THE GPR17RECEPTOR AS A NEW POTENTIAL PHARMACOLOGICAL TARGET TO RESTORE OLIGODENDROGLIAL DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: New insights on the mechanisms at the basis of amyotrophic lateral sclerosis (ALS) come from the demonstration that motor neuron (MN) degeneration is linked to dysfunction/death of oligodendrocytes. As a consequence, oligodendrocyte precursor cells (OPCs) increased proliferation, but failed to replace degenerating oligodendrocytes, resulting in the presence of immature/dysfunctional oligodendrocytes. Thus, restoring oligodendrocyte function and promoting OPC maturation have emerged as interesting approaches to prevent MN degeneration. An important regulator of OPC differentiation is GPR17, a P2Y-like receptor specifically expressed by a sub-population of OPCs in transition to pre-oligodendrocytes, but not in mature cells. Previous data obtained in different models of neurodegeneration have shown that an abnormal increase of GPR17expression is associated to myelin defects. Moreover, recent studies suggest that GPR17is a promising pharmacological target for the treatment of neurodegenerative diseases characterized by oligodendrocyte dysfunction. With this work, we proposed to characterize GPR17alterations in the SOD1G93A mouse model of ALS and to assess in vitro whether this receptor could be exploited as a target to restore impaired oligodendrocyte function.

Materials and methods: SOD1G93A mice and control SOD1wild-type mice have been sacrificed at early pre-symptomatic stage (P7/P10), pre-symptomatic stage (P30), symptomatic stage (P90) and late symptomatic stage (P120) to characterize GPR17expression in the spinal cord by western blot and immunohistochemistry together with different oligodendroglial markers (i.e. NG2, GSTϖ). Primary OPC cultures have been prepared from spinal cord of P7SOD1G93A, control SOD1wild-type and wild-type mice using anti-PDGFRα MicroBeads and MACS technology. Differentiation of primary OPCs has been assessed by immunocytochemistry, in presence or absence of the non-selective GPR17antagonist montelukast.

Results: Our results showed decreased levels of the mature oligodendrocyte marker GSTϖ in lumbar spinal cord of SOD1G93A mice at late symptomatic stage, indicating degenerative changes in oligodendrocytes. In parallel, GPR17expression was found significantly increased at pre-symptomatic stage as compared to SOD1wild-type mice and this alteration persists at the late symptomatic phase, mainly in the ventral spinal cord. The receptor seems to be early involved in the disease, as also suggested by its high expression in P7/P10 SOD1G93A mice. Interestingly, primary OPCs from SOD1G93A mice showed a lower differentiation capability with respect to OPCs from wild type mice; no differences were detected in the proliferation rate. Of note, the non-selective GPR17antagonist montelukast, an oral drug already approved by FDA, was able to rescue OPC differentiation defects in vitro.

Discussion and conclusions: Here, we demonstrated that, during the late symptomatic stage of the disease, GPR17expression is strongly up-regulated in OPCs displaying an immature phenotype in the spinal cords of SOD1G93A mice, thus indicating a block of oligodendroglial differentiation. Furthermore, we highlighted the GPR17receptor as a new potential target that could be exploited to restore the impaired OPC differentiation observed in cultures from SOD1G93A mice spinal cords. Globally, our data provided important information on the possibility to retard motor neuron degeneration via entirely novel, GPR17-targeted, pharmacological approaches, thus setting the basis for future *in vivo* strategies.

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