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THE COMPANY OF Biologists

COMMENTARY

Epithelial cell division – multiplying without losing touch

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ABSTRACT

Epithelia are compact tissues comprising juxtaposed cells that function as mechanical and chemical barriers between the body and the environment. This barrier relies, in part, on adhesive contacts within adherens junctions, which are formed and stabilized by E-cadherin and catenin proteins linked to the actomyosin cytoskeleton. During development and throughout adult life, epithelia are continuously growing or regenerating, largely as a result of cell division. Although persistence of adherens junctions is needed for epithelial integrity, these junctions are continually remodelled during cell division. In this Commentary, we will focus on cytokinesis, the final step of mitosis, a multiparty phenomenon in which the adherens junction belt plays an essential role and during which a new cell–cell interface is generated between daughter cells. This new interface is the site of intense remodelling, where new adhesive contacts are assembled and cell polarity is transmitted from mother to daughter cells, ultimately becoming the site of cell signalling.

KEY WORDS: Epithelial cells, Adherens junctions, Cytokinesis

Introduction

Epithelia function as mechanical and chemical barriers between the body and the environment. Mono- or multi-layered, these compact tissues are spatially organized, and each cell is tightly bound to its neighbours through various cell–cell contacts. In particular, intercellular junctions within tight or septate and adherens junctions define the limits between the apical and basal membrane, thereby conferring an intrinsic polarity to the cell. In vertebrates, tight junctions act as the diffusion barrier and are apical to adherens junctions, whereas in invertebrates, the diffusion barrier is ensured by septate junctions that are basal to adherens junctions (Fig. 1) (Matter and Balda, 2003; Tepass and Hartenstein, 1994; Tepass et al., 2001). Adherens junctions serve an adhesive role and are involved in maintaining tissue integrity, and we will focus on this type of junction in this Commentary. Adherens junctions are formed and stabilized by E-cadherin (also known as CDH1 in mammals and Shotgun in *Drosophila*) and clusters of catenin proteins that are linked to the actomyosin cytoskeleton. Thus they form an adherens junction belt between the apical and the basolateral domains of the epithelial plasma membrane. These domains have a distinct composition of transmembrane proteins and lipids. Transmembrane proteins are specifically localized to either domain, depending on sorting signals that are deciphered by specialized intracellular trafficking machinery (Apodaca et al., 2012). Although the mechanisms through which lipids are trafficked in cells are not yet fully elucidated, data support the idea that the distribution of phosphoinositides is polarized along the apical-basal axis and contributes to the establishment and maintenance of cell polarity (Martin-Belmonte and Mostov, 2008; Shewan et al., 2011).

In all epithelial cells, the adherens junction belt contributes both to the global cell polarity and the mechanical barrier function of the epithelium. Although the persistence of adherens junctions is needed for epithelial integrity throughout development and adulthood, adherens junctions are continually remodelled during tissue morphogenesis, in part through E-cadherin turnover, which contributes to junction formation and maintenance (reviewed in Baum and Georgiou, 2011; Friedl and Zallen, 2010; Guillot and Lecuit, 2013b; Herszterg et al., 2014). Even so, little is known with regard to how tissue integrity is maintained when an epithelial cell divides, in particular during cytokinesis (when the mitotic cell separates into two cells), which is initiated during the later stages of cell division (Fededa and Gerlich, 2012; Glotzer, 2005; Glotzer, 2010; Green et al., 2012; Robinson and Spudich, 2004).

Following sister chromatid separation, the anaphase spindle mediates the assembly of an actomyosin contractile ring that is connected to the plasma membrane at the cell equator (Box 1). Actin and non-muscle myosin II (Myo II) then generate the contractile tension that is needed for ring constriction; this then leads to the local ingression of the plasma membrane at the equator (i.e. cleavage furrowing) until a narrow intercellular bridge, stabilized by the midbody, separates the sister cells. Abscission eventually resolves the bridge, thereby generating two distinct cells. Therefore, the dividing cell is subjected to various forces that are exerted through its own cytoskeleton (reviewed by Cadart et al., 2014; Kunda and Baum, 2009; Lancaster and Baum, 2014). In cultures of isolated cells, cells are round and exhibit a stiff actomyosin cortex during prometaphase, but upon entry into cytokinesis, cortical tensions become asymmetric – tension at the poles is relaxed, whereas the equator undergoes contraction. This softening of the polar cortex allows furrow ingression. Whether similar cortical tensions are applied during epithelial cell cytokinesis within a tissue context, and how neighbouring cells accommodate and/or impact on these cell changes are unknown. At the same time, the adherens junction belt and the polarity of the dividing cell need to be remodelled to some extent in order to allow the formation of a new membrane between the two daughter cells. Furthermore, adherens junctions and appropriate cell polarity must be established on this newly formed membrane in order to maintain tissue integrity. Although the molecular factors and mechanisms that control cytokinesis have been identified in studies of isolated cells, little is known regarding the maintenance and transmission of adhesive contacts during epithelial cell division. Four studies in *Drosophila* have recently begun to shed light on how adherens junctions are remodelled during cell division in order to allow proper

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Journal of Cell Science (2014) 127, 5127–5137 doi:10.1242/jcs.151472

