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Stimulation of the LXR pathway improves remyelination in aged mice after lysolecithin-induced demyelination

Myelin is a highly-specialised membrane which tightly wraps around axons, thereby insulating and nurturing them. In the central nervous system (CNS), myelin is synthesised by oligodendrocytes. Myelin is harmed by a variety of causes, ranging from hereditary and autoimmune diseases to trauma and nutritional deficiencies. The most common demyelinating disease of the CNS in humans is multiple sclerosis (MS), in which an autoimmune inflammatory incursion targets and destroys the myelin sheath. After such a demyelinating insult, phagocytes are recruited to the lesion to remove the resulting myelin debris. The efficiency and temporary regulation of this process are crucial for subsequent remyelination and lesion repair. In aged animals, remyelination occurs less efficiently than in young animals. Thus far, the reduced remyelination rate observed in old animals has been attributed to a slower recruitment of phagocytes into the lesion and an impaired phagocytosis. As a consequence, there are changes in the cytokine/chemokine environment and inhibitory proteins derived from myelin debris persist in the extracellular environment, thereby preventing remyelination. In this study, we are particularly interested on the role that the lipid overload in phagocytes can have in remyelination. When removing myelin debris, phagocytes are faced with very high amounts of lipids in their cytoplasm. We show that the phagocytes of old mice accumulate high amounts of lipids in their cytoplasm after a lysolecithin-induced demyelination. Such quantities of lipids can induce lipotoxicity through various mechanisms, which lead to cellular damage and activation of inflammatory pathways. This, in turn, creates a hostile environment for correct remyelination, leading to impaired lesion repair. Hence, we suggest that the impairment in the lipid handling plays an important role in the inefficient remyelination observed in old animals. To further confirm our hypothesis, we investigated one of the mechanisms by which lipids are expelled from cells. The Liver-X receptor (LXR), a nuclear transcription factor, has been seen to be crucial for this process. The LXR detects oxysterols, which are cholesterol derivatives, and initiates the transcription of a set of genes that promote cholesterol efflux. Activation of this pathway by synthetic LXR agonists ameliorates the clinical course of experimental autoimmune encephalomyelitis, the most widely-used MS model. In old mice treated with the LXR agonist GW3965, we observed less lipid accumulation in the cytoplasm of phagocytes and better lesion repair. Therefore, stimulation of the LXR pathway can be used to counteract the impaired remyelination seen in aged mice. In conclusion, we suggest that a failure in the lipid handling mechanisms is partly responsible for the impaired remyelination observed in aged animals and propose the LXR pathway as a possible target for enhancement of remyelination.