Selectively manipulating protein modifications

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Protein activity is strictly regulated. Incorrect or poor protein regulation can lead to uncontrolled growth and thus cancer or chronic inflammation. Members of the Institute of Veterinary Biochemistry and Molecular Biology from the University of Zurich have identified enzymes that can regulate the activity of medically important proteins. Their discovery enables these proteins to be manipulated very selectively, opening up new treatment methods for inflammations and cancer.

For a healthy organism, it is crucial for proteins to be active or inactive at the right time. The corresponding regulation is often based on a chemical modification of the protein structure: Enzymes attach small molecules to particular sites on a protein or remove them, thereby activating or deactivating the protein. Members of the Institute of Veterinary Biochemistry and Molecular Biology from the University of Zurich in collaboration with other Institutes have now discovered how the inactivation of a protein, which is important for medicine, can be reversed.

New group of ADP-ribosylhydrolases identified

An important protein modification is ADP-ribosylation, which is involved in certain types of breast cancer, cellular stress reactions and gene regulation. So-called ADP-ribosyltransferases attach the ADP ribose molecule to proteins, thereby altering their function. In recent

years, many ADP-ribosyltransferases have been discovered that can convey single or several ADP-riboses to different proteins. Enzymes that can remove these riboses again, however, are less well known. Professor Michael Hottiger's team of researchers has now identified a new group of such ADP-ribosylhydrolases. The scientists discovered that a so-called macrodomain is responsible for removing the ADP-riboses in human proteins, but also in the bacterium Archaeoglobus fulgidus.

"We therefore assume that the reversal of the modification takes place in a similar way in different species," explains Michael Hottiger.

Biomedically relevant: inactivation of the modified enzyme GSK3β

The researchers also prove that ADP-ribosylhydrolases can remove the ADP-ribose of the intensively studied enzyme GSK3β, which regulates the synthesis of storage substances and is important in the progression of various diseases. ADP-ribosylation deactivates GSK3β, which can be reversed again by the newly identified enzyme. "Our discovery enables ADP-ribose modification to be manipulated and tested selectively, and new treatment methods developed for diseases such as inflammations or cancer," concludes Michael Hottiger.

More information: Florian Rosenthal, Karla L.H. Feijs, Emilie Frugier, Mario Bonalli, Alexandra H. Forst, Ralph Imhof, Hans C. Winkler, David Fischer, Amedeo Caflisch, Paul O. Hassa, Bernhard Lüscher and Michael Hottiger. Macrodomain-containing proteins are novel mono-ADP-ribosylhydrolases. *Nature Structural & Molecular Biology*. March 10, 2013. Doi 10.1038/nsmb.2521

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