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Molecular Components of the Adherens Junction

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Abstract

Adherens junctions serve to couple individual cells into various arrangements required for tissue structure and function. The central structural components of adherens junctions are transmembrane adhesion receptors, and their associated actin-binding/regulatory proteins. The molecular machineries that organize these adhesion receptor complexes into higher order junction structures, and the functional consequences of this junctional organization will be discussed.

I. Overview

The adherens junction (AJ) is a structure that links membrane and cytoskeletal components at discrete contact regions. As its name implies, the molecular components of this junction are required for basic cell-cell adhesion. The consequences of this adhesion, that is, the organization of adhesive units into higher order structures or “junctions”-- are more far-reaching. For example, *junctional* adhesions are critical for processes such as epithelial cell polarization, where the AJ contributes to a landmark that defines an apical/basolateral axis, to tissue morphogenesis, where AJs effectively couple the cytoskeletons of adjacent cells so that they can undergo coordinated movements. In this review, we discuss the ultrastructural and molecular organization of AJs. Other sections of this issue will focus specifically on adherens junction dynamics/regulation (9), the role of adherens junctions in organogenesis (18), and the relationship between AJs and other junction systems (5). To complement these sections, we will highlight the issue of junctional versus non-junctional organizations of adhesion components [1]. We consider evidence that the molecular components required for the adhesive function of AJs provide basic cell-cell adhesive activity independently of their junctional organization. Only after these core adhesive components are organized into junctional structures, are “extra-adhesive functions” served, such as cell polarization and intercellular coupling for purposes of tissue morphogenesis.

II. The ultrastructural tradition of the adherens junction

Although AJs are observed in various cell contexts (e.g., intercalated disk/fascia adherens of cardiac myocytes; paranodal loops/intracellular junctions of Schwann cells), and have historically encompassed cell-substratum adhesions (e.g., focal contacts, [2], the most well known example is the zonular adherens junction, or *zonula adherens* (ZA) of polarized

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epithelial cells (Figure 1A). The ZA was described by Farquhar and Palade as the intermediate component of a tripartite, junction complex, commonly found between the apices of most simple epithelia [3]. The two other components of this complex, the more lumenally localized zonula occludens (or tight junction) and the basally localized desmosome are compositionally and functionally distinct and are discussed elsewhere (in this series, 2, 3, 6 & 10). At the electron microscopic level, the AJ is a region where membranes appear perfectly parallel over an intercellular space of ~200 Å and extending between 0.2–0.5μm in length [3]. Deep-etch electron microscopy reveals that the intercellular space of the AJ is connected by numerous cylinder-like projections [4], (Figure 1B) and may reflect higher order structures of the transmembrane adhesive components (cadherins and nectins) discussed below. The cytoplasmic side of the adherens contact is characterized by a plate-like densification or "plaque" into which numerous microfilaments (4–7nm in diameter) feed.

At the ZA, actin microfilaments are particularly prominent and appear to be continuous with the bundle of actin filaments that encircle the cytoplasmic surface of the contact region. While the zonula adherens is continuous or "belt-like" in most epithelia, outside of the tripartite junctional complex, adherens junctions are often discontinuous, or 'spot-like'. These latter types of adherens contacts can be seen scattered along the entire lateral surface of epithelial cells [5] and in non-epithelial cell types such as the synaptic junctions of neurons [6,7] or the tenticle-like processes between mesenchymal cells [8]. While spot and zonular adherens junctions appear to be fundamentally similar structures, these differences likely suit different purposes. For example, spot-like junctions may favor anchoring, while a zonular "belt-like" junction enables coordination of epithelial sheet movements (described in section VI). In epithelia, these arrangements of AJ superstructure may also reflect different stages of junctional maturation [8–11].

As predicted from the ultrastructure, three classes of proteins are required for this AJ structure: 1) adhesion receptors spanning the intercellular space of the junction and comprising the adhesive bond (e.g., cadherin and nectin-type adhesion receptors), 2) a cytoskeletal network anchoring the adhesive components (e.g., actin), and 3) cytoskeleton/membrane "plaque" proteins that serve to link the adhesive components with the cytoskeleton (e.g., catenins and afadin). Numerous regulatory proteins can affect these core structural components, such as growth factor receptors and kinases (e.g., EGFR and src-family members) and regulators of actin dynamics (e.g., Rho and Rap family GTPases, myosin, formins. etc). Indeed, it has become clear that these regulatory components are as central to AJ structure/function as the structural components themselves, affecting assembly, trafficking, stability and higher order junctional organizations of the core adhesive components discussed below.

III. Core structural components for adhesion and junction formation

Adherens junctions consist of two basic adhesive units: the cadherin/catenin and nectin/afadin complexes (Figure 2). Broadly speaking, these adhesive complexes link a homophilic recognition event with the underlying actin cytoskeleton, and distinct contributions of each complex to AJ structure/function have emerged.

