BREAKAGE–REPLICATION/FUSION PROCESS

Genomes are frequently shaped by several mechanisms that generate massive structural complexity. The most relevant ones are breakage–fusion–bridge (BFB), chromothripsis, and what a recent paper in Nature Genetics by Zhang et al. (1) calls the "breakage–replication/fusion" cycle. These mechanisms are related, but are not the same.

BFB (breakage–fusion–bridge) is a cyclical process: a broken chromosome end fuses to another end, forms a dicentric chromosome, breaks again during mitosis, and repeats the cycle. This process generates inverted duplications and amplifications, and it is very common in cancer, as suggested by the abundance of foldback junctions in tumor genomes.

Chromothripsis, instead, is primarily a catastrophic fragmentation event: a chromosome (or a chromosome arm) is shattered into many pieces in a single crisis and then stitched back together in a chaotic order. This nicely explains the famous oscillating copy-number patterns, but by itself it does not naturally explain copy-number gains, high-level amplifications, or complex insertions.

Zhang et al. propose a third concept: the breakage–replication/fusion cycle. The key idea is that if a broken DNA end enters S phase and gets replicated before being repaired, a single end can generate two "sister" ends, which can then fuse in different ways. Breakage–replication/fusion is not a new concept, but it is the first time that this long-known phenomenon is formalized as a general mechanism with clear genomic signatures and recognized as a major driver of structural complexity in cancer genomes, human disease, and genome evolution.

This has several important consequences:

- replication of one broken end can produce two adjacent, parallel breakpoints
- fusion of these replicated ends can directly generate duplications, foldbacks, and amplifications
- in the same cycle, short insertions derived from ssDNA can be incorporated at the junctions

In this framework, chromothripsis can be the initiating fragmentation event, but much of the subsequent complexity, including segmental gains and amplifications, can be built by breakage–replication/fusion cycles acting on the fragments. And many structures that have traditionally been interpreted as products of multi-generation BFB cycles may, in fact, arise from replication–fusion of broken fragments in a much more direct way.

So perhaps we should think less in terms of a single, isolated "chromosome catastrophe", and more in terms of what broken DNA ends do when they are allowed to replicate.

1. https://www.ncbi.nlm.nih.gov/pubmed/41482535