Cadherins constitute a superfamily of cell–cell adhesion molecules expressed in many different cell types that are required for proper cellular function and maintenance of tissue architecture. Classical cadherins are the best understood class of cadherins. They are single membrane spanning proteins with a divergent extracellular domain of five repeats and a conserved cytoplasmic domain. Binding between cadherin extracellular domains is weak, but strong cell–cell adhesion develops during lateral clustering of cadherins by proteins that link the cadherin cytoplasmic domain to the actin cytoskeleton. Understanding how different regions of cadherins regulate cell–cell adhesion has been a major focus of study. Here, we examine evidence of the structure and function of the extracellular domain of classical cadherins in regard to the control of recognition and adhesive contacts between cadherins on opposing cell surfaces. Early experiments that focused on understanding the homotypic, Ca++-dependent characteristics of cadherin adhesion are discussed, and data supporting the widely accepted cis- and trans-dimer models of cadherins are analyzed.

Keywords  Cadherin · Cell–cell adhesion · Calcium · Structure · Dimer
proto-cadherin family is included (Frank and Kemler 2002). Cadherins are expressed in many cells and tissues, and are evolutionarily conserved in vertebrates and invertebrates (Kemler 1992; Takeichi 1995; Gumbiner 1996). Here we focus on a subset of cadherins, the classical cadherins, that are the best described and understood. We focus on the structure and function of the extracellular domain that controls recognition and adhesive contacts between cadherins on opposing cell surfaces.

Classical cadherins, of which E-, P-, N-, and R-cadherin are members, were shown to mediate segregation of different cell populations in early studies. Segregation was based on homophilic adhesion in which cells expressing one cadherin subtype (E-cadherin for example) segregated in suspension from cells expressing a different cadherin subtype (P-cadherin). Cadherin-mediated homotypic adhesion appears to depend on binding specificity, Ca\(^{++}\)-dependence, and molecular contacts of cadherins and cadherin–cadherin adhesion. Sequence analysis of classical cadherins reveals that they have five tandemly repeated domains in the extracellular domain, termed extracellular cadherin repeats 1–5 (EC1–5) (Fig. 1) with EC1 at the amino terminus (Hatta et al. 1988). When synthesized, cadherins contain signal and precursor peptides that are cleaved during processing and maturation of the protein in the endoplasmic reticulum (ER) and Golgi. The precursor peptide is cleaved before cell surface presentation of the cadherin, and cleavage is required for adhesive function (Ozawa and Kemler 1990).

How do cadherin extracellular domains interact to form cell–cell adhesions? The most prevalent models describe two cadherins within the same membrane forming a lateral or cis-dimer and that this dimer promotes adhesion.

**Fig. 1.** Schematic of a classical cadherin. The schematic depicts the domain organization of a classical cadherin. Five extracellular repeats (EC1–5) are preceded by a precursor peptide which is cleaved during maturation. Ca\(^{++}\)-binding sites (+ marks) are located at each EC junction. EC5 is followed by a single transmembrane segment and a highly conserved cytosolic domain which associates with members of the catenin protein family. Monoclonal antibody binding regions are marked with numbered black bars above the repeats and correspond to binding sites of (1) ECCD-1, (2) PCD1 and NCD1, and (3) DECMA. Disulfide bonds are shown in EC5 as gray brackets. A close view of EC1 also shows the histidine-alanine-valine (HAV) tripeptide as well as the highly conserved first seven residues of the mature protein including Trp2.