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Specific oxidation regulates cellular functions

Hydrogen peroxide is a dangerous metabolic product that can damage cellular components through oxidation. This, however, is not its only role in the cell, as scientists had assumed for a long time. Scientists from the German Cancer Research Center (DKFZ) have now discovered how this small molecule also transmits specific signals in the cell: Enzymes called peroxiredoxins catch the free hydrogen peroxide molecules and use them to specifically oxidize other proteins. Hydrogen peroxide thus regulates, for example, the activity of an inflammation-promoting transcription factor and hence controls important cellular functions.

Hydrogen peroxide (H_2O_2) is a strong oxidizer and is used as a bleaching agent for hair and teeth, and as a wound disinfectant. In addition, H_2O_2 also forms in the body, for example as a metabolic product of cellular respiration. It belongs to a group of chemicals called reactive oxygen species (ROS), which scientists suspect to have a damaging effect on cells and their components. For example, they are believed to play a role in carcinogenesis, degenerative diseases, and even aging. Body cells contain large quantities of enzymes called peroxiredoxins that degrade H_2O_2 and have been believed to act as a protection against the supposedly dangerous H_2O_2 molecules.

About ten years ago, research results showed that things are not quite as simple as that: “Under most conditions, H_2O_2 is not an undesired side product but rather an essential chemical messenger that plays an important role in regulating the way in which body cells respond to signals from outside such as hormones and growth factors,” says Dr. Tobias Dick of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). “We know today that the body’s own H_2O_2 is vital for signal processing in a healthy organism.” H_2O_2 transmits signals by oxidizing specific proteins at particular sites, thereby alternatively turning them on or off. Dick and his co-workers have now been the first to show the molecular mechanisms behind this signaling through specific oxidation in human cells.

This mechanism has long been enigmatic for scientists: A signaling molecule needs to act specifically. How can a tiny molecule like H_2O_2, which is hardly any larger than a water molecule (H_2O), specifically oxidize particular proteins while leaving others completely unaffected? And why is it that the relatively small amounts of H_2O_2 that are produced for signaling are not immediately captured by peroxiredoxins before H_2O_2 can even react with target proteins?

Dick’s team has now shown that the solution is as simple as it is elegant. The DKFZ researchers proved that H_2O_2 is in fact captured by peroxiredoxins immediately after forming. What happens next, however, came as a surprise: The peroxiredoxins used H_2O_2 to oxidize other proteins. This means that they do in fact catch H_2O_2, though not in order to prevent its oxidative effect but rather to orderly direct them to very specific targets. Unlike the tiny H_2O_2 molecule, peroxiredoxins can interact specifically with other proteins. Thus, they are able to target and oxidize other proteins in order to regulate their function. The oxidative alteration of the target proteins is only temporary and does not cause any damage.

The researchers used an example to demonstrate the mechanism: They identified the transcription factor STAT3, which regulates inflammatory processes and can promote tumor

development, as a prominent target protein of one peroxiredoxin. They were able to show that the peroxiredoxin transmits the oxidative effect of H_2O_2 to STAT3. The oxidation status of STAT3, in turn, determined how efficiently the transcription factor regulates gene activity. Contrary to all previous assumptions, the researchers were able to exclude the possibility of direct and spontaneous oxidation of STAT3 by free H_2O_2.

“Tumor cells produce larger quantities of H_2O_2 and use oxidative signals at higher levels than normal cells in order to drive their own growth,” says Mirko Sobotta, first author of the publication. “Now that we have identified the peroxiredoxins as key players in specific oxidation, we can target them in order to interfere with cancer-relevant oxidative signals.”

The new study does not only unravel a fundamental problem of biology but it also uncovers a new level of regulation for the cancer-relevant transcription factor STAT3. The research project is part of the Collaborative Research Center 1036 (SFB 1036), which pursues research on basic mechanisms of cellular regulation within the DKFZ-ZMBH alliance.

Sobotta, M.C., Liou, W., Stöcker, S., Talwar, D., Oehler, M., Ruppert, T., Scharf, A.N., and Dick, T.P. (2014). Peroxiredoxin-2 and STAT3 form a redox relay for H_2O_2 signaling. Nature Chemical Biology 2014, DOI: 10.1038/nchembio.1695.

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