# Phosphoproteomic analysis of metformin signaling in colorectal cancer cells elucidates mechanism of action and potential therapeutic opportunities


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## Abstract

Background

The biguanide drug metformin is a safe and widely prescribed drug for type 2 diabetes. Interestingly, hundreds of clinical trials have been set to evaluate the potential role of metformin in the prevention and treatment of cancer including colorectal cancer (CRC). However, the “metformin signaling” remains controversial.

Aims and Methods

To interrogate cell signaling induced by metformin in CRC and explore the druggability of the metformin-rewired phosphorylation network, we performed integrative analysis of phosphoproteomics, bioinformatics, and cell proliferation assays on a panel of 12 molecularly heterogeneous CRC cell lines. Using the high-resolute data-independent analysis mass spectrometry (DIA-MS), we monitored a total of 10,142 proteins and 56,080 phosphosites (P-sites) in CRC cells upon a short- and a long-term metformin treatment.

Results and Conclusions

We found that metformin tended to primarily remodel cell signaling in the long-term and only minimally regulated the total proteome expression levels. Strikingly, the phosphorylation signaling response to metformin was highly heterogeneous in the CRC panel, based on a network analysis inferring kinase/phosphatase activities and cell signaling reconstruction. A “MetScore” was determined to assign the metformin relevance of each P-site, revealing new and robust phosphorylation nodes and pathways in metformin signaling. Finally, we leveraged the metformin P-site signature to identify pharmacodynamic interactions and confirmed a number of candidate metformin-interacting drugs, including navitoclax, a BCL-2/BCL-xL inhibitor. Together, we provide a comprehensive phosphoproteomic resource to explore the metformin-induced cell signaling for potential cancer therapeutics. This resource can be accessed at https://yslproteomics.shinyapps.io/Metformin/.