Chapter 4
Structure and Function of Cadherin Extracellular Regions

Lawrence Shapiro

Abstract Cell-surface glycoproteins of the cadherin superfamily are defined by the presence of extracellular cadherin (EC) β-sandwich domains in their extracellular regions. EC domains adopt a fold similar to immunoglobulin domains, but most EC domains ligate calcium through stereotyped sites positioned between successive domains; Ca^{2+}-binding at these sites rigidifies cadherin extracellular regions. Although the superfamily is highly diverse and may serve numerous functions, the best-characterized members are the vertebrate "classical" cadherins, which mediate cell–cell adhesion via homodimerization between their membrane-distal EC1 domains. Nonclassical and invertebrate cadherins have evolved distinct mechanisms for cell recognition and adhesion, and are only now beginning to be understood.

Keywords Cadherin • Classical cadherin • Extracellular cell adhesion • Crystal structure crystallography • Cell adhesion • Adherens junctions

4.1 Introduction

Cadherins embody a large family of cell surface proteins, the best characterized of which function in cell–cell recognition and adhesion (Nagafuchi et al. 1987; Ogou et al. 1983; Takeichi 1990, 1991). In mediating this function, cadherins bind between cells through their extracellular regions, the structure and function of which are the topic of this review. Cadherin extracellular regions are diverse in structure (Fig. 4.1) (Nollet et al. 2000; Shapiro and Weis 2009) and, as described here, serve varied remarkable functions. Extracellular regions of cadherins are characterized by the presence of distinctive protein domains of ~100 amino acids called extracellular cadherin (EC) domains (Hatta et al. 1988; Overduin et al. 1995; Shapiro et al. 1995a, b). The number of EC domains in the extracellular regions of various cadherins varies widely, however, distinctive EC domain sequences can be

L. Shapiro (✉)
Department of Biochemistry and Molecular Biophysics, Columbia University, New York, NY 10032, USA
e-mail: shapiro@convex.hhmi.columbia.edu

S.T. Suzuki, S. Hirano (eds.), *The Cadherin Superfamily*,
DOI 10.1007/978-4-431-56033-3_4

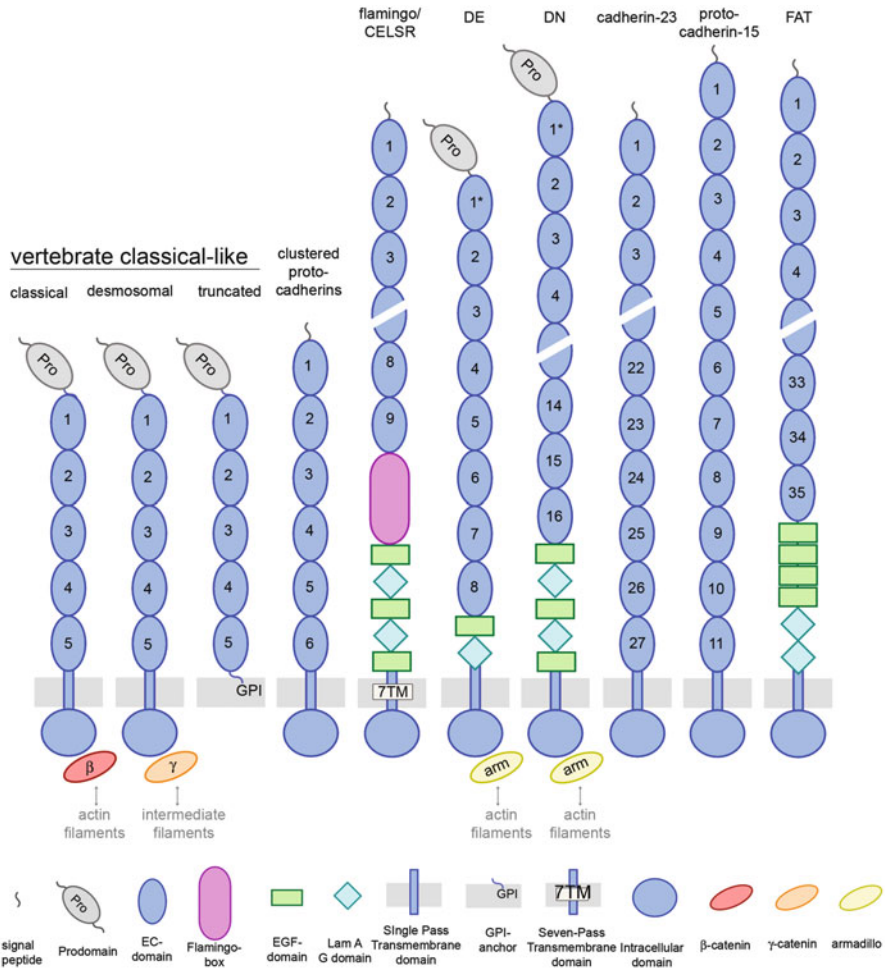

Fig. 4.1 Schematic diagram of domain arrangements in numerous cadherin subclasses. EC domains are numbered, and domains of other types are shown in the legends

detected in cadherins from widely varying species, including vertebrates, invertebrates, and some single-celled animals (Nollet et al. 2000; Posy et al. 2008b).

