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Cancer metabolism meets systems biology: Understanding metabolic master regulators

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Abstract

Pyruvate kinase activity is controlled by a tightly woven regulatory network. The oncofetal isoform of pyruvate kinase (PKM2) is a master regulator of cancer metabolism. PKM2 engages in parallel, feed-forward, positive and negative feedback control contributing to cancer progression. Besides its metabolic role, non-metabolic functions of PKM2 as protein kinase and transcriptional coactivator for c-MYC and hypoxia-inducible factor 1-alpha are essential for epidermal growth factor receptor activation-induced tumorigenesis. These biochemical activities are controlled by a shift in the oligomeric state of PKM2 that includes acetylation, oxidation, phosphorylation, prolyl hydroxylation and sumoylation. Metabolically active PKM2 tetramer is allosterically regulated and responds to nutritional and stress signals. Metabolically inactive PKM2 dimer is imported into the nucleus and can function as protein kinase stimulating transcription. A systems biology approach to PKM2 at the genome, transcriptome, proteome, metabolome and fluxome level reveals how differences in biomolecular structure translate into a global rewiring of cancer metabolism. Cancer systems biology takes us beyond the Warburg effect, opening unprecedented therapeutic opportunities.

Biography

Fabian V. Filipp is an Assistant Professor of Systems Biology and Cancer Metabolism at the University of California, Merced. He leads the Program for Quantitative and Systems Biology and is editor of the Journal of Metabolomics and Systems Biology. His research group employs genomics, transcriptomics, proteomics, metabolomics, and fluxomics tools to mechanistically decipher human metabolic disease. His developed methods in NMR spectroscopy, structural and chemical biology led to high-resolution insights into structure, dynamics, and function of the lipogenesis machinery in human cancer progression.

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