Stem and progenitor cells from the central nervous system: basic aspects and clinical relevance

Células-tronco e progenitores no sistema nervoso central: aspectos básicos e relevância clínica

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ABSTRACT
Aberrant neurogenesis has been correlated with different pathologies such as neurodegenerative diseases, epilepsy, Down syndrome and depression. This review discusses the involvement of neural stem cells and neuroprogenitors in the development and maturation of the nervous system. In particular, the functional relevance of these cells to the central nervous system at both the physiological and pathological contexts is highlighted, along with new therapeutic strategies based on modulation of adult neurogenesis.

Descriptors: Stem cells; Central nervous system/cytology; Central nervous system/physiology; Neurons/cytology; Tissue therapy

RESUMO
Distúrbios no processo de neurogênese têm sido correlacionados com diferentes patologias, como doenças neurodegenerativas, epilepsia, síndrome de Down e depressão. Nessa revisão, discute-se o envolvimento de células-tronco neurais e neuroprogenitores ao longo do desenvolvimento e maturação do sistema nervoso. São destacadas a relevância dessas células ao funcionamento do sistema nervoso central nos contextos fisiológico e patológico, bem como novas estratégias terapêuticas baseadas na modulação da neurogênese pós-natal.

Descritores: Células-tronco; Sistema nervoso central/citologia; Sistema nervoso central/fisiologia; Neurônios/citologia; Terapia tissular

STEM CELLS AND THE DEVELOPMENT OF THE NERVOUS SYSTEM
Stem cells (SC) are undifferentiated cells with the capacity to self-renew and to originate mature and specialized progenitor cells⁴⁻⁵. According to their differentiation capacity, SC are classified as: totipotent, capable of generating embryonic and extra-embryonic cells, e.g., zygote; pluripotent, capable of generating specific cells originated in the three germ layers, e.g., embryonic SC (ESC); multipotent, with limited capacity to generate different types of specialized cells, e.g., most of adult SC (ASC), such as mesenchymal cells; and oligo- and unipotent, cells with a limited potential for differentiation, e.g., hematopoietic SC⁶⁻⁷. Presently, the clinical use of SC is limited to ASC transplants, especially those derived from bone marrow and umbilical cord blood, for hematopoietic system reconstitution⁸⁻⁹.

SC may originate progenitor cells, which have a limited capacity for self-renewal and cellular differentiation. In the literature, SC and neural progenitors are referred to as neural precursor cells⁴⁻⁸.

In the central nervous system (CNS), neural SC (NSC) and neuroprogenitors are involved in the generation of neurons, astrocytes and oligodendrocytes⁴⁻⁸, and play an important role in the maturation of this system in the fetal and postnatal phases, as well as in maintaining their physiological integrity during the adult phase⁹ (Figure 1).

During embryonic development, the nervous system is initially divided into prosencephalon [forebrain], mesencephalon [midbrain], rhombencephalon and caudal portion of the neural tube. During later phases, the prosencephalon (primitive anterior encephalon) divides into telencephalon and diencephalon, and the rhombencephalon originates the metencephalon and myelencephalon. At later stages, the telencephalon...
originates the cerebral cortex, basal ganglia, hippocampal formation, amygdale and olfactory bulb; the diencephalon originates the thalamus, hypothalamus, subthalamus, epithalamus, retina and optic nerves and tract. The metencephalon originates the pons and the cerebellum, while the myelencephalon gives rise to the bulb. The caudal portion of the neural tube will originate the spinal cord, while the mesencephalon (mid encephalon) has no subdivisions in the mature adult form\(^{(10-11)}\).

A large part of the interneurons of the neocortex, hippocampus and olfactory bulb derive from the subventricular zone (SVZ) of the ganglionic eminence situated in the telencephalon region of embryos\(^{(12)}\). In adults, this SVZ continues as an important neurogenic site\(^{(9)}\). Corticogenesis involves the participation of two distinct populations of neurons. One of them consists of neurons that migrate radially, which arise from the neocortical ventricular neocortical zone and probably originate the pyramidal neurons of the neocortex. Another population is formed by neurons that arise from the ganglionic eminences, which migrate tangentially to the neocortex and probably differentiate into non-pyramidal cortical neurons\(^{(13)}\).

The ganglionic eminences are regions where the basal ganglion originates, and they may be subdivided into medial ganglion eminence (MGE), lateral ganglion eminence (LGE) and caudal ganglion eminence. The LGE cells migrate anteriorly and ventrally, originating neurons in the corpus striatum and olfactory bulb. The MGE neurons migrate dorsally towards the neocortex through the neocortical subventricular zone, where they differentiate into transitory granular neurons in the marginal zone and into interneurons that express gamma-aminobutyric acid (GABA), parvalbumin, calretinin or somatostatin in the cortical layer\(^{(13-15)}\).

Cells from the MGE and LGE have distinct behaviors. The MGE cells migrate extensively in vitro and, in vivo, they have the unique capacity of penetrating and dispersing throughout the adult cerebral parenchyma. LGE cells migrate less extensively in cultures and do not have the capacity to disperse throughout the adult brain. LGE cells are not capable of migrating the long distances of the SVZ in the postnatal and adult CNS, suggesting that SVZ originates in the lateral ventricle of the adult and in the LGE in the embryo\(^{(16)}\).

