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Interplay between tight junctions & adherens junctions

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A B S T R A C T

Cell-cell adhesions are critical for the development and maintenance of tissues. Present at sites of cell-cell contact are the adherens junctions and tight junctions. The adherens junctions mediate cell-cell adhesion via the actions of nectins and cadherins. The tight junctions regulate passage of ions and small molecules between cells and establish cell polarity. Historically, the adherens and tight junctions have been thought of as discrete complexes. However, it is now clear that a high level of interdependency exists between the two junctional complexes. The adherens junctions and tight junctions are physically linked, by the *zonula occludens* proteins, and linked via signaling molecules including several polarity complexes and actin cytoskeletal modifiers. This review will first describe the individual components of both the adherens and tight junctions and then discuss the coupling of the two complexes with an emphasis on the signaling links and physical interactions between the two junctional complexes.

1. Introduction

The interactions between cells are important for the assembly and maintenance of three dimensional tissues. Ultrastructural studies reveal that cells are connected by multiple junctional complexes, including the tight junctions, adherens junctions, gap junctions, and desmosomes. These junctions are arranged with the tight junctions nearest the apical (lumen exposed) portion of the cell and the adherens junctions immediately underneath the tight junctions. Both the gap junctions and desmosomes are located more basally. Of these junctional components, the tight junctions and adherens junctions have been highly studied and are the subject of this review. It is appreciated that tight junctions are multiprotein complexes found in regions where membranes of two cells join together. The tight junctions have two functions: 1) a fence function, which prevents mixing of membrane lipids between the apical and basolateral membranes and 2) a gate function, which regulates the passage of molecules and ions between cells. In contrast, the adherens junctions contain two subcomplexes: the nectin-based adhesions, which form the first attachment of cells to their neighbors and the cadherin-based adhesions which mediate strong cell-cell adhesion.

While the adherens junctions and tight junctions have historically been studied as discrete complexes, evidence suggests a high level of interdependency. The formation of tight junctions is dependent on the cadherin- and nectin-based adhesions. Conversely, mutated tight junction proteins delay the maturation of adherens junctions [1]. Hence, these junctions are not discrete but highly interdependent. This review will first describe the main constituents of adherens junctions and tight junctions and then will focus on connections and interplay between the two junctions.

2. Adherens junctions

The adherens junctions are comprised of two families of transmembrane spanning, adhesive receptors: the cadherins and the nectins (Fig. 1). The extracellular regions of these proteins mediate adhesion of cells to their neighbors while the intracellular regions interact with an array of proteins. These intracellular proteins control the assembly and dynamics of adherens junctions by modulating connections with the actin cytoskeleton and stimulating signaling pathways.

2.1. Cadherin-based adhesions

There are over 20 members of the cadherin superfamily. Epithelial cadherin, or E-cadherin, is found primarily in epithelial tissues and is the focus of this review. E-cadherin has five immunoglobulin-like extracellular cadherin repeat domains that mediate the adhesion of cells to adjacent cells [2]. To mediate adhesion, cadherins first form *cis*-dimers with cadherins on the same cells [3–5]. Contact with an adjacent cell is then initiated by the formation of *trans*-dimers with cadherins on neighboring cells across the paracellular space [3,4]. *Trans*- and *cis*- cadherin dimers mediate strong adhesion, thereby preventing the separation of cells.

Like the N-terminal domains, the E-cadherin cytoplasmic tail is

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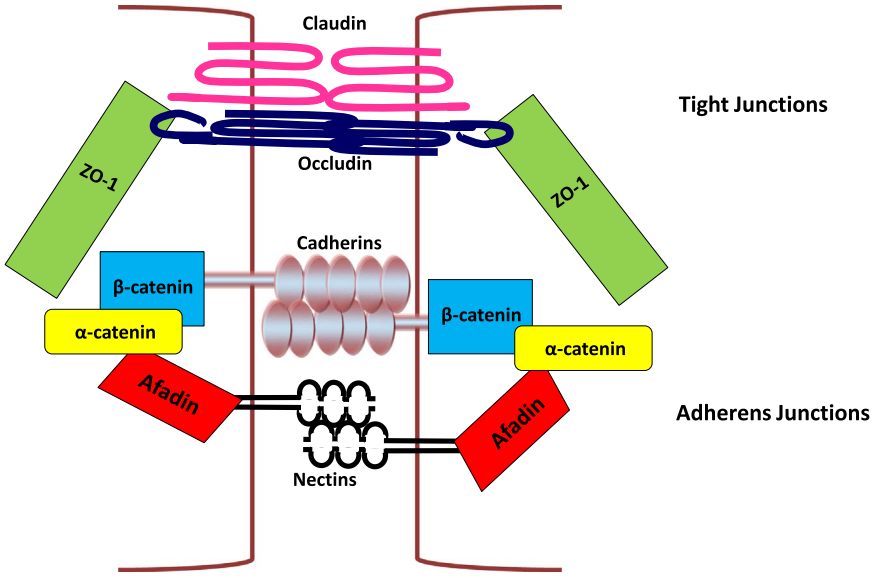

