

Spotlight

Can developmental signals shatter or mend our genomes?

Yimiao Qu¹ and Kyle M. Loh ^{1,*}

Consensus holds that most cells in the embryo are genetically identical and have healthy genomes. However, embryonic cells with abnormal chromosomes are surprisingly frequent. In a recent publication, de Jaime-Soguero *et al.* report that extracellular developmental signaling pathways, including BMP, FGF, and WNT, can promote or prevent chromosome instability in certain cell types.

We often implicitly assume that almost all cells in the body have identical genomes, and that cells chiefly differ from one another by virtue of the genes that they express. This assumption has been challenged in developmental biology: cells with abnormal chromosomes are surprisingly frequent in the embryo [1,2]. The prevalence and types of chromosomal abnormality, the developmental stages in which they arise, and how long they persist, remain fascinating questions that warrant exploration. Present estimates suggest that 12–50% of blastomere cells in early cleavage-stage human and mouse embryos, when the embryo comprises two to eight cells, carry chromosomal abnormalities [1,2]. The preponderance of chromosomal aberrations may appear shockingly high. However, this comports with how many embryos ultimately fail to successfully complete development. In fact, some hypothesize that frequent chromosome abnormalities principally underlie low fertility in humans [3].

de Jaime-Soguero *et al.* supply an intriguing potential explanation for chromosome

abnormalities in embryos [4]. They found that developmental signaling pathways (BMP, FGF, and WNT) regulate chromosome segregation in human and mouse pluripotent stem cells (PSCs) undergoing cell division. While these extracellular signals are known to guide cell-fate decisions by regulating gene expression [5], this study reveals their unexpected roles in regulating chromosome segregation [4]. In PSCs, WNT and BMP preserve normal chromosomal segregation, whereas FGF fosters chromosomal instability [4]. This has broad implications for developmental biology, because BMP, FGF, and WNT are turned on and off in complex timings and combinations as PSCs differentiate into myriad cell types [5]. Thus, this begs the question of whether chromosomal stability dynamically changes in stem and progenitor cells, or in their differentiated progeny, as a consequence of whether combinations of BMP, FGF, or WNT are brought to bear on a given cell type for varying durations *in vivo* or *in vitro*.

Mechanistically, how do these developmental signaling pathways regulate chromosome segregation? To address this here, we first provide background regarding DNA replication. During cell division, cells contend with the staggering challenge of faithfully replicating the billions of bases in the genome. Multiple factors can conspire to impede DNA replication, thereby causing replication stress. If left unresolved, replication stress causes double-stranded DNA breaks and structurally abnormal chromosomes that can then mis-segregate during mitosis [6,7]. Consequently, defects in chromosome structure can translate into aberrations in chromosome number [6,7]. The authors suggest that FGF impedes the progression of DNA replication forks, thereby causing replication stress and increasing double-stranded DNA breaks [4]. Conversely, BMP and WNT appear to alleviate replication stress induced by stalled replication

forks [4]. Thus, these developmental signals oppositely affect replication stress in PSCs.

Perturbations in these developmental signaling pathways can trigger mild replication stress [4]. Severe replication stress arrests cell cycle progression, whereas cells with mild replication stress can escape these checkpoints, allowing cells with under-replicated DNA to proceed into mitosis, where under-replicated DNA leads to chromosome missegregation [6,7]. It is imperative to test whether BMP, FGF, and WNT similarly impact replication stress and chromosome missegregation in early embryos. If so, perhaps the replication stress caused by developmental signals is mild enough to bypass checkpoints and persist through cell division, contributing to prevalent chromosome missegregation in embryos.

Curiously, BMP, FGF, and WNT do not universally regulate chromosome stability across all cell types [4]. Instead, their effects are concentrated in certain cell types, including PSCs. After 1 or 2 days of PSC differentiation into primitive streak, endoderm, mesoderm, and ectoderm cells, these developmental signaling pathways become less potent at regulating chromosome segregation [4], despite their continued importance in guiding cell fate [5]. However, the direct molecular targets that BMP, FGF, and WNT act on to influence replication stress in PSCs remain mysterious, as does understanding why these pathways fail to act on these targets in most differentiated cell types.

de Jaime-Soguero *et al.*'s findings extend beyond basic developmental biology to the field of regenerative medicine. Worryingly, chromosomal abnormalities have been noted in human PSCs [8], thereby imperiling cell replacement therapies. FGF2, which fosters chromosomal instability [4], is ubiquitous in human PSC culture media [9]. If FGF2 underlies chromosome instability in human PSCs, this would be consequential.

