Sticky worms: adhesion complexes in *C. elegans*

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**Summary**

*Caenorhabditis elegans* is a powerful model system for investigating the establishment, regulation and function of adhesive structures in vivo. *C. elegans* has several adhesion complexes related to those in vertebrates. These include: (1) epithelial apical junctions, which have features of both adherens and tight junctions; (2) dense bodies, which are muscle-attachment structures similar to focal adhesions; (3) fibrous organelles, which resemble hemidesmosomes and mediate mechanical coupling between tissues; and (4) a putative dystrophin-glycoprotein complex that has potential roles in muscle function and embryogenesis. Recent work has increased our understanding of these structures and has given new insights into the functions of their vertebrate counterparts.

**Introduction**

Adhesion complexes play key roles in many events, including cell migration, differentiation, proliferation, apoptosis and growth cone guidance. The underlying strategies used to accomplish cell adhesion are remarkably similar in *Caenorhabditis elegans*, *Drosophila* and humans (Hynes and Zhao, 2000). Therefore, studies in relatively simple organisms such as *C. elegans* have the potential to reveal much about the basic, conserved molecular mechanisms that mediate and regulate cell adhesion.

Several aspects of *C. elegans* make it highly amenable to in vivo studies of cell adhesion. Its small size, simple body plan, optical transparency, invariant cell lineage, fast generation time and genetic manipulability facilitate the analysis of adhesion complexes. Forward genetic screening has identified numerous proteins that are important for cell adhesion in *C. elegans*, including integrins (Williams and Waterston, 1994), a classical cadherin (Costa et al., 1998) and many others. Furthermore, analysis of the *C. elegans* genome has identified numerous putative adhesion receptors, many of which have vertebrate homologs [see Cell Science at a Glance article in this issue, pp. 1867-1870 (Cox et al., 2004)] (Hutter et al., 2000). Several adhesion complexes in *C. elegans* are similar to those in vertebrates, including: epithelial apical junctions, which have traits of adherens and tight junctions; integrin-mediated dense bodies, which orchestrate sarcomere assembly and are similar to focal adhesions; hemidesmosome-like fibrous organelles, which anchor intermediate filaments and mechanically couple tissues; and a putative dystrophin-glycoprotein complex, which may link the extracellular matrix (ECM) and actin cytoskeleton in epithelial cells, neurons and, potentially, muscle. These complexes have been studied predominantly during epithelial and muscle morphogenesis. Cell adhesion also plays an important role in the nervous system of *C. elegans*, particularly in synapse formation (reviewed by Broadie and Richmond, 2002; Jin, 2002) and growth cone guidance (reviewed by Branda and Stern, 1999; Cooper, 2002); however, these topics are beyond the scope of this review.

**C. elegans apical junctions**

Epithelial junctions in *C. elegans* and higher eukaryotes are strikingly similar in composition and function, but have some overall differences in organization (Fig. 1A) (reviewed by Knust and Bossinger, 2002; Müller and Bossinger, 2003). In the epithelia of *C. elegans* (which include the epidermis, pharynx, intestine and vulva), a single, electron-dense region is typically restricted to the apical contact zone between cells (Fig. 1B) (Priess and Hirsh, 1986; Leung et al., 1999). This *C. elegans* apical junction (CeAJ) has several domains with distinct multiprotein complexes (Fig. 1A).

The apical region of CeAJs contains a cadherin-catenin complex that mediates adhesion and anchorage to the actin cytoskeleton. Because of its similarity to adherens junctions of other organisms, we refer to this as the adherens junctional domain. More basal is a domain containing the Discs large (Dlg) homolog, DLG-1, and its binding partner, AJM-1. The DLG-AJM-containing domain regulates adhesion and might also regulate paracellular permeability.

In cells of the intestine and pharynx, a region apical to the adherens junctional domain has a composition that is similar to that of the vertebrate tight junction and the subapical region (SAR) in *Drosophila*. This SAR-like region contains a PAR-3–PAR-6–PKC-3 complex and at least one homolog of Crumbs, a transmembrane protein that regulates cell polarity in *Drosophila* and vertebrates (reviewed by Müller and Bossinger, 2003). Although the PAR-atypical PKC (aPKC) complex regulates cell polarization in the one-cell *C. elegans*...
embryo (reviewed by Ohno, 2001; Etienne-Manneville and Hall, 2003), its functional role in C. elegans epithelia is not known. C. elegans has one Crumbs homolog (crb-1) and a second Crumbs-like gene (crl-1 or eat-20). Loss-of-function studies indicate that neither is essential for epithelial development (Bossinger et al., 2001), although EAT-20 is necessary for proper muscle pumping in the pharynx (Shibata et al., 2000). Thus, the function of the SAR-like region remains unclear. Accordingly, we focus here on describing recent progress in understanding the adherens junctional and DLG-AJM domains.

