CHRONIC EFFECTS OF UV ON HUMAN SKIN

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INTRODUCTION

UV radiation causes a number of chronic degenerative changes in the skin, mainly in Caucasian populations as a result of its action on keratinocytes, melanocytes and components of the dermal stroma including fibrous tissues (collagen, elastin) fibroblasts and blood vessels. Among the degenerative changes, skin cancers are the most dreadful perspectives, but photoaging is of the most important general concern for the population.

MECHANISMS OF UV CARCINOGENESIS

There is abundant evidence that UV causes damages by direct photochemical effects and oxidative effects[1]. There is also evidence that activated oncogenes and mutated tumor-suppressor genes are present in some skin cancers[2-3]. From a review of the animal studies, it has been found that the effectiveness is to peak in the UVB range, that UVA is also carcinogenic at a much lower level of effectiveness[4]. It is believed that UVC is not effective for human carcinogenesis and that visible light will not play a significant role. Also from animal studies, the immune system may be deeply altered[5]. The suppression of systemic responses may favor the malignant cell proliferation and the metastatic processes. In man, beside anecdotal reports, no firm assessment can be made. Figure 1 represents the most comprehensive scheme to illustrate the complexity of carcinogenesis

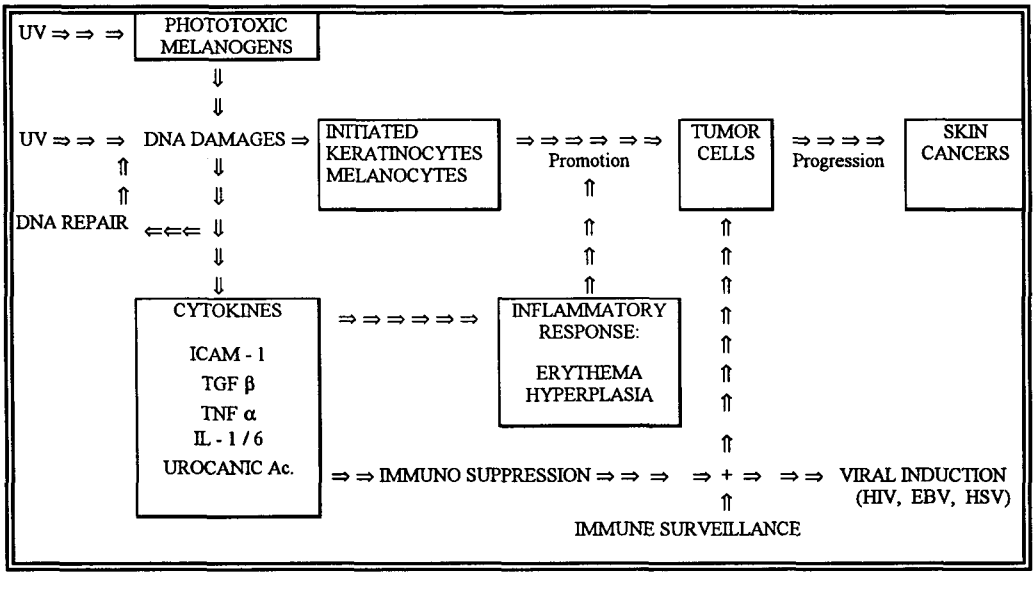

Figure 1. Scheme adapted from Ref. 5, modified to include melanin and melanocytic system.

Following irradiation, one can observe the production of p53 protein[2], the expression of a tumor suppressor gene which blocks the cell division in G1, allowing the DNA damages to be repaired[6]. The p53 protein is rapidly induced and has normally a very short half-life. If the damage is unreparable, the p53 pushes the cell into programmed cell death, called apoptosis (sunburn cells)[3]. Loss of normal function of the product of the p53 gene is usually caused by missense point mutations. The mutations in the p53 gene are very common alterations[8] and 5 specific loci of the gene have been found target for UV-induced lesions. The mutated p53 accumulates in the nucleus and is correlated with more aggressive tumors, metastasis and lower 5-year survival rate[6]. The discovery of the role of the p53 gene and other genes involved in the control of cell division is of a major importance to the understanding of the photocarcinogenesis process[7] as illustrated on the following figures 2 and 3.

