

AUTOPHAGY ABNORMALITIES IN MUTANT CELLS ISOLATED FROM GAUCHER'S LYSOSOMAL STORAGE DISEASE

***Ozlem Oral*^{1**}, *Parisa Sarafi*², *Aysel Yuces*³, *Serap Dokmeci*^{2*}, *Devrim Gozuacik*^{4*}**

¹SABANCI UNIVERSITY, Nanaotechnology Research and Application Center, 34956 Tuzla, Istanbul, Turkey;

²HACETTEPE UNIVERSITY, Faculty of Medicine, Department of Medical Biology, 06100, Ankara, Turkey;

³HACETTEPE UNIVERSITY, Faculty of Medicine, Departments of Child and Adolescent Psychiatry, Gastroenterology, Hepatology and Nutrition Unit, 06100, Ankara, Turkey;

⁴SABANCI UNIVERSITY, Faculty of Engineering and Natural Sciences, Molecular Biology, Genetics and Bioengineering Program, 34956 Tuzla, Istanbul, Turkey

* Equally contributing corresponding authors: dgozuacik@sabanciuniv.edu, semre@hacettepe.edu.tr

**ozlemoral@sabanciuniv.edu

Considering their involvement in the degradation and recycling of biomolecules, secretion, plasma membrane repair, cell signalling and energy metabolism, lysosomes are the most important organelles for cellular homeostasis and organismal health. The function of lysosomes depend on coordinated action of lysosomal hydrolyses and lysosomal membrane-bound proteins. Mutations on the coding region of these proteins cause defective lysosomal functions, accumulation of un-metabolized target substrates in the cells and finally coming out of lysosomal storage disease. Substrates are transported to lysosomes through different mechanism such as endocytosis, phagocytosis or autophagy. Macroautophagy (autophagy herein) is a conserved cellular pathway, that lead to the engulfment of portions of cytoplasm and organelles and that subsequently delivers the cargo to lysosomes for degradation. Gaucher's 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. To explore the contribution of autophagy abnormalities to the Gaucher's disease, we analyzed the expression of autophagy and/or lysosome-related genes and proteins in fibroblast cells isolated from patients with different mutations. Although we observed an increase in the expression of Beclin1, Atg5, Atg12, Atg4C, LC3, p62, LAMP1 and LAMP2 in control cells under autophagy-stimulating starvation condition, however in cells isolated from Gaucher's disease patients, autophagy/lysosome-related gene upregulation was perturbed. We also observed a mutation-type dependent accumulation of some autophagy proteins. Moreover, while there was a clear lysosome and lysosomal protein accumulation and an increase in lysosome numbers in starved-patient cells, these lysosomes were defective in cathepsin activity. Moreover, biochemical and morphological analyses revealed abnormalities

of autophagy in mutant cells. Contribution of autophagy abnormalities to the disease phenotype will be discussed.