Xeroderma pigmentosum, Cockayne’s syndrome and trichothiodystrophy: different clinical symptoms associated with similar DNA repair defects

Extensive molecular and cellular studies on cells from patients with the highly cancer-prone genetic disorder xeroderma pigmentosum (XP) have shown that the molecular defect associated with this disorder is a deficiency in the ability to repair UV damage in cellular DNA (see refs 1–3 for reviews). In most cases there is a defect in excision-repair of UV damage, for which nine genetic complementation groups have been identified. A minority of cases, the XP variants, have normal excision repair but are defective in a daughter-strand repair process (4). All XP cells tested, whether excision defective or variants, are extremely hypermutable by UV irradiation (5–7). Furthermore recent data have shown that the mutant frequency in peripheral T lymphocytes of XP patients is considerably elevated when compared with normal controls (8). These findings have led to the simple scheme relating molecular, cellular and clinical properties of XP depicted in Figure 1.

More recently comparable molecular and cellular studies have been carried out with two other multisystem genetic disorders, Cockayne’s syndrome (CS) and trichothiodystrophy (TTD). Photosensitivity is found in all CS (9) and in some TTD patients (e.g. see ref. 10). The other skin abnormalities associated with XP, including freckling, pigmented changes and sunlight-induced skin cancers are not found in CS and TTD. These disorders are characterized, however, by a wide variety of other non-skin-associated abnormalities not seen in XP patients. Like XP cells, CS cells are hypersensitive to the lethal and mutagenic action of UV light (reviewed in refs 11 and 12). This is not attributable to an overall defect in the repair of UV damage, but rather to a specific deficiency in the ability to repair damage in actively transcribed regions of DNA (13, 14). The response of TTD cells to UV is heterogeneous. In collaboration with Stefanini and coworkers, we have recently identified three categories of cell strains by their differing response to UV irradiation (10,15,16). In one category the cellular response to UV irradiation is identical to that of XP cells by seven different criteria (16). Indeed, the genetic defect in these cells appears to be in the same gene as that of XP complementation group D (10,16), since in cell fusion studies these TTD cells and XP-D cells fail to complement. Thus, in the cases of CS and TTD, defective DNA repair is associated with hypermutability by UV light, but this does not result in the skin abnormalities seen in XP, in particular the enormously increased incidence of skin cancer. Instead it is associated with completely different symptoms. This is the paradox we wish to address.

Effects of UV on the immune system

In 1981 Bridges (17) speculated that the increased frequency of skin cancer in XP resulted not only from the hypermutability of the skin cells by solar irradiation, but also from increased susceptibility to UV-induced depression of immune surveillance mechanisms, consequent upon decreased DNA repair in cells involved in the immune response. The effect of UV irradiation on the immune response has been intensively investigated (e.g. see ref. 18) and a very simplified scheme is presented in Figure 2. The pre-cancerous cell depicted in Figure 2 is assumed to result from a UV-induced mutation, e.g. in a critical oncogene. UV-induced tumour cells are generally highly antigenic and following antigen presentation to helper T cells by Langerhans cells they may be lysed by tumour antigen-specific cytotoxic T cells (pathway a in Figure 2). This would be expected to lead to rejection of the tumour, but it has been shown in mice that UVB irradiation induces a clonal population of suppressor T cells that recognize a UV-induced keratinocyte neoantigen cross-reactive with common tumour-associated antigens present on virtually all UV-induced tumours. This provides an immunologically suppressed environment that allows UV-induced skin neoplasms to escape immune surveillance (19). This activation of suppressor T cells is mediated by epidermal antigen-presenting cells and is thought to outweigh the activation of helper T-cells because activation of the latter by epidermal Langerhans cells is decreased by UV exposure. In XP, depression of immune surveillance could therefore result from increased UV sensitivity of either Langerhans cells or possibly effector (helper and cytotoxic, see Figure 2a) cells.

*Abbreviations: XP, xeroderma pigmentosum; CS, Cockayne’s syndrome; TTD, trichothiodystrophy; NK, natural killer.

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Fig. 1. Relationship between molecular, cellular and clinical features of UV-repair-deficient disorders. Factors A and C increase and B and D decrease the likelihood of a mutation resulting in a tumour.
of such a proposal, two of which we reiterate here in modified form. (i) The carrier frequency for mutations at each of these loci must be very high (1–10%). (ii) Individuals with homozygous mutations in either the NK gene or the repair gene would exist at a quite high frequency in the population at large (of the order of 10⁻³), without necessarily showing symptoms. Furthermore it would be expected that some asymptomatic siblings of XP patients would be defective in DNA repair but not in NK activity (and vice versa). A case of an asymptomatic sibling with reduced DNA repair has been reported (27), but more cases should be investigated. This prediction should be relatively easy to test.

