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Significance of Molecular Autophagic Pathway in Gaucher Disease Pathology

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Abstract : Autophagy is an evolutionary conserved lysosome-dependent catabolic pathway, responsible for the degradation of long-lived proteins, abnormal aggregates and damaged organelles which cannot be degraded by the ubiquitin-proteasome system. Lysosomes degrade the substrates through the activity of lysosomal hydrolases and lysosomal membrane-bound proteins. Mutations in the coding region of these proteins cause malfunctional lysosomes, which contributes to the pathogenesis of lysosomal storage diseases. Gaucher disease is a lysosomal storage disease resulting from the mutation of a lysosomal membrane-associated glycoprotein called glucocerebrosidase and its cofactor saposin C. The disease leads to intracellular accumulation of glucosylceramide and other glycolipids. Because of the essential role of lysosomes in autophagic degradation, Gaucher disease may directly be linked to this pathway. In this study, we investigated the expression of autophagy and/or lysosome-related genes and proteins in fibroblast cells isolated from patients with different mutations. We carried out confocal microscopy analysis and examined autophagic flux by utilizing the differential pH sensitivities of RFP and GFP in mRFP-GFP-LC3 probe. We also evaluated lysosomal pH by active lysosome staining and lysosomal enzyme activity. Beside lysosomes, we also performed proteasomal activity and cell death analysis in patient samples. Our data showed significant attenuation in the expression of key autophagy-related genes and accumulation of their proteins in mutant cells. We found decreased the ability of autophagosomes to fuse with lysosomes, associated with elevated lysosomal pH and reduced lysosomal enzyme activity. Proteasomal degradation and cell death analysis showed reduced proteolytic activity of the proteasome, which consequently leads to increased susceptibility to cell death. Our data indicate that the major degradation pathways are affected by multifunctional lysosomes in mutant patient cells and may underlie in the mechanism of clinical severity of Gaucher patients. (This project is supported by TUBITAK-3501-National Young Researchers Career Development Program, Project No: 112T130).

Keywords : autophagy, Gaucher's disease, glucocerebrosidase, mutant fibroblasts
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