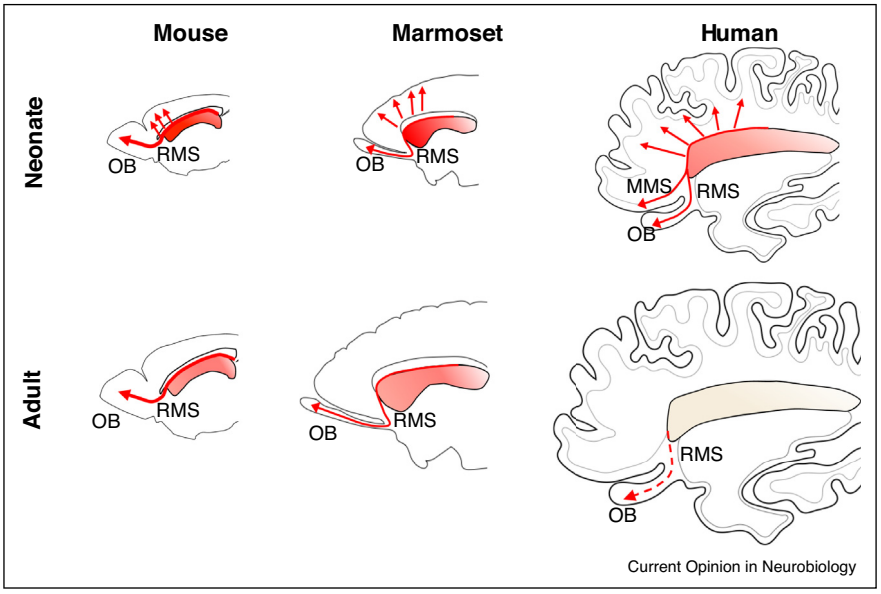
At a single cell level, a neuroblast extends its leading process and then forms a swelling in this process, which is followed by somal translocation. The growth cone of the leading process contains Shootin 1b, which couples F-actin retrograde flow and generates traction force [36]. The swelling harbors activated RhoA signaling, which promotes saltatory movement [31]. Neuroblasts form the filopodium-like lateral protrusion (FLP), a specialized protrusion formed from the proximal leading process during migration termination, to deaccelerate migration [34•]. Moreover, the primary cilium in the swelling changes its direction and subcellular localization, which may reflect changes in the microtubule network during migration [27]. It is possible that these machineries work with other cytoskeletal regulators [37–40] to achieve coordinated saltatory movement of migrating neuroblasts (Figure 1c).

While neuroblast migration in the postnatal brain has been studied most intensively in rodents, it is also observed in primates, including humans. Neonatal common marmosets show unique V-SVZ cytoarchitectures and neuroblast migration toward the OB and cerebral cortex [6,41], similar to those in human infants [42••], indicating that common marmosets are a useful model to understand human V-SVZ neurogenesis and neuroblast migration in the postnatal brain, even outside the RMS-OB system. In humans, neurogenic potential in the V-SVZ is only maintained during the neonatal and infant period and it declines thereafter. Neuroblasts born in the lateral ventricle walls migrate extensively into the OB through the RMS and into the prefrontal cortex through the medial migratory stream (MMS) [43]. Furthermore, periventricular regions in human infants harbor a large number of neuroblasts, a portion of which forms chain-like aggregates that associate with blood vessels or orient radially towards cortical regions such as the cingulate gyrus [42••]. Secretagogin + cells and serotonergic fibers are observed in the human V-SVZ-OB pathway [25,26••]; therefore, some of the mechanisms for postnatal neuroblast migration are likely to be evolutionarily conserved and amenable to the development of new strategies for endogenous neuronal regeneration in the injured human brain (Figure 2).

Migratory mechanisms in injured postnatal brain

Brain injuries cause the loss of cells and trigger various changes in the affected tissue, which positively and negatively influence neuroblast migration. For example,

