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EDITORIAL

Two decades of chromosomal instability and aneuploidy

Stefano Santaguida

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Chromosomal instability (CIN) and the resulting aneuploidy are recognized as hallmarks of cancer. Over the last two decades, the work of several labs has significantly contributed to the molecular understanding of the causes of aneuploidy. Additionally, insights have been gained into how aneuploidy and CIN impact cell physiology in both untransformed and cancer cells, shedding light on their roles in tumorigenesis and cancer progression (Bakhoum and Cantley 2018; Ben-David and Amon 2020; Chunduri and Storchova 2019; Garribba and Santaguida 2022; Levine and Holland 2018; Santaguida and Amon 2015; Vasudevan et al. 2021). This Special Issue of *Chromosome Research*, titled "Aneuploidy and Chromosome Instability," features excellent and up-to-date contributions from experts in the field, covering various aspects of the intricate relationship between aneuploidy and CIN.

The fidelity of chromosome segregation and the cell's ability to prevent errors during this process are under the surveillance of the spindle assembly checkpoint (SAC), an evolutionarily conserved mechanism that delays anaphase onset until all chromosomes are properly aligned on the metaphase plate (Musacchio 2015). Nevertheless, chromosomes lagging in anaphase can elude detection by the SAC, remaining unnoticed during cell division and posing a significant risk to mitotic fidelity. The discovery of the mechanism responsible for the formation of lagging chromosomes occurred just over 20 years ago and served as the catalyst for a series of new research inquiries, spanning from the exploration of correction mechanisms to the understanding of factors that amplify these errors in cancer cells. This breakthrough was achieved through the seminal work of Daniela Cimini, who, in this Special Issue, reflects on all the new avenues of investigation that originated from that important discovery, including studying the consequences of aneuploidy (Cimini 2023).

Comprehensively analyzing the effects of aneuploidy on cell physiology had long been hindered by the absence of suitable model systems for systematic study. A seminal paper by Eduardo Torres in 2007 provided the first comprehensive characterization of the effects of gaining an extra chromosome in the budding yeast *Saccharomyces cerevisiae*. This landmark paper laid the foundation for studying aneuploidy and significantly contributed to identifying and characterizing aneuploidy-associated phenotypes, starting a completely new field of investigation. In his review, Eduardo Torres focuses on several aspects of the effects of gaining an extra chromosome, giving a

Responsible Editor: Stefano Santaguida.

S. Santaguida
Department of Experimental Oncology at IEO, European Institute of Oncology IRCCS, Milan, Italy

S. Santaguida (✉)
Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
e-mail: Stefano.santaguida@ieo.it

broad and detailed overview of the results obtained by several researchers in the field (Torres 2023).

One of the significant advancements in early yeast studies involved the creation and characterization of stable isogenic aneuploid strains. Similar methodologies were subsequently applied in mammalian cells, utilizing approaches such as microcell-mediated chromosome transfer (MMCT) or the crossing of mice with Robertsonian translocations. These techniques complemented efforts aimed at inducing random chromosome mis-segregation, resulting in cell populations with mixed chromosome assortments. In their review, Susanne Lens and colleagues comprehensively explore these models and discuss novel strategies for inducing, eliminating, or selecting specific chromosomal gains and losses in both human and murine cell systems (Truong et al. 2023).

An important barrier to the propagation of aneuploid cells is given by the activation of the tumor suppressor p53. Although aneuploidy and TP53 gene inactivation strongly co-occur in tumors, very little is known about the routes leading to the activation of p53 in aneuploid cells. Further, it is poorly understood whether and how TP53 inactivation would constitute a permissive condition required for the dissemination of aneuploid cells. These important aspects of the biology of aneuploid cells together with the intertwined relationship between aneuploidy and p53 activation are summarized in the review by Marques and Kops (Marques and Kops 2023).

A major consequence of aneuploidy both in yeast and in human is CIN. Mark Burkard and colleagues provide an authoritative review on how CIN is quantified and offers a historical perspective on the methods utilized in the past for detecting and measuring CIN in cancer cells. They also discuss considerations for CIN measurement and reflect on open questions in the field (Lynch et al. 2024).

CIN is a pervasive feature of human cancer, is a key driver of intratumor heterogeneity (ITH), and is characterized by an elevated occurrence of chromosomal segregation abnormalities. Aneuploidy, along with CIN and ITH, has been strongly correlated with unfavorable prognoses in cancer. However, our comprehension of their intricate interactions and their respective impacts on therapy resistance in cancer patients remains limited. In their review, Sarah McClelland and colleagues tackle this problem and undertake an intriguing endeavor to disentangle the individual and combined contributions of aneuploidy, CIN, and ITH to the development of resistance in cancer (Andrade et al. 2023).

CIN might also lead to the generation of micronuclei, which are potent activators of cGAS, a double-strand nucleic acid sensor able to trigger an inflammatory response. Nevertheless, the molecular pathways responsible for CIN-induced inflammatory response remain poorly understood. Moreover, recent findings indicate that cancers with CIN manage to evade this inflammatory response, thus evading immune surveillance. In their review, Floris Foijer and collaborators explore the signaling pathways associated with sensing CIN and their complex interactions (van den Brink et al. 2023).

