A Ring-like Template for Abscission

In the October 7th issue of Cell, Gromley et al. (2005) show that a ring-like structure containing the centrosomal protein centriolin acts as a local recruitment site for the membrane fusion machinery that controls abscission.

The most obvious event in animal cell cytokinesis is ingression of the cleavage furrow, which is powered by the actomyosin contractile ring and which effects the majority of the physical task of cell division. While furrowing will likely never lose its cachet, it is increasingly clear that much of what happens during furrowing is directed toward the mechanistically distinct event abscission, in which daughter cells actually become physiologically distinct. Obviously, abscission must involve some topological transformation of the plasma membrane. Strikingly, recruitment of centriolin to the midbody ring is dependent on the components of the plasma membrane. Recent reports that the midbody contains variouss proteins involved in membrane trafficking (Low et al., 2005) substantiates this hypothesis by demonstrating that the centriolin-containing midbody ring is clearly evident later in cleavage, five or more micrometers from the plasma membrane. Strikingly, recruitment of centriolin to the midbody ring is dependent on the components of the centrosomal complex, MKLP1 and MgcRacGAP (Mishima et al., 2002), the same players that control as-"the midbody ring," which serves as the site of centriolin recruitment as well as the point at which secretory vesicles eventually accumulate within the midbody. The midbody ring is equivalent to the so-called Flemming body, a phase-dense structure that bulges outward in the approximate middle of the midbody, like the neck of a chicken choking on a particular stale donut (Figure 1). Gromley et al. (2005) note that centriolin begins accumulating in a ring-like structure not long after the onset of furrowing and show that the centriolin-containing midbody ring is clearly evident later in cleavage, five or more micrometers from the midbody. The midbody ring is equivalent to the so-called Flemming body, a phase-dense structure that bulges outward in the approximate middle of the midbody, like the neck of a chicken choking on a particular stale donut (Figure 1). Gromley et al. (2005) note that centriolin begins accumulating in a ring-like structure not long after the onset of furrowing and show that the centriolin-containing midbody ring is clearly evident later in cleavage, five or more micrometers from the midbody. The midbody ring is equivalent to the so-called Flemming body, a phase-dense structure that bulges outward in the approximate middle of the midbody, like the neck of a chicken choking on a particular stale donut (Figure 1). Gromley et al. (2005) note that centriolin begins accumulating in a ring-like structure not long after the onset of furrowing and show that the centriolin-containing midbody ring is clearly evident later in cleavage, five or more micrometers from the midbody. The midbody ring is equivalent to the so-called Flemming body, a phase-dense structure that bulges outward in the approximate middle of the midbody, like the neck of a chicken choking on a particular stale donut (Figure 1).

Centriolin was originally identified as a marker of centrosome maturation, such that newly made daughter centrioles possess none until cells enter mitosis (Gromley et al., 2003). But surprisingly, depletion of centriolin by siRNA had no detectable effect on microtubule organization but instead results in a consistent delay or suppression of abscission. The phenotype of centriolin depletion, however, is much different than that of many other late cytokinesis defects in which the furrow ingress to various extents, and then rapidly regresses, such that the daughter cells rapidly become a single, binucleate cell. Instead, cells depleted of centriolin remain connected by a long cytoplasmic bridge for hours, indicating that the problem isn’t that they can’t maintain the constriction, but rather cannot sever it.

