REVIEWS

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Mitochondria and Cancer

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Abstract

Mitochondria generate energy through cellular respiration and regulate various cellular processes such as heat production, generation and detoxification of reactive oxygen species, metabolism, apoptosis, and calcium homeostasis. In human cells, large numbers of mitochondria are present, each containing multiple copies of mitochondrial DNA. Variations in mitochondrial DNA have been associated with the onset and progression of various diseases, including neurological, cardiovascular, and metabolic disorders and also several cancers. These variants can be important drivers of cancer and may play a crucial role in tumor development. Additionally, mitochondrial copy number changes and structural variations, such as deletions can be associated with different types of cancer. Therefore, understanding the fundamental mechanisms is highly crucial. The molecular genetic correlations of mitochondrial DNA alterations and cancer, emphasize the importance of mitochondrial integrity in maintaining cellular homeostasis. Gaining knowledge of these associations can help us comprehend cancer processes as well as potential routes for targeted treatments and prevention, while further investigation is still required.

Keywords: Mitochondria, cancer, mitochondrial genome, mitochondrial DNA variations

Structure and Function of Mitochondria

Mitochondria are organelles found in eukaryotic cells, which are responsible for generating energy in the form of adenosine triphosphate (ATP) through a process called cellular respiration (1). They are commonly referred to as the "powerhouses" of the cell because of their role in producing ATP, which is essential for a wide range of cellular functions, including metabolism, growth, and movement (2).

Organization of mitochondria is in the form of four morphologically and functionally distinct parts: (i) the outer membrane, permeable to ions and small molecules, whose traffic is mediated by specific

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transporters and channels; (ii) the intermembrane space, the region between the matrix and the cytosol, where important processes such as the exchange of proteins, lipids, metal ions and initiation of the apoptotic pathway occur; (iii) the inner membrane, comprised of respiratory complexes in its inward folds (cristae), which surrounds the matrix and enables the transport of ions, metabolites, proteins through specialized transporters; (iv) the matrix, containing mitochondrial DNA (mtDNA) and proteins, which are associated with important biochemical pathways such as the citric acid cycle and beta-oxidation of fatty acids (3-6). The process of cellular respiration involves a series of chemical reactions that take place within these compartments, which ultimately result in the production of ATP (7).

The oxidative phosphorylation system includes five protein complexes and two electron carriers embedded in the inner mitochondrial membrane (5). During respiration, electrons from nicotinamide adenine dinucleotide + hydrogen (NADH) and succinate are transferred to ubiquinone via complexes I and II, then pass through complex III, cytochrome c, and end at complex IV. The energy from electron transfer through complexes I, III, and IV pumps protons from the mitochondrial matrix to the intermembrane space which in turn activates ATP synthesis in complex V (7-11). The structure of mitochondria and energy metabolism is summarized in Figures 1a and 1b, respectively.

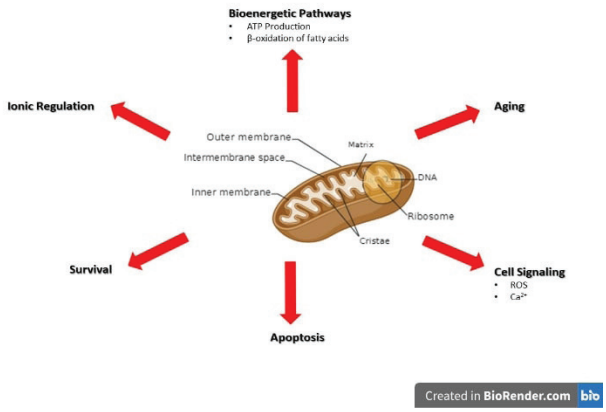

Figure 1A
Represents morphological and functional organization of mitochondria.

