REVIEW ARTICLE

Patterns in Space: Coordinating Adhesion and Actomyosin Contractility at E-cadherin Junctions

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Abstract

Cadherin adhesion receptors are fundamental determinants of tissue organization in health and disease. Increasingly, we have come to appreciate that classical cadherins exert their biological actions through active cooperation with the contractile actin cytoskeleton. Rather than being passive resistors of detachment forces, cadherins can regulate the assembly and mechanics of the contractile apparatus itself. Moreover, coordinate spatial patterning of adhesion and contractility is emerging as a determinant of morphogenesis. Here we review recent developments in cadherins and actin cytoskeleton cooperativity, by focusing on E-cadherin adhesive patterning in the epithelia. Next, we discuss the underlying principles of cellular rearrangement during Drosophila germband extension and epithelial cell extrusion, as models of how planar and apical-lateral patterns of contractility organize tissue architecture.

Keywords: E-cadherin, contractility, actomyosin, morphogenesis, cell extrusion, tension

INTRODUCTION

Epithelia cells are organized into sheets that form the covering layers of organs such as the colon and mammary gland. This requires cell-cell adhesion, supported notably by the E-cadherin adhesion receptor (Harrison et al., 2011). Coupling of cadherin adhesion to the actin cytoskeleton further reinforced adherenseness (Ratheesh & Yap, 2012; Desai et al., 2013; Hong et al., 2013). Such reinforcement (Ladoux et al., 2010) is essential as epithelial contacts constantly experience mechanical stress during cellular turnover (Toyama et al., 2008; Mao et al., 2013), tissue overcrowding (Farhadifar et al., 2007; Eisenhoffer et al., 2012), and growth factor- (Pollack et al., 1998) or morphogen-induced (Howard et al., 2011) remodeling.

We have long appreciated that association of E-cadherin with the actin cytoskeleton plays an important role in allowing cadherin junctions to resist these mechanical stresses. Of note, E-cadherin adhesion transmits tension to shape the epithelium (Martin et al., 2010; Rauzi et al., 2013; Gomez et al., 2011) and its dysregulation contributes to diseases, such as tumor progression to invasion and metastasis (Rodriguez et al., 2012; Thiery, 2002; Jeanes et al., 2008; Wijnhoven et al., 2000). For many years, this was thought to reflect passive binding of cadherin/catenin complexes to cortical actin filaments, a process that led to stabilization and reinforcement of adhesion. Recent developments indicate, however, that cadherins can also control the dynamics of actomyosin cytoskeleton and can, indeed, support assembly of the junctional cytoskeleton. In this review article we consider the cellular and molecular mechanisms that allow cadherin adhesion to integrate with the contractile actin cytoskeleton. In particular, we draw attention to coordinated patterns of adhesion and contractility that serve to maintain and shape epithelia. We first outline the diversity of E-cadherin adhesion patterning that drives epithelial cohesion, and then discuss molecular and cellular mechanisms that coordinate adhesion and actomyosin contractility. Finally, by comparing the processes of polarized epithelial elongation and cellular extrusion, we delineate how adhesive and contractility patterning determines tissue organization.

E-CADHERIN AS AN ADHESION RECEPTOR

In this review we focus on E-cadherin, the prototypical classical cadherin in epithelia. Like other classical cadherins, E-cadherin is a Type 1 membrane glycoprotein that functions as part of a dynamic membrane-spanning macromolecular complex (Takeichi, 1991; Halbleib & Nelson, 2006). It has an extracellular (EC) domain that is responsible for adhesive recognition, binding to the ectodomains of other E-cadherin molecules presented on neighboring cells (Leckband & Prakasam, 2006; Takeichi, 1991). E-cadherin has five EC domains and forms...
trans adhesive homodimers through its membrane-distal EC1 domains (Harrison et al., 2010). E-cadherin receptors on the same cell surface can also undergo cis-interactions (Harrison et al., 2011). The combination of these trans- and cis-interactions has the capacity to generate lateral arrays of cadherins, forming adhesive clusters. Indeed, disruption of residues that mediate trans-interactions prevents the formation of clusters at cell–cell junctions (Hong et al., 2011) (Figure 1). Lateral clustering may serve to amplify cadherin adhesive strength (Yap et al., 1997), as in vitro studies suggest that individual E-cadherin bonds are relatively weak (Perret et al., 2002). Clustering may then strengthen adhesion by increasing avidity, and these clusters may correspond to the electron-dense puncta identified at adherens junctions (AJ) (Miyaguchi, 2000), although this has yet to be established by immunoelectron microscopy.