### Adherens junctional domain

Classic cadherins are calcium-dependent homophilic cell-cell adhesion receptors linked to the actin cytoskeleton through β-catenin, which binds to α-catenin. Cadherins also bind to p120 catenin (p120ctn), which has a complex role in regulating cadherin function (reviewed by Anastasiadis and Reynolds, 2000). C. elegans has a cadherin-catenin complex consisting of the classical cadherin, HMR-1A, HMP-2 (β-catenin), HMP-1 (α-catenin) and JAC-1 (p120ctn) (Fig. 2A) (Costa et al., 1998; Pettitt et al., 2003). These proteins have low overall sequence similarity to their vertebrate homologs, but have conserved functional domains and protein-protein interactions (reviewed by Simske and Hardin, 2001; Pettitt et al., 2003).

The C. elegans HMR-HMP complex was identified through its essential role in morphogenesis of the hypodermis (Costa et al., 1998) (reviewed by Simske and Hardin, 2001), a specialized epidermis that forms the outer layer of the worm. Epidermal cells are born on the dorsal side of the embryo after gastrulation and adhere to form a cell sheet. The free edges migrate to the ventral midline, where they seal through the formation of adhesive junctions in a process called ventral enclosure (Fig. 2B) (Williams-Masson et al., 1997). The formation of junctions is rapid (taking fewer than 15 minutes) and is mediated by contact between actin-rich protrusions (see Movie 1, http://jcs.biologists.org/supplemental/) (Raich et al., 1999). Junction formation in cultured cells occurs more slowly, but is similarly initiated by cell protrusions (reviewed by Vasioukhin and Fuchs, 2001). Circumferential actin filament bundles (CFBs) anchor to CeAJs and their contraction aids the four-fold elongation of the embryo into a worm-like shape (Fig. 2B).

hmr-1-null mutants exhibit a ‘hammerhead’ (Hmr) phenotype (Movie 2, http://jcs.biologists.org/supplemental/), in which epidermal cells fail to enclose the anterior, and cells spill out of this region (Costa et al., 1998). hmp-1-null and hmp-2-null embryos exhibit a more mild ‘humpback’ (Hmp) phenotype (Movie 3, http://jcs.biologists.org/supplemental/), in which embryos enclose but form abnormal bulges when they attempt to elongate (Costa et al., 1998). However, hmp-1-null or hmp-2-null embryos that also lack maternal hmp-1 or hmp-2 exhibit the more severe Hmr phenotype. JAC-1, like the Drosophila p120ctn homolog (Myster et al., 2003), positively modulates cadherin-catenin function in C. elegans but is not essential for development (Pettitt et al., 2003).

The putative four-pass transmembrane protein VAB-9 also localizes to the adherens junctional domain (Simske et al., 2003). VAB-9 has Drosophila and vertebrate homologs (BCMP1) and is distantly related to claudins, which are tetraspan cell adhesion receptors that localize to vertebrate tight junctions (Tsukita et al., 2001; Colegio et al., 2002). vab-9-null mutants are viable but have a ‘variably abnormal’ (Vab) phenotype, characterized by elongation and body-shape defects. VAB-9 requires HMR-1 for its localization and regulates CFB attachment to CeAJs (Simske et al., 2003), although the mechanisms involved are unclear.

Several proteins have emerged as potential regulators of the adherens junctional domain including APR-1, Rho family GTPases and semaphorins. APR-1, a homolog of the APC tumor suppressor, localizes to epidermal cell borders, and mutants exhibit Hmr-like phenotypes in addition to defects in cell fate specification, among others (Hoier et al., 2000). The potential role of APR-1 in regulating the HMR-HMP complex has not been explored. Rho-family GTPases are key regulators of adherens junctions in other systems (reviewed by Van Aelst and Symons, 2002). C. elegans homologs of Cdc42 (CeCDC-
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42) and Rac-1 (CED-10) localize to epidermal cell borders (Chen et al., 1996), and Rho-family GTPases appear to regulate actomyosin contractility during elongation (Wissmann et al., 1997; Wissmann et al., 1999). Beyond this, the role of Rho-family GTPases in CeAJs is not understood. Interestingly, depleting the semaphorin MAB-20/Sema2A causes formation of ectopic epidermal cell contacts during morphogenesis (Roy et al., 2000). Abnormal contacts might be an indirect consequence of increased protrusive activity, although a more direct role for MAB-20/Sema2A causes formation of ectopic epidermal cell contacts during morphogenesis (Roy et al., 2000). Abnormal contacts might be an indirect consequence of increased protrusive activity, although a more direct role for MAB-20/Sema2A causes formation of ectopic epidermal cell contacts during morphogenesis (Roy et al., 2000).

*C. elegans* also has homologs of many proteins that localize to adherens junctions in other organisms, including ATN-1 (α-actinin), DEB-1 (vinculin), PES-7 (IQGAP) and ZO-1 (Y105E8A.26), but their roles at CeAJs are unclear (McMahon et al., 2001) (T. Tuskey, M. Köppen and J.H., unpublished). Several other proteins regulate epidermal cell migration during enclosure, including components of a conserved Arp2/3 complex (Sawa et al., 2003), an N-Wasp homolog (Sawa et al., 2003), GEX-2 and GEX-3 (Soto et al., 2002), and EVL-20/Arl2 (Antoshechkin and Han, 2002); however, a role for these proteins in cell junction formation has not been demonstrated.

