Mechanics of cell division and cytokinesis

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Accurate cell division is critical during the development of both unicellular and multicellular organisms. At the joint ASCB EMBO 2017 meeting in Philadelphia, new and exciting work on several aspects of cell division were presented at the "Mechanics of Cell Division and Cytokinesis" Minisymposium.

Multiple mechanisms ensure proper division plane specification and successful cytokinesis. First, during mitosis, animal cells often "round up" and lose cell–substrate adhesions, leaving retraction fibers in place. **Christina Dix** (Baum lab, University College London) provided insight into mitotic cell rounding and found that focal adhesion complexes were disassembled while integrins, which connect mitotic cells to the underlying substrate, remained at the cell surface within retraction fibers. In this way, integrins may provide a "memory" of cell–substrate contact sites to facilitate cellular respreading and successful cytokinesis.

Dividing cells contain mechanisms to correctly orient and position the mitotic spindle, which is important for division plane specification. Yet little is known about how spindle positioning feeds back into cell cycle progression to prevent anaphase onset when the spindle is improperly positioned. **Joshua Sandquist** (Grinnell College) identified a critical interaction between Myosin10, an actin-based motor that functions in spindle orientation, and the cell cycle regulatory kinase Wee1 as a potential mediator of this feedback. This Myosin10–Wee1 interaction is essential for coordinating spindle orientation with anaphase onset and preventing chromosome segregation before the spindle is properly oriented.

Once oriented, signals from the mitotic spindle promote contractile ring assembly at the division plane via equatorial activation of the small GTPase RhoA. This signaling comes from both the spindle midzone (equatorial stimulation) and the astral microtubules (polar relaxation). **Ingrid Adriaans** (Lens lab, University Medical Center Utrecht) showed that at the spindle midzone, two redundant pathways are involved in RhoA activation in human cells in vitro: one dependent on the central spindle and Polo-like kinase 1 (Plk1) and the other dependent on cortical Aurora B activity and centralspindlin (a complex composed of Mklp1 and MgcRacGAP) oligomerization. Her results suggest that Plk1 activity allows the dynamic exchange of centralspindlin between the central spindle and the equatorial cortex, thereby ensuring equatorial RhoA activation. **Esther Zanin** (Ludwig-Maximilians University) found that TPXL-1 (*Caenorhabditis elegans* Tpx2 homologue) on the astral microtubules provides the elusive inhibitory signal for polar relaxation by preventing the assembly of contractile ring components at the cell poles. TPXL-1 is known to localize to the centrosomes and promote Aurora A kinase activity and astral microtubule growth. In this way TPXL-1 was essential for polar clearance of contractile ring components and may be our first insight into the molecular mechanism(s) of astral-mediated polar relaxation.

Following the correct positioning and activation of contractile ring components, the ring must constrict to divide the cell into two. Two presentations used mathematical modeling to provide more insight into the mechanics and regulation of this important process. **Lam Nguyen** (Jensen lab, Caltech) visualized the 3D structure of the contractile ring in yeast cells by electron cryotomography (ECT). Based on these detailed filamentous actin (F-actin) organization data and input from the literature, 16 mechanistic coarse-grain models were explored to model the structure and constriction mechanisms of the actomyosin ring. The model that fitted best with in vivo experimental data revealed that both bipolar and membrane-attached unipolar myosin molecules exist in the ring; membrane tension is likely primarily generated by interactions between bipolar myosin-II and F-actin and transmitted to the membrane via unipolar myosins. Modeling results from **Daniel Cortes** (Amy Maddox lab, University of North Carolina) and collaborators found the best fit when F-actin depolymerization was added to their model to account for the dynamic actin meshwork; they validated their model using light-sheet microscopy to image contractile ring dynamics and quantify the levels of contractile ring proteins during cytokinesis in *C. elegans*.

Another major theme to emerge from this Minisymposium is that cytokinesis is differentially regulated in different cell types and in symmetric versus asymmetrically dividing cells. **Tri Pham** (Cabernard lab, University of Washington) presented a biophysical characterization of asymmetrically dividing *Drosophila* larval neuroblasts. His data, based on atomic force microscopy, pressure measurements, and live cell imaging, provided a two-step model explaining the generation of sibling cell size asymmetry: biased relocalization of myosin allowed the neuroblast cortex to expand first on the apical side, driven by cell internal pressure. Subsequently, contraction of the actomyosin ring led to an expansion of the basal cortex and the continuation of apical expansion. These results highlight the dynamic relationship between genetically controlled myosin relocalization, internal pressure, and active constriction in the formation of physical asymmetry during asymmetric cell division. **Tim Davies** (Canman lab, Columbia University) presented his work in the early

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C. elegans embryo on cytokinetic diversity or cell type–specific mechanisms that regulate cytokinesis in the early *C. elegans* four-cell embryo. Using a combination of rapid conditional genetics, live cell imaging, and embryo microdissection, he found that the two symmetrically dividing cells were more dependent on F-actin levels than the two asymmetrically dividing cells. Moreover, he found that both cell intrinsic and cell extrinsic, Src-dependent cell fate regulatory mechanisms underlie these cell type differences.

The meeting also highlighted some interesting findings in the regulation of cytokinesis during neurogenesis and in aging stem cells. **Diana Vargas-Hurtado** (Basto lab, Institut Curie) showed that the morphology of the mitotic spindle changed during murine neurogenesis. She found that early mouse neural progenitors contained longer astral microtubules, interacting with the cell cortex, whereas at later stages, the central spindle gained in robustness at the expense of astral microtubules in a Tpx2-dependent manner. These results indicate unexpected modifications used by neural progenitors to build a bipolar spindle, which could impact the progenitors' ability to correctly segregate chromosomes. Age-related changes in cytoskeletal dynamics also were shown to impact cytokinesis in germline stem cells (GSCs) within the *Drosophila* testis. **Kari Lenhart** (DiNardo lab, University of Pennsylvania) reported that whereas young GSCs consistently completed cytokinesis, separating from their daughter cells, a significant rate of abscission failure occurred in older flies, impacting the ability to form functional sperm. To complete abscission, an F-actin–rich ring needed to be disassembled at the intercellular bridge between GSC–daughter cell pairs. This age-dependent F-actin disassembly mechanism was regulated through Jak/STAT signaling, highlighting a role for a niche-dependent signaling pathway in controlling stem cell cytokinesis.

In summary, this is an exciting time to work on cell division. Though this important cellular process is nearly always actomyosin-dependent, there exist critical variations from one cell type and/or model system to the next. This perspective represents a fundamental change in the way we view cell division and suggests that cell type differences are likely the rule rather than the exception.