UV-B radiation: a health risk in the Arctic?

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Seasonal stratospheric ozone depletion in the Arctic has raised the question of whether the associated increases in ultraviolet-B (290–320 nm) constitute a significant health risk in Arctic populations. Increases in skin cancer in Europe and the USA from excess UV-B resulting from ozone depletion have been predicted. Skin cancer is, however, rare in Inuit populations.

UV-B also causes a selective down regulation of the immune system which may be a natural regulatory mechanism evolved to prevent autoimmune attack on sunlight-altered skin. The action spectrum for UV-B immunosuppression implicated a unique skin photoreceptor molecule, urocanic acid (UCA), which isomerizes from the *trans* to the *cis* isomer on exposure to UV-B, the *cis* isomer being immunosuppressive. This form of immunosuppression is important in skin cancer and possibly in infectious diseases.

The epidemiology of non-Hodgkin's lymphoma shows a relationship with UV exposure, postulated to be via the immunosuppressive effects of UV-B. Cancers which show an excess in Inuit populations include nasopharyngeal and salivary gland cancer. Genetic factors appear to be involved, but these are thought to be virally related cancers possibly associated with the high viral load in these populations. In several studies on non-Arctic populations, salivary gland cancer has been linked to ultraviolet exposure. A potential role for UV-B exposure in these cancers in the Arctic needs to be explored.

In view of the high levels of POPs in some Arctic regions, potential interactions between the immunosuppression caused by some of these pollutants and the effects of UV-B need to be investigated.

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Introduction

Seasonal stratospheric ozone depletion in the Arctic has raised the question of whether the associated increases in ultraviolet-B (290–320 nm) constitute a significant health risk to Arctic populations (De Fabo et al. 1995). The enhanced UV-B levels are predicted to be large, sporadic and associated with other stressors, e.g. cold and isolation, with high viral levels in some populations and, in some cases with pollutants well-described in the Arctic, such as PCBs and heavy metals (Table 1).

Skin cancer

There is a clear association between sunlight exposure and non-melanoma skin cancer, well supported by laboratory studies implicating UV-B as a carcinogen (Armstrong & Kricker 1995). There is also an epidemiological association between sunlight exposure and malignant melanoma, but the nature of the relationship is less clear and studies are hampered by inadequate animal models (Armstrong & Kricker 1993). There is epidemiological evidence that intermittent exposure to sunlight can be a critical factor in

Table 1. Increased UV radiation in the Arctic.

Characteristics
- Seasonal
- Sporadic
- Large
- Accompanied by other stressors

UV effects on health
- Skin cancer
- Eye cataracts
- Immunosuppression
  - Reduced immunity to infectious agents
  - Possible co-factor for non-Hodgkin's lymphoma
  - Probably role in certain autoimmune diseases

Combinatorial factors
- Viruses: high viral loads in some Arctic populations; high levels of virally associated cancers
- Pollutants: persistent organic pollutants, heavy metals
- Environmental stressors: cold, isolation

the development of malignant melanoma (Autier et al. 1997). A role for UV-A (320–400 nm) in melanoma development has been proposed but is not yet clarified (Miller et al. 1998).

The action spectrum for skin cancer formation (squamous cell carcinomas) has been established in mice (de Gruijl et al. 1993) and has been used to predict increases in skin cancer in Europe and the USA by excess UV-B resulting from ozone depletion 1979–1994 (de Gruijl et al. 1993; Slaper et al. 1996). These have been predicted to be on the order of 10% within 60 years. This number is a conservative estimate because it assumes full compliance with the Montreal protocol and amendments and does not take into

account ageing of the populations and other factors.

Skin cancer rates in the Arctic are in general low, however, because of the low UV-B levels relative to equatorial regions (Henriksen et al. 1989) and skin cancer is rare in Inuit populations (Miller & Gaudette 1996), consistent with the findings that skin pigmentation is protective against skin cancer. A recent study of cancer risk in Danes working in Greenland indicated, however, an elevated risk of melanoma in females, postulated as a result of excessive UV exposure (L. G. Nielsen et al. 1997)

