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The Causes and Consequences of Aneuploidy in Eukaryotic Cells

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1. Introduction

Correct transfer of genetic information to daughter cells is essential for successful propagation of any organism. Three processes are involved in maintenance and propagation of genetic information: DNA replication, DNA damage repair and chromosome segregation. Error in any of these processes might result in cell death, or, in another scenario, in survival of cells with altered genetic information. This might be reflected either by single nucleotide changes as well as small insertions and deletions; or it might lead to larger alterations in the structure and number of chromosomes, together called aneuploidy. In this chapter, our current knowledge on causes and consequences of aneuploidy in human cells and relevant model organisms will be summarized.

2. What is aneuploidy?

Aneuploidy describes any karyotype that differs from a normal chromosome set (called euploidy) and its multiples (called polyploidy). Aneuploidy can occur either by chromosome gains and losses due to chromosome segregation errors, a so called "whole chromosomal" aneuploidy, or due to rearrangements of chromosomal parts, often accompanied by their deletion and amplification, that is referred to as a "structural" or "segmental" aneuploidy (Fig. 1). Frequently, a combination of both structural and numerical chromosomal changes can be found, in particular in cancer cells (composite aneuploidy). Aneuploidy and its link to various pathologies has been known for more than a century.

Aneuploidy often reflects chromosomal instability (CIN), which is an ongoing defect in faithful transmission of chromosomes [1, 2]. Chromosomally instable cells accumulate new karyotype alterations as they proliferate and they are always aneuploid. In contrast, not every aneuploidy is linked to CIN, some cells can remain in a stable aneuploid status for multiple generations. This is well documented by the fact that patients with trisomy syndrome (e.g. trisomy of chromosome 21 in Down syndrome) usually show stable karyotype [3]. CIN, and consequently aneuploidy levels are often elevated in high-grade tumors and can be considered a reliable marker of high malignancy and drug resistance at least in some cancer types [4] [5].

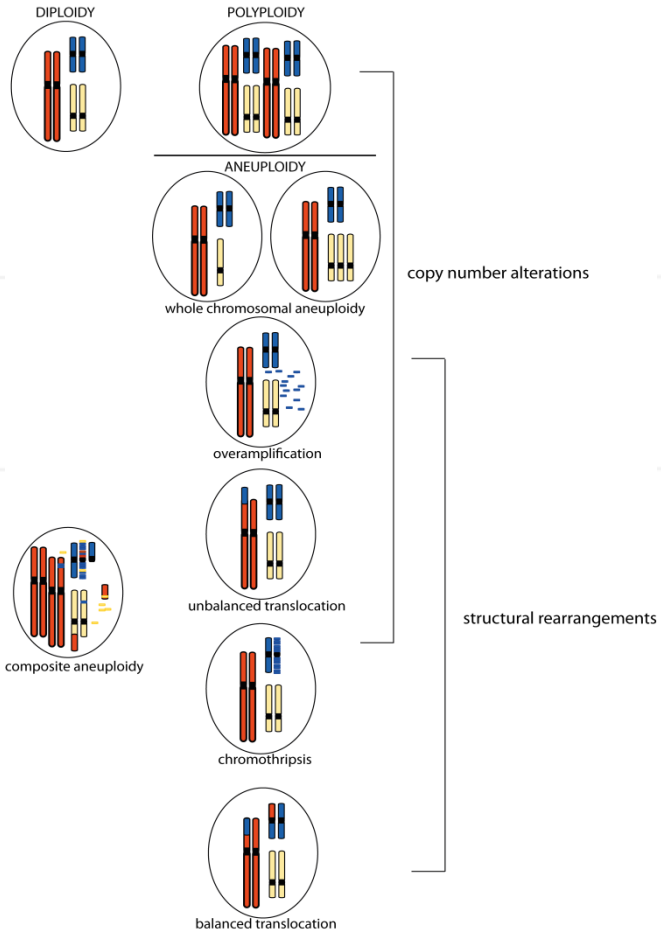


Fig. 1. Types of aneuploidy and copy number changes in eukaryotic cells.

2.1 Whole chromosomal aneuploidy

Whole chromosomal aneuploidies might arise due to random and sporadic chromosome missegregation events that occur with low frequency during any cell division. The missegregation levels range from 1/1000 to 1/10000 for human cells, and 1/10000 – 1/100000 for budding yeast in laboratory conditions and can increase in response to endogenous and exogenous agents that impair mitotic functions. The frequency of aneuploidy *in vivo* is difficult to estimate and likely depends on the type of tissue, but it might be as high as 1-2% abnormal numbers per chromosome.

Missegregation errors can occur also in germline cells. Aneuploid germinal cells that arise due to a chromosome segregation error in meiosis give rise to aneuploid embryos that show significant defects and frequently die during embryonic development. In fact, a whole chromosome aneuploidy is one of the major causes of spontaneous miscarriages [6]. There

are only few types of aneuploidies that are compatible with survival. Various aneuploidies of sex chromosomes usually do not interfere with the survival and manifest with rather mild growth alterations, mild mental disability and infertility [7]. The effect of sex chromosome abnormalities is relatively low and does not interfere with viability due to the small genetic contribution of chromosome Y and due to X chromosome silencing via an epigenetic mediated pathway [8].

