Researchers find protein induces non-shivering muscle heat generation

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(Medical Xpress)—A team of researchers working in Ohio has found evidence that suggests that the protein sarcolipin, normally a calcium regulator pump, also serves as a means of causing muscles to generate body heat independent of shivering. In their paper published in *Nature Medicine*, the team says their results show that energy heat derived from brown fat burning white fat stores, or muscle shivering, are not the only means the body has of keeping warm.

The traditional view of thermogenesis, where energy stores are burned to keep the body warm, is that brown fat grabs resources from white fat and burns it or muscles contract and relax rhythmically producing shivering, are the only two means mammals have for maintaining warmth when it's colder outside than inside their bodies. This new research shows that there is a third way as well, and it involves the protein sarcolipin, which the researchers say, causes otherwise idle muscles to burn energy which creates heat which also helps to keep the body warm.

The researchers came to this conclusion by studying the impact of brown fat, muscles and sarcolipin on heat generation in mice. First they genetically caused a small group of mice to cease producing sarcolipin, then they removed all of their brown fat. They also removed the brown fat from another small test group still able to produce sarcolipin. Afterwards, all of the mice in both groups were subjected to a 4 °C cold test environment. The mice that weren't producing sarcolipin died within ten hours, those that were, even without the aid of their brown fat,

survived. This proves, the team says, that sarcolipin does indeed induce idle muscle to produce heat, enough obviously to keep mice alive in a cold cage.

But there was another, perhaps even more intriguing, finding as well. The team reports that the mice that had their ability to produce sarcolipin removed tended to gain weight as well when put on a high fat diet; so much so that they grew to become 33 percent heavier than mice that continued to produce sarcolipin. This, the team says, might just have implications in the human world as it seems plausible that increased amounts of sarcolipin production might result in more energy burning and thus weight loss. That hasn't been tested yet, but it most certainly will be, both by this team and others searching for a way to help people lose weight despite inappropriate diets or limited exercise regimens.

More information: Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals, *Nature Medicine* (2012) doi:10.1038/nm.2897

Abstract
The role of skeletal muscle in nonshivering thermogenesis (NST) is not well understood. Here we show that sarcolipin (Sln), a newly identified regulator of the sarco/endoplasmic reticulum Ca2+-ATPase (Serca) pump1, 2, 3, 4, 5, is necessary for muscle-based thermogenesis. When challenged to acute cold (4 °C), Sln−/− mice were not able to maintain their core body temperature (37 °C) and developed hypothermia. Surgical ablation of brown adipose tissue and functional knockdown of Ucp1 allowed us to highlight the role of muscle in NST. Overexpression of Sln in the Sln-null background fully restored muscle-based thermogenesis, suggesting that Sln is the basis for Serca-mediated heat production. We show that ryanodine receptor 1 (Ryr1)-mediated Ca2+ leak is an important mechanism for Serca-activated heat generation. Here we present data to suggest that Sln can continue to interact with

Serca in the presence of Ca2+, which can promote uncoupling of the Serca pump and cause futile cycling. We further show that loss of Sln predisposes mice to diet-induced obesity, which suggests that Sln-mediated NST is recruited during metabolic overload. These data collectively suggest that SLN is an important mediator of muscle thermogenesis and whole-body energy metabolism.