The cadherin/catenin 'core' adhesion complex

Classical cadherins were the first family of adhesion molecules found in the adherens junction (e.g., as in Figure 1F). These molecules are type I, single-pass transmembrane glycoproteins that mediate Ca^{2+}-dependent intercellular adhesion. Specific adhesive binding is conferred by the cadherin ectodomain, which engages an identical molecule on the surface of an adjacent cell [12, 13]. The cadherin cytoplasmic domain mediates key structural and signaling activities required for adhesion through its association with three distinct proteins known as catenins [14]. β-catenin (or the highly homologous γ-catenin/plakoglobin) are arm-repeat proteins

[15] whose direct binding to cadherin is crucial for full adhesive function [16, 17]. Specifically, β-catenin binding to cadherins appears to be a prerequisite for adhesion due to its role in protecting the cadherin cytoplasmic domain from proteolysis in vitro [18], as well as enhancing the efficiency of endoplasmic reticulum to cell surface transport [19]. More important, β-catenin or plakoglobin contains binding information for the one member of the cadherin/catenin 'core adhesive complex' that contains an actin-binding domain, α-catenin [20–22]. α-catenin is a vinculin homologue that can bind F-actin in vitro [21], and is crucial for actin polymerization at or near AJs in vivo [11]. For years, α-catenin was thought to "hardwire" the cadherin/β-catenin complex to the actin cytoskeleton, in large part because the β-catenin and actin-binding domains in α-catenin are found at different ends of the protein, as well as evidence that an E-cadherin/α-catenin fusion protein could rescue adhesion [23, 24]. However, recent studies reveal that α-catenin is an allosteric protein in vitro, unable to bind β-catenin and F-actin simultaneously [25]. Although it is formally possible that cellular modification of α-catenin could allow its binding to *both* β-catenin and F-actin, a compelling new model has been proposed, whereby the cadherin/catenin complex is not stably attached to F-actin filaments. Instead, highly clustered cadherin/β-catenin complexes generate high local concentrations of a soluble pool of α-catenin that drives changes in actin dynamics (also discussed in section V).

Cadherins also associate with $p120^{ctn}$, which belongs to a subfamily of armadillo proteins whose molecular diversity through splicing and phosphorylation suggests important roles in the finely-tuned regulation of cadherin adhesions [26]. For example in vertebrate systems, p120 regulates cadherin surface levels by antagonizing endocytosis [27,28] perhaps through masking endocytic signals in the cadherin cytoplasmic (juxtamembrane) domain [29]. Other studies demonstrate that p120 is required for something that goes beyond controlling steady-state levels of cadherins. Specifically, $p120^{ctn}$-cadherin binding plays a key role in the conversion of weak cell-cell adhesions into strong, more "compacted" adhesions, likely through its effects on cadherin clustering [30], and the local assembly of actin [31]. In contrast to α-catenin, which can affect actin properties through direct binding, p120 does not bind actin directly, but instead regulates actin dynamics through its ability to inhibit Rho [31–33], and Discussed in V).

In summary, the cadherin/catenin "core adhesive" complex contains components that mediate homophilic recognition across the intercellular cleft (cadherin), actin association (α-catenin) and/or regulation of actin dynamics (p120ctn/α-catenin), and stabilization of the complex at the cell surface (p120ctn/β-catenin) (Figure 2, left side).

The Nectin-Afadin adhesion complex

Nectin is a member of the IgG superfamily of calcium-independent adhesion molecules. The nectin subfamily (i.e., nectins 1–4) contains an extracellular domain comprised of three IgG-like loops, and a cytoplasmic domain, which contains a C-terminal PDZ binding motif in most variants [34]. Like cadherins, nectins form lateral homodimers that can engage in both homophilic and heterophilic adhesion with other nectins or nectin-like receptors. The cytoplasmic domain of nectin interacts with an actin-binding protein known as AF6/afadin [35,36], thereby providing an alternate way to couple AJs to actin. Afadin is a modular protein that has been also found to interact with Ras/Rap-family GTPases, as well as other actin-binding proteins such as ZO-1 and α-catenin [37]. Similar to α-catenin, afadin knock-outs reveal an essential role in epithelial organization [36,38]. Thus, like the cadherin/catenin adhesive unit, the nectin-afadin complex contains components that can mediate intercellular adhesion and actin association (Figure 2, right side).

