Adaptation to food deprivation as a clue for treating metabolic diseases

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When people are deprived of food, a number of biological mechanisms are set in motion to adapt the body's metabolism to the conditions of scarcity. One of these processes has been revealed by a team of Belgian researchers, led by professor Karolien De Bosscher (VIB-Ghent University). The scientists discovered how three important proteins collaborate on a genetic level to provide a response to long-term fasting. The insights are published in the leading scientific journal *Nucleic Acids Research*, and could ultimately be put to use in clinical environments to treat metabolic diseases more efficiently.

As the research covered multiple aspects of gene regulated metabolic processes, several parties were involved. While conducted in the Jan Tavernier lab (VIB-Ghent University, specialized in medical biotechnology) and in close cooperation with the Claude Libert lab (VIB-Ghent University, focusing on inflammation), it is also the result of a long-standing collaboration with the team of professor Bart Staels at the Institut Pasteur de Lille (France), a prominent scientist in the field of metabolic diseases.

Protein with a new function

The researchers uncovered that long-term fasting triggers specific proteins. One of those recognizes the stress hormone cortisol, another one senses the amount of fatty acids (important energy sources), and a third protein called 'AMPK' detects cellular energy. Particularly the

discovery of AMPK teaming up with these other sensors within the cell nucleus in a state of food deprivation came as a real surprise.

Prof. Karolien De Bosscher (VIB-Ghent University): "Together with the other proteins, AMPK plays a more direct role than previously assumed. Apart from functioning outside a cell's nucleus as an energy sensor, we found the protein inside the nucleus as well, in a complex with the other two proteins. This complex stimulates the expression of metabolic genes coding for metabolic enzymes, which in turn control the sugar and fat metabolism. In short, AMPK plays a crucial role in a coordinated defense response to food deprivation."

Mimicking the effects

By better understanding the interactions of the three essentials proteins, the research teams hopes it will eventually be possible to mimic their effect in a controlled environment.

Prof. Karolien De Bosscher (VIB-Ghent University): "During former studies, we had already built up quite some knowledge about these proteins. After all, they have an impact on the body's metabolism in their individual state as well. However, this research with which my PhD student Dariusz Ratman graduated, shows how they are actually collaborating on a genetic level. We hope that understanding these effects will allow us to treat metabolic diseases more efficiently."

Mapping out AMPK

Especially the surprising location where AMPK was found, can form the basis for further steps. Although medication aimed at activating AMPK in its known function – as an energy sensor outside a cell's nucleus – already exists, for example to treat type 2 diabetes, side effects can

occur. That is why the researchers hope to contribute to the development of a more specific treatment to tweak AMPK in its genetic function as well.

Prof. Karolien De Bosscher (VIB-Ghent University): "Controlling AMPK's activity in the cell's nucleus, where it binds with the other proteins, could open up whole new treatment options. But first, there is still quite some work ahead. We are currently performing new experiments to fully figure out these novel genetic processes. Charting all these genes is far from a piece of cake, but we have high hopes that it will eventually lead to new therapeutic possibilities."

More information: Dariusz Ratman et al. Chromatin recruitment of activated AMPK drives fasting response genes co-controlled by GR and PPARα, *Nucleic Acids Research* (2016). DOI: 10.1093/nar/gkw742

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