Chapter 9

Parenchymal Neuro-Glio-Genesis Versus Germinal Layer-Derived Neurogenesis: Two Faces of Central Nervous System Structural Plasticity

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/56100

1. Introduction

The discovery of neural stem cells (NSCs) at the beginning of the nineties led many people to consider definitively broken the dogma of a static central nervous system (CNS) made up of non-renewable elements [1-3]. In parallel, the occurrence and characterization of adult neurogenesis in the olfactory bulb and hippocampus [3-5] triggered new hopes for brain repair. Twenty years after, the dream of regenerative medicine applied to brain/spinal cord injuries and neurodegenerative diseases is still very far [6,7]. As a matter of fact, adult neurogenesis in mammals occurs mainly within two restricted areas known as 'neurogenic sites' [3,8]: the forebrain subventricular zone (SVZ); reviewed in [9] and the hippocampal dentate gyrus (subgranular zone, SGZ); reviewed in [10]. As a direct consequence of such topographical localization, most of the CNS parenchyma out of the two 'classic' neurogenic sites remains substantially a non-renewable tissue. Actually, most of the traumatic/vascular injuries and neurodegenerative diseases do occur in 'non-neurogenic' regions and no efficacious therapies capable of restoring CNS structure and functions through cell replacement are at present available. Thus, two decades after the discovery of NSCs and the reaching of a satisfactory characterization of adult neurogenic sites, a gap remains between the occurrence of stem/progenitor cells in the CNS of adult mammals and their effective capability to serve in brain repair. Several aspects do converge in explaining this gap [11], partially accounting for the heterogeneity of CNS structural plasticity in mammals (summarized in Table 1)

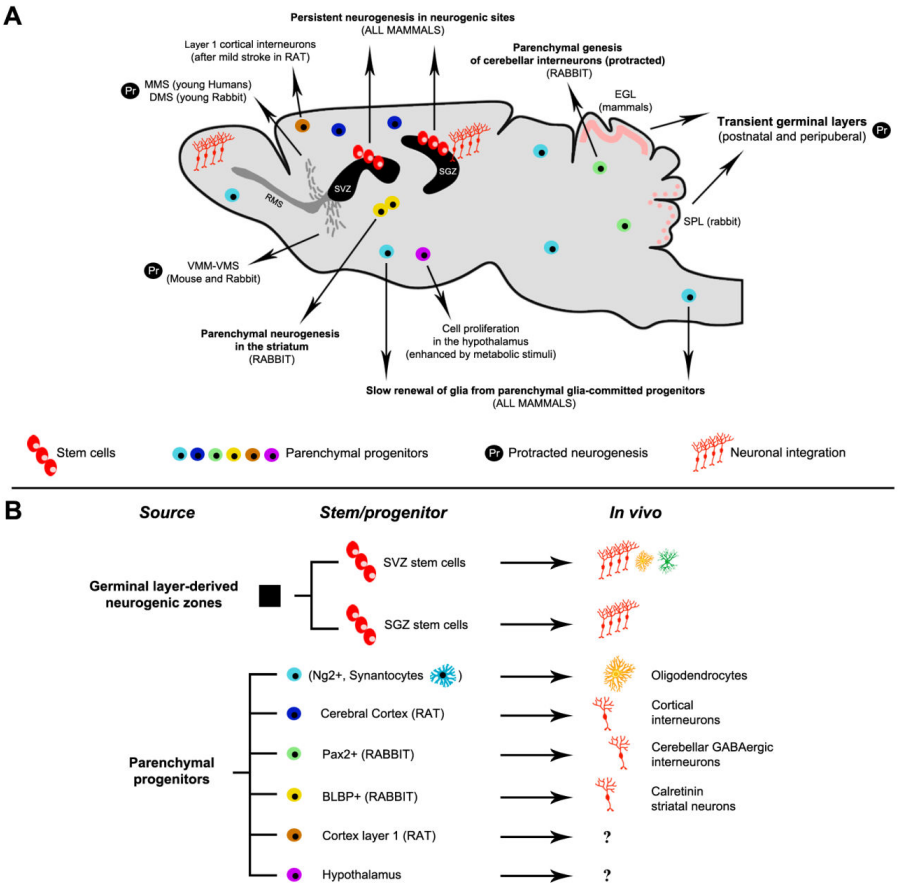

Figure 1. Heterogeneity of postnatal / adult neurogenic processes in different mammals by considering different aspects and mammalian species. B, Schematic summary of the main sources (progenitor cells) of adult mammalian neurogenesis, its outcome in vivo / in culture system, and its possible activation after lesion. In the case of many parenchymal regions, some of these steps are still obscure. BLBP, brain lipid-binding protein; EGL, external germinal layer; GABA, c-aminobutyric acid; Ng2, nerve / glial antigen 2 proteoglycan; NPY, Neuropeptide Y; SGZ, subgranular zone; SPL, subpial layer; SVZ, subventricular zone; VMM, ventral migratory mass; VMS, ventrocaudal migratory stream; MMS, medial migratory stream; DMS, dorsal migratory stream. Adapted from Ref [30].

In this chapter the neurogenic/gliogenic potential of the mammalian brain parenchyma *in vivo* will be analyzed with particular reference to variables involved in its heterogeneity (e.g., animal species, age, CNS regions; see Figure 1 and Table 1). In particular, these variables do determine the tissue environment in which stem/progenitor cells are immersed, what seems to be extremely important for their activity and outcome. In addition, the origin and nature of stem/progenitor cells would also contribute to their neurogenic/gliogenic potential. It is now well known that cells may have a broader potential than they normally exhibit in vivo when