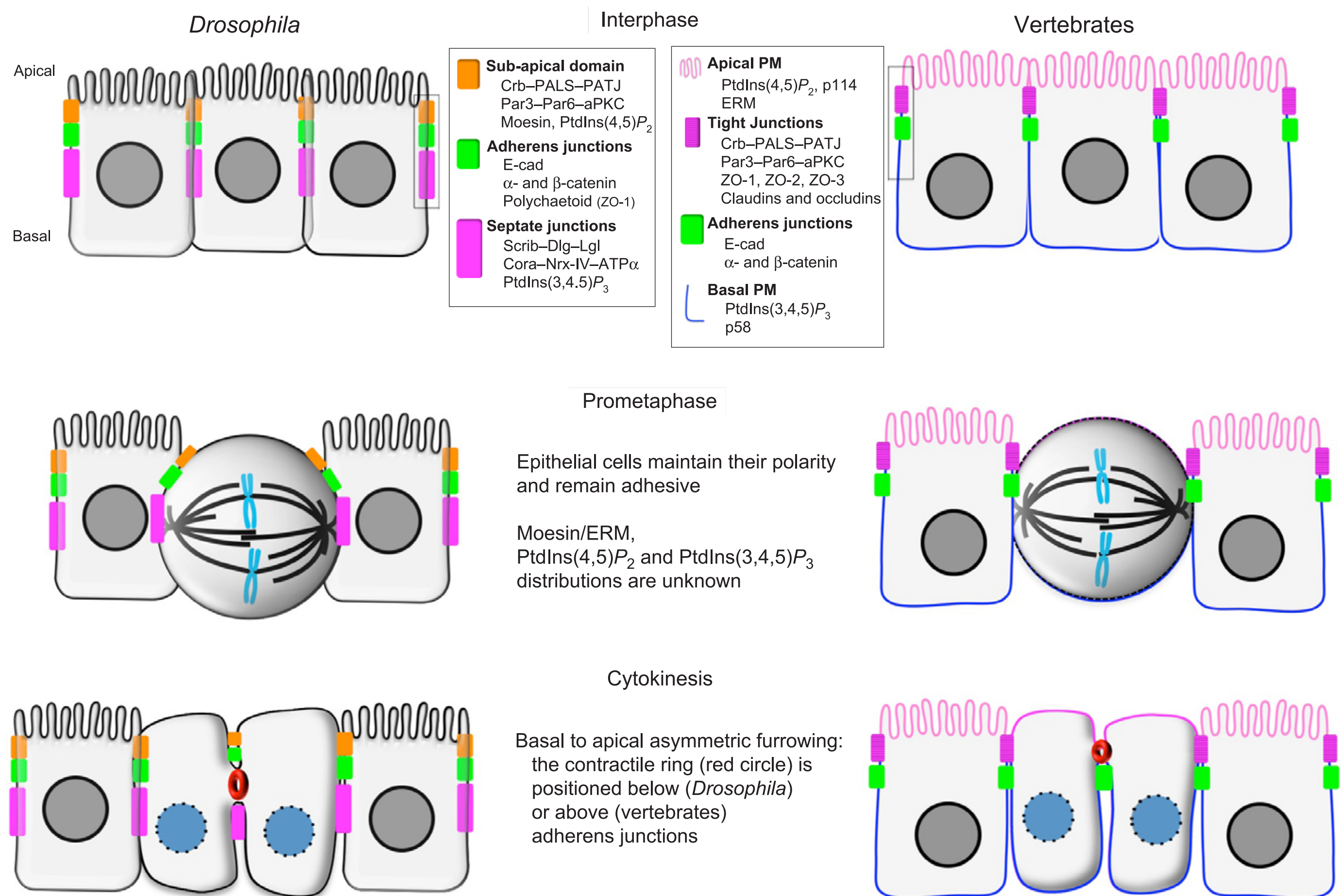

Fig. 1. Distribution of apical-basal polarity markers during mitosis. Epithelial cells in *Drosophila* (left) and vertebrates (right) maintain their apical-basal distribution and composition of junctional complexes, polarity markers and phosphoinositides (listed in the insets) during interphase, prometaphase and cytokinesis. A fundamental difference between these epithelia is the position of the diffusion barrier relative to the adherens junction belt: septate junctions (orange) are apical in *Drosophila*, whereas tight junctions (purple) are basal in vertebrates. A major difference between species is the final position of the midbody relative to adherens junctions, below and above the adherens junctions in *Drosophila* and vertebrates, respectively. aPKC: atypical protein kinase C; Cora: Coracle; Crb: Crumbs; Dlg: Discs large; E-cad: E-cadherin; ERM: ezrin, radixin and moesin; Lgl: Lethal (2) giant larvae; Nrx-IV: Neurexin IV; p58: also known as 58-kDa antigen (Reinsch and Karsenti, 1994); p114: also known as p114RhoGEF or ARHGEF18; PALS: protein associated with Lin7, also known as Stardust in *Drosophila*; PATJ: protein associated with tight junctions; PtdIns(4,5)P_2: phosphatidylinositol 4,5-bisphosphate; PtdIns(3,4,5)P_3: phosphatidylinositol 3,4,5-trisphosphate; Scrib: Scribble; ZO: Zona occludens.

partitioning of cell polarity markers and adhesive complexes *in vivo* (Founounou et al., 2013; Guillot and Lecuit, 2013a; Herszterg et al., 2013; Morais-de-Sá and Sunkel, 2013a). Other excellent recent reviews have discussed the forces involved in spindle positioning during mitosis (Almonacid et al., 2014; Kotak and Gönczy, 2013; McNally, 2013) and the mechanics of cytokinesis (Herszterg et al., 2014; Morais-de-Sá and Sunkel, 2013b). Therefore, this Commentary will focus on the dynamics of polarity maintenance and its transmission to the daughter cell interface; we will discuss the role of adherens junctions during the progression of the cleavage furrow, the anchoring of the contractile ring and the formation of the new adhesive interface, and, finally, how abscission resolves cytokinesis and leads to the new membrane interface behaving as a signalling platform between daughter cells.

Maintenance of polarity during epithelial cytokinesis?

Because cells in an epithelium remain mechanically connected to their neighbours while they divide, this raises the question of how they can divide without weakening the barrier function. Several studies in different model systems suggest that epithelial cells maintain their apical-basal polarity and remain adhesive during division (Fig. 1). Indeed, several transmembrane proteins or associated proteins remain at their appropriate apical-basal localization throughout mitosis, e.g. E-cadherin in Madin-Darby canine kidney (MDCK) cells (Baker and Garrod, 1993; Reinsch and Karsenti, 1994), desmoplakin, ZO-1 and vinculin in MDCK cells (Baker and Garrod, 1993) and mammalian skin (Devenport et al., 2011), as well as E-cadherin, Crumbs and Notch in pupal *Drosophila* epithelium (Founounou et al., 2013). By contrast, the localization of the apical determinants (Par3/Bazooka, aPKC and Par6) during mitosis appears to depend on the cellular context, as it is unaffected in *Drosophila* embryo ectoderm (Guillot and Lecuit, 2013a), whereas it is partially depolarized in *Drosophila* ovary follicular epithelial cells (Morais-de-Sá and Sunkel, 2013a). Thus, although the aforementioned studies collectively imply that there is no global change in the apical-basal membrane polarity of dividing epithelial cells, formal demonstration still awaits – for instance, investigations using time-lapse microscopy. In particular, the localization of the components of septate junctions in invertebrates

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Journal of Cell Science (2014) 127, 5127–5137 doi:10.1242/jcs.151472

Box 1. Brief overview of cytokinesis

Numerous studies have led to the identification of the core molecular machinery underlying cytokinesis in isolated cells, and the readers should refer to previous excellent reviews on this topic (Fededa and Gerlich, 2012; Glotzer, 2005; Glotzer, 2010; Green et al., 2012; Robinson and Spudich, 2004), bearing in mind that this field is rapidly growing. Briefly, following sister chromatid separation, cytokinesis starts with signalling between the anaphase spindle and the cell cortex to generate an equatorial zone of active RhoA. The central spindle forms in the midzone between sister chromatids, recruits Ect2 – a guanine nucleotide exchange factor for Rho GTPases – and loads it onto the plasma membrane in order to promote the localized activation of RhoA at the equator, as well as phosphorylation of Myo II. There, active RhoA induces the assembly of the contractile ring – a filamentous network composed of formin-nucleated actin filaments, Myo II, membrane-associated septins that form linear heteromeric filaments and the filament cross linker anillin. Myo II forms bipolar filaments that bind to and exert forces on actin filaments, leading to ring constriction (Fig. 2). As the ring constricts, the spindle midzone matures to form the midbody, which organizes the intercellular bridge. Upon abscission, the bridge is eventually resolved, thereby generating two distinct cells.

or tight junctions in vertebrates during mitosis, and thus the transmission and/or maintenance of the diffusion barrier from mother to daughter cells, remains largely unexplored.