IV. Junctional versus non-junctional organization of core adhesive components

Both nectins and cadherins have been localized by immuno-EM to the ZA structures discussed above [12,35]. While the nectin/afadin complex is mainly localized to the ZA region [39], there is a substantial amount of non-ZA cadherin/catenin complexes that run the entire length of the epithelial lateral membrane [40]. Whether the lateral surface is comprised of numerous spot-like AJs, or diffuse, non-junctional cadherin complexes may be difficult to answer, but it is clear that cadherins do not need to be organized into a ZA for basic adhesive activity, since most cadherin-based adhesion assays are performed in fibroblastic L-cells or CHO cells, which lack obvious ZA structures [41,42]. This suggests that non-junctional cadherin complexes serve to mediate basic cell-cell adhesion between cell membranes, while nectin/afadin-mediated co-organization with cadherin/catenin complexes may be required for higher order junctional structures (such as the ZA). Indeed, while nectins mediate a form of Ca^{+2}-independent adhesion that can be measured by aggregation assays [35], Ca^{+2}-dependent cadherin adhesion appears to be the major means of epithelial cohesion, as evidenced by the exquisite sensitivity of epithelial contacts to calcium chelators [43], and their more robust adhesive capacity [44,45]. In addition, AF6/afadin null mice show a complete loss of the tripartite junctional complex (which contains the ZA) and overall epithelial structure without significantly altering the subcellular localization of E-cadherin [36,38]. Thus, it appears that nectin/afadin driven ZA formation and cadherin-based adhesions can be uncoupled, and while cadherin-based adhesion is certainly required for junction formation, it appears to be insufficient for organizing a ZA structure. Perhaps the importance of afadin in junction organization makes sense given recent evidence that the cadherin/catenin complex may not be stably anchored to the actin cytoskeleton [25,59]. Whether nectin/afadin adhesive complexes can be directly linked to F-actin, and how the nectin/Afadin complex collaborates with the cadherin complex to direct ZA formation is not clear. Many potential physical links between the nectin-cadherin adhesion systems have been identified, the most direct being between afadin and α-catenin or $p120^{ctn}$ [46,47].

An important implication of the above findings is that the differential organization of cadherins may serve distinct functions: Diffusely distributed, non-junctional cadherin/catenin complexes may be more crucial for transient contacts that accompany intercellular movements, such as border cell migration [48] or convergence extension rearrangements [49]. Co-organization of cadherin/catenin and nectin/afadin complexes into higher order ZA-structures may suit other functions, such as compaction of cell membranes for polarity establishment and coordination of epithelial morphogenetic events (discussed in VI below).

V. AJ/ZA formation as a multi-step process

Cadherins/catenin-mediated adhesion as a pre-requisite for junction formation

Many lines of investigation indicate that AJ formation may depend on a multi-step assembly process. For example, in mesenchymal cell cultures that are in a dynamic state of forming/breaking contacts, close contacts can be seen (Figure 1C), but electron dense accumulation is only observed in a subset of these contacts (Figure 1D&E). These images suggest that basic cell-cell adhesion precedes plaque formation, which reflects a denser organization of the microfilament system [8]. The molecular events that drive these ultrastructural changes are beginning to be elucidated. Cadherin/catenin complexes can be formed early in the biosynthetic pathway [50, 51], and appear to localize at the cell contact concurrently, suggesting that these proteins arrive at the membrane as a complex [52]. Dimerization of cadherin ectodomains has been shown to be required and sufficient for adhesive activity [42, 53, 54], but the extent to which these dimers form laterally or across the intercellular membrane space is not yet resolved

[55]. Since forced clustering of cadherin ectodomains is sufficient to increase adhesive strength [56], there is much focus on how the cadherin cytoplasmic domain and associated catenins mediate clustering. In this regard, engagement of cadherin receptors on an adjacent cell may induce lateral clustering of cadherins via the $p120^{ctn}$ binding, juxtamembrane region [30]. Since cadherin mutants lacking the p120-binding domain fail to mediate robust adhesion [31, 57], cadherin clustering is considered an early event in AJ assembly. It should be pointed out that any critical role of p120 in adhesion seems at odds with evidence that it is not required for ZA formation in flies and worms. Given the complexity of actin at the ZA and actin regulation, it is likely that multiple redundant mechanisms will be required to coordinate a productive, junctional actin belt. Moreover, this redundancy also exists within the cadherin molecule itself, where both juxtamembrane ($p120^{ctn}$-binding) and β-catenin/α-catenin-binding regions independently contribute to cadherin adhesive activities [16] 24, 30].

Actin association and organization

How the cadherin/catenin complex interacts with actin, and is incorporated into junctional structures is a critical question whose answer depends on the particular stage of junction assembly. For example, the manner in which actin is localized to the AJ appears to change over the course of junction maturation. More specifically, actin filaments approach initial cell contacts “end-to-membrane” (perpendicularly) through local Arp2/3-dependent polymerization, while mature contacts are characterized by a “side-to-membrane” (parallel bundles) relationship [10,11,58]. Recent data suggest that α-catenin may play a critical role in this transition of actin assemblies, as α-catenin can compete with and inhibit Arp2/3-dependent actin polymerization [25], and α-catenin dimers can preferentially bind and bundle actin filaments in vitro [21,25]. Thus, cadherin/catenin clustering at immature cell contacts would generate a high, local concentration of cadherin-free α-catenin that could both antagonize branched actin arrangements (i.e., as found in lamellapodia/filipodia) and promote the organization of parallel actin bundles [25,59], as observed in mature ZA ultrastructures (Figure 2, left).

