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Soluble tyrosinase is an endoplasmic reticulum (ER)-associated degradation substrate retained in the ER by calreticulin and BiP/GRP78 and not calnexin.

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Abstract

Tyrosinase is a type I membrane protein regulating the pigmentation process in humans. Mutations of the human tyrosinase gene cause the tyrosinase negative type I oculocutaneous albinism (OCAI). Some OCAI mutations were shown to delete the transmembrane domain or to affect its hydrophobic properties, resulting in soluble tyrosinase mutants that are retained in the endoplasmic reticulum (ER). To understand the specific mechanisms involved in the ER retention of soluble tyrosinase, we have constructed a tyrosinase mutant truncated at its C-terminal end and investigated its maturation process. The mutant is retained in the ER, and it is degraded through the proteasomal pathway. We determined that the mannose trimming is required for an efficient degradation process. Moreover, this soluble ER-associated degradation substrate is stopped at the ER quality control checkpoint with no requirements for an ER-Golgi recycling pathway. Co-immmunoprecipitation experiments showed that soluble tyrosinase interacts with calreticulin and BiP/GRP78 (and not calnexin) during its ER transit. Expression of soluble tyrosinase in calreticulin-deficient cells resulted in the export of soluble tyrosinase of the ER, indicating the calreticulin role in ER retention. Taken together, these data show that OCAI soluble tyrosinase is an ER-associated degradation substrate that, unlike other albino tyrosinases, associates with calreticulin and BiP/GRP78. The lack of specificity for calnexin interaction reveals a novel role for calreticulin in OCAI albinism.

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