GPR17-expressing oligodendrocyte precursor cells differentially react to damage in experimental autoimmune encephalomyelitis and cuprizone-induced demyelination.

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In the central nervous system (CNS), oligodendrocytes provide support and insulation to axons thanks to the production of a myelin sheath, ensuring correct transmission of nerve impulses (White et al., 2014). In demyelinating disorders, such as multiple sclerosis, oligodendroglial precursor cells (OPCs) are known to proliferate and participate to remyelination. However, while disease progresses, this process becomes less and less efficient, eventually resulting in blockade of oligodendroglial maturation (Ozawa et al., 1994). Promoting myelination via a specific action on key molecules involved in OPC differentiation has been thus increasingly recognized as a promising strategy to foster endogenous re-myelination (Rovaris et al., 2006). In this respect, the G protein-coupled receptor GPR17 has recently emerged as a key regulator of oligodendrogenesis. In the CNS, GPR17 specifically decorates a subset of early bipolar NG2-positive OPCs, reaches its maximal expression in immature/pre-oligodendrocytes and it is then downregulated before terminal maturation (Fumagalli et al., 2011). Any alterations in this precise expression pattern result in myelination defects (Fumagalli et al., 2015). Here, we characterized the expression of GPR17 in two different models of demyelination: Experimental Autoimmune Encephalomyelitis (EAE) which is characterized by global immune responses against myelin components and strong inflammation, and cuprizone-induced demyelination, characterized by local damage induced by a toxic agent. In the spinal cord of EAE mice we observed a marked upregulation of GPR17 in the OPCs accumulating at demyelinating lesions; similarly, a clear accumulation of GPR17 expressing cells was observed in the corpus callosum of cuprizone-fed mice during both the initial de-myelination and the subsequent re-myelination phases. Then, to investigate in more detail the contribution of GPR17 expressing cells to re-myelination, we used the first inducible reporter GPR17-iCreERT2xCAG-GFP mouse line (Viganò et al., 2016; Bonfanti et al., 2017) in which, upon tamoxifen treatment all cells expressing GPR17 at that very precise moment become permanently fluorescent (GFP+ cells), and their final destiny can then be clearly determined. In both models, we observed a strong increase in the number of GFP+ cells, suggesting that GPR17-expressing cells react to the insult and expand their pool. However, only in the cuprizone model the reacting GFP+ cells actually differentiated to mature oligodendrocytes, thus contributing to re-myelination. In the EAE model, significant maturation of GFP+ cells occurred only in the gray matter which is minimally affected by damage, to suggest that the inability of white matter reacting GFP+ cells to maturate be due to the presence of a strong local inflammatory environment blocking cells at immature stages and preventing terminal maturation. Our data open new directions to treat diseases, such as MS, which are characterized by both demyelination and inflammation and suggest that remyelinating approaches should be combined to therapies controlling inflammation, in order to achieve effective myelin repair and retard neurodegeneration. Sponsored by Fondazione Italiana Sclerosi Multipla 2013/R/1 to MPA.

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