Whole chromosome aneuploidy: Big mutations drive adaptation by phenotypic leap

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Despite its widespread existence, the adaptive role of aneuploidy (the abnormal state of having an unequal number of different chromosomes) has been a subject of debate. Cellular aneuploidy has been associated with enhanced resistance to stress, whereas on the organismal level it is detrimental to multicellular species. Certain aneuploid karyotypes are deleterious for specific environments, but karyotype diversity in a population potentiates adaptive evolution. To reconcile these paradoxical observations, this review distinguishes the role of aneuploidy in cellular versus organismal evolution. Further, it proposes a population genetics perspective to examine the behavior of aneuploidy on a populational versus individual level. By altering the copy number of a significant portion of the genome, aneuploidy introduces large phenotypic leaps that enable small cell populations to explore a wide phenotypic landscape, from which adaptive traits can be selected. The production of chromosome number variation can be further increased by stress- or mutation-induced chromosomal instability, fueling rapid cellular adaptation.

Keywords:
adaptation; aneuploidy; population; stress

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Introduction

An *E. coli* cell contains a single DNA molecule of five million base pairs. *Saccharomyces cerevisiae* (budding yeast), a unicellular eukaryote, has a DNA content of 24 million base pairs in its diploid form. This number increases to six billion base pairs in humans, providing the genetic coding to support their unsurpassed functional complexity. One of the important evolutionary advances in eukaryotes seems to be segmentation of the genome into multiple DNA molecules, which form highly compact, organized structures called chromosomes. With the increasing amount of DNA, the workload of DNA segregation during cell division increases accordingly. Eukaryotes utilize intricate machinery, consisting of the mitotic spindle and the kinetochore associated with each segregating chromosome, to ensure accurate transmission of genomic information [1, 2]. Along with this machinery, a sensitive monitoring system (the spindle assembly checkpoint, SAC), has evolved to deal with errors and perturbations of spindle mechanics [3, 4]. Even so, chromosome segregation remains a weak link in genome transmission: in a normal yeast population, aneuploidy represents a large proportion of the genetic variations that occur (see below).

Errors in genome transmission are usually harmful to the fitness of an individual cell or organism but, in a population with a large number of individuals, imperfect genome transmission produces genetic variants, which are essential for adaptive evolution under selection. The most commonly considered genetic variants during evolutionary processes are point mutations. Chromosome segregation also produces genetic variants; not in single gene sequences, but in the copy number of chromosomes, which contain hundreds of genes. This genetic variation is referred to as whole chromosome aneuploidy [5–8]. In this review, ''aneuploidy'' refers to whole chromosome number variation, without including segmental chromosome aneuploidy. By changing the dosage of many genes, aneuploidy leads to dramatic consequences. In humans, aneuploidy is primarily recognized in diseases such as Down's syndrome [9] and cancer [10]. The role of aneuploidy in these two diseases is drastically different (see below).

Moreover, there are many other cases where aneuploidy is not pathological, but a physiological state [11–13]. It is speculated that such physiological aneuploidy may have beneficial effects for cells or organisms. In this review, we propose a model to explain how aneuploidy can be an effective mode of adaptation during somatic evolution, where the population size is usually restricted. The rate of production of aneuploids is not always constant, and we discuss the findings that certain environmental stressors could induce chromosome instability (CIN), leading to resistance to stress itself or increased evolvability to a broad spectrum of cytotoxic reagents.

