Short and long-term effects of chromosome mis-segregation and aneuploidy.

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Preface

Chromosome mis-segregation generates aneuploid daughter cells, which contain an incorrect chromosome number. Although aneuploidy interferes with proliferation of untransformed cells, it is also, paradoxically, a hallmark of cancer, a disease defined by increased proliferative potential. These contradictory effects are also observed in mouse models of chromosome instability (CIN). CIN can inhibit and promote tumorigenesis. Recent work has provided insights into the cellular consequences of CIN and aneuploidy. Chromosome mis-segregation *per se* can alter the genome in many more ways than causing the gain or loss of chromosomes. The long-term effects of aneuploidy are caused by gene-specific effects and a stereotypic aneuploidy stress response. Importantly, these recent findings provide insights into the role of aneuploidy in tumorigenesis.

Introduction

The term "aneuploidy" was coined by Gunnar Tackholm in 1922[1]. He studied the karyotypes of meiotic cells of F1 hybrids from crosses between different rose species. He noted that in meioses of a subset of these F1 hybrids "*bivalent and univalent chromosomes are not a multiple of seven* (author's note: the haploid chromosome number of the genus Rosa)*. In many instances this is also the case for their somatic karyotypes. Because it is necessary to coin a term for a chromosome number that is not a multiple of the base chromosome number, I will call this condition aneuploidy. Henceforth, aneuploidy refers to hyper and hypoploid chromosome numbers*."[1].

Whereas aneuploidy is a frequent outcome of meioses in progeny of interspecies crosses, it rarely arises during the mitotic divisions that form the soma and during meiosis of intraspecies crosses. This is because surveillance mechanisms that prevent chromosome mis-segregation, such as the spindle assembly checkpoint (SAC) (BOX 1), are in place[2-6]. Although these safeguard mechanisms are well characterized, the cellular consequences of their failure and what happens to cells in which these safeguard mechanisms failed and that have become aneuploid is only beginning to be understood. The reason for why we lack a detailed understanding of the consequences of chromosome mis-segregation is that studying faulty chromosome segregation and the resultant aneuploidies is difficult. Chromosome mis-segregation is a rare event and hence difficult to capture. The analysis of the products of chromosome mis-segregation, cells with aneuploid genomes, is equally tricky. Studying small changes in gene dosage – chromosome gains or losses result in a 50% change in gene expression[7-16] – is difficult. Dissecting the complex consequences of hundreds if not thousands of such small changes in gene expression occurring simultaneously is even more challenging. With the development of ever more sophisticated live cell imaging tools and quantitative genome-wide methods we are, however, beginning to

make headways. We now appreciate that chromosome mis-segregation can have a dramatic impact on genome integrity, causing DNA damage and genomic rearrangements. We are also making progress towards understanding the impact of an unbalanced karyotype on cell and organismal physiology. It has now become clear that the phenotypes of aneuploid cells are composites of phenotypes caused by specific gene imbalances and general aneuploidy associated traits caused by simultaneous changes in gene dosage of many genes, which have little effects when varied individually. Advances in understanding the immediate and long-term effects of chromosome mis-segregation are urgently needed. Whole chromosome gains and losses have a dramatic impact on human health. They are the leading cause of miscarriages and mental retardation in humans and a hallmark of cancer.

In this review, we will first discuss the detrimental effects of chromosome mis-segregation and aneuploidy on cell physiology. We will describe recent findings that show that the process of chromosome mis-segregation has dramatic effects on genome integrity causing DNA damage and activation of p53. We will next summarize our current understanding of how an altered karyotype affects the cell's proteome and physiological state. We will end with a discussion of links between chromosome mis-segregation, aneuploidy and cancer, reviewing recent evidence suggesting a causative role for chromosome mis-segregation and aneuploidy in tumorigenesis.

Aneuploidy is rare in normal tissues.
When aneuploidy is present throughout the organism it is known as **constitutional aneuploidy.** Such aneuploidies are caused by chromosome segregation errors during germ cell formation, usually during meiosis (reviewed in REF[17]). **Somatic aneuploidy** is the result of mitotic errors and describes a condition in which only a fraction of cells in an organism harbors an abnormal karyotype. Most constitutional aneuploidies cause embryonic lethality, the most notable exception in humans being Trisomy 21 (Down Syndrome). The consequences of high levels of somatic aneuploidy are also severe. Patients with the rare human syndrome, *mosaic variegated aneuploidy* (MVA), which is, amongst other mutations, caused by mutations in *BUB1B*, a gene required for accurate chromosome segregation (reviewed in REF[5], Box1) exhibit growth retardation, microcephaly and childhood cancers[18].

Given the profound adverse effects of aneuploidy on human health it is not surprising that cells with an unbalanced karyotype are rare. In budding and fission yeast, for example, chromosome loss rate is estimated to be between $1x10^{-5}$ and $1x10^{-4}$ per generation[19-22] (Table 1). Primary and non-transformed tissue culture cell lines exhibit a chromosome mis-segregation rate of approximately $\sim 2.5x10^{-2}\%$[23] per chromosome. Extending this result to all chromosomes suggests a chromosome loss or gain rate of ~1% [23,24] (Table 1).

The degree of aneuploidy observed in tissues is in agreement with these mis-segregation frequencies. Mouse lymphocytes and mouse and human keratinocytes exhibit aneuploidy frequencies of around 3%[25,26]. However, mammalian brain and liver were reported to exhibit significantly higher levels of aneuploidy. Fluorescent in situ hybridization (FISH) analyses suggested that as many as 50% of liver cells in humans are aneuploid[27-29]; spectral karyotyping (SKY)[30] or FISH[25,30-33] studies reported 20 – 33% of brain cells to be aneuploid. However, subsequent single cell sequencing analyses contradicted these previous results and revealed that the brain and liver have low levels of aneuploidy similar to those seen in other tissues[26,34,35] (Table 1). The overestimation of aneuploidy by FISH and SKY is likely due to hybridization and chromosome spreading artifacts, respectively. Furthermore, even a low frequency of artifacts for a single chromosome can lead to a gross overestimation of aneuploidy when extrapolated across all chromosomes.

Chromosome segregation defects are more frequent during meiosis and the effects on reproductive success significant (reviewed in REF[17]). In humans, approximately 35% of spontaneous abortions, 4% of stillbirths and as many as 25% of all zygotes are aneuploid[17,36,37] (Table 1).

Together, these observations indicate that constitutional and somatic aneuploidies are rare but when they occur, their impact on health is dramatic. In what follows we will summarize our current understanding of how the immediate and long-term effects of chromosome mis-segregation cause decreased fitness, disease and even death.

Immediate effects of segregation errors

There are two consequence of chromosomes mis-segregation: a faulty mitosis occurs and the resulting daughter cells are aneuploid. Recent studies indicate both outcomes have a dramatic impact on cells.

Chromosome mis-segregation causes DNA damage.

To understand the immediate consequences of chromosome mis-segregation, the frequency of chromosome mis-segregation events was increased by interfering with mitotic spindle function[38]. In such abnormal mitoses, mis-segregating chromosomes frequently lag behind during anaphase and can become entrapped and damaged in the cleavage furrow during cytokinesis (Figure 1). The broken chromosomes elicit a DNA damage response. Their repair via non-homologous end-joining during the following G1 phase of the cell cycle can but may not always lead to translocations and deletions[38,39].

Lagging chromosomes sometimes also do not catch up with the other chromosomes in time to be incorporated into the reforming nucleus. Such

chromosomes then form their own micronuclei[40-43] (Figure 1). These micronuclei are not just miniature nuclei as they are not fully functional[39] .DNA replication proceeds slowly in micronuclei[39,43]. Given the importance of a functional nuclear envelope for efficient DNA replication[44], defects in nuclear import[39-41] or irreversible nuclear envelope collapse[45] could be responsible for this inability of micronuclei to properly replicate their DNA (Figure 1). The consequences on DNA integrity are dramatic: DNA damage levels are high in micronuclei and their repair leads to extensive DNA rearrangements[39,46], as elegantly demonstrated by combining life cell imaging and single cell sequencing techniques[46]. The complex chromosomal rearrangements that form in micronuclei are reminiscent of chromothripsis[47,48,49], which has been observed in approximately 3% of cancers and is prevalent in osteosarcomas (35%) and aggressive neuroblastomas (18%)[48,49]. Chromotripsis has also been observed in some human congenital diseases[50] where, as in cancer, it might provide the fuel for rapid genome evolution.

