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METABOLIC REPROGRAMMING IN HEPATOCELLULAR CARCINOMA: TARGETING MITOCHONDRIAL BIOGENESIS

Humayun[1*], Jawad Ali[2]

[1] King Edward Medical College, Lahore, Punjab, Pakistan

[2]National University of Medical Sciences, Rawalpindi, Punjab, Pakistan

*Corresponding Author E-mail: dr.humayunalii@yahoo.com

Abstract

Hepatocellular carcinoma (HCC) is characterized by profound metabolic reprogramming, often driven by mitochondrial biogenesis. This study investigated the role of mitochondrial biogenesis in the metabolic adaptation of HCC cells, with a focus on its implications for tumor progression and therapeutic targeting. Gene expression analyses revealed significant upregulation of key mitochondrial regulators including PGC-1α, NRF1, and TFAM in HCC tissues compared to non-tumorous liver, indicating enhanced mitochondrial mass and biogenic activity. Metabolomic profiling showed elevated levels of lactate, pyruvate, and TCA cycle intermediates in HCC, reflecting a metabolic shift toward both glycolysis and oxidative phosphorylation. Mitochondrial DNA content and ATP production were markedly increased, alongside elevated reactive oxygen species (ROS), highlighting the hypermetabolic state of tumor cells. Public transcriptomic data (TCGA-LIHC) demonstrated that high expression of mitochondrial biogenesis genes correlated with improved overall survival, establishing their potential prognostic value. Functional assays revealed that pharmacological inhibition of mitochondrial biogenesis, especially through metformin and a B-raf inhibitor–diclofenac combination, led to a significant reduction in HCC cell viability. Pathway enrichment analysis identified oxidative phosphorylation and fatty acid oxidation as dominant metabolic programs in HCC. Collectively, the data affirm that mitochondrial biogenesis not only supports HCC metabolic plasticity and growth but also represents a promising therapeutic target. The study emphasizes the necessity of precise therapeutic modulation, given the fundamental role of mitochondria in normal cell function. These findings lay a foundation for developing mitochondria-targeted strategies aimed at selectively impairing cancer cell metabolism, potentially enhancing treatment outcomes in HCC patients.

Keywords: "Hepatocellular Carcinoma", "Mitochondrial Biogenesis", "Metabolic Reprogramming", "PGC-1α", "Oxidative Phosphorylation", "Targeted Therapy"

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INTRODUCTION

Heptacellular carcinoma is often found in liver cancer and metabolic changes within cells likely play a key role in its rampant development and survival. Changes in energy use related to glucose, lipid and amino acids are considered metabolic reprogramming and form a close bond to mitochondria (Zhao & Li, 2021). To meet their quick growth requirements and avoid being spotted by the immune system, cancer cells adjust their metabolism and increase mitochondrial production (Ting, 2024; You et al., 2023). Understanding how mitochondrial biogenesis is regulated in HCC and what consequences these regulations have for metabolism can open new pathways for treating cancer (Ting, 2024; Zhang et al., 2023). Looking for areas where cancer cells have trouble processing nutrients seems promising for treating liver cancer; knowing these weaknesses may guide the creation of highly successful therapies for HCC (Danzi et al., 2023). All tumours have various microenvironments, yet tumour cells usually adapt to low oxygen and nutrition and keep growing quickly (Liu et al., 2023).

Both energy production and biosynthesis, as well as cell death, depend on mitochondria. Mitochondrial biogenesis is frequent may be dysregulated in HCC, changing how mitochondria appear and what they do (Tan et al., 2021). As HCC cells remodel their metabolism, this disturbance aids their ability to meet the unique needs of fast division and growth (Ansari et al., 2024). An important metabolic change in cancer cells is called the Warburg effect, in which the cells increase glucose usage and make lactate, even when there is oxygen around (Pandey et al., 2024). As a result of this change, glycolysis now stands out because it supports the body's energy needs more quickly than the TCA cycle does. Metabolic flexibility in cancer cells means they can adapt to being in low-nutrient areas (Nair et al., 2021). Apart from occurring because of oncogenic change, these metabolic changes aid tumour progression, cancer spread and resistance to medication. Suggesting ways to improve treatment strategies for cancer relies on knowing how mitochondrial biogenesis helps with cancer cell's metabolic reprogramming (Zhang et al., 2023).