Aneuploidy is a widespread genetic variation in nature

Early studies on aneuploidy related it solely to disease states, which suggest that aneuploidy is unlikely to be persistent in populations as a result of the detrimental effect on fitness. In recent years, the advent of genome technology, especially comparative genome hybridization and DNA sequencing, reveals a different picture (Table 1). In lab strains of *S. cerevisiae*, it was estimated that 8% of the strains from the genome-wide ORF knockout library were aneuploid [14]. Aneuploidy has also been identified in wild yeasts isolated from the environment such as oak tree soil [15]. In industrial yeast strains, the deviation of DNA content from euploidy is a common feature that was first documented decades ago [16]. High-resolution genomic analysis techniques such as array-based comparative genomic hybridization (aCGH) and next-generation sequencing has revealed the detailed genome structure and copy number variation, which includes whole chromosome aneuploidy, in strains used for diverse industrial applications, such as sake and beer brewing [15, 17, 18], wine fermentation [18], and sherry-wine aging [19]. In pathogenic yeast/fungi, aneuploidy is associated with drug resistance [5, 20]. For example, more than 50% of fluconazole-resistant *Candida albicans* isolates from patients were found to harbor either whole chromosome or segmental duplication of Chr 5 [21]. Whole chromosome aneuploidy was also found in fluconazole-resistant strains of another pathogenic yeast, *Cryptococcus neoformans* [22].

Beyond yeast and fungi, aneuploidy has been documented in many other contexts. It is long thought that due to their erroneous transmission during meiosis, aneuploid karyotypes are unlikely to be maintained during long-term adaptation and speciation in natural history. However, an outlier exists. Leishmaniasis is a form of clinical pathology, ranging from disfiguring cutaneous lesions to fatal visceral infection, caused by different *Leishmania* protozoan parasites associated with varied pathological features [23]. Interestingly, it has been found that four different *Leishmania* species/strains have little variation in DNA sequence, yet exhibit dramatic differences in chromosome copy numbers [24]. The aneuploid *Leishmania* can still perform sexual reproduction [25], but the mechanistic details have yet to be elucidated.

In multicellular organisms such as mammals, aneuploidy is present in both the germline and somatic tissues. Germline aneuploidy is rare and, when present, causes severe developmental abnormalities. In humans, chromosome number variation in fertilized oocytes causes rare birth defects such as Down's syndrome (trisomy 21, incidence of one in 2,000 births), Edwards syndrome (trisomy 18, one in 6,000 births), and Patau syndrome (trisomy 13, less than one in 10,000 births). However, it is intriguing that several studies have reported that aneuploidy is highly prevalent in the early blastomeres of developing human or mouse embryos [26, 27], raising the question as to at what stage aneuploidy impairs developmental programs and how aneuploid cells are cleared during later development. On the other hand, aneuploidy in somatic cells is not rare at all. Aneuploidy is a hallmark of cancer, one of the leading causes of death. It is present in more than 70% of tumors (Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer, http://cgap.nci.nih.gov/Chromosomes/Mitelman and [28, 29]). Evidence indicates that aneuploidy may drive tumorigenesis through its adaptive effect in a cell population (see below). But somatic aneuploidy is not limited to cancer cells – work in recent years has revealed that several normal human tissues bear a surprisingly high-level diversity of karyotypes. For example, normal human liver contains 25–50% aneuploids [13]. In the fetal brain, it has been estimated that 30–35% of neurons are aneuploid [30, 31]. Compared with animal organisms, plants such as *Arabidopsis thaliana* tolerate germline

Table 1. Examples of aneuploidy associated with environmental stress

Species		Conditions	Associated stress	Ref.
S. cerevisiae	Lab	Gene deletion	Various growth defects	[14, 35]
		Environmental stress	Proteotoxic stress	[42]
	Industrial	Sake production (1/9)[a]	Ethanol, high sugar (osmotic stress)	[15, 18]
		Wine production (4/26)[a]	Ethanol, acetaldehyde, high sugar	[15, 18, 19]
		Beer brewing (3/4)[a]	Ethanol, high sugar	[17, 18]
C. albicans		Fluconazole resistance (21/42)[a]	Membrane defect	[21]
C. neoformans		Fluconazole resistance	Membrane defect	[22]
Leishmania		Different species		[24]
Human		Most cancer	Growth restriction, immune attack	http://cgap.nci.nih.gov/Chromosomes/Mitelman and [28, 29]
		Liver	Metabolic stress	[13]

[a] Frequency of aneuploidy reported in parentheses (aneuploids/total tested).

aneuploidy well, which can cause substantial phenotypic variations [32, 33]. In summary, aneuploidy is observed from yeasts to humans. With the increasing application of quantitative DNA technology, it is likely that further evidence will emerge from diverse contexts illustrating the widespread existence of aneuploidy.