In addition to producing ATP, mitochondria are also involved in several other important cellular processes such as heat production, generation and detoxification of reactive oxygen species (ROS), regulation of

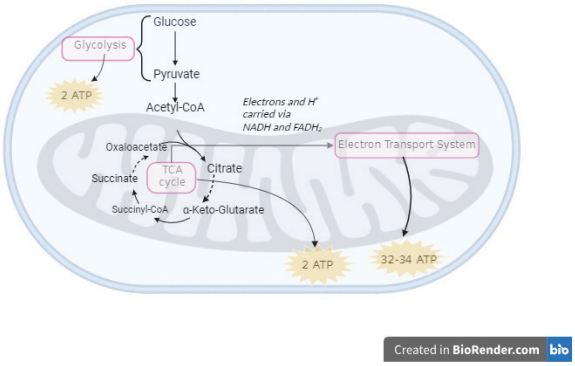

Figure 1B
Illustrates and summarizes the energy metabolism pathways (Glycolysis, Tricarboxylic acid (TCA) cycle and Electron transport system (ETS), FADH2: Flavin adenine dinucleotide) Adapted from: Libretext 2020 120 & Koklesova 2022 121 (Created in Biorender.com)

intracellular calcium (important for muscle contraction and other cellular processes), lipid metabolism, synthesis of steroid hormone, certain amino acids and heme (9). Mitochondria also play a role in apoptosis (programmed cell death), which is an important process for removing damaged or unwanted cells from the body. Mitochondria release certain proteins that trigger the apoptotic pathway when a cell is damaged or no longer needed in mammalian cells (12).

Mitochondria have their DNA, known as the mitochondrial genome or mtDNA, which is separate from the cell's nuclear DNA (nDNA), and are believed to have originated from free-living bacteria that were engulfed by ancestral eukaryotic cells in a process called endosymbiosis (13). This is supported by the fact that mitochondria have their ribosomes, and the structure of their DNA is similar to that of bacteria (14).

Mitochondrial Genome

Margit Nass and Sylvan Nass first described and isolated mitochondrial DNA in 1963 (15). However, the first complete mtDNA sequence was published 18 years later in 1981 as the mtDNA Cambridge reference sequence (CRS) (16, 17). Currently, the revised CRS (rCRS—revised Cambridge Reference Sequence), a modified version of the sequence presented by Anderson et al., is used for nucleotide numbering of the mitochondrial genome (16-19).

The mtDNA is a circular double-stranded DNA molecule that is typically between 16,000 and 20,000

base pairs long, depending on the organism (20, 21). In humans, the mitochondrial genome contains no histones and is only 16,569 base pairs long (2, 7). There are no introns in the mitochondrial genome and all genes are adjacent to each other with few exceptions. It consists of a total of 37 genes, including 13 polypeptides encoding four of the five complexes (complexes I, III, IV, and V) that make up the oxidative phosphorylation system discussed previously, as well as 22 transfer RNAs (tRNA) and 12S and 16S ribosomal RNAs (rRNA) required for mitochondrial protein synthesis. Along with mitochondrial genes, nuclear genes also play a role in the assembly mechanism of oxidative phosphorylation complexes (5, 7, 11, 22).

The two mtDNA chains, named light (L) and heavy (H), are quite different in their base composition. The heavy chain is rich in purines and the light chain is rich in pyrimidines. The distribution of genes in the two chains is asymmetrical. The L-chain contains only the ND6 gene and some t-RNA-encoding genes, while the 12S and 16S ribosomal RNAs and tRNAs and most of the genes encoding proteins are located on the H-chain (13, 23, 24). The approximately 1 kb long non-coding region (Displacement loop, D-loop) contains the H-chain replication origin and promoters required for the transcription of both chains. The mitochondrial DNA is illustrated in Figure 2.

The genetic code of mitochondrial DNA shows some differences compared to the universal genetic code. The “UGA” stop codon in the human nuclear code encodes tryptophan, and the “AUA” (isoleucine) is encoded as methionine in the mitochondrial genome. “AGA” and “AGG”, which encode arginine, are arguably known as non-standard stop codons in mitochondria (19).

Mitochondrial DNA has a 10-20 times faster evolution rate than the nDNA and is therefore, more susceptible to mutations (25). Lack of protective histones, lack of intronic regions, ineffective repair mechanisms, high replication speed in mtDNA, and low fidelity of mtDNA polymerase are the reasons for the higher incidence of mtDNA mutations (25-27).

