Breaking Through Resistance:
Mitochondrial Import in Pancreatic Cancer

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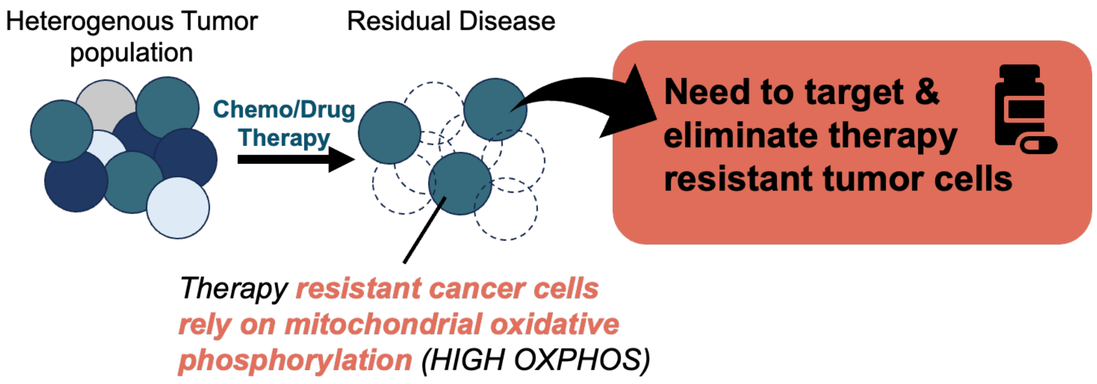
Background

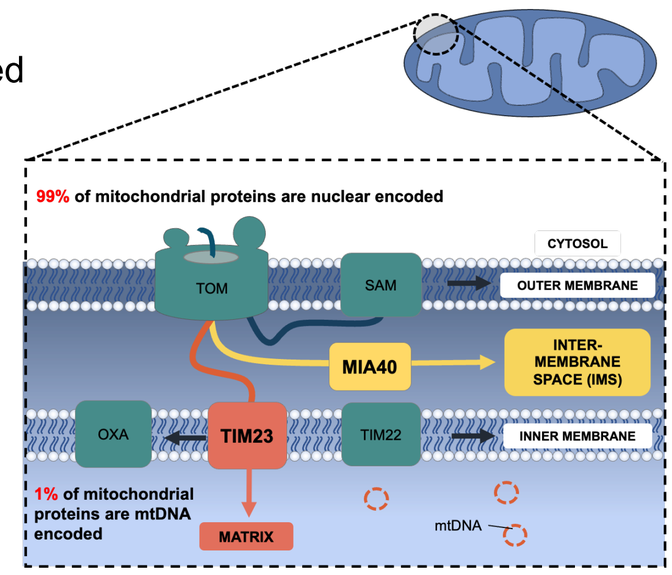
Pancreatic cancer will be the second deadliest cancer by 2030. However, treatment efficacy is limited by chemoresistance[1].

- Recent studies suggest that **therapy-resistant cancer cells rely on oxidative phosphorylation (high OXPHOS)** and other essential mitochondrial functions[2]. This has also been confirmed in pancreatic cancer[3,4].
- However, targeting mitochondrial dependence has been challenging due to off-target toxicity[5].
- Thus, there is an urgent need for alternative ways to overcome these obstacles and to exploit mitochondrial dependence effectively.



Among all the five mitochondrial import pathways, the MIA40 pathway (targeting proteins to the IMS) and TIM23 pathway (targeting proteins to the matrix) are upregulated in pancreatic cancer[6,7].

- Cancer cells with an upregulated MIA40 and TIM23 pathway share characteristics with therapy-resistant cancer cells[7,8,9].
- Why cancer cells are reliant on these mitochondrial import pathways, *and perhaps other mitochondrial biogenesis pathways*, remains unclear.



How does mitochondrial biogenesis - *particularly protein import* – drive tumorigenesis and chemoresistance in pancreatic cancer?