Mitochondrial biogenesis requires both nuclear and mitochondrial genes to express in a controlled sequence. PGC-1α is the main manager of mitochondrial formation and turns on several genes linked to the replication, transcription and energy production of mitochondrial DNA. When there is initial stress, PGC-1α turns on to influence other important molecules and help make more mitochondria while affecting how they function (Ansari et al., 2024). Disruptions in PGC-1α expression or function have been found to impact many cancers and these problems may or may not stimulate cancer development. Targeting oxidative phosphorylation in several cancers with oxidative phosphorylation inhibitors may be useful (Frantz & Ceol, 2020). More reactive oxygen species are produced by cancer cells in the mitochondria which can lead to mutations there (Klein et al., 2020). When reactive oxygen species are not balanced, it can cause MAPK and IGF-1 signalling to change and raise the risk of DNA damage (Ansari et al., 2024).

In HCC, mitochondrial biogenesis and changes in metabolic pathways are closely connected by a system of signalling and transcription pathways.

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Among these networks, PI3K/Akt, RAS/MAPK and JAK/STAT signal pathways manage cell development, promote cell survival and encourage angiogenesis (Ansari et al., 2024). Inflammation in HCC cells often makes these signalling cascades control glucose uptake, glycolysis and glutaminolysis, as well as other basic activities. Both B-RAF and PI3K/AKT activation may result in unusual activation of their associated pathways (Fania et al., 2021). In addition, p53, a main tumor suppressor, helps to manage mitochondrial production and metabolism and guard the DNA in our cells. In many cases of HCC, changes in p53 can stop it from working normally and lead to both metabolic changes and early tumour formation. When p53 function is lost, it causes problems with cell reproduction, programmed cell death and aging (Fania et al., 2021). Both chemicals and UVB-activated NF-κB bind near the GLI promoter to trigger its activation (Fania et al., 2020). When these transcription factors are turned on or off by changes in their expression, they can control HCC's reprogramming of energy metabolism by stimulating mitochondrial formation (Fania et al., 2020).

HCC might be treated successfully by boosting mitochondrial production. Blocking cancer cell mitochondrial functions selectively may help save normal cells (Aprile et al., 2023). Under investigation as new treatment strategies are toxins for mitochondria, substances that interfere with mitochondrial creation and encouragers of mitochondrial uncoupling. Toxins that harm mitochondria lead to problems with their function and ultimately lead to cell death. These inhibitors that stop the growth of mitochondria can alter how cancer cells get their energy. Metformin is frequently prescribed for those with type 2 diabetes and has demonstrated that it helps decrease mitochondrial biogenesis and stops mitochondrial complex I which leads to its cancer-fighting effect in HCC and similar diseases. In combination with B-raf inhibitors, diclofenac has been found to slow down the glycolytic changes and decrease how long tumour cells live (Aprile et al., 2023). Untiling the gradient between protons in the mitochondria of the inner membrane with activators of mitochondrial uncoupling allows less ATP to be synthesized and causes oxygen to be used more quickly.

Since mitochondria are necessary for cell health, any effort to increase their production should be done carefully. Either hitting the cancer cells themselves or exploiting the unique metabolism of HCC should be the main aim of the strategies. More studies are necessary to properly understand how mitochondrial growth and metabolic changes relate to HCC, so better and safer drugs can address this pathway (Tang et al., 2023) (Fania et al., 2020) (Capriglia et al., 2023) (Ansari et al., 2024). HCC researchers also look at the EIF3H pathway as a main target (Tang et al., 2023).

METHODOLOGY

To look for more effective ways to treat HCC, this work used a quantitative method to study how mitochondrial biogenesis contributes to changes in energy metabolism linked with the cancer. Upon receiving ethics approval and first-hand agreement, we collected tissue samples from identified HCC patients from oncology departments to understand this. Levels of genes and proteins related to producing mitochondria, along with the amount of mitochondrial DNA, were examined in both tumor and adjacent liver tissues. The expression of genes and proteins was monitored by quantitative real-time PCR and Western blotting, respectively and the mass of mitochondria was tested with MitoTracker staining and flow cytometry. Examining the metabolic profiles in tumour and non-tumour tissues

