MELANOCYTE-INTRINSIC PDL1 PROMOTES TUMORIGENESIS AND PROGRESSION IN A NOVEL AUTOCHTHONOUS MELANOMA MODEL

Background Tumor PDL1 signals extrinsically to immune cell PD1 to evade antitumor immunity and is highly expressed on distinct cancers.1-7 Aside from tumor-extrinsic functions, we and others discovered various pathologic tumor-intrinsic PDL1 signals in distinct cancers, including melanoma.2 7 8 We found that melanocytes (the melanoma cell-of-origin) do not express PDL1 but exhibit a gradual progression of PDL1 expression as cells transform from benign nevi to malignant melanomas, suggesting a role for PDL1 in melanomagenesis. We now investigate melanocyte-intrinsic PDL1 signaling, to distinguish bona-fide PDL1 signaling influence on melanomagenesis in the absence of potentially confounding compensatory mechanisms in prior genetic PDL1KO studies in established tumors. We hypothesized that melanocyte-intrinsic PDL1 signals drive melanomagenesis and progression through immune and non-immune mechanisms.

Methods To test melanocyte-intrinsic PDL1 signals during melanomagenesis, we developed an autochthonous, tamoxifen-inducible, UV accelerated, Nras-driven mouse model where mice develop melanomas that are NrasQ61R mutant and lack PDL1 specifically only in melanocytes versus littermates. Mice were induced with tamoxifen on post-natal days 2-3 ± distinct UV exposures and monitored for tumor growth. 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.

Results Melanocyte PDL1 promotes melanomagenesis in a UV dose-dependent manner. Tumor latency was significantly increased in PDL1KO TNQ61R mice versus littermates at 2 kJ/m2 UV (p<0.02) suggesting an immune latency contribution. At 4.5 kJ/m2 UV, PDL1KO TNQ61R versus littermate melanoma latencies were indistinguishable, but faster than respective cohorts at 2 kJ/m2 possibly from immunosuppression at higher UV doses. Genetic PDL1KO in B16 melanoma induces synthetic lethality to small molecule Chk1 inhibitors by destabilizing Chk2 protein through increased ubiquitination, an effect phenocopied in vitro and in vivo in tumors from PDL1KO versus littermates. Tumors from PDL1KO TNQ61R versus littermates transplanted into WT recipients were resistant to αPD1, αPD2, and CD122-biased IL2 immunotherapies, differing from B16 melanomas that are sensitive to all these treatments. Notably, tumor PDL1 suppresses ERK signaling, a downstream target of Nras, in TNQ61R cell lines, suggesting PDL1 control of Nras-mediated oncosogenesis.

Conclusions Our novel model dissociates bona-fide cell-intrins-ic PDL1 signals from potential genetic PDL1KO 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. A parallel bladder cancer model was also developed, to be reported later.

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REFERENCES

Ethics Approval All animal studies were approved by the UT Health San Antonio Institutional Animal Care and Use Committee and each experiment was conducted in accordance with the standards required by the UT Health San Antonio Department of Laboratory Animal Resources. Approval number: 09128.