ANTI-PDL2 USES IL17-DRIVEN INTERFERON-GAMMA TO TREAT AGED BUT NOT YOUNG CUTANEOUS MELANOMA-BEARING MICE, AND TREATS OTHER TUMORS IN AN AGE- AND TME-DEPENDENT MANNER

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Background: Immune checkpoint blockade (ICB) with αPD1, αPDL2, αCTLA4 and αLAG3 is FDA-approved but agents fail to treat up to ~80% of all cancers. PDL2 is a second PD1 ligand but little is reported on αPDL2 cancer immunotherapy. Age is the biggest risk for cancer, yet little few age affects on ICB are reported. We previously reported that αPDL2 treats melanoma in aged but not young mice. Here we provide mechanistic insights, outcomes in other cancers and human data.

Methods: We tested αPDL2 ICB and mechanisms in WT, IFNγKO and IL17KO mice in B16F10 (B16) and Nras mutated melanomas, ID8agg ovarian cancer and MB49 bladder cancer. We tested αPDL2 in aged (18-33 months) and young (3-8 months) mice. Tumors were analyzed by flow cytometry plus UMAP. Human PBMC and tumor samples were from commercial and institutional sources. TCGA data were mined.

Results: αPDL2 ICB was ineffective in young mice with transplanted SQ B16 or NRAS-mutated melanoma, but remarkably effective in both in aged. αPDL2 efficacy was host IFNγ-dependent as expected, but also unexpectedly host IL17-dependent, which induced IFNγ. αPDL2 promoted IFNγ production by CD8+, CD4+ and γδ T cells and induced Treg fragility all in a host IL17-dependent manner. A cellular IL17 source for αPDL2 efficacy, mechanism for age-related IL17-driven IFNγ and contributions from Treg fragility are under study but not yet established. αPDL2 failed to treat transplanted orthotopic ovarian cancer in young or aged, but treated young mice bearing transplanted heterotopic, SQ bladder cancers, demonstrating αPDL2 is not efficacious only in aged or melanoma and that young skin is not necessarily hostile to αPDL2. TCGA data showed IL17 and PDL2 expression significantly increases by age in all cancers generally and specifically in melanomas. PDL2 protein increase by age was confirmed in human PBMC and primary tumors in linDR+CD141+ cDC1 but not on cDC2, plasmacytoid DC or other myeloid cells, T cells or B cells by flow cytometry. Both TCGA and flow data sets corroborated mouse data.

Conclusions: αPDL2 is effective in aged but not young melanoma-bearing hosts and requires IL17 for efficacy. IL-17 is necessary for improved IFNγ production which is a likely αPDL2 efficacy mechanism. αPDL2 is a promising ICB approach meriting additional studies of mechanisms and effects on distinct tumors and TME. As age effects were confirmed in humans, it could be especially useful in aged hosts, or selected ICB failures (e.g., αPDL1) as we previously reported.

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