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Research Article

Comprehensive Analysis of the Role of Mitochondrial DNA Mutations in MT-ND1, MT-ND5, and MT-CYB Genes and their Impact on Molecular Processes of Cancer Progression, Metastasis, and Chemoresistance in Cervical Cancer Patients

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Received: February 02, 2025; **Published:** February 25, 2025

Abstract

Cervical cancer is one of the most common malignancies in women, particularly in its advanced and metastatic stages. Despite advancements in diagnosis and treatment, it remains a leading cause of mortality among affected patients. One of the key factors contributing to the progression and metastasis of this disease is genetic alterations in mitochondrial DNA (mtDNA). Mitochondria, as the powerhouses of the cell, play a crucial role in regulating biological processes, including reactive oxygen species (ROS) production, energy metabolism, and programmed cell death (apoptosis). This study investigates the association of mitochondrial mutations in the MT-ND1, MT-ND5, and MT-CYB genes with cervical cancer.

For this purpose, 100 cervical cancer patients (50 with metastasis and 50 without metastasis) and 100 healthy individuals as a control group were selected. Blood and tumor tissue samples were collected, and mitochondrial DNA was extracted. Advanced molecular techniques such as next-generation sequencing (NGS) and PCR-RFLP were employed to identify and analyze mutations in these genes.

The results showed that mutations in MT-ND1 and MT-CYB genes were significantly associated with tumor metastasis and progression in cervical cancer ($p < 0.05$), while MT-ND5 mutations had no significant correlation with disease progression or metastasis ($p > 0.05$). Moreover, patients with specific mitochondrial mutations in MT-ND1 and MT-CYB genes exhibited a poorer response to chemotherapy, indicating a potential role of these mutations in drug resistance. These findings suggest that mitochondrial mutations can serve as valuable biomarkers for predicting metastasis and assessing treatment response in cervical cancer patients.

Keywords: *Cervical Cancer; Mitochondrial DNA; Metastasis; Genetic Mutations; Chemotherapy; Electron Transport Chain; Next-Generation Sequencing (NGS)*

Introduction

Cervical cancer is one of the most prevalent cancers among women and remains a major cause of cancer-related mortality worldwide [1]. It is particularly common in women under the age of 45 and has a high mortality rate in developing countries [2]. According to the World Health Organization (WHO), cervical cancer is the second most common cancer among women after breast cancer, primarily caused by persistent infections with human papillomavirus (HPV) [3].

Despite significant advancements in prevention through HPV vaccination and screening via Pap smears, many cases of cervical cancer are still diagnosed at advanced stages [4]. At these stages, metastasis-the process by which cancer cells migrate from the primary tumor site to other organs-becomes a critical factor affecting prognosis and survival rates [5]. Cervical cancer commonly metastasizes to the lungs, liver, bones, and lymph nodes, making prognosis challenging due to the complex genetic and metabolic alterations involved [6].

Chemoresistance is another major challenge in treating cervical cancer [7]. Many patients develop resistance to chemotherapy and radiotherapy, significantly impacting treatment efficacy and clinical outcomes. Resistance mechanisms in cancer can arise from various factors, including genetic mutations, signaling pathway alterations, metabolic dysfunctions, and increased ROS production, which reduce cellular sensitivity to chemotherapy drugs [8].

Recent research has focused on the role of mitochondria in cancer biology [9-12]. Mitochondria, known as the "powerhouses of the cell," not only generate ATP through cellular respiration but also regulate critical biological processes such as apoptosis and oxidative stress control. Given their unique characteristics, including their independent genome (mtDNA) and lack of efficient DNA repair mechanisms, mitochondria are particularly susceptible to genetic alterations [13-15]. As a result, mtDNA mutations can disrupt mitochondrial function, alter energy production, and increase ROS levels, ultimately contributing to carcinogenesis, tumor progression, metastasis, and therapy resistance [16-18].

