

Classical and desmosomal cadherins at a glance

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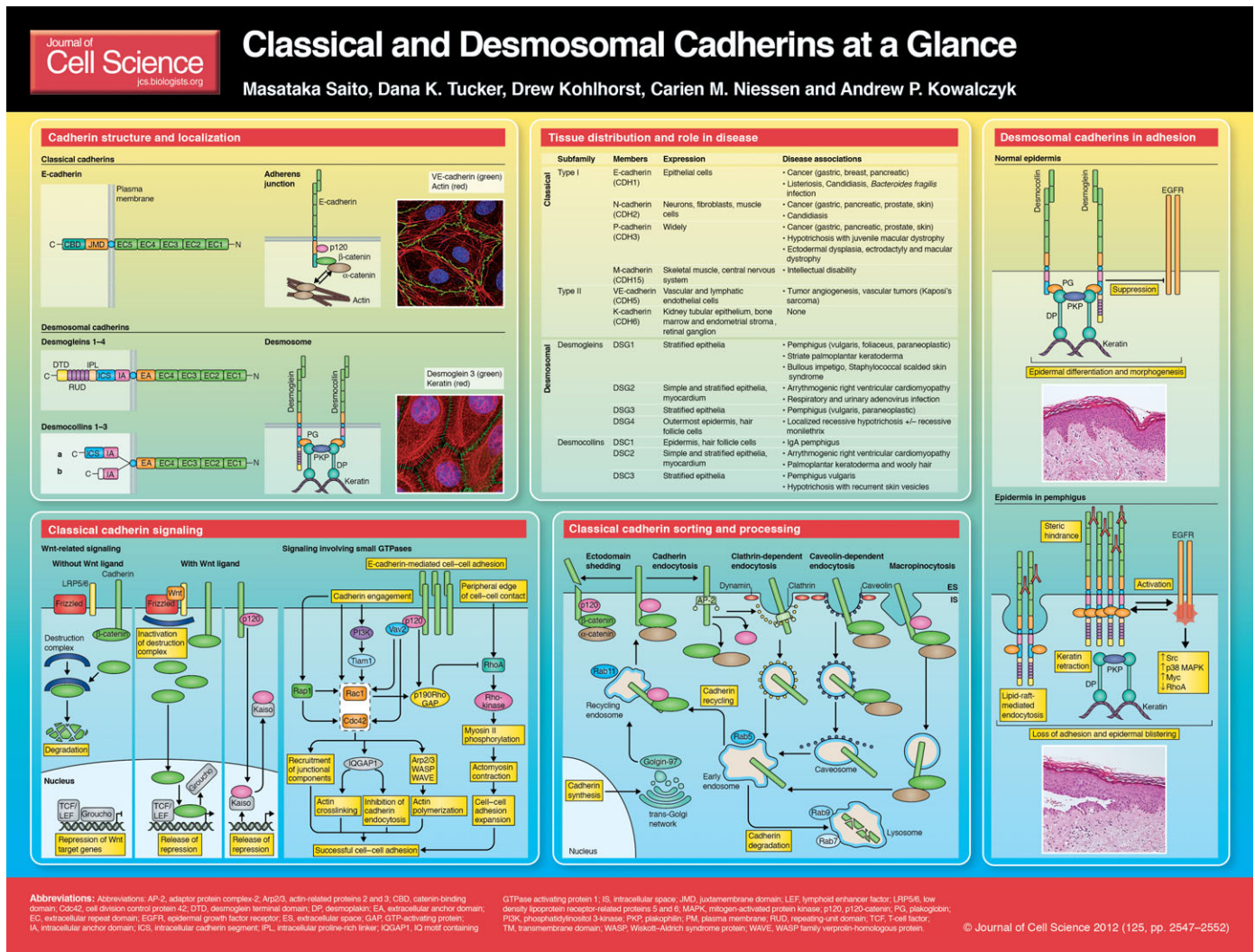
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Journal of Cell Science 125, 2547–2552
 © 2012. Published by The Company of Biologists Ltd
 doi: 10.1242/jcs.066654

