European Journal of Cell Biology 103 (2024) 151410

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Damage control of epithelial barrier function in dynamic environments

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ARTICLE INFO

Keywords:
tight junctions
septate junctions
barrier function
epithelial cells

ABSTRACT

Epithelial tissues cover the surfaces and lumens of the internal organs of multicellular animals and crucially contribute to internal environment homeostasis by delineating distinct compartments within the body. This vital role is known as epithelial barrier function. Epithelial cells are arranged like cobblestones and intricately bind together to form an epithelial sheet that upholds this barrier function. Central to the restriction of solute and fluid diffusion through intercellular spaces are occluding junctions, tight junctions in vertebrates and septate junctions in invertebrates. As part of epithelial tissues, cells undergo constant renewal, with older cells being replaced by new ones. Simultaneously, the epithelial tissue undergoes relative rearrangement, elongating, and shifting directionally as a whole. The movement or shape changes within the epithelial sheet necessitate significant deformation and reconnection of occluding junctions. Recent advancements have shed light on the intricate mechanisms through which epithelial cells sustain their barrier function in dynamic environments. This review aims to introduce these noteworthy findings and discuss some of the questions that remain unanswered.

1. Architecture and molecular components of occluding junctions

1.1. Architecture of tight junctions

Vertebrate epithelial cells have specialized type of occluding junction known as tight junctions (TJs), located just apically to adherens junctions (AJs) (Fig. 1A). In TJs, the plasma membranes of adjacent epithelial cells closely appose to each other, revealing a series of focal contacts or 'kissing points' in ultrathin sections. These focal contacts are considered cross-sections of a continuous belt-like structure, known as TJ strands, which are observed in freeze-fracture replica electron microscopy. TJ strands intricately anastomose, forming a network. The relationship between the TJ strand network structure and barrier function has been discussed elsewhere (Saito et al., 2023). At locations where three cells meet, TJ strand networks from three cell-cell junctions connect to the central sealing element, creating a specialized structure termed tricellular tight junctions (tTJs) (Higashi and Miller, 2017; Bosveld et al., 2018; Higashi and Chiba, 2020). TJs, in conjunction with tTJs, encircle the apical border of the cells, playing a crucial role in contributing to the epithelial barrier function.

1.2. Transmembrane proteins of tight junctions

TJs and tTJs consist of various transmembrane proteins. Among them, claudin family proteins serve as the backbone of TJ strands (Furuse et al., 1998a, 1998b). Claudins play a crucial role in the formation of TJ strands, establishing a permeability barrier for ions and small molecules (Otani et al., 2019). Specific combinations of multiple claudin subtypes, differentially expressed in each epithelial tissue (Mineta et al., 2011; Morita et al., 1999; Tsukita and Furuse, 1999), determine the paracellular permeability of ions and small molecules. The TJ-associated MARVEL protein (TAMP) family, consisting of occludin, tricellulin, and MarvelD3, is also incorporated into TJ strands (Furuse et al., 1993; Ikenouchi et al., 2005; Raleigh et al., 2010; Steed et al., 2009). Occludin is localized at branching points of TJ strands (Van Itallie et al., 2017) and increases the branching points of the TJ strand network in epithelial cells (Saito et al., 2021). Tricellulin shares the branch-forming function with occludin (Cording et al., 2013; Saito et al., 2021) and is required for connecting TJ strands to the central sealing element at tTJs (Nayak et al., 2013; Sugawara et al., 2021). MarvelD3 influences the morphology of the TJ strand network when co-expressed with claudin-1 in fibroblasts (Cording et al., 2013) but does not alter the branching patterns of the TJ strand network in epithelial cells (Saito

Abbreviations: TJ, tight junction; tTJ, tricellular tight junction; SJ, septate junction; tSJ, tricellular septate junction; pSJ, pleated septate junction; sSJ, smooth septate junction; AJ, adherens junction; CAM, cell adhesion molecule; PAC, pre-assembled apical compartment.

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https://doi.org/10.1016/j.ejcb.2024.151410
Received 30 December 2023; Received in revised form 27 March 2024; Accepted 30 March 2024
Available online 3 April 2024
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et al., 2022). Junctional adhesion molecule (JAM)-A belongs to the JAM family of the immunoglobulin superfamily (Martìn-Padura et al., 1998). It has recently been reported that claudin-deficient cells maintain a size-selective barrier for macromolecules, disrupted only in claudin/JAM-A-deficient cells (Otani et al., 2019). Given that claudin-deficient cells also retain close membrane apposition with ~6-nm intervals (Otani et al., 2019), it is likely that JAM-A can create a permeability barrier against macromolecules independently of claudins. Whether other JAM family proteins (JAM-B, JAM-C, JAM-4, ESAM, CAR, CLMP/ASAM, and JAM-L) share this function should be elucidated in future studies. Angulins (angulin-1/lipolysis-stimulated lipoprotein receptor [LSR], angulin-2/immunoglobulin-like domain containing receptor [ILDR] 1, and angulin-3/ILDR2) also belong to the immunoglobulin superfamily, specifically localizing at tTJs of various epithelial tissues and being responsible for barrier maintenance at tTJs (Higashi et al., 2013; Masuda et al., 2011; Sugawara et al., 2021).

1.3. Scaffolding proteins of tight junctions

ZO family proteins (ZO-1, ZO-2, and ZO-3) are scaffolding proteins with multiple domains (Gumbiner et al., 1991; Haskins et al., 1998; Stevenson et al., 1986) and bind to the TJ transmembrane proteins via their PDZ domains. ZO-1 and ZO-2 share essential roles in TJ formation in epithelial cells (Otani et al., 2019; Umeda et al., 2006) and the proper establishment of epithelial polarity (Otani et al., 2019). ZO-3 cannot substitute for the TJ-establishing role of ZO-1/2 (Umeda et al., 2006) and is dispensable for TJ formation in vivo (Adachi et al., 2006; Xu et al., 2008). Cingulin family proteins, cingulin (Citi et al., 1988) and JACOP/paracingulin/cgnl1 (Ohnishi et al., 2004), are localized at TJs by interacting with ZO-1 (Pulimeno et al., 2011; Umeda et al., 2004) and tether myosin-2 cytoskeleton to TJs (Rouaud et al., 2023). Cingulin was reported to be dispensable for barrier function and TJ structure (Guillemot et al., 2012; Maupérin et al., 2023). The evolutionally conserved polarity protein complex PAR-3/PAR-6/aPKC is also localized at TJs and is required for the establishment of epithelial apicobasal polarity (Izumi et al., 1998; Suzuki et al., 2001).

1.4. Architecture of septate junctions

Epithelia of most invertebrates have a different type of occluding junction, called septate junctions (SJs). SJs are observed as a ladder-like structure between adjacent epithelial cells, made up of septa spanning the intercellular space of 15–20 nm in cross-sections. Septa are observed as strands in tangentially cut sections using a tracer impregnation technique. The morphology of the SJ strands varies among phyla and epithelial types (Jonusaite et al., 2016). They can be single or double and pleated or smooth. SJ strands in many species have side projections. In the endodermal tissues of Echinoderm, an anastomosing network of SJ strands was reported (Green et al., 1979). Among many types of SJs, pleated SJ (pSJ) (Fig. 1B) and smooth SJ (sSJ) (Fig. 1C) in *Drosophila* have been most characterized, which are observed in the ectoderm and endoderm, respectively (Izumi and Furuse, 2014). Both pSJ and sSJ are observed as dozens of parallel strands without branching in freeze-fracture replica electron microscopy.

1.5. Transmembrane proteins of septate junctions

SJs contain small four-membrane-path proteins: Megatrachea/pickle (Mega) (Behr et al., 2003), sinuous (Sinu) (Wu et al., 2004), and kune-kune (Kune) (Nelson et al., 2010) in pSJs and snakeskin (ssk) (Yanagihashi et al., 2012) and Tsp2A (Izumi et al., 2016) in sSJs. Other cell adhesion molecules (CAMs) neurexin IV (NrxIV) (Baumgartner et al., 1996), Na/K ATPase (Genova and Fehon, 2003), and fasciclin III (FasIII) (Woods et al., 1997) constitute pSJs and Mesh (Izumi et al., 2012) and FasIII are components of sSJs. Gliotactin (Auld et al., 1995; Schulte et al., 2003), Bark beetle (Bark)/Anakonda (Ana) (Byri et al., 2015; Hildebrandt et al., 2015), and M6 (Zappia et al., 2011; Dunn et al., 2018) are the molecular components of tricellular septate junctions (tSJs).

1.6. Scaffolding proteins of septate junctions

The cytoplasmic side of SJs is associated with many scaffolding proteins, including coracle (Cora) (Fehon et al., 1994), scribble (Scrib) (Bilder and Perrimon, 2000), lethal giant larvae (Lgl) (Strand et al., 1994; Bilder and Perrimon, 2000), discs large (Dlg) (Woods and Bryant,

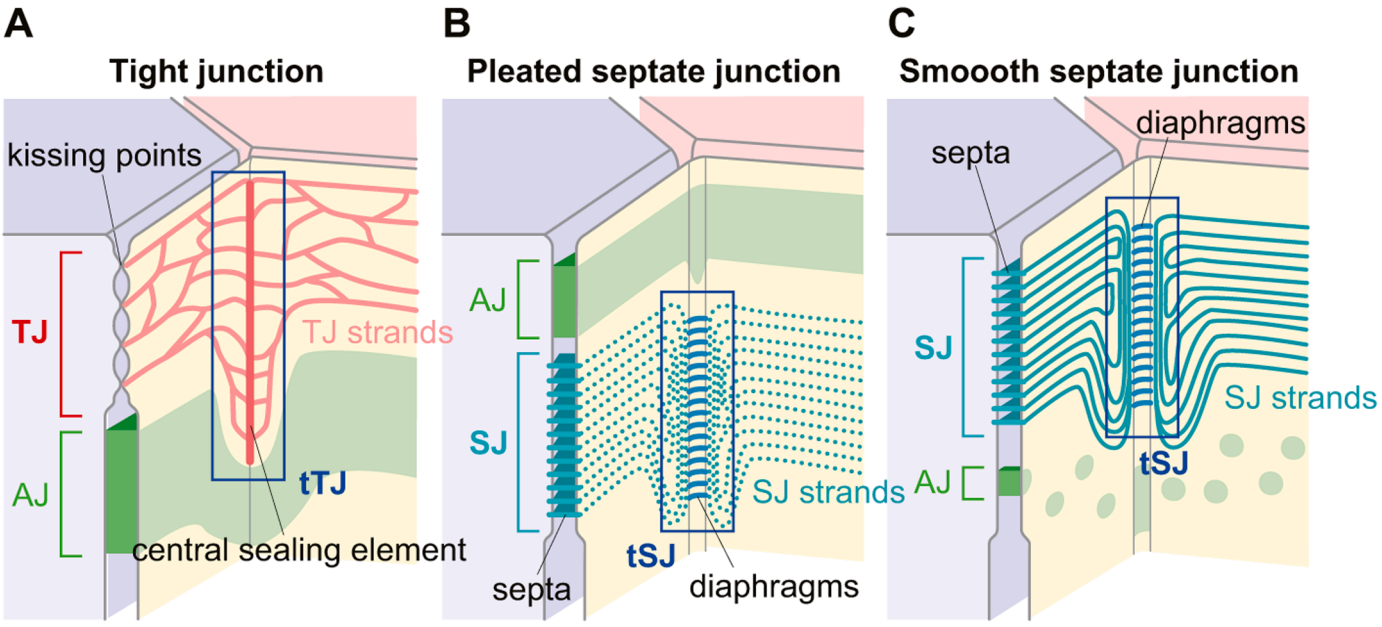


Fig. 1. Architecture of occluding junctions. A-C. Organization of tight junctions in vertebrate epithelium (A), pleated septate junctions in *Drosophila* ectodermal epithelium (B), and smooth septate junctions in *Drosophila* endodermal epithelium (C). TJ, tight junction; AJ, adherens junction; tTJ, tricellular tight junction; SJ, septate junction; AJ, adherens junction; tSJ, tricellular septate junction.

1991), and varicose (Vari) (Wu et al., 2007).

2. Barrier maintenance during dynamic remodeling of epithelial cells

Epithelial tissues maintain homeostasis by renewing their cells. New cells are produced by cell division within the cell sheet or by insertion from the apical or basal side of the cell sheet. Old cells are removed from the cell sheet by cell extrusion. These processes cause an imbalance of intercellular tension. Thus, the epithelial cells need to rearrange the occluding junctions around them to alleviate the imbalance of junctional tension. Indeed, the occluding junctions are newly assembled where the barrier function is bleached during cell rearrangement.

