Study advances knowledge of what happens in our cells after exercise

December 10 2021, by Ivy Shih

Illustration of a fingerprint produced using the phosphoproteome of one of the

study participants. Each square represents a phosphosite, and the color represents how different that phosphosite is to the other subjects. Credit: Elise Needham.

An international team of researchers has developed a new approach to pinpoint which proteins in our cells are most critical for increasing sugar absorption after exercise—an important benefit of exercise that can help maintain good blood sugar levels.

The results of this work are published in the December issue of the international research journal *Nature Biotechnology*, the result of a global collaboration by scientists at the University of Sydney and the University of Copenhagen.

By measuring proteins directly in human muscles using cutting-edge technology called mass spectrometry, the researchers discovered that each person has their own unique 'fingerprint' of protein activities.

The method they have developed identifies changes to proteins that differ across study participants in the same way that sugar absorption does.

Using this method, they uncovered a mechanism by which exercise increases the uptake of sugar into muscles following insulin stimulation, providing new understanding into this complex process.

"We all know that exercise is good for us, but it also helps to prevent specific diseases. For example, it improves the ability of our muscles to absorb sugar from the blood following a meal," said senior co-author Professor David James, ARC Laureate and Leonard P. Ullmann Chair of Metabolic Systems Biology at the Charles Perkins Centre and the University's Faculty of Medicine and Health and Faculty of Science.

"When this process fails, it is called 'prediabetes'—a risk factor for many diseases including heart disease, type 2 diabetes, and some types of cancers. Researchers don't know what causes prediabetes, but if they did, they could design drugs to treat this condition before it triggers disease."

Opening protein 'doors'

Sugar absorption by muscle is carried out by a collection of molecular machines called proteins.

This process begins with the binding of the small protein insulin to other proteins—receptors—on the surface of fat and muscle cells. This triggers a cascade of thousands of protein signals inside the cell—a process termed 'phosphorylation'. Ultimately these phosphorylation signals open protein "doors", bringing sugar into the cells.

Currently we know that in prediabetes many of these signals are defective, but we don't know which ones are most important to fix.

Elise Needham, Ph.D. candidate at the University of Sydney and lead author of the study, said a key challenge has been in the complexity of phosphorylation.

"Exercise involves thousands of changes to phosphorylation signals, and we do not know which are the most important for regulating the beneficial effects of exercise," said Ms Needham.

"To tackle this challenge, we developed a method called 'personalised phosphoproteomics'."

Using this approach, the team uncovered a new mechanism by which human muscle cells coordinate the response to exercise and insulin.

"Differences between individuals means that there is considerable biological variation in phosphorylation—like a molecular 'fingerprint'," said senior co-author Dr. Sean Humphrey, at the Charles Perkins Centre.

"This reduces the likelihood of identifying the most important responses. Instead of viewing this as an obstacle, we used it to our advantage".

The researchers also believe the technology can help identify other important molecular switches. For example, in the future, personalized phosphoproteomics will enable the comparison of diseased cells with healthy cells, helping to uncover the causes of complex disease.

More information: Elise J. Needham et al, Personalized phosphoproteomics identifies functional signaling, *Nature Biotechnology* (2021). DOI: 10.1038/s41587-021-01099-9

Provided by University of Sydney