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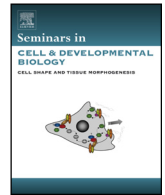

Review

Animal cell cytokinesis: The role of dynamic changes in the plasma membrane proteome and lipidome

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ABSTRACT

In animal cells, cytokinesis is characterised by the formation of the mitotic spindle that signals the assembly of an actomyosin ring between the spindle poles. Contraction of this ring drives ingression of the cleavage furrow, and culminates in the formation of a thin intercellular bridge between the daughter cells. At the centre of this bridge is the midbody, which is thought both to provide a site of attachment for the plasma membrane furrow and act as foci for the spatial and temporal control mechanisms that drive abscission. This review will focus upon recent studies that offer new insight into these events, in particular studies that elaborate on the mechanism of attachment between the furrow plasma membrane and the underlying cytoskeleton, and how dynamic changes in membrane composition might underpin key aspects of cytokinesis.

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Abbreviations: ALIX, apoptosis-linked gene-2 interacting protein X; ANCHR, abscission/NoCut Checkpoint Regulator; CHMP, charged multivesicular body protein; CPC, chromosome passenger complex; ESCRT, Endosomal Sorting Complex Required for Transport; GFP, green fluorescent protein; GUV, giant unilamellar vesicles; LBPA, lyso-bisphosphatidic acid; PI3P, phosphatidylinositol 3-phosphate; PI4P, phosphatidylinositol 4-phosphate; PI4,5P$_2$, phosphatidylinositol 4,5-bisphosphate; PI3,4,5P$_3$, phosphatidylinositol 3,4,5-trisphosphate; RBD, Rho binding domain.

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1. Introduction

Cytokinesis drives the physical scission of the daughter cells at the completion of mitosis. In animal cells, cytokinesis begins in anaphase with the reorganisation of the mitotic spindle and proceeds via the formation of a contractile ring at a site positioned equatorially between the two spindle poles; contraction of this ring drives the formation of a cleavage furrow. After completion of furrowing, a thin intercellular bridge, that has at its centre the midbody, separates the daughter cells. The midbody provides both a means to anchor the ingressed furrow and acts as a platform for the regulated assembly of the abscission machinery. Abscission involves regulated membrane trafficking into the intercellular bridge followed by the step-wise assembly of the Endosomal Sorting Complex Required for Transport (ESCRT)-machinery that is believed to catalyse the final scission event [1–4].

It is apparent, even from an overly simplified synopsis such as the above, that cytokinesis involves structural upheavals and dynamic membrane remodelling events at many stages, from early furrow ingression, through stable anchoring of the furrow to scission. We are fortunate from a range of genetic screens and proteomic analyses to have a reasonably detailed idea of the genes/proteins involved, and many excellent reviews have over the past few years provided a wide-ranging and clear analysis of the steps and players in animal cell cytokinesis. These include central spindle assembly, cleavage plane specification, the assembly and constriction of the actomyosin ring and the mechanics and regulation of abscission [4–6].

By way of contrast, this review will focus mainly on events at the plasma membrane during cytokinesis; as most of the experimental work I will discuss has utilised mammalian cells in culture, this review will focus largely on animal cell cytokinesis. Specifically I will discuss: how the membrane of the furrow may be anchored to the intracellular machinery during furrowing and abscission and how this interaction is regulated. How does RhoA get activated at specific spatial coordinates to drive the equatorial furrow? How do the physico-chemical properties of the plasma membrane change and control aspects of furrowing and abscission? And how is the temporal control of cytokinesis achieved? Recent studies have provided fascinating insight into these areas.

2. How does the plasma membrane engage the furrow machinery?

2.1. Centralspindlin–a multi-tasking complex that links the plasma membrane to the spindle and spatially activates RhoA in the furrow