How α-catenin is regulated during these distinct steps of junctional maturation is currently unclear, but α-catenin is known to interact with a number of proteins that may help coordinate these different actin organizations. For example, α-catenin binds to formin-1, which can nucleate unbranched actin filaments at cadherin contacts [60]. α-catenin can also bind ZO-1 [61], possibly during the assembly process, where it may support the formation of linear actin cables [62]. Moreover, α-catenin may indirectly associate with actin via afadin, where α-catenin is crucial for the recruitment of nectin/afadin complexes to AJs [46]. Lastly, it should be noted that numerous other actin-binding and signaling components have been localized to cadherin-contacts, such as α-actinin [63], beta 2 spectrin, ankyrin [64], cortactin [65], Arp2/3 [66], Ena/Vasp [67], Wave and Wasp ([68] and reviewed in [69,70]). The extent to which these structural and signaling proteins contribute to the junctional and/or non-junctional organization of cadherins is not yet resolved.

Stable incorporation of the complexes into junctional structures

If the AJ is largely comprised of these core structural components, the number of signaling molecules that have been localized to AJs (or all along the lateral membrane), which can affect the stable incorporation of the core adhesive complexes into junctional structures, is far greater. It may be useful to think of these factors as non-stoichiometric binding partners of the junctional complex, and broadly speaking, these factors fall into two categories: growth factor receptors/phosphatases/kinases and Rho-family GTPases and their regulators. For example, growth factor receptor tyrosine kinases such as EGFR [71], src family kinases [72,73] and tyrosine phosphatases (PTPs) [74] can be localized specifically to the adherens junction, and can interact directly with and/or modify components of the cadherin core complex, such as β-catenin

[75], p120^{ctn} [26], or the cadherin cytoplasmic domain [76]. Phosphorylation of the cadherin/catenin complex can either affect complex formation (reviewed in [77]) or modulate the complex in a way that affects its organization into higher order junction structures ([18], reviewed in [55]).

An interesting example of a protein that affects the junctional organization of cadherin/catenin complexes is the product of the Neurofibromatosis 2 locus, merlin. Merlin is a member of the ERM family of membrane/cytoskeletal linker proteins that plays a critical role in AJ formation. Specifically, *Nf2*−/− cells show diffusely localized cadherin/catenin complexes that fail to concentrate at stereotypic cell-cell junctions [78]. How merlin organizes non-junctional cadherin/catenin complexes into junction structures is not precisely known. Interestingly, although merlin can bind and stabilize actin filaments in vitro [79], it remains unclear whether merlin drives AJ formation by directly stabilizing actin filaments at junctions, or by inhibiting EGFR activation [80], which is known to have consequences for the organization of cadherin/catenin complexes [71,75,81].

More recent evidence indicates that mechanisms are in place to organize the apical actin cytoskeleton, which place actin organization “upstream” of, and therefore a prerequisite for AJ stabilization. Specifically, in the absence of the fly protein, Bitesize (BS), a synaptotagmin-like protein (which bind to Rab proteins involved in exocytic/membrane trafficking events), the AJ forms but cannot be stabilized [82]. The ERM actin-binding protein, moesin, can directly interact with BS, and appears to be critically required for the stabilization of the AJ, perhaps through an ability to inhibit Rho [83]. Of interest, localization of BS to the ZA region depends on the polarity protein Par3, which is consistent with evidence that loss-of-function mutations in Par3 do not affect the assembly of cadherin/catenin cell surface complexes, but rather prevent cadherin/catenin recruitment into a mature ZA [84,85]. Thus while initial cadherin/catenin adhesions appear to form in the absence of a Par3/BS/moesin mechanism, stabilization of the ZA is critically dependent on these players.

