
Epithelial junctions and attachments*

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Abstract

A distinctive feature of polarized epithelial cells is their specialized junctions, which contribute to cell integrity and provide platforms to orchestrate cell shape changes. The chapter discusses the composition and assembly of *C. elegans* cell-cell and cell-extracellular matrix junctions, proteins that anchor the cytoskeleton

*Edited by James M. Kramer and Donald G. Moerman. Last revised January 29, 2005. Published January 13, 2006. This chapter should be cited as: Labouesse, M. Epithelial junctions and attachments (January 13, 2006), WormBook, ed. The *C. elegans* Research Community, WormBook, doi/10.1895/wormbook.1.56.1, <http://www.wormbook.org>.

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and mechanisms involved in establishing epithelial polarity. The focus remains cellular and does not properly deal with epithelial cells in the context of the developing embryo.

1. Introduction

The interest in epithelial junctions and their associated cytoskeletal elements is recent. Essentially none of the genes mentioned in this chapter were known, let alone discussed, when *C. elegans* II was released. This chapter introduces the main players, and addresses cell adhesion, cytoskeletal anchoring, epithelial polarity and fibrous organelle assembly with a focus on cellular function. For developmental aspects or for a more comprehensive coverage of cell adhesion, the reader should consult the chapter on Epidermal morphogenesis and reviews (Cox et al., 2004; Ding et al., 2004).

2. Approaches to identify junctional and cytoskeletal components

The first reagents used to visualize junctional/cytoskeletal components were obtained approximately 20 years ago when Francis and Waterston prepared monoclonal antibodies (mAbs) against insoluble membrane-associated embryonic extracts (Francis and Waterston, 1985; Francis and Waterston, 1991). Some of these mAbs turned out to recognize junctional components (LET-805/myotactin, AJM-1, VAB-10, recognized by MH46, MH27 and MH5 mAbs, respectively) or intermediate filaments (IFs; MH4 and MH33 mAbs), and proved in some cases useful for cloning by means of phage display.

Since then, genes encoding junctional or cytoskeletal components have been identified in screens for larval defects (*sma-1*, *mua-3*, *mua-6*, *vab-10*), elongation defects causing embryonic lethality (*hmr-1*, *hmp-1*, *hmp-2*, *spc-1*, *zen-4*, *mup-4*, *pat-* genes), or variably penetrant sub-lethal body morphology defects (*vab-10*, *ifb-1*, *vab-19*). Chromosomal deficiencies have also been used to scan the genome for regions containing loci potentially required for embryonic morphogenesis (*let-413*, *vab-10*). With some exceptions (*let-805*/myotactin, *ajm-1*), all genes identified through these screens turned out to encode proteins with clear homologues in vertebrates and insects (see Table 1, Figure 2).

Several junction and cytoskeleton components have also been identified in diverse RNAi screens, a number that should increase. Table 1 is a list of junctional/cytoskeletal proteins, that is unlikely to be complete. A promising source for additional adhesion proteins will be to mine the *C. elegans* genome (Hutter et al., 2000).

Table 1. Genes are grouped (different shadings) according to their subcellular localization and/or function (see also Figure 2).

Gene	Homology or (domains)	Expression pattern	Subcellular localization	Phenotype	Identification method	Reference
<i>act-5</i>	Actin	Int.	Apical	Larval let; gut lumen def.	RNAi	Gobel et al., 2004
<i>erm-1</i>	Ezrin-radixin-moesin (FERM domain)	Most epithelia	Apical	Larval let; gut constriction	RNAi	Gobel et al., 2004; Van Furden et al., 2004
<i>eps-8</i>	EPS8 (PTB, SH3)	Int. (also many other cells)	Tip of int. microvilli, PM in embryos	Emb; larval let; ab. Int.brush border	Homol. + del	Croce et al., 2004
<i>sma-1</i>	β_H -spectrin	Ep., int., P., E.c.	Apical	Elongation def.	Larval def.	McKeown et al., 1998; Norman and Moerman, 2002
<i>spc-1</i>	α -spectrin	Ubiq.	Apical, basolateral	Emb; elongation def.	Emb	Moorthy et al., 2000; Norman and Moerman, 2002
<i>unc-70</i>	β_G -spectrin	Ubiq.	Basolateral	Larval let	Larval def.	Hammarlund et al., 2000; Moorthy et al., 2000

Gene	Homology or (domains)	Expression pattern	Subcellular localization	Phenotype	Identification method	Reference
<i>nfm-1</i>	Merlin (FERM domain)	Int.	Basolateral	Unknown	RNAi	Gobel et al., 2004
<i>hmr-1</i>	E-cadherin	Ep., int., P.	CeAJ	Emb; ventral enclosure def.	Emb	Costa et al., 1998; Raich et al., 1999
<i>hmp-1</i>	α -catenin	Ep., int., P.	CeAJ	Emb; elongation def.	Emb	Costa et al., 1998; Pettitt et al., 2003; Raich et al., 1999
<i>hmp-2</i>	β -catenin	Ep., int., P.	CeAJ	Emb; elongation def.	Emb	Costa et al., 1998; Raich et al., 1999
<i>jac-1</i>	P120-catenin	Ep., int., P.	CeAJ	None alone	RNAi	Pettitt et al., 2003
<i>vab-9</i>	BCMP1 claudin	Ep., int., P.	CeAJ	Elongation def.	Larval def.	Simske et al., 2003
<i>apr-1</i>	APC	Ep., int., P.	CeAJ	Emb; ventral enclosure def.	m.b.	Hoier et al., 2000
<i>dlg-1</i>	Discs Large (PDZ, SH3, GuK)	All epithelia	CeAJ	Emb; elongation def.	RNAi	Bossinger et al., 2001; Firestein and Rongo, 2001; Koppen et al., 2001; McMahon et al., 2001; Segbert et al., 2004
<i>ajm-1</i>	Novel (coiled coil)	All epithelia	CeAJ	Emb; elongation def.	mAb + e.s.	Bossinger et al., 2001; Koppen et al., 2001; Priess and Hirsh, 1986
<i>clc-1</i>	Classical claudin	P.	CeAJ	Permeability def.	RNAi	Asano et al., 2003
<i>lad-1/ sax-7</i>	L1CAM (FN3 + Ig rep)	All epithelia	CeAJ	Partial Emb; elongation def.	Larval screen; Homol. + del	Chen et al., 2001; Sasakura et al., 2005; Wang et al., 2005
<i>let-413</i>	Scribble (LRR, PDZ)	Ubiq. up 350-c, all epithelia	Basolateral	Emb; elongation def.	Df screen	Bossinger et al., 2004; Legouis et al., 2000; Legouis et al., 2003
<i>par-3</i>	PAR-3 (PDZ)	Early embryo; int., spermT.	Apical	Emb; gastrulation def.; Ste	RNAi	Aono et al., 2004; Nance et al., 2003; Nance and Priess, 2002
<i>par-6</i>	PAR-6 (PDZ)	Early embryo; int.	Apical	Emb; gastrulation def.	RNAi	Nance et al., 2003; Nance and Priess, 2002
<i>crb-1</i>	Crumbs	Int.	Apical	None alone	RNAi	Bossinger et al., 2001; Segbert et al., 2004
<i>zen-4</i>	MKLP1 kinesin	Unknown in epithelia	Unknown	Emb; no buccal cavity	Emb	Mishima et al., 2002; Portereiko et al., 2004; Raich et al., 1998
<i>cyk-4</i>	RhoGAP (PH,	Unknown in	Unknown	Emb; no	Emb	Jantsch- Plunger et