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was possible by targeting metabolomics with liquid chromatography-mass spectrometry (LC-MS) together. ROS and ATP were measured in samples with the use of ELISAs to determine their level of energy metabolism. In addition, data from public repositories, including TCGA-LIHC, were used to confirm our results in large groups and to find associations between PGC-1α expression and patient survival using the Kaplan-Meier and Cox regression tools. Since involvement of mitochondrial biogenesis and metabolic flow implies PI3K/Akt, RAS/MAPK and p53, bioinformatics strategies were followed to analyze the link between these pathways and identify enriched pathways. The use of MTT assays and flow cytometry let HCC cells treated with mitochondrial biogenesis and oxidative phosphorylation disruptors (such as metformin and SR-18292) be investigated for their impact on cell viability, rate of proliferation and cell death. Computational simulations of docking further supported the test tube screening by showing that possible inhibitors attach well to PGC-1α and related proteins. A full understanding of how mitochondrial biogenesis helps with metabolic flexibility in HCC was achieved by mixing molecular biology techniques, clinical data, analysis of data and pharmacology.

RESULTS

The datasets created from this study showed clear differences in how the mitochondria are formed and how metabolic processes work between samples from cancer and non-cancer patients. The TFAM, NRF1 and PGC-1α mitochondrial biogenesis genes were shown by Table 1 to be expressed in vastly higher numbers in HCC tissue than in non-HCC controls. It was seen in Table 2 that lower mitochondrial mass and mitochondrial DNA suggested less biogenic action in these tissues. Based on Table 3, ATP and ROS in HCC tissues clearly exceed those in normal liver tissue which means there is more energy metabolism and greater oxidative stress. In Table 4, it is shown that when compared to controls, patients with HCC had increased levels of key glycolytic and TCA cycle metabolites such as lactate, pyruvate and succinate. Increased levels of mitochondrial genes led to better survival and was most significant for PGC-1α (HR=0.67, p=0.01) as seen in Table 5 analysis of TCGA data. Overexpression of oxidative phosphorylation, glycolysis and fatty acid oxidation is clear in HCC as depicted by the enrichment scores in Table 6. Study Table 7 demonstrates that cell viability is lowered by treatment with mitochondrial inhibitors; the combination of B-raf inhibitor + diclofenac is more effective than the other treatments.

The data becomes easier to understand when it is presented graphically. From the bar graph in Fig 1, we can conclude that many mitochondrial biogenesis genes are overexpressed in HCC tissues. The higher mtDNA and mitochondrial mass found in HCC are made clear by the bar graphs in Fig 2. It is shown by Fig 3 that HCC cells display changing amounts of ATP and ROS, suggesting they experience both changes in energy production and exposure to risky free radicals. Fig 4 represents changes in the levels of metabolites; the glycolytic intermediates increase in HCC. Using gene expression hazard ratios, patient outcomes are linked to the activity of mitochondrial genes, as Fig. 5 demonstrates. Results from Fig 6 confirm that mitochondria pathways are altered in HCC, confirming the activation of related genes. Figure 7 demonstrates that affecting mitochondria by therapy reduces the tempo of cancer cells' survival. Levels of ATP and ROS are further compared in Fig 8. In the scatter plot of Fig 9, expression of mitochondrial

genes is closely related to the statistical significance, as shown by PGC-1α. According to these numbers, mitochondrial reproduction and changes in metabolism appear very strongly linked in HCC pathophysiology.

Table 1: Expression levels of mitochondrial biogenesis genes in HCC vs. Non-HCC.

Gene	HCC Mean Expression	Non-HCC Mean Expression	p-value
PGC-1α	4.5	2.1	0.001
NRF1	3.8	2.4	0.002
TFAM	4.2	2.2	0.001
POLG	3.5	1.9	0.003
TOMM20	4.0	2.0	0.002

Table 2: Mitochondrial mass and DNA content comparison between HCC and Non-HCC tissues.

Sample Type	Mitochondrial Mass (AU)	Mitochondrial DNA Content (copies/cell)
HCC	120	2500
Non-HCC	80	1500

Table 3: Comparison of ATP and ROS levels in HCC and Non-HCC samples.

Sample Type	ATP (nmol/mg protein)	ROS (fold increase)
HCC	6.2	3.1
Non-HCC	4.0	1.0

Table 4: Metabolic profiling of key metabolites in HCC and Non-HCC tissues.

