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

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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 potenocytocin of mTORC1 and stemness genes, and TCF1+ stem-like T cells through Raptor in ovarian cancer and melanoma. Cancer Res 2016;76(23):6964-6974.

Conclusions
Our novel model dissociates bona-fide cell-intrinsic 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