UV induced immunosuppression

UV-B also causes a selective down regulation of the immune system which may be a natural regulatory mechanism evolved to prevent auto-immune attack on sunlight-altered skin (Noonan & De Fabo 1992) (Fig. 1). First described in animals (Noonan, Kripke et al. 1981; De Fabo & Noonan 1983; Noonan & De Fabo 1992), a very similar immunosuppression by UV-B with a dose-response comparable to that in mice has also been described in humans (Cooper et al. 1992; Selgrade et al. 1997) and appears to be independent of pigmentation. This form of immunosuppression redirects the cell-mediated immune response such that a down regulatory rather than an effector response is initiated. This redirection of the immune response occurs via functional
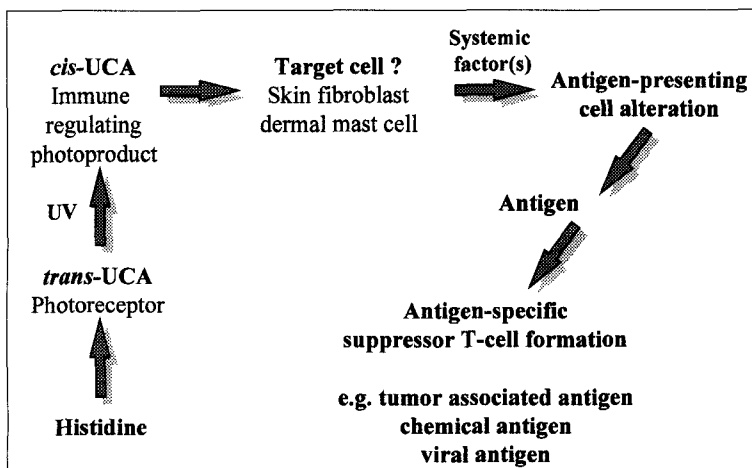

Fig. 1. Working hypothesis for the mechanisms of initiation of UV induced immuno-suppression. The photoreceptor molecule, urocanic acid (UCA), produced enzymatically in the stratum corneum as the *trans* isomer from the precursor, histidine, is isomerized to the *cis* by ultraviolet-B radiation. *Cis*-UCA causes an alteration to antigen presenting cells which results in the formation of down-regulatory or suppressor T cell immune response to incoming antigens. The target cell for the action of *cis*-UCA has not yet been identified although evidence supports a role for both skin fibroblasts and dermal mast cells.
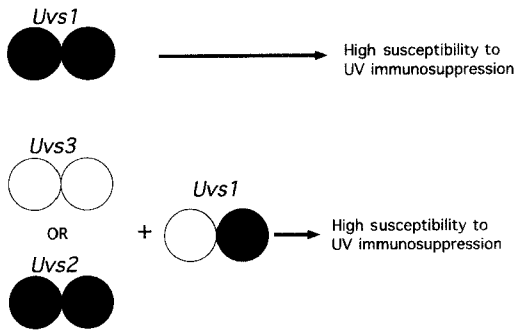
Fig. 2. Scheme derived in inbred mice for genetic control of susceptibility to the immunosuppressive effects of UV-B radiation. The action of three independent loci has been described. *Uvs1* and *Uvs2* are automsomal genes and *Uvs3* is an X-linked gene(s). The recessive epistatic action of *Uvs3* or *Uvs2* confers high susceptibility when *Uvs1* is heterozygous. Black circles represent C57BL/6 alleles (high susceptibility mouse strain) and white circles represent BALB/c alleles (low susceptibility mouse strain). There is evidence that differing susceptibilities to UV immunosuppression exist in man, but as yet these have not been shown to have a genetic basis. If genetic differences for this UV-B effect do exist in humans, they need to be investigated in Arctic populations.
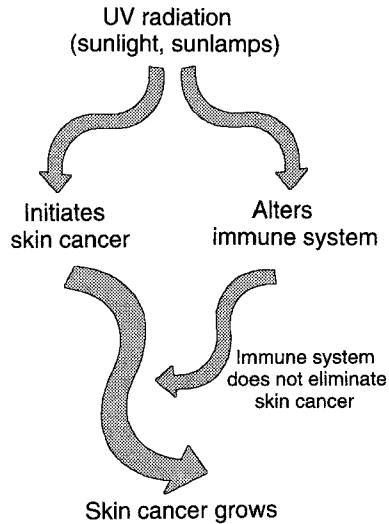

Fig. 3. Scheme for development of skin cancer in experimental animals. Ultraviolet-B radiation plays at least two independent roles, causing neoplastic transformation of skin cells and initiating immunosuppression which prevents the immune elimination of nascent skin tumours.

alterations to antigen presenting cells, either in the skin at the site of UV irradiation, or at distant sites, e.g. the spleen via the generation of a series of mediators, not all identified as yet (Noonan, Kripke et al. 1981; Noonan, De Fabo et al. 1988; Ullrich 1995).

