# Androgen Receptor Blockade in Prostate Cancer Drives Tumour-Fuelling Inflammation Through STING

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Abstract

Background: Inflammation plays major roles in prostate cancer, particularly in metastatic castration-resistant prostate cancer (mCRPC), which is invariably lethal. The senescence-associated secretory phenotype (SASP), associated CXCL1/2/8 secretion, chemoattracts myeloid cells exacerbates oncogenic inflammation. How endocrine therapy impacts oncogenic inflammation in mCRPC remains unknown.
Methods: We performed STING IHC and Hyperplex IF in mCRPC as well as syngenetic tumour model STING KO experiment.
Results: As current evidence suggests that the STimulator of Interferon Genes (STING) is involved in the SASP, we interrogated the role of STING in mCRPC. we found that elevated STING mRNA associates with poorer overall survival and androgen resistance. STING protein levels are heterogeneous across both tumour and stromal cells. In vivo patient-derived xenograft and patient biopsy studies revealed that AR blockade induces STING expression, alongside signatures of EMT, IL6-JAK-STAT3, IFNα and NF-κB signalling. High STING expression in mCRPC biopsies is also associated with SASP factor expression and inflammation associated signatures. Finally, STING knockout syngeneic tumour models significantly increases activated CD8+ T cells.
Conclusions: Overall, we identified a subset of mCPRC characterised by enriched STING+ tumour cells that results of AR blockade induces STING with resultant SASP and IL6/JAK/STAT and NF-κB signalling to drive tumour growth.

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