EC domains have topology similar to immunoglobulin domains (Overduin et al. 1995; Shapiro et al. 1995a), although arrangements of their hydrophobic core residues are distinct (Shapiro et al. 1995b). Two β -sheets are formed by seven strands; the immunoglobulin strand-topology nomenclature has been adopted for cadherin domains, with one sheet formed from strands ACFG, and the other by strands BED. The N-terminal A strand enters at the "top" of the domain, whereas the C-terminus of the final G strand exits through the "bottom", with the long-axis of the domain running parallel to the β-strands. Thus, EC domains can be efficiently assembled as contiguous repeats. For most, but not all EC domains, binding sites for

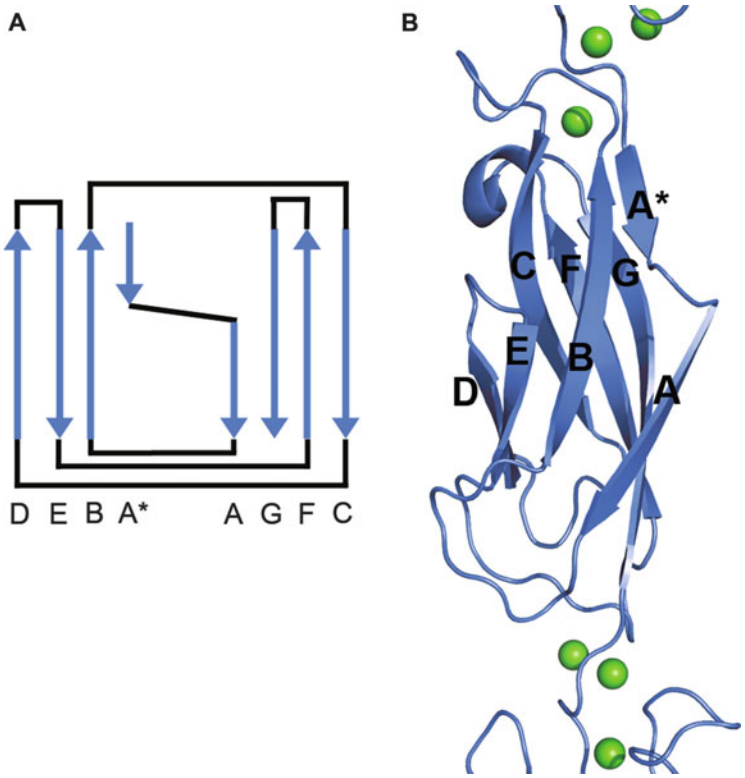

Fig. 4.2 Folding topology and role of Ca^{2+} binding by EC domains. The folding topology of an EC domain is shown schematically in (**a**). The topology is identical to immunoglobulin domains (in which the *A* strand can also associate with either sheet in different cases), and the immunoglobulin β-strand nomenclature is used. Panel (**b**) shows a ribbon diagram of a "middle" (EC2) cadherin domain, showing the classical role of Ca^{2+} ligation in rigidifying the connections between successive EC domains

Ca^{2+} ions are situated at each end of the domain (Boggon et al. 2002). Because Ca^{2+} ligands are donated from both preceding and following EC domains, Ca^{2+} ligation serves to rigidify the overall ectodomain structure (Boggon et al. 2002; Harrison et al. 2011; Fig. 4.2). Thus, cadherin EC domains provide a platform from which loops can be elaborated, as for immunoglobulin domains, and Ca^{2+} binding provides a mechanism to rigidify an overall superstructure of tandemly repeated EC domains.

Cadherins of vertebrates have been the most extensively studied. Numerous vertebrate cadherin subfamilies can be identified by phylogenetic analysis (Nollet et al. 2000; Posy et al. 2008b), including the classical cadherins, which appear in two distinctive sequence clusters referred to as type I and type II classical cadherins. Type I cadherins, including N-, E-, P-, and R-cadherins are broadly expressed, and mediate Ca^{2+}-dependent adhesion with primarily (but not exclusively) homophilic

specificities (Katsamba et al. 2009). Their homophilic specificity makes cadherins ideal for formation of cell layers composed of a single cell type. The distinctive specificities of different type I classical cadherins are also thought to provide a driving force for the separation of cell layers (Hatta et al. 1987; Hatta and Takeichi 1986; Hirano et al. 1987; Nagafuchi et al. 1987; Duguay et al. 2003). Thus, type I cadherins commonly mediate homophilic adhesion between cells of various layers, and also play a role in mediating the relationships between layers, which can involve either separation or heterophilic adhesion.

Type I cadherins provide the transmembrane intercellular adhesive components of actin-attached adherens junctions (Harris and Tepass 2010; Meng and Takeichi 2009; Yap et al. 1997; Yonemura 2011). The formation of such junctions is among the most remarkable functions of cadherin ectodomains, where the combination of trans interactions (between cadherins on apposing cells) and cis interactions (between cadherins on the same cell) underlies an ordered junction structure (Harrison et al. 2011). Remarkably, the structure of these ordered assemblies appears to be encoded in the extracellular region itself, as type I cadherins lacking their cytoplasmic domain can spontaneously assemble junction-like structures between cadherins presented on juxtaposed membrane surfaces (Harrison et al. 2011; Taveau et al. 2008).

Another subfamily of vertebrate cadherins, the desmosomal cadherins (Delva et al. 2009; Garrod 2010; Holthofer et al. 2007; Koeser et al. 2003; Lewis et al. 1994), also form ordered intercellular attachments at desmosome junctions. Desmosomal cadherins, which include two subgroups, desmocollins and desmogleins, have structures (as inferred by sequence analysis) expected to be highly similar to type I classical cadherins (Posy et al. 2008a). However, structures of functional desmosmal cadherin ectodomains have not yet been obtained. Desmosomes are extremely dense and form junction superstructures that appear well-ordered in the extracellular space, suggesting the presence of lateral interactions between cadherin ectodomains (He et al. 2003; Al-Amoudi et al. 2007; Al-Amoudi and Frangakis 2008). Although sequence conservation suggests that their adhesive binding will likely be similar to that of type I cadherins (Posy et al. 2008a), the nature of potential lateral interactions among desmosomal cadherins remains unknown. Furthermore, as desmosome junctions contain both desmocollins and desmogleins (Chitaev and Troyanovsky 1997; Delva et al. 2009; Franke et al. 1994; Nollet et al. 2000), the roles and interactions of members of either subfamily remain unknown; thus the specific architecture of desmosomes remains largely to be determined.