Cell–cell contact is central to cell polarity, tissue organization and compartmentalization of organ systems. Cadherins are a large superfamily of cell–cell adhesion molecules that are fundamental determinants of how and when cells interact, migrate and undergo morphogenetic conversions (Gumbiner, 2005; Halbleib and Nelson, 2006; Hulpiau and van Roy, 2011; Niessen et al., 2011; Pokutta and Weis, 2007; Saburi and McNeill, 2005). The activity of cadherins was originally appreciated in the context of compaction of epithelial cells during development (Takeichi, 1988). Since these early studies, the discovery of many additional cadherin superfamily members has resulted in a plethora of publications describing their structure and function in a wide range of molecular interactions and cellular activities. Many cadherins operate to mechanically couple adjacent cells by

mediating cell–cell interactions within highly ordered junctional complexes. These complexes include the actin-associated adherens junctions, intermediate-filament-associated desmosomes, intercalated discs between cardiomyocytes, and a variety of other related junctions with tissue-specific functions (Delva et al., 2009; Franke, 2009; Niessen and Gottardi, 2008; Niessen et al., 2011). Cadherin-based adhesive intercellular junctions drive tissue morphogenesis during development and are essential for the maintenance of adult tissue architecture in virtually all complex tissues (Gumbiner, 2005; Stepniak et al., 2009).

In addition to mediating cell adhesion, cadherins function as signaling scaffolds that regulate cell motility, proliferation and gene expression. As outlined in this Cell Science at a Glance poster article, cadherins participate in the regulation of a number of



(See poster insert)

cellular networks including membrane trafficking pathways, growth factor signaling, Rho family GTPase activities, cytoskeletal remodeling, and gene-expression programs. Recent work has revealed that these regulatory and signaling pathways are often altered in human diseases with compromised cadherin function. This Cell Science at a Glance article aims to highlight the characteristics of classical and desmosomal cadherins, the cellular machinery with which these adhesion molecules interact and the diseases that directly result from compromised cadherin function.

The cadherin superfamily

Cadherins comprise a large superfamily with over 350 members (Hulpiau and van Roy, 2009; Hulpiau and van Roy, 2011). The most salient feature of this superfamily is the presence of a variable number of successive extracellular cadherin (EC) repeat domains, each comprising ~110 amino acids, that are rigidified by binding three Ca^{2+} ions at linker regions between these domains (Boggon et al., 2002; Ciatto et al., 2010; Hulpiau and van Roy, 2009). Sequence similarity has been used to categorize cadherins into subfamilies that include classical, desmosomal and proto-cadherins and a variety of other cadherin subfamily members that exhibit a wide range of activities and binding partners. Here, we restrict our focus to the classical and desmosomal cadherins.

The ectodomain of both classical and desmosomal cadherins comprises five highly conserved EC domains (EC1–EC5), with the most membrane-proximal (EC5) domain of the desmosomal cadherins sometimes being referred to as the extracellular anchor (EA) domain (Boggon et al., 2002; Delva et al., 2009; Shapiro and Weis, 2009). The type I and type II classical cadherins were originally named on the basis of the tissues within which they were first identified [e.g. type I, epithelial (E)-cadherin and neural (N)-cadherin, type II vascular endothelial (VE)-cadherin and kidney (K)-cadherin; CDH1, CDH2, CDH5 and CDH6, respectively]. However, their expression is not always restricted to these tissues (see Poster) (Gumbiner, 2005; Leckband and Prakasam, 2006). Desmosomal cadherins, the desmogleins and desmocollins, are expressed primarily in epithelial tissues and cardiac muscle (Green and Simpson, 2007; Hulpiau and van Roy, 2009; Nollet et al., 2000). In humans, there are four desmoglein (*DSG1–DSG4*) and three desmocollin (*DSC1–*

DSC3) genes. All three desmocollin gene products are subjected to alternative splicing to generate the type ‘a’ form and the shorter type ‘b’ form. Both desmocollin isoforms localize to desmosomes, although the shorter ‘b’ form lacks the intracellular cadherin segment (ICS) domain, where plakoglobin binds, and thus might have less extensive cytoskeletal linkages (Green and Simpson, 2007; North et al., 1999).

