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Repetitive irradiation with sub-erythemal UV dose induces changes in human epidermis on three cellular levels: DNA structure, epigenetic DNA methylation and gene expression

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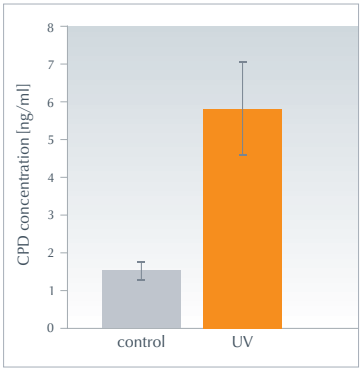
STUDY AIM
Investigation of DNA damage and epigentic DNA changes in the epidermis after repetitive irradiation with suberythmal doses of UV.

SUBJECTS
32 healthy female Caucasian subjects (Fitzpatrick phototypes 1 to 4, mean age 52 yrs.)

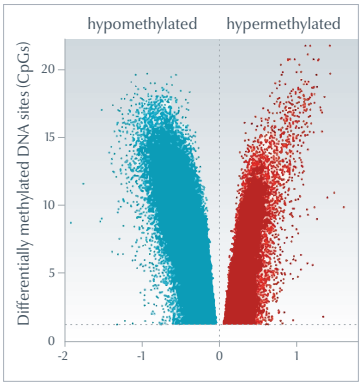
METHODS
Subjects were repetitively irradiated with 0.9 MED (90% of the required minimal dose causing erythema) on the lower back on three consecutive days. After 24h of the last irradiation session, suction blisters were taken from control and treated area. The obtained epidermis was analyzed for DNA damage via CPD ELISA kit and the epigenetic changes were investigated via differential DNA methylation analysis of 850.000 CpGs which have been profiled on the MethylationEPIC array platform.

RESULTS
- The repetitive exposure to 0.9 MED, revealed a 390% increase in CPD level in the UV-treated samples compared to control samples
- The methylation status of 850,000 CpGs in the human genome was analyzed and 171,000 CpGs (20%) were shown to be differentially methylated upon UV irradiation.

CONCLUSION
This study demonstrates that the repetitive irradiation with 0.9 MED on three consecutive days does not only induce potentially mutagenic photolesions, but also changes the epigenetic methylation pattern of DNA.



Increase in CPD levels (DNA photodamage) after UV irradiation compared to non-irradiated control



UV irradiation changed the epigenetic methylation pattern in epidermal DNA

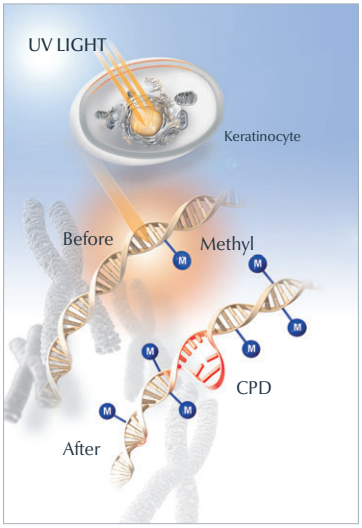
BACKGROUND INFORMATION

UV-induced DNA changes (CPDs and hypermethylated CpG islands) are potentially mutagenic and can result in actinic keratosis and non-melanoma skin cancer.

Solar ultraviolet radiation causes skin cancers derived from epidermal melanocytes (melanoma) and keratinocytes (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)). Epidemiology has shown a relationship between sunburn (erythema) and malignant melanoma (MM), especially with childhood exposure. There is also evidence for such a relationship for BCC. The epidemiology for SCC supports a role for chronic low dose (sub-erythemal) solar UV exposure [1].

Non-melanoma skin cancer is initiated by UV-induced DNA damage, in particular the cyclobutane pyrimidine dimer (CPD) that results in characteristic cytosine to thymine transition mutations in key regulatory genes such as p53 [2].

DNA methylation is a covalent epigenetic modification of cytosines within CpG dinucleotides. The deregulation of the normal methylome is a major hallmark of human cancers and frequently characterized by widespread CpG island promoter hypermethylation [3]. CDH1 promoter hypermethylation increases from normal skin to actinic keratosis and cutaneous squamous cell carcinoma [4].



[1] Young AR et al., Sub-optimal Application of a High SPF Sunscreen Prevents Epidermal DNA Damage in Vivo. Acta Derm Venereol 2018; 98: 880–887 | [2] Brash DE. UV signature mutations. Photochem Photobiol 2015; 91: 15–26 | [3] Baylin, S. B. & Jones, P. A. A decade of exploring the cancer epigenome – biological and translational implications. Nat. Rev. Cancer 11, 726–734 (2011) | [4] Chiles, M. C., Ai, L., Zuo, C., Fan, C.-Y. & Smoller, B. R. E-cadherin promoter hypermethylation in preneoplastic and neoplastic skin lesions. Mod. Pathol. 16, 1014–1018 (2003)