not occur in cells expressing tagged Artemis cDNA that were treated with an ATM inhibitor — strong evidence for a role of ATM in this process.

The authors formulated an intriguing model for biphasic rejoining of DSBs in which ATM hyperphosphorylates Artemis, activating its nuclease and end-processing abilities. Other proteins — such as 53BP1, H2AX, Nbs1 and Mre11 — might provide a scaffold that keeps Artemis at the DSB site and/or activate ATM.

Regardless of how accurate this model proves to be, the identification of Artemis as a downstream component of the ATM signalling pathway has gone a long way towards explaining AT radiosensitivity.

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NPG Executive Editor,
European Journal of Human Genetics

🌐 **References and links**
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CANCER GENETICS

Tumour suppressor super models

The tumour suppressor p53 binds DNA and activates transcription to control the cell cycle and apoptosis, and is mutated in over 50% of human cancers. Mutations in *TP53* also cause Li–Fraumeni syndrome, which predisposes patients to a broad spectrum of malignancies, particularly sarcomas and carcinomas. However, the range of tumours seen in Li–Fraumeni syndrome and spontaneous cancers cannot be explained simply by a loss of wild-type p53; for example, mice that lack p53 develop lymphomas and sarcomas but not carcinomas, and these tumours tend not to metastasize. Furthermore, p53 is an unusual tumour suppressor because it is commonly altered through missense mutation rather than deletion. Now, two research groups have generated mouse models that closely resemble Li–Fraumeni syndrome and have used these models to investigate why the *TP53* mutations seen in human cancers are so oncogenic.

Kenneth Olive and co-workers produced mice with missense point mutations in two of the most commonly mutated p53 codons in human cancer: $Trp53^{R172H}$ affects the overall structure of the p53 DNA-binding domain, and $Trp53^{R270H}$ affects a residue that makes direct contact with DNA. Although $Trp53^{R270H/-}$ and $Trp53^{R172H/-}$ mice developed distinct tumour spectra, both developed different tumour phenotypes compared with $Trp53^{-/-}$ mice, indicating that missense *Trp53* mutants have pro-tumorigenic or oncogenic functions that cannot be explained simply by the loss of wild-type p53. In particular, strains carrying these two mutant alleles developed metastatic carcinomas and are therefore more accurate models of Li–Fraumeni syndrome.

The possibility that mice carrying *Trp53* missense mutations could be used as models of Li–Fraumeni syndrome was further supported by work carried out by Gene Lang and colleagues, who also generated mice that possessed the $Trp53^{R172H}$ structural mutation (which they refer to as $Trp53^{515A}$). However, the results from the two laboratories show that the same *Trp53* mutation causes different tumour spectra in different mouse strains; whereas Olive and co-workers found that $Trp53^{R172H/+}$ mice developed more carcinomas than $Trp53^{+/-}$ mice, Lang *et al.* show that $Trp53^{R172H/+}$ mice developed metastatic tumours.

Lang and colleagues also found that $Trp53^{R172H/R172H}$ and $Trp53^{R172H/+}$ mouse embryonic fibroblasts grow faster, have more DNA synthesis and have greater transformation potential than $Trp53^{+/+}$, $Trp53^{+/-}$ or $Trp53^{-/-}$ cells, supporting the idea that p53 mutant proteins function differently to wild-type p53. So, how do missense mutant p53 proteins exert their oncogenic effects?

p53 interacts with its family members p63 and p73, which themselves activate several p53 target genes in response to DNA damage. Both groups found evidence that $p53^{R172H}$ interacts with and inhibits endogenous p63 and p73 in cell lines that are derived from mouse tumours expressing this protein. Lang and colleagues also found that the disruption of p63 and p73 causes increased transformation of $Trp53^{-/-}$ cells and augments DNA synthesis to levels seen in $Trp53^{R172H/R172H}$ cells. The researchers conclude that the ability of mutant p53 to bind and inhibit p63 and p73 could explain why mutant p53 is more detrimental than the lack of p53, and why *TP53* missense mutations — rather than deletions of *TP53* — are so commonly found in human tumours.

Jenny Bangham

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