Because of actin’s proximity to the adherens junction, it is perhaps not surprising that members of the Rho (e.g., CDC42, Rac and Rho) and Rap subfamilies of small GTPases can influence cadherin mediated cell-cell adhesion and AJ structure/function. Certainly, their well-defined effects on actin polymerization can regulate adhesion and junction organization indirectly, since AJ structure requires an intact microfilament system [86]. However, studies have revealed that cadherins and nectins are not only targets of Rho and Rap-family GTPases, but that cadherin and nectin engagement events are sufficient to activate these GTPases, suggesting a mutually interdependent relationship (reviewed in [87,88]). How adhesion-receptor ligation activates small GTPases, and what are the key effector steps that result from this activation, are questions under intense investigation. Of interest, core structural components of both nectin/afadin and cadherin/catenin complexes can directly bind to regulators of Rho-family GTPases. For example, a RapGEF (C3G) directly binds E-cadherin [89], while PDZ-GEF can bind β-catenin’s C-terminal PDZ-binding motif [90]. As GEFs catalyze the exchange of GDP for GTP and thus activate their cognate GTPases, local recruitment of these GEFs to core components of the cadherin/catenin complex may explain how cadherin engagement locally activates Rap, and why loss of Rap prevents the normal circumferential distribution of the cadherin/catenin complex/ZA structure [91]. Moreover, the nectin binding partner, afadin, has a Rap binding domain, and as such is a Rap effector. It is possible that Rap binding to afadin prevents endocytosis of non-transengaged cadherins. Taken together, these observations may explain how cadherin-based adhesions (through local activation of Rap) positively reinforce nectin functions at the AJ [47]. Lastly, p120^{ctn} can bind to p190Rho-GAP, which may explain how p120^{ctn} in the vicinity of cadherin complexes can locally inhibit Rho to promote AJ assembly [33]. Thus while it is clear that core components of cadherin/catenin and nectin/afadin complexes can interact with regulators of Rho and Rap-family GTPases, it will be important

to understand how these interactions affect distinct molecular steps in the junctional assembly process.

Positioning of the ZA within the tripartite junctional complex

Vinculin is a α-catenin related molecule that can bind α-catenin and actin, and localizes to both AJs and focal contacts [92]. Importantly, vinculin binding to α-catenin is not important for basic cell-cell adhesion [93], but rather for positioning the ZA next to the tight junction [94]. Thus, recruitment of vinculin to the adherens junction might be important for ZA assembly, which would in turn coordinate tight junction alignment with AJ formation. Like vinculin, ZO-1 has α-catenin and actin binding activities [61] and is also required for ZA formation and positioning [62]. Specifically, the MAGUK homology region of ZO-1 (aa1-871) is sufficient to promote belt like AJs and TJs, and segregate these junctions. Thus, ZO-1 and vinculin may specifically contribute to ZA formation and the sorting out of AJs/TJs junctions.

VI. Important functions of the AJ/ZA

While many molecular components of the adherens junction mediate the basic adhesiveness of cells, the organization of these adhesive complexes into higher order junctional structures, like the ZA in polarized cells, serves functions beyond adhesion. There are numerous morphogenetic events that occur throughout development that depend on coordinating the movements of adjacent cells. For example, gastrulation begins with an epithelial invagination event that requires the coupling of cell ZA structures, while cell sorting within an epithelium appears to be driven by differences in adhesion (reviewed in [95]). How the ZA structure is modified to drive these different types of intercellular movements is an active area of investigation. Recent examples that emphasize ZA functions are discussed below, because they highlight new molecular components that affect AJ structure/function.

AJ proteins in contact-dependent signaling

One of the best examples where the junctional arrangement of cadherin/catenin complexes may serve “extra-adhesive” functions is the phenomenon of contact mediated growth inhibition. For example, while cadherin abundance can certainly inhibit growth through antagonizing β-catenin signaling [96], it has become clear that homophilic engagement and/or clustering of cadherins *alone* are sufficient to transducer growth inhibitory signals [97,98]. Specifically, engagement of surface cadherins with recombinant, cadherin ectodomain-coupled beads can inhibit full activation of the EGFR [97]. Since the ERM family member, merlin, plays roles in both the concentration of cadherins at cell junctions [78] and the control of EGFR activation by restricting its localization [80], it appears that the co-organization of cadherins and growth factor receptors into higher order junction structures has biological consequences that are distinct from--and in addition to--cadherin expression levels alone.

AJ proteins in cell sorting and invaginations

Echinoid (Ed) is an Ig-type molecule in flies that, like nectin, binds afadin and colocalizes with cadherin/catenin complexes at the ZA. Of interest, Ed −/− cells strongly segregate from Ed+/− cells, perhaps because Ed−/− cells accumulate higher levels of cadherin/catenin complexes and junctionally-associated actin, while the apposing +/− cells show reduced cadherin/catenin and actin levels [99]. This shows that Echinoid is required to balance the expression levels and/or junctional accumulation of cadherins between adjacent cells, and suggests that modulation of Ed functions may drive tissue sorting events that depend on differential adhesive states [100].

Epithelial sheet invaginations that accompany gastrulation are also critically dependent on AJ components. Specifically, ventral furrow formation in flies is directed by a pathway that

recruits RhoGEF2 to the ZA region, which in turn recruits myosin 2 to allow constriction of the ZA [101]. Targeting of RhoGEF2 appears to be mediated by redundant mechanisms, and T48, new transmembrane protein with a C-terminal PDZ-binding domain helps concentrate both RhoGEF2 and cadherin/catenin complexes apically to coordinate this process [102].