The apical-basal plasma membrane composition of phosphoinositides during epithelial cell division is even less characterized than that of polarity proteins. As the cortical localization of polarity markers discussed above relies on the membrane-localization of specific phosphoinositides, one might predict that the localization of polarity proteins during mitosis would mirror that of phosphoinositides. Observations of MDCK cells grown as cysts revealed that phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2] is a crucial determinant of the apical surface (Fig. 1). During epithelial cell polarization, the apically localized lipid phosphatase, phosphatase and tensin homolog (PTEN), induces the apical segregation of PtdIns(4,5)P_2, which in turns recruits annexin 2 and the Cdc42–Par6–aPKC polarity complex (Martin-Belmonte et al., 2007). Reciprocally, phosphatidylinositol (3,4,5)-trisphosphate [PtdIns(3,4,5)P_3] localizes to and regulates the formation of the basolateral membrane in MDCK cysts (Gassama-Diagne et al., 2006). In *Drosophila* follicular epithelium also, PtdIns(4,5)P_2 defines the apical surface and PtdIns(3,4,5)P_3 the basolateral surface. Indeed, loss of the *Drosophila* phosphatidylinositol-4-phosphate 5-kinase Skittles reduces PtdIns(4,5)P_2 levels and impairs apical targeting of the polarity determinant Par3, thus causing the disassembly of adherens junctions and formation of an apically active actomyosin contractile ring that results in apical constriction, i.e. epithelial morphological changes reminiscent of the epithelial–mesenchymal transition (EMT) (Claret et al., 2014). Although the lipid kinases found in vertebrates and in insects are different (PTEN versus Skittles), the function of apical PtdIns(4,5)P_2, and probably that of basolateral PtdIns(3,4,5)P_3, in tissue integrity appears to be evolutionarily conserved.

In addition to their role in apical-basal polarity, phosphoinositides have major roles in cytoskeletal remodelling and membrane trafficking throughout cytokinesis of isolated cells, as highlighted in previous reviews (Brill et al., 2011; Echard, 2012; Janetopoulos and Devreotes, 2006; Logan and Mandato, 2006; Nezis et al., 2010). However, their role in epithelial cell cytokinesis remains unknown, and it is unclear, for example, whether apical-basal segregation of PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3 is preserved during epithelial cell mitosis. It is well established that, in *Schizosaccharomyces pombe* (Zhang et al., 2000), *Drosophila* S2 cells (Ben El Kadhi et al., 2011; Roubinet et al., 2011) and isolated mammalian cells (Abe et al., 2012; Dambournet et al., 2011; Emoto et al., 2005; Field et al., 2005; Kouranti et al., 2006), PtdIns(4,5)P_2 is the only phosphoinositide that is obviously enriched at the plasma membrane of the cleavage furrow. There, PtdIns(4,5)P_2 is essential for the recruitment of anillin (also known as ANLN in mammals and Scraps in *Drosophila*), which then interacts with components of the actin cytoskeleton, including F-actin, Myo II, RhoA, Ect2 [a guanine nucleotide exchange factor (GEF) for Rho GTPases] and septins (Box 1; Fig. 2) to trigger contractile ring assembly and constriction (Chesneau et al., 2012; D'Avino et al., 2009; Piekny and Maddox, 2010). A recent lipidomic approach to study the changes in lipid composition and localization at the onset of cytokinesis in isolated cells revealed that glycosphingolipids have a key role in controlling cortical stiffness during mitosis (Atilla-Gokcumen et al., 2014). Based on these data, one could anticipate that PtdIns(4,5)P_2 and glycosphingolipids, which are enriched at the apical plasma membrane in polarized epithelial cells during interphase, exert important roles in cytokinesis. This raises the question of how PtdIns(4,5)P_2 and glycosphingolipids are targeted to and/or locally generated in the PtdIns(3,4,5)P_3-enriched basolateral domain where furrowing initiates? Addressing these fascinating issues requires reliable probes that allow detection of the dynamic localization of specific lipids or glycolipids during mitosis in combination, for example, with optogenetic tools that are able to inactivate gene products in a defined temporal and spatial manner (Idevall-Hagren et al., 2012).

A role for adherens junctions in cleavage furrow progression

As described above, the plasma membrane composition differs along the apical-basal axis and, very probably, in the furrowing membrane, thus raising the question of how is furrowing progression in epithelial cells spatially controlled? In isolated cells or epithelial cells that divide orthogonally to the plane of the epithelium, i.e. when the contractile ring does not bisect the adherens junction belt during cytokinesis, the actomyosin ring is assumed to typically contract in a symmetric manner, termed 'symmetric furrow ingression' (Founounou et al., 2013). However, symmetric furrowing might not be the rule. For example, in isolated cells that remain adhered to the substratum throughout cell division, furrowing is asymmetric (Fishkind and Wang, 1993). A more physiological example is that of the contractile ring of the *Caenorhabditis elegans* zygote, which follows a symmetry-breaking mechanism, promoting 'asymmetric furrowing' (Maddox et al., 2007; Tse et al., 2012). Similarly, epithelial cytokinesis is generally characterized by an initially unequal ingression of the cleavage furrow along the apical-basal axis when the cell divides parallel to the plane of the epithelium, i.e. when the contractile ring bisects the adherens junction belt. From here on, we will focus on this type of planar epithelial cell division. In most cases, unequal ingression (or 'asymmetric furrowing') proceeds from the basal to the apical membrane, such as in MDCK cells that are grown as a monolayer (Reinsch and Karsenti, 1994), cultured hepatocytes (Kojima et al., 2001), as well

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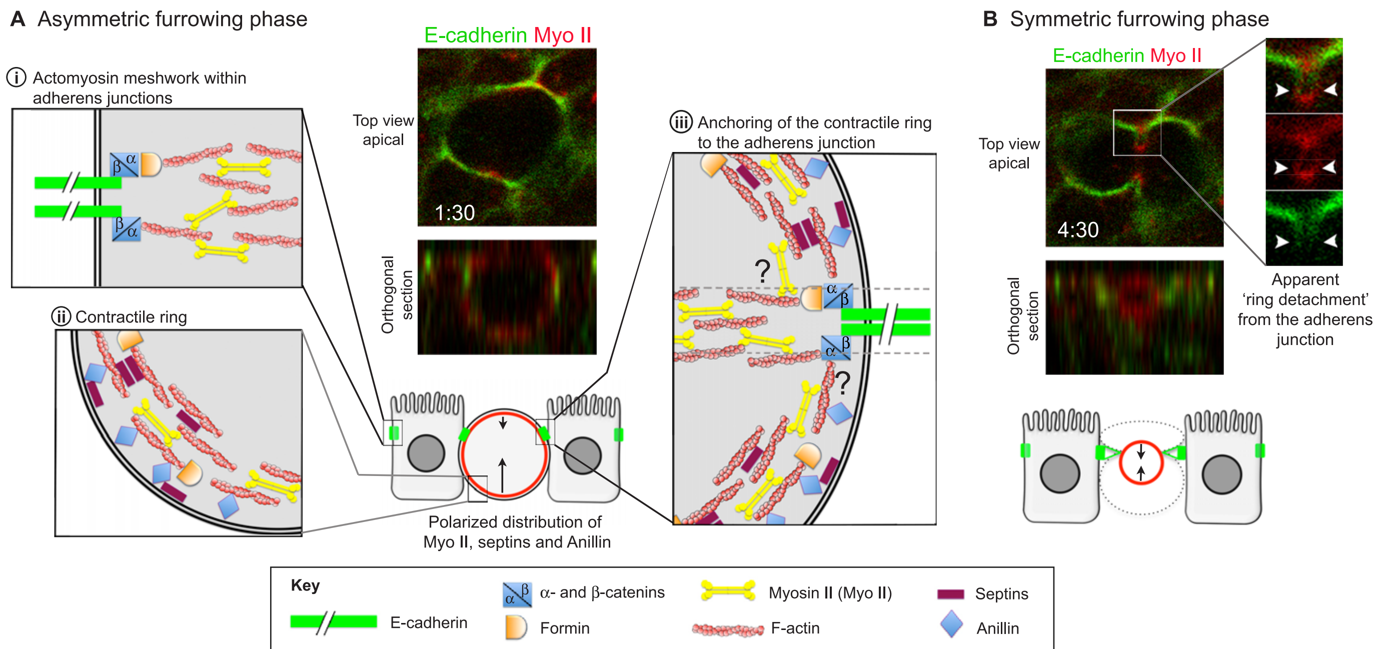