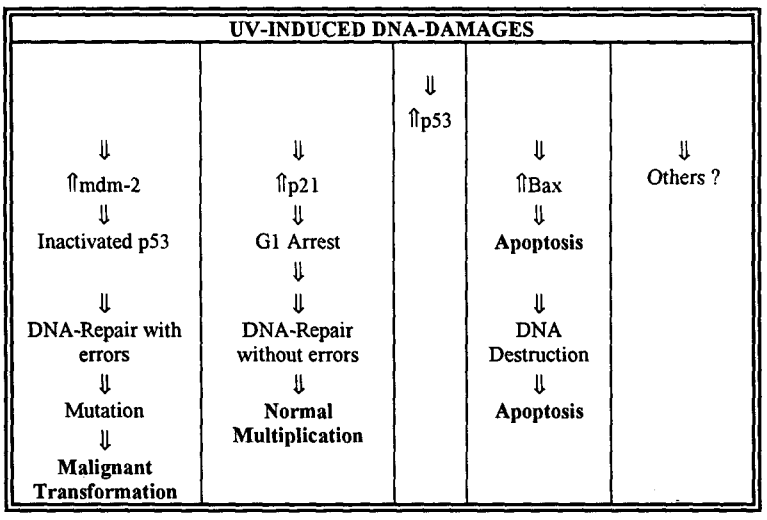

Figure 2. Molecular events following UV irradiation.

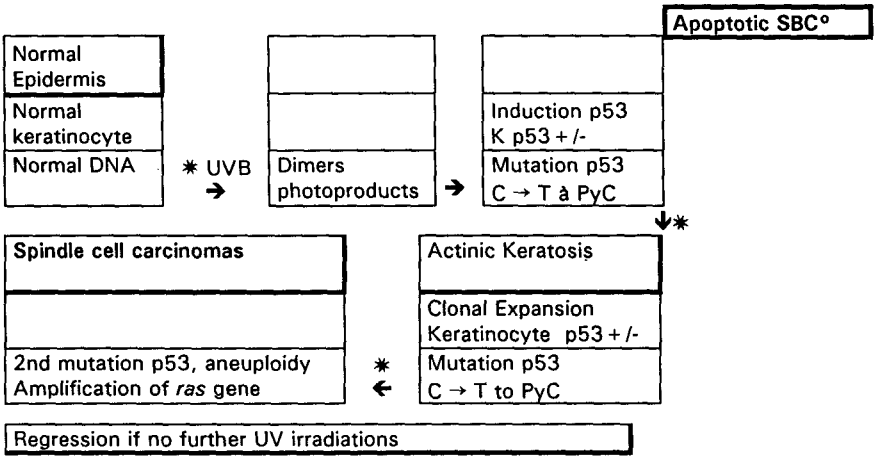

Figure 3: Synthetic aspects of steps initiating photocarcinogenesis

Benign lesions induced by solar exposures

Freckles and **solar lentigo** are pigmented macules occurring on the sun-exposed skin of Caucasians. Their prevalence is increased in highly sun-sensitive skin. Freckles occur commonly in children and are considered as marker for high sensitivity in most of the melanocompromized subjects. Solar lentigo increase with age, and are characterized by an increased number of melanocytes and increased concentration of melanin in the basal layer. An increased risk of melanoma has been observed in relation to freckling in childhood and an increased risk for non melanocytic skin cancer has been found in relation with freckling and prevalence of solar lentigo[9].
Melanocytic nevi are benign proliferations of melanocytes associated, in white populations, with phenotypic indicators of constitutional high sensitivity to the sun. They occurs mainly on body sites, maximally or intermittently exposed to the sun. There number and size are inconsistently associated with multiple sunburns in early life. They are associated with an increased risk for cutaneous melanoma. Precursors of melanins may induce DNA damages by photosensitization reaction[10] and might be responsible for melanocytic proliferation and melanoma.
Solar keratosis are benign proliferations of epidermal keratinocytes. They are very common on permanently exposed body sites in elderly people, in Caucasian populations living in areas of high ambient solar irradiance. They have been considered as phenotypic indicators of cutaneous sun-sensitivity and estimates of total sun-exposure. They are strongly associated with a risk of non-melanocytic skin cancers and are considered as precancerous lesions. They are also regularly associated with signs of dermal sun-induced degeneration (heliodermatosis).