Centralspindlin, a heterotetramer comprised of a dimer of the kinesin-6 motor protein MLKP1 and a dimer of a Rho-GTPase activating protein MgcRacGAP (Cyk4), is a well-established regulator of cytokinesis [7]. MKLP1 is composed of an amino-terminal motor domain joined to a carboxy-terminal globular domain via a parallel coiled-coil and a long linker domain [8]. This long linker domain interacts with the amino terminus of MgcRacGAP that is in turn assembled from an amino terminal coiled-coil domain, a putative C1 domain (see below) and a carboxy-terminal RhoGAP domain. This complex localises to the centre of the spindle midzone in anaphase where, together with other proteins it participates in the formation of antiparallel arrays of microtubules and the midbody (for detailed review, see [7]). Phosphorylation of MgcRacGAP/Cyk4 by Polo-like kinase-1 facilitates the interaction of this complex with the Rho guanine nucleotide exchange factor ECT2. This drives the activation of the small GTPase RhoA and initiates the formation of the furrow and the assembly of the actomyosin ring [7]. Centralspindlin is also involved in the recruitment of some of the abscission machinery prior to the final cleavage event [9]. Thus, the multi-functional centralspindlin complex has come to be regarded as the 'conductor of the cytokinetic orchestrator' [7,10]. The constriction of the actomyosin ring proceeds until the daughter cells remain separated only by a thin intercellular bridge, rich in microtubules, with the midbody at its centre. One of the mysteries of this process is how the plasma membrane of the furrow is linked to the midbody. Recent studies have identified a key role for the centralspindlin complex in this association.

A number of proteomic and genetic studies have identified a long list of proteins known to be involved in cytokinesis or associated with midbodies [11]. Lekomtsev and colleagues examined these components for the presence of membrane-association motifs, and identified a poorly characterised but evolutionary-conserved C1 domain in MgcRacGAP (shown schematically in Fig. 1A) [12]; C1 domains are known to function as lipid-binding domains, raising the interesting possibility that a similar function may be integral to the function of MgcRacGAP. Mutations within this C1 domain, including point mutants within the structural 'core' of the protein, impaired cytokinesis, suggesting that this C1 domain played a functional role [12]. Careful analysis of the myriad of functions of MgcRacGAP revealed that the C1 domain was not required for the formation of the centralspindlin complex nor did deletion of the C1 domain impair either localisation of the complex or the recruitment of other cytokinetic regulators, suggesting that this domain had hitherto played an unrecognised role in cytokinesis [12]. Using GST-fusion proteins, Lekomtsev and colleagues revealed that the C1 domain selectively interacted with phosphatidylinositol-4, 5-bisphosphate ($PI4,5P_2$) and phosphatidylinositol-4-phosphate (PI4P), lipids known to be enriched in the furrow of dividing cells (Section 5 below). Importantly, depletion of both of these lipids using engineered selective phosphatases resulted in the release of a fluorescently tagged C1 dimer from the plasma membrane, and mutations in the putative lipid binding domains of MgcRacGAP impaired both cytokinesis and lipid binding *in vitro*. These observations suggest that the ability to bind to the plasma membrane may be a key function of the C1 domain.

In an elegant series of experiments Lekomtsev tested this hypothesis by replacing the atypical C1 domain of MgcRacGAP firstly with a typical C1B domain from protein kinase Cα. Typical C1 domains are characterised by tight binding to phorbol esters (or diacyglycerol) that forms a hydrophobic surface that interacts with membranes. Depletion of endogenous MgcRacGAP impaired cytokinesis; expression of the MgcRacGAP-C1B hybrid rescued this effect, but only upon addition of phorbol esters [12]. A similar restoration of cytokinesis was observed if a distinct membrane targeting sequence was substituted. Such observations suggest that the atypical domain of MgcRacGAP is involved in membrane tethering of centralspindlin, and this tethering is essential for completion of cytokinesis [12]. This was supported by live-cell imaging, which revealed that in cells expressing wild-type MgcRacGAP, the plasma membrane remains associated with the midbody until abscission. By contrast MgcRacGAP mutants with defective C1 domain function, while still localising to the midbody, did not support association of the plasma membrane and the midbody; the plasma membrane was frequently observed to detach from the midbody, leading to furrow regression and cytokinesis failure [12]. These data implicate centralspindlin as a point of attachment of the plasma membrane to the midbody, and suggest a model in which the ingressing furrow can physically bind the midbody at a key step, stabilising the furrow and perhaps allowing the assembly of the abscission machinery once this association is established (Fig. 1B).

Interestingly, MKLP1 has been shown to interact with the GTPase Arf6 [13]. Like many small GTPases, Arf6 is associated with

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