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Recent advances and applications of mitochondria in tumors and inflammation

Hui Liu[1*†], Mengmeng Pan[1†], Yumeng Li[1], Zhen Huang[1], Hanying Li[1], Chenguang Zhang[1], Chunlei Guo[1] and Hui Wang[1*]

Abstract
Mitochondria are bilayer membrane organelles with basic metabolic activity. They are considered hubs for biosynthesis, bioenergy, and signaling functions, coordinating major biological pathways. Mitochondria are coupled to the oxidation of fatty acids and pyruvate through electron transport chains and have historically been considered the primary source of cellular energy. Recent studies have depicted that mitochondria are centers that promote inflammatory responses and play a crucial role in combating pathogenic infections. Moreover, mitochondria provide the basis for tumor synthesis metabolism, control redox and calcium homeostasis, participate in transcriptional regulation, and control cell death. Mitochondria are involved in all steps of tumorigenesis. This review discusses the relationship between mitochondria (including mitochondrial metabolism and mitophagy) and tumors, and the relationship between mtDNA and inflammation, as well as its clinical application in inflammatory diseases. More importantly, the application and targeted treatment strategies provide more opportunities for the development of new anticancer drugs.

Keywords Mitochondria, Metabolism, Inflammation, Tumor

Introduction

Mitochondria are organelles in eukaryotes responsible for cellular respiration and have a bilayer membrane. They contain an outer membrane, a highly folded inner membrane, a stromal space surrounded by an inner membrane, and an intermembrane space between the inner and outer membranes. There are usually hundreds or thousands of mitochondria in a cell. Mitochondria are crucial for respiration in all tissues [1]. They arise from innate symbiosis, and a unique feature of mitochondria is circular, double-stranded, supercoiled genetic material called mitochondrial DNA (mtDNA). mtDNA encodes 13 protein subunits of the ETC complex and a set of transfer and ribosomal RNAs; thus, mitochondrial function is highly dependent on mtDNA function [2]. Human mtDNA is a 16.6 kb circular double-stranded DNA molecule that retains an independent genome that encodes 37 genes [3]. Appropriate inflammatory signals mediated by mtDNA are associated with various human diseases, particularly infectious/inflammatory diseases and cancer. The transfer of mtDNA between the tumor and surrounding somatic cells can be achieved through the horizontal transfer of mtDNA and is related to the occurrence and progression of tumors [4, 5].

Mitochondria generate cellular energy through glycolysis, tricarboxylic acid (TCA) cycle, and oxidative

†Hui Liu and Mengmeng Pan contributed equally to this work.

*Correspondence:
Hui Liu
hsdliuhui@163.com
Hui Wang
immuneweb@163.com
[1]Henan Key Laboratory of Immunology and Targeted Drug, Henan Collaborative Innovation Center of Molecular Diagnosis and Laboratory Medicine, School of Medical Technology, Xinxiang Medical University, Xinxiang, China

phosphorylation (OXPHOS) [6, 7]. Mitochondria are also involved in bioenergy metabolism and cellular balance, including ATP production through electron transfer and oxidative phosphorylation, metabolite oxidation through the TCA cycle, β-oxidized fatty acid decomposition, reactive oxygen species (ROS) generation, and initiation and execution of cell apoptosis. Mitochondria are the main energy suppliers and power sources of cells and are key hubs for regulating various key metabolites, playing a crucial role in epigenetic regulation [8–11]. Moreover, mitochondria regulate calcium (Ca^{2+}) homeostasis and autophagy, which execute cell death. Mitochondrial dynamics and energy play a central role in proinflammatory signaling, and when mtDNA leaks from damaged mitochondria into the cytoplasm, it becomes an essential driving factor for inflammation. Mitochondria are vital organelles that control innate immunity and inflammatory responses [12].