On the other side of the plasma membrane, the cadherin cytoplasmic tails interact with the catenins (Desai et al., 2013; Aberle et al., 1996) and a range of proteins that link the cadherin receptor to the cytoskeleton (Kovacs et al., 2002, 2011; Maddugoda et al., 2007; Smutny et al., 2011), cell signaling (Ratheesh et al., 2012; McLachlan et al., 2007; Ren et al., 2009), and trafficking (Bryant & Stow, 2004; Levayer et al., 2011; Fujita et al., 2002). Here we will focus on the actin cytoskeleton.

PATTERNING CADHERIN ADHESION RECEPTORS WITHIN EPITHELIAL CELL–CELL JUNCTIONS

E-cadherin adhesion receptors organize at epithelial cell–cell junctions to form larger-scale structures that are commonly termed AJ. To date, four types of AJ have been described: the Zonula adherens (ZA), Lateral AJ (LAJ), Punctate AJ (PAJ) and also Spot AJ (SAJ). It should be emphasized that these types of junctions have been principally identified based on their morphology. While there is emerging evidence of biochemical differences that may distinguish them (Taguchi et al., 2011), it is likely that they represent a spectrum of ways in which cadherins can undergo lateral organization in the membrane at cell–cell junctions. Further, fundamental adhesion units within all these AJ appear to be clusters of cadherins whose higher-order organization depends largely on the cytoskeleton through a variety of mechanisms. These disparate junctional patterns can then be thought to reflect how the cytoskeleton can organize cadherins within cell–cell contacts.

Zonula adherens

The ZA is typically found in simple polarized epithelia as a dense band of E-cadherin located in the apical region of cell–cell junctions (Miyaguchi, 2000). The ZA was originally identified by electron microscopy as discrete electron-dense regions between cells (Hirokawa & Heuser, 1981; Miyaguchi, 2000; Farquhar & Palade, 1963). By immunofluorescence microscopy it is commonly interpreted to be represented by a ring-like band of E-cadherin (Meng et al., 2008) that, on closer inspection, comprises densely packed E-cadherin clusters (Smutny et al., 2011). In vertebrates, the ZA localizes just basal to the tight junction that is responsible for regulating paracellular permeability. In contrast, the ZA in Drosophila is located apical to the septate junctions, the invertebrate equivalent of vertebrate tight junctions (Meng & Takeichi, 2009).

The concentrated ring of E-cadherin at the ZA lies immediately proximate to the junctional actin cytoskeleton that is distinguished by the presence of dense bundles oriented parallel to the ZA (Kovacs et al., 2011; Yonemura, 2011). The requirement for this junctional cytoskeleton has been demonstrated in many experiments across different model systems, where dispersion of the E-cadherin clusters at the ZA occurred when the junctional cytoskeleton was perturbed with laser nanoscissors (Cavey et al., 2008), acute exposure to hepatocyte growth factor (Mangold et al., 2011), or disruption of F-actin regulators found at junctions (Kovacs et al., 2011; Maddugoda et al., 2007; Smutny et al., 2011).

Lateral adherens junctions

Although apical ZA are often prominent features in simple epithelia, especially when analyzed by immunofluorescence microscopy, E-cadherin receptors are also present elsewhere at epithelial cell–cell contacts. Cross-section of mammalian tissues such as the rat colonic crypt revealed that cadherin–catenin adhesion complexes distribute throughout the apico–lateral region of cell–cell...
contacts (Larsson, 2006). Distribution of E-cadherin adhesive clusters below the ZA and throughout the lateral junctions is also evident in primary (Vaezi et al., 2002) and transformed cell lines (Kametani & Takeichi, 2007). In primary keratinocytes and Caco-2 cells (Figure 2), lateral AJ form after the apical AJ has assembled (Vaezi et al., 2002). Following initial contact, rho-associated protein kinase (ROCK)-dependent cortical contractility (Zhang et al., 2005) promotes the gradual formation of actin-rich lateral contacts that protrude downwards in an apical-to-basal direction. Lateral AJ then appear as the lateral interface expands (Figure 2), suggesting that assembly of lateral AJ coincides with, and may contribute to, growth in cell height (Vaezi et al., 2002).

