Astrocytes control neurogenesis in the central nervous system

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Glial cells comprise most of the non-neuronal cells of the brain and include oligodendrocytes, radial glia and astrocytes. Among them, astrocytes represent the major cell population in the central nervous system (CNS). Their functions are diverse and include almost every aspects of nervous system function, from cell birth and death to migration and cell-cell interactions that connect and integrate the working elements of the CNS. (CASTELLANO-LOPEZ; NIETO-SAMPEDRO, 2001)

The strong interactions of these cells with cell partners, through gap junctions for instance, has long been considered as an illustration of a kind of inertia of an astroglial syncytium. However, patch-clamp experiments showed rapidly the presence of various types of channels either voltage-dependent or independent on the astroglial cell surface. Numerous astroglial functions were discovered with rapid developing technologies in the field of optical and electronical imaging, including the constitution of brain architecture during development.

Embryonic astrocytes of the radial glia, serve as railways for migration of immature neurons of the periventricular zone towards the external layers of the cerebral cortex. Astrocytes are involved in the formation of the blood brain barrier and their active role in the formation and plasticity of synapses between neurons has been demonstrated (HAYDON, 2001). Astrocytes has in addition the unique capacity in the CNS, to stock glucose and represent therefore, a major source of energy for neurons and their secreted growth factors are essential for the surviving of neural functions.

A dogma which has been contested during these last years, was the unalterability of neurons from birth to death. Two brain areas, the subventricular zone and the hippocampus subgranular zone contain stem cells which give rise to new neurons all along life, even through adulthood. For a review, see Alvarez-Buylla, Garcia-Verdugo and Tramontin (2001), and Alvarez-Buylla, Seri and Doetsch (2002) ; for primates, see Eriksson and others (1998), and Kornack and Rakic (1999, 2001). With the discovery of adult neurogenesis, in at least a few brain regions, an increasing number of publications reported also newly generated neurons in other regions of the adult CNS (GROSS, 2000; GRASSI ZUCCONI; GIUDITTA, 2002). Thus, it appeared that adult brain contains also stem cells in other brain regions like striatum or spinal cord which have the capacity to give rise to the different cell types of the CNS, including neurons. However, these cells remained quiescent in the normal physiological environment and were not functionally relevant because neuronal regeneration did normally not occur at detectable levels after lesions, except in the

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olfactory bulb (MURRAY; CALOF, 1999; ASTIC; SAUCIER, 2001). From these observations it has become clear that neurogenesis can in principle also occur in the adult mammalian brain, but the environment there is much less favourable for neurogenesis and/or survival of new neurons than during development (LIM et al., 2000). Local environment is responsible for adult stem cells ability to proliferate and differentiate and an hostile environment has to be overcome either by the supplying of positive growth factors (NAKATOMI et al., 2002) and/or by the blocking of inhibitory signals (LIM et al., 2000). That has still to be demonstrated and the mechanisms involved to be characterized.

A paper of the group of Fred Gage, one of the pioneers in the field with Sam Weiss and Arturo Alvarez-Buylla, has recently evidenced the role of astrocytes in the control of neurogenesis in the adult hippocampus. To visualize the stem cells time course, the authors utilized a previously described technique which allowed the clonal isolation of rat adult hippocampus stem cells; they transfect them with a retrovirus which permit the expression of a fluorescent marker (GFP) in their lineage. In the presence of Fibroblast factor 2 (FGF-2), these cells proliferate and keep undifferentiated. The authors observed after deprivation of FGF, a spontaneous differentiation of 1-2% of these cells into neurons (MAP-2+),oligodendrocytes (GALC+) and astrocytes (GFAP+). When laminin, retinoic acid and foetal calf serum were added, the percentage could reach 5%. However, when these cells were grown over a newborn astrocytes monolayer, more than 10% of new astrocytes and neurons could be observed. If the monolayer only contained fibroblasts, nothing happened. If the monolayer mainly contained neurons, a differentiation towards oligodendrocytes was observed, whereas over a hippocampus astroglial monolayer, a neurogenic effect was evident. It could therefore be concluded that astrocytes might produce soluble and transmembranous factors, able to favour differentiation of adult stem cells into neurons. This effect appeared optimal with newborn astrocytes and appeared rather specific to hippocampal astrocytes.

Transplantation of immature stem cells, derived either from embryonic or from adult brain, highlights the difficulties of these cells to generate neurons. Their default pathway, seems to be the generation of astrocytes in line with the discovery that adult neural stem cells, exhibit many features of astrocytes. (DOETSCH et al., 1999; SERI et al., 2001; IMURA; KORNBLUM; SOFRONIEW, 2003)

The characterization of factors which probably induce the outgoing of stem cells from the cell cycle and their engagement into a specific lineage, opened an important field for reconstitutive therapy for neurodegenerative diseases.

O controle da neurogênese pelos astrócitos no sistema nervoso central

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