AJ proteins in cell polarity

A strong interdependent relationship exists between junction formation and the establishment of apical-basolateral polarity. While basolateral proteins receive their polarized spatial cue upon initial cell-cell contact formation [103], apical domain establishment requires ZA formation [104]. Indeed the ZA (together with the tight junction) serves as a structural landmark for cell polarization by providing spatial cues for multi-protein signaling complexes crucial for apical domain formation (e.g., Par3/Par6/aPKC; see section 5 for more complete discussion), as well as docking sites for vesicle transport (e.g., Sec6/8 complex, [105,106], reviewed in [107]. While the C-terminus of β-catenin can interact with Par3, nectins 1&3 and Echinoid can also bind this protein [99,108], indicating there are multiple redundant binding partners for the recruitment of Par3 to the ZA region. Perhaps redundant targeting mechanisms make sense in terms of junctional co-assembly of cadherins with nectins/Echinoid, as junctional organization would create a high local concentration of overlapping (e.g., Par3) binding partners. This would ensure that polarity complexes are recruited to the ZA region, and not where these proteins are diffusely distributed along the lateral membrane.

Summary

The AJ is a structure that links core adhesive components to the underlying microfilament system. While intercellular adhesion is a central function of AJ components, it is becoming increasingly clear that the organization of these core components into higher order junction structures serves other functions, from coordinating cell sorting and invagination events, to generating contact-dependent growth and polarity signals. Indeed, the variety of these AJ functions is now reflected in the diverse and extensive molecular complexity of this structure, as highlighted in this review. Since the ZA/AJs were originally defined as structures at the EM level, and most current studies localize components to “AJs” at the light microscopic level, this issue of junctional versus non-junctional organization of adhesive components has remained poorly resolved. The challenge will be to find molecules that specifically regulate non-junctional adhesions, as well as those required for ZA assembly, as defined at the ultrastructural level, or in systems where the ZA is well delineated from lateral membrane contacts.

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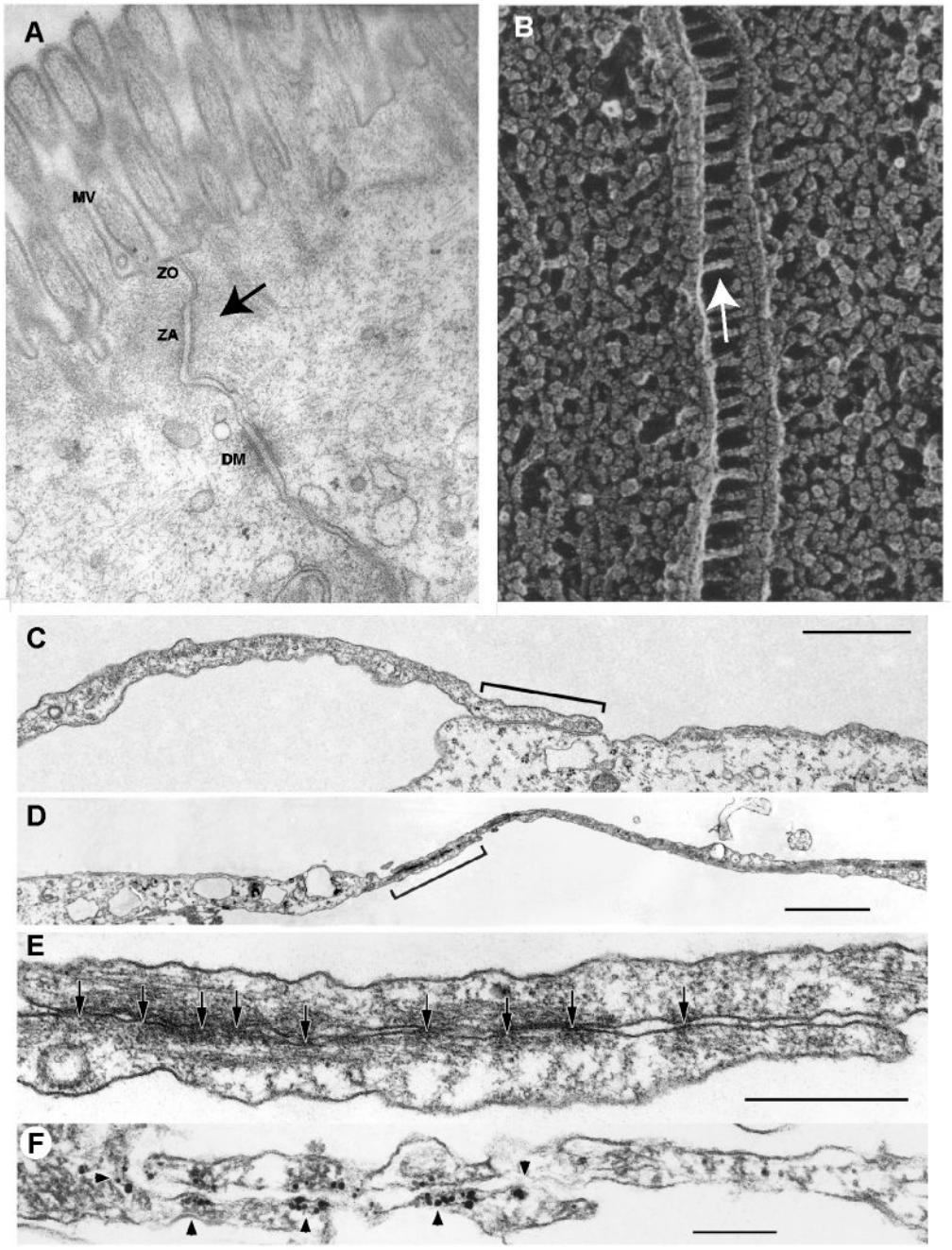

