Causes and consequences of aneuploidy in cancer

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Abstract | Genetic instability, which includes both numerical and structural chromosomal abnormalities, is a hallmark of cancer. Whereas the structural chromosome rearrangements have received substantial attention, the role of whole-chromosome aneuploidy in cancer is much less well-understood. Here we review recent progress in understanding the roles of whole-chromosome aneuploidy in cancer, including the mechanistic causes of aneuploidy, the cellular responses to chromosome gains or losses and how cells might adapt to tolerate these usually detrimental alterations. We also explore the role of aneuploidy in cellular transformation and discuss the possibility of developing aneuploidy-specific therapies.

Aneuploidy
The presence of an abnormal number of chromosomes, either more or less than the diploid number. Aneuploidy is associated with cell and organismal inviability, cancer and birth defects.

Chromosomal instability
(CIN). A persistently high rate of gain and loss of chromosomes.

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Numerical and structural chromosome abnormalities are the most obvious and most distinguishing characteristics of cancer genomes (FIG. 1). In recent years, we have learned important details about how structural or segmental rearrangements can have an impact on tumour development through the activation of oncogenes and the inactivation of tumour suppressors[1]. By contrast, the role of numerical, whole-chromosome aneuploidy during tumour development is considerably less well-understood[2,3]. As a point of nomenclature, we shall hereafter refer to whole-chromosome aneuploidy as just 'aneuploidy'. As discussed below, numerous animal models, as well as a human cancer predisposition syndrome, make it clear that aneuploidy can predispose to tumour development, and the underlying mechanisms that drive tumorigenesis are now an active area of research[4,5].

There has been an intense focus on the causes and consequences of chromosomal instability (CIN), because it is a common feature of many cancers[6–8]. However, it is important to distinguish aneuploidy (the 'state' of the karyotype) from CIN (the 'rate' of karyotypic change). Although CIN leads to aneuploidy, not all aneuploid cells exhibit CIN; some cells are aneuploid with a uniform, stable karyotype — a phenomenon that has received much less attention than CIN. Recent large-scale DNA copy number analyses highlight how common recurrent aneuploidy is in human cancer[9].

The genes and pathways that are deregulated by whole-chromosome aneuploidy are largely unknown, and the impact of these genomic alterations may be complex[2]. Unlike balanced translocations, for which the breakpoint regions can be cloned and sequenced, the genes on the aneuploid chromosomes that contribute to tumorigenesis are more difficult to identify owing to the large genomic regions that are affected and the potential requirement for multiple altered genes to act cooperatively. However, understanding the role of aneuploidy in specific cancers is crucial for understanding disease pathogenesis and may also lead to new avenues for treatment.

This Review focuses on recent progress in understanding how aneuploidy contributes to the phenotypes of human cancers. We discuss recent progress in defining how tumour cells develop CIN. We describe how aneuploidy is usually detrimental to cellular and organismal survival owing to the resultant gene expression imbalances, and we discuss the specific adaptations that cells might need to tolerate it. Given that aneuploidy is not just tolerated but is remarkably common in cancer, we revisit the debate over whether aneuploidy is a cause or a consequence of malignant transformation. This question remains highly relevant because it raises the fundamental question of whether CIN itself is selected for by cancer cells, as is the case for other types of 'mutator' mutations that occur in some tumours. But we will also highlight the complexities of trying to identify which genes of aneuploid chromosomes might be responsible for driving oncogenesis. Finally, we will review the potential development of aneuploidy-specific therapeutics that target either common characteristics of aneuploid cells (irrespective of their specific chromosome content) or alternatively that target cells based on the specific genes that are affected by the aneuploidy.
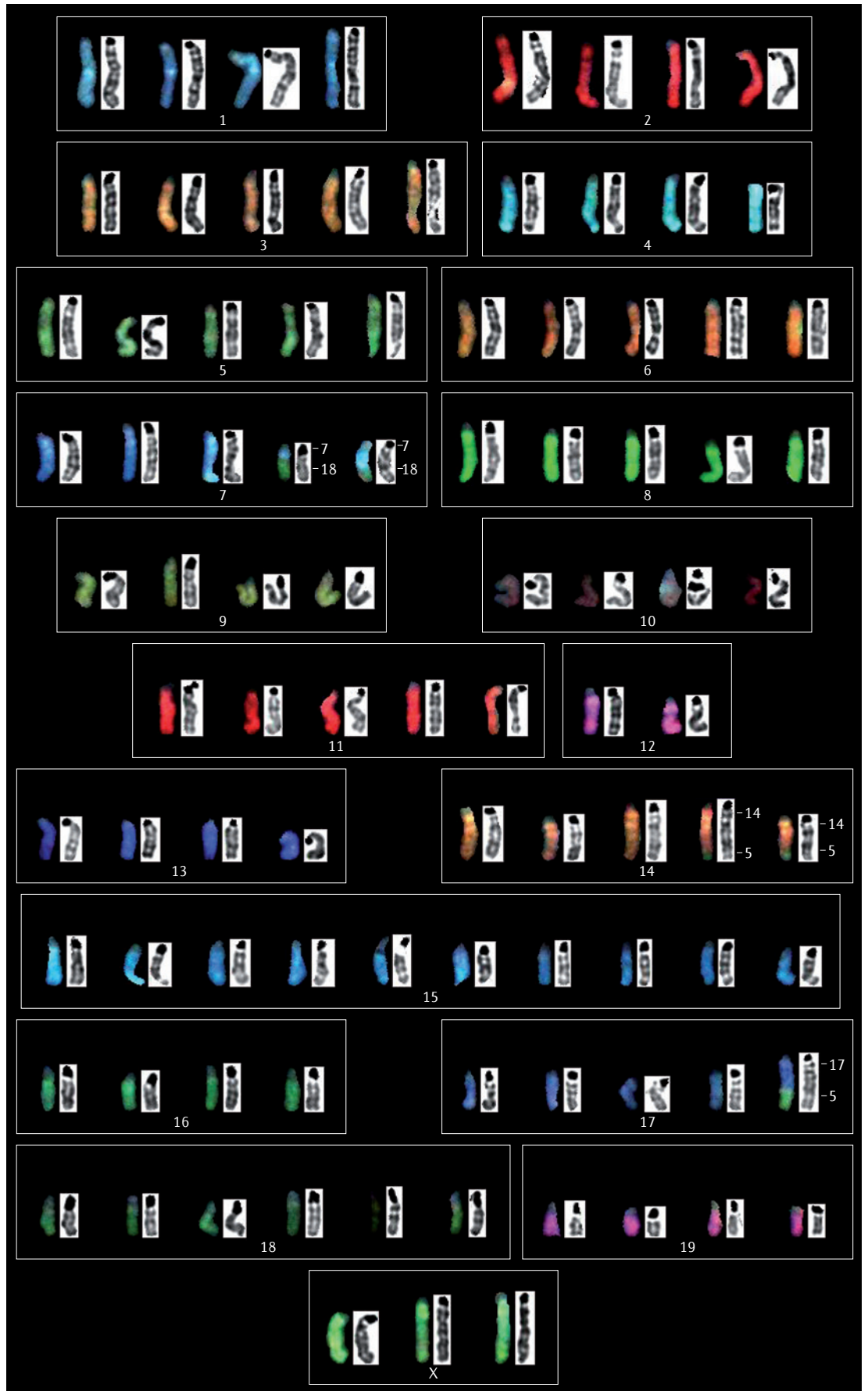
◀ Figure 1 | **Chromosomal instability.** Spectral karyotyping (SKY) chromosome painting of a near-tetraploid mouse tumour demonstrates both numerical and structural chromosomal abnormalities. Image courtesy of E. Ivanova, Belfer Institute for Applied Cancer Science, Dana–Farber Cancer Institute, Boston, Massachusetts, USA.

Widespread aneuploidy in cancer

There is strong evidence for a high frequency of aneuploidy in cancer. A recent, comprehensive study by Beroukhim and colleagues[9] examined the prevalence of somatic copy number alterations (SCNAs) in cancer and discovered that one-quarter of the genome of a typical cancer cell is affected either by whole-arm SCNAs or by the whole-chromosome SCNAs of aneuploidy. By contrast, only 10% of a cancer cell genome is affected by focal SCNAs. Furthermore, most of these whole-chromosome SCNAs showed strong evidence for preferential gain or loss (but not both) across cancer lineages, implying a selective process, rather than random alterations. This evidence for a high frequency of aneuploidy in cancer is reinforced by analyses of the Mitelman Database, which is the largest repository of cytogenetic information on human cancers and contains the results from over 60,000 cases[10,11]. Whole-chromosome alterations are recurrently observed in several cancer types. For example, the gain of chromosome 8 is seen in 10–20% of cases of acute myeloid leukaemia (AML), as well as some solid tumours, including Ewing's Sarcoma and desmoid tumours[12–16] (TABLE 1).