Chromosome mis-segregation causes p53 activation
Errors in chromosome segregation result in p53 activation. Increased levels of p53 and expression of p53 responsive genes were detected following chromosome mis-segregation that resulted in a G1 arrest[51]. Consistent with a role of p53 in causing the arrest, G1 arrest was alleviated by p53 inactivation. Moreover, p53 also limits the proliferation of cells experiencing high levels of chromosome mis-segregation in the embryo. Mutant mice lacking the gene encoding the spindle assembly checkpoint component Mad2 die at embryonic day 6.5[52]. Similarly, *MAD2*$^{-/-}$ mouse blastocysts die in culture within 5 days but when p53 is deleted blastocysts remain viable for many weeks[53]. Thus, p53 plays a central role in preventing cell cycle progression following chromosome mis-segregation.

Which aspect of chromosome mis-segregation causes p53 activation remains a key unanswered question, for which consensus hasn't been reached yet. One study [38] has suggested that DNA damage during cytokinesis causes p53 activation (Figure 2a). However, in another study[51], DNA damage following chromosome mis-segregation was not detected and it was proposed that aneuploidy *per se* activates p53 (Figure 2b). Similarly, another group[54] observed p53 activation in SAC-deficient MEFs but not DNA damage. Instead, this group reported that reactive oxygen species (ROS) were elevated following chromosome mis-segregation. High levels of ROS caused activation of the DNA damage checkpoint kinase ATM and of p53 (Figure 2c). It is noteworthy that increased levels of ROS have also been observed in aneuploid budding yeast strains[11].

What could be the reason for these different results? DNA damage occurring during chromosome mis-segregation is likely to be transient and could have been

missed in some studies. Differences in experimental procedure could also determine whether or not p53 is activated. Some approaches used to generate aneuploid cells involve arresting cells in pro-metaphase for prolonged periods of time. Arresting cells in pro-metaphase for more than 90 minutes causes a p53-dependent G1 arrest when cells are released from the cell cycle block irrespective of whether or not chromosomes had been mis-segregated[55]. The mechanisms whereby prometaphase length causes p53 activation are not understood, but multiple events could contribute (Figure 2d). Prolonged prometaphase arrest causes apoptosis and hence a DNA damage response[56], telomere uncapping[57], p38 activation[55] and a decrease in Mdm2 levels, which targets p53 for degradation[58-60]. All these events could lead to p53 activation.

In summary, which aspects of chromosome mis-segregation – there could be multiple - activate p53 remains to be clearly defined. Interestingly, p53 activation has not been observed in cells with constitutional aneuploidies[61], which suggests that p53 activation is an immediate consequence of chromosome mis-segregation and is attenuated in cells with constitutional aneuploidies or is only elicited by specific aneuploid karyotypes.

Long-term effects of an altered karyotype

Changes in chromosome composition cause a multitude of phenotypes and have long-term effects. The reason is that changes in the copy number of genes located on autosomes largely, although not universally, result in a corresponding change in gene expression. A systematic analysis of budding yeast strains carrying single additional chromosomes showed that approximately 80% of genes that are present in an additional copy are expressed at an accordingly increased level[11]. The genes that do not show increased expression predominantly encode proteins that function in multi protein complexes such as the ribosome[11]. Similar observations were made in fission yeast, *Arabidopsis thaliana*, and mammalian cells[10,12,13,15,16,62-66] but the principle that gene copy number determines abundance of gene product may not be universal. **Dosage-compensation** mechanisms such as those described for sex chromosomes, may exist for autosomes in *Drosophila melanogaster* and in some plants[67-71].

Which aspects of gaining and losing whole chromosomes cause the phenotypes observed in aneuploid cells and organisms? Although studies in budding yeast have shown that the presence of 5 additional centromeric plasmids interferes with microtubule – kinetochore attachment[72], gaining or losing DNA *per se* is generally not considered as the major cause for phenotypic changes associated with aneuploidy. This was demonstrated by introducing large amounts of mammalian DNA into budding yeast cells. Little or not proteins are synthesized in budding yeast from this foreign DNA because, even if the mammalian genes were transcribed, the yeast splicing machinery cannot splice mammalian

mRNAs. Introducing mammalian DNA in the form of yeast artificial chromosomes (YACs) as large as approximately 13% of the yeast genome (1.6Mb) has little impact on the fitness of yeast strains[14]. This observation, together with the fact that autosomal dosage-compensation mechanisms are not in place indicates that the phenotypes that are observed in aneuploid yeast cells are caused by changes in the expression of genes located on the aneuploid chromosomes.

The finding that in budding yeast all aneuploidy-associated phenotypes analyzed to date are attenuated by increased ploidy[14,73] further indicates that it is relative levels of gene dosage that are mainly responsible for the phenotypes associated with an altered karyotype. Phenotypes caused by the gain of single chromosomes are drastically attenuated in diploid yeast cells compared to haploid yeast cells[14,73]. Thus, polyploidy represents an aneuploidy-tolerating condition. This is illustrated by the observation that tetraploid yeast strains exhibit a 200-fold increase in chromosome loss compared to diploid yeast strains, yet proliferation is only mildly impaired[22]. In cancers too, an increase in genome-wide ploidy (many cancers are tetraploid) probably protects cancer cells from the adverse effects of aneuploidy allowing them to take advantage of potential beneficial traits conferred by altered dosage of specific oncogenic drivers.

In what follows we will provide examples for how changes in copy number of specific genes (gene specific effects) interfere with development and cause diseases. We will then describe how simultaneously changing the copy number of many genes that on their own have little impact on cellular functions cause a generic set of phenotypes known as the aneuploidy associated stresses.

Gene specific effects of aneuploidy

Changes in gene copy number have been linked to many diseases (reviewed in ref[74,75]). For example, duplication of the *APP* gene (encoding amyloid beta precursor protein) has been implicated in early onset Alzheimer's disease[76], deletion of one copy of *PMP22* (the gene encoding peripheral myelin protein 22) is the cause of Charcot-Marie-Tooth 1A neuropathy[77]. While examples of changes in gene copy number causing developmental abnormalities and diseases are numerous, dramatic effects of gaining or losing single genes on cellular fitness are less common. The best-known example is the β-tubulin gene in *Saccharomyces cerevisiae.* An additional copy of this gene is lethal[78]. Only a handful of other genes have been shown to reduce fitness when present at an additional copy under standard growth conditions[79]. Similarly, only few genes were found to reduce fitness when present at one copy instead of two. In budding yeast only 184 genes (3% of the yeast genome) are haploinsufficient for growth under optimal growth conditions[80]. This number is higher in fission yeast[81] (455 genes), most likely because fission yeast predominantly propagates as a haploid whereas budding yeast as diploid, which presumably causes haploinsufficiency to be under strong negative selection[81].

Understanding how changes in gene dosage of individual genes impact development and organismal functions will be important for developing strategies to improve the lives of individuals with Down Syndrome. Two recent studies suggest that some of the defects caused by an additional copy of chromosome 21 are reversible. It was found that the cognitive deficiencies in mouse models of Down Syndrome can be ameliorated by a Hedgehog agonist therapy[82]. Silencing one copy of chromosome 21 by targeting the X chromosome inactivating Xist RNA to one of the three copies of this chromosome greatly improved proliferation and neural rosette formation in pluripotent Down Syndrome stem cells[83]. These findings open potential new avenues for the development of therapies for the treatment of Down Syndrome.

Aneuploidy-associated stresses

A 50% change in expression of the majority of genes individually has little if any impact on cellular fitness. In contrast, the same change in dosage of many such genes simultaneously contributes to the decrease in fitness of cells with unbalanced karyotypes and is responsible for traits shared by cells with different aneuploidies[84] (Figure 3). We refer to these general traits as the aneuploidy-associated stresses. Thus far they have only been studied in cellular models of aneuploidy, but they probably contribute to the myriad of phenotypes observed in aneuploid organisms.

Transcriptional and post-transcriptional responses to aneuploidy.

Studies of aneuploid budding yeast, fission yeast, and plants, as well as aneuploid primary, untransformed mouse and human cells have revealed a conserved gene expression response to the aneuploid state[14,85-87] (Figure 3). Transcripts associated with cell growth, proliferation, and nucleic acid metabolism are down-regulated, while transcripts associated with stress and membranes functions are up-regulated. These transcriptional alterations are reminiscent of the environmental stress response (ESR) first described in budding yeast[88,89] (Figure 3). The ESR is triggered by several stresses and/or slowed growth, and the gene expression pattern commonly observed in aneuploid cells is likely the result of cellular stress as well as a reflection of the sluggish proliferation of aneuploid cells[85,87].

