Review

Exploring Chromosomal Instability and Chromoanagenesis as Engines of Genomic Evolution

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Review

Exploring Chromosomal Instability and Chromoanagenesis as Engines of Genomic Evolution

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Summary: Advances in sequencing techniques have revealed extreme chromosomal diversity and underscored the importance of chromoanagenesis in macroevolution, speciation, and the context of cancer and tumor progression. Evolution is essential for adapting to the environment, preparing for future pressures, ensuring survival, and generating diversity. Here we discuss some events like chromothripsis and other chromosomal rearrangements, emphasizing their roles as driving forces in genomic evolution from cancer to speciation.

Keywords: chromoanagenesis; chromothripsis; chromosomal instability; micronucleus; genome evolution; macroevolution; speciation; gametogenesis; embryogenesis; cancer

1. Introduction on Evolution and Chromoagenesis

Evolution is intricately linked to the capacity to change and adapt. It manifests along a spectrum, with some species evolving rapidly while others exhibit notably slower rates of change. A few animal species are known for their highly efficient DNA repair mechanisms and are referred to as 'living fossils' due to their incredibly low species diversity and minimal differences from their fossil relatives [1,2]. In the other side, some species exhibit extreme cases of genomic evolution, with chromosomal evolution being one of the most visible and impactful changes. One of the mysteries of structural genome evolution is its extreme temporal irregularity. For many organisms, it is known that periods of very slow genome changes alternate with explosions of chromosomal rearrangements, resulting in rapid and complete reshuffling of the linkage groups and gene orders [3]. These types of evolution are known as rapid chromosomal change [4,5], extensive chromosome evolution [6], fast karyotype evolution [7], karyotypic mega-evolution [8], or runaway chromosomal evolution [9]. Events like whole genome doubling favor rapid and drastic changes in karyotype due to their genomic instability [10,11]. Furthermore, such explosive evolution is now known to be associated with chromoanagenesis, a process of chromosome rebirth from chaos, resulting from a catastrophic event. Chromoanagenesis is an umbrella term that to describe the full spectrum of large-scale rearrangement [12]. The most frequent and well-studied example is chromothripsis, where hundreds of chromosome fragments are reorganized, duplicated or removed. In addition, other complex rearrangements include chromoplexy, chromoanasynthesis. These drastic chromosomal evolutions have recently been well described in disease such as cancer [12–14] or in the case of rare diseases [15,16] but is also known in evolution [17] from numerous groups of organisms like mammals [5], plankton [18], fungi [19] or plants [20–22].

2. Chromoagenesis, a Chromosome Rebirth

Chromoanagenesis is a term describing the complex chromosomal rearrangements chromothripsis, chromoplexy and chromoanagenesis (Figure 1).

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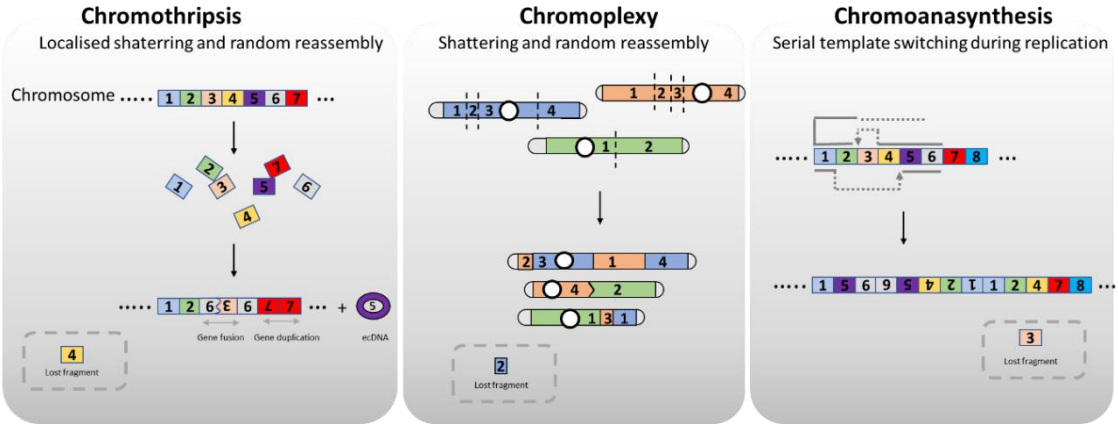

Figure 1. Types of chromoanagenesis.

Chromothripsis is a chromosomal instability phenomenon, a genomic catastrophe, where hundreds of chromosomal rearrangements occur during one single event in a localized region of one or two chromosomes. It was first described by Stephens *et al* [23] in a patient with chronic lymphocytic leukemia. It is now found in 40-80% of all tumors [24]. It was also rapidly identified in patients with congenital malformations, developmental disorders or carrying apparently balanced rearrangements [15–17]. Chromothripsis involve a pulverization of the chromosome in several fragments that can reorganized in a different order during the next mitosis [25,26]. Chromothripsis is known to drive tumorigenesis by disruption or loss of tumor suppressor, generation of oncogenic fusions and amplification of oncogene through extrachromosomal DNA (ecDNA) [12,27].