Interactions between cadherins

In classical cadherins, the EC1 domains engage homophilically in trans interactions through the exchange or swap of their N-terminal β -strands (Harrison et al., 2010). The formation of this strand-exchange dimer involves the insertion of the conserved EC1 Trp2 residue of one cadherin into the hydrophobic pocket located in EC1 of a partner cadherin. The residues that flank Trp2 form additional interactions that stabilize the formation of this dimer. In addition, other regions within EC1 participate in lateral cis interactions with a region of the EC2 domain of a neighboring molecule. Cooperativity between the strong trans-dimers and weak cis interactions is necessary for the production of stable and higher-ordered junctional structures (Harrison et al., 2011). Desmosomal cadherins also have the Trp2 residue and hydrophobic pocket required for the EC1 trans β -strand swap but lack sequences that are similar to the cis interface sequences of the type I cadherins. However, visualization of the three-dimensional organization of native desmosomes has revealed that desmosomal cadherins do participate in cis interactions (Al-Amoudi et al., 2007). Additionally, the desmosomal cadherins have been reported to interact both homophilically and heterophilically (Green and Simpson, 2007; Thomason et al., 2010).

Classical and desmosomal cadherins at cell–cell junctions

The intracellular domains of classical and desmosomal cadherins specify whether they are tethered to the actin or intermediate filament cytoskeleton (Delva et al., 2009; Shapiro and Weis, 2009). The cytoplasmic domain of classical cadherins directly binds to the armadillo protein family members p120-catenin and β -catenin, and interacts indirectly with α -catenin, a member of the vinculin superfamily (Shapiro and Weis, 2009). Binding of p120-catenin to the cadherin juxtamembrane (JMD) domain stabilizes the cadherin complex by preventing cadherin internalization and

degradation (Davis et al., 2003; Xiao et al., 2003) (see Poster). The mechanism by which classical cadherins are linked to the actin cytoskeleton was assumed to be a static bridge formed by α -catenin binding to both F-actin and cadherin-bound β -catenin (Gates and Peifer, 2005; Kwiatkowski et al., 2010). More recent studies challenge this model and demonstrate that α -catenin cannot bind β -catenin and F-actin simultaneously (Drees et al., 2005; Yamada et al., 2005). Although the precise mechanism of coupling cadherins to the actin cytoskeleton remains elusive, numerous observations indicate that this linkage is crucial in mediating adherens junction assembly, maintenance and adhesion (Hartsock and Nelson, 2008; Kwiatkowski et al., 2010; Pokutta and Weis, 2007; Taguchi et al., 2011; Yonemura, 2011; Yonemura et al., 2010).

The cytoplasmic domains of desmosomal cadherins are coupled to intermediate filaments through associations with the β -catenin-related armadillo protein plakoglobin, and the plakophilins (Al-Amoudi et al., 2011; Carnahan et al., 2010; Hatzfeld, 2007). Desmoplakin (DP), a member of the plakin family of cytolinker proteins, links the desmosomal cadherin complex to the cytoskeleton by binding plakophilins and plakoglobin at its N-terminus and intermediate filaments at its C-terminus (Desai et al., 2009; Thomason et al., 2010) (see Poster). The linkage between the intermediate filament cytoskeleton and desmosomal cadherin complexes is crucial to tissues that experience substantial mechanical stress, such as the myocardium and stratified epithelia (Simpson et al., 2011).

