TARGETING M2-TUMOR ASSOCIATED MACROPHAGES IN PROSTATE CANCER

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Background: Prostate cancer is a leading cause of cancer-related deaths of men in the U.S., and in the past year, over 30,000 men died from this disease. While localized prostate cancer is highly treatable by surgical resection and radiation, cancer that has metastasized remains incurable. Alternatively activated macrophages, also known as M2-macrophages, primarily scavenge debris and in the process, promote angiogenesis and wound repair. M2-macrophages are phenotypically similar to M2 tumor-associated macrophages (M2-TAMs) have been reported to associate with solid tumors such as prostate cancer to facilitate epithelial to mesenchymal transition (EMT), tumor invasiveness, metastasis, and resistance to therapy. As an invasive species within the tumor microenvironment, this makes M2-TAMs an ideal therapeutic target in prostate cancer. The purpose of this project is to develop novel therapeutics that will directly target M2-TAMs for destruction and subsequently attenuate prostate tumor growth, progression, and metastasis. Our hypothesis is to determine if targeting of M2-TAMs by using enriched surface antigens that are targeted by antibody-drug-conjugates (ADCs), be an effective therapy for lethal prostate cancer while simultaneously eliciting an immune response.

Methods: To identify novel surface antigens expressed on M2-macrophages, we developed a novel method of creating homogenous populations of human macrophages from $CD14^+$ monocytes *in vitro*. Our homogenous M1 macrophages secrete pro-inflammatory cytokines and our M2 macrophages secrete anti-inflammatory cytokines as well as VEGF. We then performed solid-phase extraction of *N*-linked glycopeptides (SPEG) followed by liquid chromatography-tandem Mass Spectrometry (LC-MS/MS) on our homogenous macrophage populations.

Results: We discovered five novel peptides that are enriched exclusively on M2-macrophages relative to M1 macrophages and $CD14^+$ monocytes. Lastly, we determined if these surface antigens, found enriched on M2 macrophages, were also expressed in human metastatic castrate-resistant prostate cancer (mCRPC). Using mCRPC tissues from rapid autopsies supplied by the Departments of Urology and Surgical Pathology, we were able to determine M2-macrophage infiltration by using immunohistochemistry and flow cytometry. The studies described here outline a method of altering the tumor immune microenvironment. To target these cells, antibodies against enriched M2-macrophage surface antigens will be constructed into antibody drug conjugates (ADCs) and then tested *in vitro* and in a syngeneic prostate tumor mouse model. **Conclusions**: By identifying specific markers on M2-TAMs, we predict that this method of targeting will provide a better prognosis for patients who have been diagnosed with lethal prostate cancer.

Conflict of Interest: The authors declare no competing interests

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