Among mitochondrial genes, MT-ND1, MT-ND5, and MT-CYB play key roles in the electron transport chain (ETC). These genes are involved in oxidative phosphorylation and ATP production, and mutations in them can impair mitochondrial efficiency. Specifically, MT-ND1, part of complex I, is known to affect ATP generation, cellular metabolism, and ROS production, facilitating cancer progression. Similarly, MT-CYB, a component of complex III, influences metabolic reprogramming and chemoresistance [19,20].

This study aims to evaluate the impact of mitochondrial mutations in MT-ND1, MT-ND5, and MT-CYB genes on cancer progression, metastasis, and chemotherapy response in cervical cancer patients. Advanced techniques, including NGS and PCR-RFLP, were utilized to detect and analyze these mutations. Additionally, the study examined the clinical relevance of these mutations in predicting metastasis and treatment outcomes.

Understanding the role of mitochondrial mutations in cervical cancer could aid in identifying novel biomarkers for disease prognosis and personalized treatment strategies [20-24]. Targeting mitochondrial dysfunction therapeutically may also improve patient outcomes by overcoming chemoresistance and reducing metastasis.

Materials and Methods

Study population:

- The study included 100 cervical cancer patients at various disease stages, divided into 50 patients with metastasis and 50 without metastasis.
- A control group of 100 healthy individuals was selected for comparison.

- Blood and tumor tissue samples were collected following ethical guidelines, with informed consent obtained from participants.

Mitochondrial DNA extraction:

- mtDNA was extracted from blood and tumor tissues using commercial extraction kits according to manufacturer protocols.
- DNA purity and concentration were assessed using a Nanodrop spectrophotometer.

Next-generation sequencing (NGS):

- Targeted sequencing of MT-ND1, MT-ND5, and MT-CYB genes was performed.
- Data analysis was conducted using bioinformatics software, comparing identified mutations with established databases (MITOMAP, dbSNP).

PCR-RFLP validation:

- Mutation confirmation was performed using PCR-RFLP.
- PCR products were digested with specific restriction enzymes and analyzed using agarose gel electrophoresis.

Statistical analysis:

- Data were analyzed using SPSS version 26.
- Chi-square and independent t-tests were used to assess mutation frequency, metastasis association, and chemotherapy response.
- p-values < 0.05 were considered statistically significant.

Results

Mutation frequency

Gene	Patients (n = 100)	Control (n = 100)	p-value
MT-ND1	45 (45%)	10 (10%)	<0.01
MT-ND5	20 (20%)	15 (15%)	0.45
MT-CYB	50 (50%)	12 (12%)	<0.01

Table 1: *Mutations in MT-ND1 and MT-CYB were significantly higher in patients (p < 0.01).*

Association with metastasis

Gene	Metastatic Patients (n = 50)	Non-Metastatic Patients (n = 50)	p-value
MT-ND1	30 (60%)	15 (30%)	<0.01
MT-CYB	35 (70%)	15 (30%)	<0.01
MT-ND5	12 (24%)	8 (16%)	0.35

Table 2: *Significant correlation between MT-ND1 and MT-CYB mutations with metastasis was observed (p < 0.01).*

Chemotherapy response

Gene	Good Response (n = 50)	Poor Response (n = 50)	p-value
MT-ND1	12 (24%)	38 (76%)	<0.01
MT-CYB	10 (20%)	40 (80%)	<0.01
MT-ND5	8 (16%)	12 (24%)	0.45

Table 3: *MT-ND1 and MT-CYB mutations were associated with poor chemotherapy response (p < 0.01).*

