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Review

The therapeutic contribution of nanomedicine to treat neurodegenerative diseases *via* neural stem cell differentiation

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ABSTRACT

The discovery of adult neurogenesis drastically changed the therapeutic approaches of central nervous system regenerative medicine. The stimulation of this physiologic process can increase memory and motor performances in patients affected by neurodegenerative diseases. Neural stem cells contribute to the neurogenesis process through their differentiation into specialized neuronal cells. In this review, we describe the most important methods developed to restore neurological functions *via* neural stem cell differentiation. In particular, we focused on the role of nanomedicine. The application of nanostructured scaffolds, nanoparticulate drug delivery systems, and nanotechnology-based real-time imaging has significantly improved the safety and the efficacy of neural stem cell-based treatments. This review provides a comprehensive background on the contribution of nanomedicine to the modulation of neurogenesis *via* neural stem cell differentiation.

1. Introduction

The dogma of a static brain was destroyed when Smart and Leblond showed for the first time that glial cells are dividing throughout the mouse brain parenchyma [1]. A few years later, Altman and Das reported the migration of postnatally born neuroblasts from the subventricular zone to the olfactory bulb, providing the first strong evidence of neurogenesis in the adult brain [2]. Important discoveries were made in the following decades, such as the presence of adult-born neurons in the dentate gyrus of rats [3] and in the vocal control nucleus of birds [4], but the perception of neurogenesis has drastically changed only since the 1990s. One of the most important discoveries was the observation that the proliferation of progenitor cells, and the subsequent number of newborn neurons, was dynamic. Several factors such as hormonal stress [5], age [6], and alcohol [7] could modulate this process. The improvement of immunohistological techniques represented another step forward in the description of neurogenesis by providing more sensitive analyses [8,9]. Moreover, the ability to isolate, cultivate, and differentiate neuronal precursor cells *in vitro* provided crucial data on the cellular and biomolecular mechanisms involved in adult neurogenesis [10–12].

In humans, the evaluation of neurogenesis was initially performed by the quantification of the number of cells expressing neuroblast markers such as doublecortin (DCX) or polysialylated-neural cell adhesion molecule (PSA-NCAM) in postmortem brains [13]. These markers were found in significant amounts in two regions of the brain: the subgranular zone (SGZ) and the subventricular zone (SVZ) (Fig. 1). These markers are highly expressed during the fetal and perinatal phases, then expression dramatically decreases during the first postnatal months, and finally slowly declines throughout life [14]. Human adult neurogenesis was recently confirmed by Spalding and colleagues [15]. They measured the annual neuron turnover (1.75%) and concluded that neurons were generated during adulthood at similar rates in humans and mice.

The discovery of adult neurogenesis also showed the limits of this physiologic process. Indeed, neurogenesis is restricted to small areas of the brain (the SGZ and SVZ), called niches, and its impact

Abbreviations: CNS, central nervous system; NSC, neural stem cells; SVZ, subventricular zone; SGZ, subgranular zone.

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on the adult organism is very limited.

The identification of neural stem cells (NSC) and their role in adult neurogenesis motivated researchers to explore the regenerative potential of these cells. The design of therapeutics able to modulate the differentiation of NSC, and consequently the rate of neurogenesis, represents a promising strategy in the treatment of many neurodegenerative diseases. In this review we underline the significant advancements achieved from the conception to the clinical application of therapies targeting NSC differentiation. We review the therapeutic potential of NSC and analyze how their differentiation could contribute to the treatment of neurodegenerative disorders. Although much progress has been made, issues are still associated with the therapeutic use of NSC. In this review, we will underline how nanomedicine can contribute to the improvement of NSC-based therapy.

2. Neural stem cells

2.1. Definition

The current definition of NSC, related to their peculiar biological properties, was based on retrospective *in vitro* studies [10,16,17]. "*We define a neural stem cell as a stem cell derived from any part of the nervous system and which primarily makes cells expressing neural markers (those of astrocytes, oligodendrocytes and neurons) in in vitro culture*" [18].

While there was evidence of adult neurogenesis, the cells involved were not characterized until the end of the 1990s. At that time, NSC were identified and their role in neurogenesis was understood and described.

