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Chromosome Dynamics in Cancer: From Mitotic Errors to Genomic Catastrophes and Therapeutic Vulnerabilities

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Abstract

Chromosome dynamics—including segregation fidelity, nuclear architecture, micronuclei formation, and chromothripsis—plays a central role in cancer evolution, intra-tumoral heterogeneity, and therapy resistance. Defective mitosis and subsequent chromosomal mis-segregation rapidly generate aneuploidy and structural rearrangements, accelerating tumor adaptation under selective pressures. Micronuclei serve as both a biomarker and a mechanistic driver of genomic chaos, often leading to catastrophic events such as chromothripsis. Moreover, the rupture of micronuclear envelopes can activate the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS- STING) innate immune pathway, further shaping the tumor microenvironment and response to immunotherapy. Advances in live-cell imaging, single-cell genomics, clustered regularly interspaced short palindromic repeats-based (CRISPR) functional screens, and 3D genome mapping have elucidated how chromosomal instability (CIN) shapes tumor evolution and provides targetable vulnerabilities. This review synthesizes current understanding of chromosome dynamics in cancer, integrating mechanistic insights with translational implications, and proposes strategies for exploiting these processes therapeutically.

Keywords: Chromosomal instability (CIN), Micronuclei, Chromothripsis, cGAS–STING pathway, Tumor evolution, Aneuploidy

Introduction

Fundamentally, cancer is defined by the genomic chaos that drives its progression. Chromosomal instability (CIN) is a hallmark of many malignancies, driving aneuploidy, structural rearrangements, and rapid clonal evolution [1,2]. Mitotic errors such as lagging chromosomes, merotelic attachments, and spindle assembly defects not only generate genomic diversity but also create micronuclei, which are prone to DNA damage and can undergo chromothripsis [3,4]. Importantly, recent work has highlighted the critical role of micronuclei in activating the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway due to the exposure of missegregated DNA to the cytoplasm, linking CIN to tumor-intrinsic inflammation and immune evasion [5]. Collectively, these processes, in turn, underpin tumor progression, metastasis, and therapy resistance.

Recent technological advances—including live-cell imaging, single-cell sequencing, clustered regularly interspaced short palindromic repeats (CRISPR) screens, and 3D genome mapping—have allowed unprecedented insight into chromosome dynamics. The integration of mechanistic, imaging, and genomic approaches now enables a comprehensive understanding of how mitotic errors translate into genomic chaos and how these vulnerabilities can be targeted therapeutically [6–8].

This review explains current knowledge on chromosome dynamics in cancer, from segregation errors and micronuclei formation to chromothripsis and nuclear architecture alterations, highlighting their mechanistic interplay and translational potential.

Chromosome Segregation Errors and Genomic Instability

Accurate chromosome segregation during mitosis is essential for genome stability. Errors in this process—such as lagging chromosomes, merotelic attachments, or spindle assembly checkpoint (SAC) failures—lead to aneuploidy and structural

rearrangements [6]. Beyond structural errors, aneuploidy itself drives tumor heterogeneity by creating subclonal populations with variable proliferative and survival advantages, a key factor in resistance [1,9].

Critically, Thompson *et al*. [10] demonstrated that lagging chromosomes in breast cancer cells frequently mis-segregate, forming micronuclei that are prone to DNA damage. Over time, these events fuel structural rearrangements and chromothripsis, establishing a direct link between mitotic errors and catastrophic genome alterations. Moreover, chromosomal missegregation can disrupt tumor suppressor loci and amplify oncogenes, conferring selective growth advantages under stress or therapeutic pressure [11]. Furthermore, this rampant instability is frequently tolerated or even facilitated by the concurrent inactivation of key tumor suppressors like tumor protein 53 (*TP53*), which normally prevent the cell cycle progression under conditions of severe CIN [12].

Mechanistically, CIN arises from both structural and numerical chromosomal errors. SAC defects, centrosome amplification, and kinetochore dysfunction contribute to misaligned chromosomes, whereas defective DNA damage response pathways exacerbate structural instability [6,13]. For instance, defects in the mitotic motor protein kinesin family member 18A (KIF18A) have been linked to an increase in merotelic attachments and subsequent CIN [14]. Collectively, these errors accelerate tumor evolution, enhancing adaptability and therapy resistance.

Controversy in aneuploidy

Although many agree that aneuploidy drives rapid adaptation and heterogeneity [1,9], its overall impact remains disputed. Aneuploidy-related stress [7] can impose major fitness costs proteotoxic, metabolic, and replication stress-often slowing growth compared to near-diploid cells. Yet it can also provide advantages when gene dosage boosts certain oncogenes, such as gains on *8q* or *20q* [15]. The prevailing view, supported by Sansregret *et al*. [1], is that tumors with *TP53* inactivation [12] can tolerate the initial fitness loss, and the added genetic variability enhances evolution under treatment pressure. Future studies should define "aneuploidy signatures" that predict when the net effect is harmful or beneficial.

