Cold Spring Harbor Perspectives in Biology
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Junctional Music that the Nucleus Hears: Cell–Cell Contact Signaling and the Modulation of Gene Activity

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Cell–cell junctions continue to capture the interest of cell and developmental biologists, with an emerging area being the molecular means by which junctional signals relate to gene activity in the nucleus. Although complexities often arise in determining the direct versus indirect nature of such signal transduction, it is clear that such pathways are essential for the function of tissues and that alterations may contribute to many pathological outcomes. This review assesses a variety of cell–cell junction-to-nuclear signaling pathways, and outlines interesting areas for further study.

The evolution of multicellular life forms has to a significant extent involved refinements of each cell's capacity to sense the state of its directly contacting neighbors. This exchange of information often occurs within tissues, with the result that gene activity in the nucleus is altered or maintained accordingly. In this article, we focus on how signals arise at cell–cell junctions and are transduced to the nucleus; we do not include discussion of mechanical/cytoskeletal signals influencing nuclear decisions, and the reader is directed to a recent review of this topic (Ingber 2008).

An issue that arises when addressing cell–cell junction(s), referred to as CCJ(s), -to-nuclear signals, is that homotypic or heterotypic junctional proteins responsible for conferring adhesive activity are often in a much larger complex of proteins. These interactions may be either in *cis* (interacting within the plasma membrane of the cell) or *trans* orientations (interacting through ectodomain contacts extended between cells). Most of these transmembrane proteins are likely to have the potential to contribute to downstream signaling events, and many may associate with one another only under specific physiological conditions. For example, certain receptor tyrosine kinases (RTKs) associate with particular cadherins, and when associated are relevant to that cadherin's functions (Wheelock and Johnson 2003; Andl and Rustgi 2005). In this

Editors: W. James Nelson and Elaine Fuchs
Additional Perspectives on Cell Junctions available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a002923
Cite this article as *Cold Spring Harb Perspect Biol* 2009;1:a002923

article, we discuss relationships such as these in the context of CCJ-nuclear signaling. A topic not represented here is the CCJ signaling of immune surveillance cells, for example, pathways activated following leukocyte–endothelia contact. This area is of great basic and biomedical interest, but is addressed elsewhere (Dustin 2007).

We focus on signaling by a select number of junction types, including adherens, desmosomal, and tight junctions, and to a lesser extent, gap junctions. Details of the structure and function of each of these junctions are presented in other articles (see Meng and Takeichi 2009, Delva et al. 2009, Furuse 2009, and Goodenough and Paul 2009, respectively). These junctions are often represented in textbooks as distinct entities in the context of epithelial tissues, but their structures and how they respond to or generate signaling cues vary according to cellular context. Select components within these junctions may be shared, for example between desmosomal, adherens, and tight junctions, and in some instances, intimate physical proximities are likely to advance these junctions' functional interrelation. Further, different cell types show less common junctional organizations (Straub et al. 2003; Wuchter et al. 2007), such that the total spectrum of CCJ signals is likely to be impressive, and far beyond what is currently known or understood. Given the interdependence of cell neighbors in forming and maintaining cell groupings, high diversity and sophistication arose in complex organisms, both in CCJ structures themselves and their associated nuclear signaling pathways. Compared with the knowledge accumulated over the past two decades on cell–extracellular matrix signaling via integrins (Abram and Lowell 2009), we know less about signals initiated from forming or mature cell–cell contacts in epithelial, neural, or endothelial tissues. Thus, as the field moves forward, there is the potential to achieve a deepened understanding of how the cell–extracellular matrix and cell–cell adhesion systems are coupled in a signaling context, and how they collectively relate to the adhesion, motility, and differentiation of cells and tissues.

ADHERENS AND DESMOSOMAL JUNCTIONS

Adherens junctions are comprised of a number of transmembrane proteins, including the classic cadherins (see Meng and Takeichi 2009) and nectins, which are members of the distinct Ig (immunoglobulin) family of adhesion proteins/receptors (Fig. 1) (Takai et al. 2008a; Takai et al. 2008b). In some cases, cadherins and nectins associate through intracellular proteins, including p120-catenin bound to the juxtamembrane domain of cadherin and afadin bound to nectin (Ogita and Takai 2008). RTKs are also present at adherens junctions, although unlike cadherins and nectins, they are not viewed as adhesion proteins, but rather as signaling entities instructing, responding, or working in parallel with other signal generators within the cadherin/nectin macromolecular complex.

Desmosomal junctions contain additional members of the cadherin superfamily, represented in the transmembrane polypeptides of the desmocollin and desmoglein subfamilies (Fig. 2) (Green and Simpson 2007; Holthofer et al. 2007; Garrod and Chidgey 2008) (see also Delva et al. 2009). Desmosomal cadherins bind catenins that are different from those found in complex with classic cadherins at adherens junctions (Hatzfeld 2007). There are, however, catenins such as plakoglobin that are found at more than one junction (Zhurinsky et al. 2000). This may occur more often than realized as β-catenin, which is generally thought to bind only cadherins at adherens junctions, is also found at desmosomes under certain conditions (Bierkamp et al. 1999). In addition, p120-catenin has been identified at desmosomal junctions (Kanno et al. 2008), and ZO-1, generally found at tight junctions, associates with adherens junctions during their assembly (Itoh et al. 1993; Muller et al. 2005). Finally, p0071-catenin was first characterized in association with desmosomal cadherins but also localizes to adherens junction (Hatzfeld et al. 2003; Calkins et al. 2003). Such examples of catenins being shared across junctional types may reflect a means to

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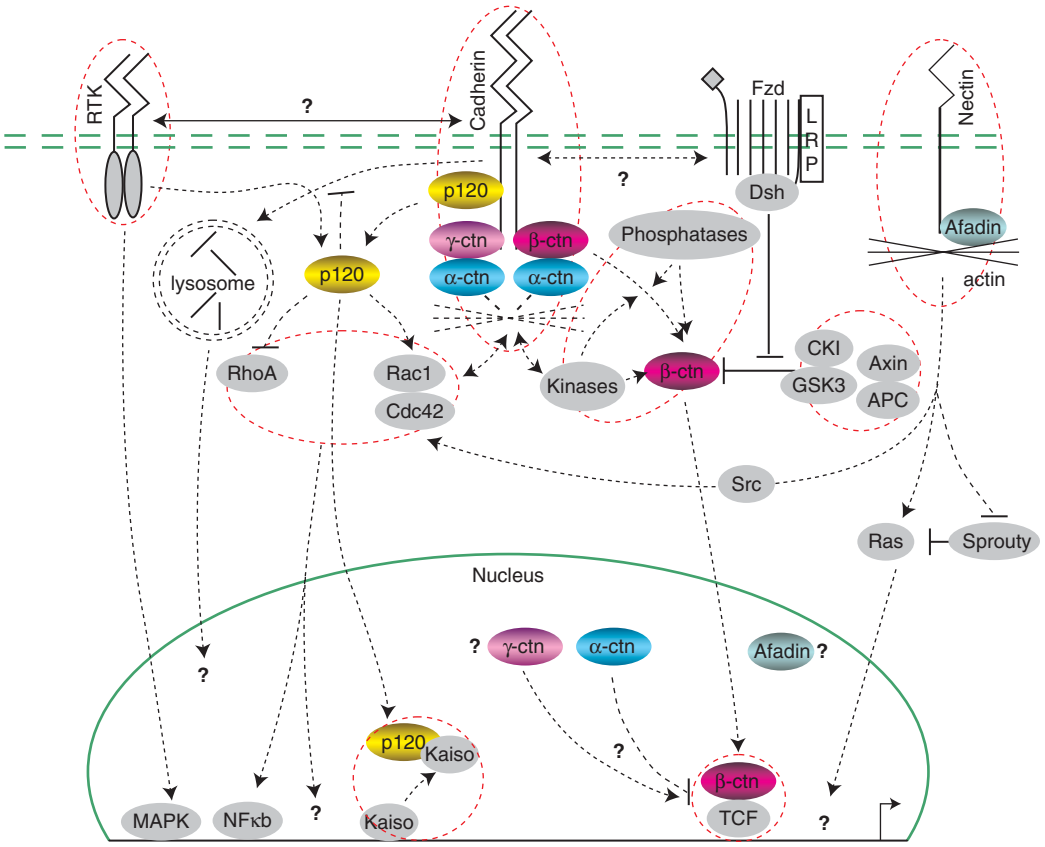

Figure 1. Adherens junction signaling to the nucleus. Proteins binding to the intracellular regions of cadherins include catenins, with β-catenin further associating with α-catenin and perhaps indirectly/dynamically with actin microfilaments. The structurally related p120-catenin subfamily is proposed to modulate cadherin lateral clustering, cadherin endocytosis, and activities of Rho-family GTPases. β-catenin acts in various ways within the nucleus, including as a transcriptional coactivator in conjunction with LEF/TCF, whereas p120-catenin relieves Kaiso-mediated gene repression. Other catenins have also been observed in the nucleus, where they have putative or shared roles in transcriptional regulation. Signaling from the nectin/afadin complex to the nucleus may occur indirectly through Ras or Rho, or more directly through afadin's potential association with chromatin or transcriptional modulators. Some evidence has indicated that receptor tyrosine kinases/growth factor receptors, or the frizzled/LRP complex, modulate signals initiated from the adherens junction and vice versa. Dotted circles highlight select signaling entities where research has been focused over the past decade.

coordinately regulate distinct cell–cell contacts, to enhance cross talk between junctions, or to provide additive junctional signals directed to other cellular compartments such as the nucleus.

