

Bankhead-Coley Cancer Research Program

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Bridge (1-year project)*

Project Title: Mechanisms of Bladder Cancer Progression

Project Summary: Bladder cancer (BCa) is the costliest cancer to treat due to the heterogeneity in tumor progression and frequent recurrence. HYAL1 hyaluronidase degrades hyaluronic acid (HA), a glycosaminoglycan. HYAL1 and HA stimulate BCa growth, invasion, and angiogenesis and are accurate markers for BCa. We hypothesize that HA and HYAL1 inhibitors cripple BCa growth and metastasis and that HYAL1 expression is transcriptionally regulated.

HYAL1 inhibitor, sulfated-HA (sHA) and HA synthesis inhibitor, 4-methylumbelliferone (4-MU), inhibit BCa growth by inducing cell cycle arrest and apoptosis, respectively. They are non-toxic and have antitumor activity. To examine the mechanism of sHA and 4-MU action, we are evaluating their effects on membrane proximal signaling events induced by the cell surface HA-HA receptor interaction in BCa cells. We will also test the effect of sHA, 4-MU, HA and HA-oligosaccharides on normal bladder cells. We will perform cDNA microarray and microRNA analyses to examine the global changes in gene expression induced by sHA or 4-MU in BCa cells (Aim 1). The regulation of HYAL1 expression is unknown. We identified HYAL1 promoter and showed that DNA methylation regulates HYAL1 expression in BCa. To identify any enhancer/repressor elements that regulate HYAL1 expression, we will analyze up to 5-kb sequence up stream of the HYAL1 transcription start site by cloning and reporter assays in BCa and normal urothelial cells. EMSA and ChIP assays will be performed to identify the possible regulators of HYAL1 transcription in the far up stream region. We will also characterize any demethylase activity in BCa and normal urothelial cells that might be involved in regulating HYAL1 promoter methylation (Aim 2).

This study should reveal how HYAL1 and HA inhibitors control BCa through intracellular signaling and potential of these inhibitors as BCa treatments. Analysis of how HYAL1 expression is regulated in BCa may suggest ways to control it.