Metabolic dependencies in prostate cancer: regulation and targeting of lipogenesis

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Cancer cells overcome growth factor dependence by deregulating oncogenic and/or tumor-suppressor pathways that in turn affect their metabolism. It is not clear, however, whether human prostate tumors develop a similar metabolic response to different oncogenic drivers or if particular oncogenic events result in distinct and specific metabolic reprogramming. To determine whether driving oncogenes differentially affect prostate tumor metabolism, a metabolomics profiling study was performed in human prostate cancer cells transformed by MYC or AKT1, in tumors from transgenic mice with MYC and AKT expressed in the prostate under the probasin promoter, and in human prostate tumors in which either the MYC or AKT pathways were found to be activated. Integrative analysis of these metabolomic datasets revealed that AKT1 activation was associated with accumulation of aerobic glycolysis metabolites, whereas MYC overexpression was associated with dysregulated lipid metabolism. Overall, these results demonstrate that unique metabolic abnormalities in prostate cancer are associated with different oncogenes and that metabolic profiling, which can be performed in tissue or serum, may be useful in inferring driving oncogenes in metastatic disease. In addition, de novo lipogenesis also contributes to the tumorigenic phenotype induced by Fatty Acid Synthase-driven prostate cancers as well as in those arising in the context of the metabolic syndrome. These lipogenic tumors are targetable by suppressors of lipogenesis such as AMPK activators and by inhibitors of lipogenic enzymes.