2.1. Barrier maintenance of dividing cells in the epithelial cell sheet

Epithelial barrier function is maintained even in the epithelia which proliferate rapidly, including developing epithelia and vertebrate intestinal epithelium. In these epithelia, cells undergo division within the epithelial sheet, giving rise to new daughter cells.

The initial indication of TJ maintenance in dividing epithelial cells was established through thin-section electron microscopy of fixed intestinal epithelium in mice (Jinguji and Ishikawa, 1992). Subsequent evidence came from ZO-1 immunostaining of Madin-Darby canine kidney (MDCK) cells (Baker and Garrod, 1993; Reinsch and Karsenti, 1994) and live imaging of ZO-1 in the surface epithelium of gastrula-stage *Xenopus* embryos (Higashi et al., 2016). During cytokinesis initiation, the dividing cell (D) retains TJ and tTJs with the surrounding cells (Fig. 2A). An actomyosin-based contractile ring forms orthogonal to the junctional plane, leading to the ingression of the basal plasma membrane towards the apical plane. Simultaneously the apical plasma membrane constricts inward and cells neighboring the cleavage plane (N) are pulled between daughter cells, preserving the TJs between daughter and neighboring cells ($TJ_{D\text{-}N}$). As $TJ_{D\text{-}N}$ persists between the midbody and neighboring cells, a new TJ between the neighboring cells ($TJ_{N\text{-}N}$) forms underneath the midbody. Two new tTJs are established at the newly formed tricellular vertices between daughter cells and neighboring cells before midbody abscission. This coordinated maintenance of $TJ_{D\text{-}N}$ and the formation of new $TJ_{N\text{-}N}$ and tTJs ensure the integrity of the epithelial barrier around the dividing cell.

In contrast, the maintenance of barrier function in dividing epithelial cells within *Drosophila* ectodermal epithelium follows a distinct mechanism from that observed in vertebrates, as demonstrated by live imaging of pupal dorsal thorax epithelium (Daniel et al., 2018; Wang et al., 2018; Wittek et al., 2020; Esmangart de Bournonville and Le Borgne, 2020) (Fig. 2B). As the contractile ring constricts from the basal to apical side in the dividing cell (D), the plasma membrane near the apical plane associated with the contractile ring invaginates inward as a thin membrane process. The membrane of the cells neighboring the cleavage plane (N) detaches from the cleavage furrow of the dividing cells at the apical AJ level (Founounou et al., 2013; Guillot and Lecuit, 2013; Herszterg et al., 2013). However, membranes remain attached at a lower level where the SJ between the dividing cell and neighboring cells ($SJ_{D\text{-}N}$) is located, and $SJ_{D\text{-}N}$ is maintained until the midbody is formed. On the new interface between daughter cells, a new SJ ($SJ_{D\text{-}D}$) and two new tSJs are assembled apical to the midbody. Subsequently, the midbody moves in the basal direction, disentangling the membranes of the daughter cells and neighboring cells. Although the mechanism is different from vertebrate epithelium, the coordinated maintenance of old $SJ_{D\text{-}N}$ and the establishment of new $SJ_{D\text{-}D}$ ensure the preservation of permeability barrier function in *Drosophila* ectoderm.

2.2. Cell insertion to the pre-existing cell sheet

An alternative way to increase cell number within the epithelium involves the insertion of cells into the pre-existing cell sheet. It has been recognized that the cells are inserted by the process called radial intercalation. Recent discoveries have uncovered new types of cell insertion, namely PAC (pre-assembled apical compartment) integration and multicellular rosette-guided collective intercalation.

Radial intercalation is observed in developing epithelia, where newly differentiated epithelial cells lacking apical membrane and occluding junctions are incorporated into the epithelial cell sheet either from the basal side (Campbell et al., 2010; Deblandre et al., 1999; McMahon et al., 2008; Stubbs et al., 2006; Voiculescu et al., 2007) or apical side (Pfannenstein and Macara, 2023). The intercalation of multiciliated cells (MCCs) into the skin of *Xenopus* embryo has served as a good model for studying the molecular mechanisms of radial intercalation (Collins et al., 2021; Sedzinski et al., 2017, 2016; Ventura et al., 2022; Werner et al., 2014) (Figs. 3A and 4). Precursors of MCC extend filopodia-like processes toward the cell vertices from the basal side and integrate with tricellular or multicellular junctions. The intercalation primarily occurs at multicellular junctions and the four-fold vertices created by the collapse of two tricellular junctions. Throughout the intercalation process, TJs and tTJs are continuously maintained and new TJ ($TJ_{MCC\text{-}EC}$) and tTJs are rapidly established between the MCC and surrounding

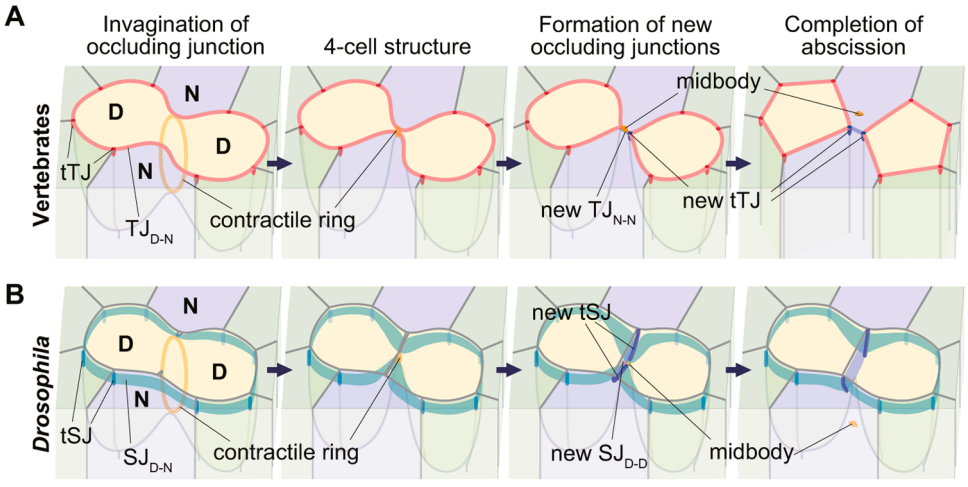


Fig. 2. Reorganization of occluding junctions in dividing epithelial cells. A-B. Remodeling of occluding junctions during cytokinesis in the vertebrate epithelial cell (A) and the *Drosophila* ectoderm epithelial cells (B). D, dividing cell; N, the cells neighboring the cleavage plane; $TJ_{D\text{-}N}$, pre-existing tight junctions between dividing cells and neighboring cells; $TJ_{N\text{-}N}$, newly formed tight junction between the neighboring cells; tTJ, tricellular tight junction; $SJ_{D\text{-}N}$, pre-existing septate junctions between dividing cells and neighboring cells; $SJ_{N\text{-}N}$, newly formed septate junction between the neighboring cells; tSJ, tricellular septate junction.

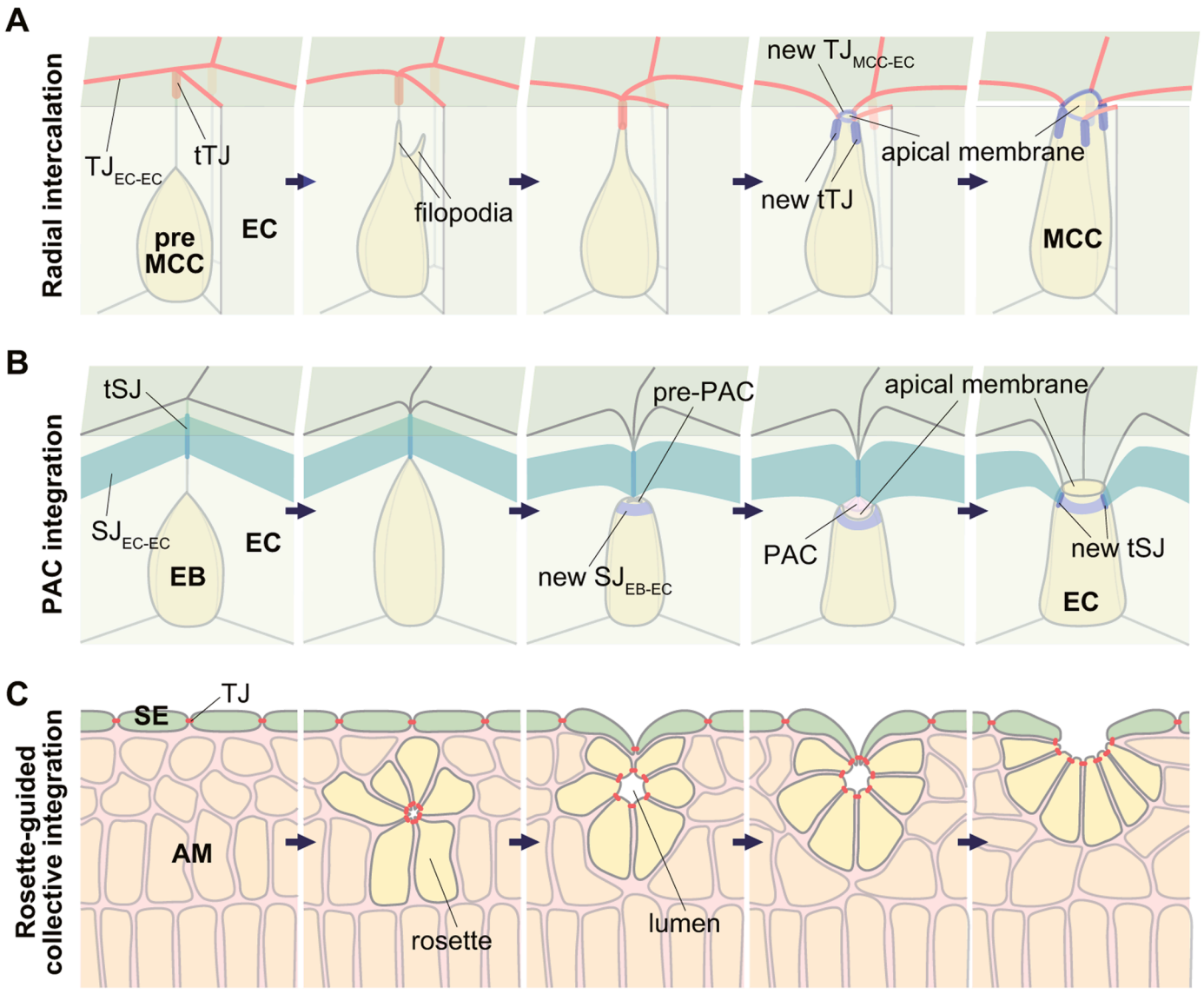


Fig. 3. Reorganization of occluding junctions during cell insertion. A. Remodeling of tight junctions during radial intercalation of *Xenopus* multiciliated cell into the surface epithelium. MCC, multiciliated cell; EC, epithelial cell; $TJ_{EC\text{-}EC}$, pre-existing tight junctions between surface epithelial cells; $TJ_{MCC\text{-}EC}$, newly formed tight junctions between the multiciliated cell and surrounding epithelial cells; tTJ, tricellular tight junction. B. Remodeling of septate junctions during integration of the *Drosophila* enteroblast into midgut epithelium. EB, enteroblast; EC, enterocyte; $SJ_{EC\text{-}EC}$, pre-existing septate junctions between the enterocytes; $SJ_{EB\text{-}EC}$, newly formed septate junctions between the enteroblast and surrounding enterocytes; tSJ, tricellular septate junction; PAC, pre-assembled apical compartment. C. Remodeling of tight junctions during integration of mouse axial mesodermal cells into surface endoderm. SE, surface endoderm; AM, axial mesoderm, TJ, tight junction.

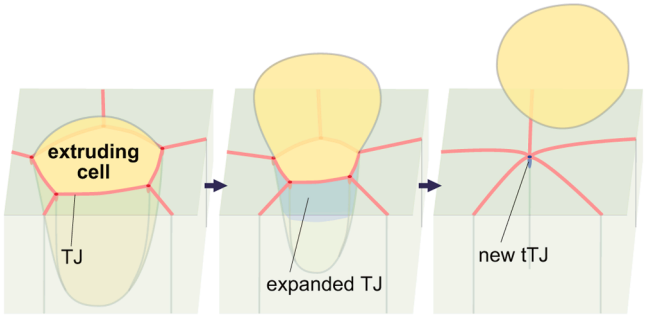


Fig. 4. Reorganization of occluding junctions during cell extrusion. Remodeling of tight junctions during cell extrusion of mouse enterocytes. TJ, tight junction; tTJ, tricellular tight junction.

epithelial cells.

