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Review paper

Mitochondrial RNAs in Oncology: Review of Interventions and Innovative Diagnostic Approaches in the Biogenesis of Human Cancers

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Abstract

Background and Aim: Cancer is the greatest public health challenge of the 21st century, with most patients diagnosed at advanced stages. Recent research highlights non-coding nuclear-encoded mitochondrial RNAs (mtRNAs) as potential biomarkers for cancer diagnosis. This study explores the mtRNA family and their diagnostic applications in oncology, including chromatin-associated mitochondrial RNAs (mt-caRNA), long non-coding mitochondrial RNAs (ncmtRNA), mitochondrial messenger RNA (mito-mRNA), mitochondrial transfer RNA (mito-tRNA), mitochondrial microRNAs (mito-miRNA), and circular mitochondrial RNAs (circ-mtRNA).

Methods: A comprehensive search in PubMed and Google Scholar (2022-2024) yielded 21 articles related to "Diagnosis", "Oncology", "Cancer", and "Mitochondrial RNA".

Results: Changes in mtRNA levels impact cancer progression by affecting mitochondrial protein synthesis and apoptosis. mt-caRNAs facilitate mitochondrial-nuclear communication, and ncmtRNAs like ncmtRNA-LDL805 influence mitochondrial bioenergetics in lung diseases. Specific mtRNA changes could be therapeutic targets against metastasis. QUCO-1 binds mtRNA, causing mitochondrial dysfunction, apoptosis, cell cycle arrest, and reduced proliferation in colorectal cancer cells. Reduced circ-mtRNA expression is linked to tumor size and recurrence. Targeting AsncmtRNAs with ASOs suppresses breast cancer cell proliferation and induces apoptosis.

Conclusion: Mitochondrial RNAs (mtRNAs) play a role in cell biogenesis and mitochondrial regulation, potentially providing new diagnostic and predictive cancer methods.

Keywords: *mtRNAs, Oncology, Cancer, Diagnosis*

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Introduction

Cancer is the greatest human public health challenge of the 21st century [1]. Most patients are diagnosed in advanced stages, underscoring the significant importance of diagnostic approaches [2], [3], [4]. Recent research has introduced non-coding nuclear-encoded mitochondrial RNAs (mtRNAs) as potential biomarkers for cancer diagnosis [2], [5]. In this study, we describe the mtRNA family and their diagnostic approaches in oncology, including chromatin-associated mitochondrial RNAs (mt-caRNA) [6], long non-coding mitochondrial RNAs (ncmtRNA) [7], [8], mitochondrial messenger RNA (mito-mRNA) [9], mitochondrial transfer RNA (mito-tRNA) [5], [10], [11], mitochondrial microRNAs (mito-miRNA) [12], and circular mitochondrial RNAs (circ-mtRNA) [11], [13].

1. *Chromatin-Associated Mitochondrial RNAs*

Recent research indicates that these molecules originate from the nuclear genome and bind to it, forming part of the caRNA family [6]. These molecules preferentially attach to promoter regions, and their binding levels change in response to environmental stresses, such as diabetes [6]. Suppressing certain non-coding types of these RNAs in human endothelial cells reduces the expression of RNA molecules that regulate cellular adhesion [6]. Additionally, many mt-caRNAs are translocated to the nucleus under cellular stress and disease conditions, identifying these molecules as messengers responsible for mitochondrial-nuclear communication and linking mitochondrial genome transcription products with nuclear transcription regulation [6].

2. *Long Non-Coding Mitochondrial RNAs*

The levels of mitochondrial non-coding RNAs (ncRNAs) increase in type 2 alveolar epithelial cells of both mice and humans when exposed to cigarette smoke. These molecules potentially play a significant role in mitochondrial biogenesis in human lung cells, possibly linking them to lung diseases [7]. They mediate mitochondrial bioenergetics in type 2 alveolar epithelial cells in response to cigarette smoke exposure; however, this response might diminish in smoking-related abnormalities like chronic obstructive pulmonary disease (COPD) or non-small cell lung cancer (NSCLC) due to their reduction [7]. The mitochondrial long non-coding RNA (lncRNAs) family comprises sense (SncmtRNA) and antisense (ASncmtRNA) members [8]. Suppression of ASncmtRNAs using antisense oligonucleotides (ASOs) halts proliferation and induces apoptosis in tumor cells, but not in normal cells [8]. A 2023 study using RNA sequencing (RNAseq) on MDA-MB-231 breast cancer cells revealed no significant differences in mRNA levels, although proteins responsible for genomic integrity were downregulated in tumor cells and upregulated in normal cells. This inverse effect of ASncmtRNA likely contributes to tumor cell suppression and protection of normal cells [8].

3. *Mitochondrial Messenger RNA*

Given the fundamental relationship between DNA and proteins, with mRNA serving as the primary intermediary, targeting mitochondrial mRNA translation could yield beneficial anti-cancer effects [14]. Aggressive cancers often exhibit increased metabolic flexibility, with this metabolic switch facilitating tumor growth being pharmacologically targetable through inhibition of mitochondrial mRNA translation [14]. These specific mtRNA alterations could serve as therapeutic targets against metastatic cancers [14].

