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REVIEWS

Cell-based therapies for the preterm infant

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Abstract

The severely preterm infant receives a multitude of life-saving interventions, many of which carry risks of serious side effects. Cell therapy is an important and promising arm of regenerative medicine that may address a number of these problems. Most forms of cellular therapy use stem/progenitor cells or stem-like cells, which have the capacity to migrate, engraft and exert anti-inflammatory effects. Although some of these cell-based therapies have made their way to clinical trials in adults, little headway has been made in the neonatal patient group. This review discusses the efficacy of cell therapy in preclinical studies to date and their potential applications to diseases that afflict many prematurely born infants. Specifically, we identify the major hurdles that must be overcome before cell therapies can be safely used in the neonatal intensive care unit.

Key Words: *bronchopulmonary dysplasia, cell therapy, human amnion epithelial cells, mesenchymal stromal cells, prematurity*

Introduction

Preterm birth is defined as birth before 37 weeks of gestation [1]. The incidence of preterm birth is associated with prenatal mortality, neonatal morbidity and childhood disability. Preterm birth remains the leading cause of neonatal deaths in children under 5 years of age, second only to pneumonia [2]. Although there has been a gradual decline in the perinatal mortality as the result of improvements in overall clinical management, the mortality rate of preterm infants born at 32–36 weeks has remained 3- to 5-fold higher compared with that of term infants [3,4]. The mortality rate in infants born at 22–23 weeks is more than 3-fold higher than those born at 28 weeks [5]. There are a multitude of complications associated with being born preterm, many of which are indirect consequences of life-saving interventions, including respiratory distress syndrome and bronchopulmonary dysplasia (BPD). Cell therapy may be a suitable adjuvant therapy for indications in which inflammation and tissue damage prevail. In this review, we will identify the most common diseases that affect premature infants who are amenable to cell therapy. We will describe current clinical management as well as preclinical evidence of efficacy with the use of cell therapies.

Respiratory diseases

Premature infants born at 33–36 weeks' gestation are more than 4 times as likely to have neonatal respiratory morbidity compared with their term counterparts [6]. These respiratory complications include respiratory distress syndrome, BPD and secondary pulmonary hypertension. Respiratory distress syndrome is the single most important cause of illness and death in preterm infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs. BPD is commonly associated with mechanical ventilation and oxygen therapy of severely preterm infants, which results in abnormal lung development, decreased lung compliance, oxidative stress and inflammation [7]. Collectively, these respiratory disorders have serious adverse long-term health consequences on the severely preterm infant including abnormal lung and airway development and increased susceptibility to respiratory disease [8].

Ventilation is considered a major pillar of critical care medicine in premature infants, especially for those with respiratory diseases. Although ventilation strategies have become less injurious over the years [9,10], the deleterious effects on underdeveloped organs can be profound. A high fraction of inspired oxygen (FiO_2)

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is associated with increased incidence of BPD [11] and retinopathy of prematurity [12], whereas low FiO_2 induces hypoxic ischemic encephalopathy and necrotizing enterocolitis [13]. Consequently, many clinical centers now emphasize low lung volume and avoiding endotracheal ventilation [14,15].

Current clinical management for respiratory diseases in preterm infants includes suppressing lung inflammation and infection, and improving pulmonary function. For example, surfactant is widely used in preterm infants to reduce the risk of developing respiratory distress syndrome [16]. Corticosteroids suppress pulmonary inflammation and improve pulmonary function. Systemic postnatal corticosteroids are used early ($\leq$7 days) to prevent the development of BPD [17] and are used later (>7days) to treat pulmonary diseases [18]. Caffeine is recommended for reducing the numbers of apneic attacks in preterm infants [19] and for the prevention of BPD in very low birth weight infants [20]. Although there are advances in treatments, some therapies have no advantages or even have significant adverse effects. For example, systemic corticosteroids use, though effective, can cause adverse effects of neurodevelopment [17,18], and inhaled corticosteroid administration neither prevents nor treats BPD [21].

Neurological diseases

Challenges faced by the premature infant are not limited to respiratory conditions. Common neurological diseases associated with preterm birth include intraventricular hemorrhage, periventricular leukomalacia and sequelae such as cerebral palsy and cognitive impairment. The premature brain is highly susceptible to hypoxia. Most brain insults occur secondary to perinatal hypoxia or asphyxia. An estimated 20–25% of infants with very low birth weight (<1500 g) have intraventricular hemorrhage, which has been attributed to alterations in cerebral blood flow to the immature and fragile germinal matrix microvasculature and secondary periventricular venous infarction [22]. Risk factors of intraventricular hemorrhage include severe respiratory distress syndrome and patent ductus arteriosus, which can induce intraventricular hemorrhage through fluctuations in blood flow [23].

Another common neurological disorder in premature infants is periventricular leukomalacia, which can either occur in isolation or in conjunction with intraventricular hemorrhage. The pathological hallmark for periventricular leukomalacia is the focal and diffuse periventricular depletion of immature premyelinating oligodendroglia, which are highly vulnerable to ischemic and inflammatory injuries [24].

The pathogenesis of neurological diseases in preterm infants is largely caused by immaturity of the brain structure and cells as well as the unstable cerebral blood flow. Management is currently confined to screening for sequelae such as posthemorrhagic hydrocephalus. Because of the significant adverse effects of short- and long-term sequelae in later life, clinical trials have focused on prevention strategies. For example, phenobarbital, indomethacin and ibuprofen are used to prevent intraventricular hemorrhage [25]. Phenobarbital is used for stabilization of blood pressure and free radical production. Indomethacin is used to promote microvascular maturation and blunt fluctuations in cerebral blood flow by closing patent ductus. Ibuprofen is used to improve autoregulation of cerebral blood flow. However, meta-analysis showed no difference in the incidence and severity of intraventricular hemorrhage after intervention [25,26].

Gastroenterological diseases

Necrotizing enterocolitis (NEC) is another inflammatory disease that primarily affects premature infants. It is the leading cause of gastrointestinal mortality and morbidity in preterm infants. The incidence of necrotizing enterocolitis in preterm birth is reportedly 9 times greater than that of term birth [27]. The etiology of NEC is different in term compared with preterm infants. In term infants, hypoxia-ischemia is a common precursor for NEC [13] and usually is associated with other diseases such as congenital heart disease [28]. In contrast, the etiology and pathogenesis of NEC in preterm infants is not completely understood. It is, however, acknowledged that the disease is multifactorial.

Inflammation was recently reported to be the dominant underlying cause of NEC [29]; other risk factors include intestinal immaturity, abnormal intestinal microbial colonization and hypoxic ischemic injury [30]. Immature motility, digestion, absorption, barrier function and immune defence contribute to the high incidence of NEC in preterm infants [31]. Premature enterocytes have an excessive and inappropriate inflammatory response to postnatal bacterial colonization in which inflammation further increases intestinal permeability. A pathological microbial colonization increases the risk of NEC in preterm infants by inducing an inflammatory response [32]. Vascular regulators such as nitric oxide and endothelin, consequent to hypoxic ischemic injury, can further compound NEC by altering the microvascular environment [33].

Current clinical treatments include abdominal decompression, bowel rest, broad-spectrum intravenous antibiotics and intravenous hyperalimentation; surgical interventions are required for infants with severe NEC [31]. Control of inflammation in NEC is