Cerebral white matter is vulnerable to ischemic insults, and aging is a major risk factor to exacerbate white matter damage in stroke. Three recent studies provide insights into potential therapeutic approaches that may be used to ameliorate age-related white matter responses after stroke.

**Sozmen et al (Nogo receptor blockade overcomes remyelination failure after white matter stroke and stimulates functional recovery in aged mice. Proc Natl Acad Sci USA. 2016;113:E8453–E8462. doi: 10.1073/pnas.1615322113)** investigated the roles of Nogo/NgR1 signaling in remyelination after white matter stroke. This study used a mouse model of white matter stroke by injecting L-Nio into the corpus callosum region. L-Nio is a nonselective inhibitor of all nitric oxide synthase isoforms, and L-Nio injection induces focal ischemia by vasoconstriction. With this model, the authors first demonstrated that oligodendrocyte precursor cells proliferated in the damaged white matter region. However, those oligodendrocyte precursor cells failed to mature into oligodendrocytes but instead differentiated toward astrocytes. Because Nogo/NgR1 signaling regulates oligodendrocyte precursor cell differentiation, the authors then examined the expression levels of NgR1-binding molecules after white matter stroke in both young (>2.5 months old) and aged (24 months old) mice by assessing their mRNA levels in subcortical white matter region. In both young and aged mice, white matter stroke increased the levels of NgR1 ligands and decreased the ones of endogenous NgR1 inhibitors, but those changes were more significant in aged mice. Finally, to study the roles of NgR1 ligands in white matter repair, the authors used NgR(OMNI)-Fc, an engineered soluble hybrid of NgR1/NgR2 that binds and neutralizes several NgR1 ligands. Even in aged mice, animals that receive NgR(OMNI)-Fc exhibited a greater number of mature oligodendrocytes along with enhanced motor recovery under the conditions of white matter stroke. These data demonstrated the negative effects of NgR1 ligands in white matter repair after injury, but the NgR1 actions can be neutralized by clinically relevant engineered compounds.

Besides axonal/oligodendrocyte damage, aging may worsen the glymphatic dysfunction after white matter injury. **Venkat et al (White matter damage and glymphatic dysfunction in a model of vascular dementia in rats with no prior vascular pathologies. Neurobiol Aging. 2017;50:96–106. doi: 10.1016/j.neurobiolaging.2016.11.002)** compared young rats (male, 3–4 months old) with retired breeder rats (male, 6–8 months old), focusing on white matter dysfunction after injury. In this study, rats were injected cholesterol crystals into cerebral blood vessels via internal carotid artery, as a rat model of multiple microinfarction that shows similar pathologies observed in vascular dementia patients. As expected, retired breeder rats exhibited worsened white matter dysfunction after cholesterol crystal injection, such as decreased myelin thickness/axon density and cognitive decline. The authors also investigated the glymphatic system, which is an effective waste clearance pathway to remove metabolic wastes and neurotoxins from the brain parenchyma. The retired breeders with multiple microinfarctions showed a decreased and delayed cerebrospinal fluid penetration and clearance via paravascular pathways, which was accompanied with dilated perivascular spaces and decreased expressions of a water-channel AQP4 (aquaporin 4). Therefore, AQP4-dependent glymphatic dysfunction in aged brains may be associated with worse outcomes after white matter damage, raising the possibility that AQP4-related pathways may be a target for treating white matter injury in aged brains after cerebrovascular injury.

mouse optic nerve, which is a pure and fully myelinated white matter tract, using 3-dimensional electron microscopy. Three-dimensional reconstruction blocks from serial 3-dimensional images demonstrated significant differences in the axonal structure of optic nerves between young (1-month-old) and aged (12-month-old) mice. Aged optic nerves showed a smaller number of axons, but those axons exhibited larger diameters wrapped with thicker myelin sheaths. In addition, although the authors’ previous reports confirmed that aged optic nerve tracts did not have any conduction delay, the 3-dimensional electron microscopic analysis revealed that aging increased nodal length and internodal distances in mouse optic nerves. Besides architectural organization changes in myelinated axons, aged optic nerves had fewer mitochondria, whose shape was instead longer and larger. These changes in mitochondria in aged optic nerves led to an increase in oxidative stress markers and less ATP level, which may result in making axons more vulnerable to a metabolic attack, such as ischemic stress.

Taken together, these three recent studies support age-dependent architectural and functional changes in white matter. To find a way to reverse or ameliorate these deleterious changes in a clinically relevant manner, further studies are warranted to understand how these mechanisms operate in the context of white matter damage and repair after stroke.
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