Figure 2



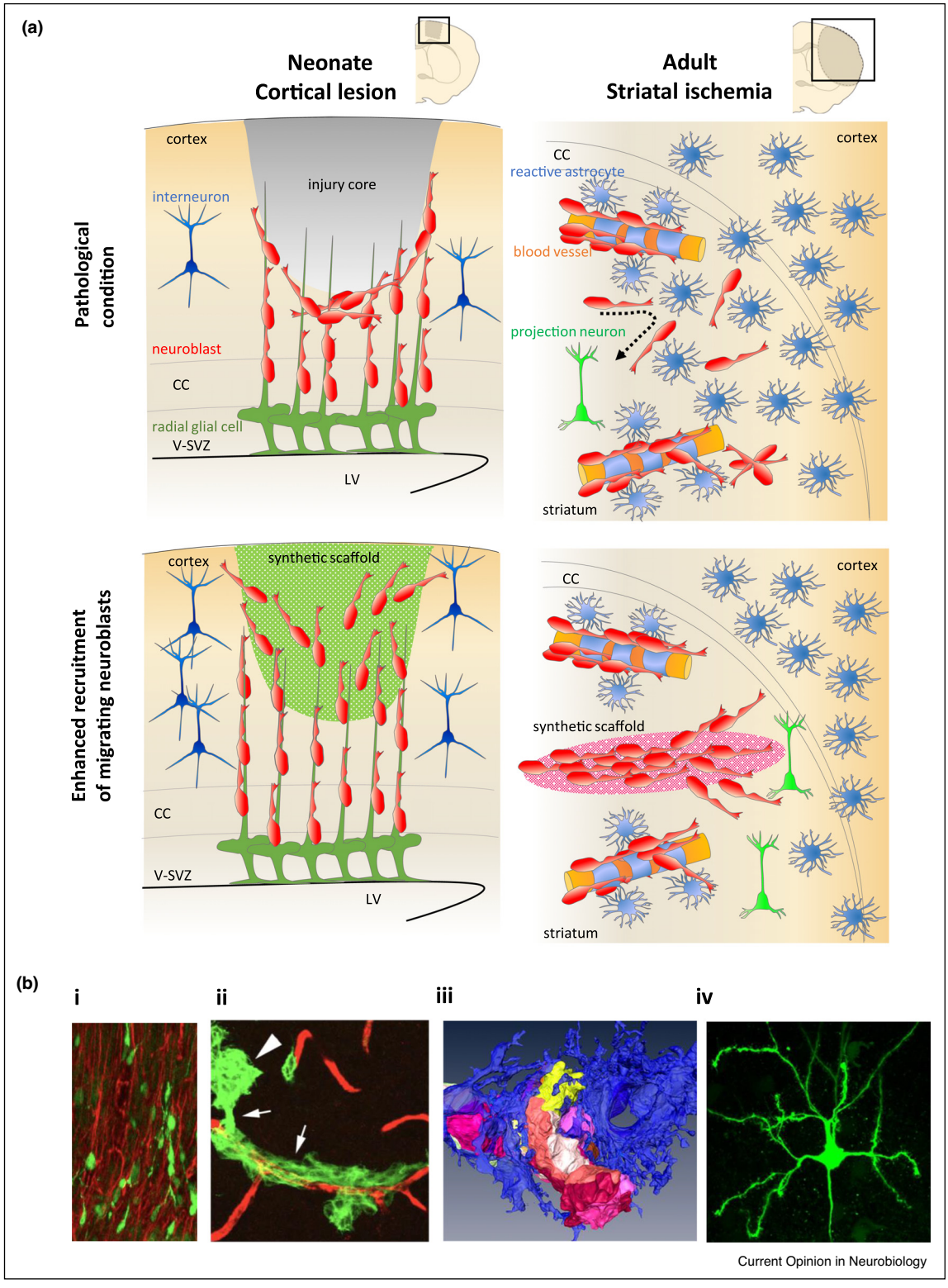
Comparison of neurogenic capacity and neuroblast migratory stream in mice, marmosets and humans. Sagittal views of the brain at the level of the RMS and OB in each species at different ages are illustrated. Neonatal mice have a high level of NSC proliferation in the V-SVZ and newly generated neuroblasts migrating into the OB through the RMS and into the cortex. Adult mice have decreased levels of neurogenesis in the V-SVZ and reduced neuroblast migration into the OB but not the cortex. Neonatal marmosets show active neuroblast migration in the RMS and cortex, while adult marmosets have decreased levels of neurogenesis in the V-SVZ, very low levels of neuroblast migration in the RMS, and no migration towards the cortex. Human neonates have an active pool of NSCs in the V-SVZ and three migrating streams, the RMS, MMS and frontal cortex. In adult human, no or very low levels of neurogenesis in the V-SVZ and neuroblast migration are observed.

while reactive astrocytes have neurotoxic effects and form glial scars [44], inflammation induces secretion of chemoattractants [24] and activation of quiescent NSCs [45], which eventually differentiate into neuroblasts [46].

