Screening of primary cancer-associated fibroblast drug sensitivity to guide rational design of cancer-associated fibroblast-targeted antibody-drug conjugates in prostate cancer

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Background:

Cancer-associated fibroblasts (CAFs) are a prominent stromal cell population within the prostate tumor microenvironment (TME) that perform a wide array of roles in prostate cancer (PCA) progression and therapeutic resistance. Given the importance and diversity of these roles, therapies that target CAFs have the potential to improve disease control and increase survival for patients with PCa. Prior attempts to develop CAF-directed therapies, including antibody-drug conjugates (ADCs), for PCa have not been successful. However, there was no high-level data on the therapeutic sensitivities of CAFs to guide cytotoxic payload selection for these therapies. We therefore aimed to investigate the sensitivity of CAFs to three unique classes of chemotherapy to determine whether specific agents may be preferred as cytotoxic payloads in CAF-targeted therapies.

Methods:

Using six unique populations of high FAP and low FAP expressing primary CAFs that were derived from prostatectomy specimens of three patients with PCa, we evaluated the treatment effect of three commonly used cytotoxic payloads: the tubulin inhibitor monomethyl auristatin E (MMAE), the DNA alkylating payload SG3199, and the DNA intercalator PNU-159682 (PNU) using an area under the curve (AUC) treatment strategy. We also performed similar analysis on prostate tumor cell lines (22Rv1) to compare the sensitivity of tumor cells and CAFs to the evaluated treatments.

Results:

Analysis of dose-response data demonstrated that primary PCa CAFs were more sensitive to SG3199 and PNU than MMAE at the evaluated doses. There was also more heterogeneity of in the sensitivity of different CAF cell populations to MMAE than to SG3199 or PNU. Prostate tumor cells were more sensitive to MMAE treatment than the CAFs.

Conclusions:

Our data suggests that MMAE, which is a commonly used cytotoxic payload for ADCs that target tumor cells, may be a suboptimal payload for CAF-directed therapies. This finding may explain the prior failure of previous CAF-targeted therapies that utilized MMAE as the cytotoxic payload. SG3199 or PNU appear to induce greater and less heterogeneous CAF cytotoxicity. Future research should evaluate these agents as well as other cytotoxic agents as payloads in CAF-targeted therapies for PCa treatment.

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Conflicts of Interest Disclosure Statement:

S.G.Z. reports unrelated patents licensed to Veracyte, and that a family member is an employee of Artera and holds stock in Exact Sciences.