Autosomal trisomies have a much larger effect and only trisomy of chromosome 13 (Edwards syndrome), trisomy of chromosome 18 (Pateu syndrome) and trisomy of chromosome 21 (Down syndrome) are compatible with survival [9]. In all cases the presence of an extra chromosome copy results in a complex pathologic phenotype (for example there is up to different 72 pathological features linked to trisomy 21) that often severely impair quality of life. Down syndrome with mental disability, frequent heart defects, multiple facial and dactylic alterations and early onset lymphomas (among other pathologic features) is the only trisomy compatible with survival untill adulthood. The reasons for the dramatic effect of the trisomies as well as the molecular mechanisms underlying the phenotypes are not fully understood [10]. Accordingly, no targeted therapy is available for trisomy syndrome patients despite several decades of intense research.

Congenital trisomy leads to embryonic death also in mice, indicating that whole chromosomal aneuploidy is generally not well tolerated and leads to detrimental changes in organism physiology. In some cases, mosaic aneuploidy or aneuploidy only within a part of a tissue can be identified suggesting that low levels of aneuploidy might be better tolerated or even beneficial.

2.2 Structural aneuploidy

Recent large-scale screens of the human genome by deep sequencing, single nucleotide polymorphism analysis (SNP) and comparative genomic hybridization (CGH) revealed a fascinating and dynamic genomic landscape with multiple copy number changes of various chromosome regions. In principal there are two major types of copy number changes that usually cover a sequence from approximately one kilobase to several megabases.

First, copy number variations (CNV) describe congenital abnormalities in gene copy numbers that usually affect segments of individual chromosomes. Their identification suggests an unanticipated plasticity of the human genome and it has been proposed that CNVs represent an important factor that affects the outcome of complex, multifactorial genetic traits ([11], for review see [12]). Many of the subchromosomal CNVs identified so far are functionally linked to various pathological phenotypes that are frequently related to neurological defects. The second type of structural changes called somatic copy number alterations (SCNA) was uncovered by large scale deep sequencing that revealed a puzzling dynamic landscape of copy number changes of human genome and reflects the variability within somatic cells of a single individual [13]. SCNAs are found in both normal tissues and, at much higher frequency in human cancers, in particular in leukaemias and lymphomas.

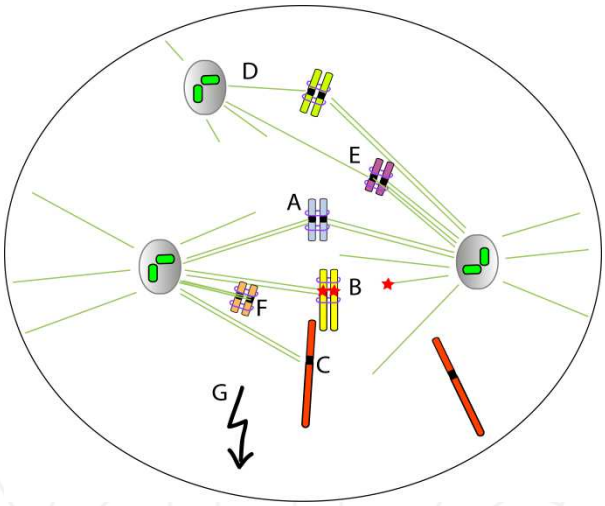
3. Causes of aneuploidy

As aneuploidy describes broad spectra of numerical and structural chromosome changes, multiple different mechanisms may lead to the emergence of aneuploid karyotypes.

3.1 Whole chromosome aneuploidy

Whole chromosome aneuploidy results mostly from chromosome segregation errors, thus generating daughter cells that have lost or gained an individual chromosome (or few of them). This can occur even during normal unpertubed cell division or after an exposure to endogenous or exogenous damaging agents. Live cell microscopy of cells missegregating their chromosomes suggests that spontaneously arising aneuploid cells often die or arrest in a p53 dependent manner [14]. Even if the aneuploids survive, they are likely outgrown by fitter euploid cells (see below).

The frequency of aneuploidy is significantly enhanced by gene mutations that impair chromosome segregation. Such a mutation leads to both aneuploidy as well as to a general chromosomal instability phenotype (CIN). This has been observed for mutations of genes that affect cell cycle regulation, mitotic spindle checkpoint and sister chromatid cohesion. Increased frequency of cells with abnormal karyotype and CIN phenotype might be also due to mutations that disrupt the capacity of cells to activate the p53 pathway or to undergo apoptosis. However, this is likely not sufficient as a knock out of p53 does not increase aneuploidy and chromosome instability in human cells [15].



A. Normal, amphitelic attachment, B. Kinetochore or microtubule defect that interferes with correct attachment, C. Defect in sister chromatid cohesion hinders correct attachment, D. multiple centrosomes lead to formation of multipolar spindles, which in turn interferes with normal chromosome segregation, E. merotelic attachments are not recognized by spindle assembly checkpoint and often remain uncorrected, resulting in lagging chromosomes and aneuploidy, F. syntelic attachments lead to incorrect chromosome segregation, G. defects in SAC interfere with error recognition and repair.

Fig. 2. Schematic depicting the mitotic spindle defects that lead to whole chromosomal aneuploidy

The most obvious triggers of chromosome missegregation are defects of the spindle. During cell division, the genetic information carried on chromosomes is equally divided into the two daughter cells. The elaborate mitotic spindle consists of microtubules emanating from the spindle poles formed by microtubule organizing centers (called centrosomes in

mammalian cells and spindle pole bodies in yeast) that attach to a proteinaceous structure, so called kinetochore, that forms at the centromeric DNA of each chromosome. Defects in kinetochore composition, microtubule dynamics or in spindle pole function lead to increased frequency of chromosome segregation errors (Fig. 2). Correct chromosome segregation is surveyed by complex machinery called spindle assembly checkpoint (SAC). Components of SAC, such as Bub1, Bub3, BubR1, Mad1, Mad2, Mad3, Mps1 and CENP-E, recognize incorrectly attached or empty kinetochores and trigger cell cycle delay until all chromosomes are properly attached to microtubules and aligned at the metaphase plate [16]. The cell cycle delay is executed via inhibition of the anaphase promoting complex-cyclosome (APC/C), whose activity is required for the metaphase-to-anaphase progression [17]. Defects in SAC lead inevitably to high chromosome missegregation levels both *in vitro* and *in vivo* and thus to aneuploidy.