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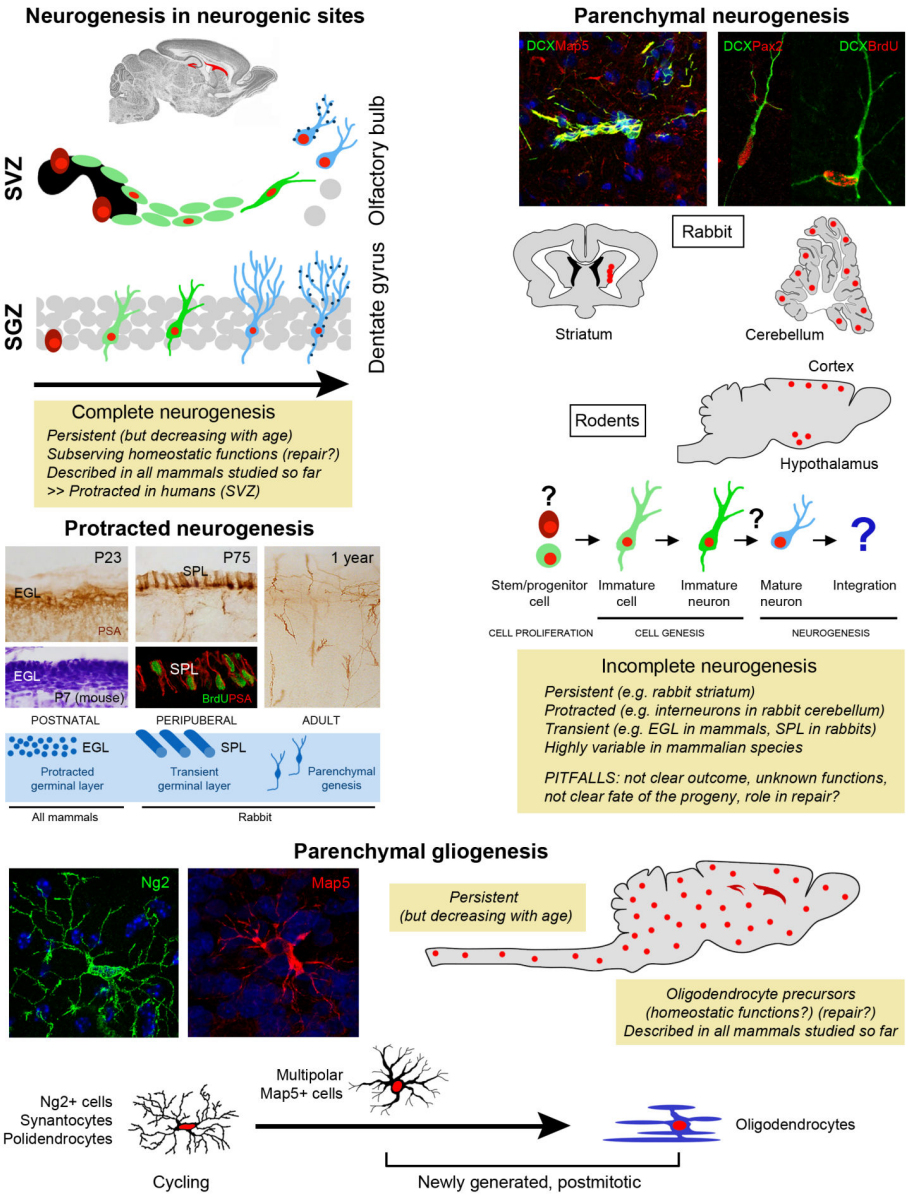

Figure 2. Schematic summary of the features and location of different neurogenic/gliogenic processes occurring spontaneously in the CNS of postnatal and adult mammals. Red dots indicate newlyborn cells. SVZ, subventricular zone; SGZ, subgranular zone; EGL, external germinal layer; SPL, subpial layer (rabbit); PSA, PSA-NCAM; Map5, microtubule-associated protein 1B; P23, postnatal day 23. Question marks indicate lack of knowledge about the origin, late differentiative steps, and final integration of newly generated parenchymal neurons. Adapted from Ref [32].

exposed to a different environment, either in vitro or in vivo [29]. Hence, in order to avoid one of the most common misunderstandings, namely the confusion between occurrence of *de novo* cell proliferation in the CNS tissue and existence of true gliogenic/neurogenic processes, here the attention will be focused on the outcome(s) of the newly generated progeny [30].

A. Variables affecting the nature and features of adult neurogenesis	
Animal species (animal world)	*General plasticity and persistent neurogenesis are usually reduced across phylogeny; in parallel, the reparative/regenerative potential is also reduced*
Animal species (mammals)	*Unlike previous belief and current bias, remarkable differences in the location and extension of adult neurogenesis do exist among mammals*
Age	*Some neurogenic processes are extensions of delayed developmental programs (postnatal/protracted neurogenesis) whereas others persist throughout life (persistent neurogenesis). All neurogenic processes are progressively reduced with age*
Microenvironment (niche)	*A well defined neural stem cell niche sustains neurogenesis in neurogenic sites (SVZ, SGZ), whereas a niche has not been characterized in parenchymal neurogenesis*
Origin of stem/progenitor cells	*Neurogenic sites (SVZ, SGZ) directly derive from persistence and modification of pre-existing, embryonic germinal layers, whereas for parenchymal cell genesis such direct link is not clear*
Location in the CNS	*Location either within a germinal layer-derived niche or in the parenchyma redirects to the two previous points; in parenchymal neurogenesis many variations are linked to local cues of the different CNS regions involved*
Function	*In physiology: linked to the different ecological niches of the animals (present in all animals)* *In repair: linked to the species; in invertebrates and non-mammalian vertebrates the physiological function is associated with function in repair, whereas in birds and mammals it is only linked to physiology/homeostasis of specific systems*

B. Main differences between cell genesis in adult neurogenic sites and in the parenchyma		
	Neurogenic sites	***Parenchyma***
Location	*Restricted*	*Widespread*
Primary progenitor cells	*Stem cells*	*Progenitors*
Microenvironment	*Stem cell niche*	*Mature neuropil*
Origin	*Germinal layer-derived*	*No direct link with germinal layers*
Fate (progeny)	*Mainly neurons (some astrocytes and oligodendrocytes)*	*Mainly glial cells (some neurons)*
Fate (process)	*Complete*	*Incomplete*

Table 1. Heterogeneity of adult neuro-glio-genesis

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Since developmental changes also account for loss of CNS reparative/regenerative capacities and neuro-glio-genic potential, a paragraph will be devoted to the progenitor cell developmental origin. Then, a brief summary of comparative adult neurogenesis will be given. Evolutionary explanations can provide an understanding of the logic followed (or not) by neurogenic processes through phylogeny, also accounting for the failure in mammalian CNS repair/regeneration and scarce usefulness of adult neurogenesis as a possible solution for brain repair [31,32].

