Researcher studies protein's link to heart disease

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(Medical Xpress)—The largest protein known to exist in the human body functions as a molecular spring, and University of Arizona researchers are gaining new insights into its role in heart disease.

Many heart conditions are well-characterized on a clinical level, for example blockages leading to a heart attack, or weakened heart muscle leading to heart failure, but our understanding of what causes these conditions on a cellular and molecular level is still extremely limited.

Henk Granzier, professor of physiology, molecular and cellular biology, and biomedical engineering, uses cutting-edge technology to look inside cells and analyze titin, a protein roughly 100 times the size of typical proteins found in muscle, and the role it plays in the heart's cycle of pump and fill.

After earning his doctorate in physiology and bioengineering from the University of Washington, Granzier conducted his postdoctoral training at the University of Texas with Kuan Wang, who discovered titin in the late 1970s.

The average human adult has roughly 1 pound of titin in the body, and while the protein stands out for its size as a chain of almost 40,000 amino acids, its role was a mystery when it was first discovered.

"Despite the fact that we have so much of it, titin was discovered late relative to other abundant proteins in the body," Granzier says. "It's so much larger than normal proteins that it's hard to detect titin with normal biochemical techniques. At the beginning, scientists were skeptical it was even a protein.

"Now we know it's a very important protein for the structure of contractual units in the muscle. As the heart pumps, it has to both squeeze and then expand again to fill itself. That filling aspect of the cycle has been largely ignored by scientists until recently. In fact, studies conducted during the last few years have shown that amazingly half of the patients with heart failure have as cause of their deadly disease a malfunction in the filling phase."

Granzier's research, conducted with the support of four major National Institutes of Health grants, uses an integrative approach that spans a wide range of levels from molecular biology, single molecule biophysics, cellular physiology, muscle mechanics and whole heart physiology.

Additionally, it uses models that mimic human disease. His lab's focus is on titin's role in biomechanical sensing and signaling, cardiomyopathy, and diastolic function or disfunction.

"Titin is quite important for understanding diseases since it can be mistuned or mutated," says Granzier, who also holds the Norville Endowed Chair in Sarver Heart Center's Molecular Cardiovascular Research Program.

Problems that can arise in titin involve changes or mistuning in the spring aspect, essentially creating a stiff heart muscle that won't perform properly, or mutations that can happen in titin, because it has such a large gene, that effectively shorten the protein to the degree that it loses functionality.

"Now scientists like myself are thinking about how to use this knowledge," says Granzier. "The next frontier is how to use the understanding of the basic biology of titin to come up with therapies to help patients."

Provided by University of Arizona