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Review

Mitochondrial DNA-targeted therapy: A novel approach to combat cancer

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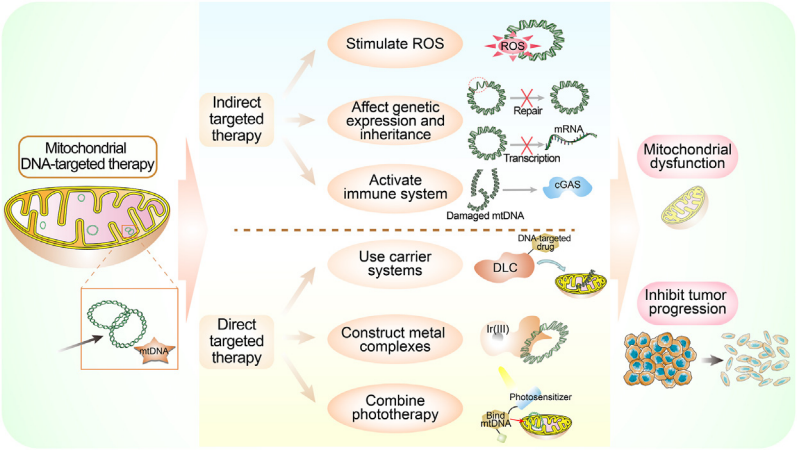
GRAPHICAL ABSTRACT



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ABSTRACT

Mitochondrial DNA (mtDNA) encodes proteins and RNAs that are essential for mitochondrial function and cellular homeostasis, and participates in important processes of cellular bioenergetics and metabolism. Alterations in mtDNA are associated with various diseases, especially cancers, and are considered as biomarkers for some types of tumors. Moreover, mtDNA alterations have been found to affect the proliferation, progression and metastasis of cancer cells, as well as their interactions with the immune system and the tumor microenvironment (TME). The important role of mtDNA in cancer development makes it a significant target for cancer treatment. In recent years, many novel therapeutic methods targeting mtDNA have emerged. In this study, we first discussed how cancerogenesis is triggered by mtDNA mutations, including alterations in gene copy number, aberrant gene expression and epigenetic modifications. Then, we described in detail the mechanisms underlying the interactions between mtDNA and the extramitochondrial environment, which are crucial for understanding the efficacy and safety of mtDNA-targeted therapy. Next, we provided a comprehensive overview of the recent progress in cancer therapy strategies that target mtDNA. We classified them into two categories based on their mechanisms of action: indirect and direct targeting strategies. Indirect targeting strategies aimed to induce mtDNA damage and dysfunction by modulating pathways that are involved in mtDNA stability and integrity, while direct targeting

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strategies utilized molecules that can selectively bind to or cleave mtDNA to achieve the therapeutic efficacy. This study highlights the importance of mtDNA-targeted therapy in cancer treatment, and will provide insights for future research and development of targeted drugs and therapeutic strategies.

1. Introduction

Mitochondria play critical organelles roles in various aspects of biological processes such as energy generation, immune responses, programmed cell death and metabolism of various bioactive molecules including calcium, iron-sulfur cluster, one-carbon units, nucleotide, amino acid and lipid metabolism (Huertas et al., 2017; Li et al., 2018; Lu et al., 2018; Spinelli & Haigis, 2018; Zhang et al., 2020). Various factors such as free radical production, mtDNA mutation, etc., can cause mitochondrial dysfunction. Mitochondria with abnormal function has also been implicated in the development of various diseases, and have long been proposed as driving forces for malignant transformation (Bennett et al., 2022; Iske et al., 2020; Kim et al., 2017; Ma et al., 2018). Recent research highlighted that mitochondria can be regard as an important target for cancer therapy.

Mitochondrial DNA is a fundamental indicator of mitochondrial function. It encodes 37 coding genes, including 13 essential subunits of oxidative phosphorylation (OXPHOS) complex proteins and RNAs (22 tRNAs and 2 rRNAs) required for protein synthesis (Fig. 1). (Guerra et al., 2017) Mitochondrial DNA plays an irreplaceable role in the maintenance of metabolic activity and cellular function. Mitochondrial DNA mutations and copy number alterations have been found to be closely related to the acceleration of tumor development (Hu et al., 2016; Smith et al., 2022b). For example, Tid1 knockdown in gastric cancer cells leads to a decrease in mtDNA copy number, which regulates cell migration and invasion (Wang et al., 2020). Reduced mtDNA content has been found to be associated with the induction of a progressive phenotype of breast cancer and the promotion of tumor formation (Aminuddin et al., 2020; Singh et al., 2009). In addition, a 4977-bp deletion from 8470 to 13,459 bp in mtDNA has been proved as a major inducement in the carcinogenesis of hepatocellular carcinoma and colorectal cancer (Aminuddin et al., 2020). Mutation and microsatellite instability in the non-coding D-loop region of mtDNA would contribute to laryngeal cancer (Wang et al., 2021). These observations highlight the significant association between mtDNA and cancer progression.

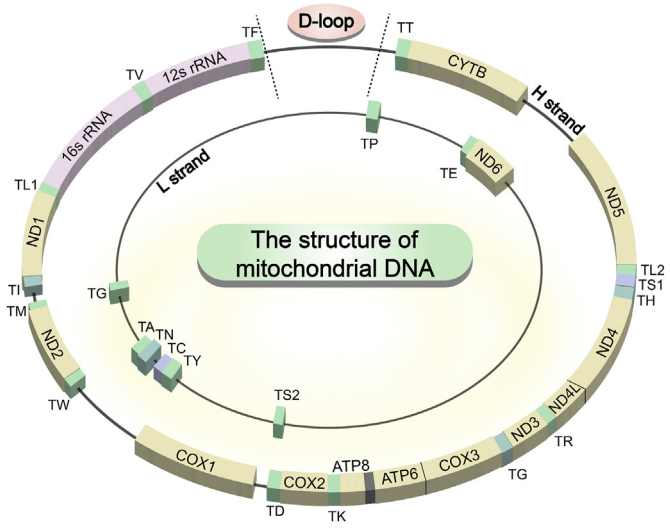

Fig. 1. The detailed structure of mtDNA. The whole mtDNA sequence included a total of 37 coding genes and a D-loop region. And the coding genes including 13 essential proteins (ND1, ND2, ND3, ND4, ND4L, ND5, ND6, CYTB, COX1, COX2, COX3, ATP6 and ATP8), 22 tRNAs (TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL1, TL2, TK, TM, TF, TP, TS1, TS2, TT, TW, TY and TV) and 2 rRNAs (12s rRNA and 16s rRNA).

Compared to the nuclear genome (nDNA), the lack of histone protection, the void of introns and a weak DNA repair ability, together makes mtDNA more vulnerable to damages, thereby leading to single-strand breaks, abasic sites, oxidative base damage and DNA crosslinking (Hou et al., 2018; Pustylnikov et al., 2018). Several endogenous factors such as oxidative stress (Nadalutti et al., 2022), enzyme-induced damage (Geden et al., 2021), and the absence of repair mechanisms (Boguszewska et al., 2020), as well as some exogenous factors such as industrial byproducts including alkylating agents, aldehydes and polycyclic aromatic hydrocarbons, therapeutic drugs including nucleoside analogues, and radiation (Cline, 2012), may introduce mutations in mtDNA. On the other hand, changes in key genes that are associated with the stability of the mtDNA genome are the main endogenous factors that cause mtDNA mutation. It has been demonstrated that numerous genes participate in the generation of mtDNA mutations, such as SLC25A4 (Finsterer & Zarrouk-Mahjoub, 2018), FBXL4 (Alsina et al., 2020), thymidine kinase 2 (Laine--Menéndez et al., 2021) and so on. P53 is an important regulator of normal mitochondrial and cellular physiology, and its aberrant expression affects mitochondrial function, mitochondrial biogenesis, mtDNA abundance and tumor suppressor activity (Bergeaud et al., 2013; Koczor et al., 2012; Yadav et al., 2015). It has been reported that P53 could bind to glycogen synthase kinase 3β, mitochondrial transcription factor A (TFAM) and mtDNA regulatory D-loop region and participate in stimulating mtDNA repair to maintain mtDNA content in HepG2 cells (Vadrot et al., 2012). Loss of P53 can lead to increased susceptibility of mtDNA to mutations (Wu et al., 2018). Furthermore, ANKLE1 is an endonuclease involved in response to DNA damage stimulus, and its ectopic expression could cause mtDNA instability and cleavage in breast epithelial-derived cells (Przanowski et al., 2023). These risk factors may result in the accumulation of mtDNA mutations and significantly increase the likelihood of tumor progression.

Considering its important role in cancer development, mtDNA-targeted therapies have emerged as promising strategies in cancer treatment recently. The application of immunotherapy by inducing mtDNA release, targeted therapy by constructing mitochondria-targeted complexes and combination of chemotherapy and photodynamic therapy (PDT) have greatly promoted the progress of anticancer targeting mtDNA. Here, we reviewed the mtDNA-targeted cancer treatment strategies and summarized the significant progress. Initially, we provided an overview of the association between mtDNA mutations and tumorigenesis. Then we elucidated the vital messenger role of mtDNA in biological processes, which is conducive to a deeper understanding of the mechanisms, efficacy, physiological response and prognosis of targeted therapeutic strategies. Finally, we screened relevant studies in recent years based on the criterion of causing mtDNA damage and leading to cancer cell death. Based on the pathways of mtDNA damage caused by the therapeutic strategies mentioned, we classified the included studies into two categories, namely the indirect targeted therapy and direct targeted therapy. Meanwhile, we summarized the main success of these studies in two tables (Tables 1 and 2). We hope this study will provide useful insights for researchers interested in mtDNA-targeted treatment.

2. mtDNA mutations: a trigger for cancerogenesis

Mutations in the mitochondrial genome constitute a significant component of the cancer mutant genome (Ju et al., 2014). mtDNA dysfunction and gene mutations are closely related to tumorigenesis and can confer different degrees of advantages to cancer cells depending on

Table 1
Summary of indirect targeting therapies in recent years.