2. Developmental origin of adult neurogenic/gliogenic processes

What makes it possible the remarkable neurogenesis occurring in neurogenic sites is their direct origin from embryonic germinal layers which retain stem/progenitor cells along with the 'niche' environment allowing their activity [10,33]. The SVZ and SGZ actually are remnants of their embryonic counterpart, from which they maintain several cellular and molecular aspects [9] in parallel with an adaptation to the changing anatomy of the postnatal and adult brain [34,35].

During development, the CNS originates from the neuroepithelium, pseudostratified epithelial cells that maintain contact with both the ventricular and pial surfaces. As brain thickness increases, neuroepitheial cells transform into radial glia [33,36]. Beside their classic role as scaffolding for migrating neurons during embryogenesis and their subsequent transformation into parenchymal astrocytes of the mature CNS [37,38], radial glia cells behave as stem cells, leading to the genesis of astrocytes, neurons [39,40], and, to a lesser extent, oligodendrocytes [41]. Thus radial glial cells not only serve as progenitors for many neurons and glial cells soon after birth, but also give rise to adult SVZ stem cells that continue to produce neurons throughout adult life [41]. The origin of astrocytes that function as neural progenitors in the adult hippocampus has not been determined experimentally. A connection to radial glial cells, has been suggested even in the hippocampal SGZ [42,43]. The relationship of adult NSCs to their developmental precursors offers clues to the unique characteristics that distinguish these germinal astrocytes from other astroglial cells in the brain parenchyma [33]. Indeed, parenchymal astrocytes lose very early their stem cell potential (around postnatal day 10 in mice [44]), although they can still proliferate in the severe gliosis induced after lesion [45], and resume multipotentiality *in vitro* [46].

On the other hand, gliogenesis persists throughout the CNS in the form of parenchymal cell genesis capable of creating new oligodendrocytes and, to a lesser extent, astrocytes, throughout life [12,15]. Most of this gliogenic activity is attributed to synantocytes/polydendrocytes (Ng2+ cells; see below) which are widespread in the CNS tissue and whose origin is still partially obscure. Oligodendrocytes originate from migratory and mitotic embryonic precursors which progressively mature into postmitotic myelin-producing cells. The sequential expression of developmental markers defines distinct phenotypic stages in the oligodendrocyte lineage, characterized by proliferative capacities, migratory abilities and changes in morphology. Most knowledge on this issue comes from studies on the rodent embryonic spinal cord. The first

oligodendrocyte-committed cell appears at embryonic day 12 (E12) in two columns in the ventral ventricular zone of the motor neuron progenitor domain [47], which is defined by the expression of Olig2 [48]. The embryonic oligodendrocyte precursors are identified by their expression of platelet-derived growth factor alpha receptor (PDGFRα) [49]. The appearence of the oligodendrocyte lineage-associated markers Olig2 (essential for oligodendrocyte specification and differentiation) and PDGFRα (which permits the expansion of the original precursor population) is dependent on the concentrations of Sonic hedgehog (Shh) [50,51]. One or two days after their appearance, PDGFRα+ cells exit the ventricular zone and expand by local proliferation and migration first in the ventral spinal cord region and then dorsally [52]. Finally, they occupy the entire parenchyma by the time of birth [49]. A dorsal source of oligodendrocyte precursors was also shown to contribute to oligodendrogenesis in the spinal cord and hindbrain [53,54]. Fate mapping experiments revealed a double source of oligodendrocyte precursors in the forebrain: cells expressing oligodendrocyte lineage markers, such as Olig1, Olig2, Sox10 and PDGFRα, first appear ventrally, in the neuroepithelium of the medial ganglionic eminence, and then migrate laterally and dorsally into all parts of the developing forebrain by E16 to birth [55]. However, several studies have provided evidence for a dorsal and later source of oligodendrocyte precursors in the lateral and/or caudal ganglionic eminence(s), which constitute a second wave of cells invading the cortex only by E18 [54,56]. Nevertheless, adult oligodendrocyte derive only by dorsal precursors, since medial ganglionic eminence-derived precursors were demonstrated to completely disappear after birth [56]. On the whole, it is thought that a unique oligodendrocyte population can derive from progenitor domains defined by different signaling molecules, in contrast to what has been established for neuronal specification during embryonic development, where different parts of the ventricular zone generate distinct types of neurons. In the rodent CNS, once PDGFRα+ cells have left the ventricular zone, they start to be termed 'oligodendrocyte progenitor cells' and acquire their most typical marker: an integral membrane chondroitin sulphate proteoglycan named Ng2 (nerve/glial antigen 2). Ng2 expression becomes detectable only at E14 [57], thus, from E17 to adulthood all PDGFRα+ cells are Ng2+, and, conversely, all the parenchymal (non-vascular) Ng2+ cells are PDGFRα+ [57,58]. Early embryonic Ng2+/PDGFαR+ OPCs are small, undifferentiated, proliferative and motile cells [59]. During embryogenesis, their morphology changes rapidly from a simple oval or polygonal cell body with few unbranched processes to a more differentiated and branched shape with a smaller cell soma [57,60].

Coming back to adult neurogenesis, non mammalian vertebrates including fish, amphibians, and reptiles harbor a more widespread genesis of neurons in the parenchyma. Such processes, due to their location, are apparently independent from the primitive germinal layers. Nevertheless, recent studies which analysed in more detail the origin of adult neurogenesis in fish show that all neurogenic processes likely originate from remnants of the germinal layers; reviewed in [61]. Teleost proliferation zones reflect a general proliferation pattern along the ventricular walls of the brain, distinctly localized in all its subdivisions along the rostrocaudal axis. Between 12 and 16 distinct proliferation zones have been recognized in different teleost species [61]. Hence, across different animal classes, most stem cell populations retain contact to the ventricular system, and they appear as neuroepithelial cells, radial glial or astroglial cell types. The different shapes of these progenitors have been suggested to be a secondary

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consequence of the architecture of the developing parenchyma overlying the ventricular stem cell zone of the embryo [9]. This common pattern across animal species, along with data reported above on the origin of cycling glial progenitors in mammals, indirectly suggests that adult parenchymal neuro-glio-genesis ultimately derives from embryonic germinal layers, yet being able to persist independently in some cases.