Classical cadherin sorting and processing

Cadherins assemble into robust adhesive intercellular junctions, but these complexes exhibit considerable plasticity and undergo dynamic cycles of assembly and disassembly (Niessen et al., 2011). For example, proteolytic processing of cadherin ectodomains provides a rapid mechanism for cadherin inactivation and turnover (Cavallaro and Dejana, 2011; Seifert et al., 2009). Furthermore, the highly regulated delivery and retrieval of cadherins to and from the cell surface by membrane trafficking pathways is crucial for controlling the adhesive potential of the cell surface (Chiasson and Kowalczyk, 2008). Distinct endocytic mechanisms have been implicated in cadherin regulation, including clathrin-, caveolae-, lipid-raft- and

macropinocytotic-mediated internalization (Delva and Kowalczyk, 2009). The cues that select cadherins for a specific internalization pathway are not well understood, although substantial progress has been made for classical cadherins. For example, E-cadherin and VE-cadherin are typically internalized through clathrin-dependent pathways (Ivanov et al., 2004; Izumi et al., 2004; Le et al., 1999; Xiao et al., 2005). The clathrin adaptor protein complex 2 (AP-2) has been shown to associate with the cytoplasmic domains of VE-cadherin and E-cadherin and appears crucial for endocytosis of classical cadherins (Chiasson et al., 2009; Sato et al., 2011). p120-catenin appears to modulate the access of clathrin adaptors to the cadherin tail by masking endocytic signals and thereby preventing cadherin recruitment into clathrin- and AP-2-enriched membrane domains (Chiasson et al., 2009; Xiao et al., 2005). In the case of E-cadherin, a putative dileucine AP-2-binding motif has been shown to regulate endocytosis and lysosomal targeting (Miyashita and Ozawa, 2007a; Miyashita and Ozawa, 2007b). Interestingly, this same dileucine motif is also important for polarized delivery of E-cadherin to the basolateral membrane (Miranda et al., 2003; Miranda et al., 2001). Beyond AP-2 and clathrin, other molecules that have been implicated in cadherin endocytosis include Hakai (also known as CBL1), an E3 ubiquitin ligase, which promotes ubiquitylation and endocytosis of E-cadherin (Fujita et al., 2002), and β -arrestin, which promotes internalization of VE-cadherin (Gavard and Gutkind, 2006). Further analysis of cadherin cytoplasmic tail sequences is likely to reveal numerous regulatory motifs that are used in a tissue- and differentiation-specific manner to control cadherin trafficking to and from the plasma membrane.

Growing evidence suggests that cadherin-mediated adhesion is tightly coupled to membrane trafficking pathways. For example, mutations in regulators of membrane trafficking, such as Rab11, a member of the Ras superfamily of monomeric G-proteins, and dynamin, a GTPase responsible for endocytosis in eukaryotic cells, result in substantial alterations in cadherin distribution and phenotypes that can, at least in part, be explained by altered adhesion (Niessen et al., 2011). Furthermore, ablating p120-catenin gene (*Ctnd1*) expression leads to decreased steady state cadherin levels in most tissues analyzed, presumably because of increased cadherin endocytosis and turnover (Davis

and Reynolds, 2006; Elia et al., 2006; Oas et al., 2010; Perez-Moreno et al., 2006). Type I gamma phosphatidylinositol-4-phosphate 5-kinase (PIPKI γ) modulates E-cadherin trafficking by binding directly to E-cadherin and preventing the association of cadherin with the adaptor protein complex 1 (AP-1), a clathrin adaptor complex that is important for delivery of newly synthesized and recycled receptors to the plasma membrane. Interestingly, a mutation in E-cadherin that prevents binding to PIPKI γ leads to hereditary gastric cancers (Ling et al., 2007). Thus, growing evidence suggests that altered cadherin trafficking is detrimental to normal tissue development and homeostasis.

