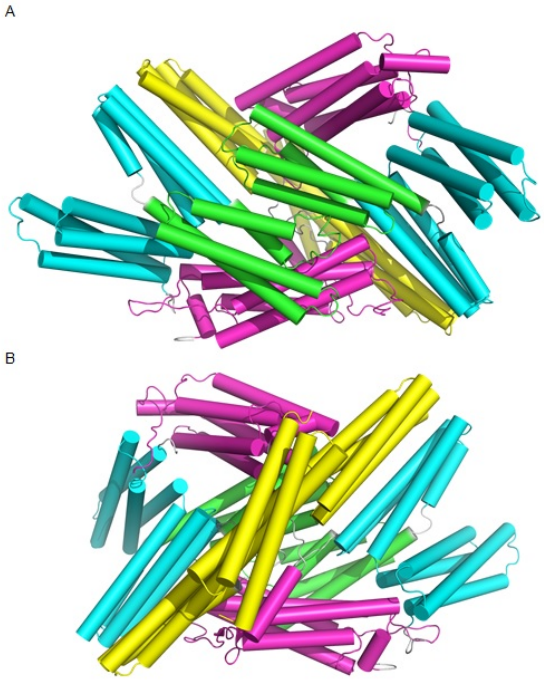
The Long-Sought Structure of α-Catenin Defines Its Functions for Cell-Cell Interactions

Cells bind each other using specialized cell surface adhesion complexes called adherens junctions. These complexes direct the formation of tight, Velcro-like contacts that are essential for the development, architecture, maintenance, and function of tissues in all higher organisms. Adherens junctions are made up of three types of proteins: (1) Cadherin receptors that span the cell membrane and direct the binding of cells to each other using domains that project to the outside of the cell. (2) β-catenin binds to the tail domains of cadherins, which are found on the inside of the cell. (3) α-catenin then binds to β-catenin. The term catenin is derived from the Latin word for chain, 'catena', and forming a chain is what cadherin, β-catenin, and α-catenin literally do. The adhesion complex is stabilized by the binding of α-catenin, the end of the chain, to the molecular framework of the cell, the cytoskeleton. Without this link, cells would simply be amorphous soft assemblies. Furthermore, when cadherins, β-catenin, and/or α-catenin are altered, there are marked changes in cell signaling, growth, and migration, which can result in abnormalities and cancer.



Full-length α-catenin crystal structure reveals its dimeric asymmetric arrangement. The individual domains are colored individually (dimerization domain in yellow, vinculin binding domain in green, M-fragment in cyan, and the F-actin binding domain in magenta). A: View onto the vinculin binding domains. B: View onto the dimerization domains.

The exact mechanism by which α-catenin provides links to the cytoskeleton and the cadherin/β-catenin complex has puzzled scientists for a long time. Rangarajan and Izard from the Florida campus of The Scripps Research Institute (TSRI) have now solved this puzzle by determining the structure of α-catenin. The remote data collection robotics, tunability of wavelengths, and stable beam conditions at SSRL's Beam Line 11-1 greatly contributed to the successful data collection of the weakly diffracting α-catenin crystals. The automated crystal mounting system facilitated remote screening and validated data collection strategies for obtaining accurate phases to medium resolution (5.5 Å), using the protein crystals soaked in a tungsten cluster derivative. This step was essential for solving the structure. The work was published in the February 2013 edition of the journal *Nature Structural & Molecular Biology.*

α-catenin forms links to the cytoskeleton by binding to a protein called F-actin (the "F" stands for filament), which is found in species ranging from yeast to humans. It has been a paradox for scientists that α-catenin cannot bind to F-actin while also bound to β-catenin, although it is able to bind to F-actin on its own. In other words, the binding of α-catenin to F-actin and β-catenin exclude each other in the test tube. How does α-catenin bind to F-actin versus β-catenin, and how is the final link in the chain stabilized in cells?

To resolve this paradox, Rangarajan and Izard crystallized nearly full-length human α-catenin and determined its structure, which explained why α-catenin cannot bind simultaneously to F-actin and β-catenin. Specifically, in its unbound state, α-catenin was shown to be an asymmetric dimer in which the two subunits have remarkable differences in their architecture. The two subunits together appear to create the binding site for F-actin. Binding of β-catenin to α-catenin disrupts the interaction of the two subunits. This change in α-catenin's architecture dramatically reduces the binding affinity for F-actin.

How are cadherin/β-catenin and α-catenin/F-actin complexes linked together in cells? This part of the puzzle was resolved when Rangarajan and Izard realized that another cytoskeleton protein called vinculin, which can also bind to F-actin, plays a critical role in this process [1]. Specifically, the comparison of the structures of dimeric α-catenin alone and in its complex with pre-activated vinculin established that vinculin binding did not disrupt the α-catenin dimer. In fact, both partners of the vinculin/ α-catenin complex were capable of binding to F-actin, a scenario that would stabilize adhesion complexes.

Reference

[1] E. S. Rangarajan, T. Izard, "The Cytoskeletal Protein α-Catenin Unfurls upon Binding to Vinculin", *J. Biol. Chem.* **287,** 18492 (2012)

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