Lateral E-cadherin clusters are often dynamic (Kametani & Takeichi, 2007; Vaezi et al., 2002; Hong et al., 2013). In transformed cells, lateral cadherin clusters flow in a basal-to-apical direction (Kametani & Takeichi, 2007; Hong et al., 2010), a process that involves an α-catenin-mediated interaction with linear F-actin cables that are also oriented in a basal-to-apical direction. Myosin II activity is responsible for the F-actin flow (Zhang et al., 2003; Kametani & Takeichi, 2007). As cadherin flow was most evident in transformed cells, Kametani and Takeichi (2007) proposed that it might represent a cell–cell contact sliding mechanism for cellular locomotion in cancer metastasis. Consistent with this idea, cadherin flow was only observed in untransformed MDCK cultures when collective cell migration was initiated during wound healing (Kametani & Takeichi, 2007), but not seen in confluent cultures.

**Punctate adherens junctions**

PAJ have been described as sites of nascent contact where spots of concentrated E-cadherin are linked to linear F-actin bundles oriented towards the plasma membrane (Yonemura, 2011; Taguchi et al., 2011; Twiss et al., 2012). As cell contacts first assemble, multiple E-cadherin clusters appear along the newly forming contact and rapidly associate with small bundles of actin filaments arrayed perpendicular to the plasma membrane (Vasioukhin et al., 2000) (Figure 3a). The density of PAJs increases as contacts lengthen, through the formation of new PAJ at the edges of the contacts (Yamada & Nelson, 2007) (Figure 3b). The subsequent increase in E-cadherin density at junctions helps to establish the ZA. This coincides with a reorganization of the actin cytoskeleton, with bundles becoming oriented parallel to the cell–cell contacts. Additionally during wound closure, contraction of multiple PAJ together coincides with recruitment of the actin-binding protein, epithelial protein lost in neoplasm (EPLIN) (Taguchi et al., 2011), which is thought to reinforce the coupling of E-cadherin to the actin cytoskeleton. This leads to the closure of the wound (Abe & Takeichi, 2008) and also contributes to formation of the relatively immobile ZA (Taguchi et al., 2011).

**Spot adherens junctions**

SAJ were first described in Drosophila embryos as patches of closely apposed membranes found in the early and mid stages of embryonic development (Tepass & Hartenstein, 1994). Subsequent immunofluorescence analysis revealed that they correspond to prominent spots of DE-cadherin that exist within the apical-most region of cell–cell contacts (Cavey et al.,

![Figure 2](image-url) E-cad clusters distribute laterally during heightening of cell–cell contacts. (a) Initial contact formation. (b) Distribution of E-cadherin clusters laterally during lateral expansion of cell contacts forming the LAJ. (c) LAJ formation in E-cad-GFP expressing Caco-2 cells with endogenous E-cad depleted.

![Figure 3](image-url) Initial contact formation process. (a) Formation of PAJ upon initial contact of two cells. (b) Increase PAJ density to establish the Zonula Adherens.
During and shortly after gastrulation, SAJ become concentrated at apical cell–cell junctions and subsequently fuse into the continuous ZA in the posterior endoderm and the ectoderm (Tepass & Hartenstein, 1994). However, even after fusion, discrete, high-intensity foci of transgenically expressed DE-cadherin-GFP can be identified within the ZA (Cavey et al., 2008). These correspond to stable foci of cadherin, as analyzed by FRAP (Fluorescence recovery after photobleaching), that contrast with the more rapidly turning over cadherin population found elsewhere within the ZA. Strikingly, these SAJs persist at junctions even after inhibition of F-actin polymerization by Latrunculin A, whereas the rest of the ZA was lost. This led to the concept that DE-cadherin might be organized at junctions through two distinct F-actin pools: a latrunculin-resistant pool that stabilized adjacent SAJs and a second dynamic population that constrained lateral movement of SAJ (Cavey et al., 2008; Sako et al., 1998). Interestingly, latrunculin-resistant foci of F-actin can also be found at vertebrate epithelial cell–cell junctions (Tang & Brieger, 2012), suggesting that these stable F-actin foci may not be confined to Drosophila.

BUILDING A CONTRACTILE APPARATUS AT CADHERIN JUNCTIONS

As we have seen, in their various junctional guises E-cadherin adhesion receptors are closely associated with, and influenced by, the actin cytoskeleton. This functional cooperativity arises from at least three processes: physical associations between cadherin molecular complexes and actin filaments; active regulation of junctional actin assembly at cadherin junctions; and the junctional recruitment of non-muscle Myosin II to form a mechanically active actomyosin network that exerts tensile force on adhesion.

Binding cadherin complexes to cortical actin: the role of α-catenin?