How do cells become aneuploid?

In an adult human, millions of cell divisions occur every minute, and the maintenance of a diploid karyotype requires the proper segregation of chromosomes with every cell division. However, the chromosome segregation machinery is imperfect, and *in vitro* estimates suggest that normal, diploid cells missegregate a chromosome once every hundred cell divisions[17,18]. The basal rate of spontaneous chromosome missegregation *in vivo* is an unknown but important quantity that could vary between cell types. Even if this *in vivo* rate is extremely low, strong selective pressure could enable the proliferation of rare aneuploid cells under certain conditions, as discussed below.

The disruption of multiple genes and pathways has been implicated in increasing the rate of chromosome gains and losses above the basal rate and generating CIN[7]. These mechanisms include defects in the kinetochore–microtubule attachments and dynamics, centrosome number, spindle-assembly checkpoint (SAC) and chromosome cohesion (FIG. 2). These causes of CIN have been reviewed and discussed in detail elsewhere, so we will only focus on recent progress[7,19].

Merotelic attachments. Merotelic attachments occur when a single kinetochore attaches to microtubules that arise from both poles of the spindle. They occur frequently in cancer cell lines and can lead to the missegregation of chromosomes[19–22] (FIG. 2a). Several mechanisms have been proposed to explain why tumour cells have an increased frequency of merotelic attachments[22–27].

We will focus on two key causes in this Review: an increased number of centrosomes and hyperstabilized kinetochore–microtubule attachments[23,25,28].

Centrosome amplification often occurs *in vivo* in tumours and has a strong correlation with CIN[29–32]. Although centrosome abnormalities have long been correlated with CIN, only recently has the underlying mechanism been clarified. Because of early experiments by Theodor Boveri[33], it has generally been assumed that extra centrosomes generate chromosome segregation errors by inducing multipolar cell divisions[34]. However, we now know that multipolar cell divisions are rare and that when they occur most of the progeny eventually die. This is because multipolar spindles are often transient intermediates, and cancer cell lines with centrosome amplification usually cluster extra centrosomes during mitosis, enabling the formation of a pseudo-bipolar spindle[23,24,32,35,36]. The centrosome clustering enables cells to survive but appears to come at the cost of an increased frequency of merotelic attachments[23,24] (FIG. 2b). Indeed, the presence of supernumerary centrosomes increases the frequency of merotelic attachments and chromosome segregation errors[23]. Centrosome amplification and merotelic attachments have been observed in primary human tumours and are therefore plausible causes of the CIN. In the future, it will be important to define precisely how centrosome amplification affects the dynamics of spindle microtubules. It will also be important to determine whether centrosome amplification increases the rate at which merotelic attachments are formed or whether it impairs the error correction mechanisms that fix them.

Another proposal linking merotelic attachments and CIN is based on the observation that the efficient correction of kinetochore–microtubule attachment errors requires the release of incorrectly attached microtubules, which is the rate-limiting step in error correction[28] (FIG. 2a). Thus, interactions that inappropriately stabilize microtubule attachments might be expected to increase chromosome missegregation errors and to generate CIN. Measuring spindle microtubule dynamics in live mitotic cells[25] showed that the kinetochore–microtubule attachments were more stable in cancer cell lines with CIN than in a non-cancerous, diploid cell lines and that manipulating the stability of the kinetochore–microtubule attachments in either cell type was sufficient to alter the rates of CIN[28]. It is not yet clear why cancer cells would develop more stable kinetochore–microtubule attachments. Although technically challenging, it would ultimately be important to examine kinetochore–microtubule attachment stability *in vivo* for roles in CIN and tumorigenesis. It would also be of great value eventually to compare tumour cells with their cells of origin.

Spindle assembly checkpoint defects. A compromised SAC, which arrests cells with improper spindle kinetochore attachments, can lead to CIN and aneuploidy[37,38] (FIG. 2c). Mouse models demonstrate that these spindle checkpoint defects can promote tumorigenesis but also illustrate that there is no simple correlation between chromosome missegregation rates and the probability

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Kinetochore
A large protein complex that assembles at centromeres. It is composed of inner and outer regions that contain >80 proteins, which are required for spindle attachment, chromosome movement and regulation of the mitotic checkpoint.

Centrosome
An organelle that serves as the main microtubule-organizing centre of the cell, as well as a regulator of cell cycle progression.

Spindle assembly checkpoint
(SAC). A highly conserved surveillance mechanism in mitosis and meiosis that minimizes chromosome loss by preventing chromosomes from initiating anaphase until all kinetochores have successfully captured spindle microtubules.

Merotelic attachments
Abnormal kinetochore–microtubule attachments that occur when a single kinetochore attaches to microtubules that arise from both poles of the spindle.

Table 1 | **Specific, recurrent chromosome gains and losses in human cancer**

Chromosome	Gains		Losses	
	Cancer type	**Frequency (%)**	**Cancer type**	**Frequency (%)**
1	Multiple myeloma	22/385 (5.7)	Adenocarcinoma (kidney)	14/610 (2.3)
	Adenocarcinoma (breast)	27/323 (8.4)		
2	Hepatoblastoma	29/65 (44.6)		
	Ewing's sarcoma	21/181 (11.6)		
3	Multiple myeloma	81/385 (21)	Melanoma	36/72 (50)
	Diffuse large B-cell lymphoma	25/197 (12.7)	Adenocarcinoma (kidney)	43/610 (7.0)
4	Acute lymphoblastic leukaemia	187/1817 (10.3)	Adenocarcinoma (kidney)	12/610 (2.0)
5	Multiple myeloma	84/385 (21.8)		
	Adenocarcinoma (kidney)	48/610 (7.9)		
6	Acute lymphoblastic leukaemia	206/1817 (11.3)	Adenocarcinoma (kidney)	19/610 (3.1)
	Wilms' tumour	44/232 (19.0)		
7	Adenocarcinoma (kidney)	222/610 (36.3)	Acute myeloid leukaemia	144/1026 (14)
	Adenocarcinoma (intestine)	40/125 (32.0)	Juvenile myelomonocytic leukaemia	30/50 (60)
8	Acute myeloid leukaemia	206/1026 (20.0)	Adenocarcinoma (kidney)	29/610 (4.8)
	Chronic myeloid leukaemia	253/808 (31.3)		
	Ewing's sarcoma	62/181 (34.2)		
9	Multiple myeloma	98/385 (24.2)		
	Polycythaemia vera	41/166 (24.7)		
10	Acute lymphoblastic leukaemia	173/1817 (9.5)	Astrocytoma	21/234 (9.0)
	Adenocarcinoma (uterus)	22/62 (35.5)	Multiple myeloma	14/385 (3.6)
11	Multiple myeloma	82/385 (21.3)		
12	Chronic lymphocytic leukaemia	305/884 (34.5)	Multiple myeloma	11/385 (2.9)
	Wilms' tumor	85/232 (36.6)		
13	Acute myeloid leukaemia	31/144 (21.5)	Multiple myeloma	52/385 (13.5)
	Wilms' tumor	34/232 (14.7)		
14	Acute lymphoblastic leukaemia	198/1817 (10.9)	Adenocarcinoma (kidney)	67/610 (11.0)
			Meningioma	49/508 (9.6)
15	Multiple myeloma	94/385 (24.4)		
16	Adenocarcinoma (kidney)	92/610 (15.1)	Multiple myeloma	14/385 (3.6)
17	Adenocarcinoma (kidney)	102/610 (16.7)		
	Acute lymphoblastic leukaemia	161/1817 (8.9)		
18	Acute lymphoblastic leukaemia	185/1817 (10.2)	Adenocarcinoma (kidney)	22/610 (3.6)
	Wilms' tumour	35/232 (15.1)		
19	Multiple myeloma	94/385 (24.4)	Adenocarcinoma (breast)	20/323 (6.2)
	Chronic myeloid leukaemia	79/808 (9.8)	Meningioma	16/508 (3.1)
20	Hepatoblastoma	28/65 (43.1)		
	Adenocarcinoma (kidney)	60/610 (9.8)		
21	Acute lymphoblastic leukaemia	363/1817 (20.0)		
	Acute megakaryoblastic leukaemia	59/168 (35.1)		
22	Acute lymphoblastic leukaemia	77/1817 (4.2)	Meningioma	355/508 (69.9)
X	Acute lymphoblastic leukaemia	225/1817 (12.4)		
	Follicular lymphoma	34/274 (12.4)		
Y				