In the field of tumor, mitochondria not only provide energy support for the rapid proliferation of tumor cells, but also affect the survival and death of tumor cells by regulating apoptosis, autophagy and other processes. In addition, the changes of mitochondrial metabolites have also been confirmed to be closely related to the remodeling of tumor microenvironment and tumor progression. Similarly, in the field of inflammation, mitochondria also show its unique role. Mitochondria regulate the initiation and resolution of inflammatory response by producing reactive oxygen species ROS and participating in the activation of inflammasome. This article will focus on the role of mitochondria in cancer and inflammatory diseases, exploring existing knowledge in this field to avoid resistance to treatment and control the development of tumors and inflammation.

Mitochondrial functional diversity: disease mechanisms and new strategies for targeted therapy

As an energy factory of eukaryotic cells, mitochondria 'core function is to generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), and participate in metabolic regulation, calcium ion signaling, reactive oxygen species (ROS) balance and programmed cell death regulation. In recent years, studies have found that mitochondria maintain their functional integrity through dynamic network remodeling (fusion and division), while the dysregulation of mitochondrial quality control mechanisms (such as mitophagy and unfolded protein response) is closely related to aging, neurodegenerative diseases (such as Alzheimer's disease and Parkinson's disease) and metabolic syndrome [13]. For example, mutation or deletion of mtDNA can lead to ATP synthesis disorder, which in turn triggers apoptosis or necroptosis, a process that is particularly prominent in myocardial ischemia-reperfusion injury [14]. In addition, mitochondria participate in tumor microenvironment regulation through metabolic reprogramming, and the "Warburg" of cancer cells relies on mitochondrial cytoplasmic metabolic coupling, providing a new strategy for targeted cancer therapy [15]. Studies have illustrated that many cancer cells can oxidize glucose via OXPHOS in fully functioning mitochondria. Disrupting glucose-6-phosphate isomerase can completely block the "Warburg effect" and activate the oxidative phosphorylation (OXPHOS) pathway, which has minimal impact on tumor growth under hypoxic conditions [16]. Tumor cells rely on mitochondria for energy to sustain their proliferation and utilize them to manage the production and release of ROS, tumor proteins, and paracrine metabolites. Moreover, they regulate Ca^{2+} homeostasis and autophagy and trigger cell death. In addition, cancer cells can influence their metabolism through endogenous and extracellular plasma mechanisms, leading to TCA cycle enzyme dysfunction, electron respiratory chain leakage, and subsequent oxidative stress, along with abnormal carcinogenic and anticancer signaling that can induce mitochondrial dysfunction [17–21].

In conclusion, the diversity of mitochondrial functions and its pivotal role in diseases have opened up a new direction for the development of precision therapies targeting mitochondria (such as Mito antioxidants and mtDNA editing technology).

Mitochondrial dysfunction and its role in inflammation and tumor development

Chronic inflammation is considered an important factor in the occurrence of tumors. Cytokines, free radicals, and inflammation related enzymes in the inflammatory environment can promote gene mutations and the proliferation, survival, and invasion of tumor cells [22]. There have also been studies showing that as humans age and the number of cell divisions increases, when telomeres become shorter to a certain extent, the mitochondrial TERRA-ZBP1(TERRA is a non coding RNA found on human telomeres, while ZBP1 is a zinc finger protein that can bind DNA and RNA.) complex activates innate immune responses, thereby promoting tumor suppression mechanisms in the body and effectively killing cancer cells [30]. Next, we will elaborate on the important role of mitochondria in inflammation and tumors [23]. Next, we will introduce in detail the important roles that mitochondria play in inflammation and tumors.

Mitochondria and tumors

Mitochondrial dysfunction: drivers and targets of cancer

Cancer cells are highly proliferative and invasive, making their eradication challenging. Mitochondria influence all processes related to tumor development, including

mitochondrial biogenesis and turnover, fission and fusion dynamics, susceptibility to cell death, regulation of oxidative stress, metabolism, signal transduction, and the process from malignant tumor transformation to metastasis. Mitochondrial dysfunction can lead to tumor cell death [20]. Mitochondrial dysfunction caused by mtDNA mutations, abnormal TCA cycle enzyme function, electron respiratory chain leakage and subsequent oxidative stress, and abnormal carcinogenic and tumor suppressive signals can alter cellular metabolic pathways, disrupt redox balance, and cause tumor cells to resist apoptosis and treatment, thereby promoting the development of various human cancers [17, 24].

