

Dissecting SHMT2 Function as a Metabolic Driver of Lymphomagenesis

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Abstract: We find that the serine hydroxymethyltransferase-2 gene (SHMT2) is amplified in approx. 30% of human B cell lymphomas and that SHMT2 can act as a driver of lymphoma development in vivo. SHMT2 is therefore a first metabolic enzyme that can act as an oncogene in vivo. We propose a study to dissect the metabolic effects of SHMT2 activation in lymphoma, its contribution to lymphoma progression, and we will explore therapeutic implications of SHMT2 activity. The Wendel lab (MSKCC) has developed a new murine model of follicular lymphoma that captures the early stages of the disease and is ideally suited to study genetic drivers of lymphoma development and progression and characterize their biochemical and gene expression effects as well as test new therapies in genetically engineered tumors. The Birsoy lab (Rockefeller) will investigate the mechanistic effect of SHMT2 activation on lymphomagenesis using a combination of metabolomics and in vivo CRISPR-Cas9 based genetic screening approaches. A better understanding of the role of SHMT2 in Myc amplified lymphoma cells will also enable identification of new therapies in these cancers. The Birsoy lab has expertise in metabolomics and CRISPR screens and is ideally suited to carry out these studies.