Commentary

How important are somatic mutations and immune control in skin cancer? Reflections on xeroderma pigmentosum

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One of the key pieces of evidence in favour of the somatic mutation theory of cancer comes from the hereditary disease xeroderma pigmentosum (XP). Cells from such patients are deficient in the repair of DNA damage caused by a wide variety of mutagens including far u.v. light (FUV) and photochemical sensitization by psoralens and near u.v. light (PUVA). The cells, in consequence, are killed or mutated by doses very much lower than those required for cells from normal individuals. XP individuals themselves show a high incidence of skin tumours on areas of skin exposed to light, which is commonly said to reflect the relative hypersensitivity to sunlight-induced mutation to malignancy, (i.e., initiation), in cells of the skin.

This has been an attractive interpretation but I suggest it may be an oversimplification, at least when viewed quantitatively. Should not one also take into account the likelihood that skin cancer (particularly squamous cell carcinoma) rarely appears except when normal control processes in the skin are impaired. It is well known, for example, that skin cancer is common in patients undergoing strong immunosuppressive therapy (1) implying that potentially malignant cells are present in normal skin more often than is generally realized and suggesting that some sort of immune process normally plays a role in controlling their growth into overt neoplasms. Earlier, Dupuy and Lafforet (2) had found evidence for impaired cell-mediated immunity (including an inability to obtain sensitization to dinitrochlorobenzene) in XP patients and hypothesized that this might contribute to their proneness to develop skin cancer. Subsequently, Bridges and Strauss (3) discussed evidence that DNA damage such as that produced by FUV and PUVA can cause breakdown of immune control in the skin of animals. They suggested that the elevated rate of squamous cell carcinoma observed in psoriasis patients undergoing recent PUVA therapy (4) might be attributable to such an effect rather than to mutation, since squamous cell carcinomas, at least within the first 2 years after commencement of PUVA therapy, seem to arise only in individuals who have either had previous skin cancer or a history of radiation exposure. They referred to this effect of PUVA as promotion, but perhaps a better term would be pseudopromotion or permissive cocarcinogenesis as defined by Berenblum (5).

Three new papers provide strong support for the view that immune control is of paramount importance for skin cancer. Firstly, Strauss et al. (6) have shown that about half of more than 100 psoriasis patients undergoing PUVA treatment had an impaired cell-mediated immune response to dinitrochlorobenzene applied to the skin. Of about 400 patients treated over the last 4 years, 6 developed cutaneous tumours, often multiple. In two of these patients, tumours were diagnosed after the skin test had been recorded; both had given abnormally low responses. Moreover, in both patients lesions began to regress when PUVA treatment was discontinued (6). This study shows clearly that the state of the skin was crucial for the appearance and progression of tumours, although it does not permit the immune impairment to be regarded as causative rather than as reflecting some other primary disturbance.

A second relevant study by Jennings and Spradbrow (reported at the Fourth International Congress of Immunology, 1980, and following up earlier work by Spradbrow (7)) was carried out with Hereford cattle. In Australia these animals are extremely prone to ocular squamous cell carcinoma, presumably sunlight-induced; up to 20% incidence has been recorded. It was found that these tumours could be cured or arrested with a single intramuscular injection of a phenol-saline extract of allogeneic tumour, (i.e., from a genetically different animal of the same species), but not of autochthonous tumour, (i.e., from the same animal). After treatment with allogeneic extract a new cell-mediated response to phenol-saline extracts of squamous cell carcinoma was detected.

Finally, to return to XP, Al-Saleem et al. (8) treated nine such patients presenting with inoperable skin tumours. They hypothesized (as others have done, see (3)) that suppressor lymphocytes might be involved in controlling skin tumours. Following treatment with indomethacin (to neutralize overproduction of prostaglandins by suppressor cells) and steroids (to eliminate suppressor cell precursors) they observed regression of tumours in 8 patients; in three the regression was complete.

These papers clearly reveal the immunological nature of the mechanisms that exist for the control of skin cancer and allow the conclusion that, although an initiated tumour cell is presumably required (and the
number of such cells may well be increased by mutagens), the appearance of a tumour is very rare unless the skin is damaged and the tumour controlling mechanisms (probably immunological in nature) are impaired. DNA damaging agents such as FUV and PUVA seem to be able to cause such impairment so that they may give rise to tumours by pseudopromotion as well as by initiation. It is not possible to say at present whether the DNA damage acts in any specific way to impair immune control, or whether the immunological status of the skin is simply altered as a result of its cytotoxic and cytostatic action, for example, on lymphocytes (9) or Langerhans cells (10).

A strong argument that it is actually DNA damage that is primarily responsible for the impairment of immune control comes from the great rapidity with which multiple tumours appear in XP patients treated with PUVA compared with normal individuals (c.f. 11, 12).

This observation is satisfactorily explained only by assuming that PUVA acts as a pseudopromotor allowing the appearance of already existing foci of neoplastic cells and that XP patients, because of their DNA repair deficiency, are hypersensitive to the immunological impairment as well as to the initiating activity of PUVA. The impairment in cell-mediated immunity observed in XP patients by Dupuy and Lafforet (2) may well, in the light of this, be attributable to unavoidable chronic exposure to light rather than to a primary immunological deficiency.

It follows from the above arguments that the elevated frequency of skin cells transformed by some sort of somatic mutation, while it may be necessary, may in itself not be sufficient to account for the development of the multiple tumours often observed in XP patients (and, at a lower frequency, in psoriasis patients undergoing PUVA therapy). At least as important, and perhaps more so, is the unrepaired damage in other cells such as lymphocytes or Langerhans cells (c.f. 9,10) which allows transformed cells to develop into tumours by impairing immune control processes in ways so far not understood.

One final piece of evidence for such an interpretation may be derived from another sun-sensitive hereditary disease, Cockayne syndrome, believed also to have an associated repair deficiency. Fibroblasts from these patients are hypersensitive to u.v. (13), to the same extent as excision-defective XP cells but rather more so than variant XP cells, known to be defective in some post-replication repair process. Only for one strain of Cockayne syndrome cells has u.v. mutability so far been studied (14). In this strain, however, hypermutability by u.v. was clearly shown, comparable in extent to that in XP variants (15). Unlike XP patients (including variants), Cockayne syndrome patients do not exhibit any XP-like freckling, hyperkeratoses, or skin neoplasms. Does this not argue that something more is required for the early appearance of multiple skin neoplasms as found in XPs than an elevated frequency of somatic mutations, something like impaired immune control perhaps? Consequently, I suggest that the elevated skin cancer rate in XP patients in no way accurately reflects the actual increase in mutation frequency in exposed skin, but is likely to exaggerate it greatly.

From the point of view of the XP patient, this realization offers the hope that even if somatic mutation due to illumination is impossible to avoid totally, it may be possible to enhance the immune control processes in the skin so as to block the outgrowth of such cells into tumours.

References