Aggressive tumors possess the distinctive ability to adapt and effectively manage ongoing CIN. These tumor-promoting effects of CIN are complemented by tumor-suppressing effects, the latter presenting specific vulnerabilities possibly exploitable in cancer therapy. In their review, Veronica Rodriguez-Bravo and Brittiny Dhital offer a thorough overview of the contrasting impacts of CIN on tumor promotion and suppression. They also provide insights into the current understanding of the mechanisms implicated in the adaptation and propagation of cancer cells harboring CIN (Dhital and Rodriguez-Bravo 2023).

Importantly, our current understanding of the causes and consequences of CIN and its link to cancer is derived by studies done in established cell lines. The lack of appropriate disease-specific CIN has been recently surpassed with the development of patient-derived cell cultures and organoids. In their review, Stephen Taylor and colleagues describe their progress building a living biobank of patient-derived ovarian cancer models, predominantly from high-grade serous ovarian cancer, one of the most chromosomally unstable tumor types (Nelson et al. 2023).

Besides being recognized as hallmarks of cancer, CIN and aneuploidy are also associated with the aging process and are detectable in the aging brain. Cristina Montagna and her colleagues provide an overview of advanced methodologies utilized to study aneuploidy and CIN in non-tumor somatic tissues. They also contemplate the importance of understanding the prevalence and specific consequences of aneuploidy and CIN in the aging brain, highlighting the need for further scientific investigation (Albert et al. 2023).

This Special Issue of *Chromosome Research* offers a comprehensive overview of the field. As the guest editor, I wish to express my heartfelt gratitude to the colleagues who contributed excellent reviews to this Special Issue. I am also deeply appreciative of all the colleagues who served as reviewers, offering insightful and constructive comments that greatly enhanced the process. I am also indebted to both the Editor-in-Chief Dr. Beth A. Sullivan and Executive Editor Dr. Rachel O'Neill for their guidance and expertise during the assembly of this Special Issue. It is my sincere hope that this Special Issue will spark further discussions and research efforts to move forward our understanding of the causes and consequences of aneuploidy and CIN, ultimately advancing the field as a whole.

References

Albert O et al (2023) Chromosome instability and aneuploidy in the mammalian brain. Chromosome Res 31:32. https://doi.org/10.1007/s10577-023-09740-w

Andrade JR, Gallagher AD, Maharaj J, McClelland SE (2023) Disentangling the roles of aneuploidy, chromosomal instability and tumour heterogeneity in developing resistance to cancer therapies. Chromosome Res 31:28. https://doi.org/10.1007/s10577-023-09737-5

Bakhoum SF, Cantley LC (2018) The multifaceted role of chromosomal instability in cancer and its microenvironment. Cell 174:1347–1360. https://doi.org/10.1016/j.cell.2018.08.027

Ben-David U, Amon A (2020) Context is everything: aneuploidy in cancer. Nat Rev Genet 21:44–62. https://doi.org/10.1038/s41576-019-0171-x

Chunduri NK, Storchova Z (2019) The diverse consequences of aneuploidy. Nat Cell Biol 21:54–62. https://doi.org/10.1038/s41556-018-0243-8

Cimini D (2023) Twenty years of merotelic kinetochore attachments: a historical perspective. Chromosome Res 31:18. https://doi.org/10.1007/s10577-023-09727-7

Dhital B, Rodriguez-Bravo V (2023) Mechanisms of chromosomal instability (CIN) tolerance in aggressive tumors: surviving the genomic chaos. Chromosome Res 31:15. https://doi.org/10.1007/s10577-023-09724-w

Garribba L, Santaguida S (2022) The dynamic instability of the aneuploid genome. Front Cell Dev Biol 10:838928. https://doi.org/10.3389/fcell.2022.838928

Levine MS, Holland AJ (2018) The impact of mitotic errors on cell proliferation and tumorigenesis. Genes Dev 32:620–638. https://doi.org/10.1101/gad.314351.118

Lynch A, Bradford S, Burkard ME (2024) The reckoning of chromosomal instability: past, present, future. Chromosome Res 32:2. https://doi.org/10.1007/s10577-024-09746-y

Marques JF, Kops G (2023) Permission to pass: on the role of p53 as a gatekeeper for aneuploidy. Chromosome Res 31:31. https://doi.org/10.1007/s10577-023-09741-9

Musacchio A (2015) The molecular biology of spindle assembly checkpoint signaling dynamics. Curr Biol 25:R1002-1018. https://doi.org/10.1016/j.cub.2015.08.051

Nelson L et al (2023) Exploiting a living biobank to delineate mechanisms underlying disease-specific chromosome instability. Chromosome Res 31:21. https://doi.org/10.1007/s10577-023-09731-x

Santaguida S, Amon A (2015) Short- and long-term effects of chromosome mis-segregation and aneuploidy. Nat Rev Mol Cell Biol 16:473–485. https://doi.org/10.1038/nrm4025

Torres EM (2023) Consequences of gaining an extra chromosome. Chromosome Res 31:24. https://doi.org/10.1007/s10577-023-09732-w

Truong MA, Cane-Gasull P, Lens SMA (2023) Modeling specific aneuploidies: from karyotype manipulations to biological insights. Chromosome Res 31:25. https://doi.org/10.1007/s10577-023-09735-7

van den Brink A, Suarez Peredo Rodriguez MF, Foijer F (2023) Chromosomal instability and inflammation: a catch-22 for cancer cells. Chromosome Res 31(19). https://doi.org/10.1007/s10577-023-09730-y

Vasudevan A et al (2021) Aneuploidy as a promoter and suppressor of malignant growth. Nat Rev Cancer 21:89–103. https://doi.org/10.1038/s41568-020-00321-1