White matter responses are increasingly recognized as a vital part of stroke pathophysiology. Acute stroke therapies cannot be successful without also protecting white matter. And any attempt at promoting stroke recovery cannot be accomplished without restoring white matter connectivity as well. Hence, a full understanding of white matter biology is essential in stroke research. Three recent articles provide powerful insights into how oligodendrocyte precursor cells (OPCs) remain functional and contribute to white matter homeostasis, even in the adult central nervous system.

Hughes et al (Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. Nature Neuroscience. 2013;16:669–676) examined the mechanisms by which OPCs maintain their density in the adult brain. To observe OPCs in adult brains in vivo, the authors developed a line of transgenic mice that express a membrane-anchored form of enhanced green fluorescent protein under the control of the NG2 promoter. The chondroitin sulfate proteoglycan NG2 can be used as a marker for OPCs, and using these transgenic mice, the authors performed in vivo 2-photon imaging of OPCs in the mouse somatosensory cortex. Their analysis showed that NG2-positive OPCs extended motile filopodia and reorganized their processes, indicating that OPCs actively survey their local environment. In addition, OPC’s position was not fixed, and in response to loss of OPCs through death or differentiation, neighboring OPCs migrate and proliferate to preserve their density in adult brain. Finally, long-term imaging revealed that some OPCs could directly differentiate into oligodendrocytes without proliferation. Taken together, adult OPCs may maintain a constant density in the central nervous system to participate in regeneration and repair of oligodendrocyte throughout life.

OPC differentiation is an indispensable requirement for oligodendrogenesis even in the adult brain. But the precise mechanisms as to what factor(s) regulate the cell differentiation still remain unclear. Mei et al (Stage-specific deletion of Olig2 conveys opposing functions on differentiation and maturation of oligodendrocytes. J Neurosci. 2013;33:8454–8462) suggest that a basic helix–loop–helix transcription factor Olig2 has a stage-specific regulatory role for OPC differentiation. The authors developed 2 lines of transgenic mice: (1) CNP-Cre;Olig2flox/flox that shows ablation of Olig2 in only OPCs and (2) PLP-Cre;ER;Olig2flox/flox in which the Olig2 gene is conditionally ablated in immature (eg, newly generated) oligodendrocytes. Using these 2 kinds of transgenic mice, this study revealed the stage-specific opposite functions of Olig2 that this protein in OPCs may promote the differentiation of OPCs, whereas Olig2 in newly generated oligodendrocytes inhibits the maturation process into myelinated oligodendrocytes. Olig1 is a highly homologous transcription factor to Olig2, and this factor may contribute to the stage-specific roles of Olig2. Olig1 expression was reduced on Olig2 deletion in OPCs but was increased when Olig2 was deleted in immature oligodendrocytes. Interestingly, Olig1 overexpression in Olig2-deficient OPCs rescued the differentiation phenotype in vitro. Taken together, Olig2 may act with Olig1 as an activator for OPC differentiation at the early stage, but after the appropriate number of newly generated oligodendrocytes is emerged, this same protein may work as a repressor of myelin gene expression.

Finally, there may be crosstalk between stem/progenitor cell biology in oligodendrogial and neuronal systems. These pathways may potentially provide overlapping mechanisms in both white and gray matter remodeling during and after stroke. A recent study by Rafalski et al (Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. Nat Cell Biol. 2013;15:614–624) described a novel mechanism underlying OPC generation from neural stem cells (NSCs). The authors examined the roles of SIRT1, one of the sirtuin family (SIRTs). SIRTs are NAD+-dependent deacetylases, which connect stress stimuli and energy metabolism to lysine deacetylation, and because SIRT1 is upregulated in a mouse model of multiple sclerosis in regions of inflammation, the SIRT1 protein was hypothesized to participate in the regulation of adult oligodendrocytes. The authors prepared a line of transgenic mice in which exon 4 of the Sirt1 gene is flanked by loxP sites with Nestin-Cre-ER. This NestinCreER,Sirt1flox/flox mouse line showed the specific deletion of the SIRT1 protein in adult NSCs when mice were injected with tamoxifen. SIRT1 inactivation in NSCs increased the production of OPCs in the adult brain, indicating that SIRT1 proteins may regulate oligodendrogenesis from NSCs. In addition, using mouse models of demyelinating injuries, such as lysolecithin-induced demyelination of the corpus callosum or chronic experimental autoimmune encephalomyelitis, the authors demonstrated that SIRT1 inactivation in NSCs enhanced the rate of remyelination after the injury. Finally, microarray, quantitative real-time polymerase chain reaction, and Western blot analyses revealed that platelet-derived growth factor receptor α and its downstream Akt and p38 mitogen-activated protein kinase signaling might participate in the oligodendrocyte expansion after SIRT1 inactivation in NSCs.

Oligodendrocytes comprise the major cell type for white matter function, and in the adult brain, OPCs may serve as the central stem/progenitor cell system for sustaining white matter homeostasis during and after stroke. Emerging new ideas that define the biology of OPC renewal may eventually lead us to new stroke therapeutics for acute protection and recovery.
Stroke Literature Synopses: Basic Science

*Stroke*. 2013;44:e89; originally published online July 9, 2013; doi: 10.1161/STROKEAHA.113.002244

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/8/e89

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/