Fig. 2. Role of adherens junctions in cleavage furrow progression and ring anchoring. Illustrated here is a two-phase model for cleavage furrow progression in epithelial cells. (A) Asymmetric furrowing phase. As shown in the images of the pupal notum in the middle, the initial constriction is asymmetric and the contractile ring (*MyoII*::MyoII–mCherry, red) remains associated with the adherens junction belt (E-cadherin–GFP, green) 1 min 30 s after the start of contractile ring constriction. Image courtesy of N. Founounou; reproduced with permission from Elsevier (Founounou et al., 2013). (i) Schematic illustration of adhesive contacts between cells that are supported by adherens junctions and mediated by adhesion molecules, such as E-cadherin (green), which links the actin cytoskeleton through β- and α-catenins. α-catenin is important for recruiting and organizing a meshwork of cytoskeletal proteins, including F-actin filaments and formins, which are involved in the polymerization of actin and Myo II mini-filaments (Kobielak et al., 2004). This cortical meshwork is confined within the plane of the adhesive belt. (ii) Schematic illustration of the contractile ring as a network composed of F-actin filaments, Myo II filaments, septin filaments and the crosslinker Anillin (see also Box 1). Based on their ability to bind phosphoinositides and to bundle actin filaments (Mavrakis et al., 2014), septins are shown here at several locations within the contractile ring. (iii) Hypothetical modes of anchoring the contractile ring to the adherens junction belt. Whether the two actomyosin networks actually mix or not is an open question. It is conceivable that the two meshworks connect through the binding of F-actin to α-catenin and/or the binding of Myo II mini-filaments to F-actin. As the initial apical and basal rates of contractile ring constriction differ and correlate with the polarized distribution of Myo II, septins and Anillin, we propose that the ring anchors to the adherens junctions, but behaves as two hemi-rings with distinct constrictive properties. (B) Symmetric furrowing phase. As the ring constricts, live imaging reveals an apparent detachment of the contractile ring (*MyoII*::MyoII–mCherry, red) from the belt of adherens junctions (E-cadherin–GFP, green; arrowheads point to the apparent ring detachment). This step coincides with the disappearance of the polarized distributions of Myo II, septins and Anillin, and symmetric furrowing. The image was taken 4 min and 30 s after the start of contractile ring constriction. Image courtesy of N. Founounou; reproduced with permission from Elsevier (Founounou et al., 2013).

as *in vivo* in mouse intestine (Fleming et al., 2007; Jinguji and Ishikawa, 1992) and vertebrate neuroepithelium (Das et al., 2003; Dubreuil et al., 2007; Kosodo et al., 2004). More recently, asymmetric furrowing has also been observed in *Drosophila* ovary follicular epithelium (Morais-de-Sá and Sunkel, 2013a), embryo ectoderm (Guillot and Lecuit, 2013a) and pupal notum (Founounou et al., 2013; Herszterg et al., 2013). This basal-to-apical asymmetric furrow ingression results in the apical positioning of the midbody (Figs 1, 2). Although additional means of positioning the midbody apically can also be achieved through apical extrusion in the absence of asymmetric furrowing (Herszterg et al., 2013), apical positioning has been shown to result from unequal furrow ingression in most of the cases that have been reported so far (Founounou et al., 2013; Guillot and Lecuit, 2013a; Herszterg et al., 2013; Le Page et al., 2011; Morais-de-Sá and Sunkel, 2013a; Reinsch and Karsenti, 1994). In the *C. elegans* zygote, asymmetric furrowing relies on septins and Anillin-1, which organize an asymmetric contractile ring structure (Maddox et al., 2007). In *Drosophila* epithelial cells, time-lapse analysis has revealed that the apical versus basal composition of the contractile ring, with regard to Myo II, septins and Anillin, changes throughout cytokinesis (Founounou et al., 2013; Guillot and Lecuit, 2013a; Morais-de-Sá and Sunkel, 2013a). However, despite the transient polarized distribution of these factors and the fact that septins and Anillin regulate the rate of actomyosin contraction, they are dispensable for unequal furrow ingression in *Drosophila* (Founounou et al., 2013; Guillot and Lecuit, 2013a; Herszterg et al., 2013; Morais-de-Sá and Sunkel, 2013a). Thus, how is asymmetry achieved in these epithelial cells? Interestingly, the contractile ring remains closely associated with apically localized adherens junctions (Guillot and Lecuit, 2013a; Morais-de-Sá and Sunkel, 2013a). In epithelial cells of the *Drosophila* embryo ectoderm (Guillot and Lecuit, 2013a) or follicular epithelium (Morais-de-Sá and Sunkel, 2013a) that have mutations in the gene encoding β-catenin or that have been depleted of E-cadherin or α-catenin, furrow ingression becomes symmetric, leading to the notion that adherens junctions are essential for asymmetric furrowing. This notion is further supported by the observation that the polarized assembly of adherens junctions in otherwise non-epithelial, non-polarized *Drosophila* S2 cells is sufficient to recruit the midbody to the site of adherens junctions components (Morais-de-Sá and Sunkel, 2013a). Thus, adherens junctions contribute to

asymmetric furrowing, raising the question of how the contractile ring anchors to and ultimately bisects the adherens junction belt.

Anchoring the contractile ring to the adherens junction belt

During cytokinesis, at the level of the adhesive belt, two distinct contractile actomyosin meshworks coexist. The first one is organized by adherens junctions and lies within their plane (Fig. 2Ai), whereas the second meshwork is the cytokinetic contractile ring that is positioned orthogonally to the plane of the adherens junction belt (Fig. 2Aii). Because these two contractile meshworks differ in their composition, how are they able to connect (Fig. 2Aiii)? Time-lapse analysis and quantitation of the parameters of ring constriction have revealed that, in epithelial cells of *Drosophila* pupal notum, furrowing proceeds in two phases. In the first phase (Fig. 2A), furrow ingression is asymmetric from the basal to the apical surface and ultimately leads to apical positioning of the midbody. During this phase, the apical and basal domains of the contractile ring differ in protein composition, as judged by the polarized distribution of Myo II, septins and Anillin (see above), and in their rates of constriction. This gives the impression of two hemi-rings that are anchored to and separated by adherens junctions. Interestingly, in the developing *Drosophila* male germline (an example of incomplete cytokinesis) in the absence of Anillin and/or septins, an E-cadherin–catenin complex, owing to its ability to bind to actin filaments (Desai et al., 2013; Hartsock and Nelson, 2008; Weis and Nelson, 2006), is able to substitute for Anillin and/or septins in order to locally anchor the contractile ring (Goldbach et al., 2010). By analogy, we propose that the adherens junction belt anchors the contractile ring through α-catenin (Fig. 2Aiii). This local change in the mode of anchoring at the level of adherens junctions would contribute to separating the intrinsic properties of the apical and basal domains of the contractile ring, thereby participating in asymmetric furrow ingression.