3. Comparative adult neurogenesis and brain repair

Unlike mammals, other classes of vertebrates including fish, amphibians, and reptiles, harbor a more widespread adult neurogenesis in the parenchyma. In these animals, stem and progenitor cells, in addition to their role in physiological plasticity, also participate in brain repair and regeneration. Failure in mammalian brain repair after traumatic, vascular, and neurodegenerative injuries is due to: i) a strong reduction in the extension of neurogenic regions within the whole CNS; ii) a substantial lack of CNS reparative/regenerative capacity; iii) the fact that adult neurogenic sites subserve specific physiological functions rather than brain repair; for review, see [11,62,63]. It is important to note that although the occurrence of good neurogenic potentials would generally favor brain repair (at least by making available stem/progenitor cells) there is not a direct, linear relationship between occurrence of stem/progenitor cells and repair/regeneration, the latter processes strongly depending on the tissue environment and/or tissue reactions; for selected examples of neurogenesis and regeneration see [64].

Neurogenic processes are detectable in wide regions of the CNS in invertebrates and non-mammalian vertebrates [61,65,66], whereas in mammals they are restricted to two privileged areas (neurogenic sites) and the remaining CNS is largely made up of non-renewable tissue [30,67,68]. The state of substantial 'general plasticity' and cell renewal existing in the oldest living metazoans, so that all cell types, including neurons, are balanced in their production and loss [69,70], is progressively reduced in vertebrates, although fish and amphibians still maintain remarkable regenerative capacities [71,72]. Then, in birds and mammals a transition between regeneration permissive and non-permissive stages occurs soon after birth, and highly-restricted spots of adult neurogenesis subserve homeostatic functions in specific neural circuits [73,74]. The decrease in neurogenic abilities occurs in parallel with topographical/numerical restriction of germinal layer-derived stem cell niches, whereas the decrease in regenerative abilities occurs in parallel with other aspects: the impossibility to re-access to embryonic developmental programs during adulthood [75], the lack of differentiated cells capable of dedifferentiation [76], the development of a strong immune surveillance [77] and the consequent tissue reactions, most of which detrimental (reviewed in [11,64]). In some cases, the stem cells found in the CNS of non-mammalian vertebrates are deployed for postnatal development of parts of the brain until the final structure is reached. In other cases, postnatal neurogenesis continues into adulthood leading to a net increase of the number of neurons with age. Finally, in other cases, stem cells fuel neuronal turnover. An example is the protracted development of the cerebellar granular layer in mammals, which in adult teleosts actually

becomes a persistent neurogenesis, where the granular layer continuously grows and no definite adult cerebellar size is reached [61].

In addition, when considering mammals, the failure in CNS repair is a result of evolutionary constraints in which the injured tissue would not favor a strategy of regeneration but rather one of minimizing further damage (e.g., gliotic reaction [78]). Hence, as a consequence of multiple, converging aspects, CNS regenerative capacity in mammals could have reached a point of non-return, in parallel with the persistence of some neurogenic processes which remain mainly focused on physiological functions (e.g., cell renewal/addition in selective neural circuits linked to learning/memory tasks [73,74]).

An increased consciousness that the scarce reparative capacity of the mammalian CNS depends on multiple aspects should indicate that it is very unlike the finding of a single molecular factor or pharmacological treatment capable of eliciting repair/regeneration. Comparative results from vertebrate species of different classes have demonstrated that adult neurogenesis is widespread among vertebrates but is employed by different species in different functional contexts [74,79,80], and a growing number of reports show a remarkable heterogeneity even among mammals [17-19]. This variability concerns both the organization/extension/function of the two neurogenic sites and many examples of parenchymal neurogenesis; reviewed in [30] (see below). This fact, along with our still incomplete knowledge of adult neurogenesis in humans (especially within the parenchyma), partially hampers the reaching of well established 'common rules' which might be used in the translation of experimental preclinical data to human medicine. Thus, dealing with mammalian CNS structural plasticity, high levels of heterogeneity involving different 'types' of neurogenic processes should be taken into account.

4. Heterogeneity of cell genesis in the mammalian CNS

We now know that 'classic' neurogenic sites are consistently present in all mammals studied, although with some differences, particularly when the outcome(s) of the neurogenic process are involved [30]. The occurrence of a rostral migratory stream which is active throughout life in rodents but temporally restricted to the postnatal period in humans [81] is a prototypical example of variability among mammals. Indeed, in humans this neurogenic process seems to fall in a delayed developmental process rather than adult neurogenesis (see below).

In addition to neurogenic sites, studies carried out during the last two decades revealed the presence of local, parenchymal progenitors which retain some proliferative capacity in most of the mature mammalian CNS [12,14,15,17-19,82] (Figure 1). This fact suggests that structural plasticity involving *de novo* cell genesis in the CNS could be more widespread than previously thought. As a consequence of the increasing number of reports investigating adult neurogenesis in mammals, our perception of this biological process has gained new perspectives and nuances; for deeper analysis see [30,66,83,84]. What was previously thought as "the genesis of new neurons in restricted brain areas endowed with NSCs", can now be intended as a highly heterogeneous phenomenon (summarized in Figures 1 and 2), whose heterogeneity depends

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on several variables (see Table 1). The main elements of heterogeneity can be summarized as follows: i) the location of progenitors (gathered within restricted neurogenic sites or widely spread out in the parenchyma); ii) the nature of the progenitors (*bona fide* NSCs versus different types of progenitors); iii) the genetic and molecular features of the progenitors (cell lineage: neuronal-like versus glial-like; identification of differentiative stages dependent on the available markers); iv) the existence or not of well characterized neurogenic niches (absence of niches or occurrence of atypical/non-identified niches in the parenchyma?); v) the extension in time after birth (protracted, transient persistent neurogenesis); vi) the ultimate fate of the progeny in terms of cell lineage (neuronal versus glial; astrocytic versus oligodendrocytic); vii) the ultimate fate of the progeny in terms of cell integration into circuits (complete versus incomplete neurogenesis); viii) the spontaneous occurrence of the process versus its injury-induced appearance. This latter point could be considered a further step beyond the so-called 'constitutive' neurogenesis, namely the spontaneous, continuous genesis of new neurons as part of a physiologic, homeostatic process [85].