How signals cross the membrane following *trans*-cadherin ectodomain contact is not well understood. The relevance of cadherin *cis*-dimerization to subsequent *trans* interactions is proposed in some but not all models (Brieher et al. 1996; Yap et al. 1997; Yap et al. 1998; Patel et al. 2003; Yap and Kovacs 2003; Troyanovsky 2005; Troyanovsky et al. 2007; Nelson 2008), with higher order clustering possibly correlating with raised levels of interacting phosphatases, kinases, or small GTPases (see also Watenabe et al. 2009). This may be similar to models of RTK clustering and activation in which cytoplasmic kinase domains come in closer proximity to initiate signaling.

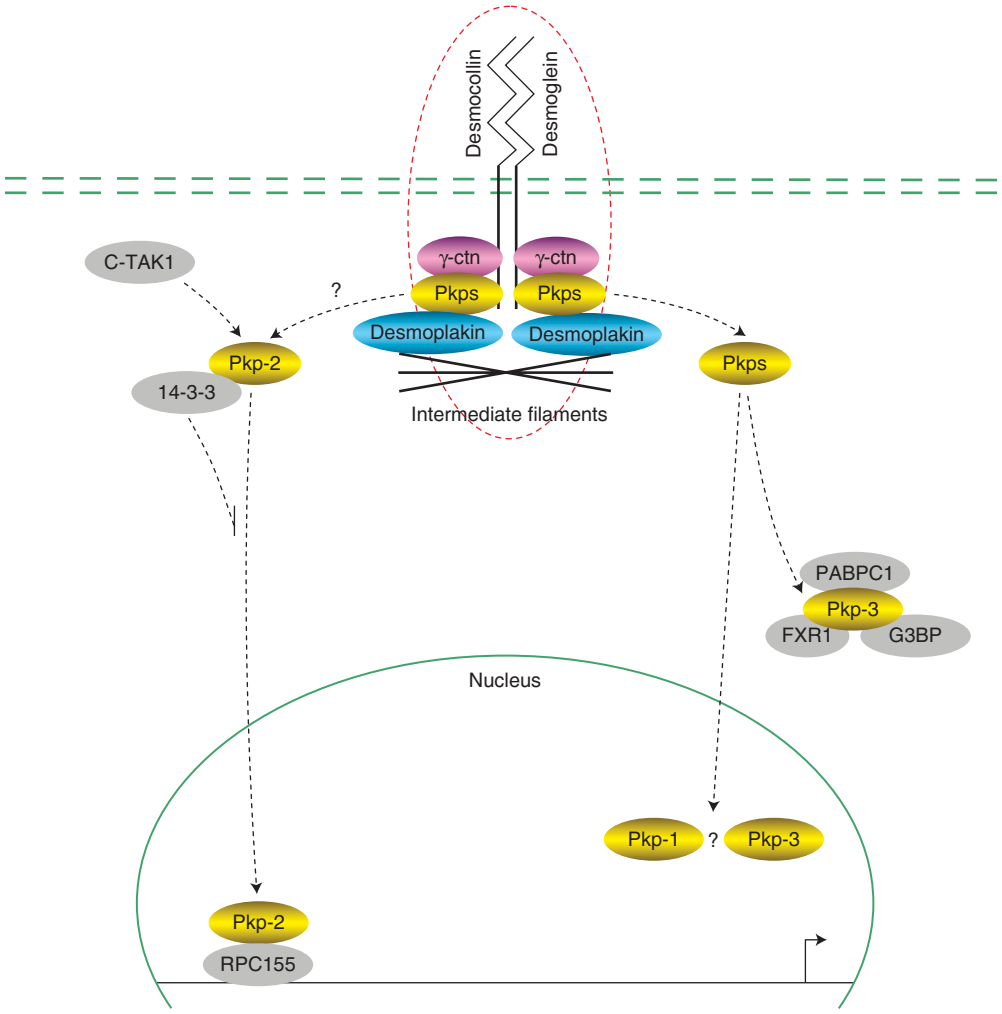

Figure 2. Desmosome junction signaling to the nucleus. Desmosomes are adhesive plaques containing the transmembrane cadherin superfamily members desmocollin and desmoglein, as well as intracellular binding partners such as plakoglobin (γ-catenin), plakophilins (Pkps), and desmoplakin. A number of desmosomal catenins have been localized to the nucleus although the functional relevance remains to be elucidated. Plakophilin-2, for example, has been found to reside within the PolIII complex and to associate with RPC155 and the transcription factor TFIIIB.

Following ectodomain engagement, transmembrane signaling might occur through displacement of adhesion molecules relative to the plasma membrane, perhaps exposing or removing an intracellular binding site, or displacements relative to other transmembrane polypeptides, analogous to that occurring between the α- and β-integrin subunits on binding extracellular matrix.

Our focus here is on the nuclear signaling pathways that are initiated at cell–cell junctions. From a conceptual perspective, it seems that evolution would favor signals passing in both directions, thereby informing nuclear as well as cell–cell contact decision-making in a reciprocal manner. This would include still incompletely understood concepts such as contact inhibition, where chromosomal

replication/cell division slows with increased cell–cell association or, conversely, the lessening or remodeling of cell–cell contacts in cells initiating gene programs that favor a migratory phase or epithelial-to-mesenchymal transitions.

CATENIN SIGNALING

A signaling trajectory that might at first seem obvious between cell–cell junctions and downstream nuclear events is that involving β-catenin. β-catenin binds the distal (carboxy-terminal) domain of cadherin cytoplasmic tails via β-catenin's central Armadillo domain (Huber and Weis 2001; Xu and Kimelman 2007). Concomitantly, β-catenin binds to α-catenin via its amino-terminal domain (Pokutta and Weis 2000). A recent model proposes that the cadherin–β-catenin complex may locally enrich α-catenin (Yamada et al. 2005; Drees et al. 2005; Weis and Nelson 2006), which when released forms homodimers capable of lowering Arp 2/3 activity (Yamada and Nelson 2007). This is then expected to reduce actin branching and cellular protrusive activity within the microenvironment, facilitating contact formation and stability.

Another major role of β-catenin is in the canonical Wnt signaling pathway (Clevers 2006; Gavert and Ben-Ze'ev 2007; Huang and He 2008; Barker 2008; Mosimann et al. 2009) (see also Heuberger and Birchmeier 2009; Cadigan and Peifer 2009). Following Wnt-ligand association with the plasma membrane receptor–coreceptor complex of Frizzled–Lrp, a signaling pool of β-catenin is formed that is not bound to cadherin. This process involves Wnt-ligand-directed inactivation of an intracellular β-catenin destruction complex (involving components such as GSK3β, CK1α, Axin, and APC), that in the absence of Wnt ligand would otherwise basally suppress the Wnt pathway (see Cadigan and Peifer 2009 for details). Once stabilized, a number of poorly understood events allow β-catenin to enter the nucleus to activate Wnt target genes important in many developmental and pathological contexts (Suh and Gumbiner 2003; Gottardi and Gumbiner 2004; Mosimann et al. 2009). Activation occurs on β-catenin's association with TCF/LEF transcription factors resident at TCF/LEF consensus binding sites within Wnt target gene promoters.

It was envisaged that β-catenin released from the cadherin complex, perhaps in response to specific phosphorylation events (Daniel and Reynolds 1997; Potter et al. 2005; Sallee et al. 2006; Alema and Salvatore 2007), might also enter a signaling pool and activate Wnt target genes (Perez-Moreno et al. 2003; Nelson and Nusse 2004; Bienz 2005; Perez-Moreno and Fuchs 2006). However, unless Wnt signals are already active, it remains reasonable to ask how β-catenin released from cadherin escapes the destruction complex. Indeed, in a number of contexts, it appears that cadherin loss alone may not be sufficient to activate β-catenin signaling (Caca et al. 1999; van de Wetering et al. 2001; Herzig et al. 2007), even as cadherin loss increases Wnt signals activated by other means (Gottardi et al. 2001; Kuphal and Behrens 2006).

Evidence has accumulated over the past decade that β-catenin released from cadherin is associated with increased Wnt pathway activity in some experimental contexts, such as in response to RTK or Src activity (Nelson and Nusse 2004; Bienz 2005; Lilien and Balsamo 2005; Brembeck et al. 2006; Gavert and Ben-Ze'ev 2007; McLachlan and Yap 2007). Src is capable of phosphorylating β-catenin at tyrosine 654, and reducing its association with cadherin (Roura et al. 1999). Most studies have been correlative, with the dissociation of β-catenin from cadherin occurring concurrent with increased transcriptional activity from endogenous Wnt gene targets or luciferase reporters. However, the kinases examined may well have produced effects beyond β-catenin release from cadherin. For example, activation of Akt and/or inhibition of GSK3β could result in β-catenin stabilization and modulation of the Wnt endogenous genes or reporter constructs by an alternative upstream path (Larue and Bellacosa 2005).

