

## Investigating the cross-talk between microglia and oligodendrocyte progenitors in brain ischemia

E. Bonfanti<sup>1\*</sup>, P. Gelosa<sup>1,2</sup>, M. Lombardi<sup>3</sup>, M. Cimino<sup>4</sup>, L. Dimou<sup>5</sup>, L. Sironi<sup>1,2</sup>, C. Verderio<sup>3,6</sup>, M.P. Abbracchio<sup>1</sup>, M. Fumagalli<sup>1</sup>.

<sup>1</sup> Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan 20133, Italy

<sup>2</sup> Centro Cardiologico Monzino, Milan 20138, Italy

<sup>3</sup> Istituto Clinico Humanitas, Humanita Mirasole SpA, Milan, Italy

<sup>4</sup> Department of Biomolecular Sciences, University of Urbino, Urbino 61029, Italy

<sup>5</sup> Molecular and Translational Neuroscience, Department of Neurology, University of Ulm, Germany

<sup>6</sup> CNR, Institute of Neuroscience, Milan, Italy

\* presenting author: [elisabetta.bonfanti@guest.unimi.it](mailto:elisabetta.bonfanti@guest.unimi.it)

Oligodendrocytes, the myelin-forming cells in the brain, are severely affected by ischemia (Arai et al. 2009, Biol Pharm Bull), contributing to stroke-associated deficits. The possibility to implement spontaneous post-injury repair mechanisms still represents an unexplored field.

Recent data obtained by fate-mapping analysis using the conditional GPR17-iCreER<sup>T2</sup>xCAG-eGFP transgenic mice, showed that the subpopulation of adult Oligodendrocyte Progenitor Cells (OPCs) expressing the GPR17 receptor (GFP<sup>+</sup>-cells) represent “a reserve pool” that is maintained for repair purposes after brain damage (Viganò et al. 2016, Glia). Accordingly, our data demonstrated that, after brain ischemia, GFP<sup>+</sup>-cells actively respond to injury increasing their proliferation rate and migratory capacity. However, at later stages, only a few percentage of these cells undergo maturation. This limited post-stroke repair is likely due to local unfavourable inflammatory milieu mediated by macrophages and resident microglia, which participate to post-ischemic inflammation assuming both detrimental and beneficial phenotypes.

Here, we aimed at: (i) characterizing the spatio-temporal distribution of GFP<sup>+</sup>-cells in relation to microglia and macrophage polarization after brain ischemia in the middle cerebral artery occlusion MCAo, rodent model; (ii) exploring the cross-talk between microglia and OPCs, by assessing how vesicles released extracellularly (EVs) by microglia, polarized toward the pro- and anti-inflammatory states, influence OPC behaviour.

*In vivo* studies showed that GFP<sup>+</sup>-cells accumulate at the border of the ischemic lesion starting from 72h after ischemia, when immune cells show both pro- and anti-inflammatory features. One week after stroke, the absolute number of pro-inflammatory cells increases, whereas immune cells with anti-inflammatory phenotype were found to be decreased. *In vitro* studies pointed out that EVs produced by pro-inflammatory microglia limit OPC proliferation. On the contrary, 48h exposure to EVs from either pro- or anti-inflammatory microglia (but not resting cells) promote OPC maturation and myelination. Interestingly, EVs from pro-regenerative cells also increased OPC migration. These data suggest that EVs contain signals able to influence OPC proliferation, migration and maturation. Shedding light on the mechanisms by which microglia activation interferes with the regeneration potential of OPCs is important for developing therapeutic interventions to implement functional recovery after stroke.

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