Journal club

A FOUR-LANE HIGHWAY TO CANCER

Aneuploidy — a cellular state characterized by the gain or loss of entire chromosomes or large chromosomal fragments — is commonly found in biopsies from a wide range of solid tumours. Moreover, the degree of aneuploidy in malignant cells is linked to key clinico-pathological features, including genomic instability, propensity to metastatic dissemination and patient survival (Ganem *et al.*). During the past decade, several laboratories worldwide — including ours — have intensively investigated the molecular mechanisms through which cancer cells acquire gross chromosomal alterations, and how these abnormalities can be tolerated (which does not occur in normal, non-transformed cells) (Castedo *et al.*).

One paper published a few years ago in *Nature Genetics* (Zack *et al.*) studied somatic copy number alterations in 4,934 cancers from

“ a frequent mechanism through which transformed cells become aneuploid ... may involve whole-genome duplication ”

The Cancer Genome Atlas Pan-Cancer data set. This was the first attempt to investigate aneuploidy in a systematic manner across such a large number of clinical samples, and it culminated in the discovery of recurrent patterns of alterations in somatic copy number. Perhaps the most surprising finding of this work, however, was that whole-genome duplication (tetraploidization) was detected in as many as 37% of cancer specimens analysed. Notably, whole-genome duplication correlated with particularly high rates of other somatic copy number alterations, as well as with several unrelated oncogenic events (such as mutations in tumour protein p53 (*TP53*)) (Zack *et al.*).

This result suggests that a frequent mechanism through which transformed cells become aneuploid and form aggressive tumours may involve whole-genome duplication, followed by imperfect de-duplication events (Santaguida *et al.*) — a hypothesis that had been put forward earlier but received limited attention so far (Vitale *et al.*). The fact that tetraploid cancer cells are subjected

to natural immunosurveillance (and hence do not go unrecognized by the immune system as their aneuploid counterparts do) lends further support to this possibility (Senovilla *et al.*). Thus, it seems that (at least at the beginning of its course) the road leading to cancer via aneuploidy often has four, not just two, lanes.

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