INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal disorder characterized by hypersensitivity of the skin to sunlight specifically to ultraviolet (UV) which can lead to high rate of susceptibility to skin cancer and other kinds of neurodegenerative problems. Compared to normal individuals, XP patients have a more than 1000-fold increased risk of developing skin cancer on sun-exposed areas of their body. Genetic and molecular analyses have revealed that the repair of UV-induced DNA damage is impaired in XP patients owing to mutations in genes that form part of a DNA-repair pathway known as nucleotide excision repair (NER). XP is, therefore, regarded as a convincing human example of the link between DNA repair deficiency and cancer risk. However, this relationship has not been examined in detail in humans due to the limited number of XP patients and their frequent early death due to skin cancer and neurological problems. For these reasons are required the generation of equivalent animal models to determine their exact molecular mechanisms.

As described in other chapters, cell fusion studies have revealed that there are seven different genetic complementation groups in XP (denoted XPA through XPG) as well as an XP-variant form (XPV). A defect in one of the seven genes (XPA to XPG), involved in the NER pathway, can cause XP and the loss of function of the eighth gene, XPV, results in clinical XP phenotype, including predispositions to skin cancer. The recently developed technology of targeted gene replacement in mouse embryonic stem (ES) cells has provided investigators with the ability to generate mutant mouse strains defective in specific gene(s) of interest. To date, several such defective animals showing XP have been reported. These animal models exhibited characteristic features that mimic XP patients and provided a very useful experimental system for studying how DNA repair mechanisms affected tumourogenesis, development and ageing in humans.

XPA-DEFICIENT MOUSE MODELS

The XPA genetic group (defective in the XPA gene) comprises one of the largest groups among XP patients whose skin cancers are the most severe among all the known groups of XP. XPA gene encodes a protein involved in the initial damage-recognition stages of NER and the stabilization of the multiprotein repair complex assembled at DNA damage sites. Mice defective in the highly conserved Xpa gene (as well as a number of other XP mutant mice) have been generated by conventional gene targeting and have proven to be attractive models for human disease. In particular, exposure of the shaved dorsal skin of mice to UV light results in multiple skin lesions...
that typically progress to tumors. A wealth of information from several Xpa-deficient strains of mice is in agreement with the epidemiological data confirming that XPA results in a marked predisposition to cancer in the sun-exposed skin.\(^6\) The Xpa mutant mice of 8–10 wks were irradiated on the back with UV-B at a dose of 5 J/cm\(^2\) three times weekly for 10 wks (total dose: 150 J/cm\(^2\)). More than 30% of the irradiated mice developed tumors of melanocytic origin that metastasized to the lymph nodes. Histologically, the proliferated cells exhibited lentigo maligna melanoma or nodular melanoma. Immunohistochemistry confirmed that the tumor cells were characteristic of melanoma. Non-irradiated mice did not develop skin tumors spontaneously. This mouse model is useful for studying the photobiological aspects of human melanoma, since the mice developed melanoma from epidermal melanocytes only after UV exposure.\(^2\)

Xpa-deficient mice are also prone to spontaneous and carcinogen-induced tumorigenesis in their internal organs besides skin cancer. For example, Xpa mice appeared to develop internal tumors with a much higher frequency and shorter latency times than normal mice upon exposure to several different carcinogens. Treatment with benzo[\(\alpha\)]pyrene (B[\(\alpha\])P) by gavages resulted in an increased development of generalized T-cell lymphomas mainly occurring in the spleen, whereas exposure via the diet resulted in a higher incidence of forestomach tumors compared to their wild-type counterparts.\(^7\)\(^8\) These experimental data are in good agreement with the epidemiological data pointing to a 10-20-fold increase in the incidence of internal neoplasms in XP patients compared to normal individuals. The fact that sensitivity of Xpa mice to carcinogens is high, it suggests that this mouse model is an excellent candidate for carcinogenicity testing.

**XPC-Deficient Mouse Models**

The most common XPC form of XP in North America and Europe is that associated with the genetic group C.\(^10\) An Xpc mutant mouse was generated by replacing exon 10 of the Xpc gene with a PolII-NEO selection cassette.\(^11\) In order to assess if deletion of the Xpc gene results in an enhanced predisposition to UV radiation-induced skin cancer, Xpc\(\sim/-\) animals as well as Xpc\(+/-\) and Xpc\(+/+\) littermates were irradiated with a cumulative dose of \(\sim 140\) KJ/m\(^2\) of UV-B radiation over an 18-wk period. Xpc mutant mice were highly predisposed to UV-B radiation-induced skin cancer and all the Xpc\(\sim/-\) animals had developed skin tumors by 25 wks of irradiation while all control animals (Xpc\(+/-\) and Xpc\(+/+\)) were free of tumors.\(^12\)\(^13\) Longer periods of observation revealed that Xpc\(+/-\) animals were at increased risk of developing skin tumors after exposure to UV radiation. The latency time for the appearance of skin cancer was reduced in Xpc\(+/-\) compared with wild type littermates, with Xpc\(+/-\) animals manifesting a 50% skin cancer incidence by 50 wks after irradiation. This is considerably earlier than Xpc\(+/+\) mice, where the 50% skin cancer incidence reached only 90 wks after irradiation. The result that the Xpc heterozygous mutant state conferred an increased predisposition to UV-induced skin cancer has important implications for human health. The fact that no mutational inactivation of the remaining Xpc allele in tumors originating in heterozygous mutant animals has been observed, suggests that the increased predisposition associated with the heterozygous state is due to an allelic insufficiency, or haploinsufficiency. This could imply that humans carrying a heterozygous mutation in XP genes may be at increased risk to cancer associated with exposure of sunlight.

Further studies revealed that Xpc mutant mice are fertile and have no detectable developmental or neurological abnormalities.\(^15\) Prolonged observation has also failed to find any evidence of an enhanced predisposition to spontaneous internal cancers in this Xpc mutant animals older than 1.5 years. Anatomical analyses of mice of this age and older have revealed no other gross abnormalities.

In order to examine whether Xpc mutant mice are predisposed to cancers in other tissues associated with exposure to chemical carcinogens, animals such as, Xpc\(\sim/-\) and littermate controls were treated with 2-acetylamino-fluorene (2-AAF) or N-OH-AAF.\(^14\) The results show that Xpc\(\sim/-\) animals, irrespective of the Trp53 genotype, were more predisposed to 2-AAF- or N-OH-AAF-induced liver and lung tumors. Among Xpc\(\sim/-\) Trp53\(+/+\) animals, 67% of the mice manifested benign or malignant tumors in the lungs or liver at 15 months posttreatment.