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Title: Role of FXIIIa in Colorectal Cancer Peritoneal Metastasis

Cancer has been dubbed by clinicians and scientists as the “wound that never heals.” The peritoneum is a thin layer of tissue that covers our internal organs similar to our skin but on the inside. The peritoneum is one of the most common sites of colon cancer spread, also known as peritoneal metastasis (PM). This occurs in one out of every 5 patients with colon cancer metastasis. Surgeons have long noted the predilection of peritoneal cancer metastasis to wounds, very often being the first site of detectable disease in patients with PM. This proposal aims to uncover the interaction between the earliest events of colorectal cancer spread and wound healing, namely cancer stem cell promotion and coagulation, respectively. The cancer stem cell (CSC) hypothesis postulates that tumors arise from a small subset of cells with self-renewal ability. In this model, CSCs ability for self-renewal, resistance to chemotherapy, and laying dormant, accounts for the most challenging clinical presentations of metastasis, ineffective chemotherapy, and tumor reappearance. Clot formation can occur due to a number of different conditions, most commonly after injury to stop bleeding. However, abnormal blood clotting in the deep veins also occurs and is a common problem in patients with cancer. This observation led many to the realization that cancer induces a state of abnormal clotting. An essential step of blood clotting is meshing the proteins that form the clot together, also known as fibrin, and chemically linking them together in order to form a stable blood clot. The process of linking fibrin molecules together is called fibrin cross-linking, and is performed by the enzyme factor XIIIa. We hypothesize that the chemical stabilization of blood clots by Factor XIIIa (FXIIIa), which induces clot stabilization, promotes CRC stem cells in patients with PM.

Our preliminary data suggests a significant promotion of the CSCs in CRC cell lines cultured in cross-linked fibrin (XLF) treated with pathologically relevant levels of FXIIIa in vitro. In this proposal, we advocate for a groundbreaking approach by targeting FXIIIa in CRC PM, addressing a critical gap in the treatment of this pervasive disease, with an unmet clinical need. Furthermore, we introduce novel nonsaccharide glycosaminoglycan mimetics (NSGMs) aimed at FXIIIa, which hold the promise to significantly advance current therapeutic options.