Hematopoietic Cell Therapy for Metabolic Disease

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The lysosome, an intracellular organelle responsible for the intracellular sorting, recycling, and digestion of organic molecules, was first described 50 years ago by Christian de Duve.[1] All known lysosomal storage diseases (LSD) are single gene defects and with few exceptions are autosomal recessive in inheritance. Loss of functional activity of lysosomal enzymes results in accumulation of substrates, such as glycoproteins or mucopolysaccharides (MPS).[2] The clinical manifestations of LSD vary depending on the specific enzymatic deficiency, level of residual activity, and site of substrate accumulation (Tables I and II). Variability in disease severity is observed in patients with the same disorder, because small differences in enzyme activity may result in marked differences in clinical disease.[2-5]

THERAPY OF METABOLIC DISORDERS

In general terms, a reduction in substrate accumulation may be achieved through enhanced substrate degradation, slowing the rate of substrate production, or an altered immune response to substrate. The delivery of enzyme may be achieved by exogenous enzyme administration, via allogeneic hematopoietic stem cell transplantation (HCT) or potentially by autologous HCT after ex vivo genetic correction. Alternatively, the activity of unstable enzymes may be enhanced with "chaperone" molecules.[6] The second approach, termed "substrate reduction therapy," includes agents such as miglustat, an inhibitor of ceramide glucosyltransferase, the primary enzyme responsible for glycosphingolipid biosynthesis. This agent has been shown to have activity in patients with Gaucher disease.[7] Alteration of the immune response to substrate accumulation may be critical in the amelioration of the cerebral form of adrenoleukodystrophy (ALD). Modulation of central nervous system (CNS) inflammation is thought to be one of the mechanisms responsible for disease stabilization after HCT.[8]

ENZYME REPLACEMENT THERAPY

Enzymes destined for lysosomal localization acquire a mannose 6-phosphate (M6P) recognition signal, which facilitates their transportation to the lysosome (Figure 1).[9] The potential of enzyme replacement therapy (ERT) to provide beneficial effects was supported by the discovery of M6P receptors on the plasma membrane of cells, and documentation that lysosomal enzymes in the environment bind to these receptors, resulting in internalization into the lysosome.[10] After intravenous administration the serum half-life of lysosomal enzymes is short (10 to 20 minutes). Of importance, poor penetration of these enzymes into the cerebral spinal fluid and brain has been documented and is a major limitation of this approach. The initial focus in the development of ERT has therefore been to target diseases for which there is little CNS involvement.[6] Clinical applications of ERT have been summarized elsewhere.[6,11]

CELLULAR THERAPY OF LYSOSOMAL DISORDERS

HCT for Mucopolysaccharides

The ability of hematopoietic cells from unaffected individuals to "cross-correct" deficient fibroblasts was initially documented by Neufeld et al,[12] providing proof of principle for efficacy of cellular therapy. As microglial cells, which are hematopoietically

ALD	Adrenoleukodystrophy	M6P	Mannose 6-phosphate
CNS	Central nervous system	MAPC	Multipotent adult progenitor cell
ERT	Enzyme replacement therapy	MLD	Metachromatic leukodystrophy
GLD	Globoid cell leukodystrophy	MPS	Mucopolysaccharidosis, mucopolysaccharide
HCT	Hematopoietic stem cell transplantation	MRI	Magnetic resonance imaging
LSD	Lysosomal storage disease	MSC	Mesenchymal stem cell

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Table I. Storage diseases treated with blood and marrow transplantation

	Lysosomal SD		Sphingolipidoses	
	MPS I	MPS VI	GLD	MLD
Syndrome	Hurler	Maroteaux-lamy	Krabbe	
Incidence*	1:100,000	1;235,000	1:141,000	1:92,000
Deficiency	α-l-iduronidase	Arylsulfatase B	Galactocerebrosidase I: infantile form II: juvenile form III: adult form	Arylsulfatase a I: late infantile II: juvenile III: adult
Phenotype	Hepatosplenomegaly	Hepatomegaly		
Visceral	Upper airway complications Respiratory infections		Severe vomiting	
	Valvular dysfunction Hernias	Valvular dysfunction Hernias		
Skeletal	Dysostosis multiplex	Dysostosis multiplex		
Neurologic	Mental retardation Hydrocephalus	None	Seizures, hypertonia, Ataxia, spasticity	Hypotonia, seizures Irritability, ataxia
Other	Corneal clouding	Corneal clouding	Vision loss	Blindness
Treatment				
ERT	In clinical trials	In clinical trials		
HCT	3y OS ~70% for HLA Matched related and unrelated transplants	Visceral Improvement	Neurologic Improvement	Neurologic Deterioration or improvement
Problems	Reports of high graft failure Poor correction of skeletal and heart disease	Orthopedic problems Progress	Symptomatic infants are unlikely to benefit from HCT	Persistence of peripheral neuropathy
Animal models	Mouse, dog, cat	Cat, rat, dog, mouse	Mouse, sheep, dog, monkey	Mouse

OS, overall survival; *HCT*, hematopoietic stem cell transplantation; *ERT*, enzyme replacement therapy.
*Incidence per number of live births (http://www.lysosomallearning.com).

derived, engraft within the brain, HCT could prove efficacious in continuous delivery of enzyme within the CNS.[13]

Hurler syndrome (MPS I)

Hurler syndrome, caused by a severe deficiency in α-L-iduronidase, is the LSD for which the greatest experience exists in the therapeutic application of HCT. As such, it is illustrative of the biologic and practical issues encountered in the use of transplantation for these diseases. The spectrum of manifestations of Hurler syndrome includes organomegaly, corneal clouding and airway compromise due to accumulation of glycosaminoglycans.[14] Substrate also accumulates within the myocardium and causes thickening of the valves.[15] Although neurologic development may be normal in infancy, by the second year of life progressive developmental delay is typically observed. Orthopedic complications include valgus deformities of the knees, hip dysplasia, severe kyphoscoliosis, odontoid hypoplasia, carpal tunnel syndrome, and trigger digits.[16]

Transplantation for MPS I was first pioneered by Hobbs et al,[17] who observed resolution of the organomegaly and improvement in corneal clouding several months after donor-derived hematopoietic engraftment. Heterozygous to normal serum levels of α-L-iduronidase are routinely achieved after HCT. Although the anticipated decline in cognitive function is arrested,[18] recipients over 2 years of age at transplantation have inferior neurologic outcomes compared with those undergoing transplantation at an earlier age.[19] The experience at the University of Minnesota with HCT by use of HLA-matched related donors for Hurler syndrome since 1990 provides a context for what can be achieved by this therapeutic approach (Figure 2). However, most affected children do not have a suitable HLA-matched related donor. Therefore we and others have explored the potential of HCT with alternative donors. The survival rate of patients with Hurler syndrome who have undergone unrelated HCT appears decreased in comparison to what is observed with related donors (data reported by the National Marrow Donor Program; Figure 3). The use of umbilical cord blood (UCB) transplantation has also extended this treatment option.[20] Although these results are encouraging, a larger experience with longer follow-up will prove instructive regarding differences in unrelated marrow and unrelated UCB transplantation outcomes. Dual therapy with ERT before and during HCT for Hurler syndrome has been explored at the University of Minnesota with the intention of improving regimen-related toxicity by reducing the glycosaminoglycan burden.[21,22] However, not all manifestations of Hurler syndrome are corrected by HCT. Although storage material diminishes in the myocardium and the coronary arteries, valvular thickening does not resolve.[15] Furthermore, the capacity of HCT