The Purinergic System as a Target for Demyelinating Diseases

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Demyelination (i.e., loss of integrity of the myelin envelope ensheating neuronal processes) leading to impaired nerve conduction and neurological deficits is not only a feature of multiple sclerosis (MS), but represents a common feature of several neurodegenerative diseases including stroke, Alzheimer's and amyotrophic lateral sclerosis. On this basis, the identification of new pharmacological targets to foster remyelination represents a new approach to repair the brain and spinal cord. Our laboratory has been involved for several years in the characterization of a new purinergic receptor, GPR17, that is espressed on the Oligodendrocyte Precursor Cells (OPCs, the myelin forming cells) that are still present in the adult CNS (Ciana et al., 2006; Lecca et al., 2008; Fumagalli et al., 2011; Coppi et al., 2013).
Specifically, GPR17 orchestrates the transition of early OPCs to mature myelinating cells acquiring the tipical mature marker MBP (myelin basic protein). Knock in and knock out esperiments on cultured OPCs have shown that GPR17 is needed to undertake differentiation, but that, at a certain maturation stage (when cells express the pre-oligodendrocyte marker O4), GPR17 has to be downregulated to allow cells to complete differentiation. Indeed, GPR17 is never present on MBP-expressing mature oligodendrocytes (Daniele et al, 2014; Fumagalli M. et al., under revision, 2015). More recently, by utilizing the first GPR17 transgenic reporter mouse line for fate mapping studies, where the final destiny of GPR17-expressing precursors can be actually visualized by confocal microscopy (Vigano' F et al., submitted), we have univocally proved that OPCs, that have espressed GPR17 in their earlier life, indeed undergo myelination, and that their processes ensheat neuronal endings. Based on these findings and independently of us, FAST FORWARD, a non profit arm of the National Multiple Sclerosis Society USA, has proposed GPR17 as a "model receptor" for new remyelinating strategies for both MS and other neurodegenerative diseases (see also Eberini et al., 2011).
In an attempt to shed light on the mechanisms that regulate the critical and time dependent expression of GPR17 during OPC differentiation, we have recently identified by bioinformatic analysis a new microRNA (miR-X), that putatively regulates multiple components of the myelination machinery, such as NG2, GalC, APC and, besides GPR17, additional purinergic receptors including $P2X_2$, $P2X_4$ and $P2Y_6$ (MiRWalk). Both the forced expression and the silencing of miR-X strongly altered OPC maturation in culture, in parallel to marked changes of key oligodendrocyte genes, including GPR17, MAP5 and MBP. Levels of miR-X were altered in both spinal cord tissues from experimental autoimmune encephalomyelitis (EAE) mice (a rodent model of human multiple sclerosis, MS) and in the cerebrospinal fluid of MS patients, suggesting that it could be a hallmark of the disease (Lecca D et al., in preparation). Globally, these data suggest that miR-X participates to OPC maturation and that its dysregulation may contribute to demyelination and/or defective remyelination. Understanding the molecular links between miR-X, GPR17 and other genes involved in myelination will provide novel therapeutic means to enhance endogenous CNS reparative capabilities in both MS and other neurodegenerative diseases by simultaneously targeting multiple components of the same molecular pathway.
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