

## Adherin' with cadherin

Adhesion molecules of cell junctions can interact with the cytoskeleton in unexpected ways, particularly in neural cells.

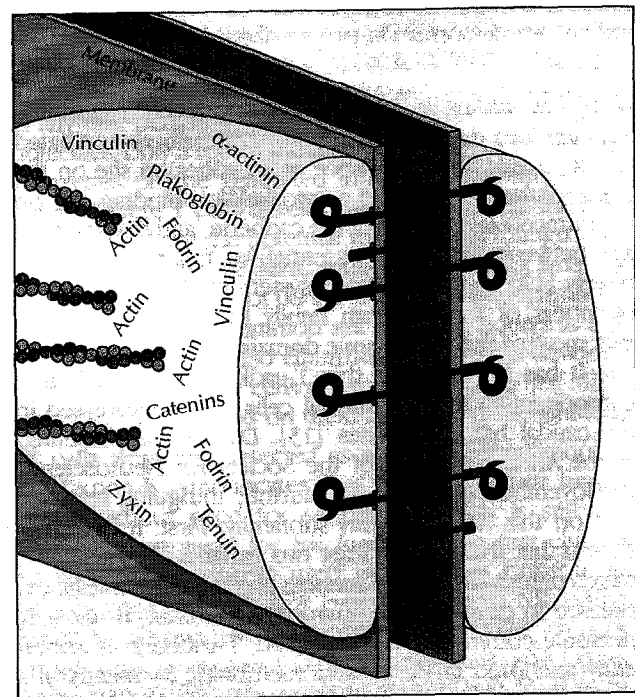
Adhesive interactions between cells occur at highly specialized multimolecular membrane domains known, collectively, as cell junctions. Of the various types of cell junction, the most prominent and mechanically stable are adherens-type junctions and desmosomes. Recent investigations have clearly established gross similarities between these two types of junction: they are both complex structures associated with many different molecules segregated into three major domains, namely an integral membrane domain, a submembrane plaque, and cytoskeletal filaments to which the submembrane plaque is anchored.

Among the many molecular components of adherens-type junctions (see [1]) for a review) and desmosomes, there are both components that are presumed to play a regulatory role, such as protein kinases and proteases, and components that are directly involved in the transmembrane interactions involved in the adhesion between cells at the junctions. The latter components largely differ between junctions. Thus, the cytoskeletal filaments to which desmosomes are anchored are intermediate filaments, whereas adherens-type junctions are anchored to actin filaments, apparently through  $\alpha$  actinin and vinculin (Fig. 1) In the case of the transmembrane molecules of the junctions — cadherins in adherens-type junctions [2] and desmogleins/desmoplakins in desmosomes [3] — there is a remarkable overall degree of sequence similarity in their extracellular portions which mediate cell-cell interactions, but distinct differences between the cytoplasmic tails, which are presumed to provide the linkage to the cytoskeletal filaments.

Cadherins are key components in the two major cellular manifestations of cell adhesion: selective cell sorting, and the mechanical cytoplasmic response including the interaction with the force-generating microfilament system. The significance of both processes is evident from the classic experiments of Holtfreter and coworkers who showed, nearly 40 years ago, that suspended embryonic cells tend to re-aggregate selectively into histotypically defined configurations [4]. A modern and molecularly more defined version of such experiments by several researchers including Takeichi and colleagues in 1988 [5] showed that transfection of different cadherins into mesenchymal cells induces an apparent epithelialization and selective sorting of the cells into homotypic aggregates both *in vitro* and *in vivo* (for review see [6]).

At about the same time, it was shown that although the binding site(s) on cadherins is located at the extracellular amino terminus of the molecule, the cytoplasmic carboxyl tail is essential not only for the transmembrane

linkage to cytoskeletal filaments but also for the adhesive function itself. Thus, cadherins produced in cells transfected with DNA from which segments encoding parts of the cytoplasmic tail of the molecule had been removed lost the capacity to mediate specific cell adhesion [7] (Fig. 1). The basis for this effect has not yet been clarified and several alternative mechanisms may be considered, including a direct effect of the cytoplasmic tail on the extracellular binding affinity or the effective augmentation of binding as a result of cytoskeleton-dependent oligomerization.