Gene	Homology or (domains)	Expression pattern	Subcellular localization	Phenotype	Identification method	Reference
	GAP)	epithelia		buccal cavity		al., 2000; Mishima et al., 2002; Portereiko et al., 2004
<i>ifa-1</i>	IF	R., V. Ut., E.c., P., P-I. v.	FO	Larval let	Bioch.; RNAi	Dodemont et al., 1994; Karabinos et al., 2001; Karabinos et al., 2003
<i>mua-6/ifa-2</i>	IF	Ep., R., V. Ut.,	FO	Muscle detach.	Larval def.	Dodemont et al., 1994; Hapiak et al., 2003; Karabinos et al., 2001; Karabinos et al., 2003
<i>ifa-3</i>	IF	Ep., R., P-I. v.	FO	Emb; muscle detach	Bioch.; RNAi	Dodemont et al., 1994; Karabinos et al., 2001; Karabinos et al., 2003; Woo et al., 2004
<i>ifb-1</i>	IF	Ep., R., V. Ut., P., P-I. v.	FO	Emb; muscle detach	Vab / RNAi	Dodemont et al., 1994; Karabinos et al., 2001; Karabinos et al., 2003; Woo et al., 2004
<i>ifc-1</i>	IF	Ep., R., P., int.	FO in ep.?, CeAJ in P., apical in int.	Partial lethality	mAb + e.s.	Karabinos et al., 2001; Karabinos et al., 2003; Karabinos et al., 2004
<i>ifc-2</i>	IF	P., int.	Cytoplasmic + CeAJ	Weak lethality in adults	mAb + e.s.	Karabinos et al., 2002; Karabinos et al., 2004
<i>ifb-2, ifd-1, ifd-2, ife-1</i>	IF	Int.	Apical	None alone/ partial larval let in triple knock-down	mAb + e.s.	Bossinger et al., 2004; Dodemont et al., 1994; Karabinos et al., 2001; Karabinos et al., 2003; Karabinos et al., 2004
<i>let-805</i>	Novel (FN3 repeats + TM)	Hyp syncytia, P cells, P.	FO	Emb; muscle detach	mAb + e.s.	Hresko et al., 1999
<i>mup-4</i>	Matrilin-like (VWA+EGF rep.; TM)	Hyp syncytia, P cells, P.	FO	Emb; muscle detach	Emb	Gatewood and Bucher, 1997; Hong et al., 2001
<i>mua-3</i>	Matrilin-like (LDL+ VWA+ EGF rep.; TM)	Hyp syncytia, P cells, P.	FO	Muscle detach	Larval def.	Bercher et al., 2001; Plenefisch et al., 2000
<i>vab-19</i>	Kank (ANK rep.)	Hyp syncytia, P cells, P.	FO	Emb; muscle detach	Vab screen	Ding et al., 2003
<i>vab-10A</i>	Plakin (CH rep.; SPEC, PLEC rep.)	Hyp syncytia, P cells, P.	FO	Emb; muscle detach	Df & larval screens	Bosher et al., 2003; Plenefisch et al., 2000
<i>vab-10B</i>	Plakin (CH	Hyp syncytia,	Between FO in	Emb; ep.	Df & larval	Bosher et al., 2003

Gene	Homology or (domains)	Expression pattern	Subcellular localization	Phenotype	Identification method	Reference
	rep.; SPEC rep.; GAR	P cells, P., R., int., muscles, NS	ep. apical in gut	thickening	screens	
<i>mel-11</i>	MBP (ANK rep.)	Epidermis	CeAJ	Ste; enclosure def.	Suppressor	Piekny et al., 2003; Wissmann et al., 1999; Wissmann et al., 1997
<i>ptp-3</i>	Protein phosphatase (TM)	Epidermis	CeAJ	Body morphology def.	Homol. + del	Harrington et al., 2002
<i>cdc-42</i>	Cdc42 GTPase	Epidermis.	CeAJ	Unknown	Homol.	Chen et al., 1996; Chen et al., 1993; Chen et al., 1993
<i>ced-10/rac-1</i>	Rac GTPase	Epidermis	CeAJ	Ced; Mig; Emb	Larval screen	Chen et al., 1993; Ellis et al., 1991; Reddien and Horvitz, 2000; Soto et al., 2002
<i>pak-1</i>	P21-activated kinase	Epidermis	CeAJ	Unknown	Homol.	Chen et al., 1996

Abbreviations: ab., abnormal; ANK rep., ankyrin repeat; APC, Adenomatosis Polyposis Carcinoma; bind., binding; Bioch., biochemical approach; CeAJ, *C. elegans* Apical Junction; Ced, Cell Death abnormal; CH, calponin homology domain; def., defect; del, deletion screen; detach., detachment; Df, deficiency; E.c., excretory cell; EGF rep., repeats found in the Epidermal Growth Factor; Emb, embryonic lethal; ep., epidermis; e.s., epitope screening; FERM, domain found in Band 4.1, ezrin, radixin, moesin proteins; FN3 rep., fibronectin type III repeats; GAR, growth arrest protein-2 related repeat; Homol., homology; IF, intermediate filament; Ig rep., immunoglobulin superfamily repeat; int., intestine; LDL rep., Low Density Lipoprotein receptor A repeats; let, lethal; LRR, Leucine-Rich repeat; mAb, monoclonal antibody; Mb, membrane; m.b., molecular biology; Mig, migration defective; P., pharynx; PDZ, PSD-95/Disc Large/ZO-1 homology domain; PH, pleckstrin homology domain; P-I. v., pharynx-intestinal valve; PLEC rep., plectin repeat; PM, plasma membrane; PTB, phosphotyrosine-binding domain; R, rectum; rep., repeats; RNAi, RNA interference; SH3, src homology domain type 3; SPEC rep., spectrin repeat; spermT., spermatheca; TM, transmembrane domain;; ut. Uterus; Vab, variably abnormal; V., vulva; VWA, von Willebrand Factor A repeats.

3. Epithelial cytoskeleton

All three cytoskeletal networks can be found in *C. elegans*, in contrast to *Drosophila* which lacks intermediate filaments (IFs; Figure 1A). Except for IFs (see below), the expression and potential functions of individual cytoskeletal proteins in epithelia have not yet been fully characterized.