Mitochondrial metabolic plasticity: new mechanisms of tumor drug resistance and targeted intervention breakthrough

Mitochondria play a vital role in tumor growth and development, as they control abnormal energy metabolism in malignant cells and regulate cell death via apoptosis and necrosis [25]. The plasticity of mitochondrial metabolism is now recognized as a hallmark of cancer, as it is crucial for tumor resistance. The acquisition of cancer resistance is associated with TNT-mediated mitochondrial metastasis. Mitochondria with diverse functions can be exchanged between tumor and normal cells within the microenvironment via TNTs(Tunneling Nanotubes) [18, 26]. Cancer cells exhibit numerous metabolic abnormalities related to mitochondria and other subcellular organelles. These distortions facilitate tumor growth and survival while displaying unique traits that increase susceptibility to certain anticancer drugs. Recent studies found that lithium carbonate revitalizes tumor-reactive $CD8^{+}$T cells by shunting lactic acid into mitochondria, thus inhibiting tumor [27]. Targeting CH25H(Cholesterol 25-Hydroxylase) can eliminate the immunosuppressive function of macrophages, enhance the number and activation of infiltrating T cells, and synergistically improve antitumor efficacy with anti-pd-1 [28].

The ultimate goals of conventional chemotherapy, targeted anticancer agents, radiotherapy, and immunotherapy are to induce the death or permanent inactivation of malignant cells (either through cell aging or terminal differentiation), either directly or as a result of immune mechanisms [29]. However, the most notable aspects are that [1] regulating mitochondrial regulatory cell death (RCD) involves powerful metabolic components rather than purely structural ones; [2] several metabolic aspects of mitochondrial biology can also influence therapeutic responses [30]; [3] metabolic enzymes within mitochondria (such as mutated IDH2) are utilized to develop anticancer drugs to promote terminal cell differentiation [31]. Consequently, various treatments have established compensatory metabolic networks to support cancer cell survival. This metabolic shift may offer a target for developing new effective drugs against cancer cells. Besides controlling various forms of RCD, mitochondria also influence the cancer cell response to treatment through metabolic reprogramming. Tumor microenvironmental conditions, including hypoxia, alterations in nutrient supply, and cancer cell metabolic changes, increase the biogenesis requirements of tumor cells, increase energy needs, and promote adaptation to the tumor microenvironment [32]. The tumor microenvironment can profoundly affect mitochondrial activity, provide adaptive metabolic responses, enable tumor cell survival, and promote metastasis [31, 33]. However, the mechanisms underlying the metabolic flexibility of various cells in the TME remain unclear.

Tumor duality of mitochondrial autophagy

Autophagy serves as the primary degradation system within cells, enabling the transport of damaged cytoplasmic and mitochondrial organelles to the lysosomes for degradation [34, 35]. Recent studies have highlighted the intricate interplay between autophagy and apoptosis, particularly involving caspase-8 and caspase-3. Caspase-8, a key initiator of extrinsic apoptosis, can directly cleave autophagy-related (ATG) proteins such as Beclin-1, thereby modulating autophagic flux. This cleavage disrupts the Beclin-1/Bcl-2 complex, promoting autophagy initiation [36]. Caspase-3, an executioner caspase, further amplifies mitochondrial dysfunction by cleaving pro-survival proteins and enhancing ROS production, which synergizes with autophagy to drive tumor cell death. Notably, cancer cells with defective apoptosis pathways (e.g., p53 mutations) are more susceptible to autophagy-dependent cell death, as observed in SKOV-3 ovarian cancer cells compared to A2780 cells, where differential Peff compliance intervals reflect altered mitochondrial membrane permeability and metabolic plasticity [37–39].

The role of selective autophagy adaptors, such as p62/SQSTM1, extends beyond cargo recognition. p62 interacts with Keap1 to activate Nrf2 (Nfe2l2), which transcriptionally upregulates antioxidant genes (e.g.,NAD(P)H quinone dehydrogenase 1, NQO1) and mixed-function oxygenases, modulating epithelial-mesenchymal transition (EMT) and metabolic reprogramming. During EMT, autophagy markers like LC3-II and Beclin-1 are upregulated, facilitating mitochondrial turnover and mitigating oxidative stress. Conversely, mesenchymal-epithelial transition (MET) is associated with reduced autophagic activity, highlighting context-dependent roles of autophagy in metastasis [40].

