PD-1 INHIBITS BYSTANDER T CELL ACTIVATION AND PROTECTS FROM ACTIVATION INDUCED CELL DEATH

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Background Immune checkpoint inhibition (ICI) targeting PD-1/PD-L1 is being increasingly applied and for longer periods of time. Aside from rapid response to antigen stimulation, memory T cells can also be directly activated and perform effector functions via cytokine signaling alone in the presence of high concentrations of inflammatory or immunostimulatory cytokines due to expression of CD132/CD122 receptor complexes.1-3 These ‘bystander-activated’ T cells can therefore amplify T cell effector responses particularly in aged individuals where a higher proportion of memory T cells exists.4 While the role of PD-1/PDL-1 on antigen-specific T cell responses has been extensively characterized, its role in bystander T cell responses is less clear.

Methods We examined the role of the PD-1/PD-L1 pathway during bystander activation using multiple mouse and human model systems. T cells from mice treated with high-dose (HD) rhIL-2 were evaluated for bystander activation using flow cytometry for NKG2D, CD69, granzyme B, CD25, Ki67, and PD-1 expression. Mouse T cells from control or TCR-transgenic OT-1 mice (which are specific for ovalbumin and thus not antigen-experienced) were stimulated in vitro with rhIL-2 or anti-CD3/28 to model bystander versus TCR-stimulated signaling. Activation, proliferative, and apoptotic responses (via annexin V staining) were assessed at various time-points. Effects of PD-1 blockade or loss was also assessed. We compared these results gating on PD1+ and PD1- T cell populations and subsequently repeated the same procedure using human T cells isolated from human PBMCs. We then assessed human T cells isolated from patients undergoing HD rhIL2 treatment for cancer, gating on PD1+ and PD-1- activated T populations.

Results Significantly reduced activation and proliferative responses were observed by activated PD-1+ bystander T cells compared to the PD-1- populations in both the mouse and human T cells following HD IL2 treatment in vitro or in vivo. PD-1- bystander-activated T cells also had increased apoptosis via activation induced cell death (AICD). Concurrent blockade or absence of PD-1 signaling in the mouse models resulted in greater activation responses comparable to PD-1- cells, but this also resulted in increased AICD and cell loss.

Conclusions The PD-1/PD-L1 pathway also inhibits antigen-nonspecific bystander-activated memory T cell responses and protects cells from AICD. While blockade of this pathway can result in increased bystander activation and effector functions, it also leads to increased AICD and T cell loss. These findings imply possible consequences of continuous PD-1 blockade application on the maintenance of the finite memory T-cell pool.

REFERENCES