**Fig. 1.** An adherens-type junction showing cadherins (green), some of which are truncated (darker green). The different components making up the plaque (yellow) are indicated. Actin chains (red) emerge from the plaque.

Attempts to identify the intracellular partner(s) of cadherins brought to light a group of cytoplasmic polypeptides, denoted catenins, which apparently bind to the cytoplasmic tail of cadherins and link them to the actin-containing microfilament network [8,9]. This finding was based mainly on the coimmunoprecipitation with cadherin molecules of three distinct catenins,  $\alpha$ ,  $\beta$  and  $\gamma$ , with apparent molecular weights of 102, 88 and 80 kD, respectively. It was shown that catenin binding by the epithelial cadherin, uvomorulin, depends on the presence

of the 72 carboxyl-terminal amino acids of uvomorulin [10]. Catenins, however, are also expressed in cells that contain little or no cadherin [10].

In addition to their junctional association with the cytoskeleton through catenins and vinculin, cadherins may also be involved in long-range compartmentalization of the plasma membrane and induction of cell surface polarity. McNeill *et al.* [11] have shown that introduction of uvomorulin into non-polarized mesenchymal cells not only leads to the acquisition of an epithelioid morphology but also induces segregation of Na<sup>+</sup>-K<sup>+</sup>-ATPase into the basolateral aspects of the cells, along with the fodrin-based membrane cytoskeleton. In that paper as well as in follow-up studies by the same group (WJ Nelson, personal communication), evidence is presented that the induction of polarity in cells, manifested in the basolateral distribution of the Na<sup>+</sup>-K<sup>+</sup>-ATPase, is not (or not just) attributable to the presence of a tight junctional barrier for lateral diffusion or to targeted transport from the Golgi but rather to specific retention and stabilization of the molecule in the uvomorulin-induced basolateral domain. In contrast, Na<sup>+</sup>-K<sup>+</sup> ATPase, inserted into the apical domain is, presumably, rapidly turned over and lost.

All of the studies so far discussed produced data in line with the idea that the transduction of cadherin-mediated signals requires the presence of an adhesion site on the extracellular domain and a cytoskeleton-binding site on the intracellular domain of the cadherin, and that the linkage between the two is essential for function. The discovery [12] that the nervous system contains 'truncated' members of the cadherin family (T-cadherins), which lack most of the cytoplasmic domain, is therefore intriguing. It has been shown that T-cadherin is a prominent component in many neuronal cells and is expressed in the caudal half of somites [13]. Data to be presented at the Annual Meeting of the Society for Neuroscience in November 1991 will add further intriguing information on this new cadherin subfamily. First, it has been shown that there are at least two variants of T-cadherin, which differ in their 3' sequences and are differentially expressed in developing embryos (M Sacristan, B Ranscht, personal communication). Second, T-cadherin is apparently anchored in the plasma membrane by means of a glycosyl phosphatidyl inositol glycan instead of a transmembrane domain but can still induce Ca<sup>2+</sup>-dependent cell aggregation in transfected cells (DJ Vestal, B Ranscht, personal communication). The basis for the apparent discrepancy between these findings and those suggesting that the intact carboxyl-terminus is essential for adhesive function is not yet clear.

Taken together the recent data imply that cadherin-mediated transmembrane interactions may occur by at least three alternative mechanisms. One of those is, most likely, the focal transmembrane linkage found in adherens-type junctions and involving catenins, vinculin,  $\alpha$ -actinin and actin. Another mechanism is less focal associating of cadherins with the fodrin-based membrane cytoskeleton; and the third uses a lipid-dependent anchor-

age mechanism. It is conceivable that future characterization of the cadherin family will reveal yet more mechanisms. A promising hunting ground could be the eight new cadherins recently identified in rat brain together with six new human cadherins [14]. It will require extensive studies to elucidate the entire spectrum of anchorage mechanisms of the various cadherins and to determine their particular contributions to cellular morphogenesis and polarity and to the control of cell dynamics, growth and differentiation.

## References

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