Just as kinases bind and act on the cadherin–catenin complex, so too do a variety of phosphatases that dephosphorylate both cadherins and catenins (Lilien et al. 2002; Sallee et al. 2006; McLachlan and Yap 2007). The phosphatases involved are numerous and include membrane-spanning receptor-type phosphatases such as DEP-1, PTPmu, LAR, and VE-PTP, as well as cytoplasmic phosphatases including PTP1B and Shp-2. In addition to the opposing impact of kinases and phosphatases on catenin signaling, a further means of promoting β-catenin's displacement from the larger cadherin–catenin complex toward a nuclear signaling pool involves the β-catenin-binding protein BCL9-2, a homolog of the human protooncogene product BCL9 (Brembeck et al. 2004; Brembeck et al. 2006). In response to RTK activation, direct or indirect β-catenin phosphorylation at tyrosine 142 occurs (e.g., via the RTK Met versus the cytoplasmic tyrosine kinases fer or fyn), decreasing β-catenin's association with α-catenin in favor of BCL9, and promoting β-catenin nuclear entry and activity. Such examples have brought attention to the likely interrelation of adherens junction states, inclusive of secondary protein modifications, with transcriptional outcomes (see also Heuberger and Birchmeier 2009).

Because the Wnt pathway impinges directly or indirectly on multiple classes of genes and produces various cellular responses (proliferation, differentiation, stem-cell maintenance), the impact of increased β-catenin signaling cannot be predicted without knowing the molecular details of the tissue or larger developmental programs involved (Clevers 2006; Gavert and Ben-Ze'ev 2007; Huang and He 2008; Barker 2008; Mosimann et al. 2009). However, in the case of RTK effects on the cadherin–catenin complex in particular, assessments have generally been made of endogenous β-catenin gene targets such as cyclin-D1 and c-myc, whose increased expression in many cases correlates with increased cell-cycle progression under normal and pathological conditions. Even though a large number of factors are contributory, decreased E-cadherin levels or function in many carcinomas is correlated with increased proliferation. Thus, the field will continue to be interested in the biological roles of catenin nuclear signals originating from the cadherin–catenin macromolecular complex in future studies of normal or diseased cells and tissues.

OTHER CATENINS

Cadherins bind a number of other catenins distinct from β-catenin that may be involved in CCJ signaling to the nucleus. One of these is plakoglobin (γ-catenin), which being very similar in structure to β-catenin, competes with β-catenin for binding to the membrane-distal region of cadherin tails, and can associate with α-catenin (Zhurinsky et al. 2000). In common with β-catenin, signaling pools of plakoglobin have been found to respond to signals initiated by Wnt ligands (thereby escaping destruction), although plakoglobin's nuclear role has been characterized as either activating, repressive, or relatively neutral in nature probably because of context issues (Merriam et al. 1997; Kodama et al. 1999; Kolligs et al. 2000; Williams et al. 2000; Charpentier et al. 2000; Shtutman et al. 2002; Maeda et al. 2004; Garcia-Gras et al. 2006; Dusek et al. 2007; Shimizu et al. 2008; Martin et al. 2009). Although less studied than β-catenin, it is possible that plakoglobin once dissociated from the cadherin complex might also represent a signaling entity arising from cell–cell junctions. Interestingly, plakoglobin is further present in association with the desmoglein and desmocollin cadherin family members (Garrod and Chidgey 2008), the principal transmembrane proteins conferring adhesive activity at desmosomal junctions. Thus, a signaling pool of plakoglobin could conceivably arise from either of these cell–cell junctions, or perhaps coordinately from both.

Loss of desmosome-associated desmoplakin in mouse cardiomyocytes was associated with increased levels of plakoglobin in the nucleus and a reduction in β-catenin-mediated Wnt signaling. This led to fibroadipocytic replacement of cardiac myocytes that mimics

the human genetic condition arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) (Garcia-Gras et al. 2006). Additional evidence showed that plakoglobin entered the nucleus to modulate some Wnt/β-catenin target genes (Maeda et al. 2004), and that it might modulate cellular Src activity (Yin et al. 2005). Correlative links have also been made between misdirected desmocollin (3a and 3b) expression in transgenic mice and altered keratinocyte differentiation, with altered β-catenin stability and, thereby, Wnt activity being a possible basis of the phenotype (Hardman et al. 2005). Thus, desmosome-to-nuclear communication occurs in pathologic/experimental contexts, and presumably also under physiologic conditions.

α-Catenin, which is structurally unrelated to the other catenins (Kobielak and Fuchs 2004; Pokutta et al. 2008), binds to β-catenin within the cadherin–catenin complex, and independently modulates, and associates with the actin cytoskeleton (Yamada et al. 2005; Drees et al. 2005). Phosphorylation of α-catenin at tyrosine 148 increases its affinity for β-catenin (Burks and Agazie 2006), whereas β-catenin phosphorylation at tyrosine 142 lowers its affinity for α-catenin (Piedra et al. 2003). Just as the absence or presence of these secondary modifications represent points that might assist β-catenin release into a signaling pool, so might α-catenin be released in response to upstream kinases/phosphatases to modulate cytoskeletal or perhaps nuclear outcomes. α-Catenin has been observed in the nucleus (Giannini et al. 2004; El-Bahrawy et al. 2002), and reports suggest it may modulate β-catenin nuclear signaling (Giannini et al. 2004). Although the mechanisms are uncertain, genetic ablation of α-catenin alters NFκB, HH, MAPK, and Wnt signaling pathways (Kobielak and Fuchs 2006; Lien et al. 2006; Vasioukhin et al. 2001; Merdek et al. 2004; Hwang et al. 2005). Further studies may reveal activities of α-catenin that strengthen its position as a nuclear signaling entity, whereas additional work will be needed to determine if α-catenin originating from the cadherin–catenin complex contributes to CCJ-nuclear signaling.

p120 Subfamily

The p120-catenin subfamily includes p120, and the ARVCF-, δ-, and p0071-catenins (Hatzfeld 2005; Reynolds 2007; McCrea and Park 2007). Each binds weakly to the membrane proximal tail region of classic cadherins, and some members, such as p120, also interact with desmosomal cadherins (desmoglein 3) (Kanno et al. 2008). Interestingly, p120 subfamily members have a prominent role in determining the rate of cadherin endocytosis (Kowalczyk and Reynolds 2004; Xiao et al. 2007), and thus in determining the state of cadherin-mediated contacts.

p120 subfamily members directly or indirectly modulate small GTPases such as Rac1 and RhoA (Anastasiadis et al. 2000; Noren et al. 2001; Yap and Kovacs 2003; Wolf et al. 2006; Anastasiadis 2007) (see also Watanabe et al. 2009). This activity functionally distinguishes p120 family members from β-catenin and plakoglobin. An open question is the extent to which p120 members modulate small GTPases in the immediate molecular vicinity of the cadherin complex (Braga 2002). Although cadherin association appears to lower their capacity to modulate Rac1 or RhoA, p120 subfamily members may cycle on-and-off cadherins to modulate local GTPases and thereby cytoskeletal structures. Once fully dissociated from cadherin, p120 subfamily members could diffuse elsewhere to activate small GTPases whose downstream impact may include the modulation of gene activity via effects on cell-cycle progression (Villalonga and Ridley 2006; Wolf et al. 2006).

The most established outcome of p120 entry into the nucleus is loss of gene repression conferred by Kaiso, a POZ/zinc-finger family member. This outcome is conceptually analogous to β-catenin relieving TCF/LEF mediated repression, although the underlying mechanism involving p120 is different (Kelly et al. 2004; Daniel 2007). Although results relating to Kaiso's functions in Wnt signaling and TCF/LEF differ (Ruzov et al. 2009a; Ruzov et al. 2009b; Iioka et al. 2009), other evidence suggests that p120-catenin assists in

de-repressing select Wnt/β-catenin target genes whose promoters have both TCF/LEF and Kaiso binding sites (Kim et al. 2004; Park et al. 2005; Spring et al. 2005; van Roy and McCrea 2005; Park et al. 2006). In addition to Kaiso, recent work revealed that the transcriptional repressor Glis2 associates with p120 (Hosking et al. 2007). Glis2 and Src promote p120's localization to the nucleus, and functional studies suggest that Glis2 participates in neuronal differentiation. Thus, as for β-catenin, we should consider the possibility that p120 has a nuclear function on its dissociation from cadherin. A recent report documented the nuclear- and p120-catenin-dependent entry of a cadherin cyto-domain fragment generated by presenilin, with consequent effects on Kaiso-mediated gene repression (Ferber et al. 2008). Recent results further indicate that, in common with β-catenin and plakoglobin, p120 subfamily members are stabilized in response to upstream Wnt signals (Park et al. 2006; JY Hong and PDM, unpublished results). This suggests an integrated network of catenin downstream effects, including those involving gene regulation. Such integrated responses could arise on Wnt-ligand signaling (Wnt-ligand–Frizzled–LRP complex formation), or in response to local kinase or other activities at CCJs. More work is required to address the validity of this latter possibility, as the graphic dissociation of multiple catenins into signaling pools is not often reported in response to stimuli.