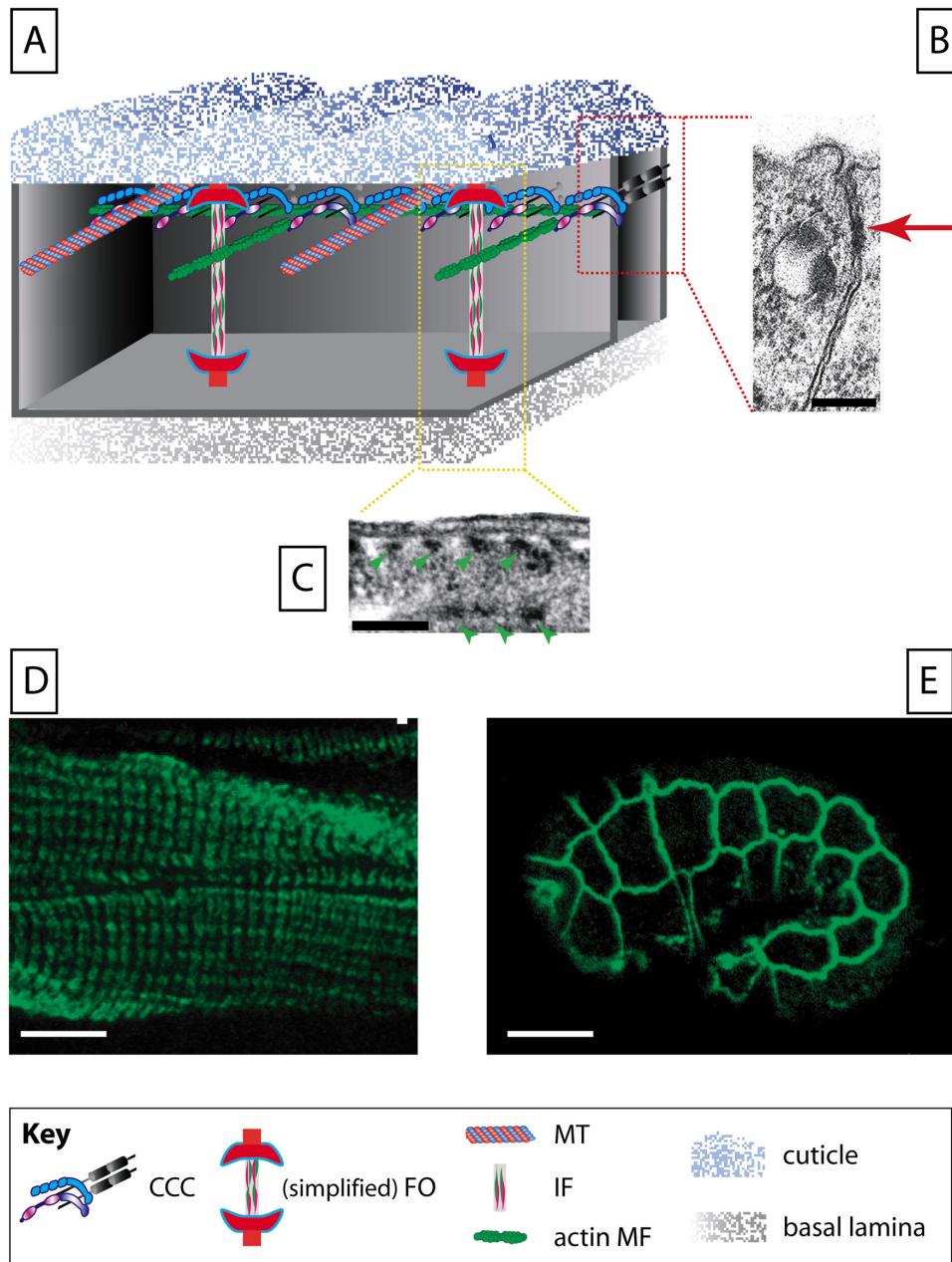


Figure 1. A schematic view of a non-seam epidermal cell. (A) All epidermal cells contain actin microfilaments and microtubules, but only dorsal and ventral epidermal cells contain intermediate filaments. In addition to cortical actin MFs, there are circumferential MF bundles, which are intermingled with MTs, and at least in embryos are less apical than MTs. It is unclear whether IFs are closer to MTs or to MFs. The cell-cell adhesion complex known as the CeAJ (*C. elegans* apical junction) has been simplified for clarity, leaving only the cadherin-catenin complex (CCC; for further details, see Fig. 3A). There are more CeAJs than actin MF bundles. Dorsal and ventral cells establish fibrous organelles (FOs), which are junctions with the extracellular matrix that mechanically couple muscles to the cuticle. For the sake of clarity, several FO components were not drawn. (B) Transmission electron micrograph of the adhesion complex between two adjacent epidermal cells in embryos (picture, courtesy of Dr. Renaud Legouis). Note that a single electron dense area can be observed (red arrow). (C) Transmission electron micrograph of FOs in the dorsal epidermis of embryos (green arrowheads, electron dense plaques). (D) Adult stained with the MH5 mAb showing the VAB-10A pattern in adults (a FO component). (E) Mid-staged embryo stained with the MH27 mAb showing the AJM-1 pattern (a CeAJ component) in the epidermis. Scale bars, 100 nm (B), 1 μ m (C), 10 μ m (D, E).

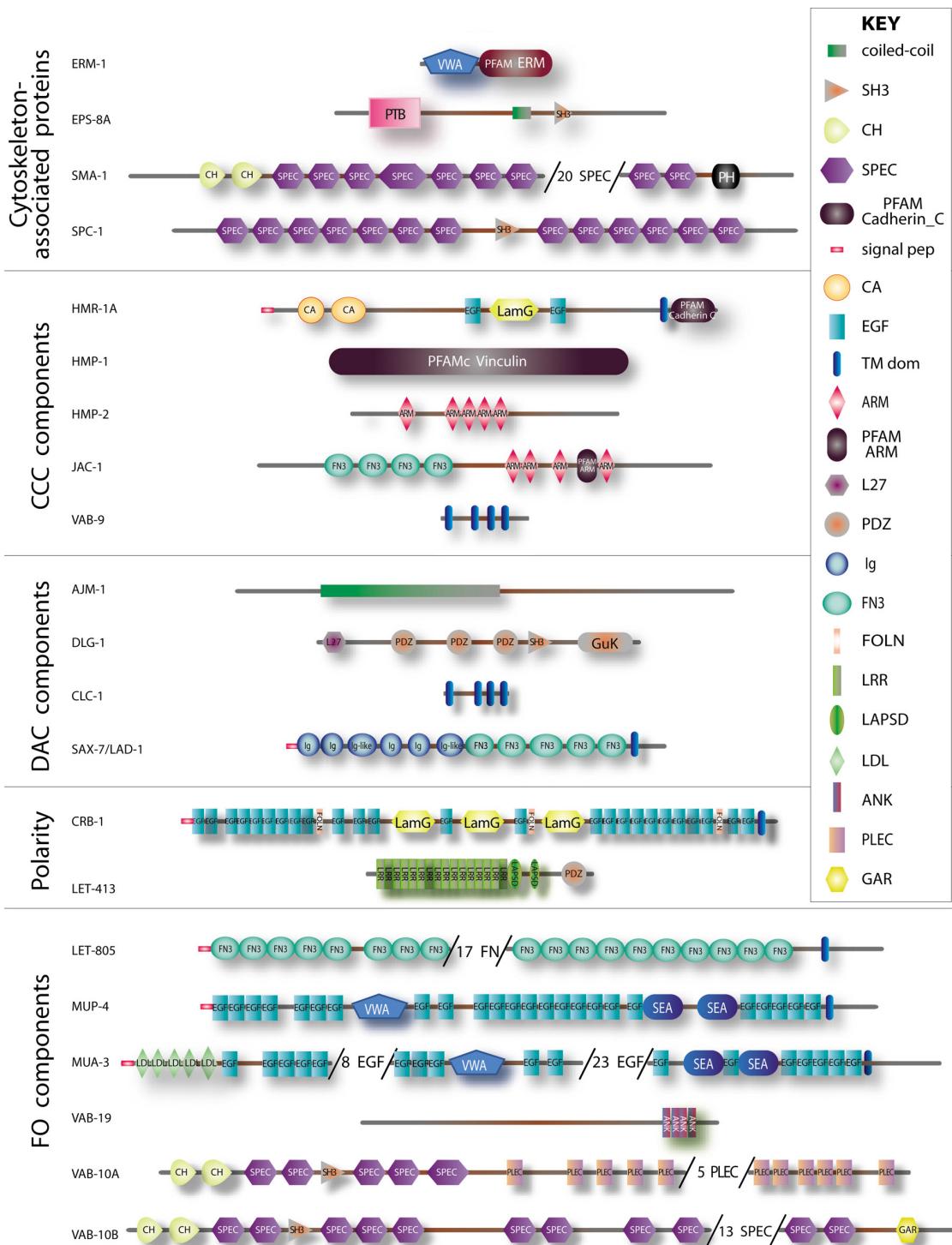


Figure 2. Structure of some epithelial junctional and cytoskeletal proteins. Schematic representation of the main epithelial-specific proteins that are further discussed in the text based on predictions made by the SMART software (smart.embl-heidelberg.org) for the longest existing isoform (for PAR-3 and PAR-6 see [Asymmetric cell division and axis formation in the embryo](#)). To fit proteins on a single page, some repeats were omitted in very large proteins (numbers in parentheses). Proteins are grouped as in [Table I](#) according to their membrane domain or presumptive function. The key for domains is shown on the left, except for those big enough to use larger fonts, and refer to SMART or PFAM domains (see [Table I](#)). Other symbols: ARM, armadillo repeat; CA, cadherin repeat; CCC, Cadherin/Catenin Complex; DAC, DLG-1/AJM-1 Complex; FO, Fibrous organelle; FOLN, Follistatin-N-terminal-like domain; LamG, laminin G domain; LAPSD, LRR and PDZ associated specific domain; L27, LIN-2 and LIN-7 domain; signal pep, signal peptide; TM dom, transmembrane domain.