Due to the multifaceted aspects of the above mentioned processes, some problems of terminology can also be raised (see Refs. [30,32]). A common misunderstanding consists of a different use of the word 'neurogenesis', which can be intended either as 'genesis of neurons' or as 'genesis of neural cells', i.e. neurons and glia. Embryonic neurogenesis, namely the process of building up the whole CNS, involves both neuro- and glio-genesis, occurring in largely overlapping and strictly intermingled phases, whereas neurogenesis and gliogenesis can occur separately in the adult. The landscape is even more complex, since research on adult neurogenesis brought developmental neuroscience within the mature brain, and the intermix of structurally plastic changes involving cell genesis/differentiation with the fully assembled adult tissue is accompanied by a previously unexpected intermix of cell lineages (e.g., newly formed neuroblasts arising from astrocytic-like stem cells *in vivo*). For this reason, in this review article, when not speaking of well characterized cell lineages, the notion of 'cell genesis' instead of 'neurogenesis' will be used, since in most 'neurogenic' processes different cell types can be considered among the progenitors, and different progenies can be generated. Hence, apart from detailed knowledge gathered around the activity of SVZ and SGZ neurogenic sites, many aspects of parenchymal cell genesis remain obscure and/or unesplored, as a consequence of the heterogeneity depicted above. In the last few years, parenchymal neuro-glio-genesis was among the most studied, yet less known, issues, due to the widespread location of the progenitor cells and to the substantial lack of markers which specifically identify their real origin as well as the stage-specific steps of their differentiation. As a consequence, the presence/absence of neurogenic processes within different CNS parenchymal regions in different mammalian species is still quite controversial and debatable. In most cases, parenchymal cell genesis occurs at low levels, at the limit of technical detection. Furthermore, in some cases it is very difficult to show its final outcome(s), most of the parenchymal neurogenesis appearing 'incomplete' as to the final differentiation/integration of the progeny [30] (Figure 2). Finally, to correctly classify both germinal layer-derived and parenchymal neurogenesis some other aspects should be taken into account, such as the temporal extension of 'protracted'/'transient'developmental neurogenic processes with respect to a 'constitutive'/'persistent' neurogenesis [30]. A further aspect is that of lesion-induced neuro-glio-genesis, namely the genesis

of new cells as a consequence of different types of CNS injury [18,25,26,86] or altered homeostasis [87]. This is an important point since many lines of research in the field of neural repair directed to manipulate stem cells in the perspective of intracerebral transplantation did not produced substantial therapeutic innovations. As an alternative, another approach might be that of stimulating/modulating the endogenous sources of cell progenitors present both in germinal layer-derived stem cell niches (SVZ and hippocampus) and in the parenchyma.

5. Parenchymal neurogenesis

Spontaneous (constitutive) parenchymal neurogenesis can be considered as a very rare phenomenon in mammals, and its regional location has been shown to be dependent on the animal species, age, and physiological/pathological states [30]. Different examples of neurogenesis occurring outside the two neurogenic sites have been described in rodents [17,82], rabbits [18,19] and monkeys [22,88]. Remarkable differences can be observed between closely related orders (e.g., rodents and lagomorphs [18,19]), between species (e.g., rat and mouse [17,23,89,90]), and even different strains [91,92].

Most parenchymal neurogenesis described in adult rodents seems to occur spontaneously at very low levels, rather being elicited/enhanced after specific physiological or pathological conditions [17,82,86,87] (see below). Dayer and colleagues [17] showed the occurrence of new neurons in the deep layers of the rat cerebral cortex. By labelling newlyborn cells with multiple intra-peritoneal injections of BrdU and using markers of both immature and mature neurons to characterize the new cells through a detailed confocal analysis at different survival times, they demonstrated genesis of new GABAergic interneurons in both neocortex and striatum. At 4-5 weeks survival time, the 0.4 +/- 0.13% of the BrdU+ cells were mature NeuN+ neurons in the neocortex. Morphologic and phenotypic analyses assert these cells belong to different categories of cortical interneurons. Interestingly, although several BrdU+/DCX+/Tuc4+ neuroblasts were identified close to the SVZ periventricular region, the great majority of cortical BrdU+ cells were positive for Ng2. From these data the Authors suggested that adult cortical newborn interneurons might originate from *in situ* progenitors. Other examples of spontaneous parenchymal neurogenesis have been described in lagomorphs. In rabbits, newly generated neurons are spontaneously produced in other regions of the adult brain starting from local, parenchymal progenitors. In the caudate nucleus, newly formed neuroblasts form longitudinally-arranged, doublecortin (DCX) and PSA-NCAM immunoreactive striatal chains similar to the SVZ chains [18]. These neuroblasts are generated from clusters of proliferating cells which express the astroglial marker brain lipid binding protein (BLBP), and about 1/6 of surviving cells differentiate into calretinin striatal interneurons. Always in rabbits, in sharp contrast with our common knowledge concerning the CNS of other mammals studied so far, a remarkable genesis of cells is detectable in the peripuberal, and to a lesser extent, adult cerebellar cortex [19]. Systemically-administered BrdU detected at different post-injection survival times (up to two months) reveals newly generated PSA-NCAM+/DCX+/Pax2+ interneurons of neuroepithelial origin homogeneously distributed in the cerebellar cortex. Thus, in the striatal and cerebellar parenchyma of lagomorphs new neurons are generated

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independently from the remnants of germinal layers, yet their final outcome and their role in the adult neural circuits remains obscure; reviewed in [30].