PAC integration is recently discovered form of cell intercalation observed in the adult midgut of *Drosophila* (Chen and St Johnston, 2022; Galenza et al., 2023). Unlike mammalian intestinal stem cells (ISCs) embedded in the epithelial cell sheet at the crypt base, *Drosophila* adult midgut stem cells are positioned between the basolateral membranes of enterocytes (ECs) at the basal side, without facing the intestinal lumen. Enteroblasts (EBs) that differentiate from ISCs undergo PAC integration and become enterocytes (Fig. 3B). Initially, EBs associate with the pre-existing SJ between enterocytes ($SJ_{EC\text{-}EC}$) at the tricellular vertices of enterocytes. Subsequently, a sausage-shaped membrane structure, named pre-PAC, forms near the interface between the EB and SJ. The pre-PAC is covered with short microvilli and associated with filamentous actin (F-actin), which are characteristic to the apical membrane. In contrast to the previously observed vacuolar apical compartments (VACs) of MDCK cells (Vega-Salas et al., 1987), the lumen of the pre-PAC is continuous with the extracellular space. In the next step, the pre-PAC

matures into a PAC, an extracellular space surrounded by the apical membrane of EB and the basolateral membranes of ECs. While $SJ_{EC\text{-}EC}$ continues to maintain barrier function, restricting the diffusion of molecules from the apical lumen to the PAC, a new SJ between the EB and EC ($SJ_{EB\text{-}EC}$) is formed to complete the seal of the PAC lumen. As $SJ_{EC\text{-}EC}$ shrinks, $SJ_{EB\text{-}EC}$ grows. Ultimately, the PAC opens to the intestinal lumen and $SJ_{EC\text{-}EC}$ is lost. The smooth transition from $SJ_{EC\text{-}EC}$ to $SJ_{EB\text{-}EC}$ maintains barrier function during the integration and maturation of the nascent apical membrane. Early electron microscopy studies have also revealed PAC-like structures in vertebrate epithelial tissues including the human oviduct (Hagiwara et al., 1997) and human nasal mucosa (Boysen and Reith, 1980). In these tissues, stem cells are located at the basal side of the epithelium (Carter et al., 2004; Paik et al., 2012) and newly differentiated cells must be intercalated into the surface epithelium. It is plausible that a mechanism similar to PAC-mediated insertion of EBs might mediate the radial intercalation of new cells in these tissues although the process of how TJs are reorganized during the insertion remains to be elucidated.

Multicellular rosette-guided collective intercalation is a process of mesenchymal-epithelial transition (MET) recently identified in the axial mesoderm of the mouse embryo (Gredler and Zallen, 2023). Axial mesoderm (AM) cells are derived from epiblast epithelium by epithelial-mesenchymal transition. They reside beneath the surface endoderm epithelium (SE) at the distal surface of mouse embryos. Between embryonic day 7 (E7) and E8, these mesenchymal cells undergo MET and intercalate into the surface endoderm, contributing to the formation of the node and notochordal plate. Prior to the intercalation, axial mesoderm cells polarize and form a multicellular rosette structure at the basal side of the surface endoderm (Fig. 3C). At the center of the rosette, a lumen surrounded by apical membranes and tight junctions is formed, expanding into a spherical or tunnel-like structure. Subsequently, the rosette approaches the surface endodermal cells, leading to the basal deformation and incorporation of some endodermal cells into the rosette structure. As the rosette fuses with the endodermal epithelium, the central lumen becomes continuous with the apical space and axial mesoderm cells converge with the surface epithelium. During the formation of the rosette as an intermediate structure, axial mesoderm cells prepare to integrate into the surface epithelial cells without compromising barrier function by establishing tight junctions around the lumen. A similar rosette-like structure is also observed in the lateral plate mesoderm of chick embryos during MET, contributing to the generation of coelomic epithelium (Abboud Asleh et al., 2023). The rosettes of lateral plate mesoderm cells coalesce with each other, generating two pseudostratified epithelial layers of coelomic epithelium.

2.3. Cell extrusion from the epithelial sheet

The removal of aging cells from the epithelial sheet, known as cell extrusion or cell shedding, occurs either apically or basally (Guan et al., 2011; Madara, 1990; Marchiando et al., 2011; Rosenblatt et al., 2001; Ventrella et al., 2023). Even in rapidly turning over tissues such as the vertebrate intestines, where millions of cells are renewed daily, barrier function is essentially maintained. An electron microscopy study of naturally extruding cells in the intestines of rats and hamsters have provided insights into the mechanisms of barrier maintenance (Madara, 1990). At the tips of the villi in the intestinal epithelium, extruding cells maintain their cell-cell junctions with surrounding cells. As the extruding cell moves upward and extends into the intestinal lumen, TJs expand to the basolateral membrane. Below the extruding cell, surrounding cells form new TJs, ensuring the continuity of barrier integrity without leaving a transient hole. In vivo live imaging of ZO-1 in the mouse intestine has confirmed these observations, showing that TJs redistribute to the basolateral side of extruding cells and seal the extracellular space until the extrusion is complete, both in physiological and pathological shedding situations (Guan et al., 2011; Marchiando et al., 2011).

In the *Drosophila* midgut, dying cells undergo a distinct type of cell death called erebosis and are not immediately extruded from the epithelium (Ciesielski et al., 2022). After losing most of their organelle and cytoskeleton, erebotic cells remain in the epithelial sheet. Given that sSJ proteins around the erebotic cells are reduced, it is likely that surrounding cells employ a unique mechanism to compensate for junctional integrity, hereby maintaining the barrier function of the midgut.

2.4. Cell intercalation and rearrangement of occluding junctions

When epithelial tissues experience global or local tension, occluding junctions must adapt to the increased tension to preserve barrier function. In elongating epithelial tissues, cells exchange their positions to intercalate to each other, which requires a reorganization of occluding junctions. The mechanisms underlying the response of occluding junctions to changes in tension remain largely unclear. The rearrangement of cells occurs in three stages: the contraction of one junction, the formation of a four-way junction, and the elongation of the newly formed junction. It has been reported that the tSJ protein M6 and the phosphatidyl inositol phosphatase PTEN play roles in the resolution of the four-way junction structure (Bardet et al., 2013; Ikawa et al., 2023).

2.5. Cell growth and expansion of occluding junctions

Cell growth also requires the rearrangement of occluding junctions. It has been recently shown that newly synthesized claudin molecules are consistently incorporated into the TJ strand network from the basolateral side (Van Itallie et al., 2019), suggesting the adaptability of vertebrate epithelium to cell growth. In contrast, given that *Drosophila* SJs consist of unbranched strands, it is presumed to be challenging to introduce new components from the side of the strands. A recent report demonstrated that new SJ proteins are added from the apical side in primary epithelial cells (Babatz et al., 2018). However, in subperineurial glial cells, which undergo extensive growth without dividing during the larval stage, new SJ strands are added from both apical and basolateral sides. Moreover, in these cells, SJs are initially assembled as highly corrugated and folded strands, later stretched out to accommodate rapid cell growth.

3. Molecular mechanisms to maintain barrier function during epithelial rearrangement

The epithelial barrier is maintained by proper organization of occluding junction proteins and it is well accepted that the actomyosin cytoskeleton contributes to preventing breaches in barrier function (Turner et al., 2014; Citi et al., 2014; Arnold et al., 2017; Varadarajan et al., 2019; Shigetomi and Ikenouchi, 2019; Horowitz et al., 2023). Different cytoplasmic actin isoforms, non-muscle myosin II motors, and their regulators play essential roles in the regulation of epithelial integrity and barrier function (Naydenov et al., 2016; He et al., 2020; Ivanov et al., 2022; Rouaud et al., 2023). However, in each situation of dynamic rearrangement of epithelial cells explained above, it is plausible to think that newly formed cell-cell interfaces during dynamics of epithelium suffer small breaks of barrier function and that there are specific molecular mechanisms to reestablish a barrier at these sites. It has begun to be understood how epithelial cells (re)build TJs at barrier breach sites and this section focuses on recent findings uncovering the barrier repairing mechanisms.

3.1. Proteinases and EpCAM/Claudin-7

It has been known that proteinase activity can induce the formation of new TJs on membranes lacking TJs, such as pancreatic β cells, the basolateral membrane of MDCK cells, and the human colon adenocarcinoma cell line HT-29 (Cohen et al., 1985, 1990, Faff et al., 1987, 1988;

in't Veld et al., 1984; Lynch et al., 1995; Orci et al., 1973; Polak-Charcon et al., 1978; Talmon et al., 1984). Additionally, membrane-anchored serine proteinases (MASPs) and endogenous proteinase inhibitors have been implicated in maintaining epithelial barrier function (Buzza et al., 2013, 2010; Holt-Danborg et al., 2019; Leyvraz et al., 2005; List et al., 2009, 2002; Szabo et al., 2023, 2019; Szabo and Bugge, 2018; Wu et al., 2017). Our recent model proposes an explanation for how proteinases regulate barrier function in MDCK II cells (Higashi et al., 2023; Varadarajan et al., 2023) (Fig. 5). MASPs including TMPRSS1/hepsin, TMPRSS4, TMPRSS14/matriptase/ST14, and PRSS8/prostasin play a key role in cleaving the transmembrane protein EpCAM, which forms a complex with claudin-7 localized on the basolateral membrane. At the sites of barrier loss, MASPs are activated by an as-yet-unknown mechanism, leading to the cleavage of EpCAM. This disrupts the EpCAM/claudin-7 complex, allowing released claudin-7 to polymerize and generate new TJ strands, contributing to the rapid repair of damaged TJs. Notably, at the tips of the villi in the mouse intestine, claudin-7 becomes insoluble to detergent around the shedding cells, which suggests that claudin-7 is polymerized at the cell extrusion sites. Both EpCAM and claudin-7 have been implicated in TJ barrier maintenance (Ding et al., 2012; Guerra et al., 2012; Kozan et al., 2015; Ladwein et al., 2005; Lei et al., 2012; Salomon et al., 2017; Sivagnanam et al., 2008; Tanaka et al., 2015; Tatum et al., 2010; Wu et al., 2013), providing further support for this hypothesis. In future studies, it will be crucial to assess the conservation of this proteinase-mediated mechanism in other epithelial contexts.

3.2. Rho activation and actomyosin reorganization

The small GTPase Rho plays a crucial role in regulating the formation and maintenance of TJ barrier integrity (Arnold et al., 2017; Citi et al., 2014; McCormack et al., 2013; Quiros and Nusrat, 2014; Shigetomi and Ikenouchi, 2019; Terry et al., 2010; Varadarajan et al., 2019). At the sites of TJ breaches in the surface epithelium of *Xenopus* gastrula-stage embryos, Rho GTPase is transiently activated. Active Rho induces ZO-1 accumulation and actomyosin reorganization, which reinstate the undercoat structure of TJs and prevent further TJ breaks (Reyes et al., 2014; Stephenson et al., 2019) (Fig. 5). The transient activation of Rho, referred to as Rho flare, is initiated by p115-RhoGEF and calcium flashes mediated by mechanosensitive calcium channels (Chumki et al., 2022; Varadarajan et al., 2022). This suggests that changes in membrane tension may serve as a trigger for Rho activation. Dynamic changes in active Rho levels and F-actin are also observed during the remodeling of cell-cell junctions in MCF-7 cells and MDCK II cells, respectively (Gupta et al., 2021; Tokuda et al., 2014).

3.3. Molecular mechanisms to detect septate junction barrier breaks

The loss of SJ or tSJ proteins in the *Drosophila* midgut leads to an abnormal increase in the cell numbers of ISCs and EBs. While the accumulation of EBs results from their failure to integrate into the luminal surface (Chen and St Johnston, 2022; Galenza et al., 2023), as explained earlier, the loss of the SJ barrier also induces the proliferation of ISCs (Resnik-Docampo et al., 2017; Xu et al., 2019; Izumi et al., 2019; Chen et al., 2020). Although various signaling pathways, including JNK, MAP kinase, atypical PKC, Hippo, and JAK-Stat, have been implicated in this regulation, it remains unknown how the barrier defect is detected in the epithelial cells, leading to the alteration of ISC fate in a non-cell autonomous manner. A recent study has proposed that *Drosophila* pupal wing imaginal disc epithelial cells detect SJ defects through the tumor necrosis factor (TNF) signal (de Vreede et al., 2022). The TNF receptor Grindelwald (Grnd) is normally localized on the apical surface. However, in wings where SJ proteins Dlg or Scrib are mutated, Grnd can bind to Eiger, the TNF ligand circulating in the hemolymph and bathing the basolateral side of the epithelium, inducing a JNK-mediated apoptosis signal. A similar receptor-ligand-based mechanism might detect barrier loss and relay the mitotic signal to the ISCs. Another recent study has discovered that in *Drosophila* pupal notum, reduced SJ integrity alters the traffic route of the SJ component, shifting it from degradation to recycling, thereby restoring the barrier function (Esmangart de Bournonville et al., 2024).

