Abstract

Project Code: RSA5980066

Project Title: บทบาทการยับยั้งของ nuclear factor erythroid2-related factor2 (Nrf2) ต่อความเสื่อมสภาพของผิวหนังในเซลล์ผิวหนัง human melanocytes ที่เพาะเลี้ยงร่วมกับ human keratinocytes และในผิวหนังของหนู

Investigator: รศ. ดร. พญ.อุไรวรรณ พานิช ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

E-mail Address: uraiwan.pan@mahidol.ac.th

Project Period: 3 years

Ultraviolet radiation (UVR) (both UVA and UVB rays) is considered the most important environmental factor responsible for cutaneous photodamage associated with premature aging or photoaging and photocarcinogenesis. UVA irradiation plays a role in premature aging of the skin through triggering oxidative stress-associated stimulation of matrix metalloproteinase-1 (MMP-1) responsible for collagen degradation and subsequently compromised skin integrity, a hallmark of photoaged skin. Moreover, UVB has been recognized to play a role in photodamaged skin through apoptosis and DNA damage of skin cells including melanocytes (MC). Keratinocytes (KC) surrounding MC have been shown to influence MC responses via the paracrine effects. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a crucial transcription factor that regulates gene expressions of important antioxidant enzymes. It is also suggested that oxidative stress mediated by UVR has been found to induce apoptosis, DNA damage and MMP-1 in association with modulation of mitogen activated protein kinases (MAPKs) pathway. Hence, investigation of compounds targeting Nrf2-regulated antioxidant defense to combat oxidative stress could provide insight into development of a promising pharmacological approach to help delay skin photoaging. We investigated the photoprotective effects of sulforaphane (SFN), a well-known Nrf2 inducer, and hispidulin (HPD), which has traditionally been used to treat skin problems and possessed abilities to penetrate the skin, on UVA-induced MMP-1 and the phosphorylation of MAPKs through Nrf2-regulated antioxidant defenses in mouse skin. Our observations demonstrated that, upon oxidative insults induced by UVA irradiation, Nrf2 deficiency resulted in hyperactivation of MMP-1 activity through activation of MAPK/AP-1 signaling. Both HPD and SFN, potent Nrf2-activators, were shown to have photoprotective effects against repetitive UVA, reducing MMP-1 induction and restoring collagen formation, possibly via inactivation of MAPK/AP-1 signaling pathways. Furthermore, to study the paracrine effects of KC on MC, by using MC-KC co-culture systems, KC was observed to provide a rescue effect on UVB-mediated MC damage, although depletion of Nrf2 in KC reversed its protective effects on MC in a paracrine fashion in association with elevation of ROS levels and activation of MAPK pathways in MC. In conclusion, Nrf2 could influence UVA-mediated MMP-1 upregulation through the MAPK/AP-1 signaling cascades in KC and indirectly regulate paracrine protective effect of KC on UVB-mediated MC damage.

Keywords: Ultraviolet radiation, photoaging, oxidative stress, nuclear factor E2-related factor 2 (Nrf2), keratinocytes, melanocytes