PD-1 BLOCKADE ADMINISTERED BEFORE OR AT THE TIME OF T CELL ACTIVATION ENHANCES ANTI-TUMOR IMMUNITY

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Background Immune checkpoint inhibitors as monotherapies have been a successful treatment strategy for some cancer types, but have not been as effective at treating immunologically “cold” tumors. This is likely due to low tumor mutational burden, a highly immunosuppressive microenvironment, and low numbers of infiltrating CD8+ T cells. Our group has implemented DNA vaccines as a means to generate antigen-specific CD8+ T cells. We and others have shown that PD-1 blockade in combination with T cell activating agents (vaccines) are more effective when these agents are administered simultaneously. However, optimal scheduling of vaccination in combination with checkpoint blockade and mechanisms thereof have not been thoroughly explored. Therefore, we sought to address whether adminstering PD-1 blockade prior to, simultaneously, or after immunization would affect anti-tumor immunity.

Methods C57Bl/6 mice were inoculated with E.G7-OVA, PD-L1hi tumors. Mice received naïve OT-1 splenocytes (with TCRs specific for SIINFEKL peptide) by adoptive transfer and were then immunized with SIINFEKL peptide. PD-1 blockade was administered to mice either at the same time as peptide immunization, two days prior, or two days later. In a separate model, isolated OT-1 CD8+ T cells were co-cultured with dendritic cells and activated in the presence of SIINFEKL peptide and PD-1 blockade. These resulting pre-activated T cells were then assessed for phenotype and IFNγ secretion in vitro and were adoptively transferred to tumor-bearing mice and assessed for tumor growth kinetics and tumor infiltrating lymphocyte (TIL) analysis.

Results Mice receiving pre- or simultaneous- treatment of PD-1 blockade had prolonged survival and delayed tumor growth in comparison to the control and late PD-1 blockade treatment groups. OT-1 CD8+ T cells activated in vitro in the presence of PD-1 blockade exhibited greater IFNγ secretion, and mice receiving transferred OT-1 CD8+ T cells pre-activated in the presence of PD-1 blockade exhibited greater anti-tumor responses than control mice or mice receiving late administration of PD-1 blockade. Mice receiving transferred T cells pre-activated in the presence of PD-1 blockade had an increased percentage of CD8+ TILs exhibiting an effector-memory and short-lived effector phenotype.

Conclusions These results indicate PD-1 blockade may be best employed when administered before or at the same time as T cell activating agents such as vaccines, and that blockade affects the phenotype and function of T cells at the time of vaccine activation.