Chromoplexy, in another hand, tends to involve less pieces of chromosome but implicates more chromosomes, frequently 5 or even more [28]. It leads to multiple interchromosomal and intrachromosomal translocations and deletions.

Chromoanasynthesis is replication-based process with local rearrangement and altered gene copy number due to serial fork stalling or template switching, or microhomology-mediated break-induced replication [29]. It involves duplications and deletions and it is associated with replication stress.

Other events of chromosome instability (CIN) are associated with chromothripsis as the Breakage-fusion-bridge (BFB) cycle or the newly described seismic amplification [30–32].

3. Molecular Mechanisms to Generate Genome Rearrangements, Source for Evolution

The origin of chromoanagenesis is not fully understood yet. However, concerning chromothripsis, it seems clear that nuclear envelope rupture (NER) from a micronucleus is responsible for the chromosome pulverization. During mitosis, a lagging chromosome or a chromosome fragment resulting from an unrepaired dsDNA break (DSBs), can produce the formation of micronuclei (Figure 2). When a full or piece of chromosome is late during the nuclear envelope (NE) formation, it is not clustered with the other chromosomes. Then a proper NE forms around this one, forming a separate small nucleus close to the main nucleus, known as micronuclei (MN) [33].

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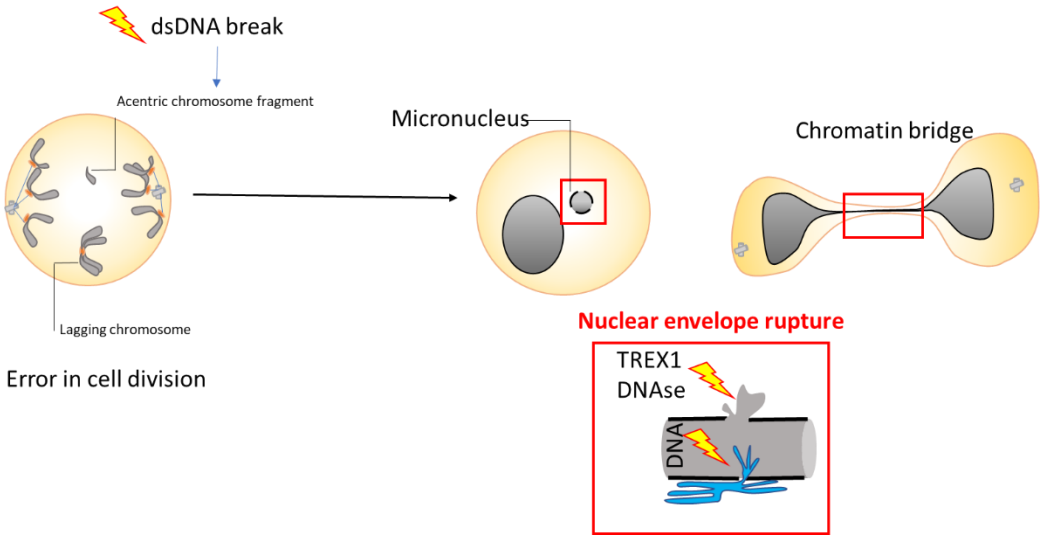

Figure 2. Origin of chromoanagenesis. Error in cell division, which involve physical separation of chromosomes, can lead to the formation of micronuclei, a separate nucleus containing the lagging chromosome. A fragment of chromosome resulting from double-strand DNA damage can also lead to micronuclei formation. Micronuclei present a defective nuclear envelope that tend to disrupt. NE can also disrupt due to chromatin bridges. During nuclear envelope rupture, DNA is exposed to cytoplasmic DNAse or to the endonuclease TREX1 associate with the reticulum endoplasmic, resulting in chromosome fragmentation.

Micronuclei formation is now recognized as a major event that triggers chromosome shattering, followed by the aberrant reassembly of the fragments [25,26,34]. NER happens on micronuclei, where the envelope is fragile and tends to disrupt without possibility of proper repair [35,36]. The nuclear envelope of micronuclei often lacks sufficient nuclear pores and normally is associated with is delayed DNA replication and repair [25,37,38]. This envelope can rupture exposing the chromatin to cytosolic factors [36,37]. Factors contributing to this rupture include the loss or mislocalization of the nuclear lamina component lamin B1 [36,39], depletion of nuclear envelope proteins (Figure 3) [37] or activation of ATR pathway to clear damaged DNA [40]. Experimental evidence suggests that chromosomes from ruptured micronuclei undergo chromothripsis, a process of chromosome shattering and rearrangement [25,26].

