

INVOLVEMENT of AUTOPHAGY ABNORMALITIES in GAUCHER LYSOSOMAL STORAGE DISEASE

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Lysosomes are important organelles for cellular homeostasis with their involvements in degradation of biomolecules, cell signaling and energy metabolism, which are related to health and diseases. The function of lysosomes depend on coordinated action of lysosomal hydrolyzes and lysosomal membrane-bound proteins. Mutations on the coding region of these proteins cause defective lysosomal functions and accumulation of un-metabolized substrates, which contributes to the pathogenesis of lysosomal storage diseases. Substrates are transported to lysosomes through different mechanism such as endocytosis, phagocytosis or autophagy. Autophagy is a conserved cellular pathway, that lead to the engulfment of portions of the cytoplasm and organelles and then delivers the cargo to lysosomes for degradation. Autophagic degradation is relies on the ability of lysosomal membrane fusion with autophagic vesicle membrane, therefore disorders in lysosomal action may directly effect on autophagy. Gaucher disease is a lysosomal storage disease resulting from the mutation of a lysosomal membrane-associated glycoprotein glucocerebrosidase (GBA) and GBA cofactor of saposin C. The disease leads to the intracellular accumulation of glucosylceramide and other glycolipids. In order to show, the effect of autophagy abnormalities to the Gaucher disease, we analyzed the expression of autophagy and/or lysosome-related genes and proteins in fibroblast cells isolated from patients with different mutations. We observed significant attenuation in autophagy/lysosome-related gene in patient fibroblast cells. We also observed a mutation-type dependent accumulation of some autophagy proteins. Moreover, there was a clear lysosome and lysosomal protein accumulation and an increase in lysosome numbers in starved-patient cells. Biochemical and morphological analyses of autophagy revealed some abnormalities in mutant cells, suggesting that autophagy is directly affected in Gaucher patient cells. **(This project is supported by TUBITAK-3501-National Young Researchers Career Development Program, Project No: 112T130)**