E-Cadherin: A Distant Member of the Immunoglobulin Superfamily

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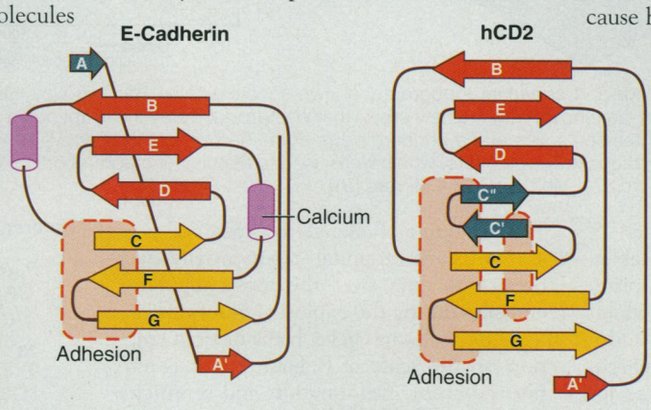
In a pioneering experiment at the beginning of this century, H. V. Wilson found that sponge cells of different species segregate when mixed artificially. This was the first demonstration that cells can choose the identity of their neighbors (*1*). This skill depends solely on the properties of the individual cells, in particular on the specific adhesiveness of cells to other cells. This adhesiveness is governed by receptor glycoproteins on the cell surface and is critical to the process of development and morphogenesis.

Cell-cell adhesion is also important for processes other than development. The best known examples of cell adhesion molecules are from immune cells, in which the surface receptors mediate, for example, adhesion to antigen-presenting cells and the endothelial cells of the vasculature. Indeed, immune-cell adhesion receptors are the only cell adhesion molecules for which atomic structures have been solved, specifically the CD2 (*2*) and E-selectin (*3*) adhesion domains. In this issue of *Science*, Overduin and co-workers report the first structure of an adhesion molecule important for development outside the immune system (*4*). The new solution structure of the amino-terminal domain of epithelial cadherin (E-cadherin) reveals some surprises and new insights into cell-cell adhesion.

In the past, cell adhesion molecules (CAMs) have been classified into families on the basis of their amino acid sequences (*5*). Three of these families are important during morphogenesis—CAMs with homology to the integrin superfamily, the immunoglobulin (Ig) superfamily, and the cadherin superfamily (*6*). Other families of adhesion molecules include the selectins, which recognize carbohydrates on the surfaces of target cells in inflammatory responses, and the little known addressins, which direct the migration of lymphocytes to lymph nodes (*7*).

Only integrins and cadherins require calcium to perform their adhesion function; CAMs from the Ig superfamily do not. Rather, these CAMs primarily mediate adhesion via contacts with other CAMs from the Ig superfamily. The best known example is the interaction of CD2 from T cells with CD58 of antigen-presenting cells. Some CAMs from the Ig superfamily also form contacts with CAMs from the integrin superfamily.

Until recently, the cadherins were considered a separate family of adhesion molecules. Cadherins are single-chain transmembrane polypeptides. The extracellular portion usually consists of five homologous domains of about 110 residues. The short cytoplasmic tail interacts with the cytoskeleton by means of proteins called catenins.



E-cadherin and CD2. The secondary structures and topology of the adhesion domains of E-cadherin (**left**) and human CD2 (**right**). Arrows, β-strands; cylinders, helices; dashed lines, putative adhesion surfaces. The two faces of the β-barrel are red and yellow.

The adhesive function of cadherins is primarily localized in the first amino-terminal domain, and it is this domain of E-cadherin that Overduin and co-workers have solved (*4*). Their first unexpected result is that the structure shows remarkable similarity to the Ig fold (although there is no sequence homology), the well-known sandwich structure of Ig variable or constant domains as found in the Ig superfamily (see figure). However, in contrast to these structures, the fold of cadherin resembles more a barrel than a sandwich and exhibits two small helices in place of the irregularly structured B-C and E-F loops of molecules from the Ig superfamily.

The second surprise is that the putative adhesion interface is on the same side of the molecule as in the Ig-type adhesion molecule CD2 (see figure). It is centered around the end of the F-strand of the β-sheet and contains a conserved His-Ala-Val sequence. The side chains of the histidine and the valine are exposed on the surface, whereas the alanyl side chain points to the protein interior. Residues flanking the His-Ala-Val sequence seem to determine the specificity of the adhesion. In CD2, the F-G, C-C′, and C-C″ loops as well as some nearby residues form the adhesion site (*8*). The adhesion sites of cadherin and CD2 are at positions analogous to the contact sites between the variable domains of heavy and light chains in Igs (*9*).

The third striking observation concerns the binding site of calcium, which is required for cadherin adhesiveness. Overduin and co-workers identified the binding site in the linkage region between domains 1 and 2. It is not close to the putative site of adhesion, yet calcium binding induces a conformational change at the adhesion face. This effect is not yet understood. The primary result of calcium binding is stabilization of the positions of the five extracellular domains relative to each other, because homologous calcium binding sites are present at the linkage regions between all extracellular domains.

The new structure of a cadherin adhesion domain unveils a dominance of the Ig structural motif among cell adhesion molecules and more generally among receptor molecules. Previously, the growth hormone receptor structure was found to be built of domains related to this evolutionarily successful motif (*10*); in this case, too, no sequence homology exists. Many proteins of the extracellular matrix are built of structural motifs related to the Ig fold, the fibronectin–type III domains, for example. The three-dimensional structure of the cadherin adhesion domain will certainly stimulate analysis by site-directed mutagenesis of the surface residues important for adhesion contacts and may lead to an understanding of the specificity of adhesion in developmental processes.

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