In another case, NER happens in cells with a chromatin bridge, where telomere fusion connects two daughter cells [41]. This implies the generation of additional tension forces affecting the NE during movement, leading to NER that can last up to two minutes [42]. Cells can also experience transient NER of their nuclei during migration [43–46]. Interestingly, immune attack can fail and contribute to mutagenesis. Cytotoxic T lymphocytes often fail to kill target cells during one-on-one interaction, leading to transient NER and subsequent DNA damage [47]. Such 'failed' attacks then contribute to the generation of genomic diversity and progression toward resistance. Additionally, certain viruses, such as human papillomavirus (HPV) and Epstein–Barr virus (EBV), have been implicated in the formation of micronuclei, leading to chromothripsis in infected cells. These viral interactions might have played a role in chromosomal rearrangements, evolution, and speciation [48,49].

Remarkably, a study using CRISPR-Cas9 gene editing has shown that a single DSB can trigger a cascade of events resulting in the formation of micronuclei and chromosome bridges [50]. Such simple DSBs can be amplified into far more extensive genomic alterations during subsequent mitosis, leading to a myriad of genomic diversity.

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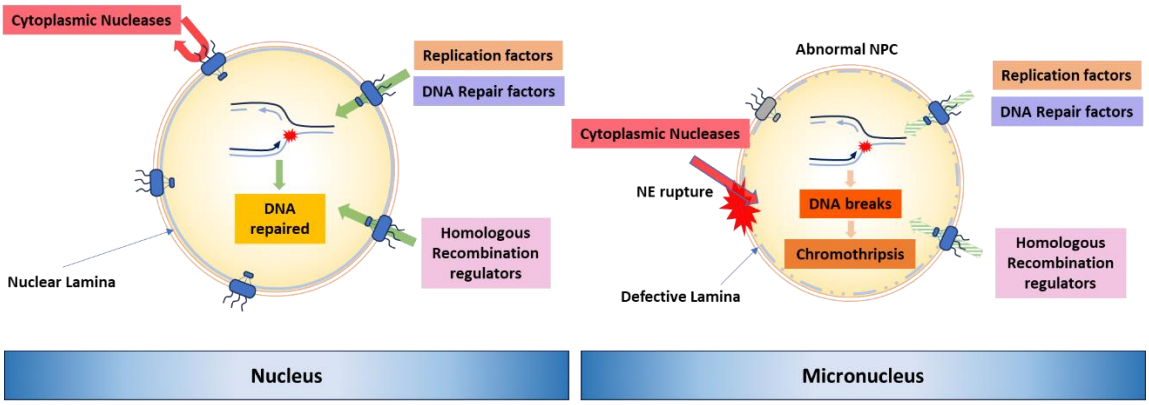

Figure 3. DNA metabolism in the micronuclei. Micronuclei exhibit a nuclear envelope (NE) that lacks sufficient nuclear pore complexes and shows abnormal lamina formation. These abnormalities cause issues with nuclear protein import and frequent NE ruptures. When the NE ruptures, cytoplasmic components, as nuclease TREX1, invade the micronucleus, while soluble nuclear components and DNA can leak out.

During NER, DSBs can occur due to the entry of cytoplasmic nucleases such as TREX1 [41,51], errors in DNA repair or replication [12,52]. Such breaks can lead to chromosome pulverization and fragmentation. Several mechanisms have been proposed to explain the complexity of new genomic rearrangements. One of such mechanisms is non-homologous end joining (NHEJ), which can lead to reciprocal translocations following DSBs [53,54]. Studies indicate that translocations are more frequent in mammalian cells lacking NHEJ components like Ku70 and ligase Xrcc4, suggesting that alternative end-joining (alt-EJ) mechanisms might facilitate these translocations [55]. These processes often involve modifications at break sites, typically resulting in deletions. Other common features of DNA junctions formed by end-joining could include microhomology [55]. A novel model, fork stalling and template switching (FoSTeS), has been introduced to explain the complexity and microhomologies at breakpoints of non-recurrent duplications and deletions associated with genomic disorders [56]. This model is related to another called microhomology-mediated break-induced replication (MMBIR), which is based on break-induced replication and accounts for various complex rearrangements, mainly involving duplications and deletions [56–58].

Interestingly, samples with events of whole genome doubling (WGD) are associated with the presence of chromothripsis [12]. WGD has been shown to induce replication stress as well as DSBs [59]. Furthermore, during proliferation, WGD+ cells, which have extra centrosomes, exhibit chromosomal instability during proliferation, leading to an elevated rate of chromosome mis-segregation and the rapid accumulation of both numerical and structural abnormalities [60].

