GPR17, a key receptor involved in oligodendrogenesis: implications for re-myelination strategies

G.T.Coppolino[1], D. Lecca[1], D. Marangon[1], F. Viganò[2], C. Parravicini[1], I. Eberini[1], R. Magliozzi[3], R. Furlan[4], L. Dimou[2], M.P. Abbracchio[1]

[1] Dept. of Pharmacological and Biomolecular Sciences, University of Milan, Italy
[2] Physiological genomics, Institute for Physiology and Ludwig-Maximilians University Munich, Germany
[3] Neurology Section of Department of Neurological and Movement Sciences, University of Verona, Policlinico G.B. Rossi, Verona, Italy
[4]San Raffaele Scientific Institute, Milan, Italy

Multiple Sclerosis (MS) is a chronic immune-mediated disease in which the immune system directs an abnormal response against endogenous myelin proteins. In the central nervous system (CNS), myelin is an insulating lipidic structure produced by oligodendrocytes, which is responsible of fast axonal electric transmission. During MS, demyelination disrupts neuronal conductance, leading to motor symptoms, and impairs oligodendroglial functions. Under these conditions, oligodendrocyte precursor cells (OPCs) are recruited at the site of injury to remyelinate damaged axons, but this process is often defective.

Although MS has been studied for centuries, there are several unmet needs that include development of treatments aimed to further delaying progression, providing neuroprotection and promoting remyelination.

In the last years, we have been studying GPR17, a G protein-coupled receptor activated by both uracil nucleotides and cysteinyl-leukotrienes, mediators involved in inflammatory responses in the CNS.

GPR17 is highly expressed in both OPCs and immature oligodendrocytes, it is required to start physiological oligodendroglial differentiation, whereas at later differentiation stages it has to be progressively downregulated to allow cells' terminal maturation. Moreover, GPR17 is markedly up-regulated in rodent models of cerebral trauma, brain ischemia and in lysolecithin-induced focal demyelination. These data suggest that GPR17 takes part in the pathological mechanisms of demyelination either as a consequence of the disease or contributing to the lesion. Since little is known about GPR17 in a primary demyelinating disease like MS, the aim of this work was to characterize GPR17 alterations both in murine MS models and in human MS lesions.

In mice with Experimental Autoimmune Encephalomyelitis (EAE), we observed a marked and persistent upregulation of GPR17 in the OPCs accumulating at demyelinating lesions. Conversely, no GPR17 upregulation was found in a model characterized by a much lower degree of inflammation, i.e. cuprizone-induced demyelination. In a similar way to EAE, in autoptic samples from MS patients, many GPR17-positive activated cells accumulated at the border of active lesions, in parallel with a marked increase of CXCL12 levels, a chemokine that has been recently demonstrated to interact with GPR17 and to promote OPC differentiation in vitro not only via its well-characterized receptors CXCR4 and CXCR7, but also via GPR17.

Thus, CXCL12 may represent one of the key inflammatory factors triggering a persistent upregulation of GPR17 in both rodent EAE and human MS. We speculate that, as a result of chronic inflammation, CXCL12 accumulating at demyelinating lesions markedly upregulates GPR17, which initially promotes OPC differentiation, but then prevents the physiological downregulation of this receptor eventually resulting in inhibition of terminal OPC maturation to myelinating cells. These findings may have implications for the design of novel pharmacological approaches aimed at overcoming the re-myelination block typical of chronic demyelinating diseases.

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