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Neutrophil Extracellular Traps Promote Metastases after Surgery

Surgery is a crucial intervention and provides a chance of cure for patients with cancer. The perioperative period is characterized by an increased risk of accelerated growth of micrometastatic disease and formation of new metastatic foci. My research focuses on understanding the mechanisms underlying this phenomenon. The AHPBA research award allowed me to study one of the mechanisms, specifically the role of neutrophils in surgery-induced acceleration of metastatic growth.

Neutrophils, first-line responders after surgical stress, may play an important role in linking inflammation to cancer progression. In response to stress, neutrophils can expel their protein-studded chromatin to form local snares known as neutrophil extracellular traps (NET). In the work supported by this award, and under the supervision of Dr. Allan Tsung, I asked whether, as a result of its ability to ensnare moving cells, NET formation might promote metastasis after surgical stress. Consistent with this hypothesis, we found that in patients undergoing liver resection for metastatic colorectal cancer, we observed that increased postoperative NET formation was associated with a >4-fold reduction in disease-free survival. In like manner, in a murine model of surgical stress, we observed an increase in NET formation that correlated with an accelerated development and progression of metastatic disease. These effects were abrogated by inhibiting NET formation in mice through either local treatment with DNAse or inhibition of the enzyme peptidylarginine deaminase, both of which have the potential to be used in clinical investigations. Furthermore, mechanistic investigations in vitro indicated that mouse neutrophil-derived NET triggered HMGB1 release and activated TLR9-dependent pathways in cancer cells to promote their adhesion, proliferation, migration, and invasion.

This research can ultimately lead to the development of specific new therapeutic interventions aimed to target NET formation in the perioperative period and ultimately improve long-term oncological outcomes.