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editorial

A balancing act: focus on aneuploidy

Faithful chromosome segregation is crucial for the viability of cells and organisms, as evidenced by the fact that in humans only one autosomic trisomy—and no autosomic monosomies—allow survival into adulthood. Cells therefore use sophisticated mechanisms to ensure that each daughter receives an intact copy of the genome during cell division. Eukaryotic chromosomes have a specialized region known as the centromere, which recruits a complex proteinaceus structure—the kinetochore—that binds spindle microtubules to enable the separation of chromosomes during mitosis. The mitotic checkpoint and the machinery that controls kinetochore–microtubule attachment ensure correct chromosome segregation. However, several processes can lead to aneuploidy—the deviation from a haploid chromosomal number—such as defects in mitotic checkpoint proteins or sister chromatid cohesion, incorrect or hyperstabilized chromosome-spindle attachments, centrosome amplification or defects in cytokinesis.

Aneuploidy is a major health concern. It is the leading cause of mental retardation and spontaneous miscarriage, and the current trend towards advanced maternal age has increased the frequency of trisomic fetuses by 71% in the past ten years [1]. Furthermore, most solid tumours and about 50% of haematopoietic cancers are aneuploid. During the past few years, the cell-cycle, cancer and fertility fields have therefore made a substantial effort to understand the causes and consequences of aneuploidy.

To bring together knowledge from different viewpoints and highlight recent advances in this exciting field, this issue of EMBO *reports* features four reviews on aneuploidy. An article by Rolf Jessberger analyses the process of oocyte meiosis and how it becomes less accurate with age, and reviews by Holland & Cleveland, Pfau & Amon and Swanton & colleagues focus on aneuploidy in the context of cancer.

An overarching theme is the importance of intact sister chromatid cohesion to ensure the fidelity of chromosome segregation. In mammalian oocytes—which remain arrested in meiosis for up to four decades in humans—cohesin is loaded onto chromosomes during development and is probably not turned over for the life of the oocyte. Progressive loss of cohesin or 'exhaustion' seems responsible for the dramatic increase in aneuploid eggs with age. Similarly, defects in cohesion proteins are frequently found in various types of cancer.

As will become apparent in the three cancer-related reviews, it is important to distinguish between aneuploidy and chromosomal instability (CIN)—a high rate of gain or loss of chromosomes. CIN leads to aneuploidy, but stable aneuploidy can occur without CIN, which is associated with a good prognosis in cancer and occurs in normal brain and liver tissue. An outstanding question is how and whether aneuploidy and CIN predispose to tumorigenesis. Technological advances have allowed the characterization of CIN status of a variety of cancers, underscoring the prevalence of aneuploidy. However, whether aneuploidy is a driving cause of tumour formation remains unclear. Despite the extensive association of aneuploidy with tumours *in vivo*, extensive data from yeast, mouse and human cell culture indicate that abnormal chromosome content provides a growth disadvantage *in vitro*, and the presence of CIN in some tumours correlates with good prognosis: this is the so-called 'aneuploidy paradox'.

In this review series, the Cleveland, Amon and Swanton groups provide their own particular views on this paradox. CIN could endow tumour cells with extreme evolvability that is beneficial *in vivo*, but would be a growth disadvantage under the constant, rich conditions of cell culture. On the other hand, aneuploidy could interfere with cell proliferation—as seen *in vitro*—and would be selected against; further mutations or chromosomal alterations would allow cells to overcome this restriction and reveal their full tumorigenic potential. According to this view, CIN would allow cells to overcome the negative effects of aneuploidy and promote tumorigenesis below a certain threshold. However, as Swanton and colleagues discuss, the nonlinear relationship between the extent of CIN and cancer prognosis suggests that, beyond this threshold, CIN would become unfavourable owing to the accumulation of deleterious genomic alterations.

An increase in genomic material is generally accompanied by an increase in the expression of proteins encoded there, leading to altered metabolic properties, imbalances in the cell proteome and proteotoxic stress due to an overloading of protein degradation pathways. These effects imply that therapeutically targetable pathways would be common in a variety of aneuploid tumour cells. Initial proof-of-principle screens show promise in this regard and, as discussed in these reviews, have led to potential drug candidates.

Swanton and colleagues provide a much needed—but rare—translational perspective into the issue of aneuploidy and CIN. Their review highlights the prognostic value of CIN assessment in human tumours, evaluates the methods used to analyse CIN and provides insights into how it could be therapeutically targeted.

We hope this selection of comprehensive reviews will contribute to a better understanding of the complexities of aneuploidy and its causes. The possibility of targeting this imbalanced state in cancer therapy and harnessing our increasing knowledge to alleviate fertility problems are exciting prospects. We look forward to future developments in this fast-moving field.

REFERENCE
1. De Souza E *et al* (2010) *J Med Screen* **17:** 170–175

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