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Different populations of endoplasmic reticulum mannosidase I/Man1b1 play distinct roles in the proteostasis network of the vertebrate secretory pathway

Statement of Problem: Although inherited information exists within a genetic material, defects in the encoded proteins are responsible for manifestations associated with abnormal biology. Therefore, a need exists to mechanistically define the proteostasis systems responsible for managing the cellular proteome as a means to eventually identify novel therapeutic sites for disease intervention. To this end, we have monitored the fates of newly synthesized proteins that are translocated into the secretory pathway, many of which are subjected to asparagine(N)-linked glycosylation. In addition to facilitating proper protein folding, modification of the appendage flags misfolded N-glycoproteins for elimination by "ER-associated Degradation" (ERAD). The currently accepted flagging mechanism involves the opportunistic cleavage of alpha-1,2-mannose units. Although this crucial event was initially thought to involve ER mannosidase I (Man1b1), recent evidence indicates that the protein is not a component of the mammalian glycoprotein quality control interactome, localizes to post-ER compartments, and does not require enzymatic activity to promote N-glycoprotein degradation.

Methodology & Theoretical Orientation: The present study sought to define the contribution of Man1b1 to the operation of an apparently "unconventional" ERAD client recruitment system. The effects of wildtype and selectively mutated forms of recombinant human Man1b1 on the fates of selected ERAD clients were monitored through the use of pharmacologic inhibitors, metabolic radiolabeling, immunoprecipitation, and western blotting.

Findings: Distinct populations of Man1b1 have identified that exhibit different intracellular trafficking patterns, unique functional partners, and unique client specificities.

Conclusion & Significance: An unexpected level of functional plasticity exists in the proteostasis network of the secretory pathway, extending the role of a specific mannosidase beyond that of limits of Glycobiology.

Biography

Sifers helped pioneer the initial mechanistic analysis of the biological systems that manage glycoprotein homeostasis (i.e. glycoproteostasis) in the mammalian secretory pathway. Using alpha1-antitrypsin deficiency as a medically relevant paradigm and client, his lab characterized the processes of chaperone-assisted glycoprotein folding as a means of conformation-based intracellular retention and proposed and characterized the mannose timer hypothesis as an initial step in N-glycan-targeted proteolysis (quality control). Subsequently, his team identified the underlying contribution of the unfolded protein response (UPR) and elucidated how compromised quality control can function as an etiologic agent of infantile liver cirrhosis.

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