Under such pathological conditions, V-SVZ-derived neuroblasts migrate toward lesions by using the surrounding scaffold cells and modifying cellular signaling, similar to the migration mode of neuroblasts in the RMS (Figure 3a, b). Neuroblasts express β1-integrin in the ischemic striatum and use chain migration toward the lesion [47•]. Involvement of other adhesive molecules, such as PSA-NCAM and N-cadherin, in forming neuroblast chains in the injured brain is unknown; however, the intrinsic properties of migrating neuroblasts in the RMS are preserved at injury sites. Similarly, the majority of migrating neuroblasts in an injury closely associate with scaffold cells, astrocytes or blood vessels [9,10,48]. Blood vessel-guided neuroblast migration is facilitated by ligand-receptor interaction, such as β1-integrin-expressing neuroblast adherence to laminin-rich blood vessels [47•]. In the injured striatum, BDNF promotes neuroblast migration [49]. Because injury induces expression of BDNF in vascular endothelial cells and TrkB in reactive astrocytes, lesions may recapitulate a permissive environment for neuroblast migration, as in the RMS [19]. Reactive astrocytes enwrap neuroblasts, thereby hampering their migration toward a lesion [50••]. However, migrating neuroblasts express Slit1 and remodel the morphology of Robo2+ astrocytes to facilitate migration, similar to how Slit1+ migrating neuroblasts in the RMS repel Robo2 + astrocytes [17]. Injury also recapitulates the developmental stage of the brain to acquire new scaffolds, including the emergence of radial glial fibers in the neonatal cerebral cortex [51••]. During normal development, radial glial cells are embryonic NSCs that guide radially migrating neuroblasts toward the cortical plate by providing fibers that form a migratory scaffold into the cortical plate [52]. Persisting radial glial fibers in a cortical injury promote migration of neuroblasts by exerting N-cadherin-mediated adhesion along the fibers in the injury [51••], similar to that during corticogenesis. Taken together, it appears that in pathological conditions, migrating neuroblasts use various endogenous scaffolds and coordinated signaling interactions to promote their migration.

Chemokines in the developing cortex act as intracortical or RMS migration cues [53] and are secreted from cells in lesion areas. There are classically known combinations of injury-derived chemokines and interacting neuronal receptors, for example, SDF1-CXCR4, Angiopoietin-1-Tie2, MCP1-CCR2, and CXCL13-CXCR5, which may be involved in changing the direction of neuroblast

Figure 3



Neuroblast migration under pathological conditions and its enhancement by various treatments in the neonatal and adult mouse brain. **(a)** Schematic drawings of a cortical lesion in a neonate (Left) and a stroke model in an adult (Right) are illustrated. The region within the square in each coronal section shown above is magnified below. Dark colored brain regions indicate the injured area. NSCs in the V-SVZ are activated by injury to generate neuroblasts. Neonates have a higher capacity to activate neurogenesis than adults. Injured neonatal brain contains radial glial fibers that support neuroblast migration towards the lesion. However, radial glial fibers disappear before a sufficient number of neuroblasts

migration [23,24]. In addition, the OB-localized chemokine, prokineticin 2 [21], is expressed in activated microglia [54]. In spite of the expression of these attractive factors, most neuroblasts do not reach lesions, indicating the existence of inhibitory mechanisms that impede their migration (Figure 3a).

In the normal brain, the final destination of migrating neuroblasts and the differentiated neuronal subtypes are defined within the organized architecture of the V-SVZ-RMS-OB pathway. Although a lesion site attempts to recapitulate the RMS-like environment, the natural repair mechanisms do not achieve functional recovery of the damaged brain, especially in adults, which have less capacity for post-injury neurogenesis than neonates. Neuroblasts in the injured brain migrate in an inconsistent direction and tend not to reach the lesion site [48,50••,55]; therefore, most neuroblasts fail to achieve correct positioning and cannot survive until they further mature and integrate into the local network. In the striatum, endogenous V-SVZ-derived Slit1+ neuroblasts halt migration in the periphery of an infarcted area in the medial striatum as they decrease Slit1 expression [50••]. However, this can be overcome by augmenting the potential of neuroblast migration; Slit1-overexpressing neuroblasts extend their migration to the lateral striatum and eventually differentiate into both interneurons and projection neurons, which project into the globus pallidus [50••] (Figure 3a). As a consequence, successful integration of newly generated neurons into the local neuronal network and functional recovery are achieved [50••]. It is important to understand how neuroblasts terminate their migration in the pathological environment to further promote neuronal migration and to accomplish correct neuronal localization to reorganize the fractured neuronal network.

Recent studies using human and non-human primates have demonstrated important similarities and differences in the mechanisms of postnatal neuroblast migration between primates and rodents. As described above, during early postnatal human development, neuroblasts migrate extensively throughout the frontal lobe [42••], which suggests the importance of postnatal neuroblast migration in cortical development. Common marmosets [6], as well as piglets [56•], which exhibit similar brain structure and impairment of cortical development under hypoxia as humans, may become useful animal models and provide new insights into neuroblast migration in primates under pathological conditions. Cerebral organoids, generated from induced pluripotent stem cells of patients with neuronal migration disorders, as well as grafting of human cells into the rodent brain, will further provide precise mechanisms of human neuroblast migration [57•].