4. Chromosomal Instability and Macroevolution

In the wild, organisms can show an impressive change in number of chromosomes between closely related species. This enormous karyotypic diversification indicates that chromosomal evolution is an active and recurrent process. Such changes are also associated with chromoanagenesis-like rearrangements. Recent advances in sequencing technology and bioinformatics software, along with their reduced costs, have enabled the detailed characterization of highly complex chromosomal rearrangements mostly in human tumor samples. While the human genome is well-mapped, reference templates for other species are necessary to fully understand genomic complexity. There is no doubt that in the near future, chromoanagenesis will be described in the genomic evolution of several species, especially those showing huge karyotype diversification. In fact, a recent study has shown the importance of chromoanagenesis in adaptation as observed between marine annelids and the terrestrial clitellates. This study provides evidence of punctuated genomic change via chromoanagenesis leading not only to the origin of a new animal lineage but also to adaptive genomic changes facilitating the colonization of new habitats [61].

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The case of tuco-tuco, a small neotropical rodent in the family Ctenomyidae found in South America, shows an extraordinary chromosomal variability. With 70 species with a diploid number varying from 10 to 70 chromosomes, it is one of the most speciose and chromosomally variable rodent genera of the world [62]. Within the genus, several types of chromosomal rearrangements were described such as Robertsonian translocations, inversions, heterochromatin additions and deletions, as well as complex rearrangements [62–64]. In Corydoras fish genus (Siluriformes: Callichthyidae) diploid numbers range from n = 44 to n = 102 and have extensive chromosomal rearrangements [65]. Similar diversity is found in Muntjac deer (Artiodactyla: Cervidae) with karyotypes ranging from n = 3 to n = 23 [66] and drastic chromosomal rearrangements [5]. In plants, the greatest range of within-genus karyotype variation is found in Carex, where haploid chromosome numbers range from n = 6 to n = 66 [67,68]. Lepidoptera is an order of winged insects that includes butterflies and moths. Despite this general stability, some genera of butterflies and moths exhibit remarkable variation in chromosome numbers. For instance, in the clade comprising the genera ((Polyommatus + Neolysandra) + Lysandra) (Lepidoptera, Lycaenidae), an array of chromosomally diverse species emerged within less than 5 million years of evolution. In these species, the haploid chromosome numbers range from n = 10 to n = 226 [3]. Lepidoptera evolution involves fission and fusion of chromosomes, but also some species present much more complex rearrangements of their chromosomes [3,69].

The selective breeding of new species with enhanced production and improved flavor is foundational to modern agriculture and livestock farming and such new species are often associated with chromosomal aberrations. In plants as coffee [70] or grape [71], in cattle [72] or in yeast [73], selective pressure applied during selection is associated with massive changes in their chromosome organization. However, such selection is often associated with a decrease in resilience and a loss of advantages in the wild. For example, cattle breeding is associated with dysfunction in fertility, notably due to Robertsonian translocation, a common type of translocation [72]. In the case of black and white tempranillo, different grape varieties, a genomic study has shown events of complex chromosomal exchanges between three chromosomes [71], that are likely a chromoplexy pattern. However, even though these new species were selected for their gustative values, in term of stiffness, such chromosomal changes are associated with issues in viability of gametes [74]. In yeast, the 'Guinness strains' exhibit polyploidy and chromosomal aberrations. Presumably due to the effects of aneuploidy, all 16 known Guinness strains show poor sporulation [73].

Extreme conditions found in the laboratory, such as the use of haploid induction in plants, biolistic transformation, mutagenesis, or irradiation, can result in both chromothripsis and chromoplexy. In plant, such events were observed in *Arabidopsis thaliana* [75,76], poplar trees [21,77], maize [78], rice [78] or potatoes [79]. In *C. elegans*, chromoanasynthesis was observed after a mutagenesis screen [80,81]. Interestingly, ecDNA known to be associated with chromothripsis can serve as a mechanism of resistance for organisms such as yeast for copper resistance or plants for glyphosate resistance [82].

5. Chromosomal Instability in Cancer

An intriguing aspect lies in the similarity and parallelism between the history of genomic complexity in tumors and genome evolutionary changes. Both are shaped by drastic events like chromosome rearrangements and the gain or loss of chromosomes, which drive their evolution and adaptation to new environments and pressures. WGD is an early event in tumorigenesis [83–87], promoting genome diversity and chromosomal instability [88], similar to what has been observed before the diversification of vertebrates [89,90] and in plants [91]. Interestingly, genome duplication can occur multiple times during tumor development, resulting in highly complex cancer genomes [84,92]. Furthermore, chromothripsis increased with whole-genome duplications in most cancer types [93].

Cancer genomes are complex, heterogeneous, and highly rearranged. Between 80-97% of tumors exhibit detectable CIN and complex chromosomal rearrangements [92,94]. Notably, chromothripsis is observed in 40-80% of tumors, chromoplexy in 10%, and chromoanasynthesis in 5%

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[23,24,28,30,95,96]. Thus, chromoanagenesis plays a crucial role in driving tumor evolution. Furthermore, tumor progression, in another word, evolution, is associated with increased complexity and genomic large-scale reorganization within the metastatic lesions [83–87,97], accelerating the odds of developing resistance to anti-cancer therapies [98]. Importantly, chromothripsis is associated with the formation of circular extrachromosomal DNA (ecDNA) as well as with segmental deletion, supporting the amplification of oncogenes as well as the disruption or loss of tumor suppressor, highlighting their pivotal role in tumor evolution [12,27,34,99].