Associations between specific chromosome gains and losses and specific cancers were identified using the Statistical Associations in Cancer Karyotypes (STACK) website[11]. STACK filters the non-biased karyotype data from the Mitelman Database, which contains karyotype data from many sources, to remove any partially characterized or redundant karyotypes, as well as karyotypes that were not near-diploid. The significance of the correlation between a specific karyotype aberration and a specific tumour class are then calculated using the hypergeometric test. Of note, significant associations have also been described between amplifications and deletions of chromosome arms and specific tumour classes[9].

of developing cancer[4]. Additionally, it remains unclear how often SAC defects occur in human tumours. The rare human cancer predisposition syndrome mosaic variegated aneuploidy (MVA) is caused by inactivation of the SAC protein BUBR1, demonstrating the relevance of the mouse models to human cancer[5], but SAC gene mutations are extremely rare in human cancer[39–43]. Furthermore, many CIN cancer cell lines that were previously thought to have SAC defects were recently shown by large-scale imaging experiments to have normally functioning checkpoints[17,44,45]. Although SAC gene mutations are rare, there is evidence of SAC gene silencing by methylation[46,47]. It will be interesting to determine the contribution of these silencing events to the CIN phenotype and to tumour development.

Chromosome cohesion defects. Accurate chromosome segregation is achieved through carefully orchestrated interactions between the mitotic spindle, kinetochores and cohesion[48,49] (FIG. 2d). Mutations in four genes that are involved in sister chromatid cohesion, including subunits of the cohesion complex, were identified in colorectal tumours through the sequencing of human homologues of genes that are known to cause CIN in budding yeast[50]. The functional consequences of these specific mutations have yet to be tested experimentally. However, recent work from Solomon *et al.*[51] identified inactivating mutations in stromal antigen 2 (*STAG2*) and reduced expression of its protein product in human cancer cell lines, xenografts and primary tumours. *STAG2* encodes one of the two human orthologues of the yeast SCC3 cohesin subunit, which is a component of the cohesion complex that may form a ring structure around sister chromatids. They also showed that the inactivation of *STAG2* in human cell lines results in defective sister chromatid cohesion and an increase in aneuploidy. This work suggests an *in vivo* role for cohesion defects in aneuploidy and cancer progression. However, cohesion has multiple cellular roles, including regulation of transcription[52]. Further work needs to be done in primary tumours to determine the precise contributions of these various aspects of cohesin function to tumorigenesis. It would also be interesting to know at what point during tumour evolution *STAG2* is mutated.

Detrimental effects of aneuploidy

The deleterious effects of aneuploidy, particularly at the level of the organism, are well-established in many species, including *Drosophila melanogaster*, *Caenorhabditis elegans*, mice, plants and humans. In these species, organism-wide aneuploidy is usually lethal[53]. A key issue is whether aneuploidy per se, regardless of the specific chromosome complement of a cell, causes a specific detrimental effect on fitness.

In vitro differences in growth rate, metabolism, cell cycle kinetics and cell size have been observed in aneuploid cells. Torres *et al.*[54] used a chromosome transfer strategy and selectable markers to generate aneuploid yeast strains with a single extra chromosome (BOX 1). All of the aneuploid strains proliferated more slowly than the wild-type cells, although in some cases the differences were modest and only apparent in co-culture experiments. The aneuploid yeast cells demonstrated a delay in the G1 phase of the cell cycle, increased sensitivity to drugs targeting protein synthesis and folding, and metabolic changes with increased glucose uptake and use[54]. These aneuploid yeast cells also exhibited modest but statistically significant increases in genomic instability with elevated rates of point mutations, mitotic recombination and loss of whole chromosomes, as well defective DNA repair[55]. The systematic nature of this work represents a major advance in the field and not only demonstrates that aneuploidy is detrimental to haploid yeast that has been grown under non-selective conditions, but it also begins to elucidate the mechanisms that lead to these growth defects[54–56].

Detrimental effects due to aneuploidy have also been described in mammalian cells. Williams *et al.*[57] established mouse embryonic fibroblast (MEF) cell lines with trisomy for chromosomes 1, 13, 16 or 19 (BOX 1). Notably, all of the trisomic embryos, with the exception of mice that were trisomic for chromosome 19, died *in utero*. Analysis of the MEF cell lines that were established from these embryos, however, showed that cell proliferation was impaired in all trisomic MEFs compared with the diploid MEFs. The trisomic cells were larger in size and also exhibited metabolic alterations with increased glutamine uptake and ammonium ion production. Unlike haploid yeast, the aneuploid MEFs did not display sensitivity to proteasome inhibitors. The functional implications of these metabolic abnormalities are not yet clear, but they could reflect broadly similar physiological alterations to those that occur in aneuploid yeast.

Studies of the effects of aneuploidy in humans are limited to the few karyotypes that are compatible with viability (BOX 1). Trisomy of chromosome 21 in patients with Down's syndrome is the only autosomal trisomy that is viable in humans. Individuals with two other trisomies, trisomy 13 and trisomy 18, can survive to birth but do not typically live beyond the first few years of life[58]. Some studies have suggested that cells with trisomy of chromosome 21 display a proliferation defect in culture relative to non-isogenic diploid cells[59]. However, other data are harder to interpret. Rare patients are born with mosaic aneuploidy, in which some cells are euploid but others have a specific trisomy. Mosaicism can involve trisomies of chromosomes other than 13, 18 and 21. Intriguingly, these patients can exhibit stable levels of mosaicism over time, strongly suggesting that the aneuploid cells can proliferate comparably to the diploid cells *in vivo*[60]. Furthermore, aneuploidy is common in a number of normal cell types within the body, including hepatocytes, neural progenitor cells and neurons[61,62]. Thus, stable aneuploidy can be observed in both normal and cancerous tissues in humans. To understand why apparently detrimental karyotypes can be observed in tissues, it is important to dissect the cellular response to aneuploidy and potential mechanisms of cellular adaptation that enable cell survival and proliferation.
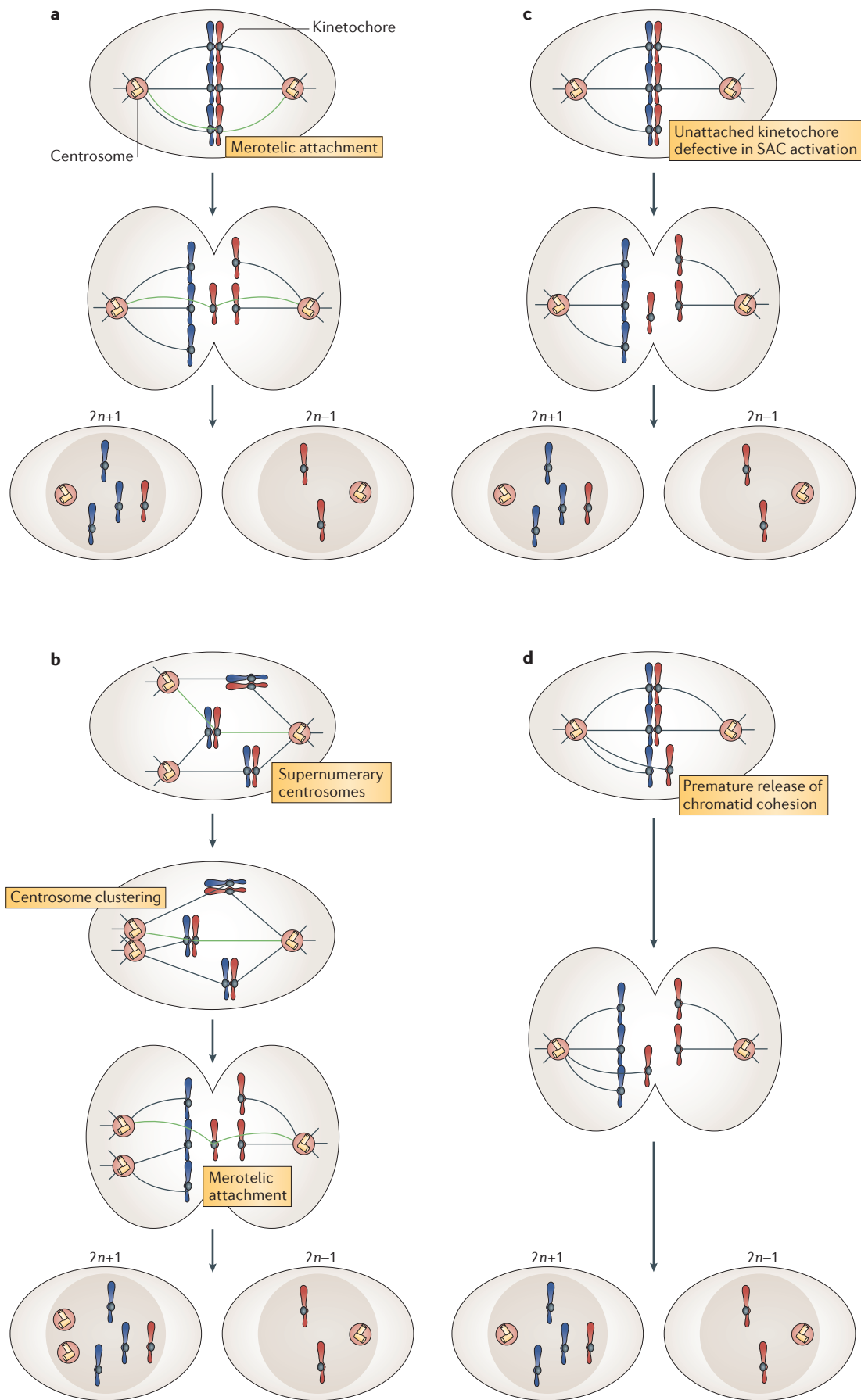
Mosaic variegated aneuploidy
A rare, recessive condition that is characterized by growth restriction, microcephaly, childhood cancer and constitutional mosaicism for chromosomal gains and losses.