Micronuclei and Chromothripsis

Micronuclei are extranuclear bodies containing lagging or missegregated chromosomes. Initially considered mere markers of CIN, they are now recognized as active contributors to genomic instability. DNA within micronuclei experiences replication stress and subsequent nuclear envelope rupture, initiating cycles of breakage-fusion-bridge that rapidly leading to DNA fragmentation and chromothripsis—a phenomenon characterized by localized, catastrophic chromosomal rearrangements [3,4].

Chromothripsis often results in complex rearrangements that simultaneously delete tumor suppressor genes and amplify oncogenes, providing a rapid route to malignant transformation. The formation of micronuclei links mitotic segregation errors directly to these catastrophic events, emphasizing a continuum from missegration to genomic chaos. Studies by Bakhoum *et al*. demonstrated that tumors with frequent micronuclei formation exhibit high structural variation and enhanced metastatic potential, underscoring the functional significance of these nuclear structures [16].

A newly recognized dimension of micronuclei is their role in stimulating the cGAS-STING pathway. When the micronuclear envelope ruptures, the exposed double-stranded DNA in the cytoplasm is recognized by the cyclic GMP-AMP synthase (cGAS) sensor, leading to the activation of STING and the production of pro-inflammatory cytokines, which can paradoxically promote tumor progression, metastasis, or influence response to immunotherapy [5,17].

Micronuclei formation and chromothripsis thus serve as both mechanistic drivers of cancer evolution and potential biomarkers for aggressive disease. Their occurrence reflects underlying mitotic defects, DNA repair inefficiencies, and nuclear architectural vulnerabilities, integrating the processes described in Section "Chromosome Segregation Errors and Genomic Instability".

Controversy in cGAS-STING function

The activation of cGAS-STING by micronuclear rupture is well established [5,17], but its role in cancer remains debated. It argues that sustained activation creates a pro-inflammatory state that drives senescence or anti-tumor immunity, often linked to better immunotherapy response [18]. Another group, supported by studies like Bakhoum *et al*. [16], suggests that chronic, low-level STING activity instead promotes metastasis by inducing cytokines such as Interleukin-6 (IL-6) and C-X-C motif chemokine ligand 10 (CXCL10) that enhance invasiveness and immunosuppression [19]. Overall, the outcome depends on how often and how strongly cGAS-STING is activated, as well as the tumor microenvironment, determining whether CIN-driven inflammation suppresses tumors or supports metastasis.

Nuclear Architecture and Chromatin Organization

The fate of the mis-segregated chromosome in a micronucleus, whether it undergoes chromothripsis or activates cGAS-STING is fundamentally dictated by the physical integrity and organization of the nucleus.

The 3D organization of the genome influences chromosome dynamics and the susceptibility to segregation errors. Disrupted nuclear architecture, altered chromatin compartments (A/B), and misfolded topologically associating domains (TADs) can promote missegration and facilitate chromothripsis [16,20]. Chromatin remodeling factors such as enhancer of zeste homolog 2 (EZH2) and lysine-specific demethylase 1 (LSD1) further modulate genome stability by influencing replication timing and chromatin compaction, linking epigenetic regulation to mitotic fidelity [7].

Altered nuclear architecture, particularly defects in nuclear envelope components like Lamin A or Lamin C, can create significant physical and mechanical stress during mitosis, predisposing chromosomes to lagging and micronucleus formation [21]. These structural perturbations integrate seamlessly with molecular defects in mitotic regulators, emphasizing the interplay between nuclear organization and CIN. Furthermore, disruptions in the telomere maintenance mechanisms are also deeply intertwined with chromosome dynamics, frequently leading to end-to-end fusions and anaphase bridges, which are precursors to chromothripsis [22].

Implications for Tumor Evolution and Therapy Resistance

CIN and resultant micronuclei formation accelerate tumor evolution by generating subclonal heterogeneity. McGranahan & Swanton highlighted that CIN- driven heterogeneity allows selective clonal expansion under therapy, facilitating drug resistance [11,23]. Tumors with high CIN often display adaptability to DNA-damaging agents, targeted therapies, and chemotherapeutics, representing a major clinical challenge.

From a clinical standpoint, CIN creates both profound challenges and non-oncogene opportunities. While it fosters resistance, it also exposes tumor-specific vulnerabilities. For example, CIN-positive tumors rely on SAC components, DNA damage response pathways, and cell-cycle checkpoints for survival, providing potential targets for selective intervention [7]. The increased basal stress in highly aneuploid cells, termed aneuploidy-associated stress, makes them hypersensitive to inhibition of specific metabolic or signaling pathways, a vulnerability that can be exploited [7].

