Development of a Preclinical Model of Surgically-Induced Inflammation in Malignant Mesothelioma

Richard W. Davis IV, Joann Miller, Manolis Papasavvas, Asteri Klampatsa, Steve Albelda, Keith Cengel, Theresa Busch

Inflammation is a well-known consequence of surgery, defined by the increase of pro-inflammatory cytokines (such as IL-6), stress hormones (such as cortisol) and acute phase proteins (such as C-reactive protein and fibrinogen). This inflammation can detract from the benefit of surgical resection due to its propensity to initiate pro-tumoral events such as immunosuppression, angiogenesis, and metastasis. As surgery is often followed by other therapies in a multi-modality setting, it is important to understand the consequence of surgery-induced inflammation on subsequent treatment. One such post-surgical therapy is intraoperative photodynamic therapy (PDT), which excels at the eradication of superficial localized or regionally diffuse malignancies. PDT is often combined with surgery in order to remove residual disease after macroscopic complete resection, with our ongoing investigation of malignant pleural mesothelioma (MPM) serving as one example. Study of the effect of surgery-induced inflammation on subsequent treatments would be facilitated by a clinically-informed animal model of surgery-induced inflammation in the context of combinational therapy. In this talk, we will discuss the preclinical and clinical effects of surgical resections on inflammatory markers in MPM. IL-6 levels were increased in the serum of MPM patients at the time of macroscopic complete resection (prior to initiation of PDT). Additionally, patients showed significant increases in surgically-induced cortisol levels. In the preclinical setting, surgery-induced increases in IL-6 were replicated in the tumor tissue, with trending increases at 4 hours post-surgery reaching significance 16 hours post-surgery compared to tumor controls. Serum levels of surgically resected mice showed trending increases in IL-6 at this 16 hour time point. Addition of PDT to surgically resected mice showed significantly increased IL-6 levels 19 hours post-surgery in serum and trending increases in the tumor tissue. Lastly, we will outline the design of a new pre-clinical model we term tumor incision (TI). This model of inflammatory response to surgery improves the resection model because the TI model allows all mice to enter the study with tumors of the same size. In contrast, when resection is used, it is necessary to allow tumors in the resection groups to grow larger in order to accommodate resection while still providing size-matched tumors for PDT between PDT-alone and surgery/PDT-treated groups. Thus, TI minimizes the effects of variables that are introduced as a function of increasing tumor size, such as hypoxia and expression of PDT resistance factors. This TI model replicates the induction of IL-6 in surgically-resected mice. Use of this model has begun to define targetable mechanisms in the interplay between surgically-induced inflammation and PDT towards the goal of generating lasting responses in patients.