In cancers, some transcripts have been found to be more abundant in cancers with a high degree of aneuploidy. A gene expression signature derived from this study (known as “CIN70”) had been proposed to function as a marker of chromosomal instability in cancer. However, subsequent research has demonstrated that CIN70 more accurately reflects the proliferation rate of tumors, rather than intrinsic CIN[91,92]. A comparison of high-CIN and low-CIN cancer cell lines identified a set of transcriptional changes distinct from CIN70 but similar to the ESR observed in primary aneuploid cells. Interestingly, an ESR was not

observed when comparing the transcriptomes of highly aneuploid breast tumors to near-diploid breast tumors. These findings led to the proposal that two types of aneuploidy exist in cancers: 1) continuously changing karyotypes that, like aneuploidies in primary cells, have a negative impact on cellular fitness and 2) selected, stable aneuploid karyotypes that have evolved to support maximal proliferation and in which the stresses caused by aneuploid karyotypes are suppressed. It is important to note that the gene expression changes caused by CIN in cancer and by aneuploidy in primary cells are related but not identical. For instance, genes annotated to the mitotic cell cycle are very strongly down-regulated in trisomic fibroblasts, while in high-CIN cancer cell lines, cell cycle genes are moderately down-regulated but RNA metabolism genes are strongly suppressed. The cause of these differences is at present unknown.

Recently, an additional gene expression signature shared among aneuploid budding yeast strains was identified[11]. This signature, named the aneuploidy-associated protein signature (APS), is characterized by the up-regulation of proteins but not transcripts of genes involved in oxidative stress response. The strength of the APS correlates with the degree of aneuploidy, suggesting that the degree of karyotype imbalance cause an increase in ROS. Which aspect of the aneuploid condition is responsible for elevated ROS remains to be determined. However, hyper-activation of the proteasome, through inactivation of the proteasome-associated deubiquitinating enzyme Ubp6 suppresses the APS[11], raising the interesting possibility that proteotoxicity, a hallmark of the aneuploid state to be discussed next, contributes to the APS (Figure 3).

Aneuploidy causes proteotoxic stress

In healthy cells, a complex regulatory network maintains cellular protein homeostasis (proteostasis) by ensuring that proteins are present only in their fully active form and at appropriate levels[93,94]. Chaperone-mediated folding pathways facilitate the folding of proteins; protein degradation pathways - autophagy and the ubiquitin proteasome system (Box 2) - ensure that mis-folded proteins are eliminated (reviewed in REF[95-99]). When these systems become limiting or are impaired, unfolded and misfolded proteins accumulate resulting in **proteotoxic stress** (Figure 4). This stress is met by a multi-pronged response aimed at increasing the protein quality control capacity of the cell.

Aneuploidy impacts all protein quality control pathways in the cell. Analysis of budding yeast strains carrying single additional chromosomes (disomic yeast strains) showed that at least one chaperone, the chaperone Hsp90 (reviewed in REF[100]) is limiting in several different disomic yeast strains[73]. Aneuploid immortalized and tumorigenic human cells[101] are also defective in HSP90-mediated protein folding. Reduced protein folding capacity was suggested to be caused by a reduced ability to activate a HSF1-induced heat shock response[101]. On the other hand, it was found that basal levels of expression of the HSF1

target HSP72 were increased in aneuploid MEFs[61]. Primary mouse cells may respond differently to folding stress than immortalized and cancerous human cell lines. Despite these differences, all types of mammalian cell lines carrying one or two additional chromosomes analyzed to date are more sensitive to the HSP90 inhibitor 17-N-allylamino-17-demethoxygeldanamycin (17-AAG)[61,101] than euploid cells, indicating that Hsp90 is limiting in several aneuploid cells.

Aberrant karyotypes also impact protein degradation pathways, including ubiquitin-mediated proteasomal degradation of short-lived proteins and autophagy-mediated removal of protein aggregates. Some disomic budding yeast strains exhibit sensitivity to the proteasome inhibitor MG132[14]. Furthermore, hyperactivation of proteasomal degradation by deleting the proteasome-associated deubiquitinating enzyme *UBP6* attenuates the aneuploidy induced changes in cellular protein composition and improves their fitness[11,63]. Unlike some disomic budding yeast strains, mammalian aneuploid cells do not exhibit increases sensitivity to proteasome inhibitors[61]. Recent studies indicate that proteasome-mediated degradation is increased in aneuploid mammalian cells [101], suggesting that proteasome activity is up-regulated in cells with abnormal karyotypes[101] . Autophagy on the other hand appears to be insufficient in aneuploid mammalian cells. Trisomic MEFs and aneuploid human cells exhibit increased sensitivity to the lysosome inhibitor chloroquine[10,61]. Furthermore, the gene expression signature of aneuploid human cells is similar to that of cells in which lysosomal degradation is inhibited[87]. Our unpublished data indicate that autophagosomes accumulate within lysosomes without evidence of lysosome mal-function (SS and AA, unpublished results). It thus appears that autophagy is a major route of clearance of mis-folded proteins in aneuploid mammalian cells.

Why is proteotoxicity a universal feature of aneuploid cells? The comparison of haploid yeast strains carrying an additional chromosome (disomic strain) with diploid yeast strains carrying an extra copy of the same chromosome (trisomic strain) provided insight into this question. All phenotypes indicative of proteotoxic stress are greatly reduced in trisomes compared to disomes suggesting that changes in the relative ratio of proteins are a major source of proteotoxicity in aneuploid cells. In haploid cells an extra copy of a gene leads to a doubling of gene expression. In diploid cells the relative increase or decrease in expression is only 50%. While this difference may be of little consequence for proteins that fold spontaneously, it has profound consequences for proteins that require chaperones to reach their native conformation. Many protein complex subunits are unstable unless bound to their partners, and will often bind to chaperones to remain soluble until they associate with their binding partners[102]. Thus, in aneuploid cells every single subunit produced from the additional gene copy will require the continuous engagement of chaperones to remain in a soluble state and will be need to be eventually degraded when a binding partner cannot be found. This latter point is illustrated by the analysis of the proteome of aneuploid

cells. In disomic budding yeast strains approximately 20 percent of proteins do not exhibit increased expression when gene dosage is doubled even though transcript levels are up-regulated according to gene copy number[13,63]. The vast majority of proteins whose expression does not scale with gene number are subunits of multi-protein complexes[10,11,14,63]. The ribosome is especially worth mentioning in this context. Increasing the copy number of ribosomal genes does not lead to a corresponding increase in protein levels[11]. Given that ribosomal proteins constitute about 20% of total protein in yeast (http://www.proteomaps.net) eliminating ribosomal subunits produced from excess gene copies alone could place a burden on the cell's protein quality control pathways.

At first glance it may seem surprising that changing the expression of genes by 50 percent challenges the cell's protein quality control pathways. Granted, gaining or losing whole chromosomes causes changes in the expression of hundreds sometimes thousands of genes but why does the cell not simply continuously increase protein quality control activity as occurs during heat shock? A recently discovered feature of gene expression control, that is coordinate expression of genes that function in complexes, could explain the inability of cells to adapt to the aneuploid state. It was shown that expression of subunits that assemble into a complex is coordinated[103]. This indicates that rather than maintaining a large protein quality control reservoir to keep a large pool of unassembled protein complex subunits in a soluble state, cells have evolved to minimize the need for protein quality control pathways to assemble complexes. When subunits of complexes are continuously produced in the incorrect stoichiometries as occurs in aneuploid cells the protein quality control pathways of the cells are challenged, and proteotoxic stress ensues.

Aneuploidy inhibits cell proliferation.

Decreased proliferation is another characteristic of aneuploid cells[10,13,14,16,51,54,104-107]. Aneuploid fission yeast strains derived as progeny from triploid meioses delay in G1[104]. Haploid budding yeast strains disomic for one or two chromosomes or harboring complex aneuploidies proliferate slowly and many such strains also show a G1 delay[14,106].

Chromosome mis-segregation and aneuploidy also interfere with proliferation in mammalian cells. MEFs harboring hypomorphic mutations in the SAC gene *BUBR1*[107], or carry mutations in the SAC target Cdc20 that render it insensitive to checkpoint regulation[54], or that interfere with the chromosome segregation process (through depletion of the kinesin MCAK or upon Monastrol wash-out exhibit proliferation defects. Some mutations that increase chromosome mis-segregation, for example cells heterozygous for a deletion in CENP-E[108], Rae1[109], or Bub3[109], have not been reported to decrease cell proliferation. This could be due to the fact that only a small fraction of cells in the population mis-

segregate chromosomes causing the ensuing proliferation defect to be subtle and thus missed. Proliferation defects are also observed in cells harboring constitutive aneuploidies. Trisomy 21 human fibroblasts or MEFs trisomic for chromosome 1, 13, 16 or 19 divide more slowly although a specific cell cycle delay could not be identified[16]. However, other trisomic human cells show a G1 delay[10] indicating that, as in yeast, G1 delay is a common occurrence in aneuploid mammalian cells.