It is intriguing to consider that activities of the cadherin and Wnt pathways may be more closely linked than presently recognized. For example, in addition to reports of Wnt pathway activation having effects on cadherin function (Bradley et al. 1993; Hinck et al. 1994b; Hinck et al. 1994a; Yanagawa et al. 1997; Shariatmadari et al. 2005; Ulrich et al. 2005; Wodarz et al. 2006), there are indications of physical associations between Wnt and cadherin/protocadherin pathway components (Medina et al. 2004; Qin et al. 2005; Hay et al. 2009), suggesting that cadherins are likely to modulate canonical (β-catenin mediated) or noncanonical (alternative) Wnt pathways. As cadherin-mediated adhesion is required for neighboring cells to engage in multiple ligand–receptor interactions, for example those occurring at varied cell synapses or contacts, cadherins contribute to quite indirect yet essential effects on downstream/nuclear signaling. Although not addressed in this article in detail, it is also important to note that the cadherin superfamily is diverse in structure and thus function, with the unifying element being the presence of cadherin-like repeats within the extracellular domain (Hulpiau and van Roy 2009). Some members appear to act more as signaling receptors (or ligands), as opposed to combined adhesion/signaling receptors. Interesting examples include the Dachsous and FAT cadherins (see also McNeill et al. 2009), the putative ligand and receptor of the newly characterized Hippo pathway, which shows a central and conserved role in tissue growth and size control in both vertebrates and invertebrates (Zhao et al. 2008). A further interesting subgroup of cadherins covered elsewhere is the protocadherins (Morishita and Yagi 2007). Protocadherins are expressed in multiple cell types but most prominently in neural tissues, and appear to regulate a number of signaling pathways relevant to cytoskeletal functions or gene activity (Medina et al. 2004; Unterseher et al. 2004; Yang et al. 2005; Chen and Gumbiner 2006; Wang et al. 2008).

Plakophilin Subfamily

A third class of catenins are the plakophilins (PKPs) (Hatzfeld 2007). Plakophilins contain a central Armadillo domain, similar to the β-catenin and p120-catenin subfamilies. In the case of plakophilins, however, the amino-terminal domains mediate interactions with desmogleins or desmocollins. A number of plakophilins have been localized to the nucleus (Mertens et al. 1996; Schmidt et al. 1997). For example, PKP2 associates with desmosomal cadherins and components of the PolIII transcriptional complex, such as RPC155 and the transcription factor TFIIIB (Mertens et al. 2001), and has been found to influence β-

catenin-mediated Wnt signaling (Chen et al. 2002). The intracellular localization of PKP2 is modulated through phosphorylation by the serine kinase Cdc25C-associated kinase 1, which promotes the association of PKP2 with 14-3-3 proteins and localizes PKP2 to junctions rather than the nucleus (Muller et al. 2003). Another PKP family member, PKP1b, is mostly localized to the nucleus, whereas the alternatively spliced isoform PKP1a is mostly at junctions, suggesting that RNA processing of PKP family members affects PKP nuclear functions (Schmidt et al. 1997). Thus, plakophilins appear to function at both the desmosome and nucleus, although it remains unknown if plakophilins enter a signaling pool as a consequence of dissociating from desmosomal cadherins (*bona fide* junctional–nuclear signaling).

Another Perspective Relating to Junctional–Nuclear Catenin Signaling

As presented above, catenins may transduce signals to the nucleus on their dissociation from cell–cell junctions. An alternative view, not incompatible with the first, is that cell–cell junctions and nuclear components compete for catenin binding. Thus, when the level of cadherin is relatively high, catenins may be sequestered away from nuclear complexes (Choi et al. 2006). In experimental contexts, this has been shown to occur for β-catenin in which downstream Wnt pathway activity (e.g., transcription from endogenous Wnt gene targets or luciferase reporters) is suppressed upon cadherin cyto-domain sequestration of β-catenin (Heasman et al. 1994; Sanson et al. 1996; Orsulic et al. 1999). In such a case, the degree of catenin nuclear signaling might be modulated by the expression of cadherin, or through changes in cadherin–catenin affinity states or physical access. For example, in epithelial-to-mesenchymal transitions, the transcriptional repressors Snail and Slug repress E-cadherin expression (Peinado et al. 2007; Alves et al. 2009). If another cadherin does not sequester the population of catenin that would become available, and this population escapes metabolic destruction, effects on gene expression or small GTPase activity may result. Whether increased junctional–nuclear signaling results from catenin dissociation from cadherins (initial control at the protein level) and/or from increased catenin signaling pools that arise because of reduced cadherin expression (initial control at the transcriptional level), nuclear decisions are sensitive to the state of cadherin–catenin cell–cell contacts.

Receptor Tyrosine Kinases (RTKs)/Growth Factor Receptors

Cadherins and Ig-family adhesion receptors such as nectins (see the following) have been linked to the functions of growth factor receptors/RTKs (Comoglio et al. 2003). Examples include the roles of N-cadherin in neurite outgrowth (Williams et al. 1994; Sanchez-Heras et al. 2006) and of the Ig-family member N-CAM in tumor cell adhesion (Cavallaro et al. 2001). In the context of neural cells, N-caherin is thought to facilitate FGF receptor dimerization and signaling in a manner that is independent of FGF ligand (Doherty et al. 2000; Skaper et al. 2001). This relationship also appears to be independent of N-cadherin adhesive activity (Utton et al. 2001) and to involve N-cadherin and FGF receptor clustering (Williams et al. 2002). Work in epithelial and endothelial cells has indicated physical and functional interactions between N-cadherin or another classic cadherin, with the FGF receptor (Nieman et al. 1999; Kim et al. 2000; Suyama et al. 2002; Erez et al. 2004). N-cadherin–FGF-receptor interactions appear to involve interactions through their ecto-domains (Kim et al. 2000; Suyama et al. 2002; Sanchez-Heras et al. 2006), although in some contexts this association is difficult to detect at the biochemical level (Kim et al. 2005). Enhanced MAPK-ERK signaling correlates with N-cadherin-mediated cell surface retention and clustering of the FGF receptor, as well as an increase in FGF ligand responsiveness (Suyama et al. 2002). Regardless of the specific molecular underpinnings, N-cadherin's interaction with RTKs is likely relevant to

its functional association with more dynamic/motile cell states in physiologic and pathologic contexts (Wheelock et al. 2008), and shows the role of cadherin signaling both in the context of localized phenomena such as cytoskeletal rearrangement and proliferative signaling by gene activity.

Cell–cell contact, presumably mediated by cadherins, has been shown to reduce cell proliferation promoted by the EGF ligand (Qian et al. 2004). E-cadherin has been found in complex with the EGF, FGF, and cErbB2 receptors (Ochiai et al. 1994; Fedor-Chaiken et al. 2003; Qian et al. 2004; Bryant et al. 2005). E-cadherin ligation reduces Stat 5b proliferative signaling downstream of the EGF receptor (Perrais et al. 2007), and FGF-induced MAPK signaling and receptor internalization (Bryant et al. 2005). In keratinocytes and mammary epithelial cells, however, E-cadherin was found to activate the EGF receptor (Fedor-Chaiken et al. 2003), which on cell–cell contact occurred even in the absence of EGF ligand (Pece and Gutkind 2000). In endothelial cells, VE-cadherin associates with, and reduces VEGF receptor activity, an effect that may occur with the cell-density dependent phosphatase PTP1 (Grazia Lampugnani et al. 2003). This VE-cadherin–RTK interaction appears to occur indirectly via cytoplasmic domain interactions, requiring β-catenin as reported also for the E-cadherin–EGF-receptor interaction (Hoschuetzky et al. 1994). Analogous to some cadherin–RTK contexts, VE-cadherin limits VEGF-receptor internalization, thereby lowering PLCγ/MAPK downstream signaling in response to growth signals (Lampugnani et al. 2006). This is similar to the effects of the E-cadherin–FGF-receptor complex, but not the N-cadherin–FGF-receptor complex. Several possibilities have been proposed for how cadherins might alter RTK (or other receptor) signaling, such as lateral receptor clustering to facilitate RTK auto-activation, alteration of ligand–RTK interactions, or modulation of RTK endocytosis.