In rodents, the MGE is a transient structure in brain development that appears approximately on the tenth embryonic day (E10), persisting until embryonic day 16 (E16), when it then unites with the LGE\(^{(13)}\). One study demonstrated that MGE in E13.5 embryos is the primary germ region for neocortical neurons, which will then differentiate into different types of interneurons\(^{(13)}\). On the other hand, LGE cells, during the same embryonic period, do not migrate to the neocortex, but differentiate into neurons of the corpus striatum or migrate ventrally to the olfactory tuberculum and bulb.

**POSTNATAL NEUROGENESIS**

As is true during the embryonic phase, during the adult phase, the brain also displays NSC and neuroprogenitors. These cells are better characterized in the SVZ, situated between the lateral ventricle and the corpus striatum parenchyma, and in the subgranular layer of the dentate gyrus in the hippocampus, although they may also be found in other regions of the CNS, such as the cerebellum\(^{(13,17,19)}\). It is believed that these neuroprogenitors play a vital role in the CNS homeostasis.

In the hippocampus, NSC and neuroprogenitors may be isolated and maintained in vitro by primary culture. Under specific conditions, different specialized CNS cells may originate from these neuroprogenitors, including pyramidal neurons\(^{(19-21)}\). Nevertheless, in terms of treatment, the applicability of transplantation of NSC and of isolated neuroprogenitors from the hippocampus for the treatment of certain neurological diseases, such as epilepsy, is still under discussion\(^{(22)}\).

Another important, although less discussed, neurogenic site in the postnatal phase is the cerebellum. This structure represents merely 10% of the total encephalon volume, but more than half the CNS neurons are present in this region. In humans, the cerebellum is one of the first structures to differentiate and its maturation is finalized during the postnatal phase. In rodents, the cerebellum reaches maturation 15 days after birth. This late development of the cerebellum...
makes it more vulnerable to irregularities stemming from external factors, including the development of mutations. From a scientific viewpoint, however, the late maturation process facilitates the study of development of this important CNS structure, as well as the study of the biology of neural progenitors(23).

**CLINICAL IMPLICATIONS**

The precise control of the neurogenic process is critically important for the maturation and function of the nervous system. During development, changes in the process can be incompatible with life, often resulting in spontaneous miscarriages. The inhibition of neurogenesis, accompanied by excessive apoptosis of neuroprogenitors during the prenatal phase, is related to hippocampal hypoplasia noted in Down syndrome patients(24). During the adult phase, this same phenomenon is related to the development of neurodegenerative diseases. In Parkinson’s disease, for example, depletion of dopaminergic neuronal circuitry is the result of a neurogenic deficiency observed in both the SVZ and the subgranular zone of the dentate gyrus, as attested in post mortem brain samples(25). Additionally, many drugs used to treat depression induce neurogenesis in the hippocampus, suggesting that the reduction of hippocampal neurogenesis in adults may be involved in the pathophysiology of psychiatric disorders(26).

Conversely, increased neurogenesis is not necessarily beneficial and may be associated with other pathologies. Some studies suggested that exacerbated hippocampal neurogenesis in response to postnatal cerebral injury is related to the development of epilepsy. Convulsions induced in animal models of temporal lobe epilepsy cause aberrant migration and differentiation of neuroprogenitors. In addition, the newly generated granular neurons display abnormal morphology and do not integrate properly in the hilus and molecular layer of the dentate gyrus, forming reverberating excitatory neuronal circuits. These circuits contribute towards the installation of spontaneous and recurrent seizures characteristic of epilepsy(22,27).

Although the mechanisms controlling neurogenesis are not completely elucidated, especially during the postnatal phase, it is known that modifications in this process are involved in several pathologies. For this reason, new therapeutic strategies focused on the neurogenic process have been tested in preclinical and clinical trials.

**THERAPEUTIC RELEVANCE**

A growing number of in vitro studies of self-renewal and differentiation of fetal and adult NSC have been published in the medical literature, thus contributing to the knowledge of mechanisms and factors controlling the biology of these cells and applications to gene and cell therapies(1). Advancements in this direction have been made primarily in terms of new cancer treatments and procedures for restoration of damaged tissues. In Neurology, more specifically, the application of SC and neuroprogenitor cells has been studied with the intention of treating neurodegenerative diseases, multiple sclerosis, stroke, cancer, and traumas(28). Studies with SC deriving from bone marrow have shown an attenuation of functional loss in experimental models of cerebral ischemia. One of the current hypotheses suggests that transplanted cells induce a release of trophic factors and/or modulation of inflammatory cytokines in the damaged regions, which could provide a favorable environment for regeneration of the damaged tissue(29). In this sense, SC could be used not only to replace damaged cells, but also as a source of biopharmacologicals.

In Brazil, basic and preclinical studies of experimental cell therapy have been using primarily ASC obtained from bone marrow or other alternative sources such as the umbilical cord, adipose tissue and dental pulp. Although clinical studies are scarce, protocols with bone marrow SC in heart diseases have been shown promising results(30). Nevertheless, studies addressing the biology of NSC and potential cell therapy applications in neurological diseases are still rare.

**CONCLUSIONS**

The process of neurogenesis is a great target for the development of new therapeutic strategies in Neurology. However, more basic and preclinical studies must be performed to elucidate the yet unexplored aspects of NSC, their possible therapeutic role in different pathologies and the mechanisms involved. Therefore, improvement of techniques and methods for isolating, characterizing and cultivating SC and progenitors from the CNS should catalyze studies on NSC biology and ensuing applications in Medicine.

**ACKNOWLEDGEMENTS**

The authors thank the financial support given by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes) to students Daniela Emi Suzuki, Márcia Cristina Leite Pereira and Luciana Janjoppi.

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