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Cell adhesion receptors in *C. elegans*

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C. elegans has numerous putative cell adhesion receptors, many of which have vertebrate homologues. The simple body plan of *C. elegans*, its optical transparency and genetic tractability

make it well suited for the study of adhesion receptors and their associated complexes (reviewed by Cox and Hardin in this issue, pp. 1885-1897). We focus here on receptors that are likely to directly mediate adhesion either between cells or to the extracellular matrix; for information on other cell surface receptors please refer to Hutter et al. (Hutter et al., 2000).

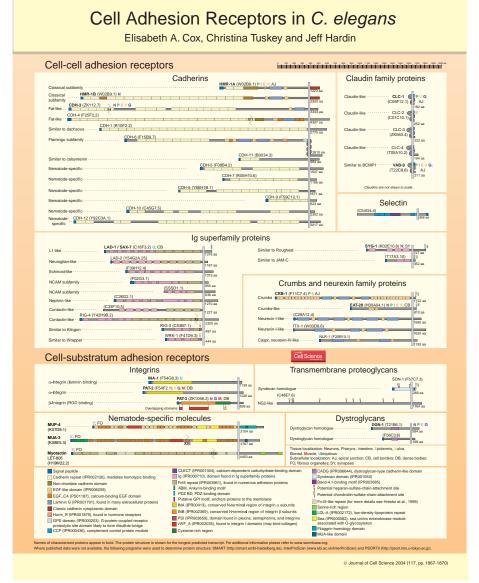
Cell-cell adhesion receptors

Cadherins

Cadherins are calcium-dependent, homophilic, cell-cell adhesion receptors that regulate morphogenesis, pattern formation and cell migration (reviewed in Tepass, 1999; Vleminckx and Kemler, 1999). *C. elegans* is predicted to express 13 putative transmembrane proteins with extracellular cadherin repeats (Hill et al., 2001).

cadherin genes have been functionally characterized: hmr-1 and cdh-3. hmr-1 encodes two isoforms: HMR-1A, which is crucial during epidermal morphogenesis (reviewed by Cox and Hardin, 2004); and HMR-1B, which might participate in neural development (Broadbent and Pettitt, 2002). The HMR-1 cytoplasmic domain binds catenins and promotes the formation of adherens-junction-like adhesions (reviewed by Cox and Hardin, 2004). The C. elegans Fat-like cadherin CDH-3 is expressed in epithelial and neurectodermal cells and is important for morphogenesis of the epidermal cell at the tip of the tail (Pettitt et al., 1996). A second Fat-like cadherin, CDH-4, is neuronally expressed, but its function is not understood (Hill et al., 2001).

The C. elegans genome encodes several other predicted proteins that have sequence similarity in their extracellular domains to Drosophila and vertebrate cadherins. This does not extend to the cytoplasmic domains, which indicates that different proteins might act downstream. CDH-1 is primarily neuronally expressed (Hill et al., 2001), and is similar to *Drosophila* Dachsous. which was identified through its role in imaginal disc morphogenesis (reviewed in Tepass, 1999). CDH-6 has sequence similarity Flamingo, which to participates in planar cell polarity in Drosophila (reviewed in Takeichi et al., 2000). CDH-11 has extensive similarity to human brain proteins of the calsyntenin family, which might participate in synaptic transmission (Vogt et al., 2001). Whether CDH-1, CDH-6 and CDH-11 have functions similar to those of their homologues is not known. The remaining putative cadherins (CDH-5, CDH-7, CDH-8, CDH-9, CDH-10 and CDH-12) have not been characterized, and are probably nematode specific because they lack obvious homologues in other organisms.



(See poster insert)

Immunoglobulin superfamily cell adhesion molecules (IgCAMs)

IgCAMs are single-span transmembrane proteins that mediate cell-cell adhesion via homophilic or heterophilic interactions. The *C. elegans* genome encodes numerous immunoglobulindomain proteins that might function as cell-cell adhesion receptors (reviewed in Teichmann and Chothia, 2000; Hutter et al., 2000).