An important question regarding the proliferation defects of aneuploid cells is whether they are the consequence of copy number changes of a few especially harmful genes, or whether they are brought about by copy number alterations of many genes that cause no growth defect when varied individually. As with most if not all aneuploidy-associate phenotypes the answer is likely to be that both contribute. For example, a single additional copy of chromosome VI causes lethality in haploid budding yeast cells because a single additional copy of the β-tubulin encoding gene *TUB2* is lethal[78]. Such cases are however rare, at least in budding yeast. A genome-wide study in budding yeast determined the upper copy number limit of every gene in the budding yeast genome and identified 55 genes that are not tolerated at more than 5 copies per haploid genome[110]. Changes in copy number of these most dosage sensitive genes are however insufficient to drive the proliferation defects of aneuploid cells[84]. Introducing an additional copy of these dosage sensitive genes into yeast strains did not recapitulate the growth defects of yeast strains carrying an additional copy of the chromosome the genes are located on. This finding indicates that the proliferation defects of aneuploid budding yeast cells are largely caused by simultaneous gene copy number changes that independently are benign at least under standard growth conditions.

So if it is not only individual genes that at altered dosage impair proliferation in aneuploid cells, which other aspects of the aneuploid condition do? Aneuploidy-induced proteotoxicity appears to contribute to the proliferation defect of aneuploid cells. In budding yeast increasing protein quality control not only improves protein homeostasis but also cellular fitness. Deleting *UBP6* improves proliferation in 11 out of 13 disomic yeast strains under conditions of heat stress (growth at 37°C)[11]. In mammalian cells, increased chaperone expression also improves fitness. Overexpression of the heat shock transcription factor HSF1 not only rescues the folding defect of human aneuploid cells but also their proliferation defect[101]. Although other aspects of HSF1 biology that are beyond its role in protein folding might contribute to improved proliferation of aneuploid cells upon HSF1 overexpression, this remarkable finding points to a link between aneuploidy-induced proteotoxicity and proliferation defects[101]. Whether other aneuploidy-associated stresses contribute to the reduced proliferative abilities of aneuploid cells remains to be determined.

Aneuploidy in cancer
90% of solid tumors and 50% of blood cancers are aneuploid[111,112]. Whether and how aneuploidy promotes tumorigenesis has been an active area of research and discussion. The realization that mutations in genes regulating chromosome segregation are rare in cancers[113-115] together with the observation that aneuploidy inhibits proliferation, suggests that aneuploidy is a by-product of tumorigenesis that interferes with the process rather than causes it. Indeed, loss of tumor suppressors has been shown to cause chromosome instability. RB inactivation not only deregulates the G1 – S phase transition but also compromises centromere function, which leads to chromosome instability and hence aneuploidy[116,117]. Loss of function mutations in APC cause deregulation of the Wnt pathway and decrease chromosome segregation fidelity[118].

While aneuploidy can be a byproduct of oncogenic transformation there is mounting evidence that aneuploidy can promote tumorigenesis. The analysis of cancer genomes indicates that loss of tumor suppressor genes and gain of oncogenes drive karyotype changes such as whole or partial chromosome gains and losses creating the clonal aneuploid karyotypes characteristic for a specific cancer[119]. However, the analysis of specific aneuploid karyotypes and mouse models of CIN revealed that aneuploidy can both promote and inhibit tumorigenesis. Mice trisomic for part of chromosome 16 are resistant to *Apc*^{Min} induced colon cancer[120]. Individuals trisomic for chromosome 21 are less likely to develop solid tumors compared to the euploid population[121]. This tumor protective function of trisomy 21 has been attributed to the triplication of the DSCR1 gene[122]. Trisomy 8, on the other hand, appears to promote hematopoietic malignancies. 25% of chronic myeloid leukemias (CML), 10–15% of acute myeloid leukemias (AML) and 5% of acute lymphoblastic leukemias (ALL) harbor an additional copy of chromosome 8[123]. MYC, a key driver of hematopoietic malignancies, is located on chromosome 8 and could be the reason for the prevalence of additional copies of chromosome 8 in blood cancers[124].

Studies of mouse models of chromosomal instability (Supplementary Table 1), the condition that spawns aneuploid karyotypes, too show that akin to other forms of genomic instability such as reduction of telomerase activity[125 126], CIN can promote and inhibit tumorigenesis. A prime example for this dual role of CIN in tumorigenesis is the motor protein Cenp-E[108]. Animals heterozygous for a *CENP-E* deletion harbor increased levels of aneuploidy[108] and are significantly less likely to develop spontaneous liver tumors and 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors[108] (see also Supplementary Table 1). However, the same animals exhibit an increase in the incidence of spleen lymphomas and lung adenomas[108]. Many other mouse models of CIN have been described to promote or inhibit tumorigenesis in a manner that depends on the cell type and genetic background in which the abnormal karyotype arises. They are summarized in Supplementary Table 1.

Recent studies revealed a perhaps general principle whereby aneuploidy can promote tumorigenesis[127]. In a *K-RAS*-driven model of lung cancer, continuous *K-RAS* expression is required for tumor maintenance. Upon repression of *K-RAS* tumors regress. When chromosome mis-segregation is induced in K-RAS driven tumors through the overexpression of the SAC factor Mad2, the disease relapsed quickly. This finding suggests that the karyotype heterogeneity created by increased CIN facilitates the emergence of *K-RAS* independent tumors[127].

While increased karyotypic instability can facilitate the evolution of advantageous karyotypes, it of course is much more likely to generate disadvantageous ones. A recent study[128] illustrates this double edged nature of CIN. Mice lacking one copy of *CENP-E* exhibit an increase incidence of spleen and lung tumors. Increasing chromosome mis-segregation in these mice by interfering with spindle assembly checkpoint function decreased tumor formation by increasing cell death[128]. These findings indicate that low rates of chromosome mis-segregation can promote tumorigenesis by increasing the likelihood of generating a tumor-promoting karyotype. However when chromosome mis-segregation rates become too high, tumor cells cannot “hold on” to such tumorigenesis-promoting karyotypes. Instead cells with inviable karyotypes are continuously generated leading to cell death and hence tumor suppression.

Conclusions and future directions

Research over the last 5 years has provided significant insights into the immediate and long-term consequences of chromosome mis-segregation and has provided concrete hypotheses as to how CIN and aneuploidy could promote tumorigenesis. Chromosome mis-segregation can lead to structural alterations of chromosomes. These alterations and the genomic instability that arises from the aneuploid state *per se*[129,130] are likely drivers of tumor evolution. We now also understand that aneuploid karyotypes negatively impact cellular fitness but rare favorable variants can provide a survival advantage as has been seen in microbial evolution studies[131-133].

Understanding how certain karyotypes promote specific aspects of tumorigenesis will be important next steps in understanding the role of aneuploidy in tumorigenesis. It should also be determined whether the gene-specific phenotypes and general stresses caused by the aneuploid state can be exploited in cancer therapy. Synthetic negative interactions between proteotoxic and energy-stress inducing compounds and aneuploidy have been described[61]. Strategies that first select for a specific karyotype to then eliminate it have been reported recently in inhibiting the growth of aneuploid fungal pathogens and several central nervous system cancer cell lines [134] Aneuploidy is a hallmark of cancer yet is rare in normal tissues. Compounds that target the aneuploid state

therefore have ideal therapeutic properties: broad spectrum efficacy and high specificity. A large-scale effort is now required to identify such compounds.

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Box 1: Mechanisms that prevent chromosome mis-segregation.
The process of chromosome segregation is tightly controlled by the spindle assembly checkpoint (SAC, also known as the mitotic checkpoint), an evolutionary conserved surveillance mechanism that prevents the mis-segregation of chromosomes[5,135] (see the figure). When the sister kinetochores attach to microtubules emanating from only one spindle pole (syntelic attachment) or only one of the two sister kinetochores attaches to microtubules (monotelic attachment) the SAC is activated and inhibits anaphase onset. When all kinetochores have attached to microtubules emanating from opposite poles, known as amphitelic attachment or bi-orientation the SAC is silenced and anaphase commences (see the figure). Syntelic and monotelic microtubule – kinetochore attachments recruit core components of the SAC - MAD1, MAD2, BUB3, BUBR1 and the checkpoint kinases AURORA B, BUB1 and MPS1. The recruitment of these proteins catalyzes the inhibition of the anaphase-promoting complex/cyclosome (APC/C^{CDC20}), an E3 ubiquitin ligase that triggers the metaphase to anaphase transition (left panels).

Inhibition of APC/C^{CDC20} is brought about by the incorporation of the APC/C activator CDC20 into the mitotic checkpoint complex (MCC), composed of the checkpoint proteins MAD2, BUBR1, BUB3, and CDC20 itself. Once all kinetochores achieve amphitelic attachment, the SAC is turned off and APC/C^{CDC20} is activated. APC/C^{CDC20} then targets SECURIN and CYCLIN B for degradation by the 26S proteasome. This leads to loss of sister chromatid cohesion and inactivation of CDK1. These events trigger chromosome segregation and mitotic exit, respectively (right panels).

