Molecular mechanism of autophagic pathway in Gaucher cells

Oral O.,[1] Sharafi P.,[2] Yuce A.,[3] Gozuacik D.,[4] Dokmeci (Emre) S.[2]

[1]Sabanci Univ. Nanotech. Res. and Appl. Center, Istanbul, Turkey

[2]Hacettepe Univ. Faculty of Medicine, Dept. of Medical Biology, Ankara, Turkey

[3]Hacettepe University, Faculty of Medicine, Dept. of Child and Adolesc. Psychiatry, Gastroenterol. Hepatol. and Nutr Unit, Ankara, Turkey

[4]Sabanci Univ. Faculty of Eng. and Nat. Sciences, Mol. Biol., Genetics and Bioeng. Program, Istanbul, Turkey

Background and objectives: Lysosomes regulate cellular homeostasis via degradation and recycling of biomolecules. Lysosomal hydrolyzes and lysosomal membrane-bound proteins are two main actors for functional lysosome and any mutation on the coding region of these proteins cause accumulation of un-metabolized target substrates in the cells and finally coming out of lysosomal storage disease (LSD). Gaucher's disease is a LSD resulting from the mutation of a lysosomal membrane-associated glycoprotein glucocerebrosidase (GBA) and GBA cofactor of saposin C. The disease cause intracellular accumulation of glucosylceramide and other glycolipids. Autophagy is a conserved cellular pathway, leading to the engulfment of portions of cytoplasm and organelles and subsequently delivers the cargo to lysosomes for degradation. Although the relevance of autophagy is shown in different LSDs, the underlying molecular mechanism in Gaucher disease is poorly understood.

Materials and Methods: Here, we investigated molecular significance of autophagic pathway in fibroblasts cells obtained from Gaucher patients. First**,** we analyzed the expression of autophagy and/or lysosome-related genes and proteins and then carried out active lysosome staining by using confocal microscopy analyses. In order to test autophagic flux, we used the differential pH sensitivities of RFP and GFP in mRFP-GFP-LC3 probe. Finally, we investigated lysosomes in detail by performing enzymatic activity tests.

Results: We observed significant attenuation in the expression of key autophagy-related genes and accumulation of their proteins in mutant cells. We found inhibition of autophagosomes to fuse with lysosomes, that is associated with lysosomal pH and reduced enzyme activity.

Conclusion: Our data indicate that autophagic pathway is directly affected by mulfunctional lysosomes and may underlie the mechanism of clinical severity of Gaucher patients**.**

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