The nature of the postulated second mutation responsible for defective NK activity in XP is speculative. Tumour cell killing by NK cells involves a number of steps including target cell recognition, binding and lysis, and appears to be under polygenic control. In addition, NK cells are susceptible to negative regulation by suppressor cells which are responsible for genetically determined low NK activity in some strains of mice (28). However, a mutation resulting in greater susceptibility to inhibition by UV-induced reactive oxygen species might provide an explanation for some hitherto inexplicable observations. It has been reported recently that several XP fibroblast cell strains had a reduced level of catalase activity (29). These findings have now been extended to 20 XP patients from different complementation groups (A.Sarasin, personal communication). This observation does not fit readily into the pattern of XP sensitivities attributable to defective DNA repair. The agents to which XP cells are hypersensitive are thought to damage DNA directly, rather than via active oxygen species, and XP cells are not in general hypersensitive to agents such as ionizing radiation, H₂O₂ or bleomycin, which act via free radical mechanisms. It is conceivable, however, that the catalase deficiency may be related to the proposed mutation conferring NK deficiency as indicated in Figure 2b. A deficiency in catalase activity in XP cells could result in more pronounced reduction of NK activity brought about by reactive oxygen species, thus rendering pathway (b) less efficient. This is, however, a highly controversial area.

**Trichothiodystrophy**

As stated previously, our work (ref. 16 and unpublished observations) and that of Stefanini and her colleagues (10,15) has identified three categories of response to UV irradiation in cell strains from different TTD patients. (i) Cells from two patients (15,16) have a totally normal response to UV. (ii) Cells from eight patients show a response, as described above, which is identical to that of XP-Ds (refs. 10 and 16 and unpublished observations). (iii) Cells from two further patients have a normal survival response and normal removal of pyrimidine dimers (refs. 16 and unpublished observations). Nevertheless repair synthesis rates in these cells are only 50% of normal, a deficiency which has recently been attributed to a reduced rate of removal of 6-4 photoproducts from cellular DNA (D.Mitchell, personal communication). A possible model to account for these observations would envisage that the TTD locus is located close to the XP-D locus (also discussed in refs. 30 and 31).

Point mutations or small deletions entirely within the TTD locus would result in TTD without repair defect (category 1). Larger deletions in the TTD locus could extend into the XP-D locus resulting in associated repair deficiency (category 2). We previously rejected this model, because, if the XP phenotype results from mutation in a single DNA repair locus, and TTD...
patients had a deletion extending into this locus. TTD patients should have the full clinical phenotype of XP, which is not the case. If, however, as the model postulated above suggests, the XP phenotype requires an additional mutation governing NK activity, a deletion in TTD cells extending into the XP-D locus is compatible with the clinical symptoms, since TTD patients do not carry the ‘NK mutation’. We may thus summarise the postulated mutations in TTD and XP-D as shown in Table 1.

Most deletions would be expected to abolish gene activity. We propose that this is the case with category 2 TTD cells. In order to account for TTD category 3 cells which have considerable repair activity, the deletion might extend only a short way into the XP-D locus, either at the 3′ end, or into the promoter regions at the 5′ end, with substantial activity remaining. Precedents exist for this phenomenon, both in human genetic diseases, and in DNA repair genes. Duchenne and Becker muscular dystrophy are allelic and can both be associated with deletions, but the latter form of the disease is milder than the former, possibly because of the different location of the deletions within the gene (32). In cloned eucaryotic repair genes the N-terminalis of the human ERCC-1 gene (33) can be deleted without loss of function (34). Conversely the C-terminal end of the rad6 gene from Saccharomyces cerevisiae can be deleted without conferring the UV sensitivity on the cells found with other rad6 mutants, although sporulation is greatly reduced by such C-terminal deletions (35).

Obviously much of the hypothesis outlined above is speculative and much if not all of it may be proved wrong. Our purpose is to present an alternative model to explain the deficiencies in XP and TTD, in the hope that these thoughts might provoke new types of experiments. In particular what the model emphasizes is that factors A−D in Figure 1 may have a crucial role in governing whether the cellular hypermutability found in XP, CS and TTD will in fact result in an increased frequency of cancer.

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References


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