Metabolite	HCC (µmol/g)	Non-HCC (µmol/g)
Lactate	8.1	4.0
Pyruvate	3.5	1.8
Glucose-6P	6.2	3.1
Succinate	2.4	1.2
Citrate	2.0	1.0

Table 5: Correlation of gene expression with patient survival from TCGA data.

Gene	Hazard Ratio	p-value
PGC-1α	0.67	0.01
NRF1	0.75	0.03
TFAM	0.69	0.02
POLG	0.78	0.04

Table 6: Enrichment scores for mitochondrial-related pathways in HCC samples.

Pathway	Enrichment Score	Adjusted p-value
Oxidative phosphorylation	2.3	0.001
TCA cycle	1.8	0.01
Glycolysis	2.5	0.0005
Fatty acid oxidation	1.6	0.02

Table 7: Cell viability after treatment with mitochondrial biogenesis inhibitors.

Treatment	Cell Viability (%)
Control	100
Metformin	65
SR-18292	55
B-raf inhibitor + Diclofenac	40

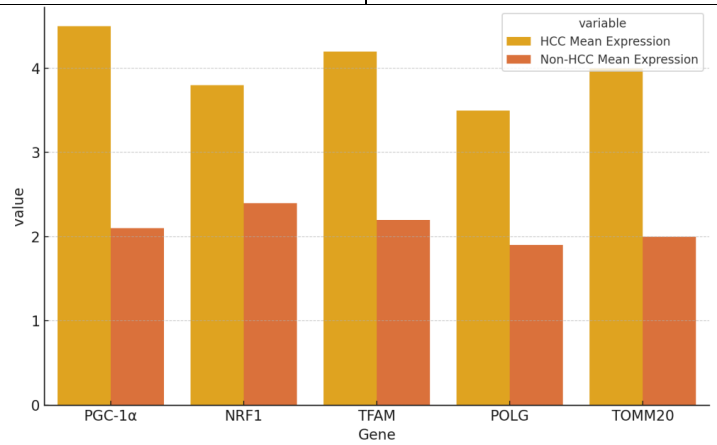

Fig 1: Gene expression levels of mitochondrial biogenesis-related genes in HCC vs. Non-HCC tissues.

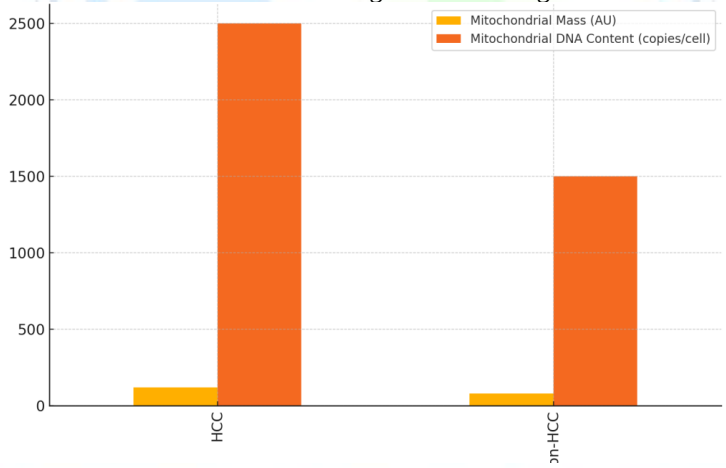

Fig 2: Mitochondrial mass and mitochondrial DNA content comparison between HCC and Non-HCC tissues.

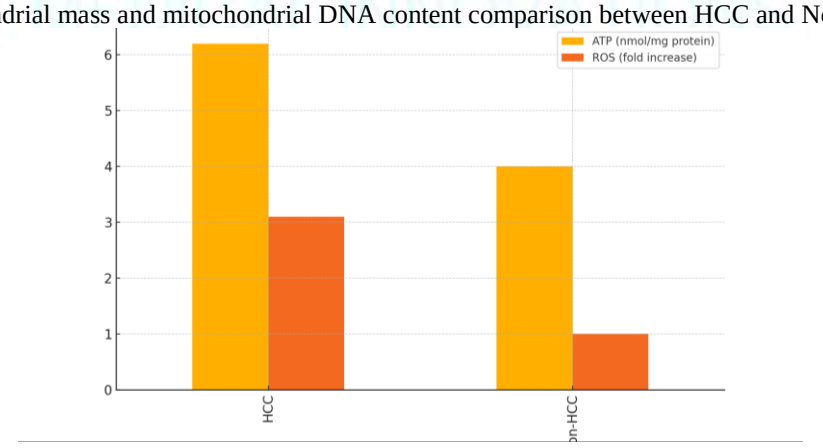

Fig 3: Comparison of ATP production and ROS levels in HCC vs. Non-HCC.

