Dissecting the Metabolic Regulation of Tumor Initiating Stem Cells

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Abstract: Metabolic reprogramming has emerged as a hallmark of cancer, exhibiting a profound impact on tumor progression. Changes in nutrient utilization are required to maintain the bioenergetic and biosynthetic demands of cancer cells and can be therapeutically targeted to treat human malignancies. However, the metabolic adaptations that occur during the early stages of cancer, including how stem cells respond to oncogenic stress during tumor initiation, are still poorly understood. Moreover, several classes of metabolites can regulate epigenetic processes and signal transduction, introducing the possibility that metabolites may directly influence transformation. To address these issues, we examine the consequences of metabolic reprogramming during tumor initiation in an autochthonous model of squamous cell carcinoma (SCC), among the most common and life-threatening cancers worldwide. By overexpressing Sox2, an essential transcription factor induced by SCC- initiating stem cells, we present preliminary data suggesting that altered *α*-ketoglutarate (*α*KG) levels and serine/glycine metabolism dependencies may act together to drive oncogenesis. First, we propose to establish techniques that enable the direct assessment of metabolism in epidermal stem cells while experiencing oncogenic stress and in fully formed tumors. We will test for metabolic vulnerabilities during the early stages of malignant transformation. Finally, we will investigate the impact of metabolic reprogramming on histone and protein methylation, linking candidate metabolites to transcriptional programs and pathways that establish cancer stem cell identity. Together, this work will improve our basic understanding of how metabolic reprogramming participates in tumor initiation, potentially identifying therapeutic avenues for preventative treatment.