REVIEW

Actin filament association at adherens junctions

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Abstract : The adherens junction (AJ) is a cadherin-based and actin filament associated cell-to-cell junction. AJs can contribute to tissue morphogenesis and homeostasis and their association with actin filaments is crucial for the functions. There are three types of AJs in terms of the mode of actin filament/AJ association. Among many actin-binding proteins associated with AJs, α-catenin is one of the most important actin filament/AJ linkers that functions in all types of AJs. Although α-catenin in cadherin-catenin complex appears to bind to actin filaments within cells, it fails to bind to actin filaments *in vitro* mysteriously. Recent report revealed that α-catenin in the complex can bind to actin filaments *in vitro* when forces are applied to the filament. In addition to force-sensitive vinculin binding, α-catenin has another force-sensitive property of actin filament-binding. Elucidation of its significance and the molecular mechanism is indispensable for understanding AJ formation and maintenance during tissue morphogenesis, function and repair. J. Med. Invest. 64 : 14-19, February, 2017

Keywords **:** *Adherens junction, Actin filament, α-catenin, Force-sensitivity*

INTRODUCTION

The adherens junction (AJ) is a cadherin-based and actin filament-associated cell-to-cell junction typically found in epithelial tissues. AJs are also found in fibroblasts, cardiac muscles and neurons. Cadherins connect adjacent cells and actin filaments transmit forces through interaction with myosin II. Therefore, AJs can contribute to tissue morphogenesis and homeostasis and their association with actin filaments is crucial (1-3). During embryogenesis, tissue regeneration and wound repair AJs support morphogenesis mechanically as well as are remodeled dynamically. For transmission of forces, actin filament/AJ association should be strong. On the other hand, dynamic remodeling of AJs requires weak association leading to quick dissociation of AJ components. It is natural to think that strength of actin filament/AJ association is regulated according to cellular context.

Ultrastructural analyses showed that the AJs are characterized as a membrane region at the interface of two adjacent cells with opposing membranes typically ~20 nm apart, with an intercellular space spanned by cadherin's extracellular domains, and with a dense undercoat associated with actin filaments at the cytoplasmic surface (4-8). There are typically three types of AJs (Figure 1). Punctate forms of AJs are called punctum adherens (PA, Figure 1A, D) (4, 9, 10). They are also called spot AJ, spot-like AJ, punctum, punctate AJ, nascent junction, primordial AJ or focal adherens junction, depending on their situation. PAs found in the intercalated discs tandemly connecting cardiac muscle cells have been called fascia adherens. Zonula adherens (ZA, Figure 1B, E) is a belt-like AJ encircling the cell completely at the apical/basolateral border in highly polarized epithelial cells. The tight junction (TJ) forms apically close to the ZA based on ZA formation. PAs are found in early stages of junction development and transformed into ZAs in highly polarized epithelial cells (11). Therefore, it is quite often that PAs are considered as premature forms of AJs and ZAs as matured forms of AJs. However, PAs are not always primary forms of AJs because PAs are found in various tissue cells such as cardiac muscles, keratinocytes in stratified epithelium, many organisms in stages during development (6, 11-15). The third type of AJs is found at the corner where several cells meet in polarized epithelial cell sheets. Three cells are connected at their corner through a tricellular AJ (Figure 1C, F). Adhesion molecules and the mode of their binding are not yet known (16). The corner can consist of four or more cells and show highly dynamic behavior during cell rearrangement found during morphogenesis (17-19).

ULTRASTRUCTURE OF ACTIN FILAMENT/AJ ASSOCIATION

At ZAs, actin filaments form bundles and run parallel to the plasma membrane (20) (Figure 1B, E). Because ZAs encircle epithelial cells at their apex, ZA-associated actin filament bundles form a circular structure called the circumferential actin bundles. This structure can contract by the interaction with myosin II, leading to apical constriction typically seen in epithelial morphogenesis during development. At PAs actin filaments associate with the plasma membrane in a perpendicular manner (6, 11, 15, 21-24), enabling direct transmission of forces through AJs to adjacent cells (Figure 1A, D). When forces are reduced by inhibiting myosin II activity, PAs cannot be maintained and are converted into ZAs (25, 26). Normally PAs convert into ZAs during sheet formation of highly polarized epithelial cells (11, 15, 23). PAs are known to fuse each other and form the continuous belt of the ZA during the process with dynamic changes of actin filament association. The molecular mechanism involved in the process is almost unknown. Because the mode of actin filament association is completely different, regulation of the association should be required. The mode of actin filament/AJ association at the tricellular junctions is similar to that at PAs in that actin filaments penetrate the undercoat of the AJ at relatively high angles (Figure 1C, F).

Received for publication October 31, 2016 ; accepted February 6, 2016.

