TELOMERES

Fusing breaks

Telomeres protect chromosome ends from fusion, and loss of telomeres can lead to genomic instability and tumour formation. However, telomere loss can also cause apoptosis. Carol Greider and colleagues now show that short telomeres can inhibit tumorigenesis by fusing to DNA double-strand breaks, preventing oncogenic chromosome translocations.

The authors studied a mouse model that was null for both ataxia-telangiectasia mutated (*Atm*) — which is involved in signalling the presence of DNA double-strand breaks and has a role in telomere maintenance — and telomerase RNA (*mTR*) — which maintains functional telomere length. $Atm^{-/-}mTR^{+/+}$ mice frequently have unrepaired breaks near the T-cell-receptor loci, and consequently develop thymic lymphoma. Late-generation $Atm^{-/-}mTR^{-/-}$ mice have short telomeres and survive longer than $Atm^{-/-}mTR^{+/+}$ mice because of an increase in apoptosis and a decrease in thymic lymphoma. But what happens in early generation $Atm^{-/-}mTR^{-/-}$ mice, in which short telomeres are not yet causing apoptosis, but DNA double-strand breaks are accumulating?

To the authors surprise, first generation $Atm^{-/-}mTR^{-/-}$ mice also had increased survival compared with $Atm^{-/-}mTR^{+/+}$ mice, and they found that the mice developed fewer thymic lymphomas than expected. The authors ruled out increased apoptosis, decreased cell growth or proliferation as mechanisms for decreased tumour formation, suggesting that the phenotype was due to decreased tumour initiation, not decreased tumour growth. Telomere length decreased and the number of telomere-signal-free ends of chromosomes — which signify increasing genomic instability — increased in subsequent generations of $Atm^{-/-}mTR^{-/-}$ mice. The total number of chromosome translocations was similar in $Atm^{-/-}mTR^{+/+}$ and $Atm^{-/-}mTR^{-/-}$ mice, but 15–25% of chromosomes in the tumours of $Atm^{-/-}mTR^{-/-}$ mice had internal telomere signals at translocation junctions. The defining factor was that the number of translocation events involving the T-cell-receptor loci were higher in first-generation $Atm^{-/-}mTR^{-/-}$ mice, and many of these translocations contained telomeres at the translocation junctions.

So in this model, short dysfunctional telomeres readily fuse with DNA breaks, and this fusion competes with the formation of oncogenic translocations, and therefore decreases tumour initiation. In later generations, the higher rate of telomere dysfunction and increased genomic instability overrides the protective effect of telomere fusion to translocation sites. These findings might be particularly relevant in the development of human tumours in which a lack of DNA-repair pathways have a role.

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References and links

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FURTHER READING Feldser, D. M., Hackett, J. A. & Greider, C. W. Telomere dysfunction and the initiation of genome instability. *Nature Rev. Cancer* **3**, 623–627 (2003)

WEB SITE

Carol Greider's lab: http://www.mbg.jhmi.edu/FacultyDetails.asp?PersonID=367

TUMORIGENESIS

Stability check

The nucleolar protein nucleophosmin (NPM) is mutated or translocated in several human haematological malignancies including myelodysplastic syndrome (MDS). By studying the role of NPM in mice, Pier Paolo Pandolfi and colleagues have shown that it is essential for mouse embryogenesis and that it might also have a role in the pathogenesis of human MDS.

Knocking out *Npm1* was lethal at around embryonic day 12. Studies revealed that this was at least partly caused by NPM being required for successful forebrain and haematopoetic development. The initiation of apoptosis — which was attributed to centrosome abnormalities — and ribosome-biogenesis defects in $Npm1^{-/-}$ tissues was accompanied by a marked upregulation of p53 that probably contributed to this phenotype.

On a cellular level, NPM was shown to be crucial for maintaining genomic stability, as $Npm1^{-/-}$ cells underwent a p53-mediated cell-cycle arrest caused by tetraploidy, as well as a significant degree of centrosome amplification and defects in the mitotic spindle. Furthermore, *Npm1* gene dosage is important for this function, as similar genomic defects were seen in $Npm1^{+/-}$ cells, and resulted in those cells being more susceptible to oncogenic transformation both *in vitro* and *in vivo*. The authors therefore suggest that the genetic instability that is caused by NPM deficiency — leading to unrestrained centrosome duplication and consequent aneuploidy — could contribute to tumorigenesis. This is particularly significant as $Npm1^{+/-}$ cells reflect the situation that occurs in human cancers in which the *NPM1* locus is translocated or deleted.

Because NPM was shown to be haploinsufficient, the authors wanted to find out if haematopoiesis was affected in $Npm1^{+/-}$ mice. Indeed, analysis of the blood and bone marrow of these mice revealed several dysplastic features that were reminiscent of the pathogenesis of human MDS. As the *NPM1* locus on chromosome 5 is subject to structural aberrations in patients with MDS, the authors propose that NPM dysfunction might be a participating factor in the pathogenesis of this multigenic disease.

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References and links

ORIGINAL RESEARCH PAPER Grisendi, S. *et al*. Role of nucleophosmin in embryonic development and tumorigenesis. *Nature* 6 July 2005 (doi:10.1038/nature03915)

WEBSITES

Pier Paolo Pandolfi's laboratory: http://www.mskcc.org/mskcc/html/10345.cfm

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