How Does Calcium Impact Cardiac Mitochondria?

The ability of a cardiac cell to work hard and continuously depends on the energy-producing function of its mitochondria. Calcium is key to proper mitochondrial function—but only in the right amounts. Too much calcium leads to cell death; too little suppresses production of the fuel a cell needs to function.

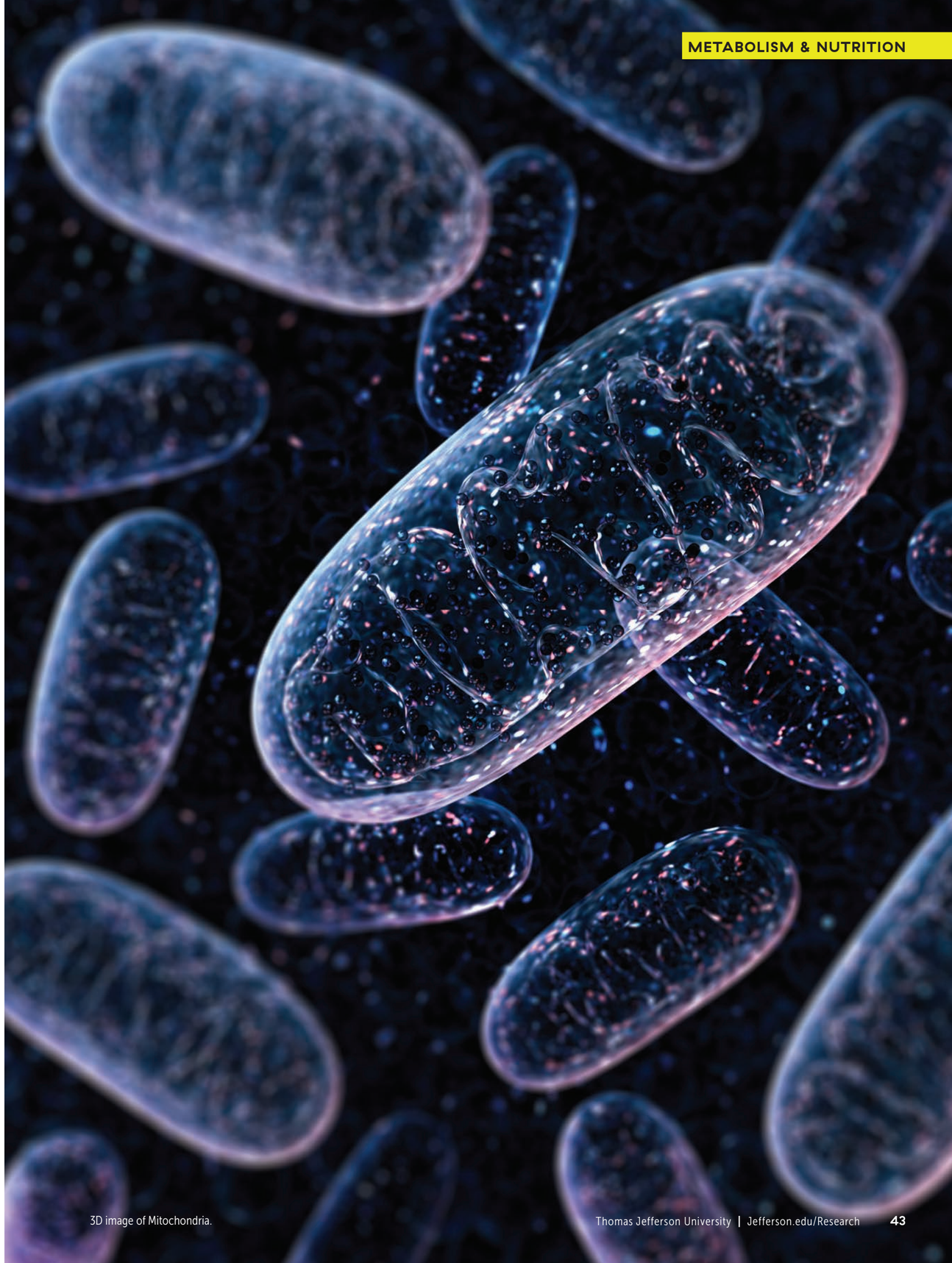
Research collaborators **Shey-Shing Sheu, PhD**, professor of medicine, and **Gyorgy Csordas, MD**, research associate professor of pathology, anatomy and cell biology, are studying the mechanisms by which cardiac mitochondria use calcium and other molecules. And they are shedding light on how dysfunction in those mechanisms contribute to ischemic heart disease, cardiac arrhythmias and heart failure. Currently, Drs. Sheu and Csordas are engaged in three related NIH-funded studies.

The first study is probing the function of the mitochondria's inner membrane, which regulates the transport of ions and metabolites including calcium. The opening of an inner-membrane structure called the permeability transition pore (PTP) can cause mitochondrial swelling that, if sustained, leads to cell death. The researchers are working to determine, among other mechanistic questions, how increased calcium concentration opens the PTP. "In addition," Dr. Sheu says, "the study is exploring whether different forms of the PTP could provide a relief valve for excess calcium. That would offer a potential target for drugs that prevent cardiac cell damage."

The second study explores the role that excessive activation of a specific protein—called dynamin-related protein 1—plays in persistent PTP opening. "This work will help us better understand how a healthy heart can perform perpetually in the face of enormous workload and what goes wrong to lead to heart failure," explains Dr. Sheu.

Finally, the third study seeks to better understand how the calcium released from a cellular structure called the sarcoplasmic reticulum of dyadic junction—which initiates muscle contraction—enters the mitochondria. As Dr. Csordas explains, the researchers believe that the new knowledge gained in this study will help explain how this process contributes to regulating the energy metabolism of the heart—and factors into the dysregulation that leads to cardiac disease. ■

> **"The study is exploring whether different forms of the PTP could provide a relief valve for excess calcium. That would offer a potential target for drugs that prevent cardiac cell damage."**
>
> Shey-Shing Sheu, PhD



3D image of Mitochondria.