The mammalian target ofrapamycin(mTOR)controls oligodendrocyte maturation by fine-tuning the activityof GPR17 receptor viaG protein-coupled receptor kinases.

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In the adult central nervous system (CNS), neural progenitor cells expressing the proteoglycan NG2 (NG2 cells, also known as Oligodendrocyte Precursor Cells, OPCs) dispersed throughout the parenchyma serve as a primary source of myelinating cells in demyelinated lesions, such as multiple sclerosis (MS). The Gi-protein-coupled receptor GPR17, activated by both uracil nucleotides (e.g. UDP-glucose) and cysteinyl-leukotrienes (e.g. LTD_4) (Ciana et al., 2006), has recently emerged as an important player in oligodendrogliogenesis (Lecca et al., 2008; Chen et al., 2009). In both brain and spinal cord, GPR17 was found on parenchymal NG2 cells in transition from precursors to premyelinating phenotypes, whereas it is not present on mature myelinating oligodendrocytes. Previous data in cultured OPCs showed that, at early differentiation stages, GPR17 activation by endogenous ligands promotes (while inhibition by antagonists or silencing RNAs impairs) OPC differentiation (Fumagalli et al., 2011). Altogether, these data point at GPR17 as a key functional modulator of oligodendrocyte maturation.
Here, we used primary OPC cultures to investigate the mechanisms underlying GPR17 endogenous regulation. This is quite important since GPR17 is upregulated at injury sites in both a demyelinating in vivo model (Boda et al., 2011) and in multiple sclerosis (MS) patients (Chen et al., 2009), which, could, in turn, cause defective myelination. In line with these findings, we have recently shown that GPR17 forced over-expression at late differentiation stages, obtained by transfecting cultured OPCs with a GFP-GPR17 fusion vector, indeed impairs terminal cell maturation. This suggests that the receptor has a stage specific function in controlling OPC differentiation and that it needs to be down-regulated/desensitized in late immature oligodendrocytes to allow their terminal maturation. Physiologically, GPR17 down-regulation may occur through agonist-induced receptor phosphorylation via G-protein coupled receptor kinases (GRKs) (Daniele et al., 2011), which are altered in MS (Vroon et al., 2005), and may, in turn, be controlled by the mTOR pathway, that indeed plays a pivotal role in oligodendrocyte maturation (Tyler et al., 2009). On this basis, we used rat primary OPCs to first assess the ability of GPR17 agonists to induce GPR17 desensitization/internalization. Through a radioactive cAMP assay, we demonstrated a loss of GPR17 responsiveness after prolonged exposure to both UDP-glucose and LTD_4. Moreover, we showed that the same agonists induce the direct physical association of GPR17 with GRK2, which in turn phosphorylates the receptor, suggesting a role for GRK2 in GPR17 regulation. Interestingly, we also demonstrated that the inhibition of the mTOR pathway by rapamycin determines a significant reduction of GRK2 levels, with parallel increases in GPR17 expression and strong impairment of OPC maturation. Globally, these data suggest that dysregulation of these interconnected pathways leading to aberrant GPR17 overexpression may prematurely block OPC maturation at a pre-immature stage. Altogether these results will help developing new pharmacological or biotechnological strategies to stimulate and/or implement the reparative potential of OPCs that are still present in the CNS.

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