Besides mutations in spindle assembly checkpoint and in mitotic spindle genes, aneuploidy is also increased in cells that carry mutant alleles of genes important for sister chromatid cohesion. Sister chromatid cohesion is maintained by evolutionary conserved cohesin rings that hold the two newly replicated chromatids together until they are separated during mitosis. Cohesion is essential for the maintenance of structural integrity of chromosomes and for proper attachment of chromosomes to the mitotic apparatus [18, 19]. The functional relevance of sister chromatid cohesion and aneuploidy has been underscored by finding that age-dependent defects in sister chromatid cohesion lead to increased frequency of aneuploid oocytes in older women, thus decreasing the chances of conceiving a healthy embryo [20, 21]. Recently, it was shown that inactivation of STAG2, which codes one of the cohesin subunits, leads to aneuploidy in human cells [22].

The widespread aneuploidy in cancer suggests that the majority of cancer cells should carry a mutation that compromises maintenance of chromosomal stability. There is over a hundred of genes identified in budding yeasts in screens aimed to identify factors avoiding CIN, most of them conserved and with multiple human orthologues. Yet mutations in these genes are not very frequent in tumors. Thus, it is possible that aneuploidy might be triggered by other events as well. Recent observations suggest that increased ploidy instigates chromosomal instability in both budding yeast [23] and human cells [24]. The hypothesis that tetraploidy facilitates CIN and subsequently tumorigenesis is supported by several *in vivo* data such as the observation that early pre-malignant stages of several tumors are characterized by increased levels of tetraploid cells [25].

Tetraploidy can arise spontaneously, by a sporadic cytokinesis error or due to cell-cell fusion induced by viral activity [26]. The list of mutations and defects that trigger formation of tetraploid cells has continuously increased in the past years. For example, telomere shortening most likely enhances the aneuploidy levels also via promoting tetraploidy as it has been shown that progressive telomere shortening leads to the accumulation of tetraploid cells in p53 deficient cell lines. It remains to be addressed in future experiments whether these mechanisms indeed contribute to the occurrence of aneuploid cells and potentially to tumorigenesis in humans.

3.2 Causes of structural aneuploidy

Whereas whole chromosomal instability and whole chromosomal aneuploidy are mostly linked to the defects in mitotic spindle function, the structural aneuploidy is generally

viewed as a consequence of DNA breakage. The inherited CNVs are likely generated through meiotic unequal crossing over or nonallelic homologous recombination (NAHR) mediated by flanking repeated sequences or segmental duplications [27]. The somatic SCNA may arise by multiple mechanisms acting on a primary DNA damage. This might lead to the breakage-fusion-bridge cycle, where the broken chromosomes can join, thus forming a bi-centric chromosome that will be inevitable exposed to massive pulling forces upon attachment to microtubules during mitosis. The opposing pulling forces cause a chromosome breakage, thus providing new DNA break points for yet another fusion. Hence, once destabilized, the genome may undergo several rounds of structural changes.

The priming DNA breakage can occur by multiple mechanisms, but the relative importance remains unclear. The identified brake sites are both recurrent, e.g. they occur at specific hotspots, or random, thus suggesting a nonspecific mechanism of DNA damage (oxidative free radicals, ionizing radiation, or spontaneous DNA backbone hydrolysis). The non-random DNA breaks can arise near telomeres, as the DNA ends get exposed due to telomere attrition and become free for the double strand break repair, mostly via non-homologous end joining with another chromosome, thus generating a bi-centric chromosome. However, it should be noted that telomere shortening is not the only factor in genomic instability and tumor formation[28]. The primary break can be also formed at chromosome fragile sites, where DNA fork is frequently posing during replication stress and might eventually disassemble, thus exposing vulnerable DNA [29]. Surprisingly, the breakpoints identified at sites of copy number changes in cancer cells mostly do not overlap with the mapped fragile sites, thus suggesting other factors influencing the DNA strand breaks. The increasingly detailed map of human DNA will certainly bring new insight into the possible links between DNA secondary structure and sites of DNA breaks [13]. For example, recent large-scale genome profiling studies of breakpoints in cancer cells identified spatial clusters that are significantly enriched for potential G-quadruplex-forming sequences [30].

Recently, occurrence of DSBs in a close vicinity of centromeric DNA has been observed during mitosis in human cells *in vitro*. These pericentromeric breaks occur due to the merotelic attachments, where one kinetochore attaches to microtubules emanating from both spindle poles, thus exposing a chromatid to opposing pulling forces[31]. Similar pericentromeric breaks were observed also in tumor cells *in vivo*, and whole arm changes that could result from this type of breaks are frequently found in cancerous genomes. Furthermore, it has been suggested that lagging chromosomes can be damaged when the lagging DNA gets trapped within the cleavage furrow and brakes due to the forces of the actomyosin ring during cytokinesis [32]. Further research will be required to address how frequently these mitotic DNA breaks occur *in vivo* and whether they can explain the chromosomal rearrangements observed in tumors.

