Ubiquitin-Specific Protease 38 (USP38) Contributes to Cellular Stress Responses in Melanogenesis

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Abstract

Melanogenesis is a tightly regulated biological process responsible for melanin production and maintenance of skin pigmentation. Cellular stress responses, including oxidative stress and mitochondrial dysfunction, are known to influence melanocyte homeostasis. Although ubiquitin-mediated protein degradation plays an important role in pigmentation regulation, the involvement of deubiquitinating enzymes (DUBs) remains poorly understood. Ubiquitin-Specific Protease 38 (USP38) recently shows therapeutic potential for malignant such as lung cancer, gastric cancer, potential regulator of cellular stress pathways, but its role in melanogenesis has not been fully characterized. This study investigated the USP38 expression in skin through melanin regulation by melanocyte stress responses. Using USP38-overexpressing in B16-F10 melanoma cells revealed inducing mitochondrial fragmentation and increasing mitochondrial reactive oxygen species (ROS), indicating mitochondrial dysfunction and oxidative stress. RNA sequency and qPCR analysis indicated USP38 primarily influences cellular stress pathways rather than directly regulating the transcription of melanogenesis-related genes. Overexpressing USP38 leads to increased melanin, while knockout of USP38 significantly reduces melanin production *in vitro*. These findings demonstrate that USP38 contributes to cellular stress responses in melanogenesis by linking oxidative stress, mitochondrial dysfunction, and proteostasis, highlighting USP38 as a potential therapeutic target for pigmentary disorders.

Keywords

Oxidative stress, ROS, mitochondrial dysfunction, melanocyte, TYR, MiTF, DCT.