The action spectrum for UV-B immunosuppression in mice differs from the carcinogenesis action spectrum (De Fabo & Noonan 1983) and implicates a unique skin photoreceptor molecule in the initiation of this effect. The photoreceptor urocanic acid (UCA) is located in the stratum corneum and isomerizes in mammals, including humans, from the *trans* to the *cis* isomer on exposure to UV-B. UCA is formed in the stratum corneum. An accumulation of evidence indicates that the *cis* isomer of UCA is immunosuppressive (Norval et al. 1989; Noonan & De Fabo 1992), similar to the effects of UV-B radiation.

Genetically determined susceptibility to UV induced immunosuppression

We and others have shown in mice that there are genetically determined susceptibilities to UV

induced immunosuppression (Kurimoto & Streilein 1994; Noonan & Hoffmann 1994a, b) (Fig. 2). This effect appears to be a complex trait, and is controlled by a number of interacting *Uvs* (UV susceptibility) genes. Recently, we have found that the number of dermal mast cells, multipotent inflammatory cells, is a determinant of susceptibility to UV induced immunosuppression (Hart et al. 1998) suggesting that the *Uvs* genes are mast cell related.

We have recent evidence indicating that mice with genetically determined high susceptibility to UV immunosuppression showed enhanced skin cancer development, consistent with the concept that the immunosuppressive effects of UV-B play an important role in UV carcinogenesis, preventing the immunologic rejection of highly antigenic skin cancers (Kripke 1990) (Fig. 3). Skin cancer patients show enhanced susceptibility to UV immunosuppression, suggesting these studies may be also be relevant to humans (Streilein et al. 1994).

In a number of studies with humans, immunosuppression was not observed in all individuals, suggesting the possibility of genetically determined differences in susceptibility to UV immunosuppression (Streilein et al. 1994; Skov et al. 1998). Further studies are needed to establish if

these differences are genetically determined since such genetic differences may represent risk factors for UV induced immunosuppression.

Dietary factors and UV-B induced immunosuppression

UV immunosuppression in mice can be increased by increasing dietary histidine (Reilly & De Fabo 1991) via increases in skin UCA levels. Fish, a staple in some Arctic populations, is relatively high in histidine. High dietary fat has also been demonstrated to enhance UV induced immunosuppression in experimental systems (Black et al. 1995) and may also be a factor in Arctic populations.

Non-Hodgkin's lymphoma and UV-B radiation

There is an accumulation of epidemiological evidence that non-Hodgkin's lymphoma shows a relationship with UV exposure, postulated to be via the immunosuppressive effects of UV-B. Several studies have found a correlation between skin cancer and the occurrence of non-Hodgkin's lymphoma (Levi, Randimbison et al. 1996; McMichael & Giles 1996; Melbye et al. 1996). In the USA, non-Hodgkin's lymphoma does not show a latitude gradient in contrast to skin cancer, suggesting that an effect of UV-B radiation may be as a co-factor rather than as a primary causative agent of this disease (Hartge et al. 1996). An excess of lymphatic malignancies in Danish women working in Greenland has been reported, raising the question of a role for excess UV-B (L. G. Nielsen et al. 1997). Lymphoid malignancies are, however, rare in Inuit populations (N. H. Nielsen et al. 1996).

Combinatorial effects

Viruses: Irradiation with UV-B is well described as reactivating latent viral infection and in depressing virus-specific cell-mediated immunity (el Ghorr & Norval 1996). The consequences of these actions for the Arctic have not been investigated. Cancers which show an excess in Inuit populations include nasopharyngeal and salivary gland cancer (N. H. Nielsen et al. 1996). Genetic factors appear to be involved, but

these are thought to be virally related cancers possibly associated with the high viral load in these populations. Interestingly, in several studies on non-Arctic populations salivary gland cancer has been linked to ultraviolet exposure (Levi, La Vecchia et al. 1998) although a latitude gradient has not been demonstrated and again UV-B may play a role as a co-factor. A potential effect of UV-B exposure in these cancers in the Arctic needs to be explored.

Pollutants: A number of persistent organic pollutants may be immunosuppressive. There is no information available on potential combinatorial effects between these agents and the immunosuppression caused by UV-B. In view of the high levels of POPs (Persistent Organic Pollutants) in some Arctic regions, such potential interactions need to be investigated (AMAP 1998).