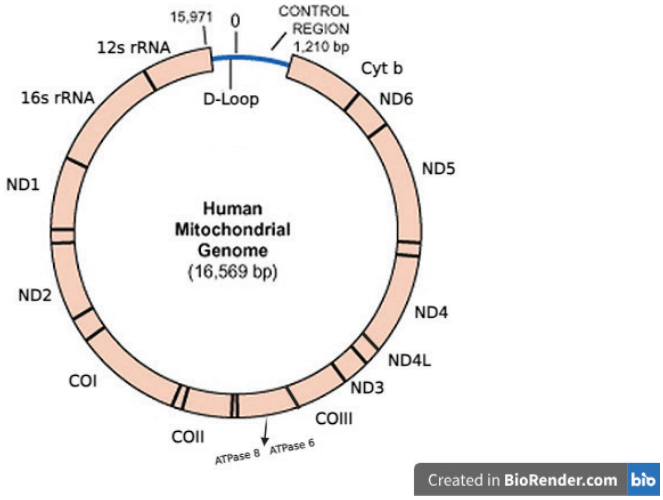

Figure 2
Mitochondrial DNA
The mitochondrial genome is represented in the figure. Cyt b: Cytochrome B; ND6: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 6; ND5: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 5; ND4: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 4; ND4L: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 4L; ND3: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 3; COIII (or MTCO3): Mitochondrially Encoded Cytochrome C Oxidase III; ATPase 6 (or MT-ATP6): Mitochondrially Encoded ATP Synthase Membrane Subunit 6; ATPase 8 (or MT-ATP8): Mitochondrially Encoded ATP Synthase Membrane Subunit 8; COII (or MTCO2): Mitochondrially Encoded Cytochrome C Oxidase II; COI: or MTCO1): Mitochondrially Encoded Cytochrome C Oxidase I; ND2: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 2; ND1: Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 1; 16s rRNA: 16S ribosomal RNA; 12s rRNA: 12S ribosomal RNA. Adapted from: Cold Spring Harbor Laboratory's DNA Learning Center 2024 122 (Created in Biorender.com)

Unlike the nuclear genome, which is inherited according to Mendelian inheritance laws, the mitochondrial genome shows matrilineal inheritance (28). This is because the developing embryo receives the majority of its cytoplasm and organelles, including its mitochondria, from the egg cell (29).

Heteroplasmy and Threshold Effect

There are hundreds to several thousand mitochondria in every human cell. Each mitochondrion contains up to ten copies of mtDNA packaged in nucleoprotein structures called nucleoids (30). Cells and tissues that need more energy usually have more mtDNA. Mostly, all mtDNA copies are identical and this is called homoplasmy (31, 32). However, errors that occur during mtDNA replication or repair can result in the formation of a mutant mtDNA molecule, and these can proliferate clonally by unknown mechanisms, eventually resulting in a metastable state called heteroplasmy (33, 34). In heteroplasmy, mutant and wild-type genomes coexist at different rates in the same organelle/cell/tissue (35). It has been shown that a low level of heteroplasmy can also occur in normal cells, and therefore the mutation load of mtDNA must exceed the minimum critical biochemical threshold (usually 70-90%) for mitochondrial dysfunction to occur in a tissue (31, 32). Since the energy requirements of tissues and organs are different from each other, the symptomatic effect of mutant mtDNA ratio differs according to organs (33).

In some cases, heteroplasmy can be benign and have no noticeable effect on the organism. In other cases, it can lead to mitochondrial diseases or disorders, which can affect a wide range of functions in the body that rely on energy production (36). As a result, mutations in the mitochondrial genome have been implicated in a variety of diseases, including neurodegenerative disorders, metabolic disorders, and aging. Additionally, mitochondrial haplotypes refer to a set of genetic variations or polymorphisms that are inherited together on the mtDNA from a single parent or ancestor and are used to trace maternal lineages and evolutionary population history (37-40). The analysis of mitochondrial haplogroups has been used to investigate a range of topics, including human migration patterns, genetic diversity within populations, and the association between specific haplogroups and disease susceptibility, including cancer (41-43).

Mitochondrial Variants and Cancer Relationship

In literature, mitochondrial mutations have been associated with different mitochondrial diseases that mostly affect the nervous system and muscle tissues (44, 45). Primary mtDNA diseases are mostly due to maternally inherited point mutations and large deletions that usually occur de novo during embryonic development (46-55). Recently, it was shown that mitochondrial dysfunction plays a key role in diseases such as Alzheimer's, major depressive disorder, and coronary artery disease (56-61). However, precise mechanisms of pathogenesis are still unknown.

