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Views and Reviews

The Cytoplasmic Domain of Adherens-Type Junctions

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ADHERENS JUNCTIONS: A DIVERSE GROUP OF HOMOLOGOUS CELL CONTACTS

Adherens junctions (AJ) comprise a unique and widespread family of cellular contacts which displays a stable association, within the cells, with actin-containing microfilaments [Geiger et al., 1987]. As discussed in several previous articles [Burridge et al., 1988; Woods and Couchman, 1988] AJ may be formed with different surfaces and assume a rather diverse morphology. They may be found in areas of plasmallemal contact with the surrounding extracellular matrix (ECM) as well as in regions of apparently direct intercellular interactions [Geiger et al., 1985]. Examples for the former type include focal contacts of cultured cells [Burridge and Fath, 1989], myotendinous junctions [Tidball et al., 1986], dense plaques of smooth muscle [Geiger et al., 1981; Small, 1985], basal adhesions to basement membranes (distinct from the intermediate filament-associated hemidesmosomes), etc. To the latter subfamily of AJ belong structures such as the *zonula adhaerens* of polar epithelia, also called "intermediate junctions" or "belt desmosomes" [Staehelin, 1974], endothelial junctions [Franke et al., 1988], *fascia adhaerens* of cardiac myocytes [Tokuyasu et al., 1981], and spot adhesions (or puncta adherentia) in other cell types. AJ are clearly distinct in structure, molecular composition, and function from tight junctions, gap junctions, and desmosomes [Staehelin, 1974; Geiger, 1983].

THE MOLECULAR CONSTITUENTS OF AJ

In recent years much data has been accumulated on the molecular composition of the different types of AJ. As mentioned above, the primary structural common denominator of all AJ is the apparent association with the periphery of the microfilament system. Further studies indicated that the interface between the actin-based network and the junctional membrane may be regarded as a highly specialized organelle. A large variety of proteins was detected in these regions, some common to all AJ, while others distinguish between cell-matrix and cell-cell contacts, or even display a cell type specific expression and distribution.

New information regarding AJ constituents and their topological interrelationships is rapidly accumulating. It appears, therefore, somewhat premature to propose, at present, a comprehensive model for AJ structure. Yet, it may be useful to provide a list of the major proteins which were so far localized along AJ of the different types (see Table I). Among these proteins, vinculin is commonly considered as the hallmark of all AJ [Geiger et al., 1985] and is broadly used for their identification and definition. While the reader is referred to the specific literature dealing with the individual proteins, we would like to focus here on the experimental approaches which were successfully employed to reveal this multitude of components and to assign them to specific subtypes of junctions or junctional subdomains.

The identification of new AJ molecules in the past relied heavily on the fortuitous immunocytochemical localization of different cellular proteins for which antibodies were available. In many cases (such as the discovery of vinculin [Geiger, 1979] or talin [Burridge and Connell, 1983]) there was essentially no previous information on the function of the protein when first isolated,

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TABLE I. Major Components of Adherens-Type Junctions

Molecule	Polypeptide MW (kDa)	Presence in C-C AJ	Presence in C-S AJ	Reference
Cadherin(s)[a]	120–140	+	−	Takeichi, 1988 (rev.)
Integrin(s)[a]	100–200[b]	−	+	Hynes, 1987 (rev.)
Actin	43	+	+	Geiger et al., 1985 (rev.)
α-Actinin	100	+	+	Lazarides and Burridge, 1975
Catenins α, β, γ	102,88,80	+	−	Kemler and Ozawa, 1989
FC-1	60	−	+	Oesch and Birchmeier, 1982
Fimbrin	63	−	+	Bretcher and Weber, 1980
Paxillin	68	−	+	Turner et al., 1990
Plakoglobin	83	+	−	Cowin et al., 1986
Radixin	82	−	+	Tsukita et al., 1989a
Talin	215–235	−	+	Burridge and Connell, 1983
Tensin	200,150	−	+	Wilkins et al., 1986
Tenuin	400	+	+	Tsukita et al., 1989b
Vinculin	116	+	+	Geiger, 1979
Zyxin	82	+	+	Crawford and Beckerle, 1991
200 K	200	+	+	Maher and Singer, 1983
30B6 antigen	175	+	+	Rogalsky and Singer, 1985
70 kD	70	−	+	Tsukita and Tsukita, 1989
$p60^{src}$	60	+	+	Rohrschneider, 1980
$p120^{v\text{-}gag\text{-}abl}$	120	?	+	Rohrschneider and Najita, 1984
$p80,p90^{v\text{-}gag\text{-}yes}$	80,90	+	+	Gentry and Rohrschneider, 1984
Protein kinase C	82	?	+	Jaken et al., 1989
CDPII	80	−	+	Beckerle et al., 1987

[a]Cell-specific members of multigene families.
[b]Heterodimers of diverse α and β chains.

while in others there was ample information on the proteins and their activity but the assignment to AJ was novel (i.e., protein kinase C [Jaken et al., 1989], Ca^{2+}-activated protease II [Beckerle et al., 1987], etc.). An extreme example for the identification of a new AJ molecule based on its subcellular localization is the discovery of the 82 kDa protein (zixin) by Beckerle [1986], which was initiated by the extensive labeling of focal contacts with a nonimmune rabbit serum followed by the use of this serum for the identification of the new junctional protein.

