Unraveling VPS13A pathways: from Drosophila to human

Thesis: Francesco Pinto, 2018

14th November 2018, 11:00 h in the Aula of the Academiegebouw (after will follow a reception in the Spiegelzaal of the Academiegebouw)

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Abstract:

Chorea-Acanthocytosis (ChAc) is a rare human neurodegenerative disease caused by homozygous mutations in the VPS13A gene. Until now no treatment is available and it is not known why mutations in this specific gene lead to neurodegeneration. We established and validated a suitable model organism, Drosophila melanogaster, to study ChAc. Drosophila melanogaster Vps13 mutants showed shortened life span, decreased climbing ability and the presence of vacuoles in the brain. Furthermore, Vps13 mutant flies were sensitive to proteotoxic stress and accumulated ubiquitylated proteins. We performed immunoprecipitation experiments coupled to mass spectrometry (IP-MS) in fly heads using control and Vps13 mutant flies to obtain a list of possible Vps13 interactors and Galectin was identified as a possible candidate. The Interaction between Vps13 and Galectin was validated via immunoprecipitation in cultured insect cells. In addition, we showed that human VPS13A is associated with mitochondria and, through its FFAT domain, interacting with the ER protein VAP-A. These results suggest a role in the formation of ER-mitochondria membrane contact sites. Interestingly, in cells treated with fatty acid, VPS13A translocates from mitochondria to newly synthesized lipid droplets influencing their motility and size. Our data are discussed and reveal an emerging role of VPS13A in preventing neurodegeneration.