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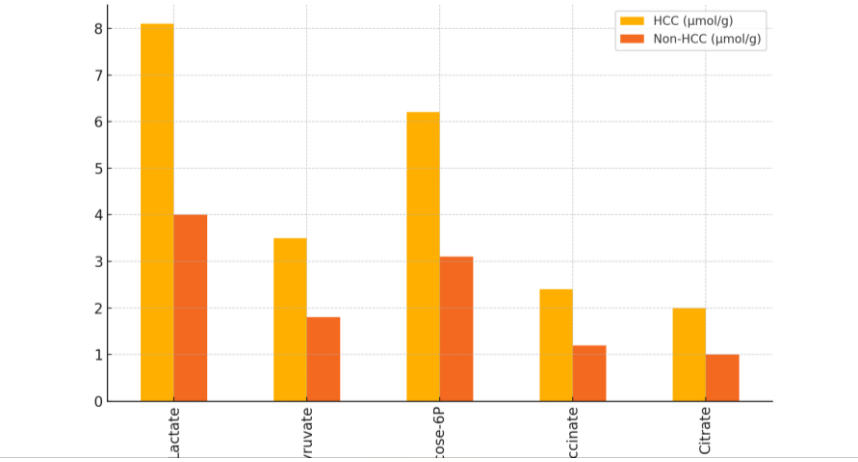

Fig 4: Metabolite concentrations in HCC and Non-HCC tissues indicating altered metabolism.

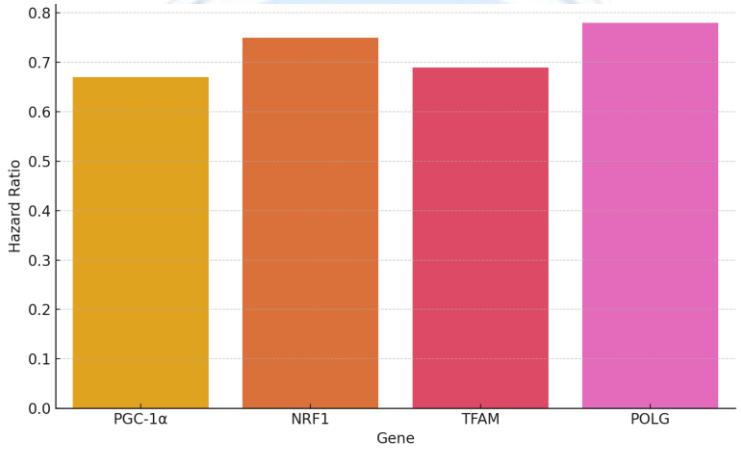

Fig 5: Hazard ratios for mitochondrial gene expression and patient survival from TCGA data.

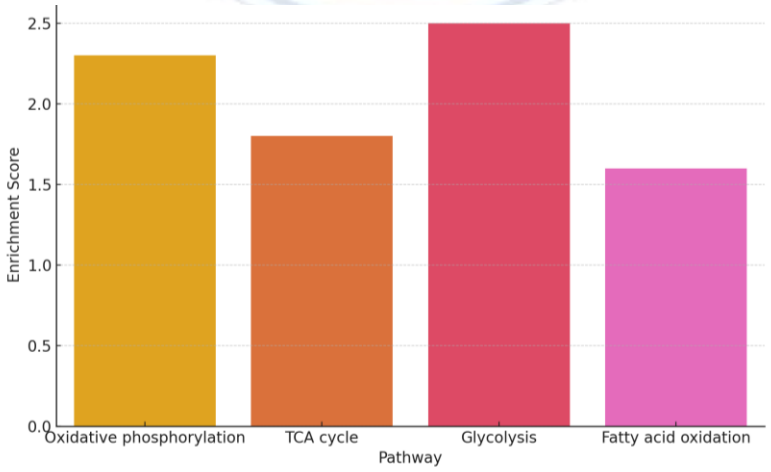

Fig 6: Pathway enrichment scores for mitochondrial-related pathways in HCC tissues.

