The contractile ring

Ann L. Miller

What is the contractile ring? During cell division, the contractile ring generates the constricting force to separate one cell into two cells. Formed during cytokinesis, the last step of cell division, the contractile ring is composed of filamentous actin (F-actin) and the motor protein myosin-2, along with additional structural and regulatory proteins. The contractile ring forms under the surface of the plasma membrane and is linked to the plasma membrane such that, when it constricts, it creates a cleavage furrow that partitions the cell in two.

Why should you care about the contractile ring? The formation of the contractile ring must be regulated with spatial and temporal precision to ensure that the cleavage furrow is positioned properly and the chromosomes and organelles are distributed equally to each daughter cell. Successful execution of cytokinesis is necessary during development as well as for maintenance of adult tissues. Cytokinesis failure can lead to abnormalities in the correct number of chromosomes, which can promote birth defects and tumor formation.

How is the contractile ring positioned in the cell? To ensure that the contractile ring forms between the separating chromosomes, the cell ingeniously uses the microtubules of the mitotic spindle to perform both the physical separation of the chromosomes and the specification of the contractile ring. The contractile ring forms at the cell equator perpendicular to the axis of chromosome separation, allowing the contractile ring to pinch the daughter cells apart between the separating chromosomes.

What are the molecular cues that position the contractile ring? The localized activation of the small GTPase Rho at the cell equator controls the position of the contractile ring. Transmission of the signal to activate Rho from the microtubules to the cell cortex is achieved via Rho regulators that concentrate on spindle microtubules at the cell equator. The best characterized complex of Rho regulators during cytokinesis is the centralspindlin complex, which consists of the kinesin-6 family member MKLP-1 and the GTPase-activating protein (GAP) MgcRacGAP (Figure 1). Centralspindlin interacts with the guanine nucleotide exchange factor (GEF) Ect2. Due to the plus-end-directed motor activity of MKLP-1, centralspindlin and Ect2 accumulate at regions of microtubule overlap at the cell equator both in the midzone region of bundled microtubules between the separated chromosomes and on equatorial astral microtubules. By concentrating Ect2's GEF activity at the cell equator, this complex delivers a signal that locally stimulates Rho activity, which in turn activates formation of the contractile ring. MgcRacGAP promotes GTPase flux — the cycling of Rho between the active and inactive states — leading to a tightly focused Rho activity zone. Additionally, GEF-H1, MyoGEF, and p190RhoGAP are involved in Rho regulation during cytokinesis. There is also evidence that the small GTPases Rac and Cdc42 may be activated in regions outside the Rho zone during cytokinesis, and MgcRacGAP can downregulate Rac in order to reduce branched actin nucleation induced by Arp2/3 during cytokinesis.

Do any additional mechanisms help determine contractile ring position? The centralspindlin–Ect2 complex delivers a positive signal that stimulates cytokinesis, but other work has suggested that dynamic polar astral microtubules deliver inhibitory signals (the molecular nature of which is not known) that induce relaxation at the polar cortex, indirectly leading to equatorial contraction. Indeed, the equatorial stimulation and polar relaxation mechanisms may work together.

How is the timing of contractile ring initiation regulated? The temporal control of contractile ring assembly is regulated by mitotic kinases to ensure that the contractile ring is initiated only after anaphase onset once the chromosomes have separated. During metaphase, centralspindlin is unable to bind microtubules due to inhibitory phosphorylation of MKLP-1 by Cdk1/cyclin B. At anaphase onset, when Cdk1's activity rapidly declines, this inhibitory phosphorylation is not maintained, allowing centralspindlin to bind microtubules. While Cdk1 plays an inhibitory role, Plk1 and Aurora B both promote cytokinesis. Prior to anaphase, Plk1 is localized to centrosomes and kinetochores, but, upon anaphase onset, it relocalizes to the spindle midzone where it phosphorylates MgcRacGAP, creating a docking site for Ect2 to bind centralspindlin. Aurora B's kinase activity is stimulated at anaphase onset, and it forms a phosphorylation gradient centered on the midzone. Aurora B phosphorylates both components of centralspindlin. Phosphorylation of MKLP-1 promotes clustering of centralspindlin, which is required for stable accumulation at microtubule plus ends, while phosphorylation of MgcRacGAP promotes MgcRacGAP's GAP activity towards Rho.