Kinetochores that attach to microtubules that emanate from both spindle poles are referred to as exhibiting merotelic attachments and are thought to be the major cause of aneuploidy in mammalian cells[136]. These types of kinetochore – microtubule attachments are not recognized by the SAC but instead are converted into amphitelic attachments through the action of Aurora B and Mps1

kinases. The protein kinases convert merotelic attachments into amphitelic ones by destabilizing microtubule kinetochore interactions by phosphorylating outer kinetochore components.

Box 2: Cellular protein quality control

Proteins must adopt a defined three-dimensional structure to be functional. A complex network of chaperone systems ensures that polypeptides reach their functional conformation. However, even after adopting the folded conformation, proteins are at risk of unfolding, because the energy barrier between folded and unfolded or mis-folded conformations is not insurmountable. Stress conditions or intrinsic instability can further contribute to protein mis-folding.

Mis-folded proteins either reengage chaperones to reattempt correct folding or are degraded. Degradation is mediated by ubiquitin-mediated proteasomal degradation. The concerted functions of E1, E2 and E3 enzymes brings about the ubiquitination of the misfolded protein thereby targeting the mis-folded protein for degradation by the proteasome[98,99] (see the figure, top).

When folding load exceeds chaperone capacity and/or when the ubiquitin–proteasome system is compromised, mis-folded/unfolded proteins can form aggregates. Such aggregates are cleared by autophagy. Deubiquitinating enzymes (DUBs) and E3 ubiquitin ligases remodel ubiquitin chains that are then able to bind ubiquitin receptors, such as p62/SQSTM1 and NBR1[98]. Autophagosomal membranes then form around the ubiquitianted aggregates[98]. Once encapsulated into autophagosomes, protein aggregates are delivered to lysosomes where they are degraded (see the figure, bottom).

Figure legends:

Figure 1: Lagging chromosomes experience DNA damage

(a) Accurate chromosome segregation leads to the equal partitioning of the genome and the generation of two euploid daughter cells, with a balanced, diploid karyotype (depicted as 2N in figure).

(b) Merotely, defined as a kinetochore that attaches to microtubules emanating from both spindle poles, can cause chromosomes to lag behind in the spindle midzone during anaphase. Such lagging chromosomes can have multiple fates. They can be trapped in the cytokinetic furrow and break during cytokinesis (top). They can form their own micronucleus that is either accurately segregated (middle) or mis-segregated (bottom). Irrespective of how micronuclei are segregated their DNA is poorly replicated and experiences significant damage in the subsequent cell cycle. 2N+x and 2N-x indicate aneuploid karyotypes in which an undefined number of chromosome(s) has been gained (+x) or lost (-x).

Figure 2: Multiple mechanisms could be responsible for p53 activation following chromosome mis-segregation.

(a) Chromosomes trapped in the cytokinetic furrow are damaged and cause activation of the DNA damage checkpoint pathway and hence p53 activation[38]. 2N+x and 2N-x indicate aneuploid karyotypes in which an undefined number of chromosome(s) has been gained (+x) or lost (-x).

(b) Aneuploidy *per se* causes activation of p53 through p38 by an unknown mechanism[51].

(c) Aneuploidy causes metabolic changes that lead to an increase in ROS. ROS activates the DNA damage checkpoint kinase ATM which in turn activates p53[54].

(d) Prolonged mitotic arrest causes p53 activation. When cells are arrested in pro-metaphase for more than 1.5 hours, cells activate p53 upon release from the pro-metaphase block[55]. How p53 activation occurs is not understood but could result from, partial activation of apoptosis, telomere uncapping (through the loss of telomere capping protein TRF2), p38 activation or Mdm2 down-regulation that occur during prolonged mitotic arrest[57].

Figure 3: The aneuploidy-associated stresses

The aneuploid state elicits a number of cellular responses. Proteotoxic and energy stress have been proposed to cause activation of the APS, which involves the up-regulation of proteins required for oxidative stress response and energy homeostasis. Aneuploidy also leads to slowed proliferation and an associated environmental stress response (ESR)-like response, in which stress response genes are up-regulated and cell proliferation genes are down-regulated. Aneuploid cells also activate p53, leading to impaired proliferation or apoptosis. This could be the result of genomic instability and activation of the DNA damage kinase ATM, activation of the stress kinase p38, prolonged cell cycle arrest, altered energy homeostasis or a combination thereof.

Figure 4: Protein quality control is limiting in aneuploid cells.

(a) In euploid cells protein quality-control and feedback mechanisms ensure that equal amounts of protein complex subunits are produced. Chaperones promote protein folding and maintain complex subunits that lack a binding partner in a soluble state. Eventually, excess and mis-folded subunits are degraded by the proteasome.

(b) In aneuploid cells protein stoichiometries of protein complex subunits are altered. Every subunit encoded by an unbalanced chromosome that functions in a protein complex lacks its binding partner(s) and must rely on cellular chaperones to remain soluble and, if no binding partner is found, on cellular proteases for its eventual degradation. This can lead to an increased burden on the cell's protein quality-control systems.

Table 1 – Frequency of aneuploidy

	Method of detection	**Incidence of aneuploidy or chromosome mis-segregation rate**	**Refs.**
Mitotic division			
Saccharomyces cerevisiae	Plasmid and YAC loss	0.001-0.01%	[19-22]
Schizzosaccharomyces pombe	Minichromosome loss	$1x10^{-4}$	[137]
Human tissue culture cells	FISH	~1%	[23,24]
Mouse keratinocytes	Single-cell sequencing	2.7%	[26]
Human keratinocytes	Single-cell sequencing	0%	[26]
Human and mouse brain	Single-cell sequencing	3-5%	[26,34]
Human and mouse liver	Single-cell sequencing	~5%	[26]
Human tissue culture cells displaying CIN	FISH	20-100%	[23]
Cancer	SKY	>85%	[6,138]
Meiotic divisions			
Saccharomyces cerevisiae	YAC mis-segregation	~4%	[19]
Schizzosaccharomyces pombe	Minichromosome loss	~4%	[139]
Drosophila melanogaster	SKY	~0.1%	[140-142]
Mouse fertilized eggs	SKY	1-2%	[143]
Human Sperm	SKY	1-4%	[144,145]
	FISH	1-3%	[146]
Human Oocytes	SKY	10-35%	[147,148]
	FISH	20-70%	[147,148]
	CGH	30-75%	[149,150]
Zygotes (human)	FISH, SKY	5-25%	[17]
Spontaneous abortions (human)	SKY	35%	[17,36,37]
Stillbirths (human)	SKY	4%	[17,36,37]
Newborns (human)	SKY	0.3%	[17,36,37]

Note: Plasmid, mini-chromosome and YAC loss measure mis-segregation rates; SKY, FISH and single cell sequencing measure incidence of aneuploidy

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This study shows that HSP90-mediated protein folding is reduced aneuploid mammalian cells providing a link between aneuploidy and proteotoxic stress.

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By analyzing genome sequence data from cancerous and normal tissues, this study provides evidence that aneuploidy drives tumorigenesis through losses of tumor suppressor genes and gains of oncogenes.

128. Silk, A. D. *et al.* Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors. *Proceedings of the National Academy of Sciences* **110,** E4134–41 (2013).
This study suggests that while low levels of chromosome mis-segregation can accelerate the generation of karyotypes that promote tumorigenesis, high rate of chromosome gain and loss leads to tumor suppression and cell death.

127. Sotillo, R., Schvartzman, J.-M., Socci, N. D. & Benezra, R. Mad2-induced chromosome instability leads to lung tumour relapse after oncogene withdrawal. *Nature* **464,** 436–440 (2010).
This study shows that tumor relapse after oncogene withdrawal is accelerated under condition of increased chromosome mis-segregation in a KRAS-driven model of lung cancer. This finding indicates that aneuploidy can facilitate the emergence of resistant karyotypes that confer an evolutionary advantage to the tumor.

Supplementary information: Table: Mouse models of chromosomal instability

Glossary:

Chromothripsis: A process in which entire chromosomes are shattered and then stitched together in a seemingly random manner, leading to dozens sometimes even hundreds of rearrangements within a single chromosome.
Dosage compensation: Alteration of mRNA or protein expression to compensate for variation in DNA copy number.
Proteotoxic stress: A cellular stress elicited by unfolded/mis-folded proteins.
Chromosomal instability (CIN): a condition in which the rate of chromosome mis-segregation is elevated.
Merotelic attachment: An incorrect microtubule–kinetochore attachment where a kinetochore attaches to microtubules emanating from both spindle poles.
Spectral karyotyping (SKY): A cytogenetic technique utilized to simultaneously visualize all chromosomes in a cell by employing different fluorescently labeled probes for each chromosome.

