Expression of GPR17 receptor in a murine model of perinatal brain neuroinflammation and its possible interaction with Wnt pathway

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Oligodendrocyte precursor cells (OPCs) are generated in specific germinal regions and progressively maturate to myelinating cells. Oligodendrocytes (OLs) differentiation is regulated by a complex interplay of intrinsic, epigenetic and extrinsic factors, including Wnt and the G protein-coupled receptor referred to as GPR17 (Mitew et al., 2014). This receptor responds to both extracellular nucleotides (UDP, UDP-glucose) and cysteinyl-leukotrienes (Ciana et al., 2006), endogenous signaling molecules involved in inflammatory response and in the repair of brain lesions. GPR17 is highly expressed in OPCs during the transition to immature OLs, but it is down-regulated in mature cells. Accordingly, GPR17-expressing OPCs are already present in mice at birth, increase over time, reach a peak at P10, before the peak of myelination, and then decline in the adult brain (Boda et al., 2011). Of note, in cultured OPCs, early GPR17 silencing has been shown to profoundly affect their ability to generate mature OLs (Fumagalli et al., 2011, 2015). Myelination defects characterize many brain disorders, including perinatal brain injury caused by systemic inflammation (Favrais et al., 2011), which is a leading cause of preterm birth. It has already been suggested that an imbalance in the Wnt/β-catenin/TCF4 pathway could be involved in the maturation arrest of OLs that is observed in premature infants (Yuen et al., 2014). No data are currently available on GPR17 in perinatal brain injury and on its possible interaction with Wnt pathway.

Based on these premises, the aim of this work was to assess if the maturational blockade of OLs due to mild systemic perinatal inflammation, induced by intraperitoneal injections of interleukin-1β (IL-1β), is accompanied by defects in GPR17 expression and whether the Wnt pathway is involved in the regulation of GPR17.

Data showed that in newborn mice exposed to IL-1β, which induces a blockade of oligodendrocyte maturation, GPR17 expression is not affected at early time point (P5), but it is downregulated at P10, when its expression should be maximal.

Moreover, in vitro studies revealed that the maturation blockade of the oligodendroglial cell line Oli-Neu, after treatment with a Wnt Agonist II, is accompanied by a severe inhibition of GPR17 expression.

In conclusion, our data have shown that myelination defects observed in perinatal brain injury are associated with defects in GPR17 expression; further studies are needed to characterize the molecular link between Wnt pathway and GPR17 receptor.

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