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Alfredo Quiñones-Hinojosa and Nader Sanai

Embryonic Human Stem Cells: Present and Future

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Cleo Choong and Mahendra S. Rao

Human embryonic stem cells (hESCs) are stable in terms of their pluripotency, karyotype, global gene expression, ability to repair DNA and maintain telomerase levels, and growth characteristics. hESCs offer a renewable source of a wide range of cell types for use in research and cell-based therapies to treat disease. Characterization of cell populations that differentiate from them provides important information on early differentiation events and critical data for subsequent downstream manipulations. A strategy that has evolved in using cells is to develop a master bank of cells from which a working bank is generated, which is then used to generate appropriate cell types for screening, drug discovery, or therapeutic use. Appropriate cells are purified or enriched by one of several selection techniques, and such purified populations are used for most purposes. In this review, the authors discuss recent results and review the progress that has been made in the field, with a focus on using embryonic stem cells for neural targets.

The Human Brain Subventricular Zone: Stem Cells in This Niche and Its Organization

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Alfredo Quiñones-Hinojosa, Nader Sanai, Oscar Gonzalez-Perez,
and Jose Manuel Garcia-Verdugo

The human brain harbors stem cells in the subventricular zone (SVZ). The authors have collected postmortem and intraoperative tissue from adult human patients and found that it contains a unique ribbon of astrocytes that proliferate in vivo and can function as neural stem cells in vitro. Furthermore, they have conducted an anatomic, cytoarchitectural, and ultrastructural study in complete postmortem brains to define the precise organization of the lateral walls of the human lateral ventricles. With immunohistochemistry, the authors mapped a proliferative glial fibrillary acidic protein (GFAP)-positive ribbon of astrocytic cells in the human SVZ. In this article, the authors report on four main types of SVZ walls in the human brain. Types A through C line the striatum from dorsal (type A), to middle (type B), to ventral (type C) regions along the lateral wall of the lateral ventricle. Type D wall lines the floor of the temporal horn over the hippocampus. Understanding the organization of the adult human SVZ represents a necessary first step in understanding cellular proliferation, precursor migration, and the neurogenic niche of the largest known germinal region in the adult human brain.

Astrocytic Stem Cells in the Adult Brain

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Eric D. Laywell, Dennis A. Steindler, and Daniel J. Silver

The adult mammalian brain harbors a population of neural stem cells (NSCs) that are responsible for persistent neurogenesis in the olfactory system and hippocampus and may also play a role in tumorigenesis. Here, the authors review the evidence that NSCs within the adult brain are a special type of astrocyte. In addition, the authors examine the phylogenetic and ontogenetic relations between this astrocyte stem cell and related members of the astrocytic family. Finally, the authors compare and contrast the functional characteristics of NSCs and hematopoietic stem cells and review the potential oncogenic transformation of astrocyte NSCs that may underlie brain tumorigenesis as seen in glioblastoma and other primary brain tumors.

Brain Tumors

Brain Tumor Stem Cells: Identification and Concepts

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Sheila Singh and Peter B. Dirks

The study of human brain tumors has characteristically emphasized the molecular and cellular analysis of the bulk tumor. There is increasing evidence in brain tumors and other malignancies that the tumor clone is functionally heterogeneous, however, existing in a cellular hierarchy based on small subpopulations of stem cells. These concepts were first definitively demonstrated in human acute myelogenous leukemia, in which regeneration of a diversely heterogeneous human leukemia cell population in a xenograft mouse model occurred only after injection of a rare relatively homogeneous population of leukemic cells that expressed hematopoietic stem cell markers. Recently, through advances in understanding of normal neural stem cell biology, the use of techniques for cell purification by flow cytometry, and the development of cell functional assays *in vivo*, the time was made ripe for several groups to characterize brain tumor stem cells (BTSCs). The BTSC resides in the cell fraction expressing the neural precursor cell surface marker CD133.

Platelet-Derived Growth Factor—Mediated Gliomagenesis and Brain Tumor Recruitment

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Elena I. Fomchenko and Eric C. Holland

Platelet-derived growth factor (PDGF) is a growth factor family of ligands and receptors known to activate phosphatidylinositol 3-kinase, mitogen-activated protein kinase, Jak family kinase, Src family kinase, and phospholipase C γ signal transduction pathways, some of which have been causally linked to glioma formation. Extensive involvement of PDGF in development and its implication in a variety of pathologic conditions, including gliomagenesis, are mediated not only by autocrine effects but by paracrine effects. Many researchers view brain tumors as clonal entities derived from the cancer stem cell; however, recent documentation of the importance of the tumor microenvironment for glioma initiation and progression as well as the ability of neural stem or progenitor cells to migrate toward the sites of injury or tumor formation reveals additional complexities in brain tumorigenesis. Paracrine effects of PDGF in animal models of gliomagenesis, continued adult neurogenesis capable of increasing in response to brain injury, and the growth factor—rich environment of brain tumors suggest that recruitment may play a role in gliomagenesis. In this view, glioma formation involves recruitment of cells from the adjacent brain and possibly other sites.

