Sphingolipidoses comprise the most prevalent group of lysosomal storage disorders. The most frequent is Gaucher disease (GD), where it occurs the storage of the glycosphingolipid glucosylceramide (GlcCer) due to a deficiency in the enzyme glucocerebrosidase (GCase). GD is a multi-systemic disorder affecting most organs, resulting in cytopenia, hepatosplenomegaly and skeletal abnormalities (1). Only recently, lysosomal integral membrane protein, type 2 (LIMP-2) has been identified as the receptor involved in the intracellular sorting and trafficking of the enzyme GCase to lysosomes (2). Deficiency of LIMP-2 causes Action Myoclonic-Renal Failure (AMRF), which clinically differs from GD. AMRF patients present renal dysfunction and failure, myoclonic epilepsy and ataxia with progressive neurological impairment (3,4). The marked phenotypic difference between GD and AMRF prompted us to study more closely the abnormalities in GCase and the functionally related lipid abnormalities in human and tissues of LIMP-2 KO mice as well as the efficaccy of glycosphingolipid substrate reduction therapy to treat AMRF disorder. Recently developed fluorescent activity-based-probes allowed a sensitive and specific visualization of active GCase, showing a cell-type specific gradient in deficiency of functional GCase along LIMP-2 deficient tissues. By doing the lipidomic analysis, the principal substrate of GCase, GlcCer, did not correlate with the extent of the enzyme deficiency. Another outspoken lipid abnormality in LIMP-2 KO mice is the elevation of GlcSph,the lyso-form of GlcCer which correlates with GCase deficiencies in tissues. By the first time, it was also documented another metabolite abnormality in LIMP-2 KO mice, i.e. elevated levels of glucosyl-cholesterol were seen in LIMP-2 KO mice tissues. These findings help to understand the remarkable difference in clinical and biochemical manifestation associated with primary GCase deficiency in Gaucher patients when compared to the secondary GCase deficiency in AMRF patients. All together, the results also suggest that combined measurements of chitotriosidase and GlcSph can be used for convenient differential laboratory diagnosis of AMRF and GD.

1 - The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York, NY: McGraw-Hill; 7th ed. 1995:2641–2670; 2 - Cell 2007, 131:770–83; 3 - Hum Mol Genet 2008, 17:2238–43; 4 - Am J Hum Genet 2008, 82:673–84