Results

1 Panc-1 cells are high OXPHOS, whereas MIA PaCa-2 cells are more glycolytic

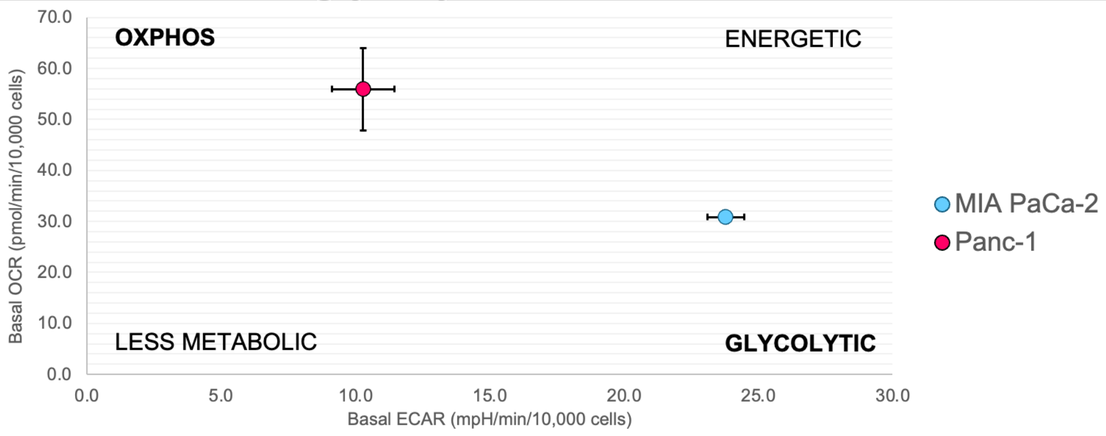


Figure 1: Energy map depicting basal OCR versus basal ECAR plot normalized to 10,000 seeded cells. Error bars represent standard deviation.

2 High OXPHOS Panc-1 cells are more sensitive to mitochondrial import pathway inhibitors compared to low OXPHOS tumor cells.

- Overall, both Panc-1 and MIA PaCa-2 cell lines are more susceptible to the Complex-I inhibitor Rotenone, the chemotherapeutic agent Gemcitabine and inhibitors targeting mitochondrial import (MitoBloCKs) compared to other compounds tested.
- However, among these, only the MitoBloCKs selectively eradicate high OXPHOS Panc-1 cells compared to more glycolytic MIA PaCa-2 cells.

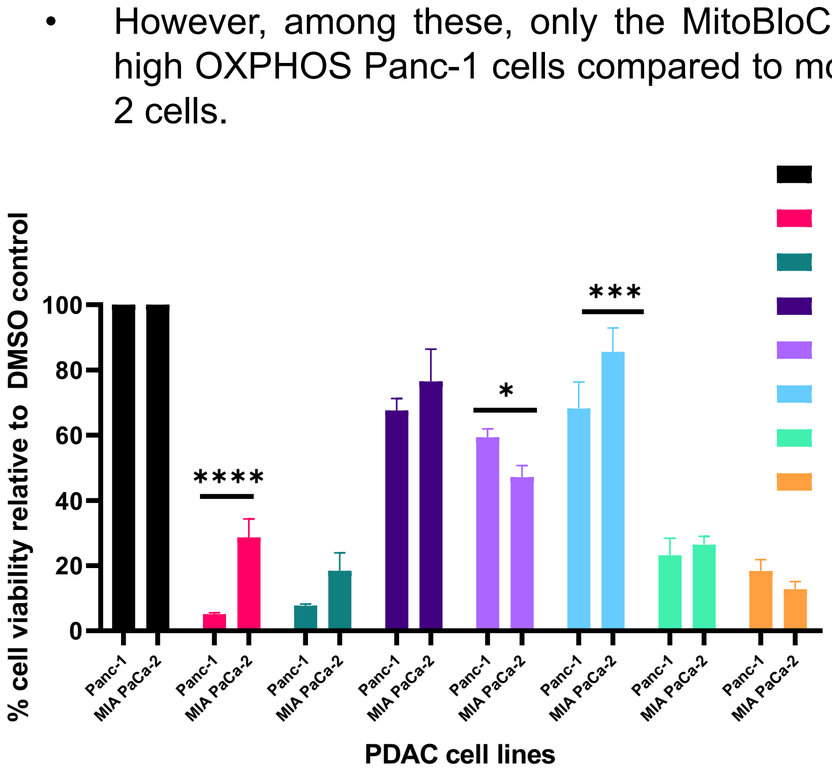
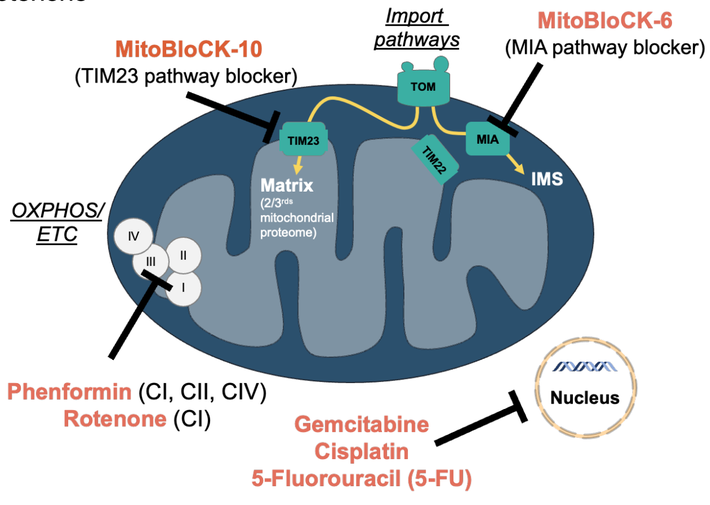


