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Exploring neurogenesis outside the niche: atypical locations of mammalian neural stem/progenitor cells

L. BONFANTI[1], A. MACKAY-SIM[2]

[1] Department of Veterinary Morphophysiology and Scientific Institute of the Cavalieri-Ottolenghi Foundation, University of Turin, Italy;
[2] National Centre for Adult Stem Cell Research, Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Australia

Adult neurogenesis, namely the capacity of generating new nerve and glial cells throughout life, is a phylogenetically highly conserved feature that challenges the dogma of the nervous system as a static, non-renewable tissue (Gage, 2000). Yet, unlike invertebrates and non-mammalian vertebrates, in which neurogenesis persists in wide regions of the central nervous system (CNS), in adult mammals it is mainly restricted to two specific brain sites: the forebrain subventricular zone and the hippocampal dentate gyrus (Gage, 2000; Kriegstein and Alvarez-Buylla, 2009). It is now clear that the persistence of neurogenesis in these zones depends on stem cells which reside in niches as vestigial remnants of embryonic germinal layers (Kriegstein and Alvarez-Buylla, 2009). This fact leaves the remainder of the CNS as a non-renewable tissue substantially incapable to repair damage coming from neurodegenerative diseases, ischemic/traumatic lesions.

In the last few years, the persistence of neurogenesis has been observed also in other CNS sites and in sensory organs, in addition to the neurogenic zones quoted above. The most striking example, known for many years, is that of olfactory receptor neurons which are continuously renewed in the olfactory mucosa (see article by Mackay-Sim, in this issue). Other examples have subsequently emerged and this special issue deals specifically with these less studied stem/progenitor cells responsible for adult neurogenesis in niches outside the forebrain and hippocampus. The review by Locker et al. summarizes a decade of research on quiescent stem cells in the mammalian retina, also taking into account the advances made in animal models of stem cell-mediated retinal regeneration. The article by Metzger gives an overview of the development, structure and function of the enteric nervous system, focusing on the persistence of neural stem cells in the gut. Pardal et al. report on stem cells existing in the carotid body, a chemoreceptor organ of the peripheral nervous system that supports neurogenesis in response to hypoxemia. Finally, Miura and Barlow address the issue of the continuous renewal of taste receptor cells, a type of electrochemically excitable cells which are epithelial in origin but capable of releasing neurotransmitter onto afferent nerve fibers. Proliferating/quiescent progenitor cells have been demonstrated to occur even in diverse regions of the adult CNS out of the forebrain and hippocampus (Nishiyama et al., 2009; Ohira et al., 2009). These additional neurogenic sites also raise the issue of comparative studies in mammalian species and in other animal groups. The occurrence of neurogenesis within the mature brain parenchyma, not related with persistent germinal layers, can be frequently found in non-vertebrate species which harbour disperse, highly active niche-like neurogenic sites in widespread CNS regions (Kaslin et al., 2008) accounting for remarkable regenerative capacity (Zupanc, 2009). By contrast, most local

Corresponding Author: Luca Bonfanti, Dipartimento di Morfofisiologia Veterinaria, via Leonardo da Vinci 44, 10095 Grugliasco (TO), Italy - Email: luca.bonfanti@unito.it

progenitors of the non-neurogenic parenchyma in the mammalian CNS, in spite of their proliferative capacity, only exhibit neural stem-like potentialities *in vitro* but do not produce neurogenesis *in vivo* (Nishiyama et al., 2009; Ponti et al., in this issue). The article by Boda and Buffo in this issue reviews recent updates concerning these cells, and how their potential could be increased in specific pathological/experimental conditions (see also Ohira et al., 2009), in the perspective of using such endogenous sources for brain repair. Nevertheless, also this clear distinction between an atypical, *potential* neurogenesis from parenchymal progenitors (that does not exhibit fully or spontaneously *in vivo*) and a constitutive, topographically-restricted, *actual* neurogenesis (intended as a spontaneous neurogenesis from germinal layer-derived neurogenic sites) seems not to be an absolute rule in mammals. In fact, the spontaneous, parenchymal genesis of new neurons has been observed to occur in certain CNS regions of lagomorphs, such as the rabbit striatum (Luzzati et al., 2006) and cerebellum (see article by Ponti et al., in this issue).