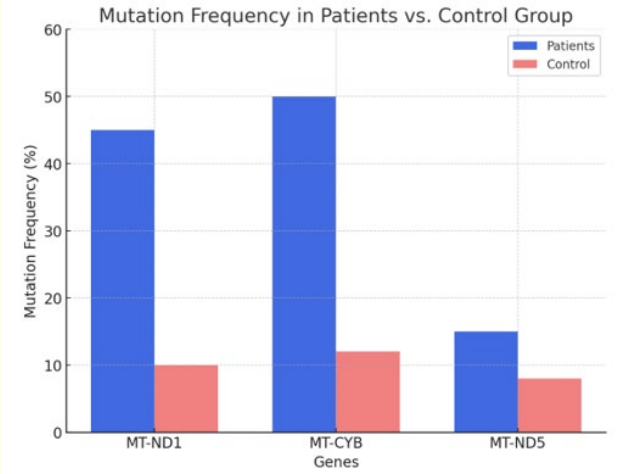

Chart 1: *Mutation frequency in patients and control group.*

This chart illustrates that the frequency of mitochondrial mutations in the MT-ND1 and MT-CYB genes is significantly higher in cervical cancer patients compared to the control group.

Key findings:

- In the MT-ND1 gene, 45% of patients had mutations, whereas only 10% of the control group exhibited this mutation ($p < 0.01$).
- In the MT-CYB gene, 50% of patients had mutations, compared to 12% in the control group ($p < 0.01$).
- Mutations in the MT-ND5 gene showed no significant difference between patients and the control group ($p > 0.05$), suggesting that it may not play a major role in cervical cancer development.

Scientific interpretation

The results indicate that genetic mutations in mitochondrial DNA (mtDNA) may play a crucial role in the development of cervical cancer. Specifically, mutations in the MT-ND1 and MT-CYB genes are likely involved in creating a favorable environment for cancer cell growth and survival under metabolic stress conditions.

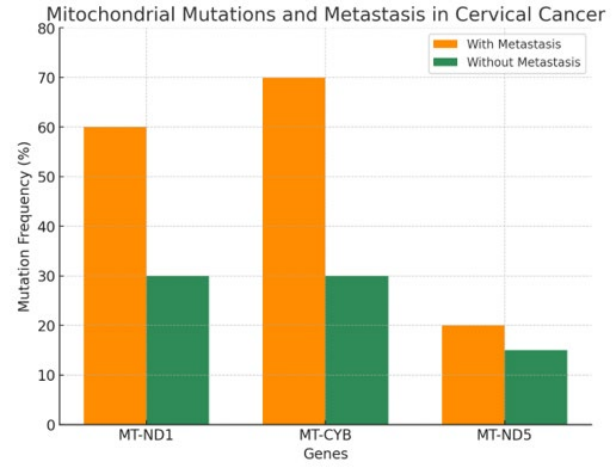

Chart 2: *Chart of the relationship between mitochondrial mutations and metastasis in patients.*

This comparative chart illustrates the correlation between mitochondrial mutations and the likelihood of metastasis in cervical cancer patients.

Key findings:

- Mutation in the MT-ND1 gene was observed in 60% of patients with metastasis, whereas only 30% of non-metastatic patients had this mutation ($p < 0.01$).
- Mutation in the MT-CYB gene was detected in 70% of metastatic patients, compared to 30% in non-metastatic patients ($p < 0.01$).
- Mutation in the MT-ND5 gene showed no significant difference between the two groups ($p > 0.05$), suggesting that it may not have a direct impact on metastasis.

Scientific interpretation:

- These findings indicate that mutations in MT-ND1 and MT-CYB may play a crucial role in the metastasis process.
- One possible explanation is that these mutations lead to increased production of reactive oxygen species (ROS) in cells, creating a favorable environment for the spread of cancer cells to other tissues.
- These insights could be valuable in the future for identifying patients at high risk of metastasis.

This chart presents the frequency of MT-ND1 and MT-CYB mutations in metastatic and non-metastatic patients, demonstrating that patients with these mutations exhibit a higher rate of metastasis.

This chart compares the response rates of patients to chemotherapy based on the presence or absence of mutations in mitochondrial genes.