Why is aneuploidy, which defines an "abnormal" genome, widespread in nature?

"Abnormal" karyotypes can be beneficial under abnormal environmental conditions

The effect of aneuploidy on fitness is context-specific [6]. Aneuploidy is thought to induce abnormality due to an imbalance in gene dosage. It is assumed that the "normal" functionality of molecular complexes or pathways made of more loosely interacting molecules relies on the correct stoichiometry of their protein components. When the normal stoichiometry is skewed, the functionality in terms of efficiency, timing, or specificity of the system could be reduced or altered in some way. However, normalcy is relative and, in the context of physiology, it refers to the preferred state or the state of highest fitness under a given condition. Thus, a cell with a genome imbalanced (i.e. with suboptimal stoichiometry) for one condition, say the "normal" environment, may indeed have the altered functionality that gives rise to optimal fitness under an altered, for instance, stressful condition [6, 34]. In many cases, the prevalence of aneuploidy, as discussed above, has indeed been found in association with stress (Table 1). For example, the wine brewing/aging process imposes potent proteotoxic stress due to high concentrations of ethanol and acetaldehyde [19]. Fluconazole impairs the synthesis of ergosterol, an essential component of the cell membrane of *C. albicans* [35]. Even the normal tissue environment in an animal organism is usually repressive for cellular proliferation, which cancer cells must overcome (see below).

The mechanism by which aneuploidy can bring adaptive phenotypic change has been extensively studied in single cell organisms. Aneuploidy can cause changes in expression patterns in different ways, manifested at both the mRNA [14, 34, 36–40] and protein [34, 41] levels. Although altered chromosome stoichiometry leads to expression pattern changes for many genes, in some cases the adaptive effect of aneuploidy can be attributed to a dosage change for a single gene. For example, a homozygous deletion of the *RPS24A* gene on yeast Chr V causes a growth defect. However, large, fast-growing colonies occasionally appear among a group of small colonies. It was found that cells in these large colonies had gained a copy of Chr IX, carrying a *RPS24B* gene that is 97% identical in sequence to *RPS24A* [14]. An advantage of achieving adaptive functions through aneuploidy, over that through mutations of specific genes, is that genes contributing to the same physiological outcome may be present on the same aneuploid chromosome. This allows a combination of adaptive dosage changes to two or several genes through a single chromosome dosage change. In *C. albicans*, the fluconazole resistance associated with Chr V duplication can be mimicked by increasing the dosage of *ERG11* (encoding the drug target) and *TAC1* (encoding a regulator of the drug efflux system), which are both located on this chromosome [21, 35]. Euploid budding yeasts can adapt to the lethal-level Hsp90 inhibitor, radicicol, by gaining Chr XV [42]. Much of the enhanced resistance is due to the synergistic effect of the increased dosage of two genes located on Chr XV: *STI1*, encoding an Hsp90 co-chaperone and *PDR5*, encoding a drug pump [42].