	Strategies for targeted therapy	Drugs, compounds or key genes used	The core of therapeutic strategy (Characteristics of mtDNA targeting)	Cancer	year
Wang et al. (Wang et al., 2023)	Influence genetic functions of mtDNA, increasing ROS	TFAM and gemcitabine	Inhibition of TFAM results in mitochondrial dysfunction, amplifies gemcitabin-induced oxidative stress, and augments cytotoxicity.	Pancreatic cancer	2023
Yin et al. (Yin et al., 2023)	Activate immunity	Raddeanin A	It could bind to TDP-43, induce mtDNA leakage, and ultimately enhance DC-mediated antigen cross-presentation and T cell activation.	Melanoma and colon cancer	2023
Xiao et al. (Xiao et al., 2022)	Activate immunity	PLGA@Icaritin NPs	Resulted in overproduction of oxidative-mitochondrial DNA, which activates the release of DAMPs	Gastric cancer	2022
Li et al. (Li et al., 2022)	Activate immunity	(BPA + CPI)@PLGA NPs	The release of mtDNA caused by mitochondrial metabolism disorder further activated the cGAS/STING signal pathway	Liver cancer	2022
Witkowska et al. (Witkowska et al., 2022)	Activate immunity	Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-9H-carbazole-1-carboxylate; 3-((*tert*-butoxycarbonyl) amino)-2-hydroxy-9H-carbazole-1-carboxylic acid	It induced the release of mtDNA into the cytosol by increasing the permeabilization of the mitochondrial IM, which could lead to cell death-associated inflammation	Colon cancer and osteosarcoma	2022
Zhao et al. (Zhao et al., 2022)	Activate immunity	A herpesvirus-mimicking nanoparticle (named Vir-ZM@TD)	Vir-ZM@TD evaded rapid clearance in the blood circulation and mimicked the serial infection processes of herpesvirus, including TFAM deficiency-triggered mtDNA stress, as well as the release of Mn2+ from organelles into the cytosol, priming cGAS-STING pathway-mediated innate immunity.	Breast carcinoma	2022
Yan et al. (Yan et al., 2022)	Activate immunity	RocA	RocA promoted NK cell infiltration by activating cGAS-STING signaling via targeting mtDNA.	NSCLC	2022
Benedetti et al. (Benedetti et al., 2022)	Increase ROS	Acyclovir	The continuous generation of ROS caused dose-dependent damage to mtDNA	NSCLC	2022
Somuncu et al. (Somuncu et al., 2022)	Increase ROS, influence genetic functions of mtDNA	3,3'-[(1,1′-Biphenyl)-4′,4′-diyl)bis (azo)]bis [4-amino-1-naphthalenesulfonic acid](CR)	CR was a high-affinity binder to the Pol γ protein, causing mitochondrial dysfunction by inhibiting Pol γ activity and oxidative mtDNA damage repair.	Colonic carcinoma	2022
Wang et al. (Wang et al., 2022a)	Influence genetic functions of mtDNA	CircRNAs	miR-1182/TFAM axis was inhibited, resulting in transcriptional repression of ND1 and ATP6	NSCLC	2022
Kong et al. (Kong et al., 2022)	Influence genetic functions of mtDNA	The combination of epoxomicin and cisplatin	Inhibition of TFAM and POLRMT function, affecting mitochondrial genome transcription	ovarian carcinoma	2022
Guo et al. (Guo et al., 2022)	Influence genetic functions of mtDNA, increase ROS	VB12- sericin-PBLG-IR780	VB12- sericin-PBLG-IR780 could significantly inhibit the expression of ATP synthase and lead to ROS generation.	Gastric cancer	2022
Hu et al. (Hu et al., 2021)	Activate immunity	ATM protein inhibition	ATM inhibition potently activated the cGAS/STING pathway and enhanced lymphocyte infiltration into the TME by TFAM, leading to mtDNA leakage into the cytoplasm.	Breast carcinoma and melanoma	2021
Jiang et al. (Jiang, Guo, et al., 2021)	Activate immunity, metal complexes	MSN-Ru2+/Fe2+	MSN-Ru2+/Fe2+ could enter mitochondria to bind with mtDNA due to the lipophilic and DNA affinity of Ru2+ complex. Oxidative mtDNA is able to escape from the tumor cells and results in the reactivated immunoresponse of macrophages against cancer cells.	Pancreatic cancer	2021
Panchangam et al. (Panchangam et al., 2021)	Increase ROS	Novel C–N-cyclometalated 2H-indazole-Ir(III) complex	Increased ROS damage mtDNA. And mtDNA may also be damaged as a target during metal delivery.	Triple negative mammary gland cancer	2021
Koshikawa et al. (Koshikawa et al., 2021)	Increase ROS, carrier system	A five-ring PIP-TPP	It localized in the mitochondria in HeLamtA3243G cells and induced mitochondrial ROS production, mitophagy and apoptosis in a mutation-specific fashion	Cervical carcinoma	2021
Li et al. (Li, Zhang, et al., 2021)	Influence genetic functions of mtDNA, Activate immunity	Zalcitabine	Zalcitabine-induced TFAM degradation could trigger oxidative DNA damage, mtDNA release to the cytosol, and subsequent activation of the CGAS-STING1 pathway	Pancreatic cancer	2021
Cheng et al. (Cheng et al., 2020)	Activate immunity	Overexpression of Lon	Upregulation of Lon induced the secretion of extracellular vehicles, which carry mtDNA and PD-L1.	Oral squamous cell carcinoma	2020
Pandey et al. (Pandey & Verma, 2020)	Influence genetic functions of mtDNA	Violacein and silver nanoparticles	Dyad drug system could structurally bind and inhibit TFAM at the interface of TFAM-DNA complex during replication and thus can hinder majority of pathways contributing to cancer proliferation.	Pan-carcinoma	2020
Bonekamp et al. (Bonekamp et al., 2020)	Influence genetic functions of mtDNA	IMTs	IMT1 and IMT1B significantly reduced the levels of mtDNA transcriptions and respiratory chain subunits in tumor cells by inhibiting POLRMT.	NSCLC, cervical carcinoma and ovarian carcinoma	2020
	Increase ROS	Gemcitabine	Gemcitabine depleted the cellular pool of deoxyribonucleotides and inhibits the synthesis of	Insulinoma	2019

(*continued on next page*)

Table 1 (*continued*)

	Strategies for targeted therapy	Drugs, compounds or key genes used	The core of therapeutic strategy (Characteristics of mtDNA targeting)	Cancer	year
Inamura et al. (Inamura et al., 2019)			mtDNA , resulting in the acceleration of ROS generation in mitochondria.		
Fan et al. (Fan et al., 2017)	Influence genetic functions of mtDNA	miR-199a-3p	The up-regulation of miR-199a-3p expression could inhibit mitochondria by inhibiting TFAM transcription	Breast carcinoma	2017

the mutation types, locations, and heteroplasmy level. The composition of this network involves alterations in gene copy number, aberrant gene expression, and mtDNA epigenetic modifications that frequently impact cancer occurrence and malignant transformation through metabolic regulation, reactive oxygen species (ROS) generation, intercellular interaction, and other mechanisms. Here we provide a concise overview of the intricate relationship between mtDNA damage, gene mutations, and cancer progression, to clarify the status of mtDNA as a biomarker in tumors and its value as a therapeutic target.

Abnormal gene expression of mtDNA is the most common manifestation of mitochondrial genome changes, which often causes imbalance of ROS level, changes of cellular metabolism, and the transformation of tumor energy form. Research findings have demonstrated that mutations in mtDNA can impact the constituents of electron transport chain, thereby resulting in elevated levels of ROS (Smith et al., 2022a). In most cases, Complex I is preferentially affected, accompanied by silencing of complex III and complex V (Kim et al., 2022). Abnormal ROS levels can promote tumor initiation and growth by inducing mtDNA mutations, genomic instability, metabolic reprogramming, and activation of oncogenic signaling pathways (Kuo et al., 2022). Furthermore, metabolic alterations serve as a crucial mechanism in regulating tumorigenesis following mtDNA mutations. Schöpf et al. (Schöpf et al., 2020) studied the alterations in mitochondrial metabolism and mtDNA in prostate cancer tissue samples. They found that malignant tissue samples have lower “NADH-pathway” capacity and stronger succinate oxidation than benign tissue samples, especially in high-grade tumors. The accumulation of harmful mtDNA mutations, particularly in mitochondrial complex I genes, and the presence of mtDNA heteroplasmy causes it and contributes to the development and aggressiveness of prostate cancer. This study has emphasized that mtDNA mutations can induce metabolic reprogramming in tumor tissues, leading to high-risk transformation of tumors. In addition, deregulation of enzymes caused by mtDNA mutations can lead to the accumulation of intermediate products in cancer cells, accelerating tumorigenesis (Badrinath & Yoo, 2018). From the perspective of energy generation, mtDNA mutations may affect the cellular energy capacity, increase oxidative stress, indirectly lead to cancer aggravation, and also have an energy programming effect on cancer metabolism that depends on OXPHOS (Carew & Huang, 2002; Davis et al., 2014).

Epigenetic changes in mtDNA are modifications that affect the expression or function of mtDNA without altering its sequence, including mtDNA methylation, RNA methylation, and histone modifications (Wagner et al., 2022). Some studies have shown that epigenetic changes in mtDNA can promote tumor progression by affecting various aspects of mitochondrial function and communication. In colorectal cancer, Feng et al. (Feng et al., 2012) observed a significant correlation between the expression change of ND2 and clinical pathological stage, and they identified that demethylation of D-loop plays an important regulatory role in this process. In addition, 8 mtDNA aberrantly methylated sites were found to be associated with enhanced invasion and metastasis of breast cancer (Han et al., 2017). And this potentially malignant methylation in D-loop region can be maternally inherited. The progression of bone metastatic tumors of renal cell carcinoma was also shown to be related to the methylation status of mtDNA D-loop region, and could be induced by hypoxic microenvironment (Liu, Tian, et al., 2022). However, even though mtDNA methylation may be used as a marker to predict cancer progression, its relationship with cancer remains to be further elucidated. Mitochondria retain their own replication, transcription, and translation systems, and abnormal methylation modifications of their own mitochondrial RNA may also affect mtDNA and mitochondrial function by regulating the stability and structure of mitochondrial transcription. rRNA methylation is mainly affected by mitochondrial rRNA methyltransferases, including mitochondrial large subunit methyltransferases (MRM1, MRM2, MRM3, TRMT61B) and mitochondrial small subunit methyltransferases (TFB1M, TRMT2B, NSUN4, METTL15) (Lopez Sanchez et al., 2020). Abnormalities of mitochondrial rRNA methyltransferases have been found to be associated with diabetes, Alzheimer's disease, and breast cancer (Couch et al., 2016; Koeck et al., 2011). mtDNA lacks histones, but mtDNA binding proteins can serve as targets for post-translational modifications, mainly involving TFAM, mitochondrial single-stranded binding protein and DNA polymerase γ (POL γ), which participates in mitochondrial transcription (Chatterjee et al., 2022). Histone modifications can affect the accessibility, replication, and transcription of mtDNA, and may promote cancer progression by regulating OXPHOS, mitochondrial biogenesis, apoptosis, and retrograde signaling in cancer cells.

The change in mtDNA copy number level is also important for cancer progression. So far, an increase or decrease in mtDNA copy number has been observed in various cancers, which may represent the potential role of mtDNA copy number in cancer progression (Li, Sundquist, et al., 2021, p. 13). In recent years, researchers have tried to utilize it as a biomarker for cancer diagnosis and efficacy prediction. Zhang et al. (Zhang et al., 2023) investigated the correlation between leukocyte mtDNA copy number and clinical outcomes in breast cancer patients, revealing for the first time that high mtDNA copy numbers are associated with worse prognosis in hormone receptor-positive cases. And they proposed using mtDNA copy number as a biomarker to predict prognosis. In addition, Sun et al. (Sun et al., 2018) attempted to demonstrate that increased mtDNA copy number can promote the metastasis of microsatellite-stable colorectal cancer cells by increasing mitochondrial OXPHOS level. Similarly, Reznik et al. (Ed et al., 2015) found that a large number of tumor tissues exhibit alterations in the content of mtDNA, manifested as depletion (bladder cancer, breast cancer, esophageal cancer, head and neck squamous cell carcinoma, kidney cancer) or accumulation (lung cancer), which is closely related to the regulation of tumor pathology and patient survival. The association between mtDNA copy number and tumor progression is undoubtedly authentic. On the contrary, some studies have shown that the change in mtDNA copy number was not sufficient to serve as a clinical marker for cancer assessment (Haja Mohideen et al., 2015). Therefore, the clinical value of mtDNA copy number remains to be further clarified.