Long term expansion and differentiation into neural lineages of specific cells isolated from the brain hinted the existence of adult NSC [10,12]. NSC are characterized by the ability to self-renew and to differentiate into neurons, astrocytes, and oligodendrocytes [19,20]. It has long been postulated that adult neurogenesis originated from these tri-potent NSC, which are mostly restricted to the SVZ and the SGZ (Fig. 2A). Unlike other somatic stem cells, the information regarding the localization and the properties of NSC precursors is very limited. The embryonic origins of NSC are not well understood. Adult SGZ-NSC could originate from the ventral hippocampus during the late fetal stage [21], while adult SVZ-NSC are regionally specified at an early embryonic stage [22,23].

2.2. Biological functions

The role of adult somatic stem cells is normally related to the modulation of homeostasis in the tissues. When adult NSC were discovered, it was initially assumed that their function was exclusively to provide a regenerative source of new neurons and glial cells in pathological conditions. Instead, evidence suggested that the primary function of adult NSC was to confer additional plasticity to the brain. Direct and indirect mechanisms were described to regulate such plasticity [24] (Fig. 2B). Intrinsic transcriptional programs directed to gene expression or external signals triggering an intracellular cascade greatly impact the behavior of NSC. Consequently, the identification of the origin of the niche signals is challenging (e.g., the role of calcium levels on the activity of postnatal developing regions [25–27]). Although NSC are multipotent *in vitro*, recent genetic fate-mapping and clonal lineage-tracing of NSC have highlighted the lack of similarities between NSC differentiation *in vitro* and *in vivo* [28]. The niche environment seems to limit adult NSC differentiation. In the adult SGZ, NSC can generate dentate gyrus granular cells while in the adult SVZ, NSC produce neuroblasts, which migrate to the olfactory bulb where they differentiate into interneurons [29]. Moreover, NSC localization in the niches would determine the type of cells derived from NSC. In the SVZ, ventral NSC mostly develop into calbindin-expressing cells, whereas dorsal NSC develop into thyrosine-hydroxylase-expressing cells [30]. These two markers are associated with two different cell types: long-axon and dopaminergic neurons,

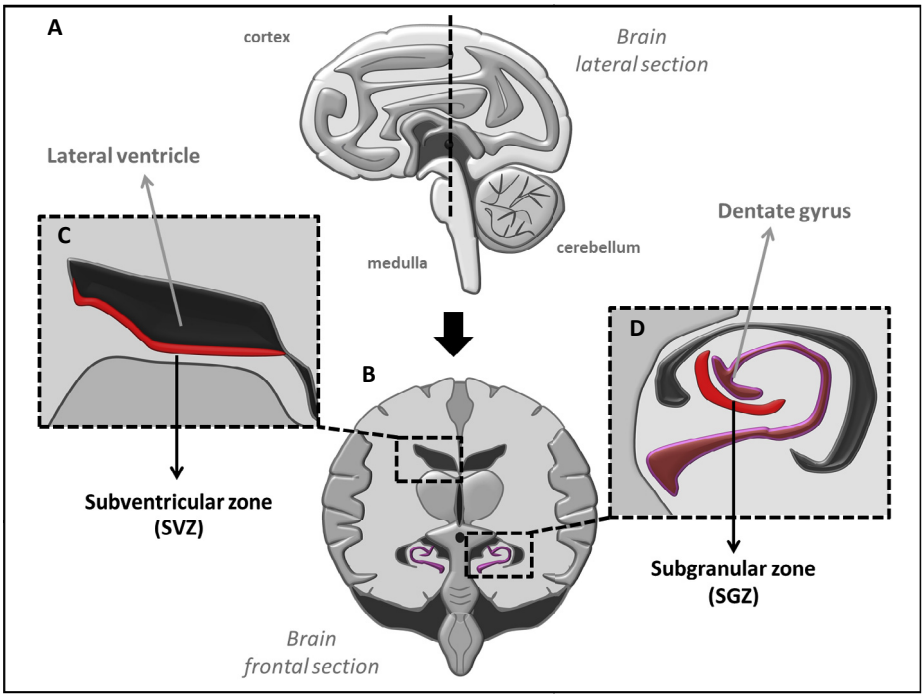

Fig. 1. Neural stem cell niches in the brain. Localization of the subgranular (SGZ) and subventricular (SVZ) zones in an adult human brain. A, lateral section of the brain. B, frontal section of the brain. C, subventricular zone, highlighted in red. D, subgranular zone, highlighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)