In Search of the Medulloblast: Neural Stem Cells and Embryonal Brain Tumors

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Charles G. Eberhart

Medulloblastomas have a cellular and molecular phenotype similar in many ways to that of neural stem cells. Indeed, it has long been believed that a medulloblastoma

can arise from transformed neural stem cells. Recent analyses of murine transgenic lines has confirmed that cells of the external germinal layer (EGL) can be transformed into a medulloblastoma, generally in association with activation of the Hedgehog signaling pathway. Stem or progenitor cell populations outside the EGL, however, are also likely the cells of origin for a subset of medulloblastomas. Many nonnodular tumors, for example, express markers suggesting that they derive from the ventricular zone germinal layer and show evidence of Wnt pathway activation. Understanding the role of developmental signaling pathways, such as Hedgehog and Wnt, in the initiation and growth of embryonal brain tumors may lead to novel therapies for these highly malignant lesions. In addition, because such pathways are required in neural stem cells, their blockade may prove particularly effective in ablating the stem-like cells within medulloblastomas that are critical for tumor propagation. In support of this concept, inhibition of a third pathway important in stem cells, Notch, seems to deplete the stem-like tumor fraction and block formation of xenografts.

Stem Cells as Vehicles for the Treatment of Brain Cancer

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Khubaib Y. Mapara, Charles B. Stevenson, Reid C. Thompson,
and Moneeb Ehtesham

Stem cell therapy represents a promising new therapeutic modality for infiltrative gliomas. The promise of this emerging technology centers on the potent migratory tropism exhibited by stem cells for disseminated foci of intracranial pathologic findings. This important characteristic, which has been validated in a wide set of preclinical studies, forms a foundation for the use of transplanted stem cell populations as vehicles for the delivery of tumor-toxic molecules to sites of intracranial tumor. Nevertheless, although experimental models using this technique to target brain tumors have shown encouraging results, many concerns and questions remain to be addressed before realistic clinical implementation of this strategy can begin. Key among these are an inadequate understanding of the specific tropic mechanisms that govern stem cell migration toward invasive tumors and the need to identify appropriate tissue sources and culture processes for the generation of adequate therapeutic stem cell populations. Despite these limitations, the use of stem cells as vectors for the treatment of brain tumors holds significant promise and may prove to be an important therapeutic modality for patients with malignant glioma.

Neurorestoration

The Adult Neural Stem Cell Niche: Lessons for Future Neural Cell Replacement Strategies

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Daniel A. Lim, Yin-Cheng Huang, and Arturo Alvarez-Buylla

Transplantation of neural stem cells (NSCs) and the mobilization of endogenous neural precursors in the adult brain have been proposed as therapies for a wide range of central nervous system disorders, including neurodegenerative disease (eg, Parkinson's disease), demyelinating disorders (eg, multiple sclerosis), stroke, and trauma. Although there is great hope for the success of such therapies, the clinical development of NSC-based therapies is still in its infancy. A greater understanding of how to control the proliferation, migration, differentiation, and survival of NSCs and their progeny is critical for the development of cell replacement therapies. NSCs are partially regulated by the specialized microenvironment—or “niche”—in which these cells reside. The adult rodent brain retains NSCs in two separate niches that continually generate new neurons: the subventricular zone (SVZ) of the lateral ventricle and the dentate gyrus subgranular zone (SGZ) of the hippocampus. Similar niches may be found in the human brain. In this article, the authors briefly review their current understanding of the SVZ and SGZ niches. Lessons learned from these niches may allow one to manipulate NSCs better in culture for therapeutic transplantation and possibly even to mobilize endogenous precursors to repair diseased or injured brain.

Glial progenitor–based repair of demyelinating neurologic diseases

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H. Michael Keyoung and Steven A. Goldman

Demyelinating diseases of the brain and spinal cord affect more than one-quarter million of Americans, with numbers reaching more than two million across the world. These patients experience not only the vascular, traumatic, and inflammatory demyelinations of adulthood but the congenital and childhood dysmyelinating syndromes of the pediatric leukodystrophies. Several disease-modifying strategies have been developed that slow disease progression, especially in the inflammatory demyelinations and in multiple sclerosis in particular. Yet, currently available disease modifiers typically influence the immune system and are neither intended to nor competent to reverse the structural neurologic damage attending acquired demyelination. Fortunately, however, the disorders of myelin lend themselves well to attempts at structural repair, because central oligodendrocytes are the primary, and often sole, victims of the underlying disease process. Given the relative availability and homogeneity of human oligodendrocyte progenitor cells, the disorders of myelin formation and maintenance may be especially compelling targets for cell-based neurologic therapy.