Beclin 1 is a key protein involved in autophagy initiation, and its expression level is positively correlated with autophagy activity (such as LC3II levels) [41]. At present, there are two main molecular regulatory mechanisms of

autophagy in mammals. The first is Parkin dependent, involving PINK1/Parkin mediated autophagy, and the second is Parkin independent, involving mitochondrial phagocytosis of BNIP3/Nix, FUNDC1, etc. through the following pathways. Other non classical pathways mediate autophagy mechanismsGradually discovered, such as BCL2L13, PHB2, FKBP8, and DRP1 mediated mitosis [42]. The GTPase Drp1 is frequently upregulated in many cancers, and overexpression of Drp1 can activate the cGAS STING pathway and promote autophagy, LC3B is a widely used autophagy marker that regulates mitochondrial quantity and quality by eliminating mitochondria to basal levels to meet cellular energy requirements and prevent excessive ROS production [43]. Studies have found that PINK1 mediated mitophagy processes transport PD-L1 to mitochondria for degradation. Paclitaxel can inhibit PINK1 dependent mitosis, promote the expression of atad3a, and then affect the protein balance of PD-L1. Atad3a is not only a resistance factor of ICI combination therapy, but also a potential target to improve the effect of chemotherapy and immunotherapy by blocking the mitochondrial distribution of PD-L1 [44].

Since mitochondrial autophagy degrades dysfunctional mitochondria and limits ROS production, its function has been linked to tumor suppression. The accumulation of Parkin deficiency-induced mitochondrial dysfunction reduces mitochondrial OXPHOS, increases ROS production, and increases glycolysis, promoting tumor development [45]. Autophagy defects are emerging as a potential cause of various diseases, and interventions targeting autophagy may have therapeutic potential. Several synthetic and natural compounds, including lacinol A, promote mitochondrial autophagy [46]. Mitochondria are critical for iron metabolism and cell death. Studies have confirmed that glioblastoma (GBM) cells have a high iron requirement for tumor growth and invasion [47]. Sirtuin-3 (SIRT3) is a deacetylase in mitochondria that regulates mitochondrial mass and function and inhibits the accumulation of ferrous and ROS in the mitochondria, thereby triggering mitochondrial autophagy. SIRT3 knockdown in GBM cells resulted in the upregulation of the mitochondrial autophagy pathway, sensitizing glioblastoma to iron death [48]. Nrf2 (nuclear factor erythroid 2-related factor 2) is a key regulatory factor in iron metabolism. NRF2 regulates the competitive binding between p62 (SQSTM1) and Keap1, forming a positive feedback loop and promoting the clearance of damaged mitochondria. Small molecule PMI induces autophagy independently of the PINK1/Parkin pathway by disrupting the NRF2 Keap1 interaction [49, 50].(Flowchart 1).

Mitochondria and inflammation

Mitochondria play a crucial role in cellular homeostasis and are easily damaged by inflammatory mediators released during host defense [51, 52]. It is generally accepted that a controlled inflammatory response is beneficial and part of the normal response to tissue damage [52, 53]. However, if dysregulated, it becomes harmful and leads to various diseases in which inflammation and tissue damage/stress maintain each other, causing septic shock [52, 54, 55]. As a result, understanding the balance between beneficial and harmful inflammasome activation is required to develop new therapies for patients with inflammatory diseases [56].