Another family of vertebrate cadherins that function in cell adhesion is the type II family of classical cadherins (Patel et al. 2006; Shimoyama et al. 1999). Their structures are similar overall to type I cadherins (Patel et al. 2006), but their expression patterns differ. In general, type II cadherins, encoded by 13 different genes conserved in vertebrates (Nollet et al. 2000), are coexpressed in subsets together (Marthiens et al. 2005; Price et al. 2002). Thus, although a given cell type usually expresses a single type I cadherin, such as N- or E-cadherin (Hatta and Takeichi 1986; Hirano et al. 1987; Nakagawa and Takeichi 1998; Takeichi 1991,

1995), most type II cadherin-expressing cells produce a small set of type II cadherins. A well-studied example can be found in the spinal cord, where motor neuron cell bodies are grouped together in structures called motor pools; each motor pool innervates an individual muscle. Each motor pool expresses a distinct combination of type II cadherins, and these distinct sets of type II cadherins function to hold the cells of each motor pool together through homophilic adhesion, while separating them from cells of other motor pools (Patel et al. 2006; Price et al. 2002). Misexpression of type II cadherins in this system disrupts motor pool organization (Patel et al. 2006; Price et al. 2002). Overall, the coexpression of type II cadherins has complicated their functional analyses. As a result, less is known about their function than for type I cadherins.

Numerous other branches of the cadherin family are also found in vertebrate genomes, and have been functionally characterized to varying degrees. A group of proteins referred to, sometimes confusingly, as protocadherins is also represented (Nollet et al. 2000). Many protocadherins appear to function in cell–cell adhesion, but there are two notable classes of outliers. First, is a group of extremely large cadherins that help to form filamentous signaling structures (Ahmed et al. 2006; Kazmierczak et al. 2007). In a key example, the hair cells of the inner ear produce stereocilia, which are linked at their apex by a thin helical structure called the "tip-link". This structure, which is required for hearing, is composed of a complex between the very large proteins cadherin-23 (27 EC domains) and protocadherin-15 (11 EC domains) (Ahmed et al. 2006; Kazmierczak et al. 2007; Elledge et al. 2010; Sotomayor et al. 2010). There is binding at the tips between these two large cadherins that extend from adjacent stereocilia (Sotomayor et al. 2012), however, the cable-like structure they produce is tuned to sensing vibration and transmitting it to the hair cells via associated ion channels to produce neural representations of sound (Kazmierczak et al. 2007). Similar proteins are found in other sensory systems as well, but their functions remain unknown (Seiler et al. 2005).

Another important outlying example is found in a distinctive set of genes arranged in three clusters that encode the α, β, and γ "clustered" protocadherins, highly specialized proteins that help to mediate neural self-recognition and self-avoidance (Hayashi and Takeichi 2015; Thu et al. 2014; Chen and Maniatis 2013; Yagi 2012). These proteins are functionally distinct from the majority of cadherins, still mediating cell–cell recognition, but primarily to activate avoidance between neurites emanating from the same neuron, while allowing interaction between neurites of different neurons (Lefebvre et al. 2012; Chen et al. 2012). Thus, cell–cell recognition by cadherins can mediate avoidance as well as adhesion. The mechanism by which protocadherins enable self-recognition by processes from the same neuron remains unclear but, as described below, preliminary structure/function studies give clues about their remarkable function.

4.2 Vertebrate Classical Cadherins

Extracellular regions of classical cadherins protrude from opposing cell surfaces and form trans adhesive homodimers through their membrane-distal EC1 domains (Fig. 4.3). The cadherin/cadherin interface that mediates this interaction has been characterized in detail from atomic resolution structures of numerous classical cadherins (Harrison et al. 2011; Shapiro et al. 1995a; Boggon et al. 2002; Haussinger et al. 2004; Parisini et al. 2007). All classical cadherins share a common binding mechanism in which the most N-terminal portion of the β strand A, called

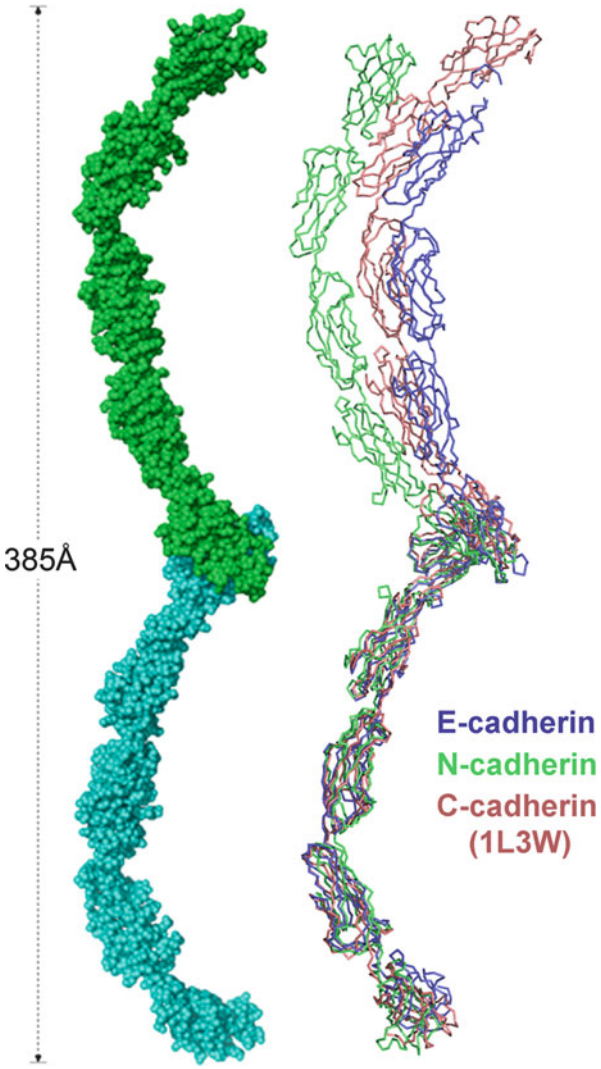

Fig. 4.3 Crystal structures of the full adhesive ectodomains in the adhesive dimer conformation for N-, E-, and C-cadherin structures. *Left*, C-cadherin adhesive dimer structure in space-filling representation. *Right*, Superposition of all three dimer structures, showing their variability. Only the lower molecule is used in the superposition, and the variation of the upper molecules represents mainly angular differences at the adhesive interface

the A* strand, swaps between EC1 domains of the adhesive partner protomers, a form of 3D domain swapping (Bennett et al. 1995). Conserved hydrophobic anchor residues located on the A* strand—Trp2 for type I cadherins and Trp2 and Trp4 in type II cadherins—dock into a conserved hydrophobic pocket in the body of the adhesive partner EC1 domain in trans (from the apposed cell). These conserved anchoring Trp residues are necessary for cell adhesion, and point mutation at these residues provides a convenient knockout for classical cadherin function (Harrison et al. 2005; Meng and Takeichi 2009; Patel et al. 2003; Shapiro and Weis 2009; Troyanovsky et al. 2003; Patel et al. 2003).

