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Targeting hexosamine biosynthesis pathway for the treatment of desmoid tumors

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Cancer cells rewire metabolic pathways and energy production to support the enhanced proliferation, invasion and resistance to treatment. The three main glucose metabolism pathways that support growth of cancer cells are: a) the glycolysis pathway for energy production; b) the pentose phosphate pathway for biomass production; and c) the hexosamine biosynthesis pathway (HBP) for protein glycosylation. Activation of HBP leads to altered glycosylation of oncogenes, transcription factors and kinases in many types of cancer. These aberrations contribute to increased proliferation and survival of tumor cells, and are associated with resistance to therapy. Therapeutic targeting of GFPT2 (glutamine-fructose-6-phosphate transaminase 2, the first and rate-limiting enzyme in HBP) and the enzymes that act downstream of HBP exhibits anti-tumorigenic effect, and modulates sensitivity to chemo-, radio- and immunotherapy. Most of the studies of HBP focused on carcinomas and the role of HPB in sarcoma has not been extensively explored. We recently reported a remarkable enrichment of genes involved in HBP in a subset of leiomyosarcoma (LMS) and demonstrated that expression of GFPT2 in LMS is associated with poor clinical outcome. We identified the c-Myc oncoprotein as a potential target of HPB that may be stabilized by aberrant glycosylation in LMS.

Here we present data to support a new direction of research related to metabolic reprogramming and glycosylation in desmoid type fibromatosis (DTF). In addition to the previously reported expression of GFPT2 in a subset of LMS, we performed a large-scale screening of GFPT2 protein expression by immunohistochemistry in 260 primary specimens of 32 types of soft tissue lesions. In this screening, we observed near universal expression of GFPT2 protein in DTF, and a significant association of GFPT2 protein expression with DTF compared to other types of soft tissue tumors. Next, we further explored a possible activation of HBP in DTF based on the analysis of a previously published 3SEQ transcriptomic dataset from our lab that is composed of 53 specimens of 10 types of fibrotic lesions including DTF (PMID: 24342436). Gene Set Enrichment Analysis of this dataset identified HBP as the only glucose metabolism pathway enriched in DTF compared to the other types of fibrotic lesions. Gene Set Enrichment Analysis also demonstrated a significant enrichment of multiple REACTOME glycosylation-associated pathways in DTF. Our analysis also identified ATF6 (activating transcription factor 6) as a possible target regulated by aberrant glycosylation in DTF. Interestingly, ATF6 transcription factor is a glycoprotein that has been demonstrated to underlie the resistance to chemotherapy in osteosarcoma, to have a pro-oncogenic role in primary liver cancers and has been proposed as a therapeutic target in cystic fibrosis.

Our study offers new insights into metabolic reprogramming and mechanisms of tumorigenesis in DTF. Since targeting HBP can provide therapeutic benefit in preclinical models of carcinoma, our next goal is to confirm the activation of HBP in DTF by *in vitro* studies, which will provide a rationale to explore the potential of therapeutic targeting of this pathway in DTF.