Two C. elegans IgCAMs, LAD-1 and SYG-1, have been functionally characterized. LAD-1 is one of three L1CAM homologues in C. elegans. In vertebrates and Drosophila, L1CAMs participate in neural development and might also have roles in epithelia (reviewed in Crossin and Krushel, 2000). LAD-1 localizes to cell-cell contacts, and perturbing its expression phenotypes ranging uncoordinated movement to embryonic lethality (Chen et al., 2001). The function of the other two C. elegans L1CAM homologues, LAD-2 (similar to Drosophila Neuroglian) and F39G12.4 (similar to *Drosophila* Echinoid), is unknown. The other characterized C. elegans IgCAM, SYG-1, specifies the site of formation of some synapses and has similarity to Drosophila IrreC and vertebrate NEPH1, which participate in many developmental events (Shen and Bargmann, 2003).

C. elegans has several genes encoding proteins similar to IgCAMs implicated in neural development; whether they have similar functions in C. elegans is not known. F02G3.1 and SSSD1.1 have extracellular domains similar to the vertebrate neural cell adhesion molecule NCAM. C26G2.1 has sequence similarity to vertebrate nephrin, which is required for neural and kidney development in mice and humans (Putaala et al., 2001). C33F10.5 and RIG-4 are similar to vertebrate contactin. which is required for maintaining neuronal paranodal junctions (reviewed in Tepass et al., 2002). Two GPIanchored IgCAMs, RIG-3 and WRK-1, have sequence similarity, respectively, to Drosophila Klingon and Wrapper, which have been proposed to mediate cell adhesion (reviewed in Teichmann and Chothia, 2000).

Additionally, one uncharacterized *C. elegans* IgCAM (T17A3.10) has structural similarity to JAM-C, an adhesion receptor in vertebrate tight junctions (reviewed in Ebnet et al., 2004).

Claudin-like proteins

Claudins are tetraspan, homotypic cellcell adhesion receptors that mediate paracellular permeability in vertebrate tight junctions (reviewed in Tsukita and Furuse, 2002). The C. elegans genome encodes several claudin-like proteins, including CLC-1, CLC-2, CLC-3 and CLC-4. CLC-1 localizes to epithelial cell junctions in the pharynx, where it regulates barrier function (Asano et al., 2003); the remaining CLC proteins are uncharacterized. VAB-9, a divergent claudin-like protein most similar to vertebrate BCMP1 (brain cell membrane protein 1), localizes to epithelial cell contacts and interacts with the cadherincatenin complex during epidermal morphogenesis (Simske et al., 2003).

Crumbs and neurexin family proteins

Crumbs and neurexin family proteins both have extracellular EGF repeats and laminin G domains, but have different expression patterns and functions. C. elegans has two Crumbs-like proteins, CRB-1 and EAT-20. Drosophila Crumbs is a Notch-like receptor that localizes to the apical domain of epithelia, where it promotes apical identity and zonula adherens formation (reviewed in Tepass et al., 2002). In C. elegans, CRB-1 has a similar localization, although RNAi directed against it does not cause an observable phenotype (Bossinger et al., 2001). EAT-20 localizes to the apical surface of epithelial cells in the pharynx and null mutants exhibit feeding defects (Shibata et al., 2000).

Three *C. elegans* proteins fall into the neurexin family, which consists mostly of putative neural cell adhesion receptors (Bellen et al., 1998). C29A12.4 and ITX-1 are homologous to vertebrate neurexin I, while NLR-1 is homologous to *Drosophila* Neurexin IV and vertebrate Caspr. Neurexin IV and Caspr localize to specialized neural septate-like

junctions, suggesting a conserved role in mediating cell-cell contact (Bellen et al., 1998); the functions of *C. elegans* neurexins are unknown.

