Depleting Tumor-infiltrating Mesenchymal Stem Cells to Overcome the Immunosuppressive Microenvironment and Enhance Immunotherapy Efficacy in Prostate Cancer

Brennen WN[1], Krueger TE[1], and Isaacs JT[1, 2]

[1]Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and [2]The Brady Urological Institute, The Johns Hopkins School of Medicine, Baltimore, MD, United States

Abstract: Prostate cancer is characterized by T-cell exclusion – i.e. poor infiltration of effector cells into tumors, which explains the poor responses to immunotherapy. Instead, T-cells restricted to the adjacent stroma and benign areas are characterized by anergic and immunosuppressive phenotypes. Therefore, in order for immunotherapy to produce robust anti-tumor responses in prostate cancer, this exclusion barrier and immunosuppressive microenvironment must first be overcome. We have identified mesenchymal stem cells (MSCs) in primary and metastatic human prostate cancer tissue. MSCs have significant immunosuppressive properties with numerous effects on the innate and adaptive immune system. Collectively, these properties prevent infiltration of cytotoxic effector cells into malignant foci and suggest MSCs represent a critical upstream node critical for promoting an immunosuppressive microenvironment that effectively blocks robust responses to immunotherapy. Thus, we hypothesize that MSCs recruited to malignant lesions actively suppress an immune response and selective depletion of this population can restore immunologic recognition and elimination of malignant cells via broad re-activation of cytotoxic pro-inflammatory pathways while suppressing regulatory T-cell (Treg) and myeloid-derived suppressor cell (MDSC) function.

Conflicts of Interest: The authors declare that no conflicts of interest exist.

Funding: Prostate Cancer Foundation (PCF) Young Investigator Award (WNB), Patrick C. Walsh Prostate Cancer Research Fund (WNB), SKCCC Cancer Center Support Grant (CCSG) developmental funds [P30 CA006973, (WNB)], and NIH-Prostate SPORE Grant P50 CA058236 (JTI). Additionally, we would like to acknowledge the Department of Defense Prostate Cancer Research Program [W81XWH-10-2-0056 and W81XWH-10-2-0046 Prostate Cancer Biorepository Network (PCBN)], the NIH-Prostate SPORE Grant Pathology Core (P50 CA058236), the Flow Cytometry core, and the Tissue Services Core supported by the SKCCC CCSG (P30 CA006973) for their services and assistance, in addition to acknowledging the use of tissues procured by the National Disease Research Interchange (NDRI) with support from NIH grant 2 U42 OD011158.