3.1. Actin

C. elegans has five closely related actins (ACT-1-5). In the epidermis, actin is found at the cell cortex, and, starting at the 1.5-fold stage, in circumferential bundles located under the furrows of the embryonic sheath, a structure thought to maintain the shape of the embryo during elongation (Costa et al., 1997; Priess and Hirsh, 1986). The specific molecular composition, organization and polarity of these bundles have not been established. In the intestine, actin microfilaments are enriched at the lumen (Gobel et al., 2004; Van Furden et al., 2004).

3.2. Microtubules

There are nine α -tubulins (TBA-1-9) and six β -tubulins (TBB-1-6) in the *C. elegans* genome. Microtubules are oriented circumferentially in dorsal (hyp7) and ventral (P cells) epidermal cells, where they might be intermingled with actin microfilament bundles, but are less well-organized in lateral seam cells (Costa et al., 1997; Priess and Hirsh, 1986). In the intestine, microtubules are enriched at the prospective lumen (Leung et al., 1999). How the microtubule cytoskeleton is anchored to the plasma membrane is not known.

3.3. Intermediate filaments

Among the eleven individual IFs (IFA-1-4, IFB-1-2, IFC-1-2, IFD-1-2, IFE-1), three (IFB-1, MUA-6/IFA-2 and IFA-3) are expressed in the epidermis, where they form short filaments between the apical and basal membranes located circumferentially at the interface between body wall muscles and the cuticle (Bartnik et al., 1986; Francis and Waterston, 1985; Francis and Waterston, 1991). *In vitro* polymerization suggests that IFB-1 forms obligate heteropolymers with IFA-2 and IFA-3, reminiscent of the vertebrate keratin system (Karabinos et al., 2003). Expression studies and genetic analysis further suggest that IFB-1/IFA-3 is the major heteropolymer in the embryonic epidermis, while IFB-1/MUA-6 is critical in the larval epidermis (Hapiak et al., 2003; Karabinos et al., 2003; Woo et al., 2004), with a possible minor contribution from IFC-1 (Karabinos et al., 2004). In the pharynx, IFA-1 forms heteropolymers with IFB-1 and is essential for feeding, while in the intestine three out of the four intestinal IFs must be removed to affect feeding and survival (Bossinger et al., 2004; Karabinos et al., 2001; Karabinos et al., 2003; Karabinos et al., 2004).

4. Apical junction components

Despite apparent differences, *C. elegans* epithelial cells look very similar to their vertebrate and fly counterparts. Although transmission electron microscopy identifies a single electron-dense junction in *C. elegans* (Figure 1B, 1E), whereas flies and vertebrates possess two junctional complexes, recent cellular and genetic analyses establish that worm epithelial cells do contain two molecularly and functionally distinct junctional complexes. These two complexes together are commonly referred to as the CeAJ (*C. elegans* Apical Junction; Figure 3A).

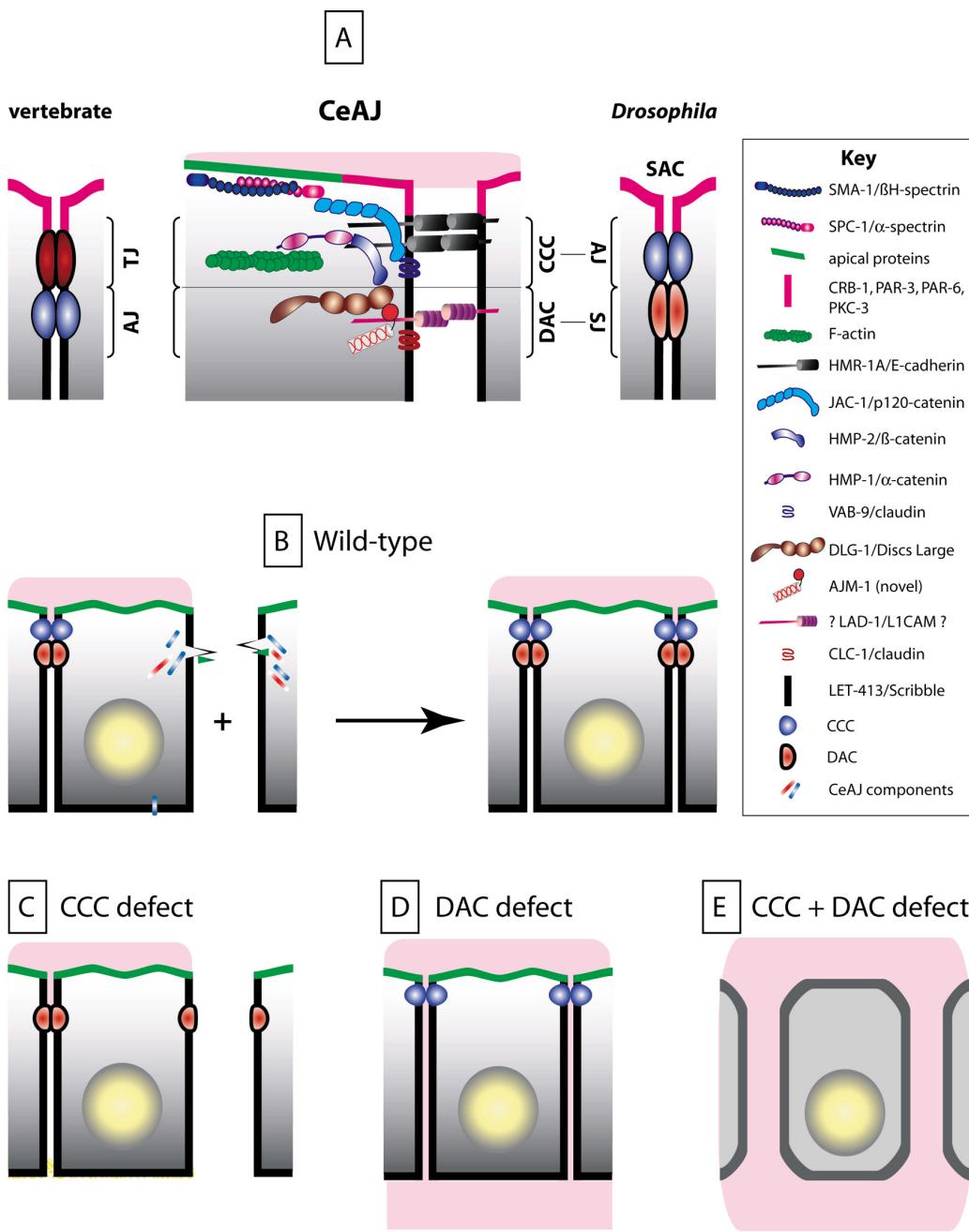


Figure 3. The CeAJ and cell-cell adhesion. (A) Schematic representation of known components CeAJ components. Like in vertebrates and *Drosophila*, *C. elegans* epithelial cells contain two adhesion complexes, the cadherin-catenin (CCC) and the DLG-1/AJM-1 (DAC) complexes. *C. elegans* is unique in three respects: (i) there is a single electron-dense area in the CeAJ (see Figure 1B); (ii) LET-413 does not colocalize with DLG-1 (as its homologue Scribble in *Drosophila*); (iii) PAR-3, PAR-6, PKC-3 and CRB-1 are present at the apical membrane in tubular organs (the existence of apical polarity determinants in epidermal cells is an open question). CeAJs from different epithelia contain the same set of proteins; notable differences concern the identity of the classical claudin-like protein (CLC-1 present in the pharynx, vulva and spermatheca; CLC-2 present in the lateral epidermis). The DAC complex might correspond to the electron-density in the CeAJ. Indeed, immunogold staining experiments localize AJM-1 at the electron density, and removal of DLG-1 or AJM-1 compromise the formation or the integrity, respectively, of the electron dense area of the CeAJ (Koppen et al., 2001; McMahon et al., 2001; Rostaing et al., 2004). Similar electron microscopy experiments with CCC components should clarify this point. (B) Once born, epidermal cells rapidly establish CeAJs (CCC, blue ball; DAC, red ellipse), which remain stable unless cells fuse. During ventral enclosure (+ sign), ventral epidermal cells extend actin-rich filopodial extensions towards the ventral midline (green triangles), where they must assemble a new CeAJ with their contralateral homologues through a cadherin/ HMR-1-dependent recruitment of other CCC, and presumably DAC, components (elongated rectangles; Raich et al., 1999). A similar actin-based process for junction formation has also been described in vertebrates (Vasioukhin et al., 2000). (C) Ventral cells in zygotic *hmr-1*, maternal and zygotic *hmp-2* or maternal and zygotic *hmp-1* mutants can extend towards the ventral midline but fail to establish junctions. However, adhesion remains normal elsewhere between cells that already had assembled a CeAJ. (D) Cell-cell adhesion is not impaired in mutants lacking the DAC. Paracellular gate function is defective in animals lacking the claudin-like protein CLC-1, a putative DAC component: pharyngeal cells fail to prevent a small fluorescent dye to leak between adjacent cells (pink material infiltrating between cells). (E) In animals lacking a CCC and a DAC protein (HMP-1 and DLG-1, or VAB-9 and DLG-1), cell adhesion is not maintained, causing epithelial cells to round up.