Cadherins and catenins in Wnt-related signaling

Studies using fly, frog and mammalian model systems have demonstrated that the Wnt family of secreted protein ligands are master mediators of cell–cell signaling events and gene modulation during embryogenesis, adult tissue maintenance and regeneration (Sylvie et al., 2012). Altered expression, mutation or misregulation of Wnt pathway components affects tissue morphogenesis and induces multiple diseases, most notably cancer (Heuberger and Birchmeier, 2010). The cadherin-binding protein β -catenin has a central role in canonical Wnt signaling (Heuberger and Birchmeier, 2010; Logan and Nusse, 2004; MacDonald et al., 2009). In the absence of Wnt ligands, cytoplasmic β -catenin (β -catenin not associated with adherens junctions) is recruited into a destruction complex that consists of adenomatous polyposis coli protein (APC), axin-bound casein kinase 1 and glycogen synthase kinase-3. Following sequential phosphorylation within the destruction complex, β -catenin is targeted to and degraded by the proteasome (Clevers, 2006; Heuberger and Birchmeier, 2010). Therefore, in the absence of Wnt ligands, cytoplasmic β -catenin is degraded and levels remain low (see Poster).

In the presence of Wnt ligands, receptor binding by the co-receptor complex of Frizzled (a G-protein-coupled receptor) and the lipoprotein-receptor-related proteins 5 and 6 (LRP5/6) leads to inactivation of the destruction complex. Therefore, cytoplasmic β -catenin levels are stabilized, leading to interactions with T-cell factor (TCF) or lymphoid-enhancer factor (LEF) transcription factors. The interaction of β -catenin with TCF releases the transcriptional

repressor Groucho [the transducin-like enhancer (TLE) proteins in humans] from the complex, thereby resulting in the activation of Wnt target genes (Heuberger and Birchmeier, 2010; Xue and Zhao, 2012). p120-catenin also regulates gene expression albeit through a different mechanism. Binding of p120-catenin to the transcriptional repressor Kaiso relieves its repression of, among others, Wnt-responsive genes, resulting in enhanced gene expression (Heuberger and Birchmeier, 2010). Thus, β -catenin and p120-catenin have central roles at both cell–cell junctions and in the nucleus, and cadherin adhesive activity is likely to provide a key input into this signaling axis (Maher et al., 2009).

Cadherins in receptor tyrosine kinase signaling

Cadherins exhibit reciprocal regulatory relationships with receptor tyrosine kinases (RTKs) to modulate cell adhesion, migration and proliferation (Cavallaro and Dejana, 2011; Niessen et al., 2011). For example, E-cadherin has been found to form complexes with the epidermal growth factor receptor (EGFR) (Fedor-Chaiken et al., 2003), and VE-cadherin has been shown to associate with the vascular endothelial growth factor receptor 2 (VEGFR2) (Carmeliet et al., 1999; Lampugnani et al., 2003). Cytoplasmic associations with Src family and other kinases further modulate both cadherin and catenin tyrosine phosphorylation (Niessen et al., 2011). Not surprisingly, a number of transmembrane and cytoplasmic phosphatases are also enriched at cell–cell junctions, and the phosphorylation status has been reported to modulate cadherin–catenin interactions and catenin signaling (Cavallaro and Dejana, 2011). Interestingly, cadherin endocytosis is regulated by both RTKs and Src (Trojanovsky, 2009). Likewise, VEGF receptor endocytosis and signaling is regulated by VE-cadherin, demonstrating a bidirectional regulation of adhesion and signaling activities (Lampugnani et al., 2006).

Desmosomal cadherins also exhibit reciprocal regulation with RTKs, particularly the EGFR (Simpson et al., 2011). This regulation is especially interesting in the case of desmogleins, where DSG1 has been shown to suppress EGFR activity in order to drive epidermal differentiation (Getsios et al., 2009). Furthermore, inhibition of EGFR stabilizes desmogleins at the cell surface by preventing desmoglein endocytosis