Emerging Technologies to Study Chromosome Dynamics

Technological advances are transforming our understanding of chromosome dynamics:

Live-cell imaging and molecular tracers

Allows visualization of mitotic errors, lagging chromosomes, and micronuclei formation in real time, increasingly combined with sensors for DNA damage or cGAS-STING activation [5,6].

Single-cell genomics (scRNA-seq, scDNA-seq)

Resolves intratumoral heterogeneity, maps aneuploid subclones, and identifies structural rearrangements with unprecedented resolution [3,11,24].

CRISPR-based functional screens

Identify genes essential for chromosomal stability (e.g., regulators of spindle assembly or kinetochore function) and potential therapeutic targets [7].

3D Genome mapping (Hi-C, single-cell Hi-C)

Reveals aberrant nuclear architecture and disrupted chromatin compartments linked to segregation errors [16,20].

Computational modeling

Predicts the impact of CIN on tumor evolution and therapy resistance, enabling adaptive treatment strategies and understanding the kinetics of chromosome mis-segregation [1,25].

Integration of these approaches allows multi-dimensional analysis of chromosome dynamics, bridging mechanistic insights with clinical applications.

Translational Opportunities and Therapeutic Implications

CIN and micronuclei provide both biomarkers and therapeutic targets. Strategies include:

Exploiting synthetic lethality

Targeting vulnerabilities in CIN-high tumors, such as SAC inhibition (e.g., inhibition of Aurora A/B or centromere-associated protein E [CENP-E]) or DNA repair pathway targeting, which cells with massive DNA damage rely on [7,26].

Mitotic checkpoint kinase inhibition: Highly aneuploid cells operate with a *tightly tuned* mitotic timing and are particularly vulnerable to agents that *further disrupt* the mitotic clock. Inhibitors targeting Aurora A (e.g., Alisertib) or Aurora B (e.g., Barasertib) exploit this, forcing premature mitotic exit and catastrophic cell death in CIN-high cells, as demonstrated in preclinical models [7,26].

DNA repair targeting: CIN-induced genomic chaos often leads to reliance on specific DNA repair pathways. Tumors with high levels of DNA breaks from chromothripsis show increased dependency on poly(ADP-ribose) polymerase (PARP) and ataxia telangiectasia and Rad3 related/checkpoint kinase 1 (ATR/CHK1) signaling. Targeting ATR (e.g., Berdamstat) or PARP (e.g., Olaparib) can create synthetic lethality by pushing these already-stressed cells past a critical threshold of DNA damage [27].

Targeting aneuploidy-associated stress

Inhibiting pathways like the proteasome or specific metabolic enzymes that highly aneuploid cells are addicted to for survival [7].

Aneuploid cells exhibit constitutive proteotoxic stress and increased reliance on the proteasome for clearing misfolded proteins [7]. This renders them hypersensitive to Proteasome Inhibitors (e.g., Bortezomib), an existing class of drugs that can be repurposed for CIN-high solid tumors.

Modulating the cGAS-STING axis

Developing approaches to either suppress chronic cGAS-STING signaling that promotes inflammation and metastasis, or to enhance it to trigger effective anti-tumor immunity, particularly in combination with immunotherapy [17,28].

Monitoring chromothripsis signatures

Using complex structural variation patterns as predictive or prognostic biomarkers for aggressive disease and drug response [6].

Micronuclei signatures as biomarkers: The presence of circulating tumor DNA (ctDNA) with chromothriptic patterns (detectable via low-coverage whole-genome sequencing of blood) serves as a potent prognostic biomarker, often correlating with aggressive disease and poor outcome in lung and breast cancer [29]. Furthermore, the frequency of micronuclei observable in patient-derived circulating tumor cells (CTCs) is being explored as a dynamic predictor of metastatic risk [16].

These approaches exemplify how fundamental insights into chromosome dynamics can be translated into precision oncology interventions.

Future Directions

Key areas for future research include:

- Elucidating the molecular determinants that dictate micronuclei fate—specifically, which ones lead to chromothripsis versus cGAS-STING activation.
- Defining the comprehensive relationship between nuclear architecture, chromatin topology, and the initiation of chromothripsis.
- Integrating longitudinal patient data (e.g., liquid biopsy) with mechanistic studies to validate CIN metrics as robust, dynamic biomarkers for treatment selection.
- Developing therapies that specifically target the vulnerabilities created by CIN without causing unacceptable toxicity in normal, stable cells.

Conclusion

Chromosome dynamics is a central driver of cancer evolution, influencing heterogeneity, therapy resistance, and metastasis. From segregation errors to micronuclei formation and chromothripsis, the interplay of mitotic fidelity, nuclear architecture, and DNA repair defines tumor behavior. Cutting-edge technologies have illuminated these processes, providing opportunities to translate mechanistic insights into targeted therapies. By integrating basic science with clinical application, the field moves toward exploiting chromosome dynamics as both a predictive biomarker and a therapeutic vulnerability, thereby navigating the future towards more effective and personalized cancer treatment.

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