How is the contractile ring assembled? When Rho is specifically activated at the equatorial cortex, it promotes actin polymerization and myosin-2 activation via Rho effector proteins. A conformational change occurs when Rho is in the active, GTP-bound state, such that only Rho–GTP can interact with and activate its downstream effector proteins. Rho–GTP promotes actin filament assembly by activating formins, specifically mDia2, which nucleate linear, unbranched actin filaments. Formin is autoinhibited by an intramolecular interaction between the amino and carboxyl termini; Rho–GTP binding to formin releases this autoinhibition. Rho–GTP promotes myosin-2 assembly by activating the kinases ROCK and Citron, which then activate myosin-2 via two mechanisms. First, they phosphorylate its regulatory light chain (rMLC) directly, promoting its assembly into bipolar filaments and activating its motor activity. Second, they phosphorylate and inhibit myosin phosphatase, indirectly promoting rMLC phosphorylation (Figure 1). In addition to *de novo* actin polymerization and myosin-2 bipolar filament formation, cortical flow of F-actin and myosin-2 may

assist the equatorial accumulation of actomyosin.

Are there other components of the contractile ring besides F-actin and myosin-2? There are multiple additional proteins in the contractile ring that play important functional roles. Profilin binds actin monomers and increases the elongation rate of actin filaments generated by formin. Cofilin is an actin-severing protein that destabilizes actin filaments in the contractile ring. Profilin and cofilin are important for the dynamic assembly and disassembly of actin filaments observed in the contractile ring. Anillin is a scaffolding protein that binds F-actin, myosin-2, septins, Rho, and MgcRacGAP, and contains a pleckstrin homology domain. Anillin is important for the organization and recruitment of structural and signaling proteins to the contractile ring and may be involved in tethering the contractile ring to the plasma membrane. One of the proteins Anillin recruits to the contractile ring is septin. Septins are filament-forming GTPases involved in stabilizing the contractile ring and restricting the spread of the cleavage furrow.

How does the contractile ring actually contract? The traditional model for how the contractile ring components generate the force to separate the cell (the 'purse-string' model) is that bipolar filaments of myosin-2 use their motor activity to move along two antiparallel actin filaments, causing them to slide past each other. Within the context of a contractile ring, many myosin-2 motors sliding many actin filaments would lead to constriction of the contractile ring. However, the geometry of F-actin and myosin-2 in the contractile ring is controversial, and in fact it is likely that alternative organizations of F-actin and myosin-2 exist and function in contraction. Importantly, as the ring constricts, the cross-sectional area of the contractile ring remains constant, suggesting that F-actin disassembly must balance ongoing F-actin polymerization. Indeed, F-actin disassembly is required for furrow ingression and may contribute to force production. The actin filament severing activity of cofilin and the ATPase activity of myosin-2 are required for F-actin disassembly in the contractile ring. Studies in mammalian cells and yeast suggest that the contractile ring is a dynamic structure in which F-actin and myosin-2 are continuously assembled and turned over. In contrast, recent work in *Caenorhabditis elegans* showed that myosin-2 does not actually turn over via exchange with a cytoplasmic or cortical pool, but instead the contractile ring is progressively disassembled over time. Further, this study proposed that the contractile ring may be organized in discrete contractile modules that are arrayed in series around the ring such that cells with a larger circumference have more contractile modules, and thus the rate of constriction is proportional to the initial circumference of the ring.

