Enzymes from dangerous bacteria become important tools for protein chemistry

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A research group at Umeå University, together with researchers in Munich, have identified two enzymes from the pathogenic Legionella bacteria that are very useful in chemically modifying proteins to be used in medical drugs. The result of the study is presented in the chemical journal *Angewandte Chemie International Edition*.

Bacteria infecting cells from the inside use specific chemical reactions to overtake the host cell's labeling strategy and can therefore make the cell into a suitable environment for the bacteria to multiply. To achieve this, the bacteria pumps out various enzymes in the host cell, which act as chemical catalysts and modify the host cell's own proteins. This leads to the proteins not being able to perform their tasks, alternatively start performing other tasks than they were originally set out to do.

One of these bacterial enzymes are present in the Legionella bacteria and is called AnkX. It starts the immobilisation of a small, so called phosphocholine moiety, on some of the host cell's proteins and, further along in the course of the infection, the bacteria sends out a new enzyme, called Lem3, to remove the small moiety. At the present, it is unknown why there is an enzyme that then removes the moiety from the proteins of the host cells.

"What is so interesting with the chemistry of intracellular bacteria is how it is so different in comparison to our own cell's chemistry. Here we have a unique chance at producing enzymes that can be used specifically in biochemistry, cell biology and biotechnology without having

overlapping reactivity with our own cells' enzymes," says Christian Hedberg, research group leader at the Department of Chemistry and corresponding author of the study.

In the daily research, intense work is being performed in trying to understand the chemical courses of event in infections but sometimes you also find specific applications.

"The idea to use the AnkX-Lem3 system for labeling proteins arose by coincidence when we were studying how AnkX modified certain proteins with phosphocholine. We saw that AnkX did not care particularly about which three-dimensional structure the protein had, just that the amino acid recognition sequence in the protein was correct. That made us realise the possibility to use the system in modifying any protein, as long as the amino acid recognition sequence of eight amino acids that AnkX recognises has been added genetically," says Hedberg.

The study also shows the possibility of finely adjusting the reactivity in the system. With AnkX it is possible to add a marking and with Lem3 it can be removed. This opens up for completely new applications – for instance by turning on and off a protein's function at certain times by first adding AnkX and then Lem3.

"This makes the AnkX-Lem3 system unique. There is no other enzymatic labeling system based on a short peptide sequence that it reversible," says Hedberg.

A future potential medical use can be to develop very selective labelings of biomolecules, for instance for binding of cancer drugs to particular antibodies to reduce the side effects.

Christian Hedberg's research group at Umeå University has collaborated with Aymelt Itzen's research group at the Technische Universität

München. The research team has utilised a broad scientific angle in the study – organic synthesis, biochemistry and molecular biology have all walked hand in hand. The German researchers have performed the biochemical characterisation.

Without the opportunity to produce a large variety of Legionella enzymes and various protein substrates, the study had not been possible. One of the crucial factors was the Protein Expertise Platform (PEP) in the KBC Building at Umeå University.

"Without PEP, we would not have been able to keep up such a fast pace of work in this project. We have been able to pass on time-consuming routine work to specialists," says Christian Hedberg.

More information: "Covalent Protein Labeling by Enzymatic Phosphocholination." *Angew. Chem. Int. Ed.*, 54: 10327–10330. doi: 10.1002/anie.201502618

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