Key protein drives 'power plants' that fuel cells in heart and other key body systems

4 August 2015

Case Western Reserve University scientists have discovered that a protein called Kruppel-like Factor 4 (KLF4) controls mitochondria—the "power plants" in cells that catalyze energy production. Specifically, they determined KLF4's pivotal role through its absence—that is, the mitochondria malfunction without enough of the protein, which in turn leads to reduced energy. This decline is particularly problematic in the heart because lower energy can lead to heart failure and death.

The researchers' findings appear in the August edition of *The Journal of Clinical Investigation* (*JCI*). In addition to an article detailing the research, the edition also features a First Author Perspective piece from Xudong Liao, PhD, an assistant professor of medicine in the area of cardiovascular medicine at Case Western Reserve University School of Medicine.

"Some cells are incredibly dependent on mitochondria, particularly the heart and brain," Liao said. "The brain is working all the time, too, even while we are sleeping, so it is particularly sensitive to mitochondrial function. Cancer also hijacks mitochondrial machinery to drive its spread. Therefore, the identification of KLF4 as a major regulator of mitochondria health may have implications beyond those we detailed in this article."

Mitochondria are described as "power plant" structures because they convert sugars and lipids to adenosine triphosphate (ATP), the energy currency for all cells. The number of mitochondria, their ability to produce energy, and their repair and/or removal when damaged constitute some of the key aspects of mitochondria's lifecycle. The investigators found that KLF4 controls these critical aspects of mitochondrial biology.

"Xudong made the observation several years ago that mice lacking KLF4 in the heart developed profound heart failure in response to stress," said senior author Mukesh Jain, MD, the Ellery Sedgwick Jr. Chair and Distinguished Scientist, and director of the Case Cardiovascular Research Institute, Case Western Reserve University School of Medicine. "In this most recent research, he looked into the mechanisms for why the heart had failed so quickly and made the exciting observation that KLF4 controls major aspects of the mitochondrial biology."

The initial hint that KLF4 regulates mitochondrial biology came from genome-wide studies that revealed a strong signature for KLF4's control of mitochondrial genes. Next, Liao and his colleagues compared the effects of cardiac stress on normal mice and on those lacking KLF4 in their hearts. The normal mice adapted to the stress and didn't succumb to heart failure for weeks. In contrast, half the KLF4-deficient mice died of heart failure within a week; the rest experienced severe declines in the heart's ability to contract and pump blood.

Further investigation revealed massive mitochondrial damage and energy reduction. From there, the researchers showed that KLF4 also regulates mitochondrial biogenesis (production of new mitochondria) and mitophagy (mitochondrial repair and maintenance).

"Mitochondria have their own life cycle, and KLF4 controls it," Jain said. "Increasingly, there is a view that mitochondrial dysfunction is a major contributor to many forms of heart failure. The heart has an unrelenting need for energy and thus any mitochondrial dysfunction will impair the heart's ability to pump blood."

In addition to examining the role of mitochondria in other organ and system function, the researchers also plan to search for ways to increase the amount of KLF4 in cells involved in the heart's work. "If we could target compounds to enhance KLF4 in specific tissues, we may be able to ameliorate disease," Jain said.

Provided by Case Western Reserve University