The lagging chromosomes are often left behind the main chromosome mass during cell division. These chromosomes, even if segregated properly, often form a micronucleus surrounded by its own nuclear envelope, hence isolated from the main nucleus. Recently, it has been shown that the replication of DNA trapped in the micronuclei is often defective, most likely due to the unbalanced sources of DNA replication machinery [33]. In several cases, a total "pulverization" of such a chromosome or chromosome part can be observed (called chromothripsis). The chromosome can get again reassembled and joins with the main

chromosome mass during the next mitosis. Such abnormally reassembled chromosomes are observed in some specific tumor types at low frequency[34], and might also lead to copy number alterations, as some parts of the chromosome are lost or amplified.

4. Consequences of aneuploidy

The severe consequences of abnormal chromosome numbers in trisomy syndromes as well as the link of aneuploidy to cancer clearly suggest remarkable effects of aneuploidy on the physiology of eukaryotic cells. Recently, several model systems have been carefully analyzed in respect to the consequences of copy number changes. This research brought a plethora of observations of the phenotypes of aneuploid cells, but so far only a little understanding about the underlying molecular mechanisms.

4.1 Growth defect of aneuploid cells

Whole chromosomal aneuploidy has a detrimental effect in nearly all organisms analyzed so far, which is most frequently manifested by the remarkably slow growth or even cell death. Various developmental abnormalities and growth defects have been shown in many different organisms starting from *Schizosaccharomyces pombe* [35], *Saccharomyces cerevisiae* [36], Drosophila [37], *Caenorhabditis elegans* [38], mouse [39] and human [9]. This is in particular remarkable in response to monosomy, where one homologous chromosome is missing. Monosomy is nearly non-existent in normal, non-cancerous human cells, most likely due to a frequent haploinsufficiency of many human genes. In contrast, diploid budding yeasts cells with monosomy can survive, as there are only few haploinsufficient genes [40]. Yet, even in this case a population of cells with a normal diploid karyotype will be quickly selected [41]. Cancerous cells often show a monosomic pattern for individual chromosomes. However, as monosomy in tumor cells is often accompanied by multiple additional changes within their composite karyotype, we can assume that the haploinsufficiency is compensated for by other genomic changes.

Not only a loss of chromosomes detrimental; a presence of extra chromosomes impairs cell growth as well. The first studies linking aneuploidy to the decreased fitness of eukaryotic cells were conducted in primary fibroblasts from Down syndrome patients that were shown to proliferate more slowly than euploid control cells *in vitro* [42]. Moreover, aneuploid embryos are often characterized by slow intrauterinal growth and a lower birth weight. Similarly, trisomic human cells generated *in vitro* by a single chromosome transfer show frequently a slow growth, which is also observed in mouse trisomic cells obtained by selection of cells after Robertsonian translocation [39]. Experimentally generated disomic budding yeasts show a significant growth delay as well [36].

What exactly causes the growth defect that is often observed in cells with an extra chromosome remains an open question. It has been shown that it is not simply the presence of extra DNA, as an artificial chromosome engineered from non-transcribed human DNA does not cause a growth delay in budding yeasts [36]. Thus, an increased expression of the extra genes is necessary to trigger the detrimental effect. There are at least two principal possibilities. First, the phenotypic changes might be due to an effect of individual de-regulated gene(s) that affect pathways important for cell survival. As an example, disomy of chromosome 6 in budding yeast is not viable, whereas other disomies are, and the likely

explanation is the increased expression of *TUB2* and *ACT1*, which were previously shown to interfere with cell viability [36]. Further lines of evidence support this idea. For example, some regions of the genome are rarely amplified, which might be due to the presence of a gene whose over-expression would not be compatible with survival. Addition of an extra chromosome might be also advantageous, if for example a specific gene supporting proliferation is carried on the extra chromosome.

The second possibility is that the defect of aneuploid cells is due to a cumulative effect of low but chronic overexpression of many genes. For example, over-expression of up to a few thousands of genes on a single human chromosome might bring the cellular homeostasis out of balance. It has been found that the gene expression analyzed on the level of mRNA roughly corresponds to the gene copy numbers in most of the organisms analyzed so far. This suggests that all the genes of the extra chromosome are transcribed and likely also translated, thus leading to the presence of extra proteins. One of the current models hypothesizes that the overexpression of extra copies of specific genes might lead to accumulation of useless proteins that impair general cellular proteostasis. This interesting option is discussed in more details below.

4.2 Protein homeostasis in aneuploids

The hypothesis of impaired protein homeostasis in aneuploid cells originates mostly from recent analysis of artificially prepared haploid yeast strains with a single disomic chromosome. The presence of an extra chromosome significantly decreases the growth rates and renders the cells sensitive to drugs that target transcription, translation and protein degradation via the proteasome. Thus, it was proposed that the presence of an extra chromosome leads to imbalances in protein composition that might be partially compensated for by increased protein degradation. This conclusion is further supported by the fact that disomic budding yeasts that evolved to improve their growth rates often acquired mutations in Ubp6 gene [43]. This gene encodes a ubiquitin-specific protease that removes ubiquitin from ubiquitin chains and negatively regulates proteasomal degradation. Thus, increased permissivity of the proteasome improves the growth of artificially prepared disomic budding yeast [43]. Rapid development in proteomics enabled analysis of protein levels in budding yeast cells. Interestingly, using the model disomic cell lines, Torres et al. [43] showed that although the transcript levels correspond to the copy number changes, the corresponding protein levels are partially compensated, that means expressed at levels more similar to the abundance identified in normal haploid cells. This compensatory effect was observed in approximately 20 % of proteins and significantly more often for subunits of multimolecular complexes. However, it remains unclear whether the increased proteasome activity improves the cellular growth by enhancing the compensatory effect, or rather by a more general increase of turnover of cellular proteins. Moreover, no similar compensatory effects were detected by analysis of aneuploid budding yeasts with a more complex karyotype [44], leaving the question whether the compensation of protein levels occurs and affects growth of aneuploid cells open for future experiments.