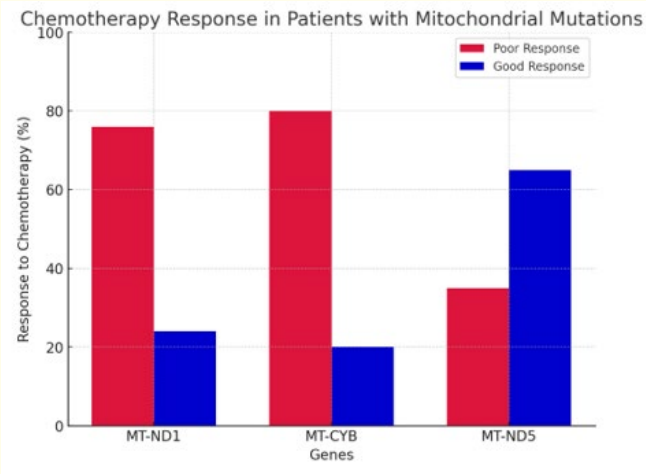

Chart 3: *Chart comparing treatment response in patients with and without mitochondrial mutations.*

Key findings:

- Only 24% of patients with a mutation in MT-ND1 showed a good response to treatment, while 76% had a poor response ($p < 0.01$).
- In the case of MT-CYB, 80% of patients with this mutation showed a poor response to chemotherapy ($p < 0.01$).
- Mutation in MT-ND5 did not have a significant impact on treatment response ($p > 0.05$).

Scientific interpretation:

- These results indicate that mutations in MT-ND1 and MT-CYB may lead to drug resistance in cervical cancer.
- A possible mechanism is that mitochondrial mutations disrupt cellular energy metabolism, making cancer cells more resistant to chemotherapy-induced stress.
- These findings emphasize that analyzing mitochondrial mutations can be effective in selecting targeted therapeutic strategies for patients.

Overall conclusions from chart analysis:

1. MT-ND1 and MT-CYB mutations are associated with a higher risk of cervical cancer.
2. These mutations are significantly correlated with metastasis, making them potential biomarkers for predicting metastasis risk.
3. Patients with these mutations show weaker responses to chemotherapy, indicating their potential role in predicting drug resistance.
4. Mutation in MT-ND5 did not show a significant correlation with any of these factors, suggesting a lesser role in disease progression.

This chart demonstrates that patients with mutations in MT-ND1 and MT-CYB are predominantly in the group that exhibited a poor response to chemotherapy.

Discussion

This study found that mutations in MT-ND1 and MT-CYB are associated with metastasis and chemotherapy resistance in patients with cervical cancer. These findings indicate that genetic alterations in mitochondrial DNA play a crucial role in molecular processes related to cancer progression, particularly in metastasis and resistance to treatment.

Previous studies have shown that mitochondria play multiple roles in cancers, including energy production, apoptosis regulation, and controlling reactive oxygen species (ROS), which can damage cancer cells and increase their metastatic capacity [26-30]. The mitochondrial mutations examined in this study, MT-ND1 and MT-CYB, may actually induce functional changes in mitochondria that enhance cancer cell survival and migration to distant areas of the body.

This study demonstrated a significant association between these mutations and both increased metastasis and chemotherapy resistance in patients with cervical cancer [25,28].

Comparison with similar studies:

- *Scientific Reports* found that mutations in MT-ND1 and MT-CYB in breast cancer were associated with increased metastatic ability and chemotherapy resistance [27]. These results are similar to our findings, where MT-ND1 and MT-CYB mutations were significantly correlated with metastasis and reduced response to chemotherapy in cervical cancer. Zhou., *et al*. concluded that changes in these genes may lead to excessive ROS production, facilitating metastatic processes [27]. The same results were observed in our study, where MT-ND1 and MT-CYB mutations increased ROS levels and facilitated cancer cell migration.
- The other study showed mitochondrial mutations in MT-ND5 and MT-ND1 in lung cancer led to chemotherapy resistance and increased metastasis rates. In this study, MT-ND1 mutations were particularly associated with metabolic alterations and reduced response to chemotherapy drugs. These findings are similar to our study, as we also found that MT-ND1 and MT-CYB mutations were significantly linked to weaker responses to chemotherapy.
- Additionally, *Cancer Research* investigated the role of mitochondria in developing drug resistance in colorectal cancer. They found that mutations in MT-ND1 and MT-CYB altered metabolic signaling pathways, making cancer cells resistant to chemotherapy [12]. These results align with our study, as we also observed that mitochondrial mutations in MT-ND1 and MT-CYB reduced chemotherapy sensitivity in cervical cancer patients.
- Moreover, *Nature Communications* concluded that mitochondrial mutations in different cancers could serve as biomarkers for predicting metastasis and treatment resistance [29]. These findings support our study, highlighting that mitochondrial DNA alterations may serve as predictive biomarkers for disease prognosis and response to therapy.