In summary, although cadherin and Ig-family adhesion protein interactions with RTKs (as well as phosphatases) are incompletely understood, they represent a link between adhesive junction components and signaling pathways that modulate cell growth and a host of other processes. Further, although some of these relationships may not be dependent on cell–cell adhesion per se, others appear adhesion- or contact-responsive, such as E-cadherin-mediated growth arrest via effects on EGF-receptor interactions (Perrais et al. 2007). Interestingly, the FGF receptor appears to associate more with nonjunctional cadherins or Ig-family (N-CAM) adhesion proteins in cell lines derived from a number of sources (e.g., epithelial, myoblastic, and fibroblastic) (Sanchez-Heras et al. 2006). Further, N-cadherin and the PDGF receptor associate to promote cell movements at the leading edge of cells, with their cytoplasmic domain interactions occurring indirectly via β-catenin and NHERF (Theisen et al. 2007). These considerations indicate that much remains to be learned about how adhesive-protein–RTK signaling is engineered within cells, while already suggesting an intimate cell-surface interplay that ultimately modulates gene activity.

Small GTPases

We will discuss briefly junction-mediated effects on small GTPases (see by Watanabe et al). Cadherin-mediated adhesion has been shown to modulate Rac and less directly Rho and Cdc42, with these GTPases reciprocally contributing to determining cell–cell junction states (Anastasiadis 2007; Yap and Kovacs 2003; Braga and Yap 2005; Yap et al. 2007). Junctional effects on small GTPases (or the reverse) are complex, as differences are apparent as a function of cell type and context. Most of the effects studied have been within the junctional area itself, or cytoplasmic effects that largely relate to cytoskeletal structure–function.

Although GTPase effects are thought to be compartmentalized, including a proportion of those acting at cell–cell contact sites, it is likely that some GTPase signals contribute directly to longer-range signaling to the nucleus. Future studies might address,

for example, the impact of junctionally activated (or inhibited) small GTPases on cell cycle progression. In such cases, it is likely that p120-catenin subfamily members (Anastasiadis 2007), or other molecular players such as PI3 kinase or Akt (Yap and Kovacs 2003; Yap et al. 2007) (see the following), would act as intermediates. Importantly, Rho, Rac, and Cdc42 are known to play roles in cell cycle progression (Coleman et al. 2004; Villalonga and Ridley 2006), and each is responsive to cadherin-mediated cell–cell contact in context-dependent manners (Yap and Kovacs 2003; Burridge and Wennerberg 2004; Yap et al. 2007; Anastasiadis 2007). Thus, as we learn more from future studies, small GTPases are likely to become recognized players in CCJ-nuclear signaling.

PI3 Kinase and Akt

In addition to small GTPase signals arising from CCJs, other signaling mediators such as PI3K and Akt have attracted attention (Larue and Bellacosa 2005; Giehl and Menke 2008). For example, the survival of melanoma cells is enhanced by N-cadherin through an Akt-dependent mechanism (Li et al. 2001), whereas reduced N- or VE-cadherin function in endothelial, granulose, or hepatocellular carcinoma cells results in apoptosis (Peluso et al. 1996; Makrigiannakis et al. 1999; Erez et al. 2004; Gwak et al. 2006; Jiang et al. 2007). E-cadherin also promotes cell survival, inclusive of cancer contexts (St Croix and Kerbel 1997; Kantak and Kramer 1998; Kang et al. 2007). As junctional molecules such as cadherins allow for multiple ligand–receptor interactions, it is not possible in many cases to conclude that cell survival effects are mediated as a direct consequence of cadherin cytoplasmic domain interactions. However, the involvement of cadherin–catenin complexes in producing intracellular signals suggest that direct cadherin effects are contributory and perhaps even predominant in some instances. In this regard, strong evidence has accumulated that PI3 kinase and Rac activation results following cadherin–cadherin *trans* interactions, and that the cadherin cytoplasmic domain is involved (Kovacs et al. 2002; Goodwin et al. 2003). Future work will be required to determine the relative impact of such signals locally, relative to those that might quickly reach the nucleus to modulate gene programs.

NECTIN BASED SIGNALING

Thus far, our discussion has largely taken place from a cadherin-centric perspective. However, it is clear that other adhesive transmembrane polypeptides, such as the Ig-family member N-CAM, also modulate signaling pathways reaching the nucleus (Williams et al. 1994; Choi et al. 2001; Little et al. 2001). Although we will not discuss N-CAM further, we will summarize evidence that the nectin Ig-family of adhesion receptors have important roles in junction formation in epithelia, fibroblasts, and neurons (Takai and Nakanishi 2003; Takai et al. 2008a; Sakisaka et al. 2007). Heterophilic *trans* interactions between nectin1 and nectin3 occur at synaptic junctions (Mizoguchi et al. 2002; Togashi et al. 2006), whereas homophilic N-cadherin *trans* interactions are from both sides of the synapse. Nectins bind several cytoplasmic proteins including afadin, which binds actin, and the cell polarity protein Par3. Indirectly, nectins associate with α-catenin, annexin II, IQGAP1, and ZO1. This latter ZO1 interaction is relevant to nectin's roles in tight junction formation (Ooshio et al. 2007). With respect to signaling, nectin3 associates in *cis* with the integrin α(v)β(3), which appears important for peripheral cytoskeletal organization and activity, and formation of adherens and tight junctions (Sakamoto et al. 2006; Ozaki et al. 2007; Sakamoto et al. 2008). PKC, FAK, and c-Src participate in nectin function downstream of α(v)β(3) (Ozaki et al. 2007; Sakamoto et al. 2008). The fact that nectins interact with components of both the adherens junction (cadherins through α-catenin–afadin associations), tight junctions (ZO1), and α(v)β(3) integrin, appears to provide an example of junctional cross talk. Nectin3 has also been found in *cis* association with the PDGF, but not the

EGF receptor, raising the question whether nectin modulates RTK signaling or vice-versa, and if this nectin complex might also include cadherin or α(v)β(3) integrin (unpublished in Sakisaka et al. 2007). A number of studies have further established functional links between nectins and the activation of the small G proteins Rap1, Cdc42, and Rac through c-Src (Ogita and Takai 2006; Kawakatsu et al. 2005).

It has been proposed that distinct nectin-like (Necl) transmembrane molecules link nectin pathways directly with the nucleus. Much of the focus has been on Necl5, which appears to contribute to contact-mediated inhibition of cell growth, and is capable of binding in *trans* to nectin3 in confluent cell culture. In nonconfluent cells, however, Necl5 associates in *cis* with the PDGF receptor, and α(v)β(3) integrin. These binary associations appear to influence Rap1 and Rac signals involved in cell movements, and Ras signals that induce cell proliferation (H. Amano et al. unpublished; Sakisaka et al. 2007; Minami et al. 2007; Kakunaga et al. 2004). Once cells reach higher densities, Necl5 is thought to engage in heterotypic interactions with nectin3, reducing Ras-mediated proliferative signaling and enhancing signals that strengthen junctions through cadherin and cytoskeletal reorganization. Necl5 is also associated with Sprouty, a negative regulator of growth factor signaling through inhibition of Ras (Kajita et al. 2007). In subconfluent cells, Necl5 appears to block Sprouty inhibition of Ras, favoring a proliferative cell state. In confluent cells, Necl5 is endocytosed more rapidly, and this reduction in Necl5 levels is proposed to allow Sprouty to inhibit Ras, leading to slowed cell proliferation. Finally, recent work indicates that the nectin–afadin complex contributes to PDGF-induced cell survival through the PI3K-Akt signaling pathway (Kanzaki et al. 2008). Cadherins have also been linked to cell survival signaling (Peluso et al. 1996; Kantak and Kramer 1998; St Croix and Kerbel 1997; Makrigiannakis et al. 1999; Gwak et al. 2006; Jiang et al. 2007; Wheelock et al. 2008), and as above noted, associate with RTKs. Prosurvival effects arise from Akt and β-catenin signaling in the case of N-cadherin (Li et al. 2001), and Akt signaling upon E-cadherin association with ErbB4 (Kang et al. 2007). Given the previously noted associations that have been resolved between cadherins and nectins, it may well be that their respective downstream signals are coordinated or interdependent.

GAP JUNCTIONS

Among CCJs, gap junctions represent a unique nonadhesive connection formed from the docking of two hemichannels (or connexon, a hexameric cluster of various connexin isoforms), allowing direct intercellular communications between adjacent cells (Fig. 3) (see Goodenough and Paul 2009). Such an exchange of chemical or electrical signals has been implicated in a broad spectrum of biological events, including metabolic and ion homeostasis, synchronization of muscle contraction, and cell proliferation, survival, differentiation, and migration (Wong et al. 2008; Harris 2007; Mese et al. 2007).

Unlike many classical outside-in signaling pathways, in which ligands bind receptors to trigger events such as phosphorylation or oligomerization and ultimately alter gene expression, gap junctions or hemichannels function as gate keepers to permit molecular diffusion in their opened conformation and prevent such diffusion in closed states (Harris 2007). Entering signaling entities include calcium and other critical metabolites or second messengers that may alter gene expression through known (e.g., CxRE dependent) or unknown mechanisms (Rodriguez-Sinovas et al. 2007).

