studies on psychosocial aspects of prenatal diagnosis.

DEFECTIVE PROCESSING OF LYSOSOMAL ENZYMES

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Lysosomal enzymes are synthesized at the rough endoplasmic reticulum as glycosylated precursors of high molecular weight. In the endoplasmic reticulum and following in the Golgi complex they undergo a series of modifications that involve cleavage of the amino-terminal signal peptide, disulfide binding, oligosaccharide processing and subunit association. Mannose 6-phosphate residues added in the Golgi complex serve as a signal for recognition by mannose 6-phosphate specific receptors. The receptor-ligand complexes are routed to a prelysosomal acidic compartment, where the lysosomal enzymes and receptors dissociate. The receptors return to the site, where they bind lysosomal enzymes (within or distal to the trans-Golgi). A second mannose 6-phosphate receptor dependent pathway ensures receptor-mediated endocytosis of (exogenous) lysosomal enzymes. The pathways for receptor-mediated transport of endogenous and exogenous lysosomal enzymes are connected and both involve clathrin-coated vesicles. The lysosomal enzymes released from the receptors are transported to lysosomes, where they undergo a limited proteolysis, termed maturation. It has become apparent that defective activity of a lysosomal enzyme in a lysosomal storage disease can be caused by one of the following reasons: 1. Defective synthesis of the lysosomal enzyme polypeptide. 2. Defective transport of the newly synthesized lysosomal enzyme to lysosomes. 3. Instability of the lysosomal enzyme polypeptide within the lysosomes. 4. Deficiency in a cofactor required for activation of the lysosomal enzyme or for presenting the substrate. 5. Synthesis of a catalytically inactive lysosomal enzyme polypeptide. A single mutation may affect several of these parameters, e.g. catalytic activity and stability or transport properties and stability.
The lysosomal storage disorders in which different mutations have been identified by studying the biosynthesis and processing of lysosomal enzymes comprise the following disorders: M. Tay-Sachs (1,2), Pompe (3,4), fucosidosis (5), metachromatic leukodystrophy (6), Gaucher (7), Fabry (8) and Maroteaux-Lamy (9). The analysis of the molecular defects in lysosomal storage disorders using the recently cloned cDNAs for lysosomal enzymes will provide an increased understanding of the requirements for synthesis, processing, stability and transport of lysosomal enzymes under normal conditions.

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BONE MARROW TRANSPLANTATION FOR THE TREATMENT OF LYSOSOMAL STORAGE DISEASES

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Replacement treatment by the use of pure enzymes in various lysosomal storage diseases (LSD) has as yet not produced permanent clinical improvement. Brady et al have attempted this in both Gaucher's disease (1) and Niemann-Pick Disease (2) using enzyme made from human placenta. Neither has implantation of fibroblasts (3) or amnion-epithelial cells (4) given any beneficial effects.
In this paper evidence will be produced to show that a successful bone marrow transplantation (BMT) can produce an everlasting source of enzyme. When the missing enzyme can be demonstrated in the white cells, and that this treatment can be clinically effective.
In Wolman's Disease a satisfactory graft resulted in an adequate level of acid esterase and acid lipase both in the white cells and in liver biopsy along with mobilisation and disappearance of cholesterol from the liver (5).
In GM_1 gangliosidosis a stable white cell engraftment led to the disappearance of the hepatosplenomegaly but there was no improvement in the neurological regression, so that the patient died fourteen months after the graft, thus not altering the natural history of the disease (6).
In Niemann-Pick Disease type B (non-neurological) a successful graft has led to some diminution in the stored sphingomyelin within 80 days of BMT. Hopefully the adequate engraftment of normal marrow will continue to produce a normal white cell level of the missing enzyme, sphingomyelinase, which will lead to the disappearance of the hepatosplenomegaly in time, as has occurred in all other cases of LSD so far transplanted.
Five cases of Gaucher's Disease have been successfully engrafted with complete resolution of the hepatosplenomegaly, clearing of the lung infiltrate and slow improvement in the radiological appearances of the bones, clinically a very satisfactory result (7).
The results in the mucopolysaccharidoses (MPS) seem to very in the different types. In all the hepatosplenomegaly resolved, if there is corneal clouding this improves, there is improvement in the cardiac signs if there is evidence of cardiac involvement. Similarly joint mobility improves but there have been very differing results so far as the CNS involvement is concerned.
Six consecutive cases of Hurler's Disease (MPS I) have all shown that the expected regression in intellectual performance has not occurred, three to six years (average 4.6 years) after the graft and three children are already in normal schools. But the evaluable cases of Hunter's Disease (MPS II) continue to regress. Similarly twins transplanted for San fillipo-B Disease (MPS IIIB) are not deteriorating nearly five years after grafting, but one child with San fillipo-A (MPS IIIA) is. (8). Although all these