Co-culture
A cell culture containing a mixture of two different cell types.

Proteasome inhibitors
A class of drugs, including MG132 and bortezomib, that block the action of proteasomes, which are cellular complexes involved in protein degradation.

a

Kinetochore

Centrosome

Merotelic attachment

2n+1   2n−1

b

Supernumerary centrosomes

Centrosome clustering

Merotelic attachment

2n+1   2n−1

c

Unattached kinetochore defective in SAC activation

2n+1   2n−1

d

Premature release of chromatid cohesion

2n+1   2n−1

◄ Figure 2 | **Pathways to aneuploidy.** There are several pathways by which a cell may become aneuploid. **a** | Merotelic attachments. A single kinetochore can attach to microtubules that arise from both poles of the spindle. If the merotelic attachments are not corrected before anaphase, then both sister chromatids can missegregate towards the same pole to generate aneuploid cells, or they can lag in the spindle midzone and be excluded from both daughter nuclei. The efficient correction of these kinetochore–microtubule attachment errors requires the release of incorrectly attached microtubules, which is the rate-limiting step in error correction[7,22,28]. In normal cells, microtubules are frequently released from kinetochores prior to anaphase to promote the correction of incorrect attachments and to prevent chromosome missegregation. Slow release rates due to kinetochore–microtubule attachment defects may increase the likelihood that merotelic attachments will persist and lead to chromosome missegregation[25,28]. **b** | Supernumerary centrosomes. Cells with centrosome amplification usually cluster extra centrosomes during mitosis to form a pseudo-bipolar spindle that can result in an increased frequency of merotelic attachments. **c** | Spindle assembly checkpoint (SAC) defects. A compromised SAC could allow cells to enter anaphase with unattached or misaligned chromosomes. As a result, both copies of one chromosome may end up in a single daughter cell. **d** | Chromosome cohesion defects. Chromosomes can be missegregated if sister chromatid cohesion is lost prematurely or if it persists during anaphase.

Cellular responses to aneuploidy

A major focus of current research is to determine how cells respond at the transcriptional or proteomic level to gene expression imbalances that are caused by aneuploidy. In particular, some of these studies address the question of whether aneuploidy causes transcriptional and protein expression changes in direct proportion to the copy number alteration of the DNA or whether the cell minimizes the effects of aneuploidy through dosage compensation. There is also the more complex possibility of gene expression effects beyond the chromosomes that are affected by aneuploidy through altering feedback loops of transcriptional regulators or through epigenetic effects[53]. The possibility that cells induce a specific transcriptional stress response to aneuploidy has also been raised[54]. Beyond the importance of this point in understanding the basic physiology of aneuploidy, this is also a crucial concept. If aneuploidy triggers a common stress response and all aneuploid cells need to develop specific adaptations in order to proliferate with their altered genomes, this opens the possibility that aneuploidy itself may be targeted as a cancer therapy.

Transcriptome effects. Two recent studies in aneuploid yeast strains — which were generated using different methods (BOX 1) — used gene expression microarrays to investigate the effects of aneuploidy on the transcriptome. Both studies report that gene expression, in general, is proportional to gene dosage in aneuploid yeast. Interestingly, Torres *et al.*[54] also found that many yeast strains showed a common gene expression signature. This signature was originally described by Gasch *et al.*[63] as an environmental stress response (ESR) in yeast that has been grown under stressful conditions and at slow growth rates. When normalized for growth rate in phosphate-limited conditions, the aneuploid strains showed increased expression of genes related to ribosomal biogenesis and nucleic acid metabolism[54]. Pavelka *et al.*[64] only identified this ESR signature using their most stringent analysis, and it was not correlated with either growth rate or number of aneuploid chromosomes.

However, the different approaches used in these studies for strain construction, selection, growth and data analysis make a direct comparison difficult. One issue, discussed below, is whether the strains being studied are genetically stable. The genetic heterogeneity of unstable strains might mask gene expression patterns that are detectable in stable strains. Thus, although both studies agree that aneuploidy can induce a general transcriptional response beyond the copy number alteration of the affected chromosome (or chromosomes), it is less clear whether this response mainly reflects the impaired growth of some strains or whether it reflects a specific aneuploidy-sensing mechanism that is wired into cells.

Proteome effects. The effect of aneuploidy on the proteome is also controversial. The stoichiometry of certain protein complexes, such as the ribosome, is maintained by the proteolysis of subunits that fail to assemble into the complex[65,66]. In the absence of mechanisms for compensation, aneuploidy could lead to an excess of uncomplexed proteins and proteotoxic stress[54,67] (FIG. 3). Proteotoxic stress results from the accumulation of unfolded, misfolded and aggregated proteins in a cell and can lead to the activation of factors and pathways that are designed to mitigate the burden of these unfolded proteins. This includes the ubiquitin–proteasome and chaperone pathways and could place an energetic burden on aneuploid cells.

The above yeast transcriptome studies also looked for dosage compensation at the level of the proteome. Providing evidence for dosage compensation, Torres *et al.*[54] found that most proteins examined (13 of 16) did not scale with gene copy number and that these proteins were members of multi-protein complexes. Consistent results were subsequently found in a more global proteome analysis[67], leading the authors to hypothesize that increasing protein degradation to compensate for gene copy number abnormalities may be a general response to aneuploidy. In further support of this hypothesis, the group found that some of their aneuploid yeast strains were more sensitive to proteasome inhibitors than the isogenic euploid control cells[54].

By contrast, Pavelka *et al.*[64] found that chromosome copy number generally scaled with protein abundance, that proteomic changes clustered among similar karyotypes and that there was minimal dosage compensation for core complex proteins. The reason for these differences is not completely clear; however, differences in the sensitivities of the protein detection techniques[68,69] — namely, stable isotope labelling by amino acids in cell culture (SILAC) and multidimensional protein identification technology (MudPIT) mass spectrometry — and/or the stability of the aneuploid yeast strains used[55,70] are potential explanations.

When characterizing cellular responses to aneuploidy with the aim of defining a cellular state or vulnerability that might form the basis of an aneuploidy-specific cancer therapy, it is important to know whether the findings from yeast can be generalized to higher eukaryotes. Preliminary data imply that aneuploid cells that are derived from diploid HCT116 human colon

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Dosage compensation
The counterbalancing of gene and protein imbalances that arise from unequal numbers of chromosomes, such as sex chromosomes in normal cells or potentially any chromosome in aneuploid cells.

Environmental stress response
(ESR). A gene set signature defined in yeast that has been grown under stressful conditions and at slow growth rates.

Proteotoxic stress
Results from the accumulation of unfolded, misfolded and aggregated proteins in a cell.