Environmental stressors: It has been well described that stressful environmental conditions can be immunosuppressive. In the overwintering populations in the Antarctic, depression of cell-mediated immunity is well described and increased shedding of herpes virus and expansion of latent Epstein-Barr virus infected B cells have been reported (Tingate et al. 1997). The effect of combined environmental stressors and UV-B radiation on the immune system has not been investigated.

Conclusions

The long-term health implications of the large sporadic increases in UV-B in the Arctic are not yet clear and coordinated health investigations are urgently needed to address this issue. Of particular consideration are the effects on the immune system by UV-B in combination with stressors and pollutants known to be in the Arctic. The implications of increased UV-B on the high viral load of many Arctic populations also needs investigation.

References

AMAP (Arctic Monitoring and Assessment Programme) 1998: *AMAP assessment report: Arctic pollution issues.* Oslo: AMAP.
Armstrong, B. K. & Kricker, A. 1993: How much melanoma is caused by sun exposure? *Melanoma Res. 3,* 395–401.

Armstrong, B. K. & Kricker, A. 1995: Skin cancer. *Dermatol. Clin. 13*, 583–594.

Autier, P., Dore, J. F., Gefeller, O., Cesarini, J. P., Lejeune, F., Koelmel, K. F., Lienard, D. & Kleeberg, U. R. 1997: Melanoma risk and residence in sunny area. EORTC Melanoma Co-operative Group. European Organization for Research and Treatment of Cancer. *Br. J. Cancer 76,* 1521–1524.

Black, H. S., Okoite-Eboh, G., Gerguis, J., Urban, J. I. & Thornby, J. I. 1995: Dietary fat modulates immunorespon-siveness in UV-irradiated mice. *Photochem. Photobiol. 62,* 964–969.

Cooper, K. D., Oberhelman, L., Hamilton, T. A., Baadsgaard, O., Terhune, M., LeVee, G., Anderson, T. & Koren, H. 1992: UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, $CD1a^-DR^+$ epidermal macrophage induction, and Langerhans cell depletion. *Proc. Natl. Acad. Sci. (USA) 89,* 8497–8501.

De Fabo, E. C. & Noonan, F. P. 1983: Mechanism of immune suppression by ultraviolet irradiation in vivo. I: Evidence for the existence of a unique photoreceptor in skin and its role in photoimmunology. *J. Exp. Med. 158,* 84–98.

De Fabo, E. C. et al. 1995: Effects of increased ultraviolet radiation in the Arctic. In E. C. De Fabo (ed.): *Proceedings of a series of IASC (International Arctic Science Committee) workshops on UV impacts in the Arctic, held in Copenhagen, Greenland, and Washington, D.C. (1993–1995).* Oslo: IASC.

de Gruijl, F., Sterenborg, H., Forbes, P., Davies, R., Cole, C., Kelfkens, G., van Weelden, H., Slaper, H. & van der Leun, J. 1993: Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. *Cancer Res. 53,* 53–60.

el Ghorr, A. A. & Norval, M. 1996: The effect of UV-B irradiation on secondary epidermal infection of mice with herpes simplex virus type 1. *J. Gen. Virol. 77,* 485–491.

Hart, P. H., Grimbaldeston, M. A., Swift, G., Jaksic, A., Noonan, F. P. & Finlay-Jones, J. J. 1998: Dermal mast cells determine susceptibility to UVB-induced systemic suppression of contact hypersensitivity responses in mice. *J. Exp. Med. 187,* 2045–2053.

Hartge P., Devesa, S. S., Grauman, D., Fears, T. R. & Fraumeni, J. F. 1996: Non-Hodgkin's lymphoma and sunlight. *J. Natl. Cancer Inst. 88,* 298–300.

Henriksen, K., Stamnes, K., Volden, G. & Falk, E. S. 1989: Ultraviolet radiation at high latitudes and the risk of skin cancer. *Photodermatology 6,* 110–117.

Kripke, M. 1990: Effects of UV radiation on tumor immunity. *J. Natl. Cancer Inst. 82,* 1392–1395.

Kurimoto, I. & Streilein, J. W. 1994: Characterization of the immunogenetic basis of ultraviolet-B light effects on contact hypersensitivity induction. *Immunology 81,* 352–358.

Levi, F., La Vecchia, C., Te, V., Randimbison, L. & Erler, G. 1998: Incidence of invasive skin cancers following basal cell skin cancer. *Am. J. Epidemiol. 147,* 722–726.

Levi, F., Randimbison, L., Te, V. & La Vecchia, C. 1996: Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br. J. Cancer 74,* 1847–1850.

