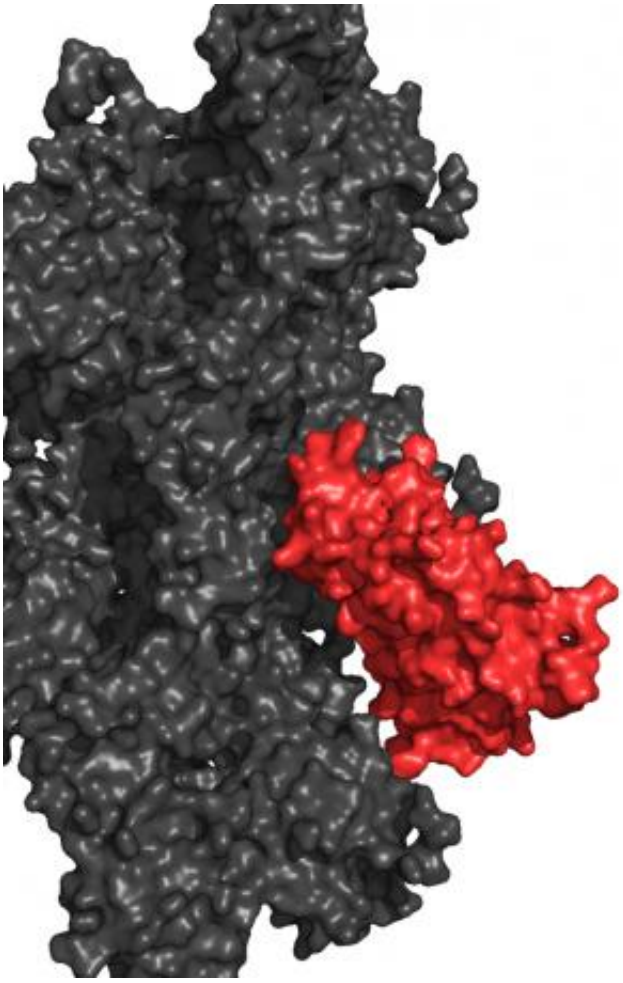
Researchers develop new model of cellular movement

April 18 2014, by William Davis



Proteins actin and vinculin bind together at a site identified by researchers at the UNC School of Medicine. The interaction of the proteins plays an important role in cell movement. Credit: UNC/Campbell Lab

(Phys.org) —Cell movement plays an important role in a host of biological functions from embryonic development to repairing wounded tissue. It also enables cancer cells to break free from their sites of origin and migrate throughout the body.

A new study led by Sharon Campbell, PhD, professor of Biochemistry and Biophysics at the UNC School of Medicine and member of UNC Lineberger Comprehensive Cancer Center, deepens the understanding of a pair of proteins – vinculin and actin – that work together to allow a cell to migrate throughout the body. The study, published in the journal *Structure*, proposes a new model for understanding how these proteins bind together to facilitate cell movement. This team effort was conducted in collaboration with the labs of UNC Lineberger members Keith Burridge, Nikolay Dokholyan, and Richard Superfine, as well as with Edward Egelman's laboratory at the University of Virginia.

The best model for the interaction between vinculin and actin dates back to 2006, when researchers used low-resolution electron microscopy data and computational modeling to identify potential sites where these proteins bind together. Campbell's team revised that model using data from a combination of higher-resolution electron microscopy, computer-generated molecular modeling, and the creation of mutant variants of vinculin.

"Our data supported a unique surface that was important for actin binding," said Campbell. "Identification of this actin binding surface on vinculin has enabled us to dissect how this critical interaction controls how cells respond to force and move. This, in turn, will help us better understand how disregulation leads to disease."

Cell movement plays an important role in cancer research because of the role of metastasis in tumor development. In many cancers, the greatest threat to the patient comes not from the original tumor but from the

cancer cells that migrate and form new tumors throughout the body. Campbell says there is some data on vinculin's role in promoting metastasis, but there is a need for more research to determine the link.

"By helping us better understand how cell movement is regulated, we can better understand metastasis," said Peter Thompson, lead author of the Structure paper and graduate student in the Campbell lab.

To create the model, researchers developed mutants of vinculin that disrupted the actin/vinculin interaction. The model identified a new face of the protein that contains a site where actin and vinculin bind together, a distinct, second and stronger interaction, than the previously described binding site from the old model.

"Our data suggest that there's a face on the vinculin tail that has been ignored by the previous model, and that it is very important," said Thompson.

Earlier research by Campbell's lab determined some of the consequences of vinculin physically binding to the actin that makes up the cytoskeletal matrix within a cell. Acting as a molecular clutch, vinculin engages with actin to transfer force and help control cellular motion.

As vinculin is an extremely abundant protein with roles in a variety of biological processes, a greater understanding of the protein's function could have broad medical implications, including with heart disease.

"In your cardiovascular system – your heart and arteries – the cells that form these organs need to stick together tightly. They do this in part by forming cell-to-cell adherens junctions," said Thompson. "Vinculin creates a critical physical link between the actin cytoskeleton and these junctions. If you disrupt that, the hypothesis is that cells no longer respond appropriately to force and the organ suffers."

Provided by University of North Carolina at Chapel Hill School of Medicine