Box 1 | Experimental models of aneuploidy

Torres et al.[54] used a chromosome transfer strategy with drug selection to engineer haploid yeast cells with a single extra chromosome (a). If a mating partner lacks the karyogamy gene (KAR1) then nuclear fusion does not occur, but sometimes individual chromosomes are transferred from one nucleus to the other during these failed matings. These rare transfers can then be selected for using different selectable markers (shown in yellow and green in the figure). Using this technique, the authors generated 13 of the 16 possible disomic strains. Building on previous methodology[56], Pavelka et al.[64] induced meiosis in yeast strains with an odd ploidy (3n or 5n), which produces aneuploid progenies at high frequencies, and then isolated aneuploid strains without any drug selection (b). Using this technique, the authors generated 38 stable aneuploid strains (12.5% of spores analysed) with 35 distinct karyotypes. Williams et al.[57] used a technique that takes advantage of Robertsonian translocations to generate aneuploid mouse embryonic fibroblasts (c). Compound heterozygous mice strains carrying Robertsonian translocations between the blue and green chromosomes and between the red and green chromosomes were mated with wild-type mice. Between 7 and 40% of the resulting progeny were

trisomic for the chromosome that is common to the two Robertsonian translocations (the green one) because of a meiotic non-disjunction event in the male germline. Using this technique, the authors generated cell lines with trisomy for chromosomes 1, 13, 16 or 19. Tissue samples from individuals with aneuploidy, such as trisomy 21 in Down's syndrome, can also be used to model and study aneuploidy (d). Of note, tissue samples that are obtained from an individual with mosaic aneuploidy can include both diploid and aneuploid cells, which are otherwise isogenic and could be used for a direct comparison. Microcell-mediated chromosome transfer (MMCT) is a technique that allows the transfer of a specific chromosome from a donor cell line into a host cell line[114–116] (e). The donor cells contain one chromosome with a selectable marker. Microcells are generated in the donor cells by causing micronucleation through the treatment with colcemid. Treatment of these micronucleated cells with cytochalasin B followed by centrifugation results in enucleation and formation of microcells. The microcells are then purified by filtration and are fused to recipient cells using polyethylene glycol. Selection in antibiotics follows fusion.
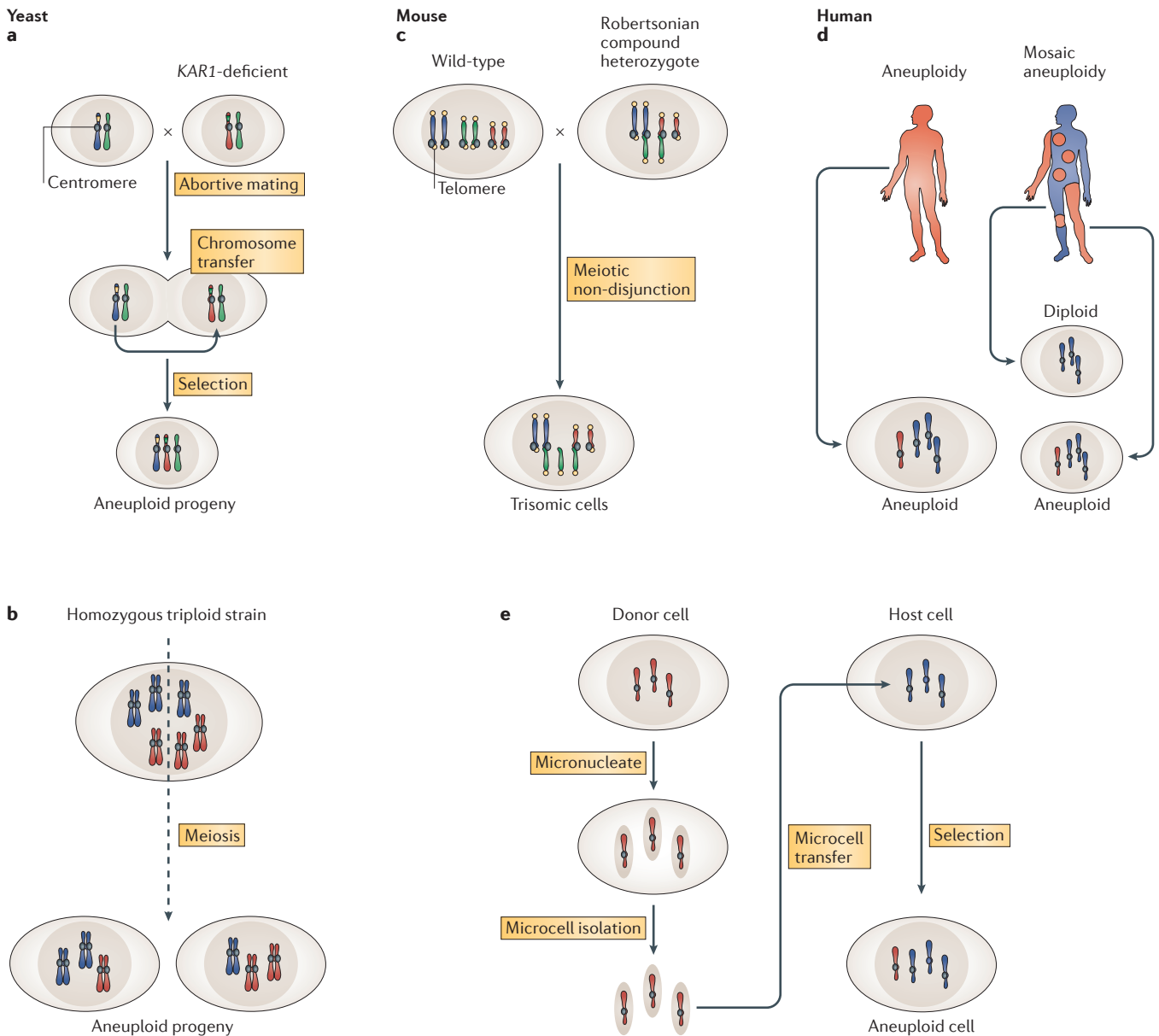
Robertsonian translocation
A chromosomal abnormality in which two acrocentric chromosomes become joined by a common centromere.

Reactive oxygen species
(ROS). Ions or small molecules — including oxygen ions, free radicals, inorganic peroxides and organic peroxides — that are highly reactive owing to the presence of unpaired valence shell electrons. They are a by-product of the normal metabolism of oxygen and have important roles in cell signalling. Increased levels owing to environmental stress can result in damage to cells.

cancer cells do show some evidence of protein-level dosage compensation and display an upregulation of the autophagy pathway (Z. Storchova, Max Planck Institute of Biochemistry, Martinsried, Germany, personal communication). Taken together, these results imply that aneuploid cells may share adaptive cellular responses of dosage compensation at the level of the proteome, but the details of the extent, importance and mechanism of this compensation remain to be elucidated.

Tolerance of aneuploidy

Given the frequent observation of aneuploidy in both cancerous and normal tissues, a key question is how cells can adapt to tolerate an apparently detrimental aneuploid genotype. One simple mechanism that enables aneuploidy to be tolerated is to increase the number of chromosome sets: the gain or loss of a single chromosome will be expected to have a larger impact in a haploid cell compared with in a diploid or in a tetraploid cell. Indeed, diploid yeast strains with an extra chromosome are far less sensitive to drugs that target protein synthesis and protein folding relative to isogenic haploid strains with the same chromosome gain[54]. Furthermore, tetraploid yeast can tolerate a nearly 1,000-fold increase in the rate of chromosome gain or loss without major impairment in the kinetics of cell cycle progression[71]. Similarly, tetraploid mammalian cells, which exhibit CIN and

Euploid cell

Aneuploid cell

Figure 3 | **Proteotoxic stress.** Aneuploidy can lead to imbalances in protein stoichiometry. In this illustration, two proteins that have genes located on different chromosomes function in a complex. Maintaining the correct number of each subunit is regulated by multiple pathways, including protein degradation by the ubiquitin–proteasome pathway and by chaperone-mediated sequestration. In aneuploid cells, as indicated by the additional red chromosome, the imbalances in protein stoichiometry are amplified and may overwhelm these protein quality-control pathways, leading to protein misfolding and aggregation.

aneuploidy, have a near-normal growth rate compared with isogenic diploid cells[23]. In fact, buffering the effects of aneuploidy and facilitating a combination of whole-chromosome aneuploidies, which would otherwise be lethal in diploid cells, could be one mechanism by which genome doubling promotes transformation[72].

Because cells typically accumulate many genetic changes during tumorigenesis, studies in different systems have aimed to define genetic backgrounds that are permissive for aneuploidy. For example, one genetic screen identified mutations in the deubiquitylating enzyme UBP6 in some spontaneously fast-growing aneuploid yeast strains[67]. The unbiased identification of a deubiquitylating enzyme in this screen reinforces the view of the importance of the proteasome-mediated protein degradation pathway in aneuploid cells.