Using Drosophila as another excellent model for analysis of the effects of aneuploidy, recent research revealed a significant buffering of genes in aneuploid regions [45, 46]. The authors also identified that the buffering is more efficient for differentially expressed genes than for genes that are expressed ubiquitously. Remarkably, the buffering of copy

number changes on both autosomes and sex chromosomes occurs on the transcriptional level, making the Drosophila model significantly different from mammalian and yeast model systems. Further research will be required to confirm the buffering on transcriptional level in Drosophila (and the lack thereof in yeasts and mammalian cells) and to identify the reasons of the differences.

4.3 Global response to aneuploidy

One of the interesting questions is whether aneuploidy elicits a specific physiological response in eukaryotes, or whether its effects depend on the extra chromosomes due to a deregulation of cellular pathways depending on the specific karyotype combination. Addressing this question is important as the existence of a specific response to aneuploidy, or the identification of essential adaptations that are required for survival of aneuploid cells might provide new targets for therapy of aneuploid tumors.

The most comprehensive analysis so far was performed in two different models of budding yeast aneuploids. Microarray analysis of haploid disomic budding yeasts shows a common gene expression pattern [36] that was identified previously as the environmental stress response (ESR) signature [47]. Moreover, an increased expression of ribosomal biogenesis and nucleic acid metabolism genes and down-regulation of carbohydrate energy metabolism genes were determined under growth conditions that normalized the growth differences between euploid and aneuploid strains [36]. Using budding yeast with complex aneuploidies that originated from aberrant meiosis of polyploid cells, Pavelka et al. revealed the ESR expression pattern in three out of five analyzed strains, but only when the highest stringency analysis was applied [44]. No other specific pathway deregulations were identified. Thus, although it appears that the rather general stress response is often activated in disomic budding yeast, no clear expression pattern shared by different types of aneuploid cells was identified. The differences in the two studies might be explained by the a difference between disomic and complex aneuploidies. Moreover, possible genome instability of aneuploid cells [48] might mask gene expression patterns.

There is only limited data regarding the effects of aneuploidy on gene expression in other eukaryotes. Using model trisomic human cells that were created by transfer of individual chromosomes into both normal and transformed human cells, no specific pathway deregulation was identified [49], although it should be noted that the complex pattern of transcriptional deregulation was not analyzed in detail. Another study used trisomic mouse embryonic fibroblasts (MEFs) harboring an extra chromosome 1, 13, 16, or 19 [39]. Similarly, microarray analysis of mRNA levels revealed a gene-dosage dependent increase of mRNA levels of genes encoded on the extra chromosomes, as well as other deregulations, but no specific expression pattern in these trisomic MEFs [39]. Analysis of transcriptional data from Drosophila cells with various segmental and chromosomal aneuploidies identified no general response to the chromosome number changes [45, 46]. Thus, further research will be required to address the question whether all eukaryotic cells show a unified response to aneuploidy, or whether this is something to be observed only in budding yeast.

Recent results obtained from a drug sensitivity screen using the above mentioned MEF cells suggest that there is a common defect in aneuploid cells. The authors tested approximately 20 drugs inducing genotoxic, proteotoxic as well as energy stress; most of them showed no

specific effect except for AICAR, chloroquine and 17-AAG [50]. AICAR induces energy stress, leading to the activation of the AMP-activated protein kinase AMPK1, whereas 17-AAG is a derivative of Geldanamycin, which inhibits the heat shock responsive chaperone Hsp90. Chloroquine, also used as an anti-malaric drug, was found to inhibit autophagy, a protein degradation pathway. These results correspond with the previously observed changes in energy metabolism and protein homeostasis in aneuploid budding yeast, thus pointing out these molecular processes as the possible pitfalls of aneuploidy. The authors also showed that these three identified compounds inhibit growth of aneuploid cancer cell lines significantly more than the growth of euploid cancer cell lines [50]. Thus, the drugs that inhibit growth of trisomic cells might potentially be useful for treatment of highly aneuploid cancer types. Indeed, autophagy inhibiting drugs are currently tested for cancer treatments.

4.4 Benefits of aneuploidy

Aneuploidy can also provide benefits to the cells as is documented by the fact that aneuploidy conveys resistance to antimycotic drugs in the human pathogene *Candida albicans* [51]. Aneuploid and polyploid strains of budding yeast *Saccharomyces cerevisiae* can be frequently found in nature, and multiple laboratory strains, in particular the ones that contain various deletions, show some degree of aneuploidy [52]. The association with a deletion mutation suggests that aneuploidy arises as a consequence of these mutations or that it might provide some compensation of the effect of specific mutations.

The decision whether aneuploidy will be beneficial or detrimental is likely influenced by the type of aneuploidy and the type of selection imposed by the environment. Experimentally created budding yeast cells that contain one extra chromosome show a significant growth impairment and increased sensitivity to numerous drugs [36], however, *in vitro* evolution lead to selection of fast growing cell populations adapted to disomy [43]. Aneuploid budding yeasts that arose via meiosis of triploid parents do not show a remarkable growth defect, and their karyotype confers an increased phenotypic variability, as assessed by altered sensitivity to multiple drugs in comparison to the original euploid wild type [44]. The sporulation efficiency of triploid parents is very low and thus likely only karyotype combinations with the least detrimental effect on viability survive. The various compositions arising from the meiosis could lead to chromosome combinations that provide a compensation of the imbalances. Moreover, aneuploid cells might be chromosomally unstable, thus allowing continuous "reinvention" of the karyotype composition during various drug treatments, a phenomenon that resembles the enhanced resistance acquisition in chromosomally unstable composite aneuploid cancer cells [5] [53]. Further investigations should address the mechanisms of the increased fitness in aneuploid cells.