McMichael, A. J. & Giles, G. G. 1996: Have increases in solar ultraviolet exposure contributed to the rise in incidence of non-Hodgkin's lymphoma? *Br. J. Cancer 73,* 945–950.

Melbye, M., Adami, H. O., Hjalgrim, H. & Glimelius, B. 1996: Ultraviolet light and non-Hodgkins lymphoma. *Acta Oncol. 35,* 655–657.

Miller, A. B. & Gaudette, L. A. 1996: Cancers of skin, bone, connective tissues, brain, eye, thyroid and other specified and unspecified sites in Inuit. *Acta Oncol. 35,* 607–616.

Miller, S. A., Hamilton, S. L., Wester, U. G. & Cyr, W. H. 1998: An analysis of UVA emissions from sunlamps and the potential importance for melanoma. *Photochem. Photobiol. 68,* 63–70.

Nielsen, L. G., Frisch, M. & Melbye, M. 1997: Cancer risk in a cohort of Danes working in Greenland. *Scand. J. Soc. Med. 25,* 44–49.

Nielsen, N. H., Storm, H. H., Gaudette, L. A. & Lanier, A. P. 1996: Cancer in circumpolar Inuit 1969–1988: a summary. *Acta Oncol. 35,* 621–628.

Noonan, F. P. & De Fabo, E. C. 1992: Immunosuppression by ultraviolet B radiation: initiation by urocanic acid. *Immunol. Today 13,* 250–254.

Noonan, F. P., De Fabo, E. C. & Morrison, H. 1988: *Cis*-urocanic acid, a product formed by ultraviolet B irradiation of the skin initiates an antigen presentation defect in splenic dendritic cells in vivo. *J. Invest. Dermatol. 90,* 92–99.

Noonan, F. P. & Hoffman, H. A. 1994a: Susceptibility to immunosuppression by ultraviolet B radiation in the mouse. *Immunogenetics 39,* 29–39.

Noonan, F. P. & Hoffman, H. A. 1994b: Control of UVB immunosuppression in the mouse by autosomal and sex-linked genes. *Immunogenetics 40,* 247–256.

Noonan, F. P., Kripke, M. L., Pedersen, G. M. & Greene, M. I. 1981: Suppression of contact hypersensitivity in mice by ultraviolet irradiation is associated with defective antigen presentation. *Immunology 43,* 527–533.

Norval, M. & el Ghorr, A. A. 1996: UV radiation and mouse models of herpes simplex virus infection. *Photochem. Photobiol. 64,* 242–245.

Norval, M., Simpson, T. & Ross, J. 1989: Urocanic acid and immunosuppression. *Photochem. Photobiol. 50,* 267–275.

Reilly, S. & De Fabo, E. C. 1991: Dietary histidine increases mouse skin urocanic levels and enhances UVB-induced immune suppression of contact hypersensitivity. *Photochem. Photobiol. 53,* 431–438.

Selgrade, M. K., Noonan, F. P., Smith, M. V., Jeevan, A., Cooper, K. D. & Koren, H. 1997: Quantitative inter-species comparisons of the immunosuppressive effects of ultraviolet radiation (UVR). Abstract distributed at the 11th International Conference on Carcinogenesis and Risk Assessment.

Skov, L., Hansen, H., Dittmar, H. C., Barker, J. N., Simon, J. C. & Baadsgaard, O. 1998: Susceptibility to effects of UVB irradiation on induction of contact sensitivity, relevance of number and function of Langerhans cells and epidermal macrophages. *Photochem. Photobiol. 67,* 714–719.

Slaper, H., Velders, G. J. M., Daniel, J. S., de Gruijl, F. R. & van der Leun, J. C. 1996: Estimates of ozone depletion and skin cancer incidence to examine the Vienna Convention achievements. *Nature 384,* 256–258.

Streilein, J. W., Taylor, J., Vincek, V., Kurimoto, I., Shimizu, T., Tie, C. & Golomb, C. 1994: Immune surveillance and sunlight-induced skin cancer. *Immunol. Today 15,* 174–179.

Tingate, T. R., Lugg, D. J., Muller, H. K., Stowe, R. P. & Pierson, D. L. 1997: Antarctic isolation: immune and viral studies. *Immunol. Cell Biol. 75,* 275–283.

Ullrich, S. E. 1995: Modulation of immunity by ultraviolet radiation: key effects on antigen presentation. *J. Invest. Dermatol. 105,* 30S–36S.