INHERITED PREDISPOSITION TO CANCER: RELATIONSHIP TO DNA DAMAGE PROCESSING

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INTRODUCTION

There is an increasing realisation that many cancers can occur in individuals who carry an inherited predisposition to the disease. This was suspected from the existence of "cancer families" in which many relatives present with the same pattern of disease, often with an earlier than average age of presentation. More recently the isolation of the genes that are defective in some of these individuals has allowed a more detailed analysis of biochemical defects in their cells. A common feature of the cancer-prone individuals is the presence of abnormalities in the way cells process DNA damage. Indeed there is some evidence that the ability to repair DNA damage, as evidenced by the reduction in the amount of chromosome damage, may almost be a general feature of all cancer predisposition (see below). In this article I will examine some rare inherited cancer-prone syndromes that have alterations in the way DNA-damaging agents are handled and consider the role of these processes in more common diseases.

UV-SENSITIVE SYNDROMES AND SKIN CANCER.

It has been recognised for many years that the ultra violet (UV) component of sunlight is highly toxic and mutagenic to human cells and that UV can reduce the immunocompetence of irradiated animals. This has been linked to the induction of skin cancers by the observations that more than 90% of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) occur on exposed parts of the body and the incidence of melanomas is highest in countries where fair skinned individuals are exposed to high levels of sunlight (e.g. Australia).

Our knowledge of the processes that are important in this link between UV and skin cancer has been greatly facilitated by the existence of rare individuals who exhibit severe over-reactions to sunlight. The "classic" UV-sensitive syndrome is xeroderma pigmentosum (XP). The defects associated with this syndrome lead to an abnormal erythema response to sunlight, the life expectancy is reduced by about 30 years and the median age for first skin cancer is around 50 years lower than in normal individuals[1]. These individuals can also have an impaired immune system and premature neuronal death can lead to neurological defects. Cells from XP individuals have a reduced ability to perform nucleotide excision repair which normally removes the regions of DNA that are damaged by UV light. Six of the genes that are mutated in individuals with this disorder have been cloned and in most cases their function has been at least partially characterised within the nucleotide excision repair process. An important finding within this characterisation is that the proteins encoded by some of these XP genes are part of a complex (TFIIH) that is involved in transcription[2]. This has led to the UV-sensitive syndromes being also labelled as "transcription syndromes".

XP individuals have a very clear proneness to skin cancer on exposed parts of the body and this is perhaps the clearest and best characterised situation in which a susceptibility to a significant carcinogen is linked to a cancer-prone syndrome. However, the association is not this simple since there are individuals who are defective in aspects of the nucleotide excision repair pathway, with cells that show some UV sensitivity but who are not prone to cancer. These are people with Cockayne syndrome and trichothiodystrophy. This suggests that the gene mutations in these individuals have more widespread effects than simply reducing the efficacy of nucleotide excision repair. It is clear that the extent and nature of the repair defects are not identical in the three syndromes and much effort is going in to relating this to the clinical observations.

ATAXIA TELANGIECTASIA: AN IONISING RADIATION-SENSITIVE SYNDROME

Among the several features that characterise the recessively inherited syndrome ataxia telangiectasia (A-T) there is a very high susceptibility to lymphoma, leukaemia and other cancers of childhood and young adults[3] (Table 1). It was also recognised by clinicians in the 1960s that individuals with symptoms associated with A-T exhibit an extreme sensitivity to ionising radiation given for the treatment of their cancers. Severe tissue damage was observed at doses of radiation that would not be expected to cause any side effects. Subsequent analysis of lymphocytes and fibroblasts from these A-T patients showed them to be much more sensitive to the killing effects of ionising radiation than cells from normal individuals (Figure 1). These cells have been extensively investigated over the last 25 years and several defects in the cells have been noted (Table 2), including an increased incidence of spontaneous and radiation-induced chromosome aberrations.

Ataxia (reflection of cerebellar degeneration and progressive neuromotor deterioration)
Telangiectasia in the conjunctivae (occasionally in facial skin)
Absence or degeneration of thymus.
Reduced T-cell response
Growth retardation
Premature ageing
Predisposition to lymphoid leukaemias and lymphomas
Acute sensitivity to ionising radiation

Table 1 – Some clinical characteristics of ataxia telangiectasia

Acute sensitivity to ionising radiation
Chromosome instability
Reduced inhibition of DNA replication after irradiation
Delayed increase in stability of p53 protein after irradiation
A greater G2 accumulation 24 hour post-irradiation
Altered incidence of apoptosis after irradiation
Increase in induction of specific chromosome aberrations by radiation
Defective recovery in delayed plating experiments (PLDR)
Reduced recovery capacity after low dose rate irradiation

