Special Lectures ❷

TMEM165; a new key player in Golgi glycosylation and cellular Mn^{2+} homeostasis

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François Foulquier is currently Research Director at CNRS institute in France (Centre National de la Recherche Scientifique). Dr. Foulquier received his PhD in Biochemistry at the University of Lille in 2003. From 2003-2007, he was a postdoctoral Marie-Curie fellow at KU-Leuven (Belgium) with Pr. G. Matthijs. During his postdoc, his research has focused on identifying and characterizing the molecular bases of Congenital Disorders of Glycosylation (CDG) that are severe inherited diseases in which aberrant protein glycosylation is a hallmark. The discovery of genes not directly involved in the glycosylation process such as COGs/ TMEM165 let him to investigate the molecular mechanisms by which the regulation of the glycosylation process at the ER/ Golgi levels occurs. Dr. Foulquier now runs a laboratory of 10 scientists at the Structural and Functional Glycobiology Unit (UGSF) in Lille. His current work is aimed at understanding the impacts of vesicular trafficking, pH and Mn^{2+} ER/ Golgi homeostasis on the regulation of the glycosylation process. Additionally, Dr. Foulquier was awarded the CNRS 2011 Bronze Medal for his contribution on CDG. His work is currently supported by national (French National Agency) and european grants. He won Mizutani research grant in 2015.

Congenital disorders of glycosylation (CDG) are severe inherited diseases in which aberrant protein glycosylation is a hallmark. From this genetically and clinically heterogenous group, a significant subgroup due to Golgi homeostasis defects is emerging. We previously identified TMEM165 as a Golgi protein involved in CDG. Extremely conserved in the eukaryotic reign, the molecular mechanism by which TMEM165 deficiencies lead to Golgi glycosylation abnormalities was enigmatic. As GDT1 is the ortholog of TMEM165 in yeast, both gdt1Δ null mutant yeasts and TMEM165 depleted cells were used. We highlighted that the observed Golgi glycosylation defects due to Gdt1p/TMEM165 deficiency result from Golgi manganese homeostasis defect (**Figure 1** panels A and B). We discovered that in both yeasts and mammalian Gdt1p/TMEM165 deficient cells, Mn^{2+} supplementation could restore a normal glycosylation. We also showed that TMEM165 was a Mn^{2+} sensitive protein. When exposed to high Mn^{2+} concentrations, we demonstrated that TMEM165 was targeted and degraded in lysosomes. Remarkably, the variant p.E108G recently identified in a novel TMEM165-CDG patient, was found to be insensitive to Mn^{2+} supplementation. This study not only provides novel insights into the molecular causes of glycosylation defects observed in TMEM165-deficient cells but also suggests that TMEM165 is a key determinant for the regulation of Golgi Mn^{2+} homeostasis (**Figure 1**).

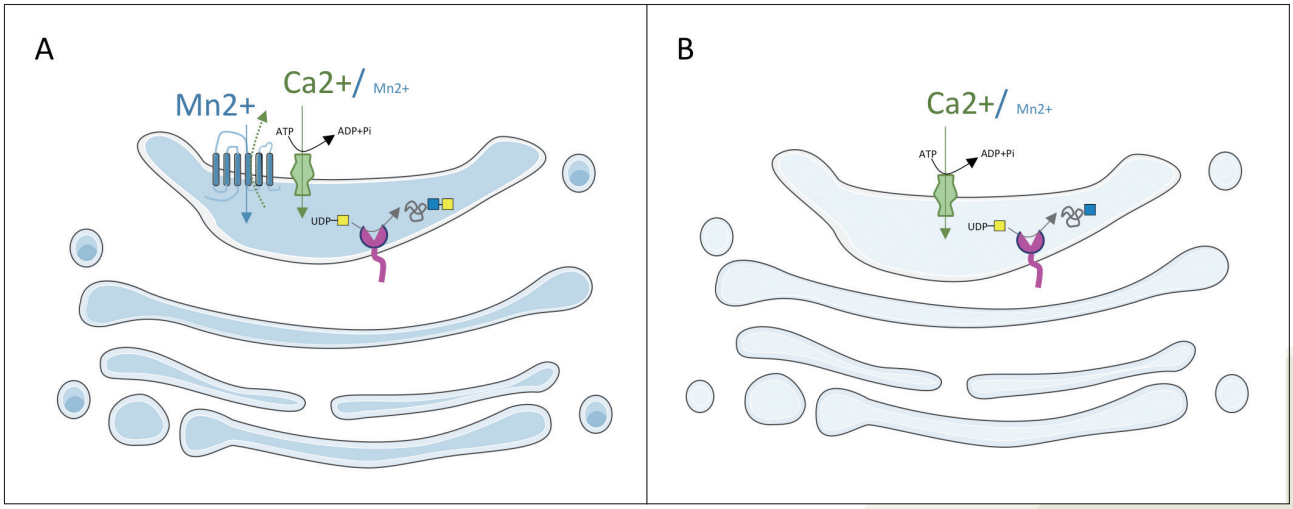

Figure 1

A Proposed model for the function of TMEM165 in regulating Golgi together with the Ca^{2+}/Mn^{2+} ATPase SPCA1. The Mn^{2+} concentration in the Golgi permits the Mn^{2+}-dependent galactosyltransferases to transfer galactose residues from UDP-Gal to glycoconjugates.

B Proposed model where TMEM165 is deficient. The lack of TMEM165 leads to a decreased Golgi level of Mn^{2+}. The lack of Golgi Mn^{2+} impacts the activity of Golgi galactosyltransferases and leads to the appearance of undergalactosylated glycoconjugates. Blue square: GlcNAc and yellow square: galactose.