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Review

Mechanisms of cell–cell interaction in oligodendrogenesis and remyelination after stroke

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ABSTRACT

White matter damage is a clinically important aspect of several central nervous system diseases, including stroke. Cerebral white matter primarily consists of axonal bundles ensheathed with myelin secreted by mature oligodendrocytes, which play an important role in neurotransmission between different areas of gray matter. During the acute phase of stroke, damage to oligodendrocytes leads to white matter dysfunction through the loss of myelin. On the contrary, during the chronic phase, white matter components promote an environment, which is favorable for neural repair, vascular remodeling, and remyelination. For effective remyelination to take place, oligodendrocyte precursor cells (OPCs) play critical roles by proliferating and differentiating into mature oligodendrocytes, which help to decrease the burden of axonal injury. Notably, other types of cells contribute to these OPC responses under the ischemic conditions. This mini-review summarizes the non-cell autonomous mechanisms in oligodendrogenesis and remyelination after white matter damage, focusing on how OPCs receive support from their neighboring cells.

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Contents

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1. Introduction

From the newborn period to adulthood, stroke is a serious disease without a cure in most cases. Stroke in newborns can lead to cerebral palsy (CP), cognitive deficits, and serious neurological dysfunctions which affect the entire lifespan of the patient (Pierrat et al., 2005). In adults, stroke remains the leading cause of disability around the world (Demaerschalk et al., 2010). In developing potential therapies for stroke, protection and regeneration of neurons have been major goals in clinical care and in neuroscience research. It is now well known that targeting neurons alone is inadequate therapy for optimizing the likelihood of a good outcome, and that it is essential to support the entire neurovascular unit, consisting of neurons, glia, endothelial cells, and pericytes. It is apparent that in hypoxic–ischemic injury, not only is grey matter injured but white matter is also damaged. Hence, white matter repair is also important in the process of functional neurological recovery. In recent years, there has been an increasing number of studies concerning white matter injury in stroke, and a greater understanding of the importance of white matter involvement in this disease. However, much is still unknown regarding the physiology of white matter injury and repair in stroke, and a better understanding of these processes is needed in order to develop therapeutic interventions to treat white matter injury.

Oligodendrocyte precursor cells (OPCs) are immature forms of oligodendrocytes, the key source of myelin production, and thus are essential for repair of damaged white matter after ischemic injury. It is reported that the white matter of animal models and human patients with hypoxia/ischemia (HI)-induced brain injury contains an increased number of OPCs (Levine, 1994; Mandai et al., 1997), possibly an adaptive response that increases remyelination. Additionally, enhanced proliferation, migration and differentiation of OPCs are seen in the peri-infarct region (Gregersen et al., 2001; Mandai et al., 1997). Given the important role that OPCs play in remyelination and white matter injury repair, understanding OPCs characteristics, including mechanisms involved in proliferation, migration, and differentiation, is essential in exploring new evidence involving white matter protection and repair.

When hypoxic and/or ischemic injury is introduced, cells within the neurovascular unit react to the insult and these reactions may make the microenvironment more or less favorable for neuronal repair, vascular remodeling, and remyelination. For example, activated microglia and macrophages participate in multiple stages of repair. Macrophages clear up the debris after demyelination and improve efficacy of remyelination thereafter (Copelman et al., 2001). In addition to this phagocytic activity, there is some evidence that macrophages benefit remyelination by secreting a wide variety of trophic factors. In a model of induced demyelination, mice with reduced expression of macrophages have reduced expression of insulin-like growth factor 1 (IGF-1) and transforming growth factor beta 1 (TGFβ1), as well as delayed recruitment of OPCs that express the platelet-derived growth factor receptor alpha (PDGFRα) (Kotter et al., 2005). Recent research has shown that microglia/macrophages exhibit two distinct phenotypes after brain injury—as, pro-inflammatory M1 cells and anti-inflammatory/immunoregulatory M2 cells. In a demyelination model, OPC differentiation was enhanced *in vitro* with M2 cell conditioned media and impaired *in vivo* after intra-lesional M2 cell depletion (Miron et al., 2013), suggesting that "M2 cell" promotes OPC differentiation. Macrophages and microglia play important roles in both OPC proliferation and differentiation. Other cells, such as astrocytes, neurons, and endothelial cells, also participate in different aspects of repair. Understanding cellular interactions during and after stroke may pave the way to find