Contrary to conventional wisdom, functional mitochondria are essential for the cancer cell. Although mutations in mitochondrial genes are common in cancer cells, they do not generally inactivate mitochondrial energy metabolism but rather alter the mitochondrial bioenergetic and biosynthetic state (62). It has been reported that the rate of individuals with somatic mutations in the nuclear and/or mitochondrial genome may differ between 13% and 63% depending on the type of cancer (63, 64). Additionally, it is possible to identify mtDNA variations in a single tumor type or different cancer types (65).

Somatic mutations that may be associated with tumorigenesis have been reported in many mitochondrial genes, particularly those encoding the mitochondrial respiratory chain proteins (64, 66, 67). These mutations include both synonymous and non-synonymous somatic mtDNA alterations (63, 68). In general, the most common variations associated with carcinogenesis are in complex I genes (69). In contrast, the number of somatic variations reported for complex III (cytochrome b, mt-CYB gene), which is solely encoded by mtDNA, is scarce, except for bladder cancer (70). Among the protein-coding genes, complex I and IV mutations are thought to be more potent in inducing carcinogenesis (67, 71).

Both the coding and non-coding sections of the mtDNA have been found to include mutations in all forms of cancers including glioblastoma (72, 73). Strong selection is applied to tumor cells as a result of metabolic dysregulation and its aftereffects. Therefore, it appears that obtaining somatic mtDNA mutations that affect oxidative phosphorylation is another way to promote tumor growth (63).

Various cancers have been associated with mtDNA mutations in D-loop and other mitochondrial genes. Particularly those in the genes ND4 and ND5 that encode the subunits of Complex I of the respiratory chain, have been linked to several malignancies, including those of the liver and kidney (76). These alterations frequently increase cellular proliferation and apoptosis resistance, advancing cancer. Moreover, conflicting data links the ND3 G10398A

mutation to an increased risk of cancer, particularly breast cancer (77, 78) and the T16519C mtDNA control region variant is associated with endometrial cancer (79). Also, mutations in ND5, ATP6, and ATP8 are frequently observed in breast cancer (66). Additionally, a synonymous T6777C SNP in cytochrome c oxidase subunit 1 (CO1), seems to lower the incidence of ovarian cancer along with variants in several nDNA mitochondrial genes (80, 81). In colorectal cancers, rRNA point mutations are more common than tRNA and both non-synonymous and synonymous mutations can be observed in all mitochondrial genes; controversially, in stomach and lung cancers, point and indel mutations are detected in tRNA (82, 83). Furthermore, D310 instability is also commonly detected, especially in bladder, breast, colorectal, head and neck, and lung cancers (66). Finally, the mtDNA control region variant C150 has been associated with an increased risk of human papillomavirus (HPV) infection and cervical cancer (64, 84).

The polymorphic D-Loop region is thought to be critical for modulating mtDNA transcription and replication. D-loop polymorphisms have been linked to an increased risk of numerous cancers, including breast, cervical, skin, liver, stomach, and colon (85). In addition, our study suggested that some unique mitochondrial variations may be evaluated as prospective cancer biomarkers for the risk and progression of brain tumors and that the D-loop individual variations in mtDNA may play a crucial role in glioma biology (86). Therefore, in cancer research, the analysis of the non-coding D-loop control region as well as the coding regions of the mitochondrial genome is also important (87, 88). Somatic mutations of the D-loop region are detected more frequently in advanced cancers (89). In several tumors, increased mutation numbers have been associated with poor prognosis (90).

Although mutations in tRNAs encoded by mitochondria have been reported frequently in other respiratory chain diseases, the number of variations associated with cancer is quite low (22). This is because tRNA mutations affect secondary structures and alter mitochondrial function by causing instability in the stem and loop regions (68, 91). Similarly, the impacts of rRNA mutations are substantially more severe than alterations in protein-coding genes, making rRNA modifications uncommon (22).

