INTRODUCTION

Cell-cell interaction is one of the fundamental processes required for development. It is natural to postulate that certain molecules should mediate this interaction. Cell adhesion molecules are good candidates to act as mediators of at least some parts of the interaction, and a large number of studies on cell adhesion molecules have been carried out to elucidate their developmental roles extensively (for review see Hynes and Lauder, 1992).

Cadherins are a group of cell adhesion proteins that mediate Ca\(^{2+}\)-dependent cell-cell adhesion. The adhesion properties – the homophilic nature of the activity, the high specificity of the interaction and the tissue specificity of the expression – led to the hypothesis that various cadherins might mediate specific cell-cell adhesion and play a pivotal role in the formation and maintenance of tissues (for review see Takeichi, 1991). Indeed, many cadherins and cadherin-related proteins have been identified in various tissues of different organisms (for review see Suzuki, 1996). The initial studies appeared to support this hypothesis, but subsequent studies have indicated that the story is not as simple as expected. Nevertheless, the features of these new proteins are very intriguing, and they appear to play a variety of important roles during morphogenesis and other biological processes. I will describe some of the recent findings and discuss their potential implications. In this commentary, I will focus on the recently identified protocadherins.

STRUCTURAL PROPERTIES OF PROTOCADHERINS AND THE CADHERIN SUPERFAMILY

Members of the cadherin superfamily (cadherins) are characterized by their unique extracellular domains, which are primarily composed of multiple repeats (cadherin repeats) of a cadherin specific motif (cadherin motif). The motif is about 100 amino acids in length and consists of multiple, highly conserved amino acids and short amino acid sequences. The three-dimensional structural model has recently been determined (Overduin et al., 1995; Shapiro et al., 1995). One interesting result of the structural studies is that cadherins are classified into two groups based on their extracellular domain features (Fig. 1): the classical cadherin type, including classical cadherins, desmosomal cadherins and HPT/LI-cadherin; and the protocadherin type, including vertebrate protocadherins, Drosophila fat and Drosophila DE-cadherin. Cadherins of the classical cadherin type share essentially the same extracellular domain structure, consisting of five cadherin repeats, each with its own characteristic features. Importantly, these cadherins share the cadherin repeats that show the characteristic features of the third and fifth repeats (EC3 and EC5) of classical cadherins: EC3 has one amino acid deletion near the C terminus and the DRE sequence in the middle of the repeat is replaced by a DFE or DYE sequence; EC5 contains the characteristic four cysteine residues. Cadherins of the protocadherin type, on the other hand, contain more than five cadherin repeats in their extracellular domains: the sequences are very similar to each other, and none of them contains the characteristic features of the EC3 or EC5 of the classical type cadherins (Sano et al., 1993).

The cytoplasmic domains of protocadherins, but not classical cadherins, are variable. Especially, the protocadherin type are highly variable and contain various cytoplasmic sequences. There has even been a report of a protocadherin...
FUNCTIONAL PROPERTIES OF PROTOCADHERINS

Classical cadherins were initially identified as the molecules that mediate cell-cell adhesion, and a recent knockout mouse experiment has proved the role of classical cadherins in embryogenesis (Larue et al., 1994). In contrast, the biological role of protocadherins is elusive, although a large number of protocadherins are expressed in a variety of organisms. Transfection experiments have indicated that protocadherins were localized at cell-cell contact sites in a Ca²⁺-dependent manner and showed cell aggregation activity similar to the classical cadherins, indicating that protocadherins have homophilic interaction activity. Many cell adhesion properties of the transfectants are similar to those of classical cadherins, but protocadherins also show unique properties that have not been reported for the classical cadherins (Obata et al., 1995; Sago et al., 1995). One noticeable difference is that the cell adhesion activity of protocadherins appears to be weaker than that of classical cadherins. The weak cell adhesion activity is not a characteristic property of protocadherins; some classical cadherins do not show strong cell adhesion activity (Tanihara et al., 1994). To date, no one has shown directly the homophilic interaction of cadherins in vitro, and this has been an enigma for cadherin research for many years. However, a consensus is now emerging in this field that the homophilic interaction activity of the cadherin extracellular domains is intrinsically very weak and that cadherins need to make clusters on the cell surface to generate strong cell adhesion activity. Recently Shaprio et al. (1995) even proposed a zipper model based on the crystal structure of a cadherin repeat.

Classical cadherins directly or indirectly associate with catenins and other proteins (Ozawa et al., 1989; Reynolds et al., 1994; Hoschuetzky 1994; Brady-Kalnay et al., 1995). The interaction appears to play a major role in cadherin clustering, which generates the strong cell adhesion activity and may participate in other activities (Matsunaga et al., 1988; Dantzig et al., 1994). Protocadherins, on the other hand, do not interact strongly with cytoskeletal proteins; thus, protocadherins are easily extracted with detergent and the localization at cell-cell contact sites is very labile. Therefore, the cell adhesion activity of protocadherins is predicted to be weaker than that of classical cadherins, and indeed, the activity is weak as described above. The chimeric Pcdh2 with E-cadherin cytoplasmic domain showed stronger cell adhesion activity (Obata et al., 1995), which is consistent with this notion.

It appears that these cadherins do not have a role in typical cell-cell adhesion because of their weak cell adhesion activity and labile localization at cell-cell contact sites. However, considering other features such as the capability of homophilic interaction and the expression of many protocadherins with different cytoplasmic sequences in various organisms, protocadherins may have a role in more general cell-cell interactions. In this context, the interaction between the cytoplasmic domains of cadherins and the cytoplasmic proteins is very interesting. If protocadherins play an important role as predicted, it should be exerted through the interaction between the cytoplasmic domains and the cytoplasmic proteins. Our recent results suggest that the cytoplasmic domains of protocadherins interact with several cytoplasmic proteins that are different from the known catenins (Sago et al., 1995). Characterization of the proteins should provide useful information about the biological role of protocadherins.

Furthermore, it may be noteworthy that heterophilic interaction of E-cadherin has recently been reported by Cepek et al. (1994). If heterophilic interaction is a common property among
cadherins, the whole story of cadherin function should be rewritten.

CONCLUDING REMARKS

We now know that a variety of cadherins are expressed in various tissues of different organisms and that their properties are highly divergent. It is evident that classical cadherins including E-cadherin are just a part of the cadherin superfamily. The major unanswered questions regarding protocadherins, and many other new cadherins as well are: (1) what activity do they actually exert in vivo and (2) what processes are they involved in? Circumstantial evidence suggests that they play an important role, but we do not know much about their function. I think several promising approaches are available now to elucidate their role. The knockout mouse and transgenic mouse approaches may provide an important clue. Indeed, our recent preliminary results indicated that ectopic expression of Pcdh2 resulted in the deformation of retinal tissue structure. Furthermore, characterization of the molecules that interact with the cytoplasmic domains may yield interesting information.

Recent studies on classical cadherins have revealed fundamental information regarding the structural and functional properties of cadherins. A structural and functional model of classical cadherins is now available, but we still have many important unanswered questions.

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REFERENCES


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