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Tricellular junctions: a hot corner of epithelial biology

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As the result of an intricate interplay between mechanical and biochemical cues, coordinated cell dynamics are at the basis of tissue development, homeostasis and repair. Numerous studies have addressed the interplay between these two inputs and their impact on cellular dynamics. These studies largely focus on bicellular junctions (BCJs). Recent works have illuminated that tricellular junctions (TCJs), the junctions where three cells contact, play important roles in epithelial tissues beyond their well-known structural function in preserving epithelial barrier integrity. Indeed, TJCs have recently been implicated in the regulation of collective cell migration, division orientation, cell proliferation and cell mechanical properties. More generally, the TCJ distribution aligns with the cell shape and mechanical stress orientation within the tissue, while their number encapsulates the packing topology. Importantly, known regulators of growth signalling and of cell mechanical properties are also localized at TCJs. Therefore, TCJs emerge as spatial sites to sense and integrate biochemical and mechanical inputs to guide epithelial tissue dynamics.

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Introduction

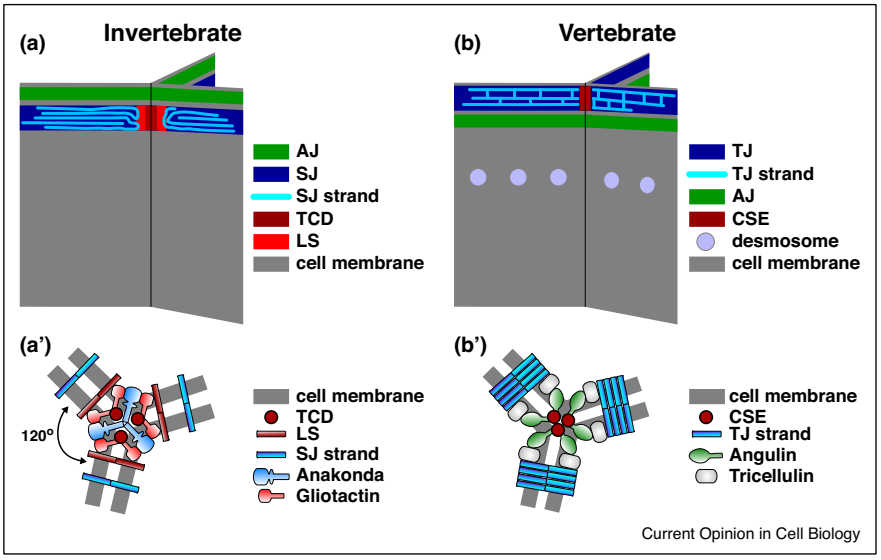
As selective permeability barriers epithelial tissues cover organs separating them from the external milieu. To ensure barrier function cells are packed and form adhesive contacts along their apical-basal axes, at both the bicellular junctions (BCJs) and at the tricellular junctions (TCJs). In vertebrate tissues, cell–cell adhesion is mediated by the apical tight junctions (TJs), basal-lateral adherens junctions (AJs) and the desmosomes, while in invertebrate tissues adhesion is mediated by the apical AJs and the basal-lateral septate junctions (SJs) (Figure 1a,b) (reviews [1–6]). Numerous works have focused on the roles of BCJ mechanical properties, their formation and remodelling in promoting tissue dynamics and regulating epithelial packing (reviews [7–9]). Recent studies show that epithelial tissue dynamics and mechanics can be understood, if TCJ function is taken into account. After a brief description of the TCJ structure in vertebrate and invertebrate systems, we will focus on the emerging roles of TCJs in epithelial cell division, migration, mechanics and stem cell maintenance.

TCJ structure, protein composition and regulation

Vertebrate and invertebrate TCJ structure and formation are best characterized at the level of the TJ and SJ, respectively. In vertebrate and invertebrate model systems TCJ channels are present along the apical-basal axis at the contact interfaces between three cells. They are formed by a series of stacked diaphragms, tricellular channel diaphragms (TCD) in invertebrates or a central sealing element (CSE) in vertebrates (Figure 1a,b) (reviews [5,[21••]]). In vertebrates, the bicellular TJs form strands that attach to the CSE [10], while in invertebrates the bicellular SJ strands connect to the diaphragm along the apical-basal axis forming a lateral limiting strand (LS) at the tricellular contact interface [11–13]. At the molecular level, in vertebrates, Tricellulin mediates the connection between the TJ strands and CSE via the Angulin proteins (Angulin 1–3) [14–17]. In invertebrates, the molecular link between the LS and the TCD is proposed to be mediated by the Gliotactin (Gli) protein [18,19], while the connection between the TCD and Gli is mediated by the Anakonda (Aka) transmembrane protein [20,21••]. On the basis of experimental data and computer simulations, the geometry of the TCJ is proposed to facilitate the self-organization of the extracellular domains of Aka proteins from three adjacent cells into a tripartite septum in the TCJ lumen (Figure 1a′) [21••].

