SIRPα BLOCKADE SYNERGIZES WITH RADIATION THERAPY IN MURINE BREAST CANCER MODELS

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Background Focal tumor radiation-therapy (RT) induces an immunogenic cell-death associated with endogenous adjuvants that promote uptake of cancer antigens by conventional dendritic cells (cDCs). The expression of CD47 is markedly increased in a high proportion of breast cancers (BC) and correlates with poor-prognosis molecular subtypes. CD47 interaction with SIRPα on cDCs and macrophages provides a negative signal that inhibits phagocytosis of dying cancer cells, hindering cross-presentation of tumor-derived antigens and activation of anti-tumor T cells. Thus, we hypothesized that the "don't-eat-me" signal mediated by CD47/SIRPα acts as a barrier to RT-induced anti-tumor immunity. Using two mouse BC models refractory to immune-checkpoint blockade, we investigated the effects of RT combined with SIRPα blockade on the development of anti-tumor immunity.

Methods BALB/c or C57BL/6 mice were inoculated subcutaneously in one or both flanks with respectively TSA and AT-3 BC cells. RT was delivered to one tumor, 8Gy on 3 consecutive days once tumor volume reached 60–80mm³. SIRPα-blocking (MY1,1) or isotype antibodies were given one day prior to RT and every 3 days thereafter. Some mice received PD-L1-blocking Abs (BioXcell) every 3 days starting one day after RT completion. cDC depletion experiments were performed on AT-3 bearing C57BL/6 mice using the inducible diphtheria toxin-dependent CD11c-DTR model.²

Results SIRPα-blockade alone did not inhibit TSA tumor growth, but significantly improved tumor response to RT ($p < 0.05$), leading to complete regression of the irradiated tumor in 50–60% of the mice. In addition, SIRPα-blockade + RT combination significantly inhibited the growth ($p < 0.05$) of contralateral non-irradiated tumors (abscopal response), suggesting that it induced a systemic anti-tumor immune response. Consistent with systemic immune activation, the percentage of PD1+CD4 T cells was increased in the spleen of mice treated with anti-SIRPα compared to control Abs ($p < 0.01$), regardless of RT. In the myeloid compartment, cDC1 and macrophages showed increased PD-L1 expression. However, addition of anti-PD-L1 to RT + anti-SIRPα did not further improve abscopal responses. In the AT-3 model, SIRPα blockade significantly improved tumor control induced by RT ($p < 0.01$) but no complete regression was observed. Depletion of cDC in AT-3 bearing mice abrogated the benefit of the combination of SIRPα blockade to RT.

Conclusions Overall, our results support the hypothesis that SIRPα-blockade potentiates the ability of RT to induce anti-tumor T cell responses and improve local and systemic tumor control. We are currently investigating the mechanisms of RT interaction with SIRPα blockade to provide the rationale for translating these findings to the clinic

REFERENCES

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