Junctional organization and, indeed cadherin adhesion itself, require an intact actin cytoskeleton. Such a physical association would also seem to be necessary for classical cadherins to generate junctions that can resist mechanical stress. Decades of research have focused on addressing whether cadherins interact with actin filaments and, if so, how this may occur. For many years, a favored model postulated that α-catenin mediates stable association between the cadherin–catenin complex and the actin cytoskeleton (Rimm et al., 1995; Torres et al., 1997; Kofron et al., 1997; Hinck et al., 1994; Ozawa & Kemler, 1992). This was substantially based on the demonstration that purified α-catenin can bind to, and bundle, F-actin (Rimm et al., 1995).

Our confidence in this model was disrupted by the demonstration that a simple quaternary complex could not be reconstituted in vitro (Drees et al., 2005; Yamada et al., 2005). These studies demonstrated that recombinant α-catenin bound to β-catenin as a monomer and showed high affinity for F-actin only as a homodimer (Drees et al., 2005). As the β-catenin binding site and homodimerization domain of α-catenin overlap, this suggested that β-catenin and F-actin could not interact simultaneously (Pokutta & Weis, 2000; Koslov et al., 1997; Yamada et al., 2005; Drees et al., 2005). It was postulated instead that binding to β-catenin might serve to concentrate α-catenin at junctions, thereby promoting α-catenin dimerization upon dissociation from the cadherin/catenin complex (Drees et al., 2005). Although this provided a molecular basis for the dynamic regulation of junctional actin, it did not provide a straightforward explanation of how the actin cytoskeleton enables adhesion to resist and transmit tensile forces.

This question was then addressed in Drosophila embryos, where, as mentioned earlier, DE-cadherin was thought to exist both as a monomeric population and a clustered population (SAJ) (Cavey et al., 2008). Interestingly, depletion of α-catenin increased the lateral movement of cadherin clusters in the plane of the membrane, but did not overtly affect clustering itself. Further, nanoblot of cortical actin revealed that this increase in lateral movements might reflect the failure of E-cadherin clusters to tether to the actin cytoskeleton when α-catenin was depleted (Cavey et al., 2008). This suggested that α-catenin could mediate physical linkages between cadherins and cortical actin. One possibility was that these were of low affinity, difficult to detect in vitro, but amplified when cadherins were organized into larger scale structures such as clusters. More recently, detailed structure–function analysis of Drosophila α-catenin showed that a cadherin/α-catenin chimera was capable of substantially rescuing an α-catenin knockdown phenotype (Desai et al., 2013), consistent with earlier studies in Drosophila (Sarpal et al., 2012; Pacquelet & Rorth, 2005) and in tissue culture systems (Yonemura et al., 2010; Nagafuchi et al., 1994; Imamura et al., 1999; Kametani & Takeichi, 2007). This suggested that, although α-catenin can affect other aspects of cellular behavior independently of cadherin adhesion (Schlegelmilch et al., 2011; Benjamin et al., 2010), it plays a major role in cadherin biology by coupling E-cadherin receptors to the actin cytoskeleton.

However, it is unlikely that α-catenin is the only mechanism that can physically link cadherins to the actin cytoskeleton. A range of other actin-binding or actin-regulatory proteins have been identified at junctions. These include molecules such as EPLIN (Abe & Takeichi, 2008), Myosin VI (Mangold et al., 2012, 2011), Arp2/3 (Kovacs et al., 2002), and formins (Kobiljak et al., 2004; Carramusa et al., 2007). Together, these suggest that the functional cooperation between cadherins and the actin cytoskeleton is not just a product of physical association through one mechanism. Instead it may reflect a dynamic, versatile molecular apparatus that...
can associate with, but also regulate, the junctional cytoskeleton. To explore these possibilities, we now review the regulation of actin at cadherin junctions.

**Regulation of junctional actin dynamics**

Actin is synthesized in cells as monomeric globular actin (G-actin), which is an ATPase that self-assembles into polymeric filamentous actin (F-actin) upon binding to ATP (Dominguez & Holmes, 2011). Nucleotide hydrolysis by F-actin is one of the main factors regulating the transition between G- and F-actin. Actin filament nucleation represents a key rate-limiting step in actin assembly as the initial formation of dimers and trimers is energetically unfavorable; but once nucleated, elongation of F-actin is rapid and diffusion-limited (Pollard et al., 2000). In vitro, at physiological concentration, ATP-loaded actin monomers join the fast-growing barbed (or +) end of the filament. ATP hydrolysis takes place in the filament and ADP-actin monomers dissociate faster from the pointed (or −) end. This steady-state mechanism of actin polymerization and depolymerization is known as actin filament treadmilling (Kuhn & Pollard, 2005). However, the intrinsic dynamics of treadmilling are slow and cannot account for the dynamics of filament assembly observed within cells. Hence, numerous actin regulatory proteins are found to be involved in the control of actin cytoskeleton dynamics (Pollard et al., 2000).