The heterogeneity in parenchymal neurogenesis adds to that described for neurogenic processes occurring in adult neurogenic sites, which have been related to adaptation to ecological pressures [80]. At present, this is one of the most satisfactory functional explanations for adult neurogenesis in the entire phylogenetic tree, along with multiple, genetically-determined variables spanning from the brain anatomy/developmental history to the animal lifespan [93]. This range of possibilities can also be increased by non-genetic variables, such as experience-dependent cues [79,80].

Among the unsolved issues of parenchymal neurogenesis are the numerous reports which have not been confirmed by further studies or by other laboratories [22,23,26,94-96], along with a series of data which have been denied in studies trying to reproduce the same results [24,97-99]. Without entering in the scientific and technical discussion about these controversies, it is evident that we still not grasp the real limits of parenchymal neurogenesis and that further studies are required before finally accept or deny the existence of some neurogenic processes.

A case placed in between the spontaneous and experimentally-induced neurogenesis, is that of the hypothalamus. Several publications based on experiments carried out on rodents have been reporting data on this brain region as a new site for adult constitutive neurogenesis in mammals (for review see [100]). Under physiological conditions, both in rats [101] and mice [102,103], proliferative activity does occur in the ependymal layer of the third ventricle and within the surrounding parenchyma. In rats, Xu and collaborators using electron microscopy and immunohistochemistry showed that tanycytes lining the 3rd ventricle proliferate and express molecules usually found in glial, stem-like progenitor cells, such as BLBP and nestin. The presence of putative neural progenitors was further supported by the isolation of cells able to give rise to neurospheres from the hypothalamus. One month after BrdU injection, proliferating cells, some of which expressing Hu protein, were detected in the surrounding parenchyma. Similar results were obtained in mice [102], yet in both rodent species no clear evidence has supported constitutive and complete hypothalamic adult neurogenesis under physiological conditions. A significant increase in hypothalamic proliferating cells can be obtained by performing i.v. delivery of BrdU (350% more positive nuclei, in comparison to i.p. treated animals), nevertheless, in spite of such cell proliferation the level of neurogenesis in the intact hypothalamus seems to be arrested at a very premature stage. On the other hand, growth factor infusion [82,101,104] or certain experimental conditions/models, such as prolonged heat exposure [105] and the mutant mice investigated by Pierce and Xu (2010), seem to increase neurogenesis in the hypothalamus. Intracerebroventricular infusion of insulin growth factor I in rats [104] triggered an intense proliferation along the 3rd periventricular area and in the parenchyma of the caudal hypothalamus. As concerns the genesis of new neurons, after i.v. treatment with bFGF in rats [101], and CNTF in mice [82], it was shown that proliferation induced by growth factors can be followed by genesis of newborn neurons. Detailed morphological and molecular analyses of the 3rd periventricular region of these animals showed interesting architectural similarities with the SVZ neurogenic niche (e.g., proliferating astroglial cells contacting the ventricle by an apical process bearing a single cilium), with

tanycytes as primary proliferating elements lining the 3rd ventricle [104]. Yet, additional studies are necessary to clearly demonstrate/confirm whether hypothalamic newborn neurons generated after physiological/pathological stimulation actually become part of the pre-existing circuits playing a role in energy-balance mechanisms.

Taking into account the multifaceted aspects dealing with parenchymal neurogenesis, difficulties encountered in such type of research are not only technical. They are also linked to the occurrence of processes placed in the middle between two well characterized extremes of structural plasticity, such as synaptic plasticity, and 'complete' adult neurogenesis. In a recent review article [30] five levels have been dissected in the neurogenic processes in order to critically evaluate/compare different parenchymal neurogenic events (see also Figure 2). The subsequent steps span from cell division to possible integration of specified/differentiated elements into the CNS tissue, and according to this view, only when any of the five steps are filled the neurogenic process should be classified as 'complete'. As a result, all the parenchymal neurogenic processes described until now can actually be considered as incomplete. This could explain why many claims of neurogenic processes were subsequently refuted because not sustained by experimental evidence. The piriform cortex is one of those regions in which results reported by different researchers are quite controversial; see for example [88,106-108]. Since long time, this cortical region is known to harbor a population of neurons immunoreactive for PSA-NCAM and DCX [108-110], which are two markers highly expressed in newly generated neurons but also present in non newly generated cells [110]. Indeed, deeper investigations have shown that the piriform cortex contains a population of immature, non-newly generated neurons which display very few (or no) synapses and are frequently ensheathed by glial lamellae [108]. These cells, by remaining in an immature state for indeterminate time, can represent a 'reservoir' of neurons that could possibly be recruited into the preexisting neural circuits although not generated *ex novo* [111].

In conclusion, alternative and multiple forms of plasticity involving neurons can overlap within the so-called non-neurogenic tissue, affecting preexisting cells/circuits and increasing the complexity of the whole picture of brain structural remodeling.

6. Lesion-induced (reactive) neurogenesis

Brain lesions have been shown to stimulate neurogenesis in normally non-neurogenic regions such as the neocortex and the striatum. In the neocortex these responses are limited to specific conditions such as targeted apoptosis or mild ischemia [23,86,112,113]. By contrast, several lesion paradigms, associated to both strong or mild degeneration and inflammation, have been shown to induce neurogenesis in the striatum [25,28,114]. It is unknown if lesioned neocortex and striatum have distinct needs for immature neurons or if the neocortical tissue response is more detrimental for neurogenesis. This fundamental point reveals our very poor knowledge of lesion-induced neurogenesis. Indeed, despite an intense research, we have only little information regarding the nature, fate and potential of the progenitors stimulated by brain lesions, the mechanisms that trigger their activation and eventually their functional role.