Table 2 – Some reported features of cells from AT homozygotes

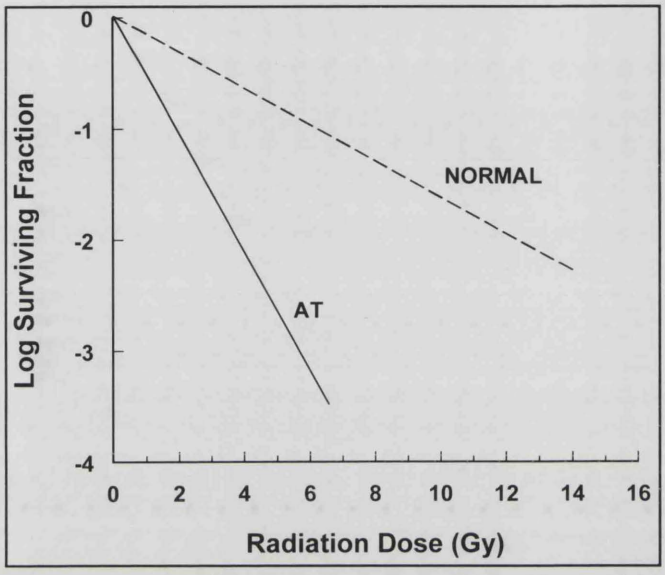

Fig. 1 – Cell survival after treatment with ionising radiation for fibroblasts taken from normal and ataxia telangiectasia individuals

A major breakthrough in the study of this disease came last year with the cloning of the gene mutated in AT sufferers[4]. This gene has been labelled the *ATM* gene (AT mutated). Although it is too early for the formal confirmation of the function of this gene, the comparison of the predicted amino acid sequence of the protein suggests that this molecule may have a widespread role in intra-cellular signalling. Similarities have been noted between the ATM protein and proteins involved in several signalling processes including some that control the cell cycle. In addition there is some similarity between the ATM protein and the catalytic sub-unit of the DNA-dependent protein kinase which is influential in the rejoining of DNA double-strand breaks[5] and this may be an important part of the link between DNA repair and this cancer-prone syndrome.

GERM LINE MUTATIONS IN THE TP53 GENE

The *TP53* gene encodes the p53 tumour suppresser protein that is frequently inactivated in many types of cancer. The p53 protein is an important part of the cellular response to DNA damage through its controlling action on cell cycle progression and apoptosis[6] although the data relating p53 status and sensitivity to carcinogenic agents is mixed. Some studies show that p53 does not influence cellular sensitivity to agents such as ionising radiation and cis-platinum[7] while others show that cells having no p53 function are resistant to these agents[8]. However, even if cells lacking functional p53 are not sensitive to the killing effects of these agents they do transform more readily in culture[9], suggesting that they may be more likely to undergo mutations in their genes.

Humans with germline mutations in the *TP53* gene include those with the rare Li-Fraumeni syndrome in which cancer incidence is >90% by the age of 50. The tumour types associated with this syndrome include sarcoma, germ cell tumours and melanoma[10] with breast cancer becoming important in those that survive the increased risks of childhood cancer. It has been demonstrated experimentally that mice that lack functional p53 also have an increased incidence of tumours[11] and, importantly, they are much more prone than normal mice to radiation-induced tumours[12].

INHERITED PREDISPOSITION TO COLON CANCER

Colorectal cancer is the third most common cause of death from cancer in the UK in both men and women and it has been estimated that 5-13% of cases may be associated with an inherited form, hereditary non polyposis colorectal cancer (HNPCC). A feature of tumours that arise within HNPCC is that they demonstrate instability in microsatellite regions of their DNA. In particular this is seen where there are repeats of specific di-nucleotides in the DNA sequence. Thus they appear to have an inability to replicate their DNA correctly or they cannot correct mistakes once they occur so they have been ascribed a replication error phenotype (RER). It is now known that most HNPCC is associated with mutations in the *hMLHl* and *hMSH2* genes[13] that are homologous to the *mutL* and *mutS* genes in bacteria. These bacterial genes are involved in the so-called mismatch repair system which corrects mismatches of bases in DNA[13]. Defects in this system result in an increased accumulation of mutations in bacteria, presenting a so-called "mutator" phenotype. Tumours arising within HNPCC have an associated high mutation rate in expressed genes[14] and it is suggested that tumour development is facilitated by an increased instability of oncogenes and tumour suppressor genes. As well as being important in correcting spontaneous errors in the DNA, the mismatch repair system is implicated in the repair of DNA damage caused by some cytotoxic agents although the impact of a defect in mismatch repair is such that cells have an increased tolerance to cytotoxic base analogues in their DNA[15].

It has been found that 0.5% of the population is heterozygous for mutations in the *MSH2* gene but no homoygotes have been identified. Somatic cells of HNPCC heteroygotes usually have normal mismatch repair in *in vitro* assays although there is one report of a HNPCC family where the heterozygotes have a mutator phenotype[16]. It therefore appears that the nature of the predispostion is likely to be predominantly one of a "two-hit" type, in which the inherited defect is a mutation in one allele which increases the likelihood of the appearance of cells with both alleles mutated or lost in order to form a tumour[13]. The relevance to this review is, therefore, that there is a DNA-processing defect in the tumours that arise in individuals with this cancer pre-disposition although it is not yet clear whether heterozygous carriers exhibit an altered susceptibility to external carcinogens.

