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# Is UV radiation beneficial in postburn wound healing?

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SUMMARY

Currently strict ultraviolet (UV) light avoidance strategies and utilizing sunblock containing products are generally advocated during the reepithelialization process as well as after wound closure. These recommendations are guided by a common appreciation of UV radiation as a predominant cause of skin cancer development. It is possible however that the currently accepted practice of near continuous UV protection abrogates the normal cutaneous response to injury, with melanocyte redistribution and pigmentation creating hypopigmented scars. We hypothesize that judicious UV exposure might in fact be beneficial for wound healing and skin homeostasis. UV light should be investigated as a potential modulator of keratinocyte–melanocyte cross-talk in wound healing. In vitro studies will have to prove whether UV radiation induced melanocyte activation might have a stimulatory paracrine effect on keratinocyte proliferation which could beneficially affect wound healing. We further hypothesize that UV exposure to wounds might stimulate and restore normal melanocyte distribution and melanin content in reepithelialized wounds preventing hypopigmentation. Furthermore, exposure of reepithelialized wounds to UV light might exert a photo protective effect in the skin by the production of melanin. This in turn may protect the epidermis from UV-induced damage and carcinogenesis. It is therefore proposed that moderate UV exposure should be commenced early in the healing process of cutaneous wounds. At present, current practice and literature do not support the notion that UV-sun block is necessary in postburn scar management. Burn scars do not seem to exert an enhanced risk for melanomagenesis, the occurrence of which has only very rarely been reported in burn scars. Different mutations in susceptibility genes or in genes involved in the control of the cell cycle or maintenance of cellular integrity which are UV radiation independent are involved in the initiation and promotion steps of skin cancer.



## Introduction

Burn wound healing and subsequent scar management is both lengthy, complicated and yet somewhat varied in its practice. Currently strict ultraviolet (UV) light avoidance strategies and utilizing sunblock containing products with SPF values of at least 15 is generally advocated during the reepithelialization process as well as after wound closure [1]. After healing and resolution of the hyperaemic appearance of the burn wound, scars often appear hypopigmented and further sun protection is emphasized in an effort to minimize UV induced skin cancer risk. This recommendation is guided by a common appreciation of UV radiation as a predominant cause of skin cancer development. This prompted us to survey all German speaking burn centres on the incidence of melanoma identified in their patients. The results of this survey failed to detect any melanoma in follow up visits in the year 2008 with a total number of approx. 6900 patient contacts. Surprisingly, a recent Medline search yielded only one review describing melanoma arising in a burn scar [2]. In this text, an incidence of 14 cases of malignant melanoma arising in postburn scars is reported over the period from 1941 until 2007. The incidence of melanoma in the general population of Central Europe is reported to be between 10 and 16 cases per 100,000 [3]. With such a discordance in the incidence of melanoma rates arising in these differing populations, it seems reasonable to question whether an increased risk of melanoma truly exists in reepithelialized wounds and scars after burn injury. It is possible that the currently accepted practice of near continuous UV protection abrogates the normal cutaneous response to injury, with melanocyte redistribution and pigmentation creating hypopigmented scars.

UV-induced DNA photoproducts in cutaneous derived keratinocytes are known to cause mutations in susceptible genes resulting in the development of both squamous cell and basal cell carcinomas. While implicated in both forms of skin malignancy, mutations in the p53 tumor suppressor gene appears to be more strongly associated with the development of squamous cell carcinomas [4]. Marjolin ulcers, skin cancers associated with burn scars,

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chronic wounds and protracted inflammatory states are most commonly squamous cell in origin and numerous publications can be found describing these associations [5,6]. It is however generally appreciated that the appearance of squamous cell carcinoma in these skin conditions is due to prolonged activation and excessive mitotic activity in keratinocytes rather than UV induced [7]. In contrast to UV-induced cellular damage, UV-induced melanin has long been known to protect keratinocytes from UV damage [8], a result of its inherent photo protective effects as well its antioxidant properties.

## The hypothesis

We hypothesize that judicious UV exposure might in fact be beneficial for wound healing and skin homeostasis. We further hypothesize that UV exposure of wounds might stimulate and restore normal melanocyte number and distribution in reepithelialized wounds while preventing hypopigmentation. Furthermore, exposure of reepithelialized wounds to UV light might exert a photo protective effect in the skin by the production of melanin by melanocytes. It is therefore proposed that moderate UV exposure should be commenced early in the healing process of cutaneous wounds.

## Evaluation of the hypothesis

### *Keratinocyte–melanocyte interaction in the skin*

In normal adult epidermis an orderly spatial distribution of melanocytes can be found and melanocyte mitosis rarely occurs. Under certain conditions however, like those found in the healing wound, UV radiation causes melanocytes to proliferate [9]. Keratinocyte-derived growth factors like basic Fibroblast Growth Factor (bFGF), Nerve Growth Factor (NGF) and Melanocyte Stimulating Hormone (MSH) alpha are known to stimulate melanocyte growth, regulating both their distribution and morphology as well as stimulating the production of melanin [10,11]. Interestingly, keratinocyte-induced melanocyte proliferation cannot be substituted by keratinocyte conditioned medium but rather requires close cell to cell contact in which melanocytes interact via dendritic processes with adjacent keratinocytes. In addition melanocyte proliferation is considered to be strongly regulated as in vitro experiments have demonstrated that melanocyte/keratinocyte ratios reflect the original ratio found in the skin biopsy from which the keratinocytes were obtained [12]. There is some evidence that in turn, keratinocyte proliferation which is essential for wound closure can be stimulated by melanocytes. Melanocytes are known to secrete a variety of keratinocyte growth factors like IL-1, IL-6, IL-8 and TGF alpha after UV stimulation, all of which are known to be mitogenic for epidermal keratinocytes [13]. In addition, keratinocyte proliferation is stimulated by MSH, secreted in both an autocrine as well as a paracrine fashion by neighbouring melanocytes. This mitogenic effect may be enhanced by UV exposure as MSH receptors on keratinocytes are upregulated by UV radiation [14].

