Overcoming the lesion microenvironment to promote regeneration in the ageing central nervous system

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Abstract

Remyelination following CNS demyelination restores rapid signal propagation and protects axons; however, its efficiency declines with increasing age. Both intrinsic changes in the oligodendrocyte progenitor cell population and extrinsic factors in the lesion microenvironment of older subjects contribute to this decline. Microglia and monocyte-derived macrophages are critical for successful remyelination, releasing growth factors and clearing inhibitory myelin debris. Several studies have implicated delayed recruitment of macrophages/microglia into lesions as a key contributor to the decline in remyelination observed in older subjects. Here we show that the decreased expression of the scavenger receptor CD36 of aging mouse microglia and human microglia in culture underlies their reduced phagocytic activity. Overexpression of CD36 in cultured microglia rescues the deficit in phagocytosis of myelin debris. By screening for clinically approved agents that stimulate macrophages/microglia, we have found that niacin (vitamin B3) upregulates CD36 expression and enhances myelin phagocytosis by microglia in culture. This increase in myelin phagocytosis is mediated through the niacin receptor (hydroxycarboxylic acid receptor 2). Genetic fate mapping and multiphoton live imaging show that systemic treatment of 9–12-month-old demyelinated mice with therapeutically relevant doses of niacin promotes myelin debris clearance in lesions by both peripherally derived macrophages and microglia. This is accompanied by enhancement of oligodendrocyte progenitor cell numbers and by improved remyelination in the treated mice. Niacin represents a safe and translationally amenable regenerative therapy for chronic demyelinating diseases such as multiple sclerosis.

Biography

Khalil Rawji is a postdoctoral fellow at the Wellcome-MRC Cambridge Stem Cell Institute at the University of Cambridge and is funded by the Multiple Sclerosis Society of Canada. He completed his BSc (Hons. Dist.) in Life Sciences and his MSc In Neuroscience at Queen's University in Kingston, Ontario. He subsequently obtained his PhD in Neuroscience with Dr. Wee Yong at the University of Calgary in Alberta, Canada in 2018. He is interested in understanding how ageing impacts regeneration in the central nervous system and is exploring novel regenerative strategies for diseases such as multiple sclerosis.

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