Cadherin adhesions, formed by both E-cadherin and N-cadherin receptors, are sites of dynamic actin assembly (Kovacs et al., 2002, 2011; Tang & Brieher, 2012; Verma et al., 2004; Drees et al., 2005; Lambert et al., 2002; Vasioukhin et al., 2000). This has been demonstrated by studies that use incorporation of G-actin to identify sites of actin nucleation (Yamada & Nelson, 2007; Tang & Brieher, 2012) as well as FRAP studies with GFP-actin (Kovacs et al., 2011; Yamada & Nelson, 2007). This implies that cadherin junctions are sites where the ensemble of actin assembly components might be found. Accordingly, here we discuss the various actin regulatory proteins that are implicated in the formation, maintenance, and remodeling of cadherin junctions.

**Cadherin junctions and actin nucleation**

A variety of molecules are now known to be able to catalyze the rate-limiting step of actin nucleation. Of these, the Arp2/3 complex and formins, have been identified at cadherin junctions. Formins are a family of related proteins that share highly conserved formin homology (FH1 and FH2) domains (Liu et al., 2010). Formins nucleate new filaments and remain associated with their growing ends, where they cooperate withprofilinin to promote monomer addition and rapid elongation of long, unbranched filaments (Chesarone et al., 2010) such as those found in stress fibers (Watanabe et al., 1999). Of this family, both formin-1 (Kobiela et al., 2004) and mDia1 (Carramusa et al., 2007) have been implicated in E-cadherin junctions, being thought to promote linear actin cable assembly to support E-cadherin cell–cell contact integrity. Furthermore in Drosophila embryos, the formin diaphanous assemblies the apical actin network that connects the medioapical actin network to junctional actin filaments and also confines E-cadherin at junctions (Mason et al., 2013). Overexpression of constitutively-active formin transgenes in Drosophila can also further restrain the lateral movement of E-cadherin clusters in early embryonic epithelia (Cavey et al., 2008).

Together, these findings identify roles for formins at cadherin junctions, but these may not be the only mechanism for actin nucleation. Indeed, inhibition of formin activity using a broad-spectrum chemical inhibitor (SMIFH2) (Rizvi et al., 2009) did not affect the ability of MDCK cells to reassemble a junctional actin cytoskeleton following treatment with latrunculin (Tang & Brieher, 2012). Instead, Arp2/3 was found to be responsible for junctional F-actin assembly.

The Arp2/3 complex is a seven-protein assembly that nucleates new actin filaments while bound to existing filaments (Pollard, 2007) thus creating branched actin networks (Gournier et al., 2001; Rouiller et al., 2008). Arp2/3 can associate with E-cadherin (Kovacs et al., 2002) and is found both newly forming contacts (Verma et al., 2004; Kovacs et al., 2002; Herszterg et al., 2013) and mature junctions (Kovacs et al., 2011; Bernadskaya et al., 2011). In nascent contacts, Arp2/3 generates protractive membrane activity for cell surface extension between contacting cells (Verma et al., 2004) and in mature E-cadherin junctions Arp2/3 catalyzes F-actin assembly (Kovacs et al., 2011) necessary for contractility to generate junctional tension (Verma et al., 2012). Additionally, Arp2/3-nucleated actin filaments promote de-novo cadherin contact formation during cell division in Drosophila embryos (Herszterg et al., 2013).

**Post-nucleation regulation at cadherin junctions**

Dynamic regulation not only encompasses the stage of filament nucleation, but also includes other events in actin assembly. One example is found at the junctional cytoskeleton of the ZA. As noted above, this is distinguished by prominent actin filament bundles (Kovacs et al., 2011; Yonemura, 2011). Interestingly, junctional bundles require Arp2/3 activity, but Arp2/3 does not localize to the bundles. Instead, it is found at the junctional membrane along with a pool of cortical actin filaments (Kovacs et al., 2011). This suggests that junctional bundles arise from filaments that are nucleated at the membrane, a process that implies that post-nucleation steps of actin assembly may also be regulated. One factor in this process is the actin regulator, N-WASP, which is found at the ZA and is necessary for perijunctional bundles to form. N-WASP is best understood for its capacity to stimulate Arp2/3 activity (Weaver et al., 2002), however at the ZA it appears to act at a post-nucleation step.
to stabilize newly formed actin filaments, thereby allowing their organization into perijunctional bundles. Interestingly, upregulation of N-WASP at the cell cortex can also restrain movement of E-cadherin clusters in the early embryonic epithelia of Drosophila (Cavey et al., 2008), suggesting that it may also affect junctions in flies.

