Better understanding of hydrogen peroxide regulation can lead to new insights into disease development

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The team of prof. Joris Messens at the VIB-VUB Center for Structural Biology has provided new insights into the regulation of an important intracellular messenger molecule, hydrogen peroxide (H_2O_2), whose dysregulation has been linked to the development of several diseases, including cancer.

To fine-tune levels of H_2O_2, cells can sense changes in the concentration of H_2O_2 and respond by activating specific DNA regulation mechanisms. In bacteria, a protein called OxyR functions as such a H_2O_2-sensor. The exact mechanism of how OxyR senses H_2O_2 and changes its DNA binding properties, however, has hitherto remained unexplored.

By combining protein X-ray crystal structures with supporting molecular biological and biochemical experiments, Dr. David Young and Dr. Brandán Pedre together with international collaborators and co-workers of the Messens lab have provided new insight into this question. They have uncovered the precise H_2O_2 binding site and the conformational changes that OxyR uses to bind to DNA and stimulate the regulation of the cellular H_2O_2 concentration.

"Previously, the H_2O_2-induced structural change of OxyR has led to the development of fluorescence-based genetically encoded H_2O_2 sensors, offering a way to visualize compartment-specific endogenous H_2O_2 in real time in living cells in various pathological conditions," explains Dr.

David Young (VIB-VUB). Brandán Pedre (VIB-VUB) adds: "This new insight in the structural details of the OxyR protein not only clarifies how the cell arms itself against H_2O_2 changes but will also enable us to create more sensitive and specific OxyR-based fluorescent biosensors. Such sensors will help us to better understand how aberrant H_2O_2 signaling leads to disease and, in the long run, identify new drug targets."

More information: Brandán Pedre et al. Structural snapshots of OxyR reveal the peroxidatic mechanism of H2O2 sensing, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1807954115

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