In the process of mtDNA mutation and disease induction, the level of mtDNA heteroplasmy significantly impacts the clinical progression of the disease. Generally speaking, only when the mutant heteroplasmy of mtDNA reaches a certain proportion can it induce disease. In recent years, scholars have conducted a more in-depth analysis of this dynamic evolutionary process. Wallace et al. (Picard et al., 2014) conducted a study in 2014 to assess the impact of varying level of mtDNA tRNALeu

Table 2
Summary of direct targeting strategies in recent years.

	Strategies for targeted therapy	Drugs or compounds used	The core of therapeutic strategy (Characteristics of mtDNA targeting)	Cancer	year
Mukerabigwi et al. (Mukerabigwi et al., 2023)	Carrier system	TF@CNM + DOX	Design tumor and mitochondrial dual targeting multiprodrug to improve intracellular ros level and solve multi-drug resistance in cancers.	Breast carcinoma	2023
Yao et al. (Yao et al., 2023)	Carrier system	PIP-TPP (CCC-h1005)	CCC-h1005 can be used to treat many cervical cancers harboring high copies of the target variant	Cervical carcinoma	2023
Faria et al. (Faria et al., 2022)	Carrier system	PEI–DQA/TAT/pDNA, MTS-CPP/pDNA	Polymer and peptide delivery systems increased mitochondrial localization of targeted therapy.	Cervical carcinoma and lung cancer	2022
Luo et al. (Luo et al., 2022)	Carrier system	NP(Pt)@AL	The activity of thioredoxin reductase 1 inhibited by AL and the adducts of Pt (II) with mtDNA can costimulate ROS and reactivate the mitochondrial pathway of apoptosis.	Ovarian carcinoma	2022
Tsuji et al. (Tsuji et al., 2022)	Carrier system	novel PIP-TPP (CCC-021-TPP)	CCC-021-TPP caused cell senescence, accompanied by significant induction of anti-apoptotic BCL-XL	NSCLC	2022
Mondal et al. (Mondal et al., 2022)	Direct bonding	Ym155	Ym155 binds mtDNA leading to mitochondrial dysfunction, including a decrease in OXPHOS and TCA cycle intermediates, and an increase in mitochondrial permeability.	Lung cancer	2022
Wang et al. (Wang et al., 2022c)	Metal complex	Zn (II)–cryptolepine–cyclen	It showed efficient plasmid DNA intercalation, and has a high binding affinity to mtDNA to cleave DNA, further causing mitochondrial damage, and can be used for cisplatin resistance	Lung cancer	2022
Echevarría et al. (Echevarría et al., 2022)	Metal complex, PDT	A family of Ir (III) complexes	Complexes [1a] Cl and [3a] Cl were able to cause severe cleavage on mtDNA, resulting in the inhibition of the expression of mitochondrial genes.	Prostate cancer and melanoma	2022
Bajpai et al. (Bajpai et al., 2022b)	Metal complex	Cholesterol-based chimeric nanoparticles consisting of cisplatin, camptothecin, and tigecycline	Particles localized efficiently into the mitochondria of cancer cells within 6 h, simultaneously impairing mtDNA, mt-Top1, and mitochondrial ribosomes.	Breast carcinoma, cervical carcinoma and lung cancer	2022
Jiang et al. (Jiang, Guo, et al., 2021)	Activate immunity, metal complexes	MSN-Ru2+/Fe2+	MSN-Ru2+/Fe2+ could enter mitochondria to bind with mtDNA due to the lipophilic and DNA affinity of Ru2+ complex. Oxidative mtDNA is able to escape from the tumor cells and results in the reactivated immunoresponse of macrophages against cancer cells.	Pancreatic cancer	2021
Muhammad et al. (Muhammad et al., 2021)	Carrier system	c,c,t -[Pt-(NH3)2Cl2 (TPP) (Dox)] (PPD)	Enhanced mitochondrial localization and overcoming cisplatin resistance	Breast carcinoma	2021
Koshikawa et al. (Koshikawa et al., 2021)	Increase ROS, carrier system	A five-ring PIP-TPP	It localized in the mitochondria in HeLamtA3243G cells and induced mitochondrial ROS production, mitophagy and apoptosis in a mutation-specific fashion	Cervical carcinoma	2021
Zhang et al. (Zhang et al., 2021)	PTT, PDT	IR780@Pt NPs	Massive ROS generation and photothermal effects under 808 nm laser irradiation resulted in MMP loss, significantly reduced cellular ATP production, decreased cellular GSH levels, mtDNA damage, and mitochondrial dysfunction.	Osteosarcoma and cervical carcinoma	2021
Nair et al. (Nair et al., 2020)	Carrier system	A folic acid anchored *p*-sulfo-calix [4] arene capped hollow gold nanoparticles was meticulously loaded with Dox and Mt-Dox.	Overcomed off-target effects and eradicated both nDNA and mtDNA	Cervical carcinoma and lung cancer	2020
Chen et al. (Chen et al., 2020)	Carrier system	Choil-TPP	It could inhibit the transcription of mtDNA and damage mtDNA.	pancreatic cancer	2020
Yang et al. (Yang et al., 2020)	Carrier system, PTT	Pt (IV)-NPs contain IR780	Pt (IV)-NPs could markedly facilitate cancer-specific mitochondrial targeting, inducing mitochondrial dysfunction and mtDNA damage, thus greatly increasing the Pt accumulation in cisplatin resistant cancer cells.	Lung cancer	2020
Liu et al. (Liu et al., 2020)	Direct bonding	Pentamidine	Pentamidine targets AT sequences in mtDNA, resulting in decreased transcription levels of mitochondrial coding genes, decreased mtDNA, and changes in mitochondrial morphology and function	Prostate cancer	2020
Qin et al. (Qin et al., 2020)	Metal complex	Cyclometalated iridium (III) complexes	Ir complexes induced an increase in intracellular ROS levels, a reduction in ATP production, mtDNA damage, an increase in lipid eroxidation levels, and proteasomal activity inhibition	Lung cancer	2020
Li et al. (Li, Wu, et al., 2020)	Metal complex, PDT	Dinuclear Ir(III)-containing luminescent metallohelices	It had stronger mtDNA binding affinity and better PDT effect. And mtDNA were cleaved by the generated intracellular $^1O_2$.	Breast carcinoma and lung cancer	2020
	Metal complex			Lung cancer	2019

(*continued on next page*)

Table 2 (*continued*)

	Strategies for targeted therapy	Drugs or compounds used	The core of therapeutic strategy (Characteristics of mtDNA targeting)	Cancer	year
Cao et al. (Cao et al., 2019)		Ir3: [Ir (dfppy)2 (dppz)](PF6); Ir4: [Ir (ptz)2 (dppz)](PF6)	Complexes Ir3 and Ir4 bound to mtDNA, intercalated to mtDNA in situ and induced mtDNA damage, resulting in decline of mitochondrial membrane potential, disability of adenosine triphosphate generation, disruption of mitochondrial energetic and metabolic status		
Chen et al. (Chen et al., 2018)	Carrier system	peptide nucleic acids coupled with TPP	It targeted the D-loop regulatory region of mtDNA.TPP is a DLC for mitochondrial targeting, and PNA can bond to DNA and RNA targets efficiently	Lung cancer	2018
Wang et al. (Wang et al., 2018)	Carrier system, PTT	Nanoparticles: a core–shell –SS–shell architecture are composed of a core of Fe3O4 colloidal nanocrystal clusters, an inner shell of PDA functionalized with TPP, and an outer shell of methoxy poly (ethylene glycol) linked to the PDA by disulfide bonds.	The magnetic core can increase the accumulation of nanoparticles at the tumor site. A photothermal effect is generated from the PDA photosensitizer using NIR, leading to a dramatic decrease in mitochondrial membrane potential. Simultaneously, the loaded Dox can enter the mitochondria and subsequently damage the mtDNA.	Melanoma	2018
Hu et al. (Hu et al., 2017)	Carrier system, PCT	UCNP core combined with mesoporous silica and Ru2+ complex.	Under NIR irradiation, the accumulated H2O2 in intratumoral mitochondrion will react with Fe2+ to efficiently generate localized –OH radicals which cause mtDNA damage.	Liver cancer	2017
Yang et al. (Yang et al., 2017)	Direct bonding, PDT	D112	D112 bound to mtDNA, and induced mtDNA damage, ROS production and complex I inhibition.	Breast carcinoma	2017
Pokrzywinski et al. (Pokrzywinski et al., 2016)	Carrier system	mitoTEMPOL, mitoquinone and mitochromanol-acetate conjugated to TPP+	Reduced mitochondrial function by affecting mtDNA integrity and oxidative respiration.	Breast carcinoma and lung cancer	2016

(UUR) 3243 A > G mutation on gene expression profile, signaling pathway and epigenetic changes in cells. Their findings suggested that the degree of heteroplasmy has differential effects on cell phenotype. This variability of heteroplasmy negated the concept of "single mutation-single disease", providing an explanation for clinical variability in mtDNA diseases. In 2019, Wallace et al. (Kopinski et al., 2019) further delved into a more comprehensive examination of the impact of heteroplasmy level on the nDNA. They incorporated nuclear NAD+/NADH levels, changes in histone modifications, mitochondrial intermediates, and alterations in redox states into the intricate network of "mtDNA-nDNA". This perspective enhances our understanding of the process by which mtDNA mutations cause diseases and plays a crucial role in guiding the appropriate utilization of mtDNA as a biomarker.

The alterations in mtDNA can affect various aspects of mitochondrial function and cellular homeostasis, including energy generation, ROS production, metabolic reprogramming, epigenetic regulation and nuclear gene expression. Moreover, the level of mtDNA heteroplasmy can modulate the phenotypic variability and severity of mtDNA diseases. Therefore, mtDNA damage and gene mutations are important factors that contribute to cancer development and progression. Besides, the interactions between mtDNA and other cellular components, such as nDNA, immune system, and neighboring cells, can also influence the tumorigenicity, metastasis, chemoresistance, and immunogenicity of cancer cells.

3. The messenger role of mtDNA: basis and concerns of targeted therapy

As an important intermediate medium, mtDNA can extensively communicate with extramitochondrial biological systems and trigger a series of biological effects, especially when its stable state is disrupted. Understanding how mtDNA interacts with other components will help reveal the mechanism, effect prediction and prognosis evaluation of mtDNA-targeted therapies. Here, we discuss the important role of mtDNA in intercellular and intracellular communication.