4.1. The cadherin-catenin complex (CCC)

This complex is analogous in composition and to a large extent in function to the cadherin-catenin complex found in flies and vertebrates (Costa et al., 1998). The CCC includes homologues of the classical E-cadherin (**HMR-1**), α -catenin (**HMP-1**), β -catenin (**HMP-2**), p120-catenin (**JAC-1**), and a distant claudin superfamily member (**VAB-9**; Costa et al., 1998; Pettitt et al., 2003; Simske et al., 2003; for further details, see **The cadherin superfamily**). The CCC is the most apical within the CeAJ (Koppen et al., 2001; McMahon et al., 2001).

4.2. The DLG-1/AJM-1 complex (DAC)

This complex is defined by two membrane-associated proteins, a *Drosophila* Discs-large homologue (**DLG-1**), and a new coiled-coil protein (**AJM-1**; Bossinger et al., 2001; Firestein and Rongo, 2001; Koppen et al., 2001; McMahon et al., 2001). **DLG-1** and **AJM-1** form a bona fide complex since they interact *in vitro* and are mutually dependent on each other for proper localization *in vivo* (Koppen et al., 2001; McMahon et al., 2001; Segbert et al., 2004).

The number of additional proteins belonging to the DAC and how **DLG-1/AJM-1** is anchored to the membrane is not known. The claudin homologues **CLC-1** or **CLC-2**, or the L1-CAM homologue **LAD-1/SAX-7**, which colocalize with **AJM-1**, might in some tissues fulfill this role (Asano et al., 2003; Chen et al., 2001).

4.3. Additional proteins not assigned to a particular complex

Several signaling proteins localize at the CeAJ or should do so based on homology, but their specific function is seldom known (Table 1; see Cox et al., 2004 for more references). Among them, the APC homologue **APR-1** might be part of the CCC, since its *Drosophila* counterpart colocalizes with Armadillo/ β -catenin, and since *apr-1* null mutants display an embryonic phenotype reminiscent of the ***hmr-1*** ventral enclosure defect (Bienz and Hamada, 2004; Hoier et al., 2000).

5. Cell adhesion, microfilament anchorage and gate function

In vertebrates and *Drosophila*, adherens junctions maintain cell-cell adhesion and anchor actin microfilaments, while tight junctions (septate junctions in *Drosophila*) ensure a paracellular gate function. In addition, both junctional complexes contribute to maintenance of cell polarity and act as signaling platforms (Braga, 2002; Tsukita et al., 1999). In this framework, what is known about the cellular functions of the two CeAJ complexes?

5.1. Cell-cell adhesion

Mutations inactivating the CCC affect cell-cell adhesion, but only in certain circumstances. Mutations in ***hmr-1*/E-cadherin**, or simultaneous loss of zygotic and maternal ***hmp-1*/ α -catenin** or ***hmp-2*/ β -catenin** prevent the stable assembly of new CeAJs during the morphogenetic movement known as ventral enclosure (for further details, see **Epidermal Morphogenesis**; Costa et al., 1998; Raich et al., 1999). Surprisingly however, such mutations do not impair cell adhesion among other epidermal cells or intestinal cells (Figure 3C).

The absence of the **DLG-1/AJM-1** complex does not cause major cell adhesion defects, despite the absence of a detectable electron density in **DLG-1** deficient embryos, or the presence of localized bubble-like separations between adjacent **AJM-1** deficient cells (Figure 3D; Koppen et al., 2001; McMahon et al., 2001). Expression of a truncated form of the putative DAC component **LAD-1/SAX-7** leads to morphogenetic defects that could be interpreted as adhesion defects (Chen et al., 2001). Identification of null alleles in this gene confirm that it is required in different ways for normal embryonic morphogenesis; in particular it is required for muscle attachment (see below), although the exact nature of the adhesion defect has not been established (Wang et al., 2005).

The unexpected observation that cell adhesion remains largely unaffected when one CeAJ complex is missing suggests that *C. elegans*, like vertebrates, might contain redundant adhesion systems (Sakisaka and Takai, 2004). The two CeAJ complexes likely cooperate to maintain cell adhesion, since simultaneous loss of a CCC and DAC components causes severe adhesion defects in the epidermis and the intestine (Figure 3E; Segbert et al., 2004; Simske et al., 2003; L. McMahon and M. Labouesse, unpublished results).

5.2. Paracellular gate function

The strong sequence similarity between DLG-1 and Discs Large, which in *Drosophila* associates with septate junctions, and the occurrence of vacuoles in *ajm-1* and *dlg-1* null mutants, raised the possibility that the DAC could perform a role analogous to septate junctions in maintaining paracellular gating (Koppen et al., 2001). Indirect support for this view has come from the observation that a low-molecular weight fluorescent dye can diffuse between pharyngeal cells in animals lacking CLC-1, a possible DAC component (Figure 3D; Asano et al., 2003).

5.3. Actin anchoring

In the epidermis, the CCC complex is essential to anchor the circumferential actin bundles, since lack of HMP-1/α-catenin or HMP-2/β-catenin causes them to detach from the CeAJ (Figure 4B; Costa et al., 1998). Consistent with the observation that drugs inhibiting actin polymerization prevent embryonic elongation (Priess and Hirsh, 1986), *hmp-1* and *hmp-2* mutations block elongation, while loss of JAC-1/p120 catenin enhances the elongation defect of a weak *hmp-1* mutation (Costa et al., 1998; Pettitt et al., 2003). The presence of redundant adhesion systems in *C. elegans* has made it possible to separate the actin anchoring and the cell-cell adhesion functions of the CCC.

