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Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells

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Abstract

Recent work in neuroscience has shown that the adult central nervous system contains neural progenitors, precursors, and stem cells that are capable of generating new neurons, astrocytes, and oligodendrocytes. While challenging previous dogma that no new neurons are born in the adult mammalian CNS, these findings bring with them future possibilities for the development of novel neural repair strategies. The purpose of this review is to present current knowledge about constitutively occurring adult mammalian neurogenesis, to highlight the critical differences between ''neurogenic'' and ''non-neurogenic'' regions in the adult brain, and to describe the cardinal features of two well-described neurogenic regions—the subventricular zone/olfactory bulb system, and the dentate gyrus of the hippocampus. We also provide an overview of currently used models for studying neural precursors in vitro, mention some precursor transplantation models, and emphasize that, in this rapidly growing field of neuroscience, one must take caution with respect to a variety of methodological considerations for studying neural precursor cells both in vitro and in vivo. The possibility of repairing neural circuitry by manipulating neurogenesis is an intriguing one, and, therefore, we also review recent efforts to understand the conditions under which neurogenesis can be induced in non-neurogenic regions of the adult CNS. This work aims toward molecular and cellular manipulation of endogenous neural precursors in situ, without transplantation. We conclude this review with a discussion of what the function might be of newly generated neurons in the adult brain and provide a summary of current thinking about the consequences of disturbed adult neurogenesis and the reaction of neurogenic regions to disease.

Contents

Abbreviations: BDNF, brain-derived neurotrophic factor; BLBP, brain lipid binding protein; BMP, bone morphogenetic protein; BrdU, bromodeoxyuridine; CNS, central nervous system; Dcx, doublecortin; DG, dentate gyrus; EGF, epidermal growth factor; FGF-2, fibroblast growth factor-2 (basic fibroblast growth factor); GABA, gamma amino butyric acid; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; HVC, high vocal center; IGF-I, insulin-like growth factor-I; NeuN, neuron-specific nuclear protein; PDGF, platelet-derived growth factor; PSA-NCAM, polysialylated neural cell adhesion molecule; RMS, rostral migratory stream; SGZ, subgranular zone; SVZ, subventricular zone; TGFα, transforming growth factor-α; VEGF, vascular endothelial growth factor

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1. Introduction

Contrary to previously held beliefs about the static nature of the adult brain, it is in fact capable of generating new neurons that can integrate into its complex circuitry. However, the recent development of new techniques has resulted in an explosion of research demonstrating that neurogenesis, the birth of new neurons, constitutively occurs in two specific regions of the adult mammalian brain (olfactory bulb and hippocampal dentate gyrus), and that there are significant numbers of multipotent neural precursors, or ''stem cells,'' in many parts of the adult mammalian brain (Altman and Das, 1965; Altman, 1969; Reynolds and Weiss, 1992; Lois and Alvarez-Buylla, 1993; Palmer et al., 1995) (and see reviews in McKay, 1997; Gage, 2000; van der Kooy and Weiss, 2000; Alvarez-Buylla et al., 2001).

The rise of precursor cell biology has brought new life to neural transplantation and the consideration of cellular replacement strategies to treat diseases of the brain. The idea of ''making new neurons'' is appealing for neurodegenerative diseases or selective neuronal loss associated with chronic neurological or psychiatric disorders. One goal of neural precursor biology is to learn from this regionally limited, constitutive neurogenesis how to manipulate neural precursors toward therapeutic neuronal or glial repopulation. Elucidation of the relevant molecular controls might allow both control over transplanted precursor cells and the development of neuronal replacement therapies based on the recruitment of endogenous cells.

This review deals with adult neurogenesis; cellular repair of the adult mammalian central nervous system (CNS); what is known about the location, behavior, and function of precursor cells in the adult brain. In the context of CNS regeneration, this information lies at the core of all attempts to guide neuronal or glial development from neural precursors in the adult CNS for therapeutic purposes. These topics are also important for at least two other reasons: (1) adult neurogenesis and precursor cell function might play an important role for the function of the healthy and diseased brain and might underlie particular aspects of neuronal plasticity, as defined by the adaptation of circuitry in response to functional demands; (2) precursor cell biology in the adult CNS also appears to recapitulate some of the molecular, cellular, and other requirements for neuronal development in the developing brain.

A substantial body of research regarding constitutively occurring neurogenesis provides insight into the potential for and limitations of neuronal replacement therapies based on manipulation of neural precursors. Recent work has partially elucidated the normal behavior of endogenous adult precursors, including their ability to migrate to select brain regions, differentiate into neurons, integrate into normal neural circuitry and, finally, functionally integrate into the adult brain. Research is also beginning to identify and describe molecular and activity-related controls over constitutively occurring neurogenesis. The location, identity, and differentiation potential of endogenous adult precursors are beginning to be understood. In this review, we will outline the few examples of normally occurring neurogenesis in the adult mammalian CNS; briefly describe adult neural precursors; discuss a few lines of recent research demonstrating that endogenous neural precursors can be induced to differentiate into neurons in regions of the adult brain that do not normally undergo neurogenesis. Throughout this review, as the many challenges facing studies of adult mammalian neurogenesis are presented, we highlight the fact that constitutive neurogenesis occurs in discrete regions of the adult mammalian brain; that limited neurogenesis can be induced under certain conditions in normally ''non-neurogenic'' regions; but that any claims of constitutive or induced adult neurogenesis must be supported by rigorous, multi-level, and critical analysis.

2. Defining neural stem cells, progenitors, and precursors

Rigorously defined, adult CNS ''stem cells'' exhibit three cardinal features: (1) they are ''self-renewing,'' with the theoretically unlimited ability to produce progeny indistinguishable from themselves; (2) they are proliferative, continuing to undergo mitosis (though perhaps with quite long cell cycles); (3) they are multipotent for the different neuroectodermal lineages of the CNS, including the multitude of different neuronal and glial sub-types. Multipotent progenitors of the adult brain are proliferative cells with only limited self-renewal that can differentiate into at least two different cell lineages (multipotency) (Gage et al., 1995b; Weiss et al., 1996b; McKay, 1997). Lineage-specific precursors or progenitors are cells with restriction to one distinct lineage (e.g., neuronal, astroglial, glial, oligoden-