Xeroderma Pigmentosum Knockout Mice: An Immunologic Tale

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The exciting report by Miyauchi-Hashimoto, Horio, and Tanaka in this issue (p 343) presents a novel system, xeroderma pigmentosum (XP) knockout mice, permitting the examination of the interaction of ultraviolet (UV) and DNA repair on immune function in an intact animal. This innovative technique may provide new answers to old questions about XP.

Patients with xeroderma pigmentosum (XP) have more than a 1000-fold increased risk of developing cancer on sun-exposed skin (Kraemer *et al*, 1994a). This recessive disorder has clinical sun sensitivity that is associated with increased sensitivity to killing of cultured skin cells after exposure to UV (Kraemer *et al*, 1994b; Cleaver and Kraemer, 1995). In 1968, James Cleaver (Cleaver, 1968) reported that XP cells are defective in DNA excision repair, a process whereby cells mend DNA that is damaged by UV. Cleaver showed that XP cells have impaired ability to remove DNA photoproducts produced by UV exposure. Subsequent studies have demonstrated that seven different molecular defects (XP complementation groups A through G) may result in clinical XP (Cleaver and Kraemer, 1995).

The symptoms of most XP patients consist of redness, freckle-like pigmentation, atrophy, and telangiectasia, which eventually lead to premalignant and malignant lesions. These are generally confined to sun-exposed parts of the body (skin and anterior eye), and sun protection appears to be effective in preventing most of these abnormalities.

Since XP cells are also hypermutable following UV exposure, the marked increase in skin cancer is usually ascribed to UV-induced mutations in the skin cells. This somatic mutation theory of carcinogenesis is supported by the observation that the types of mutations induced in UV-treated plasmids transfected into XP cells (C to T and CC to TT) are typical of UV damage (Levy *et al*, 1995). These same mutations appear frequently in skin cancers obtained from XP patients [(Levy *et al*, 1995), and references therein].

Symptoms of severe immune deficiency such as multiple infections are not usually observed in XP patients. There have been scattered reports, however, of abnormalities in tests of immune function (Dupuy and Lafforet, 1974; Wysenbeek *et al*, 1986; Norris *et al*, 1990; Mariani *et al*, 1992). These range from mild defects in cellular immunity to combined immunodeficiency (Goldstein *et al*, 1990). More recently, some patients had impaired natural killer cell activity and reduced interferon production (Gaspari *et al*, 1993).

The experimental studies in mice of Kripke (1990, 1991) demonstrated that UV radiation may have profound effects on the immune system. These alterations include impaired ability to reject experimentally transplanted skin cancers. Recent studies utilizing DNA repair enzymes to reverse specific types of UV damage have shown that some of these effects are dependent on the presence of UV photoproducts in DNA (Vink *et al*, 1996).

Sun exposure may alter the immune system in XP patients. Some severely sun-exposed Egyptian XP patients had impaired ability to develop skin contact sensitization (Morison *et al*, 1985). Clinical studies of the skin of XP patients indicated that epidermal Langerhans cells *in vivo* were particularly sensitive to depletion by UV (Jimbo *et al*, 1992). These observations raise the possibility that immune abnormalities may contribute to the high frequency of UV-induced cancer in DNA repair–deficient XP patients.

An extensive series of elegant experimental studies led by Tanaka resulted in the cloning of the human gene that is defective in XP complementation group A (Tanaka *et al*, 1990) and culminated in the production of mice in which the function of the murine XPA gene is eliminated (Nakane *et al*, 1995). The XPA knockout mice were shown to have markedly increased sensitivity to UV induction of skin cancer, thus strongly linking the XPA gene defect to skin cancer in an intact animal.

The report by Miyauchi-Hashimoto *et al* describes examination of the response of the immune system in these animals to UVB exposure. They found that the XPA knockout mice were hypersensitive to UVB or psoralen plus UVA induction of inflammation as assessed by ear swelling or cellular infiltration of the skin. Of particular note, as in the humans with XP, markers of Langerhans cells disappeared at low UV doses and showed delayed reappearance. The XPA knockout mice had a normal induction of contact hypersensitivity but had greatly enhanced UVB induction of local and systemic immunosuppression.

These results have implications for theories of carcinogenesis in XP patients and suggest that UV-induced immunosuppression may play a role in human skin cancer development. In addition, the XPA knockouts can serve as models for detailed examination of the contribution of DNA repair to other immune mechanisms such as interferon induction, natural killer cell activation, or elaboration of interleukins. Further, additional knockout strains of mice inactivating other DNA repair genes are being developed. For example, patients with Cockayne syndrome have clinical and cellular UV hypersensitivity and hypermutability as in XP but do not develop skin cancer (Kraemer *et al*, 1994b; Cleaver and Kraemer, 1995). Perhaps Cockayne syndrome knockout mice may have different immune surveillance than the XPA knockouts. The XPA knockout mice should also be useful for studies of the effect of agents such as liposomes containing DNA repair enzymes, retinoids, or immune enhancers on immune function and UV-induced skin cancers. The tale of the use of XP knockouts for immune studies is just beginning.

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