1488 MELANOMA CELL-OF-ORIGIN PDL1 PROMOTES EARLY TUMOR PROGRESSION AND DISTINCT IMMUNE OUTCOMES IN A NOVEL AUTOCHTHONOUS NRAS-MUTANT MELANOMA MODEL

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Background Tumor-intrinsic PDL1 signals are drivers of treatment resistance in distinct aggressive tumors, such as melanoma.[1–3] Melanocytes, the melanoma cell-of-origin do not express PDL1 at baseline but exhibit a stepwise progression of PDL1 expression as cells transform from benign nevi to malignant melanomas, suggesting PDL1-driven contributions to melanomagenesis. We now investigate melanocyte-intrinsic PDL1 signaling in melanomagenesis. We hypothesized that melanocyte-intrinsic PDL1 signals drive melanomagenesis and early progression through distinct immune and non-immune mechanisms.

Methods We developed a novel autochthonous mouse model that develops $NRAS^{Q61R}$-mutant melanomas lacking PDL1 only in melanocytes ($PDL1^{KO}$ TN^{Q61R}) and littermate controls ($PDL1^{+/+}$ TN^{Q61R}). We induced mice with 4-OH tamoxifen ± UV exposure to accelerate melanoma development. We established transplantable cell lines from derived tumors and SQ challenged into WT BL6 mice for *in vivo* treatment studies and studied PDL1 signaling *in vitro*. We analyzed PDL1 influences on TIL content by 30-color spectral flow cytometry and assessed bulk and spatial transcriptomic dynamics.

Results We observed significantly increased tumor latency in $PDL1^{KO}$ vs. $PDL1^{+/+}$ TN^{Q61R} mice at 0 kJ/m^2 and 2 kJ/m^2 UVB ($p<0.02$), suggesting melanocyte/tumor PDL1 promotes melanomagenesis. Strikingly, melanocyte PDL1 effects on tumor latency were abrogated at 4.5 kJ/m^2, suggesting immune contributions, *e.g.,* from local immunosuppression. We derived transplantable cell lines from autochthonous tumors. Transplanted NRAS cell lines exhibited distinct tumor microenvironments (TMEs) shaped by PDL1 status versus B16 melanomas in WT BL6 mice. $PDL1^{KO}$ TN^{Q61R} tumors had decreased overall CD45+ immune infiltrate in autochthonous tumors and transplanted tumors with specific decreases in CD8+ and CD4+ T cells while CD11b+ myeloid cells were increased. Importantly, our TN^{Q61R} transplantable tumors recapitulate the T cell immune landscape in autochthonous TN^{Q61R} tumors, demonstrating the utility of transplantable tumors from our model in phenocopying the *de novo* tumor TME. These findings contrast with prior findings in B16 melanomas in which tumor $PDL1^{KO}$ results in increased CD8+ and CD4+ TILs and decreased CD11b+ TILs. Tumor PDL1 promotes sensitivity to anti-PDL1 *in vivo* in distinct transplantable TN^{Q61R} melanoma cell line UVB backgrounds. Our model allows studies of PDL1 signals in melanomagenesis and progression and distinguishes *bona fide* tumor cell-intrinsic PDL1 signals and influences on the TME.

Conclusions Our novel model distinguishes *bona-fide* cell-intrinsic PDL1 signals from potential genetic $PDL1^{KO}$ compensation confounding effects, allows studies of earliest PDL1 signals in melanomagenesis and progression, helps understand if PDL1 affects NRAS-driven oncogenesis, and helps test immunotherapy and small molecule treatment effects.

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