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Review

Mesenchymal stem cells as cellular vectors for pediatric neurological disorders

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ABSTRACT

Lysosomal storage diseases are a heterogeneous group of hereditary disorders characterized by a deficiency in lysosomal function. Although these disorders differ in their etiology and phenotype those that affect the nervous system generally manifest as a profound deterioration in neurologic function with age. Over the past several decades implementation of various treatment regimens including bone marrow and cord blood cell transplantation, enzyme replacement, and substrate reduction therapy have proved effective for managing some clinical manifestations of these diseases but their ability to ameliorate neurologic complications remains unclear. Consequently, there exists a need to develop alternative therapies that more effectively target the central nervous system. Recently, direct intracranial transplantation of tissue-specific stem and progenitor cells has been explored as a means to reconstitute metabolic deficiencies in the CNS. In this chapter we discuss the merits of bone marrow-derived mesenchymal stem cells (MSCs) for this purpose. Originally identified as progenitors of connective tissue cell lineages, recent findings have revealed several novel aspects of MSC biology that make them attractive as therapeutic agents in the CNS. We relate these advances in MSC biology to their utility as cellular vectors for treating neurologic sequelae associated with pediatric neurologic disorders.

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1. Introduction

Children suffer from a variety of hereditary disorders that manifest as a profound deterioration in neurological function with age. Among these disorders the lysosomal storage diseases (LSDs) are most common. LSDs represent over 40 genetic disorders that result from defects in lysosomal function, which leads to accumulation of glycosaminoglycans, glycoproteins, or sphingolipids in organs throughout the body. Although rare, collectively these diseases have an incidence of approximately 1 in 7000–8000 live births (Winchester et al., 2000). Depending upon the specific enzyme deficiency, distinct patterns of substrate accumulation occurs in organs resulting in a wide spectrum of clinical symptoms (Moses, 1990). Additionally, the time of onset to disease, which ranges from infancy to adulthood, as well as the degree of clinical involvement is influenced both by the specific inherited genetic mutation and the level of enzyme deficiency. In some LSDs abnormal accumulation of storage material occurs within cells of the brain and spinal cord, making neuro-degeneration a prominent feature of these disorders. Biochemical and pathological studies indicate that specific neural cell types possess different sensitivities to accumulated storage material, making distinct brain regions susceptible to disease. For example in Gaucher disease, which is caused by a deficiency of glucocerebrosidase, significant neuronal losses have been observed within the basal ganglia, nuclei of the midbrain, cerebellum, dentate nucleus, and hypothalamus (Espinas and Faris, 1969; Kaye et al., 1986). A recent analysis of autopsy samples from patients with all three forms of Gaucher disease indicated that neuronal loss predominated in type 2 and 3 patients but patients with type 1 disease presented with astrogliosis (Wong et al., 2004). In contrast, patients with Niemann–Pick type C (NPC) typically exhibit widespread neuronal atrophy at early stages of the disease but at later stages Purkinje neurons in the cerebellum become uniquely sensitive to degeneration (Walkley and Suzuki, 2004). Alternatively, Sandhoff and Tay–Sachs patients exhibit widespread apoptosis throughout the cerebral cortex, cerebellum, and brain stem that affects neurons, oligodendrocytes, astrocytes, Purkinje cells, micro-glia, and vascular pericytes (Huang et al., 1997).

A subset of LSDs, the leukodystrophies, manifests as a profound degeneration of white matter due to defects in myelin metabolism. For example, metachromatic leukodystrophy (MLD), one of the most common leukodystrophies, results from the inability to degrade sulfated glycolipids due to a deficiency of the lysosomal enzyme arylsulfatase A (Gieselmann, 2008). Some MLD patients have normal arylsulfatase A activity but lack an activator protein that is involved in sulfatide degradation (Kolter and Sandhoff, 2005). Both defects result in the intra-lysosomal accumulation of sulfatide compounds in neural and non-neural tissues. Pathological features include diffuse demyelination and metachromatic-staining granules in glial cells and macrophages. Central and peripheral myelination is abnormal with widespread loss of myelinated oligodendroglia in the CNS and segmental demyelination of peripheral nerves (Gieselmann, 2008; Gieselmann and Krageloh-Mann, 2010). Symptoms typically manifest during peak periods of myelin formation in post-natal development resulting in progressive loss of both motor and cognitive functions followed by death in approximately five years. However, the onset of the disease may be delayed until adolescence or adulthood depending on the degree of enzyme deficiency. Recently, several new causative mutations have been identified for this disorder (Cesani et al., 2009; Galla et al., 2013; Luzi et al., 2013).

In summary, many LSDs present with neurological sequelae but the cause and extent of neuro-degeneration are dictated by the nature of the accumulated storage material and its relative toxicity to different cell types. Consequently, developing a single therapeutic approach to treat neurologic sequelae associated with LSDs is difficult since the therapy must reduce accumulated storage material in a variety of cell types localized within different anatomical regions of the brain. Presently, hematopoietic stem cell transplantation (HSCT) and umbilical cord blood transplantation (UCBT) attempt to achieve this result by providing the CNS with a continuous supply of micro-glial cells with normal lysosomal functions *via* the circulation. However, since the overall efficacy of these approaches remains uncertain, alternative treatment strategies designed to more efficiently target the CNS are under development.

2. Cell-based therapies for lysosomal storage diseases

Over the past 25 years HSCT has been used to treat many types of sphingolipidosis and mucopolysaccharidosis (Krivit,