**Building the contractile apparatus**

Non-muscle Myosin II (here myosin for short) is a dominant generator of contractile force in non-muscle cells. Three non-muscle myosins (A–C) are found in vertebrates, whereas only one gene is found in Drosophila and Caenorhabditis elegans (Vicente-Manzanares et al., 2009). Despite this, all are actin-binding proteins that cross-link and contract actin filaments. They exist as heterohexamers, consisting of two pairs each of heavy chains that bear actin-binding head domains and coiled-coil rod (tail) domains, regulatory light chains, and essential light chains that stabilize the heavy chain structure. Myosin II assembles into antiparallel bipolar filaments through interactions between their coiled-coiled domains (Vicente-Manzanares et al., 2009). These filaments then bind to actin through their head domains and the ATPase activity of the head enables a conformational change that moves actin filaments to generate contractile force (Tyska & Warshaw, 2002; Vicente-Manzanares et al., 2009).

A major effect of myosin contractility is the generation of tension on junctional actin networks. However, it is increasingly evident that cortical tension plays an important role in the regulation of the contractile actomyosin apparatus. Tension itself can promote the recruitment and stabilization of Myosin II at junctions (Fernandez-Gonzalez et al., 2009), suggesting that it exists as part of a positive feedback network. One mechanism for this impact of tension may lie in the observation that myosin binds preferentially to pre-stressed actin filaments through interactions between their coiled-coil rod (tail) domains, regulatory light chains, and essential light chains that stabilize the heavy chain structure. Myosin II assembles into antiparallel bipolar filaments through interactions between their coiled-coiled domains (Vicente-Manzanares et al., 2009). These filaments then bind to actin through their head domains and the ATPase activity of the head enables a conformational change that moves actin filaments to generate contractile force (Tyska & Warshaw, 2002; Vicente-Manzanares et al., 2009).

Myosin contractility can also affect the integrity and organization of the actin networks to which it binds. In particular, contractile stresses can disassemble actin networks (Haviv et al., 2008; Ideses et al., 2013). The precise impact of such contractile stress may depend on the precise organization of F-actin. For example, in sarcomeres of skeletal and cardiac muscles, myosin minifilaments segregate toward the pointed ends of F-actin and crosslink at the barbed end. This configuration supports tensile forces only and promotes the organization of actin filaments to produce contraction. However in less organized actomyosin networks, interactions between F-actin and Myosin II can generate local tension and compression. Compressive stresses are relieved through filament buckling and subsequent severing, keeping only tensile forces (Murrell & Gardel, 2012). These patterns of compression and tension ultimately reorganize the actomyosin networks. However, the role of F-actin disassembly by Myosin II remains unknown in many cadherin-mediated processes such as cell–cell intercalation, extrusion, and wound closure (Reymann et al., 2012).

**MORPHOGENETIC IMPLICATIONS OF CONTRACTILE AND ADHESION PATTERNING**

What then are the functional consequences of coupling contractility to E-cadherin adhesion? E-cadherin adhesion couples cells together and resists actomyosin contractility generated at the cell cortex. Ultimately, producing tension at junctions (Fernandez-Gonzalez et al., 2009) that is transmitted across epithelia (Martin et al., 2010). These tensile stresses can be measured from the local recoil at sites of nanoablation (Fernandez-Gonzalez et al., 2009; Verma et al., 2012; Levayer & Lecuit, 2013) and also deduced from planar flows of Myosin II (often in the medio–apical planes of the cells), as revealed by live-cell imaging (Roh-Johnson et al., 2012). The spatial patterning of adhesion and contractility critically influences the morphogenetic outcome of epithelial tissues. Here we discuss how such coordinated patterning influences biological outcomes. We focus on two examples: planar polarized patterning during Drosophila germband extension and apical–lateral patterning during cell extrusion.

