Background

Appendiceal Adenocarcinoma (AA) is a rare cancer that most commonly metastasizes to the peritoneal cavity. Very few preclinical models of AA exist. Patient-derived xenograft (PDX) models have the advantage of maintaining molecular and histologic features of human tumors as well as inherent intratumoral heterogeneity.

Most PDX models involve engraftment of tumors in the subcutis of immunodeficient mice. However, heterotopic tumor implantation may alter tumor growth and behavior. We hypothesized that orthotopic engraftment in the peritoneal cavity would more faithfully recapitulate the tumor microenvironment in metastatic AA. Improved preclinical modeling is critical for studying tumor biology of human cancers and accurately predicting patient responses to novel therapies.

Methods

- Three AA PDX tumor models were developed to compare the peritoneal cavity and subcutis.
- Tumor size was measured over time to calculate and normalize tumor growth.
- Tumors were removed and RNA sequencing was performed.
- H&E and immunohistochemical (IHC) staining was performed. Ki-67 staining was used to evaluate cell proliferation. Serial sections were stained with human marker KU80, GI epithelial marker CDX2, and mesenchymal marker vimentin.
- Slides were scanned with an Aperio AT2 whole slide digital scanner. Images were deconvoluted and merged using HALO v3.6.

Results

1.) Increased Appendiceal Adenocarcinoma Tumor Growth Rate In Peritoneal Microenvironment

- Table 1: Normalized growth measures for peritoneal and subcutaneous PDX. 2/3 of the tumor models evaluated showed a faster growth rate in the peritoneal cavity.

2.) Increased Appendiceal Adenocarcinoma Tumor Cell Proliferation In Peritoneal Microenvironment

- Fig. 4 shows increased proliferative activity in the peritoneal tumors compared to subcutaneous PDX.

3.) Human Appendiceal Adenocarcinoma Cells Persist in PDX Murine Models

- Fig. 5 indicates persistence of human tumor cells in the peritoneal cavity of PDX mice.

4.) Murine Stroma Replaces Human Stroma in Appendiceal Adenocarcinoma PDX Tumors

- Fig. 6 demonstrates replacement of human stroma by murine cells in PDX tumors.

Conclusions

1.) Orthotopic engraftment in the peritoneal cavity is superior to subcutaneous engraftment in preclinical PDX models due to improved tumor cell persistence and proliferation

2.) Murine stroma derived from the peritoneal cavity more faithfully recapitulates tumor microenvironment derived stroma in human patients and plays a role in supporting tumor growth.

References

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