The other, seemingly more systematic approach, was to try and isolate AJ (or at least get an enriched fraction) and then to either purify individual proteins and characterize them or prepare monoclonal antibodies and use them to study individual molecules. This approach was used, for example, to identify constituents present in the isolated AJ of liver tissue [Tsukita and Tsukita, 1989] or in *fascia adhaerens* of cardiac muscle. The latter approach enabled the identification of A-CAM/N-cadherin [Volk and Geiger, 1984], as well as the 200 kDa protein [Maher and Singer, 1983].

Apparently, each of these approaches has its advantages and limitations; one of the difficulties for the specific assignment of AJ molecules stems from the fact that highly conserved proteins which are common among those which carry vital functions are often "immunosilent" and thus may not be readily identified or localized with antibodies. The subcellular assignment of molecules to different junctions and junctional subdomains presents a challenge of a different nature. While in principle one may conduct a high-resolution immunoelectron-microscopic mapping of all junctional components, such analysis is quite demanding and has so far been conducted for only a relatively small number of molecules (i.e., α-actinin, vinculin, and talin [Beckerle et al., 1989; Geiger et al., 1981; Chen and Singer, 1982]). Thus, it may sometimes be difficult to distinguish an extracellular component of the junction which is not readily available for antibodies from a genuine membranal or a cytoplasmic component (see, for example, recent studies on fibulin which was initially identified as a cytoplasmic molecule [Argraves et al., 1989] and later localized on the outer cell surface as well as in the ECM [Argraves et al., 1990]). Moreover, within the junction proper, it may be important to determine whether a protein is uniformly distributed throughout the junction or peripherally associated with it like α-actinin which can be removed from AJ by actin depolymerization [Avnur et al., 1983] and whether an apparent intercellular contact is indeed direct or else bridged by extracellular linking molecules.

AJ DYNAMICS AND THE DILEMMA OF SUBCELLULAR MOLECULAR SORTING

AJ differ from other organelles in that they are not separated from the rest of the cytoplasm by a lipid membrane and their peripheral cytoplasmic components (i.e., actin, α-actinin, vinculin, etc.) readily exchange with the cytoplasmic diffusible pool [Geiger et al., 1984; Kreis et al., 1985]. This feature suggests that the assembly of the AJ complex and/or its modulation depends on the availability of potent binding sites for cytoplasmic junctional molecules at the endofacial surfaces of the junction itself rather than on an active and directional transport mechanism. In view of the fact that different AJ in the same cells (cell-cell vs. cell-matrix) contain different molecules (for example plakoglobin [Cowin et al., 1986] and cadherins [Takeichi, 1988; Geiger et al., 1985], which are present in the former, talin [Burridge and Connell, 1983; Geiger et al., 1985] and integrins [Damsky et al., 1985] associated with the latter), one may assume that sorting mechanisms exist at the cytoplasmic aspects of the two AJ subfamilies. Based on the rationale that the primary event leading to specific assembly of AJ is the interaction with the external surface, it was proposed that the aggregation and immobilization of the respective transmembrane receptors, namely, integrins and cadherins, induce the selective and local accretion of the correct intracellular components. Thus, the cytoplasmic domains of the two types of "contact receptors" play a key role in the selective establishment of the transmembrane linkage in AJ. In the following section we will briefly review the role of the two cytoplasmic domains and their molecular reactivities.

THE CYTOPLASMIC DOMAINS OF CADHERINS AND INTEGRINS ARE ESSENTIAL FOR THEIR ADHESIVE ACTIVITY

Cadherins are a family of single chain receptors for Ca^{2+}-dependent cell-cell adhesion [reviewed by Takeichi, 1988]. Their N-terminal amino acids are exposed on the external cell surface and contain the putative homophilic binding site. They are followed by a typical transmembrane sequence and a cytoplasmic C-terminal tail [Hatta et al., 1988]. Recent studies have established the presence of several homologous members of the cadherin family, classified according to their tissue of origin or to their primary sequence, in AJ of different cells. Sequence comparison revealed that the cytoplasmic domain of cadherins is the most highly conserved region along the molecules. Moreover, modifications of such sequences, as observed in the cadherin-related desmosomal membrane molecule, desmoglein 1 [Koch et al., 1990], and desmocollins (Mechanic et al., 1991), completely alter the binding properties and lead to a totally different set of interactions with the intermediate filament system.

Members of the integrin family, notably the $\alpha_5\beta_1$ fibronectin receptor and the $\alpha_v\beta_3$ vitronectin receptor, have actually been localized in structurally defined cell-matrix adhesions [reviewed by Hynes, 1987]. Integrins of the β_2-subfamily, which are implicated in cell-cell interactions in lymphoid cells [Kishimoto et al., 1987], will not be further discussed here [for review, see Larson and Springer, 1990].

