THE MUCOLIPIDOSES: MULTIPLE HYDROLASE DEFICIENCY DISEASES.
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I-cell disease (mucolipidosis II) is a severe inherited lysosomal storage disease characterized clinically by profound psychomotor retardation, severe Hurler-like skeletal changes, progressive limitation of joint mobility, gingival hyperplasia , hernias, and frequent upper respiratory infections. Abnormalities are evident soon after birth, and death from pneumonia or heart failure usually occurs between the ages of 2 and 8 years (1-3). Mucolipidosis III is a related disorder distinguished principally by its later onset, a somewhat milder course, mild to absent mental retardation, and survival of affected patients to adult life (1,4,5). Cultured fibroblasts from patients with both of these disorders display large inclusions on phase microscopy that gave rise to the name I-cell disease (6,7).

Unlike cells cultured from patients with lysosomal storage diseases due to single enzyme deficiencies, I-cell disease fibroblasts show reduced levels of many acid hydrolases (8,9). However, culture medium surrounding these fibroblasts has elevated levels of these hydrolases, and the body fluids of affected patients have enormously elevated levels of these hydrolases (9,10). A lysosomal membrane leak which allows escape of these enzymes was suggested to explain these findings. When Hickman and Neufeld (11) tested this hypothesis, they found that I-cell fibroblasts take up and retain normal lysosomal enzymes in a normal manner. They found, however, that I-cell fibroblasts secrete abnormal lysosomal hydrolases which, though catalytically active, were not recognized and taken up by normal human fibroblasts. These studies led Hickman and Neufeld to propose that lysosomal enzymes are normally modified by the addition of a component, which is shared by a whole family of hydrolases and accounts for their recognition and uptake by normal fibroblasts. I-cell disease was proposed to result from a defect in this recognition component leading to the failure of lysosomal hydrolases to localize properly. Hickman et al (12) suggested that the recognition component may be carbohydrate, based on the knowledge that most lysosomal enzymes are glycoproteins, and the finding that gentle periodation of one lysosomal enzyme preferentially inactivates uptake activity compared to catalytic activity.

Lysosomal hydrolases exist in high-uptake forms, i.e. forms which are rapidly pinocytosed by human fibroblasts, and low-uptake forms which are taken up no more rapidly than can be accounted for by nonspecific (bulk-phase) endocytosis (13,14). Recent studies from this laboratory (14) showed that treatment of high-uptake forms of the enzymes with alkaline phosphatase destroyed their susceptibility to pinocytosis by fibroblasts. Furthermore, D-mannose-6-phosphate is a potent inhibitor of pinocytosis of lysosomal hydrolases by fibroblasts. These observations led us to suggest that high-uptake forms of lysosomal hydrolases are phosphoglycoproteins, and that a phosphohexosyl group on the enzyme may be the common recognition marker on lysosomal enzymes that is masked or defective in I-cell disease enzymes.

The unusual freeze-sensitivity of I-cell fibroblasts led us to suspect that I-cell fibroblasts possess an abnormality in their plasma membrane, in addition to a maturation defect in lysosomal enzymes. This hypothesis was tested and verified by demonstrating that certain enveloped viruses acquire abnor-

mal properties when grown in fibroblasts from patients with mucolipidosis II or mucolipidosis III (15). Neuraminidase treatment of the abnormal viruses produced in I-cell fibroblasts corrects the phenotypic abnormalities of the virus completely. Since the I-cell viral glycoproteins are not abnormal, an abnormality in membrane glycolipids of the I-cell viral membranes is suspected. Neuraminidase was recently added to the list of enzymes diminished in I-cell disease fibroblasts (16), a finding that may explain the abnormal membrane properties of certain I-cell viruses and their phenotypic correction by treatment of the viruses with neuraminidase.

While the many abnormalities found in cells from patients with mucolipidoses II and III have provided a number of exciting insights into lysosomal enzyme physiology and biochemistry, the nature of the basic defect leading to these many findings has not yet been established.

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