An alternative way in which cells could adapt to aneuploidy is to impair signalling pathways that limit the proliferation of aneuploid cells. In support of this model, Thompson *et al.*[17,73] have demonstrated that the *in vitro* missegregation of chromosomes in diploid human cells leads to a cell cycle delay with nuclear accumulation of the antiproliferative tumour suppressor proteins p53 and p21. Deletion of the p53 gene (*TP53*) allowed the propagation of viable aneuploid cells, suggesting that the p53 pathway has an important role in limiting the growth of aneuploid human cells. These data fit well with the observation that many tumour cells exhibit both aneuploidy and defects in the p53 pathway[74]. It is unknown whether this permissive genetic background must precede aneuploidy or whether it can develop as an adaptation to aneuploidy to help overcome the initial cell sickness. However, the knockout of *TP53* in human cells does not itself lead to aneuploidy[75]. Also, the presence of aneuploid cells in some normal human and mouse tissues suggests that there are exceptions in which p53 is not activated, or not activated to high levels, in aneuploid cells[61,62,76,77]. Furthermore, the field is at an early stage, and there are important mechanistic questions about how chromosome missegregation activates p53. One recent study suggests that p53 activation is mediated by reactive oxygen species (ROS) that are generated in the aneuploid cells. The ROS possibly could be related to increased metabolic flux, but precisely why aneuploidy generates ROS remains to be determined[78]. A potential signalling mechanism is through ROS-mediated activation of the DNA damage response protein ataxia telangiectasia mutated (ATM)[79], which then activates p53 by a non-canonical (CHK1- and CHK2-independent) mechanism[78]. Thus, although many details still remain to be elucidated, this work presents evidence for an intriguing mechanism whereby the ATM–p53 pathway maintains genomic stability not only as a well-characterized antiproliferative response to double-stranded DNA breaks but also to aneuploidy.
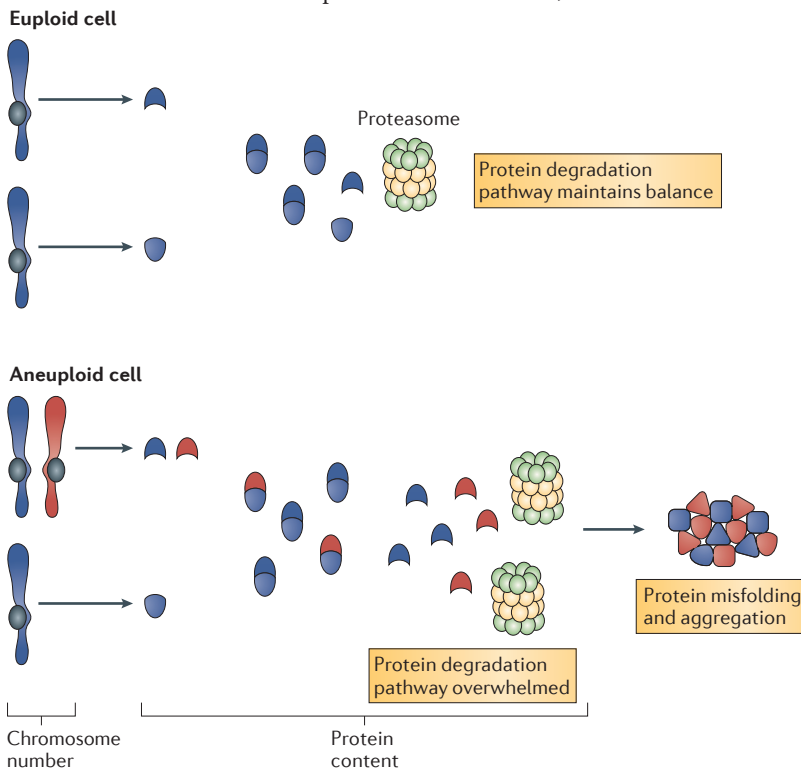
Why do cells become aneuploid?

Aneuploidy as a driver and passenger of tumorigenesis. A long-standing debate has centred on whether the widespread aneuploidy that is observed in cancers is a cause or a consequence of cancer[34,80–82]. In other words, is aneuploidy

a driver or a passenger in the transformation process and, more generally, why do cells become aneuploid?

Work by several groups has shown that cancer cell lines with CIN missegregate a chromosome *in vitro* every one to three cell divisions, which is substantially higher than the rate in non-transformed cells[17,37]. Because

cancer cells are often defective in pathways that regulate genome stability, one possibility is that aneuploidy is collateral damage — or a passenger — in the transformation process[83] (and hence that the more recurrent aneuploidies are simply more tolerated than other chromosomes in the setting of gross CIN). For example, inactivation of the retinoblastoma-associated protein (RB) leads to CIN and aneuploidy, as recently reviewed[84–86]. Although the most studied function of RB relates to its repression of E2F-regulated genes and control of the cell cycle, recent *in vitro* and *in vivo* studies also demonstrate that the loss of this tumour suppressor gene enhances genomic instability, including CIN[86]. This genomic instability is likely to be generated through multiple mechanisms, and three recent studies showed that RB loss leads to defects in chromosome condensation and cohesion, abnormal centromere structure and accumulation of DNA damage[83,87,88]. Depletion of RB also causes the overexpression of MAD2, a mitotic checkpoint protein whose dysregulation leads to CIN[89,90].

The alternative, but not mutually exclusive, possibility to the passenger hypothesis is that aneuploidy has a driving role in adaptive evolution by providing a fitness advantage under specific circumstances[91] and thus could be a positively selected driver of tumorigenesis.

Advantages of aneuploidy in mammalian tumorigenesis. Aneuploidy can be an effective mechanism for generating phenotypic variation and adaptation under a strong selective pressure in yeast (BOX 2). However, to what extent do these findings apply to the frequent observation of aneuploidy in mammalian cells and cancer? Although the roles of aneuploidy in disease pathogenesis are unknown, the yeast studies suggest that the effects could be complex and could potentially involve the altered expression of multiple genes and/or pathways[92] or an increased mutation rate[55]. Despite this potential complexity, understanding the roles of these whole-chromosome aneuploidies in specific cancers could provide important insight into pathogenesis as well as lead towards new therapies.

The first studies investigating trisomy as a driver of tumorigenesis used a mouse model of chemically induced skin papillomas and squamous cell carcinomas[93]. Recurrent and stable trisomy of mouse chromosome 7 in these tumours caused duplication of a mutated *HRAS* allele, suggesting that the nonrandom duplication of chromosome 7 is an important mechanism by which the mutated *HRAS* allele is overexpressed. Similarly, germline and somatic mutations of the *MET* protooncogene, which is located on human chromosome 7, occur in human papillary renal carcinomas. These tumours are characterized by stable trisomy of chromosome 7, and nonrandom duplication of the chromosome that bears the mutated *MET* gene has been demonstrated in tumours from patients with hereditary renal carcinomas[94,95]. Likewise, trisomy of chromosome 4 is commonly observed in the M2 and M4 subtypes of acute myeloid leukaemia, and one study has demonstrated that trisomy of chromosome 4 can lead to an increased dosage of a mutant *KIT* allele[96,97].

Box 2 | Aneuploidy advantages in yeast

Although an extra copy of a chromosome alters the expression of many genes, a growth advantage under the appropriate selective pressures can be provided by a single relevant gene on this chromosome. For example, Hughes *et al.*[117] showed that haploid *Saccharomyces cerevisiae* strains with deletions of single genes frequently compensate by becoming aneuploid (diomsic) for a whole chromosome harbouring a close paralogue of the deleted gene.

Similarly, Pavelka *et al.*[64] compared 38 aneuploid budding yeast strains to euploid controls under various stress conditions and drug exposures and found that various aneuploid strains grew more robustly in rich media and in the presence of various antiproliferative drugs. Further analysis showed that strains with similar karyotypes displayed similar growth patterns in the different environments. Whole-genome sequencing suggested that no additional mutations occurred in the aneuploid strains, supporting the conclusion that the enhanced growth properties were due to aneuploidy. The group also demonstrated that, of the genes that were amplified by aneuploidy of chromosome XIII, resistance to the tumorigenic compound 4-nitroquinoline-1-oxide (4-NQO) was solely due to amplification of *ATR1*. This work demonstrates that even one gene on an aneuploid chromosome can be responsible for a novel phenotype, supporting the hypothesis that aneuploidy can contribute to tumorigenesis by amplifying or deleting a single oncogene or tumour suppressor.