Fig. 1. Schematic of the adherens junctions and tight junctions. The adherens junctions are composed of the nectin-based adhesions and the cadherin-based adhesions. The extracellular domains of nectins dimerize with nectins on neighboring cells and the cyotplasmic tail recruits afadin. Similarly, cadherins bind to cadherins on adjacent cells. The cadherin cytoplasmic tail recruits β-catenin which in turn binds α-catenin. More apical to the adherens junctions are the tight junctions. The main constituents of the tight junctions are two transmembrane spanning proteins, occludin and claudin. Occludin recruits ZO-1, an actin binding protein, that can during the formation of cell-cell junctions bind to the adherens junction protein, α-catenin. The brown lines indicate the plasma membranes of two adjacent cells.

highly conserved and mediates interactions with the catenin proteins and other actin cytoskeletal binding proteins [6,7]. Catenins recruited to the cadherin cytoplasmic domain include β-catenin, α-catenin, and p120-catenin (Fig. 1). The interaction between E-cadherin and β-catenin retains β-catenin at sites of cell-cell contact. Under these conditions, E-cadherin prevents β-catenin from entering the nucleus, binding the transcription factor, Lef, and stimulating transcription [8]. In addition, β-catenin binds α-catenin, [7] which links E-cadherin to the actin cytoskeleton. α-Catenin is an actin bundling protein. The Nelson laboratory suggested α-catenin was unable to bind β-catenin and actin filaments simultaneously [9]. However, it is now widely appreciated that α-catenin binds both β-catenin and actin filaments, but this event is restricted to cells under force [10]. A third catenin, p120-catenin directly binds to the E-cadherin juxtamembrane domain [6,11,12]. This interaction stabilizes E-cadherin at the plasma membrane, promotes cadherin clustering, and stimulates the Rho family GTPases [13]. Subsequently, the Rho family GTPases bind effector proteins and modulate actin dynamics.

2.2. Nectins

The nectin family contains four members each with several splice variants [14]. The nectin extracellular domain contains three Ig-like loops, followed by a single pass transmembrane domain, and a cytoplasmic tail [15]. The Ig-like loops are necessary for the dimerization of nectins. Similar to the cadherins, nectin dimerization occurs through the formation of *cis* dimers followed by *trans* dimer formation across cell-cell junctions [15].

Like cadherins, nectins mediate cell-cell adhesion and facilitate the establishment of apical-basolateral polarity. This adhesion is fundamentally different from the cadherins in two ways. First, nectin dimers are unable to support strong cell-cell adhesion, thereby rendering cadherins as the major cell-cell adhesion receptor in adherens junctions. Second, unlike cadherins, nectins can form homophilic interactions with the same family member and heterophilic interactions with related family members [16].

The cytoplasmic tails of nectins are involved in protein-protein interactions (Fig. 1). At the C-terminus of nectins, a PDZ binding motif binds afadin [15,17]. Afadin is an actin binding protein that anchors the nectins to the actin cytoskeleton. The nectin-afadin interaction is essential for adherens junction maturation, as loss of afadin delays cadherin localization to cell-cell junctions and weakens adherens junctions [18]. In addition to afadin, nectins interact with cell polarity proteins, such as partitioning-defective homolog 3 (Par3) [15,19]. This interaction ensures the correct spatial and temporal localization of Par3 and the subsequent establishment of apico-basolateral polarity.

3. Tight junctions

The most apical of all the junctional components are the tight junctions (Fig. 1). The tight junctions have two functions. They have a barrier or gate function that regulates the passage of ions, water, and macromolecules through the regions between cells (i.e. paracellular space). Tight junctions also have a fence function that establishes and maintains cell polarity by restricting the distribution of lipids within the membrane.

Tight junctions are composed of greater than 40 proteins that are either transmembrane proteins or cytoplasmic actin-binding proteins. The former are responsible for establishing cell-cell contact in the intercellular space, while the latter serve as a link to the actin cytoskeleton. The primary constituents in the transmembrane group are the claudins, occludin, and junctional adhesion molecules (JAMs). The primary cytoplasmic actin binding proteins in the tight junctions are the *zonula occludens* (ZO) proteins.

3.1. Claudins

The claudins form the backbone of tight junctions and are the most important components of the tight junctions. They regulate the gate function of tight junctions by restricting the elements that pass by their size. The claudins have four transmembrane domains, with the N-terminus and the C-terminus in the cytoplasm [20,21]. These domains are arranged such that there are two large extracellular loops and a cytoplasmic tail. Extracellular loop 1 contains several charged amino acid residues that regulate paracellular charge selectivity [22]. The

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