**Cadherin-independent mechanisms for mediating cell-cell adhesion**

Since inactivation of cadherins and catenins in mice (Larue et al., 1994; Riethmacher et al., 1995), *Xenopus* (Heasman et al., 1994) and *Drosophila* (Tepass et al., 1996; Uemura et al., 1996) disrupts early embryonic cell adhesion, it is surprising that this is not the case in *C. elegans*. Other putative cadherins in *C. elegans* (Cox et al., 2004; Hill et al., 2001) could act redundantly with HMR-1. However, the only other cadherin characterized to date is the Fat-like cadherin, CDH-3, which regulates morphogenesis of the epidermal cell (hyp10) at the

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**Fig. 2.** The cadherin-catenin complex in *C. elegans*. (A) Diagram of the cadherin-catenin complex in *C. elegans*. This complex consists of HMR-1A (cadherin), HMP-2 (β-catenin), HMP-1 (α-catenin) and JAC-1 (p120ctn). (B) A time course showing localization of the cadherin-catenin complex during epidermal morphogenesis in *C. elegans*. Confocal images of a living embryo expressing a JAC-1–GFP fusion protein. During ventral enclosure (a–b), edges of the epidermal cell sheet extend around the embryo, meet at the ventral midline, and seal through the formation of cell junctions. Note that JAC-1–GFP is not present at the leading edge of migrating epidermal cells, but is rapidly recruited to the contact region between cells at the ventral midline. Other adherens junctional components show a similar localization during enclosure. After ventral enclosure, contraction of the epidermis helps to drive the four-fold elongation of the embryo (c,d). Nomarski images of similarly aged embryos are shown for comparison (e–h). A Nomarski movie (Movie 4, http://jcs.biologists.org/supplemental/) showing development of a wild-type embryo is available online. In all images, anterior is left. Bar, 10 μm.
The strongest *Drosophila* and vertebrate homologs are listed. For the null phenotype, the stage of arrest is indicated and the drawing represents abnormalities in the electron-dense region, as observed by TEM (see text for details).

**DLG-AJM domain**

The DLG-AJM domain lies basal to the adherens junctional domain (Fig. 1) and plays a role in adhesion and, potentially, in paracellular permeability. DLG-1 is a membrane-associated guanylate kinase (MAGUK; Fig. 3) that has homologs in *Drosophila* (Dlg) and vertebrates (hDlg/SAP97). *Drosophila*Dlg regulates formation of adherens and septate junctions (reviewed by Müller and Bossinger, 2003), and is also important for synapse formation (Budnik, 1996) and preventing follicular cell overgrowth during oogenesis (Goode and Perrimon, 1997). Like *Drosophila*Dlg, vertebrate SAP97 localizes to epithelial cell contacts, acts as a tumor suppressor, and aids assembly of synaptic junctions (reviewed by Fujita and Kurachi, 2000). Mice with a partial deletion of SAP97 exhibit cleft palates (Caruana and Bernstein, 2001), highlighting its importance in morphogenesis.

**AJM-1** is a novel coiled-coil protein (Fig. 3) (Köppen et al., 2001). The coiled-coil region is similar to that of the keratin-binding protein trichohyalin (E.A.C. and J.H., unpublished), and its topology is predicted to be similar to that of the vertebrate tight junction proteins cingulin and JEAP (S. Citi, personal communication). DLG-1 is necessary for the proper localization of AJM-1 and physically interacts with AJM-1 in vitro (Bossinger et al., 2001; Firestein and Rongo, 2001; Köppen et al., 2001; McMahon et al., 2001).

Loss of DLG-1 or AJM-1 causes embryonic arrest at the two- to three-fold stage of elongation, which appears to be accompanied by necrotic cell death (C. Lockwood and J.H., unpublished) (Bossinger et al., 2001; Firestein and Rongo, 2001; Köppen et al., 2001; McMahon et al., 2001). Additionally, loss of DLG-1 results in leakage of cytoplasm from the tail and ventral midline during elongation (McMahon et al., 2001) and abnormalities in actin bundles of the pharynx and epidermis (Firestein and Rongo, 2001).

The precise function of the DLG-AJM domain is not known, but transmission electron microscopy (TEM) analysis has provided some insights. In *ajm-1* null mutants, junctions occasionally separate, leaving paracellular gaps of 50-200 nm (Köppen et al., 2001). This is speculated to cause loss of solute gating, leading to osmotic shock (Köppen et al., 2001). By contrast, embryos subject to RNAi directed against *dlg-1* exhibit loss of electron-dense material from CeAJs (Firestein and Rongo, 2001; McMahon et al., 2001), indicating that DLG-1 might act as a scaffold for the formation of this material. Intriguingly, epithelial cell membranes nonetheless remain closely apposed. They may be held together by the HMR-HMP complex, which remains intact in *dlg-1(RNAi)* embryos (Bossinger et al., 2001; McMahon et al., 2001). In light of this, it is interesting that the severity of the adhesion phenotypes induced by loss of DLG-1 or AJM-1 is enhanced by RNAi directed against the adherens junctional component *vab-9* (Simsek et al., 2003). This suggests that the adherens junctional and DLG-AJM domains act together to promote epithelial integrity.