This special issue of *Archives Italiennes de Biologie* is focused on two aspects of atypical neurogenesis in mammals, concerning: i) atypical locations of adult neurogenesis not strictly belonging to the CNS (retina, olfactory mucosa, carotid body, taste receptor cells, enteric nervous system); and ii) potential neurogenesis from local, germinative layer-independent progenitor cells located in different regions of the CNS, including additional neurogenic areas existing in non-rodent species. Putting together these aspects, the regulation of neo-neurogenesis in mammals is gaining more elements of complexity. First of all, it is becoming increasingly clear that basal levels of neurogenic activity may be hardly detectable with current technological tools, but levels can increase dramatically under specific physiological, experimental, and pathological stimuli (Ohira et al., 2009). Other issues for the field are the evidence for neurogenesis *in vivo* but a lack of positive identification of the putative stem/progenitor cells in the tissue of origin (e.g. rabbit cerebellar neurogenesis), whereas in other tissues quiescent progenitor cells have been identified (e.g. Ng2+ parenchymal progenitors and human spinal cord central canal stem/progenitor cells; see article by Varghese et al.). Thus, in this expanded view of persistent neurogenic processes, the microenvironment in which stem/progenitor cells live (or are placed) is fundamental in defining their potential. In some cases, such as the olfactory mucosa, a stem cell niche has already been defined (see the article by Mackay-Sim), whereas in others this represents a widely open field of research. The picture emerging from this special issue is that of a theme (the persistence of neurogenic processes) with many variations linked to different variables: the environmental locations (defined by the cellular and molecular composition of different anatomical locations), the type of tissue, the age, and the species. In this context, the goal could be that of trying to understand if "atypical niches" are required to allow the neurogenic process to persist at different locations and at different developmental stages through the "adaptation" of stem cells to highly different tissue environments. In this issues, the article by Leto et al. explores how the prospective white matter can act as a postnatal niche in providing instructive information for determining the fate choices of a common population of multipotent cerebellar progenitors. In the highly heterogeneous picture of CNS structural plasticity raised by these studies, an alternative scenario consists of some immature neurons in the adult brain that are held over from early development maintaining their immaturity in a "standby mode" (article by Gomez-Climent et al., in this issue). Although this type of event could not be classified as "adult neurogenesis", the possible outcomes can be very similar since these immature neurons could represent a further possibility for the adult CNS for recruiting new substrates for synaptic contacts even within the assembled neuronal circuitries.

This Special Issue brings together new insights in a field which is gaining increasing interest and unexpected heterogeneity, and is intended to underline the multifaceted features of neurogenesis persisting in sites of the adult nervous system that are outside the now well known, "classic" neurogenic sites described in the mouse brain (Gage, 2000; Kriegstein and Alvarez-Buylla, 2009). The variety of stem/progenitor cell-tissue interactions represents a new frontier in the highly ramified field of structural plasticity, adult neurogenesis, and brain repair. For instance, further understanding of multifaceted stem cell/tissue interactions could maybe explain some outcomes described in experimental conditions, such as the establishment of atypical perivas-

cular niches after intravenous injections of neural stem cells (Pluchino et al., in this issue).

Specific knowledge about the variety of stem/progenitor cells and their niches in the adult nervous system could contribute to new strategies aimed at circumventing the failure in regeneration and repair that characterizes most of the mammalian nervous system. For this reason, in some contributions of this special issue the possible outcomes of atypical neurogenic locations in the perspective of alternative strategies for therapeutic approach are also discussed.

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