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Research Report

The promise of stem cells for neural repair

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ABSTRACT

The realization that the adult nervous system develops from multipotential stem cells and that cells with stem-like properties are retained in the adult CNS has provoked an intense search for ways to utilize their potential for therapeutic treatments of multiple neurological disorders. Transplantation of neural stem cells or more restricted progenitors to replace cells lost to injury or disease may facilitate functional recovery in a spectrum of neurological disorders. Alternatively, expansion and recruitment of endogenous progenitors may be effective in treating widespread cell loss in the adult CNS. A major challenge to the development of effective stem cell therapies is to direct the fate of the newly generated cells to specifically replace those lost to disease. Insights from developmental research are providing molecular targets for regulating the differentiation of neural stem cells and their progeny in areas of injury to the adult CNS. Given the commonality of processes mediating the assembly of multicellular systems, the approaches developed in the CNS will likely be applicable for selective cell replacement in the auditory system.

1. Introduction

The generation of interconnected neurons and glia in a functional nervous system from the relatively few cells of the embryonic neural tube requires the exquisitely coordinated control of cell proliferation, fate determination, and connectivity. Our increased understanding of these processes is leading to insights important for therapeutic repair. During development, the nervous system arises in a spatially and temporally stereotyped pattern from cells, including stem cells with the ability to give rise to many different cell types and divide extensively. Studies on stem and progenitor cells in the developing nervous system have identified environmental signals such as growth factors that regulate the fundamental process of development. It is the enormous potential of stem cells to repair damage or disease in the adult nervous system, however, which has focused intense current interest on stem cells as potential resources for regenerative medicine. In the brain and spinal cord, which together comprise the central nervous system (CNS), the high level of cellular complexity and the apparent failure of the adult CNS to functionally recover after most injuries or insults suggested that this tissue lacked stem cells or other precursors. Studies over the last two decades have, however, clearly demonstrated that the adult CNS retains stem cells as well as more restricted precursors and that these cells have substantial potential for extensive cellular replacement. The goal for the future is to harness that potential for functional restoration. It seems likely that similar principles will apply to the functional repair in all multicellular neural systems. Thus, insights from studies on stem cells in the CNS may well provide valuable pointers for the development of regenerative strategies in systems such as the ear.

The adult mammalian (CNS) is composed primarily of three major differentiated cells types—neurons, astrocytes,

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and oligodendrocytes. Neurons are the functional unit of the CNS, responsible for making specific connections that allow information flow in the nervous system. In addition, astrocytes, identified through the expression of a particular intermediate filament protein known as glial fibrillary acidic protein (GFAP), provide both trophic and structural support to neurons. Oligodendrocytes are the source of myelin, the fatty insulation that surrounds axons protecting them from environmental stressors and facilitating rapid electrical conduction. The CNS also contains microglial cells derived from peripheral tissue and a number of different precursor cells including neural stem cells.

