Coenzyme A plays leading role in nitric oxide function so essential to cell metabolism

January 14 2015

Case Western Reserve and University Hospitals (UH) Case Medical Center researchers and physicians have discovered that the molecule known as coenzyme A plays a key role in cell metabolism by regulating the actions of nitric oxide. Cell metabolism is the ongoing process of chemical transformations within the body's cells that sustains life, and alterations in metabolism are a common cause of human disease, including cancer and heart disease. Their findings about the mechanisms of action for coenzyme A, as well as discovering a new class of enzymes that regulate coenzyme A-based reactions, appear in the Dec. 15 edition of the *Proceedings of the National Academy of Sciences* (*PNAS*).

"The governing role of coenzyme A in nitric oxide function was completely unknown and unanticipated before this study," said senior author Jonathan Stamler, MD, professor of medicine, Case Western Reserve University School of Medicine, and director, Harrington Discovery Institute at UH Case Medical Center. "Nitric oxide operates in every cell and tissue of the body to influence cell function. We are trying to work through the basic control of nitric oxide biology to elucidate the machinery underlying its mechanisms of action."

Coenzyme A sets into motion a process known as protein nitrosylation, which unleashes nitric oxide to alter the shape and function of proteins within cells to modify cell behavior. The purpose of manipulating the behavior of cells is to tailor their actions to accommodate the ever-changing needs of the body's metabolism.

In addition, Case Western Reserve and UH investigators identified hundreds of proteins regulated by coenzyme A-driven protein nitrosylation. Many of the newly discovered targets of nitrosylation were noted to influence cellular energy production. Because coenzyme A itself serves as a source of energy for cells, the authors concluded that nitrosylation might influence the major building blocks of cells such as fats and sugars.

"We are trying to understand how nitrosylation works in ensuring that nitric oxide achieves its specificity in regulating cell function. We have found new enzymes that regulate nitrosylation by coenzyme A," Stamler said. "We know that aberrant protein nitrosylation is a common cause or contributor to disease. We anticipate that these new enzymes may play a role."

During their research, investigators studied yeast in making their discoveries about coenzyme A and also a new class of enzymes that control the ability of coenzyme A to nitrosylate proteins. These newly found enzymes have a profound effect on cell metabolism, particularly in sterol (cholesterol) synthesis, by regulating the signal mechanism of cell metabolism and protein nitrosylation. Alternations in cholesterol levels are a common cause of atherosclerosis and Alzheimer's.

"We are excited to say that these new classes of enzymes potentially provide entry into metabolic regulation in mammals and offer new pathways and new possibilities for understanding cell metabolism," Stamler said. "This new class of enzymes is present in every living cell, and it governs metabolic signaling molecules and regulates cellular metabolism in organisms from bacteria to humans."

In terms of next steps, Stamler and fellow researchers will work to identify the specific functions of each enzyme in the class of enzymes they discovered during the course of this investigation.

The fundamental basic discoveries of this new class of enzymes and of coenzyme A function could open a new avenue of scientific research. His findings anchor the development of new therapeutic approaches for patients with heart and other diseases.

"Cell metabolism is a hot topic today because alterations in cell metabolism serve as a signature for a whole variety of diseases," Stamler said. "Our findings about these cell metabolism mechanisms promise new understanding of health and disease."

Provided by Case Western Reserve University