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Skin tight: cell adhesion in the epidermis of *Caenorhabditis elegans*

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The powerful genetics, genomics and microscopy tools available for *C. elegans* make it well suited to studying how epithelial cells adhere to one another and the extracellular matrix, and how the integrated, simultaneous activities of multiple cell adhesion complexes function to shape an organism. Recent studies using forward and reverse genetics have shed light on how phylogenetically conserved cell adhesion complexes, such as the cadherin/catenin complex, claudins, the Discs large complex and hemidesmosome-like attachment structures, regulate epithelial cell adhesion, providing new insights into conserved cell adhesion mechanisms in higher eukaryotes.

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Abbreviations

aPKC	atypical protein kinase C
CCC	cadherin/catenin complex
CeAJ	<i>C. elegans</i> apical junction
ECM	extracellular matrix
FO	fibrous organelle
GFP	green fluorescent protein
Hmp	humpback
Hmr	hammerhead
IF	intermediate filament
MAGUK	membrane-associated guanylate kinase
Mua	muscle attachment
RNAi	RNA interference
ZP	zona pellucida

Introduction: *C. elegans* as a model system for studying epithelial adhesion

Epithelia play a key role in orchestrating the overall architecture of animals. The dynamic adhesive properties of epithelia are especially important in embryos, where adhesion complexes are regulated at an exquisitely refined level to achieve the changes in form associated with morphogenesis. Because of its simplicity, optical

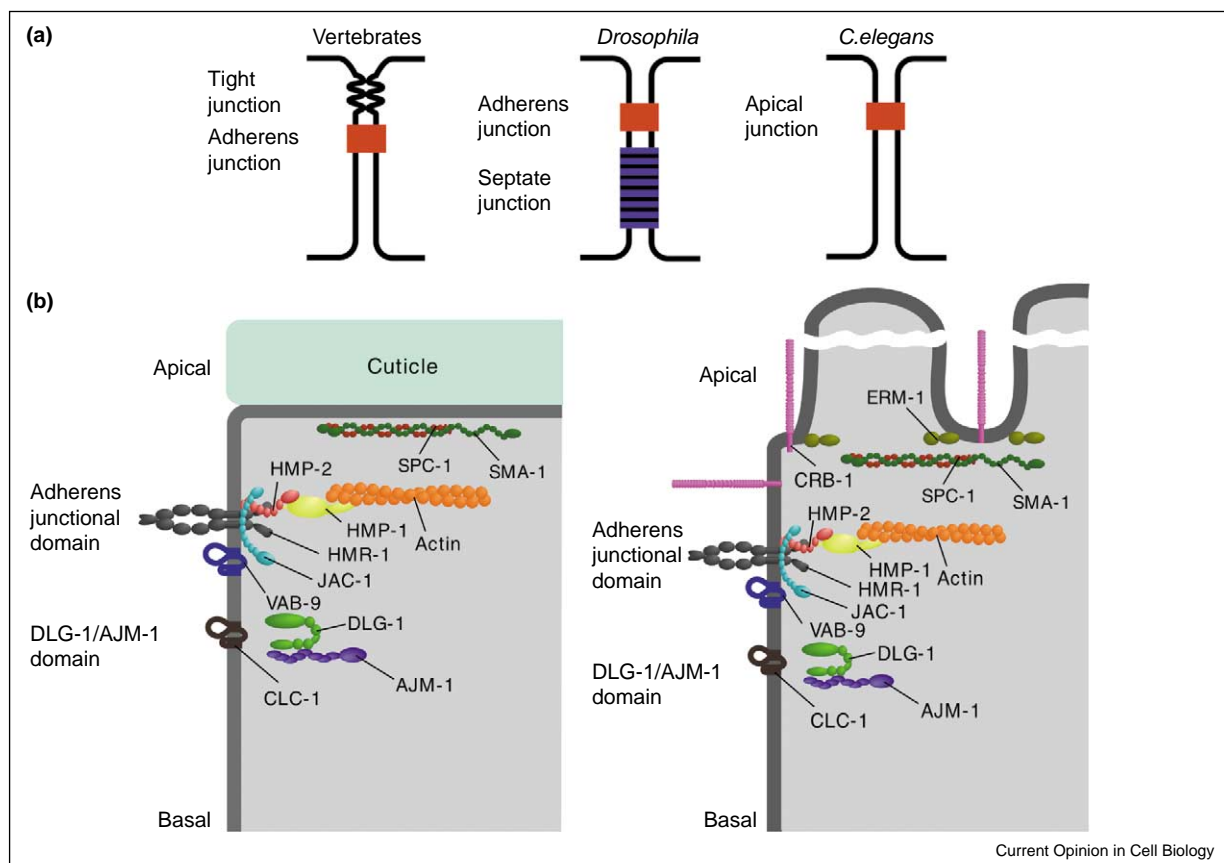
transparency, stereotypical cell lineage and suitability for both forward and reverse genetics, the *C. elegans* embryo is a convenient system for analyzing dynamic changes in epithelial cell adhesion *in vivo*. Analysis of the *C. elegans* genome indicates that it has many adhesion proteins in common with other organisms [1[•],2,3,4[•]]. Moreover, unlike *Drosophila*, which has no intermediate filaments (IFs), *C. elegans* expresses a number of IFs ([5,6[•],7[•]]), allowing powerful genetic approaches to the study of IF-containing adhesion complexes similar to those in vertebrates. Recent reviews have summarized studies of all of the major adhesion complexes in *C. elegans* [1[•],3,8^{••}], including muscle dense bodies, which attach muscle cells to the basal lamina. Dense bodies contain many of the proteins found at focal contacts in vertebrates, including integrins and their associated proteins, such as integrin-linked kinase (ILK; see the article by Grashoff *et al.* in this issue). Here, we focus primarily on the embryonic epidermis, or hypodermis, of *C. elegans* as a model for understanding how multiple adhesion complexes are integrated in epithelial cells during embryonic development.

