CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

The Hexoasmine Biosynthetic Pathway Tunes YAP Signaling to Promote Glioblastoma Growth and Confer Poor Patient Prognosis

Sagar R. Shah MS, PhD; Christopher Saeui; Kevin Yarema; Alfredo Quinones-Hinojosa MD

Introduction

Alterations in metabolic flux is one of the hallmarks of cancer. Apart from the energetic demands for cancer cell survival, tumor growth and progression is driven by increased glucose consumption. This hyperactive glycolytic cycle subsequently generates substrates for the hexosamine biosynthetic pathway (HBP), a master regulator of glycoconjugate biosynthesis necessary for post-translational modification of proteins. Accumulating evidence has shown that defects in HBP signaling activate oncogenic factors via glycosylation to drive tumor growth and progression.

Methods

Patient-derived glioblastoma cells and tissues were utilized to evaluate HBP activity using metabolomics, western blotting of total and glycosylated proteins, PCR, and other in vitro functional assays. Manipulations of molecular targets was conducted using lentiviral -based shRNA and overexpression vectors or small molecular inhibitors. Expression profiling, GSEA, Kaplan-Meier analyses was performed using patient clinical data sets such as REMBRANDT and TCGA. Tumor growth and targeting was conducted using intracranial and subcutaneous GBM xenograft models.

Results

Our study demonstrates that hyperactivity of HBP leads to increased production of the sugar metabolite UDP-GlcNAc, which confers poor GBM patient prognosis. Specifically, UDP-N-acetylgalactosamine pyrophosphorylase (UAP), the central regulator of UDP-GlcNAc synthesis, drives GBM cell proliferation, stemness, migration, and invasion by enhancing YAP stability via O-GlcNAcylation, a post-translational modification event. Furthermore, targeting HBP signaling using a proprietary small molecule inhibitor or genetic inhibition of UAP attenuates tumor growth and progression.

Conclusions

Impairment in metabolic pathways regulating cellular energetics can lead to alterations in molecular networks that govern cell survival and growth. Our study demonstrates that hyperactivation of HBP drives GBM growth and progression through modulation of UAP-YAP signaling. Furthermore, our analyses provides insights into activation of oncogenic networks by global cellular O-GlcNAcylation, which leads to tumor aggressiveness and poor patient outcome. Furthermore, our potent proprietary small molecule inhibitors of HBP signaling offer a novel opportunity for the management and treatment of cancer, including glioblastoma.

Learning Objectives

By the conclusion of this session, participants should be able to:
1) understand the relevance of hexosamine biosynthetic pathway in cancer,
2) appreciate the molecular basis of oncogenic activation by altered metabolic flux,
3) identify viable treatment options and targets for HBP/UAP-YAP-driven tumor growth.

[Default Poster]