3.1. The interactions between mtDNA and nDNA

The extensive interactions between mtDNA and nDNA include the expression regulation of related nuclear genes and the maintenance of mtDNA stability under nuclear regulation (Kosmider et al., 2019; Yamazoe et al., 2021; Zhou et al., 2010). mtDNA can influence nDNA expression through various pathways. These pathways include activating related signaling pathways during damage, directly acting on nDNA through ROS generated by mitochondrial dysfunction, or integrating mtDNA into nDNA to form nuclear mitochondrial sequences (NUMTs). The influences on the expression nuclear genes may confer both advantages and disadvantages for the vital functions of cells. Han et al. (Han et al., 2021) found an increase in stemness-associated genes, such as OCT4, NANOG, and SOX2, after the depletion of mtDNA in Hep3B/rho0 cells, causing the obtaining and maintaining of cancer stem-like properties. And Lee et al. (Lee et al., 2015) discovered the pivotal roles that the activation of retrograde NUPR1-granulin pathway after mitochondrial dysfunction played in human liver cancer. Moreover, the process of epithelial-mesenchymal transition has also been shown to be associated with the activation of the TGF-β-c-Jun/AP-1 signaling pathway caused by mitochondrial dysfunction (Yi et al., 2015). NUMTs are fragments of mtDNA that have been transferred and integrated into nDNA. When exogenous or endogenous factors cause DNA double-strand break (DSB), mtDNA can integrate into nDNA through microhomology-mediated end joining, retro-transposition, endocytosis of mitochondria-derived vesicles, encapsulation of mtDNA in the nucleus, and other pathways, affecting the structure and regulation of nDNA genetic information (Gaziev & Shaikhaev, 2010). Some studies have shown that these integrated sequences are involved in processes such as carcinogenesis and aging (Wei et al., 2022). Therapeutically, we hope that mtDNA damage caused by mtDNA-targeted therapy can induce the expression of genes related to cell death. It has been reported the alteration of mtDNA copy number can initiate retrograde signaling, which causes the impairment of the expression profile of nuclear genes and modifies cell physiology and morphology (Abd Radzak et al., 2022). In addition, the immune- and

stress-related genes have been found the most highly differentially expressed in mtDNA-deleted 4T1/rho0 cells, which might be the basis of immune activation (Grasso et al., 2020).

In addition to affecting the gene expression of nDNA, mtDNA damage can also activate DNA damage response (DDR) to promote mtDNA repair and regulate cellular senescence and apoptosis activities. mtDNA damage can activate the DDR of nDNA to repair mtDNA and maintain mtDNA stability. mtDNA damage can be sensed by different molecules and pathways that translocate to the nucleus and modulate the expression of nuclear genes that are involved in mtDNA replication, repair, and turnover, such as p53, ataxia telangiectasia mutation (ATM) protein, and NF-κB (Lee & Paull, 2020; Shin et al., 2022). Moreover, the nuclear DDR can also regulate the availability of nucleotides for mtDNA synthesis by balancing the nucleotide pool (Rai, 2010). The DDR can regulate the nucleotide pool by activating enzymes that synthesize or salvage nucleotides, such as RNR (Zuo et al., 2022), and/or by inhibiting enzymes that degrade or consume nucleotides, such as SAMHD1, DUT, and PARN (Murphy & Kleiman, 2020; St Gelais et al., 2012). In addition, the nuclear DDR can also influence the communication between the nucleus and the mitochondria by modulating the expression of proteins that mediate mitochondrial-nuclear crosstalk, or altering the localization of proteins that shuttle between the two organelles (Fairbrother-Browne et al., 2021). Therefore, the nuclear DDR is an important mechanism for maintaining mitochondrial function and integrity after mtDNA damage. As another important double-stranded DNA in cells, the interactions between mtDNA and nDNA merit more research. And it is an aspect worth paying attention to after the disruption of mtDNA homeostasis caused by either therapeutic reasons or natural factors.

3.2. The role of mtDNA in intercellular transfer

Similarly, mtDNA is crucial for cell-to-cell communications. Cancer cells with mtDNA depletion can obtain functional mtDNA from adjacent cells to repair mitochondrial function, including stromal cells and tumor cells. At the same time, some mtDNA carrying certain pathogenic mutations can be transferred to other cancer cells. These mechanisms of intercellular transfer include tunneling nanotubes (TNTs), cell fusion, gap junction channels (GJCs) and extracellular vesicles (EVs), and occur under physiological and pathological conditions (Fig. 2). (Liu, Sun, et al., 2022; Valenti et al., 2021a) TNTs are slender, membrane-enclosed tubular connections that enable the intercellular transfer of various molecules and organelles, including mtDNA, between distant cells (Dubois et al., 2020). The generation of TNTs primarily involves two mechanisms, namely filopodial interplay and cell dislodgement, which additionally necessitate the modulation of cortical actin dynamics, plasma membrane deformation and curvature (Turos-Korgul et al., 2022). The movement of mtDNA and mitochondria within TNTs is contingent on the cytoskeleton elements, predominantly F-actin and microtubules, and can be influenced by cytoskeletal composition, membrane dynamics, molecular motors, oxidative stress and extracellular signals (Dagar et al., 2021). TNTs-mediated mtDNA transmission can modulate the metabolic and genetic diversity of tumor cells and influence their proliferation, metastasis and adaptation (Marlein et al., 2019). For example, cancer-associated fibroblasts can donate functional mitochondria and mtDNA to prostate cancer cells via TNTs and increase their glycolytic activity and chemoresistance, promoting their malignant transformation (Ippolito et al., 2019). Furthermore, another study reported that glioblastoma (GBM) cells can transmit mutated mitochondria and mtDNA to neighboring primary astrocytes via TNTs, modulating metabolism, facilitating cancer progression and tumor metabolism adaptation to the microenvironment (Valdebenito et al., 2021). As another important pattern, GJCs are composed of connexin (Cx) proteins that form hexameric hemichannels on each cell membrane (Valenti et al., 2021b). However, owing to the pore size restriction, they preclude the passage of organelles and usually assist in TNT-mediated mitochondrial transfer (Liu, Sun, et al., 2022). Cx43 is an important regulator of TNT generation, which has been reported to act in the mechanism of mitochondrial transfer between mesenchymal stem cells and epithelial cells in asthma inflammation (Yao et al., 2018).

EVs-mediated pattern can transfer mtDNA or mitochondria-related components by fusing with the plasma membrane or endocytosis, affecting the functions of the recipient cells. Takenage et al. (Takenaga

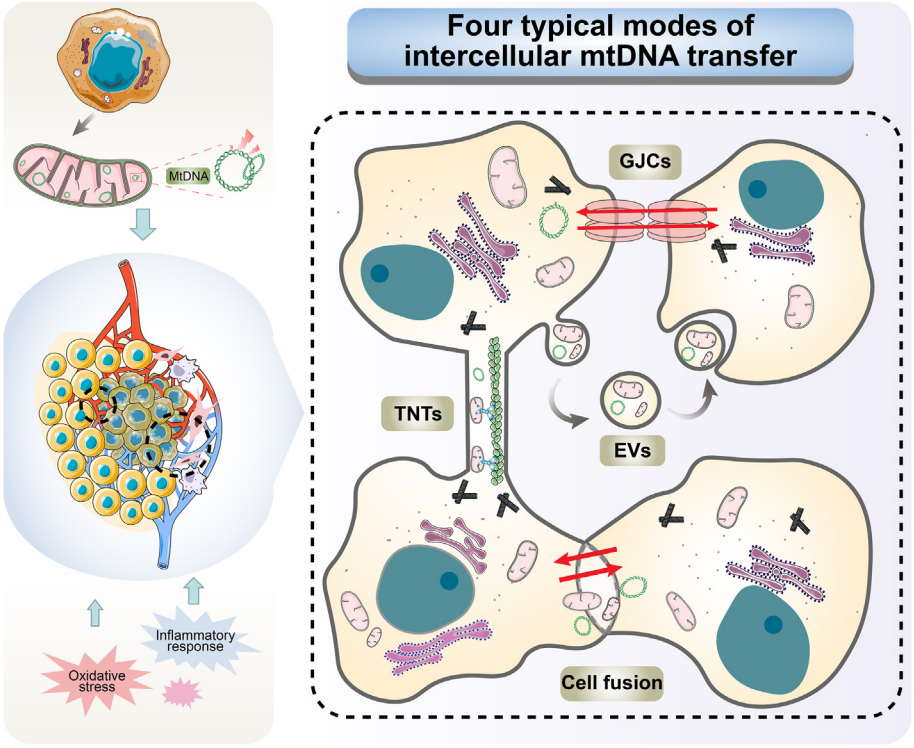

Fig. 2. Schematic diagram of four typical modes of intercellular mtDNA transfer. Stimulation of TME tissues by endogenous factors, such as damaged mtDNA in tumor cells, or exogenous factors like oxidative stress, inflammatory response and pathological stimuli can trigger intercellular transfer of mtDNA. mtDNA transfer mainly includes four typical forms: tunneling nanotubes (TNTs), cell fusion, gap junction channels (GJCs) and extracellular vesicles (EVs). Multiple mechanisms frequently co-exist and synergistically interact in TME.

et al., 2021) have revealed that metastasis-enhancing pathogenic mtDNA derived from metastatic tumor cells is transferred to low-metastatic tumor cells via EV to promote the metastatic potential of tumors. And in the treatment of breast cancer, EVs can carry intact mtDNA and act as infectious mediators between cancer-associated fibroblasts and cancer cells, rescuing breast cancer cells with OXPHOS defects induced by hormone therapy (Sansone et al., 2017). The findings suggest a strong correlation between EVS-mediated mtDNA transfer and the development of tumors as well as the acquisition of drug resistance. Moreover, EVs that remain in the extracellular environment may have a close association with mtDNA-mediated immune and inflammatory responses in TME. TNTs, EVs and GJCs represent the main pathways of mtDNA intercellular transfer in tumor tissues, but there are often multiple patterns co-existing and synergizing in reality (Yang et al., 2023). In addition, mtDNA can also be transferred between cells through cell fusion. It has been demonstrated that the formation of hybrid cells through spontaneous fusion between pre-malignant (IMR90 E6E7) and malignant (IMR90 E6E7 RST) mesenchymal cells facilitate the metastatic dissemination of tumors (Brito et al., 2021). Nevertheless, it is important to note that cell fusion involves the sharing of a large number of organelles and cellular structures, and cannot be solely attributed to mtDNA or mitochondrial exchange.

In the recent studies, intercellular transmission of mtDNA is usually associated with functional repair and remodeling of cells with mitochondrial dysfunction. In cancer cells, intercellular mitochondrial transfer can modulate the bioenergetics, metabolism, oxidative stress, gene expression and signaling pathways of tumor cells and non-tumor cells in the TME, affecting the tumorigenicity, metastasis, chemoresistance and immunogenicity of tumor cells and other phenotypes (Berridge et al., 2015). Intercellular mtDNA transfer is an emerging phenomenon that has important implications for understanding and treating mitochondrial diseases. As a dynamic and complex process, it has beneficial or detrimental effects on both donor and recipient cells depending on the context and direction of transfer. Also, it offers new insights into the molecular mechanisms and consequences of mitochondrial dysfunction and communication in different cell types and tissues, penning new avenues for developing novel therapeutic strategies based on manipulating intercellular mtDNA transfer to enhance or inhibit mitochondrial function in target cells (Valenti et al., 2021a).

