Synopsis of Original Research Paper

Reversible skin color control by palmitoylation of melanin synthesis-related enzymes

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Palmitoylation is a lipid modification involving the attachment of palmitic acid to a cysteine residue, thereby affecting protein function. We investigated the effect of palmitoylation of tyrosinase, the rate-limiting enzyme in melanin synthesis, using a human 3-D skin model system and melanocyte culture. The palmitoylation inhibitor, 2-bromopalmitate (2-BP), increased melanin content and tyrosinase protein levels in melanogenic cells by suppressing tyrosinase degradation. The palmitoylation site was Cys^{500} in the C-terminal cytoplasmic tail of tyrosinase. The non-palmitoylatable mutant, tyrosinase (C500A), was slowly degraded and less ubiquitinated than wild-type tyrosinase. Screening for the DHHC (Asp-His-His-Cys) family of proteins for tyrosinase palmitoylation suggested that DHHC2, 3, 7, and 15 are involved in tyrosinase palmitoylation. Knockdown of DHHC2, 3, or 15 increased tyrosinase protein levels and melanin content. Taken together, tyrosinase palmitoylation at Cys^{500} by DHHC2, 3, and/or 15 regulate melanogenesis by modulating tyrosinase protein levels. Additionally, we developed a facile auto-S-palmitoylation assay for DHHC activation using NBD-palmitoyl-CoA. This assay elucidates the effect of DHHC posttranslational modification and disease-related point mutations on DHHC activation.