This study not only provides an explanation for this defect, it also reveals the existence of a structure the authors term the “midbody ring,” which serves as the site of centriolin recruitment as well as the point at which secretory vesicles eventually accumulate within the midbody. The midbody ring is equivalent to the so-called Flemming body, a phase-dense structure that bulges outward in the approximate middle of the midbody, like the neck of a chicken choking on a particular stale donut (Figure 1). Gromley et al. (2005) note that centriolin begins accumulating in a ring-like structure not long after the onset of furrowing and show that the centriolin-containing midbody ring is clearly evident later in cleavage, five or more micrometers from the midbody. Strikingly, recruitment of centriolin to the midbody ring is dependent on the components of the centrosomal complex, MKLP1 and MgcRacGAP (Mishima et al., 2002), the same players that control assembly of the contractile ring (Somers and Saint, 2003). While most studies have focused on localization of centrosomal centriole to the spindle midzone and just beneath the contractile ring, in fact MKLP1 and MgcRacGAP also localized in a tight spot in the center of the midzone (see Figure 5 in Somers and Saint, 2003) before the onset of furrowing, suggesting that the midbody ring might be templated at the same time as the contractile ring.

In contrast to the contractile ring, once formed, the midbody ring maintains a constant size. Further, it is remarkably stable, in that components of it persist as a coherent structure well into the next cell cycle. Thus, while both the beginning and end of cytokinesis depend on macromolecular rings, many of the features of the two rings are distinctly different.

These differences reflect their different roles: the contractile ring dynamically narrows the cell to the point where abscission can take place, while the midbody ring acts as a landing site for machinery involved in

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membrane fusion. Accordingly, the exocyst complex and SNARE proteins localize to the midbody ring in a centriolin-dependent manner, and their knockdown by RNAi mimics the abscission phenotype resulting from centriolin knockdown.

The deposition of this machinery is followed by a dramatic and rapid recruitment of secretory vesicles to the midbody ring (Figure 1). These vesicles apparently then undergo heterotypic fusion with the PM and (presumably) homotypic fusion with each other, thereby accomplishing abscission. Remarkably, the vesicles are recruited from only one of the daughter cells. The basis for this asymmetry is unknown, although it is reminiscent of previous work showing that the mother centriole of one of the daughter cells is transiently recruited to the midbody region shortly before abscission (Piel et al., 2001). However, Gromley et al. note that they do not consistently observe such centriole translocation, suggesting that whatever changes in the microtubule cytoskeleton direct asymmetric vesicle recruitment, they are not strictly dependent on en mass centriole movement per se. Conceivably, centrosome translocation might reflect a recruitment process in which centriolin is dragged off the centriole (by MKLP1) in large patches, sometimes giving a tug sufficient to haul the centriole with it, sometimes not. If indeed centriolin recruits in clots, and if its arrival at the midbody in sufficient quantity also signals the cessation of recruitment, then it might explain how vesicle targeting might be made asymmetric: presumably one cell or the other would be first to contribute the requisite centriolin clot.

By identifying the midbody ring, characterizing its role, and showing that centriolin is one of its key components, Gromley et al. (2005) have unified several disparate observations—the inhibition of cytokinesis by centrosome ablation (Khodjakov and Rieder, 2001), the localization of secretory proteins to the midbody (Low et al., 2003), and the accumulation of membrane in the midbody region (Skop et al., 2001). As described by the authors, this study also supports the notion that the terminal stages of animal cell division resemble in many ways cytokinesis in both plants, which is driven by vesicle fusion, and budding yeast, which is finished by local concentration of the exocyst complex at the bud site.

Finally, these findings underscore the mechanistic difference between the beginning and end of cytokinesis in animal cells. In fact, it would probably make sense for cell biologists to stop referring to abscission as “late cytokinesis” or the “completion of cytokinesis.” We are talking about two mechanisms, fundamentally different from one another as the process of spindle assembly is from furrow formation, not two different stages of one process. The progression of the cytokinetic furrow helps to create the preconditions for abscission, just as the geometry of the mitotic apparatus influences the development of the furrow. Of course, it may be that cells vary in the extent to which contractile furrowing is temporally segregated from abscission: in the HeLa cells studied by Gromley et al., abscission begins long after the furrow has reduced itself to a slender canal; in large embryonic cells with a fast cell cycle, vesicle delivery and fusion may overlap with some or all of furrowing (Danilchik et al., 2003). It will therefore be of considerable interest to follow the distribution of
centriolin and other midbody ring components in other model systems.

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