Researchers discover new enzymes central to cell function

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Doctors have long treated heart attacks, improved asthma symptoms, and cured impotence by increasing levels of a single molecule in the body: nitric oxide.

The tiny molecule can change how proteins function. But new research featured in *Molecular Cell* suggests supplementing nitric oxide—NO—is only the first step. Researchers have discovered previously unknown enzymes in the body that convert NO into "stopgap" molecules—SNOs—that then modulate proteins. The newly discovered enzymes help NO have diverse roles in cells. They may also be prime therapeutic targets to treat a range of diseases.

The discovery represents a paradigm shift for biologists in the field, says study lead Jonathan Stamler, MD, professor of medicine at Case Western Reserve University School of Medicine and President, University Hospitals Harrington Discovery Institute.

"Nitric oxide has been implicated in virtually all cellular functions, and too much or too little is widely implicated in disease, including Alzheimer's, heart failure, cancer, asthma and infection," he explained. "The prevailing view in the field is that too much or too little NO is due to activity of enzymes that make NO, called NO synthases. However, the new findings suggest that NO synthases operate in concert with two new classes of enzymes that attach NO to target proteins, and raise the possibility of literally hundreds of enzymes mediating NO-based signaling."

The enzymes work together to control proteins through a process called S-nitrosylation. Stamler and colleagues describe a chain reaction. First, NO synthases make NO. Then, a new class of enzymes—SNO synthases—convert NO into SNOs, that attach to proteins and modulate their function. A third class transfers the SNOs to additional proteins that control numerous additional cellular functions, including growth, movement and metabolism, and also protect cells from injury. Without SNO synthases, cells can't use NO. And there are potentially hundreds of different SNO-generating enzymes that make thousands of different SNOs.

NO signaling in cells is essentially designed to make SNOs—lots of them.

"This opens the field to new understanding and opportunity, as hundreds of enzymes likely carry out signaling inside cells through this process. Each of these enzymes could potentially be targeted specifically in disease," Stamler said.

With so many enzymes in the new model, it now makes sense why drugs that increase NO levels are not interchangeable. "The assumption is that they all work the same way to increase NO. But our findings suggest that NO itself is just the first step. It's all in what the cell does with NO and which SNO it's converted into," Stamler said. "Administration of NO cannot replicate the function of SNOs carried out by these new enzymes."

The groundbreaking study finally explains how NO can have so many different functions in cells. By converting NO into different SNOs, cells can achieve different results.

The next step for researchers will be to identify individual SNO synthases in different tissues and their specific roles in disease, says

Stamler. The new enzymes could serve as therapeutic targets for drug developers. For example, excessive S-nitrosylation is strongly associated with Alzheimer's and Parkinson's diseases, but NO is also needed for normal brain function, including memory.

"The assumption has been that one has to block NO production to stop this from happening. But the treatments don't work," he said. Since NO has such sweeping effects inside cells, blocking it has major side effects. Under the new model, researchers could target disease-specific SNO synthases working downstream of NO.

"Now we know that we can block S-nitrosylation without altering NO production," Stamler said. "This provides a new horizon of therapeutic opportunities, and changes perspective in the field."

More information: Seth, et al. "A Multiplex Enzymatic Machinery for Cellular Protein S-nitrosylation." *Molecular Cell*.

Provided by Case Western Reserve University

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