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SPOTLIGHT

Beyond selection: How chromosome 12 gain dominates stem cell genomes

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Trisomy of chromosome 12 is frequently observed across many pluripotent stem cell lines. In this issue, Narozna et al. (https://doi.org/10.1083/jcb.202501231) reveal that trisomy 12 in human-induced pluripotent stem cells (iPSCs) is driven by ongoing missegregation events due to sub-telomeric erosion, which, coupled with a modest growth advantage, results in rapid population takeover.

The rise of trisomy 12: Beyond simple selection

The gain or loss of entire chromosomes or chromosome segments designated as aneuploidy is a defining feature of many human cancers (1). Yet, how such aneuploidy naturally emerges remains unclear. Most experimental systems rely on transformed or tumor-derived cells, which already harbor extensive chromosomal abnormalities, making it difficult to study the origins and consequences of aneuploidy. To overcome this limitation, Narozna et al. (2) turned to human-induced pluripotent stem cells (iPSCs), which spontaneously acquire chromosomal abnormalities in roughly one third of cultures. Among these changes, trisomy 12 is one of the most common whole-chromosome gains, traditionally attributed to arbitrary replication or segregation errors, followed by selection for cells whose extra chromosome provides a proliferative advantage (3, 4). Here, Narozna et al. challenge this paradigm by showing that selection alone cannot explain the rapid takeover of trisomy 12 in iPSC cultures (5). Using dual-color centromeric DNA-FISH (for chromosomes 12 and 10), they examined samples from the AICS-0012 iPSC line obtained across 170 days in culture (57 passages). This enabled them to precisely define the critical window in which chromosome 12 status shifted from near diploidy (~6% trisomy) to almost complete trisomy (~100%). Surprisingly, this shift required ~13 passages in culture, contradicting the rate obtained from theoretical computation, which predicted only 38% of the cells to become trisomic by this time. This discrepancy revealed that selection alone cannot account for the abrupt culture-wide increase in the frequency of trisomy 12, suggesting a mechanism driving ongoing missegregation events is at play.

Missegregation and micronuclear capture: Chromosome 12 route to trisomy

To investigate this, Narozna et al. examined mitotic figures of cells during the transition to near-complete trisomy 12. Remarkably, chromosome 12 specifically exhibited a high frequency of anaphase bridging, representing ~55% of all bridges during key transition passages, and a 13-fold enrichment over random expectation (~4.3%). In contrast, such events were rare in pre-transition (diploid) passages, where chromosome 12 bridges accounted for only 3% of anaphase cells. Given the high missegregation rate of chromosome 12, they hypothesized that it might frequently be sequestered into micronuclei, a well-known signature of chromosome instability in cancer cells (6). Tracking missegregation over time, they found a striking enrichment of chromosome 12 (12.9%) into micronuclei specifically during the transition passages compared with only 4.4 % for chromosome 10 (which served as a control). Thus, they identified a critical window in which chromosome 12 was especially susceptible to micronuclear capture. These micronuclei were large and predominantly decorated by lamin B1, indicative of an intact membrane structure (7). Notably, chromosome 12 bridges were preferentially found in the periphery of the metaphase plate during mitosis, a location more susceptible to micronucleation (8). The lack of 5-ethynyl-2′-deoxyuridine labeling in micronuclei indicated that chromosome 12 does not undergo DNA replication when missegregated, although it has been reported that micronuclei from peripheral chromosomes do not exhibit replication defects (9). Consistent with this observation, mitotic figures of cells during the trisomic transition window showed a 3:2 ratio of chromosome 12 signals separating during anaphase. Importantly, some mitotic events had the third chromosome 12 at a distance from the metaphase plate, as would be expected from the joining of an unpaired and unreplicated single chromatid originating from a previous micronucleation event.

Fragile ends, big consequences: From sub-telomeric loss to trisomy 12 dominance

In light of the above, a critical question remained: why is chromosome 12 susceptible to anaphase bridging? Prior studies have shown that chromosome 12p (short arm of chromosome 12) harbors some of the