**Planar coordination of adhesion and contractility during polarized epithelia elongation: Germband Extension**

As noted above, a number of studies in Drosophila and C. elegans embryos have identified an actomyosin network at the apical poles of cells (often called a medioapical network) that generates pulsatile contractility to drive apical constriction (Martin et al., 2009) when coupled to AJ (Roh-Johnson et al., 2012). A number of morphogenetic events depend critically on dynamic cooperativity between local adhesion and contractility of cells (Levayer & Lecuit, 2012) rather than on external forces on tissue (Bertet et al., 2004) and local tissue growth (Irvine & Wieschaus, 1994).

This is exemplified by germband extension in the Drosophila embryo, where temporal control of cellular contractility at both the medioapical and junctional regions (Rauzi et al., 2010) leads to formation of multicellular rosettes that causes the epithelia covering of embryos to shrink in the dorsal–ventral axis and elongate in the anterior–posterior axis (Bertet et al., 2004; Blankenship et al., 2006) (Figure 4). Rosette formation is also responsible for neural tube closure in chick embryos and convergent extension of xenopus embryo as well (Kim et al., 2010; Nishimura et al., 2012), thus implying that it may be a conserved mechanism of cellular patterning.

Rosette formation entails planar-polarized shrinkage of cadherin junctions, often those with a dorsal–ventral
Figure 4. Model of Polarized Epithelial Elongation: Germband-Extension in Drosophila Embryo. (a) Shrinkage of dorsal–ventral junctions (green arrows) is a critical step in cell–cell intercalation. (b) Direction of polarized epithelial elongation in a drosophila embryo (red arrow). (c) Medioapical actin network anchors on DE-cadherin, where DE-cadherin distribution is planar polarized. Medioapical actomyosin contraction and its planar polarized flow into DV junction stabilize shortened DV junction length.

(DV) orientation (Fernandez-Gonzalez et al., 2009; Blankenship et al., 2006). Such junctional shrinkage reflects flow and contractile activity of Myosin II that is, in turn, influenced by the patterning of cadherin adhesion at junctions (Rauzi et al., 2010). First, contraction of the medioapical actomyosin network pulls upon E-cadherin clusters at AP junctions (Levayer & Lecuit, 2013) to shrink the DV junctions (Rauzi et al., 2010). This is attributed to DE-cadherin’s planar-polarized distribution, being relatively enriched at AP junctions but depleted by endocytosis at the DV junctions (Levayer et al., 2011). This anisotropic distribution of DE-cadherin clusters then causes biased movement of the contractile medioapical network, leading it to flow into the shrinking DV junction (Rauzi et al., 2010) (Figure 4c).

The regulatory influence of cadherin is revealed by the demonstration that overexpression of DE-cadherin throughout junctions reduced the planar-polarized distribution of tension across the medioapical network thus decreasing the flow of medioapical Myosin II into junctions (Levayer & Lecuit, 2013). This reinforces the notion that anisotropic distribution of E-cadherin clusters at AP versus DV junctions is required for generating polarized flow. Local destruction of the medioapical network by laser nanoablation also randomized Myosin II flow into AP, as well as DV, junctions (Levayer & Lecuit, 2013; Rauzi et al., 2010). Taken together, these suggest that the directionality of myosin flow emerged from the interaction between anisotropic E-cadherin distribution and the properties of medioapical actomyosin network. It emphasizes that the planar polarized distribution of adhesion influences the spatial patterns of contractility exerted on junctions and, ultimately, across epithelia (Levayer & Lecuit, 2013).

Dynamic cooperation between junctions and the contractile apparatus is further emphasized by the sequence of events that follow the flow of medioapical myosin toward junctions. A junctional pool of actomyosin is also present in these cells (Fernandez-Gonzalez et al., 2009) and, indeed, the flow of medioapical actomyosin into DV junctions results in its apparent merger with the junctional actomyosin pool. Strikingly, this merging of myosin pools coincides with the stabilization of the shortened DV junction, rather than recoil to its previous length (Rauzi et al., 2010). Thus effective shrinkage of DV junctions appears to involve a ratchet-like process, where successive cycles of medioapical actomyosin contraction and junctional stabilization progressively shorten the junctions. How myosin flow into junctions may stabilize their length remains to be elucidated. One possibility is that myosin may cooperate with other F-actin cross-linking proteins.
found selectively at the adherens junctions, but not in the medioapical cortex, leading to a change in pattern of contractility. Importantly, epithelial elongation requires shrinkage of not just one but most of the DV junctions present in the epithelium (Figure 4a). This apparently involves contractile Myosin II puncta flowing into pairs of DV junctions in an alternating fashion (Levayer & Lecuit, 2013). This alternating flow is attributed to transient asymmetric fluctuations in DE-cadherin levels between pairs of DV junctions that are initiated by alternating E-cadherin endocytosis events. As cadherin endocytosis itself is triggered by entry of medioapical Myosin II puncta flowing into junctions (Levayer & Lecuit, 2013), this further emphasizes how planar polarized adhesion and contractility cooperates to drive germband extension.

