Study finds fat hormone's long-sought link to heart protection

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One of the many advantages of maintaining a normal body weight is having healthy fat, which in turn supports a healthy heart. Fat tissue is increasingly seen as more than just a storage depot - it's also an active secretory organ that normally produces high levels of a cardioprotective hormone called adiponectin. How adiponectin protects the hearts of healthy people has long been a mystery, and now a team led by Barbara Ranscht, Ph.D. and Pilar Ruiz-Lozano, Ph.D. at Sanford-Burnham Medical Research Institute (Sanford-Burnham) reveals that the protein T-cadherin is the receptor that anchors adiponectin to heart cells. This new study, published November 1 in *The Journal of Clinical Investigation*, helps answer the longstanding question about how adiponectin prevents stress-induced damage in the heart.

"Whereas healthy people usually have high adiponectin levels circulating in their bodies, obese fat is different from healthy fat. Obese fat produces less adiponectin, reflected in lower levels of adiponectin found in serum," explained Dr. Ranscht, professor in Sanford-Burnham's Tumor Microenvironment Program and senior author of the study. "Many clinical studies correlate low adiponectin levels with an increased risk for heart disease, stroke and other cardiovascular dysfunctions."

Dr. Ranscht's laboratory previously studied T-cadherin for its role in brain development and cancer, and had noted T-cadherin's abundant expression in the heart when discovering this molecule in the early nineties. The best way to determine T-cadherin's role in heart protection is to see what happens when the protein is missing, so Dr. Ranscht and colleagues engineered mice that lacked T-cadherin and looked at their hearts. They found that adiponectin was no longer able to bind to heart tissue, leaving more hormone flowing in the bloodstream. The researchers then exposed T-cadherin-deficient animals to cardiac stress by restricting blood flow. Without the ability to bind adiponectin to the heart, mice with mutant T-cadherin suffered from increased cardiac damage and experienced the same symptoms as mice lacking adiponectin under those conditions.

To further prove T-cadherin's partnership with adiponectin in cardiac protection, the researchers attempted a rescue experiment. It was known that administering adiponectin to adiponectin-deficient mice reverses stress-induced heart damage. If T-cadherin were indeed necessary for mediating adiponectin-induced cardioprotection, then this rescue should not work in T-cadherin-deficient mice. Therefore, the researchers first had to generate a mouse model that lacks both the hormone and the receptor. Indeed, adding adiponectin to the double mutant mice did not rescue the stress-damaged hearts, underscoring the importance of T-cadherin for adiponectin functions in the heart.

How do adiponectin and T-cadherin collaborate to promote healthy hearts? Adiponectin is known to activate a cascade of molecular events converging on a protein called AMP-activated protein kinase (AMPK), which in turn regulates energy usage in the cell. This study showed that T-cadherin is required for adiponectin-induced AMPK activity.

According to Dr. Ranscht, the next steps will be to test if T-cadherin is necessary for adiponectin's other beneficial functions in metabolism and inflammation, and to identify the pathways connecting T-cadherin to AMPK activation in the heart. "Our work shows that T-cadherin is necessary for adiponectin functions, but we still don't know how T-cadherin transmits the adiponectin-binding signal into the cell. We are now searching for proteins that might functionally associate with T-cadherin and thus form the molecular link between T-cadherin and AMPK."

More information: Denzel MS, Scimia M-C,

Zumstein PM, Walsh K, Ruiz-Lozano P, Ranscht B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. *The Journal of Clinical Investigation*. November 1, 2010.

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