Pan-cancer analysis of mutation-associated metabolic reprogramming using genome-scale metabolic models

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Metabolic reprogramming is considered a hallmark of cancers, and plays an important role in cancer development and progression partly as a consequence of somatic mutations. A representative product of metabolic reprogramming in cancers is oncometabolites that are metabolites that show abnormal accumulation, induces malignancy, and are produced by metabolic gene mutations. However, metabolic pathways that are affected by mutations in key cancer genes are yet to be characterized. The aim of this study was therefore to characterize metabolic pathways and their metabolites that are affected in response to somatic mutations in multiple cancers. For this, we reconstructed genome-scale metabolic models (GEMs) for 948 cancer patients across 17 cancer types using patient-specific omics data from Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium. We next present a novel computational pipeline to identify key metabolites and metabolic pathways associated with somatic mutations, which was validated using relevant literature and multi-omics data of acute myeloid leukemia samples. Our computational pipeline and its prediction outcomes can be valuable resources for future cancer studies.