

878

BET INHIBITION SENSITIZES IMMUNOLOGICALLY-COLD RB-DEFICIENT PROSTATE CANCER TO IMMUNE CHECKPOINT BLOCKADE VIA DNA DAMAGE-INDUCED STING/NF- κ B/TYPE I IFN SIGNALING

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Background Non-T cell-inflamed immunologically “cold” tumor microenvironments (TME) are associated with poor responsiveness to immune checkpoint blockade (ICB), and can be sculpted by tumor cell genomics. We have previously described how Retinoblastoma (Rb) tumor suppressor loss of function, one of the most frequent alterations in human cancer and associated with lineage plasticity, poor prognosis and therapeutic outcomes, promotes an immunosuppressive TME *in vitro* and *in vivo*. Here, we evaluated how inhibition of the bromo-domain and extraterminal (BET) domain family can reverse the consequences of Rb loss to enhance the efficacy of ICB.

Methods Wild-type or Rb-deficient murine MycCaP tumor cells were evaluated *in vitro* and *ex vivo* for how BET inhibition (BETi) alters DNA damage and type I IFN signaling pathways by qRT-PCR, Western blot, ELISA, and ImageStream analysis. Tumor-bearing animals were treated with BETi (alone or with STING or NF- κ B inhibition), and immune infiltration into the TME was evaluated by flow cytometry. Anti-tumor responses to BETi was evaluated in the presence or absence of T cell and/or macrophage depletion. Finally, BETi was combined with PDL1 blockade, with or without androgen deprivation therapy (ADT), and anti-tumor responses were evaluated in the presence or absence of STING/NF- κ B blockade.

Results BETi was found to increase tumor cell-intrinsic DNA damage, which induced STING/NF- κ B signaling and type I IFN expression and T cell migration in Rb-deficient tumor cells, in part due to increased baseline STING expression following Rb loss. *In vivo* BETi treatment increased T cell infiltration into the TME and suppressed Rb-deficient tumor growth that were T cell- and macrophage-dependent as well as STING/NF- κ B-dependent. BETi alone increased PD-1 expression on tumor-infiltrating T cells and PD-L1 expression on suppressive M2 and MDSC populations *in vivo*, resulting in increased susceptibility to combined BETi and PDL1 blockade in Rb-deficient tumors *in vivo*. Finally, ADT further enhanced the efficacy of BETi and ICB in a STING/NF- κ B-dependent fashion.

Conclusions These data demonstrate that BETi increases immune infiltration into the immunologically-cold Rb-deficient TME via activation of tumor cell-intrinsic STING/NF- κ B activation and type I IFN signaling within tumor cells. This results in differential macrophage and T cell-mediated inhibition of Rb-deficient prostate tumor growth and sensitization of Rb-deficient prostate cancer to ICB. This provides the mechanistic rationale to test combinations of ADT, BETi and ICB in clinical trials of Rb-deficient hormone-sensitive metastatic prostate cancer.

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