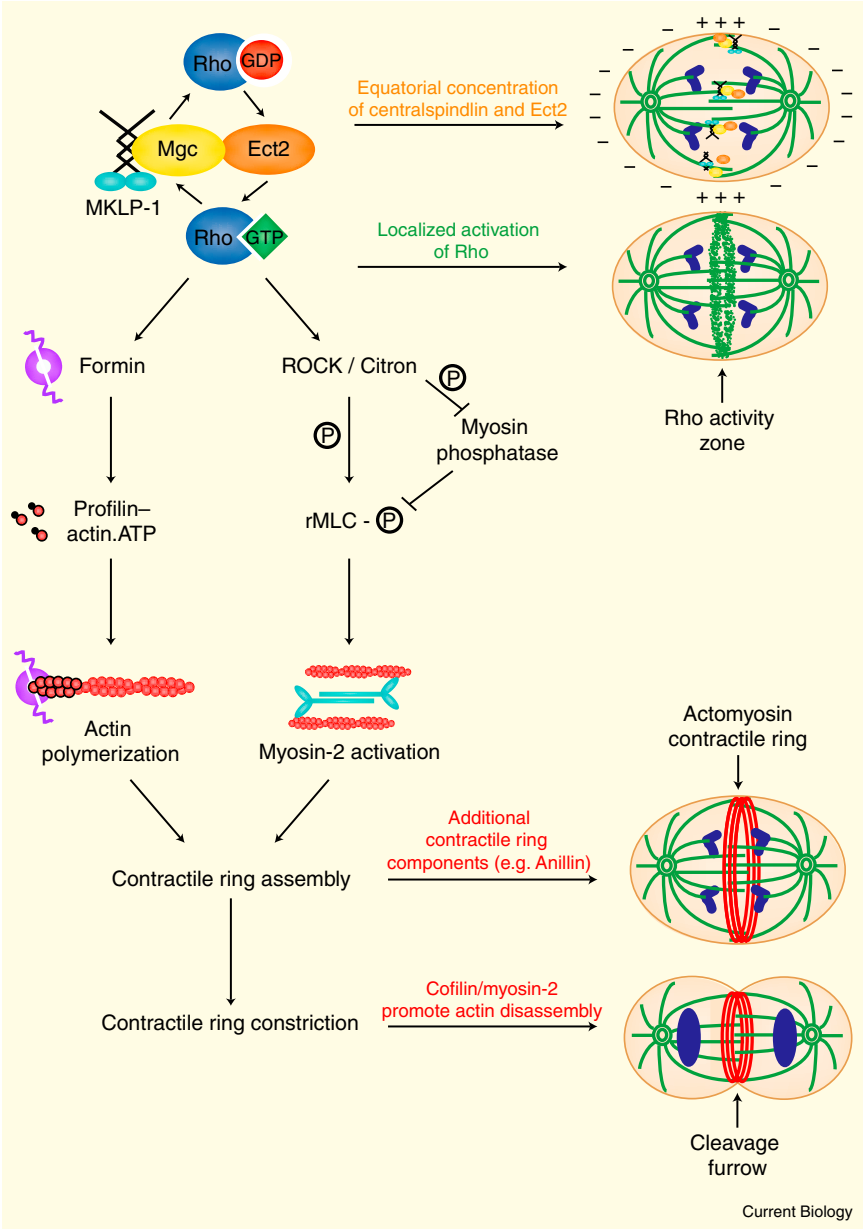

Figure 1. The molecular mechanisms of contractile ring specification, assembly, and contraction (see text for details).

How do cells finally complete cytokinesis? The contractile ring alone is not sufficient for complete cell separation; membrane insertion is also required. The contractile ring disassembles when it has constricted to its fullest extent, creating an intercellular bridge, which tethers the two daughter cells until abscission,

a process that requires the delivery of membrane vesicles to the intercellular bridge and membrane fusion events.

