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Grant Title: Enzymatic cleavage of heparan sulfate powers inflammation and associated cancer

Abstract

Chronic inflammation is a root cause of the most devastating illnesses, including metabolic disorders, autoimmune diseases and, more recently, - various types of cancer. Macrophages are dominant cellular players in chronic inflammation, known to drive pathogenesis of inflammatory diseases, diabetes and its complications, and inflammation-associated tumors. While significant progress has been made in deciphering the role of the cytokines in macrophage polarization toward chronic inflammatory phenotype, role of extracellular matrix components (including heparan sulfate and its enzymatic remodeling by heparanase enzyme) in this process only recently came to appreciation.

Our present research emphasizes previously unrecognized mechanism through which heparanase-mediated degradation of heparan sulfate (HS) modulates innate immune responses in various complex pathologies (i.e., inflammatory disease and associated cancer, diabetes and related conditions.

The objective of the present proposal was to elucidate the HS/heparanase-dependent mechanism of macrophage activation, To achieve this objective we utilized *in vivo* models of obesity/metabolic syndrome/type 2 diabetes, chemically-induced chronic colitis and associated cancer), along with the *ex vivo* and *in vitro* systems based on macrophage-derived cell line and primary macrophages.

Our findings show that heparanase-mediated cleavage of HS facilitates pro-inflammatory and pro-cancerous effects exerted by macrophages stimulated by several endo- and exogenous ligands of toll-like receptors, including components of obesogenic/diabetic milieu, as well as substances derived from necrotic cells or microbial flora. When occurring in pre-neoplastic/neoplastic tissue (i.e., in the setting of colitis-induced carcinoma, obesity/diabetes-associated breast/pancreatic tumors) these effects foster tumor progression; while the similar effects taking place in non-cancerous settings sustain pathogenesis of inflammatory diseases (e.g., chronic colitis, diabetes).

Given critical importance of macrophages in inflammation, metabolic disorders and malignancy, it is hoped that detailed understanding of these effects will promote proper tailoring of therapeutic intervention in a wide spectrum of diseases.