Background

• Immunosuppression mediated by the tumor stroma remains a major barrier in refractory tumors
• Cancer-associated fibroblasts (CAFs) are a dominant component of the pancreatic tumor microenvironment
• We sought to identify CAF-associated factor(s) responsible for the suppressive polarization of tumor infiltrating myeloid cells, which can directly inhibit antitumor CD8 T cell function
• A CAF-associated soluble factor would provide a target to reverse immunosuppression

Hypothesis

CAFs are associated with recruitment and polarization of suppressive myeloid cells, and this interaction is mediated by a CAF-associated soluble factor

Methods

CAF polarization of myeloid cells

• Bone marrow (BM) progenitors were cultured for 96 hours in normal fibroblast or CAF conditioned media
• Flow cytometry was used to assess the suppressive capacity of fibroblast conditioned myeloid cells

Suppression of T cells by CAF conditioned myeloid cells

• BM progenitors were cultured for 96 hours in normal fibroblast or CAF conditioned media
• Myeloid cells were co-cultured with CD8 T cells for 72 hours
• Flow cytometry was performed

CAF-induced myeloid polarization in vivo

• Mice were challenged with MT-4-LA tumor cells
• On day 5, mice were injected intratumorally with DMEM, normal fibroblast CM, CAF CM, or left untreated

Heat inactivation of CAF conditioned media

• BM progenitors were cultured for 96 hours in CAF conditioned media that was left at 56°C for 2 hours
• Flow cytometry was performed

Results

Results and Discussion

• CAFs can recruit myeloid cells and influence their suppressive function by promoting PD-L1 and arginase expression
• mPSC CM increased PD-L1 expression
• CAF conditioned myeloid cells reduce T cell proliferation and promotes tumor growth
• Intratumoral treatment with mPSC CM led to increased PD-L1 expression on macrophages and granulocytes
• Heat inactivation did not reduce mPSC-induced expression of PD-L1 on myeloid cells
• Our results suggest that CAFs recruit and polarize myeloid cells.
• Eventual goals include inactivating previously identified CAF-associated soluble factors with the hope of reducing local tumor immune suppression.

References


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