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Modulation of Mitochondrial Biogenesis and Apoptosis by Resveratrol in Human Hepatocellular Carcinoma Cells

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Abstract

Resveratrol, a natural polyphenolic compound found in grapes and red wine, has been shown to exert anti-cancer properties through multiple biochemical pathways. This study investigates the molecular mechanisms by which resveratrol affects mitochondrial biogenesis and apoptosis in human hepatocellular carcinoma (HepG2) cells. We observed that resveratrol induces mitochondrial DNA replication, upregulates PGC-1α and NRF1 expression, and promotes caspase-mediated apoptosis. Furthermore, it modulates Bcl-2 family protein expression and enhances reactive oxygen species (ROS) production, contributing to mitochondrial stress. These findings suggest that resveratrol may function as a potential therapeutic agent targeting mitochondrial dysfunction and apoptosis in liver cancer.

Keywords: Resveratrol, Hepatocellular carcinoma, Mitochondria, Apoptosis, PGC-1α, NRF1, Caspases, ROS, Bcl-2, Biochemical signaling

Introduction

Hepatocellular carcinoma (HCC) is among the leading causes of cancer-related deaths worldwide. Current therapeutic strategies often exhibit limited efficacy due to tumor resistance and systemic toxicity. Recent studies have highlighted the role of mitochondrial biogenesis and apoptosis in regulating cancer cell fate.

Mitochondria are not only the powerhouse of the cell but also key regulators of intrinsic apoptotic pathways. Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a stilbenoid found in red wine, has gained attention for its chemopreventive and pro-apoptotic properties. It has been shown to activate several transcriptional coactivators involved in mitochondrial function, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and nuclear respiratory factor 1 (NRF1). The aim of this study was to elucidate the molecular and cellular pathways through which resveratrol modulates mitochondrial biogenesis and apoptosis in HepG2 cells.

Materials and Methods

Cell Culture:
Human hepatocellular carcinoma cells (HepG2) were obtained from the American Type Culture Collection (ATCC) and maintained in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin under standard cell culture conditions.
Treatment with Resveratrol:
Cells were treated with varying concentrations of resveratrol (10–100 μM) for 24 and 48 hours. A vehicle control group was maintained using 0.1% DMSO.
Quantitative PCR (qPCR):
Total RNA was extracted using TRIzol reagent and reverse-transcribed to cDNA. qPCR was performed to assess expression levels of mitochondrial biogenesis markers (PGC-1α, NRF1, TFAM). Relative expression was normalized using GAPDH as a housekeeping gene.
Western Blot Analysis:
Protein extracts were subjected to SDS-PAGE followed by immunoblotting for cytochrome c, cleaved caspase-3, Bcl-2, Bax, PGC-1α, and β-actin.
Mitochondrial DNA Quantification:
Mitochondrial DNA (mtDNA) copy number was quantified using qPCR targeting mitochondrial-specific genes and normalized to nuclear DNA.
ROS Measurement:
Intracellular ROS production was assessed using the DCFDA Cellular ROS Detection Assay.
Statistical Analysis:
Data were analyzed using ANOVA followed by Tukey's test. A p-value <0.05 was considered statistically significant.

Results
Resveratrol treatment significantly upregulated the expression of PGC-1α and NRF1 in a time- and dose-dependent manner. There was a marked increase in mitochondrial DNA copy number, indicating enhanced mitochondrial biogenesis. Western blot analysis revealed increased levels of cleaved caspase-3 and decreased Bcl-2 expression, consistent with activation of apoptosis.
Moreover, ROS levels were significantly elevated following resveratrol treatment, suggesting oxidative stress as a contributing factor to mitochondrial dysfunction. Bax expression was elevated, leading to a higher Bax/Bcl-2 ratio. These molecular events were accompanied by chromatin condensation and DNA fragmentation, observed via DAPI staining (data not shown).

Discussion
Our findings demonstrate that resveratrol exerts potent biochemical effects on mitochondria in hepatocellular carcinoma cells. The increase in mitochondrial biogenesis may initially appear paradoxical in cancer therapy; however, in this context, it is accompanied by an apoptotic cascade, suggesting that mitochondrial stress is being exploited to trigger cell death.
The induction of PGC-1α and NRF1 suggests activation of a compensatory response to mitochondrial stress, while elevated ROS may push cells beyond their survival threshold. The regulation of Bcl-2 family proteins and the activation of caspase-3 confirm the intrinsic apoptotic pathway's involvement.
These results align with previous studies reporting that resveratrol enhances mitochondrial function in non-cancerous cells while promoting apoptosis in tumor cells. This dual action makes resveratrol a promising candidate for further exploration as a metabolic modulator in cancer therapy.

Conclusion
Resveratrol significantly modulates mitochondrial biogenesis and promotes intrinsic apoptosis in HepG2 cells. These effects are mediated through the upregulation of PGC-1α/NRF1 and the enhancement of ROS production, leading to mitochondrial-mediated cell death. This study supports the potential therapeutic value of resveratrol in liver cancer and encourages further investigation in preclinical and clinical settings.

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