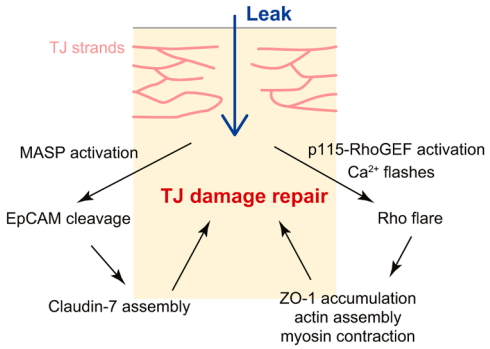


Fig. 5. Current model of tight junction repair mechanisms. See text for details.

4. Open questions

4.1. Are there common proteinase-mediated repair mechanisms for tight and septate junctions?

The recent demonstration of the proteinase-mediated TJ repair mechanism in mammalian cultured cells raises questions regarding whether similar mechanisms maintain SJs in response to minor barrier disruptions. Notably, the release of the glycosylphosphatidylinositol (GPI)-anchored protein Undicht by ADAM10-like proteinases, Kuzbanian and Kuzbanian-like, is cruicial for septate junction formation in the *Drosophila* blood-brain barrier (BBB) and trachea epithelia (Petri et al., 2019). Another GPI-anchored protein Boudin, involved in BBB SJ maintenance, is also released from cells (Hijazi et al., 2009), although the role of proteinases in this process remains unclear. Considering the upregulation of Undicht expression during the epithelial wound repair (Petri et al., 2019), investigating its localization and cleavage at SJ break sites could provide valuable insights.

4.2. How does actomyosin cytoskeleton contribute to the break and repair of tight junctions?

The actomyosin cytoskeleton associated with cell-cell junctions consists of two main populations: those aligned parallel and those connected perpendicularly to the junctions. The former population generates purse-string constriction forces, while the latter pulls junctions, inducing an interdigitated shape (Yonemura et al., 1995; Danjo and Gipson, 1998; Yamada et al., 2005; Abe and Takeichi, 2008; Martin et al., 2009; Taguchi et al., 2011; Ebrahim et al., 2013; Tokuda et al., 2014; Choi et al., 2016; Yu-Kemp et al., 2022; Miyazaki et al., 2023). However, the molecular mechanisms governing these populations and their role in barrier function are not fully elucidated. At junctions under increased tension, α-catenin undergoes extension, exposing a hidden binding surface and recruiting vinculin, an actin-binding protein (Yonemura et al., 2010). The orientation of the force inducing this change, whether parallel or perpendicular to the junctions, remains unclear.

Traditionally, it has been widely accepted that the actomyosin cytoskeleton is associated with E-cadherin-based AJs. However, a recent study unveils a distinct distribution of the circumferential actomyosin bundle parallel to junctions in mature intestinal epithelial cells, both *in vivo* and *in vitro* (Mangeol et al., 2024). This bundle is found to colocalize with ZO-1 and afadin, which are localized at TJs and upper part of AJs, respectively. This discovery raises questions about the prevalence of

similar distributions in other epithelial types and their local adaptations during changes in junctional tension amidst the dynamic reorganization of epithelia.

Increased tension induces a reduction in junctional ZO-1 at TJs and results in focal TJ breakage (Stephenson et al., 2019; Nguyen et al., 2024). ZO-1, like vinculin, is a mechanosensitive protein, and its linkage with both TJ transmembrane proteins and F-actin is crucial for preventing breaks (Rouaud et al., 2019; Schwayer et al., 2019; Belardi et al., 2020; Schmidt et al., 2023; Nguyen et al., 2024). The interplay between ZO-1-based and vinclin-based mechanosensitive mechanisms in preserving junctional integrity awaits future studies, as understanding their potential synergistic or distinct roles promises insights into how cells respond to mechanical cues and maintain barrier functions amidst varying physiological conditions.

4.3. How is the barrier function maintained at four-way junctions during cell intercalation?

In mature epithelial sheets, cells typically assume a polygonal shape and establish tricellular junctions at their vertices. The barrier function at these tricellular junctions is upheld by tTJs in vertebrates and tSJs in *Drosophila* (Higashi and Miller, 2017; Higashi and Chiba, 2020). However, during dynamic epithelial reorganization, two tricellular junctions converge to transiently create a four-way junction during cell intercalation. In this rearrangement, components of tTJ, tSJ, and tAJ along with associated bicellular components, must be reorganized while preserving barrier integrity (Choi et al., 2016; Letizia et al., 2019; Uechi and Kuranaga, 2019; Esmangart de Bournonville and Le Borgne, 2020; Yu and Zallen, 2020; Malin et al., 2022; Cho et al., 2022; Ikawa et al., 2023). While it is reasonable to hypothesize the existence of specific molecular machinery facilitating this process, no proteins concentrated specifically at four-way junctions have been reported thus far.

5. Concluding remarks

In various remodeling processes of epithelial cells, barrier function is maintained by establishing new occluding junctions at newly formed cell-cell interfaces while keeping pre-existing occluding junctions. Molecular mechanisms to regulate new junction formation is beginning to be understood. We hope that future development of new observation techniques would reveal more details of the mechanisms described here or novel mechanism in various epithelial systems.

CRediT authorship contribution statement

Tomohito Higashi: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Akira C. Saito:** Writing – review & editing, Validation, Formal analysis. **Hideki Chiba:** Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP21K06156.

References

Abboud Asleh, M., Zaher, M., Asleh, J., Jadon, J., Shaulov, L., Yelin, R., Schultheiss, T. M., 2023. A morphogenetic wave in the chick embryo lateral mesoderm generates mesenchymal-epithelial transition through a 3D-rosette intermediate. Dev. Cell 58, 951–966.e5. https://doi.org/10.1016/j.devcel.2023.03.017.

Abe, K., Takeichi, M., 2008. EPLIN mediates linkage of the cadherin catenin complex to F-actin and stabilizes the circumferential actin belt. Proc. Natl. Acad. Sci. USA 105, 13–19. https://doi.org/10.1073/pnas.0710504105.

Adachi, M., Inoko, A., Hata, M., Furuse, K., Umeda, K., Itoh, M., Tsukita, S., 2006. Normal establishment of epithelial tight junctions in mice and cultured cells lacking expression of ZO-3, a tight-junction MAGUK protein. Mol. Cell. Biol. 26, 9003–9015. https://doi.org/10.1128/MCB.01811-05.

Arnold, T.R., Stephenson, R.E., Miller, A.L., 2017. Rho GTPases and actomyosin: partners in regulating epithelial cell-cell junction structure and function. Exp. Cell Res. 358, 20–30. https://doi.org/10.1016/j.yexcr.2017.03.053.

Auld, V.J., Fetter, R.D., Broadie, K., Goodman, C.S., 1995. Gliotactin, a novel transmembrane protein on peripheral glia, is required to form the blood-nerve barrier in Drosophila. Cell 81, 757–767. https://doi.org/10.1016/0092-8674(95)90537-5.

Babatz, F., Naffin, E., Klämbt, C., 2018. The drosophila blood-brain barrier adapts to cell growth by unfolding of pre-existing septate junctions. Dev. Cell 47, 697–710.e3. https://doi.org/10.1016/j.devcel.2018.10.002.

Baker, J., Garrod, D., 1993. Epithelial cells retain junctions during mitosis. J. Cell Sci. 104 (Pt 2), 415–425. https://doi.org/10.1242/jcs.104.2.415.

Bardet, P.-L., Guirao, B., Paoletti, C., Serman, F., Léopold, V., Bosveld, F., Goya, Y., Mirouse, V., Graner, F., Bellaïche, Y., 2013. PTEN controls junction lengthening and stability during cell rearrangement in epithelial tissue. Dev. Cell 25, 534–546. https://doi.org/10.1016/j.devcel.2013.04.020.

Baumgartner, S., Littleton, J.T., Broadie, K., Bhat, M.A., Harbecke, R., Lengyel, J.A., Chiquet-Ehrismann, R., Prokop, A., Bellen, H.J., 1996. A Drosophila neurexin is required for septate junction and blood-nerve barrier formation and function. Cell 87, 1059–1068. https://doi.org/10.1016/s0092-8674(00)81800-0.

Behr, M., Riedel, D., Schuh, R., 2003. The claudin-like megatrachea is essential in septate junctions for the epithelial barrier function in Drosophila. Dev. Cell 5, 611–620. https://doi.org/10.1016/s1534-5807(03)00275-2.

Belardi, B., Hamkins-Indik, T., Harris, A.R., Kim, J., Xu, K., Fletcher, D.A., 2020. A weak link with actin organizes tight junctions to control epithelial permeability. Dev. Cell 54, 792–804.e7. https://doi.org/10.1016/j.devcel.2020.07.022.

Bilder, D., Perrimon, N., 2000. Localization of apical epithelial determinants by the basolateral PDZ protein Scribble. Nature 403, 676–680. https://doi.org/10.1038/35001108.

Bosveld, F., Wang, Z., Bellaïche, Y., 2018. Tricellular junctions: a hot corner of epithelial biology. Curr. Opin. Cell Biol. 54, 80–88. https://doi.org/10.1016/j.ceb.2018.05.002.

Boysen, M., Reith, A., 1980. Intracytoplasmic lumina with and without cilia in both normal and pathologically altered nasal mucosa. Ultrastruct. Pathol. 1, 477–485. https://doi.org/10.3109/01913128009140554.

Buzza, M.S., Netzel-Arnett, S., Shea-Donohue, T., Zhao, A., Lin, C.-Y., List, K., Szabo, R., Fasano, A., Bugge, T.H., Antalis, T.M., 2010. Membrane-anchored serine protease matriptase regulates epithelial barrier formation and permeability in the intestine. Proc. Natl. Acad. Sci. U. S. A. 107, 4200–4205. https://doi.org/10.1073/pnas.0903923107.

Buzza, M.S., Martin, E.W., Driesbaugh, K.H., Désilets, A., Leduc, R., Antalis, T.M., 2013. Prostasin is required for matriptase activation in intestinal epithelial cells to regulate closure of the paracellular pathway. J. Biol. Chem. 288, 10328–10337. https://doi.org/10.1074/jbc.M112.443432.

Byri, S., Misra, T., Syed, Z.A., Bätz, T., Shah, J., Boril, L., Glashauser, J., Aegerter-Wilmsen, T., Matzat, T., Moussian, B., Uv, A., Luschnig, S., 2015. The triple-repeat protein anakonda controls epithelial tricellular junction formation in drosophila. Dev. Cell 33, 535–548. https://doi.org/10.1016/j.devcel.2015.03.023.

Campbell, K., Casanova, J., Skaer, H., 2010. Mesenchymal-to-epithelial transition of intercalating cells in Drosophila renal tubules depends on polarity cues from epithelial neighbours. Mech. Dev. 127, 345–357. https://doi.org/10.1016/j.mod.2010.04.002.

Carter, L.A., MacDonald, J.L., Roskams, A.J., 2004. Olfactory horizontal basal cells demonstrate a conserved multipotent progenitor phenotype. J. Neurosci. . J. Soc. Neurosci. 24, 5670–5683. https://doi.org/10.1523/JNEUROSCI.0330-04.2004.

Chen, H.-J., Li, Q., Nirala, N.K., Ip, Y.T., 2020. The snakeskin-mesh complex of smooth septate junction restricts yorkie to regulate intestinal homeostasis in drosophila. Stem Cell Rep. 14, 828–844. https://doi.org/10.1016/j.stemcr.2020.03.021.

Chen, J., St Johnston, D., 2022. De novo apical domain formation inside the Drosophila adult midgut epithelium. eLife 11, e76366. https://doi.org/10.7554/eLife.76366.

Cho, Y., Haraguchi, D., Shigetomi, K., Matsuzawa, K., Uchida, S., Ikenouchi, J., 2022. Tricellulin secures the epithelial barrier at tricellular junctions by interacting with actomyosin. J. Cell Biol. 221, e202009037 https://doi.org/10.1083/jcb.202009037.

