

ON THE “NORMALIZATION” OF MOSAIC EMBRYOS

Since the foundational paper by Vermeesch’s group in 2009 (1), it has been well established that chromosome mosaicism arising during the first cell divisions of an embryo is quite common. A second important finding was that mosaic embryos can develop into healthy newborns. The key question then became: how does this “normalization” occur?

A recent paper published on BioRxiv (2), which also involves Vermeesch’s group, provides the answers.

The study uses single-cell genome-and-transcriptome sequencing (G&T-seq) on 756 cells from 112 human preimplantation embryos to investigate how chromosomal instability (CIN) affects early development.

- Widespread aneuploidy: About 50% of cells carried numerical or structural chromosomal abnormalities, observed across all developmental stages and lineages.
- Gene dosage effects: Gains and losses of DNA segments caused measurable but stage-dependent changes in gene expression. Gains typically had stronger effect than losses, indicating partial dosage compensation.
- Regulatory network perturbation: Aneuploidy in transcription factor genes altered the expression of their target genes, disrupting gene regulatory networks.
- Developmental delay: Aneuploid cells generally showed slower developmental progression compared to euploid cells within the same embryo.
- Cell competition and fitness: Aneuploid cells displayed stress signatures, reduced metabolic and ribosomal activity, and impaired proteostasis. This unfit cellular phenotype likely triggers cell competition, leading to the preferential survival of euploid cells.

Conclusion: Chromosome instability in early human embryos affects gene regulation, delays development in aneuploid cells, and activates mechanisms that may eliminate these cells, explaining how mosaic embryos can still give rise to healthy offspring.

1. <https://pubmed.ncbi.nlm.nih.gov/19396175/>
2. <https://www.biorxiv.org/content/10.1101/2023.03.08.530586v1>