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COMMENTARY

Adult neurogenesis: Is it showtime for clinical translation?

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The existence of adult stem cells was first described in tissues with high proliferation rates, such as the hematopoietic system and the intestine. Since then, stem cells have been found in almost all adult tissues, including the nervous system. Adult neurogenesis is supported by multipotent neural stem cells (NSCs), which maintain some of the cellular and molecular characteristics of their embryonic counterparts. Because of their suggestive appeal as therapeutic agents and their presumed relevance for cognition in health and disease, adult neurogenesis is attracting considerable attention from neuroscientists.

A recent study by Alvarez-Buylla and colleagues revealed evidence indicating that adult NSCs were allocated and specified early in embryonic development.[1] They also showed a lineage relationship between the embryonic and postnatal NSCs.[1] It is known that two main regions continue to generate new neurons throughout adulthood: the subventricular zone (SVZ), an extensive germinal niche containing neural stem cells (NSCs) known as B1 cells, and the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus.[2] The B1 cells have astroglial characteristics but retain important neuroepithelial properties.[3] Although this cell lineage has been suggested to contain the central NSC continuum from which differentiated neurons and glia are derived, the fate of these cells derived from progenitors and their origins remain unknown. Using BrdU labeling and *in utero* delivery of GFP-expressing retroviruses bearing at least 10^5 tags (barcodes), the authors found that the majority of the pre-B1 cells were generated from embryonic cells that divided between E13.5 and E15.5. Their results also demonstrated a direct clonal relationship between the progenitor cells that generate the olfactory bulb (OB) interneurons postnatally and those that produce neurons for other regions of the telencephalon during embryonic development.

A previous study has suggested that postnatal stem cells in distinct regions produce different types of neurons, even when they are heterotopically grafted or grown in culture.[4] By reading the barcodes of labeled cells, Alvarez-Buylla and colleagues were able to demonstrate that the positional information within individual embryonic progenitor cells, which determines the types of neurons and glia generated for different forebrain regions throughout embryogenesis, is inherited by pre-B1 cells as early as E11.5. This regional identity is maintained from the embryonic to adult stages, which may be orchestrated by a number of cell-intrinsic and -extrinsic factors.

The size of the NSCs population in the SVZ is associated with several ongoing processes, including self-renewal.[5] Maintaining the balance between NSC and NPCs (neural progenitor cells) in this area is critical to supply the brain with specific neuronal populations, both under normal conditions and after injury. The authors found that only 3.0% of clones contained B1 cells and OB neurons in the V-SVZ, which may suggest that the self-renewal of B1 cells is rare. Therefore, it is possible that the pre-B1 cells remain largely quiescent for different periods of time until they become reactivated to generate separate cohorts of neurons postnatally.

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Elucidating the rules that govern the origin and differentiation of adult neural stem cells might be important, since the generation of neural precursor cells from adult mammals may offer perspectives useful for the development of new strategies for the treatment of CNS disorders. For instance, impaired neurogenesis is an early critical event in the course of Alzheimer's disease (AD), which is characterized by memory impairments and neuronal vulnerability in the hippocampal formation and olfactory circuits.[6] The wild-type presenilin protein and the soluble form of APP (amyloid precursor protein) have both been implicated in the function of adult neurogenesis.[7] Approaches to enhance neurogenesis and/or neuronal maturation could be considered as potential stem cell-based therapies for AD. However, neuronal replacement aiming at functional restoration in AD is extremely complex, because stem cells may predifferentiate into many different types of neuroblasts *in vitro* before being subsequently implanted in a large number of brain areas.[8] Based on the report by Alvarez-Buylla and colleagues, it is clear that the neurogenic potential of embryonic progenitor cells is highly restricted by their locations. Thus, further identification of the temporal and spatial identity of these cells would shed new light on the potential use of cell-based therapy for neurological diseases in the future.

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