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Consequences of aneuploidy in sickness and in health

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A link between aneuploidy and miscarriage or cancer in humans has been known for a long time. However, only in recent years the development of experimental models of whole-chromosome aneuploidy has allowed investigators to take a closer look at how aneuploidy affects individual cells. Collectively, recent studies using these models have shown that aneuploidy induces transcriptomic and proteomic changes, chromosomal instability, and adaptation. In this article, we discuss the findings from these recent studies and present current and emerging models on how aneuploidy may be deleterious in certain contexts, but beneficial in others.

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Introduction

Fundamental to life is a cell's ability to accurately divide its genomic material evenly between its daughter cells. A number of different chromosome segregation errors can lead to inaccurate distribution of the genetic material to the daughter cells during cell division and cause defects such as chromosome rearrangements, gain/loss of defined genomic regions, and/or gain/loss of entire chromosomes (i.e., aneuploidy). All these defects can have dire consequences on the health of both individual cells and the organism in which they arise. In this article, we will specifically discuss the consequences of whole-chromosome aneuploidy, which is known to be a leading cause of miscarriage in humans, but is also found in certain healthy tissues, and is a common feature of cancer cells. Although the association between aneuploidy and miscarriages or cancer has been known for a long time, only in recent years a number of newly developed experimental models of aneuploidy have allowed a more thorough investigation and deeper understanding of how aneuploidy affects individual cells. These models consisted of various systems with defined extra chromosomes, including strains of haploid budding yeast carrying specific disomies, mouse embryonic fibroblasts (MEFs) carrying specific trisomies as a result of Robertsonian fusions, and trisomic or tetrasomic human cell lines generated via microcell-mediated chromosome transfer. Our discussion will focus on these recent studies in an attempt to highlight common themes and important differences.

Effects of aneuploidy on gene expression and protein levels

Initial studies in haploid yeast strains carrying specific disomies [1••] or MEFs carrying defined trisomies [2••] reported an increased expression of genes on the aneuploid chromosome. A later study on a large panel of aneuploid yeast strains revealed that both the transcriptomic and the proteomic profiles scaled up with the aneuploidy [3••]. Proteomic changes in aneuploid yeast were also confirmed in a recent study [4•] and a direct correlation between chromosome copy number and gene expression levels was identified in several studies using aneuploid human cells [5•,6,7••]. Moreover, one of these studies also found changes at the proteomic level to correlate with the specific aneuploidy in human cells [7••]. Thus, these studies collectively highlighted a scale-up phenomenon by which the RNAs and the proteins corresponding to genes on the aneuploid chromosome(s) are present in higher amounts compared to those found in euploid controls.

However, one study also found that the levels of some proteins (~25%) encoded on the aneuploid chromosome(s) were maintained at levels more similar to the diploid level, with protein kinases and subunits of protein complexes being the majority of those [7••]. Moreover, it was shown, both in yeast and human cells, that aneuploidy results in mis-regulation of a set of genes independent of the specific aneuploidy [4•,7••]. Indeed, at the protein level, human cells displayed downregulation of DNA and RNA metabolism pathways and upregulation of pathways linked to autophagy and lysosome function, vesicle transport, membrane synthesis, and carbohydrate and oxidative metabolic processes [7••]. In a different study, transcriptomic analysis of a number of aneuploid cell lines identified downregulation of genes linked to DNA replication, transcription, and ribosomes and upregulation of genes linked to endoplasmic reticulum, Golgi apparatus, and lysosomes [8•]. Finally, regardless of the specific disomy, aneuploid budding yeast displayed a 'gene expression signature' corresponding to upregulation of proteins involved in the oxidative stress response [4•]. These findings are consistent with a previous meta-analysis performed by Sheltzer and colleagues [9], who found that different aneuploidies arising in many different species, including yeast, plants, mice, and humans, produced certain consistent gene expression changes, independent of the aneuploidy and of the species. These changes consisted in the upregulation of genes involved in the response to stress and downregulation of genes associated with cell cycle and cell proliferation [9]. Yet, other investigators observed association in human cells between aneuploidy and upregulation of proteins involved in DNA metabolism (as opposed to the downregulation reported in [7••]) and growth [10•]. On the basis of these observations, several groups of investigators have argued that aneuploidy induces a defined gene mis-expression pattern, possibly as a result of a physiological response to the stress caused by carrying an excess of hundreds-to-thousands genes. However, an alternative, not mutually exclusive, possibility is that genes on the aneuploid chromosome may act as regulators of genes on other chromosomes; this is consistent with studies performed on colorectal cancer cell lines with or without defined aneuploidies [10•,11]. In these studies, trisomy 7 and trisomy 13 were found to induce mis-regulation of genes on chromosomes other than the aneuploid ones (in addition to those on the aneuploid chromosomes), but the genes mis-regulated in response to trisomy 7 were different than those mis-regulated in response to trisomy 13 [10•,11].

