**MOLECULAR SIGNIFICANCE of AUTOPHAGY in GAUCHER DISEASE**

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Autophagy is a lysosomal-dependent catabolic pathway contributing to cellular homeostasis by sequestering cytosolic macromolecules in double or multimembrane vesicles and deliver them to lysosomes for degradation. Gaucher disease is the most frequent lysosomal storage disorder (LSD) caused by deficiency of acid-β glucosidase and is characterized by the accumulation of glucosylceramide or other gycolipids in visceral organs or central nervous system. Although the relevance of autophagy is shown in different LSDs, the underlying molecular mechanism in Gaucher disease is poorly understood. Here, we investigated molecular significance of autophagic pathway in fibroblasts cells obtained from Gaucher patients homozygous for L296V mutation, as well as for the most common mutations, N370S, L444P, and D409H. We observed significant attenuation in the expression of key autophagy-related genes *(BECN1, ATG5* and *LC3)* and accumulation of their proteins in mutant cells. We found that decrease ability of autophagosomes to fuse with lysosomes is associated with elevated lysosomal pH and reduced lysosomal enzyme activity. Analysis of proteasomal degradation machinery showed decreased proteolytic activity of proteasome, which consequently leads to increased susceptibility to cell death. Our data indicate that both autophagic pathway and ubiquitin-proteasome system are affected by mulfunctional lysosomes and may underlie the mechanism of clinical severity of Gaucher patients. (This project is supported by TUBITAK-3501-National Young Researchers Carreer Development Program, Project No: 112T130).

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