A number of connexins appear to localize to the nucleus. For example, on immunostaining, connexin 43 has been observed in the nuclei of magnocellular neurons (Eisner and Colombo 2002), whereas its carboxy-terminal fragment localizes to cardiomyocyte and HeLa cell nuclei and correlates with decreased cell proliferation (Dang et al. 2003). Further experimentation is needed, however, to determine if physiologic gap junction–nuclear signaling occurs as a function of connexin

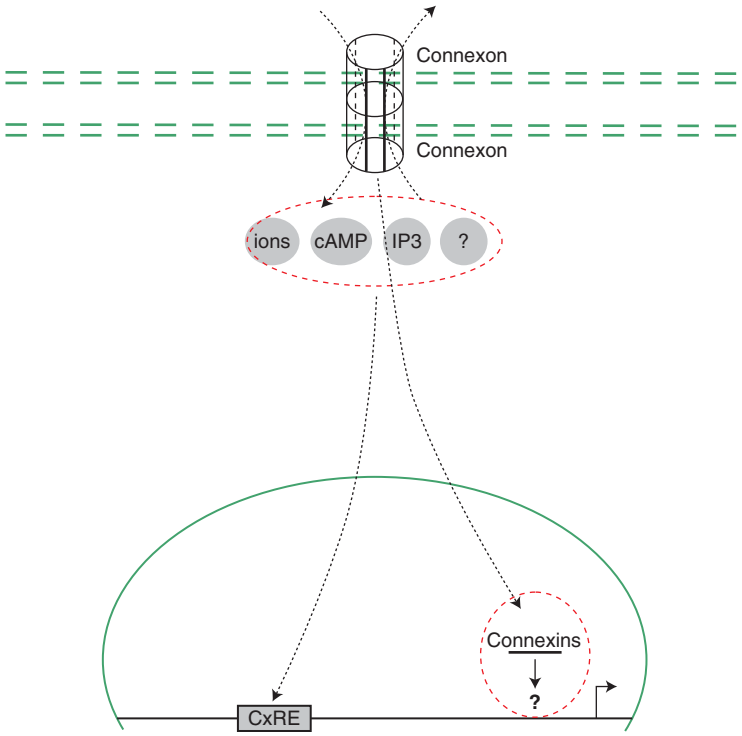

Figure 3. Gap junction signaling to the nucleus. Gap junctions are nonadhesive channels that allow regulated intercellular transmission of electrical or small molecule signals. Connexin 43, a gap junction structural component, has been observed in the nuclei of certain cells and associated with decreased cell proliferation.

or connexin-fragment entry to the nucleus, or through other proteins originally associated with plasma membrane-associated gap junctions.

TIGHT JUNCTIONS

Tight junctions (TJs) are areas of close contact between neighboring plasma membranes, where intramembrane strands at the contact sites can be visualized by freeze-fracture electron microscopy (Tsukita et al. 2001; see Furuse 2009). Tight junctions act as barriers that show both gating and fencing functions: Gating determines the paracellular diffusion of molecules according to size and charge, whereas fencing restricts lipid diffusion between the apical and basolateral intramembrane domains (Balda and Matter 2008; Cereijido et al. 2008; Paris et al. 2008; see Anderson and Van Itallie 2009). Certain proteins of the epithelial TJ show cellular localizations other than the TJ. These proteins localize to both nuclei and TJ, and tend to be involved in the regulation of cell proliferation, gene expression, and cell differentiation (Fig. 4) (Balda and Matter 2003; Matter and Balda 2007). Here, we discuss TJ proteins having both junctional and nuclear localizations, and summarize what is known about their functions, regulation, and expression.

Six TJ-associated transmembrane proteins have been identified: occludin, claudins, tricellulin, JAMs (Junction Adhesion Molecules), CRB-3 (a human homolog of *Drosophila* Crumbs), and Bves (blood vessel/epicardial substance) (Lemmers et al. 2004; Osler et al. 2005; Furuse and Tsukita 2006; Wang and Margolis 2007; Chiba et al. 2008). It remains unclear how each of these proteins interacts with components of the TJ cytoplasmic plaque

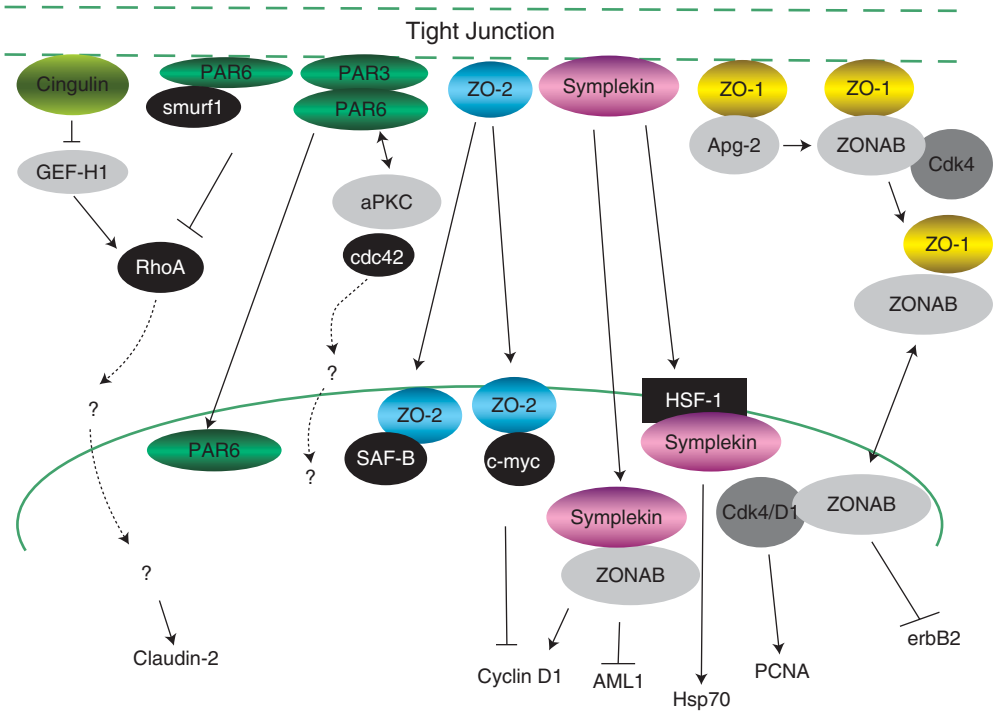

Figure 4. Tight junction signaling to the nucleus. Displayed are pathways associated with tight junctions and suggested or showed to regulate gene expression. Arrows refer to positive functional interactions that could be because of either indirect positive effects or direct physical interactions. Conversely, lines ending with a "T" are negative functional interactions reflecting indirect effects or direct physical interactions. Although most of the junctional proteins depicted associate with junctional membrane proteins, many of the transmembrane entities relevant to the indicated pathways are not known and therefore not indicated.

and how these interactions result in a protein network that controls paracellular permeability, gene expression, junctional dynamics, proliferation, and polarity. The TJ cytoplasmic plaque is formed by multiple adaptor and scaffolding proteins (e.g., ZO-1/2/3, PATJ, Pals1, PAR-3, and PAR-6), different types of signaling components such as GTP-binding proteins, protein kinases, and phosphatases, as well as transcriptional and post-transcriptional regulators (Matter and Balda 2007; Paris et al. 2008). Several proteins have dual localizations at TJs and the nucleus, including ZONAB, cdk4, symplekin, ZO-2, PAR-6, huASH1, and ubinuclein. Most of these proteins have been linked to cell proliferation, gene expression, and/or cell differentiation, and interact with and regulate transcription factors.

ZO-1 AND ZONAB IN CELL PROLIFERATION AND GENE EXPRESSION

ZO-1, the first TJ protein identified (Stevenson et al. 1986), contains distinct protein–protein interaction domains including three PDZ, an SH3 domain, and a domain homologous to yeast guanylate kinase (GUK domain) (Willott et al. 1993). ZO-1 belongs to the same protein family as DlgA (Discs large A), a *Drosophila* tumor suppressor (Tsukita et al. 1993; Woods and Bryant 1993; Fanning et al. 2007). ZO-1 is present not only in epithelial TJs, but also in fibroblasts, neurons, and astrocytes (Howarth et al. 1992), suggesting it has more general functions in cells that do not have tight junctions. Although ZO-1 has been observed in the nucleus of certain cells and conditions, some of the data is conflicting (Gottardi et al. 1996;

Balda and Matter 2000; Reichert et al. 2000; Glaunsinger et al. 2001; Matter and Balda 2003; Traweger et al. 2003). Moreover, the known signaling functions of ZO-1 do not require a nuclear pool of ZO-1, but involve interactions that occur in the cytoplasm and lead to the cytoplasmic sequestration of the dual localization protein ZONAB.