4.3 Strand-Swap Binding

The exchange of β-strands between interacting classical cadherins provides one of the clearest biological examples of the protein interaction mode referred to as "3D domain swapping" (Bennett et al. 1995). 3D domain swapping is defined by the presence of two alternative conformations, the unbound and bound states, which differ in that the "swapping" region is self-bound in the monomer, but interacts identically with its partner domain in the bound state. In the case of vertebrate classical cadherins, the swapping "domain" (the A*-strand) can dock into a binding pocket in the body of its own protomer to form a "closed"monomer (Fig. 4.4, left panel), or can dock into the pocket of a partner EC1 domain to form a strand-swapped dimer (Fig. 4.4, right panel). A necessary step in the transition of the closed monomer to the swapped dimer is rearrangement of the monomer state such that the swapping domain, the A* strand, undocks, allowing dimers to form between two open monomers. As is characteristic of 3D-domain swap binding, the swapping domain (the A* strand) is found in nearly identical residue environments in the "closed" monomer and in the swapped dimer. The closed monomer state can thus be thought of as a competitive inhibitor for the swapped dimer. This competition generally weakens interactions for 3D domain-swapped interfaces, and underlies the relatively weak binding affinities of classical cadherins (~10–100μM) (Chen et al. 2005). This property also requires that structural differences exist that stabilize the dimer and/or destabilize the monomer so that adhesive dimers are favored at points of cell–cell contact. Several factors that favor the formation of strand-swapped dimers (Posy et al. 2008b) have been identified, including a shortened A-strand, which strains to self-dock, but which is free to dock in the less geometrically constrained setting of a dimer.

Binding sites for three Ca^{2+} ions are found at interdomain linkers between each set of successive EC domains (Fig. 4.2). Glu11, a residue conserved at the base of EC1 A strands, coordinates Ca^{2+} in all classical cadherins. Anchoring of the A strand at both ends—at the base by Ca^{2+} binding to Glu11 and at the N terminus by Trp2 docking—induces strain in the shortened A strand. This strain destabilizes the closed monomer and thus favors strand-swapped dimer formation (Vendome et al. 2011; Vunnam and Pedigo 2011a, b).

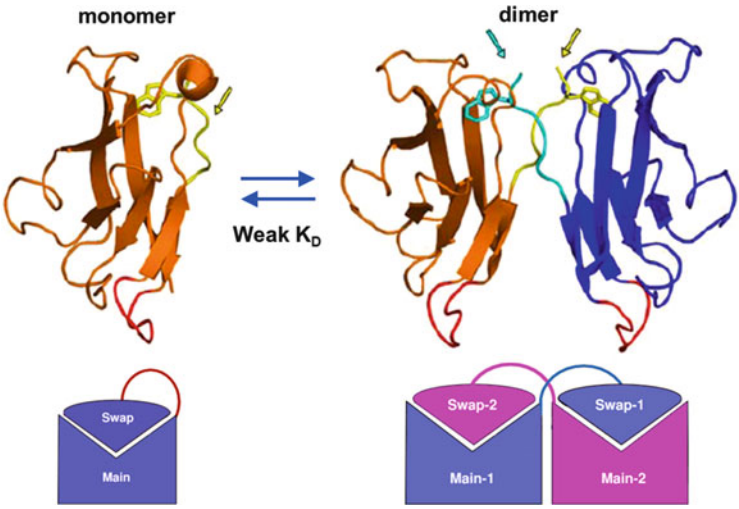

Fig. 4.4 3D domain swapping in classical cadherins. *Left*, a ribbon representation of the closed form of the EC1 domain of E-cadherin (*top*), and schematic representation of a closed monomer in 3D domain swapping. The swap domain in the *lower panel* corresponds to the swapping A* strand in the *upper panel*. In the dimer (*right*), the atomic environment of the swapped strand is nearly identical, but in the intermolecular rather than the intramolecular context shown at *left*. The similarity between the monomer structure at *left* and the dimer structure at *right* leads to small energy differences, and hence weak binding is weak. Arrows indicate the swapping A* strands

All vertebrate classical cadherins form cell-adhesive dimers through a similar strand-swapping mechanism. However, there are characteristic differences between members of the type I and type II cadherin subfamilies (Fig. 4.5). Adhesive interfaces of type I cadherins are restricted to the Trp2-acceptor pocket region near the N-terminal apex of EC1 and the partner A* strand region that includes Trp2. By contrast, in type II cadherins, two tryptophan residues, Trp2 and Trp4, anchor the swapped strand. The dimer interfaces of type II family members also extend beyond the swapping region, along the entire face of the EC1 domain. These extended interface regions mediate interactions involving conserved hydrophobic residues at positions 8, 10, and 13 (Patel et al. 2006). VE- cadherin, a divergent classical cadherin and the primary adhesion protein of the vascular endothelium (Harris and Nelson 2010), blurs the definition between type I and type II cadherins. As do type II cadherins, VE-cadherin docks Trp2 and Trp4 into the hydrophobic pocket of its partner, but as do type I cadherins it lacks hydrophobic interactions along the rest of its EC1 domain and thus has an overall dimer arrangement more similar to that of type I cadherins (Brasch et al. 2011).