Because whole-chromosome aneuploidy by definition involves large genomic segments, the impact of aneuploidy is not limited to the effects of a single gene. For example, Selmecki *et al.*[118,119] demonstrated that the *in vivo* acquisition of extra copies of an isochromosome by *Candida albicans* confers resistance to fluconazole through the action of two specific genes in a copy-number-dependent manner. *ERG11*, an ergosterol biosynthesis gene encoding the drug target, and *TAC1*, a transcriptional regulator of drug efflux pumps, independently and additively mediated resistance in these strains. Importantly, an identical karyotype could be rapidly reproduced in the laboratory by culturing *C. albicans* in the presence of fluconazole. A related study by Rancati *et al.*[92] has demonstrated that yeast cells carrying a deletion of *MYO1*, which encodes the only myosin II that is required for cytokinesis, rapidly evolve through different pathways to restore normal cytokinesis and growth. In one of these mechanisms, two upstream regulators of the cell wall biogenesis pathway were located on a chromosome that became aneuploid. Increasing the copy number of both genes together, but not either gene alone, was sufficient to result in thickening of the cell wall at the division site, thus restoring cytokinesis in unadapted *MYO1* mutants. This demonstrates the synergistic effects of small changes in gene expression and how a single genetic event, such as the gain or loss of a single chromosome, can 'bundle' the phenotypic effects from copy number alterations in multiple genes[64,91,92,118].

Finally, small-scale copy number changes in genes that are involved in DNA repair, DNA replication or mitosis might have an indirect impact on tumorigenesis by creating a mutator phenotype with increased CIN or with other forms of genomic instability, as originally suggested by Duesberg and colleagues[120,121]. Indeed, one recent study demonstrated that aneuploid yeast has increased genomic instability, including increased chromosome loss and defective DNA damage repair[55]. Thus, although aneuploidy seems to be detrimental to most cell populations, it may benefit cells that are under selective pressure by increasing the frequency of growth-promoting genetic alterations not only through chromosome missegregation but also through other mechanisms of genomic instability. Although this work did not identify any of the dysregulated genes leading to genomic instability, another recent study reported that the budding yeast *KIP3*, which is a member of the kinesin 8 microtubule motor family, is a dosage-sensitive gene that has a role in chromosome segregation[122]. Kinesin 8 proteins control chromosome congression and the spindle length in all eukaryotes. Single copy alterations of the *KIP3* gene or mutant versions of *KIP3* could toggle from a functionally null phenotype to a wild-type phenotype or to a hyperactive phenotype.

A role for aneuploidy generated by CIN has also been recently demonstrated in tumour relapse and recurrence[98]. Benezra and colleagues[90,98] induced CIN in tumour cells by overexpressing the spindle checkpoint protein MAD2 in mutant *KRAS*-driven lung tumours in mice. The combined overexpression of MAD2 and KRAS led to the formation of lung adenocarcinomas that were larger and more aggressive than the tumours that developed in mice that overexpressed only KRAS[98], indicating a key role for CIN in the tumorigenesis. The continued expression of mutant KRAS was required for tumour maintenance in these mice, which is consistent with the concept of oncogene addiction. Interestingly, the tumours that developed CIN and aneuploidy owing to transient MAD2 overexpression recurred at markedly elevated rates after the withdrawal of the *KRAS* oncogene. The relapsed tumours were highly aneuploid and exhibited activation of multiple pro-proliferative pathways, a result that is consistent with the idea that MAD2-mediated aneuploidy in the primary tumour generated diversity and an evolutionary advantage for the oncogene-driven tumours. From a therapeutic standpoint, this work also suggests that early CIN may be responsible for tumour relapse after effective induction chemotherapy.

The consequences of aneuploidy, like its causes, are often multifaceted and are likely to be context-dependent. Recent data suggest that aneuploidy can both promote and inhibit tumorigenesis[80–82]. This is clearly illustrated *in vivo* by the observation that individuals with Down's syndrome have a significantly increased risk for haematologic malignancies but a remarkably decreased incidence of solid tumours[99]. Recent work, in fact, suggests that the tumour suppressor effect of trisomy of chromosome 21 in solid tumours may be due to the overexpression of two genes that are located on chromosome 21, *DSCR1* (also known as *RCAN1*) and dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (*DYRK1A*), both of which inhibit tumour angiogenesis by suppression of the calcineurin pathway[100]. Similarly, the tumour-promoting effect of chromosome 21 in haematopoietic cells is also an active area of research[101]. Consequently, the effects of aneuploidy may depend on the specific interaction of the karyotype with the genetic context and microenvironment found in different tissues. In general, the specific roles or mechanisms of aneuploid chromosomes in specific cancers are largely unknown. However, the driving functions of aneuploidy may encompass multiple mechanisms, including amplification of a mutated oncogene, amplification of a dosage-sensitive wild-type gene, loss of a tumour suppressor gene or increase in genomic instability.

Aneuploidy as a therapeutic target

Aneuploidy is a hallmark of cancer and a highly attractive therapeutic target. Because aneuploidy is generated by different mechanisms, there are multiple promising strategies on the horizon for targeting aneuploidy (FIG. 4).

Targeting CIN. This approach requires the discovery of genetic dependencies that occur specifically in chromosomally unstable cells. Numerous studies have identified mutations that display synthetic lethality with mutations that trigger genetic instability[102,103] (FIG. 4a). This concept was also reinforced by the finding of 'ploidy-specific lethality' in yeast[71,104]. Tetraploid budding yeast has rates of chromosome loss that are more than two orders of magnitude higher than isogenic diploid strains. A small number of gene deletions were observed to be lethal in tetraploid cells but to have little or no effect in diploid cells. Most of these genes affect genomic stability, suggesting that the lethality is due in large part to the CIN phenotype of the tetraploid strains. Likewise, tetraploid mammalian cells display a CIN phenotype, which is primarily due to the presence of supernumerary centrosomes[23]. Recent studies have identified gene knockdowns that inhibit centrosome clustering and kill CIN cancer cells with extra centrosomes[105]. The most appealing candidate to come from these studies is a kinesin motor of the kinesin 14 family called HSET (also known as KIFC1)[106]. In common with the ploidy-specific lethality in yeast, *HSET* knockdown has little or no effect on normal diploid cells, but it is lethal to cells that contain extra centrosomes. Small-molecule inhibitors of kinesin motors have been described and are indeed in clinical trials, so HSET inhibitors should also be feasible to develop.

Targeting common cellular responses to aneuploidy. It would also be appealing to interfere with a general response to aneuploidy, such as the ubiquitin–proteasome, heat shock protein (HSP) chaperone and autophagy pathways[107] (FIG. 4b). What remains to be determined is how general the dependence of aneuploid cancer cells will be on these pathways. For example, clinical trials with the proteasome inhibitor bortezomib (velcade) suggest that aneuploidy alone is not sufficient to ensure clinical efficacy[108,109]. In addition, the buffering effect of diploidy or polyploidy also raises the concern over whether the magnitude of the dependence of aneuploid cells on these pathways, as observed in haploid yeast, will provide a clinically relevant therapeutic window.

Potential therapeutic targets include pathways that are either already impaired in the aneuploid cells or that are more essential for viability relative to diploid cells. Studies on the physiology of aneuploid yeast and mouse embryonic fibroblast (MEF) cells, as described above, have shown alterations in gene and protein expression with resultant proteotoxic (FIG. 3) and metabolic stress[54,57]. Thus, the initial efforts in identifying aneuploidy-selective compounds focused on drugs targeting these pathways. Although aneuploid MEFs have changes that are consistent with those that are observed in budding yeast, trisomic MEFs did not display sensitivity to proteasome inhibitors[57]. However, the general compromise of aneuploid cells might lend itself to combination therapies, and recent work has begun to validate this concept.

Chromosome congression
The process of aligning chromosomes on the spindle during mitosis.

Oncogene addiction
The dependence of a cancer cell on one overactive gene or pathway for survival, growth and proliferation.

Synthetic lethality
Two genes are synthetic lethal if mutation of either alone is compatible with viability, but mutation of both leads to cell death.

