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Spotlight

Chromosome Segregation Fidelity Integrates Information across Scales

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The influence of tissue context is an emerging theme in cell biology. Recent work reveals that tissue architecture promotes chromosome segregation fidelity in epithelia, suggesting that aneuploidy in certain cancers may arise as a consequence of disrupted tissue architecture and highlighting the shortcomings of cell culture systems.

Tissues coordinate mechanical and chemical activities across length scales to achieve robust determination of shape, size, and function. For example, at cell division, molecular-scale components build cellular-scale machines that drive the division of each cell, producing new cells that go on to structure entire tissues. Evidence from *in vivo* studies and three-dimensional culture systems indicate that information flows not only from molecules to tissues but also in the reverse direction: the broader tissue context influences many aspects of subcellular state, including cytoskeletal architecture, drug sensitivity, and gene expression.

Three-dimensional culture systems have revealed new insights into how cell division drives development, patterning (McKinley et al., 2018), and tumorigenesis, where tissue architecture can dramatically alter cells' invasive behavior (Weaver et al., 1997). However, the molecular mechanisms of cell division itself have so far largely been studied in cultured cell lines. While the checkpoints and error correction mechanisms that ensure accurate chromosome segregation have traditionally been viewed as cell-intrinsic processes, a recent study led by Kristin Knouse and Angelika Amon (Knouse et al., 2018) described in *Cell* the surprising phenomenon that three-dimensional tissue architecture increases the fidelity of chromosome segregation in epithelia. This work has broad implications for proliferation-driven processes in development and disease and draws attention to critical limitations of widely used two-dimensional culture models.

To determine the impact of tissue architecture on cell division, Knouse et al. (2018) directly compared chromosome segregation fidelity in five mouse tissues to the same five cell types shortly after dissociation from the tissue. This systematic analysis allowed patterns to emerge and was a key innovation of this work. In the mammary gland, skin, and neonatal liver, chromosome segregation errors occurred in dissociated cells, but not in the tissue context (Figure 1). The specific errors the authors quantified—lagging chromosomes that can missegregate at anaphase and micronuclei that can lead to chromosome loss—are strongly associated with aneuploidy, a common feature of many cancers. Interestingly, chromosome segregation errors were not increased by dissociation in neural progenitors or T cells, both cell types that normally divide in less structured tissues than the three epithelial contexts of mammary gland, skin, and liver. Thus, epithelial cells seem to uniquely require their well-defined tissue structure to maintain their genome integrity.

To determine which aspect of the tissue context is critical to segregation fidelity, the authors took advantage of mammary epithelial cells' amenability to growth as spheroids in Matrigel. Immature spheroids grown for two days, lacking cell polarity and an inner lumen, had a high error rate equivalent to that of dissociated mammary epithelial cells. Strikingly, when spheroids formed mature junctions after two more days in culture, chromosome segregation errors were rescued in a β1 integrin-dependent, but not cell-shape-dependent, manner. That spheroid culture could revert the error-prone cell divisions indicated that the loss of tissue structure played a direct role in mitotic errors, rather than the process of dissociating the cells or missing biochemical factors from the tissue environment.

To gain insight into how tissue architecture confers segregation fidelity, the authors turned to live imaging. Lagging chromosomes, like those observed in dissociated cells and immature spheroids, largely arise from a particular kind of incorrect attachment known as merotely, where individual chromatids are connected to microtubule bundles from both spindle poles simultaneously (Cimini et al., 2001). When cells in immature and mature spheroids were forced into early anaphase, they had equally high numbers of lagging chromosomes, indicating that in the absence of proper tissue architecture, cells were not forming merotelic attachments at a higher rate. Instead, some cells appeared less successful at correcting such erroneous attachments.

