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Spotlight

Understanding Complexity of Cancer Genomes: Lessons from Errors

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Deconstructing the events leading to cancer genome rearrangements is key to understanding tumorigenesis. In a recent issue of *Science*, Umbreit, Zhang et al. elegantly show that complex genome evolution is the result of a cascade of events initiated by a single error during cell division.

A prominent feature of cancer cells is the complexity of their genomes. This ranges from numerical chromosome changes to local genome rearrangements (Figures 1A and 1B). Alterations in chromosome numbers include aneuploidy and whole-genome duplication (Santaguida and Amon, 2015). Aneuploidy is a condition characterized by an unbalanced chromosome content acquired through gains or losses of entire chromosomes or parts of them and is present in more than 80% of tumors. Whole-genome duplication is recognized as an important intermediate in the oncogenesis of about a third of solid tumors and is a state in which cells harbor more than two sets of homologous chromosomes (e.g., tetraploidy instead of diploidy) (Figure 1A). Importantly, changes in chromosome number have long been recognized as a striking feature of a wide range of tumors, mainly because of their large—and thus relatively easily detectable—gross scale changes. On the contrary, details of the complex mutational landscape of cancer cells have remained elusive. The recent increased application of next-generation sequencing and the consequent availability of thousands of cancer genome sequencing data has started to reveal the multifaceted perturbed genome architecture of cancer cells and provide crucial insights into its organization. These efforts led to the identification of specific mutation signatures, such as chromoplexy, in which unclustered rearrangements characterize multiple chromosomes, and chromothripsis, a phenomenon in which genomes acquire tens to hundreds of rearrangements clustered within one or few chromosomes (Holland and Cleveland, 2012) (Figure 1B). Localized structural alterations may also be caused by breakage-fusion-bridge (BFB) cycles, in which broken ends of different chromatids or chromosomes fuse, generating dicentric chromosomes that eventually break (McClintock, 1941), fueling a vicious cycle in which gene amplification ramps up (Figure 1B). Interestingly, the co-occurrence of BFB cycles and chromothripsis within the same cancer genome has been recently reported (Maciejowski et al., 2015), suggesting that the two processes are intimately interwoven. Building on this, in an exciting new study in *Science*, Umbreit et al. (2020) provide a mechanistic link between the BFB cycle and chromothripsis, suggesting a unifying model for the occurrence of these two catastrophic events underlying massive genome rearrangements in cancer cells (Figure 1C).

By employing orthogonal approaches to generate chromosome bridges in transformed and immortalized human cell lines, the authors show that actomyosin contractility is responsible for chromosome bridge breakage in late interphase, a process that has been previously ascribed to the three-prime repair exonuclease 1 (TREX-1) (Maciejowski et al., 2015). Long-term live-imaging and correlative single-cell whole-genome sequencing (LookSeq—a method pioneered by Zhang et al., 2015) revealed that the immediate effects of bridge breakage were copy-number alterations and DNA damage, either in the form of simple breaks or localized complex DNA fragmentation. Furthermore, broken bridge chromosomes were also experiencing aberrant DNA replication, which led to complex rearrangements resembling chromothriptic-like signatures. This finding is remarkable for several reasons and provides a substantial advance toward our understanding of cancer genomes. First, it provides direct demonstration that chromosome bridges can undergo chromothripsis, similar to what was previously reported in micronuclei (Crasta et al., 2012; Ly et al., 2019). Second, it suggests that, like micronuclei, DNA replication abnormalities are caused by defective nuclear envelope assembly. Third, some chromosomal rearrangements displayed tandem arrays harboring numerous insertions of approximately 200 base pairs, a distinct signature that the authors named "tandem short template (TST) jumps."

Remarkably, in a series of elegant experiments, the authors reported another intriguing observation about the behavior of broken chromosome bridges during cell-cycle progression. They found that broken stubs of chromosome bridges experienced further damage as a consequence of mitotic DNA replication, likely due to the presence of under-replicated regions. Not surprisingly, fidelity of mitosis was highly compromised in cells containing such chromosomes. Chromosome mis-segregation was a frequent outcome and led to the generation of daughter cells containing a micronucleus in approximately half of the cases. This fueled further DNA damage and complex rearrangements, instigating a repetitive process of bridge formation, micronuclei generation, and chromothripsis (Figure 1C).