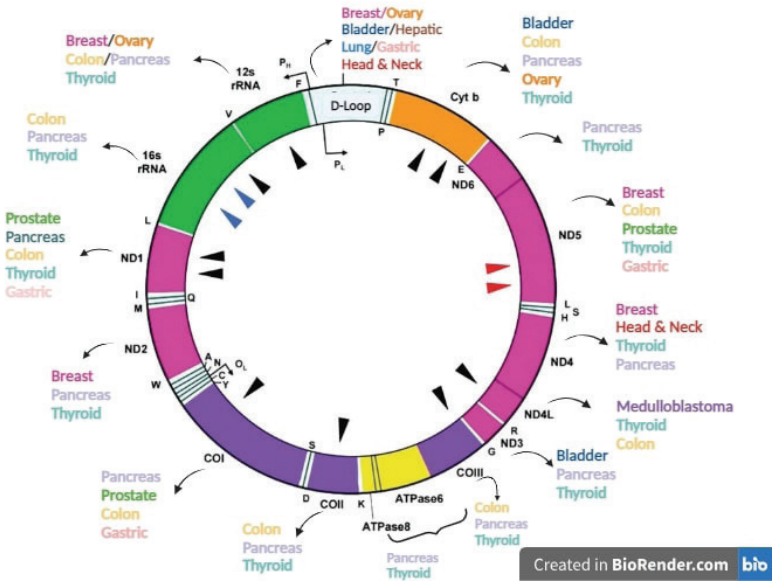

Figure 3

Mitochondrial DNA and related cancers

Human mitochondrial DNA is a ~16 kbp circular, double-stranded DNA containing 37 genes, encoding 13 electron transfer complex (ETC) component proteins, 2 ribosomal RNAs, and 22 transfer RNAs. The mutations of ETC coding regions, D-loop and rRNA genes in mtDNA were commonly found in various cancers. mtDNA mutations in each region and related cancers are illustrated. Black arrowheads represent the mtDNA somatic mutations by homoplasmic alterations; blue arrowheads are rarer heteroplasmic substitutions and red arrowheads are mixed homoplasmic/heteroplasmic variants. Adapted from: Errichiello et.al 2018 123 (Created in Biorender.com)

Furthermore, deletions detected in mtDNA have also been associated with different cancers. A 21 bp deletion causing increased cell growth due to overexpression of the mt-CYB gene has been found in bladder cancer (92, 93). The other most frequently detected structural variation is a 4977 bp deletion that has been found in different cancer types such as breast, colorectal, stomach and head & neck, comprising five tRNA genes and seven protein-coding genes (34, 66, 94). Figure 3 summarizes the mtDNA variations related to several cancers.

Mitochondrial copy number may also vary in several cancers. It has been shown that the mtDNA copy number is increased in some cancers (such as thyroid, pancreas and prostate) and decreased in others (for instance bladder, breast, colorectal and stomach), but the findings of several investigations contradict one another (64, 95). The exact mechanism of copy number variations (CNV) is still unknown. However, it is considered that the increase may be due to compensation for impaired oxidative phosphorylation, while the decrease in CNV might be caused by mutations in the D-loop region, which plays a role in replication (64, 88, 89).

Apart from mutations, structural variations and copy number changes in mitochondria, mutations in nuclear genes that are part of the mitochondrial proteome can also cause copy number and stability changes in mtDNA and thus play a role in the formation and development of cancer (96-98).

Overall, while more research is needed to understand the relationship between mtDNA mutations and cancer fully, there is growing evidence that these mutations may be important drivers of tumorigenesis and could serve as potential targets for cancer prevention and treatment.

Mitochondrial Bioenergetics and Cancer Relationship

Common disorders caused by defects in mitochondrial function are known to influence energy production in cells and can produce a wide range of symptoms across different organs. (99). Moreover, using Genome-Wide Association Studies (GWAS), mitochondrial variations were investigated to identify their possible contribution to cancer risk (100). To determine the causal link between mitochondrial-related genetic variations and various cancer types, Mendelian Randomization (MR) methodology was applied to the variants, which helps in overcoming reverse causality and confounding variables that frequently restrict observational studies. As a result, strong evidence has been discovered correlating a fundamental enzyme for the production of isoprenoid, Farnesyl Diphosphate Synthase (FDPS) expression level with the risk of breast cancer (101, 102). On the other hand, the NOP2/Sun RNA Methyltransferase 4 (NSUN4) (takes part in the assembly of the mitochondrial ribosome) expression level is associated with prostate and breast cancers (100).