(Klessner et al., 2009). This pathway might be important in disease states, such as pemphigus vulgaris and related disorders, because it is possible that the adhesive activity of cadherin would be stabilized by inhibition of EGFR activity or signals emanating downstream of the receptor (see Poster). In pemphigus vulgaris, patients generate autoantibodies (IgG) directed against desmogleins, resulting in weakened adhesion, as well as blistering in the epidermis (Amagai and Stanley, 2011). A number of studies have suggested that signaling pathways, including those mediated through EGFR, p38 mitogen-activated protein kinase (MAPK14) and Myc, among others, are activated downstream of autoantibody binding (Getsios et al., 2010; Müller et al., 2008). Although the details of how these pathways interact with desmogleins on a molecular level remain to be determined, pemphigus represents a clear example of how the desmosomal adhesion and growth factor receptor signaling pathway might be targeted therapeutically.

Role of cadherins in small GTPase signaling

Cadherin engagement exerts local control over cytoskeletal organization to regulate cell shape and polarity. This control is largely exerted through small GTPases of the Rho family. Interestingly, GTPase activation in the context of cell adhesion varies even among closely related cadherins, perhaps because of differences in cellular background. This signaling diversity makes it difficult to draw a generalized model (Braga and Yap, 2005). In the case of E-cadherin-mediated cell adhesion, cadherin engagement stimulates phosphatidylinositol 3-kinase (PI3K) (Pece et al., 1999), in response to which Tiam1, a guanine nucleotide exchange factor (GEF), activates Rac1, thereby causing Rac1 to accumulate at cell–cell contacts (Watanabe et al., 2009). Following cadherin engagement, Cdc42 is also recruited to cell–cell junctions and subsequently activated. Furthermore, E-cadherin recruits and activates Rap1, a Ras family GTPase member, which is required for Cdc42 activation (Hogan et al., 2004). p120-catenin also activates Rac1 and Cdc42 through binding to Vav2, a Rho family GEF (Noren et al., 2000). Furthermore, the Ras GTPase-activating-like protein IQGAP1 activates Rac1 and Cdc42 to subsequently induce actin cross-linking and inhibit cadherin endocytosis.

Additional junctional components are recruited to the contact site to promote actin polymerization through the actin-related protein 2/3 (Arp2/3) complex and members of the Wiskott–Aldrich syndrome protein (WASP) and WASP-family verprolin-homologous protein (WAVE) families (Watanabe et al., 2009). An additional layer of control results from Rac1 antagonizing RhoA activity through a mechanism that involves p120-catenin and p190 RhoGAP (Bustos et al., 2008; Wildenberg et al., 2006). RhoA is preferentially activated at the distal edge of cell–cell contacts (Yamada and Nelson, 2007a). Rho-kinase, an effector of RhoA, increases phosphorylation of myosin light chain and subsequent phosphorylation of myosin II, which results in actomyosin contraction, suggesting that RhoA is involved in the expansion of cell–cell adhesion sites (Watanabe et al., 2009; Yamada and Nelson, 2007a).

Cadherins targeted in human disease

A number of human diseases result from compromised cadherin function, including cancer, neuronal and mental health disorders, as well as skin and cardiovascular diseases. The loss of E-cadherin function, functionally, genetically or epigenetically, contributes to the acquisition of an invasive phenotype in a wide range of epithelial tumor types (Bex and van Roy, 2009; Carneiro et al., 2008; Wheelock et al., 2008). E-cadherin downregulation is often associated with an upregulation of N-cadherin through a process known as ‘cadherin switching’. Cadherin switching is thought to be a key event in epithelial-to-mesenchymal transition (EMT), a process in which epithelial cells lose their characteristic polarity and cell–cell junctions to become highly motile and invasive (Wheelock et al., 2008). Recent evidence also suggests that there is a role for desmosomal cadherins in tumor suppression, and additional studies to understand how this cadherin subfamily modulates the tumor phenotype are clearly warranted (Bex and van Roy, 2009; Dusek and Attardi, 2011).