Unlike in *Drosophila* and vertebrates, there is a single, apically situated electron-dense region connecting epithelial cells in *C. elegans*, the *C. elegans* apical junction (CeAJ; see Figure 1a). Although it is currently unclear exactly where specific molecular complexes localize relative to this single electron density, *C. elegans* epithelia possess several multiprotein complexes similar to those in other organisms (Figure 1b; see [8^{••},9] for other reviews). These include the following: an adherens junctional subdomain, which contains the cadherin/catenin complex (CCC); a more basal junctional domain containing the *C. elegans* homologue of Discs large and its binding partner, AJM-1 (the *DLG-1/AJM-1* subdomain); and an apical region, which, in some tissues, contains transmembrane proteins of the Crumbs family, the *C. elegans* PAR-3/PAR-6/atypical protein kinase C (aPKC) complex, and proteins that stabilize cytoskeletal attachments to the apical membrane (Figure 1b). In addition, epidermal cells in *C. elegans* also possess hemidesmosome-like attachment structures or ‘fibrous organelles’ (FOs), which couple IFs to the apical and basal surfaces of epidermal cells (Figure 1b).

The cadherin/catenin complex: epithelial sealing and actin anchorage

In *C. elegans*, the only classical cadherin is encoded by the *hmr-1* locus [10], which encodes two proteins: a longer, neuronal-specific isoform, HMR-1B, and a shorter

Figure 1



Junctional organization in epithelia of *C. elegans*. **(a)** Comparison of junctional complexes in vertebrates, *Drosophila*, and *C. elegans*. In vertebrates, the occluding junction, the tight junction, lies apical to the adherens junction, which contains the cadherin/catenin complex. In contrast, in *Drosophila*, the occluding junction, the septate junction, lies basal to the adherens junction. In *C. elegans*, a single electron-dense junctional structure, the *C. elegans* apical junction (CeAJ), is observable. **(b)** Molecular complexes associated with cell-cell junctions in *C. elegans* epithelia. Left: a schematic of an epidermal cell, which maintains an apical attachment to the cuticle. Right: a schematic of an intestinal cell, an example of a non-cuticular epithelium. The adherens junctional domain comprises the most apical domain of the junction, and contains the *C. elegans* homologues of the cadherin/catenin complex: HMR-1A/cadherin (black), HMP-1/α-catenin (yellow), HMP-2/β-catenin (red), and JAC-1/p120ctn (light blue). The claudin-like protein VAB-9 (dark blue) also localizes to this region. The adherens junctional domain is thought to link directly to the actin cytoskeleton. The more basal region of the junction consists of the MAGUK DLG-1/Disks large (green) and the novel coiled-coil protein AJM-1 (purple). Recently, claudin-like CLC proteins (brown) have been shown to localize with the DLG-1/AJM-1 domain in at least some epithelia. Apical to the junction, several proteins probably aid attachment of the apical membrane to the cytoskeleton, such as SMA-1/β_H-spectrin (dark green) and SPC-1/α-spectrin (red). Several proteins are only found near the apex in non-cuticular epithelia, such as the intestine and pharynx (right). These include the FERM domain protein, ERM-1 (olive), the Crumbs homologue, CRB-1 (pink), the Crumbs-related protein, EAT-20 (not shown), and the PAR-3/PAR-6/PKC-3 (aPKC) complex (powder blue, mauve, and pale green, respectively).

