Synopsis of Original Research Paper

Functions for mitochondrial molecules in skin aging and tumorigenesis

Teruki Yanagi

Department of Dermatology, Faculty of Medicine and Graduate school of medicine, Hokkaido University

Mitochondria exerts a central function in various cellular responses, and repeats fusion and division to change their morphology. In recent years, a group of GTP hydrolases involved with fusion and division of mitochondria has been identified. Mitofusin (Mfn) 1, Mfn 2, and OPA 1 are involved in the process of fusion, and DRP 1 (Dynamin Related Protein 1) is involved in the division process. Although it has been reported that DRP1 is essential for maintaining the cell division of malignant tumors such as malignant melanoma, the molecular function in ultraviolet-related carcinogenesis of keratinocytes is unknown. Herein we conducted experiments using clinical specimens and cultured cells to analyze the function of DRP1 in skin aging, UV-related skin disorders and cutaneous squamous cell carcinoma (SCC). We investigated cell proliferation, cell cycle, mitochondrial morphology, and MAPK signaling pathway using cutaneous SCC A431 and DJM1 cells that were transfected with shRNA vectors targeting Drp1. The Drp1 gene-knockdown SCC cells showed lower cell proliferation than scramble control cells, as assessed by direct cell counting and clonogenic assays. DNA content analysis showed Drp1 knockdown to cause G2/M arrest. Morphologically, the depletion of Drp1 resulted in an elongated,hyper-fused mitochondrial network. The MEK inhibitor PD325901 suppressed cell proliferation, as well as inhibiting the phosphorylation of ERK1/2 and Drp1(Ser616). Also, PD325901 caused the dysregulation of the mitochondrial network. In tumor xenografts of DJM1 cells, the knockdown of Drp1 suppressed tumor growth in vivo, and clinically, the expression levels of Drp1 were higher in cutaneous SCCs than in normal epidermis, and correlated positively with the advanced clinical stages. Our findings suggest that the mitochondrial division-related molecule “DRP1” may become a new biomarker in cutaneous SCC as well as a novel therapeutic target.