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Abstract

Epithelial adhesive cell-to-cell contacts contain large, plasma membrane-spanning multiprotein aggregates that perform vital structural and signaling functions. Three prominent adhesive contacts are the tight junction, adherens junction, and the desmosome. Each junction type has unique cellular functions and a complex molecular composition. In this review, we comment on recent and exciting advances in our understanding of junction composition and function.

Too tight to see

Tight junction (TJ) structures form a gasket-like seal around the cell at the apical-most aspect of the lateral plasma membrane (Figure 1) [1-4]. This seal regulates both the intermixing of apical and lateral membrane components and paracellular tissue barrier properties. TJs are responsible for both maintaining epithelial polarity and restricting the paracellular passage of ions and solutes. By freeze-fracture electron microscopy, the ultrastructure of the TJ is seen as a latticework of proteinaceous strands. It has been appreciated for some time that these stands contain claudin superfamily proteins, yet due to the lack of a claudin crystal structure, little is known concerning primary claudin interactions in TJ strands. Suzuki et al. recently provided a compelling model of the TJ structure [5]. The flagellate protist Euglena gracilis utilizes the claudin-like protein IP39 to form linear arrays that are quite similar to TJs. Purification and crystallization of endogenous IP39 arrays led to several discoveries: a) polymerization of trimeric IP39 subunits, b) antiparallel row formation, and c) heterogeneous trimer interactions, which suggest a potential mechanism for TJ strand branching.

The TJ is by far the most complex and least understood junction, due in part to the diversity and number of its molecular constituents. Indeed, discoveries of novel TJ-associated proteins continue. For example, Higashi et al. introduced the angulin family of tricellular TJ proteins [6]. The authors studied the function of lipoprotein receptor (LSR)-related proteins immunoglobulin-like domain-containing receptor1 (ILDR1) and 2, which exhibit tissue- and organ-specific expression patterns and have differing effects on barrier function, with ILDR1 and LSR being associated with tighter barriers than ILDR2. Tricellular TJ contacts occur as three cells intersect, and attempts to inventory tricellular proteins are particularly welcome given that paracellular macromolecule flux occurs largely through these contacts [7]. Prior to this finding, only tricellulin and LSR were known components of the tricellular junction.

Our growing knowledge of TJ constituents presents a further problem: how do the plethora of TJ proteins interact? Van Itallie et al. address this issue by assessing the protein complexes surrounding zonula occludens-1 (ZO-1) [8]. Using a biotin ligase proximity-labeling technique, the authors identify more than 400 potential interacting proteins, including novel TJ proteins FBP1L, US6NL, and IGS11. Truncation studies showed the ZO-1 N-terminal segments interact in proximity to signaling proteins and transmembrane components, such as claudins and occludin, while C-terminal ZO-1 interacts with actin network proteins. Therefore, ZO-1, either individually or in mass, links the transmembrane TJ components to the actin cytoskeleton. This powerful technique has the potential to help us understand the nature and function of the TJ plaque, particularly under
different biologically interesting states, such as TJ assembly or remodeling due to proinflammatory cytokine exposure.

### Adhesion under stress

Cadherin-based adhesions populate the lateral membrane below the TJ, forming homotypic transcellular interactions through their calcium-dependent ectodomains. E-cadherin is a major cadherin isoform in epithelial tissues and is involved in cellular processes such as cell-cell contact inhibition signaling, cell proliferation, actin cytoskeletal remodeling, and cell polarity establishment [9,10]. Inside the cell, E-cadherin binds to the catenin family proteins p120, α-catenin, and β-catenin. Catenins mediate cadherin-dependent functions, and the nature of the molecular mechanisms involved is the subject of intense study and debate.

A recent article by Rangarajan and Izard weighs in on this debate with an interesting comparative structural study of full-length α-catenin [11]. The β-catenin–α-catenin complex does not appear to directly bind F-actin, and, therefore, a physical link between the adherens junction (AJ) and actin network is believed to require additional interactions [12,13].

The authors observe that α-catenin forms an asymmetric dimer with a high affinity for F-actin, while the β-catenin–α-catenin complex binding interface competes for both the α-catenin dimerization domain and F-actin engagement. The authors further suggest that activated vinculin binding may mediate the link between E-cadherin and the actin network.

Several notable studies have recently reinforced the concept of a direct linkage between the AJ and the actin cytoskeleton through α-catenin, including studies of α-catenin function in *Drosophila*. Desai et al. take a mutagenesis approach and provide *in vivo* data supporting the view that α-catenin is a physical linker between the cadherin–β-catenin complex and the actin cytoskeleton [14]. In *Drosophila*, Rap1 activity has been shown to regulate cadherin-catenin interactions with the actin cytoskeleton during gastrulation, further supporting this link [15].

Using single-molecule atomic force microscopy, Rakshit et al. studied cadherin homodimer bonding under mechanical tension [16]. The authors showed that newly formed E-cadherin trans-dimers will rapidly form a "catch bond", which is strengthened under stress. Persistent E-cadherin trans-dimers will mature and exhibit high-affinity binding in the absence of force. These results suggest a physical mechanism that cadherins use to resist tensile forces as cells rearrange during cell-cell contact formation and tissue homeostasis.

These recent structural and biochemical findings exploring the AJ are fascinating, and given that both α-catenin and vinculin have recently been shown to act as tension-regulated adaptor proteins, it seems likely that the cadherin-catenin complex functions as a mechanical adhesion stress sensor [17,18]. If so, controversies surrounding the biochemical arrangement of this complex may require the study of adhesions under stress.

### Desmosome in the Spotlight

Desmosomes form intermittent spot adhesions along the lateral membrane and are anchored in the cytoplasm to intermediate filaments. These structures provide mechanical resilience to the epithelium, thus contributing to tissue homeostasis. There are two types of desmosomal cadherins, desmogleins (1-4) and desmocollins (1-3), each with several isoforms (for detailed desmosome structure, see [19]). Along with their structural role, desmosomes are emerging as centers of intracellular signaling.

Desmoglein-1 appears in recent studies as a regulator of cell differentiation. The guanylate exchange factor Bcr is a regulator of keratinocyte differentiation that acts
Conclusions

Rapid progress is being made in the exploration of cell adhesive junctions, and given the central role these junctions play in epithelial homeostasis and disease, the attention is warranted. Many of these complexes have been studied for decades but retain the ability to surprise us with novel biological functions, protein constituents, and links to disease states. That said, we expect more surprises in the years to come.

Abbreviations

AJ, adherens junction; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; ILDR, immunoglobulin-like domain-containing receptor; LEF, lymphoid enhancing factor; LSR, lipoprotein receptor; MAL, myocardin-related transcription factor; PKC, protein kinase C; TCF, T cell factor; TJ, tight Junction; ZO-1, zonula occludens-1.

Disclosures

The authors declare that they have no disclosures.

References