The specificity of classical cadherin adhesive binding is controlled by the EC1 domain, as demonstrated by experiments in which EC1 domains were shuffled between different cadherins with different specificities (Patel et al. 2006; Klingelhofer et al. 2000; Nose et al. 1990; Shan et al. 2000, 2004). Type I cadherins do not bind to type II cadherins (Shapiro and Weis 2009; Patel et al. 2006;

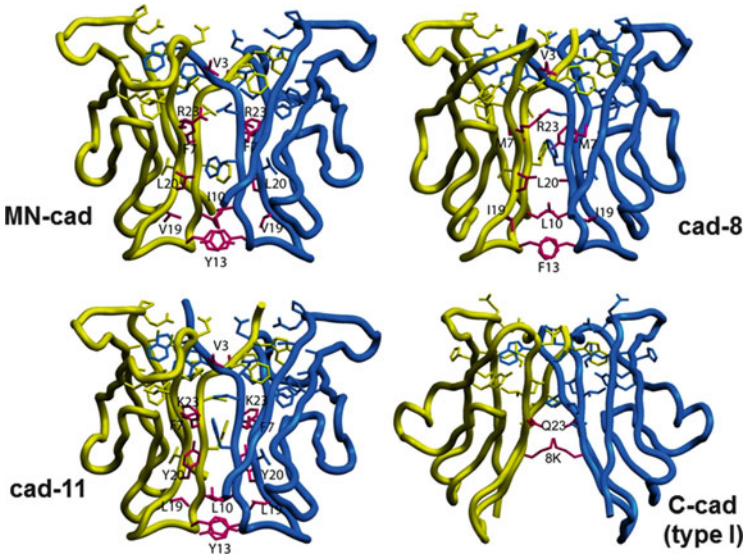

Fig. 4.5 Comparison of type I and type II cadherin adhesive interfaces. Worm diagrams are shown for three type II cadherin EC1 domain adhesive dimers: MN-cadherin, and cadherins -8 and -11. The adhesive EC1 dimer is also shown for one type I cadherin, C-cadherin. Note that the adhesive interface for type I cadherins involves only the strand-swap region, whereas type II cadherins have an extra hydrophobic interface toward the base, which zips up over the whole length of the EC1 domain

Katsamba et al. 2009; Shimoyama et al. 1999), consistent with the differences between the adhesive interface structures of these cadherin subfamilies. They are often described as having homophilic specificities, however, classical cadherins interact promiscuously within subfamilies (Katsamba et al. 2009; Patel et al. 2006; Shimoyama et al. 1999; Shimoyama et al. 2000). Type I cadherins are usually expressed singly, but type II cadherins are in general expressed in combinations; the biological effect of type II cadherin coexpression remains to be fully understood.

4.4 X-Dimers Facilitate Strand Swapping in Type I and Type II Classical Cadherins

To form strand-swapped cell-adhesive dimers requires that each partner classical cadherin protomer refold to transition from the "closed" monomer form (Fig. 4.4, left panel) to the "open" dimer form (Fig. 4.4, right panel). This conformational change can present a kinetic barrier. Indeed, in other examples of 3D domain swapping, this process can occur over very long time periods (Bennett et al. 1995). Results of single-molecule fluorescence resonance energy transfer (FRET) experiments have provided evidence for an encounter complex

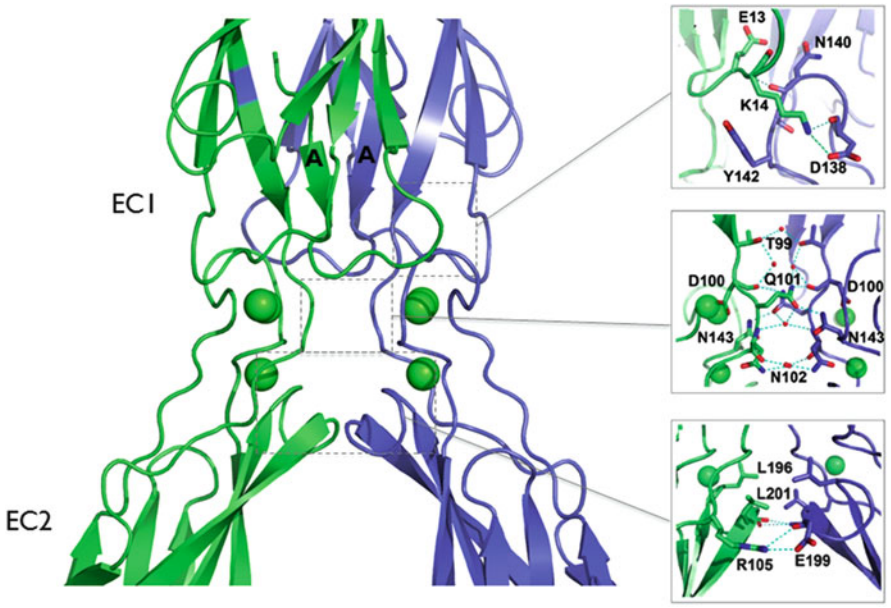

Fig. 4.6 X-dimer structure. The overall structure of the X-dimer interface is shown in ribbon representation for the E-cadherin strand swapping-incompetent mutant E89A. All strand-swapping–incompetent mutants of type I and type II cadherins determined thus far are in the X-dimer conformation. The X-interface includes the bottom of EC1, the EC1-EC2 linker, and the top of EC2; these three regions are shown in expanded view at right

intermediate. When strand swapping was ablated by a Trp2 to Ala mutation, dimers still formed between EC1 domains, with FRET distances slightly altered as compared with swapped dimers, suggesting the existence of a nonswapped dimer form. Additionally, atomic force microscopy (AFM) experiments showed the nonswapped mutant dimers to be weaker than strand-swapped, wild-type dimers, energetically consistent with a role as a binding intermediate (Sivasankar et al. 2009).

