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How enzymes regulate energy metabolism. New insights into the signalling network of cells

Mitochondria are known as the “cell‘s power plant“ fulfilling key functions for the metabolic processes in cells. An international research team led by Professor Clemens Steegborn, University of Bayreuth, currently detected a system of biochemical signals and processes interacting collectively in order to control the energy metabolic processes within cells. The scientists report on their results in the „Journal of Biological Chemistry“. These will advance the basic research in the field of signal controlled processes within cells. In addition, interesting perspectives for the development of therapeutic drugs will be established.

Prof. Dr. Clemens Steegborn
University of Bayreuth

To prevent cellular respiration from a standstill: the messenger cAMP

A key role for the energy metabolic processes within cells is assigned to cyclical Adenosine Monophosphate, in short: „cAMP“, which is acting as messenger transmitting signals that are essential for a functioning metabolism. It activates proteins within mitochondria which participate in cellular respiration thus controlling energy metabolism. The molecules of cAMP are located inside the mitochondria, the so-called matrix, which is enclosed by an inner and an outer membrane. In case of an increased quantity of cAMP molecules the energy metabolism will be stimulated. Conversely, a reduction in the cAMP molecules weakens the energy metabolism.

Controlled by enzymes: cAMP as a switch for energy metabolism

This is the point where the research results published by Steegborn in cooperation with his colleagues from Cornell University in New York and Ruhr-University in Bochum get traction.

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The scientists discovered how the reduction of cAMP contained within the mitochondria occurs. In their research they decrypted an important mechanism for regulating the messenger quantity:

- Increases of cAMP are controlled by the enzyme adenylate cyclase (sAC). This enzyme produces cAMP molecules from the cellular energy reservoir adenosyne triphosphate (ATP). In order for the enzyme to assume this catalytic function, it itself has to be activated, e.g. by bicarbonate.
- The opposite process, e.g. the reduction of cAMP levels, is initiated by another enzyme. The protein involved here originates from the family of phosphodiesterases (PDE); to be precise, an isoform of PDE2A. This enzyme must also be activated so that it may reduce the amount of cAMP contained in the mitochondria. This process is performed by molecules which aggregate along an area at the end of the protein – the N-terminus of the PDE2A molecules.

In this manner, the messenger cAMP acts as an enzyme controlled trigger which strengthens or weakens the energy metabolism. The trigger „position“ is determined by which of the two enzymes dominates: Adenylate cyclase (sAC) increases the amount of cAMP, phosphodiesterases (PDE2A) would reduce it.

From mice to men: Identical control mechanism in mammals

The scientists were particularly intrigued by the phosphodiesterases (PDE2A) present in the mitochondria. They did not only identify this enzyme in mitochondria of various cell tissues in mice and rats, but also in mitochondria of cultured human cells. „Based on our laboratory results, we can assume that this mechanism for controling energy metabolism basically operates in this fashion in all mammals“, Steegborn declares. He and his colleagues were also successful in demonstrating how the PDE2A is transported into the mitochondria. The N-terminus is responsible for allowing this particular form of phophodiesterases to pass through the protective double membrane of the mitochondria.

Which molecules within the mitochondria bind to the regulatory region of the PDE2A thus activating the enzyme, could not be determined yet. At present, Steegborn and his staff are testing the assumption that these molecules are cyclical Guanosine Monophosphate (cGMP). This is also an intracellular messenger, however, one which up to now could only be identified outside of the mitochondria, within the cytosol.

New perspectives to fight diseases, e.g. metabolic conditions

Discovering that phosphodiesterases weaken the activating impact of cAMP on cellular respiration provides new options for research into therapeutic drugs. Even today pharmaceuticals, which act as inhibitors on phosphodiesterases, are in use for other purposes.

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„Therefore, our findings provide attractive approaches for developing substances which counteract specifically the reduction of cAMP“, Steegborn declares. Consequently, such active ingredients could increase energy metabolism and contribute to successfully fighting metabolic conditions or, in addition, neuronal diseases.

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Rebeca Acin-Perez, Michael Russwurm, Kathrin Günnewig, Melanie Gertz, Georg Zoidl, Lavoisier Ramos, Jochen Buck, Lonny R. Levin, Joachim Rassow, Giovanni Manfredi, Clemens Steegborn,

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