Choi, W., Acharya, B.R., Peyret, G., Fardin, M.-A., Mège, R.-M., Ladoux, B., Yap, A.S., Fanning, A.S., Peifer, M., 2016. Remodeling the zonula adherens in response to tension and the role of afadin in this response. J. Cell Biol. 213, 243–260. https://doi.org/10.1083/jcb.201506115.

Chumki, S.A., van den Goor, L.M., Hall, B.N., Miller, A.L., 2022. p115RhoGEF activates RhoA to support tight junction maintenance and remodeling. Mol. Biol. Cell 33, ar136. https://doi.org/10.1091/mbc.E22-06-0205.

Ciesielski, H.M., Nishida, H., Takano, T., Fukuhara, A., Otani, T., Ikegawa, Y., Okada, M., Nishimura, T., Furuse, M., Yoo, S.K., 2022. Erebosis, a new cell death mechanism

during homeostatic turnover of gut enterocytes. PLOS Biol. 20, e3001586 https://doi.org/10.1371/journal.pbio.3001586.
Citi, S., Sabanay, H., Jakes, R., Geiger, B., Kendrick-Jones, J., 1988. Cingulin, a new peripheral component of tight junctions. Nature 333, 272–276. https://doi.org/10.1038/333272a0.
Citi, S., Guerrera, D., Spadaro, D., Shah, J., 2014. Epithelial junctions and Rho family GTPases: the zonular signalosome. Small GTPases 5, 1–15. https://doi.org/10.4161/21541248.2014.973760.
Cohen, E., Talmon, A., Faff, O., Bacher, A., Ben-Shaul, Y., 1985. Formation of tight junctions in epithelial cells. I. Induction by proteases in a human colon carcinoma cell line. Exp. Cell Res. 156, 103–116. https://doi.org/10.1016/0014-4827(85)90265-4.
Cohen, E., Ophir, I., Henis, Y.I., Bacher, A., Ben Shaul, Y., 1990. Effect of temperature on the assembly of tight junctions and on the mobility of lipids in membranes of HT29 cells. J. Cell Sci. 97 (Pt 1), 119–125.
Collins, C., Kim, S.K., Ventrella, R., Carruzzo, H.M., Wortman, J.C., Han, H., Suva, E.E., Mitchell, J.W., Yu, C.C., Mitchell, B.J., 2021. Tubulin acetylation promotes penetrative capacity of cells undergoing radial intercalation. Cell Rep. 36, 109556 https://doi.org/10.1016/j.celrep.2021.109556.
Cording, J., Berg, J., Käding, N., Bellmann, C., Tscheik, C., Westphal, J.K., Milatz, S., Günzel, D., Wolburg, H., Piontek, J., Huber, O., Blasig, I.E., 2013. In tight junctions, claudins regulate the interactions between occludin, tricellulin and marvelD3, which, inversely, modulate claudin oligomerization. J. Cell Sci. 126, 554–564. https://doi.org/10.1242/jcs.114306.
Daniel, E., Daudé, M., Kolotuev, I., Charish, K., Auld, V., Le Borgne, R., 2018. Coordination of septate junctions assembly and completion of cytokinesis in proliferative epithelial tissues. Curr. Biol. CB 28, 1380–1391.e4. https://doi.org/10.1016/j.cub.2018.03.034.
Danjo, Y., Gipson, I.K., 1998. Actin "purse string" filaments are anchored by E-cadherin-mediated adherens junctions at the leading edge of the epithelial wound, providing coordinated cell movement. J. Cell Sci. 111 (Pt 22), 3323–3332. https://doi.org/10.1242/jcs.111.22.3323.
Deblandre, G.A., Wettstein, D.A., Koyano-Nakagawa, N., Kintner, C., 1999. A two-step mechanism generates the spacing pattern of the ciliated cells in the skin of Xenopus embryos. Dev. Camb. Engl. 126, 4715–4728. https://doi.org/10.1242/dev.126.21.4715.
Ding, L., Lu, Z., Foreman, O., Tatum, R., Lu, Q., Renegar, R., Cao, J., Chen, Y.-H., 2012. Inflammation and disruption of the mucosal architecture in claudin-7-deficient mice. Gastroenterology 142, 305–315. https://doi.org/10.1053/j.gastro.2011.10.025.
Dunn, B.S., Rush, L., Lu, J.-Y., Xu, T., 2018. Mutations in the Drosophila tricellular junction protein M6 synergize with RasV12 to induce apical cell delamination and invasion. Proc. Natl. Acad. Sci. U. S. A. 115, 8358–8363. https://doi.org/10.1073/pnas.1807343115.
Ebrahim, S., Fujita, T., Millis, B.A., Kozin, E., Ma, X., Kawamoto, S., Baird, M.A., Davidson, M., Yonemura, S., Hisa, Y., Conti, M.A., Adelstein, R.S., Sakaguchi, H., Kachar, B., 2013. NMII forms a contractile transcellular sarcomeric network to regulate apical cell junctions and tissue geometry. Curr. Biol. CB 23, 731–736. https://doi.org/10.1016/j.cub.2013.03.039.
Esmangart de Bournonville, T., Le Borgne, R., 2020. Interplay between anakonda, gliotactin, and M6 for tricellular junction assembly and anchoring of septate junctions in drosophila epithelium. Curr. Biol. CB 30, 4245–4253.e4. https://doi.org/10.1016/j.cub.2020.07.090.
Esmangart de Bournonville, T., Jaglarz, M.K., Durel, E., Le Borgne, R., 2024. ESCRT-III-dependent adhesive and mechanical changes are triggered by a mechanism detecting alteration of septate junction integrity in drosophila epithelial cells. eLife 13, e91246. https://doi.org/10.7554/eLife.91246.
Faff, O., Cohen, E., Bacher, A., Ben-Shaul, Y., 1987. Proteinase-induced formation of focal tight junctions in HT 29 adenocarcinoma cells does not require extracellular calcium. Biochim. Biophys. Acta 905, 48–56. https://doi.org/10.1016/0005-2736(87)90007-1.
Faff, O., Mitreiter, R., Mückter, H., Ben-Shaul, Y., Bacher, A., 1988. Rapid formation of tight junctions in HT 29 human adenocarcinoma cells by hypertonic salt solutions. Exp. Cell Res. 177, 60–72. https://doi.org/10.1016/0014-4827(88)90025-0.
Fehon, R.G., Dawson, I.A., Artavanis-Tsakonas, S., 1994. A Drosophila homologue of membrane-skeleton protein 4.1 is associated with septate junctions and is encoded by the coracle gene. Dev. Camb. Engl. 120, 545–557. https://doi.org/10.1242/dev.120.3.545.
Founounou, N., Loyer, N., Le Borgne, R., 2013. Septins regulate the contractility of the actomyosin ring to enable adherens junction remodeling during cytokinesis of epithelial cells. Dev. Cell 24, 242–255. https://doi.org/10.1016/j.devcel.2013.01.008.
Furuse, M., Hirase, T., Itoh, M., Nagafuchi, A., Yonemura, S., Tsukita, S., Tsukita, S., 1993. Occludin: a novel integral membrane protein localizing at tight junctions. J. Cell Biol. 123, 1777–1788. https://doi.org/10.1083/jcb.123.6.1777.
Furuse, M., Sasaki, H., Fujimoto, K., Tsukita, S., 1998b. A single gene product, claudin-1 or -2, reconstitutes tight junction strands and recruits occludin in fibroblasts. J. Cell Biol. 143, 391–401. https://doi.org/10.1083/jcb.143.2.391.
Furuse, M., Fujita, K., Hiiragi, T., Fujimoto, K., Tsukita, S., 1998a. Claudin-1 and -2: novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. J. Cell Biol. 141, 1539–1550. https://doi.org/10.1083/jcb.141.7.1539.
Galenza, A., Moreno-Roman, P., Su, Y.-H., Acosta-Alvarez, L., Debec, A., Guichet, A., Knapp, J.-M., Kizilyaprak, C., Humbel, B.M., Kolotuev, I., O'Brien, L.E., 2023. Basal stem cell progeny establish their apical surface in a junctional niche during turnover of an adult barrier epithelium. Nat. Cell Biol. 25, 658–671. https://doi.org/10.1038/s41556-023-01116-w.
Genova, J.L., Fehon, R.G., 2003. Neuroglian, Gliotactin, and the Na+/K+ ATPase are essential for septate junction function in Drosophila. J. Cell Biol. 161, 979–989. https://doi.org/10.1083/jcb.200212054.
Gredler, M.L., Zallen, J.A., 2023. Multicellular rosettes link mesenchymal-epithelial transition to radial intercalation in the mouse axial mesoderm. Dev. Cell 58, 933–950.e5. https://doi.org/10.1016/j.devcel.2023.03.018.
Green, C.R., Bergquist, P.R., Bullivant, S., 1979. An anastomosing septate junction in endothelial cells of the phylum echinodermata. J. Ultrastruct. Res. 68, 72–80. https://doi.org/10.1016/s0022-5320(79)90143-6.
Guan, Y., Watson, A.J.M., Marchiando, A.M., Bradford, E., Shen, L., Turner, J.R., Montrose, M.H., 2011. Redistribution of the tight junction protein ZO-1 during physiological shedding of mouse intestinal epithelial cells. Am. J. Physiol. Cell Physiol. 300, C1404–C1414. https://doi.org/10.1152/ajpcell.00270.2010.
Guerra, E., Lattanzio, R., La Sorda, R., Dini, F., Tiboni, G.M., Piantelli, M., Alberti, S., 2012. mTrop1/Epcam knockout mice develop congenital tufting enteropathy through dysregulation of intestinal E-cadherin/β-catenin. PlOS One 7, e49302. https://doi.org/10.1371/journal.pone.0049302.
Guillemot, L., Schneider, Y., Brun, P., Castagliuolo, I., Pizzuti, D., Martines, D., Jond, L., Bongiovanni, M., Citi, S., 2012. Cingulin is dispensable for epithelial barrier function and tight junction structure, and plays a role in the control of claudin-2 expression and response to duodenal mucosa injury. J. Cell Sci. 125, 5005–5014. https://doi.org/10.1242/jcs.101261.
Guillot, C., Lecuit, T., 2013. Adhesion disengagement uncouples intrinsic and extrinsic forces to drive cytokinesis in epithelial tissues. Dev. Cell 24, 227–241. https://doi.org/10.1016/j.devcel.2013.01.010.
Gumbiner, B., Lowenkopf, T., Apatira, D., 1991. Identification of a 160-kDa polypeptide that binds to the tight junction protein ZO-1. Proc. Natl. Acad. Sci. USA 88, 3460–3464. https://doi.org/10.1073/pnas.88.8.3460.
Gupta, S., Duszyc, K., Verma, S., Budnar, S., Liang, X., Gomez, G.A., Marcq, P., Noordstra, I., Yap, A.S., 2021. Enhanced RhoA signalling stabilizes E-cadherin in migrating epithelial monolayers. J. Cell Sci. 134, jcs258767 https://doi.org/10.1242/jcs.258767.
Hagiwara, H., Ohwada, N., Fujimoto, T., 1997. Intracytoplasmic lumina in human oviduct epithelium. Ultrastruct. Pathol. 21, 163–172. https://doi.org/10.3109/01913129709021315.
Haskins, J., Gu, L., Wittchen, E.S., Hibbard, J., Stevenson, B.R., 1998. ZO-3, a novel member of the MAGUK protein family found at the tight junction, interacts with ZO-1 and occludin. J. Cell Biol. 141, 199–208. https://doi.org/10.1083/jcb.141.1.199.
He, W.-Q., Wang, J., Sheng, J.-Y., Zha, J.-M., Graham, W.V., Turner, J.R., 2020. Contributions of myosin light chain kinase to regulation of epithelial paracellular permeability and mucosal homeostasis. Int. J. Mol. Sci. 21, 993. https://doi.org/10.3390/ijms21030993.
Herszterg, S., Leibfried, A., Bosveld, F., Martin, C., Bellaiche, Y., 2013. Interplay between the dividing cell and its neighbors regulates adherens junction formation during cytokinesis in epithelial tissue. Dev. Cell 24, 256–270. https://doi.org/10.1016/j.devcel.2012.11.019.
Higashi, T., Chiba, H., 2020. Molecular organization, regulation and function of tricellular junctions. Biochim. Biophys. Acta Biomembr. 1862, 183143 https://doi.org/10.1016/j.bbamem.2019.183143.
Higashi, T., Miller, A.L., 2017. Tricellular junctions: how to build junctions at the TRICkiest points of epithelial cells. Mol. Biol. Cell 28, 2023–2034. https://doi.org/10.1091/mbc.E16-10-0697.
Higashi, T., Tokuda, S., Kitajiri, S., Masuda, S., Nakamura, H., Oda, Y., Furuse, M., 2013. Analysis of the "angulin" proteins LSR, ILDR1 and ILDR2–tricellulin recruitment, epithelial barrier function and implication in deafness pathogenesis. J. Cell Sci. 126, 966–977. https://doi.org/10.1242/jcs.116442.
Higashi, T., Arnold, T.R., Stephenson, R.E., Dinshaw, K.M., Miller, A.L., 2016. Maintenance of the epithelial barrier and remodeling of cell-cell junctions during cytokinesis. Curr. Biol. CB 26, 1829–1842. https://doi.org/10.1016/j.cub.2016.05.036.
Higashi, T., Saito, A.C., Fukazawa, Y., Furuse, M., Higashi, A.Y., Ono, M., Chiba, H., 2023. EpCAM proteolysis and release of complexed claudin-7 repair and maintain the tight junction barrier. J. Cell Biol. 222, e202204079 https://doi.org/10.1083/jcb.202204079.
Hijazi, A., Masson, W., Augé, B., Waltzer, L., Haenlin, M., Roch, F., 2009. boudin is required for septate junction organisation in drosophila and codes for a diffusible protein of the Ly6 superfamily. Dev. Camb. Engl. 136, 2199–2209. https://doi.org/10.1242/dev.033845.
Hildebrandt, A., Pflanz, R., Behr, M., Tarp, T., Riedel, D., Schuh, R., 2015. Bark beetle controls epithelial morphogenesis by septate junction maturation in Drosophila. Dev. Biol. 400, 237–247. https://doi.org/10.1016/j.ydbio.2015.02.008.
Holt-Danborg, L., Vodopiutz, J., Nonboe, A.W., De Laffolie, J., Skovbjerg, S., Wolters, V. M., Müller, T., Hetzer, B., Querfurt, A., Zimmer, K.-P., Jensen, J.K., Entenmann, A., Heinz-Erian, P., Vogel, L.K., Janecke, A.R., 2019. SPINT2 (HAI-2) missense variants identified in congenital sodium diarrhea/tufting enteropathy affect the ability of HAI-2 to inhibit prostasin but not matriptase. Hum. Mol. Genet. 28, 828–841. https://doi.org/10.1093/hmg/ddy394.
Horowitz, A., Chanez-Paredes, S.D., Haest, X., Turner, J.R., 2023. Paracellular permeability and tight junction regulation in gut health and disease. Nat. Rev. Gastroenterol. Hepatol. 20, 417–432. https://doi.org/10.1038/s41575-023-00766-3.
Ikawa, K., Ishihara, S., Tamori, Y., Sugimura, K., 2023. Attachment and detachment of cortical myosin regulates cell junction exchange during cell rearrangement in the Drosophila wing epithelium. Curr. Biol. CB 33, 263–275.e4. https://doi.org/10.1016/j.cub.2022.11.067.