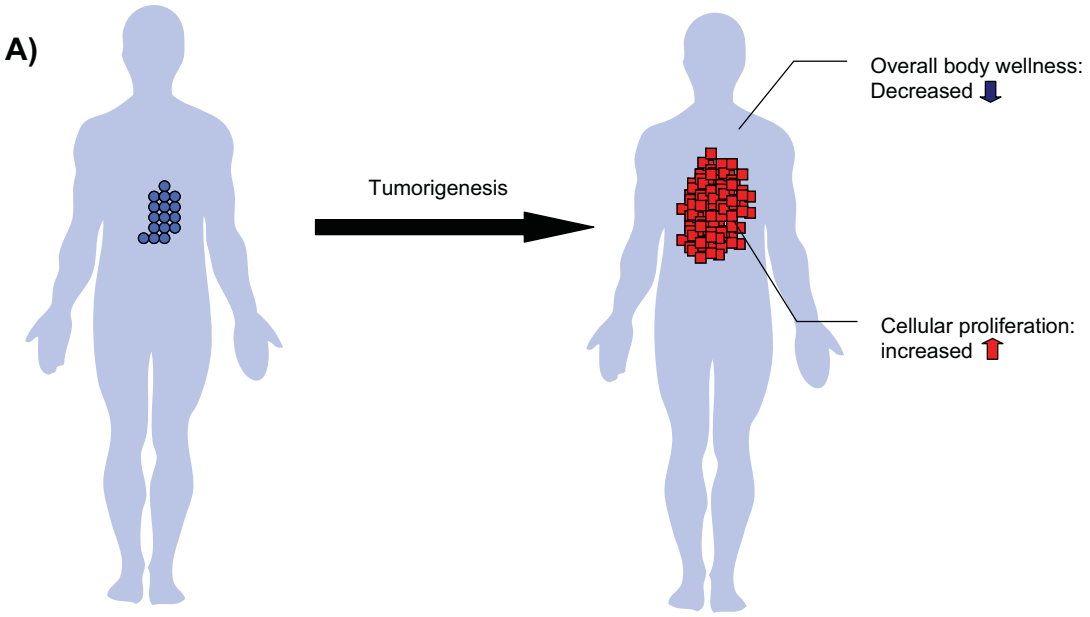
The dosage change of genes located on an aneuploid chromosome can also bring about adaptive traits by altering the expression of genes on other chromosomes. Myo1 is a motor protein required for constriction of the bud neck during cytokinesis. Deletion of *Myo1* leads to cytokinesis failure and in most cases lethality [43]. In the rare *Δmyo1* survivors, some are able to restore cytokinesis through gradual thickening of the cell wall at the bud neck. In these adapted strains, the expression of several genes involved in cell wall biogenesis is increased up to 16-fold compared to that in the isogenic wild-type haploid strain. Interestingly, these genes are located on multiple different chromosomes, but a commonly amplified chromosome in these strains is Chr XVI. It turns out that Chr XVI carries the genes encoding two upstream regulators of cell wall biogenesis, Rlm1 and its upstream activator Mkk2, a MAP kinase kinase [35]. Thus, by altering the dosage of regulatory factors, aneuploidy can cause broad gene expression changes well beyond a direct DNA dosage effect.

Even though aneuploidy can introduce adaptive traits into a population, it has also been noted that in any given environment, such as the presence of proteotoxic stress [36, 42] or a DNA damaging agent [34, 44] or low temperature [34], most of the aneuploid karyotypes tested are not adaptive. In fact, only some aneuploid karyotypes show enhanced growth compared to the euploid. This reinforces the idea that phenotypic changes generated by mutations are usually deleterious [45]. Nevertheless, mutations are a necessary ingredient of the force that drives adaptive evolution. In other words, chromosome number variation or any other type of mutation does not guarantee enhanced cell fitness, but rather the adaptive value of genetic variation is best appreciated at the population level, where the adaptive variant is selected through competition.

Aneuploidy impacts organismal versus cellular fitness differently in multicellular species

Despite evidence in unicellular organisms demonstrating how changes in chromosome stoichiometry bring about adaptation, it remains unclear whether similar mechanisms exist in metazoans. It has been shown that aneuploidy leads to gene expression variation in mammalian cell lines in a manner similar to that in yeast [39, 40, 46], but the counter argument has been that aneuploidy causes debilitating diseases such as Down's syndrome and cancer. One way to reconcile this paradox is to distinguish cellular fitness from organismal fitness.

