Squeeze play: Protein's grip like a baseball bunter's

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Like all good baseball players, the protein calmodulin appreciates the importance of maintaining a good grip. A vital regulatory protein in all plants and animals, calmodulin is known to grab hold of hundreds of different proteins inside our cells, and it typically uses a grip that would make a Little League coach proud: it holds its two clasping lobes firmly together, one atop the other, like the hands of a big league slugger.

In a surprising find, researchers from Rice University and the University of Texas Health Science Center at Houston (UT-Houston) report in the Oct. 11 issue of *Structure* the first-ever case of calmodulin using a different kind of grip, a more open grasp that's reminiscent of a batter trying to lay down a bunt.

"If your hands are together, your arms operate as one unit," said Rice co-author Kevin MacKenzie, demonstrating a swing with an imaginary bat. "But when you bunt," he said, sliding one hand up into the classic bunter's stance, "your arms operate independently, and that's what we're seeing calmodulin do in this case."

Calmodulin is a vital biochemical player in life forms that range from fungi to humans. Its utility lies in its ability to pass on signals both outside and inside of cells. It does this by carrying out one specialized function: it binds with calcium ions and changes shape when it does so. As it changes shape, it grabs hold or lets go of other proteins.

"Nature could have selected a system where each protein bound calcium

on its own, but instead it uses calmodulin for that and then has calmodulin interact with the other proteins," said MacKenzie, assistant professor of biochemistry and cell biology.

One of calmodulin's roles in muscle cells comes in regulating the flow of calcium ions into the cell. When your nerve sends a signal to your heart to beat or your arm to move, the signal causes tiny compartments of calcium inside the muscle cells to open briefly and release a burst of calcium ions that cause the muscle to contract. Then, tiny pumps throughout the cell remove the calcium and put it back in the compartments, causing the muscle to relax.

Calmodulin is known to grab hold of the valve on the compartment that opens to release the burst of ions and closes again when the compartment is being filled. This valve, known as the ryanodine receptor, or RYR1, is almost 35 times larger than calmodulin, and the team from Rice and UT-Houston used a combination of X-ray crystallography and nuclear magnetic resonance (NMR) to determine the precise structure or shape of calmodulin that binds to the receptor in the presence of calcium.

"Though calmodulin is known to bind to lots of different proteins, it usually grabs hold with both lobes or lets go with both, depending upon whether calcium is around," MacKenzie said. "With RYR1, calmodulin stays bound whether calcium's there or not, and we think this two-handed grip could play a functional role, perhaps allowing it to keep hold with one lobe at all times, but grabbing and releasing with the other to help open or close the valve."

MacKenzie said the researchers confirmed calmodulin's new grip using state-of-the-art techniques on the Gulf Coast Consortia's (GCC) powerful 800 MHz NMR in Rice's Keck Hall. MacKenzie believes the new grip plays a key role in allowing our muscles to contract and relax quickly. He said the team hopes to learn more through follow-up

investigations of the structure of calmodulin that is bound to the receptor in the absence of calcium. Preliminary results suggest that calmodulin uses yet another grip in this situation.

"The combination of X-ray crystallography and NMR residual dipolar couplings allowed us to identify both the overall structure of the complex and movements within the complex on the microsecond time-scale, which is important because that time scale is relevant for fast-twitching muscles," he said. "But it's actually pretty hard to measure motion at the microsecond time scale using NMR."

Source: Rice University