ZONAB is a Y-box transcription factor that belongs to a small family of multifunctional regulators of transcription and post-transcriptional processes (Gallia et al. 2000; Kohno et al. 2003). The Y-box factor family includes DbpA/ZONAB, DbpB/YB-1, and DbpC/contrin (Sakura et al. 1988; Lloberas et al. 1995). ZONAB controls expression of the growth factor coreceptor erbB2, cell cycle regulators such as cyclin D1 and PCNA, and regulates epithelial morphogenesis (Balda and Matter 2000; Balda et al. 2003; Sourisseau et al. 2006). Knockout experiments in mice have shown that mice deficient in DbpA/ZONAB (also called MSY3 in mice) develop normally. However, functional redundancy is indicated as DbpA/ZONAB and DbpB/YB-1 double knockout mice die earlier than animals knocked out for DbpB/YB-1 alone (Lu et al. 2006).

ZONAB binds to the SH3 domain of ZO-1, which contributes to ZONAB's regulation (Balda and Matter 2000; Balda et al. 2003). In MDCK cells, ZO-1 and ZONAB expression are inversely regulated by cell density, and results from different experimental approaches indicate that ZO-1 suppresses proliferation by inhibiting ZONAB's nuclear accumulation (Balda and Matter 2000; Balda et al. 2003). Indeed, the SH3 domain of ZO-1 that binds to ZONAB is necessary and sufficient to sequester ZONAB in the cytoplasm and reduce proliferation (Balda et al. 2003). ZONAB associates with the cell division kinase (CDK) 4, which also has a TJ-nuclear localization; thus, reduction of nuclear ZONAB levels results in reduced nuclear CDK4. Hence, the cell-density dependent accumulation of ZO-1 at TJs works to inhibit the proliferation-promoting ZONAB and CDK4 pathways.

The relative expression levels of ZONAB and ZO-1 are tightly regulated. ZO-1 is expressed at low levels in sparse cultures of MDCK cells, and its levels rises as a function of increased cell density (Balda and Matter 2000). As ZO-1 interacts with many junctional proteins and its half-life increases with greater cell–cell contact, its up-regulation seems to involve junctional stabilization (Gumbiner et al. 1991). Transcriptional mechanisms also affect ZO-1 expression. ZO-1 levels are decreased during corneal wound repair (Cao et al. 2002), in response to β–catenin (Mann et al. 1999), on experimental cell transformation and in a variety of cancers (Miettinen et al. 1994; Chen et al. 2000; Tian and Phillips 2002; Eger et al. 2004; Harten et al. 2009). Analysis of the ZO-1 promoter revealed response elements targeted during EMT (Venkov et al. 2007), as well as by signaling networks activated in neoplastic, metabolic, and viral diseases (Chen et al. 2008). In contrast to ZO-1, ZONAB/DbpA expression increases in contexts that favor proliferation, such as transcriptional regulation by E2F1, and thus is a prognostic marker for hepatocellular carcinomas (Yasen et al. 2005).

ZONAB activity is also regulated by other proteins that control its interaction with ZO-1. One such protein is Apg-2, a heat shock protein that like ZONAB binds the SH3 domain of ZO-1 (Tsapara et al. 2006). Apg-2 is a member of the Hsp110 family of chaperones in the cytosol, the nucleus, and to a lesser extent at the cell–cell junctions in MDCK cells (Tsapara et al. 2006). In response to heat shock, Apg-2 is recruited to junctions and binds ZO-1, leading to ZONAB dissociation, nuclear localization, and activation. Apg-2 depletion retards TJ assembly in calcium switch experiments using two-dimensional cultures, and affects the development of well-organized polarized cysts in three-dimensional cultures (Aijaz et al. 2007), similar to the effects of ZO-1 depletion (Aijaz et al. 2006; Sourisseau et al. 2006). However, whether this effect is due solely to Apg-2's relationship with ZO-1 and ZONAB is not clear. Nevertheless, a functional interaction of these components is further suggested by Apg-2's over-expression in hepatocellular carcinomas

(Gotoh et al. 2004), where ZONAB/DbpA is a prognostic marker (Yasen et al. 2005), and ZO-1 is down-regulated (Orban et al. 2008). Thus, it seems that liver cancer correlates with increased ZONAB activity either because of increased expression of ZONAB itself or of Apg-2, or because of down-regulation of ZO-1.

SYMPLEKIN IN mRNA PROCESSING AND CELL PROLIFERATION

Symplekin, a nuclear protein that can associate with TJs, has been linked to the machinery involved in 3′-end processing of pre-mRNA and polyadenylation (Keon et al. 1996; Takagaki and Manley 2000; Hofmann et al. 2002). In stressed cells, symplekin interacts with HSF-1 (heat shock inducible transcription factor one) to regulate hsp70 mRNA polyadenylation (Xing et al. 2004). In *Xenopus*, symplekin and an unusual poly(A) polymerase, GLD-2, are required for cytoplasmic polyadenylation (Barnard et al. 2004). Furthermore, symplekin and the polyadenylation factor CPSF-73 are targets of the small ubiquitin-like modifier SUMO (Vethantham et al. 2007). Thus, symplekin has a role in mRNA processing.

Whether symplekin's junctional localization reflects a regulatory role of cell–cell adhesion in polyadenylation is not known. As symplekin appears to bind transcription factors, it may localize to sites where those interacting transcription factors are found. This possibility is supported by the finding that symplekin interacts with ZONAB. Symplekin depletion by RNA interference reduces ZONAB nuclear accumulation, transcriptional activity, cell proliferation and expression of cyclin D1 in a ZONAB-dependent manner (Kavanagh et al. 2006). Furthermore, symplekin cooperates with ZONAB to negatively regulate intestinal goblet cell differentiation, acting via repression of the AML1 transcription factor (Buchert et al. 2009). As ZONAB is a Y-box factor, a family of multifunctional proteins that can interact with DNA as well as RNA (Kohno et al. 2003), it is tempting to speculate that the interaction between symplekin and ZONAB is not only functionally important for transcription but also for RNA processing, stability, and/or localization.

ZO-2 IN CELL PROLIFERATION AND GENE EXPRESSION

ZO-2 has the same domain structure as ZO-1 and was identified because of its interaction with ZO-1 (Gumbiner et al. 1991; Jesaitis and Goodenough 1994). ZO-2 shuttles from the cell periphery to the nucleus (Islas et al. 2002; Traweger et al. 2003; Kausalya et al. 2004), interacts with the nuclear ribonucleoprotein scaffold attachment factor-B (SAF-B) (Traweger et al. 2003) and several transcription factors (Betanzos et al. 2004; Huerta et al. 2007). ZO-2 inhibits cell proliferation by affecting transcription, translation, and degradation of cyclin D1 (Huerta et al. 2007; Tapia et al. 2009), coincident with observations that its expression is reduced in certain tumors (Chlenski et al. 2000; Fink et al. 2006; Paschoud et al. 2007). ZO-2 binds and inactivates oncogenic viral proteins (Glaunsinger et al. 2000; Lee et al. 2000; Glaunsinger et al. 2001), and its degradation is induced by HIV type 1 gp120 (Nakamuta et al. 2008). Conversely, in some epithelial and endothelial cells, ZO-2 has been reported to increase proliferation and regulate the expression of M2 pyruvate kinase (Traweger et al. 2008).

In mice, ZO-2 deficiency is embryonic lethal; embryos show decreased proliferation at embryonic day 6.5, and increased apoptosis at embryonic day 7.5, indicating an arrest in early gastrulation (Xu et al. 2008). Depletion of ZO-2 protein by RNA interference in two-cell embryos delays blastocoel cavity formation with normal cell proliferation and morphogenesis. In contrast, ZO-1 knockdown, or combined ZO-1 and ZO-2 knockdown, produces a more severe inhibition of blastocoel formation, indicating distinct but possibly overlapping roles for ZO proteins in blastocyst morphogenesis (Sheth et al. 2008). Further studies are needed to address these contradictions in ZO-2's role in cell proliferation, possibly because of different experimental systems/contexts, and to identify genes regulated

by ZO-2 in association with SAF-B or other transcription factors.

HuASH1 AND UBINUCLEIN IN CHROMATIN REMODELING AND GENE EXPRESSION

HuASH1, the human homolog of *Drosophila* ASH1 (absent, small, or homeotic discs 1), belongs to the trithorax group of transcription factors. It was found to colocalize with TJ markers by immunofluorescence (Nakamura et al. 2000). HuASH1 functions as a histone methyltransferase, an enzymatic activity involved in chromatin remodeling and gene expression (Beisel et al. 2002; Gregory et al. 2007), and interacts with HDAC1 repression complexes (Tanaka et al. 2008). It remains unknown how huASH1 is recruited to intercellular junctions, or the functional relevance of its junctional association in chromatin remodeling and gene expression.

Ubinuclein belongs to a novel family of histone chaperones conserved throughout eukaryotes (Balaji et al. 2009), and has been found to interact with viral transcription factors in the nucleus and ZO-1 at epithelial TJs (Aho et al. 2008). When overexpressed, ubinuclein prevents MDCK cells from going through cytokinesis (Aho et al. 2008). Whether and how ZO-1 might regulate the function and localization of ubinuclein, or the specifics of ubinuclein's interactions with other proteins in the nucleus, remain open questions.