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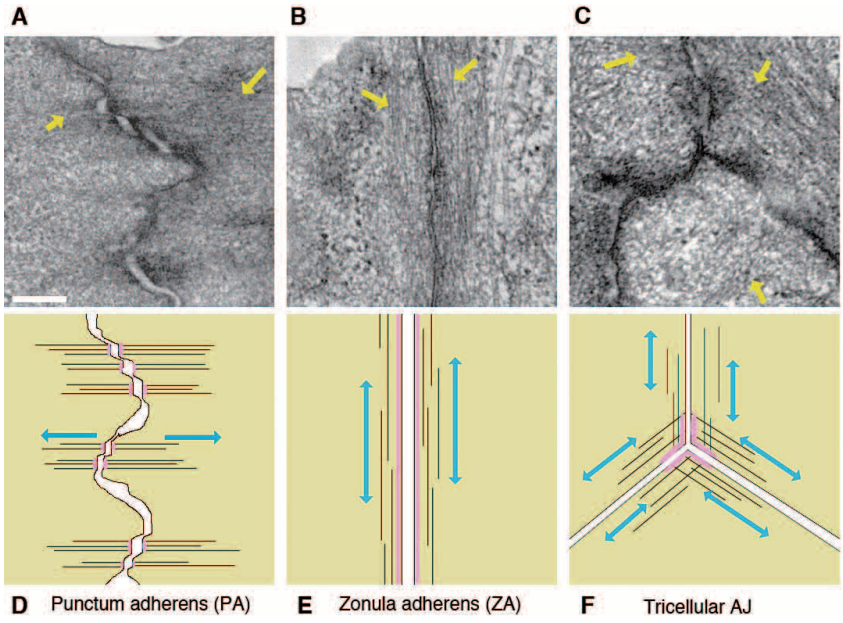

Figure 1
Three types of AJs found in MTD-1A epithelial cells. Electron micrographs (**A**-**C**) and models illustrating the mode of association of actin filaments with AJs (**D**-**F**). Yellow arrows in micrographs show actin filaments. Blue arrows in models show the orientation of actin filaments. Pink regions indicate AJs in the models. In the Punctum adherens (PA), actin filament bundles are associated with the plasma membrane perpendicularly (**A**, **D**). In the Zonula adherens (ZA), actin filament bundles run parallel to the plasma membrane (**B**, **E**). The tricellular AJ, the corner where three cells meet, is formed at both ends of the ZA in a hexagonal cell sheet. Three or more cells can form a corner. Actin filament bundles are associated with the plasma membrane at high angles. Bar, 200 nm.

AJ COMPONENTS RESPONSIBLE FOR ACTIN ASSOCIATION

The central functional unit of AJs is the cadherin-catenin complex. Cadherin binds to p120 catenin and β-catenin at its cytoplasmic region. β-catenin in turn binds to α-catenin, forming the cadherin-catenin complex (27-30). Within this complex, α-catenin has an actin filament-binding ability and it is essential for the actin filament/AJ interaction (13, 31-36). Another major adhesion molecule in AJs is nectins, which bind to an actin-binding protein AF6/afadin at their cytoplasmic region (37-38). Because afadin knockout in mouse intestinal epithelial cells showed no change in junctional and epithelial organization, importance of actin filament/afadin association in AJ is limited (39). Eplin is colocalized with actin filaments within cells and also found in ZAs but not in PAs, also showing its limited function in AJ formation (12, 40, 41). Vinculin accumulates at both focal adhesions and AJs. It has actin binding region in its C-terminus, which is exposed when vinculin is activated (42). As vinculin recruitment to focal adhesions is force-dependent (43), vinculin recruitment to AJs through its binding to α-catenin is also force-dependent (26, 44, 45). Although the cadherin-catenin complex distribution along the lateral membranes is not affected in epithelial sheets when myosin II activity is inhibited, vinculin disappears from ZAs. Inhibition of vinculin recruitment to AJs showed that vinculin is not required for PA formation and ZAs can be formed but incompletely, indicating its regulatory role (35, 46). Since vinculin is an actin-binding protein required for early development (47) and formation of PAs in cardiac muscles (48), its recruitment should increase the number of actin filaments associated with AJs, resulting in strengthening the structure and function of AJs. ZO-1 and closely related ZO-2 accumulate at PAs but not at ZAs. During TJ formation they move from ZAs to TJs (49). Because PAs can be formed without ZO-1/-2 (24), ZO-1/-2 may have a regulatory but not structural role in AJ formation. The Arp2/3 complex responsible for actin polymerization together with N-WASP, cortactin, Ena/VASP has a fundamental role in both initiation and maturation steps of AJ formation through regulation of actin polymerization although these proteins do not appear to be structural linkages between AJs and actin filaments (50-53). These structural components of AJs are summarized in Figure 2.

