A human system studying myelin phagocytosing and its effect on oligodendrocytes

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In MS lesions, myelin loss is opposed by remyelination, a repair mechanism that limits damage caused by the loss of the myelin sheath. This process, however, fails with disease progression and age, leading to the question what might be the underlying reason. iPSC-derived oligodendrocytes from RRMS patients showed no significant differences in proliferation, migration and differentiation compared to healthy controls, whereas differentiation into $O4^+$ and MBP^+ oligodendrocytes was significantly reduced after treatment with conditioned supernatant from activated PBMCs or pro-inflammatory polarized microglia.

Myelin debris clearance by blood-derived macrophages and microglia in MS lesions is essential for remyelination, as myelin debris itself can limit this process. Furthermore, the uptake of myelin by macrophages results in a rather anti-inflammatory phenotype, which itself can promote remyelination. In animal studies, an impaired cholesterol metabolism, the major component of myelin, leads to lipid accumulation and lipid droplet formation in macrophages after myelin phagocytosis, accompanied with decreased remyelination and a higher number of myeloid infiltrates. Nonetheless, the interaction of myeloid cells and oligodendrocytes at different stages of myelin processing is poorly understood.

This project aims to characterize the effects of myelin phagocytosing blood-derived macrophages and microglia on oligodendrocytes using primary (macrophages) and iPSC-derived (microglia, oligodendrocytes) human cells. Human blood-derived macrophages showed an intermediate inflammatory-profile after initial myelin phagocytosis that shifts into an anti-inflammatory phenotype after lipid droplet formation. However, so far, *in vivo* data obtained from human tissue sections showed no significant correlation between the number of lipid droplet forming macrophages and oligodendrocyte numbers in MS lesions as well as presence or absence of remyelination. Further experiment will be performed to analyse in detail the impact of myeloid cells on oligodendrocyte differentiation, myelination and cell death after myelin uptake and different stages of myelin processing.

Disclosure of conflict of interest

LSG, KH, LK, MP declare that there is no conflict of interest.

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