Despite the vast number of publications on mesenchymal–epidermal interaction, little is published on melanocyte–epidermal interaction. Co-culture 'wounding' studies including keratinocytes and melanocytes with and without UV exposure are needed to shed more light on this subject. These studies can expand our collective knowledge on the function of melanocytes as regulatory cells in wound healing as controlled by external UV light and support our hypothesis that keratinocytes and melanocytes substantially interact in skin homeostasis.

### *UV-induced photoprotection in the skin and risk assessment of UV carcinogenesis*

Moderate UV A or UV B exposure is necessary for melanin production by melanocytes [15]. It is well known that melanin exerts a protective effect on cutaneous cells by the absorption of UV spectrum wavelengths as well as scattering UV radiation [8]. UV B induced melanin also exerts an antioxidant capacity in keratinocytes and melanocytes, thereby reducing UV B induced superoxide toxicity and protecting skin cells. It has also been reported that moderate UV B induced DNA damage enhances the reparative capacity of melanocytes [16].

In contrast to these beneficial effects of UV light, epidemiologic data has long shown that low levels of skin pigmentation such as those found in lighter skinned populations (Fitzpatrick skin types I and II) are more susceptible to the development of malignant melanomas as compared to darker skinned populations [17]. Melanocytes exert a certain resistance to UV B-induced apoptosis, increasing the risk of UV-induced mutations at high UV B doses, an effect which is more pronounced in lighter skinned individuals [18]. Darker pigmented skin has been shown to be more adept at removing UV damaged apoptotic cells than lighter skin [18]. Different mutations in susceptibility genes or in genes involved in the control of the cell cycle and maintenance of melanocytic cellular integrity (p16/Rb pathway) are crucially involved in the initiation and promotion steps of melanomagenesis [19]. Further epidemiological and molecular data derived from a larger population size must be collected in order to accurately correlate the incidence of melanomagenesis in burn scars.

It is well established that with respect to keratinocytes, UV-induced DNA photoproducts are able to cause mutations in susceptible genes leading to the development of both squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [4]. In basal cell carcinomas, mutations in the p53 tumor suppressor gene were identified in only 56% of studied cases while mutations of the hedgehog pathway related genes, especially patched-1, represent the most commonly recognized pathogenic event [20]. In squamous cell carcinoma development UV-induced mutations in the p53 tumor suppressor gene is most commonly described [4]. It is interesting to note that SCC arising in burn scars (Marjolin's ulcer) usually developed in sun protected limbs, raising question as to the cause of the p53 gene mutation in this entity [5,6]. It seems clear that besides UV induced etiologic factors, additional factors substantially contribute to skin carcinogenesis. As SCC in scars can have a latency of as long as 30 years, prospective surveillance studies are very difficult to carry out. Even a precise retrospective analysis of possible carcinogenic factors can be challenging. It would be interesting to see whether xenogenic transplantation of human scar with subsequent UV exposure could decipher the pathogenesis of Marjolin's ulcer i.e. SCC in scars.

### *Hypopigmentation of scars*

Often scars after burn injuries remain paler that the surrounding skin. In general melanocytes interact with 36–40 keratinocytes via dendritic process. Dressler et al. [21] demonstrated that the ratio of melanocytes to keratinocytes was elevated after cutaneous injury, with slow improvement over time. In contrast, Velangi and Rees [22] demonstrated that there was neither a difference in number nor in melanin content in paler scars. Unfortunately, the latter authors gave no clear explanation for the hypopigmented appearance. Clinically many patients with hypopigmented scars desire an improved aesthetic result, and subsequent autologous transplantation of cultured and non cultured melanocytes has been performed with varied success [23]. As UV light can regulate melanocyte proliferation and melanin content, a clinical study seems

warranted to prospectively measure constitutive pigmentation, colour and melanosomes in postburn wounds. Aesthetic improvement of the scar by judicious UV exposure would obviate the necessity for surgical corrections of hypopigmented scars.

## Conclusion

UV light should be investigated as a potential modulator of keratinocyte–melanocyte biology in wound healing. UV-induced melanin production in melanocytes and subsequent deposition in keratinocytes will exert a photo protective effect and this in turn may protect the epidermis from UV-induced damage and carcinogenesis. In addition, in vitro studies will have to prove whether UV radiation induced melanocyte activation might have a stimulatory paracrine effect on keratinocyte proliferation which could act in wound healing. At present the literature does not support the notion that UV-sunblock is a necessary adjunct to postburn scar management.

## Conflicts of interest statement

None declared.

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