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Thermogenetics: How Proteins are controllable by heat

Protein activity can be precisely regulated via subtle changes in temperature using heat-sensitive switches. Underlying this capability is a novel modular design strategy developed by researchers at the Institute of Pharmacy and Molecular Biotechnology of Heidelberg University. The strategy allows the integration of sensory domains in various proteins regardless of function or spatial structure. This new Heidelberg approach in the field of thermogenetics is broadly applicable and opens up new possibilities for precise, non-invasive control of different cellular processes. It was developed by a research team led by Prof. Dr Dominik Niopek and Dr Jan Mathony.

Proteins are the molecular machines of the cell. They regulate nearly all vital processes and their responses are highly dynamic. To better understand these processes and their chronological sequence, scientists need tools that can be used to change individual parameters precisely and in a controlled manner. The most suitable proteins are those that can be turned on and off like technical devices. Especially attractive in this context are heat-sensitive protein switches that tightly regulate the temperature spatiotemporally and are able to deeply penetrate tissue or complex biological samples as a signal.

Until now, temperature-dependent control of proteins was considered technically difficult and highly limited. Most available methods allow only indirect control by means of gene expression. The Heidelberg researchers solved this problem. They integrated optimized variants of a plant sensory domain into natural proteins, in order to develop so-called allosteric thermoswitches. These switches respond with high precision to minimal changes in temperature within the physiological temperature window of human cells, which is between 37 and 40 degrees Celsius. Thus, protein activity can be altered to tightly control cellular functions.

“Our goal was to make temperature usable as a versatile stimulus for protein control,” explains Ann-Sophie Kröll, a doctoral candidate in Dr Mathony’s team. To verify feasibility, the new approach was first tested and refined using the *Escherichia coli* bacterium. Then the researchers transferred their strategy to mammal cells and engineered temperature-controllable CRISPR-Cas gene editors, whose activity can be finely regulated. “Using these allosteric thermoswitches, we are able to directly and reversibly control cellular functions without actively intervening in other processes of the cell,” explains Prof. Niopek, who heads the Pharmaceutical Biology department at the Institute of Pharmacy and Molecular Biotechnology.

One major characteristic of this new approach is its high modularity. In addition to the sensory domain originally used, the researchers were also able to integrate an alternative receptor module into proteins that likewise responds to temperature changes. The modular design strategy of the Heidelberg researchers thus offers a general blueprint for engineering temperature-controlled protein switches. They can be integrated independently of the function or spatial structure of the given proteins and open up new possibilities for the precise control of various cellular processes without the need to intervene in the cell, thus enabling non-invasive control.

“We want to further develop thermogenetics into a comprehensive and broadly applicable technology that can be used in future to precisely regulate nearly every protein solely through heat. We are now at the threshold of the possible in this field,” states junior research group leader Jan Mathony. According to Dominik Niopek, the results present new perspectives for basic research. “They also promise great potential for future biomedical applications,” adds Prof. Niopek.

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Publication:

A.S. Kroell, K. H. Hoffmann, N.A. Motzkus, N. Lemmen, N. Happ, B. Wolf, A.L. von Bachmann, N. Southern, F. Vogd, S. Aschenbrenner, D. Niopek, and J. Mathony: Modular engineering of thermoresponsive allosteric proteins. Nature Chemical Biology (published online 12 February 2026), DOI: 10.1038/s41589-026-02151-y.

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Further information

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