**Reconstruction of Insulin Signal Flow from Phosphoproteome and Metabolome Data**

**What is the medically relevant insight from the article?**

This research makes a significant contribution to our understanding of the role of insulin in maintaining metabolic balance, the sequence of signals involved in insulin-related signaling pathways, and the control mechanisms underlying glycolysis. The authors reconstructed the flow of insulin signals within a trans-omic network using data from phosphoproteome and metabolome analyses. Through their method that incorporated time-course data and multiple databases, they were able to identify pathways involved in insulin's acute action, specifically highlighting protein kinases, phosphorylated metabolic enzymes, and allosteric effectors as key components within this network. Additionally, they discovered specific regulatory pathways and reactions influenced by insulin, including its activation of liver-type phosphofructokinase 1—a crucial enzyme in glycolysis. Overall, this study presents an adaptable approach for reconstructing signal flow using phosphoproteome and metabolome data sources. It also has implications for enhancing our knowledge about metabolic disorders and potentially informing the development of innovative therapeutic approaches.

**Which genomics technology/ technologies were used?**

The cellular response to insulin was analyzed using a range of genomics technologies. These included genome tiling arrays for the identification of transcribed sequences, microarrays for gene expression analysis, RNA sequencing for reconstructing biochemical networks in microorganisms, metabolomics for profiling metabolites in plant functional genomics, phosphoproteomics for analyzing protein phosphorylation patterns, lipidomics for studying lipid profiles, and proteomics for examining protein expression levels.

**List and explain at least three questions/ hypotheses you can think of that extend the analysis presented in the paper.**

1. Does the signal flow of insulin differ between different cell types or tissues in a trans-omic network?

The focus of this study is on the signal flow of insulin in rat hepatoma cells. In order to expand our analysis, we can investigate whether the signal flow of insulin remains consistent across various cell types or tissues. By comparing the phosphoproteome and metabolome data from different cell types or tissues, we can identify any variations in the responsible metabolic enzymes, protein phosphorylation, and allosteric regulation in response to insulin. This would provide valuable insights into the regulation of insulin signaling specific to each cell type or tissue.

1. How is the signal flow of insulin affected under different physiological or pathological conditions?

The primary objective of this paper is to examine the signal flow of insulin in response to acute insulin stimulation. To further our analysis, we can explore how the signal flow of insulin is altered under different physiological or pathological conditions, such as fasting, obesity, or diabetes. By comparing the phosphoproteome and metabolome data from these conditions, we can identify any changes in the responsible metabolic enzymes, protein phosphorylation, and allosteric regulation. This would provide valuable insights into the dysregulation of insulin signaling in various disease states.

1. Can the signal flow of insulin be modulated by targeting specific protein kinases or allosteric effectors?

This paper identifies the protein kinases and allosteric effectors that are responsible for the signal flow of insulin. To expand our analysis, we can investigate whether modulating the activity of these protein kinases or allosteric effectors can alter the signal flow of insulin. This can be achieved through genetic or pharmacological manipulation of the protein kinases or allosteric effectors in cellular or animal models. By measuring the changes in the phosphoproteome and metabolome data, we can assess the impact on the signal flow of insulin. This would provide valuable insights into potential therapeutic targets for modulating insulin signaling.

**Devise a computational analysis strategy for (some of) the listed questions**

1. Does the signal flow of insulin differ between different cell types or tissues in a trans-omic network?

We can gather trans-omic data from different cell types or tissues under the same experimental conditions. This data should include measurements of metabolites, phosphoproteins, and gene expression levels. We then apply the reconstruction model explained in the paper and compare the results using statistical analysis.