In natural history, the appearance of multi-cellularity loosened the link between organismal evolution and cellular evolution. The former is based on the relative fitness between individuals, whereas the later can be considered the fitness between cells within an individual organism. In order to survive organismal competition, strict developmental programs tightly control cell proliferation, death, and morphogenesis in order to form and maintain homeostasis of



B) **Role of aneuploidy in disease**

	Organismal Aneuploidy	Cellular Aneuploidy
Example	Down's Syndrome	Cancer
Cellular karyotype competition	No	Yes
Cellular fitness /proliferation	↑ Example: Enhanced myeloproliferation compared to euploid ↓ Example: Reduced angiogenesis	↑ Through competition, the adaptive karyotype is seleceted. Example: Chr 8 duplication in APL
Overall body wellness	↓	↓

Figure 1. Aneuploidy can exert opposing effects on overall body wellness and cellular fitness in disease. **A:** In tumorigenesis, the cellular fitness/proliferation of tumor tissue is enhanced at the expense of overall body wellness. **B:** Aneuploidy can have different roles at the cellular versus organismal level. Organismal aneuploidy originates from karyotype alteration in parental germ line/gametes. Cellular aneuploidy results from errors in somatic cell mitosis.

functional structures. Thus, organismal fitness occurs at the expense of the proliferative ability or even viability of individual component cells. In contrast, oncogenic mutations promote the cellular proliferation and survivability of cancer cells at the expense of the fitness of the host organism (Fig. 1A). For example, the Ras protein, which controls cellular mitogenic signals, is mutated to hyperactive forms in 25% of cancers and renders abnormally high growth potential for the cancer cells harboring the mutations [47]. The extrinsic barrier to cell proliferation, such as limited vesicular accessibility, can also be lifted by enhanced expression of VEGF in tumors [47]. These examples highlight the apparent conflict between cellular versus organismal fitness.

Whole organism aneuploidy, such as Down's syndrome, originates from karyotype alteration in parental germ cells, which leads to drastic gene expression changes that disrupt the intricate, long-evolved developmental program, resulting in disease of the organism [48]. However, tumorigenesis involves fierce selection and competition between normal cells and cancer cells, as well as between cancer cells of diverse karyotypes [49, 50]. As the tissue environment for cancer cells is hostile, this presents the natural selective force that generates the different types of genetic variants that can survive and improve the fitness of the cell population at the expense of organismal fitness. As a well-known cancer hallmark, karyotype abnormality is a major source of genetic variation in cancer [10, 28].

The direct causative relationship between the specific karyotype and overproliferation phenotype of tumors has been captured in a few cases (Fig. 1B). Trisomy 8 has been observed in 12% of human acute promyelocytic leukemias (APL) [51, 52]. It has long been speculated that trisomy 8 endows the growth advantage through introduction of an additional copy of the oncogene, *MYC*. Interestingly, in an APL mouse model, 64% of the cases were trisomic for chromosome 15, which also contains the mouse *MYC*. *MYC* retrovirus transduction facilitated myeloid leukemogenesis and suppressed gain of chromosome 15. Meanwhile, the induction efficiency for APL in the heterozygous *MYC* background was reduced. Remarkably, in the heterozygous *MYC* mice where APL was inducted, preferential

