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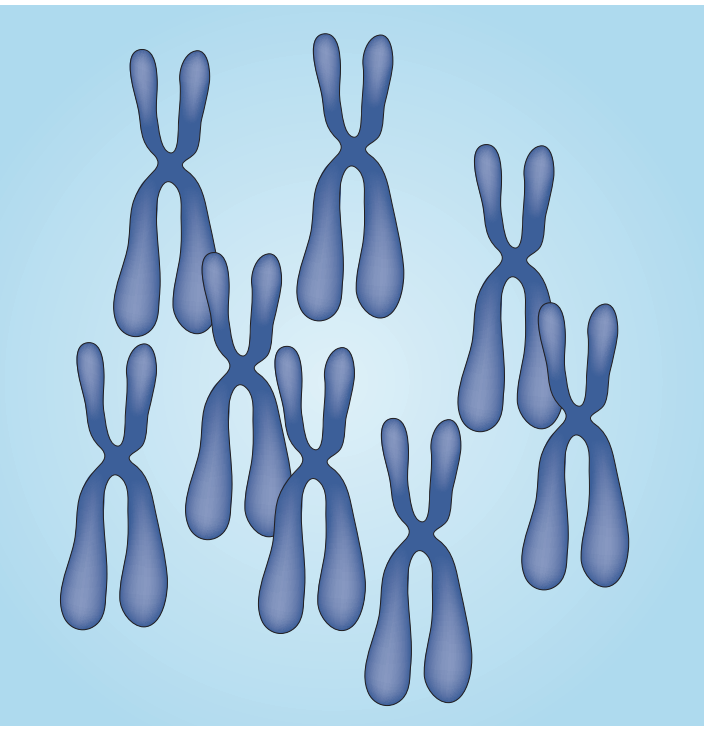
CHROMOSOMAL INSTABILITY

Coping with extra copies

> aneuploid cells have an increased dependence on the ubiquitin–proteasome pathway



Aneuploidy — an abnormal number of chromosomes — has severe consequences for an organism and is associated with developmental abnormalities and cell death. Despite these disadvantages, cancer cells are frequently aneuploid and have a high proliferative capacity, suggesting that they implement mechanisms to allow them to survive the aneuploid state. New insights into this phenomenon have been provided by a recent yeast screen that has identified novel aneuploidy-tolerating mutations.

Eduardo Torres and colleagues had previously generated budding yeast strains, each of which contained at least one extra copy of each of the yeast chromosomes (known as disomic strains). Using this panel, they found that evolved disomic strains with increased proliferation rates showed a range of genomic alterations, including point mutations, truncations, amplifications and whole-genome duplications, suggesting that the presence of extra chromosomes leads to substantial genomic changes.

Could some of these genomic changes allow yeast cells to tolerate aneuploidy? The authors selected 14 evolved disomic strains that showed decreased cell doubling times compared with their parental strains and identified 43 non-synonymous and four synonymous single nucleotide polymorphisms (SNPs) in these strains. They found little overlap in the SNPs between strains derived from the same parent, indicating that, in general, different genetic alterations lead to improved proliferation in the presence of aneuploidy. The authors identified mutations in genes involved in chromatin remodelling, stress responses, protein folding and ribosomal RNA processing, providing clues about the cellular processes that could allow aneuploidy tolerance. Intriguingly, many of the implicated genes have human homologues that are upregulated in tumours. However, Torres *et al.* did find mutations in two genes (encoding the vacuolar targeting factor Vps64 and the deubiquitylating enzyme Ubp6) that were shared between descendants of different disomic strains, suggesting that common mutations might exist that improve the proliferation of disomic strains containing different chromosome complements.

The authors then sought to characterize the mechanism by which mutations in *UBP6* contribute to the tolerance of aneuploidy. Mutation of the catalytic residue of Ubp6 led to increased proliferation of disomic strains, indicating that the deubiquitylating activity of Ubp6, which antagonizes the proteasome, normally inhibits proliferation in the aneuploid state. Moreover, when the authors examined the protein composition of disomic strains with or without *UBP6* deletions, they found that *UBP6* deletion reverted the changes in protein composition in disomic strains to a state similar to that in wild-type cells. Together, these results suggest that increased proteasomal activity contributes to the fitness of disomic strains. This is consistent with earlier observations that aneuploid yeast strains show increased sensitivity to compounds that affect protein folding and degradation, suggesting that cells may use these pathways to try to correct the protein imbalances caused by aneuploidy. The insight that aneuploid cells have an increased dependence on the ubiquitin–proteasome pathway could allow the development of novel cancer therapies and could also justify the use of clinically approved proteasomal inhibitors to treat aneuploid tumours.

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ORIGINAL RESEARCH PAPER Torres, E. M. *et al.* Identification of aneuploidy-tolerating mutations. *Cell* **143**, 1–13 (2010)
FURTHER READING Schvartzman, J.-M. *et al.* Mitotic chromosomal instability and cancer: mouse modelling of the human disease. *Nature Rev. Cancer* **10**, 102–115 (2010)