3.3. The role of mtDNA in immune activation

As a damage-associated molecular pattern (DAMP), mtDNA release and immune activation are also frequently associated with each other. The release of mtDNA is the first step in triggering immune responses and boosting immunosurveillance (Bai & Liu, 2019; Choi et al., 2020). Two mechanisms have been analyzed directed at mtDNA release, including releasing through the formation of BAX and BAK in the outer membrane and subsequent inner membrane (IM) permeabilization in apoptotic cells, and involving the oligomerization of voltage-dependent anion channel (VDAC) in the outer membrane of non-apoptotic cells (Bahat et al., 2021b). During apoptosis, apoptosis factors can inhibit the anti-apoptotic members of BCL-2 family including BCL-2 and BCL-xL, thereby unleashing BAX and BAK to cause mitochondrial pore formation in outer mitochondrial membrane, leading to release of oxidized mtDNA and activating the NLRP3 inflammasome (Paik et al., 2021; Singh et al., 2022). The activation of BAX and BAK can be induced through direct binding to a subset of BH3-only proteins named BIM, BID, PUMA and possibly NOXA (Ludwig et al., 2020). In non-apoptotic macrophages, the mechanism that ox-mtDNA could exit mitochondria via mitochondrial permeability transition pores- and VDAC-dependent channels when it was cleaved by the endonuclease FEN1 to 500–650 bp fragments has been found (Xian et al., 2022). VDAC can oligomerize under oxidative stress conditions and form large mitochondrial outer membrane pores which mediate mtDNA release in live cells (Kim et al., 2019). The release of damaged-mtDNA into the cytosol can stimulate pattern recognition receptors including Toll-like receptors and NOD-like receptors as a DAMP originated from cell itself (Bahat et al., 2021a). The cyclic GMP-AMP synthase (cGAS)-STING pathway plays an important role in leaked-mtDNA induced immune responses (Li, Zhang, et al., 2021; Zhang, Tang, et al., 2020). The cGAS is identified as a DNA sensors and can be activated by dsDNA including mtDNA, leading to the synthesis of dinucleotide second messenger 2′,3′-cyclic GMP-AMP (cGAMP) from ATP and GTP (Morimoto et al., 2021). cGAMP can finally stimulate innate immune by activating an endoplasmic reticulum-localized stimulator of interferon genes (STING), which increase production of inflammatory cytokines (Pokatayev et al., 2020; Wang et al., 2020). Besides, extracellular cGAMP can act as a soluble immune mediator in the TME to promote immune cell activation (Skopelja-Gardner et al., 2022). Extracellular release of mtDNA also plays a significant role in immune activation and inflammatory response, and is associated with the polarization and functional regulation of macrophages, dendritic cells, and T cells (Amari & Germain, 2021). The predominant pathway for mtDNA release in the TME is EV-mediated, including exosomes, microvesicles and apoptotic bodies. mtDNA can be encapsulated into EVs either through direct contact or via mitochondria-derived vesicles, resulting in extracellular release. Additionally, during apoptosis, mtDNA can also be passively released through cell membrane rupture caused by mechanical trauma (De Gaetano et al., 2021). It can be speculated that it is theoretically feasible to achieve therapy by inducing mtDNA activated immune response through targeting mtDNA. The understanding of the subsequent immune response to mtDNA-targeted therapy is of great significance for evaluating the therapeutic process.

In summary, mtDNA is not only essential for mitochondrial function, but also plays important roles in various biological processes that involve communication and interaction with other cellular components. mtDNA can regulate the expression of nuclear genes, be transferred to other cells to repair or enhance mitochondrial function, and activate immune responses by acting as a DAMP. These roles of mtDNA have implications for the development and progression of various diseases, especially cancers. As a result, understanding the mechanisms and consequences of mtDNA-mediated communication and immune activation is crucial for developing novel mtDNA-targeted therapeutic strategies.

4. Cancer therapies targeting mtDNA

4.1. Indirect targeted therapy

In this part, we discussed how to indirectly target mtDNA for cancer therapy by stimulating ROS, inhibiting POL γ and TFAM, and activating cGAS-STING pathway. These strategies exert their effects by influencing pathways that are involved in mtDNA stability and integrity instead of binding to mtDNA, thereby inducing mtDNA damage and dysfunction. The main contents of indirect targeted therapy are summarized in Fig. 3. Also, more details concerning recent indirect mtDNA-targeted researches were gathered and reported in Table 1.

4.1.1. Stimulation of ROS

ROS can be produced in mitochondria. The excessive accumulation of ROS results in mtDNA damage and mitochondrial dysfunction that may lead to severe cellular damage and apoptosis (Urbina-Varela et al., 2020; Zhang, Guo, et al., 2020). Inducing intracellular ROS accumulation to cause mtDNA damage is a viable strategy that has been developed in various studies exploring cancer therapy. Several studies have demonstrated the anti-cancer effects of different agents, such as the new Ir(III)-2-indazole complex with an isopropyl substituent which could induce mtDNA target inhibition and mitochondrion-mediated apoptosis by stimulating ROS in triple negative breast cancer (Panchangam et al., 2021). The novel VB12-sericin-PBLG-IR780 nanomicelles synthesized by Guo et al. have been proved to have anti-cancer effects by significantly inhibiting the expression of ATP synthase, inducing oxidative stress in mitochondria, increasing the generation of ROS and ultimately leading to

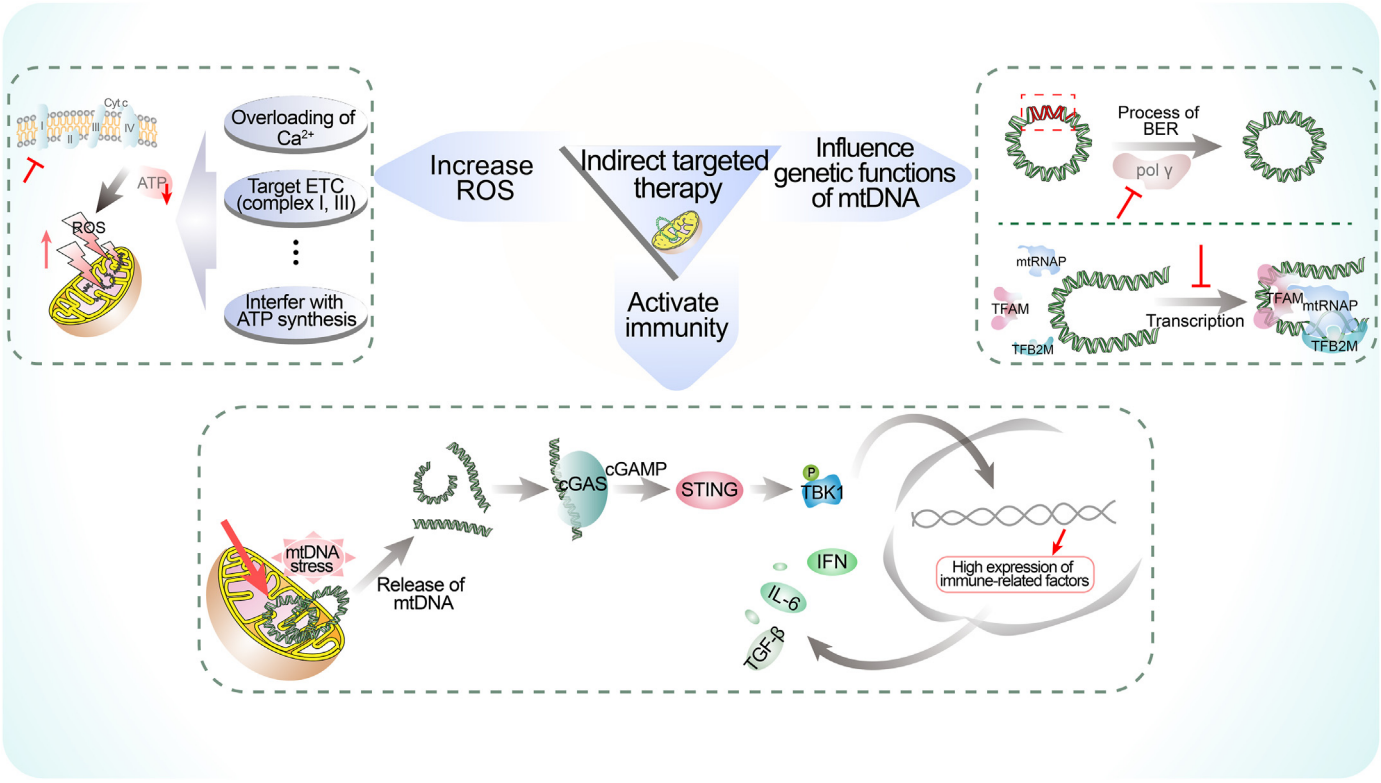

Fig. 3. The main aspects of indirect targeted therapy. We summarize the related studies of indirect targeted therapy into three categories, including increasing ROS, influencing genetic functions of mtDNA and activating immunity. Treatments that disrupt the normal states of these aspects will further cause damage of mtDNA, resulting in tumor suppression mediated by mitochondrial dysfunction. BER, base excision repair; IFN, interferon; IL-6, interleukin- 6; mtRNAP, mitochondrial RNA polymerase; TBK1, TANK Binding Kinase 1; TFAM, mitochondrial transcription factor A; TFB2M, mitochondrial transcription factor B2; TGF-β, transforming growth factor beta.

the oxidative damage of mtDNA in the presence of near-infrared (NIR) (Guo et al., 2022). In addition to that, the antiviral drug Acyclovir may inhibit the progression of cancers through mitochondrial mechanism by causing ROS-mediated mtDNA damage (Benedetti et al., 2022). The pathways that can cause increasing production of ROS can be potential targets for indirect mtDNA therapy. Several conditions including overloading of Ca2+, affecting the electron transport chain (mainly referring to complexes I and III) and interfering with the process of ATP synthesis can contribute to aberrant ROS generation, becoming possible targeting strategies (Karam et al., 2017; Sun et al., 2014; Vo et al., 2019).

4.1.2. Targeting the genetic expression and inheritance of mtDNA

The mtDNA POL γ is required for the replication and damage repair of the mitochondrial genome, and plays important roles in the biogenesis of mitochondria (De & Campbell, 2007; Siibak et al., 2017). Base excision repair is the prominent pathway for the repair of oxidative DNA lesions by excising and replacing damaged bases like 8-oxodeoxyguanine in mtDNA, using various proteins encoded in the nucleus and imported into the mitochondria (Fu et al., 2019; Zheng et al., 2020). Therefore, diminished repair capacity can be one of the factors responsible for high mutation frequencies of mtDNA which is closely related to the anti-cancer treatment (Singh et al., 2015). 3,3'-[(1,1′-Biphenyl)-4′, 4′-(diyl)bis (azo)]bis [4-amino-1-naphthalenesulfonic acid] (CR) has been identified with a high binding affinity to the POL γ protein and can cause mitochondrial dysfunction and cell apoptosis by inhibiting POL γ activity and oxidative mtDNA damage repair in MLH1 deficient human colon cancer (Somuncu et al., 2022). As one of the most significant polymerases in mtDNA synthesis and damage repair, it can become an important target of tumor therapy.

