Macrophage regulates androgen receptor activation in prostate cancer

Asmaa El-Kenawi[1*], Min Liu[2], William Dominguez Viqueira[3], Xiaoqing Yu[4], John Koomen[2], Robert Gatenby[5] and Brian Ruffell[1*]
[1]Department of Immunology; [2] Proteomics and Metabolomics Core (PMC); [3] Small Animal Imaging Lab (SAIL); [4] Department of Biostatistics ; [5] Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA

Background
Castration-resistant prostate cancer (CRPC) is a lethal stage of disease. A wealth of clinical and experimental data supports the persistence of androgen receptor (AR) signaling in many cases of CRPC, despite androgen-deprivation therapy (ADT).
Methods
Here we sought to determine the role of macrophages in CRPC using an animal model that reflects the mutational landscape of prostate cancer.
Results
Our findings showed that depleting macrophage using a neutralizing antibody against the colony-stimulating factor (CSF)-1 in combination with ADT (Lupron) significantly extended survival of mice-bearing orthotoptic prostate tumors, compared with each agent alone. To determine the mechanism by which macrophages enhance response to ADT, we performed an unbiased transcriptomic analysis of prostate tumors following macrophage depletion, and, found that macrophage infiltration was associated with molecular signatures of AR activation. This was confirmed by immunohistochemistry, with both macrophage depletion and Lupron treatment leading to reduced AR nuclear localization in prostate tumors. These findings were recapitulated in vitro, with the co-culture of macrophages and prostate cancer cells enhancing AR nuclear localization, increasing cancer cell proliferation in androgen-deprived conditions, and reducing sensitivity to the AR antagonist, enzalutamide.
Conclusion
Tumor macrophages directly promote AR activation and resistance to ADT in prostate cancer.