MtDNA immune alert

The release of mtDNA into the cytoplasm and extracellular environment activates a wide array of pattern recognition receptors and innate immune responses, including cGAS-STING, TLR9, and inflammasome formation, thereby eliciting a robust type I interferon response (Fig. 1) [3]. Recent studies have found that in patients with sepsis (sepsis) and systemic lupus erythematosus, the level of circulating free mtDNA is significantly increased and drives the systemic inflammatory response by activating the cGAS sting pathway. A multicenter clinical trial (nct04884531) confirmed that inhibitors targeting the mtDNA CGAs pathway (such as ru.521) can significantly reduce the levels of inflammatory factors (IL-6, tnf- α) and improve organ dysfunction in patients with sepsis [57]. mtDNA stress may facilitate the generation of cyclic GMP-AMP synthase (cGAS) activators triggered by the STING pathway in infectious diseases. mtDNA also contributes to the defense against bacterial invasion of odontoblasts via the cGAS-STING pathway [58]. Releasing mtDNA can activate TLR9, thereby activating the MyD88/NF-κB pathway [59]. Mitochondria are the main sites of ROS or free radical production, which are necessary for resistance to infection. Excessive ROS production may lead to cell and tissue damage and chronic inflammation in many neurodegenerative, cardiovascular, and metabolic diseases (Fig. 2). Antioxidants targeting mitochondria have been developed to reduce mitochondrial ROS production. Targeted transport of antioxidants to mitochondria can be achieved using lipophilic cations as transport carriers. The therapeutic effect of liposome-encapsulated antioxidants on liver injury and MCF-7 tumors is superior to liposomes without encapsulated antioxidants. Moreover, liposome encapsulation of NAC can persistently prevent cytokine-induced expression of pulmonary neutrophil chemoattractants, thereby protecting rats from lipopolysaccharide-induced acute respiratory distress syndrome [60].

Clinical application of mitochondria in inflammatory diseases

Excessive activation of mitochondrial fission protein drp1 is associated with intestinal epithelial barrier damage in

