Modeling the Regulation of Cancer Metabolism: Interplay between Glycolysis and OXPHOS

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Short Abstract:

Abnormal metabolism is a hallmark of cancer. In a traditional view, cancer cells largely utilize glycolysis for energy production irrespective of the presence of oxygen. Recently, increasing experimental evidence shows a critical role of actively functional mitochondria and oxidative phosphorylation (OXPHOS) in tumorigenesis and metastasis. However, how cancer cells orchestrate glycolysis and OXPHOS to facilitate malignancy is largely unknown. Through integrating mathematical modeling, bioinformatics with experiments, we show that cancer cells can acquire a stable hybrid glycolysis/OXPHOS phenotype, characterized by high activity of AMPK and HIF-1 and high metabolic activity of glycolysis and glucose/fatty acid oxidation.

Keywords **— Cancer metabolism, metabolic plasticity, hybrid metabolic phenotype, AMPK and HIF-1 signatures, gene regulatory network, metabolic pathway activity**

I. Background

ABNORMAL metabolism is an emerging hallmark of cancer [1]. Unlike normal cells, cancer cells largely depend on glycolysis to produce energy even in presence of oxygen. Emerging evidence shows that mitochondria are actively functioning in cancer cells and OXPHOS may be specifically associated with metastasis [2,3]. However, it remains elusive how cancer cells take advantage of both glycolysis and OXPHOS to facilitate malignancy.

To capture the two regimes of cancer metabolism, we develop a coarse-grained model on a core metabolism regulatory circuit, composed of AMPK, a master regulator of OXPHOS, HIF-1, a master regulator of glycolysis and ROS that can mediate the interplay between AMPK and HIF-1 [4]. Computational modeling of the AMPK:HIF:ROS circuit shows that in addition to the glycolysis and OXPHOS phenotypes, which are adopted by normal cells, cancer cells can acquire a hybrid glycolysis/OXPHOS phenotype, that can be promoted by elevated ROS production rate, stabilization of HIF-1 and regulation of oncogenes, such as MYC and c-SRC [4].

To quantify the activity of OXPHOS and glycolysis, we developed the AMPK and HIF-1 signatures by evaluating the expression of their downstream targets. Strikingly, even though the AMPK and HIF-1 gene sets are independent, we observed strong anti-correlation between AMPK and HIF-1 activities in multiple cancer types. The AMPK and HIF-1 signatures can capture the significant metabolic features of both bulk tumors and single cells [4].

To further characterize cancer metabolic activity, we extended our AMPK:HIF-1:ROS model by integrating three metabolic pathways, glucose oxidation, glycolysis and fatty acid oxidation. Our results unraveled a direct association between gene activity and metabolic pathway activity.

II. Results

A. Coupling the AMPK:HIF:ROS circuit with metabolic pathways

The modeling simulation revealed the coupling between the AMPK/HIF-1 activity and the metabolic pathway activity in different metabolism phenotypes. Particularly, the hybrid metabolic phenotype has been shown to be capable of using both glycolysis and OXPHOS for ATP production. The model further help elucidate the similarity and difference of HIF-1 and ROS in regulating the stability of various metabolism phenotypes of cancer.

B. Association of the AMPK/HIF-1 activity with metabolic pathway activity

The modeling predicted association of the AMPK/HIF-1 activity with metabolic pathway activity were supported by bioinformatics analysis of gene expression and metabolite abundance in breast and hepatocellular carcinoma samples. We showed that the evaluation of metabolic pathway activity by enzyme gene expression has more robust performance than the evaluation by metabolite abundance.

III. Conclusion

Our systems biology analysis provides signatures to assess the metabolic states of tumor samples using gene expression. Further studies are needed to evaluate the roles of the hybrid metabolic state and therapeutic strategies targeting the hybrid state.

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