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PSGL-1-DEFICIENCY SUPPRESSES TUMOR GROWTH OF ORTHOTOPIC PANCREATIC DUCTAL ADENOCARCINOMA TUMORS AND ENHANCES IMMUNE CELL INFILTRATION AND CD8⁺ T CELL RESPONSES

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Background Pancreatic ductal adenocarcinoma (PDAC) is an aggressive, poorly immunogenic cancer that is increasing in incidence. PDAC tumors are highly refractory to all currently available treatments including existing immune checkpoint blockade (ICB) therapies, demonstrate limited CD8⁺ T cell infiltration. Patient prognosis is poor with a 5-year overall survival rate of only 11%. As such, there is a critical need to develop novel approaches to improve patient outcomes. We previously demonstrated that deficiency of P-selectin glycoprotein 1 (PSGL-1) promotes enhanced CD8⁺ T cell responses that clear chronic LCMV Cl13 virus infection and inhibit the growth of PD-1 blockade resistant melanoma. Here we evaluated if targeting PSGL-1 similarly promotes CD8⁺ T cell responses to PDAC tumors to inhibit growth and metastases.

Methods 2.5x10⁴ KPC.4662 tumor cells suspended in Matrigel were injected orthotopically into the pancreas tail in 6-8 week old C57BL/6 (wildtype control) and PSGL-1^{-/-} male or female mice. PDAC tumors were collected on day 28 post-injection and assessed by flow cytometry and histology. For evaluation of metastatic potential, 2x10⁵ KPC.4662 tumor cells suspended in 1X PBS were injected intravascularly into the tail vein of control and PSGL-1^{-/-} mice. Lung metastases were assessed on day 17 post-injection.

Results At 28 days post orthotopic tumor cell injection, KPC.4662 tumor burden was reduced on average by 45% (0.74±0.27g vs 0.41±0.24g) in PSGL-1^{-/-} mice compared to control mice. Moreover, fewer mice developed non-primary tumor metastases in the intraperitoneal cavity, liver, and lungs. To assess if PSGL-1^{-/-} mice had the capability to reduce metastatic burden, KPC.4662 cells were injected intravascularly and tumor development in the lungs was assessed on day 17. PSGL-1^{-/-} reproducibly developed fewer tumors in the lungs compared to control mice as determined by histological examination. Immune infiltration (CD45⁺ cells) was markedly increased (10% vs 24%) in orthotopic tumors from PSGL-1^{-/-} mice, including an increase in Thy⁺T cells (3.1% vs 9.4%). Flow cytometry and immunofluorescence staining confirmed a significant increase in tumor-infiltrating CD8⁺ T cells in PDAC tumors from PSGL-1^{-/-}. Importantly, PSGL-1^{-/-} CD8⁺ T cells were less functionally exhausted.

Conclusions In the absence of PSGL-1, we observe significantly reduced growth of primary orthotopic PDAC tumors and decreased metastases. These findings were associated with increased CD45⁺ immune cell infiltration in the tumors and notably, increased CD8⁺ T cell effector responses. PSGL-1 therefore represents a novel target for promoting immune responses to PDAC tumors.

Ethics Approval These animal studies were conducted at Sanford Burnham Prebys with the approval of the Sanford Burnham Prebys IACUC.

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