Overview on N-linked glycosylation and Congenital Disorders of Glycosylation with a special focus on TMEM165, a new key player in Golgi homeostasis.

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Abstract:

Congenital Disorders of Glycosylation (CDG) are a rapidly growing disease family due to genetic defects of protein and lipid glycosylation. In protein N-glycosylation, two different CDG groups can be distinguished. In CDG-I, the molecular defects affect the oligosaccharidic precursor assembly pathway in the endoplasmic reticulum, leading to the presence of unoccupied N-glycosylation sites. CDG-II are due to defects in the glycan processing in the Golgi, giving rise to the presence of abnormal glycan structures on glycoproteins. To date, the CDG family comprises nearly hundred disorders. Most are due to defects in the specific glycosylation machinery, such as SLC35A1 [MIM 605634], B4GALT1 [MIM 137060] and MGAT2 [MIM 602616]. However, in the CDG-II group, defects have lately been discovered in proteins that are not only involved in glycosylation but also in other cellular functions. Among these are CDG caused by altered vesicular Golgi trafficking and/or Golgi pH homeostasis marking a new era in the CDG field.

In 2012, we reported a novel disorder in this group namely TMEM165-CDG (OMIM entry #614727). TMEM165 is a transmembrane protein of 324 amino acids belonging to a well conserved but uncharacterized family of membrane proteins named UPF0016 (Uncharacterized Protein Family 0016; Pfam PF01169). Extremely conserved in the eukaryotic reign, *GDT1* is the yeast ortholog of *TMEM165*. We highlighted that the observed Golgi glycosylation defects due to Gdt1p/TMEM165 deficiency result in fact from Golgi manganese homeostasis defect. Altogether this work allowed us to identify the Golgi protein TMEM165 as a novel cytosolic Mn2+ sensor in mammalian cells and pointed to the crucial importance of the cytosolical ELGDK motif in both Mn2+ sensitivity and function. Moreover, we demonstrated that the observed Golgi glycosylation deficiencies in Gdt1p/TMEM165 deficient cells result from a defective Golgi Mn2+ homeostasis then providing novel insights into the mechanism of the galactosylation defect observed in TMEM165-deficient cells. These findings also support the potential use of therapeutic trials of Mn2+ in TMEM165 deficient patients.

1_ Potelle S, Morelle W, Dulary E, Duvet S, Vicogne D, Spriet C, Krzewinski-Recchi MA, Morsomme P, Jaeken J, Matthijs G, De Bettignies G, Foulquier F. (2016) Glycosylation abnormalities in Gdt1p/TMEM165 deficient cells result from a defect in Golgi manganese homeostasis. ***Hum Mol Genet***. 25, 1489-500.

2_ Potelle S, Dulary E, Climer L, Duvet S, Morelle W, Vicogne D, Spriet C, Krzewinski-Recchi MA, Peanne R, De Bettignies G, Matthijs G, Marquardt T, Lupashin V, Foulquier F. (2016) Characterization of TMEM165 as a novel Golgi manganese sensitive protein involved in Congenital Disorders of Glycosylation. ***Submitted to Hum Mol Genet***.