Structural studies of strand swap-impaired classical cadherin mutants have revealed the molecular details of this encounter complex (Harrison et al. 2010). Numerous strand swap-impaired mutants adopt a similar conformation: a dimer with its interface centered around the EC1–EC2 interdomain linker (Fig. 4.6). These dimeric structures are now called “X-dimers” due to their X-like overall shape. X-dimers interact through surface residues, thus requiring no refolding for interaction. X-dimers can therefore form with fast-binding kinetics. Most importantly, in the X-dimer the A strands of each protomer are positioned in parallel to each other in close proximity, as if poised to swap (Harrison et al. 2010). Thus, X-dimers form quickly and position the EC1 domains of interacting cadherins, holding them in place to enable refolding to adopt the strand-swapped conformation. Type II cadherins (Harrison et al. 2010). The role of the X-dimer conformation

as a kinetic intermediate has been confirmed by cell biological and biophysical observations (Sivasankar et al. 2009). Mutations designed to prevent X-dimer formation, but leave strand swapping intact, fail to mediate cell adhesion (Harrison et al. 2010). The association rates of type I E-cadherin and type II cadherin-6 are dramatically slowed in such mutants such that no dimerization could be observed in short (~1 min) SPR experiments. However, in sedimentation equilibrium analytical ultracentrifugation experiments (~48 h equilibration time) wild-type binding affinities are observed (Harrison et al. 2010).

Interestingly, T-cadherin, a divergent vertebrate classical-like cadherin which is GPI-anchored and lacks a cytoplasmic region, does not interact by strand swapping. Rather, the adhesive state of T-cadherin represents an X-dimer formed between T-cadherin ectodomains from juxtaposed cells (Ciatto et al. 2010). Mutations targeting the X-dimer interface in T-cadherin abolish its function in neurite outgrowth regulation, whereas mutations targeted to the region involved in strand swapping for other classical cadherins had no effect on T-cadherin function or homodimerization (Ciatto et al. 2010). The close phylogenetic relation to type I classical cadherins suggests that T-cadherin represents a classical cadherin that has lost its ability to bind through strand swapping.

4.5 Cis Interactions, Adherens Junctions, and Desmosomes

In mature tissues cadherins localize primarily to intercellular structures with defined morphology called junctions. There are two primary junction types: adherens junctions, which are formed by classical cadherins and are linked to the actin cytoskeleton, and desmosome junctions formed by specialized desmosomal cadherins with members of two distinct subfamilies, the desmocollins and desmogleins, discussed below. Cadherin ectodomains appear to play a critical role in junction assembly. Experiments with purified classical cadherin ectodomains show that, when bound to liposomes, ectodomains alone self-assemble into structures closely resembling adherens junctions (Harrison et al. 2011; Taveau et al. 2008). Mutations at the crystallographically identified cis interface destroy these junction-like structures, suggesting a structural basis for self-assembly of adherens junctions through these cis and trans interfaces.

For classical cadherins, the lateral *cis*-interaction site shows a conservation signal above background among type vertebrate type I classical cadherins, and critically has been observed in all crystal structures of full-length type I cadherin ectodomains (Boggon et al. 2002; Harrison et al. 2011). In addition to the adhesive strand-swap interface, this lateral cis interface, formed between the base of the EC1 domain of one protomer and a region near the apex of EC2, is found in the structures of all three currently available structures of full-length cadherins, N-, E-, and C-cadherins (Fig. 4.7; Boggon et al. 2002; Harrison et al. 2011). The combination of cis and trans interactions for each cadherin molecule creates similar molecular layers within each crystal form, which likely to correspond to the fully

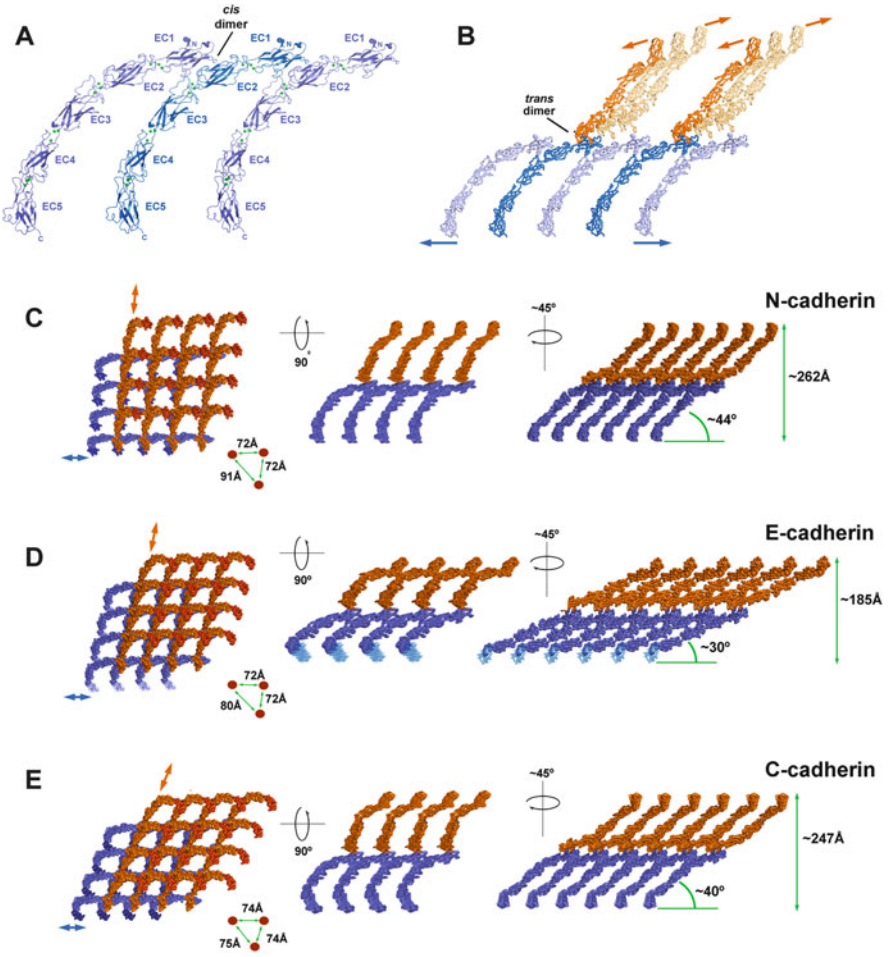

Fig. 4.7 The likely extracellular structure of adherens junctions. (**a**) The cis interface, similar among all type I cadherins investigated, is shown as it appears in crystals of N-cadherin. (**b**) The orange molecules at top, which also partake in cis interactions, attach to the blue cis interface-polymer via adhesive EC1 interactions. (**c**, **d**, and **f**) These interfaces combine to form similar lattices in unrelated crystals of N-, E-, and C-cadherins, respectively

bound state of cadherin ectodomains in adherens junctions (Boggon et al. 2002; Harrison et al. 2011). The region of EC1 involved in this cis interface is opposite to the strand-swapping site, so that cis and trans interactions can form simultaneously resulting in a continuous two-dimensional lattice with dimensions near to those expected for adherens junctions (Fig. 4.7). No sequence conservation above background level is observed for this region in other cadherin subfamilies, many of which lack elements of the interface through residue deletions. These three proteins share identities of 58 %(C/E), 58 %/(E/N), and 39 %(C/N), and it would be highly

unlikely for all three proteins to form a nearly identical interface (the cis interface) in all three unrelated crystals, arguing for its biological function.

