DISTINCT EFFICACY AND IMMUNOLOGICAL RESPONSES TO αPD-1, αPD-L1 AND αPD-L2 IMMUNOTHERAPY IN AGED VERSUS YOUNG HOSTS

Yilun Deng, Harshita Gupta, Myrna Garcia*, Aravind Kancharla, Ryan Reyes, Alvaro Padron, Tyler Curiel. University of Texas Health San Antonio, San Antonio, TX, USA

Background Aging is the biggest risk factor for cancer, yet there are limited pre-clinical/clinical data regarding aging effects on immune checkpoint (IC) inhibition (ICI) outcomes. αPD-1 can potentially block PD-L1 and PD-L2 while αPD-L1 can block PD-1 and CD80. Melanoma response to αPD-1/αPD-L1 correlates with CD8+TCF-1+ T cell stem cell (TCSC) generation. Lack of host IL-17 can lead to increased IFN-γ production.

Methods We tested αPD-1 (200 μg/mouse), αPD-L1 (100 μg/mouse) or αPD-L2 (200 μg/mouse) in aged (18–33 months) and young (3–8 months) mice challenged orthotopically with B16 (WT or PD-L1ko) or TPN61R melanoma (NRAS mutation melanoma model) (αPD-L2 only) (SQ). Tumors were analyzed by flow. We tested αPD-L2 (20 μg/ml) effects by coculturing young or aged T cells ± young or aged myeloid cells.

Results We reported that αPD-1 treats young and aged with B16 whereas αPD-L1 treats young not aged. αPD-L2 treated B16 and TPN61R melanoma in aged but, remarkably, not young, the first single agent anti-cancer immunotherapy exhibiting this property (figure 1). B16 tumors from aged had differential IC content (PD-1, PD-L1, CD80, PD-L2) versus tumors from young (e.g., more PD-L2+ tumor and stroma cells in aged mice; figure 2). Efficacy in young (αPD-1, αPD-L1) and aged (αPD-L2) correlated with increased tumor TCSC content (figure 3). αPD-L2 efficacy against B16 in aged mice required host IFN-γ and IL-17 (figure 4). αPD-1 efficacy against B16 in aged appeared to be host and tumor PD-L1 independent (figure 5). PD-L1KO B16 response to αPD-1 in aged also correlated with increased tumor TCSC content. Myeloid cell PD-L2 signaling inhibited aged but not young CD8+ T cell IL-2 production in vitro (figure 6).
Conclusions  Treatment differences in aged versus young could depend on IC, TCSC and/or host cytokine differences (IL-17/IFN-γ). αPD-1 efficacy in aged PD-L1KO mice challenged with PD-L1KO B16 suggests that PD-L2 block is sufficient for αPD-1 efficacy in aged. PD-L2 expression differences in the tumor microenvironment could also contribute to treatment efficacy differences. PD-L2 inhibitory signaling on aged but not young CD8+ T cells is a likely mechanism for αPD-L2 efficacy in aged but not young. We are now testing the role of IL-17 in αPD-L2 efficacy as it could be upstream of IFN-γ effects, and TCSC effects in aged versus young. Our work can improve cancer immunotherapy in aged hosts and provides insights into treatment failure, including in young hosts.

Acknowledgements  South Texas MSTP training grant (NIH T32GM113896), TL1TR002647, NIH T32AI138944, R01 CA231325, Waxman Grant, UL1 TR001120

REFERENCES

Ethics Approval  All animal studies are approved by UTHSA IACUC.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.234