New insights into the fuctions of fat metabolism

August 14 2017

What happens when the body's fat stores are activated? With the support of the Austrian Science Fund FWF, the biochemist Ruth Birner-Grünberger investigated the complex interaction of activation and regulation in fat breakdown, thus providing a basis for new therapeutic approaches for illnesses such as diabetes or arteriosclerosis.

After exhausting the fast energy provided by glucose (from carbohydrates), a marathon runner's body starts burning fat. When people exercise continuously at a low pulse rate, lipolysis starts after about 30 minutes. When people are hungry, the same thing happens—the fat cells receive a hormonal signal telling them to make a depot available and break down the stored lipid droplets into fatty acids. Even during fast walking, these processes occur in the body at lightning speed.

"The activation and control processes are launched within seconds. This is only possible because the proteins needed to break down the fat cells do not have to be created, but are only unlocked," says biochemist Ruth Birner-Grünberger. She studied three things: which proteins were involved in fat burning, where their interaction in fat cells occurs, and how they are mobilised or inhibited.

Phosphate acts as switch

Birner-Grünberger has been investigating lipolysis since her postdoc

period in 2002. In her research unit at the Institute of Pathology at the Medical University of Graz, she develops technologies for proteomics: "It involves trying to detect proteins based on their activity in specific metabolic processes," she says.

In a preliminary search for lipolytic enzymes in fatty tissue and in the liver, she identified several candidates: "There are several lipases, i.e. proteins that break down fat, plus other proteins that regulate the process." Particularly striking for the researchers was the amount of phosphorylation they found. Phosphorylation is a chemical modification that binds phosphates to proteins and thereby serves to activate or inhibit proteins in cells. This consumes less time and energy than launching protein synthesis or degradation anew every time. The research project was designed to answer the question as to when and where chemical modifications unlock or inhibit the proteins involved in lipolysis.

In vitro studies were not sufficient, however, to explain the interaction of the lipolytic proteins. "The biological system is complex, strictly regulated and location-dependent. We cannot achieve a complete picture by just mixing fat droplets, lipase and an activator in a test tube," explains the researcher. The scientists observed animal cells by means of a confocal laser-scan microscope.

They discovered the first steps of spatial and chemical interaction on the fat droplets in tissue cells: In order to activate the first (of three) lipases, there is a chain of command including the activator CGI58 and the regulator perilipin. When the fat cells are in a basal state, the two proteins are sitting on the lipid droplet bound together. Upon marking with phosphate, they separate; CGl58 travels to another spot on the droplet in order to activate the first lipase (ATGL). As a regulator, perilipin prevents the lipases from being activated when they are not required. This is interesting, because common illnesses such as diabetes and arteriosclerosis are encouraged by an overloaded lipid metabolism.

If the body is supplied with more energy than it can burn for a long time, it leads to the disturbance of a carefully paced and spatially balanced system.

Birner-Grünberger plans a follow-up project during which she intends to use phosphoproteomics (i.e. the global analysis of thousands of protein phosphorylation processes in cells) to understand which energetic processes are regulated simultaneously with lipolysis, such as glycogen degradation, and to observe the temporal sequence. "It looks as though fat cells are able to adjust within minutes to the fact that fatty acids are required and to how they are processed further. We not only need them for delivering energy, as in the case of exercise or hunger, but also for building cell membranes and signalling molecules." In order to carry out these analyses, the project group also developed a method for the improved evaluation of proteomics data.

More information: Anita Sahu-Osen et al. CGI-58/ABHD5 is phosphorylated on Ser239 by protein kinase A: control of subcellular localization, *Journal of Lipid Research* (2014). DOI: 10.1194/jlr.M055004

Matthias Schittmayer et al. Cleaning out the Litterbox of Proteomic Scientists' Favorite Pet: Optimized Data Analysis Avoiding Trypsin Artifacts, *Journal of Proteome Research* (2016). DOI: 10.1021/acs.jproteome.5b01105

Provided by Austrian Science Fund (FWF)