Skin cancer, the most prevalent form of cancer in Caucasians, is mostly caused by exposure to the ultraviolet (UV) wavelengths found in sunlight. UV radiation that reaches the surface of the earth from the sun is divided into two wavebands, UVB (290–320 nm) and UVA (320–400 nm), with visible light being made up of longer wavelengths. The composition of sunlight varies with latitude and time of the day, but usually is made up of about 20 times more UVA than UVB. It is critical that humans protect themselves from the damaging effects of UV radiation. Sunlight avoidance is often not practical or not observed because of work constraints or recreational activities, and therefore other means of protection from sunlight are required. Sunscreens containing UV filters are a valuable protective measure. Understanding the molecular mechanisms of photodamage that lead to skin cancer will enable the development of biological interventions that prevent these molecular mechanisms. This is likely to provide an additional powerful means of photoprotection.

In this issue of the journal, Decraene et al (2005) suggest a new possibility for photoprotection: activation of molecular photoadaption to sunlight. It is well recognized that the skin adapts to sunlight in order to reduce damage from subsequent exposures. Adaptive processes include melanin production and increased epidermal thickening, both of which attenuate the amount of UV radiation that reaches the basal cells of the epidermis. Decraene and colleagues have investigated adaptation at the molecular level, as they believe that it may be possible to activate molecular skin mechanisms through a non-damaging agent other than UV radiation does not cause damage to the skin. This would provide an additional level of photoprotection to conventional sunscreens or biological interventions that reverse damage after it has occurred. It would condition the skin into a state where UV damage is less extensive. They found that exposure to low-dose broadband UVB provided by TL 20W12 fluorescent tubes reduced apoptosis caused by a higher dose of UVB 24 h later. The mechanism of this photoadaption involved upregulation of p21/WAF1 and p53R2. These genes are both activated by p53, and are involved in cell cycle arrest and DNA repair, respectively. The low dose of photoadaptive UVB also increased and stabilized p53, as demonstrated by an increase in p53 phosphorylated at serine 15. The authors therefore propose that low-dose UVB upregulates and stabilizes p53, which induces cell cycle arrest via p21/WAF1 induction and enhancement of DNA repair via increases in p53R2. This increases the resistance of keratinocytes to a subsequent exposure to photodamaging levels of UVB as the cell is primed for DNA repair rather than division when exposed to the higher damaging UVB dose. Upregulated p21/WAF1 induces cell cycle arrest, enabling the cells to undergo DNA repair, which is also increased. These adaptive molecular mechanisms required 24 h following the low-dose exposure to allow for P53 activation. The low-dose UVB was only protective if sufficient time was allowed for p53 to activate these protective mechanisms. Therefore, this study shows that p53 helps the skin adapt to UVB by initiating protective measures.

Both UVB and UVA cause photodamage that is likely to be important for skin carcinogenesis. UVA, as well as UVB, increases levels of immunoreactive p53 protein, but predominantly in the basal layer of the epidermis (Campbell et al., 1993). Also, UVB and UVA in sunlight appear to make approximately equal contributions towards the induction of genetic mutations in p53 in human skin cancer. Similar numbers of mutations attributable to these wavebands can be found in p53 in human squamous cell carcinomas and their benign precursors actinic keratoses (Agar et al., 2004). Interestingly, UVA mutations are predominantly located at the basal layer of skin tumors, the same region in which UVA-increased levels of p53 are found. In contrast, UVB-induced mutations are restricted to the upper layers of skin tumors. Thus, UVA and UVB appear to primarily affect p53 at different depths within tumors. Whether this is because of localization of UVA photoabsorbers or some other event is unknown. This is, however, important as skin tumors are thought to arise from transient amplifying or stem cells located at the basal layer of the epidermis. In human epidermis, cells at the basal layer are less differentiated, but capable of dividing compared with the terminally differentiated cells at the surface of the skin. It is possible that p53 in basal and terminally differentiated keratinocytes may respond differently to UVB and UVA. It would be interesting to extend the studies of Decraene and colleagues to determine whether UVA as well as UVB activates p53-mediated adaptive responses to sunlight, and whether such...
adaptive responses are different in well-differentiated cells at the surface of the skin compared with basal cells at the base of the epidermis. Decraene and colleagues irradiated cultured keratinocytes isolated from human foreskins that would presumably have had little if any prior exposure to sunlight, and therefore little chance of having developed an adaptive response prior to the low-dose UVB exposure they received in this study. Adult keratinocytes may behave differently, particularly in their stratified differentiation state within skin. In a recent study it has been shown that high-dose UVA1 (340–400 nm) does not increase levels of p53 stabilized by phosphorylation at serine 15, or of p21/WAF1 (Beattie et al., 2005). It is therefore possible that UVA would not cause the photoadaptive response reported in this issue.