Cancer cells use glycolysis and the mitochondrial oxidative phosphorylation system (OXPHOS) as their principal energy sources. There is often a shift in energy metabolism from oxidative phosphorylation to glycolysis, a process known as the Warburg effect (103). This change enables cancer cells to survive and proliferate even in the absence of oxygen, a condition known as hypoxia. The specific mechanisms underlying this shift are not fully understood, however, it is thought to be linked to mutations in genes involved in mitochondrial metabolism and changes in signaling pathways (104).

There may be two classes of mutations in cancer cell mtDNA: mutations that impair OXPHOS and serve to stimulate neoplastic transformation, and those that facilitate cancer cell adaption to changing bioenergetic environments (62). Thus, tumor growth can be inhibited by modifying the production of metabolites in mitochondria or the OXPHOS genes (105). Instead of using glycolysis, a wide variety of cancer cell types rely on OXPHOS to increase their potential for tumorigenicity (106). Cancer cells upregulate the OXPHOS and TCA cycles to produce more ATP than the surrounding normal cells and develop resistance to chemotherapy (105, 107). OXPHOS allows mitochondria to produce ATP primarily by using pyruvate produced during glycolysis. Thus, mitochondrial malfunction in cancer cells can cause an increase in ROS production, contributing to genomic instability and cancer progression.

The absence of histones, inefficient DNA repair mechanisms, and proximity to ROS generated by the OXPHOS system all contribute to the high mutation rate observed in mtDNA, which is approximately 10–17 times higher than that of the nuclear genome (35). Furthermore, altered mitochondrial function can affect the expression of genes implicated in apoptosis, conferring resistance to chemotherapy and radiation therapy (108).

In summary, mitochondrial bioenergetics plays a critical role in cancer development and progression. Understanding the mechanisms underlying mitochondrial dysfunction in cancer cells and developing

strategies to target these pathways could lead to new and effective cancer treatments.

Future Aspect: Mitochondria-targeted Approaches in Cancer

Targeting mitochondrial bioenergetics has emerged as a potential therapeutic strategy for cancer treatment. For instance, extracellular citrate is imported by cancer cells to stimulate their proliferation, and it is oxidized in the mitochondrial TCA cycle to make ATP. Similar to citrate, isocitrate is an intermediate metabolite in the citric acid cycle that is present in both the cytosolic component and the mitochondria (105). On the other hand, for the past 100 years, metformin has been used to treat diabetes. Clinical investigations conducted in the past few years have demonstrated its efficacy against cancer (109). Because insulin stimulates the growth of breast cancer cells, metformin lowers insulin levels in breast cancer patients to diminish tumor cell proliferation. At the same time, it suppresses tumor progression by blocking complex I and PI3K pathway (105). On the other hand; in the form of ammonium cations, rhodamine can selectively target mitochondria because of the inner mitochondrial membrane's (IMM) negative potential, shown in MCF-7 cells- which is a widely used human breast cancer cell line (110).

Furthermore, Atovaquone is an approved antimicrobial medication that has lately shown anti-cancer activity and potential in clinical trials treating ovarian cancer (108). It reduces ATP synthesis by blocking mitochondrial complex III and increasing ROS levels, which in turn limits tumor cell proliferation (103).

Dichloroacetic acid is a novel anti-cancer drug that inhibits the TCA cycle and has been demonstrated in clinical trials to have both synergistic and inhibitory effects on liver cancer cells (109). Additionally, IACS-010759 is a small molecule of therapeutic grade that inhibits complex I of the mitochondrial electron transport chain, which is effective in treating acute myeloid leukemia (AML) and brain malignancies (103). Nevirolol is a third-generation beta-1 adrenoceptor inhibitor. Not only was it initially used to treat heart failure and hypertension, but it can also be used as a novel anti-cancer drug to treat cancer patients (111).

A recent technique known as " RNA polymerase mitochondria (POLRMT) targeting" suppresses mitochondrial transcription, depriving tumor cells of an energy source (112). Small compounds that are lipophilic and positively charged, peptide carriers, or metal complexes like ruthenium or iridium can all be used as mitochondrial targeting agents (111).