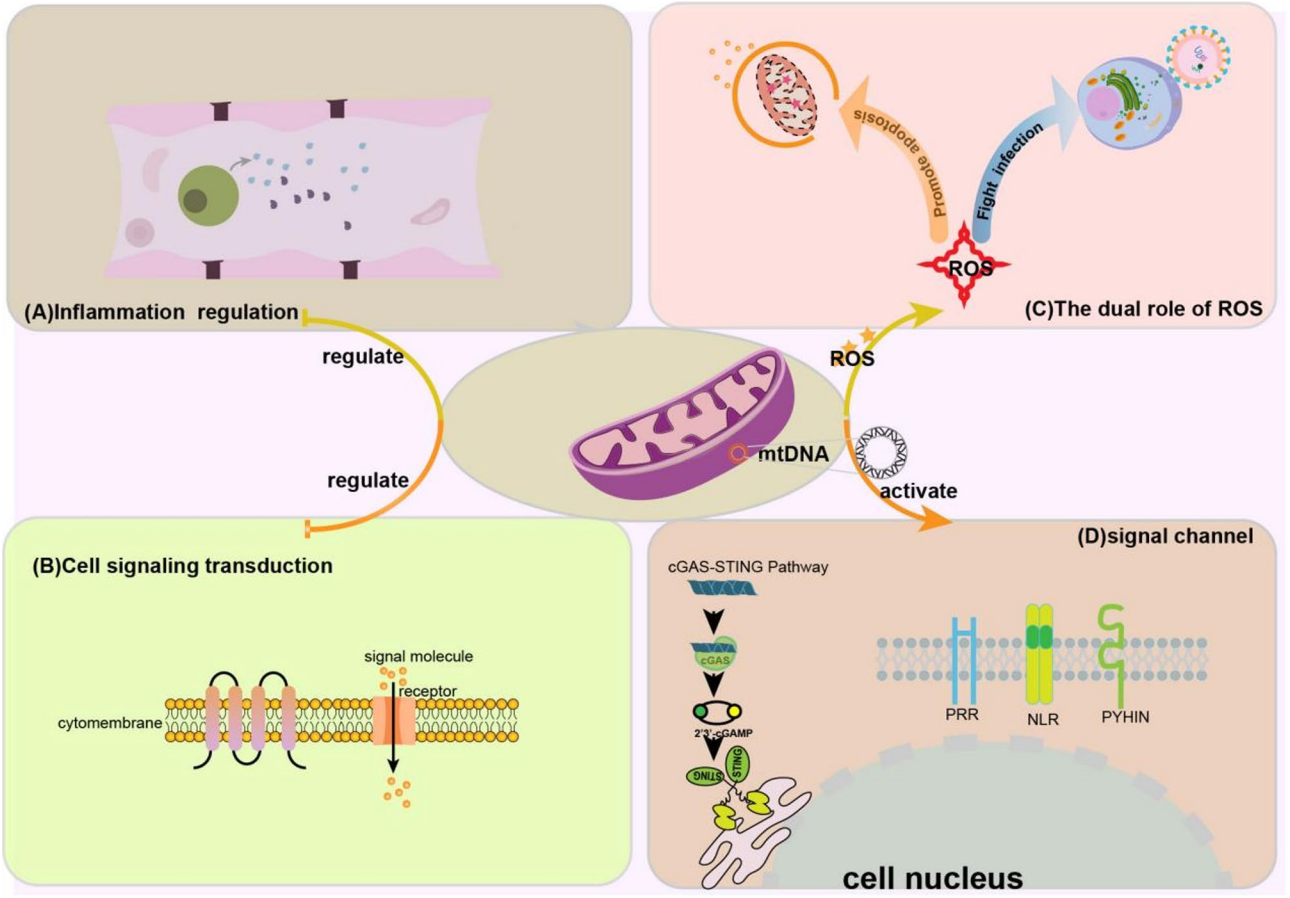

Fig. 1 (**A**) Mitochondria are a key link in inflammation regulation;(**B**) Mitochondria can regulate cellular signal transduction processes；(**C**) Mitochondria are still the main site of ROS (reactive oxygen species) or free radicals generation, and are crucial for resisting infections. However, excessive ROS generation may lead to cell and tissue damage; (**D**) Mitochondrial DNA (mtDNA) is released into the cytoplasm and extracellular environment, activating various pattern recognition receptors and innate immune responses, including the cGAS STING pathway, TLR9 receptors, and inflammasome formation, thereby triggering a strong type I interferon response.

IBD patients. A phase I clinical trial of the drp1 inhibitor mdivi-1 showed that the drug could reduce intestinal mucosal inflammation and repair barrier function by inhibiting excessive mitochondrial fission [61]. Mitochondrial reactive oxygen species (mtROS) play a key role in chronic inflammatory diseases, such as rheumatoid arthritis. The phase II clinical trial (nct05218901) published in 2024 showed that mitoq, a mitochondrial targeted antioxidant, could significantly reduce ROS levels in synovial fluid of patients, reduce the release of proinflammatory factors IL-1 β and IL-17, and delay disease progression [62] The function of mitophagy is impaired in the brain tissue of Alzheimer's disease (AD) patients, which leads to the accumulation of damaged mitochondria and the release of mtROS, activating the NLRP3 inflammasome in microglia. A population-based cohort study (2024) found that drugs that enhance mitophagy (such as urolithin a) can reduce inflammatory markers (such as GFAP) in the CSF of AD patients [63].

These studies highlight the clinical potential of targeting the mitochondrial inflammatory axis in the treatment of infections, autoimmune diseases, neurodegenerative diseases and cancer, and provide a new direction for precision medicine in the future.

Mitochondria and aging

The four core markers of aging - genomic instability, epigenetic changes, chronic inflammation, and dysbiosis - are significantly associated with the four major determinants of cancer - genomic instability, non mutagenic epigenetic reprogramming, inflammatory response, and polymorphic microbiome [64, 65]. These factors together constitute the true meta marker between aging and cancer. This viewpoint reveals the deep connection between aging and cancer, providing a new perspective for understanding these two biological phenomena [66].