2. Characterization of stem cells

A stem cell differs from other precursor or progenitor cells in two essential ways; stem cells are multipotent, giving rise to multiple cell types, and self-renewing, with a virtually unlimited ability to make more of themselves. Even within these functional definitions, there are different types of stem cells, including embryonic stem (ES) cells, fetal stem cells, and adult stem cells that continuously replenish certain tissues. Many embryonic tissues are generated from stem and progenitor cells. Once assembled, however, only a few tissues undergo extensive cell turnover in adulthood and rely on a continued source of precursors. For example, some adult tissues continue to harbor stem cells, including the blood (hematopoietic) stem cells in bone marrow that continuously produce a variety of blood and immune system cells, crypt cells that produce intestinal linings, epithelial stem cells that produce new skin cells throughout our lives, and mesenchymal stem cells (MSCs) that give rise to bone, cartilage, and connective tissue cells. These types of stem cells are found in different tissue locations and have different properties. The term" neural stem cell" (NSC) is used to describe cells that (i) can generate neural tissue or are derived from the nervous system, (ii) have the ability to self-renew, and (iii) can give rise to cells other than themselves through asymmetric cell division (Gage, 2000a). Neural stem cells are more frequent in the developing mammalian nervous system but are retained in the adult nervous system of all mammalian organisms, including humans. If stem cells capable of generating new neural cells could be successfully manipulated, a variety of neural dysfunctions are candidates for cell therapy. For example, transplantation of neural stem cells or their derivatives, recruitment of new neural cells from endogenous stem cells by pharmacological manipulations or even non-neural stem cell gene therapy are potential treatments for many neurodegenerative diseases such as Parkinson's disease, Alzheimer's diseases, and genetic disorders such as Batten's, Gaucher's, and Tay Sach's diseases. In addition, restoration of neural function after brain ischemia and spinal cord injury may be responsive to cellular therapy. Remarkably, stem cells appear to have a recognition mechanism for neural tumors and are being developed as treatment carriers. The potential for repair is not restricted to the replacement of neurons, and a promising approach is the generation of oligodendrocytes from stem cells to promote repair in diseases such as multiple sclerosis.

3. Stem cells in the CNS

It has been known for some time that continued cell division in particular regions of the adult CNS occurs. For example, in the subgranular layer of the dentate gyrus of the hippocampus (Gage, 2000a) and the subventricular zone (SVZ) of the lateral ventricles (Gage, 2000a; Luskin, 1993; Lois and Alvarez-Buylla, 1994), new neurons are generated throughout life. From the SVZ, the newly generated neurons reach their final destination in the olfactory bulb after long-distance migration through a well-defined path called the rostral migratory stream (RMS) (Luskin, 1993; Lois and Alvarez-Buylla, 1994; Alvarez-Buylla et al., 2001), although what guides this migration is not well understood. The first compelling evidence for the presence of CNS stem cells was obtained when growth factor responsive cells both from the embryonic and adult CNS were isolated (Reynolds et al., 1992a,b; Reynolds and Weiss, 1996). A critical component of the isolation of putative neural stem cells (NSCs) is their positive selection from a heterogeneous primary culture by growing the cells under conditions in which more mature cells are rapidly eliminated by cell death, while undifferentiated NSCs survive and proliferate (Bottai et al., 2003). In suspension cultures in the presence of growth factors such as epidermal growth factor (EGF) or basic fibroblast growth factor (bFGF), NSCs begin to proliferate and form small clonal clusters of cells by 2–3 days. The clusters continue to expand and generate large colonies termed neurospheres that typically measure 100–200 μm in diameter and are composed of approximately 10,000 cells. These spheres can be successfully passaged by dissociation and reculture. The secondary neurosphere cells form new clonally derived clusters that expand to neurospheres that can again be repassaged. This procedure results in a relatively consistent increase in cell number. Differentiation of neurosphere-derived cells is induced by mitogens removal and plating the progeny on an adhesive substrate either as intact clusters or dissociated cells. After several days, the majority of the cells will differentiate into neurons, astrocytes, and oligodendrocytes (Doetsch et al., 1999; Johansson et al., 1999a; Gage, 2000b).

The ability of neurosphere forming cells to give rise to different populations of neural cells has been demonstrated in vitro and in vivo (Gage et al., 1995). In culture, all three major classes of neural cells – neurons, astrocytes, and oligodendrocytes – can be obtained from neurospheres, and the relative proportions of the different cell types generated can be altered through modification of the environment in which the cells are grown. In transplantation studies, neurosphere-derived cells migrate widely throughout the CNS and generate neurons and glial cells in the developing CNS. Whether such cells functionally integrate into the CNS in a manner analogous to normal cells has yet to be defined. In general, the dispersal and integration of transplanted cells are far less effective in the normal adult CNS. Under pathological conditions, however, transplantation of NSCs appears to result in improved functional responses, although whether such improvements reflect the integration of transplanted cells or more pleiotropic effects on host cells remains to be determined. (McDonald et al., 1999). In general, the current