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Therapeutic targeting of the hexosamine biosynthesis pathway in 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. It is known that the activation of HBP leads to altered glycosylation of oncogenes, transcription factors and kinases in many types of cancer. These aberrations may lead to increased proliferation and survival of tumor cells, and may be associated with resistance to therapy. A better understanding of the role of HBP in malignancies has the potential for clinical implications. Several studies demonstrated that pharmacological inhibition of GFPT2 (glutamine-fructose-6-phosphate transaminase 2, the first and rate-limiting enzyme in HBP) and OGT (glycosyltransferase that catalyzes the addition of the O-GlcNAc in posttranslational modification of proteins) may exhibit anti-tumorigenic effect both *in vitro* and *in vivo*, and may modulate sensitivity to chemo-, radio- and immunotherapy. Most of these studies focused on carcinomas and the role of HPB in sarcoma has not been studied.

We previously performed a large-scale screening of 260 primary specimens of 33 types of soft tissue lesions. We observed near universal expression of GFPT2 in desmoid type fibromatosis (DTF) in 33 of 34 cases, independent of the mutation type of the *CTNNB1* gene. GFPT2 expression was significantly enriched in DTF compared to other types of tumors (Chi-square test $p < 0.00001$). Gene Set Enrichment Analysis of a previously published 3SEQ transcriptomic dataset composed of DTF and 9 other types of fibrotic lesions identified significant enrichment of other genes implicated in HBP and multiple glycosylation-associated pathways in DTF compared to the other types of fibrotic lesions.

To further explore the possible activation of HBP in DTF, we performed immunohistochemistry to evaluate expression of seven enzymes of the HBP and the presence of O-GlcNAc modification using well-annotated tissue microarrays with specimens of primary and recurrent DTF from over 210 patients. We also performed pharmacological inhibition of GFPT2 and OGT in cell line models to study the potential therapeutic benefit of this strategy in DTF.

This study will provide new insights into metabolic reprogramming in DTF. Modulation of glucose metabolism through HBP, either alone or in combination with other treatment modalities, is a promising direction of research. Our study will offer the first functional exploration of the role of this pathway in DTF.