Cellular aging can inhibit the initial occurrence of tumors, but the accumulation of senescent cells can also promote chronic inflammation and the development of

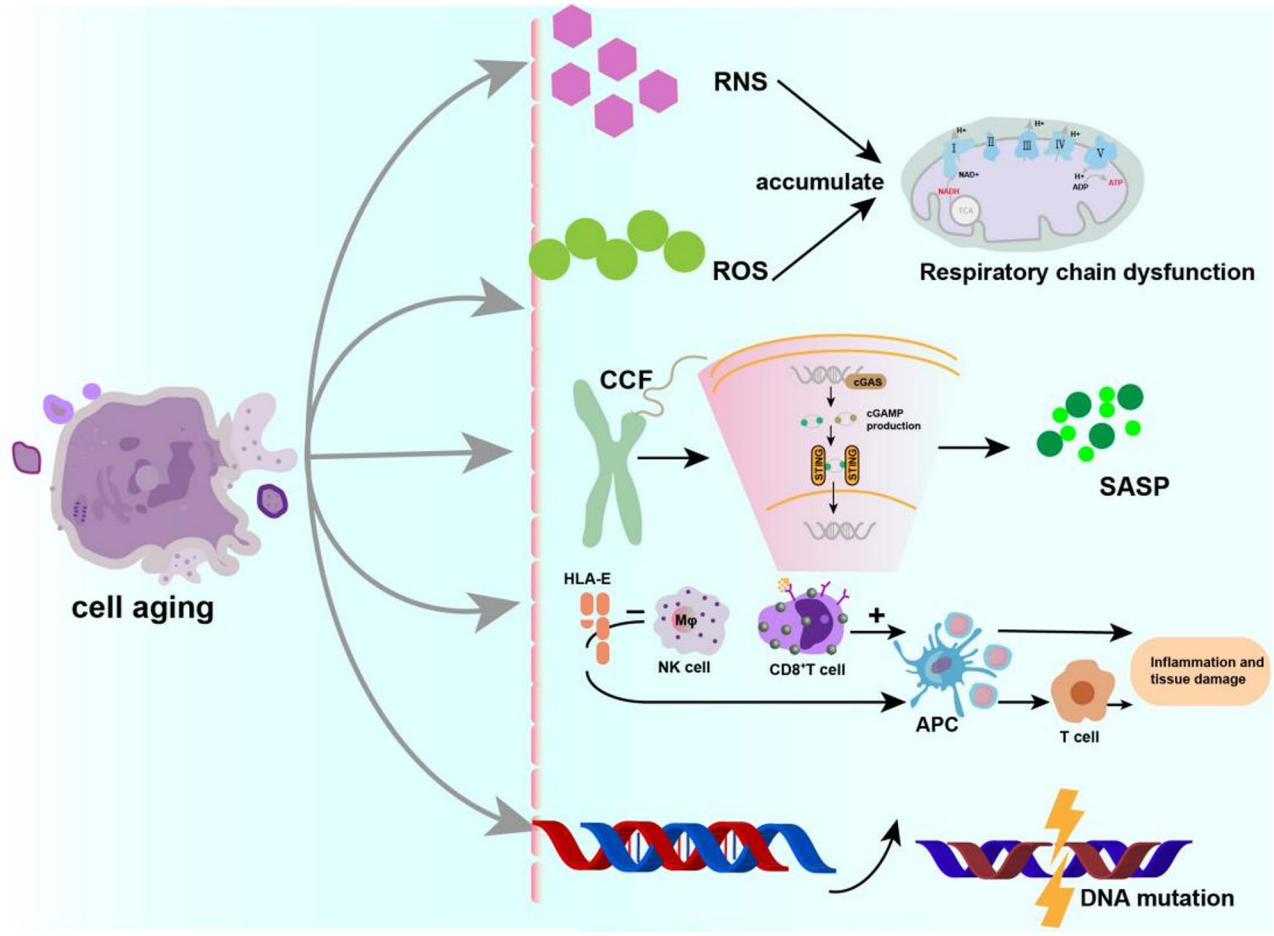

Fig. 2 Acute and chronic inflammatory diseases and aging processes are associated with the accumulation of ROS and RNS, which may be due to respiratory chain dysfunction caused by mitochondrial genome instability. Cytoplasmic chromatin fragments (CCF) extruded from the senescent nucleus trigger SASP by activating the innate immune cell sololytic DNA receptor cGAS-STING pathway. Aging cells inhibit NK and CD8 + T cell clearance by upregulating HLA-E, promoting APC mediated chronic inflammation. They can also enhance T cell activation through APCs (such as dendritic cells), leading to chronic inflammation and tissue damage. Notably, the accumulation of mitochondrial DNA (mtDNA) mutations impairs mitochondrial respiration, leading to the accumulation of mitochondrial reactive oxygen species (mtROS). This accelerates the emergence of new mtDNA mutations, leading to a vicious cycle and cellular aging

