1. Record Nr. TD18002624

Autore	G.T. Coppolino
Titolo	DYSREGULATION OF THE GPR17 RECEPTOR IN NEURO-INFLAMMATORY DISEASES: IMPLICATIONS FOR RE-MYELINATION IN MULTIPLE SCLEROSIS [Tesi di dottorato]
Editore	Università degli Studi di Milano, 2017-01-26
Lingua di pubblicazione	Inglese
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	diritti: info:eu-repo/semantics/openAccess In relazione con info:eu-repo/semantics/altIdentifier/hdl/2434/469328
Sommario	Multiple Sclerosis (MS) is a chronic immune-mediated disease in which the immune system directs an abnormal response against myelin, an insulating lipidic structure produced by oligodendrocytes 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 injury site to re-myelinate damaged axons, but this process is often defective. Many disease-modifying treatments (DMTs) are available but there are several unmet needs: delaying disease progression, providing neuroprotection and promoting re-myelination. The aim of this thesis was to characterize GPR17 alterations both in murine MS models and in human MS lesions, to assess whether this receptor, a key actor of oligodendrogenesis, can be proposed as a pharmacological target in re-myelinating strategies. GPR17 is a G protein-coupled receptor activated by both uracil nucleotides and cysteinyl-leukotrienes, mediators involved in inflammatory responses in the CNS. Under physiological conditions, GPR17 is expressed in OPCs, with maximal levels in immature oligodendrocytes and progressive downregulated in terminally

	differentiating cells. A marked GPR17 up-regulation was found in rodent models of cerebral trauma, ischemia and in lysolecithin-induced focal demyelination; suggesting that GPR17 takes part in the pathological mechanisms of demyelination either as a consequence of the disease or contributing to the lesion. 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. Furthermore, we demonstrated that the chemokine CXCL12 can also directly act as a promiscuous activator of GPR17, corroborating our hypothesis of a common pathophysiological role for GPR17 and chemokine receptors in leading the re-myelination processes. Characterizing the molecular defects of GPR17 in MS will help re-establishing its correct function in re-myelination and foster the identification of new pharmacological strategies to enhance OPCs reparative potential in MS.
Localizzazioni e accesso	http://memoria.depositolegale.it/*/http://hdl.handle.net/2434/469328