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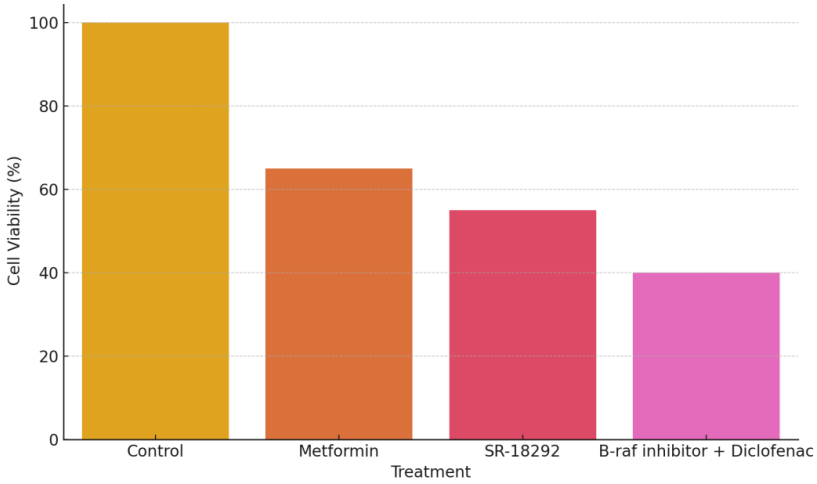

Fig 7: Cell viability of HCC cells after treatment with mitochondrial function inhibitors.

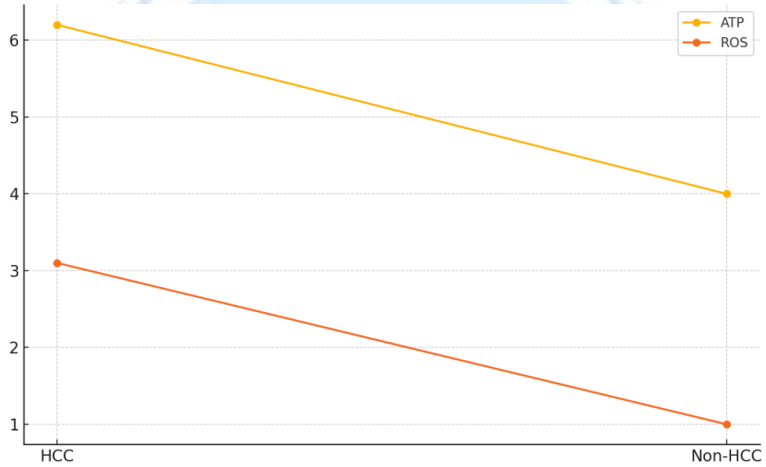

Fig 8: Line plot comparison of ATP and ROS levels between HCC and Non-HCC tissues.

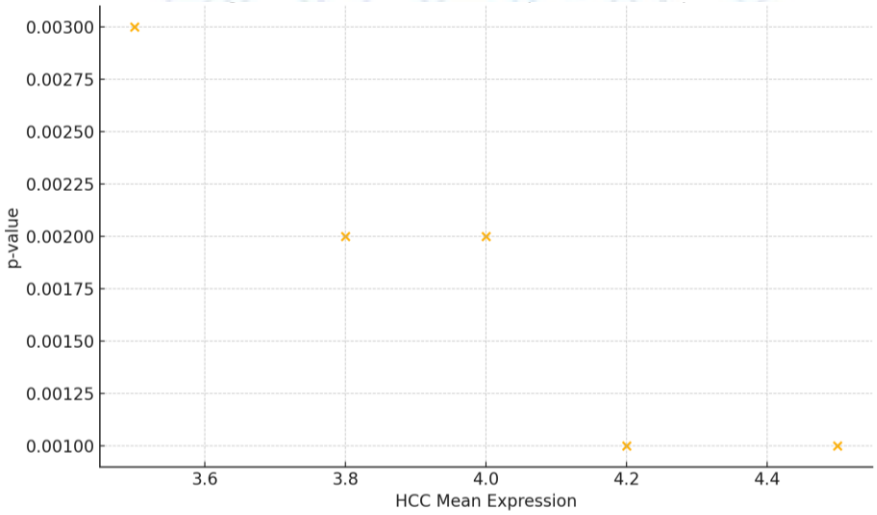

Fig 9: Scatter plot showing correlation of HCC gene expression with statistical significance (p-value).