Besides POL γ, nuclear-encoded TFAM is a high mobility group (HMG) protein and acts as a key regulator in the replication, transcription, and inheritance of mtDNA (Wen et al., 2014). It supports the maintenance and stability of mitochondrial genome and the stability of TFAM is essential for biological function in cancer progression (Lan et al., 2017). As a product of the nucleus, TFAM contains five different domains including a cleavable matrix targeting sequence, two HMG homology domains connected by a linker, a tail, and short leader sequence that is located between matrix targeting sequence and HMG1 in human and murine (Kim et al., 2018; Kozhukhar & Alexeyev, 2022). TFAM is a protein that attaches to mtDNA and regulate mitochondrial transcription process (Fu et al., 2021). The completion of the process requires the formation of a transcription initiation complex composed of TFAM, mitochondrial transcription factor B2 (TFB2M), mitochondrial RNA polymerase (mtRNAP) and promoter DNA (Fig. 4). (Uchida et al., 2017) Besides, the interaction of TFAM with 8-oxodG-containing DNA substrates has shown the important role of TFAM in regulating DNA repair, while mtDNA packaging is possibly affected by the binding between TFAM and different non-canonical DNA structures (Chew & Zhao, 2021). As TFAM plays an important role in cellular activities and is indispensable in cancer progression, its aberrant expression in colorectal cancer cells can be a helpful marker for tumor progression in colorectal cancer patients (Zhao et al., 2021). Silencing its expression can inhibit mitochondrial function and significantly reduce tumor initiation potential in colon cancer cells and KrasG12D-driven lung cancer (Wen et al., 2019). TFAM can also increase the expression of angiogenesis and invasion-related genes and play a pro-tumorigenic role (Araujo et al., 2018). Moreover, TFAM affects the sensitivity of tumor treatment. Cellular sensitivity to cisplatin treatment is correlated with microRNA-199a-3p-mediated attenuation of TFAM expression in MDA-MB-231 cells (Zhang & Wang, 2018). Similarly, TFAM modulates

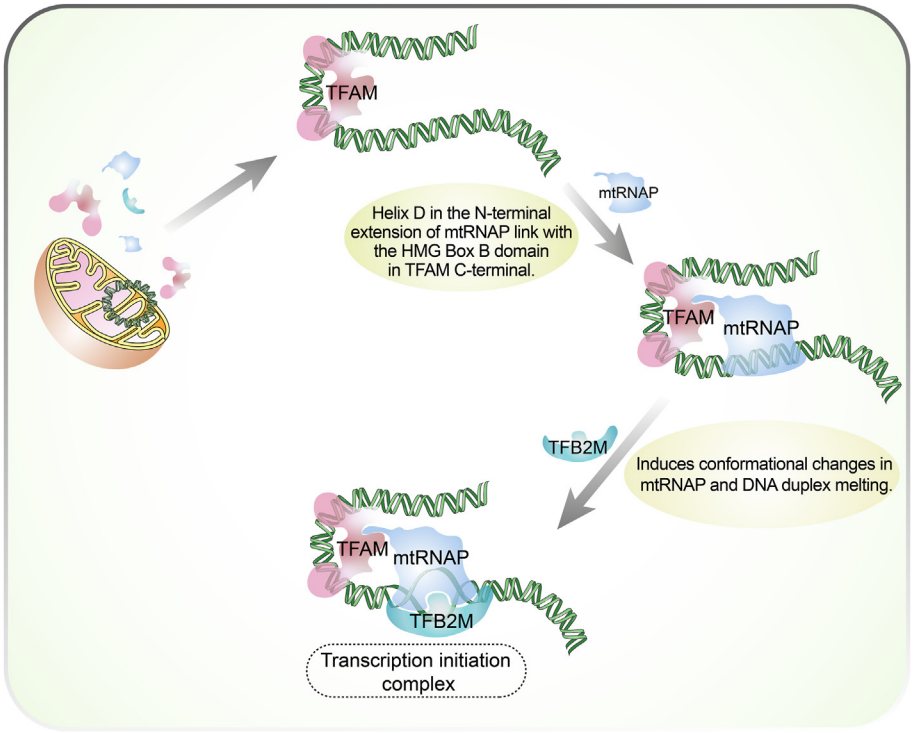

Fig. 4. Assembly of transcription initiation complexes. TFAM and three other components (TFB2M, mtRNAP and promoter DNA) form a complex on the mtDNA to start the expression process. At the beginning of the transcription, TFAM firstly binds to DNA 16–39 nt upstream of the transcription start site and induces a ~180° bend into DNA (Hillen et al., 2017; Rubio-Cosials et al., 2011). And then the helix D in the N-terminal extension of mtRNAP will link with the HMG Box B domain of TFAM, resulting in anchoring to the promoter (Hillen et al., 2017). The formed pre-IC lacks DNA specificity and transcriptional activity, unless the N-terminus of TFB2M bound to the active site of mtRNAP and induces conformational changes in mtRNAP (Morozov et al., 2015). mtRNAP, mitochondrial RNA polymerase; TFAM, mitochondrial transcription factor A; TFB2M, mitochondrial transcription factor B2.

the response of tumor cells to ionizing radiation via P53/TIGAR signaling in various cancers (Jiang & Wang, 2019). The irreplaceable position of TFAM in tumor growth and progression highlights its potential as a promising avenue for cancer treatment.

An antiviral drug for a human immunodeficiency virus infection, zalcitabine, has recently been found by causing TFAM degradation through a LONP1-dependent pathway in pancreatic cancer, resulting in triggering mtDNA stress, injury, cytosolic release and finally trigger an antiviral innate immune response via the activation of cGAS-STING1 pathway (Li, Zhang, et al., 2021). Consistent with this, Wang et al. demonstrated the pivotal role of TFAM, which exhibits high expression levels in pancreatic cancer, preserving stability of mitochondrial function and promoting biogenesis (Wang et al., 2023). Targeting TFAM inhibition may offer a potential solution to overcome resistance to gemcitabine in pancreatic cancer cells. Moreover, melatonin and the combination of epoxomicin and cisplatin can also inhibit mitochondrial functions, and ultimately promote cellular apoptosis by inhibiting TFAM (Franco et al., 2018, p. 23; Kong et al., 2022). The interactions between the expression of TFAM and other genetic activities can also be breakthrough points for targeted therapy. Up-regulation of Mir-199a-3p expression can induce mitochondrial dysfunction by inhibiting TFAM transcription in breast cancer MDA-MB-231 (Fan et al., 2017). The knockdown of Circ_0002476 caused mtDNA alterations by inhibiting Mir-1182/TFAM axis, leading to the transcriptional inhibition of ND1 (encoding the subunit of NADH dehydrogenase) and ATP6 (encoding the subunits of ATP synthase) (Wang et al., 2022a). Computer-based virtual screening have been widely used in novel drug discovery and capability prediction (Arévalo & Amorim, 2022; Song et al., 2021). The combination of violacein and silver nanoparticles that was predicted to have an anticancer activity by inhibiting TFAM as a dyad drug system (Pandey & Verma, 2020). The application of this technology will provide new strategies for the development of new TFAM-targeted drugs and solving the resistance of traditional drugs through mitochondrial pathway.

mt-RNAP, also known as POLRMT, is another important enzyme that regulates mtDNA transcription and replication. POLRMT is essential for the expression of mitochondrial genes and the maintenance of mtDNA integrity and copy number. Consequently, POLRMT is a potential target for anti-cancer therapy. Bonekamp et al. (Bonekamp et al., 2020) developed mitochondrial transcription inhibitors (IMTs), namely IMT1 and IMT1B. These compounds inhibited POLRMT non-competitively, altering its conformation, stability and activity. They could cause a significant reduction in the levels of mtDNA transcriptions and respiratory chain subunits in tumor cells, leading to dose-dependent inhibition of OXPHOS. The anti-tumor efficacy of IMTs has also been confirmed in ovarian cancer, cervical cancer and lung cancer cells.

4.1.3. *Activation of the immune system*

The interaction between mtDNA and immune system has attracted considerable attention in the recent discussion (Cushen et al., 2020; Yumnamcha et al., 2020). The manipulation of mtDNA to activate immune process represents a significant therapeutic strategy for enhancing anti-tumor effects (Mohanty et al., 2019). Two novel substituted carbazole derivatives (Ethyl 3-((*tert*-butoxycarbonyl) amino)-2-hydroxy-9H-carbazole-1-carboxylate and 3-((*tert*-butoxycarbonyl) amino)-2-hydroxy-9H-carbazole-1-carboxylic acid) synthesized by Witkowska et al. have displayed a better anticancer activity by inducing massive accumulation of mtDNA DSBs that were oxidatively damaged, increasing the permeabilization of the mitochondrial IM and stimulating the immune responses in colon and osteosarcoma (Witkowska et al., 2022).

One of the most common methods is employing some nano-carrier systems, that could activate innate immune response pathways while eliciting mtDNA damage and release. The BCP nanoparticles ((BPA + CPI) @ PLGA NPs), which combined 3-BPA and CPI-613 via a nano-drug delivery system, could not only promote the release of mtDNA by causing mitochondrial metabolism disorder, but also enhance the dimerization of STING and activation of immune (Li et al., 2022). And icaritin loading poly (lactic-*co*-glycolic acid) nanoparticles (PLGA@Icaritin NPs) could increase production of oxidative-mitochondrial DNA which followed by immunogenic cell death, and recruit infiltrating $CD4^+$ cells, $CD8^+$ T cells and cytokine to activate the anti-tumor immunity (Xiao et al., 2022). Virus-based immunotherapy, a promising method for cancer treatment, has also been used in this approach (Thomas et al., 2019). Recently, a herpesvirus-mimicking nanoparticle (named Vir-ZM@TD) is designed, in which the combinations of DNAzyme-loaded Mn-doped zeolitic

imidazolate framework-90 nanoparticles, erythrocyte membrane, RGD and HA2 peptides were used to mimic virus structure (Zhao et al., 2022). As a result, mtDNA stress was triggered by Vir-ZM@TD, releasing it into cytosol, and the sensitivity of cGAS to mtDNA was increase by Mn2+. Moreover, the natural product rocaglamide (RocA) has been shown to dramatically activate the cGAS-STING pathway and promote the cytoplasmic release of damaged mtDNA induced by itself (Yan et al., 2022).

In addition to that, using endogenous proteins to regulate mtDNA and immune system is also a potential strategy in cancer treatment. For example, overexpression of mitochondrial Lon that can accumulate ROS, increase oxidative damage of mtDNA and decrease mtDNA repair efficiency, promote mtDNA release into the cytosol and induce the secretion of extracellular vehicles carrying mtDNA, ultimately affecting the immune response in TME (Cheng et al., 2020). Besides, ATM protein has been identified as a prospective target in cancer therapy for its inhibition can enhance immune checkpoint blockade therapeutic effects by promoting cytoplasmic leakage of mtDNA, activation of cGAS-STING pathway and lymphocyte infiltration into TME (Hu et al., 2021). And Yin et al. (Yin et al., 2023) discovered the special effect of Raddeanin A in tumor immunotherapy, which is an oleanane class triterpenoid saponin isolated from Anemone raddeana Regel. It has the ability to interact with the transactive responsive DNA-binding protein 43 (TDP-43), trigger the release of mtDNA from mitochondria, and consequently enhance dendritic cells (DCs) mediated antigen cross-presentation and T cell activation. A specific protein, vaccinia virus-associated kinase 2 (VRK2), has been identified as a facilitator of mtDNA binding to VDAC, leading to the oligomerization of VDAC1 and subsequent release of mtDNA (He et al., 2021). This finding suggested that VRK2 could be a promising therapeutic target for viral infectious diseases associated with mtDNA release. Moreover, recent studies have identified VRK2 as a crucial target for enhancing tumor immunotherapy and overcoming tumor drug resistance (Chen et al., 2022; Moore et al., 2022; Peled et al., 2021; Zhu et al., 2021). However, it remains unclear whether targeting VRK2 exerts its effects via the mtDNA release pathway in cancer therapy. In conclusion, identifying and utilizing the connection between mtDNA and immune response in order to devise innovative and efficacious cancer treatment approaches is an area worth exploring.

4.2. Direct targeted therapy

The field of directly mtDNA-targeted therapy faces the challenge of preventing the impact on nuclear genes due to their genetic orthology. Nevertheless, some recent methods have overcome this problem and applied mtDNA-targeted therapy to clinical settings (Yang et al., 2022). These methods utilize mitochondrial localization molecules that can modulate the function of mtDNA by directly targeting it. This part summarized several specific strategies in the field of direct targeted therapy to mtDNA that may be extensively applied and implemented (Fig. 5). And more details of related studies about direct targeting recently were summarized in Table 2.

