have been known to transcribe in an unregulated way in yeast; if the same is true in *Tetrahymena* then their transcription betrays their existence to the genome surveillance machinery.

Herein lies the next big question, for we still do not know the mechanism that underlies the deletion itself. Based on their data and previous observations, the authors propose that the dsRNA marks the DNA to be removed in a way that is similar to that in which RNA contributes to heterochromatin formation in fission yeast and plants, and to DNA methylation in plants. By extension, they suggest that RISC-like complex might mediate deletions, although a more prosaic culprit such as a non-specific endonuclease or a recombinase cannot be ruled out at present.

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References and links

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D. simulans were the result of positive natural selection.

Together with an earlier study by Barbash *et al.*, this is one of the first analyses to pinpoint the identity of a gene that is involved in reproductive incompatibility between closely related species. It will be exciting to identify the gene or genes on the X chromosome with which *Nup96* interacts to cause male lethality, and to elucidate the molecular cause of the incompatibility between the two. It will also be interesting to see whether the strong evidence presented in this study that natural selection is involved in the genetic changes that contribute to speciation will be mirrored in other studies as more genes that are associated with hybrid inviability are identified.

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CANCER GENETICS

Who's doing the dirty work for MYC?

MYC, a basic helix-loop-helix leucine-zipper transcription factor, has to be one of the most famous oncoproteins. Among its targets are a wide range of genes that coordinate cell-cycle progression and cell growth, which sensitize the cell to apoptotic stimuli. But MYC might also promote tumorigenesis by activating the expression of genes that are involved in cellular immortalization or escape from senescence. Gandori and colleagues now show that the human Werner syndrome gene, *WRN*, is a direct target of MYC, and that MYC-driven *WRN* upregulation prevents cellular senescence and consequently leads to tumorigenesis.

Werner syndrome — a rare disorder associated with premature ageing, genomic instability and increased risk of malignancy — is caused by a loss-of-function mutation in *WRN*, which encodes a RecQ helicase implicated in mitotic recombination and repair. Also, *WRN* overexpression is seen in immortalized cell lines and might actually aid sustained proliferation. So, Gandori *et al.* wondered whether *WRN* could be a direct target of MYC.

The first clue came from expression studies — in different cell types and under different conditions, expression of the two genes was coordinated (if one went up, so did the other). Importantly, there was a short time lag between the induction of *C-MYC* and *WRN* transcription. The next clue came when Gandori and colleagues found several non-canonical MYC–MAX (MYC binds DNA as a heterodimer) binding sites in the *WRN* promoter, and *in vitro* and *in vivo* experiments showed that purified MYC–MAX complex binds to these sites.

So, MYC directly regulates *WRN* expression, but does overexpressing MYC affect the proliferation and survival of cells that lack *WRN*? To address this question, Gandori *et al.* compared

C-MYC overexpression in normal human fibroblasts with those from Werner syndrome patients. The result was clear — *C-MYC* overexpression induced senescence in 30–70% of *WRN*^{−/−} fibroblasts, whereas only ~1% of wild-type fibroblasts underwent senescence, indicating that *WRN* counteracts senescence induced by high levels of MYC. Taking a closer look at the cell cycle, the expression of cell-cycle regulatory proteins and apoptotic response in these two cell lines showed that whereas all cell types had characteristics of MYC oncogenic stimulation, cellular events that accompanied cell-cycle arrest and senescence response were limited to *WRN*^{−/−} cells.

The final evidence nailing *WRN* as the culprit came when the authors used RNA interference to remove it from normal fibroblasts in which *C-MYC* was overexpressed. Fibroblasts in which *WRN* had been knocked down proliferated poorly, and high levels of MYC not only failed to rescue this phenotype but exacerbated it.

So, Gandori *et al.* propose a model in which MYC overexpression promotes cell growth and proliferation, as well as genomic instability, which is counteracted by *WRN* — its role in DNA recombination and repair ensures cell survival (not a desirable outcome when non-*WRN*-dependent effects of MYC induce uncontrolled proliferation). In the absence of *WRN*, genetic instability increases and cell survival is compromised.

As well as adding to our knowledge of genome maintenance and cell proliferation, these findings have important implications for cancer studies. Without *WRN*, cells senesce more readily, so it is little wonder that Werner syndrome patients rarely suffer from certain types of cancer that are associated with MYC overexpression. Importantly, this study also points to a new opportunity for the treatment of human tumours that arise as a result of MYC overexpression.

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