Elucidation of molecular pathogenesis of lysosomal diseases for development of novel therapeutic strategies

○ Hitoshi Sakuraba
Dept. of Anal. Biochem., Meiji Pharmaceut. Univ.

Lysosomal storage diseases (LSDs) are genetic lysosomal enzyme deficiencies characterized by excessive accumulation of the natural substrates and a variety of clinical symptoms. In recent years a recombinant enzyme replacement therapy via intravenous administration has been established for treatment of several LSDs, and new approaches based on pharmacological chaperone, substrate depletion, stem cell therapy and gene therapy have been tried. However, elucidation of the molecular pathogenesis of LSDs should be still required for the adequate application of these techniques and development of the superior next-generation therapies. Fabry disease is an □-galactosidase (GLA) deficiency associated with triaosylceramide accumulation in affected tissues. There are two clinical forms (classical and atypical cardiac types) of the patients. In the classical patients the onset of severe pain in the extremities and hypohidrosis usually occurs during childhood, and then they develop renal, cardiac and cerebral vascular manifestations. In contrast, atypical variants have residual GLA activity and mainly develop cardiac involvement after middle age. To date, about 400 of disease-causing mutations have been identified in the GLA gene. Among them the gene abnormalities including large deletion cause the classical type disease, but the heterogeneous missense mutations are found in both classical and atypical cardiac patients. Amino acid substitutions predicted to cause large structural alterations in the catalytic and other sites by means of *in silico* modeling resulted in loss of the enzyme activity and hypersensitivity to proteolytic degradation. In contrasts, the mutant products derived from cardiac variants with putative small conformational changes were found to exhibit residual enzyme activities.