isoform, HMR-1A, which is expressed in epithelia [11]. The other components of the *C. elegans* CCC are HMP-2/β-catenin, HMP-1/α-catenin, and JAC-1/p120ctn (Figure 1b), whose conserved functional domains and protein-protein interactions indicate that they function in a manner very similar to their vertebrate and *Drosophila* counterparts [12,13**].

The *C. elegans* CCC was first identified on the basis of its essential role during morphogenesis [12,14]. During the process of ventral enclosure, the free edges of the epidermis migrate ventrally and rapidly seal as filopodia make contact at the ventral midline [14], a process that

bears striking similarities to both dorsal closure in *Drosophila* and junction formation in vertebrate cells [15–17]. *hmr-1*/cadherin null mutants and embryos depleted of both maternal and zygotic *hmp-2*/β-catenin and *hmp-1*/α-catenin function often exhibit a ‘hammerhead’ (Hmr) phenotype, as anterior ventral epidermal cells fail to make such midline contacts [12,14].

The CCC is also required for the next step in morphogenesis, elongation. As ventral enclosure completes, circumferentially oriented actin bundles in the epidermis become anchored into the CCC, and are thought to help distribute the forces that elongate the embryo, a process

that involves actomyosin-mediated cell shape changes [18[•]]. In embryos lacking zygotic *hmp-1*/α-catenin or *hmp-2*/β-catenin activity, circumferential actin filaments consistently detach from the CCC in epidermal cells, as dorsal epidermal cells are thrown into folds (the ‘hump-back’, or Hmp, phenotype) [12].

Given the clear role that the core components of the CCC play in regulating morphogenesis in *C. elegans*, it is surprising that RNA interference (RNAi) directed against the other major component of the CCC, JAC-1/p120ctn, does not cause obvious defects [13^{••}]. However, like its vertebrate counterpart [19], JAC-1/p120ctn does modulate attachment of actin filament bundles to the CCC, as deduced from its ability to enhance elongation defects in weak *hmp-1*/α-catenin mutants [13^{••}]. Similar results have been reported in *Drosophila*: loss of p120ctn has little or no phenotypic effect on its own but enhances weak mutations in CCC components [20] and a *shotgun/DE-cadherin* deletion construct lacking the juxtamembrane p120ctn binding motif can fully rescue *shotgun* mutants [21]. Since vertebrate p120ctn regulates cadherin turnover and recruitment [22], it is possible that in rapidly developing invertebrate embryos such functions are dispensable. Indeed, *C. elegans* expresses many other proteins that localize to adherens junctions in vertebrates, yet these proteins are of minor functional importance [8^{••}].

A novel associate of the CCC is a founding member of a new class of claudin superfamily proteins, VAB-9. *Bona fide* claudins are transmembrane proteins that engage in hetero- or homophilic interactions; most claudins are components of occluding junctions in both vertebrates [23,24] and *Drosophila* [25,26], and are not associated with the CCC (see [27] for a comparison of organizational differences in occluding junctions in invertebrates and vertebrates). In contrast, VAB-9 colocalizes with the CCC and requires HMR-1/cadherin function for correct localization [28^{••}]. *vab-9* nulls do not exhibit embryonic lethality, but display elongation and body shape defects and abnormal circumferential actin filament bundles, suggesting that VAB-9 affects the attachment of bundles to the CCC [28^{••}]. Although homo- or heterophilic interactions have not been conclusively shown for VAB-9 or other members of its superfamily, genetic evidence suggests that VAB-9 plays a role in cell–cell adhesion: double mutants lacking both VAB-9 and components of the DLG-1/AJM-1 complex show severe, synergistic adhesion defects [28^{••}].