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Initial studies in both cortex and striatum reported that a tiny fraction of lesion-induced neurons may differentiate into projection neurons, suggesting that endogenous neuronal progenitors may have the potential to replace degenerated neurons [23,25,115]. However, these results have not been confirmed by others [28,116]. Moreover, it is now clear that most of the lesion-induced neurons have a transient existence and, at least in the striatum, they do not express markers of projection neurons nor transcription factors involved in their specification [28,116]. Several attempts have been made to increase the survival of these cells, with little success [117]. An intriguing possibility to be explored is that lesion-induced neuroblasts occurring in multiple forms of brain injury are committed to transient neuronal types, which contribute to restorative rather than replacement mechanisms [28,63]. This idea is further supported by data showing that a transient existence often characterizes also cortical and striatal neurons generated in normal conditions [18,89].

Neuronal progenitors in the SVZ and SGZ have been shown to respond to injuries by strongly increasing their proliferation, in the SVZ, also migrating towards damaged regions [25,115]. In parallel, recent reports have showed that in the degenerated neocortex and striatum, new neurons can also be produced locally from parenchymal neuronal progenitors [28,83,113]. In the neocortex, Ohira et al. [86] showed that mild ischemia might stimulate the generation of newborn GABAergic interneurons from progenitors residing in cortical layer I. These cells were not quiescent in normal conditions as they expressed the endogeneous marker of cell proliferation Ki67 and they could be labeled with retroviral vectors. Ohira and coworkers could not define the exact nature of the parenchymal progenitors, which, intriguingly, are very close to the leptomeninges, from which neuronal progenitors have been recently isolated [118,119].

More specific lineage tracing study will be necessary to confirm the real origin of neural progenitors activated after lesion. Lineage tracing has shown that reactive astrocytes isolated from the adult neocortex can give rise to neurospheres *in vitro* [46,120]. To date, the only *in vivo* evidence that neocortical astrocytes can be neurogenic has been obtained in early postnatal mice after hypoxia/Ischemia [113]. A recent study showed that even if the neural stem cells derived from adult neocortical astrocytes maintain the capacity for self-renew when transplanted in the SVZ, they were still unable to produce neurons [121]. This observation casted some doubts over the actual role of these cells as neuronal progenitors *in vivo*. Nonetheless, this result may only indicate that the neurogenic potential of cortical and SVZ progenitors rely on distinct factors.

Another example of the *in vivo* genesis of new neurons within the lesioned brain parenchyma has been obtained in the striatum in a mice model of progressive striatal degeneration, the $Creb1^{Camkcre}Crem^{-/-}$ mutant mice (CBCM) [28,122]. In this model the SVZ acts as a source of postmitotic neuroblasts that enter the striatum from a specific subcallosal migratory stream, as individual elements. Luzzati and coworkers [28] showed that the striatum of CBCM mice contains also tightly clustered neuroblasts which originate locally from parenchymal proliferating progenitors. These cells showed features of intermediate neuronal progenitors of the SVZ and SGZ such as clustering and co-expression of glial (Sox2, Sox9, BLBP) and neuronal markers (Dlx, Sp8, DCX), and the expression of the EGFr [123-126]. This study clearly shows that the mature parenchyma can be permissive to neuronal genesis, although Luzzati and

coworkers could not trace the origin of the observed striatal parenchymal neuronal progenitors. Nonetheless, two possibilities can be considered: i) striatal neuronal progenitors could derive from the displacement of primary/intermediate progenitors from the SVZ; ii) they could represent local cells becoming neurogenic in response to neurodegeneration.

Together, these data suggests that specific degenerative conditions can stimulate the production of new neurons not only in the neurogenic niches but also in the mature brain parenchyma. This tissue has been classically considered non-permissive for neuronal progenitors, an idea mainly derived from the observation that SVZ and SGZ neural stem cells differentiate only into glial cells when transplanted into the brain parenchyma (for review, see [127]). In light on the accumulating evidence for parenchymal neurogenesis, the classical concept that the mature brain parenchyma is not permissive for the genesis of new neurons should be restricted to SVZ and SGZ progenitors. Yet, future studies should better analyze whether factors modulating the lesion-induced parenchymal neurogenic potential may differ from those acting on 'classic' neurogenic site progenitors.

7. Parenchymal gliogenesis

In the past, neurogenesis and gliogenesis had always been kept separate, the latter being considered less important than the former. In recent years, adult gliogenesis has been re-evaluated as many populations of progenitor cells with glial-like features and proliferative capacity have been shown to exist in the mature mammalian CNS [13,15]. Actually, parenchymal cell genesis in the so-called non-neurogenic regions is mainly gliogenic. In most regions of the CNS, parenchymal progenitors assure a slow process of 'constitutive' gliogenesis leading to renewal of oligodendrocytes and, to a lesser extent, astrocytes [12,15,128]. In rodents, the major population of cycling progenitors located outside the germinal niches are Ng2+ cells morphologically, antigenically, functionally distinct from mature astrocytes, oligodendrocytes and microglia [12-15]. These cells are also called 'polydendrocytes' to highlight their stellate morphology and lineal relationship to oligodendrocytes [15], 'synantocytes' [14] for their contiguity to neurons, or 'oligodendrocyte progenitor cells' (OPCs) because found able of generating myelinating oligodendrocytes [12,129,130]. Nevertheless, many polydendrocytes remain as a resident cell population of Ng2-expressing cells in the mature white and grey matter after oligodendrocytes are generated. Thus it is widely accepted they represent the fourth CNS major glial population [15], representing 2-9% of total cells [13]. In the last decade, Ng2+ cells have generated a lot of interest among neuroscientists, because they show a series of features quite unusual in OPCs. These include: i) an almost uniform distribution in both grey and white matter areas; ii) a stellate morphology; iii) an intimate association with neurons from which they receive synapses [13,14]; iv) proliferative capacity in the adult brain [13,131, 132], and v) a potential for giving rise to astrocytes and neurons that may be recruited to areas of lesion in the context of brain injury or pathology [128]. At present, it is generally accepted that polydendrocytes are OPCs, even if the demonstration that polydendrocytes differentiate into mature myelinating oligodendrocytes *in vivo* is challenging, because Ng2 expression is lost before the terminal differentiation of these cells and the appearance of mature oligoden-