Selectins

Selectins are single-span transmembrane receptors that bind cell-surface glycoproteins. In vertebrates, selectins mediate rapid and reversible adhesion of leukocytes and platelets to endothelial cells (reviewed in McEver, 2002). The *C. elegans* genome encodes one putative selectin, C54G4.4, whose function is unknown.

Cell-substratum adhesion receptors

Integrins

Integrins are $\alpha\beta$ heterodimers which form multi-protein complexes that mediate cell adhesion and signal transduction (reviewed in Zamir and Geiger, 2001). Integrins participate cell migration, proliferation, differentiation, matrix assembly and apoptosis (reviewed in Bokel and Brown, 2002). C. elegans has two α integrin genes (ina-1 and pat-2) and one β integrin gene (pat-3). αINA-1/βPAT-3 is predicted to bind laminins, while αPAT-2/βPAT-3 is predicted to bind ligands with RGD motifs (Hutter et al., 2000). α INA-1/ β PAT-3 has an important role in commissural axon navigation (Baum and Garriga, 1997). participates α PAT-2/ β PAT-3 sarcomere assembly through promoting the formation of dense bodies, which are similar to vertebrate focal adhesions (reviewed by Cox and Hardin, 2004). αPAT-2/βPAT-3 is also important for migration of distal tip cells, which direct morphogenesis of the gonad arms (Lee et al., 2001).

Transmembrane proteoglycans

The *C. elegans* genome encodes two transmembrane glycoproteins that are putative cell-substratum adhesion receptors. SDN-1 has sequence similarity to syndecans, which are single-span transmembrane proteoglycans that bind, via heparan sulfate chains, to various growth factors, enzymes and extracellular matrix molecules (Carey, 1997). Vertebrate syndecans regulate

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actin assembly, cadherin- and integrinmediated adhesion, and growth factor signaling (reviewed in Rapraeger, 2001; Yoneda and Couchman, 2003). C48E7.6 has sequence similarity to the vertebrate chondroitin sulfate proteoglycan, NG2, which regulates proliferation, cell spreading and motility, and inhibits neurite outgrowth (Levine and Nishiyama, 1996; Majumdar et al., 2002). The functions of SDN-1 and C48E7.6 are unknown.

Dystroglycans

Dystroglycan is the central component of the dystrophin-glycoprotein complex, the disruption of which has been linked to various forms of muscular dystrophy (reviewed by Ehmsen et al., 2002). C. elegans has two dystroglycan-like genes (dgn-1 and F56C3.6). Their ligand(s) are unknown, but C. elegans does express laminins, perlecan and agrin, which are ligands for vertebrate dystroglycan. DGN-1 and F56C3.6 are expressed in epithelial and neuronal cells, but not in muscle (R. Johnson and J. Kramer, personal communication). C. elegans has many other conserved dystrophinglycoprotein complex components (reviewed by Cox and Hardin, 2004), and so provides an attractive model system for studying this conserved adhesion complex.

Nematode-specific-molecules

Several putative cell adhesion receptors are components of fibrous organelles, which are analogous to vertebrate hemidesmosomes (reviewed by Cox and Hardin, 2004). MUP-4 and MUA-3 are single-span transmembrane receptors that localize to the apical epidermal surface and probably bind cuticular collagens (reviewed in Hahn and Labouesse, 2001). Myotactin is a large, single-span transmembrane protein in the basal epidermal membrane; it might bind the basement membrane or muscle cell surface proteins. MUA-3, MUP-4 and myotactin non-nematode have clear homologues.

Although many of the predicted cell adhesion receptors in *C. elegans* are just beginning to be characterized, current studies provide important insights into

their functions. *C. elegans* is a powerful model system for examining conserved roles of these proteins and elucidating how their activities are integrated to promote the development of animal form.

For more information on the genes described here, refer to http://www.wormbase.org.

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