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Review

The axon–glia unit in white matter stroke: Mechanisms of damage and recovery

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ABSTRACT

Approximately one quarter of all strokes in humans occur in white matter, and the progressive nature of white matter lesions often results in severe physical and mental disability. Unlike cortical grey matter stroke, the pathology of white matter stroke revolves around disrupted connectivity and injured axons and glial cells, rather than neuronal cell bodies. Consequently, the mechanisms behind ischemic damage to white matter elements, the regenerative responses of glial cells and their signaling pathways, all differ significantly from those in grey matter. Development of effective therapies for white matter stroke would require an enhanced understanding of the complex cellular and molecular interactions within the white matter, leading to the identification of new therapeutic targets. This review will address the unique properties of the axon–glia unit during white matter stroke, describe the challenging process of promoting effective white matter repair, and discuss recently-identified signaling pathways which may hold potential targets for repair in this disease.

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Abbreviations: WMS, white matter stroke; OPC, oligodendrocyte progenitor cells

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1. Introduction

Small vessel infarcts affecting brain white matter are an important clinical problem, accounting for up to 25% of all strokes (Arboix and Marti-Vilalta, 2009; Roger et al., 2012; Schneider et al., 2004). This percentage may grow in upcoming years due to the increasing prevalence of risk factors associated with small vessel disease, such as type II diabetes and metabolic syndrome (Bokura et al., 2008; Del Bene et al., 2013; Gouw et al., 2008). Many promising neuroprotective therapies for stroke failed the transition from animal studies to clinical trials, and a major reason for these failures may be the almost exclusive focus of preclinical studies on the neuroprotection of cerebral gray matter, with little attention to white matter tracts (Gladstone et al., 2002). A probable contributing factor is the predominant use of rodents in preclinical studies, whose white matter comprises only ~14% of total brain volume. Since white matter makes up to 50% of the volume in human brains, it is likely that the data from rodent studies misrepresents the relevance of white matter in human brain pathology (Matute, 2011; Zhang and Sejnowski, 2000). Although ischemic injuries in gray and white matter share some common characteristics, there are unique properties of stroke in white matter that are derived from the white matter elements: the axons, the oligodendrocytes that enwrap them in myelin, and fibrous astrocytes which interact with the former two. These, alongside microglia, progenitor cells and vasculature, form an intricate environment and a delicate homeostasis that is highly vulnerable to ischemic damage (Hamner et al., 2011; Matute et al., 2001; Matute, 2011; Pantoni et al., 1996; Stirling and Stys, 2010). Development of effective therapeutic strategies and identification of new targets for the treatment of white matter stroke (WMS) would require an enhanced understanding of the complex cellular and molecular architecture of white matter components. This article will review key mechanisms underlying the white matter response to ischemic WMS with focus on the axon–glia functional unit during stroke recovery.

2. The unique structure and function of brain white matter

The white matter is comprised primarily of axons and glial cells, and is devoid of neuronal cell bodies or their dendrites. Bundles of axons are topographically organized in white matter so that axons originating from specific regions form projections which occupy distinct parts of the white matter (Filley, 2010; Schmahmann et al., 2008). These tracts of axons enable rapid communication between non-adjacent brain regions as well as between peripheral and central areas.

The majority of white matter axons are enwrapped by oligodendrocytes which form segments of myelin sheaths around the axons. Myelin segments facilitate fast saltatory propagation of action potentials, and segregate the axonal membrane into defined regions: the *node* of Ranvier, where clusters of Na^+ channels "propel" the action potential along the axon (Huxley and Stampfli, 1949; Waxman and Swadlow, 1977), *paranode*, K^+ channel-rich *juxtaparanode*, and *internode* (Rios et al., 2003; Susuki and Rasband, 2008).

The lack of neuronal cell bodies and dendrites means there are no "classical" synapses in the white matter, but recent work demonstrates the existence of "axo-myelinic" synapses which involve vesicular transmitter release from axons, acting on receptors on the inner surface of the myelin sheath (Stys, 2011). Neurotransmitters released from unmyelinated white matter axons can also act on surrounding glia (Alix and Domingues, 2011). These types of signals are at the base of a bidirectional neuron–glia communication involving the secretion of endosome-derived vesicles by oligodendrocytes and their subsequent internalization by neurons through endocytosis (Fruhbeis et al., 2013). Whether this occurs in white matter is still unknown. Oligodendrocytes are also suggested to contribute to long-term axonal integrity by delivering products of aerobic glycolysis which are rapidly metabolized in axons (Funfschilling et al., 2012).

Additional important players in white matter homeostatic maintenance are fibrous astrocytes. The long processes of these cells run along axons and connect to blood vessels (Oberheim et al., 2009). White matter astrocytes are also an important source of energy, supplying axons with lactate converted from deposits of glycogen (Brown et al., 2003; Ransom and Fern, 1997). Astrocytic endfeet on brain capillaries are an important part of the blood–brain barrier (Abbott, 2005; Alvarez et al., 2013), and they also participate in regulating local microcirculation (Attwell et al., 2010; Gordon et al., 2008). In addition, astrocytic processes form contact with myelinated axons at the nodes of Ranvier, where they participate in "siphoning" of K^+ ions that accumulate following action potential generation (Kamasawa et al., 2005; Rash, 2010).

White matter microglia play an important role in neurodegeneration and inflammation. They are activated by cytokines, neurotransmitters and modulators, and can also synthesize and release many cytokines, chemokines, reactive oxygen radicals and neurotrophins which can be either injurious or beneficial to the surrounding axons and oligodendrocytes (Raivich and Banati, 2004).

The white matter components and the complex interactions among them create an optimal environment for fast transmission of signals along tracts of axons. However, the low blood flow and little collateral blood supply in deep white matter compared to gray matter make this intricate milieu highly susceptible to ischemic injuries (Iadecola et al., 2009; O'Sullivan et al., 2002), which disrupt white matter function with oftentimes devastating consequences.

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