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GENOME INSTABILITY

A robust model of fragile sites?

Genome instability frequently leads to cell death or increased incidence of cancer. At the molecular level, it is caused by chromosomal breakage at so-called fragile sites, followed by deletions, duplications and translocations, although what makes these sites prone to breakage remains unclear. In a recent study, Petes and colleagues use a *Saccharomyces cerevisiae* system to obtain molecular insights into chromosomal translocations, and show that this could provide a useful model to understand fragile sites.

Although not much is known about fragile sites, we know that the cell finds it difficult to replicate them. Further–more, chromosome breaks are found in conditions in which DNA replication is inhibited or delayed. To model the effects of inefficient replication in yeast, Petes and colleagues created a strain (GAL–POL1) in which the catalytic subunit of DNA polymerase-α was expressed from the galactose promoter, which reduced its levels to 10% of the wild type. The strain's increased sensitivity to DNA-damaging agents implied genetic instability.

To confirm that chromosomal loss and/or rearrangements occurred in this strain, the authors used the 'illegitimate mating test'. The mating type locus (*MAT*) on chromosome III ensures that wild-type cells only mate with cells of the opposite mating type. By contrast, GAL–POL1 cells mated illegitimately, and Petes and colleagues showed that this 'promiscuity' was due to inactivation of the *MAT* locus. By mating their strain with strains that carried markers on chromosome III, they showed that this inactivation was most frequently caused by an extensive deletion or complete loss of chromosome III.

Four illegitimate diploid strains were chosen for characterization so that the nature of the chromosomal rearrangements could be defined. Microarray analysis identified two sites at which chromosome III breaks occurred. Southern blot analysis and PCR showed that Ty transposable elements were present in the vicinity of these 'fragile sites'. In all types of rearrangements seen, Ty elements at fragile sites were the preferred sites for DNA breaks — altering one of the fragile sites reduced the frequency of illegitimate mating, a read-out for the level of genetic instability in these strains.

The authors put forward two main explanations for what happens at fragile sites. Low levels of DNA polymerase might result in accumulation of a single-stranded region on the lagging strand that could snap into a hairpin structure. In the process of its resolution, double-strand breaks could occur. Alternatively, one of the fragile sites that contain inverted Ty elements could form a hairpin itself. Its resolution could either induce double-strand breaks as above, or lead to the formation of a palindromic chromosome.

Although there are important differences between yeast and mammalian fragile sites, such as their size, there are encouraging similarities. For example, they are all associated with slow or late replication, and several mammalian fragile sites can form hairpin-like secondary structures. Can we count on yeast to help us solve the long-standing mystery of mitotic recombination that results in genomic instability?

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References and links

ORIGINAL RESEARCH PAPER Lemoine, F. J. & Degtyareva, N. P. *et al.* Chromosomal translocations in yeast induced by low levels of DNA polymerase: a model for chromosome fragile sites. *Cell* **120**, 587–598 (2005)