Although the CCC is clearly important for morphogenesis in *C. elegans*, it is puzzling that complete removal of its components does not abrogate cell–cell adhesion in the early embryo. *C. elegans* must presumably have other, functionally redundant adhesive complexes that act in the early embryo. Although *C. elegans* does not have a clear nectin homologue [1[•]], additional possibilities include

other cadherin-like proteins [10] and the L1CAM homologue, LAD-1 [29]. LAD-1 localizes to cell–cell contacts in the early embryo and basolaterally in epithelia, [29], so it could act in parallel with the CCC in the early embryo.

The DLG-1/AJM-1 complex: effectors in search of a partner

The basal domain of the CeAJ is characterized by the presence of DLG-1/Discs large and AJM-1, which colocalize to the electron-dense junctional region [30–33]. Like its orthologues, the *Drosophila* tumor suppressor Discs-large and vertebrate SAP97, DLG-1 is a member of the membrane-associated guanylate kinase (MAGUK) family. AJM-1 is a novel protein whose major predicted structural feature is a large coiled-coil domain [32]. Loss of either DLG-1 or AJM-1 leads to similar phenotypes: embryos arrest at about the two-fold stage of elongation, and contain swollen cells that may be necrotic [30,32]. TEM reveals that the integrity of the electron-dense region of the CeAJ is affected in both mutants: in *ajm-1* mutants, local, bubble-like separations form in this region [32], whereas removal of *dlg-1* function leads to a complete loss of electron-dense material [30,33]. DLG-1 is essential for the proper localization of AJM-1 — loss of DLG-1 function results in lateral redistribution of AJM-1 into puncta [30–33]. DLG-1 is likely to be a direct regulator of AJM-1, since the proteins interact in a yeast two-hybrid assay [32]. Recent work suggests that AJM-1 may in turn play a reciprocal role in maintaining the localization of DLG-1 in the intestine [34[•]]. In the epidermis of *ajm-1* mutants, DLG-1 localization has been reported to be normal [30,32,33], although finer-resolution imaging may reveal that similar interactions occur there.

Several studies have characterized the regulation of the DLG-1/AJM-1 complex. The LAP (leucine-rich repeat and PDZ) protein LET-413, a homologue of *Drosophila* Scribble, localizes to the basolateral membranes of epithelia through its leucine-rich repeats [35[•]]. Loss of *let-413* function leads to basal spreading of DLG-1/AJM-1 along the lateral membrane, resulting in discontinuous stretches of junctional material [30,32,36]. Like its *Drosophila* counterpart, LET-413 probably regulates apico-basal polarity more generally, at least in the intestine, since its removal also perturbs more apically situated proteins [37[•]]. The mechanism by which LET-413 acts to maintain apico-basal polarity is currently unknown.

In addition to the role of the DLG/AJM-1 complex in stabilizing the electron-dense region of the CeAJ, double mutant analysis indicates that it may also play a role in regulating adhesion. For example, *vab-9;dlg-1* and *vab-9;ajm-1* mutants frequently arrest with a ruptured epidermis, a phenotype exhibited in neither of the single mutants [28^{••}]. Similarly, simultaneous removal of DLG-1 function along with those of the apical protein

ERM-1 or CCC components results in synergistic defects in the intestine [34^{*},38^{**}]. These results suggest that the DLG-1/AJM-1 complex associates with an adhesive function that is at least partially functionally redundant with the CCC. What transmembrane protein might be responsible? One possibility is that DLG-1 interacts with *C. elegans* claudins. One *C. elegans* claudin homologue, CLC-1, co-localizes with AJM-1 in the pharynx, and its removal via RNAi leads to compromised epithelial barrier function in adults [39^{**}], consistent with this possibility. Other candidate DLG-1 interactors include LAD-1, which contains a PDZ binding motif at its C terminus [29] that could potentially interact with the PDZ motifs of DLG-1. Further studies will be necessary to determine whether CLC proteins, LAD-1 or other transmembrane proteins interact with the DLG-1/AJM-1 to regulate junctional integrity.