How can aneuploidy be advantageous? One can envision that an addition of a single chromosome triggers a stress response, as it has been shown in budding yeast. Activation of a stress response to one stress factor can potentially protect cells against another stress factors. Another possibility is that aneuploidy increases chromosomal instability and thus accelerates evolution of a clone with a karyotype that provides an advantage under specific conditions. A recent study revealed that aneuploid fission and budding yeasts indeed display an increased level of chromosome missegregation, DNA damage and mitotic recombination, compared to haploid yeast [35, 48]. Similarly, aneuploid MEF cells were able

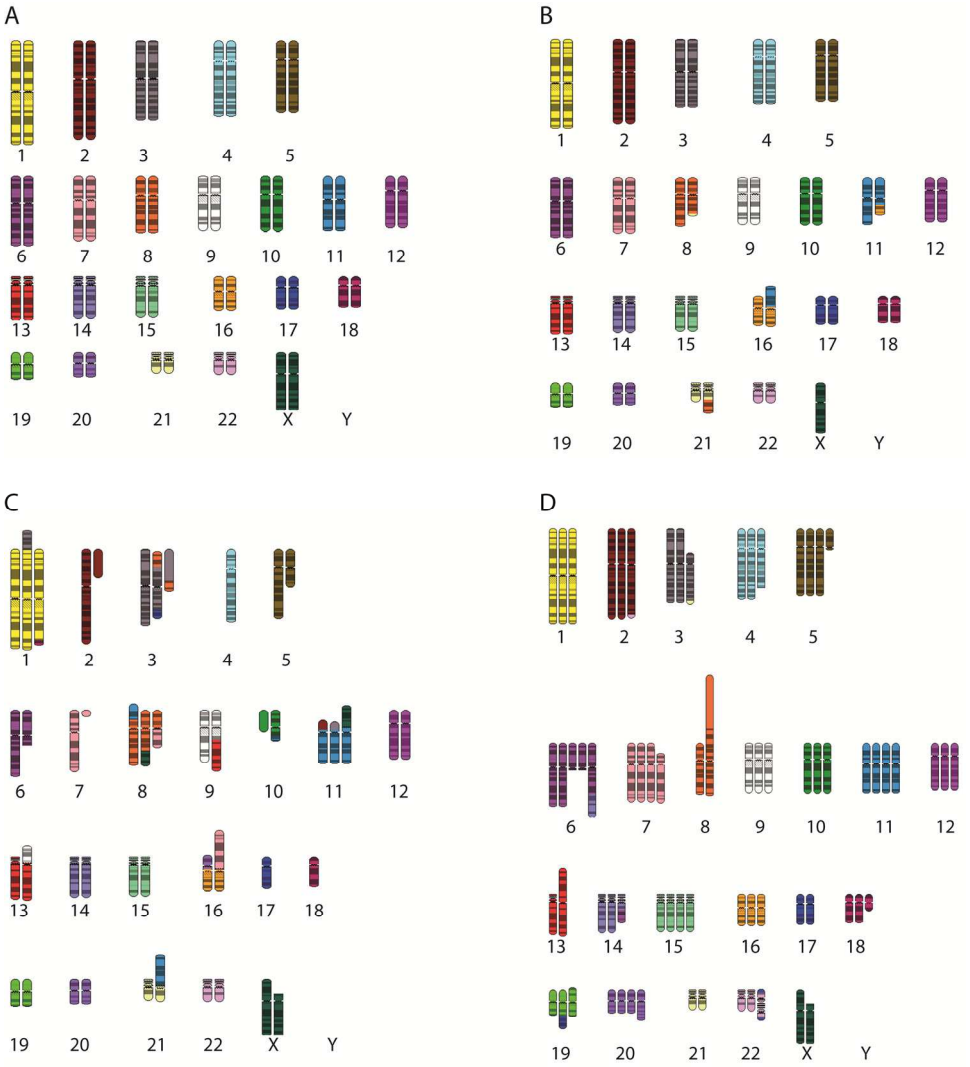
to immortalize faster than normal diploid MEFs [39]. Since immortalization is an event that requires multiple mutations of various genes leading to increased proliferation, this finding could be due to an increased mutation rate as it was observed for aneuploid yeasts. Taken together, the observations so far suggest that despite the adverse effects of addition of a single (or few) chromosome, the aneuploid cells can adapt to the situation and these adaptations may provide new characteristics that may be advantageous under specific conditions. It will be interesting to investigate what molecular mechanisms are responsible for the increased genome instability in aneuploid cells and how this can contribute to increased fitness.

5. Aneuploidy and cancer

The vast majority of cancer cells contain abnormal chromosome numbers (Fig. 3) - approximately 75 % of heamatopoietical cancers and 90% of solid tumors consists of cells with abnormal chromosome numbers [26]. Recently, a comprehensive analysis of somatic copy number alterations across human cancers revealed that nearly a quarter of the entire genome of cancer cells is affected by a whole arm or a whole chromosome copy number changes, whereas approximately 10 % shows small, site specific change, so called focal SCNAs [13]. Many of these changes are non-random, with strong preferences across cancer lineages, thus implying that selection plays an important role. The remarkable prevalence of aneuploidy in cancer has been noticed already at the end of the 19th century and aneuploidy was even proposed to trigger tumorigenesis [54]. However, with discoveries of tumor-suppressor genes and oncogenes, another view won appreciation that aneuploidy is rather a side-effect of gene mutations that are the real triggers of malignancy [25].

