Editorial

Stem Cell INVESTIGATION

Leptomeninges: a novel stem cell niche with neurogenic potential

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The meninges are composed of three membranous layers referred to as the dura mater, arachnoid mater, and pia mater. The arachnoid mater and pia mater are connected together and form the leptomeninges. The meninges not only protect the central nervous system (CNS), including the brain and spinal cord, directly with their thick outer layers but also indirectly by cushioning through the cerebrospinal fluid filled in the subarachnoid space. In addition, a previous study demonstrated that removing the meninges causes impaired cortical development (1). This suggests that the meninges have functions other than protection. In support of this idea, it is reported that the meninges modulate cortical neuron generation during early brain development by producing trophic factors such as retinoic acid (2). Thus, it is likely that they play pivotal roles in cortical neurogenesis by regulating embryonic neural stem/progenitor cells (NSPCs) (3).

In addition to these roles and effects, increasing evidence now shows that the meninges themselves function as a stem cell niche. Bifari *et al.* first reported that the leptomeninges in developing mouse brain express the NSPC marker nestin and that nestin$^+$ cells isolated from the leptomeninges exhibited activities of NSPCs, which differentiate into neurons *in vivo* and *in vitro* (4). We later showed that the leptomeninges isolated from intact brain regions in adult mice lack stem cell potential (5). These findings showed that leptomeningeal NSPCs have potential to contribute to cortical neurogenesis during early developmental stages.

Using adult mice following ischemic stroke, we previously showed that nestin$^+$ ischemia-induced NSPCs (iNSPCs) were present in the leptomeninges of ischemic areas, and they were not observed in the leptomeninges of nonischemic areas (5). Leptomeningeal cells isolated from ischemic areas produce neurosphere-like cell clusters that give rise to neural cells, including neurons (5). Furthermore, we showed that labeled leptomeningeal cells from ischemic areas migrated into post-stroke areas of the cortex and that they differentiated into doublecortin (DCX)$^+$ immature neuronal cells (6). These findings indicate that under pathological conditions, such as after ischemic stroke, leptomeningeal iNSPCs can contribute to brain repair through cortical neurogenesis.

The leptomeninges are histologically continuous with the cortical parenchyma along the blood vessels and are located at a perivascular niche as vascular pericytes (7). We showed that leptomeningeal nestin$^+$ cells spread into the cortical parenchyma, localized near CD31$^+$ endothelial cells, and expressed pericytic makers such as PDGFRβ and NG2 (5). Although the functions of pericytes remain unclear, it has been well-documented that pericytes in various organs, including the CNS, have multipotent stem cell activity (8). However, using mice at different developmental stages, including embryonic, postnatal, and adult, we recently showed that brain pericytes gradually decreased their stemness during the postnatal period and lost it by adulthood (9). Therefore, it is likely that adult brain pericytes have the features of somatic cells rather than those of tissue-committed stem cells. However, reprogramming has been reported to cause adult brain pericytes to become non-pericytic lineages, such as neuronal

lineages (10). In support of this notion, we showed that adult brain pericytes, which do not possess stem cell activity under normal conditions, reacquired stemness in response to ischemia, presumably through cellular reprogramming by mesenchymal–epithelial transition (11,12). We also showed that PDGFRβ$^+$ cells isolated from ischemic areas, including the leptomeninges, have a multipotent stem cell activity that gives rise to neuronal cells (11,12). Therefore, we proposed that brain pericytes localized along the leptomeninges to cortical parenchyma are likely the origin of leptomeningeal stem cells.

Very recently, Bifari *et al.* reported that the leptomeninges in the neonatal brain harbor radial glia-like cells resembling NSPCs in the subventricular zone (13). In addition, they showed that leptomeningeal radial glia-like neural progenitors migrate from the leptomeninges to the cortex and differentiate into functionally integrated cortical neurons. These findings were consistent with those of our previous report that showed that cortical neurons originate in part from leptomeningeal NSPCs (6). However, leptomeningeal radial glia-like neural progenitors are likely neuronal progenitors rather than NSPCs because they differentiated into neuronal lineages expressing HuC/D, DCX, NeuN, and Stab2, but not into astrocyte and oligodendrocyte lineages. Furthermore, using genetic mapping with PDGFRβ through Cre-loxP system, a technique to selectively label leptomeningeal cells, and single-cell transcriptomics, Bifari *et al.* concluded that cortical neurons are in part derived from PDGFRβ$^+$ radial glia-like neural progenitors in the leptomeninges (13). Of note, using single-cell transcriptomics, they also showed that leptomeningeal PDGFRβ$^+$ cells generate various types of clusters that exhibited features of pericytic/fibroblastic, endothelial, and microglial lineages in addition to radial glia-like lineages. However, we recently showed that PDGFRβ$^+$ pericytes isolated from post-stroke areas, including the leptomeninges, exhibited multipotent stem cell activity and that they give rise to not only neural (e.g., neurons) but also vascular lineages (e.g., endothelial cells and microglia) (11,12). Thus, it is possible that such various phenotypes exhibited by PDGFRβ$^+$ leptomeningeal cells are due to their original multipotency. Previously, we also showed that nestin$^+$/NG2$^+$/PDGFRβ$^+$ iNSPCs from ischemic areas, including the leptomeninges, which likely originated from brain multipotent pericytes, expressed a mesenchymal marker vimentin (5,6). However, vimentin is also expressed in radial glia-like cells (14). Although the relationships between pericytes, glia, and NSPCs remain unclear (15), Birbrair *et al.* divided multipotent pericytes into two subtypes (type-1 and type-2 pericytes). They further demonstrated that nestin$^+$/NG2$^+$/PDGFRβ$^+$ type-2 pericytes have the potential to differentiate into neural lineages (16). Of interest, type-2 pericytes have traits resembling neural progenitors that exhibit properties of NG2-glia (17). Therefore, it is possible that we merely look at subsets of the same PDGFRβ$^+$ leptomeningeal cells during different stages (e.g., neonatal *vs.* adult) and/or under different conditions (e.g., normal *vs.* pathological).

The precise traits of PDGFRβ$^+$ leptomeningeal cells should be clarified in further investigations. However, accumulating evidence shows that the leptomeninges that cover the entire CNS, including the brain (4-6,13,18,19) and spinal cord (20), harbor stem cell-like populations that differentiate into neuronal cells. The leptomeningeal stem/progenitor cells were observed not only during early development under normal conditions (4,13,18) but also during adulthood under pathological conditions (5,6,19,20). Thus, the leptomeninges should become a new target for treating CNS developmental disorders and diseases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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