The apical domain: not all epithelia are created equal

The tight junctions of vertebrates and the subapical region (SAR) of *Drosophila* contain two apical protein complexes that are key regulators of apical–basal polarity: first, the PAR-3/PAR-6/aPKC complex, and second, the Crumbs/Stardust/Discs-lost complex, which associates with β_H -spectrin (reviewed in [9,40–43]). Some epithelial cells in *C. elegans*, including those of the alimentary canal [31] and spermatheca [44^{**}], exhibit a similar apical region, which contains PAR-3, PAR-6 and PKC-3/aPKC, as well as the Crumbs homologue CRB-1 (Figure 1b). Although there is currently no evidence that the PAR/aPKC complex is crucial in most tissues where it is expressed, a functional role for the PAR/aPKC complex in epithelia was recently reported for the spermatheca, where it regulates polarity, including the positioning of the DLG-1/AJM-1 complex [44^{**}]. Similarly, neither the *C. elegans* Crumbs homologue (*crb-1*) nor a second Crumbs-like gene (*crl-1/eat-20*) is essential for epithelial development in *C. elegans* [31]; however, EAT-20 is required in the pharynx for proper pumping [45], and *crb-1* may interact genetically with *let-413* and *hmp-1*/ α -catenin in a complex manner in the intestine [34^{*}]. Taken together, such studies do not make it clear how these apical protein complexes function in most *C. elegans* epithelia. In addition to the PAR/aPKC and Crumbs complexes, the intestine and pharynx express proteins that probably stabilize the apical membrane by linking it to the cytoskeleton. These include the FERM domain protein ERM-1 and SMA-1/ β_H -spectrin; removal of the function of either results in tubulogenesis defects [34^{*},38^{**},46^{**}].

Surprisingly, in cuticular epithelia, such as the epidermis and the regions of the pharynx and anus that have cuticle associated with them, the PAR/aPKC and Crumbs complexes are absent ([31]; Hardin and Lockwood, unpublished). The one distinguishing feature of epithelia in

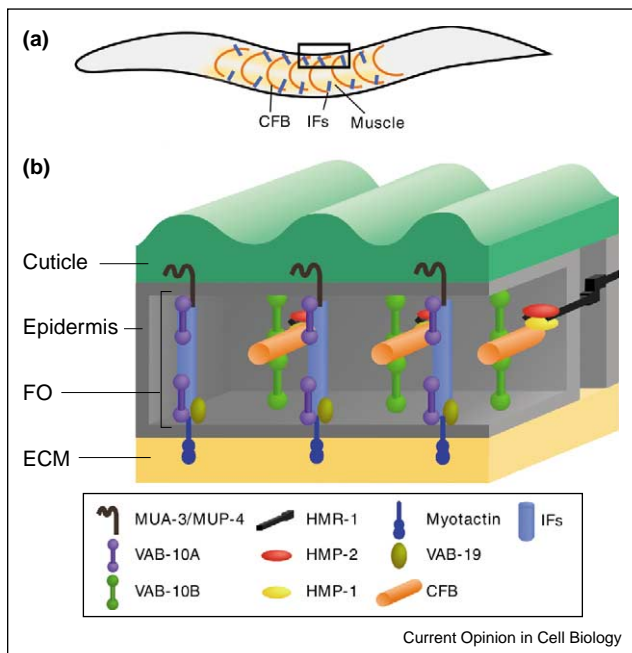
C. elegans that lack these proteins is their attachment to the cuticle, which could provide a functional substitute. Cuticular epithelia in *Drosophila* require several proteins containing domains originally identified in proteins of the mammalian zona pellucida (ZP). These ZP-domain-containing proteins are required for proper organization, including Dumpy and Piopio (reviewed in [47]); since the *C. elegans* genome encodes several ZP domain proteins (Hardin and Lockwood, unpublished), it is possible that these proteins are also important in *C. elegans*. Two apical components retained in the epidermis are SMA-1/ β_H -spectrin and SPC-1/ α -spectrin; loss of SMA-1 or SPC-1 function perturbs elongation of the embryo and results in disruption of the apical actin cytoskeleton ([48,49]; V Praitis, personal communication).

Fibrous organelles: mechanical coupling between tissues

In addition to its role in morphogenesis and as an epithelial barrier, the *C. elegans* epidermis is crucial for the efficient mechanical transduction of muscle contraction to the cuticle, which occurs through epidermal FOs. FOs, which are structurally similar to the type I hemidesmosomes of vertebrate epidermal cells (reviewed in [8^{**},50]), attach IFs basally to the underlying basement membrane and associated muscle, and apically to the cuticle (Figure 2). *C. elegans* has eleven genes that encode cytoplasmic IFs; at least three (A2, A3, B1) are essential components of FOs [6^{*},7^{*}].