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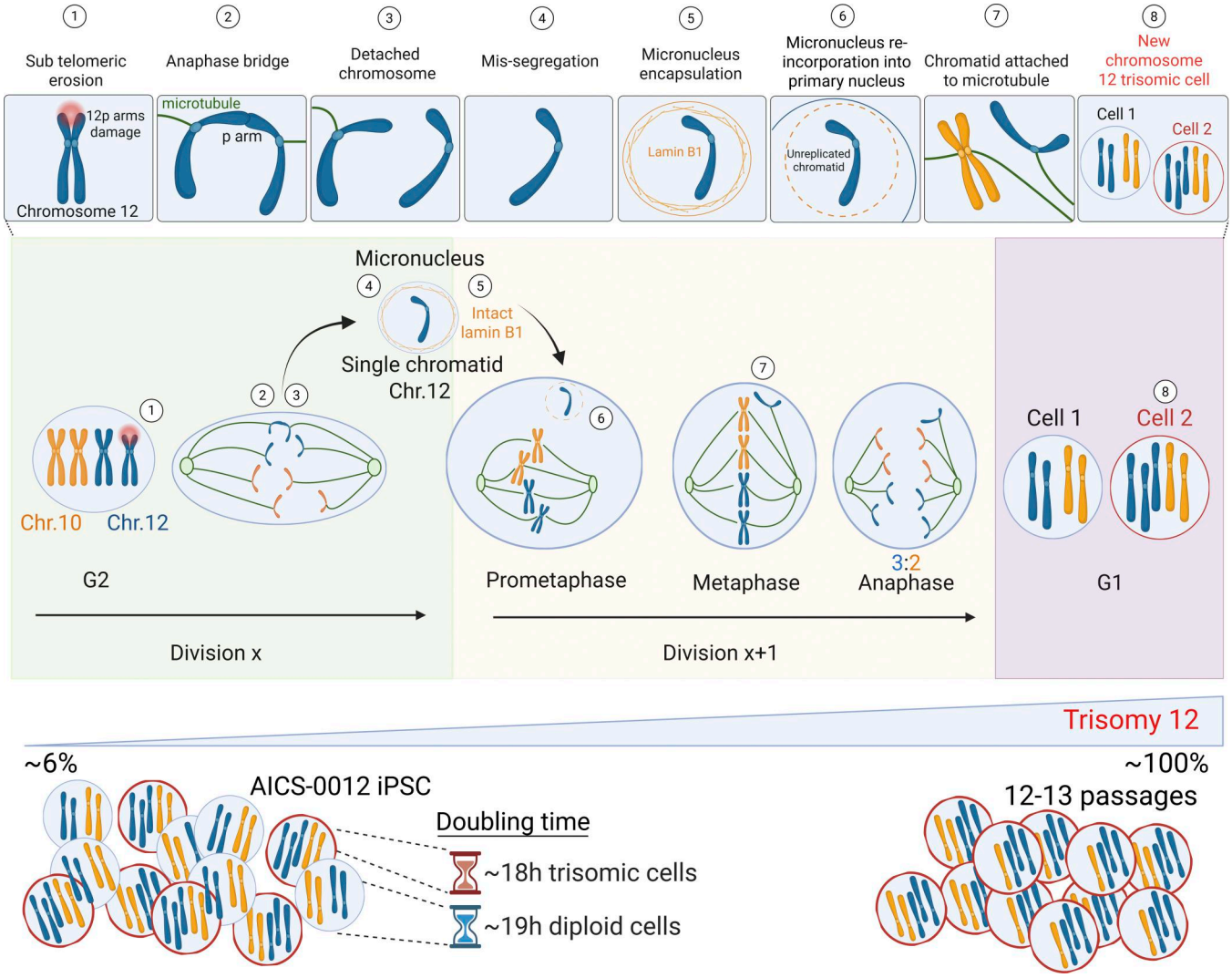

Figure 1. **Cascade of events leading to trisomy 12 dominance in iPSCs.** The different steps (1–8) illustrate how replication stress at the tip of the 12p arm (due to its shorter telomere length) could trigger anaphase bridges and micronucleation of a single chromatid (steps 1–5). The reincorporation of chromosome 12 into the primary nucleus during the subsequent mitosis results in the formation of chromosome 12 trisomic cells (steps 6–8). As this process occurs simultaneously in many cells, and together with the mild proliferative advantage of trisomic cells, the population rapidly becomes near-complete trisomic.

shortest telomeres in the genome (10), making it more susceptible to genomic instability and DNA replication stress-induced erosion. Such telomere shortening could underlie its higher tendency for bridging during anaphase. By focusing on anaphase bridges, Narozna et al. identified that bridging preferentially occurred at the p arms rather than the q arms of chromosome 12. In line with this observation, they identified that as cell divisions proceed and the trisomic population rises during critical transition passages, ~16% of 12p had lost some of their sub-telomeric region. Finally, hydroxyurea treatment accelerated the accumulation of chromosome 12 trisomy by almost twofold, directly linking replication stress with chromosome 12p instability. These experiments shed light on the cascade of events that drives trisomy 12 dominance (Fig. 1). First, replication stress intensifies in the shorter telomeres found in 12p, leading to sub-telomeric erosion. This leads to a surge in chromosome 12–specific bridging during anaphase with subsequent missegregation of one chromatid into a micronucleus. In the subsequent mitosis, the micronucleated, unreplicated, single chromatid joins the segregating chromosomes to form a trisomic cell. Occurring simultaneously in many cells during a specific timeframe, this sequence of events seeds a wave of trisomic cells that, aided by a modest growth advantage, rapidly establishes and sustains trisomy 12 dominance.

By tracking a transient biological process, the authors of this ambitious and well-executed study were able to provide a glimpse into how genomes can evolve. The observations and mechanisms described in this work open many questions, such as: why does chromosome 12 provide a selective advantage? What is the molecular mechanism that drives sub-telomeric erosion of chromosomes with shorter telomeres, such as chromosome 12p? And is this instability found in both chromosome 12 haplotypes? The latter question is of importance, as if both haplotypes are equally missegregated, it

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would be expected that the allelic ratio of the trisomic cell populations would deviate from the expected 2:1 ratio (and will be closer to 1:1). It would be interesting to see if such deviations in allelic ratio could be identified in the genomes of cancer patients, hinting on the mechanistic origins of some of cancer-related trisomies. More broadly, this work links telomere biology to whole-chromosome instability, highlighting how the discovery of trisomy 12 dynamics in iPSCs can reshape our understanding of aneuploidy in congenital disorders or cancer.

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