By contrast, during the second phase of furrow progression that initiates concomitantly with the ‘apparent’ localized loss of E-cadherin (Founounou et al., 2013), the contractile ring becomes homogenous in the protein composition and the rate of constriction, resulting in an apparently symmetric furrow ingression (Fig. 2B). This results in a midbody that is eventually positioned below the adherens junction belt (Founounou et al., 2013; Herszterg et al., 2013).

Finally, as furrowing proceeds, a new adhesive interface between daughter cells is generated, raising the question of how the coupling between furrowing and the formation of new adherens junction complexes is orchestrated and synchronized, which we will address below.

Generating a new adhesive interface

The formation of new adherens junctions between daughter cells requires the disengagement of E-cadherin complexes between mitotic and neighbouring cells at the cleavage furrow before the assembly of new E-cadherin complexes at the nascent daughter–daughter interface. However, the dividing cell is under the physical constraints of its neighbours and thus subject to multiple tensile forces. Although recent studies in *Drosophila* have shed light on the mechanical coupling between a dividing cell and its neighbours during cytokinesis (Founounou et al., 2013; Guillot and Lecuit, 2013a; Herszterg et al., 2013; Morais-de-Sá and Sunkel, 2013a), an important unsolved question concerns the timing and molecular mechanisms that underlie the disengagement of adherens junctions. A model, based on *anillin* and *septin* mutant phenotypes, suggests that junction disengagement is induced by the tensile forces that are mediated by the contractile ring, which need to reach a certain threshold to overcome the adhesive strength between mitotic cells and their neighbours (Founounou et al., 2013; Guillot and Lecuit, 2013a). In the *Drosophila* embryonic ectoderm, this adherens junction disengagement results in physical separation and the formation of a ‘hole’ between the mitotic cell and its neighbours at the edge of the furrow (Fig. 3B″) (Guillot and Lecuit, 2013a). However, in pupal notum epithelium, cohesion of membranes between mitotic and neighbouring cells appears to be maintained throughout mitosis (Founounou et al., 2013; Herszterg et al., 2013; Jinguji and Ishikawa, 1992). Indeed, concomitant with the cell-autonomous process of ring constriction, neighbouring cells exert an extrinsic tension, as shown by the accumulation of Myo II in the immediately adjacent cells on both sides of the nascent interface in alignment with the adherens junction belt (Fig. 3A) (Founounou et al., 2013; Herszterg et al., 2013). Before the juxtaposition of the daughter cell membrane during symmetric furrowing, the membranes of neighbouring epidermal cells withdraw from the interface in between the daughter cells, leading to a decrease in E-cadherin levels; however, actin polymerization takes place in the vicinity of this interface and the midbody (Fig. 3B) (Founounou et al., 2013; Herszterg et al., 2013). The molecular basis of the decrease in E-cadherin levels is currently unknown. Several hypotheses can be posed. First, a reduction in the amount of E-cadherin could be linked to the supply of new membrane components through vesicular trafficking within the ingressing membrane which, in the absence of the delivery of new E-cadherin, would result in a dilution of E-cadherin staining. Alternatively, local degradation of E-cadherin through, for example, Hakai-mediated ubiquitylation and the subsequent degradation could account for the decrease (Fujita et al., 2002). Finally, the decrease in E-cadherin staining could be due to its localized endocytosis within the ingressing membrane. In support of this latter hypothesis, endocytosis of E-cadherin has been shown to occur in mitotic cells (Bauer et al., 1998) and, in *Drosophila*, found to be initiated through activation of RhoGEF2, the formin protein Diaphanous and ROCK (Levayer et al., 2011), all of which are localized in the contractile ring.

Following this, the formation of new adherens junctions begins a few minutes after the juxtaposition of the dividing cell membrane (Fig. 3C), and the neighbouring cells actively control the length of the newly formed adhesive interface by exerting a mechanical force on it. Indeed, Myo-II–ROCK-dependent activity is responsible for the juxtaposition of the dividing cell membrane and thus the length of the new junction (Herszterg et al., 2013). In the case of this pupal notum epithelium, it remains unknown whether disengagement of the junctions occurs during furrow ingression, when E-cadherin levels are decreasing, or at a later stage, when the two membranes are closely juxtaposed (Fig. 3B,C). If tensile forces are indeed needed for adherens junction disengagement, they have to be oriented relative to the nascent plasma membrane and/or neighbouring plasma membranes, which requires pulling forces. A study using *ex vivo* cells that express E-cadherin has shown that the pulling forces which are required to separate two cells are in the range of 50–200 nN (Chu et al., 2004). By contrast, the force required to separate E-cadherin monomers or dimers is around 50 pN (Zhang et al., 2009). The range of the pulling forces required to locally

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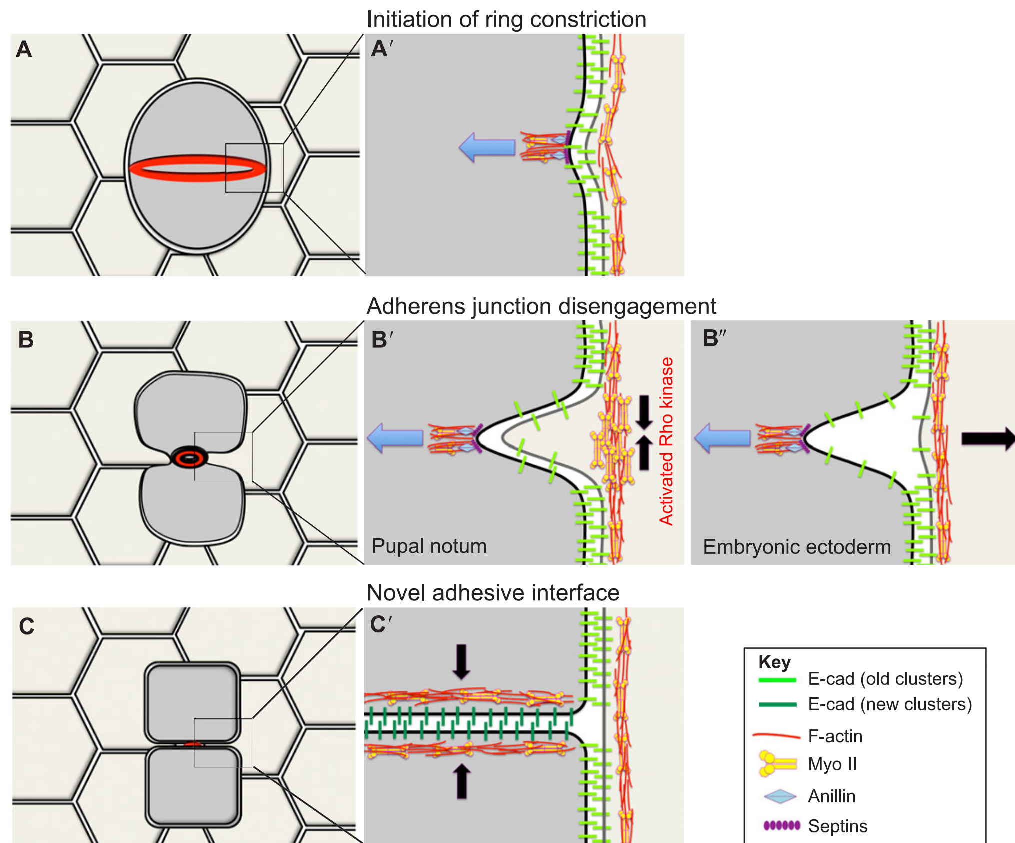