4.2.1. The application of carrier systems

How to prevent the impact on nuclear genes while targeting mtDNA has always been a problem needs to be solved. To address the challenges of targeting mtDNA specially, the use of nano-carrier systems to deliver agents specifically targeting mtDNA has gained widespread adoption in recent years (Tsuji et al., 2022). Delocalized lipophilic cations are commonly used as mitochondrion-targeted agents to construct molecule-based nano-carriers that selectively accumulate in mitochondria with a high membrane potential (Δ Ψ m) and deliver the bioactive cargo into mitochondria (Hall et al., 2021; Jiang, Zhou, et al., 2021). D112 is a cyanine molecule that was identified by the Eastman Kodak Company as a potential anti-cancer drug with high cytotoxic activity and selectivity (Yang et al., 2015). As a delocalized lipophilic cation (DLC), D112 shows promise as it can enter mitochondria preferentially, damage mtDNA, inhibit complex I and induce ROS (Yang et al., 2017). Besides, triphenylphosphonium (TPP) is the most frequently used carrier as a DLC due to its non-toxicity, easy synthesis and purification, and high stability in a biological system (Muhammad et al., 2021; Valdez-Alegría et al., 2020). It exhibits great mitochondrial aggregation by taking advantage of hydrophobicity and positive charge, with widely explored for guiding mtDNA-targeted therapy (Wang, Xiang, et al., 2020). TPP that is loaded with traditional DNA targeting chemotherapy drugs can achieve satisfactory therapeutic effects (Koshikawa et al., 2021, 2021b; Pokrzywinski et al., 2016). To overcome CDDP resistance in triple negative breast cancer cells, a mitochondrial targeting prodrug c,c,t -[Pt-(NH3)2Cl2 (TPP) (Dox)] (PPD), which conjugated PtIV to doxorubicin (Dox) and TPP cation, was synthesized by Muhammad et al. (Muhammad et al., 2021) The novel compound exhibited a superior mitochondrial localization compared to the one that is devoid of TPP and triggered mtDNA impairment, bioenergetics disruption, ROS production and necrosis induction. Moreover, nitrogen mustard chlorambucil (a DNA alkylating drug), cisplatin and other agents were also used to synthesize TPP-conjugated drugs that target mitochondria and mtDNA (Chen et al., 2020). A TPP-loaded organoarsenic prodrug system, which incorporated cisplatin and Dox (targets DNA) with t-As (interrupts the functioning of the thioredoxin system in mitochondria) via cleavable linkers, could induce mitochondria-mediated apoptosis in HepG2 (Luo et al., 2021). Pyrrole-imidazole polyamides, which are cell-permeable minor groove binders that show sequence-specific binding to double-stranded DNA and

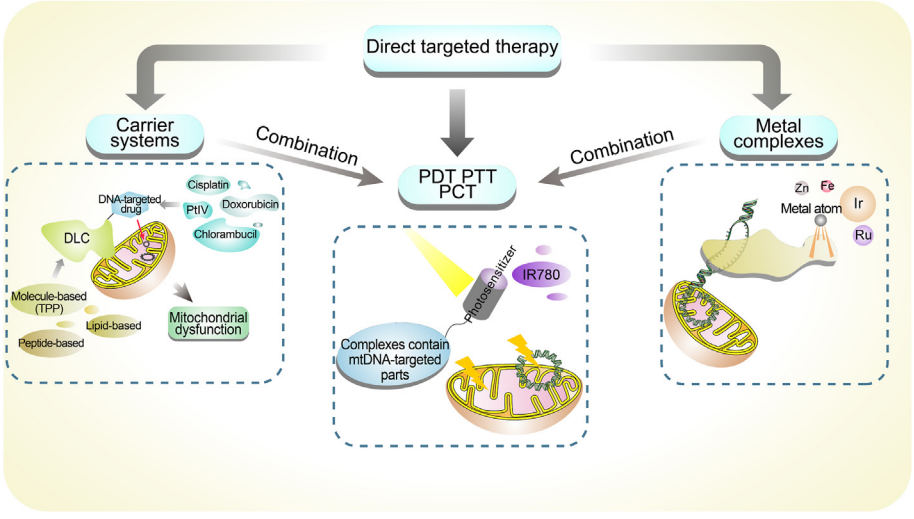

Fig. 5. The main aspects of direct targeted therapy. We summarize the relevant research into three aspects: carrier systems, metal complexes and application of phototherapy. And among the studies we included, carrier systems, metal complexes, and phototherapy frequently overlapped in their research techniques, drug construction, therapeutic effects and so on. We suspect that future research may need to enhance the integration of the three methods to develop more effective strategies. DLC, delocalized lipophilic cation; PCT, photochemotherapy; PDT, photodynamic therapy; PTT, photothermal therapy; TPP, triphenylphosphonium.

inhibit the transcription, always conjugate with TPP to target mtDNA and work well in a variety of cancers (Koshikawa, Yasui, et al., 2021). Chen et al. (Chen et al., 2018) designed a peptide nucleic acids which can bind efficiently to DNA and RNA targets to form Watson-Crick type double helix and result in interruption of transcription or RNA degradation. And the loading of TPP improves its mtDNA targeting capability, which is crucial for the mtDNA-targeted therapy.

At the same time, the novel polymer-based, lipid-based and peptide-based carrier systems for mitochondrial targeting have been developed. Faria et al. (Faria et al., 2022) designed a polyethylenimine–dequalinium polymer to load and complex a mitochondrial-gene-based plasmid, affecting gene delivery and protein expression in this organelle, and they also developed a cell-penetrating peptides based system added mitochondrial targeting sequences to achieve the efficacy of mitochondrial gene therapy. A cholesterol-based chimeric nanoparticle consisting of cisplatin, camptothecin and tigecycline was created with abilities of impairing mt-DNA, mitochondrial topoisomerase I and mitochondrial ribosomes in lung, cervical and breast cancer cells (Bajpai et al., 2022a). These kinds of delivery systems that target mitochondria have been widely developed and have great prospects in the treatment of cancers targeting mtDNA.

4.2.2. The construction of metal complexes

Complexes comprising metallic elements including Ir, Zn, Fe and Ru also play important roles in building nano-systems that target mtDNA (Nair et al., 2020; Wang et al., 2022b). Some of the metallic elements involve in chemical responses in mitochondria, while others bind DNA specifically and stabilize the complexes. Jiang et al. (Jiang, Guo, et al., 2021) have constructed a nanocatalytic medicine that induce oxidative damage in the mtDNA of tumor cells. The medicine is a Fe2+-Ru2+-loaded mesoporous silica nanoparticle named as MSN-Ru2+/Fe2+, where Ru2+ complex can bind with mtDNA and Fe2+-Fenton reagents can accelerate the intramitochondrial ROS generation by the Fenton reaction. Ir may be the most common applicational one among various metal elements because of its notable ROS generation efficiency, lifetime sensitivity to microviscosity, straightforward ligand tuning, cell permeability and photostability (Lee, Nam, et al., 2021; Qin et al., 2020). A family of Ir(III) complexes of general formula [Ir(CˆN)2(NˆN′)]Cl (NˆN′ = thiabendazole-based ligands; CˆN = ppy (2-phenylpyridinate) (Series A), or dfppy (2-(2,4-difluorophenyl)pyridinate) (Series B)) has been explored and two of them have shown anticancer activity under irradiation by inducing apoptosis through a multimodal mechanism of action that involves photocatalytic oxidation of mtDNA and mitochondrial membrane depolarization (Echevarría et al., 2022). Li et al. (Li, Wu, et al., 2020) developed metallohelices that were fabricated using the dynamic imine-coupling chemistry between aldehyde end-capped *fac*-Ir (ppy)3 handles and linear alkanediamine spacers, showing stronger DNA-binding affinities in a minor groove manner and better ability of inducing cell apoptosis under white light irradiation. These complexes also show their potential as PDT agents for cancer treatment. Additionally, cyclometalated Ir(III) complexes Ir3 and Ir4 with dipyrido [3,2- a:2′,3′- c]phenazine (dppz) ligands have shown their affinity to mtDNA and effects to damage mtDNA (Cao et al., 2019).

4.2.3. Combined with phototherapy

Phototherapy is an emerging strategy for cancer treatment that uses light to activate drugs or materials that can kill cancer cells by targeting mtDNA, which is essential for their survival and proliferation. PDT, photothermal therapy (PTT) and photochemotherapy (PCT) are three types of phototherapeutic methods that have shown promising results in recent studies. Metal complexes and DLC-based systems often intersected with the application of Phototherapy due to their unique optical and chemical properties (Hu et al., 2017; Li, Wu, et al., 2020; Wang et al., 2018). Using photosensitizers that produce ROS when exposed to light, PDT is a non-invasive modality that causes oxidative damage to the cancer cells (Shi & Sadler, 2020). And PDT offers several benefits, such as light-controlled treatment area, minimal invasiveness, low side effects and negligible drug resistance (Liu, Wang, et al., 2022; Shen et al., 2022). The mitochondria-targeted NIR photosensitizer, IR780, are widely used in the phototherapy. A multifunctional nanomedicine IR780@Pt NPs that was constructed by Zhang et al. through a supramolecular self-assembly strategy (Zhang et al., 2021). It can sufficiently induce mitochondrial dysfunction under NIR light irradiation through both photothermal and photodynamic effects, inhibiting the nucleotide excision repair pathway for the repair of DNA-Pt caused by Pt. Besides, the possibility of PDT as an adjunct to DLC-based methods has been demonstrated by Yang et al. (Yang et al., 2017) PTT that uses NIR absorbents for facilitating efficient heat production and induces cancer cell death with NIR irradiation (Nomura et al., 2020). Wang et al. (Wang et al., 2018) constructed a complex nanoparticle which contained a core-shell-SS-shell architecture with a core of Fe–O colloidal nanocrystal clusters, an inner shell of polydopamine (PDA) functionalized with TPP and an outer shell of methoxy poly (ethylene glycol) linked to the PDA by disulfide bonds. This nanoparticle can generate photothermal effect from the PDA under NIR light, ending in dramatic decreasing in MMP and Dox-mediated damage of mtDNA. And Yang et al. (Yang et al., 2020) precisely assembled IR780 with a biotin-labeled Pt (IV) prodrug derivative at a 1:1 molecular ratio, achieving mitochondria-targeted chemo-photothermal synergistic therapy under NIR irradiation in A549R tumors and almost completely eradicating the tumors. In addition, the integration of PDT and PTT has been recognized as a potential approach for achieving complete tumor ablation therapy, showing excellent tumor treatment effect (Chen et al., 2021; Li et al., 2019). PCT is a type of therapy that uses light and a photosensitizer to produce cytotoxic oxygen species within the tumors (Bossu et al., 1999). A PCT strategy of cancer therapy using NIR-assisted tumor-specific Fenton reactions has been proposed. In this study, the PCT agent, which consisted of three key components including upconversion nanoparticles core based on lanthanide-doped nanocrystals (convert NIR light to UV or visible photons to catalyze photo-Fenton reaction), mesoporous silica shell coat (load and deliver Fe2+) and Ru2+ complex on the surface of mesoporous silica shell (bind mtDNA), showed much enhanced and tumor-specific therapeutic efficacy in HegG2 cells (Hu et al., 2017). As we can see, phototherapy techniques have various forms and applications that can produce different therapeutic effects, and are highly effective in conjunction with mtDNA-targeted chemotherapy in cancer treatment.