One of the major obstacles in causatively linking CIN and aneuploidy with tumorigenesis was the lack of evidence that mutations triggering CIN are also causing cancer. For example, mutations in SAC components clearly show a CIN phenotype, and although mutations in SAC genes can be found in chromosomally unstable colon cancers, the frequency is very low [55]. Recently, an interesting link was found by identification of the causal mutations of a congenital syndrome called Mosaic Variegated Aneuploidy. MVA is a rare recessive constitutional mosaicism of chromosomal aneuploidy caused by a germline mutation in BUB1B, which encodes BubR1, a key SAC protein [56]. Approximately 25 % of cells from MVA patients carry variable monosomies and trisomies, with multiple different chromosomes involved. Importantly, the syndrome is associated with a 50% risk of early childhood cancer.

Only recently the hypothesis that aneuploidy triggers cancer could be tested more rigorously. Several mouse models have been developed to address the question whether altered chromosome numbers can trigger tumorigenesis. Most of these mouse models carry a mutation in one of the SAC genes, thus reducing the ability of cells to avoid incorrect chromosome segregation. Depending on the type of mutation, this leads to variable levels of chromosome missegregation, resulting in ongoing chromosome instability and increased frequency of cells with variable karyotypes. Indeed, many of these mouse models carrying either a deletion of one of the gene copies (as deletion of both copies is usually embryonic lethal) or a hypomorphic allele (labeled H), are more tumor-prone than the wild type



Skygrams (graphical depiction of spectral karyotyping) of normal human tissue (A); cancerous cells from acute myeloid leukemia (B), ovarian adenocarcinoma (C) and from colorectal cancer (D). Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (http://cgap.nci.nih.gov/Chromosomes/Mitelman).

Fig. 3. Variable karyotypes in cancer cells.

mouse, in particular when exposed to carcinogen. Several of the mouse models show an increased tumor incidence per se, in particular defects in Bub1, Mad1, Mad2 and others (for an excellent review on the mouse models, see [57]). Interestingly, there is no direct correlation between the probability of cancer development and the degree of aneuploidy. For example, Bub1$^{-/H}$ and Bub1$^{H/H}$ mouse models show similar levels of aneuploidy [58] as

Rae2$^{+/-}$ -Bub3$^{+/-}$ [59] or Rae2$^{+/-}$-Nup98$^{+/-}$ [60] double heterozygous mice, yet the latter ones do not show any increase in spontaneous tumorigenesis. Moreover, not all tissues are comparably prone to aneuploidy-associated tumorigenesis. Additionally, some mutations in spindle-assembly checkpoint genes were shown to prevent or at least delay the occurrence of tumors in some tissues. For example, in Cenp-E heterozygous mice the levels of spontaneous liver tumor formation are much lower than in the controls [61].

Not only gene mutations that impair the protein function, but also changing the expression levels can lead to aneuploidy and tumorigenesis. Transgenic mice engineered to overexpress Mad2 have cells with widespread chromosomal instability and develop various types of neoplasms. Interestingly, continued overexpression of Mad2 is not required for tumor maintenance, suggesting that whereas the chromosomal instability was important for initiating carcinogenesis, it is dispensable for maintaining the neoplastic phenotype [57]. Other genes were associated with cancer formation and triggering chromosomal instability as well. For example, constitutive expression of cyclin E results in karyotypic instability in mammalian cells [62] and high levels of cyclin E are correlated to breast, endometrial and skin cancers, that also show increased aneuploidy [63]. However, it should be noted when using model systems with gene mutations, it is often difficult to distinguish whether the observed effects are indeed due to chromosomal instability or due to as yet unknown function of the analyzed factor. Thus, to address the question whether tumorigenesis can be triggered by chromosomal instability and aneuploidy, it would be necessary to develop a model lacking any initial mutation, yet showing high chromosomal instability and aneuploidy.

So far only one experimental set up fulfils this condition. In this model, p53 deficient tetraploid mouse mammary epithelial cells were subcutaneously injected into a nude mouse. Tetraploid cells are inherently instable and the frequency of chromosome missegregation is significantly increased in comparison to diploids in many models analyzed so far [25]. Thus, tetraploidy alone can facilitate aneuploidy. Whereas none of the mice injected with isogenic diploid cells developed tumors, 10 out of 39 mice injected with tetraploid cells did [24]. The tumors were near-tetraploid showing multiple chromosome re-arrangements. Taken together, it appears plausible that aneuploidy and chromosomal instability itself can facilitate tumorigenesis, most likely by providing a variability that serves as a material for selection. It will be interesting to uncover the molecular mechanisms underlying chromosomal instability of aneuploid and tetraploid cells and how exactly this facilitates tumorigenesis.

6. Role of aneuploidy in neurodegeneration and aging

Recent discoveries that abnormal chromosome numbers impact on protein homeostasis has pointed out a possible link to neurodegenerative diseases and instigated the interest in the association of aneuploidy and neuropathologies. Neurons might be particularly sensitive to random genetic changes: diploid population cannot outgrow cells with abnormal karyotypes because neurons are mostly postmitotic.

