Neural stem cells after brain injury: do they originate developmentally from neural tube, neural crest, or both?

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Abstract

Although previous studies in the field of NSPC biology have focused on neuroepithelial cells that originate from the neural tube, our recent studies demonstrated that ischemia-induced NSPCs (iNSPCs) are induced in stroke-affected areas and originate, at least in part, from brain pericytes residing near blood vessels that are distributed from the leptomeninges to the cortex. Because brain pericytes, including the leptomeninges, are neural crest derivatives and iNSPCs express various neural crest markers, these findings provide a novel concept that neural crest-derived cells can play a crucial role in central nervous system (CNS) as NSPCs after brain injury.

Self-renewing multi-potential neural stem/progenitor cells (NSPCs) can be isolated from both developing and adult central nervous system (CNS). Kalyani *et al.* isolated E10.5 rat neuroepithelial cells termed *neuroepithelial stem cells* from the caudal neural tube at early stages of development.[1] Neuroepithelial cells constitute the major class of NSPCs and give rise to radial glia, which can self-renew or generate neurons directly.[2] Because radial glia can develop into various types of NSPCs, including subventricular zone astrocytes,[3] ependymal cells,[4] and oligodendrocyte precursor cells,[5] in an adult brain,[6] previous studies in the field of NSPC biology have focused on neuroepithelial cells that originate from the neural tube.

However, after brain injury, such as a cortical infarction, we demonstrated that ischemia-induced NSPCs (iNSPCs) are induced in stroke-affected areas[7-9] and originate, at least in part, from brain pericytes residing near blood vessels that are distributed from the leptomeninges to the cortex.[10] iNSPCs do not have completely identical characteristics to previously proposed NSPCs, such as subventricular zone astrocytes, ependymal cells, oligodendrocyte precursor cells, or reactive astrocytes.[10] However, iNSPCs expressing NSPC markers, such as nestin, formed neurosphere-like cell clusters with self-renewal activity and differentiated into electrophysiologically functional neurons, astrocytes, and myelin-producing oligodendrocytes,[7-10] indicating that they have stemness capacity similar to other types of NSPCs. Pericytes with multipotent progenitor activity have been identified in various organs[11] as well as in CNS.[12] Although Dore-Duffy *et al*. showed that pericyte-derived NSPCs can be isolated from the CNS of non-injured animals,[12] we hardly obtained iNSPCs from the nonischemic CNS.[7-10] Consistent with these findings, only pericytes located within the ischemic cortex/pia mater but not within the nonischemic cortex/pia mater expressed NSPC markers such as nestin and Sox2, in addition to pericyte markers such as NG2 and PDGFRβ.[10] Furthermore, iNSPCs expressed several pluripotent/undifferentiated cell markers, including Sox2, Klf4, c-myc, and Nanog, [7,10] as well as subventricular zone-derived NSPCs.[13] However, expression of various pluripotent/undifferentiated cell markers was not observed in the cortex/pia mater of non-injured animals.[7,10] These results suggest that brain injury/ischemia may increase the stemness of CNS pericytes through cell reprogramming, although we are still unaware of the signaling and/or factors essential for their induction. It was interesting to note in our recent report[10] that brain pericytes, including the leptomeninges, are neural crest derivatives[14] and iNSPCs express various neural crest markers,[15] such as Sox9, Sox10, Snail, Slug, and Twist as well as pericyte markers[10] These findings provide a novel concept that neural crest-derived cells can play a crucial role in CNS as NSPCs after brain injury. The neural crest was initially identified as a group of cells localized between the neural tube and the epidermis in the vertebrate embryo. These cells give rise to most of the peripheral nervous system and to several non-neural cell types, including smooth muscle cells, bone, cartilage, and connective tissue. Furthermore, it is known that that the neural crest has stem cell potential (neural crest-derived stem cells)[16] and that they differentiate into a variety of cell types, including neurons, glia, and smooth muscle cells.[17] These results may provide a solution to the previous puzzle that brain NSPCs can occasionally give rise to other cell types such as muscle.[12,18,19] Moreover, this result may explain the recent notion that Schwann cells, which have neural crest origin, are induced in the injured CNS.[20]

The precise source, lineage, and traits of NSPCs, which contribute to CNS repair after brain injury warrants further investigation. However, a recent study by Laranjeira et al. demonstrated that using genetic fate mapping with Sox10-marked neural crest cells gave rise to neurons and glial lineages *in vivo* in response to injury in the enteric nervous system, although there was no evidence that these cells participated in neurogenesis under steady-state conditions.[21] Based on experiments of lineage labeling of pericytes and/or neural crests by genetic means, the precise origin of iNSPCs can be clarified in future. Certainly, there are additional issues and questions to be addressed. However, researchers currently using NSPCs should consider the possibility that not only the neural tube but also the neural crest-derived NSPCs contribute to neurogenesis in CNS, particularly under pathological conditions.[10,21]

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