Biomaterials for promoting neuronal migration

For migration in injured areas, neuroblasts take advantage of endogenous scaffolds, such as blood vessels and radial glial fibers. However, these scaffolds are insufficient for continuous neuroblast migration and regeneration. The branched network morphology and low density of blood vessels are not optimal for efficient scaffolding of neuroblast migration. Radial glial fibers gradually decrease after birth and do not support neuroblast migration into the cortex in the late postnatal stage. Therefore, neuroblasts need better scaffolds to continuously migrate towards a lesion. Using biomaterials that mimic the structure and function of endogenous scaffolds is a promising approach because they enhance cell migration with the addition of cell adhesion molecules or cytokines, which remodel cytoskeletal architecture [58].

Implantation of graphene functionalized scaffolds [59] and self-assembling peptides containing BDNF and Tenascin-C enhance V-SVZ-derived neuroblast migration [60,61]. Furthermore, biomaterials applied to the injured brain can enhance functional brain repair. Blood vessel mimetic scaffolds, consisting of laminin-containing porous sponge, have been developed [62]. Furthermore, as a less invasive method, injectable hydrogel containing laminin can promote adult V-SVZ-derived neuroblasts to migrate toward a lesion [47•]. N-cadherin-Fc-conjugated porous sponge takes over the role of radial glial fibers and promotes neuroblast migration toward a cortical lesion with subsequent maturation into interneurons in the superficial layers, which leads to gait improvement [51••]. Applications of biomaterial containing vascular endothelial growth factor promotes vascularization in the injured area [63] and rewiring of neuronal connections to the local tissues with behavioral improvements [64]. Delivery of electric current to the brain in combination with these scaffolds may improve the directionality of neuroblast migration in the injured brain [65•,66]. These

(Figure 3 Legend Continued) reaches the lesion. In the post-stroke adult brain, neuroblasts migrate in chains through reactive astrocytes using blood vessels as a scaffold. Extrinsic factors secreted from surrounding cells in injured area and cell–cell interactions promote neuroblast migration. Neuroblast migration in the injured striatum is unstable and most do not reach the lesion. Manipulations of the migratory mechanisms by altering the environment using synthetic scaffolds or intrinsic cellular capacity improve neuroblast migration and neuronal regeneration. After migration termination, the neuroblasts differentiate into mature neurons in the vicinity of the injury core, which contributes to functional recovery. **(b)** Representative images of migrating neuroblasts under pathological conditions in mice. In neonatal injured brain [51••], neuroblasts (DCX + cells in green) migrate along radial glial fibers (Nestin + in red) toward a cortical lesion (i). In an adult stroke model, chain-forming neuroblasts migrate along blood vessels (arrows), while some of the neuroblasts form spherical clusters at a distance from the vessels (arrowhead) [9] (ii). Neuroblasts (red) in the chain are enwrapped by reactive astrocytes (blue) [50••] (iii). Slit1 overexpression results in long distance migration of neuroblasts and differentiation of the cells into projection neurons (DARPP32+) (iv).

studies demonstrate that biomaterials enhance functional recovery of the brain by fulfilling a scaffold role, providing a concentrated source of functional molecules and defining the migratory route (Figure 3a,b).

Conclusions

Neuroblast migration in physiological and pathological conditions share similarities, yet the extent of migration and appropriate targeting is hindered in the latter. The mammalian brain under pathological conditions is potentially more plastic than we had previously believed and the microenvironment can be remodeled to promote migrating neuroblasts. We need to better comprehend the contribution of cells and environmental factors in the injury site to the series of processes that underlie neuroblast migration to regeneration, for example, morphological changes in migrating neuroblasts, inhibitory mechanisms of neuroblast migration, and neuronal fate decisions and maturation processes. It is also important to understand the extent and underlying mechanisms of CNS regeneration in other species, such as the axolotl, which have mechanisms that sense neuronal subtype loss in injury [67], and whether higher organisms can be endowed with such mechanisms. Analyzing the interaction between neuroblasts and their microenvironment using brain organoid [57•] and primate systems [6] may provide a better model of human neuroblast migration to represent mechanisms of long-distance migration. The development of novel therapeutic strategies will be achieved once the key factors of neuroblast migration during CNS repair have been deciphered.

Conflict of interest statement

Nothing declared.

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