Mechanistically, tumors harboring high levels of CNA and chromoanagenesis have a worse prognosis than tumors with high mutation rate because of their ability to escape the immune system [100], but also to activate the cGAS-STING pathway, a pro-survival pathway for metastatic lesions [101].

6. Mitotic and Meiotic Programs as Drivers for Genome Evolution

The genome must balance stability and variability to preserve essential information while allowing adaptations to environmental changes. Accurate DNA repair and replication, during mitosis and meiosis, are crucial for maintaining and transmitting DNA through chromosomes during development and from parents to offspring. Despite programmed DSBs and meiotic recombination mixing genome information, these processes are not entirely error-free [13]. It could lead in *de novo* genomic rearrangements, such as inversions, duplications, insertions/deletions (indels), and large-scale structural changes like Robertsonian translocations and Whole Arms Translocations (WARTs), or chromoanagenesis processes, and aneuploidies. These structural changes significantly impact chromosomal and nuclear architecture [102,103]. These chromosomal rearrangements can occur during gamete formation, zygote formation, and embryo development, affecting the individual's genome, and may vary with each stage of mitosis and meiosis [104,105]. The evolutionary impact of *de novo* mutations depends on their characteristics and the context of their emergence, as tissues or time of development appearance.

Chromatin domains and compartment patterns differ among cell types, with topologically associating domains (TADs) undergoing reorganization throughout the cell cycle [106,107]. Chromothripsis reshapes gene regulation, leading to coordinated changes in the epigenetic landscape, transcription, and TADs domains. These reorganizations are crucial for genome functionality and inheritance. In cancer, TADs are commonly disturbed by chromothripsis, leading to changes in gene expression profiles [108]. Chromosomal alterations disrupting TAD architecture can lead from meiotic recombination defects to developmental deficiencies due to improper enhancer-promoter interactions [109]. Additionally, research has examined conserved chromosome territory arrangements and species-specific changes contributing to reproductive isolation and speciation [110–112].

7. Rearrangements of Chromosomes During the Initial Stages of Development

Although chromosomal rearrangements are known to occur during meiosis, the majority of documented chromoanagenesis events in animals [26,34,57,113], and all reported events in plants [75,78,114], are associated with mitotic processes, particularly during the early stages of embryonic development [75,115]. Chromosomal instability may occur during one of the initial mitotic divisions of early embryonic development, and such errors can either lead to the embryo's elimination or result in mosaicism. Mosaicism occurs when an individual has two or more genetically distinct sets of cells. Typically, it originates from a single cell that becomes the progenitor of a clone, which can sometimes cause genetic diseases, including cancer, more commonly in children than in adults [116,117]. Mosaicism, which is common in mammals including humans, can arise from unequal chromosomal division of blastomeres or the presence of different cell clones [118]. Approximately 50–70% of human cleavage embryos are aneuploid, highlighting the high levels of chromosomal instability during the generation of offspring [119,120].

Another chromosomal anomaly, the formation of a dicentric Y chromosome, leads to sterility in humans and is believed to occur early in development due to recombination between sister

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chromatids or delayed joining after a break or deletion. This can cause mosaic disorders, such as sterile males with karyotypes lacking a Y chromosome [121,122]. Dicentric chromosomes are also observed in livestock such as buffaloes, sheep, and goats [123]. Despite their formation, these chromosomes are often eliminated within a few generations due to centromeric drive, meaning they usually do not have an evolutionary impact since they are not passed on to gametes.

Most aneuploid embryos fail to develop to term, making aneuploidy in embryos a leading cause of miscarriages and infertility. Nonetheless, if chromosomal alterations occur during the formation of primordial germ cells and do not severely impair gametogenesis and fertility, these changes could be inherited and may have evolutionary significance [124]. Another key aspect to consider is the reorganization of the zygotic genome for subsequent activation from the previous maternal control. Chromosomal rearrangements impact both the physical arrangement of chromatin and the regulation of gene activity [125–127]. Research in mice has demonstrated that chromatin architecture is reprogrammed during germ cell development [128]. If the chromatin architecture is not correctly established at the onset of embryonic development, the genetic program cannot proceed, leading to the termination of the embryo's development [129,130]. Chromosomal rearrangements can also impact the genetic program beyond the directly affected sequence. However, these rearrangements can introduce new combinations of genetic patterns that contribute to genome evolution and speciation. Studies have shown that functional plasticity under a higher-order genomic organization is inherited by offspring, leading to the formation of new allelic variants on which natural selection and evolution can act [127].

