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Ultraviolet-induced decrease of leptin and adiponectin in subcutaneous fat may contribute to exacerbation of photoaging process

E Kim, D Lee, Y Kim, S Kim and J Chung *Department of Dermatology, Seoul National University College of Medicine, Institute of Human-Environment Interface Biology, Seoul National University, Seoul, Republic of Korea*

Ultraviolet (UV) exposure to the human skin significantly reduces triglycerides contents and lipid synthesis in the subcutaneous (SC) fat tissues. Leptin and adiponectin are the most abundantly expressed adipokines in the SC fat tissues. To elucidate their potential roles in photoaging, we examined the expression of leptin and adiponectin in acute UV-irradiated skin as well as photoaged skin. The expressions of leptin, adiponectin, and their corresponding receptors were significantly decreased in sun-exposed forearm skin, compared with sun-protected buttock skin of the same elderly individuals, indicating that chronic UV exposure decreases both adipokines in SC fat tissues. Acute UV irradiation also decreased the expression of leptin and adiponectin in SC fat tissue of human skin in vivo. Moreover, while exogenous leptin administration prevented UV- and TNF-α induced MMP-1 expression, it also increased TNF-α-induced decrease of type I procollagen synthesis. Adiponectin and its receptor silencing by siRNA led to an increased MMP-1 expression, which was reversed by treatment with recombinant human adiponectin. In conclusion, UV exposure decreases the expression of leptin and adiponectin, leading to the exacerbation of photoaging by stimulating MMP-1 expression and inhibiting procollagen synthesis.

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UVB-induced expression of fast-responding genes is modulated by huCOP1 in keratinocytes

B Fazekas,[1] H Polyánka,[4] G Tax,[1] K Szabó,[4] K Farkas,[4] ÁGNES Kinyó,[1] F Nagy,[2] L Kemény,[1] M Széll[3] and ÉVA Ádám[2] *1 Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary, 2 Institute of Plant Biology, Biological Research Centre, Szeged, Hungary, 3 Department of Medical Genetics, University of Szeged, Szeged, Hungary and 4 MTA-SZTE Dermatological Research Group, University of Szeged, Szeged, Hungary*

Ultraviolet (UV) B is the most prominent physical carcinogen in the environment leading to the development of various skin cancers. We have previously demonstrated that the human ortholog of the *Arabidopsis thaliana* constitutive photomorphogenesis 1 (COP1) protein, huCOP1, is expressed in keratinocytes in a UVB-regulated manner and is a negative regulator of p53 as a posttranslational modifier. However, it was not known whether huCOP1 plays a role in mediating the UVB-induced early transcriptional responses of human keratinocytes. To clarify this question we produced transgenic cell lines in which the expression of huCOP1 was stably silenced. Real-time RT-PCR array showed that the stable siRNA-mediated silencing of huCOP1 affects the UVB response of several genes within 2 h of irradiation, indicating that altered huCOP1 expression sensitizes the cells toward UVB. Pathway analysis identified a molecular network in which 13 of the 30 examined UVB-regulated genes were organized around three central proteins. Since the expression of the investigated genes was upregulated by UVB in the siCOP1 cell line, we hypothesize that huCOP1 is a repressor of the identified pathway. Several members of the network have been implicated previously in the pathogenesis of non-melanoma skin cancers; therefore, clarifying the role of huCOP1 in these skin diseases may have clinical relevance in the future.

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VE-821, a selective inhibitor of Ataxia telangiectasia and Rad3 related kinase, potentiates cell death after PUVA treatment

E Biskup, D Naym Gram and R Gniadecki *Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark*

PUVA (psoralen + UVA) is the first line therapy of early mycosis fungoides (MF). The photosynthesizing agent (eg. 8-methoxypsoralen) binds to DNA and subsequent ultraviolet A (UVA) radiation causes DNA crosslinking, DNA double strand breaks and lymphoma cell death via apoptosis. We have investigated whether pharmacologic, selective inhibition of DNA repair mechanisms would increase the effiacy of PUVA. We have employed an in vitro model of PUVA treatment of a MF cell line, MyLa 2000. In vitro PUVA pronounced G2/M cell cycle block and DNA damage measured by histone γ -H2AX phosphorylation. Since γ-H2AX phosphorylation also plays a role in DNA repair, probably by loosening the chromatin structure and recruiting repair factors such as Rad50 and Rad51,we employed KU55933 and VE-821, which are selective inhibitors of Ataxia Telangiectasia Mutated (ATM) and Ataxia Telangiectasia and Rad3 related (ATR) kinases, respectively. VE-821, but not KU55933 augmented cell death caused by PUVA by approximately 30% and released MyLa cells from the G2/M block. VE-821 also increased cell death caused by another DNA crosslinking agent, cisplatin, but not after doxorubicin (DNA intercalator) or γ-secretase inhibitor I (GSI I; proteasome and Notch signalling inhibitor with no genotoxic activity). VE-821 markedly increased, rather then blocked, H2AX phosphorylation, suggesting a different mechanism of action than targeting H2AX.

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Water filtered infrared A influences wound healing associated cytokines

NN Zoeller, M Butting, M Hofmann, S Kippenberger, R Kaufmann and A Bernd *Department of Dermatology, Venereology and Allergology, J. W. Goethe-University, Medical School, Frankfurt/Main, Germany*

The sun emission can be divided into three radiation categories: ultraviolet radiation, visible light and infrared radiation (IR). Whereas IRB (1400-3000nm) and IRC (3000nm-1mm) are absorbed by the water molecules in the atmosphere IRA (700nm-1400nm) reaches the surface. Artificial IRA radiation sources recreating the atmospheric filtering process by water-filtering the emitted IR radiation are described to beneficially influence e.g. wound healing and temperature homeostasis in vivo. Aim of our study was to characterize the effects of water filtered infrared A (wIRA) on primary dermal and epidermal cells and on organotypic tissue cultured skin equivalents. Primary fibroblasts or keratinocytes were seeded in monolayer cultures. After adherence they were irradiated with 154mW/cm^2 wIRA for 2hrs. After 24hrs of the respective treatment the cytokine profile of the cell free supernatants were analysed. Furthermore wound situations were induced first in a fibroblast monolayer and second in organotypic tissue cultured skin equivalents. After wound induction the control group was left untreated whereas the wIRA group was irradiated for 20min with 154mW/cm^2. The fibroblast monolayer was only irradiated once whereas the organotypic skin equivalents were irradiated every 24hrs for 8 days. 24hrs after each treatment the cytokine profiles of the cell free supernatants were analysed. We could show that wound healing specific cytokines e.g. GM-CSF, MCP-1, TIMP-1 were –induced after wIRA treatment whereas interleukin 29 and TNF-α were reduced. For the wound situation we observed that TGF-β1 and interleukin 6 were significantly induced after wound induction. After treatment with wIRA both cytokines were significantly reduced. The herein presented results are a first step to understand the in vivo observed wIRA dependent improved wound healing.