Recent work shows that the claudin-like protein CLC-1 colocalizes with AJM-1 in pharyngeal cell junctions, where it might regulate paracellular permeability (Asano et al., 2003). Determining whether CLC-1 or other claudin-like proteins (CLC-2, CLC-3 and CLC-4) function within the DLG-AJM domain will be an important topic for future study. Although they have not been extensively characterized, *C. elegans* has several homologs of tight and septate junctional proteins (McMahon et al., 2001; Knust and Bossinger, 2002), including Lethal giant larvae (M01A10.2), Band 4.1/Coracle (ZK270.2, C48D5.2A, T04C9.6, H05G16.2), Symplekin (F25G6.2) and Neurexin IV (F20B10.1). Identifying more components of the
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studying their functions.
indicates that importance as core elements of epithelial cell junctions and polarity. The conservation of these proteins indicates their determine its functional role in epithelial cell adhesion and has a PAR-aPKC complex, and it will be important to (Dlg/SAP-97) and LET-413 (Scribble/Erbin).
Recent insights into junctional polarity in C. elegans are derived from studies of the LAP (‘leucine-rich repeat and PDZ’) protein LET-413 (Fig. 3). LET-413 localizes through its leucine-rich repeat region to the basolateral membrane of epithelial cells and partially overlaps the DLG-AJM domain (Legouis et al., 2000; Legouis et al., 2003). Like its homologs in Drosophila (Scribble) (Bilder et al., 2000; Bilder and Perrimon, 2000) and vertebrates (Erbin) (Borg et al., 2000), LET-413 has an important role in regulating junctional organization.

In C. elegans embryos lacking LET-413, the electron-dense material at CeAJs is discontinuous, extended basally, or absent entirely (Legouis et al., 2000; McMahon et al., 2001). What accounts for this phenotype is not entirely clear, but several recent studies offer clues. First, LET-413 prevents basal diffusion of some apical CeAJ proteins, including PAR-3 and PAR-6 (Bosssinger et al., 2001). Second, although LET-413 is not necessary for apical targeting of adherens junctional components (Legouis et al., 2000; McMahon et al., 2001; Simskes et al., 2003), it does act with DLG-1 to exclude them from the basolateral membrane (Simskes et al., 2003). Third, LET-413 is important for promoting proper distribution of DLG-1 and AJM-1 and preventing them from spreading basally (Köppen et al., 2001; McMahon et al., 2001). The molecular mechanisms through which LET-413 accomplishes these functions are unknown. LET-413 could interact with a motor complex (McMahon et al., 2001) or the Rho-family GTPases (Legouis et al., 2000), although direct evidence for either possibility is lacking. Further studies on LET-413 and the identification of other regulators of CeAJ polarity are likely to clarify how epithelial cell polarity is established in vivo.

In summary, despite organizational differences between epithelial junctions in C. elegans, Drosophila and vertebrates, there are several conserved proteins that share some analogous functions (see also Müller and Bossinger, 2003). These include the HMR-HMP (cadherin-catenin) complex, DLG-1 (Dlg/SAP-97) and LET-413 (Scribble/Erbin). C. elegans also has a PAR-aPKC complex, and it will be important to determine its functional role in epithelial cell adhesion and polarity. The conservation of these proteins indicates their importance as core elements of epithelial cell junctions and indicates that C. elegans is an excellent model system for studying their functions.

Dense bodies and M-lines
C. elegans has four longitudinal muscle quadrants that underlie the epidermis (reviewed by Francis and Waterston, 1985). Muscle quadrants are first detectable just after ventral enclosure is complete and sarcomeres are evident at the two-fold stage of elongation (reviewed by Moerman and Fire, 1997). Force transduction in muscle is accomplished through anchorage of actin and myosin filaments to the muscle cell membrane. In C. elegans, mutations that perturb this process cause arrest at the two-fold stage of elongation owing to muscle paralysis (Hresko et al., 1994; Williams and Waterston, 1994; Gettnner et al., 1995). Characterization of ‘paralyzed at two-fold’ (Pat) mutants has shown that integrin attachment structures are essential for sarcomere assembly in C. elegans. Similarly, integrins are also required for the formation of functional muscles in Drosophila and mammals (reviewed by Bokel and Brown, 2002).

C. elegans is a powerful model system for exploring integrin function, in part because it has just two α-integrins (PAT-2 and INA-1) and one β-integrin (PAT-3). In C. elegans, roles for integrins in cell migration (Baum and Garriga, 1997; Lee et al., 2001), neuron fasciculation (Baum and Garriga, 1997), gonadal morphogenesis (Lee et al., 2001) and muscle tissue integrity (see below) have been documented. However, the adhesive structures organized by integrins have been most extensively examined in muscle.

