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The role of N -linked glycans in protein quality control in the early secretory pathway

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Abstract

The ER quality control machinery maintains the fidelity of the protein maturation process by sorting aberrant proteins for ER-associated protein degradation (ERAD), a process requiring retranslocation from the ER lumen to the cytosol and degradation by the proteasome. To understand the role of N-linked glycans in ERAD, degradation of wild-type (Tyr) and mutant (Tyr (C85S)) tyrosinase was examined. Here, we demonstrated that both wild-type and mutant tyrosinase were substrates of the 26S proteasome. Tyr(C85S), however, was less stable, and the cell line harboring the C85S mutation exhibited an up-regulated unfolded protein response as measured by XBP-1 mRNA splicing. Inhibiting mannose trimming or accumulating Tyr(C85S) in a monoglucosylated form led to stabilization, supporting a role for lectin chaperones in ER retention and mannose trimming in proteasomal degradation. In contrast, preventing glucose trimming caused rapid disappearance of protein. Upon closer examination employing procedures which monitored the appearance of degradation product (small peptides) rather than the disappearance of full-length protein, ablating lectin chaperone binding induced the formation of aggregates. Colocalization of tyrosinase with BiP and PDI, but not calnexin, implicated the latter two in aggregate dissolution. The fact that aggregates were disassembled and cleared from the ER at a rate similar- to non-aggregated species and degraded by the proteasome suggests a model of glycoprotein degradation in which non-lectin molecular chaperones function in the quality control of glycoproteins, at least in part, in the absence of lectin chaperones. ^

Subject Area

Molecular biology|Cellular biology|Biochemistry

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