**Epithelial extrusion**

In contrast to the planar behaviors seen during germband extension, cell extrusion involves coordination of contractility and adhesion that is patterned in the apico-lateral axis within junctions (Slatum et al., 2009). Extrusion is a process whereby minorities of cells are actively expelled from epithelia. It has been identified to drive the expulsion of apoptotic cells (Rosenblatt et al., 2001; Toyama et al., 2008), minorities of oncogene-expressing cells (Hogan et al., 2009; Leung & Brugge, 2012; Kajita et al., 2010), and also to occur during cellular over-crowding (Eisenhoffer et al., 2012; Marinari et al., 2012). A defining feature is that it is cell non-autonomous (Hogan et al., 2009) and, indeed, involves assembly of an actomyosin apparatus in the neighboring cells that facilitates expulsion to occur (Rosenblatt et al., 2001). The importance of contractility in the neighboring cells is exemplified by studies in the *Drosophila notum*, where cell extrusion is associated with the formation of a prominent contractile Myosin II cable in the neighboring cells that surround the extruding cell. Nanoablation of this actomyosin ring prevented both cell extrusion and extrusion-induced cell death (Marinari et al., 2012). A similar actomyosin ring is reported to assemble within neighboring cells when extrusion occurs in cultured mammalian epithelial cells (Slatum et al., 2009; Rosenblatt et al., 2001). But alterations in cortical contractility may not be confined to the neighboring cells, as cortical tension (Marinari et al., 2012) and contractile pulsations of junctions (Saravanan et al., 2013) were altered in extruding cells compared with non-extruding cells. Together, these suggest that contractile mechanics may be altered in both the presumptive extruding cells and their neighbors to productively force extrusion.

The patterning of adhesion and contractility during extrusion appears to be especially important to influence the direction in which extrusion occurs. Epithelial cells can be expelled either apically or basally, in the former case towards the luminal and in the latter case towards the stromal compartment (Leung & Brugge, 2012; Cagan & Aguirre-Ghiso, 2012). This is likely to be functionally important. For example, apical extrusion of oncogene-expressing cells in the colon may cause these cells to be removed from the digestive tract. In contrast, apical extrusion of equivalent transformed cells in the mammary gland allows them to proliferate in the lumena of glands and ducts (Leung & Brugge, 2012), resembling the histological feature of early-stage carcinoma-in-situ (Burstein et al., 2004) (Figure 5).

![Figure 5](image-url)  
*Figure 5.* Fate of single mutated oncogenic cells (green) within a three-dimensional cyst with a central lumen and surrounded by the extracellular matrix.
Importantly, the direction of extrusion is determined by the localization of the contractile apparatus in the neighboring cells. Active myosin localizes at basolateral region of neighboring cells, leading to constriction in this region, during apical extrusion of the target cell (Slattum et al., 2009). In contrast, during basal extrusion myosin concentrates apically to cause local constriction there (Slattum et al., 2009). Thus, the distribution of active Myosin II determines the direction of the cell extrusion. Further, this apical–lateral patterning of contractility can be regulated by microtubules. In particular, the orientation of dynamic microtubule plus-ends can influence the precise localization of myosin activity (Slattum et al., 2009). Here it is interesting that whereas extrusion commonly occurs in the apical direction in mammalian epithelia, this is reversed when cells are depleted of the tumor-suppressor adenomatosis polyposis coli (APC) gene product (Marshall et al., 2011). APC can bind microtubule plus-ends and also localize to E-cadherin junctions (den Elzen et al., 2009; Rosin-Arbesfeld et al., 2001). APC dysfunction is a major genetic driver in colon cancer but whether its impact on this opens the possibility that tension generated at junctions may feedback to modulate the molecular processes that are responsible for that tension (Fernandez-Gonzalez et al., 2009). Second, we propose that detailed spatial patterning in the coupling of adhesion and contractility is an important parameter that influences its morphogenetic outcome. This is highlighted by planar-polarized cooperativity between cadherin adhesion and contractility in germ band extension of Drosophila. Additionally, apical–lateral patterning of contractility has been suggested to direct extrusion, yet the full extent of this phenomenon remains to be uncovered. Clearly, these are interesting issues for the future.

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