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Review Article

Glial progenitor cell-based treatment of the childhood leukodystrophies

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ABSTRACT

The childhood leukodystrophies comprise a group of hereditary disorders characterized by the absence, malformation or destruction of myelin. These disorders share common clinical, radiological and pathological features, despite their diverse molecular and genetic etiologies. Oligodendrocytes and astrocytes are the major affected cell populations, and are either structurally impaired or metabolically compromised through cell-intrinsic pathology, or are the victims of mis-accumulated toxic byproducts of metabolic derangement. In either case, glial cell replacement using implanted tissue or pluripotent stem cell-derived human neural or glial progenitor cells may comprise a promising strategy for both structural remyelination and metabolic rescue. A broad variety of pediatric white matter disorders, including the primary hypomyelinating disorders, the lysosomal storage disorders, and the broader group of non-lysosomal metabolic leukodystrophies, may all be appropriate candidates for glial progenitor cell-based treatment. Nonetheless, a variety of specific challenges remain before this therapeutic strategy can be applied to children. These include timely diagnosis, before irreparable neuronal injury has ensued; understanding the natural history of the targeted disease; defining the optimal cell phenotype for each disorder; achieving safe and scalable cellular compositions; designing age-appropriate controlled clinical trials; and for autologous therapy of genetic disorders, achieving the safe genetic editing of pluripotent stem cells. Yet these challenges notwithstanding, the promise of glial progenitor cell-based treatment of the childhood myelin disorders offers hope to the many victims of this otherwise largely untreatable class of disease.

Contents

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1. Introduction

Glial progenitor cells are present throughout the adult central nervous system (CNS) and are the source of mature oligodendrocytes necessary for myelin maintenance and repair. Direct or indirect injury to oligodendrocytes and/or their progenitors results in myelin loss, and is the basis of a large number of genetic and acquired disorders of the central white matter.

The leukodystrophies in particular are heritable disorders of the CNS white matter, with or without peripheral nervous system (PNS) involvement, that have in common glial cells or myelin sheath abnormalities. As a group, their pathology is characterized by the loss of oligodendrocytes, although their specific cellular mechanisms of disease vary widely; many include significant axonal pathology. As currently defined, the hereditary leukodystrophies exclude the acquired disorders of myelin, such as multiple sclerosis, toxic and vascular disorders affecting myelin, disorders with primary neuronal involvement, and inborn errors of metabolism with predominant systemic symptoms (Vanderver et al., 2015). Instead, newer classification schemes have been proposed to better assign individual disease phenotypes into categories reflecting common pathogenic mechanisms. As such, the major childhood leukodystrophies may be defined as either lysosomal (e.g., Krabbe disease, metachromatic leukodystrophy (MLD), Tay-Sachs and the gangliosidoses, Salla disease and other sialic acidurias, and fucosidosis, among others); peroxisomal (adrenoleukodystrophy, peroxisomal biogenesis disorders); and mitochondrial (leukoencephalopathies with lactate elevation), by way of example. Other disorders may be defined by their causal cell type, such as Pelizaeus Merzbacher disease (PMD), which targets myelinating oligodendrocytes (Gow et al., 1998), and Alexander disease, which is caused by astrocytic cytoskeletal pathology (Messing et al., 2012). More traditionally, the hereditary disorders of myelin have been described in three groups according to disease histopathology (Powers, 2004). This parallel nomenclature includes, 1) the hypomyelinating disorders, characterized by decreased or absence formation of myelin, such as PMD and other primary hypomyelinating disorders; 2) the metabolic demyelinating diseases, typically characterized by enzymatic deficiency and the misaccumulation of lipid components of myelin, such as Krabbe disease and MLD; and 3) those disorders resulting from gross tissue loss, such as vanishing white matter disease and Canavan disease. The genetic and biochemical bases as well as the clinical presentations of these and other childhood myelin disorders have been extensively reviewed elsewhere (Helman et al., 2015; Parikh et al., 2015; Pouwels et al., 2014; Powers, 2004).

To address this panoply of disorders, a number of cell-based strategies have been developed to replace lost or deficient oligodendroglia and/or astrocytes, or to serve as vectors for enzyme delivery in metabolic and lysosomal storage disorders (Fig. 1). This review will focus on defining those cell types that have been developed to safely achieve effective myelin repair, the diseases for which these cells may prove specifically appropriate, and the pre-clinical studies upon which those predictions are based. We will focus particularly on the hereditary disorders of myelin, for which the development of glial cell-based therapies holds particular promise, given the well-understood molecular and cellular basis of these disorders, and the predominant involvement of glial pathology and dysmyelination in their pathogenesis.

