Proteome of an entire family

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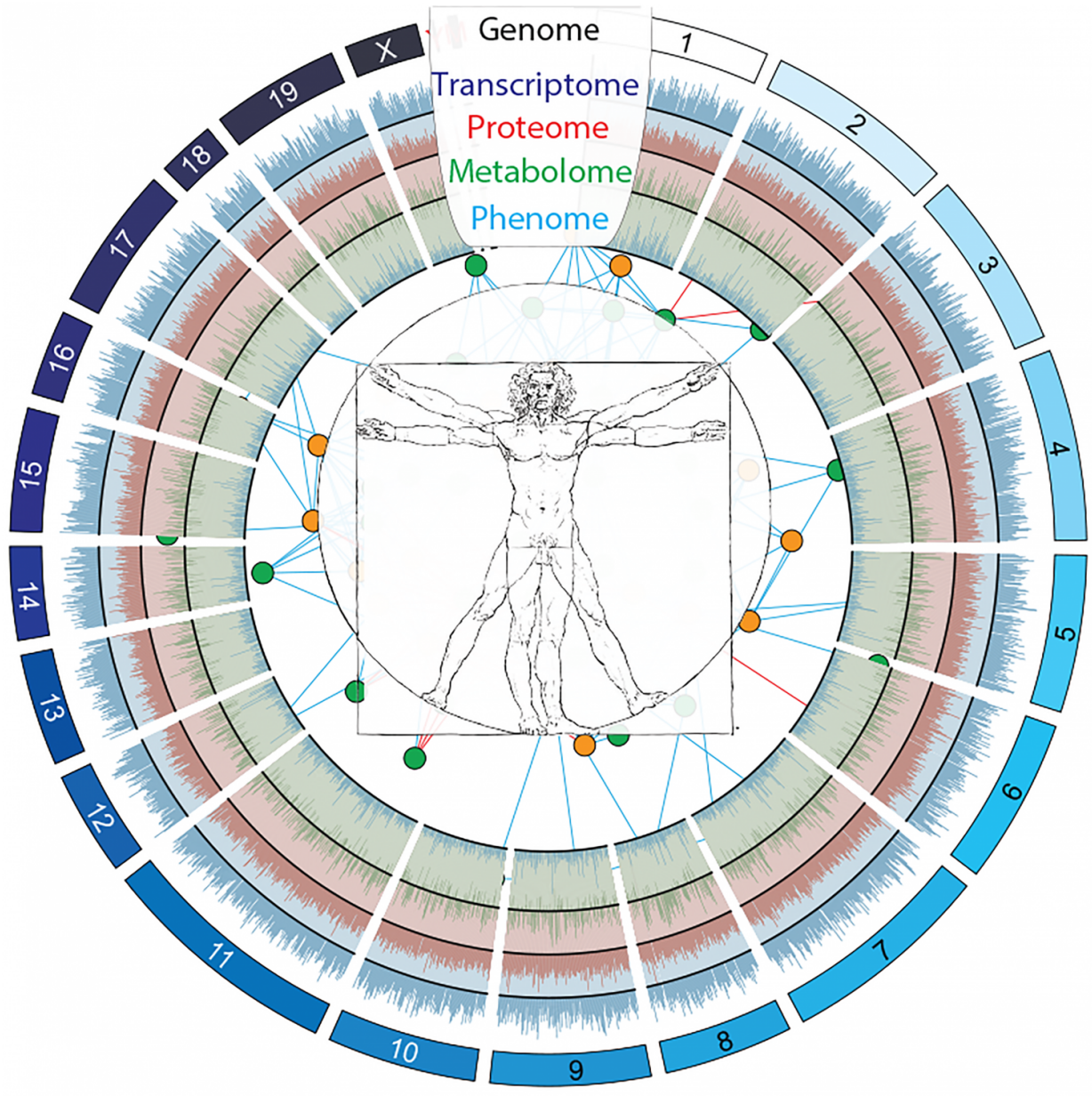

Understanding the different biological "layers" of an individual is the key to

personalized medicine. Credit: Johan Auwerx/EPFL

Scientists have won new knowledge on the molecular background of fat and energy metabolism disorders through a large-scale proteomic study with mice. The proteome is the entire set of proteins - in this case, proteins from the livers of mice. A research group specialising in proteomics, led by ETH Zurich Professor Ruedi Aebersold, and a group specialising in mitochondrial physiology and liver diseases, led by EPFL Professor Johan Auwerx, worked together on this ground-breaking project.

"As with humans, there are individual differences in mice; for example, in cholesterol metabolism or susceptibility to metabolic disorders such as fatty liver," says Evan Williams, one of the two lead authors of the study, which has been published in the latest edition of the scientific journal *Science*. Williams conducted the work as a doctoral student at EPFL and is now a postdoc at ETH Zurich. "Some of these differences could be explained genetically, but not all," he says.

Latest technique

The scientists compiled comprehensive protein data from a large group of mice to help them explain additional metabolic differences. They used a mass spectrometry measuring technique, known as SWATH-MS, developed in recent years by Aebersold's group at ETH Zurich. It allowed the researchers to measure the concentrations of a broad spectrum of liver proteins in the laboratory animals.

"It's much more complex to measure the set of proteins than to sequence the entire genome," explains Yibo Wu, postdoc in Aebersold's group and co-lead author of the study. "Using the SWATH-MS technique, it's

possible to measure thousands of different proteins in hundreds of samples." In this case, the researchers measured 2,600 different proteins in the tissue samples. In order to conduct these proteome measurements, an extensive protein database is required; Wu has played a leading role in recent years in building up such a database for mouse proteins.

Proteome complements the genome

The examined cohort consisted of 40 mice strains that date back to the same two ancestors and are therefore closely related to each other. Identical groups of mice, each consisting of representatives from these 40 strains, were fed either a high-fat diet, junk food in human terms, or a healthy low-fat diet. Over a period of weeks, the scientists charted the conventional medical (physiological) data of the mice and tested, inter alia, their performance and how quickly they reduced their weight through physical activity. As the scientists expected, the animals responded in different ways to the high-fat foods. Some of the animals developed metabolic disorders, such as fatty liver, others did not.

For the evaluation, the researchers combined the physiological data with data for genome (DNA), transcriptome (RNA) and proteome. From this combined data they were able to characterise the role of several specific proteins in fat and energy metabolism more precisely. One of these is COX7A2L. In mice this protein is responsible for the formation of supercomplexes found in mitochondria (the cell's internal 'power plants'), as the researchers found out. These supercomplexes consist of more than 100 different proteins and are responsible for providing cells with the required energy in the appropriate form. Mice with too little COX7A2L protein can't provide sufficient amounts of available energy, which impacts adversely on the whole organism.

Application in personalised medicine

This study is the most comprehensive proteomic study to date using SWATH-MS in mammals. The technique developed by ETH Zurich scientists is also ready for use in cohort studies in humans: the researchers in Aebersold's group have generated a corresponding database for thousands of human proteins. "Like the mouse strains in this study, each patient with a disease is genetically different", says ETH Professor Aebersold. "The approach we used in the mouse cohort can now be applied one-for-one in research on human diseases, and particularly for personalized medicine."

More information: "Systems proteomics of liver mitochondria function" *Science*, DOI: 10.1126/science.aad0189

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