Fig. 3. Adherens junction disengagement and the generation of a new adhesive interface. Illustrated here is cytokinesis of an epithelial cell within the context of its neighbours. Cells are viewed from the top within the plane of the adherens junctions. The zones highlighted in A, B and C are shown enlarged in insets A′, B′–B″ and C′, respectively. (A) At the anaphase-to-telophase transition, the assembled contractile ring (red circle in A, B and C) exerts pulling forces on the neighbouring cells during the initiation of furrowing (blue arrows in A′, B′ and B″). This leads to the local activation of Rho kinase in the neighbouring cell, and the subsequent accumulation of Myosin II (Myo II) at the edge of the furrow (B). Myo II accumulation drives the generation of tensile forces (black arrows in B′) on the ingressing membranes. Formation of new adherens junctions between the daughter cells requires the disassembly of E-cadherin (E-cad, light green) complexes between the mitotic cell and its neighbours at the cleavage furrow (B′ and B″), followed by the assembly of new E-cadherin complexes at the daughter–daughter interface (dark green, C′). It is dependent upon the cellular context as to whether in the areas surrounding the furrow membranes of the dividing and neighbouring cell remain connected through adhesive contacts. In *Drosophila* embryonic ectoderm, the opposing tensile forces exerted by the contractile ring in the dividing cell on one side (blue arrow in B″) and those by the neighbour cell on the other side (black arrow in B″) might bypass the adhesive strength of E-cadherin homophilic interactions, resulting in adherens junction disengagement and the appearance of a gap between the mitotic cell and its neighbour. By contrast, in *Drosophila* pupal notum and mouse intestine, the membrane of the dividing cell remains connected to that of its neighbour (shown in B′); here, the exact timing of adherens junction disengagement is presently unknown. (C) As furrow ingression proceeds and the midbody forms, tensile forces in the neighbouring cells that are induced by Myo II in the dividing cell (black arrows in C′) allow the close juxtaposition of daughter cell membranes, on which new adhesive contacts are eventually formed (dark green).

disengage adherens junctions during cytokinesis is unknown, and whether they are compatible with the pulling forces exerted by the contractile ring is yet to be established. Addressing this issue will require the development of tension sensors, enabling measurement of these forces *in situ*.

En route to abscission – the final cut

Cytokinesis can be subdivided into two main steps, with the first comprising constriction of the contractile ring, and the second comprising abscission, leading to the physical separation of the daughter cells. As constriction of the actomyosin contractile ring reaches completion, the central spindle and contractile ring mature to form the midbody and midbody ring (see Box 2 for a detailed description). Based on remarkable work in isolated cells, midbody microtubules have been proposed to have a central role in forming a scaffold for the abscission machinery (Fededa and Gerlich, 2012; Agromayor and Martin-Serrano, 2013; Green et al., 2012). This commonly accepted view has recently been revisited in a study in *C. elegans* embryos where abscission proceeds in two phases (Green et al., 2013). First, the formation of an intercellular bridge allows the cytoplasm of daughter cells to be isolated; this is delayed in the absence of septin function. In the second step (the process of abscission), the midbody and midbody ring are released into one of the daughter cells during the following cell division. This second steps relies on septins and the endosomal sorting complex required for transport (ESCRT) machinery. Strikingly, this study also found that midbody microtubules are dispensable for both steps, raising the possibility that the midbody ring itself, but not the midbody microtubules are crucial for abscission, as seen in embryos that have been depleted of the microtubule bundling protein SPD-1 (also known as PRC1 in mammals) (Green et al., 2013). Furthermore, the cell–cell interface between daughter cells remains firmly closed in embryos that lack midbody

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Box 2. Brief overview of midbody composition and abscission

The midbody comprises a densely packed antiparallel microtubule network (Glotzer, 2009; Green et al., 2012) and contains the microtubule cross linker PRC1 (Glotzer, 2009; Walczak and Shaw, 2010), the central spindlin complex comprising the kinesin Mklp1 (also known as KIF23 in mammals) and the Rho family GTPase activating protein (GAP) MgcRacGAP (also known as RACGAP1 or CYK4 in mammals; White and Glotzer, 2012), and the chromosomal passenger complex (CPC), comprising aurora kinase B, inner centromere protein (INCENP), borealin (also known as CDCA8) and survivin (also known as BIRC5) (Carmena et al., 2012). CPC stays associated with the midbody, whereas the central spindlin complex, through the ability of MgcRacGAP to bind to phosphoinositides, is required for the attachment of the midbody to the plasma membrane (Lekomtsev et al., 2012). The midbody ring retains some components of the contractile ring, such as actin filaments, Myo II, septin filaments and anillin (Gai et al., 2011; Hu et al., 2012; Kechad et al., 2012; Madaule et al., 1998). In *Drosophila* S2 cells, the N-terminal domain of Anillin, which binds to both Actin and Myo II, is required for midbody ring integrity, whereas its C-terminal domain, which binds to septin filaments, enables the attachment of the midbody ring to the plasma membrane (Kechad et al., 2012). In mammals, a similar role has been proposed for the C1 domain of the RhoGAP CYK4 (Lekomtsev et al., 2012). Although the respective contributions of the midbody and midbody ring to abscission remains unknown, the midbody is proposed to serve as a platform that allows the recruitment of the abscission machinery, which includes membrane trafficking components that narrow the intercellular bridge (Schiel and Prekeris, 2013) and the ESCRT machinery that promotes the final scission event (Agromayor and Martin-Serrano, 2013; McCullough et al., 2013). In isolated human cells, the ESCRT machinery is recruited through CEP55, which binds to the central spindlin complex in the later stages of cytokinesis. CEP55 also binds to alix (also known as CHMP4A) and ESCRT-I, which in turn recruits ESCRT-III proteins. ESCRT proteins have two main functions in abscission, they recruit the microtubule severing enzyme spastin (Lafaurie-Janvore et al., 2013; Yang et al., 2008) and polymerize to drive membrane scission (Bastos and Barr, 2010; Carlton et al., 2008; Carlton and Martin-Serrano, 2007; Elia et al., 2011; Fabbro et al., 2005; Guizetti et al., 2011; Lee et al., 2008; Morita et al., 2007; Zhao et al., 2006).