To understand how TCJs are formed and remodeled, it is essential to determine how proteins are targeted to the TCJs. Currently, the mechanisms regulating protein localization to the TCJ are poorly understood. However, the Auld lab has provided insights into this question in *Drosophila* by analyzing Gli protein localization at TCJs. The localization and protein levels of Gli are regulated by phosphorylation-dependent endocytosis and degradation facilitated by the SJ protein Discs-large (Dlg) [22–24] and the C-terminal Src kinase (Csk) [25••]. Moreover, Gli mRNA levels are regulated though a feedback mechanism that utilizes the BMP pathway to upregulate a

Figure 1



Cell–cell adhesion structures in *Drosophila* and mammals.
(a, b) Schematics showing the organization of the invertebrate and vertebrate cell–cell adhesion sites along the apical-basal axis (a, b), and cross sections of the TCJ at the level of the septate junction (SJ) and tight junction (TJ) (a', b'). In invertebrate tissues, adhesion is mediated by the apical adherens junctions (AJs) and the septate junctions (SJs), while, in vertebrate tissues, cell–cell adhesion is mediated by the tight junctions (TJs), AJs and desmosomes (reviews [1–6]). *Drosophila* SJs are located below the AJs, while the functionally equivalent structures in vertebrates, the TJs, are located above the AJs. In both invertebrates and vertebrates, at the level of the SJ or TJ, respectively, TCJ channels are present along the apical-basal axis formed by a series of stacked diaphragms, tricellular channel diaphragms (TCD) in invertebrates or a central sealing element (CSE) in vertebrates (a, b) (reviews [5,6]). In vertebrate systems, the bicellular TJs form strands that attach to the CSE [13], while in invertebrates the bicellular SJ strands connect to the diaphragm along the apical-basal axis forming a lateral limiting strand (LS) at the tricellular contact interface [11–13]. At the *Drosophila* TCJ the Aka proteins from three cells form a trimer and recruit Gli [19,21••]. In turn, Gli interacts with the LS connecting the SJs with the TCDs to form a mature TCJ (a'). In mammalian cells, the Angulin family of proteins likely interact through their extracellular Ig-like domains with the CSE, while their intracellular domains can interact with Tricellulin, which in turn connects to the TJ strands to form a mature TCJ (b') (reviews [5,6] and [14–17]).

microRNA, miR-184, which targets the 3′UTR of Gli for degradation [26].

Combined these studies show that TCJs are complex molecular structures, of which the molecular composition needs to be strictly controlled to ensure barrier integrity.

TCJ formation during epithelial tissue remodelling and division

In order to preserve barrier function during homeostasis or morphogenesis, remodelling and *de novo* formation of BCJs and TCJs needs to be coupled with local cellular dynamics such as cell elimination (extrusion, apoptosis, fusion [27,28]), addition (division, insertion [29,30]), or changes in cell positions during cell rearrangements [31]. Two studies have addressed how *de novo* TCJs are formed in the mouse ear skin epithelium [32,33••]. This multilayered epithelium is composed of an outer barrier (stratum corneum), followed by the TJ barrier (stratum granulosum), the stratum spinosum and the proliferative layer (stratum basale). Cells from the proliferative layer traverse though the stratum spinosum and stratum granulosum to finally reach the stratum corneum. Yokouchi *et al.* [33••] demonstrated that during this upward migration the cells form a 3D shape filling structure resembling a Kelvin's tetrakaidecahedron (14-sided solid with six rectangular and eight hexagonal sides) and establish Tricellulin/Angulin-1 positive TCJs with the cells of the stratum granulosum to preserve barrier integrity when entering the stratum granulosum layer. The second study addressed how the skin antigen-presenting dendritic cells, the Langerhans cells, located between the stratum spinosum and stratum basale layers, generate dendrites that penetrate the stratum granulosum to uptake antigens in the space between the stratum granulosum and stratum corneum layers and within the stratum corneum [32]. When a dendrite penetrates the TJ of the stratum granulosum layer, Tricellulin accumulates at the tricellular contact sites between two stratum granulosum cells and the dendritic cell to establish new TCJs, thus preserving barrier integrity.

In parallel to these studies on TCJ remodelling, the *de novo* TCJ formation in monolayered proliferative epithelia is emerging as an important field of research. *De novo* BCJ formation at the level of the AJs upon cell division within epithelial tissues has been characterized. Combined, these studies demonstrate that the formation of a