Non-melanocytic skin cancers
There are 2 major types of non-melanocytic skin cancers: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). They represent one half of all cancers in the white population. Ethnic background is an important determinant for the risk on non-melanocytic skin cancer in Caucasians. In people of southern European origin, born in Australia, relatively to other people born in Australia, the risk of BCC was found 0.56 for those with one southern European grand-parents, 0.17 for two, and 0.1 for three or four[11]. Among recent case control and cohort studies, the relative risk for red or light hair-color population is around 2 for BCC and 2.4 for SCC. The incidence rate of non-melanocytic skin cancers does appear to increase with proximity of the equator with similar gradients for men, women at all ages. The same pattern was observed in Australia and in USA. Epidemiological studies on migrants reveal that the incidence and the mortality is lower in migrants coming from areas of lower sun-exposure when they arrive in the high solar irradiance countries, after 10 years of age. This has shown for BCC and malignant melanoma (studies performed in Australia, Israel, and California).
Beside the skin sensitivity, the total solar exposure has been found of out-most importance. Attempts have been made to estimate the dose-response relationship between UV and SCC and BCC in retrospective cohort study in general[12]. An alternative approach is estimating a dose-response relationship in a whole population. This work has been made in the context of estimating the increase in skin cancer expected from some increment in ground level UV caused by depletion of atmospheric ozone. The results have commonly been expressed in term of biological amplification factor (BAF)[13].

Authors	Region	Sex	BAFs for BCC	BAFs for SCC
Non melanocytic skin cancer			**Incidence**	**Incidence**
Scotto et al 1983	USA	M	1.3 - 2.6	2.1 - 4.1
		F	1.1 - 2.1	2.2 - 4.3
de Gruijl & Van der Leun 1991	USA	M & F	1.4	2.5
Moan et al 1989	Norway	M	1.5 - 2.0	1.2 - 1.5
		F	1.6 - 2.1	1.6 -1.8
Melanoma			**Mortality**	
Scotto & Fears 1987	USA	M	0.4	
		F	0.5	
Pitcher & Longstreth 1991	USA	M	0.4	
		F	0.3	
Moan & Dahlback 1992	Norway	M	0.9	
		F	3.2	
	Sweden	M	1.9	
		F	2.3	
	Finland	M	1.3	
		F	2.2	

Table I. Recent estimates of BAF for non-melanocytic skin cancers and cutaneous melanoma based on geographical correlation between average annual ambient UV and skin cancer incidence of mortality.

ACTION SPECTRUM FOR PHOTOCARCINOGENESIS

Recently, two large collections of data on carcinogenicity of UV in albino hairless mice, following exposure to multiple sources emitting in the UVA, B, and C ranges, have been combined to produce the best estimate for action spectrum for skin carcinogenesis in animal strains[4]. The figure 4 reproduces the action spectrum and its adaptation to the human skin situation taking in account the absorption by the multiple layers[14]. The definition of the action spectrum is excellent in the UVB range following closely the erythema action spectrum. A large uncertainty is still observed in the UVA range which can be considered as a plateau from 340 to 380 nm. This plateau is closer from the melanogenesis action spectrum in sensitive skin than from pigmentation in darker skin[15].

In a fish model in which UV radiations are able to induce melanomas, the action spectrum is confounded with the erythema action spectrum from 290 to 315 nm, but in the UVA, the tumor develops for 10 times less dose than for the mouse non-melanocytic tumors[16]. This observation raises the possibility of a specific deleterious role of melanin in the genesis of melanocytic tumors, a point which should be linked with some specific melanin-DNA induced damages in vitro[10, 17, 18].