microtubules or are depleted of ESCRT proteins or septins (Green et al., 2013; Maddox et al., 2007), whereas these conditions cause defective abscission and multinucleation in isolated mammalian cells (Caballe and Martin-Serrano, 2011; Estey et al., 2010; Mollinari et al., 2005). Thus, at least in worms, redundant mechanisms might contribute to the formation of a stable cell–cell interface and make this cytokinetic mechanism unique. Nonetheless, the lack of a requirement for midbody microtubules in abscission is not specific to nematodes, because in mouse neuroepithelial cells and in *Drosophila* epithelial cells, the disappearance of midbody microtubules is also spatially and temporally uncoupled to abscission. First, electron microscopy studies of cytokinesis in mouse neuroepithelial cells indicate that microtubules are no longer detected in maturing midbodies that are found above the adherens junction belt (Dubreuil et al., 2007). Second, cytoplasmic intercellular bridges, also referred to as ring canals, that connect epithelial daughter cells are devoid of microtubules. Ring canals were discovered decades ago in the germline and somatic tissues of various species, including mammals (Cartwright and Arnold, 1980; Dym and Fawcett, 1971; Fawcett and Ito, 1958; Giorgi, 1978; Greenbaum et al., 2009; Pepling and Spradling, 1998; Ventelä et al., 2003). In the *Drosophila* female germline, ring canals ensure the transfer of an extensive amount of nurse-cell cytoplasm towards the oocyte. In somatic tissues, ring canals can act as direct intercellular channels through which some specific cytoplasmic proteins or protein complexes can diffuse (Airoldi et al., 2011; McLean and Cooley, 2013). In contrast to ovarian ring canals, which remain functional for several days and allow protein equilibration between follicular epithelial cells, in larval epithelia the diffusion capability of ring canals ensues for less than two cell cycles, and no function has been associated with them (McLean and Cooley, 2013). These observations raise the question as to whether ring canals are exclusively found in cells with temporally arrested cytokinesis in order to fulfill a specific function, or whether they are simply intermediates in epithelial cell abscission. In *Drosophila* wing disc epithelia, ring canals are found basal to adherens junctions (McLean and Cooley, 2013), whereas in mouse epithelia, maturing midbodies are located above adherens junctions (Dubreuil et al., 2007). Despite this difference in the final apical-basal positioning, in both cases, ring canals and maturing midbodies are found to be removed from the tensile forces that are induced by the adherens junction belt. This topology might be essential for the completion of abscission as a recent study has shown that a local reduction in tension is required to trigger recruitment of the ESCRT-III complex and abscission in isolated human cells (Lafaurie-Janvore et al., 2013). As loss of ESCRT-III can also cause multinucleation in *Drosophila* follicular epithelium (Vaccari et al., 2009), it would be interesting to monitor midbody maturation leading up to abscission and to investigate the dynamics of ESCRT-III localization in epithelial cells *in vivo*.

The process of abscission results in midbody remnants that are cellular debris and that have been proposed to regulate cell fate determination in various developmental contexts, including maintenance of stem cell identity, cellular reprogramming and tumourigenicity (reviewed by Chen et al., 2013; Schink and Stenmark, 2011). Nonetheless, *Drosophila* male germline stem cells exclude the midbody ring, whereas female germline stem cells inherit it. Thus, at least in *Drosophila* germline lineages, which are a stereotypical example for asymmetric inheritance of midbody rings, they are not dictating stem cell identity (Salzmann et al., 2014). Although the possible functions outlined above are based primarily on correlative evidence, recent work in *C. elegans* embryos has directly revealed that the asymmetric positioning of midbody remnants mediates part of the dorso-ventral axis formation (Singh and Pohl, 2014). In spite of this latter direct evidence, midbody remnants are also found to be released into the extracellular medium, to occur in interfaces between non-daughter cells and to be taken up by phagocytes for degradation in worms (Chai et al., 2012) or by adjacent cells in vertebrates (Crowell et al., 2014). Finally, in early *C. elegans* embryos, the stereotypical partitioning of midbody remnants that relies on antero-posterior polarity cues, appears to be dispensable for development (Ou et al., 2014). In conclusion, although the partitioning of midbody remnants is not random, their signalling function in given cellular contexts is still highly debated and awaits direct demonstration.

Cell–cell signalling at the new membrane interface

Although the role of midbody remnants in cell fate determination remains controversial, over the past few years it has become clear

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that cytokinesis, by generating a new cell–cell interface, opens a spatiotemporal window that enables and/or biases cell–cell communication. Probably one of the best examples is the differential activation of the Notch signalling pathway following cell division of the sensory organ precursor (SOP) in *Drosophila* pupal notum (Fig. 4) (Hartenstein and Posakony, 1989; Hartenstein and Posakony, 1990). SOPs divide asymmetrically along the antero-posterior axis to produce an anterior pIIb cell and a posterior pIIa cell (Gho and Schweisguth, 1998; Schweisguth et al., 1996). Cell fate acquisition relies on the differential activation of the transmembrane receptor Notch through its ligand Delta; Notch is activated in the pIIa cell and inhibited in the pIIb cell by Numb, which, in turn, is unequally inherited by this cell during mitosis (Cotton et al., 2013; Couturier et al., 2013; Couturier et al., 2012; Frise et al., 1996; Guo et al., 1996; Rhyu et al., 1994). Furthermore, Notch and Delta are internalized into a subset of multivesicular endosomes, marked with Smad anchor for receptor activation (Sara), which unequally partitions into the pIIa cell during cytokinesis (Coumailleau et al., 2009). In the discussion below, we will concentrate only on the Delta–Notch signalling at the newly formed daughter cell interface.