During sarcomere assembly in C. elegans, parallel bundles of actin (thin filaments) and myosin (thick filaments) link to the cell membrane through dense bodies (Z-disc analogs) and M-lines, respectively (Fig. 4A,B). Dense bodies are similar to vertebrate focal adhesions, which are integrin-based complexes that mediate linkage between the ECM and the actin cytoskeleton (Hynes, 1992). In addition to their structural role, focal adhesions also mediate cell signaling (reviewed by Zamir and Geiger, 2001; Hynes, 2002). M-lines are also integrin based and are compositionally similar to dense bodies; however, they are inherently different from focal adhesions since they anchor to myosin rather than actin.

Dense bodies and M-lines are organized by αPAT-2–βPAT-3 integrin heterodimers, which recruit numerous cytoplasmic proteins also present in focal adhesions (Fig. 5A). Like focal adhesions, dense bodies contain DEB-1/vinculin (Barstead and Waterston, 1991), ATN-1/α-actinin (Francis and Waterston, 1985; Barstead et al., 1991), CeTalin (Moulder et al., 1996), UNC-97/PINCH (Hobert et al., 1999), UNC-112/Mig-2 (Rogalski et al., 2000), PAT-4/ILK (Mackinnon et al., 2002) and PAT-6/actopaxin (Lin et al., 2003). M-lines lack actin-binding proteins (DEB-1 and ATN-1), and instead contain a novel immunoglobulin-fold protein, UNC-89 (Benian et al., 1996), that binds to myosin.

Assembly of dense bodies and M-lines
The first step in dense body and M-line assembly is recruitment of integrins to the plasma membrane, where they cluster into bands, one along the longitudinal axis of each body-wall muscle quadrant. Subsequently, these initial attachment sites segregate into a highly ordered pattern of dense bodies and M-lines (Fig. 4B).

UNC-52/perlecan, a secreted heparan sulfate proteoglycan, is the only protein known to be necessary for integrin localization to the basal muscle cell membrane (Rogalski et al., 1993; Hresko et al., 1994; Williams and Waterston, 1994; Mullen et al., 1999). Whether UNC-52 is a ligand for αPAT-2–βPAT-3, or has an indirect role in integrin recruitment, is currently unknown. Recent studies indicate that the laminin αB subunit (one of two laminin α subunits), like UNC-52,
localizes to the extracellular face of dense bodies and M-lines (Huang et al., 2003). However, rather than mediating assembly, laminin αB is necessary for restricting dense body formation to the basal membrane (Huang et al., 2003).

There are at least two distinct protein complexes that are recruited separately to nascent adhesion sites. One complex contains DEB-1/vinculin, which mediates actin filament attachment to dense bodies (Barstead and Waterston, 1991; Hresko et al., 1994). Another complex, containing UNC-112, PAT-4 and PAT-6, acts as a scaffold for the development of nascent attachment sites into dense bodies and M-lines (Rogalski et al., 2000; Mackinnon et al., 2002; Lin et al., 2003). In embryos with null mutations in these genes, UNC-52 localizes normally in the basement membrane, and integrin foci form and become associated with DEB-1, but dense bodies and M-lines do not develop.

UNC-112 has a conserved sequence present in FERM-domain proteins (Rogalski et al., 2000) that might mediate attachment to the plasma membrane (Chishti et al., 1998). Recently, Mig-2, a human homolog of UNC-112, has been shown to localize to integrin-mediated adhesions in tissue culture, where it recruits the filamin-binding protein migfilin (Tu et al., 2003). Loss of Mig-2 or migfilin impairs cell spreading and shape modulation, although cell-substratum contacts still form (Tu et al., 2003). Currently, it is unknown whether Mig-2, like UNC-112, forms a complex with ILK and actopaxin. Conversely, whether or not UNC-112, like Mig-2, provides a link to filamin is not known.

PAT-4 is the only integrin-linked kinase (ILK) homolog in C. elegans (Mackinnon et al., 2002) and participates in recruiting proteins to nascent integrin attachment sites. Surprisingly, transgenically expressed kinase-dead PAT-4 can rescue pat-4-null mutants (Mackinnon et al., 2002) and a similar result has been obtained with the Drosophila ILK homolog (Zervas et al., 2001). This suggests that ILK primarily functions as an adaptor protein rather than a kinase (Zervas and Brown, 2002). Consistent with its role as an adaptor protein in C. elegans is the observation that PAT-4/ILK binds to UNC-
112/Mig-2, UNC-97/PINCH and PAT-6/actopaxin in yeast-two-hybrid assays (Mackinnon et al., 2002; Lin et al., 2003).

PAT-6 is an actopaxin homolog that has an important role in promoting the linkage of actin and myosin filaments to dense bodies and M-lines, respectively (Lin et al., 2003). PAT-6 might directly recruit actin to dense bodies through its two tandem, unconventional calponin-homology domains and appears to recruit myosin to M-lines indirectly through binding UNC-89 (Lin et al., 2003).

Maintaining integrity of dense bodies and M-lines
Although not necessary for the formation of dense bodies and M-lines, UNC-97 is essential for their integrity (Hobert et al., 1999). UNC-97 belongs to the PINCH family of adaptor proteins, which have important roles in integrin-dependent processes in Drosophila and mammalian cells (reviewed by Wu et al., 1999). Notably, mammalian PINCH1 binds ILK, and this interaction is important for cell spreading and motility in tissue culture (Zhang et al., 2002). Similarly, UNC-97 binds PAT-4 in yeast-two-hybrid assays and is recruited to dense bodies and M-lines by PAT-4 (Hobert et al., 1999). UNC-97 also interacts with UNC-98, a C2H2 Zn-finger protein that localizes to M-lines (and possibly dense bodies) and to the nucleus (Mercer et al., 2003). UNC-98 might be involved in maintaining muscle structure, although the underlying mechanisms are not understood.

