Disorders of lysosomal metabolism / Deficiency of enzyme activators of lysosomal hydrolases

There are two types of activators:

- Saposins = SAP (sphingolipid activator protein) - these are several peptides, they contain about 80 amino acids
- GM2 activator (GM2A)

Saposins

Saposins are formed from a common precursor known as **prosaposin** (encoded by the PSAP gene), which is proteolytically cleaved into individual saposins in the early endosome phase - saposin A, B, C and D. Saposins are very stable proteins - resistant to strong proteases, high temperatures, extremely compact and rigid.

Saposins are sphingolipid-cleaving hydrolase activators

- **SAP A** - galactosylceramidase and lactosylceramidase enzyme activator
- **SAP B** - also known as GM1A, does not activate the enzyme directly, but reacts with the substrate; its function is to "pull" the glycolipid (substrate) from the lysosome membrane, i.e., without SAP B the hydrolase is active but has nothing to cleave
- **SAP C** - activates glycosylceramidase and galactosylceramidase; The function of SAP C is to activate and attach the enzyme to the membrane
- **SAP D** - participation in ceramide degradation

GM2A

The function of GM2A is to "pull" the glycolipid (GM2 ganglioside) from the membrane and allow contact of the substrate with β-hexosamidase; its function is therefore similar to that of SAP B (GM1A) - with the difference that it "pulls out" another substrate.

Diseases caused by a deficiency of lysosomal activators

In general, these diseases are very rare with the number of patients is in the tens. The deficit or mutation of activators causes the phenotype of the corresponding lysosomal sphingolipidosis.

- Prosaposin defect - there is a logical lack of all SAPs, i.e., very severe complete sphingolipidosis of the newborn, or the infant dies within 4 to 17 weeks; 6 cases described worldwide; AR disease
- **SAP A** deficiency or mutation causes the clinical picture of **Krabbe disease**
- **SAP B** deficiency or mutation causes the clinical picture of **Fabry disease** or **metachromatic leukodystrophy** (15 cases described worldwide)
- **SAP C** deficiency or mutation causes the clinical picture of **Gaucher disease** (3 cases described worldwide)
- **GM2** deficiency or mutation causes the clinical picture of **Sandhoff disease**
- **SAP D** deficit was not recorded

Activator deficiency is considered if the enzyme is functional, but there are still signs of lysosomal disease.