A number of studies have shown that the skin adapts to chronic UV exposure by inducing a range of protective mechanisms; melanin production is the best characterized of these adaptive responses. UVB initiates production of α melanocyte stimulating hormone (α-MSH) along with other paracrine factors from cutaneous keratinocytes and melanocytes, which leads to increased melanin production (Gilchrest and Eller, 1999). Synthetic potent derivatives of α-MSH are being developed to increase tanning in humans without the need for sunlight exposure as an approach to activating this photoadaptive response in order to protect from sun damage (Dorr et al., 2000). Thymine dimers, one of the forms of DNA damage caused by UV exposure, are able to activate p53, increase DNA repair, and induce melanization. Topical application of thymine dimers is able to activate these protective measures (Gilchrest and Eller, 1999; Goukassian et al., 2004). Thus, based on understanding the molecular events involved in photoadaptation, it should be possible to develop procedures that convert cells into a state that makes them less susceptible to photodamage.

In addition to UV-induced genetic mutations, UV-induced immunosuppression is an important form of damage during photocarcinogenesis. Immunosuppression also adapts to UV exposure. Exposure of humans to both low-dose UVB and UVA causes immunosuppression. Repeated exposures 24 h apart with UVA for 4 d, or UVB for 5 d are not immunosuppressive, indicating that an adaptive mechanism is activated that prevents immunosuppression from subsequent exposures (Damian et al., 1999). Higher dose UVA induces the production of interferon-γ and the antioxidant enzyme heme oxygenase-1 (HO-1), which protects from UBV-induced immunosuppression. This adaptive response occurs more rapidly than that described in this issue by Decraene and colleagues, as it can prevent immunosuppression caused by UVB exposure delivered immediately following the UVA, and HO-1 is induced immediately following high-dose UVA exposure (Allanson and Reeve, 2004). This adaptive response, increased HO-1, can also be induced by curcumin, a spice commonly used in foods that mediates this effect at least partially via the NF-κB transcription pathway (Hill-Kapturczak et al., 2001).

Study of the mechanisms of photoprotection will enable this process to be induced by biological modifiers other than UV radiation, and this approach provides considerable promise for improved photoprotection. It should be possible to develop effective strategies for this purpose that do not cause the damage that would be inflicted by UV-induced adaptation. Epigallocatechin-3-gallate (EGCG) is a phenolic compound of green tea, which is an effective chemopreventative agent. Like the low-dose UVB protocol in the study by Decraene and colleagues in this issue, EGCG up-regulates and stabilizes p53, leading to an increase in p21/WAF1 and cell cycle arrest (Hastak et al., 2005). Activation of this p53-dependent pathway is likely to be at least partially responsible for the protective effects of this compound. Artificial methods for adaptation of the skin so that it has reduced damage following exposure to sunlight, such as synthetic derivatives of α-MSH to augment melanogenesis, thymine dimers to increase DNA repair and melanogenesis, curcumin to enhance HO-1 levels, or EGCG to activate p53-dependent protective pathways, are all promising. A variety of strategies, including sun avoidance, use of sunscreens with UV filters, and biological modifiers that repair UV damage or adapt the skin so that it is less sensitive to the damaging effects of sunlight, may eventually help to reduce the incidence of skin cancer.

References


Damian DL, Barnetson RS, Halliday GM: Low-dose UVA and UVB have different time courses for suppression of contact hypersensitivity to a recall antigen in humans. J Invest Dermato 112:939–944, 1999


Hastak K, Agarwal MK, Mukhtar H, Agarwal ML: Ablation of either p21 or Bax prevents p53-dependent apoptosis induced by green tea polyphenol epigallocatechin-3-gallate. FASEB J 19:U344–U362, 2005