Adult Neurogenesis and Hippocampal Memory Function: New Cells, More Plasticity, New Memories?

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Yasuji Kitabatake, Kurt A. Sailor, Guo-li Ming, and Hongjun Song

The discovery of active adult neurogenesis in mammals, a process of generating functional neurons from neural stem cells, suggests that the adult brain is more dynamic than once imagined. The coincidence of this phenomenon occurring in the hippocampus, a region critical to the learning process, begs the question of whether adult neurogenesis is involved in memory formation. Here, the authors review rapidly accumulating evidence showing a strong correlation between certain types of memory functions and adult neurogenesis in the hippocampus. Establishment of the potential link between memory formation and adult neurogenesis is instrumental, at a basic science level, to understand the function of neural networks and is essential, at a clinical level, to develop effective therapies for various cognitive dysfunctions.

Radiation Response of Neural Precursor Cells

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John R. Fike, Radoslaw Rola, and Charles L. Limoli

Considerable data are now available regarding the radiation responsiveness of neural precursor cells that exist in the neurogenic regions of the mammalian forebrain. These cells and their progeny are extremely sensitive to irradiation, undergoing apoptosis after clinically relevant doses that do not result in overt tissue injury. In addition, there is compelling evidence that radiation significantly affects the whole process of neurogenesis and that the sensitivity depends, at least in part, on alterations in the microenvironment within which the precursor cells exist. Although provocative data exist suggesting that inflammation, oxidative stress, or morphologic relations influence neurogenesis, the precise mechanisms involved remain obscure and need to be investigated. Additionally, it is important to try to understand what these findings may mean in the context of radiation paradigms associated with the treatment of intracranial disease. Understanding how neural precursor cells respond to noxious stimuli is likely to lead to new therapeutic approaches that should restore neurogenesis and perhaps improve cognitive performance.

The Role of Stem Cells in Parkinson Disease

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Amitabh Gupta and Ted M. Dawson

Parkinson's disease (PD) affects more than 1 million people in the United States, which makes it one of the most common age-related neurodegenerative disorders, second only to Alzheimer disease. In light of this significant health problem, this review places emphasis on the exciting prospect of using stem cells as an emerging therapeutic option in

this neurologic field. To that goal, the authors first describe the clinical, genetic, and pathologic features of PD and proceed with discussing notions about disease mechanism as well as current medical and surgical treatments before focusing on the advantages, limitations, and feasibility of stem cell therapy.

Injury following trauma or stroke

Restoring Function After Spinal Cord Injury: Promoting Spontaneous Regeneration with Stem Cells and Activity-Based Therapies

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Visar Belegu, Martin Oudega, Devin S. Gary, and John W. McDonald

Although neural regeneration is an active research field today, no current treatments can aid regeneration after spinal cord injury. This article reviews the feasibility of spinal cord repair and provides an overview of the range of strategies scientists are taking toward regeneration. The major focus of this article is the future role of stem cell transplantation and simpler rehabilitative restorative approaches designed to optimize spontaneous regeneration by mobilizing endogenous stem cells and facilitating other cellular mechanisms of regeneration, such as axonal growth and myelination.

Neurogenesis After Traumatic Brain Injury

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R. Mark Richardson, Dong Sun, and M. Ross Bullock

With the hope of replacing neurons lost in traumatic brain injury (TBI), experimental models are being used to investigate TBI-induced neurogenesis. Although selectively vulnerable to TBI, the neurogenic hippocampus may have the unique ability to replace damaged neurons locally. Injury may also activate signaling pathways that induce neuroblasts from the subventricular zone to migrate to areas of focal cortical damage. Additionally, there is some evidence for local activation of latent neural progenitor cells in the injured neocortex itself. Each of these themes is discussed, with emphasis on the possibility of future therapeutic intervention.

Ischemia-Induced Neurogenesis: Role of Growth Factors

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Robert J. Dempsey and Haviryaji S.G. Kalluri

The neurogenic response in ischemic brain to growth factors is the net result of cell division and cell survival in specific regions of the brain. To increase the cell number, these physiologic processes should be active. Hence, when growth factors are infused into the brain, they might stimulate survival, cell division, or both to enhance neurogenesis. The end result is the interplay of all the endogenous factors with the infused exogenous factors. It is essential to understand the growth factors and their regulators that are expressed after ischemia if one is to pharmacologically enhance neurogenesis. It seems that a combinational therapy of factors or their inhibitors may provide powerful therapeutic potential for enhancing stroke-induced neurogenesis and restoring the damaged tissue to function.

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