5. Discussion

mtDNA has emerged as a target of cancer therapy. The alteration of mtDNA is frequently found in a variety of cancers and acts as inducement, biomarker or subsequent phenomenon in the process of tumor development, which underscores its irreplaceable position in cancer treatment. Further studying the functions of genes and encoded proteins in mtDNA is the key to elucidating mtDNA-related diseases. Mok et al. (Mok et al., 2020) have developed a new tool to manipulate mtDNA using RNA-free DddA (a double-stranded DNA deaminase) derived cytidine base editors (DdCBEs) to introduce targeted base conversions, C•G to T•A. This tool employed CRISPR-free mitochondrial base editing to precisely manipulate mtDNA and mimic disease-related mtDNA mutations. It has also been validated in five mtDNA genes (MT-ND1, MT-ND2, MT-ND4, MT-ND5 and MT-ATP8), which were stable without mtDNA deletions or copy number loss. In addition, by combining DdCBE with Cre/loxP system, Tan et al. (Tan et al., 2023) established a cell and rat resource library of mtDNA-encoded mitochondrial proteins (mt-Proteins) depletion, which can be used to study the biological functions and disease mechanisms of mt-Proteins. It provided a powerful and versatile platform for advancing mitochondrial research and therapy.

mtDNA plays a crucial role as a messenger in biological reactions. Understanding the response after mtDNA damage has important implications for drug efficacy appraisal, adverse reaction evaluation, and patient prognosis assessment. Rho0 cancer cells, which lacking mtDNA,

have been frequently used in mtDNA-related studies (Crider et al., 2012; Guerrero-Castillo et al., 2021; Kuwahara et al., 2016). Rho0 cells can be obtained by treating with low concentration of ethidium bromide, which doesn't affect nDNA synthesis (Kuwahara et al., 2016). Related researches involve cancer treatment mechanisms, cancer drug resistance, factors affecting tumor progression, TME, etc., with a wide range, showing its important role in mitochondrial researches (Gong et al., 2018; Takenaga et al., 2021; Yi et al., 2015). More information about the rho0-related studies in recent years were summarized in Table S1. Accurately describing the mechanisms of mtDNA in intracellular environment, cell communication and tumor progression is decisive in the development of mtDNA-targeted therapy, which require further investigation in future studies.

The stability and integrity of mtDNA are important for cancer targeted therapy. One of the main mechanisms of achieving favorable therapeutic outcomes by mtDNA targeting is to disrupt the stability and integrity of mtDNA. Various targeting strategies can be employed to achieve this goal, depending on the initiating or rescuing factors involved. For the initiating factors, the integrity of mtDNA can be compromised by enhancing mitochondrial oxidative stress, or by utilizing mitochondrial-targeted drug delivery systems that enhance the accumulation of DNA-damaging agents in mitochondria. For instance, nanocarriers have emerged as a promising tool for mtDNA targeting, as they offer an optimal platform for drug delivery and facilitate mitochondrial accumulation. They can physically encapsulate insoluble drugs to achieve controlled drug release, ultimately improving drug metabolism and reducing systemic drug toxicity (Luo et al., 2022). Moreover, other molecule-based, polymer-based, lipid-based and peptide-based nano-carrier systems have also been applied in this field, contributing to the advancement of cancer therapy. The development of effective mtDNA targeting delivery strategies remains a research hotspot for mtDNA-targeted cancer therapy. For the rescuing factors, cells have evolved several mtDNA repair pathways to prevent or repair mtDNA damage, including direct reversal, base excision repair, mismatch repair, translesion synthesis, and DSB repair (Li, Guan, et al., 2020). These pathways can restore the integrity and stability of mtDNA by removing the lesions or rejoining the broken strands. Inhibiting mtDNA repair pathways can increase the sensitivity of cancer cells to toxic agents, leading to an accumulation of more mtDNA mutations and a loss of mitochondrial functions (Xie et al., 2015). This mechanism has been explored by some existing studies we discussed above.

Depending on the treatment approaches, we can categorize the anticancer therapeutic strategies targeting mtDNA into “elimination strategies” (which disrupt the stability and integrity of mtDNA) and “rescue strategies” (which restore mitochondrial function through gene editing, such as providing normal mtDNA or repairing mutated mtDNA). However, most of the current mtDNA-targeted anti-cancer research focused on the “elimination strategies”, while the development of the “rescue strategies” has not been extensively explored. Gene therapy requires a nucleic acid targeting delivery system, which has been proven effective in treating some diseases (Yu et al., 2013). Yoshinaga and Numata conducted a comprehensive review of the rapidly evolving mitochondrial-targeted nucleic acid delivery vectors in recent years, categorizing them into four groups: mitochondrial targeting signal (MTS) peptides, systems based on lipophilic cations, systems based on mitochondrial fusion lipids, and physical delivery methods (Yoshinaga & Numata, 2022). Among them, the system based on MTS peptides is one of the most powerful tools. MTS peptide is a short amino acid sequence that is usually located at the N-terminus of the protein and consists of alternating hydrophobic and positively charged amino acids (Bykov et al., 2022). It has been widely employed by researchers for plasmid DNA delivery and viral gene delivery targeting mitochondria (Yoshinaga & Numata, 2022). In mitochondrial gene therapy of cancer cells, Faria et al. (Faria et al., 2022) constructed MTS-CPP/pDNA complexes and achieved promising outcomes, highlighting the potential of MTS peptide system in targeted treatment of cancer through gene therapy. In addition to the MTS peptide system, Yamada et al. (Yamada et al., 2012) designed a liposome-based carrier DF-MITO-Porter, which can deliver macromolecules more efficiently to mitochondria in cancer cells. Nevertheless, the progress towards developing mtDNA “rescue strategies” that have practical therapeutic value and clinical significance remains relatively sluggish. In the future, multi-functional carriers should be developed to enhance their capabilities in terms of mitochondrial localization, mitochondrial penetration, gene-specific editing and damage repair. And more nucleic acid delivery tools should be utilized in practical mitochondrial gene therapy experiments.

Therapeutic strategies that target mtDNA have considerable significance for anti-cancer drug research and clinical treatment. Targeting mtDNA can help overcome tumor drug resistance and complete elimination of tumors. This is because the acquisition of some biological characteristics of tumors are related to mtDNA. For example, mutations in a gene called MT-ND4 can make tumor cells resistant to cisplatin, a drug that damages DNA by forming bonds with it (Abedi et al., 2020; Alam et al., 2017; van Gisbergen et al., 2015). Cisplatin bonds are harder to removal from mtDNA than from nDNA, because mtDNA lacking a repair system called nucleotide excision repair. Therefore, it would be effective to direct cisplatin or similar compounds (Pt complexes) to the mitochondria using a carrier molecule such as TPP (Muhammad et al., 2021). At the same time, IR780 overcomes cisplatin resistance to improve the therapeutic efficacy via increasing the Pt accumulation in mitochondria and combining with phototherapy as a mito chondria-targeting phototherapy agent (Ma et al., 2019; Yang et al., 2020). Another considerable significance of targeting mtDNA lies in the close involvement of mtDNA in the disease process in clinical diseases. The presence of mtDNA has been observed to have a significant impact on a variety of clinical diseases. Mutations in any of the 37 genes encoded by mtDNA can cause mitochondrial dysfunction and disease, including cancer (Möllers et al., 2005). And the balance between mutant and WT mtDNA determines the process of mitochondrial diseases with clinical phenotypes (Lee, Lee, et al., 2021). Therefore, targeting mtDNA can be a promising candidate in drug-resistant cancer treatment and provide a wider range of strategies for clinical treatment.

However, the development and application of mtDNA-targeting drugs for anti-cancer therapy face many challenges. (i) The association between mtDNA mutations and clinical characteristics of tumors requires further elucidation. It is essential to identify the causal relationship between mtDNA alterations (including mtDNA damage, mtDNA mutation and mtDNA heteroplasmy levels) and tumor progression (including tumor occurrence, malignant transformation, tumor metastasis, tumor resistance and clinical heterogeneity of cancer patients), rather than solely simple correlations. This is of utmost importance in utilizing mtDNA as a biomarker for clinical evaluation of tumors and as a preferred target for tumor therapy. (ii) Most of the studies are still limited to validation in animal models. Only a few mtDNA-targeting drugs are in clinical trials for anti-cancer therapy, although there are already many drugs for mitochondrial therapy (Singh et al., 2021). A clinical trial of mitochondria-targeted tamoxifen (MitoTam) has been reported. MitoTam is a TPP-conjugated drug that can localize to mitochondria and induce ROS accumulation, mtDNA damage and cell injury in cancer treatment. In a clinical trial sponsored by the University of Pisa, Italy, MitoTam has achieved satisfactory results in a phase I trial and is currently being extended to a phase II trial (Dong et al., 2020). However, most of the existing mtDNA-targeting drugs were originally designed for other purposes, such as neurodegenerative diseases, viral infections, or genetic disorders (Rowe et al., 2001; Xu et al., 2022). Phototherapy may be able to achieve a faster translation to clinical application, as there are many photosensitizers for PDT that have entered clinical use or clinical trials, which have been summarized by Shi et al. (Shi & Sadler, 2020) How to promote the validation of mtDNA-targeting anticancer drugs in clinical trials is the key to mtDNA-targeted therapy. (iii) Most therapeutic strategies that activate immunity by targeting mtDNA rely on the cGAS-STING pathway to sense dsDNA. The inhibition of cGAS activity

would severely influence the efficacy of these strategies. Several factors can influence the dsDNA recognition by cGAS, including its transcriptional and post-transcriptional regulation, post-translational modifications, genetic mutations of cGAS-binding proteins and drug effects in patients with autoimmune diseases (Skopelja-Gardner et al., 2022; Yu & Liu, 2021). The combination of multiple therapies may overcome this challenge. (iv) As a promising option for combination therapy, phototherapy faces many challenges that need to be addressed. The widespread application of phototherapy requires overcoming some difficulties, such as the low ability of light to reach deep tumors, the abnormal antioxidant mechanisms that may confer resistance of tumor cells to light damage and the safety of the drugs that enable phototherapy (Shi & Sadler, 2020).

6. Conclusion

mtDNA is a key factor in various clinical pathologies, especially cancers. As a trigger, there is a causal relationship between mtDNA alterations and tumor development. Targeting mtDNA has become a promising strategy for cancer therapy. The mechanisms of the responses after mtDNA damage are crucial for developing mtDNA-targeted drugs, predicting drug efficacy, and analyzing potential drug resistance. In recent years, mtDNA-targeted therapy has rapidly developed, including direct targeting of mtDNA and indirect targeting of mtDNA through intermediate mediators. These strategies have their own characteristics in tumor treatment. Despite the challenges and limitations of mtDNA-targeted research, such as the scarcity of clinical studies and the possible resistance, we have revealed the huge potential of mtDNA as a therapeutic target for cancer treatment. We hoped this study will offer insights for future research and development of novel mtDNA-targeting drugs and strategies.

Author contributions

Yumeng Lin: Conceptualization, Investigation, Methodology, Project administration and Roles/Writing - original draft; Bowen Yang: Conceptualization and Writing - review & editing; Yibo Huang: Conceptualization and Writing - review & editing; You Zhang: Conceptualization and Writing - review & editing; Yu Jiang: Investigation and Writing - review & editing; Longyun Ma: Writing - review & editing; Ying-Qiang Shen: Conceptualization, Funding acquisition, Project administration and Writing - review & editing.

Conflict of interest

The authors declare no competing interests.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

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