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Mechanisms generating cancer genome complexity: a look back at the interphase breakage model

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Understanding the mechanims responsible for cancer genome complexity has been an important goal for many decades. Umbreit et al. recently combined live cell imaging and single cell genome sequencing to analyze the cascade of genome rearrangements following the formation of a chromosome bridge in human cells (1). Their results suggest that this bridge leads to an initial breakage-fusion-bridge (BFB) cycle, followed by additional BFB cycles interwoven with episodes of micronucleation and chromothripsis, to generate complex genome rearrangements (1).

This conclusion is strikingly consistent with the previously proposed “interphase breakage model” (2). In the 1990s, fluorescent in situ hybridization (FISH) provided unprecedented insights into the mechanisms underlying gene amplification in mammalian cells. FISH made it possible to analyze the distribution of amplified genes at the level of a single cell, just a few cell divisions after initiation of the amplification process, in model systems of cultured cells selected for resistance to a cytotoxic drug. This proved to be essential to understand the tremendous genomic instability occurring at the earlier stages of gene amplification. The earliest amplified units were organized as Megabase-long inverted repeats that could only be explained by chromatid BFB cycles (2, 3). In support of this conclusion, the “bridge” and “chromatid fusion” intermediates of BFB cycles were later observed (4), and similar structures were found in cancer cells with amplified oncogenes (5). Furthermore, co-amplified sequences alternating in metaphase chromosomes often segregated into different nuclear domains and perturbed nuclear architecture, leading to micronucleation and multiple simultaneous DNA breaks, suggesting that DNA fragments retained in the interphase nucleus could be stitchted together to generate a chromatid that would undergo additional BFB cycles (2). This “interphase breakage model” was proposed to account for the evolution of cancer genomes, particularly the rapid shortening of amplified units.

In this model, the notion of micronucleation-induced multiple DNA breaks and subsequent stitching of DNA fragments foreshadowed chromothripsis, later identified through advanced DNA sequencing methods (2, 6). Accordingly, micronucleation was next shown to cause chromothripsis (7). However, the sheer complexity of chromothripsis exceeds what was initially anticipated, and the new methods developped by Umbreit et al. now reveal the contribution of bursts of DNA replication in chromothripsis episodes (1). Interestingly, in our FISH study chromosomes with 2-4 copies of the amplification driver gene (conferring drug resistance) exhibited the same copy number of passenger (passively co-amplified) sequences, and thus could be explained by one or two BFB cycles, but chromosomes with 5-15 copies of the driver exhibited less copies of the passenger, consistent with micronucleation and chromothripsis occurring subsequently to the first or second BFB cycle, as in the study by Umbreit et al. (1, 2). Furthermore, the segregation of co-amplified markers into distinct nuclear domains was crucial to suggest the interphase breakage model. Current knowledge about nuclear organization suggests that these co-amplified markers might segregate in interphase because they belong to distinct topologically associated domains (8), or to distinct nuclear subcompartments (9), which could also explain why their co-amplification can perturb nuclear architecture. In that regard, recent PCAWG studies that analyzed chromothripsis events (10) and chromatin domains (11) in the same 2,658 tumors might provide unsuspected clues about the mechanisms that underlie complex rearrangements in cancer.

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