Online summary:

- Aneuploidy is defined as an abnormal karyotype that is not a multiple of the haploid complement.
- Chromosome mis-segregation causes DNA damage.
- Micronuclei form during chromosome mis-segregation. Chromosomes within micronuclei are underreplicated and undergo chromothripsis.
- Chromosome mis-segregation leads to p53 activation.

- The complex phenotypes caused by aneuploidy are caused by changes in the dosage of specific genes and a generic aneuploidy-associated stress response.
- Aneuploidy causes proteotoxic stress and impairs proliferation.
- Aneuploidy is a hallmark of cancer but the relationship between aneuploidy and cancer is complex. Depending on the context, aneuploidy can promote or antagonize malignant transformation.

Authors' Biographies:

Stefano Santaguida

Stefano Santaguida earned his PhD for his research carried out in the laboratory of Andrea Musacchio, at European Institute of Oncology, where he investigated the molecular mechanisms underlying spindle assembly checkpoint (SAC) function. He is currently a postdoctoral fellow in Angelika Amon's laboratory at MIT, where he studies the consequences of aneuploidy on cell physiology.

Angelika Amon

Angelika Amon obtained her PhD from the University of Vienna. She was a Whitehead Fellow from 1996 – 1999 and joined the Biology Department at MIT, where she is the Kathleen and Curtis Marble Professor of Cancer Research. Her lab studies the causes and consequences of aneuploidy in yeast and mammals.

