deficiencies by re-expressing Artemis in the patients' fibroblasts, indicating that this gene alone is responsible for the DNA-repair defects.

This is some of the first solid evidence that NHEJ mutations are lymphomagenic in humans. Only one NHEJ deficiency has been found in humans — a hypomorphic mutation in ligase IV, which is associated with leukaemia and radiosensitivity — and the *Artemis* study is the first report of a human cancer that is associated with V(D)J defects. The authors suggest that other ill-defined immunodeficiency conditions associated with lymphoma should be investigated for defects in NHEJ factors.

Kristine Novak

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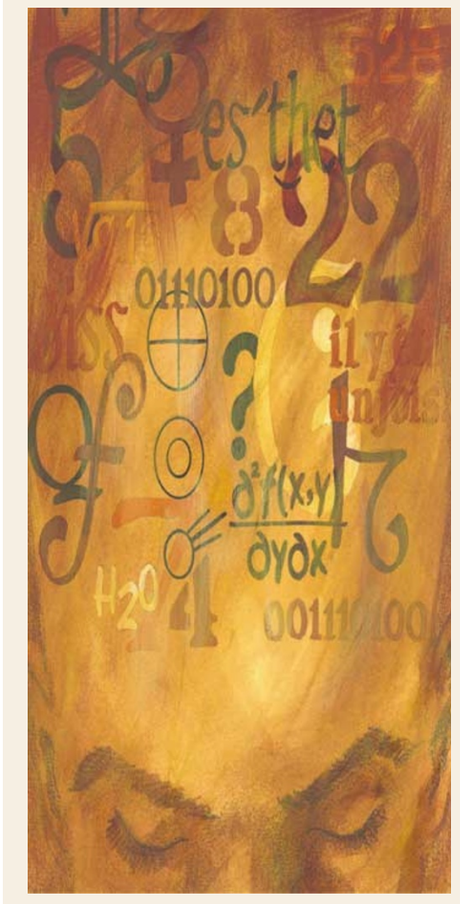

MELANOMA

Sunburn effects dissected

Being sunburnt as a child is known to increase the risk of developing melanoma in later life, but what is happening at the molecular level to initiate tumour formation? Lynda Chin and colleagues now report in the *Proceedings of the National Academy of Sciences* that components of the retinoblastoma (RB) pathway are important targets of ultraviolet (UV)-light-induced mutagenesis.

To study the molecular impact of UV-light exposure, the authors used mouse models of melanoma that were driven by an activated *Hras* transgene (*Tyr-Ras*) and loss of the tumour suppressors Arf or Ink4a (both of which are encoded by *Cdkn2a*). ARF acts to stablize p53 and the cyclin-dependent kinase (CDK) inhibitor INK4A prevents CDK4/6-dependent phosphorylation of RB, so both lead to inhibition of cell-cycle progression. INK4A has been implicated in UV-light-induced mutagenesis because UV-light signature mutations of the gene have been found in human melanoma, although the occurrence of similar mutations in non-UV-light-induced cancers has raised questions regarding this connection.

Tyr-Ras Arf$^{-/-}$ mice that were treated with UV light developed more melanomas earlier than the transgenic animals that were not exposed to UV, although these mice did develop some tumours spontaneously. Having shown that UV light cooperates with HRAS and ARF to form tumours, the authors studied the effects of UV light on the INK4A–RB axis in this model. Functional loss of Ink4a was identified in 22% of tumours that arose in UV-light-treated *Tyr-Ras Arf*$^{-/-}$ mice — which is less than the 50% observed in mice not exposed to UV light. Instead, amplification and overexpression of *Cdk6* was seen in 46% of UV-light-treated mice and in none of the non-UV-light-treated mice. Alteration of *Cdk6* was not seen in the tumours with functional loss of Ink4a and vice versa — which is consistent with the fact that both genes cause the same phenotype. Loss of Rb itself was not seen in any tumour.

In contrast to ARF, the authors observed that loss of INK4A does not cooperate with UV light to accelerate melanoma development in *Tyr-Ras Ink4a*$^{-/-}$ mice. This was a surprising finding given the widely held assumption that UV light has a broad mutagenic action. Instead, this result indicated that UV light exclusively targets the RB pathway for inactivation. So, the authors hypothesize that UV-light exposure increases melanoma risk by inactivating the RB pathway — either by means of Ink4a loss or Cdk6 amplification.

Results of this study indicate that analysis of INK4A, CDK6 and other RB-pathway components in people with a history of sunburn might be useful for the early detection of individuals who have a particularly high risk of developing melanoma. As there are no effective therapies for advanced melanoma, catching these cancers at an early stage would represent an important clinical advance.

Ezzie Hutchinson

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WEB SITE

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