Genetically Induced Tumors in the Oncopig Model Invoke an Antitumor Immune Response Dominated by Cytotoxic CD8β+ T Cells and Differentiated γδ T Cells Alongside a Regulatory Response Mediated by FOXP3+ T Cells and Immunoregulatory Molecules - DTU Orbit (13/11/2019)

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In recent years, immunotherapy has shown considerable promise in the management of several malignancies. However, the majority of preclinical studies have been conducted in rodents, the results of which often translate poorly to patients given the substantial differences between murine and human immunology. As the porcine immune system is far more analogous to that of humans, pigs may serve as a supplementary preclinical model for future testing of such therapies. We have generated the genetically modified Oncopig with inducible tumor formation resulting from concomitant KRASG12D and TP53R167H mutations under control of an adenoviral vector Cre-recombinase (AdCre). The objective of this study was to characterize the tumor microenvironment in this novel animal model with respect to T-cell responses in particular and to elucidate the potential use of Oncopigs for future preclinical testing of cancer immunotherapies. In this study, we observed pronounced intratumoral T-cell infiltration with a strong CD8β+ predominance alongside a representation of highly differentiated γδ T cells. The infiltrating CD8β+ T cells displayed increased expression of the cytotoxic marker perforin when compared with the peripheral T-cell pool. Similarly, there was robust granzyme B staining localizing to the tumors; affirming the presence of cytotoxic immune cells within the tumor. In parallel with this antitumor immune response, the tumors displayed enrichment in FOXP3-expressing T cells and increased gene expression of indoleamine 2,3-dioxygenase 1 (IDO1), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and programmed death-ligand 1 (PDL1).

Finally, we investigated the Oncopig immune system in mediating antitumor immunity. We observed pronounced killing of autologous tumor cells, which demonstrates the propensity of the Oncopig immune system to recognize and mount a cytotoxic response against tumor cells. Together, these findings suggest innate and adaptive recognition of the induced tumors with a concomitant in vivo suppression of T-cell effector functions. Combined, the data support that the Oncopig may serve as a valuable model for future preclinical testing of immunotherapies aimed at reactivating tumor-directed cytotoxicity in vivo.

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