Ikenouchi, J., Furuse, M., Furuse, K., Sasaki, H., Tsukita, Sachiko, Tsukita, Shoichiro, 2005. Tricellulin constitutes a novel barrier at tricellular contacts of epithelial cells. J. Cell Biol. 171, 939–945. https://doi.org/10.1083/jcb.200510043.

in't Veld, P.A., Pipeleers, D.G., Gepts, W., 1984. Evidence against the presence of tight junctions in normal endocrine pancreas. Diabetes 33, 101–104.

Ivanov, A.I., Lechuga, S., Marino-Melendez, A., Naydenov, N.G., 2022. Unique and redundant functions of cytoplasmic actins and nonmuscle myosin II isoforms at epithelial junctions. Ann. N. Y. Acad. Sci. 1515, 61–74. https://doi.org/10.1111/nyas.14808.

Izumi, Y., Furuse, M., 2014. Molecular organization and function of invertebrate occluding junctions. Semin. Cell Dev. Biol. 36, 186–193. https://doi.org/10.1016/j.semcdb.2014.09.009.

Izumi, Y., Hirose, T., Tamai, Y., Hirai, S., Nagashima, Y., Fujimoto, T., Tabuse, Y., Kemphues, K.J., Ohno, S., 1998. An atypical PKC directly associates and colocalizes at the epithelial tight junction with ASIP, a mammalian homologue of Caenorhabditis elegans polarity protein PAR-3. J. Cell Biol. 143, 95–106. https://doi.org/10.1083/jcb.143.1.95.

Izumi, Y., Yanagihashi, Y., Furuse, M., 2012. A novel protein complex, Mesh-Ssk, is required for septate junction formation in the Drosophila midgut. J. Cell Sci. 125, 4923–4933. https://doi.org/10.1242/jcs.112243.

Izumi, Y., Motoishi, M., Furuse, K., Furuse, M., 2016. A tetraspanin regulates septate junction formation in Drosophila midgut. J. Cell Sci. 129, 1155–1164. https://doi.org/10.1242/jcs.180448.

Izumi, Y., Furuse, K., Furuse, M., 2019. Septate junctions regulate gut homeostasis through regulation of stem cell proliferation and enterocyte behavior in Drosophila. jcs232108 J. Cell Sci. 132. https://doi.org/10.1242/jcs.232108.

Jinguji, Y., Ishikawa, H., 1992. Electron microscopic observations on the maintenance of the tight junction during cell division in the epithelium of the mouse small intestine. Cell Struct. Funct. 17, 27–37. https://doi.org/10.1247/csf.17.27.

Jonusaite, S., Donini, A., Kelly, S.P., 2016. Occluding junctions of invertebrate epithelia. J. Comp. Physiol. [B 186, 17–43. https://doi.org/10.1007/s00360-015-0937-1.

Kozan, P.A., McGeough, M.D., Peña, C.A., Mueller, J.L., Barrett, K.E., Marchelletta, R.R., Sivagnanam, M., 2015. Mutation of EpCAM leads to intestinal barrier and ion transport dysfunction. J. Mol. Med. Berl. Ger. 93, 535–545. https://doi.org/10.1007/s00109-014-1239-x.

Ladwein, M., Pape, U.-F., Schmidt, D.-S., Schnölzer, M., Fiedler, S., Langbein, L., Franke, W.W., Moldenhauer, G., Zöller, M., 2005. The cell-cell adhesion molecule EpCAM interacts directly with the tight junction protein claudin-7. Exp. Cell Res. 309, 345–357. https://doi.org/10.1016/j.yexcr.2005.06.013.

Lei, Z., Maeda, T., Tamura, A., Nakamura, T., Yamazaki, Y., Shiratori, H., Yashiro, K., Tsukita, S., Hamada, H., 2012. EpCAM contributes to formation of functional tight junction in the intestinal epithelium by recruiting claudin proteins. Dev. Biol. 371, 136–145. https://doi.org/10.1016/j.ydbio.2012.07.005.

Letizia, A., He, D., Astigarraga, S., Colombelli, J., Hatini, V., Llimargas, M., Treisman, J. E., 2019. Sidekick is a key component of tricellular adherens junctions that acts to resolve cell rearrangements. Dev. Cell 50, 313–326.e5. https://doi.org/10.1016/j.devcel.2019.07.007.

Leyvraz, C., Charles, R.-P., Rubera, I., Guitard, M., Rotman, S., Breiden, B., Sandhoff, K., Hummler, E., 2005. The epidermal barrier function is dependent on the serine protease CAP1/Prss8. J. Cell Biol. 170, 487–496. https://doi.org/10.1083/jcb.200501038.

List, K., Haudenschild, C.C., Szabo, R., Chen, W., Wahl, S.M., Swaim, W., Engelholm, L. H., Behrendt, N., Bugge, T.H., 2002. Matriptase/MT-SP1 is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis. Oncogene 21, 3765–3779. https://doi.org/10.1038/sj.onc.1205502.

List, K., Kosa, P., Szabo, R., Bey, A.L., Wang, C.B., Molinolo, A., Bugge, T.H., 2009. Epithelial integrity is maintained by a matriptase-dependent proteolytic pathway. Am. J. Pathol. 175, 1453–1463. https://doi.org/10.2353/ajpath.2009.090240.

Lynch, R.D., Tkachuk-Ross, L.J., McCormack, J.M., McCarthy, K.M., Rogers, R.A., Schneeberger, E.E., 1995. Basolateral but not apical application of protease results in a rapid rise of transepithelial electrical resistance and formation of aberrant tight junction strands in MDCK cells. Eur. J. Cell Biol. 66, 257–267.

Madara, J.L., 1990. Maintenance of the macromolecular barrier at cell extrusion sites in intestinal epithelium: physiological rearrangement of tight junctions. J. Membr. Biol. 116, 177–184. https://doi.org/10.1007/BF01868675.

Malin, J., Rosa Birriel, C., Astigarraga, S., Treisman, J.E., Hatini, V., 2022. Sidekick dynamically rebalances contractile and protrusive forces to control tissue morphogenesis. J. Cell Biol. 221, e202107035 https://doi.org/10.1083/jcb.202107035.

Mangeol, P., Massey-Harroche, D., Sebbagh, M., Richard, F., Le Bivic, A., Lenne, P.-F., 2024. The zonula adherens matura redefines the apical junction of intestinal epithelia. Proc. Natl. Acad. Sci. USA 121, e2316722121. https://doi.org/10.1073/pnas.2316722121.

Marchiando, A.M., Shen, L., Graham, W.V., Edelblum, K.L., Duckworth, C.A., Guan, Y., Montrose, M.H., Turner, J.R., Watson, A.J.M., 2011. The epithelial barrier is maintained by in vivo tight junction expansion during pathologic intestinal epithelial shedding. e1–2 Gastroenterology 140, 1208–1218. https://doi.org/10.1053/j.gastro.2011.01.004.

Martin, A.C., Kaschube, M., Wieschaus, E.F., 2009. Pulsed contractions of an actin-myosin network drive apical constriction. Nature 457, 495–499. https://doi.org/10.1038/nature07522.

Martìn-Padura, I., Lostaglio, S., Schneemann, M., Williams, L., Romano, M., Fruscella, P., Panzeri, C., Stoppacciaro, A., Ruco, L., Villa, A., Simmons, D., Dejana, E., 1998. Junctional adhesion molecule, a novel member of the immunoglobulin superfamily that distributes at intercellular junctions and modulates monocyte transmigration. J. Cell Biol. 142, 117–127. https://doi.org/10.1083/jcb.142.1.117.

Masuda, S., Oda, Y., Sasaki, H., Ikenouchi, J., Higashi, T., Akashi, M., Nishi, E., Furuse, M., 2011. LSR defines cell corners for tricellular tight junction formation in epithelial cells. J. Cell Sci. 124, 548–555. https://doi.org/10.1242/jcs.072058.

Maupérin, M., Sassi, A., Méan, I., Feraille, E., Citi, S., 2023. Knock out of CGN and CGNL1 in MDCK cells affects claudin-2 but has a minor impact on tight junction barrier function. Cells 12, 2004. https://doi.org/10.3390/cells12152004.

McCormack, J., Welsh, N.J., Braga, V.M.M., 2013. Cycling around cell-cell adhesion with Rho GTPase regulators. J. Cell Sci. 126, 379–391. https://doi.org/10.1242/jcs.097923.

McMahon, A., Supatto, W., Fraser, S.E., Stathopoulos, A., 2008. Dynamic analyses of Drosophila gastrulation provide insights into collective cell migration. Science 322, 1546–1550. https://doi.org/10.1126/science.1167094.

Mineta, K., Yamamoto, Y., Yamazaki, Y., Tanaka, H., Tada, Y., Saito, K., Tamura, A., Igarashi, M., Endo, T., Takeuchi, K., Tsukita, S., 2011. Predicted expansion of the claudin multigene family. FEBS Lett. 585, 606–612. https://doi.org/10.1016/j.febslet.2011.01.028.

Miyazaki, S., Otani, T., Sugihara, K., Fujimori, T., Furuse, M., Miura, T., 2023. Mechanism of interdigitation formation at apical boundary of MDCK cell. iScience 26, 106594. https://doi.org/10.1016/j.isci.2023.106594.

Morita, K., Furuse, M., Fujimoto, K., Tsukita, S., 1999. Claudin multigene family encoding four-transmembrane domain protein components of tight junction strands. Proc. Natl. Acad. Sci. USA 96, 511–516. https://doi.org/10.1073/pnas.96.2.511.

