Synopsis of Original Research Paper

Drug Repositioning of a HIV-1 Protease Inhibitor as an anti-melanogenic reagent targeting Nrf3

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Melanin is a pigment produced from the amino acid L-Tyrosine in melanosomes. The CNC-family transcription factor Nrf3 is expressed in the basal layer of the epidermis, where melanocytes reside. Our previous *in vitro* study using mouse melanoma B16F10 and human normal melanocytes showed that Nrf3 promotes melanogenesis by upregulating the core melanogenic gene circuit, which includes Mitf, Tyr, Tyrp1, Pmel, and Oca2. Nrf3 also induces the gene expression of several autophagosome-related factors for melanin precursor uptake by macropinocytosis, an evolutionarily-conserved fluid-phase form of endocytosis. In parallel, Nrf3 prompts autophagic degradation of melanosome for melanocyte survival. Furthermore, Nrf3-mediated melanin production is suppressed by an HIV-1 protease inhibitor nelfinavir (NFV). Here, we investigated the anti-melanogenic effect of NFV by histological and gene expression analyses using a mouse model of UV-induced hyperpigmentation. In this model, C57BL/6 mice were exposed to 130 mJ/cm^2 UV once every two days for 2 weeks. For the next 2 weeks of UV treatment, 10 μM NFV was topically applied to the right ear (UV+NFV), while the left ear received either vehicle oil (UV). Then, mouse ear specimens were fixed in formalin and embedded in paraffin. Bright-field microscopy images of none stained paraffin section were used for melanin quantification. We found that NFV treatment attenuates UV-induced melanin accumulation. Furthermore, we confirmed that NFV treatment suppressed the UV-induced gene expression of core melanogenic and autophagosome-related factors, including Mitf, Tyr, and Cln3. These results indicate the anti-melanogenic potential of NFV *in vivo*.