CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150638

Project Title:
Elevated D-2-hydroxyglutarate precedes and promotes tumor progression in inflammatory bowel diseases

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor Research Institute

Lay Summary:

Inflammatory bowel diseases (IBD), the most common forms being Crohn's disease and ulcerative colitis (UC), are characterized by chronic inflammation of the gastrointestinal tract. IBD patients are at an increased risk compared to the general public of developing colorectal cancer. Although the association between IBD and progression to colitis-associated cancer is well-established, the mechanisms driving progression from colitis to cancer remain poorly understood. Moreover, biomarkers and functional therapeutic targets to detect, predict, and prevent colitis-associated cancer are currently lacking. Accumulation of the metabolite D-2-hydroxyglutarate (D-2-HG), which is normally produced at low levels as an error product of metabolism, has been linked to oncogenesis in glioma and acute myeloid leukemia. Using a mouse model of colitis-associated cancer, we show that urinary D-2-HG is significantly increased during colitis and returned to baseline after cancer formation. Urinary level of D-2-HG during the colitis stage directly correlated with polyp number and severity of dysplasia/cancer. This pattern of D-2-HG expression may be driven by expression of hypoxia-inducible factor (Hif)1a and subsequently, D-2-hydroxyglutarate dehydrogenase (2-D-HGDH), which is an enzyme that reduces D-2-HG levels. Colonic epithelial Hif1a and D-2-HGDH expression were decreased during colitis and returned to baseline after cancer formation. Similarly, D-2-HGDH expression was decreased in actively inflamed human UC mucosal biopsies but not in matched UC-associated dysplasia. This study will determine the role of D-2-HG in preceding and promoting tumor progression during colitis. Together, our studies will identify novel mechanisms that drive progression from colitis to cancer, thereby providing novel biomarkers and functional therapeutic targets to be used to detect, predict, and potentially prevent colitis-associated cancer.