Other regulators of dense bodies and M-lines
Several other less well-characterized proteins regulate dense bodies and M-lines. The single β-G spectrin in C. elegans, UNC-70, localizes to several sites on the sarcolemmal membrane, including dense bodies and M-lines (Moorthy et al., 2000). Loss of UNC-70 results in progressive muscular dystrophy, which is associated with discontinuous dense bodies and disruption of the myofilament lattice (Moorthy et al., 2000; Hammarlund et al., 2000). Spectrin similarly localizes to Z- and M-lines in vertebrate skeletal muscle (Porter et al., 1992; Zhou et al., 1998). DIM-1 (‘disorganized muscle 1’) is a novel immunoglobulin-domain protein that localizes between and around dense bodies and stabilizes actin filament attachment (Rogalski et al., 2003).

Other integrin-mediated adhesions in C. elegans
Integrin-based adhesions can differ in morphology, composition and function (reviewed by Zamir and Geiger, 2001) (Wehrle-Haller and Imhof, 2002). Some, such as focal adhesions and dense bodies, are relatively large structures that mediate stable attachment to the ECM. By contrast, the smaller focal complexes at the leading edge of migrating cells and growth cones are rapidly turned over, permitting dynamic changes in adhesion. In addition to their role in muscle, C. elegans integrins also play a role in the formation of dynamic contacts in motile cells. For instance, migration of the distal tip cells, which directs morphogenesis of the gonad arms, is integrin dependent (Lee et al., 2001) and has recently been shown to involve CeTalin (Cram et al., 2003). Additionally, αDNA-1/βPAT-3 regulates neuronal cell migration and fasciculation (Baum and Garriga, 1997) and acts at least in part through the Nck-interacting kinase (NIK) homolog MIG-15 (Poinat et al., 2002).

There is evidence that phosphorylation of βPAT-3 is important for its function in motile cells. Integrin β tails have one or two NPXY motifs that can be tyrosine phosphorylated, which thereby modulates integrin function (reviewed by Calderwood, 2004). Interestingly, the muscle defects of pat-3-null mutants can be rescued by a pat-3 transgene that has tyrosine-to-phenylalanine mutations in its two NPXY motifs (Lee et al., 2001). However, these embryos have defects in distal tip cell migration. Further studies on the structure, regulation and signaling of integrin-mediated adhesions during developmental events in C. elegans are likely to increase our understanding of dynamic requirements for integrins in vivo.

Fibrous organelles
Muscle cells in C. elegans are mechanically linked to the cuticle through trans-epidermal attachment structures called fibrous organelles (FOs). FOs comprise an epidermal intermediate filament (IF) array that is anchored basally to the underlying basement membrane and associated muscle and apically to the cuticle (Fig. 4A). FOs are restricted to epidermal regions that overlie body wall muscles, and their formation occurs concurrently with development of muscle sarcomeres (Francis and Waterston, 1991; Hresko et al., 1994; Hresko et al., 1999). In adults, FOs form circumferential bands of 0.4 μm periodicity composed of individual attachment spots (Bercher et al., 2001) that are in register with the spacing of cuticular ridges called annuli (Fig. 4C). By contrast, there is not a strict correlation between the location of FOs and dense bodies or M-lines (Francis and Waterston, 1991). FOs also form in other areas where force is transduced to or through the epidermis, including regions of epidermal contact with intestinal, anal and vulval muscles, and mechanosensory neurons (White, 1988; Francis and Waterston, 1991).

FOs are structurally similar to vertebrate type I hemidesmosomes (Fig. 5B) (reviewed by Hahn and Labouesse, 2001), in which transmembrane receptors form a link between cytoplasmic IFs and the basement membrane (reviewed by Nievers et al., 1999). Disruption of hemidesmosomal components causes separation of the epidermis from the basal lamina, resulting in various skin-blistering diseases (Jones et al., 1998; Nievers et al., 1999). Similarly, FOs confer structural integrity to the epidermis through anchoring IFs. In vertebrate hemidesmosomes, αβ4 integrin and BPAG2 provide anchorage to the basement membrane, and plectin and BPAG1 bind IFs (reviewed by Jones et al., 1998; Nievers et al., 1999). The only conserved protein present in FOs is the plectin homolog VAB-10A (Bosher et al., 2003). FOs do not contain integrins or a BPAG2 homolog, but have other transmembrane proteins (myotactin, MUA-3 and MUP-4) that might function analogously.

Composition and assembly of FOs
The apical and basal attachment plaques of FOs have some similarities and differences in composition (Fig. 5B). VAB-10A/plectin and VAB-19/Kank appear to be present in both apical and basal attachment plaques. Apical attachments
contain the transmembrane receptors MUA-3 and MUP-4, whereas basal attachments contain myotactin. This probably reflects the need to have apical receptors specific for the collagen-rich cuticle and basal receptors specific for the basement membrane and/or muscle cell surface.

