INTRODUCTION

Resident pancreatic stellate cells (PaSCs) can transform into cancer associated fibroblasts (CAFs) upon receipt of signals from cancer cells (e.g., pancreatic ductal adenocarcinoma or PDAC cancer cells) and secrete profibrotic factors that trigger pro-tumorigenic pathways and signalling cascades.

CAFs release multiple factors which trigger pro-tumorigenic pathways and signalling cascades.

The enzyme ENPP2/ATX/Autotaxin and its substrate LPC (lysophosphatidylcholine) are secreted by CAFs into the tumour microenvironment (TME).

AXT catalyses the conversion of LPC into lysophosphatidic acid (LPA).

LPA binding to LPA receptors triggers cancer cell proliferation, migration and survival pathways.

Targeting AXT can provide avenues for novel anti-cancer therapeutic strategies in CAF-driven cancers.

METHODOLOGY

The 0082T cell line was derived from primary CAF sample 0082, provided by Dr. Andrew Lowy (University of California, San Diego) and prepared from human PDAC surgical specimens (PMID: 30837243). Western blotting was performed using MBL D322-2 ATX antibody. LPC and LPA were measured using LC-MS analysis. Conditioned media (CM) were prepared from 0082T CAF, PaSC-1 and MIA PaCa-2 cells in low nutrient (11 mM glucose and 0.5 mM L-glutamine) serum free DMEM media (5% media) and collected at 72 hours. 0082T or PaSC-1 cells were treated with 12 µM IOA-289 (ATX inhibitor) and 0.1% DMSO (vehicle control) for the preparation of CM-ATX and CM-DMSO respectively at the 72-hour time point. Growth and proliferation of MIA PaCa-2 cells were assessed upon treatment with 12 µM IOA-289 and 0.1% DMSO using time-lapse imaging (Incucyte). 1 µM Stauroporine was used as a cell death control in MIA PaCa-2 growth inhibition studies. In vivo efficacy was studied in an immuno-competent, orthotopic mouse model of pancreatic cancer using an orthotopic xenograft model which was derived from a GEMM PDAC model (Kras (G12D), P53) (9). PK/PD studies were performed following a single oral dose of IOA-289 in mice, and plasma LPA was used as a PD biomarker.

RESULTS

Pancreatic CAF secretions promote PDAC (MIA PaCa-2) proliferation

CONCLUSION

Pancreatic CAFs release abundant amounts of ATX, LPC and LPA into the TME.

PDAC cells increase their proliferation when grown in CAF secretions.

Inhibition of AXT decreases the LPA levels in plasma of both in vivo mouse models and healthy volunteer human studies.

In addition to decreasing in the LPA levels, significant decrease in tumour burden is observed in orthotopic mouse models which are generally characterised by high plasma ATX levels.

Thus, the oral ATX inhibitor, IOA-289 provides a unique opportunity to target CAF-driven ATX functions in the tumour microenvironment and intervene in pancreatic cancer progression.

REFERENCES

AUTHORS

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0082T 5X CM-DMSO
0082T 5X CM-ATXi

PANC-1 5X CM-DMSO
MIA PaCa-2 5X CM-DMSO

0.0
0.5
1.0
1.5
2.0
2.5

Relative confluency of MIA PaCa-2
✱✱
ns
ns

Figure 1: PaSCs acquire pro-tumorigenic CAF phenotype

Figure 2: 0082T CAF conditioned media (CM) is abundant in ATX protein (2A), LPC (2B), LPA (2C) and significantly increases the proliferation of MIA PaCa-2 cells relative to PDAC CM (2D). Increase in proliferation is reduced when CM is generated from 0082T CAFs treated with the ATX inhibitor, IOA-289 (CM-ATX) relative to CM from vehicle treated 0082T CAFs (CM-DMSO) (2E). Such differences in MIA PaCa-2 cell growth are not observed with CM from ATX treated PAN-1 relative to vehicle treated PAN-1 (2F). IOA-289 directly inhibits the growth of MIA PaCa-2 (2G). No difference in MIA PaCa-2 proliferation is observed with direct addition of IOA-289 along with 0082T CM as compared to treatment with 0082T CM + vehicle (2H).

Figure 3: ATX inhibition with 10 mg/kg of the small molecule IOA-289 reduced tumour burden in an orthotopic mPDA6115-luc mouse model of pancreatic cancer significantly. Similar to a standard of care gemcitabine (3A), CD8+ T cells in mice treated with 3, 10, or 30 mg/kg of IOA-289 p.o. showed sustained plasma IOA-289 levels (3B) and dose-dependent decrease in circulating 18:2 LPA (c18:2 LPA) levels with an EDT₅₀ value at 1h post dose of ~ 3 mg/kg (3C), similar sustained plasma IOA-289 levels (3D) and dose dependent decrease of c18:2 LPA in plasma (3E) was observed in healthy male volunteers (6 subjects per cohort) administered a single capsule dose (30, 60, 120, 200 and 400 mg) of IOA-289. Plasma c18:2 LPA was measured at baseline for 24 h post dose and data are normalised to baseline levels (3E-D), IOA-289 was calculated as 15 ng/mL for IOA-289 in human plasma using the PK/PD data (3F).

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REFERENCES


Conflict of Interest Statement: ZJ, AM, KS, & ML are employees and shareholders of IonCura.