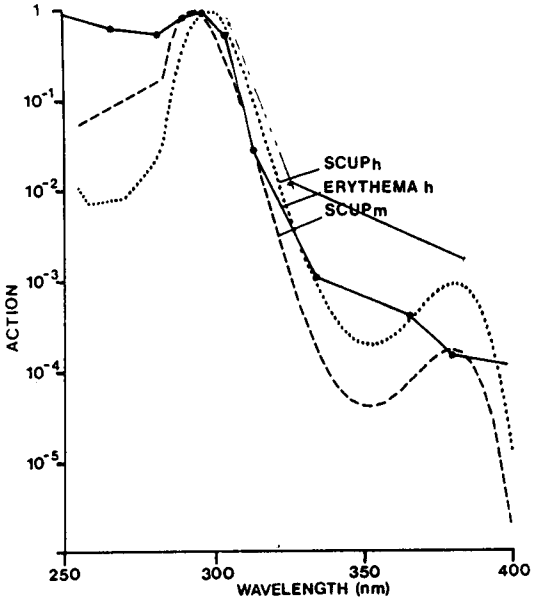

Figure 4. Estimated action spectrum ($SCUP_m$) for induction by UV of SCC in the skin of albino hairless mice (Skh-Hr1). The $SCUP_h$ is for human. On the top, the fish melanoma action spectrum is reproduced.

SKIN AGING AND ELASTOSIS

Chronic excessive UVR leads to the clinical picture recognized as photoaging. The clinical aspect is typically present on permanently exposed body sites, associating dryness, wrinkling and telangiectasia. Irregular pigmentation and solar lentigo are also observed. Histologically, this is caused by thinning of the skin, reduction in the papillary dermis thickness and replacement of the normal collagen-elastic material by elastotic bundles which lacks the elastic properties of the normal dermis. These changes are always associated with BCC and SCC and with a special form of malignant melanoma lentiginous type. The solar aging is dose-related and also related with the skin complexion. The disorders have been reproduced in hairless mice and attempts have been made to produce an action spectrum, using a specific clinical aspect of the mouse skin named sagging. Sayre and Kligman[19] have produced an action spectrum very close to the human erythema

action spectrum. However, Bissett[20] and Wulf[21] proposed a completely different action spectrum where UVA is 100 times more important. A final consensual action spectrum has not been yet obtained.

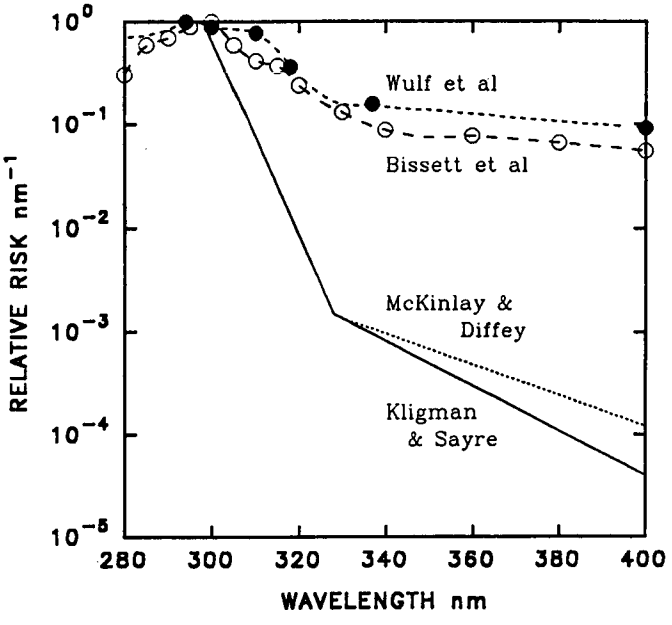

Figure 5. Mouse aging action spectra from reference 19

CONCLUSIONS

Chronic exposures and acute accidents of the skin to UV has been recognized as an important risk for skin cancers in human. Attempts have been made with mathematical models to correlate the ambient UV dose and occupational irradiations with the risk of skin cancers. Development of accurate global measurements of solar irradiance and personal dosimetry is expected in the future in order to reduce the exposure of the general population, to precise the measures to be taken for indoor and outdoor workers.

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Additional recommended readings

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