Ultraviolet Radiation (UVR)-Induced Immune Suppression: An Incentive For Sun Protection Strategies Beyond SPF

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Sun exposure is the major risk factor for cutaneous malignancy and photoaging. Protection against UVR by sunscreens is currently evaluated using a "sun protection factor", SPF, based on prevention of erythema. However, SPF is not fully reflective of UVR-induced damage and imperfectly predictive of long term consequences. One reason that this is true is due to UVR-induced suppression of the cutaneous immune system. Immune suppression is a complex phenomenon which results from both UVA and UVB parts of the spectrum, whereas erythema is more dependent on UVB wavelengths. SPF does not accurately correlate with immune protection. Therefore, there is considerable interest in developing new measurement protocols for sun protection that include immune suppression as a protection endpoint. A number of research groups are actively elucidating the mechanisms by which UVR induces immune suppression, constructing *in vitro* and *in vivo* model systems for evaluation of protection, and developing potential new strategies for product development.

The response of human skin *in vivo* is a complex interplay of many events dependent upon time (duration of exposure, time after exposure, number of exposures), wavelength, energy flux, and the individual's genetic makeup and photo-type, and previous UVR history[1,2,3]. UVR-induced immune suppression is an extremely important component of skin cancer risk, as demonstrated both in humans and other animal models[4,5].

Sunscreens are advocated as a means of preventing skin cancer, but in the USA, the consumer can compare sun protection products only by the labeled "SPF" number. Unfortunately, the SPF has been shown to correlate only poorly and not predictably with immune protection, most likely because it is not sensitive enough to UVR-induced oxidative stress[6,7,8,9,10]. In addition, the SPF measurement can not accurately predict protection given by alternative non-sunscreen ingredients such as anti-oxidants and DNA repair enzymes.

One paradigm for conceptualizing the relationship between UV wavelength and skin can be seen in figure 1.[11]

Figure 1

- UVB, UVA → direct and oxidative DNA modification → neoplastic transformation
- UVB, UVA → immuno-modulation → induction of T regulatory cells, facilitation of tumour promotion, tumour progression

In other words, shorter wave (280 to 320nm) UVB is the primary cause of direct mutagenic DNA lesions, with some contribution from longer wavelength (320 to 400nm) UVA. It should be kept in mind though, an important paper was recently published that suggested that oxidative DNA damage may be more important than originally thought and may result in mutations in the stem cell population[12].

UVB and UVA however, may contribute equally to immuno-modulation, which allows the nascent tumour cell to escape immune surveillance and destruction. This UVR-induced immune suppression can be measured by several different *in vivo* protocols, however they are all much more invasive and complicated than the current SPF protocol. For example, the contact hypersensitivity assay measures a complex function involving local cell and lymph node communication, integrates a number of cell and tissue damage and inflammatory events that occur in the skin following UV injury, tests functions other than redness, but is not practical for industry use.

How should we design a new sun protection factor?

- Must be related to skin *immune function* and reflect the current knowledge of other risk factors for skin cancer
- Must measure a short-term effect that is practical for high through-put screening during product development
- Should account for "real-life" exposure (possibly multiple sub-erythemogenic doses)
- Protection should be expressed by a value that consumers can understand and use for comparison

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