Figure 2: Mean percentage cell viability (CellTiter-Glo® 2.0 assay) of PDAC cells treated with 50 µM drugs for 72 hours. Bars represent the mean of triplicates with standard deviation normalized to the DMSO control. Statistical analysis by two-way ANOVA Tukey's multiple comparisons test. **** < 0.0001; ** < 0.001; * < 0.01; ns = non-significant. Diagram (right) illustrates mitochondrial pathways blocked by inhibitors, and the nucleus as the main target of chemotherapeutic drugs.

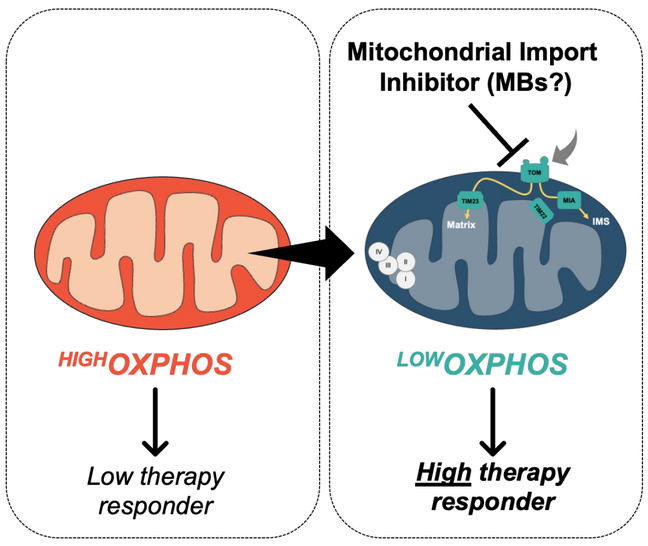


Discussion

- Mitochondrial import pathway inhibitors (MitoBloCKs) offer an *enhanced therapeutic index* by selectively targeting high OXPHOS Panc-1 cells compared to low OXPHOS tumour cells.
- This suggests that mitochondrial import pathways – specifically the TIM23 and MIA40 pathways – play distinct roles in high OXPHOS versus low OXPHOS tumor cells.
- It is unclear why Panc-1 cells are more susceptible to mitochondrial import inhibitors compared to low OXPHOS cells.

Future Work

- Using mitochondrial protein import inhibitors to induce a metabolic shift toward glycolysis (^{LOW}OXPHOS) to sensitize cells to the antitumoral activity of chemotherapeutic drugs in ^{HIGH}OXPHOS tumours[10,11].



- Future work will further investigate the relationship between metabolic rewiring, therapy resistance and mitochondrial import pathways in pancreatic cancer.
- Mitochondrial protein import pathways offer a novel target for therapeutic intervention and have the potential to be a *game-changer* in combating therapy-resistant cancers.

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