THE G2 CHROMATID DAMAGE ASSAY. A GENERAL ASSAY OF CANCER PRONENESS?

An interesting and potentially important general relationship between predisposition to cancer and a reduced ability to repair ionising radiation-induced DNA damage is suggested

by a series of studies by Sanford and colleagues[17]. In an assay which measures the disappearance of DNA damage in the G2 phase of the cell cycle by assessing chromatid aberrations, they are able to distinguish many recognised cancer-predisposing syndromes including ataxia telangiectasia, xeroderma pigmentosum and Gardner's syndrome. Thus, even in syndromes where there is no other evidence for a sensitivity to ionising radiation this assay seems to detect a defect in DNA damage processing. This has obvious implications both in terms of mechanisms underlying carcinogenesis and in the possibility that it may form a useful general test of cancer predisposition. While the results published so far are impressive, this assay is proving difficult to translate into new laboratories and it requires further evaluation.

HOW WIDESPREAD IS THE RELATIONSHIP BETWEEN DAMAGE PROCESSING DEFECTS AND CANCER?

The rarity of the obvious repair-deficient syndromes means that they are not a major public health concem. However, lesser defects caused either by heterozygosity for mutations in the genes outlined above or in mutations in genes with less influence may be much more widespread and these have the potential to be more important in the general population.

Heterozygosity for mutations in the gene responsible for ataxia telangiectasia has received the most attention in this regard. There are data to suggest that AT heterozygotes have an increased incidence of breast cancer and various calculations suggest that between 1 and 15% of all women with breast cancer are AT heterozygotes[18]. It is known that AT heterozygotes can exhibit a cellular response to ionising radiation in some assays that is intermediate between normals and AT homozygotes. For example the rejoining of DNA double-strand breaks observed after low dose rate irradiation is reduced compared with normal cells[19]. In addition, Swift[20] has observed a relationship between diagnostic X-ray exposure and breast cancer in relatives of AT homozygotes. It is therefore possible that the inability to repair DNA damage fully is an important factor in the formation of some breast cancers.

Outside the recognised syndromes there is likely to be a wide range of deficiencies that could be associated with a reduced ability to limit DNA damage by carcinogens and hence lead to an increased likelihood of cancer. For example, Grossman and Wei[21] have used damaged foreign DNA to demonstrate a reduced DNA repair capacity in patients with basal cell carcinoma, although how this is reflected in the frequency of mutations induced by UV light is yet to be determined. Also, there is a relationship between a high risk of colon cancer and low intra cellular levels of glutathione S-transferases. This is a group of enzymes that facilitate the binding of some potential carcinogens to glutathione, a process that neutralises their carcinogenic activity[22,23]. As well as protective mechanisms there may also be activating mechanisms that are important in determining how an individual will be affected by some carcinogens. For example it has been reported that the cytochrome P450, CYP2D6, which activates carcinogens in tobacco smoke is an important link in the relationship between smoking and cancer such that increasing smoking increased lung cancer risk predominantly among those with the highest CYP2D6 activity[24].

HOW USEFUL IS THIS INFORMATION?

A relationship between DNA damage processing and cancer prediposition has obvious academic importance in that it will continue to help us to understand some fundamental biochemical pathways in the cell and how they relate to carcinogenesis. At a more practical level we may be able to use a measure of DNA damage processing capacity to identify cancer-prone individuals even in situations where the specific gene involved has not been identified. This is important at the level of the individual and at a more general level where such information may be vital in order to evaluate accurately the risks associated with exposure to specific carcinogens.

Any procedure that has the potential to screen for a cancer predisposition carries with it a number of psychological, legal and ethical problems that need to be carefully considered. The advantages of screening are clear in some cases. An individual may be able to take appropriate avoidance measures if there is an obvious susceptibility to a specific carcinogen (e.g. UV and skin cancers) or there may be more general protective precautions that can be taken. For example, Ambrosone *et al*[25] have demonstrated that vitamin supplementation might be more protective in women with a family history of breast cancer than in the general population. Beyond this, however, we need to consider the effect of knowledge of a predisposition to cancers which cannot be avoided and the insurance aspects of this may not be insignificant. Clearly there is a lot to be evaluated beyond the biology.

CONCLUSIONS

Although not always clearcut, it does seem that defects in the processes that maintain DNA integrity can lead to an increased susceptibility to some carcinogens and a cancer proneness. Individuals showing a marked sensitivity to DNA damaging agents, whether they have been exposed accidentally or intentionally as part of medical treatment, have a lot to teach us about carcinogen action and tumour progression. The study of such individuals will undoubtedly facilitate the advancement of our knowledge in this area of biomedical and clinical science.

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