8. Chromosomal Instability Processes in the Germ Cells

Genome instability can have significant evolutionary consequences, leading either to extinction or rapid speciation. This process is closely tied to the emergence and establishment of chromosome rearrangements within populations. The spread and fixation of these rearrangements can be driven by their impact on gametogenesis, spermatogenesis in males or oogenesis in females. For instance, rearrangements that result in altered gametes during spermatogenesis or oogenesis, as the ones taking place in the germline, can facilitate the rapid establishment of these changes within a few generations [13]. Models of population genetics suggest that even slight reductions in viability or fertility due to these rearrangements can promote the development of divergent genetic lines, even in populations that coexist geographically. This can lead to reproductive isolation and eventually speciation.

Germline rates of *de novo* meiotic deletions and duplications are a significant source of genetic diversity, contributing to several genomic disorders. Chromosomal evolution, as deep chromosomal rearrangements or reciprocal translocations in germ lines are particularly important, as they have been observed across multiple phyla, including humans. A study in a trio family has identify *de novo* balanced rearrangements in a set of three chromosomes in a patient, mediated by simultaneous breakpoints accumulated in specific chromosomal regions and joined, resulting in a chromothripsis pattern, presumably in the germline. These translocations play a crucial role in generating genetic diversity, which is essential for the adaptive potential of populations [131–134].

Mosaicism in germ cells can have profound effects on genetic diversity and health. When chromothripsis occurs in germ cells, the resultant rearrangements can lead to significant genetic variations in gametes, potentially causing severe health problems [135]. Interestingly, many of these rearrangements, although stably transmitted in an unbalanced form from a healthy mother to her child with congenital abnormalities, are likely due to *de novo* copy-number changes of dosage-sensitive genes.

A major challenge in chromosome evolution is that new large-scale chromosome mutations must successfully go through meiosis. Even balanced chromosomal changes can harm the fertility of heterozygotes because they can mess up meiotic pairing and produce unbalanced gametes with incorrect gene dosage. However, a study has documented a case of balanced germline chromothripsis that was transmitted through three generations involving 11 healthy carriers. This suggests that chromothripsis does not always result in an abnormal phenotype. Specifically, the study

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hypothesized that truncation of the gene encoding the ataxia–telangiectasia and Rad3-related protein kinase (ATR), a vital component of the DNA damage response, might be linked to the chromothripsis event. This finding implies that germline chromothripsis may be more prevalent than currently acknowledged, underscoring its potential role in evolution and species divergence [136].

9. Gametogenesis as a Source of Chromoanagenesis

The relationship between fertility and chromosomal instability is complex and multifaceted. Abnormal chromosomes can disrupt meiosis, resulting in the production of aneuploid sperm or eggs. When these aneuploid gametes are involved in fertilization, the resulting embryos often have chromosomal abnormalities, which can lead to miscarriages or developmental issues. Additionally, chromosomal instability can impair fertility by affecting the mitotic self-renewing cells in the germ line, which are essential for the formation of gametes.

In multicellular diploid organisms like mammals, the creation of new life begins with the fusion of two haploid gametes, restoring the diploid state in the zygote. The differences between male and female meiosis and their respective products influence meiotic drive, a mechanism of natural selection [13]. Each step of gametogenesis must be meticulously regulated to ensure proper development. Male and female meiosis differ significantly in both timing and the resulting products. In males, meiosis produces four haploid spermatids, which differentiate into four spermatozoa. In females, meiosis involves asymmetric cytokinesis, resulting in one functional oocyte and two discarded polar bodies. This asymmetry during the first and second meiotic divisions affects selection processes in forming the final haploid gamete, the egg. The first division produces an oocyte and a first polar body, both with a haploid set of chromosomes but doubled DNA content. This occurs after synapsis and chromosome recombination, leading to distinct genomes for the oocyte and the polar body. The second division results in another polar body and the mature egg, each with a haploid content. In mammals, the appearance of polar bodies occurs after fertilization, as female gametes are arrested in Prophase I until triggered by fertilization. Properly clustering and separating polar bodies from parental genomes is crucial, as errors can lead to aneuploidy and the formation of micronuclei, which are common issues. Micronuclei can ultimately result in aneuploidy or chromoanagenesis events (Figure 4). Thus, polar bodies may enable rapid changes in the chromosome set, making meiotic drive a significant evolutionary force [137].

Chromothripsis has been observed during spermatogenesis and in the initial cleavages of preimplantation embryos, but not often during oogenesis [57,138]. Notably, the majority of identified chromoanagenesis events are linked with male gametogenesis [77]. Specifically, chromoanagenesis has been demonstrated to occur during meiotic divisions in spermiogenesis in humans [57,139]. While chromosomal rearrangements are also likely to arise due to errors in female meiosis, there are relatively few studies on this topic [138,140]. It has been reported that the DNA repair capacity in the male germ line is relatively low compared to somatic cells, and the mutation rate is higher during spermatogenesis than during oogenesis. The extent of these rearrangements can be substantial, potentially leading to significant evolutionary consequences [141,142]. The extensive genome reshuffling observed in rodents may be explained by chromoanagenesis events occurring in their germ lines [143,144]. The result of different meiotic segregation patterns can also be disrupted by chromosomal reorganizations involving different translocations, creating complex structures between homologous chromosomes that are difficult to resolve. This increases genome instability during meiosis. Studies in patients have described improper disjunction of chromosomes [131,145,146], which is a source of chromosomal variation and speciation.