4. *Mitochondrial Transfer RNA*

The human mitochondrion contains 20 amino acids, with 18 having unique tRNA matches, except for tRNALeu and tRNASer, which have two iso receptors [15]. Mutations or disruptions in any tRNA can impair mitochondrial protein translation [15]. Cancer cells primarily rely on oxidative phosphorylation (OXPHOS) for energy, and defective proteins can positively or negatively impact

cancer development [15]. Defective mitochondrial tRNA modifications are closely associated with mitochondrial diseases [15]. Evidence suggests a strong link between mitochondrial tRNA changes and tumor progression [15]. Recent studies show that tRNA methyltransferase 5 (TRMT5) catalyzes the modification of mitochondrial tRNA m1G37, promoting hepatocellular carcinoma (HCC) progression [15]. TRMT5 expression is upregulated in HCC and linked to poor prognosis [15]. Silencing TRMT5 reduces HCC proliferation and metastasis both “in vivo” and “in vitro”, increasing tumor cell sensitivity to chemotherapy, positioning TRMT5 as a potential oncogene and therapeutic target [15]. Additionally, small tRNA-derived RNAs (tsRNAs) play critical roles in tumorigenesis and are stable in circulation, making serum tsRNA signatures potential new biomarkers for HCC [16].

5. *Mitochondrial MicroRNAs*

Mitochondria-associated miRNAs have been identified as potential biomarkers involved in mitochondrial abnormalities [12]. These miRNAs regulate various aspects of mitochondrial homeostasis, including respiratory chain expression and assembly, mitochondrial biogenesis, antioxidant capacity, and apoptosis [12]. miRNAs translocated from the nucleus to mitochondria modulate mitochondrial genome translation [17]. mitomiR-2392, for instance, influences chemoresistance in tongue squamous cell carcinoma (TSCC) cells by reprogramming metabolism, decreasing OXPHOS, and increasing glycolysis [17]. Analyses of TSCC tumors show significant associations between miR-2392, mitochondrial gene expression, chemoresistance, and overall survival [17]. Mito-miRNAs play roles in mitochondrial DNA (mtDNA) transcription, cellular metabolism, and chemoresistance [17].

6. *Mitochondrial Circular RNAs*

Research on circRNAs has largely focused on those encoded by the nuclear genome, with limited information on mitochondria-derived circRNAs [13]. circRNAs show promise as biomarkers for various cancers [11]. The human mitochondrion encodes 13 proteins, 2 rRNAs, and 22 tRNAs [18]. Nuclear genome diversity alone cannot fully explain mitochondrial diseases [18]. Recent evidence suggests circRNAs are found in mitochondria, derived from both mitochondrial and nuclear genomes, and associated with various diseases, especially cancers [18]. These circRNAs play regulatory roles in cellular and molecular physiology and pathology [18]. mito-circRNAs are implicated in regulating mitochondrial-derived ROS production, although their exact functions remain unknown [19]. circPUM1, derived from back-splicing of the nuclear genome's PUM1 mRNA, is translocated to mitochondria and positively correlated with HIF1α accumulation under hypoxic conditions induced by CoCl2 in esophageal squamous cell carcinoma (ESCC) cell lines [20]. Suppression of circPUM1 reduces intracellular oxygen concentration, OXPHOS, mitochondrial membrane potential, increases ROS production, and mitochondrial shrinkage, leading to mitochondrial complex III dysfunction and caspase 3 dissociation [20]. Notably, circPUM1 disruption induces pyroptosis, initiating ESCC cell death [20]. Therefore, circPUM1 is crucial for maintaining mitochondrial complex III stability to enhance OXPHOS for ATP production in ESCC cells [20].

Methods

It was conducted a comprehensive search in PubMed and Google Scholar databases from 2022 to 2024, identified 21 articles relevant to the main topic of this paper. The search terms used included "Diagnosis", "Oncology", "Cancer", and "Mitochondrial RNA".

Results and Discussion

Changes in mtRNA levels are associated with cancer growth and progression [8], [10], [11], [15], [21], [22], [23], playing a significant role in mitochondrial protein synthesis, with their interventions in the mitochondrial outer membrane being an effective pathway for inducing cellular apoptosis [24], [25]. mt-caRNAs are involved in mitochondrial-nuclear communication, linking mitochondrial transcription products with the regulation of nuclear genome transcription [6]. Some ncmtRNAs, such as ncmtRNA-LDL805, mediate mitochondrial bioenergetics in type 2 alveolar epithelial cells of mice and humans exposed to cigarette smoke, potentially associated with lung-related diseases like lung cancer [7]. Recent research also suggests that specific mtRNA alterations could serve as therapeutic targets against metastasis [14]. Given the well-established potential role of mitochondria in oncology [2], [3], the regulation of mito-tRNA function is crucial due to its close association with mitochondrial diseases, particularly in cancer biogenesis [10], [15].

QUCO-1 (a fluorescent quinolinium derivative) illuminates with mtRNA under “In Vitro” conditions, inducing severe mitochondrial dysfunction and inhibition of OXPHOS in colorectal cancer (RKO) cells, leading to apoptosis, G2/M cell cycle arrest, and effective inhibition of cell proliferation upon QUCO-1 treatment [26]. Additionally, mito-miRNAs and circ-mtRNAs playing a significant role in oncology [11], [12]. For instance, reduced expression of circ-mtRNAs correlates significantly with tumor size and predicts cancer recurrence, while optimizing their translation may prevent gastric cancer progression by regulating cell proliferation, apoptosis, and tumor invasion [27]. Furthermore, it has been demonstrated that suppression of AsncmtRNAs using antisense oligonucleotides (ASOs) leads to the inhibition of proliferation and apoptosis in breast cancer tumor cells [8].

Conclusion

We have identified mtRNAs as molecules involved in the biogenesis of both normal and cancer human cells, particularly in regulating mitochondrial function, offering promising prospects for new cancer diagnostic and predictive approaches.

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Conflict of Interests

The authors declare that there are no competing interests.

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