AICAR is a cell-permeable, energy-stress-inducing compound that activates AMP-activated protein kinase (AMPK). The AMPK metabolic master regulator is usually activated in times of reduced energy avail-ability (high cellular AMP/ATP ratios) and serves to inhibit anabolic processes. Recently, aneuploid MEFs were found to be more sensitive to a combination of AICAR and the geldanamycin derivative HSP90 inhibitor 17-allylaminogeldanamycin (17-AAG) compared with isogenic diploid MEFs[107]. Both of these compounds are currently in clinical trials (see the ClinicalTrials.gov website), although trials of 17-AAG have progressed further than those of AICAR. In trisomic MEFs, which were previously shown to exhibit metabolic abnormali-ties, AICAR induced p53-mediated apoptosis. The com-bination of AICAR and 17-AAG was also synergistic and selectively lethal to aneuploid cancer cell lines relative to near-diploid cell lines. However, unlike the MEFs, cancer cell lines that lacked p53 were also sensitive to AICAR, suggesting that the mechanism (or mechanisms) of aneuploidy-selective lethality is likely to involve more than just a p53-mediated arrest. Also, HSP90 inhibition can affect multiple pathways and proteins, including oncogenic signalling, which raises the possibility that 17-AAG could be targeting more than just proteotoxic stress in the aneuploid cells[110]. Therefore, understanding the mechanisms of these drugs in aneuploid cancer cells is crucial for further advancing the therapeutic approach of aneuploidy-specific lethality. In summary, aneuploidy itself is a novel, unexploited and highly attractive treat-ment strategy in cancer therapy, and recent work has begun to validate this concept.
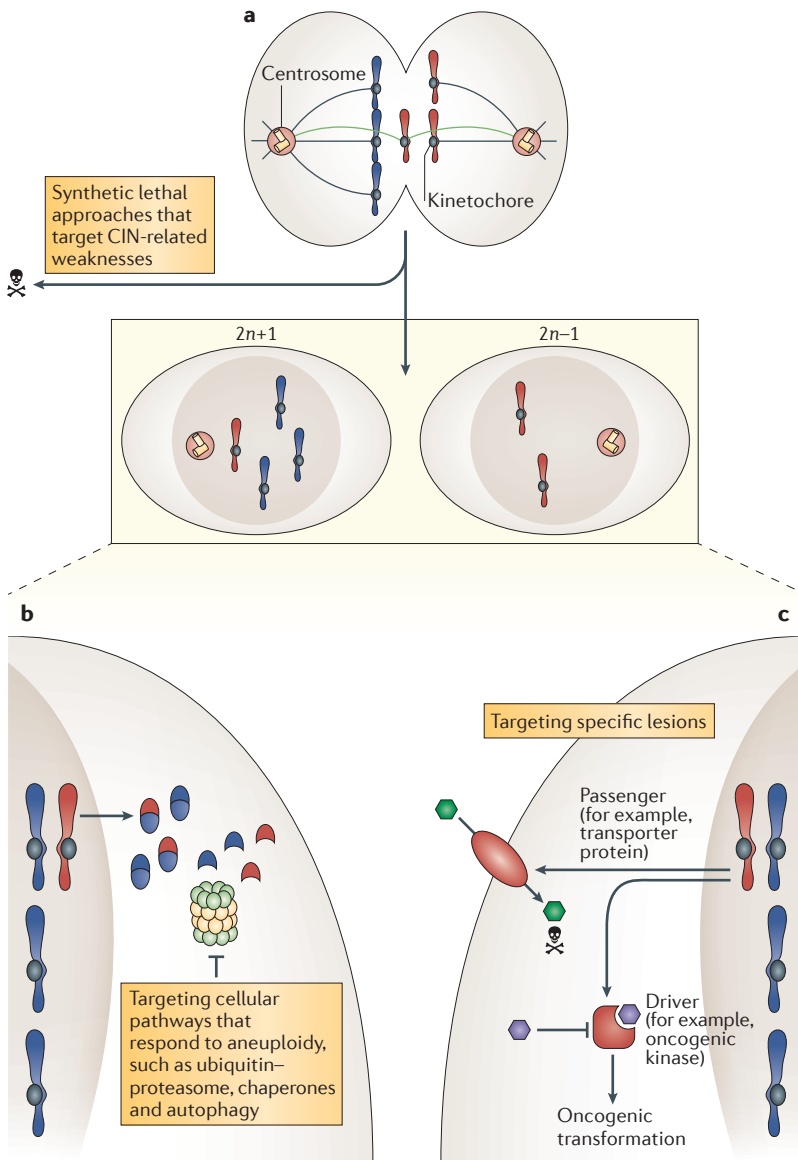
Targeting specific lesions of recurrent aneuploidies. Finally, it may be possible to target recurrent whole-chromosome aneuploidies specifically in cancer. This approach could be useful even if the global aneuploidy-targeting drugs are not achievable. We hypothesize that cancer cells with recurrent chromosome gains or losses may exhibit unique genetic dependencies owing to the simultaneous acquisition of both driver and passenger copy number change 'mutations' (FIG. 4c). The beneficial effects of the driver genes (the usual targets for targeted anticancer therapies) may be accompanied by suscep-tibilities that are conferred by the passenger genes. For example, the solute carrier family 19 (folate transporter), member 1 (*SLC19A1*) gene is located on chromosome 21 — which is trisomic or tetrasomic in almost all high-hyperdiploid cases of paediatric acute lymphoblastic leukaemia[111] — and codes for the reduced folate carrier that transports the antifolate chemotherapeutic metho-trexate into cells. Several studies have demonstrated an increased uptake and toxicity of methotrexate, which can be attributed to these additional copies of the *SLC19A1* gene, in cells with trisomy and tetrasomy of chromo-some 21 (REFS 112,113). In principle, it may be possible to target both the driver and passenger genes on the ane-uploid chromosome. Although a driver mutation is not necessarily required from a therapeutic perspective, it may be important for selection and maintenance of the aneuploid chromosome during tumorigenesis.

Conclusions and future directions

Although recent work has highlighted the frequency of recurrent chromosome gains and losses in human can-cer, the contributions of aneuploidy to the phenotypes of these cells remain less clearly defined. Despite recent

Figure 4 | **Aneuploidy-specifc therapeutic strategies.** There are multiple strategies for targeting aneuploidy. **a** | Chromosome instability (CIN). This approach requires targeting genetic dependencies in cells with CIN. For example, studies have identified mutations displaying synthetic lethality with mutations that trigger genetic instability. **b** | General cellular responses to aneuploidy. Another appealing approach is to interfere with pathways that aneuploid cells have a greater reliance on as part of their general response to aneuploidy compared with normal cells. This may include the ubiquitin–proteasome, heat shock protein (HSP) chaperones and autophagy pathways. **c** | Chromosome-specific targets. It may also be possible to target recurrent whole-chromosome aneuploidies in cancer. This could include both the driver and passenger genes on the aneuploid chromosome. For example, a driver gene could be a mutated and/or overexpressed oncogene that is required for tumorigenesis. The passenger gene could be a transporter protein that, although not required for tumorigenesis, increases the influx of a cytotoxic agent.

AICAR
Short for 5-aminoimidazole-4-carboxamide ribonucleotide, this is an activator of AMP-activated protein kinase (AMPK), which is a metabolic master regulator that is activated in times of reduced energy availability.

HSP90 inhibitor
A class of drugs, including 17-allylaminogeldanamycin (17-AAG), that inhibit the function of the molecular chaperone heat shock protein 90 (HSP90), which is involved in protein folding.

advances in defining the effects of aneuploidy on the transcriptome and proteome of cells, many important questions still remain unanswered, including what the *in vivo* causes of aneuploidy are. Although substantial work has been directed towards developing mouse models of aneuploidy using dysregulated SAC genes, how frequently spindle checkpoint defects occur in human tumours remains unclear. In light of the important role of centrosome amplification in generating CIN[23,24], animal models wherein centrosome amplification can be induced without altering other cellular signalling pathways would be of high interest. Thus, additional work needs to be focused on understanding the *in vivo* causes of aneuploidy and developing new models that reflect these causes.

Although recent work in yeast has demonstrated that aneuploidy can cause genomic instability, future work will need to address whether this also occurs in human tumours and whether the accumulation of these genomic alterations, including translocations and mutations, actually contributes to tumorigenesis. Also, what

other driver mechanisms are important in recurrent aneuploidies in cancer? For example, what is the role of trisomy of chromosome 8 in acute myeloid leukaemia? Furthermore, how are the effects of aneuploidy modulated by the cellular genetic context and tissue microenvironment?

A key question, from the standpoint of developing new therapeutics, is whether all aneuploid cells share common characteristics. Does aneuploidy trigger a common stress response and do all aneuploid cells need to develop specific adaptations in order to proliferate with their altered genomes? Alternatively, should we view aneuploid cells as being similar to Tolstoy's unhappy families, where each aneuploid cell is abnormal in its own way? A more comprehensive understanding of these effects, and the resulting physiologic responses will probably be required in order to exploit aneuploidy for therapeutic gain fully. Nevertheless, the recent advances are encouraging and hold promise for the possibility of a new, personalized, karyotype-specific approach to cancer therapy.

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FURTHER INFORMATION
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ClinicalTrials.gov: http://www.clinicaltrials.gov
Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer: http://cgap.nci.nih.gov/Chromosomes/Mitelman
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