What remains to be explored? The necessity for precise spatial and temporal control of cytokinesis to ensure that chromosome segregation and cytokinesis are coordinated is universal. Different cell sizes and geometries, the presence or absence of cell–cell contacts with neighbors, and the type of substrate on which cells are growing might influence which molecular mechanisms are most important for cytokinesis in a particular system. Nonetheless, much of the core molecular machinery is conserved in divergent species. For example, many of the proteins discussed here are also involved in regulating cytokinesis in fission yeast and budding yeast. The relative simplicity of these model systems has allowed researchers to identify a quantitative parts list of the proteins involved in cytokinesis, and these studies can be highly instructive for our understanding of how cytokinesis works in animal cells. Many important questions remain to be answered about how the contractile ring is specified, assembles, and constricts. Some of these include: what defines different populations of microtubules that deliver stimulatory and inhibitory signals to the cortex? How are certain microtubules stabilized at the cell equator? Are there additional mechanisms that regulate Rho, Rac, and Cdc42 activity during cytokinesis? What links the contractile ring to the plasma membrane? And how does the contractile ring work in a variety of *in vivo* contexts?

Where can I find out more?

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Department of Molecular, Cellular, and Developmental Biology, Program in Cell and Molecular Biology, University of Michigan, Ann Arbor, Michigan 48109, USA.
E-mail: annlm@umich.edu

Primer

Visual perception of materials and surfaces

Barton L. Anderson

The visual system relies on patterns of light to provide information about the layout of objects that populate our environment. Light is structured by the way it interacts with the three-dimensional shape, reflectance, and transmittance properties of objects. The input for vision is therefore a complex, conflated mixture of different sources of physical variation that the brain must somehow disentangle to recover the intrinsic properties of the objects and materials that fill the world.

The study of visual processes has been approached at a number of levels. Visual analysis begins with the encoding of local image properties, such as luminance, color, contrast, motion, and orientation. A large body of research into low-level vision focuses on understanding these initial stages of encoding. This initial encoding involves measurements of the *proximal stimulus* — the retinal images — which typically only provide hints as to their environmental causes. For example, a local edge of a particular contrast and orientation will elicit a specific response pattern in cells in early visual cortex, but these responses say little about its environmental source. Does this local edge correspond to an object boundary, a crease or fold in a surface, the boundary of a shadow, or a change in surface pigmentation?

To recover the *distal stimulus* — properties of the world — these low-level responses have to be transformed from an image-based representation to a representation of surfaces, materials, and objects. *Mid-level* vision is concerned with understanding how the visual system organizes image measurements into a coherent representation of surfaces and materials. This problem is hard because local low-level responses do not uniquely identify their sources; they must be interpreted relative to the context in which they are embedded. The outputs of these computations are then used by a variety of high-level visual processes, such as object recognition, face perception, the distribution and allocation of attention between objects, and cognitive processes that rely on the spatial relationships between and among objects.

The categories of low-, mid-, and high-level vision suggest that the analysis of visual information can be understood as a progressive flow from low-level feature detection to high-level scene analysis. However, this simple linear flow fails to capture the massive recurrence that occurs throughout the visual system. Although the role of feedback in visual processing remains to be fully understood, the visual system appears to be organized as a set of recurrent loops, not a simple linear chain of causation. This suggests that higher levels of processing participate in shaping the very input that they attempt to analyze. The term ‘mid-level vision’ is not intended to delineate a particular region of cortical processing, but rather, refers to the collective processes that are involved in making information about surfaces and materials explicit. In this primer, I will describe some of the ongoing areas of research into these processes, focusing on the relatively new and emerging area of material perception.

What is material perception?

Material perception is concerned with how we perceive what things are made of. Although the perception of material properties can involve all of our senses, the focus of this primer is on the problem of extracting material properties from visual information.

Different materials can be visually distinguished because (and to the extent that) they structure light in a particular, characteristic way. For example, the micro-structure of hair and fur generate particular types of texture, sheen, and orientation flow. Polished stone generates a specific pattern of specular reflections and depth from the translucent crystalline materials that compose them. Gelatins are translucent as well, but can be distinguished from other materials by their shape and the way that they move, slide, or bounce. The fact that we can distinguish material properties on the basis of