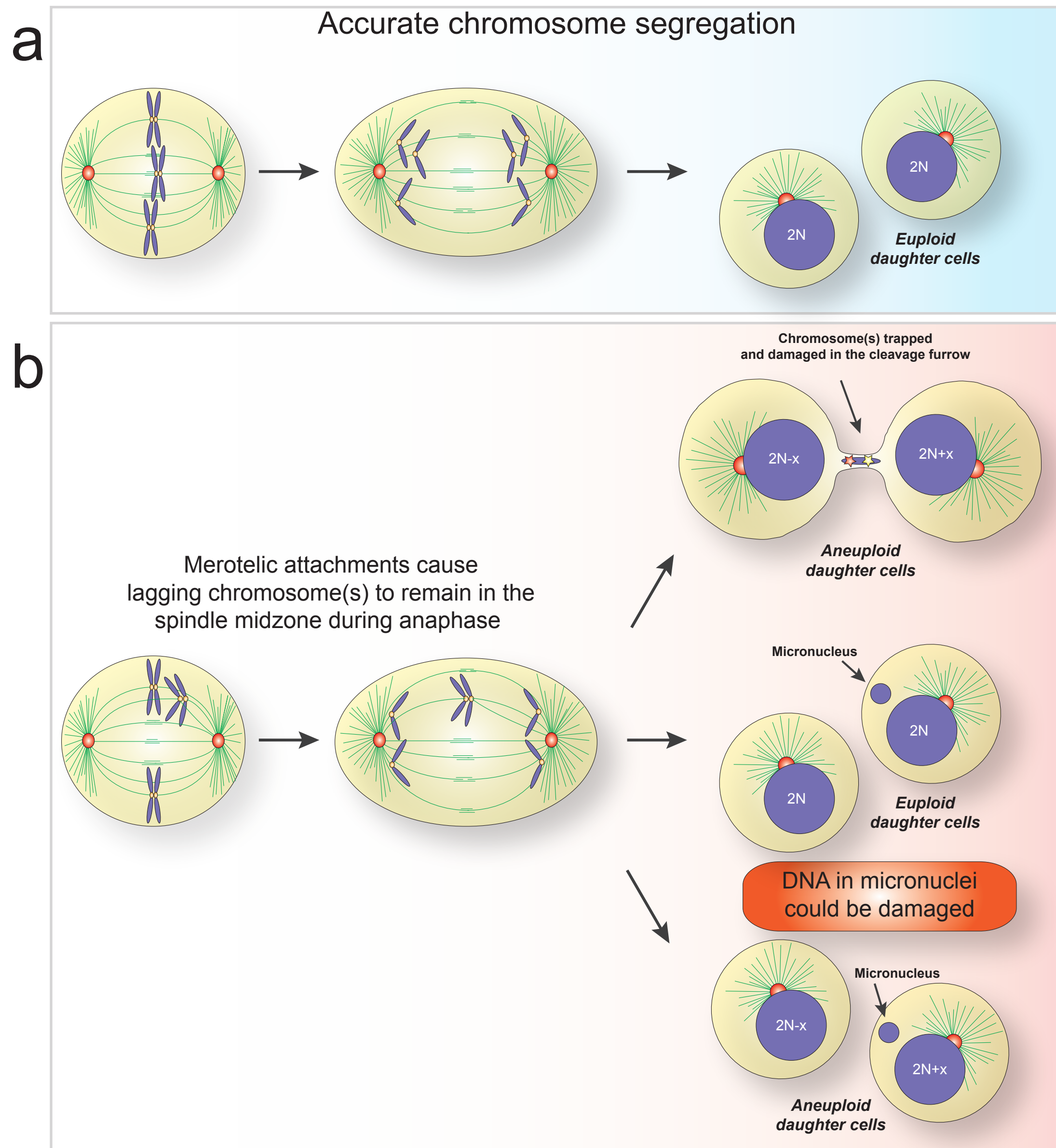


Figure 1

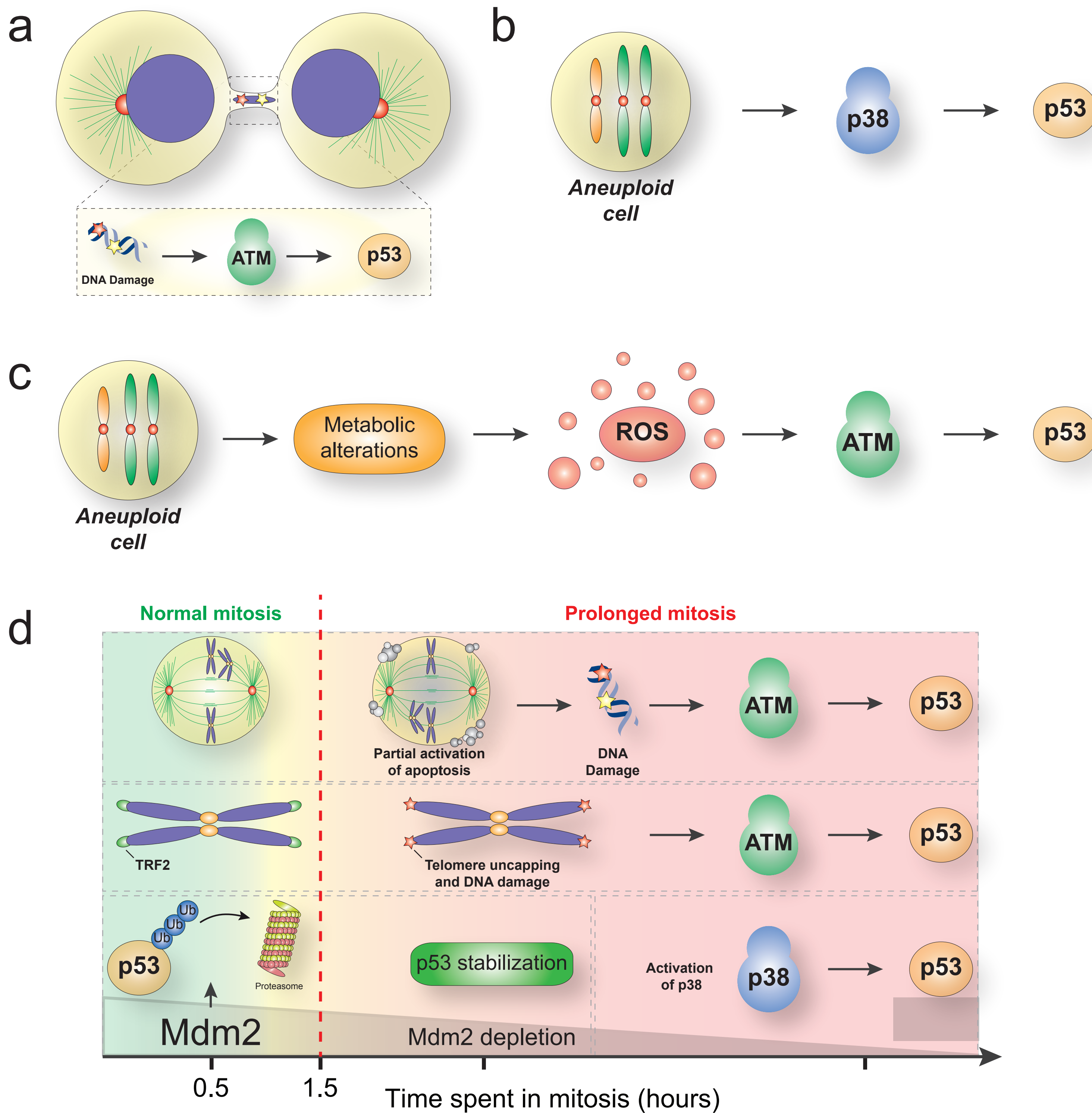


Figure 2

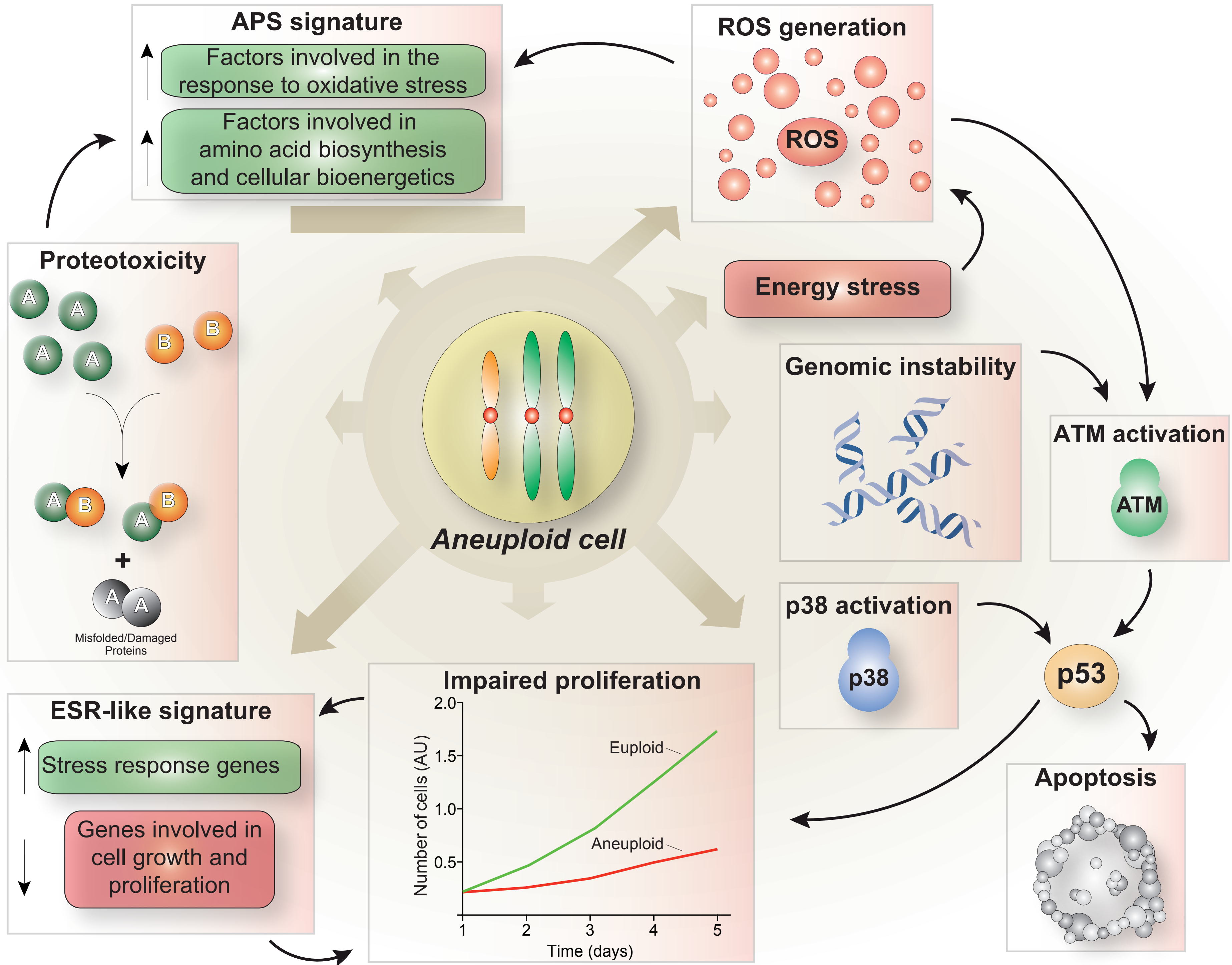
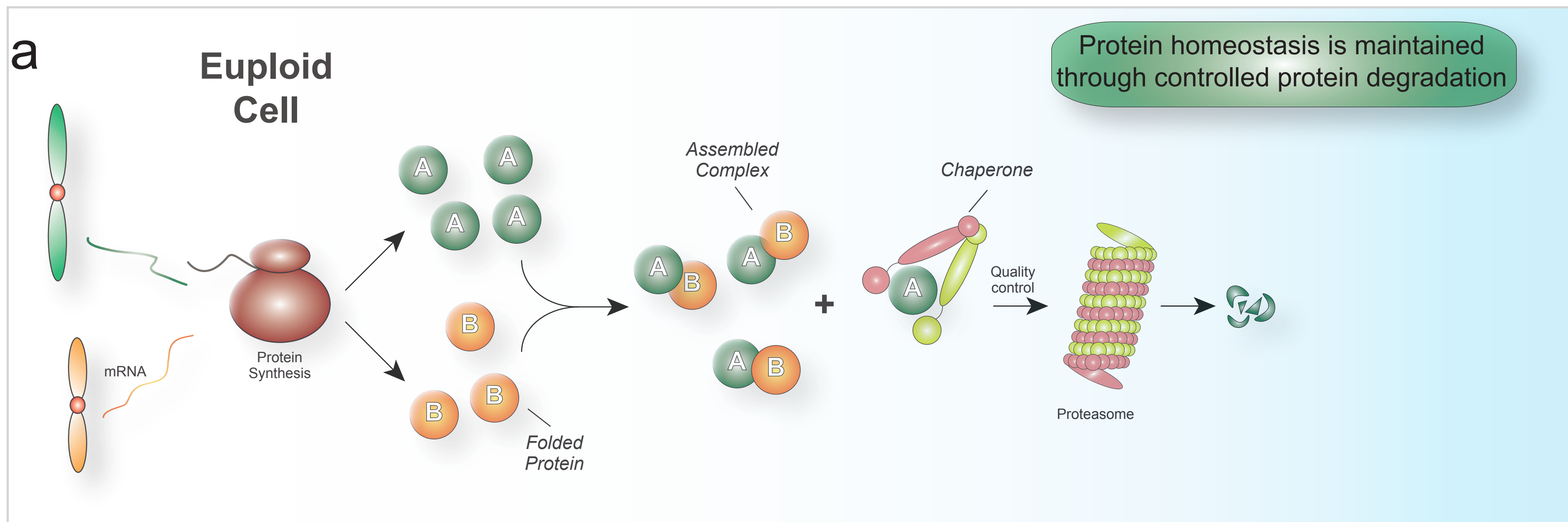


