Breaking Through Resistance: Mitochondrial Import in Pancreatic Cancer

F. van der Schans and K. Tokatlidis
School of Molecular Biosciences, University of Glasgow
x faravds ‏@‏van-der-schans.1‏@‏research.gla.ac.uk

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.

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

Results

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

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.

Future Work

• Using mitochondrial protein import inhibitors to induce a metabolic shift toward glycolysis (LOWOXPHOS) to sensitize cells to the antitumoral activity of chemotherapeutic drugs in HIGHOXPHOS 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.

References