In regions of muscle contact with the epidermis, underlying
Fig. 5. Comparison of adhesion complexes in vertebrates and C. elegans. (A) A vertebrate focal adhesion and C. elegans dense body. Only conserved proteins are shown. Focal adhesions contain numerous adaptor and signaling proteins not shown here (refer to Zamir and Geiger, 2001). A few downstream effectors are indicated by the dashed arrows. (B) A vertebrate hemidesmosome and C. elegans fibrous organelles. (For more on hemidesmosome composition, see Nievers et al., 1999; Roper et al., 2002.) Like hemidesmosomes, fibrous organelles anchor IFs through a plectin-family member (VAB-10A). The transmembrane proteins MUA-3 and MUP-4 are located apically and myotactin is located basally. VAB-19 may be located both basally and apically. The protein-protein interactions shown for fibrous organelles are speculative, since it is currently unclear whether myotactin, MUA-3 or MUP-4 interacts directly with VAB-10A or IFs. (C) The dystrophin-glycoprotein complex (DGC) in vertebrates and C. elegans. Other proteins are known to associate with the mammalian DGC (reviewed by Ehmsen et al., 2002), but have not been shown for simplicity. C. elegans does not have any clear sarcospan or nNOS homologs (Segalat, 2002). Currently, it is unclear whether the putative C. elegans DGC is present in epidermal, muscle, and/or neuronal tissues (see text for details).

Muscle initiates FO formation (Hresko et al., 1999); however, the nature of this cue is not well understood. Candidates include collagen IV (comprising EMB-9/α1 and LET-2/α2 subunits) and laminin αβ. All are produced by myoblasts, and embryos lacking these proteins exhibit phenotypes consistent with perturbed FOs, including muscle separation from the epidermis (Gupta et al., 1997; Graham et al., 1997; Huang et al., 2003). Note that, in regions of contact with non-muscle tissues, the novel ECM protein hemicentin (HIM-4) is required for FO assembly (Vogel and Hedgecock, 2001), although the mechanisms involved are not understood.

Maintaining integrity of FOs
Several proteins are important for FO maintenance, including VAB-10A, VAB-10B, VAB-19 and the transmembrane proteins MUA-3, MUP-4 and myotactin. vab-10 produces two isoforms with distinct functions (Bosher et al., 2003). As mentioned above, VAB-10A is similar to plectins, whereas VAB-10B is similar to plaksins, which are actin-microtubule crosslinking proteins. VAB-10A localizes to FOs and VAB-10B localizes to bands between FOs (Bosher et al., 2003). Loss of either VAB-10 isoform results in epidermal detachment from the cuticle and muscle and perturbation of IFs and CFBs. VAB-10A mutants exhibit a Pat phenotype, whereas VAB-10B mutants typically die in the first larval stage and have elongation and body-shape defects. In VAB-10A mutants, the number of FOs is greatly reduced, indicating a potential role in FO assembly. By analogy to vertebrate plectins, VAB-10A might mediate the link between transmembrane receptors and IFs. VAB-10B appears to regulate the thickness of the epidermis and could provide resistance against tension, although the mechanisms involved remain unclear (Bosher et al., 2003).

MUA-3 and MUP-4 are single-span transmembrane proteins that maintain adhesion between the epidermis and cuticle (Plenefisch et al., 2000; Bercher et al., 2001; Hong et al., 2001). mua-3 was identified in a screen for fragile muscle-attachment (Mua) mutants (Plenefisch et al., 2000), and mup-4 was identified on the basis of a muscle-position-defective (Mup) phenotype (Gatewood and Bucher, 1997). In mua-3 mutants, FOs form normally but the epidermis detaches from the cuticle post-embryonically (Bercher et al., 2001). mup-4-null animals exhibit a similar phenotype, but detachment occurs earlier, typically at the three-fold stage of elongation (Hong et al., 2001). MUA-3 and MUP-4 share structural similarities but do not have any clear non-nematode homologs (reviewed by Cox et al., 2004; Hahn and Labouesse, 2001). Their extracellular domains contain a von Willebrand factor type A domain, which mediates collagen binding in other proteins (Colombatti and Balduoni, 1991), whereas their cytoplasmic domains have some sequence similarity to filaggrins, which are IF-binding proteins (reviewed by Hahn and Labouesse, 2001).

Myotactin (LET-805) is a novel transmembrane protein required for adhesion between the epidermis and muscle (Hresko et al., 1999). The longest splice form encodes a single-span transmembrane protein with at least 32 fibronectin type III (FNIII) repeats in the extracellular domain and a novel cytoplasmic domain. VAB-19, an ankrin repeat protein with sequence similarity to the human tumor suppressor Kank, is also required for attachment between muscle and the epidermis (Ding et al., 2003). Recruitment of VAB-19 to FOs requires VAB-10A; however, myotactin and VAB-19 require each other for their proper final localization. In myotactin and VAB-19 mutants, IFs maintain their annular arrangement but are not restricted to the area mirroring muscle/epidermal cell contact (Hresko et al., 1999; Ding et al., 2003). Apparently as a result, shortly after muscle contraction begins, muscle detaches from the epidermis.