http://dx.doi.org/10.5772/56100

drocyte antigens. Some observations provide circumstantial evidences for the oligodendroglial fate of polydendrocytes *in vivo*. For instance, they co-express the PDGFRα, and during the first postnatal week, in the corpus callosum and cortex, they start expressing the immature oligodendrocyte antigen O4 [133]. Polydendrocytes also express the basic helix-loop-helix (bHLH) transcription factors Olig1 and Olig2, which are required for oligodendrocyte specification and differentiation [132,134] as well as Sox9 and Sox10 transcription factors. Moreover, pulse-chase labelling of proliferating cells using 5-bromo-2′-deoxyuridine (BrdU) revealed that the number of BrdU+Ng2+ cells decreases while that of BrdU+ oligodendrocytes increases over time [12,135]. Cell grafting experiments have shown that polydendrocytes give rise to myelinating cells when they are transplanted into an environment free of endogenous myelinating cells [136]. Recently, more direct evidence for the oligodendroglial fate of polydendrocytes was obtained from cell fate-mapping experiments using transgenic mice that express Cre recombinase (Cre) in Ng2-expressing cells or that express inducible Cre (CreeR), under the regulation of the Cspg4, PDGFRα or Olig2 genes, which enable determination of the fate of polydendrocytes at a given time during development [95,137,138]. These studies showed that oligodendrocytes continue to be generated in the mature brain.

Early cell-culture studies showed that OPCs purified from rat optic nerves differentiate not only into oligodendrocytes but also into process-bearing 'type-2 astrocytes' in the presence of serum factors, which led to the concept of bipotential oligodendrocyte type-2-astrocyte (O-2A) progenitor cells [139]. There are now controversial observations suggesting that bipotentiality of polydendrocytes might be real or an *in vitro* artifact [136,140,141], and most likely these cells are inherently capable of differentiating into astrocytes but are prevented from fulfilling their astroglial fate in the normal *in vivo* environment [128].

On the whole, while all of these studies consistently support the oligodendrocyte lineage of the Ng2+ cells, the genesis of astrocytes from Ng2+ cells is confirmed only during postnatal ages. All these different and sometimes controversial results may be explained by some methodological/technical differences, but may also reflect heterogeneity in progenitor cell populations⁄subpopulations (mostly not yet identified), which is far to be elucidated [98]. In this context, we have recently identified a population of multipolar glial cells immunoreactive for the microtubule associated protein 5 (Map5) [142], which share features but also differences with Ng2+ progenitor cells [19]. These multipolar, Map5+ cells are newly generated, parenchymal elements of the oligodendroglial lineage, which represent a stage-specific population of polydendrocytes (Crociara et al., in preparation; Figure 2).

8. Conclusion and future perspectives

The CNS of mammals, in spite of having lost most of its regenerative/repair capacity with respect to other phyla, is endowed with remarkable plasticity. This property is heterogeneously distributed in different regions and can manifest in different ways. A better knowledge of the various forms of spontaneous and lesion-induced structural plasticity, of their mutual relationships and of the relative underlying mechanisms is fundamental in order to figure out

new efficacious therapeutic perspectives for brain repair. During the last two decades, the discovery of neural stem cells and the studies on adult neurogenesis have opened the intriguing possibility of cell replacement-aimed therapeutic strategies. Under pressure of this perspective, studies on CNS stem cells and progenitors have increased exponentially, sometimes leading to excessive emphasis about theoretical correlations between neuro-glio-genic processes and brain repair. In this context, focusing on the 'real' neurogenic/gliogenic potential of the mammalian CNS should avoid to turn an exciting biological discovery into a therapeutic illusion. Indeed, the approach of regenerative medicine applied to the CNS is still hampered by overwhelming problems concerning the final integration of both transplanted and endogenously-induced cells [6]. The reason of this failure might be mostly due to evolutionary constraints [78], and to the fact that cell renewal typical of adult constitutive neurogenesis is primarily involved in tissue homeostasis of highly restricted regions, being hardly useful in response to external injury and neurodegenerative brain damage affecting the parenchyma [11,62]. On the other hand, the parenchymal cell genesis might represent a new plastic potential to be explored within wide regions of the CNS, including those areas affected by different neurodegenerative diseases and traumatic injuries. With respect to classic SVZ and SGZ neurogenesis, parenchymal neuro-glio-genesis does constitute an alternative source of progenitors, although with different outcomes [30]. Indeed, a vast number of reports currently published in this domain, although accurate and carried out with multiple technical approaches, do suggest that in most cases newly formed elements barely survive and do not fully integrate. In addition, the extreme heterogeneity of parenchymal neuro-glio-genesis makes the brain parenchyma a harsh territory, in which many questions remain unanswered and new ones are opened (see Box 1). For instance, beside a deep knowledge on the cell cycle and early cell lineage in neurogenic sites (see for example [143,144]), such information is starting to be gathered only in specific perenchymal regions and or situations [145,146]. Hence, further studies of parenchymal stem/progenitor cells, on their origin and their different fates and outcomes, should grant new challenges in the multifaceted field of CNS structural plasticity and repair.

- Which is the real extension of parenchymal cell genesis in the CNS of different mammals and in humans?
- Do parenchymal progenitors divide asymmetrically?
- Which are the real stemness properties of different parenchymal progenitors?
- Which stem/progenitor cells do contribute to postnatal neurogenesis but become depleted as their progeny differentiates, and which continue to replenish the stem/progenitor cell reservoir?
- Which is the origin of the different types of parenchymal progenitors?
- What is(are) the ultimate fate(s) of parenchymal neuro-glio-genesis?
- Which are the specific stimuli that can trigger quiescent parenchymal progenitor cell division and differentiation?
- Can the fate of parenchymal progenitors be altered by microenvironmental cues or it is predetermined? To which extent these changes do depend on regional localization?
- Can distinct parenchymal stem/progenitor cells be forced to produce unusual progeny if needed?
- Which are the factors leading to the progressive decrease of neurogenic and gliogenic activity with increasing age, both in neurogenic sites and parenchyma?

Box 1. Some open questions

http://dx.doi.org/10.5772/56100

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