amplification of the chromosome 15 containing the wild-type *MYC*, but not the one missing the gene, was observed. These data strongly suggest that the elevated copy number of *MYC* arising from aneuploidy directly participates in the progression of APL [53]. Another case comes from the well-characterized Down's syndrome-associated predisposition to leukemia. Down's syndrome patients have a reduced incidence of most tumors compared with the euploid population [54, 55], but their incidence of pediatric acute megakaryoblastic leukemia (AMKL) is increased 500-fold [56]. Accordingly, the mouse model of Down's syndrome, which contains a trisomic chromosome region syntenic to human chromosome 21, also shows excessive cell proliferation in myeloid linages, which may progress into AMKL [57]. Later, it was found that by deleting the trisomic copy of *Erg*, a transcription factor necessary for platelet development and stem cell function, myeloproliferation was restored to normal [58]. This case highlights that a karyotype (trisomy 21) that is detrimental at the organismal level, can still increase fitness and proliferation at the cellular level in certain contexts (Fig. 1B). In spite of a few well-studied cases, the direct causative link between karyotype and tumor phenotype in many cases remains elusive due to the high level of karyotype complexity associated with even a single cancer. This may reflect the existence of different ecological niches in a tumor [49]. In addition, different karyotypes can induce adaptation to the same stressor, as recently shown in budding yeast [34, 37]. The tools that monitor karyotype at the single cell level, such as spectral karyotyping (SKY) or single-cell sequencing [59], will provide insight into how karyotype heterogeneity evolves during tumor progression or cancer treatment. An ability to dissect the contribution of specific karyotypes to tumor phenotypes in a karyotypically heterogeneous population will be crucial for understanding the role of aneuploidy in tumorigenesis.

Aneuploidy drives adaptation in small cell populations by phenotypic leap

We propose the following model to rationalize the effectiveness of aneuploidy in rapid cellular adaptation, as observed in experimental studies in yeast. First, aneuploidy represents a readily occurring form of genetic variation in a population. The rate of chromosome missegregation in yeast is estimated to be one in 100,000 chromosome segregation events [60], which is five orders of magnitude higher than the point mutation rate per base pair per generation [61, 62]. Considering a haploid yeast genome (16 chromosomes) with a coding region of 10^7 base pairs, the rate of chromosome missgregation per cell division is likely to be ~10% of the rate of a random point mutation occurring in the genome. However, one chromosome missgregation event has 100% probability of causing a change in the expression pattern of hundreds of genes in the resulting aneuploid progeny. The spectrum of mutations in yeast was experimentally analyzed in a study where mutations were accumulated in 32 individual cultures growing for 4,800 generations in a selection-neutral process [62]. Two-hundred population bottlenecks were introduced to allow unbiased accumulation of mutations. Whole genome re-sequencing revealed 33 point mutations, with 18 being non-silent and possibly altering protein function in the affected genes. This experiment also captured two aneuploidization events, each causing a dosage change in over a hundred genes (Chromosome I and IX). In addition, other types of large changes in chromosome structure were also observed. Thus, aneuploidy and changes in chromosome structure represented a considerable portion of the genetic variation in a non-stressed yeast population.

The model presented in Fig. 2 compares the probability of adaptation caused by two classes of mutations; one with large

