Scientists elevate little-studied cellular mechanism to potential drug target

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For years, science has generally considered the phosphorylation of proteins -- the insertion of a phosphorous group into a protein that turns it on or off -- as perhaps the factor regulating a range of cellular processes from cell metabolism to programmed cell death. Now, scientists from the Florida campus of The Scripps Research Institute have identified the importance of a novel protein-regulating mechanism -- called sulfenylation -- that is similar to phosphorylation and may, in fact, open up opportunities to develop new types of drugs for diseases such as cancer.

The study was published December 11, 2011, in an advance online edition of the journal *Nature* Chemical Biology.

"With this paper, we've elevated protein sulfenylation from a marker of oxidative stress to a bona fide reversible post translational modification that plays a key regulatory role during cell signaling," said Kate Carroll, a Scripps Research associate professor who led the study. "The sulfenyl modification is the new kid on the block."

During periods of cellular stress, caused by factors such as exposure to UV radiation or chronic disease states like cancer, the level of highly reactive oxygen-containing molecules can increase, resulting in inappropriate modification of proteins and cell damage. In sulfenylation, one oxidant, hydrogen peroxide, functions as a messenger that can activate cell proliferation through oxidation of cysteine residues in signaling proteins, producing sulfenic acid. Cysteine, an amino acid

(natural protein building block), is highly oxidant sensitive.

Conventional wisdom has long held that if hydrogen peroxide does exist in the cell at any appreciable level, it represents a disease state, not a regulatory event. The new study shows that sulfenylation is actually a positive protein modification, and that it's required for signaling through the pathway, a validation of a long-held belief in some scientific circles that hydrogen peroxide functions as a general signaling molecule, not an oxidative "bad boy" to be eliminated at all costs.

A New Chemical Probe

To explore the process, Carroll and her colleagues developed a highly selective chemical probe -- known as DYn-2 -- with the ability to detect minute differences in sulfenylation rates within the cell.

With the new probe, the team was able to show that a key signaling protein, epidermal growth factor receptor (EGFR), is directly modified by hydrogen peroxide at a critical active site cysteine, stimulating its tyrosine kinase activity.

The technology described in the new paper is unique, Carroll said, because it allows scientists to trap and detect these modifications in situ, without interfering with the redox balance of the cell. "Probing cysteine oxidation in a cell lysate is like looking for a needle in a haystack," she said, "our new approach preserves labile sulfenyl modifications and avoids protein oxidation artifacts that arise during cell homogenization."

As with phosphorylation, future studies on sulfenylation will delve into the exciting discovery of new enzymes, new signaling processes, and new mechanisms of regulation.

Another broad impact of these findings, Carroll said, is to open up an

entirely new mechanism to exploit for the development of therapeutics, particularly in cancer. "It should influence the design of inhibitors that target oxidant-sensitive cysteine residues in the future," she said.

More information: "Peroxide-dependent Sulfenylation of the EGFR Catalytic Site Enhances Kinase Activity," Candice E. Paulsen et al., *Nature Chemical Biology* (2011).

Provided by The Scripps Research Institute

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