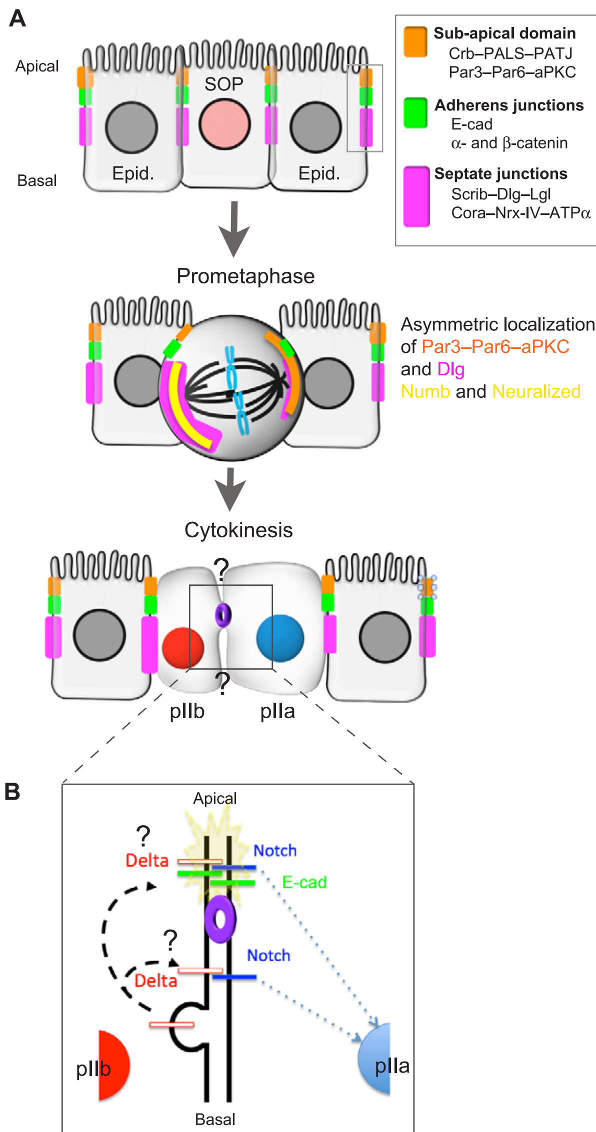

Fig. 4. Signalling at the newly formed interface of sensory organ precursor daughter cells. (A) Sensory organ precursors (SOPs) of the *Drosophila* notum divide asymmetrically, and cell fate acquisition relies on the differential activation of Notch in the pIIa cell (containing the blue nucleus) by the ligand Delta present in the pIIb cell (containing the red nucleus). The unidirectional manner of Notch signalling is partially regulated by the Notch inhibitor Numb and by Neuralized, which promotes basal-to-apical transcytosis of Delta. Both cell fate determinants localize to the anterior cortex of the dividing SOP, the cell polarity of which switches from apical-basal to antero-posterior during mitosis; the septate junction marker Dlg becomes enriched at the anterior lateral cortex, whereas the apical markers Par3, Par6 and aPKC are enriched at the posterior lateral cortex. (B) During cytokinesis, interaction between Notch and Delta might be initiated at the newly formed adherens junction and/or at the basolateral interface. aPKC: atypical protein kinase C; Cora: Coracle; Crb: Crumbs; Dlg: Discs large; E-cad: E-cadherin; Lgl: Lethal (2) giant larvae; Nrx-IV: Neurexin IV; PATJ: protein associated with tight junctions; Scrib: Scribble. Anterior is to the left and posterior to the right. Epid., epidermal cells. Purple ring represents the contractile ring. The yellow shape represents the actin-rich structure located above the midbody (Rajan et al., 2009).

Recent elegant work that made use of a functional green fluorescent protein (GFP)–Notch construct revealed that Notch signalling is initiated at cytokinesis (Couturier et al., 2012). During cytokinesis, Notch resides transiently at the apical interface, above the midbody, between the pIIa cell and pIIb cell, and Notch that has been endocytosed is delivered to the basal cytokinetic furrow. Numb, by regulating the endocytosis of Notch, removes Notch from the plasma membrane of the pIIb cell. As a consequence, Notch is exclusively activated in pIIa. Loss of Numb results in the symmetric distribution of Notch along the basal pIIa–pIIb interface, and hence symmetric Notch activation in both SOP daughter cells (Couturier et al., 2012). These data led to a model in which Numb creates an asymmetry in Notch localization along the basal pIIa–pIIb interface in order to regulate binary cell fate choice (Fig. 4B). However, whether Notch signalling is solely initiated at the basolateral interface (Couturier et al., 2013; Couturier et al., 2012) remains an open question. Indeed, Arp2/3 and Wasp control the formation of an actin-rich structure above and at the level of the midbody that is required for Delta trafficking and Notch activation in *Drosophila* SOP (Rajan et al., 2009). The cell fate determinant Neuralized, which is unequally inherited by the pIIb cell at cytokinesis (Le Borgne and Schweisguth, 2003), promotes the basal-to-apical transcytosis of Delta in epithelial cells (Benhra et al., 2010). Furthermore, the new adherens junctions at the apical side have also been proposed to act as a platform for Notch signalling during cytokinesis because Notch accumulates there in SOPs that have been depleted of the clathrin adaptor complex AP-1, and loss of AP-1 results in Notch gain of function (Benhra et al., 2011; Cotton et al., 2013). These data raise the possibility that Notch can also be activated at the apical interface above the midbody (Fig. 4B). Interestingly, SOP polarity is atypically remodelled during mitosis. Indeed, the unequal segregation of Numb requires a SOP-specific partial remodelling of the apical-basal polarity during mitosis, with the septate junction marker Discs large becoming enriched at the anterior lateral cortex and the apical determinant Par3/Bazooka becoming enriched at the posterior lateral cortex (Fig. 4A) (Bellaïche et al., 2001). This raises the possibility of an apical-basal distribution of polarity markers, i.e. apical-basal polarity, along the newly formed pIIa–pIIb interface which interacts with Delta and/or Notch, and hence results in Notch activation. Future studies aimed at analyzing membrane polarity dynamics during cytokinesis of the SOP will

help to decipher the impact of the geometry and polarity of the new adhesive interface on Delta–Notch signalling.

Another example also highlights the interplay between cytokinesis and cell fate acquisition with regards to the role of the nascent adherens junctions. In mouse neuroepithelium, cilia re-synthesis after mitosis takes place just basal to the adherens junctions rather than apical, adjacent to spot-like adherens junctions and is associated with the acquisition of a delaminating basal progenitor cell fate (Wilsch-Bräuninger et al., 2012).

Concluding remarks

By combining non-invasive and quantitative time-lapse confocal microscopy with the genetic dissection of cytokinesis, recent studies in *Drosophila* have paved the way to the understanding of the mechanics of this process in epithelial cells. However, as our knowledge increases, new challenges arise. First at the cellular level, the timing and mechanism of adherens junctions disengagement remains an open question. Being able to measure the tensile forces that operate during adherens junctions disengagement from neighbouring cells and the following formation of new adhesive contacts will help to decipher the respective contributions of the mechanics (pulling forces) and biochemistry (e.g. Ca^{2+}-dependent adhesion, membrane trafficking, protein degradation, etc.) of adherens junction components. Another challenge resides in investigating the remodelling of cell polarity and the transmission of the diffusion barrier (septate or tight junctions) from mother to daughter cells, which ensures the maintenance of tissue integrity. Another exciting challenge lies in proceeding with the molecular dissection of abscission in a tissue that is subjected to tensile forces, as it is known that tension in the intercellular bridge negatively regulates cytokinesis (Lafaurie-Janvore et al., 2013). A comparison between invertebrate (septate junctions that are basal to adherens junctions) and vertebrate (tight junctions apical to adherens junctions) epithelial cell cytokinesis will also be very informative, because in invertebrates, midbody maturation and abscission occurs basally, whereas in vertebrates, they occur apically. Further investigating the role of septate and/or tight junctions in the maturation of the midbody and abscission will also be important.

Finally, another challenge is to understand, at the tissue level, how epithelial cells can sense and decode a given mitogenic signal, sometimes at distance from the source, in order to undergo a given number of cell divisions and to orient these in order to ultimately generate (or repair) a tissue with appropriate size and shape.

Acknowledgements

We thank L. Chesneau, A. Pacquelet, J.-P. Tassan (all of the Institute of Genetics and Development of Rennes, France), T. Lecuit (Institut de Biologie du Developpement de Marseille, France) and M. Montcouquiol (NeuroCentre Magendie INSERM U 862, Bordeaux, France) for critical reading and comments.

Competing interests

The authors declare no competing interests.

Funding

The University of Rennes 1 funds S.L.B.; R.L.B. is funded by core funding from the Centre National de la Recherche Scientifique (CNRS), La Ligue contre le Cancer (Equipe Labellisée), and The National Research Agency (ANR) (Blanc SVSE2 ApiNotch).

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