Interestingly, an increasing body of evidence indicates that the adult brain cells show low levels of aneuploidy (0.5 - 0.7%) and might be viewed as a mosaic of cells with variable genotypes [64]. The level of chromosomal aneuploidy correlates with diseases affecting the brain [65]. In particular, the percentage of aneuploid cells is higher in brains from patients

with Alzheimer disease (AD) than in the healthy population. This is likely not restricted to neuronal tissues as lymphocytes and splenocytes from the AD patients are aneuploid as well and exhibit defects in mitosis and chromosomal segregation [66]. It should be noted that the the fluorescence *in situ* hybridization (FISH) of interphase cells that is used for aneuploidy evaluation in tissues of dominantly postmitotic cells is particularly prone to artifacts. So far, detailed data are lacking about the effects of the aneuploidy on neuronal cells, but the cells appear to be fully functional and the expression levels are altered according to the copy number changes [67]. The frequent occurrence of aneuploidy in the brain raises an attractive possibility that aneuploidy is required for neuronal functions, for example by contributing to the functional variability of neuronal types. On the other hand, the association of increased aneuploidy levels with AD suggests pathological effects of abnormal karyotypes in neurons.

Aneuploidy and genome instability, in particular DNA damage, are also linked to aging, as is supported by the observation that the frequency of chromosomal aberrations in senescence-accelerated strains of mice increases [68]. Similarly, frequency of aneuploidy increases with age in fibroblasts taken at successive times from the same donors as part of the Baltimore Longitudinal Study of Aging [69]. Similarly as for cancer, it remains a matter of debate whether increased levels of DNA damage and aneuploidy might be a primary trigger of cellular aging, or whether they are mere consequences of other age-associated changes. Lushnikova et al. demonstrated that aging increased specific forms of genomic instability, and proposed that the probability of accumulation of certain chromosomal abnormalities linked to cancer development might increase with aging [70].

An interesting supporting evidence of the link between aneuploidy and aging came recently from a different model. Mouse model expressing low levels of spindle assembly checkpoint protein kinase BubR1 develop progressive aneuploidy, no significant cancer increase and multiple aging-associated phenotypes [71]. Although the authors suggest that BubR1 might regulate aging, another attractive hypothesis is that aneuploidy in these cells accelerates the onset of aging.

7. Aneuploidy in stem cells

An emerging importance of aneuploidy in embryonic stem cells (ESCs) research is substantiated by two interesting phenomena. First, it was observed that the early human and mouse embryos contain remarkable numbers of chromosomally aberrant cells. Second, *in vitro* cultivation of both embryonic and adult stem cells leads to the accumulation of chromosomal abnormalities. As the usage of stem cells for human therapies is accompanied by great expectations, the causes and consequences of aneuploidy in stem cells become a subject of intense research.

Eukaryotic cells maintain genomic integrity through control checkpoint mechanisms, but ES cells differ significantly in the mechanism of cell cycle regulation and it's link to checkpoints [72]. This is most likely due to the requirement for rapid cell divisions during the early development, which is achieved by relaxing the cell cycle control and uncoupling the checkpoint control from apoptosis. The control systems are activated later, when differentiation begins [73]. The ES cells compensate the lack of checkpoint coupling to cell cycle and apoptosis by increased repair efficiency after DNA damage [74]. Nevertheless, the

lack of the checkpoint control leads to a high frequency of chromosomal mosaicism (as high as 50 %) in normal human preimplantation embryos, as was revealed by fluorescence in situ hybridization (FISH). Upon differentiation, the efficient checkpoint control and the coupling to apoptosis are established [75]. This ensures that after the cleavage stage, embryos undergo a selection that prefers euploidy, which results in lower aneuploidy levels [76] [77]. How exactly this selection occurs and what is the effect on the efficiency of the early embryonic survival remains poorly understood.

For use in therapies, large amounts of stem cells need to be prepared *in vitro*. Remarkably, stem cells acquire chromosomal aberrations in culture in a process known as culture adaptation [78] [79]. These aberrations may increase the tumorigenicity of the ES cells [80] and impair their differentiation capacity, rendering the stem cells dangerous and ineffective for therapy. Previously, it has been already shown that transplantation of human adult stem cells may result in tumor formation [81], possibly due to the chromosomal aberrations. Thus, validating the genomic integrity and developing culturing strategies that would minimize the occurrence of aneuploidy in stem cells is essential for future development of their therapeutic potential.

8. Closing remarks

More than a hundred years ago, abnormal karyotypes were suggested to have a detrimental effect on cellular physiology and ultimately to cause cancer. Now, we slowly collect information that suggest indeed abnormal chromosome number, even so minimal such as gain or loss of a single chromosome, remarkably alter physiology of eukaryotic cells. They can lead to imbalance of protein homeostasis, changes in genome stability and altered growth characteristics. To what degree these physiological changes are responsible for aneuploidy linked diseases such as Down syndrome or multiple variegated aneuploidy remains to be addressed by future experiments. The emerging association of aneuploidy with cancer and with neuropathologic diseases might provide novel opportunities for developing efficient treatments of these diseases.

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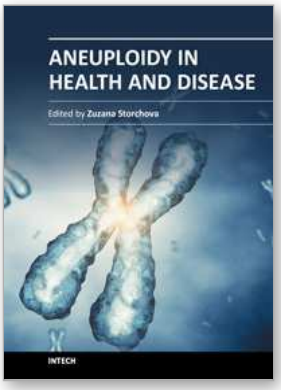

Aneuploidy in Health and Disease

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Aneuploidy means any karyotype that is not euploid, anything that stands outside the norm. Two particular characteristics make the research of aneuploidy challenging. First, it is often hard to distinguish what is a cause and what is a consequence. Secondly, aneuploidy is often associated with a persistent defect in maintenance of genome stability. Thus, working with aneuploid, unstable cells means analyzing an ever changing creature and capturing the features that persist. In the book Aneuploidy in Health and Disease we summarize the recent advances in understanding the causes and consequences of aneuploidy and its link to human pathologies.

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