

Mir-125a-3p negatively regulates oligodendrocyte precursor cells maturation and is altered in human multiple sclerosis.

Marangon Davide¹, Boda Enrica², Corinna Giorgi³, Coppolino Giusy T.¹, Parolisi Roberta², Finardi Annamaria⁴, Furlan Roberto⁴, Buffo Annalisa², Abbracchio Maria P.^{1,*}, Lecca Davide^{1,*}

¹ *Laboratory of Molecular and Cellular Pharmacology of the Purinergic Transmission, Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy.*

² *Department of Neuroscience and Neuroscience Institute Cavalieri-Ottolenghi (NICO), University of Turin, Orbassano, Turin, Italy.*

³ *European Brain Institute-Rita Levi Montalcini, Rome, Italy.*

⁴ *Institute of Experimental Neurology (INSpe), Division of Neuroscience, Milan, Italy.*

* *Equally contributed.*

In the central nervous system, oligodendrocytes provide support to axons thanks to the production of a myelin sheath. During their maturation oligodendroglial precursors (OPCs) follow a very precise differentiation program, finely orchestrated by transcription factors, epigenetic factors and microRNAs, a class of small non-coding RNAs involved in post-transcriptional regulation. Any alterations in this program can potentially contribute to dysregulated myelination, impaired remyelination and neurodegenerative conditions, as it happens in multiple sclerosis.

Recently, we identified miR-125a-3p as a new actor of oligodendroglial maturation, that could also be involved in the pathological consequences of multiple sclerosis, showing that its over-expression impairs, whereas its silencing promotes, oligodendrocyte maturation (Lecca et al., *Sci Rep*, 2016).

To shed light on the mechanism underlying this effect, we performed a microarray analysis on OPCs after miR-125a-3p over-expression. This analysis suggested that miR-125a-3p is indeed involved in the regulation of biological processes important for OPC maturation, such as cell-cell interaction and morphological differentiation. To evaluate whether miR-125a-3p modulation may influence the progression of remyelination in vivo, we overexpressed the miR-125a-3p by lentiviral approach in a focal lysolecithin-mediated demyelinating lesion in the subcortical white matter of adult mice. Interestingly, also in this case, we found that miRNA-overexpressing OPCs persisted in an immature (i.e. PDGFR α ⁺/NG2⁺) state.

Moreover, we found that miR-125a-3p levels are altered in both brain active lesions and cerebrospinal fluid of multiple sclerosis patients, suggesting that it could be a potential biomarker of disease.

The identification of a new miRNA modulating oligodendrocyte differentiation provides new findings about the complex regulation of myelination processes and we postulate that an antago-miRNA for miR-125a-3p may help promoting oligodendrocyte maturation in diseases characterized by impaired myelin repair. Sponsored by Fondazione Italiana Sclerosi Multipla 2013/R-1 project to MPA and by Fondazione Cariplo, grant n° 2014-1207 to DL.