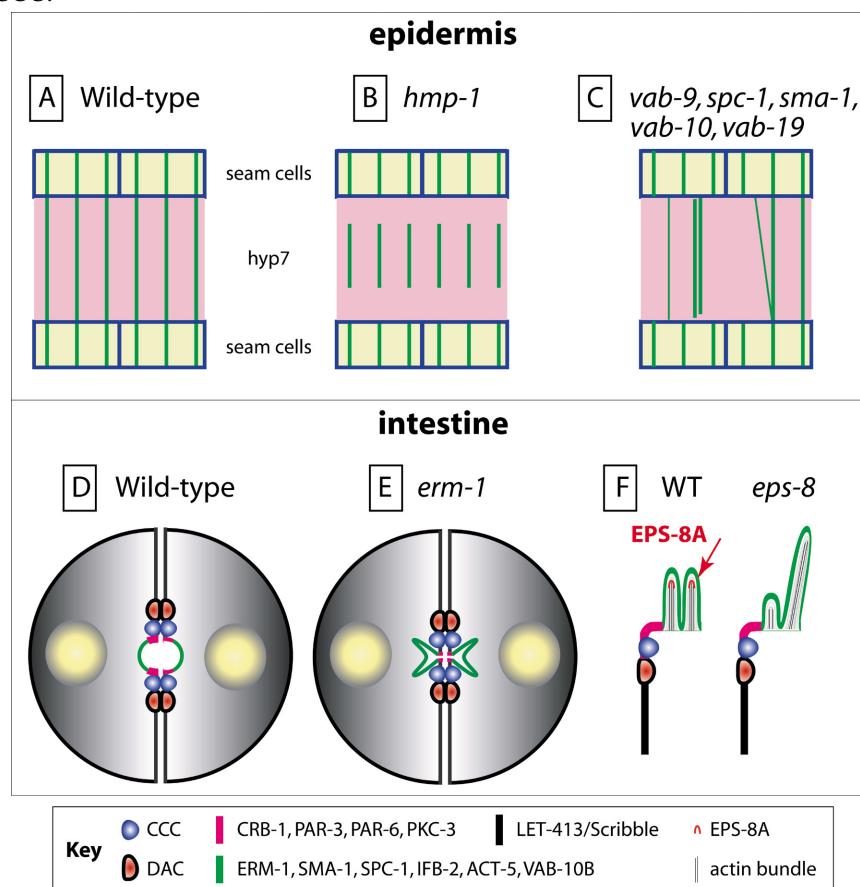


Figure 4. Anchoring of actin microfilaments. (A) Flat-mount representation of the dorsal half of an embryo (for a more complete view, see Figure 6), with seam cells (light yellow) and the main dorsal epidermal syncytium hyp7 (pink; anterior to the left, posterior to the right). Circumferential actin bundles (horizontal green lines) are anchored to the CCC (blue lines). (B) In *hmp-1* or *hmp-2* mutants, actin bundles are not attached dorsally (their attachment is not compromised ventrally and laterally); due to morphogenetic forces, they snap back to the middle of hyp7. (C) In mutants for the CCC component *VAB-9*, the apical spectrin *SPC-1/SMA-1*, the FO components *VAB-19* and *VAB-10*, MFs randomly form thicker bundles, are not properly aligned or can locally detach from the CeAJ. (D) Schematic representation of two intestinal cells. (E) *ERM-1* is required to anchor the actin cytoskeleton at the gut lumen. In animals strongly defective for *erm-1*, or partially defective for *erm-1* and *sma-1*, or *erm-1* and *act-5*, the lumen folds inside the cells, causing gut constrictions. However junctions and epithelial polarity are not affected. (F) Enlarged view of the intestinal lumen and brush border in wild-type animals (left), showing the localization of EPS-8A which binds actin barbed ends through a novel domain found at its C-terminus. In larvae homozygous for a strong *eps-8* allele or after RNAi against the *eps-8A* isoform (right), microvilli have irregular sizes and orientations or can be missing (note that RNAi against all isoforms is embryonic lethal, indicating that *eps-8* might have a maternal component).

Several proteins acting either within the CCC, at the apical membrane, or within fibrous organelles (see below) ensure the regular distribution of microfilament bundles in the epidermis (Figure 4C). For instance, in mutants affecting the CCC component **VAB-9**/claudin or the α -spectrin/**SPC-1**, microfilaments often form thicker bundles and thereby reduce elongation (Ding et al., 2003; Norman and Moerman, 2002; Simske et al., 2003).

In the intestine, the Ezrin-Radixin-Moesin homologue **ERM-1**, together with **SMA-1**/ β -spectrin, act as scaffolding proteins to anchor actin filaments at the lumen and ensure proper lumen formation (Göbel et al., 2004; Van Furden et al., 2004). In particular, strong RNAi against *erm-1* causes a severe reduction of apical microfilaments and gut lumen constrictions (Figure 4E). Although **ERM-1** is expressed in other epithelia, it only appears essential for the development of epithelia not lined by a cuticle (Göbel et al., 2004; Van Furden et al., 2004). Another protein critical for lumen formation and gut function is **EPS-8A**, the long isoform of the *C. elegans* homologue of the receptor tyrosine kinase (RTK) receptor substrate Eps8, a protein that in vertebrates links RTK and Rac GTPase signaling. **EPS-8A** is localized at the tips of the brush border intestinal microvilli, where it acts as a barbed-end actin-capping factor that stabilizes microvilli (Croce et al., 2004). When **EPS-8A** is removed by RNAi or a mutation, the gut lumen becomes strongly enlarged, causing larval lethality.

6. Assembly of apical junctions and establishment of epithelial polarity

In *Drosophila*, the interplay between three scaffolding complexes: basolaterally the Scribble/Discs Large/Lethal giant larvae complex, and apically the Bazooka/DmPAR-6/DaPKC and Crumbs/Stardust/Disc Lost complexes, specify epithelial polarity (Knust and Bossinger, 2002; Muller and Bossinger, 2003; Nelson, 2003). In *C. elegans*, the establishment of epithelial polarity may involve different mechanisms, since **PAR-3**, **PAR-6** and **PKC-3** have so far not been found in the epidermis (Bossinger et al., 2004; McMahon et al., 2001), while some other homologues of key *Drosophila* polarity proteins are not expressed in equivalent membrane domains. Current observations point to the existence of multiple, probably redundant, cues to position junctions.

6.1. Cellular processes involved in specifying polarity

The establishment of epithelial polarity often requires slightly different processes in cells that form sheets or tubes (Nelson, 2003; Zegers et al., 2003). During development of the epidermis, CeAJ components are assembled in a step-wise fashion. They are initially found along the lateral membrane, and then rapidly adopt their final apical distribution (Figure 5A). It is not clear, however, whether CeAJ components are degraded laterally, actively transported apically or prevented from docking basolaterally (McMahon et al., 2001).

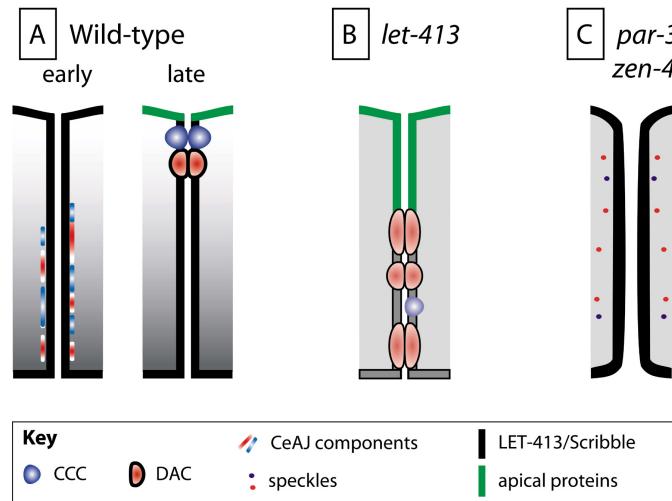


Figure 5. Establishment of epithelial cell polarity. (A) In epithelial cells forming a sheet (the epidermis), individual components of the future CeAJ are initially found along the lateral membrane (early). Subsequently, they coalesce into the CeAJ apically (late). **LET-413** is present in epithelial precursors and becomes restricted to the basolateral membrane in epithelial cells while they differentiate. (B) In *let-413* mutants, ectopic electron dense junctions are found along the lateral membrane, suggesting that **LET-413** might promote apical coalescence of CeAJ components (see A). Apical markers of the epidermis (**CHE-14**) and the intestine (**PAR-3**, **PAR-6**, **IFB-2**, **ERM-1**) also become gradually mislocalized along the lateral membrane, which might be due to the junctional defect or reflect an additional role of **LET-413**. (C) Some epithelial cells that form a tube require the activity of **PAR-3** (e.g., in the distal spermatheca), or the **ZEN-4/CYK-4** complex (in arcade cells). In animals lacking these proteins, cell polarity is not established, CeAJ components form discrete speckles, and the cytoskeleton is not enriched at the prospective apical luminal side (not illustrated).

In the intestine, the pharynx and the excretory cell, epithelial polarity appears to start by the formation of small vesicles, whose expansion contributes to form the lumen (Buechner et al., 1999; Leung et al., 1999). Microtubules and actin microfilaments are enriched at the prospective lumen, where they play a critical role in gut tubulogenesis (Leung et al., 1999). As in the epidermis, the CeAJ assembles in a step-wise manner, except that CeAJ components initially accumulate in puncta at the midline (future apical surface) to subsequently adopt a sub-apical continuous distribution (Bossinger et al., 2001; Leung et al., 1999).