2. Cellular phenotypes appropriate for treatment of the myelin disorders

2.1. Neural stem cells

Neural stem cells (NSCs) are self-renewing and multi-lineage component derivatives of the early neuroepithelium (Gage, 2000; Temple, 2001) that can generate a progeny of the three major neural phenotypes, including neurons, astrocytes and oligodendrocytes. NSCs are most prevalent in the developing brain (Keyoung et al., 2001) but also, although in relatively sparse numbers (Pincus et al., 1998), in the subependymal zone and hippocampus of the adult brain (Eriksson et al., 1998; Goldman, 1998; Kirschenbaum et al., 1994; Pincus et al., 1998). Nonetheless, they can be isolated and purified from adult (Arsenijevic et al., 2001; Pincus et al., 1997, 1998; Roy et al., 2000), as well as fetal brain (Keyoung et al., 2001; Uchida et al., 2000), and readily expanded in vitro, maintaining their phenotypic characteristics. $CD133^{+}$-defined NSCs, and in particular their $CD24^{-/lo}$ fraction, can grow as neurospheres and differentiate largely as neurons and astrocytes in vitro. Upon transplantation, NSCs can generate neurons and glia in a context-dependent fashion (Keyoung et al., 2001). As such, they constitute a source of oligodendrocyte progenitors that can be mobilized from endogenous stores to remyelinate CNS lesions (Nait-Oumesmar et al., 1999), as well as to myelinate in vivo when grafted in hypomyelinated hosts (Uchida et al., 2000; Yandava et al., 1999). However, their in vivo differentiation is difficult to instruct, allowing the potential for both heterotopic neuronal differentiation and astrocytosis; as such, NSCs are inefficient as vectors for focused oligodendrocytic and astrocytic production.

2.2. Adult glial progenitor cells

GPCs comprise an already lineage-restricted glial progenitor population, that may be better suited to treat disorders of glia, and more appropriate for myelin disease in particular (Goldman et al., 2012), although they do not carry the sustained mitotic competence and scalability of NSCs. GPCs arise from neural stem cells in the subventricular zone, and migrate during development to populate both the subcortical white matter and cortical grey matter (Wang et al., 1999; Scolding et al., 1998a). They comprise between 3 and 5% of all cells in the adult human subcortical white matter, and persist in analogous if not higher numbers in the cortex, as has been reported in the adult rodent brain (Dawson et al., 2003).

GPCs are the principal remyelinating cell type of the adult CNS and can give rise to both oligodendrocytes and astrocytes (Tripathi et al., 2010; Zawadzka et al., 2010). While glial progenitors are commonly referred to in the literature as oligodendrocyte progenitor cells (OPCs), human GPCs can give rise to oligodendrocytes or astrocytes until their terminal division, and oligodendrocytes per se are post-mitotic. As a result, the terms GPCs and OPCs refer to the same phenotype in humans; they are identical. For simplicity's sake, we have chosen to refer to both as GPCs throughout this review.

The presence of GPCs in the adult human brain was inferred in several early studies that identified immature oligodendroglia in adult brain tissue (Armstrong et al., 1992; Gogate et al., 1994). It was later that human mitotic GPCs were isolated from adult human white matter dissociates, upon transfection of cells with green fluorescent protein (GFP) placed under the control of the human early promoter (P2) for the oligodendrocyte protein cyclic nucleotide phosphodiesterase (P/hCNP2), one of the earliest proteins to be synthesized in developing oligodendrocytes (Wang et al., 1999). The GFP^{+} cells initially expressed gangliosides recognized by the monoclonal antibody A2B5 and matured as oligodendrocytes, progressing through a stereotypic sequence of A2B5, O4/sulfatide and O1/galactocerebroside expression (Bansal et al., 1989). This study (Wang et al., 1999) also confirmed that the O4 antibody against sulfatide, commonly used to identify GPCs in rodents, recognized primarily post-mitotic oligodendroglia, and not their mitotic progenitors in humans (Armstrong et al., 1992).

Importantly, when removed to low density, high purity culture, single adult GPCs isolated either by A2B5-targeted immunotagging or transfection with GFP under the control of the CNP2 promoter, revealed their multipotential nature in vitro (Nunes et al., 2003). Upon transplantation in the rat brain, cells primarily generated oligodendrocytes and astrocytes in the white matter, although also differentiated as neurons when introduced in neurogenic environments such as the prenatal olfactory stream and hippocampus (Nunes et al., 2003; Windrem et al., 2002). Together,