Interestingly, studies in several laboratories have established that the cytoplasmic domains of both cadherins [Nagafuchi and Takeichi, 1988] and β_1 integrins [Hayashi et al., 1990; Marcantonio et al., 1990] are essential not only for the transmembrane linkage to the cytoskeleton but also for an effective cell adhesion. These studies involved transfections of either intact or truncated cadherins or integrin β_1 chains into cells followed by cell adhesion assay or immunolabeling. The basis for this effect has not yet been clarified and several alternative mechanisms may be considered: a) a direct effect of the cytoplasmic region on the binding affinity outside and b) the augmentation of the effective binding constants of the respective molecules due to their cytoskeleton-dependent aggregation or oligomerization.

WHO INTERACT WITH CADHERINS AND INTEGRINS?

The identification of associated proteins is based predominantly on the co-immunoprecipitation with or direct affinity purification on the AJ receptor molecules. For E-cadherin (=uvomorulin) it had long been established that there are several cytoplasmic molecules (with apparent molecular weights of about 102 kDa, 88 kDa, and 80 kDa), which can be co-precipitated with cadherin-specific antibodies (though the antibodies react, in immunoblots, only with the cadherin band). Recently, these studies have been significantly extended. The three bands were designated catenins α, β, and γ [Kemler and Ozawa, 1989; Ozawa et al., 1989] and their interactions were shown to depend on the presence of the cytoplasmic moiety of the cadherin which is also essential for intercellular interactions [Nagafuchi and Takeichi, 1989; Ozawa et al., 1990]. It is also noteworthy that antibodies to catenins have recently become available and they do specifically react with adherens junctions (R. Kemler, personal communication). More detailed information on the fine topology of the interacting catenins is still unavailable as is the mode of interaction of the multitude of additional proteins including vinculin, plakoglobin, and others, with the cadherin-catenin complex.

The molecular interactions in cell-matrix AJ, ultimately connecting the ECM with actin, have been char-

acterized to somewhat greater extent than those of cell-cell contacts. Biochemical studies using purified proteins indicated that among the cell-matrix AJ plaque proteins integrin is specifically capable of binding to talin [Horwitz et al., 1986]. This binding was relatively weak, yet appeared specific and interestingly, was markedly reduced following tyrosine phosphorylation on integrin β_1 chain [Buck and Horwitz, 1987]. It was further shown that talin avidly binds to vinculin [Burridge and Mangeat, 1984] which apparently exhibited lower, yet significant affinity towards itself, α-actinin, and actin [Belkin and Koteliansky, 1987]. This scheme provided the "desired" continuity essential for ECM-actin linkage. There are, however, some additional observations which indicate that the linkage may, in fact, be considerably more complex: a) Cytoskeletal and plaque proteins may be involved in multiple interactions. For example, vinculin molecules lacking the talin binding site retain the capacity to associate with focal contacts, probably due to the presence of another AJ-binding domain on the deleted molecule [Bendori et al., 1989]. It is still not clear whether the latter interactions occur through resident vinculin molecules or other components, such as paxillin [Turner et al., 1990]. b) It had been reported that vinculin might be covalently linked to lipids and thus interact directly with the membrane bilayer [Burn and Burger, 1987]. Though rendered unlikely by the recent sequence data this possibility has not been directly excluded; c) in activated platelets, α-actinin was shown to pick-up lipophilic label [Rotman et al., 1982], which is normally associated only with integral membrane proteins; d) direct binding of cellular proteins, extracted in β-octyl glucoside, to a synthetic peptide corresponding to the cytoplasmic domain of integrin β_1, disclosed a new protein denoted fibulin [Argraves et al., 1989]. Later studies, however, surprisingly indicated that fibulin is, in fact, an ECM molecule [Argraves et al., 1990] and the significance of its interaction with integrin cytoplasmic domain remains unclear. e) A similar purification carried out using Triton X-100 (rather than β-octyl glucoside) indicated that α-actinin might interact with integrin β_1 cytoplasmic moiety [Otey et al., 1990]. These results are biochemically sound, yet α-actinin was detected in some significant distance from the membrane [Chen and Singer, 1982], rendering direct interaction with integrin questionable.

In conclusion, it is now apparent that molecular interactions occurring at the cytoplasmic domain of AJ are of major importance for the mechanical transmembrane linkage typical of these junctions. Moreover, in light of the correlation between AJ structure and cell behavior it is likely that long-range and long-term signal transduction events occur in them. As discussed above, recent studies employing diverse experimental approaches disclosed at least some of the junctional molecules. As an extension of these studies, it now appears feasible to determine the fine molecular topology and interactions throughout this region. A variety of experimental approaches may be employed to obtain such information. These include the use of cross-linkers for nearest neighbor mapping, examination of tyrosine-phosphorylated molecules, and the emergence of novel approaches for isolation of intact junctions. Progress along these lines will hopefully provide key information not only for the understanding of cell adhesion and cytoskeletal organization but also for the elucidation of AJ involvement in cellular dynamics, growth, and differentiation.

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