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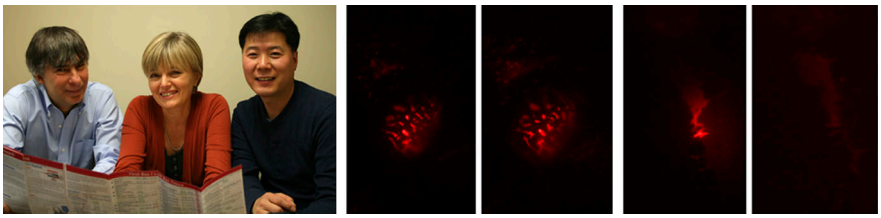
Cadherins trade bonds

Study describes how adhesion molecules rearrange their interactions to exit cell junctions.

Focal Point



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(Left to right) Sergey Troyanovsky, Regina Troyanovsky, and Soonjin Hong investigate how cadherin adhesion molecules alter their interactions with one another as they enter and exit adherens junctions. Cadherins form high-affinity, "strand-swapped" dimers directly but disassemble via a weaker "X-dimerized" intermediate. This allows cells to form strong intercellular junctions quickly but disassemble them just as rapidly. Cadherin mutants unable to X dimerize (left panels) form highly stable junctions, as indicated by the persistent red fluorescence in these time-lapse images. But cadherin mutants that can only form X dimers (right panels) turn over rapidly at intercellular contacts.

Cadherins are transmembrane, calcium-dependent adhesion molecules that assemble into adherens junctions to connect neighboring cells. Hong et al. reveal how cadherins regulate junction dynamics by changing their adhesive bonds (1).

Adherens junctions must rapidly assemble and disassemble to accommodate continuous cell movements within tissues (2). This creates a fundamental problem for cadherins, says Sergey Troyanovsky, from Northwestern University in Chicago, IL. "To quickly assemble a firm junction, the cadherin bonds must be very strong," Troyanovsky explains. "But then how can they disassemble so rapidly as well?"

Studying this question is complicated by the fact that cadherin-mediated adhesion depends not only on the adhesion molecule's extracellular domain but also on proteins such as β-catenin that bind to cadherin's intracellular tail. In 2010, Troyanovsky and colleagues developed a "tailless" cadherin mutant that could assemble junctions without binding to catenins (3), allowing the researchers to focus on the extracellular domain's contribution.

Structural models suggest that extracellular cadherin regions can form two types of dimers. The first is a strand-swapped dimer in which each cadherin inserts a tryptophan residue into a hydrophobic pocket within their partner. Two cadherins can also adopt a weaker configuration, known as an X dimer. Hong et al. made mutations to block each of these interaction modes in tailless cadherins (1).

Surprisingly, when high-affinity strand swapping was prevented—so that X dimerization was the only mode of interaction between cadherins—the adhesion proteins still formed junctions, albeit unstable ones with rapid turnover of individual cadherin molecules. On the other hand, tailless cadherins unable to X dimerize formed extremely stable junctions. "These mutants formed junctions slowly, but once the cadherins were integrated, they couldn't exit the junction," Troyanovsky says. These observations were hard to interpret until a biophysical study found that X dimerization is an intermediate step in the cadherin strand-swapping process (4). Cadherin mutants unable to form X dimers would therefore be expected to have very slow strand-swap dimer assembly and disassembly and, consequently, slow adherens junction dynamics.

> "Strand-swap-to–X dimer transition can be a key point of adherens junction plasticity."

"It looked like everything made sense," says Troyanovsky, "except that expression of the X-dimer mutants also influences the behavior of endogenous cadherin present in the same cells." Wild-type cadherin molecules also formed junctions slowly in the presence of the X-dimerization mutant. Why would this be the case if endogenous cadherin could still form X dimers? Hong et al. demonstrated that, although cadherin dimers disassemble via an X-dimerized intermediate, cadherins enter junctions and swap strands without forming an X dimer along the way. Instead, X-dimerization mutants impair adherens junction formation by forming abnormally stable, strand-swapped dimers with cadherin molecules in the same cell membrane, which are then unavailable for binding to cadherins from the neighboring cell.

Cadherins therefore assemble and disassemble junctions through distinct pathways. They form strong, strand-swapped dimers directly but shift to a weaker mode of interaction—X dimerization—when they need to break apart. Troyanovsky says that this is similar to the way that tubulin molecules change their interactions after microtubule polymerization in preparation for fast disassembly. "Our work suggests that strand-swap-to–X dimer transition can be a key point of adherens junction plasticity," says Troyanovsky.

What regulates these different interaction modes in vivo? One candidate is tension from the actomyosin cytoskeleton— myosin contraction could pull neighboring cells into a configuration that favors strand swapping and adherens junction stability. Another candidate could be the catenins and other proteins that bind the cadherin intracellular tail and organize individual cadherin dimers within adherens junctions. Catenins clearly affect cadherin dimerization because, unlike tailless mutants, full-length cadherin molecules don't form junctions at all if their X dimerization is inhibited. "The catenins prevent such abnormal cadherins from forming junctions," Troyanovsky says. "Our next step in understanding cadherin adhesion is to find out what intracellular mechanisms switch the modes of cadherin dimerization."

1. Hong, S. et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201006113.
2. Gumbiner, B.M. 2005. *Nat. Rev. Mol. Cell Biol.* 6:622–634.
3. Hong, S., et al. 2010. *Proc. Natl. Acad. Sci. USA.* 107:3528–3533.
4. Harrison, O.J., et al. 2010. *Nat. Struct. Mol. Biol.* 17:348–357.