Investigations of glycoprotein co-translational maturation in the cell

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Abstract

The earliest steps of nascent protein folding are critical to the overall folding efficiency. Folding events start as soon as the protein is translocated into the endoplasmic reticulum lumen, where the co-translational machinery ensures the fidelity of protein folding by coupling molecular chaperones, foldases and folding sensors. We seek to investigate the co-translational maturation events of disease-related glycoproteins containing different membrane topology to determine the generality and substrate specificity of this process, to hopefully provide new insight into therapeutic methods by targeting protein maturation at early stages. A variety of cell biological, biochemical, and molecular biological approaches using cell-free assays, isolated organelles and live cells have been applied in this study. The work on co-translational maturation of a type I membrane protein human tyrosinase has shown that Hsp70 family member BiP handed off tyrosinase to the lectin chaperones calnexin/calreticulin as glycans were added. The maturation pathway of the albino mutation of tyrosinase (C71R) diverges from that of the wild type co-translationally through its recognition by the oxidoreductase ERp57. The work on a type II membrane protein *influenza* neuraminidase (NA) subtype N9 has shown that calnexin co-translationally interacted with NA prior to calreticulin. This sequential manner was found to be a common feature of the ER assembly line determined by the membrane localization and soluble characteristics of calnexin/calreticulin, respectively. These interactions were required for the proper maturation of NA as NA aggregated if calnexin/calreticulin interaction was abolished by glycosylation inhibition or removal of specific glycans. Surprisingly, a subset of NA molecules can form intermolecular disulfides co-translationally supporting NA homodimerization. NA co-translational dimerization also occurs for a NA mutant lacking the critical large loop

disulfide bonds, indicating that the dimerization of the stem domain does not require proper folding of the top globular domain of NA. This represents an exception to the general rule that protein oligomerization happens after the folding of individual domains. Future work on a variety of other substrates will help illuminate a global pathway of glycoprotein co-translational maturation. ^

Subject Area

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