Interestingly, the mutant phenotype of animals lacking VAB-19, but not that of other FO components, can be suppressed by mutations in the actin-binding protein sma-1/β-H spectrin (Ding et al., 2003). This suggests, along with previous studies on VAB-10 (see above) (Bosher et al., 2003), that cross-talk between FOs and actin is essential for proper cytoskeletal patterning in the epidermis. Continued studies on FOs are likely to yield important insights into how IFs and their attachment structures regulate cytoskeletal architecture and provide mechanical stability to tissues.

Putative dystrophin-glycoprotein complex
In vertebrates, the dystrophin-glycoprotein complex (DGC) confers stability to the muscle cell membrane during cycles of muscle contraction (Campbell, 1995). It is centered around dystroglycan (Fig. 5C) (reviewed by Ehmsen et al., 2002), a transmembrane receptor that binds various ligands, including the ECM components laminin, perlecan and agrin. Dystroglycan associates with a membrane-embedded sarcoglycan complex, and forms a link to the actin cytoskeleton through binding dystrophin. In addition to actin, dystrophin binds dystrobrevin and syntrophins, which interact with nitric oxide synthase (nNOS). Mutations in DGC components and in proteins that affect the ligand-binding activity of dystroglycan are found in various forms of muscular dystrophy (reviewed by Cohn and Campbell, 2000) (Michele and Campbell, 2003).

C. elegans has many conserved DGC components (Fig. 5C), including homologs of dystroglycan (dgn-1 and F56C3.6), dystrophin (dyh-1), dystrobrevin (dyb-1), α-sarcoglycan (H22K11.4), β-sarcoglycan (K01A2.1), δ/γ-sarcoglycan
significant muscle degeneration. However, in ten-day-old assembles a DGC analogously to vertebrates and, if so, where Durbeej et al., 1998; Hemler, 1999). Whether or not Kramer, personal communication). Similarly, dystroglycan is appear to be expressed in muscle, but are expressed in epithelial and neuronal tissues (R. Johnson and J. Kramer, personal communication). Consistent with this localization is the observation that embryos lacking either gene exhibit various epithelial and neural defects (R. Johnson and J. Kramer, personal communication). Similarly, dystroglycan is present in many non-muscle tissues in mammals (reviewed by Durbeej et al., 1998; Hemler, 1999). Whether or not C. elegans assemblies a DGC analogously to vertebrates and, if so, where it is present, remain unclear.

In C. elegans, loss of DYS-1/dystrophin does not cause significant muscle degeneration. However, in ten-day-old dys-1-null animals, a small percentage (<1%) of body-wall muscle cells show an abnormal striation pattern, which may indicate the beginning of degeneration (Bessou et al., 1998). Loss of DYS-1 also results in movement defects consistent with increased muscle excitability (Bessou et al., 1998), and RNAi directed against dgn-1, δ7-sarcoglycan (F07H5.2) and syntrophin (F30A10.8) in adult worms causes a similar phenotype (Grisoni et al., 2002). Discerning the composition of dystroglycan-mediated adhesion complexes in the muscle and non-muscle tissues of C. elegans, and learning more about their precise functions, should yield important insights into the role of the DGC in development and disease.

Conclusion

Despite its small size and relative simplicity, C. elegans employs many of the same strategies for accomplishing cell adhesion as higher organisms. Most work to date has centered on defining the composition and basic roles of these structures, particularly during development. Despite this progress, there is still much to learn about how adhesion complexes in C. elegans accomplish their functions. In particular, their roles in mediating cell signaling have been largely unexamined. Since adherens junctions, focal adhesions, hemidesmosomes and the DGC all regulate cell signaling in tissue culture (reviewed by Nievers et al., 1999; Zamir and Geiger, 2001; Rando, 2001; Braga et al., 2002), it will be important to determine whether and how the analogs of these structures in C. elegans mediate signaling and how this affects in vivo events.

In the future, C. elegans might be a useful system for analyzing cross-talk between adhesion complexes. Adhesion receptor cross-talk occurs during convergent extension in Xenopus (Marsden and DeSimone, 2003) and is likely also to be important in many other in vivo events. Elongation of the C. elegans embryo, which involves the coordinated activity of adherens junctions, FOs and dense bodies, might be a useful context for studying how biochemical and physical cross-talk between adhesion receptors contributes to complex cellular events.

Additionally, C. elegans might be useful in the study of diseases involving aberrant cell adhesion, including tumor metastasis, chronic inflammatory disorders, tissue fragility disorders, muscular dystrophy, and many others. In this regard, C. elegans is beginning to be used as a model for dystrophin-mediated myopathy (reviewed by Chamberlain and Benian, 2000; Culetto and Satelle, 2000). Thus, future studies on ‘sticky worms’ have the potential to advance our understanding of the basic mechanisms underlying cell adhesion and might also give insights as to how their dysregulation contributes to disease.

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