ACTIN-BINDING ABILITY OF α-CATENIN

A member of the cadherin-catenin complex, α-catenin is an actin binding protein, which deletion leads to loss of function of the complex. Deletion of only its actin-binding C-terminal region showed weak cadherin-based cell adhesion (32, 54). At the cellular level, the behavior of the cadherin-catenin complex depends on α-catenin and actomyosin. The complex shows a flow from basal to apical along the lateral membrane of some cultured epithelial cells. This flow depends both on actin cytoskeleton and on the C-terminal region of α-catenin with actin-binding ability (14). Ectodermal cells of *Drosophila* embryos show that PAs (spot AJs) containing both the complex and actin filaments are scattered along the circumferential contractile actin meshwork. The mobility of these PAs along the meshwork is dependent both on α-catenin and actomyosin tension, indicating connecting to actin in α-catenin-dependent manner (13). In endothelial cells, the actin-binding region of α-catenin is also required for VE-cadherin stabilization and accumulation to cortical actin bundles (55). PAs were disrupted in cardiac-specific α-catenin conditional knockout mice, resulting in cardiomyopathy and susceptibility to wall rupture (56).

Although purified α-catenin protein showed actin filament binding by *in vitro* co-sedimentation assay (31), α-catenin in the complex showed almost no actin filament binding ability (57), suggesting

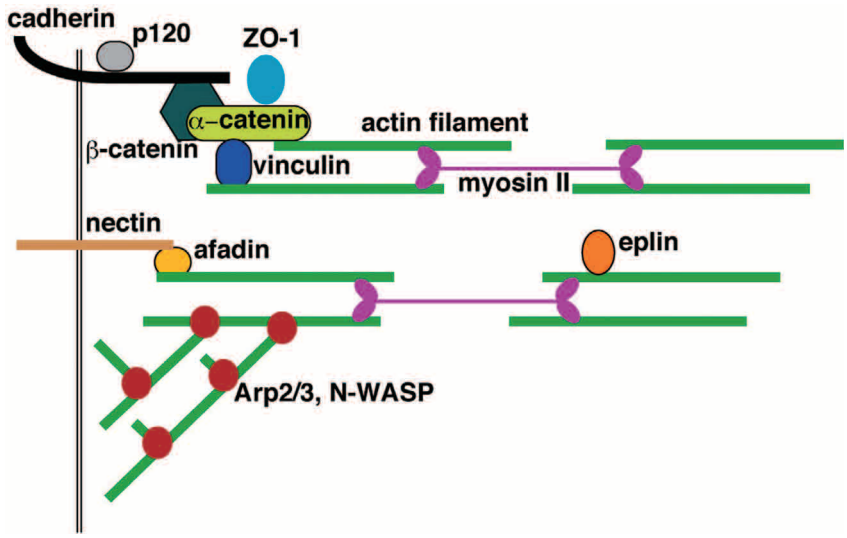

Figure 2
Structural components in AJ.
AJ components and AJ related proteins are shown. Myosin II and Arp2/3 complex-associated proteins are not included in AJ components usually.

that actin-binding protein(s) other than α-catenin associated with the complex may be responsible for regulation of actin filament/cadherin-catenin complex association. As already mentioned above, however, there is no good candidate for the protein so far. Furthermore, molecular dissection of α-catenin revealed that it has a vinculin-binding region at the central part of the molecule and also a region inhibiting the binding (35, 44). To release the inhibition within cells, the actin-binding C-terminus of α-catenin, actin filaments, myosin II activity, and cadherin binding between cells are required, indicating that vinculin/α-catenin association is force-dependent and that a possible conformational change of α-catenin when stretched unmasks the vinculin-binding region (Figure 3a). This clearly shows that α-catenin is involved in force transmission through AJs. One of the reasons why pure α-catenin but not α-catenin in the cadherin-catenin complex can bind to actin filament strongly is that α-catenin especially αE-catenin forms dimers, which enhances the actin filament binding ability because of the two actin binding regions per a dimer (57, 58) (Figure 3b, c). α-catenin exists as a monomer in the cadherin-catenin complex. This can explain the difference in the actin-binding ability between pure α-catenin and the cadherin-catenin complex *in vitro* (Figure 3d). However, because actin filament/cadherin-catenin complex association is crucial for force transmission at AJs within epithelial sheets, there should be an unknown regulatory mechanism of actin-binding ability of α-catenin in the complex. Although crystal structure of the actin-binding domain of αN-catenin was determined (59), there is no model explaining the regulatory mechanism so far.