In summary, the study by Umbreit et al. (2020) elucidates how large-scale

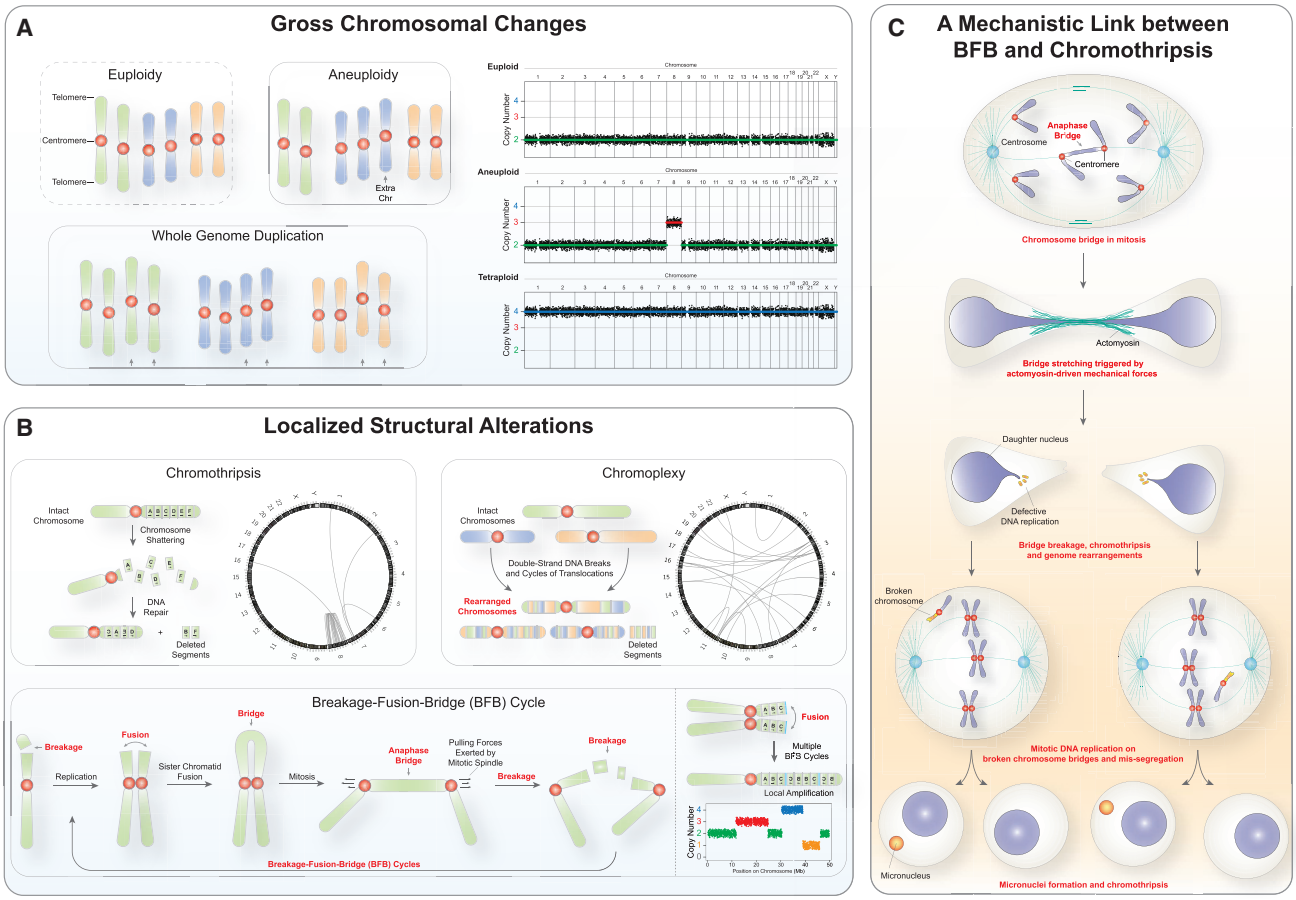

Figure 1. Genome Rearrangements in Cancer Cells

(A) Gross chromosomal changes. Aneuploidy is characterized by an unbalanced chromosome number. Whole-genome duplication by the presence of an extra set of chromosomes. Euploidy is shown as a reference. On the right, examples of segmentation plots for the three conditions are shown.

(B) Localized structural alterations. Chromothripsis displays shattering of localized genomic regions and random restitching. Chromoplexy is characterized by rearrangements involving multiple chromosomes. Circos plots show representative examples of the two processes. BFB cycle involves the repetitive fusion and breakage of chromosomes and leads to sub-chromosomal copy number alterations.

(C) A link between BFB and Chromothripsis. A chromosome bridge breaks in late interphase, generating DNA damage and structural rearrangements. In the following mitosis, a round of DNA replication leads to additional DNA damage. Chromosome bridges often mis-segregate, producing micronuclei and fueling chromothripsis.

genomic defects in cancer can be the result of a single cell division error, in which chromosome bridge formation and actomyosin-driven breakage are drivers of a mutagenic process leading to complex genome rearrangements. In the future it will be crucial to determine the causes of replication defects that lead to rapid changes of genomic landscapes. The authors propose a model in which the nuclear envelope surrounding chromosome bridges displays defects similar to those observed in micronuclei. In particular, it has been reported that micronuclei display aberrant nuclear envelope architecture and compromised integrity (Hatch et al., 2013), and this leads to depletion of nuclear pores (Liu et al., 2018). This was shown to jeopardize proper nuclear import of crucial proteins needed for faithful DNA replication, which is the underlying cause for defective DNA replication (Liu et al., 2018). Deciphering the molecular details of the causes of replication defects will be an exciting new chapter in cancer biology and holds the promise to deliver insightful results.

Another important question is whether and how exposure of cancer cells to chemotherapy or radiation therapy might accelerate the initiation and/or the progression of the catastrophic mutational processes described by Umbreit et al. (2020). Further, DNA rearrangements might lead to oncogenic gene fusion products. Thus, a substantial challenge will be to identify impactful therapeutic interventions able to selectively eradicate cancer cells harboring such complex rearrangements. Finally, a future goal will be to understand whether such rapid alterations of the genomic landscape are also responsible for congenital disorders or implicated in human development, triggered by similar genome rearrangements in the germline.

A crucial question in cancer biology is how the genome of a normal cell becomes full of rearrangements. Through the combination of live-cell imaging and single-cell whole-genome sequencing, the work from the Pellman group has started to provide mechanistic answers to this question and has heralded an important

breakthrough in the understanding of the events leading to cancer genome complexity.

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