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The molecular basis of oculocutaneous albinism type 1 (OCA1): sorting failure and degradation of mutant tyrosinases results in a lack of pigmentation.

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Abstract

Oculocutaneous albinism type 1 (OCA1) is an autosomal recessive disease resulting from mutations of the tyrosinase gene (TYR). To elucidate the molecular basis of OCA1 phenotypes, we analysed the early processing and maturation of several different types of mutant tyrosinase with various degrees of structural abnormalities (i.e. two large deletion mutants, two missense mutants that completely destroy catalytic function and three missense mutants that have a temperature-sensitive phenotype). When expressed in COS7 cells, all mutant tyrosinases were sensitive to endoglycosidase H digestion, and immunostaining showed their localization in the endoplasmic reticulum (ER) and their failure to be sorted further to their target organelles. Pulse-chase experiments showed that all mutant tyrosinases were retained by calnexin in the ER and that they were degraded at similarly rapid rates, which coincided with their dissociation from calnexin. Temperature-sensitive mutant enzymes were sorted more efficiently at 31 degrees C than at 37 degrees C, and their degradation was accelerated at 37 degrees C compared with 31 degrees C. Thus in contrast to the current concept that mutant tyrosinases are transported to melanosomes but are functionally inactive there, our results suggest that mutant tyrosinases may not be transported to melanosomes in the first place. We conclude that a significant component of mutant tyrosinase malfunction in OCA1 results from their retention and degradation in the ER compartment. This quality-control process is highly sensitive to minimal changes in protein folding, and so even relatively minor mutations in peripheral sequences of the enzyme not involved with catalytic activity may result in a significant reduction of functional enzyme in melanosomes.

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