If tissue architecture confers an advantage in correcting errors, then it should be particularly important for accurate segregation in epithelia that experience a higher baseline rate of merotelic attachments. To test this hypothesis, Knouse et al. (2018) turned to adult hepatocytes, naturally polyploid cells predisposed to merotely due to their extra centrosomes. Indeed, dissociating hepatocytes from their native tissue context led to even higher error rates than those recorded for mammary epithelial cells or keratinocytes. These findings are consistent with the authors' model that tissue architecture promotes error correction.

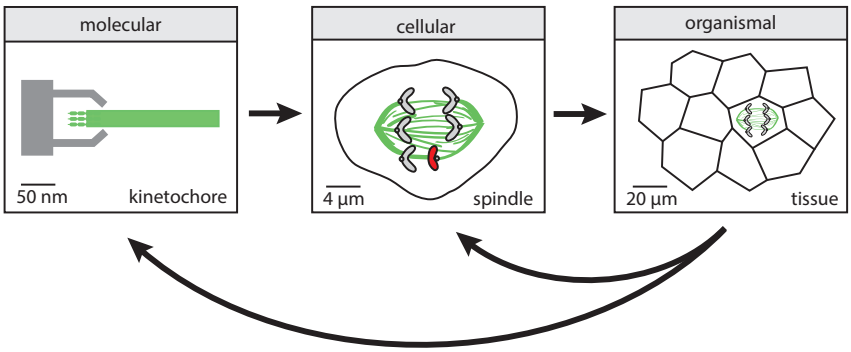

Figure 1. Chromosome Segregation Fidelity Is Controlled at Molecular, Cellular, and Tissue Scales

Knouse et al. (2018) show that when epithelial cells are dissociated from their native tissue context, chromosome segregation errors such as lagging chromosomes (red) occur more frequently. Loss of tissue architecture impairs the correction of kinetochore-microtubule attachment errors—previously thought to be regulated exclusively cell intrinsically. While the requirement of molecular-scale parts in building cellular- and organism-scale structures is clear, this study demonstrates that tissue architecture can provide critical inputs to cellular-scale and molecular-scale events, even for processes long thought to be cell intrinsic.

How tissue architecture influences chromosome segregation fidelity is far from clear. The tissue context could in principle provide inputs in the form of polarity, cytoskeletal organization, signaling downstream of β1 integrin, or a combination of all three. One intriguing lead is the known role of integrin signaling in positioning the spindle orientation machinery (Lechler and Fuchs, 2005), which may for example be required in epithelia to generate persistent tension across the spindle. For cortical positioning forces to influence error correction, they would likely have to be propagated through spindle poles and along spindle microtubules to be sensed at the kinetochore, where tension-dependent error correction is thought to occur. Experiments in *C. elegans* zygotes (Oegema et al., 2001) and cultured HeLa cells (Itabashi et al., 2012) indicate that in some contexts, kinetochores can read out force generated at centrosomes and the cortex, but how these findings extend to *in vivo* mammalian epithelia is not known. Testing this model presents the challenge of adapting physical and molecular cell biology approaches to the tissue context.

This study complements the work of others who have revealed important ways that the broader tissue context regulates the orientation and fate outcomes of cell division, layers of complexity absent in cultured cell lines (Chen et al., 2018; Tang et al., 2018). Notably, establishing error correction as a process tuned by tissue architecture provides a potential answer to the long-standing mystery of why many tumors have high rates of aneuploidy: despite varying tissues of origin and different driver mutations, disrupted tissue architecture is a universal feature of epithelial cancers.

Determining the mechanism through which tissue architecture contributes to mitotic error correction, previously thought to be cell intrinsic, will be an exciting future direction. Looking forward, revisiting core cellular processes in three-dimensional culture systems will improve our understanding of fundamental mechanisms underlying development, tissue homeostasis, and cancer pathogenesis. Cultured cell systems have provided a wealth of knowledge about molecular interactions and how they are regulated in the cellular context. Similarly, studying cells in tissue environments will transform our understanding of cell biology and how this regulation is subverted in disease.

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