Chromoanagenesis have also been observed during haploid induction in *Arabidopsis thaliana* [75]. Due to haploidy, chromosome mis-segregation can occur during gametogenesis, leading to the formation of a micronucleus containing a lagging chromosome. This chromosome, trapped within the micronucleus, undergoes fragmentation and reorganization, ultimately resulting in a shattered chromosome during meiosis (Figure 4). The viability of the meiotic process and survival of the next generation of plants can be attributed to the presence of three copies in a diploid background, where the shattered chromosome is buffered by the intact copies. Similar chromoanagenesis-like

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rearrangements have been identified as potentially influencing the genome structure of *Camelina sativa* and the genus Cucumis [22,147].

Although few cases of chromoanagenesis related to defects during gametogenesis have been described, especially in the wild [76], chromoanagenesis may be more common than currently recognized, similar to other rearrangements like Robertsonian translocations. These translocations involve the entire arms of chromosomes and occur in the acrocentric chromosomes 13, 14, 15, 21, and 22 in humans, making them the most frequent type of chromosome rearrangement in the human population and the most prevalent form of chromosomal changes observed in mammals [148]. In situations involving partial or chained-monobrachial homology, or when multiple Robertsonian translocations (Rbs) are present, synapsis can be extended but leading to meiotic failure in some cells and reduced fertility [149,150]. This phenomenon has been observed in species such as bats, shrews, mole voles, mice, and rock-wallabies, where monobrachial homology appears to restrict gene flow and possibly drive speciation [144,151–153]. In mice, various forms likely originated from whole-arm reciprocal translocations (WARTs), creating complex hybridization patterns through parental lines [154]. WARTs have been noted in the same groups as Rbs, suggesting a shared origin mechanism for these rearrangements. Occasionally, extensive rearrangements, including tandem fusions, can cause a surge in intraspecific diversity, as seen in the Evoron vole [134].

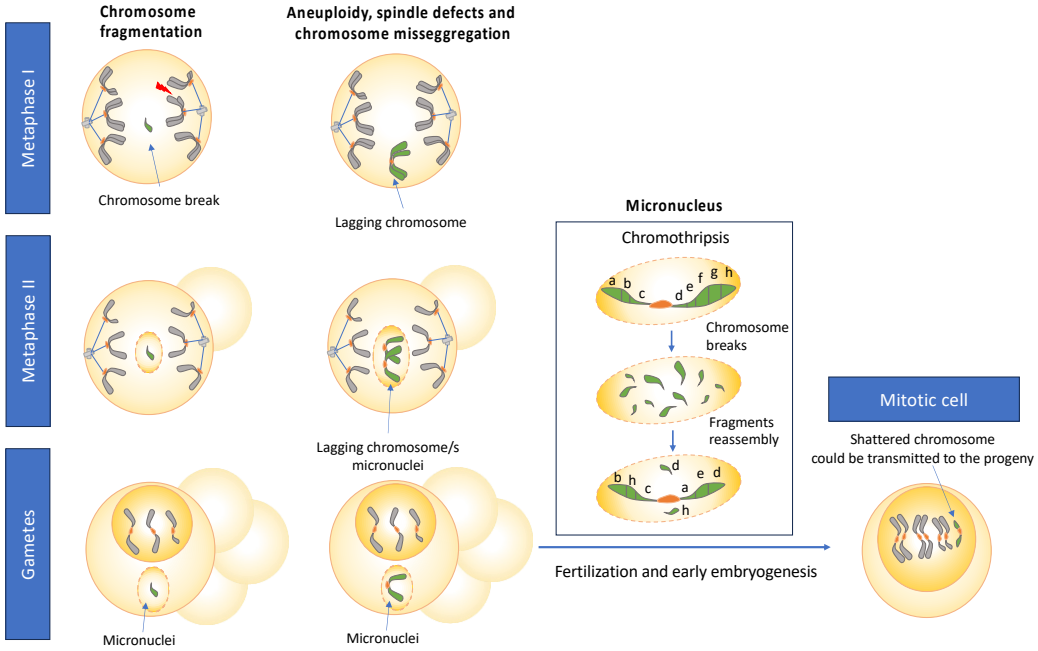

Figure 4. Proposed mechanism for chromoanagenesis during meiosis. In some cases, chromosome fragmentation, synapsis defects, spindle failures, or chromosome missegregation leads to lagging chromosomes or acentric chromosome fragments during meiosis. During meiotic division II, these missegregated chromosomes or fragments become incorporated into a compartmentalized micronucleus. DNA damage mediation, non-homologous end joining (NHEJ) repair, and restitution of the micronucleus to the euploid pole nucleus can result in aneuploidy in the zygote or during embryogenesis. Alternatively, shattered chromosomes could result from chromothripsis (represented here) and chromoanasynthesis, due to the micronucleus failing to synchronize with the mitotic divisions of the main nucleus. Chromothripsis involves DNA fragmentation and random reassembly, while chromoanasynthesis involves replication fork collapses and microhomology-mediated strand switching. Subsequently, the pulverized and reassembled chromosome forms a single unit and can be meiotically inherited by the next generation, carrying forward the clustered structural variations.