At present, methods for delivering medications that target mitochondria include surface modification of nanocarriers or chemical ligation of active pharmaceuticals by pro-mitochondrial agents (111). In contrast to traditional methods of delivering drugs to the mitochondria, mitochondria-targeted nanosystems provide the following advantages: delivering conventional medications via nanomaterials can improve drug solubility, extend drug half-life in vivo and enhance bioavailability, reduce side effects, and increase drug concentration and therapeutic index at the tumor site.

The primary method of delivering anti-cancer medications or nanoparticles to mitochondria is destroying mitochondria using mitochondria-cytotoxic peptides or peptide assemblies and combining them with chemotherapy or photothermal-promoted morphology transformation (PMT) (113). Furthermore, using nanoscale tubes, researchers proved that cancer cells can take over the mitochondria of immune cells. This discovery demonstrates how cancer cells rely on healthy cells for survival and proliferation (35).

Moreover, triphenylphosphonium (TPP) can preferentially target mammalian cells' mitochondria (111, 114). TPP-based anti-cancer drugs primarily target cancers with high membrane potential and deliver the medication to the tumor cell mitochondria for treatment. TPP's lipid solubility allows it to cross biological membranes easily. Currently, TPP is used in two ways: directly coupled with pharmaceutical compounds or modified to target mitochondrial nanosystems (111). Other TPP derivatives, alone or in combination with other therapeutic compounds, have shown promising anti-cancer properties. For example, dodecyl TPP inhibited the proliferation of suspended breast cancer stem cells in a dose-dependent manner (111, 115). However, difficulties can arise since TPP does not target all tumor cells due to its limited applicability as a mitochondrial targeting agent for tumor cells.

Furthermore, drug combinations incorporating functional peptides that target the mitochondria can increase tumor cell targeting, but they do not completely protect normal cells. Peptide-drug conjugates (PDCs) appear to respond mostly to single-factor stimuli (113). Although some studies have shown that functional peptides are biocompatible, there is still dispute about their tumor degradation rate and long-term safety. The U.S. Food and Drug Administration (FDA) has approved two PDCs for use in clinical trials: LUTATHERA (Novartis Pharmaceuticals Corporation; Basel, Switzerland)

which treats somatostatin receptor-positive pancreatic and gastrointestinal neurosecretory cancers, and PEPAXTO (Oncopeptides AB; Stockholm, Sweden) which treats recurrent bone marrow cancer (115, 117, 121).

Finally, Photodynamic therapy (PDT), photothermal therapy (PTT), chemodynamic therapy (CDT) and sonodynamic therapy (SDT) have been highly discussed in recent years (118, 119). PDT and PTT are non-invasive, easy to control, and possess low side effects but face problems of reduced depth of penetration and toxicity. On the other hand, CDT employs endogenous hydrogen peroxide but is interfered with by glutathione in tumor cells. In addition, SDT utilizes ultrasound for deeper penetration, however, the process is ineffective in hypoxic conditions. The combination of all these treatment modalities increases the overall efficacy and decreases the risk of tumor recurrence (118, 119). In summary, various mitochondria-targeted cancer therapies have been explored, each with its own benefits and limitations.

Conclusion

Mutations and alterations in mtDNA have been linked to various forms of cancer, as these genetic changes can disrupt normal mitochondrial function, leading to increased oxidative stress and impaired cellular energy metabolism. The molecular genetic associations between mtDNA mutations and cancer highlight the importance of mitochondrial integrity in maintaining cellular homeostasis. Understanding these connections provides valuable insights into the mechanisms of tumorigenesis and opens potential avenues for targeted therapies and diagnostic tools in oncology. Overall, while more research is needed to fully understand the relationship between mtDNA mutations and cancer, there is growing evidence that these mutations may be important drivers of tumorigenesis and could serve as potential targets for cancer prevention and treatment.

Conflict of Interest Statement
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Authors Contributions
GG: Conceptualization; Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing (crticial review)

ŞKY: Conceptualization; Data curation; Formal analysis; Investigation; Validation; Visualization; Writing – original draft; Writing – review & editing (crticial review)

CBA: Conceptualization; Data curation; Investigation; Project administration; Validation Supervision; Writing – original draft; Writing – review & editing (crticial review)

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