In an artificial system in which purified His-tagged cadherin ectodomains are bound to the surface of controlled-size (~200nm) Ni^{2+}-chelating liposomes, time-dependent Ca^{2+}-dependent liposome aggregation was observed, and cryo-EM analysis revealed ordered junction-like structures that resemble the layer of molecules, composed of cadherins arranged through cis and trans interfaces, observed in the unrelated crystal lattices of C- (Boggon et al. 2002), E-, and N-cadherin (Harrison et al. 2011). This liposome system, and assays using transfected cells have been employed to test the idea that the cis interface underlies lateral assembly of adherens junctions comprised of type I cadherins. Mutants compromised for binding at the cis interface of E- cadherin, but wild-type for trans strand-swap binding, showed adhesion between liposomes, but at a reduced level. In transfected cells, these cis interface-mutant cadherins a dominant phenotype in which junctions incorporating them became unstable and transient. In cells lacking wild-type cadherins, cis mutant proteins showed both diffuse localization as well as some degree of concentration at sites of cell contact, but this degree of concentration was significantly less than observed for wild-type cadherins (Harrison et al. 2011). Finally, cryo-EM analysis of adherent liposomes produced with purified cis interface-mutant cadherins showed that the ordered tooth-like structure characteristic of the wild-type reconstituted junctions was absent in the cis interface mutant junctions (Harrison et al. 2011) . Taken together, these data strongly implicate the cis interface identified in crystallographic studies in the lateral assembly of cadherin trans dimers in adherens junctions.

Remarkably, cis interactions among classical type I cadherins are too weak to be detected by analytical ultracentrifugation (detection limited to K_Ds <1 mM) or other typical solution-binding experiments, despite its apparent biological role in junction assembly revealed in mutagenesis studies with cellular or cryo-EM readouts. This apparent paradox is likely due to the significant differences expected for protein–protein interactions in solution and in the context of a membrane, where positional and rotational freedom are limited (Wu et al. 2011). Indeed, *in silico* simulation experiments suggest that when type I cadherin ectodomain dimers form in trans, their motional freedom is dramatically reduced because they are attached to one other through the adhesive interface while tethered at each end to one of the apposed cell membranes (Wu et al. 2011). Thus trans interactions between cadherins are expected to lower the entropic penalty associated with cis dimer formation (Wu et al. 2010; Wu et al. 2011), triggering a cooperative junction assembly process when two cells come into contact. The observation that cadherins do not cluster on the cell surface in the absence of an apposed cadherin-expressing cell (Gumbiner 2005; Hajra and Fearon 2002) can be at least partially explained by this model.

The self-assembly of junctions, at least in part through specific interactions of cadherin extracellular regions, could have multiple functions. Such lateral intercadherin interactions are likely to increase the mechanical stability of intercellular adhesion, and the concentration of proteins at intercellular appositions

could in principle play a critical role in signaling, although the nature of signaling at adherens junctions remains poorly understood overall. When proteins that bind one another are presented on apposing cell surfaces, their binding creates a "diffusion trap" mechanism whereby the proteins will concentrate at sites of cell membrane apposition. Cadherin assembly, however, yields a degree of concentration at junctions that is higher than can be achieved by a diffusion trap alone. The cis interface mutants described above show that adhesive binding alone, in the absence of self-assembly mediated by the cis interface, yields a substantially lower concentration of cadherin at cell–cell contacts than observed for wild-type cadherins (Harrison et al. 2011). This experiment demonstrates that cis interactions play a critical role in enhancing the localization of classical cadherins to adherens junctions, likely through assembly of small punctate junctions with bound structures produced by the cis and trans interfaces similar overall to those observed in liposome-reconstituted junctions and the N-, E-, and C-cadherin crystal structures. Large cellular adherens junctions, as observed in fluorescence microscopy, are likely to be assembled from numerous subdomains with the lattice-like structure described above. The lattice structure is directional such that any two subdomains would have to meet with an appropriate orientation to merge. Although the vertebrate type II classical cadherins are highly similar to type I cadherins and have the same adhesive mechanism as type I cadherins, they do not appear to partake in self-assembly through the cis interface described above (Brasch et al. 2011; Harrison et al. 2010; Patel et al. 2006) .

Desmosome junctions, which are extremely dense and stable structures, also assemble differently from adherens junctions formed by type I cadherins. Analyses of sequence conservation between desmosomal and type I cadherins (Thomason et al. 2010) suggest that they also adhere through a strand-swap binding mechanism—although whether the X-dimer kinetic intermediate is also used cannot be inferred by sequence comparison—but their lateral interactions are likely to differ. Both subfamilies of desmosomal cadherins, desmocollins and desmogleins, conserve the strand swap-anchoring Trp residue conserved at position 2, and hydrophobic residues corresponding to the Trp binding pocket in classical cadherins (Posy et al. 2008b; Thomason et al. 2010). Also as for type I and type II classical cadherins, mutation of Trp2 or its acceptor pocket abolishes trans binding of desmocollin 2 in cross-linking experiments (Nie et al. 2011). The structure of an EC1-domain fragment of human desmoglein-2, determined by NMR spectroscopy (pdb-ID: 2YQG) (NMR) shows a domain fold similar to that of vertebrate type I cadherins. This structure is monomeric with Trp2 self-docked, perhaps due to the inclusion of 10 residues preceding the native N terminus from a cloning artifact. Extensions of this type have been shown to prevent strand-swap dimerization in classical cadherins (Harrison et al. 2010; Haussinger et al. 2004) . Two groups have independently produced high-resolution electron microscopy tomograms of in situ desmosomes. The first of these, from the Stokes group (He et al. 2003), examined desmosomes from mouse skin embedded in plastic and sectioned. This reconstruction revealed a dense network of interacting desmosomal cadherin ectodomains, but the arrangement of ectodomains appeared far less ordered than expected from