6.2. Defining the basal position of the CeAJ

In the epidermis, the basolateral protein **LET-413**, the only *C. elegans* Scribble homologue, positions the CeAJ presumably by promoting its apical condensation (Legouis et al., 2000; McMahon et al., 2001). In **LET-413** deficient embryos, and depending on authors, **DLG-1**, **AJM-1** and **HMP-1/α-catenin**, remain lateral leading to lateral assembly of electron dense junctions (Figure 5B; Legouis et al., 2000; McMahon et al., 2001), or reach their sub-apical position less efficiently (Koppen et al., 2001). Moreover, in the epidermis as well as in the intestine, apical membrane markers progressively spread into the lateral membrane, suggesting that **LET-413** acts to maintain polarity (Bossinger et al., 2004; Koppen et al., 2001; McMahon et al., 2001; Segbert et al., 2004). Although **LET-413** biochemical activity is unknown, it has been predicted that it might act through a small GTPase. Its N-terminal leucine-rich repeats, which mediate basolateral localization, show good similarity with the Ras-interacting protein **SUR-8** (Legouis et al., 2003).

6.3. Apical proteins involved in specifying polarity and tubulogenesis

PAR-3, **PAR-6** and **PKC-3** are present at the apical membrane of tubular organs, where their role has been difficult to assess owing to their early requirement in development (Pellettieri and Seydoux, 2002). Roles for **PAR-3** and **PAR-6** in epithelial polarity have been uncovered in two specific cases. Indirect evidence in favor of a role for *C. elegans* PAR proteins in establishing cell polarity initially came from very elegant experiments in which **PAR-3** and **PAR-6** were only provided to the zygote (Nance et al., 2003). Although blastomeres after the 8-cell stage are not truly epithelial, they are polarized and require the activity of **PAR-3**/**PAR-6** to maintain cell-cell adhesion and restrict **PAR-1** and **PAR-2** to their basolateral surfaces. Lack of **PAR-3** or **PAR-6** considerably slows down ingressation of gut precursors during gastrulation (Nance et al., 2003). RNAi feeding in larvae also established that **PAR-3** is required in the distal spermatheca to specify polarity and to assemble the CeAJ (Figure 5C). In turn, absence of the CeAJ compromises signaling between the spermatheca and the germline (Aono et al., 2004).

Several observations indicate that establishing cell polarity in the intestine involves multiple parallel cues. For instance, the Crumbs homologue **CRB-1**, an apical protein in the gut, plays an ancillary role in cell polarity which can be revealed by the simultaneous knock-down of **LET-413**, **HMP-1/α-catenin** and **CRB-1** (Bossinger et al., 2004; Bossinger et al., 2001). Similarly, the Moesin homologue **ERM-1** is not essential for junction assembly or cell polarity, unless it is inactivated together with **hmr-1/E-cadherin**, in which case the CeAJ is missing in many places (as observed after the simultaneous loss of a DAC and CCC components; see Figure 3E; Speck et al., 2003; Van Furden et al., 2004).

Two new players, **zen-4** and **cyk-4**, have recently been identified as factors required for epithelialization of arcade cells during pharynx tubulogenesis (Figure 5C). Normally, arcade cells undergo a mesenchymal-epithelial transition to assemble typical CeAJs, express **PAR-3/PKC-3** at their apical membrane and create a tube (Portereiko and Mango, 2001; Portereiko et al., 2004). In **zen-4** or **cyk-4** mutants, these steps fail, perhaps because the arcade microtubule and actin cytoskeletons are disorganized (Portereiko et al., 2004). The conventional kinesin **ZEN-4/MKLP1** and the Rho GTPase-activating protein **CYK-4** were previously described to form a complex that bundles microtubules and constructs the spindle midzone during cytokinesis (Glotzer, 2001). Whether and how the functions of the **ZEN-4/CYK-4** complex in cytokinesis and epithelialization are related is not yet known.

7. Junction disassembly and cell fusion

Multiple cell fusion events occur during *C. elegans* development, which directly affect its morphogenesis and organogenesis. Confocal and transmission electron microscopy have suggested that fusion is initiated by a pore-forming mechanism originating at a single point located within or in very close proximity of a CeAJ (Mohler et al., 1998). This pore is then thought to expand by vesiculation of the membrane (Mohler et al., 1998).

While several mutants have been described that affect the decision to fuse, the only gene known to be necessary and sufficient for the fusion process itself is *eff-1* (Mohler et al., 2002). In *eff-1* mutants, cell fusion is blocked at an early step, presumably at the initiation and expansion steps (Mohler et al., 2002). Ectopic expression of **EFF-1** triggers fusion between cells that normally do not fuse, resulting in cytoplasmic mixing and the disappearance of CeAJs within one hour of expression (Shemer et al., 2004).

8. Fibrous organelles: junctions with the extracellular matrix and mechanical coupling

C. elegans dorsal and ventral epidermal cells possess a major adhesion complex, called the fibrous organelle (FO), which mediates attachment to muscles and the cuticle, or which transmits cuticle deformation to mechanosensory touch neurons (Francis and Waterston, 1991). Similar structures are also found in the pharyngeal marginal cells. FOs look ultrastructurally, functionally and to some extent molecularly like type I hemidesmosomes (HDs). In vertebrates, HDs attach the basal layer of the epidermis to the basal lamina and are essential to anchor keratin filaments (Nievers et al., 1999).

8.1. Fibrous organelles resemble type I hemidesmosomes

Transmission electron microscopy reveals the presence of regularly spaced electron densities at the apical and basal plasma membranes of the ventral and dorsal epidermis, in regions overlying body wall, vulval, uterine and anal muscles (Figure 1C–D, Figure 6A; Francis and Waterston, 1985; Francis and Waterston, 1991). These plaques, together with the dense array of filaments connecting them, correspond to FOs.

A key FO component is an isoform of the gene *vab-10*, VAB-10A, resembling plectin and BPAG1e which in HDs connect keratin filaments to integrin and BPAG2 adhesion receptors (Bosher et al., 2003; Nievers et al., 1999). Immunogold staining localizes VAB-10A to a region enriched in filaments, while genetic experiments show that VAB-10A is required to anchor IFs (Figure 6A–B; Bosher et al., 2003). Genetic and immunofluorescence experiments argue that the filaments associated with FOs correspond to the **IFB-1/IFA-3** and **IFB-1/IFA-2** heterodimers (see cytoskeleton section; Figure 6A; Hapiak et al., 2003; Karabinos et al., 2003; Woo et al., 2004). Besides VAB-10A and IFs, another presumptive FO component is **VAB-19**, which is homologous to the tumor suppressor Kank (Figure 6A; Ding et al., 2003).

The transmembrane adhesion molecules predicted to link VAB-10A and IFs are **MUA-3** and **MUP-4** on the apical side of the epidermis, and myotactin/**LET-805** on its basal side (Figure 6A; Bercher et al., 2001; Hong et al., 2001; Hresko et al., 1999). These proteins are unrelated to integrins and BPAG2, implying that HDs and FOs are not strictly equivalent (Table 1). Intriguingly, however, the extracellular domains of **MUA-3** and **MUP-4** show weak similarity to matrilins, which are components of vertebrate tendons, a structure enriched in collagens like the cuticle (Hahn and Labouesse, 2001).

Akin to the skin blistering phenotype observed in patients compromised for an HD component, mutations inactivating FO components cause the epidermis to detach from the cuticle on its apical side and from muscles on its basal side (Figure 6B–C; Bercher et al., 2001; Bosher et al., 2003; Ding et al., 2003; Hapiak et al., 2003; Hong et al., 2001; Hresko et al., 1999; Karabinos et al., 2003; Woo et al., 2004). Muscle contractions are responsible for this phenotype since inhibiting their activity strongly reduces detachment (Bosher et al., 2003; Ding et al., 2003). The ensuing detachment causes elongation defects and embryonic lethality, except in *mua-3* and *mua-6/ifa-2* mutants, which only affect larvae, suggesting that *mua-3* and *mua-6* fulfill a specialized role associated with the presence of a cuticle.

