Dysregulation of the GPR17 receptor in neuroinflammatory diseases: implications for remyelination in multiple sclerosis

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Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system, in which inflammation and myelin disruption contribute to impaired in electrical conduction.
Oligodendrocyte precursor cells (OPCs) are massively recruited to the site of injury to myelinate damaged axons, but in MS patients remyelination is often ineffective. For this reason, therapeutic strategies aimed at fostering this process could block/delay the development of the disease and the consequent disability.
We have previously shown that the membrane receptor GPR17 timely regulates the early stages of OPC differentiation, but, after reaching its highest levels in immature oligodendrocytes, it has to be down-regulated to allow terminal maturation. Any defect in its expression pattern leads to impairment in oligodendrocyte differentiation.
Interestingly, overexpression of GPR17 was found in rodent models of cerebral trauma, ischemia and in lysolecithin induced focal demyelination. Instead, little is known about GPR17 in a primary demyelinating disease such as MS. On this basis, aim of this work has been to characterize GPR17 alterations in a murine model of MS and in human post-mortem MS lesions.
In spinal cord of mice subjected to experimental autoimmune encephalomyelitis (EAE), we observed a marked and persistent upregulation of GPR17 in the OPCs accumulating at demyelinating lesions. Moreover, fate-mapping experiments with transgenic GPR17iCreERT2-GFP reporter mice showed that this increased pool of proliferating cells is blocked at an intermediate stage of differentiation, and cannot fully complete the myelination process, likely due to unfavourable inflammatory environment.
In a similar way, in post-mortem tissues from SPMS patients, many GPR17-positive activated OPCs accumulated at the border of active lesions. In particular, GPR17 was found mainly expressed by hypertrophic cells HLA (human leukocyte antigen or major histocompatibility complex) -positive at within the lesions, suggesting that GPR17 is involved in the reaction to damage in both OPCs and immune cells directly responding to inflammation.
We conclude that the coordinated presence of GPR17 at the membrane of these cells at the lesion sites could be exploited as potential new target to support endogenous remyelination through advanced pharmacological approaches.

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