Nayak, G., Lee, S.I., Yousaf, R., Edelmann, S.E., Trincot, C., Van Itallie, C.M., Sinha, G.P., Rafeeq, M., Jones, S.M., Belyantseva, I.A., Anderson, J.M., Forge, A., Frolenkov, G.I., Riazuddin, S., 2013. Tricellulin deficiency affects tight junction architecture and cochlear hair cells. J. Clin. Invest. 123, 4036–4049. https://doi.org/10.1172/JCI69031.

Naydenov, N.G., Feygin, A., Wang, D., Kuemmerle, J.F., Harris, G., Conti, M.A., Adelstein, R.S., Ivanov, A.I., 2016. Nonmuscle myosin IIA regulates intestinal epithelial barrier in vivo and plays a protective role during experimental colitis. Sci. Rep. 6, 24161 https://doi.org/10.1038/srep24161.

Nelson, K.S., Furuse, M., Beitel, G.J., 2010. The drosophila claudin kune-kune is required for septate junction organization and tracheal tube size control. Genetics 185, 831–839. https://doi.org/10.1534/genetics.110.114959.

Nguyen, T.P., Otani, T., Tsutsumi, M., Kinoshita, N., Fujiwara, S., Nemoto, T., Fujimori, T., Furuse, M., 2024. Tight junction membrane proteins regulate the mechanical resistance of the apical junctional complex. J. Cell Biol. 223, e202307104 https://doi.org/10.1083/jcb.202307104.

Ohnishi, H., Nakahara, T., Furuse, K., Sasaki, H., Tsukita, S., Furuse, M., 2004. JACOP, a novel plaque protein localizing at the apical junctional complex with sequence similarity to cingulin. J. Biol. Chem. 279, 46014–46022. https://doi.org/10.1074/jbc.M402616200.

Orci, L., Amherdt, M., Henquin, J.C., Lambert, A.E., Unger, R.H., Renold, A.E., 1973. Pronase effect on pancreatic beta cell secretion and morphology. Science 180, 647–649. https://doi.org/10.1126/science.180.4086.647.

Otani, T., Nguyen, T.P., Tokuda, S., Sugihara, K., Sugawara, T., Furuse, K., Miura, T., Ebnet, K., Furuse, M., 2019. Claudins and JAM-A coordinately regulate tight junction formation and epithelial polarity. J. Cell Biol. 218, 3372–3396. https://doi.org/10.1083/jcb.201812157.

Paik, D.Y., Janzen, D.M., Schafenacker, A.M., Velasco, V.S., Shung, M.S., Cheng, D., Huang, J., Witte, O.N., Memarzadeh, S., 2012. Stem-like epithelial cells are concentrated in the distal end of the fallopian tube: a site for injury and serous cancer initiation. Stem Cells Dayt. Ohio 30, 2487–2497. https://doi.org/10.1002/stem.1207.

Petri, J., Syed, M.H., Rey, S., Klämbt, C., 2019. Non-cell-autonomous function of the GPI-anchored protein undicht during septate junction assembly. Cell Rep. 26, 1641–1653.e4. https://doi.org/10.1016/j.celrep.2019.01.046.

Pfannenstein, A., Macara, I.G., 2023. A junction-dependent mechanism drives murine mammary cell intercalation for ductal elongation. Dev. Cell 58, 1126–1138.e4. https://doi.org/10.1016/j.devcel.2023.04.009.

Polak-Charcon, S., Shoham, J., Ben-Shaul, Y., 1978. Junction formation in trypsinized cells of human adenocarcinoma cell line. Exp. Cell Res. 116, 1–13. https://doi.org/10.1016/0014-4827(78)90058-7.

Pulimeno, P., Paschoud, S., Citi, S., 2011. A role for ZO-1 and PLEKHA7 in recruiting paracingulin to tight and adherens junctions of epithelial cells. J. Biol. Chem. 286, 16743–16750. https://doi.org/10.1074/jbc.M111.230862.

Quiros, M., Nusrat, A., 2014. RhoGTPases, actomyosin signaling and regulation of the epithelial apical junctional complex. Semin. Cell Dev. Biol. 36, 194–203. https://doi.org/10.1016/j.semcdb.2014.09.003.

Raleigh, D.R., Marchiando, A.M., Zhang, Y., Shen, L., Sasaki, H., Wang, Y., Long, M., Turner, J.R., 2010. Tight junction-associated MARVEL proteins marveld3, tricellulin, and occludin have distinct but overlapping functions. Mol. Biol. Cell 21, 1200–1213. https://doi.org/10.1091/mbc.e09-08-0734.

Reinsch, S., Karsenti, E., 1994. Orientation of spindle axis and distribution of plasma membrane proteins during cell division in polarized MDCKII cells. J. Cell Biol. 126, 1509–1526. https://doi.org/10.1083/jcb.126.6.1509.

Resnik-Docampo, M., Koehler, C.L., Clark, R.I., Schinaman, J.M., Sauer, V., Wong, D.M., Lewis, S., D'Alterio, C., Walker, D.W., Jones, D.L., 2017. Tricellular junctions regulate intestinal stem cell behaviour to maintain homeostasis. Nat. Cell Biol. 19, 52–59. https://doi.org/10.1038/ncb3454.

Reyes, C.C., Jin, M., Breznau, E.B., Espino, R., Delgado-Gonzalo, R., Goryachev, A.B., Miller, A.L., 2014. Anillin regulates cell-cell junction integrity by organizing junctional accumulation of Rho-GTP and actomyosin. Curr. Biol. CB 24, 1263–1270. https://doi.org/10.1016/j.cub.2014.04.021.

Rosenblatt, J., Raff, M.C., Cramer, L.P., 2001. An epithelial cell destined for apoptosis signals its neighbors to extrude it by an actin- and myosin-dependent mechanism. Curr. Biol. CB 11, 1847–1857. https://doi.org/10.1016/s0960-9822(01)00587-5.

Rouaud, F., Vasileva, E., Spadaro, D., Tsukita, S., Citi, S., 2019. R40.76 binds to the α domain of ZO-1: role of ZO-1 (α+) in epithelial differentiation and mechano-sensing. Tissue Barriers 7, e1653748. https://doi.org/10.1080/21688370.2019.1653748.

Rouaud, F., Huang, W., Flinois, A., Jain, K., Vasileva, E., Di Mattia, T., Mauperin, M., Parry, D.A.D., Dugina, V., Chaponnier, C., Méan, I., Montessuit, S., Mutero-Maeda, A., Yan, J., Citi, S., 2023. Cingulin and paracingulin tether myosins-2 to junctions to mechanoregulate the plasma membrane. J. Cell Biol. 222, e202208065 https://doi.org/10.1083/jcb.202208065.

Saito, A.C., Higashi, T., Fukazawa, Y., Otani, T., Tauchi, M., Higashi, A.Y., Furuse, M., Chiba, H., 2021. Occludin and tricellulin facilitate formation of anastomosing tight-junction strand network to improve barrier function. Mol. Biol. Cell 32, 722–738. https://doi.org/10.1091/mbc.E20-07-0464.

Saito, A.C., Endo, C., Fukazawa, Y., Higashi, T., Chiba, H., 2022. Effects of TAMP family on the tight junction strand network and barrier function in epithelial cells. Ann. N. Y. Acad. Sci. 1517, 234–250. https://doi.org/10.1111/nyas.14889.

Saito, A.C., Higashi, T., Chiba, H., 2023. Tight-junction strand networks and tightness of the epithelial barrier. Microsc. Oxf. Engl. 72, 213–225. https://doi.org/10.1093/jmicro/dfad008.

Salomon, J., Gaston, C., Magescas, J., Duvauchelle, B., Canioni, D., Sengmanivong, L., Mayeux, A., Michaux, G., Campeotto, F., Lemale, J., Viala, J., Poirier, F., Minc, N., Schmitz, J., Brousse, N., Ladoux, B., Goulet, O., Delacour, D., 2017. Contractile forces at tricellular contacts modulate epithelial organization and monolayer integrity. Nat. Commun. 8, 13998 https://doi.org/10.1038/ncomms13998.

Schmidt, A., Finegan, T., Häring, M., Kong, D., Fletcher, A.G., Alam, Z., Grosshans, J., Wolf, F., Peifer, M., 2023. Polychaetoid/ZO-1 strengthens cell junctions under tension while localizing differently than core adherens junction proteins. Mol. Biol. Cell 34, ar81. https://doi.org/10.1091/mbc.E23-03-0077.

Schulte, J., Tepass, U., Auld, V.J., 2003. Gliotactin, a novel marker of tricellular junctions, is necessary for septate junction development in Drosophila. J. Cell Biol. 161, 991–1000. https://doi.org/10.1083/jcb.200303192.

Schwayer, C., Shamipour, S., Pranjic-Ferscha, K., Schauer, A., Balda, M., Tada, M., Matter, K., Heisenberg, C.-P., 2019. Mechanosensation of tight junctions depends on ZO-1 phase separation and flow. Cell 179, 937–952.e18. https://doi.org/10.1016/j.cell.2019.10.006.

Sedzinski, J., Hannezo, E., Tu, F., Biro, M., Wallingford, J.B., 2016. Emergence of an apical epithelial cell surface in vivo. Dev. Cell 36, 24–35. https://doi.org/10.1016/j.devcel.2015.12.013.

Sedzinski, J., Hannezo, E., Tu, F., Biro, M., Wallingford, J.B., 2017. RhoA regulates actin network dynamics during apical surface emergence in multiciliated epithelial cells. J. Cell Sci. 130, 420–428. https://doi.org/10.1242/jcs.194704.

Shigetomi, K., Ikenouchi, J., 2019. Cell adhesion structures in epithelial cells are formed in dynamic and cooperative ways. BioEssays N. Rev. Mol. Cell. Dev. Biol. 41, e1800227 https://doi.org/10.1002/bies.201800227.

Sivagnanam, M., Mueller, J.L., Lee, H., Chen, Z., Nelson, S.F., Turner, D., Zlotkin, S.H., Pencharz, P.B., Ngan, B.-Y., Libiger, O., Schork, N.J., Lavine, J.E., Taylor, S., Newbury, R.O., Kolodner, R.D., Hoffman, H.M., 2008. Identification of EpCAM as the gene for congenital tufting enteropathy. Gastroenterology 135, 429–437. https://doi.org/10.1053/j.gastro.2008.05.036.

Steed, E., Rodrigues, N.T.L., Balda, M.S., Matter, K., 2009. Identification of MarvelD3 as a tight junction-associated transmembrane protein of the occludin family. BMC Cell Biol. 10, 95. https://doi.org/10.1186/1471-2121-10-95.

Stephenson, R.E., Higashi, T., Erofeev, I.S., Arnold, T.R., Leda, M., Goryachev, A.B., Miller, A.L., 2019. Rho flares repair local tight junction leaks. Dev. Cell 48, 445–459.e5. https://doi.org/10.1016/j.devcel.2019.01.016.

Stevenson, B.R., Siliciano, J.D., Mooseker, M.S., Goodenough, D.A., 1986. Identification of ZO-1: a high molecular weight polypeptide associated with the tight junction (zonula occludens) in a variety of epithelia. J. Cell Biol. 103, 755–766. https://doi.org/10.1083/jcb.103.3.755.

Strand, D., Raska, I., Mechler, B.M., 1994. The drosophila lethal(2)giant larvae tumor suppressor protein is a component of the cytoskeleton. J. Cell Biol. 127, 1345–1360. https://doi.org/10.1083/jcb.127.5.1345.

Stubbs, J.L., Davidson, L., Keller, R., Kintner, C., 2006. Radial intercalation of ciliated cells during Xenopus skin development. Dev. Camb. Engl. 133, 2507–2515. https://doi.org/10.1242/dev.02417.

Sugawara, T., Furuse, K., Otani, T., Wakayama, T., Furuse, M., 2021. Angulin-1 seals tricellular contacts independently of tricellulin and claudins. J. Cell Biol. 220, e202005062 https://doi.org/10.1083/jcb.202005062.

Suzuki, A., Yamanaka, T., Hirose, T., Manabe, N., Mizuno, K., Shimizu, M., Akimoto, K., Izumi, Y., Ohnishi, T., Ohno, S., 2001. Atypical protein kinase C is involved in the evolutionarily conserved par protein complex and plays a critical role in establishing epithelia-specific junctional structures. J. Cell Biol. 152, 1183–1196. https://doi.org/10.1083/jcb.152.6.1183.

