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Role of glycosylation-related genes in signaling pathways and diseases

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Congenital disorders of glycosylation (CDGs) are genetic defects affecting the assembly and degradation of asparagine (*N*)-glycans to proteins (*N*-glycosylation). Currently, it has been identified 19 types of CDG so far. Recessive mutations in *NGLY1* cause a rare, multi-system developmental disorder in human patients called NGLY1 deficiency (CDG). During endoplasmic reticulum-associated degradation (ERAD), the cytoplasmic enzyme *N*-glycanase 1 (NGLY1) is proposed to remove *N*-glycans from misfolded N-glycoproteins after their retrotranslocation from the ER to the cytosol. Using biochemical, cell-based, genetic, and genome engineering techniques, we establish the *Drosophila* Dpp and its mouse ortholog BMP4 as biologically relevant targets of NGLY1 and find, unexpectedly, that NGLY1-mediated deglycosylation of misfolded BMP4 is required for its retrotranslocation. Accumulation of misfolded BMP4 in the ER results in ER stress and prompts the ER recruitment of NGLY1. The ER-associated NGLY1 then deglycosylates misfolded BMP4 molecules to promote their retrotranslocation and proteasomal degradation, thereby allowing properly-folded BMP4 molecules to proceed through the secretory pathway and activate signaling in other cells. Our study redefines the role of NGLY1 during ERAD and suggests that impaired BMP4 signaling may underlie some of the NGLY1 deficiency patient phenotypes.

Keywords: CDG, ERAD, Glycosylation, NGLY1, BMP signaling

Short Bio: Antonio Galeone received his Master Degree in Human Biology from the University of Salento, Lecce (Italy) in 2008. In April 2012 he graduated in Nanobiotechnology at ISUFI (Istituto Superiore Universitario di Formazione Interdisciplinare), Lecce, and later performed a short-term Postdoctoral training at Italian Institute of Technology funded by the European Commission in the Pompa and Cingolani's Lab. From 2013-2018, he worked as PostDoc at Baylor College of Medicine (Houston, Texas) in the lab of Dr. Hamed Jafar-Nejad (Department of Human and Molecular Genetics). In June 2018, he has been granted by European Commission with the Marie Skłodowska-Curie individual fellowship and joined the lab of Thomas Vaccari at Universita' degli Studi di Milano (Department of Biosciences). In October 2020, Antonio has joined CNR NANOTEC, Lecce) as visiting scientist. His research mainly focuses on understanding the role of genes involved in the glycosylation process in developmental signaling pathways. Accordantly, he works to generate "avatar models" based on patient-derived alleles of congenital disorders of glycosylation (CDG).

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