

# Lysosomal Storage Diseases: Heterogeneous Group of Disorders

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## SUMMARY

The name of lysosomal storage diseases stems from the fact that in this category of disorders specific undegraded materials are stored in the lysosomes. This is usually caused by a lysosomal enzyme deficiency and leads to a cascade of pathological outcomes. Apart from deficiency of lysosomal enzymes, lysosomal storage diseases also include deficiencies in proteins necessary for enzyme functioning, proteins needed for post-translational modification of these enzymes and proteins required for export of certain compounds from the lysosomes.

Lysosomes are the cellular recycling centers responsible for the physiologic turnover of cell constituents. Lysosomal storage diseases (LSDs) mainly stem from deficiencies in lysosomal enzymes. Inadequate enzyme activity results in disruption of the degradation process and accumulation of substrates for that specific enzyme, leading to variety of pathological changes. These enzymes are primarily acid hydrolases requiring a low pH environment in order to function optimally. The combined incidence of LSDs is estimated to be in order of 1:5-8,000 live births in the USA and Europe. LSDs are generally classified by the type of accumulated compounds and include the sphingolipidoses, mucopolidoses, glycoproteinoses, and mucopolysaccharidoses. Most LSDs are inherited in an autosomal recessive manner. Over 40 LSDs have been described; most are due to mutations in genes encoding for lysosomal enzymes.<sup>1,2</sup> Molecular analysis of these diseases has identified many mutations resulting in decreased functionality which results in a wide clinical spectrum for patients. Enzyme replacement therapy or hematopoietic stem cell transplantation is used to treat some patients with LSDs. The results, while promising for some of these disorders, are still not universally successful, and many patients are not eligible for these treatments because they are too mentally or physically impaired when diagnosed.<sup>1</sup> Gene and stem cell therapies are promising but still at the trial stage for some of these disorders.<sup>3</sup>

While the initial characterization of the stored substances in these disorders led to the implication of defective

lysosomal enzymes as a common cause of pathogenesis, in few variant forms of these disorders the hydrolyzing enzymes are not deficient. Instead, mutations in genes coding for another class of proteins called “sphingolipid activator proteins” (SAPs or saposins), transport proteins, and enzymes required for the posttranslational processing of lysosomal enzymes are the cause of the disease.<sup>1,2</sup> Similarly, the pathogenicity of all LSDs is not always due to a large amount of storage of undigested substrates. The classic example of such case is globoid cell leukodystrophy or Krabbe disease where the accumulation of small amounts of a cytotoxic compound, galactosylsphingosine (psychosine), is the cause of the pathology.<sup>4</sup>

### Sphingolipid activator proteins

Sphingolipid activator proteins or saposins are crucial cofactors for the lysosomal degradation of sphingolipids. Four of the five known proteins of this class, saposins A-D, derive from a single precursor protein and show high homology. A fifth activator protein, GM<sub>2</sub> activator protein (GM<sub>2</sub>AP), is genetically unrelated. Although the main function of all five proteins lie in facilitating the enzyme hydrolysis of lipid substrates, their specificities and modes of action differ considerably.<sup>5</sup>

The four saposins A, B, C and D are produced by proteolytic processing of a single precursor protein called prosaposin. Each saposin contains about 80 amino acid residues with six equally placed cysteines, two prolines, and at least one conserved N-glycosylation site (two in saposin A, one in each saposins B, C, and D). The proteins display a structure

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of intertwined loops, with disulfide bonds between the first and sixth cysteines in the sequence, as well as between the second and fifth and the third and fourth cysteines. The bonds are necessary for the functionality of the proteins and are probably responsible for the high stability of these proteins against acid, heat, and proteolytic enzymes.<sup>5</sup>

Saposin A was identified as an N-terminal domain in the prosaposin cDNA. It is known to stimulate the enzymatic hydrolysis of galactocerebroside.<sup>6</sup> A transgenic saposin A-deficient mouse model mimics the late onset form of human globoid cell leukodystrophy. However, a human patient with saposin A deficiency, had a clinical picture similar to classical infantile Krabbe disease.<sup>7</sup>

Saposin B was found to be required as a heat-stable factor for hydrolysis of sulfatides by arylsulfatase A. It is known by many different names, such as sphingolipid activator protein-1 (SAP-1), sulfatide activator protein, and GM<sub>1</sub> ganglioside activator.<sup>8</sup> While most patients with metachromatic leukodystrophy (MLD) have defects in arylsulfatase A, some patients have defects in saposin B.<sup>9</sup> Its activator role is through the interaction with the substrates not the enzymes.

Saposin C stimulates the hydrolysis of glucocerebroside by glucocerebrosidase and galactocerebroside by galactocerebrosidase (GALC). Whereas Gaucher disease occurs mainly as a result of a deficiency of the lysosomal enzyme glucocerebrosidase activity, a rare variant form of this disease is also known in which saposin C is deficient.<sup>10</sup> Saposin D is a sphingolipid activator protein required for the lysosomal breakdown of ceramide by acid ceramidase. Transgenic saposin D-deficient mice have shown an accumulation of ceramides in the kidney and cerebellum, but do not demonstrate the phenotypic abnormalities of human Farber disease.<sup>11</sup> No specific saposin D deficiency is known in any mammalian species at this point.

GM<sub>2</sub>AP, the fifth protein of the group, shows some different structural features. With a molecular weight of about 20 kDa, it is larger than the saposins. It carries one N-glycosylation site and contains eight cysteines that form four disulfide bonds. The arrangement of these bonds is somewhat similar to that of the saposins.<sup>5</sup> A deficiency in GM<sub>2</sub>AP leads to the AB-variant form of GM<sub>2</sub> gangliosidosis, which is characterized by the accumulation of ganglioside GM<sub>2</sub> and glycolipid GA<sub>2</sub>.<sup>5</sup>

### Toxicity versus substrate buildup

In some of the lysosomal disorders, the buildup of toxic metabolites appears to play a major pathogenic role. An example of this case is Krabbe disease.<sup>4</sup> Besides galactosylceramide, which is the major substrate for GALC, patients and mouse model of Krabbe disease have elevated levels of the galactosylsphingosine, also called psychosine. Psychosine is generated by the galactosylation of sphingosine by CGT (ceramide galactosyltransferase), and its synthesis is limited to myelinating cells,

oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system.<sup>12</sup> A small amount of psychosine is generated even in normal brain during active myelination. When the lysosomal enzyme GALC is present, psychosine is degraded. However, in the absence of GALC activity, the increase levels of psychosine in the white matter of human patients and the different animal models of this disease will trigger very rapid loss of the oligodendrocytes and Schwann cells with no substantial accumulation of the primary substrate, galactosylceramide. The structural difference between psychosine and galactosylceramide is the loss of the fatty acid chain attached to the amino group of the sphingosine backbone. The pathogenesis of these disorders is still in intense investigation. However, the diagnosis of these diseases can be made in patients with relatively simple methods using blood samples or cultured skin fibroblasts. Early diagnosis will be required if the patient is to be treated successfully.

### Ethical issues

There is none to be declared.

### Competing interests

The authors declare no conflict of interests.

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