Szabo, R., Bugge, T.H., 2018. Loss of HAI-2 in mice with decreased prostasin activity leads to an early-onset intestinal failure resembling congenital tufting enteropathy. PloS One 13, e0194660. https://doi.org/10.1371/journal.pone.0194660.

Szabo, R., Callies, L.K., Bugge, T.H., 2019. Matriptase drives early-onset intestinal failure in a mouse model of congenital tufting enteropathy. dev183392 Dev. Camb. Engl. 146. https://doi.org/10.1242/dev.183392.

Szabo, R., Kawaguchi, M., Kataoka, H., Bugge, T.H., 2023. Early-onset tufting enteropathy in HAI-2-deficient mice is independent of matriptase-mediated cleavage of EpCAM. Dev. Camb. Engl. 150, dev201801 https://doi.org/10.1242/dev.201801.

Taguchi, K., Ishiuchi, T., Takeichi, M., 2011. Mechanosensitive EPLIN-dependent remodeling of adherens junctions regulates epithelial reshaping. J. Cell Biol. 194, 643–656. https://doi.org/10.1083/jcb.201104124.

Talmon, A., Cohen, E., Bacher, A., Ben-Shaul, Y., 1984. Separation of induction and expression of tight junction formation mediated by proteinases. Biochim. Biophys. Acta 769, 505–507. https://doi.org/10.1016/0005-2736(84)90337-7.

Tanaka, H., Takechi, M., Kiyonari, H., Shioi, G., Tamura, A., Tsukita, S., 2015. Intestinal deletion of Claudin-7 enhances paracellular organic solute flux and initiates colonic inflammation in mice. Gut 64, 1529–1538. https://doi.org/10.1136/gutjnl-2014-308419.

Tatum, R., Zhang, Y., Salleng, K., Lu, Z., Lin, J.-J., Lu, Q., Jeansonne, B.G., Ding, L., Chen, Y.-H., 2010. Renal salt wasting and chronic dehydration in claudin-7-deficient mice. Am. J. Physiol. Ren. Physiol. 298, F24–F34. https://doi.org/10.1152/ajprenal.00450.2009.

Terry, S., Nie, M., Matter, K., Balda, M.S., 2010. Rho signaling and tight junction functions. Physiol. Bethesda Md 25, 16–26. https://doi.org/10.1152/physiol.00034.2009.

Tokuda, S., Higashi, T., Furuse, M., 2014. ZO-1 knockout by TALEN-mediated gene targeting in MDCK cells: involvement of ZO-1 in the regulation of cytoskeleton and cell shape. PlOS One 9, e104994. https://doi.org/10.1371/journal.pone.0104994.

Tsukita, S., Furuse, M., 1999. Occludin and claudins in tight-junction strands: leading or supporting players? Trends Cell Biol. 9, 268–273. https://doi.org/10.1016/s0962-8924(99)01578-0.

Turner, J.R., Buschmann, M.M., Romero-Calvo, I., Sailer, A., Shen, L., 2014. The role of molecular remodeling in differential regulation of tight junction permeability. Semin. Cell Dev. Biol. 36, 204–212. https://doi.org/10.1016/j.semcdb.2014.09.022.

Uechi, H., Kuranaga, E., 2019. The tricellular junction protein sidekick regulates vertex dynamics to promote bicellular junction extension. Dev. Cell 50, 327–338.e5. https://doi.org/10.1016/j.devcel.2019.06.017.

Umeda, K., Matsui, T., Nakayama, M., Furuse, K., Sasaki, H., Furuse, M., Tsukita, S., 2004. Establishment and characterization of cultured epithelial cells lacking expression of ZO-1. J. Biol. Chem. 279, 44785–44794. https://doi.org/10.1074/jbc.M406563200.

Umeda, K., Ikenouchi, J., Katahira-Tayama, S., Furuse, K., Sasaki, H., Nakayama, M., Matsui, T., Tsukita, Sachiko, Furuse, M., Tsukita, Shoichiro, 2006. ZO-1 and ZO-2 independently determine where claudins are polymerized in tight-junction strand formation. Cell 126, 741–754. https://doi.org/10.1016/j.cell.2006.06.043.

Van Itallie, C.M., Tietgens, A.J., Anderson, J.M., 2017. Visualizing the dynamic coupling of claudin strands to the actin cytoskeleton through ZO-1. Mol. Biol. Cell 28, 524–534. https://doi.org/10.1091/mbc.E16-10-0698.

Van Itallie, C.M., Lidman, K.F., Tietgens, A.J., Anderson, J.M., 2019. Newly synthesized claudins but not occludin are added to the basal side of the tight junction. Mol. Biol. Cell 30, 1406–1424. https://doi.org/10.1091/mbc.E19-01-0008.

Varadarajan, S., Stephenson, R.E., Miller, A.L., 2019. Multiscale dynamics of tight junction remodeling. J. Cell Sci. 132, jcs229286 https://doi.org/10.1242/jcs.229286.

Varadarajan, S., Chumki, S.A., Stephenson, R.E., Misterovich, E.R., Wu, J.L., Dudley, C. E., Erofeev, I.S., Goryachev, A.B., Miller, A.L., 2022. Mechanosensitive calcium flashes promote sustained RhoA activation during tight junction remodeling. J. Cell Biol. 221, e202105107 https://doi.org/10.1083/jcb.202105107.

Varadarajan, S., Raya-Sandino, A., Nusrat, A., 2023. Clipping EpCAM to release Claudin-7 for the greater good of the epithelial barrier. J. Cell Biol. 222, e202211127 https://doi.org/10.1083/jcb.202211127.

Vega-Salas, D.E., Salas, P.J., Rodriguez-Boulan, E., 1987. Modulation of the expression of an apical plasma membrane protein of Madin-Darby canine kidney epithelial cells: cell-cell interactions control the appearance of a novel intracellular storage compartment. J. Cell Biol. 104, 1249–1259. https://doi.org/10.1083/jcb.104.5.1249.

Ventrella, R., Kim, S.K., Sheridan, J., Grata, A., Bresteau, E., Hassan, O.A., Suva, E.E., Walentek, P., Mitchell, B.J., 2023. Bidirectional multiciliated cell extrusion is controlled by Notch-driven basal extrusion and Piezo1-driven apical extrusion. Dev. Camb. Engl. 150, dev201612 https://doi.org/10.1242/dev.201612.

Ventura, G., Amiri, A., Thiagarajan, R., Tolonen, M., Doostmohammadi, A., Sedzinski, J., 2022. Multiciliated cells use filopodia to probe tissue mechanics during epithelial integration in vivo. Nat. Commun. 13, 6423. https://doi.org/10.1038/s41467-022-34165-0.

Voiculescu, O., Bertocchini, F., Wolpert, L., Keller, R.E., Stern, C.D., 2007. The amniote primitive streak is defined by epithelial cell intercalation before gastrulation. Nature 449, 1049–1052. https://doi.org/10.1038/nature06211.

de Vreede, G., Gerlach, S.U., Bilder, D., 2022. Epithelial monitoring through ligand-receptor segregation ensures malignant cell elimination. Science 376, 297–301. https://doi.org/10.1126/science.abl4213.

Wang, Z., Bosveld, F., Bellaïche, Y., 2018. Tricellular junction proteins promote disentanglement of daughter and neighbour cells during epithelial cytokinesis. jcs215764 J. Cell Sci. 131. https://doi.org/10.1242/jcs.215764.

Werner, M.E., Mitchell, J.W., Putzbach, W., Bacon, E., Kim, S.K., Mitchell, B.J., 2014. Radial intercalation is regulated by the Par complex and the microtubule-stabilizing protein CLAMP/Spef1. J. Cell Biol. 206, 367–376. https://doi.org/10.1083/jcb.201312045.

Wittek, A., Hollmann, M., Schleutker, R., Luschnig, S., 2020. The transmembrane proteins M6 and anakonda cooperate to initiate tricellular junction assembly in epithelia of drosophila. Curr. Biol. CB 30, 4254–4262.e5. https://doi.org/10.1016/j.cub.2020.08.003.

Woods, D.F., Bryant, P.J., 1991. The discs-large tumor suppressor gene of Drosophila encodes a guanylate kinase homolog localized at septate junctions. Cell 66, 451–464. https://doi.org/10.1016/0092-8674(81)90009-x.

Woods, D.F., Wu, J.W., Bryant, P.J., 1997. Localization of proteins to the apico-lateral junctions of drosophila epithelia. Dev. Genet. 20, 111–118 https://doi.org/10.1002/(SICI)1520-6408(1997)20:2<111::AID-DVG4>3.0.CO;2-A.

Wu, C.-J., Mannan, P., Lu, M., Udey, M.C., 2013. Epithelial cell adhesion molecule (EpCAM) regulates claudin dynamics and tight junctions. J. Biol. Chem. 288, 12253–12268. https://doi.org/10.1074/jbc.M113.457499.

Wu, C.-J., Feng, X., Lu, M., Morimura, S., Udey, M.C., 2017. Matriptase-mediated cleavage of EpCAM destabilizes claudins and dysregulates intestinal epithelial homeostasis. J. Clin. Invest. 127, 623–634. https://doi.org/10.1172/JCI88428.

Wu, V.M., Schulte, J., Hirschi, A., Tepass, U., Beitel, G.J., 2004. Sinuous is a drosophila claudin required for septate junction organization and epithelial tube size control. J. Cell Biol. 164, 313–323. https://doi.org/10.1083/jcb.200309134.

Wu, V.M., Yu, M.H., Paik, R., Banerjee, S., Liang, Z., Paul, S.M., Bhat, M.A., Beitel, G.J., 2007. Drosophila Varicose, a member of a new subgroup of basolateral MAGUKs, is required for septate junctions and tracheal morphogenesis. Dev. Camb. Engl. 134, 999–1009. https://doi.org/10.1242/dev.02785.

Xu, C., Tang, H.-W., Hung, R.-J., Hu, Y., Ni, X., Housden, B.E., Perrimon, N., 2019. The septate junction protein Tsp2A restricts intestinal stem cell activity via endocytic regulation of aPKC and hippo signaling. Cell Rep. 26, 670–688.e6. https://doi.org/10.1016/j.celrep.2018.12.079.

Xu, J., Kausalya, P.J., Phua, D.C.Y., Ali, S.M., Hossain, Z., Hunziker, W., 2008. Early embryonic lethality of mice lacking ZO-2, but Not ZO-3, reveals critical and nonredundant roles for individual zonula occludens proteins in mammalian development. Mol. Cell. Biol. 28, 1669–1678. https://doi.org/10.1128/MCB.00891-07.

Yamada, S., Pokutta, S., Drees, F., Weis, W.I., Nelson, W.J., 2005. Deconstructing the cadherin-catenin-actin complex. Cell 123, 889–901. https://doi.org/10.1016/j.cell.2005.09.020.

Yanagihashi, Y., Usui, T., Izumi, Y., Yonemura, S., Sumida, M., Tsukita, S., Uemura, T., Furuse, M., 2012. Snakeskin, a membrane protein associated with smooth septate junctions, is required for intestinal barrier function in Drosophila. J. Cell Sci. 125, 1980–1990. https://doi.org/10.1242/jcs.096800.

Yonemura, S., Itoh, M., Nagafuchi, A., Tsukita, S., 1995. Cell-to-cell adherens junction formation and actin filament organization: similarities and differences between non-polarized fibroblasts and polarized epithelial cells. J. Cell Sci. 108 (Pt 1), 127–142. https://doi.org/10.1242/jcs.108.1.127.

Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A., Shibata, M., 2010. alpha-Catenin as a tension transducer that induces adherens junction development. Nat. Cell Biol. 12, 533–542. https://doi.org/10.1038/ncb2055.

Yu, H.H., Zallen, J.A., 2020. Abl and Canoe/Afadin mediate mechanotransduction at tricellular junctions. Science 370, eaba5528. https://doi.org/10.1126/science.aba5528.

Yu-Kemp, H.-C., Szymanski, R.A., Cortes, D.B., Gadda, N.C., Lillich, M.L., Maddox, A.S., Peifer, M., 2022. Micron-scale supramolecular myosin arrays help mediate cytoskeletal assembly at mature adherens junctions. J. Cell Biol. 221, e202103074 https://doi.org/10.1083/jcb.202103074.

Zappia, M.P., Brocco, M.A., Billi, S.C., Frasch, A.C., Ceriani, M.F., 2011. M6 membrane protein plays an essential role in Drosophila oogenesis. PlOS ONe 6, e19715. https://doi.org/10.1371/journal.pone.0019715.