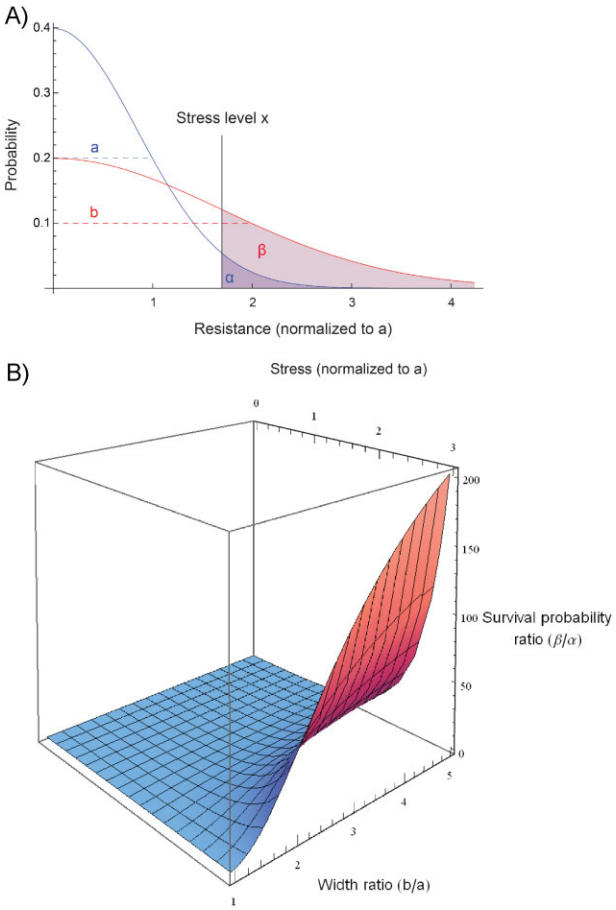


Figure 2. Potent selection favors mutation with large phenotypic variation. **A:** The fitness distribution of two classes of mutations. Class A (blue) and Class B (red) generate different amounts of phenotypic variation (shown as the different characteristic widths a and b). For simplicity, we assume that both mutations have the same skewed normal distribution of fitness (shown as varied resistance) and only one side of the distribution is shown. Under stress level *x*, only the mutants with a resistance level in the shaded area (survival probability α for Class A, β for Class B) can survive. **B:** Severe stress exaggerates the β/α ratio, and favors the survival of Class B mutants with large phenotypic variations. The three-dimensional plot demonstrates that the survival probability of Class B mutants (β) relative to Class A mutants (α) increases with either enhancement of stress (*x*) or increasing phenotypic variation of Class B mutants relative to Class A mutants; the phenotypic variation is represented by characteristic width *a* and *b*, respectively. The stress level is normalized to the characteristic width *a*. For a Class A mutation with a fitness distribution that has the characteristic width *a*, the survival probability α under stress level *x* is calculated as: $\alpha = (1/2)\,\mathrm{erfc}(x/\sqrt{2}a)$ where erfc denotes a complementary error function. The probability of survival for a Class B mutation is calculated similarly.

and the other with relatively small phenotypic variation (Fig. 2A). The relative adaptive probability between the two classes varies dramatically depending on the level of stress (i.e. selection; Fig. 2B). Aneuploidy modulates the expression of a large number of genes. One or a multiple of these changes could interact with the stress to cause large phenotypic change, akin to phenotypic leap, which enables the cell to explore a wide region of phenotypic landscape [6]. Moreover, in a diploid genetic background, i.e. the common basal ploidy for many multicellular organisms, recessive mutations will be masked, further limiting the phenotypic impact of nucleotide substitutions.

Given these considerations, we speculate that adaptive evolution in relatively small populations under a strong selective force, which limits the number of mutations with sufficient phenotypic effect to achieve adaptation, favors the selection of aneuploidy over point mutations. Certain somatic evolutionary processes, such as the clonal expansion in early tumor progression or relapse after drug treatment, may fall into this category. Gross changes in chromosomal structure represent another type of genomic change that can cause large phenotypic variation. Also, like whole chromosome aneuploidy, gross changes in chromosomal structure are frequently observed in cancer.

Chromosome instability can be induced by stress

A major cause of aneuploidy is chromosome instability (CIN), which results from errors in the chromosome segregation process during mitosis or meiosis. The rate of CIN is non-zero in well-adapted euploid cell populations and can be further increased due to genetic aberrations or under certain stressful conditions, as has recently been shown. Genes that cause CIN when mutated are called CIN genes, many of which encode components of the kinetochore, centrosome or mitotic checkpoint, which directly participate in the chromosome segregation process. In mammals, there is considerable evidence that CIN gene mutations are tumorigenic, even though the exact karyotypes that arise from these mutations have not been identified. For example, Mad2 overexpression in mice, which delays mitotic progression, promotes the occurrence of aneuploidy and leads to a wide spectrum of tumors [63]. Mutations in the checkpoint component BUB1B [64] or the centrosomal protein CEP57 [65] cause mosaic variegated aneuploidy and hereditary cancer in humans. However, CIN that is too high can inhibit tumorigenesis. In mice, the haploinsufficiency of CENP-E, a kinechore component, modestly increases CIN in various tissues [66]. It drastically increases the incidence of spleen and lung tumors in aged animals. However, in the liver, it inhibits the formation of spontaneous cancer. As the basal level of CIN is high in the liver [12, 67], it is speculated that CIN levels that are too high to even maintain the tumorigenic karyotype can suppress tumor formation [66].