FOs do not contain integrins or a BPAG2 homologue, but instead have other transmembrane proteins that probably form analogous linkages. Apically, MUA-3 and MUP-4, which both contain numerous EGF repeats, a von Willibrand factor type A domain, and two sea-urchin-enterokinase–agrin modules ([51,52]) aid attachment to the cuticle. Basally, myotactin/LET-805, a novel transmembrane protein with at least 32 extracellular fibronectin type III repeats [53], aids attachment of FOs to the basal lamina. The importance of attachment of FOs to the basal lamina is further suggested by the phenotype of embryos lacking laminin αB function, in which the epidermis separates from muscle [54^{*}]. The plectin homologue, VAB-10A, is an important component of both apical and basal FOs [55^{**}]. By analogy to vertebrate plectins, VAB-10A probably links transmembrane receptors and IFs. The *vab-10* locus also encodes a second isoform, VAB-10B, which is similar to vertebrate plakins, known actin/microtubule cross-linking proteins; VAB-10B/plakin probably makes an important contribution to the mechanical integrity of the epidermis by regulating the distance between its apical and basal surfaces [55^{**}]. Finally, the basally localized ankyrin-repeat protein, VAB-19/Kank, which requires myotactin function for its localization, appears to regulate attachment structures [56^{**}]. *vab-19* mutants have elongation defects, and, interestingly, loss of the function of SMA-1/ β_H -spectrin

Figure 2



Model for the organization of structural filaments in the epidermis.

(a) The circumferential filament bundles (CFBs) and the intermediate filament (IF)-linked fibrous organelles (FOs) show alternating patterns of localization in the larval and adult epidermis, correlating with furrows in the cuticle. **(b)** Magnified view of the CFB and FOs, revealing their spatial organization. The CFBs (orange) localize to annular furrows, and likely attach to the cadherin/catenin complex (CCC) of epithelial junctions. Essential components of the CCC include HMR-1A/cadherin (black), HMP-1/ α -catenin (yellow), and HMP-2/ β -catenin (red). Circumferential bundles are thought to contribute to the forces necessary for elongation of the embryo. Also localizing to the annular furrows is VAB-10B (green), which regulates the distance between the apical and basal surfaces of the epidermis. FOs, composed of IFs (blue) and associated proteins, localize to the annular ridges. The IFs are linked to the cuticle and basal extracellular matrix (ECM) through the transmembrane proteins MUA-3/MUP-4 (brown) and myotactin (dark blue), respectively. VAB-10A (purple) localizes to the apical and basal surfaces of FOs and is essential for their formation. VAB-19 (olive) localizes to the basal surface of FOs and plays a role in their organization. Mechanical coupling of the cuticle to the underlying muscle is necessary for completion of embryonic elongation.

partially suppresses defects in *vab-19* mutants, suggesting that VAB-19 and SMA-1 may antagonize one another during elongation.

Conclusions: *C. elegans* as a system for studying the integration of epithelial adhesion

Epithelial cell adhesion in *C. elegans* is strikingly similar to that in higher organisms, making *C. elegans* a useful system for exploring how the functions of multiple epithelial adhesion complexes are integrated, both functionally and mechanically, in an intact organism. Despite recent progress, many questions remain. The first is the extent to which various epithelial adhesion complexes depend on

one another for their formation. In some cases, there is clear independence; for example, the CCC and DLG-1/AJM-1 domains appear to form independently of one another [28^{**},30,32], even though they act synergistically in epithelial adhesion [28^{**},34^{**},38^{**}]. On the other hand, intact FOs are needed for the proper patterning and function of actin filaments in the epidermis during embryonic elongation [55^{**},56^{**}], suggesting a potentially important role for IF attachments in regulating the actin cytoskeleton. A second, related question is how epithelial adhesion complexes engage in mechanical cross-talk. For example, epidermal elongation requires SMA-1/ β H-spectrin apical to the adherens junctional domain [49], actin anchorage at the CCC [12], junctional integrity mediated by the DLG-1/AJM-1 complex [30,32,33], and linkages between FOs and the IF cytoskeleton [55^{**},56^{**}]. Using the genetic and molecular tools available in *C. elegans* it should be possible to explore how each of these multiprotein complexes contributes to the completion of complex tasks, including shaping an organism.

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