Figure 3



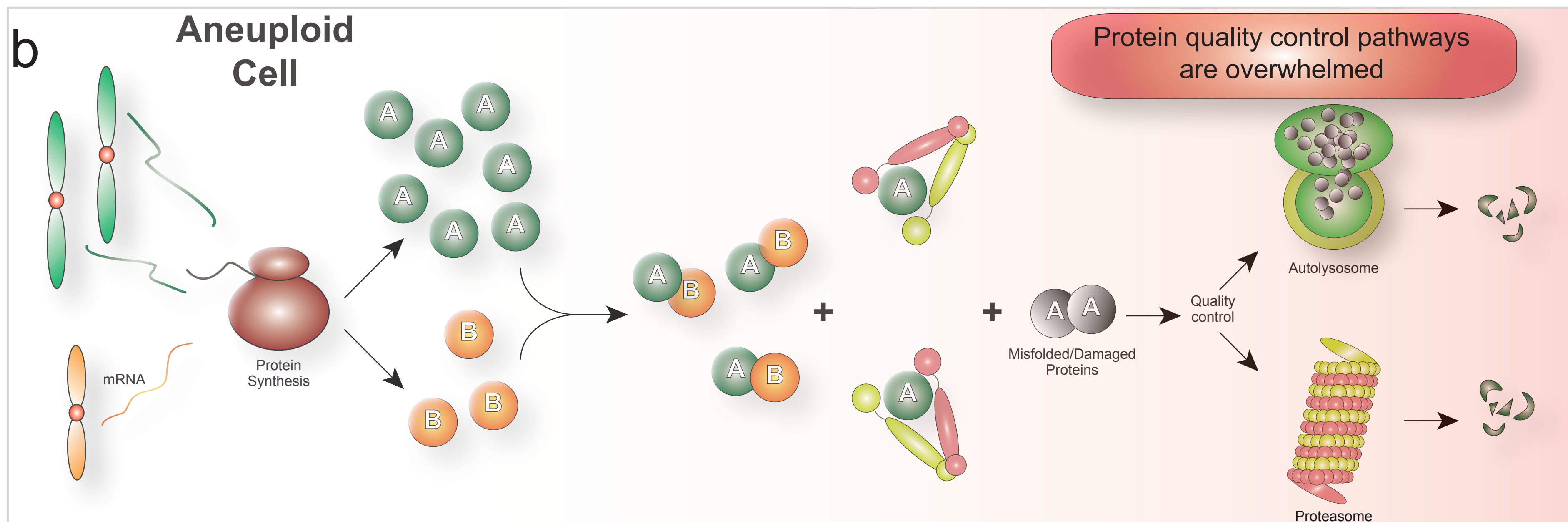
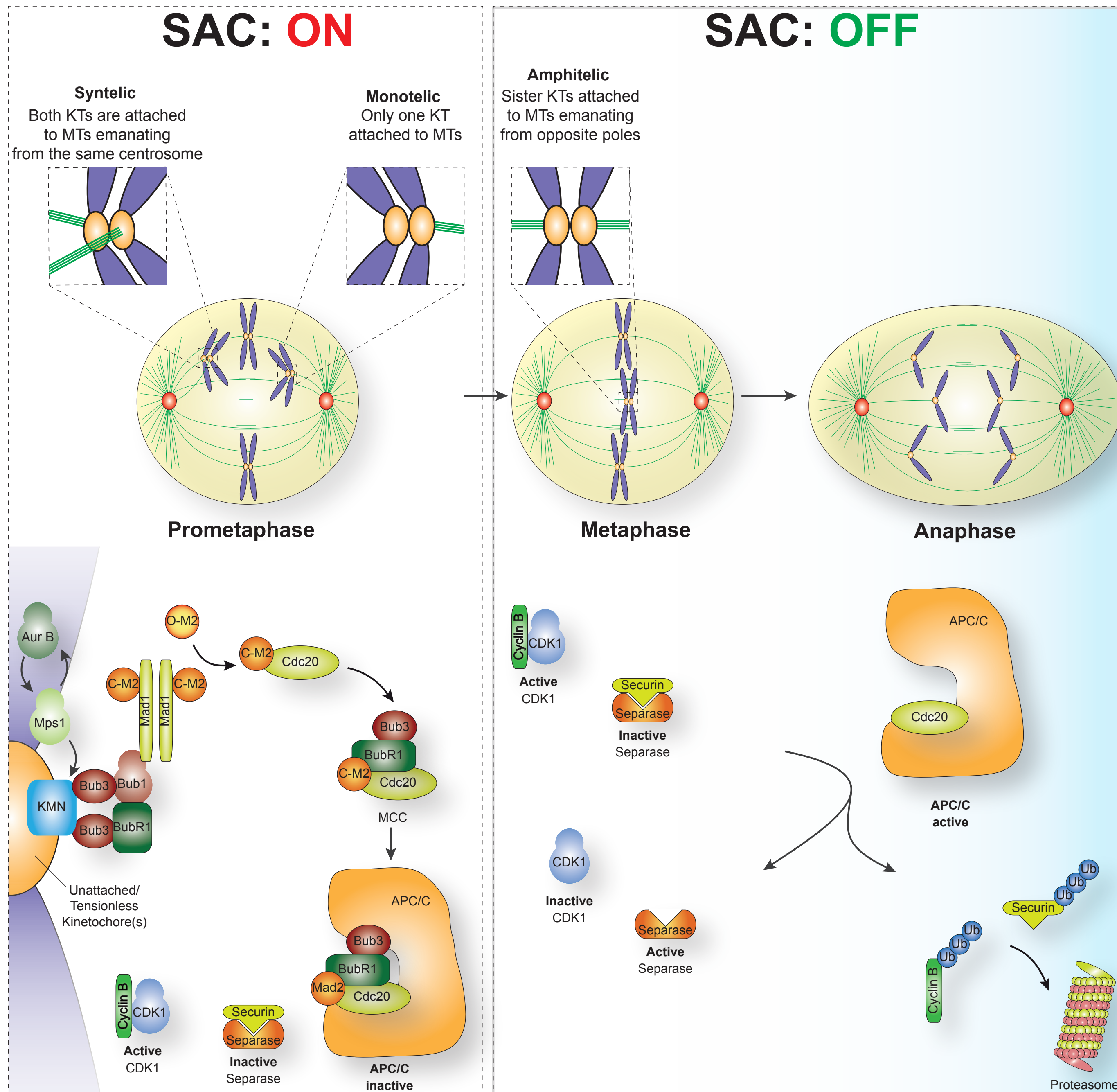
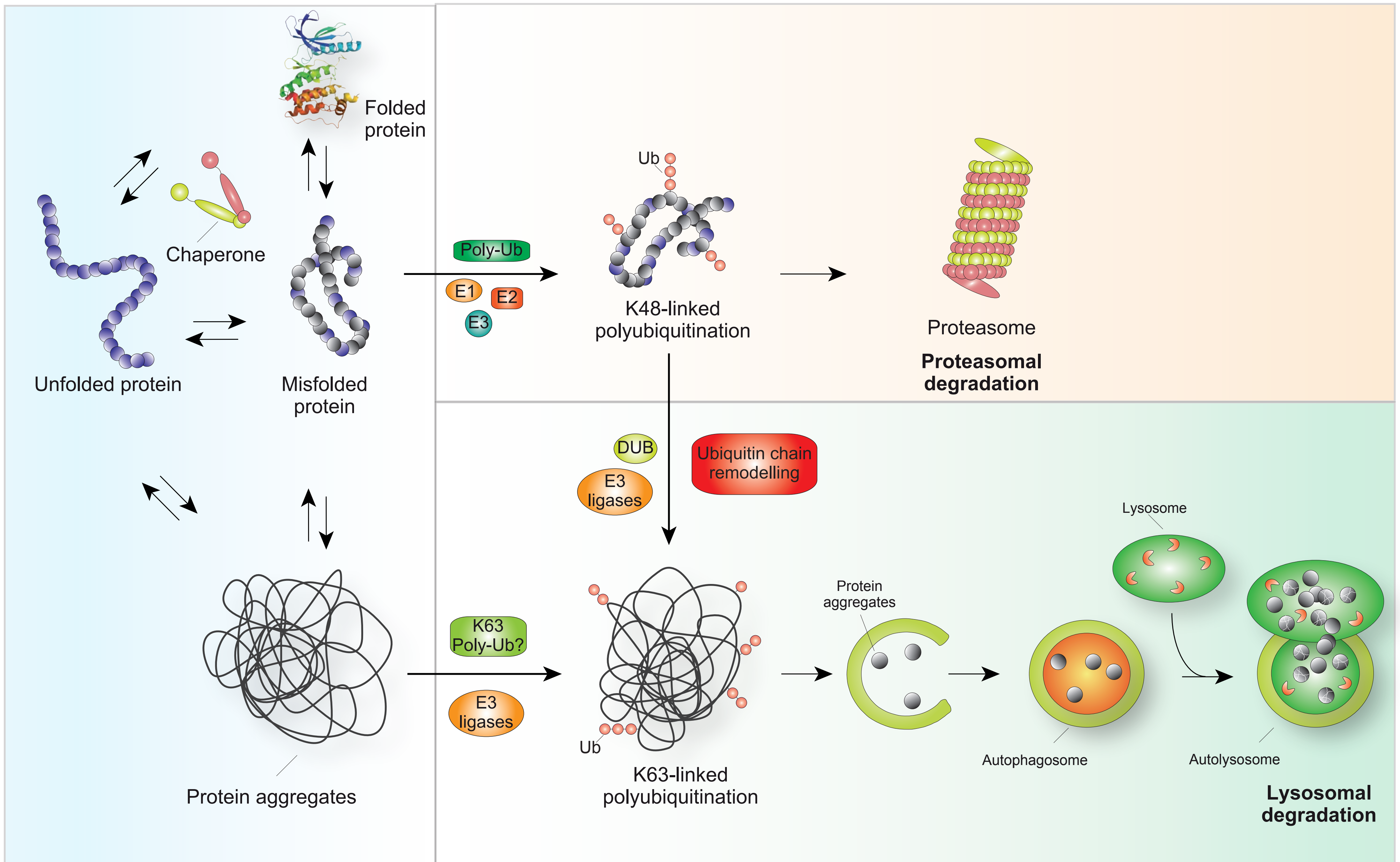


Figure 4



Box 1



Box 2