Conserved motifs in the cytoplasmic tails of human Golgi-glycosyltransferases regulate enzyme dynamics

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Golgi-resident glycosyltransferases sequentially add sugars to the growing glycan chain present on protein and lipid cargoes traversing the Golgi-stacks. The sub-Golgi localization of Golgi enzymes is maintained efficiently and mirrors the order in which they act along the Golgi-cisternae. Aberrant localization of the enzymes results in abnormal cargo glycosylation, leading to defects in function, thereby resulting in diseases such as cancer. To maintain their steady-state localization in the Golgi-cisternae, the enzymes are continuously recycled from distal (trans) to proximal Golgi-cisternae (cis) by complex recycling machinery involving COPI. Most of the Golgi-resident enzymes are type II membrane proteins, with a C-terminal enzymatic domain, a single transmembrane domain (TMD), and a short N-terminal cytosolic tail (CT). Recent studies have highlighted the importance of the CTs in the interaction with the components of the recycling machinery, contributing to the enzyme sub-Golgi localization. We have previously shown that the GOLPH3 oncogene works as an adapter, binding both, a specific motif present in the CTs of a subset of enzymes involved in glycosphingolipid metabolism, and COPI. By doing this, GOLPH3 regulates the sub-Golgi localization of enzymes bearing the GOLPH3-binding motif, thereby influencing glycosphingolipid glycosylation. Similarly, a group of O-linked glycosylation enzymes is retained in the Golgi via the binding of a motif within their CTs to δ- and ζ-subunits of COPI. The rules governing the interaction of N-terminal CTS of Golgi-enzymes with the recycling machinery resulting in a specific localization within the Golgi-cisternae are poorly understood. Here we report a novel conserved motif, namely Φ(R/K)Lxζ, enriched in the CTS of N-glycosylation enzymes. The disruption of this motif is sufficient to abolish the Golgi-localization of N-glycosylation enzymes bearing it. This leads to a decreased half-lives and lysosomal degradation of the enzymes, most probably affecting N-glycosylation quality. Our studies show that the CTS of the enzymes studied do not directly engage COPI. The next step will be to dissect the molecular details of the interaction of the enzymes CTS bearing the motif with the components of the recycling machinery. Those details will shed light on how the N-glycosylation pathway is controlled in physiopathology. Until now it was believed that all the Golgi enzymes were bulky recycled by COPI. Our finding supports a more complex scenario in which the Golgi complex is a mosaic of recycling enzyme modules (i.e., driven by specific adaptors) acting to modulate the glycan outputs of various glycosylation pathways.

References:

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