The purinergic system: a new promising target for human diseases

Investigating microglia and oligodendroglial progenitors interactions: implications for new purinergic strategies to brain repair

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Oligodendrocytes, the myelin-forming cells in the brain, are severely affected by ischemia (Arai et al., 2009), contributing to stroke-associated deficits. The possibility to implement spontaneous post-injury repair mechanisms by targeting myelin still represents an unexplored field. The membrane purinergic-like receptor GPR17 is an important regulator of OPC differentiation and myelination. GPR17 is specifically expressed in OPCs in transition to pre-oligodendrocytes, but not in mature cells and has emerged as a target to implement stroke repair through stimulation of OPC maturation (Fumagalli et al., 2016). Results obtained by fate-mapping analysis using the conditional GPR17-iCreERT2xCAG-eGFP transgenic mice showed that the subpopulation of adult OPCs expressing GPR17 (GFP+-cells) represents “a reserve pool” that is maintained for repair purposes after brain damage (Viganò et al., 2016). In particular, we recently demonstrated that, after brain ischemia, GFP+-cells actively respond to injury increasing their proliferation rate and migratory capacity. However, at later stages, only a low percentage of these cells undergoes maturation (Bonfanti et al., in press). 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+-cells in relation to microglia/macrophage polarization in transgenic mice after middle cerebral artery occlusion (MCAo); (ii) exploring the cross-talk between microglia and OPCs, by assessing how vesicles released extracellularly (EVs) by microglia, polarized toward a pro- or anti- inflammatory state, influence OPC behaviour.

In vivo studies showed that GFP+-cells accumulate at the border of the ischemic lesion starting from 72h after ischemia, when microglia and macrophages show both pro- and anti-inflammatory features. One week after stroke, the absolute number of pro-inflammatory cells increases, while myeloid cells with anti-inflammatory phenotype do not significantly change. In vitro studies showed that EVs produced by pro-inflammatory microglia only slightly limit OPC proliferation, while EVs produced by pro-regenerative microglia tend to increase it. Moreover, preliminary data showed that all types of EVs (from unstimulated, pro-inflammatory or pro-regenerative microglia) are able to induce OPC migration, indicating that EVs provide attractive guidance cues

independently of the activation state of donor microglia. Interestingly, EVs from pro-regenerative microglia have a higher chemotactic effect on the subpopulation of cells expressing GPR17. Finally, exposure to EVs from either pro- or anti-inflammatory microglia (but not resting cells) promote OPC maturation. However, EVs released by pro-regenerative cells display higher differentiation activity and significantly foster myelin deposition in an in vitro system of OPCs co-cultured with DRG neurons. Shedding light on these mechanisms is important for developing combined therapeutic interventions where a purinergic approach, aimed at implementing recovery after stroke, is potentiated by agents promoting a better microglia phenotype with pro-regenerative effects on OPCs.

Arai et al. (2009) Biol Pharm Bull 32, 1639-44

Fumagalli et al. (2016) Neuropharmacology 104, 82-93

Viganò et al. (2016) Glia 64, 287-99

Bonfanti et al. Cell Death Disease. In press

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