Reassuringly, the authors show that FGF2-induced replication stress can be alleviated in PSCs through the addition of extra nucleosides to the culture media [4]. Nucleosides are known to alleviate replication stress-induced DNA damage and chromosome missegregation [6,7]. Perhaps additional nucleosides in the culture media could help protect the genomic integrity of human PSCs destined for therapeutic use. Another fascinating aspect of this study is how the authors quantified the basal levels of chromosome missegregation in PSCs and various differentiated cell types, finding that they change in a cell type-specific way [4]. We typically evaluate the success of PSC differentiation by assaying cellular gene expression and function [5]. However, chromosome missegregation levels may eventually be important to monitor clinically in differentiated PSCs intended for therapeutic transplantation.

A fascinating question remains: what is the fate of embryonic cells with abnormal chromosomes? In healthy adult mice, chromosomally abnormal cells are rare [10], contrasting with early embryos. There are multiple ways to think about this striking difference. It might be that embryos with a high proportion of chromosomally abnormal cells usually fail to thrive and are eliminated. Alternatively, in embryos populated by fewer chromosomally abnormal cells, the abnormal cells are

progressively eliminated and winnowed out, with healthy cells proliferating to supplant them [3]. Chromosomally abnormal cells may self-destruct due to tumor suppressor p53, which helps detect genomic abnormalities [3]. Additionally, extensive genetic abnormalities may preclude cell division and differentiation. Chromosomally abnormal cells may be disadvantaged, such that neighboring cells with healthy genomes overgrow and outcompete them.

We then arrive at a speculative and dynamic view of the growing embryo. Cells are dividing, differentiating, and signaling among themselves, and occasionally developing chromosome abnormalities, but not in lockstep with one another. Chromosomally abnormal cells will usually self-destruct, be purged by other cells, or be outcompeted by healthy neighboring cells. Consequently, all surviving cells that develop into adults are those that passed through this brutal genomic stability bottleneck, thus culminating in adult animals wherein most cells have pristine genomes.

Ultimately, discovering how developmental signals, such as BMP, FGF, and WNT, regulate chromosomal stability [4] illuminates fundamental aspects of developmental biology and also has implications for the genomic safety of stem cell-based regenerative therapies.

Declaration of interests

The authors declare no competing interests.

¹Department of Developmental Biology, Institute for Stem Cell Biology & Regenerative Medicine, Stanford University, Stanford, CA 94305, USA

*Correspondence:
kyleloh@stanford.edu (K.M. Loh).
<https://doi.org/10.1016/j.tig.2024.10.006>

© 2024 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

References

- Vanneste, E. *et al.* (2009) Chromosome instability is common in human cleavage-stage embryos. *Nat. Med.* 15, 577–583
- Takahashi, S. *et al.* (2024) Embryonic genome instability upon DNA replication timing program emergence. *Nature* 633, 686–694
- Singla, S. *et al.* (2020) Autophagy-mediated apoptosis eliminates aneuploid cells in a mouse model of chromosome mosaicism. *Nat. Commun.* 11, 2958
- de Jaime-Soguero, A. *et al.* (2024) Developmental signals control chromosome segregation fidelity during pluripotency and neurogenesis by modulating replicative stress. *Nat. Commun.* 15, 7404
- Loh, K.M. *et al.* (2016) Mapping the pairwise choices leading from pluripotency to human bone, heart, and other mesoderm cell types. *Cell* 166, 451–467
- Burrell, R.A. *et al.* (2013) Replication stress links structural and numerical cancer chromosomal instability. *Nature* 494, 492–496
- Wilhelm, T. *et al.* (2019) Mild replication stress causes chromosome mis-segregation via premature centriole disengagement. *Nat. Commun.* 10, 3585
- The International Stem Cell Initiative (2011) Screening ethnically diverse human embryonic stem cells identifies a chromosome 20 minimal amplicon conferring growth advantage. *Nat. Biotechnol.* 29, 1132–1144
- Ludwig, T.E. *et al.* (2006) Feeder-independent culture of human embryonic stem cells. *Nat. Methods* 3, 637–646
- Knouse, K.A. *et al.* (2014) Single cell sequencing reveals low levels of aneuploidy across mammalian tissues. *Proc. Natl. Acad. Sci. U. S. A.* 111, 13409–13414