Our recent study in budding yeast showed that other than genetic mutations, certain stressors can escalate CIN and potentiate rapid cellular adaptation to this or other unrelated types of stress [42]. Assays using an artificial chromosome revealed that many stress conditions, including hydrogen peroxide (oxidative stress), cycloheximide (translational stress), tunicamycin (ER stress), etc., elevated the rate of chromosome loss to a level similar to that caused by benomyl, a microtubule inhibitor that disrupts the mitotic spindle. Surprisingly, radicicol, an Hsp90 inhibitor, was an exceptionally effective CIN inducer: the rate of chromosome loss was hundreds of times above the control and ~10-fold higher than that induced by benomyl, even at a radicicol concentration with only a minor effect on growth. This CIN-inducing effect is likely to be due to a crucial role for Hsp90 in kinetochore assembly [68, 69]. A high concentration of Hsp90 inhibitor resulted in the emergence of drug-resistant colonies with gains in chromosome XV. It has been noted that even though most yeast aneuploids grow more slowly than their euploid counterpart under Hsp90 inhibition [36], rare adaptive aneuploid yeasts (with Chr XV gain) can nonetheless emerge and be selected from the population with diverse karyotypes during the long-term adaptation process. More disturbingly, short-term exposure to moderate Hsp90 stress, which generates a karyotypically mosaic cell population, potentiated adaptation to unrelated cytotoxic compounds through different aneuploid chromosome stoichiometries. In the pathogenic yeast *C. albicans*, exposure to oxidative stress, heat stress and antifungal drugs elevates the rate of chromosome loss, which may also fuel the emergence of drug resistance, for which aneuploidy is one of the major contributory mechanisms [70].

The possibility of targeting Hsp90 in tumor therapy has been actively investigated in recent years [71]. A recent report showed that, in short-term cell cultures, an Hsp90 inhibitor can specifically antagonize the proliferation of certain trisomic cells, as well as CIN cell lines with high level aneuploidy, but spare the euploids [72]. This acute effect may reflect that most aneuploids are sensitive to Hsp90 inhibition. However, as in yeast, Hsp90 has been reported to be required for kinetochore function in mammalian cell lines [73, 74], raising the possibility that in long-term selection-resistant cancer cells, rare adaptive karyoytpes may appear as a result of CIN induced by the drug itself.

Summary and perspective

Aneuploidy is a genetic alteration existing in somatic cell populations. The occurrence of aneuploidy can be further increased by either mutation in CIN genes or certain environmental stress. By altering the expression of hundreds of genes at the same time, aneuploidy imposes phenotypic consequences that are, in general, much larger than those arising from random single nucleotide mutations. This phenotypic leap makes aneuploidy an important mode of adaptation for somatic cell populations. Despite the observation of aneuploidy in cancer for over a hundred years, only in a few cases has the causative relationship between specific karyotypes and tumorigenic phenotype been established. The karyotype-phenotype relationship in cancer is complicated by the complexity of karyotypes in many cases and is clearly a challenge for future research. Further, whether stress-induced chromosomal instability occurs in animal organisms and whether it could underlie rapid tumor cell evolution remains to be elucidated. It raises the question as to whether the stress

caused by drugs in fact facilitates the genetic instability that promotes the evolution of drug resistance. The observation of aneuploidy in normal tissues has gained increasing attention in recent years. It remains unclear how some normal tissues can maintain high-level karyotype mosaicism. Whether this genetic diversity is required for the functioning of these tissues or helps the cells to cope with a stressful tissue microenvironment are also interesting questions for future investigation.

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