TIGHT JUNCTION-ASSOCIATED REGULATION OF SMALL GTPases

TJs also participate in the regulation of small GTPases (see also Watanabe et al. 2009). RhoA activation affects actin organization and stimulates epithelial cell proliferation, gene expression, and differentiation (Jaffe and Hall 2002; Sahai and Marshall 2002; Nelson 2008). RhoA is down-regulated when epithelial cells reach confluence, resulting in inhibition of signaling pathways that stimulate proliferation. GEF-H1/Lfc, a guanine nucleotide exchange factor specific for RhoA, is involved in the regulation of paracellular permeability and cell proliferation (Benais-Pont et al. 2003; Aijaz et al. 2005). GEF-H1/Lfc directly interacts with cingulin, a junctional adaptor, resulting in its inhibition and thus reduced RhoA activity. In MDCK cells with reduced cingulin levels, increased claudin-2 expression is RhoA-dependent, suggesting it might be mediated by GEF-H1 signaling (Guillemot and Citi 2006).

JACOP/paracingulin, a TJ plaque protein with sequence similarity to cingulin (Ohnishi et al. 2004), interacts with GEF-H1 as well as the Rac GEF Tiam1, thereby influencing junction assembly (Guillemot et al. 2008). Tiam1 and Cdc42 have been linked to the assembly of the TJ-associated, evolutionarily conserved cell polarity signaling pathway that includes the PAR3/PAR6/aPKC complex, and is required for the formation of distinct tight and adherens junctions (Ebnet et al. 2004; Assemat et al. 2008; Iden and Collard 2008; Macara and Mili 2008).

PAR6 itself is a protein with multiple interaction partners and also shows dual localization. In different experimental systems, PAR6 was shown to interact with small GTPases such as cdc42, Rac2, Rin, Rit, and Wrch-1 (Johansson et al. 2000; Hoshino et al. 2005; Macara and Mili 2008; Brady et al. 2009), as well as p190RhoGAP (Zhang and Macara 2008). PAR6 is also part of the TGF-β-activated pathway leading to ubiquitination and degradation of RhoA (Wang and Margolis 2007). PAR6 localizes to nuclear speckles and colocalizes with Tax, a transcriptional activator of the human T-cell leukemia virus type 1 long terminal repeat (Cline and Nelson 2007). Although its nuclear functions are not clear, PAR6 does not seem to be directly involved in transcription but likely instead plays an architectural role.

TIGHT JUNCTION CROSS TALK WITH GROWTH FACTORS AND EXTRACELLULAR MATRIX PATHWAYS

The relationship of TJs with growth factor and matrix signaling is an emerging area of

research. Occludin regulates localization of the TGF-β type I receptor and thus plays a role in TGF-β-dependent dissolution of TJs during epithelial-to-mesenchymal transitions (Bose and Wrana 2006). FGF-2 fails to induce angiogenesis in JAM-A-deficient mice (Cooke et al. 2006), suggesting a role of JAM-A in FGF-2 signaling, which might be mediated by the PAR3/PAR6/aPKC complex (Ebnet et al. 2004). Additionally, EGF signaling seems to affect the expression and localization of several TJ proteins that regulate TJ assembly and barrier functions (Van Itallie et al. 1995; Basuroy et al. 2006; Wang et al. 2006; Flores-Benitez et al. 2007; Singh et al. 2007), suggesting that EGF signaling could have an indirect role in regulating TJ-nuclear signaling by modulating the activities of the PAR3/PAR6/aPKC and/or ZO-1/ZONAB pathways.

It is generally accepted that integrin signaling pathways regulate cell migration, junctional complex stability, and cell–cell interactions including those taking place at TJs (Ojakian et al. 2001). There are also examples linking TJ-ssociated proteins with integrins. For example, claudin-11 forms a complex with OAP-1, a tetraspan family protein, and with β1 integrin to regulate proliferation and migration of oligodendrocytes (Tiwari-Woodruff et al. 2001). JAMs regulate cell migration through effects on β(1) integrin or, depending on the cellular context, on α(v)β(3) integrin (Mandell et al. 2005; Naik and Naik 2006; Mandicourt et al. 2007). These results suggest that transmembrane TJ proteins may influence nuclear events through their effects on integrins. It is tempting to speculate that such relationships exist because down-regulation of ZO-1 or manipulation of ZO-1 interactions with ZONAB produce mild phenotypes in monolayers but inhibit cyst formation in three dimensional (collagen/matrigel) cultures (Umeda et al. 2004; Aijaz et al. 2006; McNeil et al. 2006; Sourisseau et al. 2006; Aijaz et al. 2007). Future studies will need to address the specific molecular mechanisms involved; for example, if/how the TJ affects gene expression profiles relevant to extracellular matrix adhesion and signaling.

ADHERENS AND TIGHT JUNCTION CROSS TALK

In revising earlier ideas in which junctions may have been viewed as rather distinct functional entities, it seems likely that in many cases shared functions occur including those involving signals directed to the nucleus. For example, the p120- and ARVCF-catenins, traditionally viewed as components of adherens junctions, also interact with ZO-1 and ZO-2 (Kausalya et al. 2004). In polarized epithelial MDCK cells, ARVCF and ZO-1 partially colocalize in the vicinity of the apical adhesion complex. Disruption of cell–cell adhesion releases ARVCF from the plasma membrane, with an increased ARVCF fraction localizing to the nucleus where it binds ZO-2 (Kausalya et al. 2004). Thus, even as the nuclear roles of ARVCF are not known, the interaction of TJ and adherens junction proteins may allow cooperation between junctions in regulating gene expression.

Cyclin D1 is an example of a gene target responsive to both TJ and adherens junction function, and which is up-regulated in many tumors (Coqueret 2002; Fu et al. 2004). Several signaling pathways that regulate cell–cell and cell–extracellular matrix adhesion have an impact on cyclin D1 expression (Shtutman et al. 1999; Tetsu and McCormick 1999; D'Amico et al. 2000; Amanatullah et al. 2001; Zhao et al. 2001; Balda and Matter 2003; Zhao et al. 2003). The identification of other genes regulated by both adherens and tight junctions should help us understand downstream cross talk occurring between adherens and tight junctions, as well as appreciate how these pathways interact with those activated by growth factors or the extracellular matrix (Balda and Matter 2003).

Junctional cross talk involving nuclear signals is further reflected in roles of the adherens junction in transcriptional regulation of TJ gene products. In endothelia, for example, the level of VE-cadherin affects that of the TJ protein claudin-5. This effect appears to occur through Akt, which phosphorylates the forkhead box factor FoxO1, and regulates the

TCF4–β-catenin transcriptional repressor complex (Taddei et al. 2008). It has been suggested that potential TCF/LEF binding sites present in the promoter of claudin-3 may account for its down-regulation in response to reduced β-catenin activity (Liebner et al. 2008). In the future, it will be interesting to further examine whether signaling pathways downstream of one junction have an impact on the expression of gene products comprising another junction.

CONCLUDING REMARKS

Although it is clear that CCJ-nuclear signaling takes place in cells and tissues, it is also apparent that our present knowledge is not satisfactory in understanding the larger roles of CCJs in transcriptional modulation. Although we are able to list a number of intriguing examples for each junction type, we are far from having a coherent picture of the networks involved at the plasma membrane, cytoplasmic, or nuclear levels. An inherent difficulty in identifying the network and its details is that downstream signals originating from cell–cell contacts are both direct and indirect, and are likely to be concurrent. For example, signals may be blocked or promoted by a component being junctionally sequestered or released from the adhesion complex to the nucleus (direct) or, alternatively, mediated through associated signaling molecules such as an RTKs, or other ligand–receptor or adaptor/signaling pairs dependent on the presence of the junction (each indirect).

One approach that has been helpful is the use of engineered contacts bearing purified adhesion receptors (coated beads, etc.). Although this is not physiologic, it assure that the physical interaction presented in *trans* is defined and, if desired, singular. Such methods, combined with the use of reagents to report pathway activation in real time, can also be useful in working out the temporal sequence of pathway activation following contact. In time, it may be that single molecule tracking methods will be used to more firmly establish the fate of individual molecules putatively traveling between junctions and the nucleus. This could assist, for example, in ascertaining if a specific catenin molecule dissociating from a cadherin complex is actually capable of reaching transcriptional regulatory regions in the nucleus. Although much work remains, we can appreciate the findings that have already been made, as they tell us of two fascinating worlds that listen to one another, one at the cell surface where cells meet and touch, and the other internal where transcriptional and proliferative/differentiation outcomes are further processed.

ACKNOWLEDGMENTS

This article is dedicated to Margaret Jean (Peggy) Wheelock, PhD (1945–2009). We thank W.J. Nelson for his critical reading, helpful comments, and patience during the review process. The laboratory of PDM is supported through funding from NIH (RO1GM52112), Texas ARP (003657-0008-2006), and UT MDACC NCI Core Grants (CA-16672). The laboratory of M.S.B. is supported through funding from the Wellcome Trust, MRC, BBSRC, AICR, and Fight for Sight.

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