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Journal club

TETRAPLOID CANCER CELL PRECURSORS

As part of their pathology course, each medical student recapitulates a basic discovery first described by Bovari around 1900. As the student stares down the microscope to discriminate between normal cells and cancer cells on a histological slide, she or he will find that cancer cells exhibit heterogeneous size (anisocytosis) and heterogeneous chromatin content (anisokaryosis), as well as abnormal, multipolar and asymmetric mitoses.

The underlying biology of this manifestation of malignant transformation has been solved over the past few years and is referred to as the 'diploid to tetraploid to aneuploid sequence'. Normal cells (which are diploid) can form tetraploid cancer cell precursors. Tetraploids then become aneuploid, through either progressive chromosomal loss or multipolar mitoses in which chromosomes are randomly distributed among more than two daughter cells.

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Accumulating, and increasingly fascinating, evidence indicates that there are several ways by which the first step of this cytological cascade — tetraploidization — can occur. Tetraploid cells contain twice the normal amount of chromosomes; a result that can arise from failed mitosis. Fujiwara *et al.* and Gascoigne and Taylor showed that tetraploid cells arise when mitosis does not lead to nuclear and cellular separation (endomitosis) as a result of misaligned, lagging chromosomes and microtubule inhibitors, respectively. Davoli *et al.* observed that cells undergo two subsequent rounds of DNA replication (endoreplication), thereby becoming tetraploid, in response to persistent telomere damage.

So, what is known mechanistically about the formation of tetraploid cells? In all of the cases described here, tetraploidization occurs through a process that is inducer- and cell type-dependent, dynamically regulated and under the control of one of the main tumour suppressor proteins, p53. Only in conditions in which p53 is inactivated and/or the apoptotic programme (which usually aborts tetraploid cells) is inactivated, can tetraploid cells be generated.

The challenge for the future is to discover strategies that preferentially kill tetraploid cells (but do no harm to their normal, diploid counterparts) or that avoid the transition from tetraploidy to aneuploidy.

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ORIGINAL RESEARCH PAPERS Fujiwara, T. *et al.* Cytokinesis failure generating tetraploids promotes tumorigenesis in p53-null cells. *Nature* **437**, 1043–1047 (2005) | Gascoigne, K. E. & Taylor, S. S. Cancer cells display profound intra- and interline variation following prolonged exposure to antimitotic drugs. *Cancer Cell* **14**, 111–122 (2008) | Davoli, T., Denchi, E.L. & de Lange, T. Persistent telomere damage induces bypass of mitosis and tetraploidy. *Cell* **141**, 81–93 (2010)