Thus, the data available so far show that aneuploidy causes upregulation of genes carried by the additional chromosome(s), as well as mis-regulation of genes mapping on other chromosomes.

Effects of aneuploidy on cell fitness and proliferation

Given the long-known association between aneuploidy and disease, it would be hard to argue against the statement that aneuploidy is an undesirable trait. However, solid evidence on how aneuploidy affects cell physiology and proliferation has only emerged over the last decade. First, haploid yeast strains carrying defined aneuploidies were shown to display a G1 delay, reduced proliferation, and reduced ability to form colonies [1••]. Subsequently, similar studies performed in MEFs carrying defined trisomies showed that aneuploid MEFs, similarly to aneuploid yeast, displayed impaired proliferation and impaired metabolism [2••].

Given its generally negative effects on cell fitness and proliferation, it is surprising that aneuploidy is a physiological, and in some cases even necessary, condition in certain healthy tissues. For instance, aneuploidy is frequently found in hepatocytes of healthy human liver [12•,13]. Perhaps more strikingly, during the development of the Drosophila rectum, papillar cells undergo endoreduplication/polyploidization and then re-enter mitosis [14,15•]. These mitoses are highly error-prone and the cell population accumulates high levels of aneuploidy, but the suppression of pre-mitotic endocycles (i.e., the reduction of aneuploidy) leads to defective rectum development and reduced organismal tolerance for a high-salt diet [15•]. Finally, the fact that aneuploidy is so commonly found in cancer cells [16,17] and does not appear to interfere with their proliferation, suggests that under certain circumstance aneuploidy may, in fact, be beneficial.

Effects of aneuploidy on chromosome stability

The question of whether aneuploidy affects chromosome stability has been debated for a long time, with reports alternatively concluding that aneuploidy induces chromosome number instability (CIN) [18–20] or that it does not [21–23]. However, in recent years, studies in aneuploid yeast strains have unquestionably shown that aneuploidy causes genomic instability [24••,25••]. On the basis of these results, a re-evaluation of the effects of aneuploidy on chromosome stability in human cells was warranted. In a recent study, amniocytes from aneuploid embryos were shown to display high rates of aneuploidy for chromosomes other than the constitutively aneuploid one [26]. In another study, both cancer cells and amniocytes carrying specific aneuploidies were shown to display high rates of mitotic chromosome mis-segregation in the form of anaphase lagging chromosomes (LCs) and chromosome number heterogeneity [27••]. LCs (chromosomes that lag behind at the spindle equator when all other chromosomes move to the poles during anaphase) are known to be the most common chromosome segregation defect seen in cancer cells [22,28]. These new findings [27••] now explain the correlation that had been previously identified between the degree of aneuploidy and the rates of LCs in cancer cells [29]. In addition to CIN, these high rates of LCs also promote chromosome structural defects, given that LCs form micronuclei (MNi) upon mitotic exit [30,31] and that MNi have been shown to accumulate DNA damage and extensive chromosome rearrangements [31–33].

To conclude, recent data strongly support a role of aneuploidy in promoting chromosome mis-segregation and chromosomal/genomic instability.

Aneuploidy and adaptability

A plethora of data indicates that aneuploidy negatively affects cellular and organismal wellness. Indeed, aneuploidy (even mosaic) is a leading cause of miscarriage and congenital defects in humans [34]. Moreover, inducing aneuploidy in mouse models by mitotic checkpoint impairment can result in increased rates of or susceptibility to tumorigenesis [35,36]. Finally, as described above, aneuploidy typically impairs cell fitness and proliferation. However, a number of studies in single cell eukaryotes revealed that aneuploidy can confer a selective advantage under stressful environmental conditions. For instance, aneuploidy is associated with acquisition of antifungal