1127 COMBINATION OF TOLL-LIKE RECEPTOR AGONISTS AND IMMUNE CHECKPOINT BLOCKADE WITH ANTI-TUMOR VACCINES CAN AFFECT ANTI-TUMOR RESPONSE

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Background T-cell checkpoint receptors are expressed when T cells are activated, and modulation of the expression or signaling of these receptors can alter the function of T cells and their anti-tumor efficacy. We previously found that T cells activated with cognate antigen increase the expression of PD-1, and this can be attenuated in the presence of multiple Toll-like receptor (TLR) agonists, notably TLR3 and TLR9. In the current report, we sought to investigate whether the combination of TLR agonists and different immune checkpoint inhibitors can further affect vaccine-mediated T cell anti-tumor immunity in a murine tumor model.

Methods The anti-tumor efficacy of the combination of TLR agonists (TLR3 and TLR9) and different immune checkpoint inhibitors, when delivered with vaccine-activated T cells, was evaluated in E.G7-OVA tumor-bearing mice. Ovalbumin-expressing E.G7 cells were implanted in C57BL/6 mice and permitted to grow until tumors were palpable (7 days). OT-1 splenocytes were then adoptively transferred and mice were immunized subcutaneously the following day with SIINFEKL (OVA) peptide alone or with TLR agonists. Antibodies blocking immune checkpoints were injected intraperitoneally the day following immunization. Mice were then followed for tumor growth.

Results Immunization of EG7-OVA tumor-bearing mice with SIINFEKL peptide vaccine, co-administered with TLR agonists and α-CTLA4, demonstrated greater anti-tumor efficacy than immunization with TLR agonists or α-CTLA4 alone. Conversely, the anti-tumor efficacy of vaccination with TLR agonists was abrogated when combined with α-PD1. We found that TLR agonists activated Tregs by suppression of PD-1 expression, and these Tregs were more functionally suppressive of CD8 proliferation. Depletion of Tregs in tumor-bearing mice led to greater anti-tumor efficacy of this combination therapy, even in the presence of α-PD1. Combining vaccination with TLR agonists and α-LAG3 or α-CTLA4 showed greater anti-tumor efficacy than with other immune checkpoint blocking antibodies (α-TIGIT, α -VISTA, or α -TIM3).

Conclusions The combination of TLR3 and TLR9 agonists, and α-CTLA4 or α-LAG3, can further improve the efficacy of a cancer vaccine, an effect not observed using α-PD1. This was mediated by activation of Tregs when α-PD1 was combined with TLR agonists. These data provide a rationale for choosing optimal combinations of TLR agonists and immune checkpoint inhibitors to improve the efficacy of anti-cancer vaccines.

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