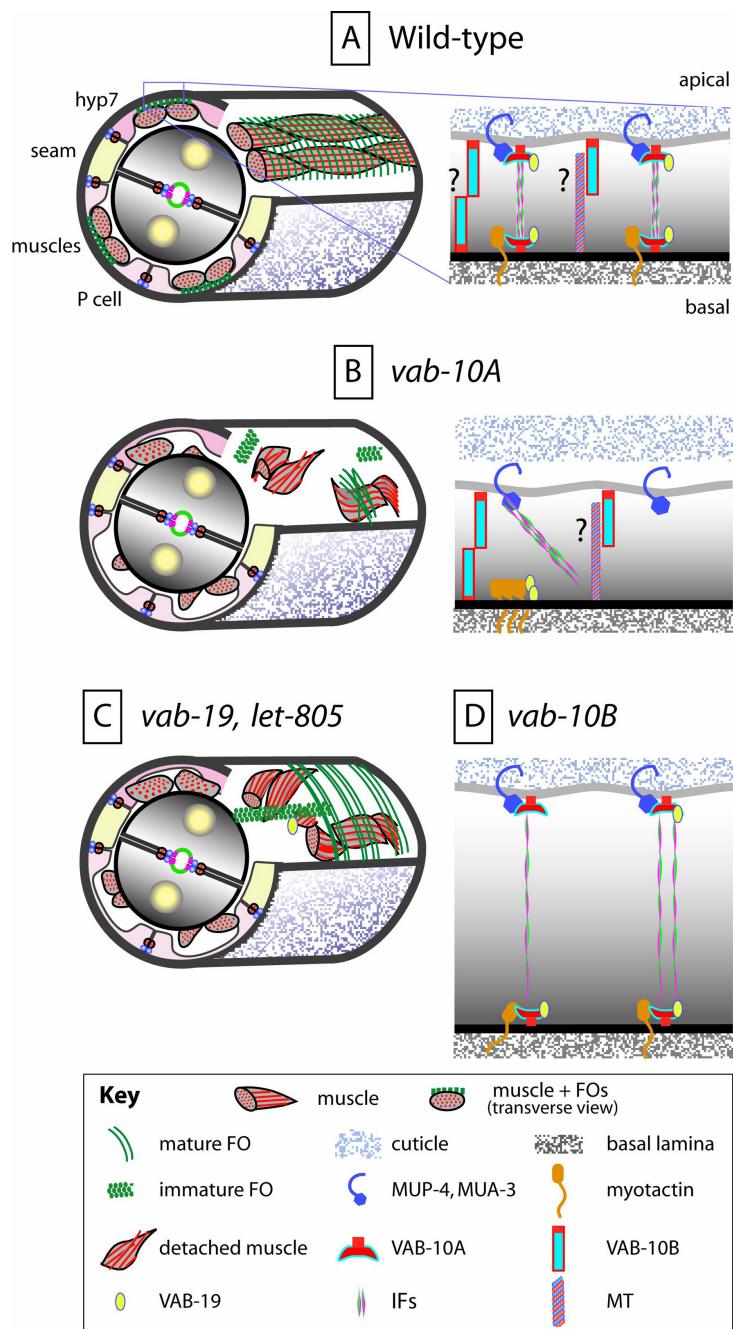


Figure 6. Structure and function of fibrous organelles. (A - left) Schematized section of an animal in which the cuticle overlaying the dorsal epidermis was removed; muscles are oriented longitudinally, fibrous organelles (FOs) circumferentially. FOs are found where muscles make contacts with the dorsal and ventral epidermis; due to FO attachments, the epidermis flattens out in regions overlying muscles (50 to 100 nm in larvae; A - right) FOs correspond to a complex formed basally by the myotactin/LET-805 receptor or apically by the homologous (see Figure 2) MUA-3 and MUP-4 receptors, the plectin/BPAG1-like VAB-10A, the ankyrin-repeat protein VAB-19/Kank, and the intermediate filament heterodimers IFB-1/IFA-2 or IFB-1/IFA-3. How these proteins interact with each other is not known, besides that MUP-4, MUA-3 and VAB-19 have potential IF-binding domains. VAB-10B, another MACF-like *vab-10* isoform present in muscle-epidermis contact areas, is found in comma embryos at the apical and basal plasma membrane. At later stages, it is unknown whether VAB-10B remains basal and apical or only apical (as in the intestine; see question marks). (B - left) In *vab-10A* mutants, muscles are not attached to the epidermis and collapse inside the embryo; FOs are strongly disorganized/absent. (B - right) At the cellular level, the epidermis detaches from the embryonic sheath (or the cuticle at later stages); IFs, myotactin and VAB-19 have a very abnormal distribution or form aggregates. (C) A similar phenotype, albeit slightly less severe, is observed in *let-805*/myotactin or *vab-19*/Kank mutants; muscles detach, and at the cellular level, FOs fail to evolve from foci to circumferential lines (left), or they stretch from one seam to the other (right). (D) In *vab-10B* mutants, the distance between the apical and basal plasma membranes increases. At least two possibilities could explain this phenotype (see question marks in A-right): either in wild-type embryos two apical and basal VAB-10B proteins form homodimers to oppose thickening, or, as it is often the case in vertebrate epithelial cells, there are apico-basally oriented microtubules that could be anchored by VAB-10B. FO integrity is also partially defective in *vab-10B* mutants, indicating that VAB-10A and VAB-10B could be mutually interdependent to maintain their organization.

8.2. Assembly of fibrous organelles

FO components initially appear as foci at the apical and basal epidermal membranes, which progressively evolve into short circumferential bands overlying muscles after the pretzel stage (Figure 6A; Francis and Waterston, 1991). FO assembly requires input from muscles (Hresko et al., 1999). It is still unclear, however, whether muscles simply stabilize FOs, or whether they induce the expression of FO components, much as *Drosophila* muscles induce the differentiation of tendon cells (Volk, 1999).

The initial assembly of FO components at the muscle-epidermis interface does not depend on other FO components, but their fine patterning does (Figure 6B–C). In the absence of VAB-10A, other components get dispersed or they aggregate into abnormal bundles (Bosher et al., 2003). Likewise, when myotactin/LET-805 is absent, FOs are not restricted to a narrow area where muscles should be and VAB-19 becomes dispersed in a broad area (Ding et al., 2003; Hresko et al., 1999). Reciprocally, when VAB-19 is absent, the distribution of IFs is enlarged and the myotactin pattern fails to evolve into a pattern of circumferential bands (Ding et al., 2003).

Maintenance of FOs depends also on VAB-10B, another VAB-10 isoform, whose distribution is intermingled with that of VAB-10A (Figure 6A, D; Bosher et al., 2003). The reason for the progressive loss of FOs in *vab-10B* mutants is unclear, and may be due to a thickening of the epidermis, and/or a failure to maintain the integrity of the actin and microtubule cytoskeleton after the two-fold stage (Landmann and Labouesse, unpublished).

9. Conclusions and future directions

Seven years ago, we knew essentially nothing about epithelial junctions in *C. elegans*. The identification of several key actors involved in building junctions thus represents a major step forward. Yet much remains to be learned, particularly in analyzing the molecular relationship between the three cytoskeletal networks and in defining how adhesion complex can modulate signaling. *C. elegans* has small cells and does not easily lend itself to biochemical analysis. Nonetheless, some recent technical developments, such as rapid cameras with better resolution, reagents that can monitor protein activity or protein-protein interaction *in vivo*, the TAP-tag method of purifying protein complexes, should allow researchers in the field to make up for those disadvantages. When combined with the traditional power of worm genetics, these techniques offer promise towards elucidating how adhesion complexes can regulate morphogenesis, or how compromising junction integrity can result in human diseases.

10. Acknowledgements

I thank past and present members of the Labouesse lab for lively and useful discussions, in particular Renaud Legouis for critical reading of the manuscript. Work in my laboratory is funded by institutional funds from the CNRS, INSERM and Hôpitaux Universitaires de Strasbourg, and by grants from the European Community, the Association pour la Recherche sur le Cancer and the Association Française contre les Myopathies.

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