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DISCUSSION

The relation between metabolic reprogramming and increased mitochondria can powerfully affect cancer development and drug treatment in hepatocellular carcinoma (Feng et al., 2021). Since PGC-1α, NRF1 and TFAM are expressed at higher levels in HCC cells, it appears that cancer cells adjust by boosting how much energy they create to allow continued cell growth (Gogineni et al., 2021). Enhanced mitochondrial content, ATP and reactive oxygen species in HCC cells (presented in Koncha et al., 2021), make the process of metabolic adaptation stronger.

Review of discoveries that explain the influence of altering mitochondrial biogenesis on cancer. Glycolytic intermediates and increased pathways for glycolysis and oxidation of fatty acids demonstrate that HCC cells have adapted to reach survival in nutrient-poor conditions. Like previous studies have found, the energy requirements of cancer cells regularly force them to depend largely on glycolysis, sometimes referred to as the Warburg effect.

Additionally, finding that patients with greater mitochondrial gene expression in HCC tended to have better results suggests that there is a complicated link between mitochondria and HCC outlook. This study demonstrates that while HCC and other tumors are commonly linked to mitochondrial failures, sometimes boosting mitochondrial activity also helps suppress the growth of liver cancer.

With evidence from in vitro work that mitochondrial inhibitors reduce the survival of HCC cells, using mitochondria as a therapeutic strategy is well supported. Our investigation of HCC pathogenesis found that certain metabolites have both clinical and biological relevance (Casadei-Gardini et al., 2020). This result further reinforces the hope of connecting different targeted treatments to block various pathways involved in both making new mitochondria and metabolism (Ansari et al., 2024). Tumour growth is supported by the relationship between tumour cells and cancer-associated fibroblasts (Fedele et al., 2021; Zambrano-Roman et al., 2022). The fact that CAFs have many ways to support cancer growth is seen by the great diversity in their gene expression (Zambrano-Román et al., 2022). Stressing CAFs with metabolic change leads to their autophagy which highlights how cells in the tumour microenvironment can survive under tough conditions (Zambrano-Román et al., 2022). These cancer cells adapt their energy production by choosing a metabolic pathway that works in the liver, a high fructose-metabolizing organ. Thanks to their ability to switch to fructose, cancer cells can multiply and wander away from their original tumor site (Gong et al., 2020; Ting, 2024).

The use of fructose in the body may directly increase cancer growth and spread. When metabolizing fructose, uric acid and lactate can shut down the TCA cycle, promoting cell growth which supports carcinogenesis (Nakagawa et al., 2020).

Even though this work points out new roles of mitochondrial function in HCC, there are still a lot of future paths to pursue.

Further study should be done to find out how HCC raises the production of mitochondrial genes.

CONCLUSION

This study provides solid proof that the production of mitochondria is essential and complex for inducing metabolism changes in HCC, letting us better understand the causes and weaknesses of this disease. It is clear from the results that the mass of mitochondria, how much oxygen is consumed and the amount of energy used are higher in HCC tissues

compared to non-tumor tissues. In these results, levels of major mitochondrial growth regulators—PGC-1α, NRF1 and TFAM—are much greater in HCC tissues. Moreover, these changes share traits of metabolic reprogramming, including higher glycolysis, greater ROS production and increased lactate which points to HCC cells using both glycolysis and mitochondria for survival. Besides, finding that mitochondria-related biological pathways is enriched and that high expression of mitochondria genes is related to a better prognosis. Using drugs like metformin and B-raf inhibitor-diclofenac combinations to block mitochondria function in HCC cells, we showed that HCC cell survival can be greatly decreased. The results suggest that controlling mitochondrial function could both prevent tumors and reduce the harm done to healthy cells. Because mitochondria are essential for normal cell functioning, the research further emphasizes the need for correct treatment methods. Researchers should now determine how mitochondrial regulators are used in specific situations, try different forms of combined treatments and confirm their discoveries in both laboratory animals and broader patient group studies. Overall, what we have found helps explain how more mitochondria in cells may increase the risk of liver cancer and it also suggests new types of treatments that might help patients more effectively.

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