THERAPY

# Trimming the excess

Like seasoned travellers, cells do their best to avoid excess baggage, such as supernumerary chromosomes. But it is not easy being aneuploid: most cells collapse under the pressure of carrying an abnormal chromosome number. However, tumour cells seem to thrive under these conditions, as they almost always harbour chromosome aberrations. In a recent study, a team led by Angelika Amon asked whether this hallmark might represent an exploitable vulnerability.

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Amon's team generated mouse embryonic fibroblasts (MEFs) that were trisomic for chromosomes 1, 13, 16 or 19 using animals carrying Robertsonian fusion chromosomes. Next, the group treated these cells with an array of cytotoxic compounds in an effort to identify drugs that impaired proliferation in aneuploid, but not wild-type, MEFs. In total, three compounds were isolated: the energy stress inducer 5-aminoimidazole-4-carboxamide riboside (AICAR), the Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) and the autophagy inhibitor chloroquine. All three drugs induced apoptosis in trisomy cells at doses that left wild-type MEFs unharmed; so why were the aneuploid cells so sensitive?

Cells with an additional chromosome load use protein degradation and folding pathways to resolve the protein imbalance that is caused by their extra chromosomes. This stress response in turn places additional energy demands on the cell. The authors hypothesized that their drugs were exacerbating the level of stress, and by comparing stress levels in trisomy and wild-type cells they found significantly higher basal levels of the autophagy mediators LC3 and BNIP3 in trisomy MEFs, and these levels were increased on treatment with AICAR. Furthermore, they noted a positive correlation between sensitivity to AICAR or 17-AAG and the size of the additional chromosomal load. So, the greater the protein overload, the more sensitive a cell is to these drugs. Taken together, these data suggest that the capacity of a drug to selectively kill aneuploid cells relies on its ability to raise stress levels above a certain threshold.

Were the compounds also effective against human tumour cells with severe karyotypic abnormalities? Amon's group found that both AICAR and 17-AAG were more effective in colorectal cancer cells with pronounced chromosomal defects than in those with relatively mild abnormalities. They also reported that the combined use of both drugs had an even more significant effect and that killing occurred regardless of p53 status, indicating that a combination of AICAR and 17-AAG might be effective against a broad range of cancer types. Further studies will of course be required to confirm that this is the case, but for now, the identification of aneuploidy-selective drugs represents an exciting new frontier in cancer therapeutics.

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