Purinergic Modulation of Adult Brain Stem-like Cell Growth and Function

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Despite previous beliefs, the generation of new neurons and new glia in the central nervous system (CNS) continues throughout life. Adult neurogenesis occurs in both classical neurogenic niches (e.g., the subventricular zone, SVZ, of the lateral ventricles) as well as in the entire brain's parenchyma, which is full of quiescent neural progenitors that are activated after injury. Two main types of adult stem-like cells have been identified: (i) proliferating reactive astrocytes; these cells remain within their lineage in vivo, but, as revealed by ex-vivo studies, re-acquire capacity for self-renewal and are potentially able to generate all the three CNS cell types, namely neurons, astrocytes and oligodendrocytes (Buffo et al., 2008); (ii) NG2-positive polydendrocytes, that can differentiate to mature oligodendrocytes participating to re-myelination after injury; these cells retain some multipotency and, under some conditions, can also generate neurons and astrocytes (Nishiyama et al., 2009). Among various neurotransmitters and growth factors, extracellular nucleotides (ATP, UTP, their break-down products and sugar nucleotides), which are released at high amounts at the sites of CNS damage (Ulrich et al., 2012) are key actors in regulating reparative responses via purinergic P2 receptors (Abbracchio et al., 2009). Regarding adult neurogenesis in CNS niches, by using a conditional GLAST::CreERT2 Rosa YFP mouse model and an *in vitro* neurosphere assay, we have recently demonstrated that the P2Y receptor agonist ADPβS promotes the proliferation of SVZ neural progenitors and sustains their progression towards the generation of neuroblasts, either directly or through the activation of parenchymal astrocytes (Boccazzi et al., see abstract presented at this meeting). Conversely, regarding parenchymal adult neurogenesis, we have recently validated the P2Y-like receptor GPR17, which is dually activated by both uracil nucleotides and cysteinyl-leukotrienes (Ciana et al., 2006), as a new target for remyelinating therapies (Lecca et al., 2008; Ceruti et al., 2009; Fumagalli et al., 2011; Boda et al., 2011; Eberini et al., 2011). Expression of GPR17 on early NG2 cells is likely driven by signals coming from neurons (see Lecca et al., abstract presented at this meeting) and reaches its maximal peak in O4-positive immature oligodendrocytes. After this stage, GPR17 has to be downregulated to allow cells to proceed towards terminal differentiation, since its forced overexpression at late NG2 differentiation stages impairs the generation of fully mature myelinating cells (see Bonfanti et al, abstract presented at this meeting). We believe that the physiological downregulation of GPR17 occurs via phosphorylation reactions followed by receptor desensitization and internalization (ibidem). We are now assessing in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis if a pathological dysregulation of these events may induce GPR17 alterations that are responsible for impaired repair of demyelinating lesions in MS (see Lecca et al. and Bonfanti et al, abstracts presented at this meeting).
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