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GENOMIC INSTABILITY

Aneuploidy stokes the fire

Whole-chromosome aneuploidy — that is, irregular numbers of individual chromosomes — is frequently observed in tumours. There is considerable debate about whether aneuploidy is a cause or merely a consequence of the interlinked phenomena of genomic instability and tumorigenesis; however, two new reports provide further evidence for a causal role for aneuploidy in both.

To determine the effect of aneuploidy on genomic stability, Sheltzer *et al.* analysed 13 haploid *Saccharomyces cerevisiae* strains that each carried an additional copy of a different chromosome. These aneuploid strains were known to have proliferative defects compared with wild-type strains, but the authors found that most aneuploid strains are also impaired in the faithful segregation of chromosomes into daughter cells. However, the genomic instability in these aneuploid cells was not only at the level of whole chromosomes. The mutation rate of specific genes (*URA3* and *CAN1*) was increased in some aneuploid lines, as shown by resistance to drugs that require the wild-type products of these genes for cytotoxicity.

What causes the increased mutation rate of these aneuploid cells? The authors found that they show increased sensitivity to multiple DNA damaging agents and also that both the resulting DNA damage and Rad52-containing DNA repair foci persist in cells. These features indicate that a defect in homologous recombination-based DNA repair might contribute to the increased rate of mutation. Indeed, DNA sequencing revealed that the focal mutations are likely to be caused by the error-prone DNA polymerase Pol ζ, which is used in a back-up repair mechanism in the absence of homologous recombination.

Why should extra copies of different chromosomes encoding different genes have such a consistent phenotypic effect? Interestingly, the addition of a chromosome consisting of unexpressed human DNA to wild-type strains did not recapitulate the effects of extra yeast chromosomes. So, although further evidence is needed, it seems that stoichiometric protein imbalances cause the cellular effects of aneuploidy, rather than merely the presence of an extra chromosome to be replicated. Consistent with this model, the detrimental effects of extra chromosomes were buffered in aneuploid diploid versus aneuploid haploid yeast cells.

In a separate study, Solomon *et al.* searched for recurrent mutations in human cancer to identify causal driving events in tumorigenesis. Using various DNA sequencing and protein expression analyses, they found somatic inactivating mutations and loss of expression of stromal antigen 2 (*STAG2*) in a subset of human tumours and cell lines. These included ~20% of glioblastomas, Ewing's sarcomas and melanomas. *STAG2* encodes a cohesin subunit that is required for sister chromatid cohesion, and engineered mutation or correction of *STAG2* alleles *in vitro* demonstrated that *STAG2* inactivation results in aneuploidy. This study adds to our growing appreciation of the role of chromosome segregation genes in aneuploidy and tumorigenesis, although a driving role for *STAG2* inactivation in cancer is yet to be verified using *in vivo* mouse models. It will also be interesting to investigate the effects of *STAG2* reactivation on the tumorigenesis of aneuploid cells.

Both reports are consistent with an emerging theme: despite aneuploidy generally being detrimental to cells, the resultant genetic heterogeneity in a cell population might provide an advantage for a subset of these cells to survive and thrive under strong selective pressures, such as those that occur during tumorigenesis.

Darren J. Burgess

ORIGINAL RESEARCH PAPERS
Sheltzer, J. M. *et al.* Aneuploidy drives genomic instability in yeast. *Science* **333**, 1026–1030 (2011) | Solomon, D. A. *et al.* Mutational inactivation of *STAG2* causes aneuploidy in human cancer. *Science* **333**, 1039–1043 (2011)

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