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10. Meiotic Specific Processes as Drivers for Chromosomal Rearrangements

Recombination is a key aspect of meiosis that increases genetic diversity during inheritance. This process is carefully programmed and controlled, particularly through synapsis, where homologous chromosomes pair up via the synaptonemal complex. Any defects in these processes can lead to chromosomal structure changes. Heterologous synapsis, for example, can reduce recombination, cause sterility, or result in improper recombination [155,156]. These alterations can lead to new chromosomal rearrangements and change the organization of topologically associating domains (TADs), both crucial for chromosome evolution [157].

In *Arabidopsis thaliana*, a case of chromoanagenesis was reported in an *asy1* mutant background, where defective meiosis led to significant chromosomal changes [76]. The ASY1 gene is a component of the synaptonemal complex that helps regulate crossover assurance and interference during meiosis. In this mutant, a dense breakpoint region on chromosome 1, associated with open euchromatin, was observed. Various types of rearrangements were identified, including those with microhomology, minor base pair additions or deletions, and perfect junctions without modifications. These rearrangements led to the loss of function in several genes and the emergence of novel genes, highlighting the evolutionary impact of such changes. The ASY1 mutation likely altered recombination patterns and caused unbalanced chromosome segregation during meiosis, especially in meiosis I. Additionally, micronuclei were observed during male sporogenesis in *asy1* mutants, serving as a source of chromoanagenesis [158].

DNA recombination is a crucial process during meiosis, leading to physical attachment between homologous chromosomes in a step called crossing-over (CO). This universal feature is essential for accurate chromosome segregation during meiosis and sexual reproduction, thereby maintaining the genome integrity of species. Moreover, meiotic recombination shuffles alleles along homologous chromosomes, generating genetic diversity in sexual gametes and offspring [159]. Understanding the mechanisms and factors involved in meiotic CO formation and resolution is important for insights into biodiversity. However, if not properly regulated, this process can lead to repair errors, resulting in sterility or miscarriages. Conversely, proper regulation of new meiotic CO formation and resolution can be adaptive, supporting species evolution and the emergence of new species. Disruptions in chromosome architecture, such as inversions, fusions, or translocations, are often linked to genetic instability and cancer due to oncogene activation and novel gene functions. Similarly, intra- or interchromosomal alterations in the germ line or during meiosis can alter normal segregation patterns, contributing to organismal evolution [160,161]. Another important aspect is that meiotic recombination between highly similar duplicated sequences can cause various genome disorders, including deletions, duplications, inversions, and translocations [133]. Although there have been no documented cases of chromoanagenesis directly linked to defects in meiotic recombination so far, it is plausible that such defects could play a role in this process, and connected with evolution.

11. Concluding Remarks

The use of new technologies such as long read DNA sequencing has allowed the discovery of another level of complexity in the genome organization.

It is undoubted that several species have not been annotated for chromosomal rearrangement events because the complexity of the chromosomal rearrangements they have experienced is beyond our current ability to resolve [69]. Furthermore, the lack of proper species mapping limits the discovery of chromoanagenesis in the evolution genome.

Evolutionary biologists have found that polyploid organisms often face a competitive disadvantage compared to their diploid counterparts, which raises questions about the persistence of this trait. One answer could be that polyploidy may help species weather catastrophic environmental changes. Increased genetic flexibility provided by multiple genomes lets polyploids make quick adjustments to new stresses and ride out catastrophic events that wipe out most normal plants and animals [162]. As for WGD, aneuploidy and CIN also are disadvantageous at first for a cell, but also offer the opportunity to adapt to new environment. CIN can offer results in the

evolution of large-scale structures such as chromoanagenesis, and can dramatically change the structure and functions of proteins, leading to the evolution of entirely new structures, adaptations, or increased fitness. As indicated by the persistence of germline chromothripsis through three generations in 11 healthy individuals, chromothripsis does not invariably lead to abnormal phenotypes [136]. This insight suggests that germline chromothripsis might be more widespread than we currently assumed, emphasizing its potential impact on evolution and species diversity. To conclude, the origin, mechanism, and potential effects of chromoanagenesis are just starting to be deciphered, marking an exciting frontier in our understanding of genetic evolution and its broader implications.

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