Differences and new findings

While many similar studies have examined mitochondrial mutations in various cancers [25-30], our study specifically focuses on cervical cancer, a topic with limited research. Our findings are consistent with existing evidence in other cancer types, reinforcing the critical role of mitochondria in treatment resistance. However, our study uniquely highlights that MT-ND1 and MT-CYB mutations play a key role in cervical cancer, whereas MT-ND5 does not show significant involvement.

Conclusion from comparative analysis

Overall, this study and similar research emphasize the importance of mitochondrial mutations in cancer progression and treatment resistance. Mutations in MT-ND1 and MT-CYB are significantly associated with metastasis and reduced chemotherapy response in cervical cancer, suggesting that they could serve as biomarkers for predicting clinical outcomes and guiding personalized treatments. Further research is necessary to develop new therapeutic strategies targeting mitochondrial dysfunction.

Final Conclusion

This study comprehensively examined the role of mitochondrial DNA mutations in MT-ND1, MT-ND5, and MT-CYB in cervical cancer progression, metastasis, and chemotherapy response. Our findings indicate that mutations in MT-ND1 and MT-CYB are strongly associated with increased metastasis and poor chemotherapy response.

Mitochondrial mutations may promote cancer progression by:

- Disrupting the electron transport chain.
- Increasing reactive oxygen species (ROS) production.
- Altering metabolic and signaling pathways.

ROS plays a key role in regulating cell invasion, metastasis, and drug resistance. Among these genes, MT-ND1, a part of Complex I in the electron transport chain, likely contributes to oxidative dysfunction, creating metabolic stress that enhances cancer cell survival and spread. Meanwhile, MT-CYB, a component of Complex III, may affect energy production and antioxidant signaling, reducing the effectiveness of chemotherapy.

Clinical Implications

These results highlight the significance of mitochondrial mutations as prognostic and predictive biomarkers in cervical cancer. Identifying these mutations in early stages can help clinicians determine high-risk patients for metastasis or chemotherapy resistance and adjust treatment strategies accordingly.

Interestingly, MT-ND5 mutations did not show a significant impact on metastasis or treatment response, suggesting a less critical role in cervical cancer progression. Future studies on other mitochondrial mutations may provide further insights into their contributions to the disease.

Therapeutic Implications

This study underscores the necessity of developing targeted therapies based on mitochondrial alterations. Possible approaches include:

1. Drugs regulating ROS production to counteract cancer cell survival advantages.
2. Compounds targeting disrupted mitochondrial electron transport chains to improve chemotherapy efficacy.
3. Precision medicine strategies incorporating mitochondrial biomarkers to personalize treatments.

Future Research Recommendations:

1. Advanced sequencing technologies (e.g. single-cell sequencing) to analyze mitochondrial mutations more precisely.
2. Genetic engineering methods (e.g. CRISPR-Cas9) to study the functional impact of specific mutations.
3. Preclinical trials to evaluate new drugs targeting mitochondrial dysfunction.

Final Thought

This study provides valuable insights into the role of mitochondria in cervical cancer progression and drug resistance. Using MT-ND1 and MT-CYB mutations as biomarkers can enhance disease prediction and optimize personalized treatment strategies, ultimately improving patient outcomes [1-30].

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Volume 14 Issue 3 March 2025