TUMORIGENESIS

Rare and informative

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URLs

XPD
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=2068

XP
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=278730

CS
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=216400 TTD
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7269

An increased risk of cancer development is found in the rare syndrome xeroderma pigmentosum (XP), whereas the development of segmental progeria (aspects of accelerated ageing) is observed in Cockayne syndrome (CS) and trichothiodystrophy (TTD). Patients with these distinct syndromes all have defects in the nucleotide excision DNA repair pathway. Remarkably, in some instances mutations in the same gene can give rise to XP, CS or TTD. In exceptionally rare cases, patients present with both XP and CS or TTD symptoms, known as XPCS or XPTTD. Mouse models of XP, CS and TTD have provided useful insights into these diseases, so to investigate how patients can develop XPCS, Jan Hoeijmakers and colleagues used a mutation found in an XPCS patient — a single point mutation (G602D) in the *XPD* gene, the product of which forms part of the TFIIH DNA repair and transcription complex — to produce an XPCS mouse that has both an increased risk of tumour development and segmental progeria.

As in patients with XPCS, the expression level of the TFIIH complex was reduced by 50% in cells of the XPCS mouse compared with wild-type cells. As XP and CS patients are hypersensitive to UV-induced DNA damage, the authors examined the UV sensitivity of XPCS mice. UV hypersensitivity was seen after 1 week in XPCS mice exposed to an environmentally relevant dose of UV for 4 days. CS patients do not have an increased risk of skin tumour development despite hypersensitivity to UV radiation, but XP and XPCS patients do. To test for a predisposition to skin cancer, the XPCS mice were exposed to a daily low dose of UV, and the incidence of tumour development was compared with another cancer-prone XP mouse model — XPA mice that have no nucleotide excision repair function. After 17 weeks, all ten XPCS mice had skin or eye tumours compared with none of the XPA mice, indicating that the XPCS mutation produces a profound increase in the risk of UV-mediated tumour development, consistent with the development of a skin tumour in the original XPCS patient at 2.5 years of age.

Why are XPCS mice, which retain some nucleotide excision repair, more cancer prone than XPA mice that have no nucleotide excision repair function? The removal of a UV-induced DNA adduct involves an incision (cut) and patch of the DNA and removal of the lesion. Through a number of experiments the authors found that although cells from both XPA and XPCS mice lack the capacity to remove UV-induced DNA lesions, XPCS cells seem to have uncoupled cut and patch mechanisms that result in persistent DNA strand breaks owing to the lesion not being patched. The authors propose that it is this characteristic that further increases the risk of tumour development.

So, although syndromes such as TTD and CS are associated with accelerated ageing and no increase in cancer risk, the XPCS mouse model shows that these two processes are not always antagonistic and can coexist. This is crucially dependent on the specific mutation that has occurred and the processes that are consequently affected.

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ORIGINAL RESEARCH PAPER Andressoo, J.-O. *et al.* An Xpd mouse model for the combined xeroderma pigmentosum/Cockayne syndrome exhibiting both cancer predisposition and segmental progeria. *Cancer Cell* **10**, 121–132 (2006)