In addition to cancers, genetic studies have identified potential roles for cadherins, including cadherin-9 and cadherin-10, in autism spectrum disorders (Morrow et al., 2008; Wang et al., 2009). Recent studies of classical cadherins (cadherin-6 and cadherin-9) reveal key functions for these adhesion molecules in axonal targeting (Rebsam and Mason, 2011). As synapses of the central

nervous system are specialized adhesive junctions, cadherins are now considered to be possible therapeutic targets in cognitive disorders (Arikath and Reichardt, 2008; Bourgeron, 2007; Yamada and Nelson, 2007b). Desmosomal cadherins and their associated plaque proteins are crucial for normal function of skin and heart. In the epidermis, inactivation of desmosomal proteins can be caused by autoantibody inhibition, mutations in the genes encoding these proteins or by proteases released during staphylococcal bacterial infection (see Poster) (Stanley and Amagai, 2006). In many of these instances, the resulting clinical presentations include epidermal fragility and blistering. However, thickening of the epidermis (hyperkeratosis) and ectodermal dysplasia can also be observed, suggesting important roles for desmosomal components in epidermal differentiation (Getsios et al., 2009; Simpson et al., 2011). Similarly, in the heart, mutations in DSG2, DSC2 and several cadherin-associated proteins, including plakoglobin, desmoplakin and plakophilin-2, lead to cardiomyopathies (Lai-Cheong et al., 2007; Thomason et al., 2010). These cardiac disorders are characterized by both alterations in the mechanical and signaling functions of desmosomes.

Recent studies have also revealed a rather remarkable and central role for cadherins in host–pathogen interactions. Indeed, a number of pathogens target cadherins in order to establish colonization of cells and tissues (Bonazzi and Cossart, 2011). Recognition of specific cadherins by bacteria often mediates either attachment of the microorganisms to the cell surface and/or internalization into the cell. For example, in listeriosis, *Listeria monocytogenes* invade host cells through a clathrin-dependent internalization process in which human E-cadherin is used as a receptor for a bacterial surface protein named internalin (Bonazzi et al., 2009). The recent identification of DSG2 as an adenoviral receptor further highlights the importance of cadherins in host–pathogen interactions (Wang et al., 2011). Collectively, these examples highlight the ways in which cadherin function is impaired or hijacked during disease.

Future perspectives

Since the discovery of cadherins over 30 years ago, overwhelming evidence has demonstrated that one of their primary functions is to establish and maintain

cell–cell adhesion on the cellular and tissue level. These adhesive events induce changes in the cytoskeleton and also initiate and modulate signaling cascades that affect gene expression programs to control growth and, in some cases, cell fate determination. In many instances, these signaling pathways feed back to modulate cell adhesion either directly or on a transcriptional and/or post-transcriptional level. The wide range of cellular functions of cadherins, and the scope of cellular signaling activities in which cadherins engage, reflect the diversity of the cadherin superfamily. A challenge for the future will be to elucidate the regulatory mechanisms that govern cadherin gene expression, trafficking and processing, and how these events integrate with other cellular signaling pathways to drive tissue patterning. Finally, further identification of cadherin dysfunction within disease states will provide important clues that will expand our understanding of how different cadherin subclasses function at the molecular and tissue level. These advances will, in turn, yield new approaches to treat human diseases that are associated with alterations in cadherin function.

Acknowledgements

We are grateful to Chantel Cadwell and Dr Christine Chiasson for critical feedback and advice during the preparation of this manuscript. We sincerely apologize to anyone whose work could not be mentioned and/or cited owing to the limited available space.

Funding

Andrew P. Kowalczyk is supported by grants from the National Institutes of Health [grant numbers R01AR048266, R01AR050501]. Drew Kohlhorst was supported by the National Institutes of Health [grant number 2K12GM000680]. Carien M. Niessen is supported by the German Cancer Foundation and the Deutsche Forschungsgemeinschaft [grant numbers SFB829, SFB832]. Deposited in PMC for release after 12 months.

A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.org. Individual poster panels are available as JPEG files at <http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.066654/-DC1>.

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