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Stem cell–based therapies for the newborn lung and brain: Possibilities and challenges

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ABSTRACT

There have been substantial advances in neonatal medical care over the past 2 decades that have resulted in the increased survival of very low birth weight infants, survival that in some centers extends to 22 weeks gestational age. Despite these advances, there continues to be significant morbidity associated with extreme preterm birth that includes both short-term and long-term pulmonary and neurologic consequences. No single therapy has proven to be effective in preventing or treating either developmental lung and brain injuries in preterm infants or the hypoxic-ischemic injury that can be inflicted on the full-term brain as a result of in utero or perinatal complications. Stem cell–based therapies are emerging as a potential paradigm-shifting approach for such complex diseases with multifactorial etiologies, but a great deal of work is still required to understand the role of stem/progenitor cells in normal development and in the repair of injured tissue. This review will summarize the biology of the various stem/progenitor cells, their effects on tissue repair in experimental models of lung and brain injury, the recent advances in our understanding of their mechanism of action, and the challenges that remain to be addressed before their eventual application to clinical care.

Introduction

Scientific, medical, and technological advances in the field of perinatal–neonatal medicine have resulted in increased survival rates for extremely low birth weight, near-term, and term infants treated in neonatal intensive care units. However, respiratory and neurologic impairments continue to constitute the major adverse outcomes of neonatal intensive care unit survivors, resulting in lifelong morbidities that include bronchopulmonary dysplasia (BPD) and several forms of brain injury. Based on a recent study from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Centers reporting on the 20-year trend in survival and outcomes of preterm infants, there have been overall modest reductions in several morbidities; however, the rates of BPD have increased.[1] Specifically, from 2009 to 2012, BPD rates increased for all gestational ages from 22 up to 27 weeks with an overall incidence rate of 45% in this age group. BPD affects at least 10,000 preterm infants in the United States each year.

The pathophysiologic features and underpinning of BPD have evolved over the last 2 decades such that the BPD of

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today is a result of "reprogramming" of normal lung growth characterized by reduced numbers of alveoli and fewer blood vessels but with less prominent fibrosis and airway lesions than the "old" BPD originally described by Northway et al.[2] Nonetheless, BPD outcomes remain associated with significant long-term pulmonary morbidities, including airway hyperreactivity, abnormal pulmonary function test results, and, in some cases, emphysematous changes that persist into adulthood. Moreover, secondary pulmonary hypertension has been reported in moderate to severe cases of BPD and is associated with increased mortality.[3,4] All in all, BPD is not just a disease of the neonatal period or even of early childhood, but rather a condition that carries lifelong consequences including the development of chronic obstructive pulmonary disease of adulthood. Specific therapies for BPD are lacking, and this disease persists despite gentler ventilation strategies and improvements in neonatal intensive care. Further, newly adopted drugs or tested therapies such as inhaled nitric oxide, antioxidants, vitamin A, caffeine, and others have either failed or have minimal effect on BPD outcomes. Steroids can decrease BPD but may be linked to long-term adverse neurologic outcomes or potentially associated with increased death rate as reported recently by the Neonatal European Study of Inhaled Steroids Trial Group.[5] Thus, the search for better treatment strategies to prevent and treat BPD continues.

Periventricular leukomalacia (PVL) is a consequence of the same perinatal insults of inflammation and oxidative damage on a developing brain that form the underpinnings of BPD. The new PVL, like the new BPD, is different, presenting with more diffuse damage in the central cerebral white matter with secondary decreases in cortical gray matter volume but without cystic changes more typical of the focal necrosis deep inside the periventricular white matter of the classic cystic PVL. In addition to the preterm brain, the full-term brain is susceptible to hypoxic-ischemic injury as a consequence of inadequate blood flow and oxygen delivery. Hypoxic-ischemic encephalopathy (HIE) occurs in 1–3 term births per 1000[6] and can result from acute blood loss secondary to placental abruption, fetal maternal hemorrhage, or prolapsed umbilical cord, among other insults. Although therapeutic hypothermia has become standard therapy for HIE, there are still a large number of infants who die or go on to develop severe neurologic impairments and cerebral palsy.[7] We are in urgent need of additional new treatments for this devastating disease, as well as new strategies to treat PVL, BPD, and other related complications of preterm birth that adversely affect the long-term normal development of these children.

Evidence of stem cell depletion in PVL and BPD

The preterm infant is exposed to several risk factors that result in tissue damage of multiple organs through common mechanisms that include inflammation, infection, and ischemia/reperfusion, all promoting the production of free oxygen radicals. In addition, the premature deprivation of protective and nutritive factors provided by the placenta and the maternal circulation plays a key role in exacerbating the injury. The common pathway of such insults leads to altered programming of development that is characterized by arrest in normal organ growth with tissue simplification. Emerging evidence suggests that loss of endogenous stem/progenitor cells required for normal cell differentiation and tissue repair may underlie the pathobiology of such injury.

Stem cells are primitive cells that can undergo self-renewal and have the potential to differentiate into multiple cell types. They are critical for normal development and also for the maintenance of normal physiology by contributing to organ repair and regeneration throughout life. Depletion or dysfunction of endogenous stem cells underlies disease development and aging. The complex architecture of the lung is maintained by the presence of rare populations of multipotent endogenous stem cells that are regulated by specific environmental signals. Their specific identification, characterization, and role in normal development and repair are being actively investigated. Further, stem cells from the bone marrow, the peripheral blood, or other tissue sources are also thought to participate in organ repair by their recruitment to sites of injury. Experimental and clinical studies support the notion that loss of circulating and tissue progenitor cells could be a mechanism underlying the abnormal developmental growth pattern in diseases such as BPD. For example, some reports have linked BPD risk with decreased endothelial progenitors in the circulation as assessed through clonogenic analysis of late outgrowth endothelial colony-forming cells (ECFCs).[8,9] In addition, lung-resident mesenchymal stem cells (MSCs) isolated from the tracheal aspirates of preterm neonates display an altered, proinflammatory phenotype,[10,11] suggesting that both depletion and dysfunction of endogenous progenitor stem cells may predispose to the development of BPD.

As in the developing lung, the developing brain is composed of progenitor cells that are critical for normal growth and repair. Premyelinating oligodendrocytes (preoligodendrocytes) are progenitor cells that are present in great abundance in the preterm brain and progressively differentiate to mature oligodendrocytes between 28 and 40 weeks gestational age to form the myelin sheath. Preoligodendrocytes, but not mature oligodendrocytes, are highly vulnerable to inflammation and oxidative stress and are preferentially lost in response to perinatal insults.[12] Loss of preoligodendrocytes results in hypomyelination of the central cerebral white matter and associated complications of gray matter loss that form the hallmark of diffuse PVL.

Altogether, accumulating evidence suggests an important role for progenitor stem cells in both supporting and maintaining normal organ growth in development and disease. Endogenous progenitor cells have been isolated from several sources and are increasingly being tested in experimental models of disease and in the case of MSCs, in several human trials including BPD. This review will summarize current knowledge on the different types of progenitor stem cells with a particular focus on the biology of MSCs and their protective role in experimental models of brain and lung injury, as well as their clinical application to date. Further, we shall summarize emerging evidence on their mechanisms of action that includes the shedding of exosomes, extracellular vesicles that carry and transmit key mediators of the MSC biologic effect.