two-dimensional EM images of desmosomes. This apparent lack of order could have arisen as an artifact of the sectioning procedure. A second more recent desmosome reconstruction was produced by the Frangakis group. This study was based on cryo-electron tomography of vitreous sections from human epidermis, and revealed a regular array of curve-shaped densities resembling classical cadherin ectodomain structures spaced at ~70Å intervals along the midline (Al-Amoudi et al. 2007). Despite this seemingly clear result, both this study and the earlier one were unable to define a molecular model for ectodomain interactions in desmosomes. A significant part of this uncertainty arises from uncertainty about the composition of the desmosomes studied. It is thought that a given desmosome will contain both desmocollins and desmogleins, but the protein compositions of the desmosomes studied by both the Frangakis and Stokes groups were unknown, and no attempt was made in either work to distinguish desmocollins from desmogliens.

4.6 "Giant" Cadherins

Both vertebrate and invertebrate genomes encode numerous proteins containing large numbers of tandem EC domains, so-called "Giant" cadherins. Relatively little is known about their structure/function relations, but early insights are exciting. The Giant cadherins protocadherin-15 (11 EC domains) and cadherin-23 (27 EC domains) provide a remarkable example. These proteins, each involved in inherited deafness, link adjacent stereocilia of sound-sensing hair cells by formation of a cable-like structure known as the tip-link. Scanning transmission electron microscopy images suggest that the tip-link is comprised of a double helix formed by two cadherin-23 molecules emanating from one stereocilium interacting at the tip with the tip of a double helix formed by two protocadherin-15 molecules emanating from adjacent stereocilium (Kazmierczak et al. 2007). Atomic resolution structures of an N-terminal EC1–EC2 fragment from cadherin-23, and its complex formed by interaction with an EC1–EC2 fragment from protocadherin-15, yield significant insights into how this head-to-tail oriented complex forms an extended handshake interaction involving both EC1 and EC2 domains. Interestingly, Pcdh 15 has an elongated N-terminus which extends as a helix beyond the body of EC1; this helix forms much of the interface with Pcdh 23 EC2. Unlike classical cadherins, there is no strand-swap interaction. The authors use molecular dynamics simulations to highlight ways in which the cadherein 23/Pcdh 15 interface is optimized to resist force in transducing vibrational signals.

Another well-studied pair of interacting giant cadherins are Fat and Dachsous, which regulate cell polarity and proliferation (Ishiuchi et al. 2009; Tanoue and Takeichi 2005). Fat is the largest cadherin, with 34 EC repeats, and binds to Dachsous, another Giant cadherin with 27 EC domains. Despite their large sizes, the mammalian proteins Fat4 and Dachsous1 are detected in intercellular spaces

contiguous with adherens junctions, raising the question of how such large molecules can be accommodated in a relatively small space, one which classical cadherins are known to traverse with only five EC domains from each adherent cell surface. A recent study of purified Fat4 and Dachsous1 ectodomains reveals that each molecule is made up of elongated sets of contiguous domains, with hairpin bends distributed at specific interdomain linkers (Tsukasaki et al. 2014). These hairpin bends appear to be associated with interdomain linker regions that lack the canonical Ca^{2+} binding sites, which normally help rigidify linkages between EC domains. Consistently, earlier work had shown that a four-domain fragment of DN-cadherin had a hairpin bend at just such a Ca^{2+}-free linker (Jin et al. 2012). Thus, Fat and Dachsous appear to bind tip to tip in the intercellular space, and have long, folded-up multi-EC ectodomains that could in principle traverse the intercellular space multiple times (Tsukasaki et al. 2014).

4.7 The Clustered Protocadherins and Neurite Self-Avoidance

The clustered protocadherins are a family of highly related vertebrate cadherin-like proteins encoded in three novel contiguous gene clusters (α, β, and γ) and are predominantly expressed in the nervous system. Protocadherins help to establish single-neuron identity to establish specific self-avoidance between neurites emanating from the same neuron. In mouse there are 58 Pcdh proteins, and each neuron expresses a defined subset of these (up to about 15) via a mechanism involving stochastic promoter choice. Neurites from the same neuron express the same Pcdhs, and thus recognize one another and repel; neurites of different neurons have different sets of Pcdhs, and hence are free to interact (no repulsion is signaled). Structure/function relationships in protocadherins remain largely obscure. Although a number of single-domain structures have been determined (pdb IDs 2EE0, 2YST, 1WYJ, 1WUZ; Morishita et al. 2006), none reveal functional recognition sites. Aggregation assays with transfected cells have shown that singly expressed Pcdhs have homophilic binding specificities, but how these specificities relate to self-avoidance in the case where many Pcdh isoforms are expressed remains unclear (Schreiner and Weiner 2010). Domain shuffling experiments suggest that Pcdh domains EC1–EC3 are crucial for trans adhesion, with domains EC2 and EC3 appearing to control protocadherin specificity in cell aggregation assays (Schreiner and Weiner 2010) . Domains EC2 and EC3 show the highest sequence diversity among individual protocadherin isoforms, consistent with the possibility of their contribution to specificity (Schreiner and Weiner 2010).

4.8 Concluding Remarks

Vertebrate classical cadherin ectodomains and vertebrate desmosomal cadherins—close relatives of classical cadherins—contain sequence elements indicative of strand-swap binding. However, other superfamily members, including protocadherins and all invertebrate cadherins, are likely to use distinct mechanisms, and these will become clear only with further structure/function studies.

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