Text by Ben Short
bshort@rockefeller.edu

Adhering to the message

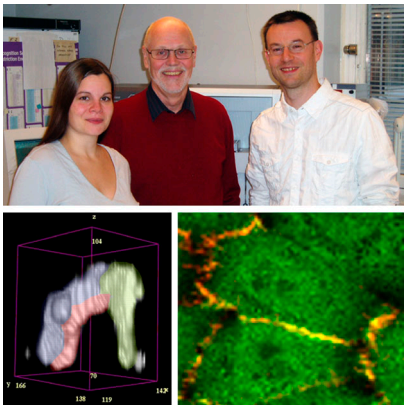
How cell adhesion molecules transmit signals across the plasma membrane.

Cells receive all sorts of messages from their surroundings. How receptors for soluble signaling factors or the extracellular matrix transmit this information across the plasma membrane is largely understood, but the mechanism by which adhesion receptors relay their interactions with neighboring cells is much less clear. Two papers now show how contact between cells expressing a cell adhesion molecule called CEACAM1 is converted into a cytoplasmic signal (1, 2).

CEACAM1 is a member of the immunoglobulin (Ig) superfamily of adhesion molecules that mediates a homophilic interaction between adjacent cells using the first of its four extracellular Ig-like domains (3). Signaling downstream of CEACAM1 regulates events as diverse as morphogenesis, cell motility, and inflammation by modulating other pathways such as MAP kinase, PI3 kinase, or Wnt signaling (4). Björn Öbrink, from the Karolinska Institute in Stockholm, Sweden, says that the precise role of CEACAM1 varies between different cell types. "This has been one of the problems in understanding CEACAM1's biology," he says.

The first step in CEACAM1 signaling involves the binding of phosphatases and kinases to the adhesion molecule's cytoplasmic domain. But how this recruitment is influenced by cell adhesion was unknown. One possibility was that—as with many growth factor receptors—signaling is initiated by changes in the oligomerization state of the transmembrane protein. Öbrink's group used electron tomography and surface plasmon resonance to look at the homophilic interactions between CEACAM1 ectodomains (1). In solution, CEACAM1 could dimerize in two different ways: monomers either lined up parallel to each other or interacted via the antiparallel association of their N-terminal-most Ig domains.

The researchers also visualized CEACAM1 ectodomains on the surface of liposomes, and saw that interactions within the same membrane were parallel, cis-dimers while the antiparallel arrangement was used by CEACAM1 molecules bridging adjacent vesicles. The liposome surfaces also contained a mix of CEACAM1 monomers and higher order clusters, but these largely rearranged into cis-dimers upon contact with neighboring membranes.



Focal Point

Two papers from Esther Klaile, Björn Öbrink, Mario Müller, and colleagues reveal how a cell adhesion molecule conveys information into the cytoplasm. Homophilic binding between CEACAM1 molecules on adjacent membranes induces the protein to form homodimers within the same membrane. CEACAM1's N-terminal Ig domain is essential for this rearrangement, as it can mediate the protein's cis and trans interactions simultaneously, as shown in the molecular electron tomogram (left). Adhesion-induced cis-dimerization of CEACAM1 (red) alters intracellular signaling pathways by preferentially recruiting the tyrosine phosphatase SHP-2 (green) over the kinase c-Src.

Could adhesion produce a similar reorganization of full-length CEACAM1 molecules in real cells? In the second study, Öbrink and colleagues measured the fluorescence resonance energy transfer (FRET) between CFP- and YFP-tagged versions of CEACAM1 in epithelial cells, discovering that adhesion between cells also induced the protein to form cis-dimers (2). "We demonstrated using both tomography and FRET that this rearrangement was a function of CEACAM1's N-terminal Ig domain," explains Öbrink. "We think that when these domains meet in trans to bridge opposing cell membranes, they allosterically induce a conformational change that causes a stronger interaction between molecules in cis."

> **"We think that these domains induce a conformational change that causes a stronger interaction."**

The team then wondered how adhesion-induced dimerization could influence cytoplasmic signaling. The tyrosine phosphatases SHP-1 and SHP-2 compete with the tyrosine kinase c-Src for a binding site on CEACAM1's cytoplasmic tail. Öbrink and colleagues found that the phosphatases prefer CEACAM1 dimers to monomers and that adhesion promoted the phosphatases' recruitment to cell contacts at the expense of c-Src.

Downstream signaling therefore depends on the extent of CEACAM1 dimerization, but Öbrink doesn't think that the cell adhesion molecule acts as a simple on–off switch. "We see a mixture of monomers, dimers, and clusters even outside of cell contacts, so there's clearly a continuous, graded signal," he says. Adhesion isn't the only factor that influences CEACAM1 signaling: a shorter isoform of the protein interferes with phosphatase recruitment (2), while calmodulin promotes dimer disassembly (5). Öbrink says that CEACAM1 doesn't seem to dimerize at all in some cell types, probably due to its association with lectins, highlighting the importance of cell context in determining CEACAM1 function.

The two papers provide the first description of a homophilic cell adhesion molecule's signaling mechanism, and the researchers think that other proteins may act in a similar way, including members of the cadherin family. "Many cell adhesion molecules bind to growth factor receptors in cis following trans homophilic binding," observes Öbrink. "That must also involve some kind of adhesion-induced conformational change."

1. Klaile, E., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200904149.
2. Müller, M.M., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200904150.
3. Watt, S.M., et al. 2001. *Blood.* 98:1469–1479.
4. Gray-Owen, S.D., and R.S. Blumberg. 2006. *Nat. Rev. Immunol.* 6:433–446.
5. Hunter, I., et al. 1996. *Biochem. J.* 320:847–853.