Figure 1. Ultrastructural features of adherens junctions

A. Transmission electron micrograph of the zonula adherens (ZA) described by Farquhar and Palade (1963) as part of a tripartite junction complex, where the ZA (black arrow) is located between the zonula occludens (ZO) and the desmosome (DM) just beneath the apical, microvillar (MV) domain. B. Quick-freeze, deep-etch image of the adherens junction between intestinal epithelial cells. Note the presence of rod-like bridging structures extending between adjacent cells at the attachment zone (white arrow). Micrographs were kindly provided by Drs. M. G. Farquhar (A) and N. Hirokawa (B) and reprinted with permission from *J. Cell Biol*. See text for references. C–F. Electron micrographs of ultrathin sections from mesenchymal cell contacts (Wuchter et al., 2007). C. “Tentacle-like” process reveals contact without electron

dense plaque structure (bracket). D&E. Different contact region at low (D) and higher magnification (E) reveals closely spaced adherens junctions characterized by dense, cytoplasmic plaques (arrows). F. Immunogold labeling shows β-catenin enrichment at these junctions (arrowheads). Micrographs were kindly provided by Dr. Werner Franke and colleagues, and reproduced with permission from *Cell Tissue Research*, Springer-Verlag.

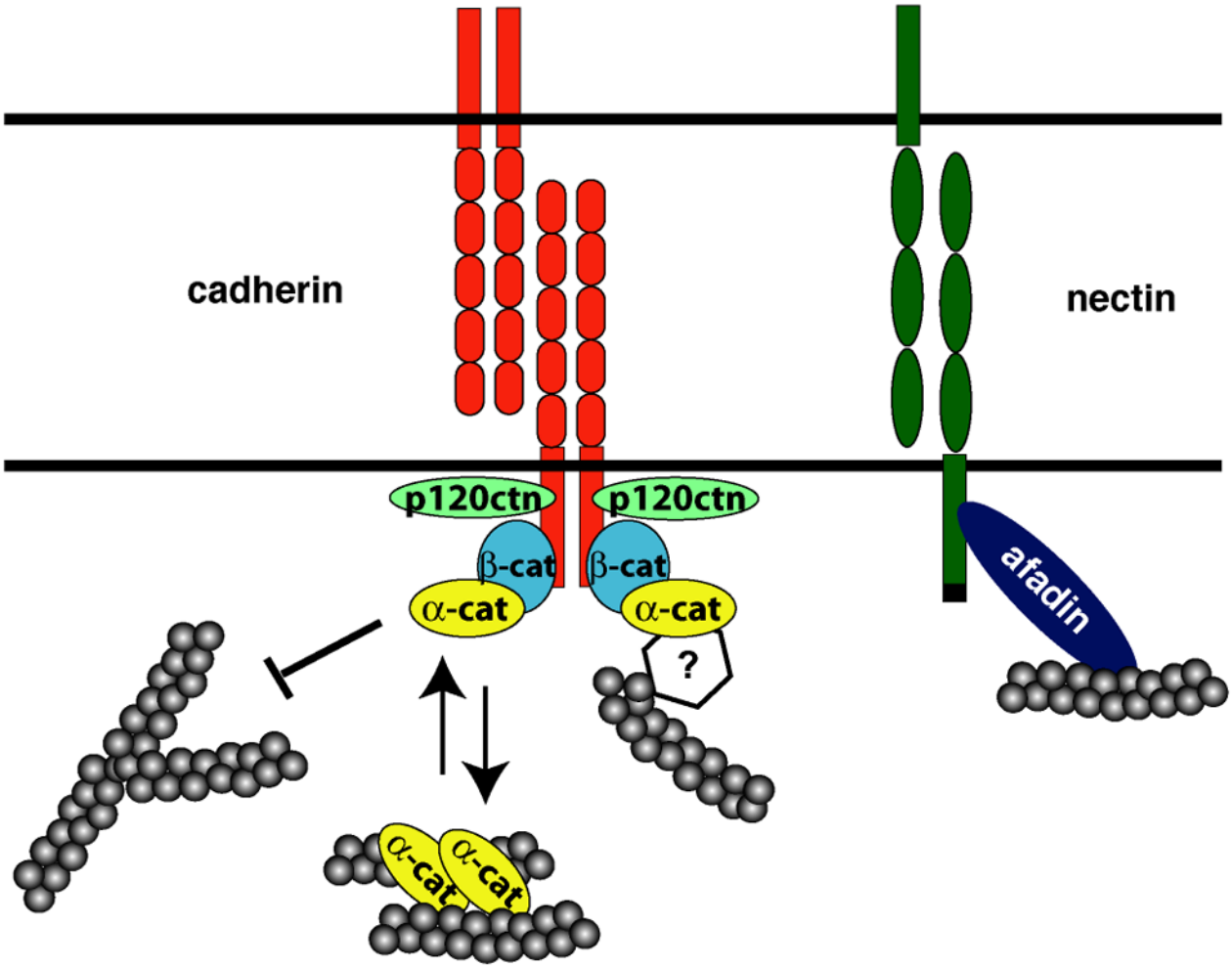

Figure 2. Core structural components for adhesion and junction formation

Cadherin and nectin homophilic adhesion receptors directly or indirectly associate with actin filaments via α-catenin and afadin, respectively. Extracellular engagement produces signals that affect actin dynamics. See text for details.

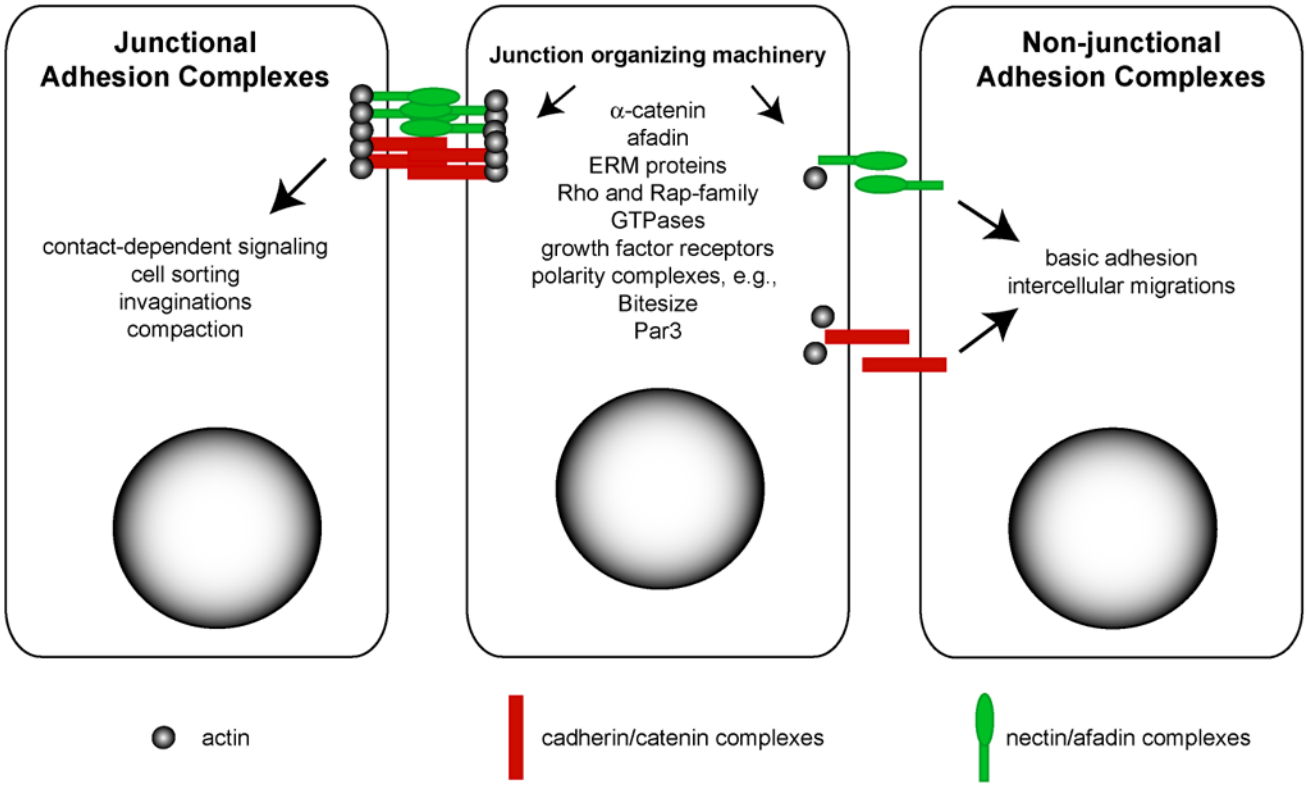

Figure 3. Junctional versus non-junctional organization of adhesive complexes and implications for function

See text for details.