Insight into the dazzling impact of insulin in cells

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Ph.D. student Sean Humphrey, from Sydney's Garvan Institute of Medical Research, is working on a mass spectrometer to uncover the phosphoproteome of a fat cell. Credit: Penelope Clay

Australian scientists have charted the path of insulin action in cells in precise detail like never before. This provides a comprehensive blueprint for understanding what goes wrong in diabetes.

The breakthrough study, conducted by Sean Humphrey and Professor

David James from Sydney's Garvan Institute of Medical Research, is now published in the early online edition of the prestigious journal *Cell Metabolism*.

First discovered in 1921, the insulin hormone plays a very important role in the body because it helps us lower blood sugar after a meal, by enabling the movement of sugar from the blood into cells. Until now, although scientists have understood the purpose of insulin at a broad level, they have struggled to understand exactly how it achieves its task.

The latest analytical devices called mass spectrometers now provide the tool that has been missing – the means of looking into the vastly complex molecular maze that exists in every single cell in the human body.

These powerful devices have opened up a field known as 'proteomics', the study of proteins on a very large scale. Proteins represent the working parts of cells, using energy to perform all essential functions such as muscle contraction, heartbeat or even memory.

Each cell houses multiple copies of between 10,000 and 12,000 protein types, which communicate with each other using various methods, the most common of which is a process known as 'phosphorylation'. Phosphate molecules are deliberately added to proteins in order to convey information, or else change the protein's function.

Each of the protein types in a cell has up to 20 potential 'phosphorylation sites', regions to which a phosphate molecule can be added. This pushes the total number of possible cell states from one moment to the next into the billions.

The authors discovered 37,248 phosphorylation sites on 5,705 different proteins, 15% of which changed in response to insulin.

"Until this study, we did not really appreciate the scale and complexity of insulin regulation," said lab leader Professor David James.

"When insulin is released from the pancreas after we eat, it travels to cells and initiates a cascade of protein phosphorylation, literally millions of interactions, some instantaneous, some taking minutes or hours. The process is so precise and intricate, and at the same time so monumental in its scope, that it's truly astounding."

Sean Humphrey, who undertook the mass spectrometry work, discovered over 1,500 phosphorylation sites that respond to insulin, and described the process as "eye opening".

"When you consider that phosphorylation is only one type of signaling – acetylation and methylation are other forms – you begin to understand the kind of complexity that faces us," he said.

In addition to cataloguing the phosphoproteome of the fat cell, the authors discovered novel regulation of a protein called 'SIN1', key to our understanding of the chain of events that occurs during insulin signaling. They have also described the mechanisms by which SIN1 influences other influential proteins within the cell, in particular one known as Akt.

"Sean's study has shed new light on how one of the most important regulators in the cell – a protein called Akt – is itself regulated," said Professor James.

"Akt not only plays a role in diabetes, but also in cancer and other diseases, and the discovery of SIN1 phosphorylation gives us useful new insights into how Akt actually functions in a cell."

"These large scale approaches are providing us with new levels of understanding of human biology that we would never have anticipated.

Without the mass spectrometer, we could not have discovered the importance of SIN1 phosphorylation in the overall insulin signaling process."

"It's an important lesson about the usefulness of this technology in allowing us to discover new things about the cell and how it regulates itself."

Provided by Garvan Institute of Medical Research