ACTIN FILAMENT/α-CATENIN BINDING AND ITS FORCE-SENSITIVITY

We suggested an idea that α-catenin in the complex may make an effective linkage with actin filament only when the filament pulls the α-catenin in a ratchet-like manner and that stretched α-catenin may further stabilize the binding (60). If there is such a mechanism, AJs can transmit forces efficiently when needed and can be remodeled easily when strong forces are not applied. Furthermore, we pointed out that this idea should be tested by *in vitro* binding assays where the dynamic association of α-catenin and the actin filament is considered (61). Along this line, α-catenin forming a complex with β-catenin has been shown to associate with actin filaments *in vitro* using a biophysical assay (62), which is developed based on optical trap to measure the lifetime of actin filament/cadherin-catenin complex bonds under tension. Purified cadherin-catenin complexes were immobilized on a glass coverslip. An actin filament was attached to two optically trapped beads and suspended above the complex. The coverslip was mounted on a motorized stage of a microscope and force was applied to the actin filament/cadherin-catenin complex bonds by moving the stage parallel to the actin filament. The beads were displaced from the optical trap if the attached actin filament bound to the immobilized cadherin-catenin complex. Then the lifetime of the bond was measured with respect to applied force. This assay revealed that actin filament/cadherin-catenin complex binding occurs under force (Figure 3d, e). A two-state catch bond model was proposed that bonds form in a weakly bound state and quickly dissociate but rapidly transition to a strongly bound state as applied force increases.

Thus, discrepancy between biochemical data and cell biological data with respect to actin filament/cadherin-catenin complex has been resolved recently. The molecular mechanism, however, that changes the actin-binding ability of α-catenin by applied forces has not been understood at all. It is quite reasonable to think that α-catenin changes its conformation under force, leading to elevated binding to actin filament. Structural, biochemical and cell biological analyses are required. In addition, the significance of the existence of such a regulation should be elucidated experimentally.

In AJs, α-catenin appears to have a central role in actin filament association. Further analyses of α-catenin as well as other proteins that may be involved in the association would be important to understand the dynamic AJ functions during tissue or organ development, wound repair and maintenance.

CONFLICT OF INTERESTS

There is no conflict of interests to declare.

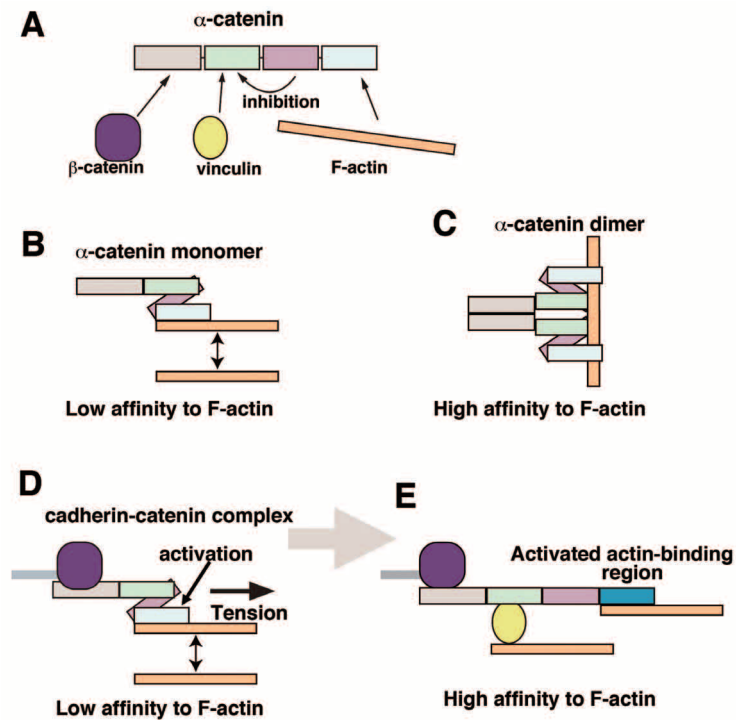

Figure 3
Actin filament/AJ association through α-catenin.
(**A**) The structure and functional domains of α-catenin, showing β-catenin, vinculin and F-actin (actin filament) binding regions (light grey, light green and light blue, respectively). The light purple domain can mask the vinculin-binding site and can unmask this site when the C-terminal actin-binding domain is pulled by actomyosin forces. (**B**) Cytoplasmic α-catenin monomer contains the C-terminal actin-binding region with relatively low affinity. Because there is no actomyosin force, cytoplasmic α-catenin would be in a folded state. (**C**) α-catenin especially αE-catenin forms dimers. The dimer has two actin-binding domains, resulting in high affinity for F-actin. (**D**) In the cadherin-catenin complex, α-catenin is monomeric and in a folded state unless it is stretched. The affinity for F-actin is low. When actomyosin forces are applied during a transient association, the conformation of the α-catenin changes (activation by tension). (**E**) When α-catenin is stretched by actomyosin forces, the vinculin-binding site is unmasked and vinculin is recruited. The conformation changes in the actin-binding domain (dark blue) would result in higher affinity to F-actin.

ACKNOWLEDGEMENTS

I thank Kisa Kakiguchi for electron microscopy. This work was supported by CREST, JST.

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