tumors. The interaction between mitochondrial dysfunction and cellular aging in the tumor microenvironment is intricate and complex, directly affecting tumor growth and immune escape. Research has shown that tumor cells induce immune cells, such as CD8 + T cells, to undergo aging, thereby evading immune surveillance and promoting tumor growth. Aging CD8 + T cells release extracellular DNA, activate the cGAS STING pathway, and trigger inflammatory responses and senescence associated phenotypes (SASP), further weakening immune surveillance function [67] Aging cells inhibit NK and CD8 + T cell clearance by upregulating HLA-E, promoting APC mediated chronic inflammation [69]. They can also enhance T cell activation through APCs (such as dendritic cells), leading to chronic inflammation and tissue damage [68, 69]. The SASP secreted by senescent cells, including pro-inflammatory cytokines, chemokines, growth factors, and proteases, can damage the tissue microenvironment, leading to organ dysfunction and the occurrence of age-related diseases. Removing mitochondria from aging cells can inhibit SASP, indicating that mitochondria may be a target for anti-aging therapy [70]. Mitochondrial derived peptides (MDPs) such as human derived peptides and MOTS-c may have dual effects in the tumor microenvironment. On the one hand, they can protect tumor cells from damage and promote tumor growth; On the other hand, they can exacerbate the aging of immune cells and suppress anti-tumor immune responses. For example, they can stimulate the secretion of inflammatory factors and may affect tumor cell metabolism through pathways such as PDK4 [71].

The integrity of mitochondrial structure and function is maintained by coordinating several processes, including biogenesis, kinetics, and mitochondrial autophagy,

collectively known as mitochondrial quality control (MQC). Impaired mitochondrial quality control and inflammation are the hallmarks of aging [72]. Inflammatory mediators can induce changes in the mitochondrial function [73]. For instance, mitochondrial dysfunction in sepsis is associated with damage to complex I, and the targeted protection of complex I has been proposed as a treatment for sepsis [74]. CRIF1 reduces doxorubicin-mediated mitochondrial dysfunction and myocardial aging by regulating PXDN [75]. The ectopic expression of the multipotent transcription factor NANOG restores mitochondrial vitality in aging cells by reconnecting metabolic pathways [76]. Targeted transcription factor EB (TFEB) by HKDC1 could maintain mitochondrial and lysosomal homeostasis and prevent cellular aging [77].

Studies have depicted that cell aging coincides with significant changes in miRNA expression profiles. MitomiRs are vital sensors of cellular aging that control mitochondrial homeostasis and affect metabolic reprogramming, redox balance, apoptosis, mitochondrial autophagy, and calcium homeostasis, all of which are closely related to aging [78]. Senescent cells accelerate inflammation by secreting proinflammatory factors crucial in promoting age-related epidemics. Giuliani et al. reported that mitomiRs, specifically let7b, miR-1, and miR-146a-5p, potentially affect the energy, oxidation, and inflammatory states of senescent cells. Among them, miR-146a is associated with inflammation-mediated aging, but not all studies have confirmed its susceptibility to mitochondria [79]. Wang et al. found that targeted delivery of miR-146a through nanoparticles can significantly reduce the production of inflammatory mediators in vitro and in vivo [80].

Aging is linked to functional defects in OXPHOS. For instance, iron chelation-induced aging involves a decrease in complex II activity. Similarly, TGF-β1 induced aging in Mv1Lu mink lung epithelial cells involves the inhibition of complex IV, leading to mitochondrial ROS production and sustained damage to MMP, thereby triggering aging. These findings emphasize that mitochondrial OXPHOS dysfunction is common in aging cells [81]. Recent studies have illustrated that cytoplasmic chromatin fragments (CCFs) extruded from the nuclei of aging cells trigger SASP by activating the innate immune cell solute DNA-sensing cGAS-STING pathway. However, the upstream signal that triggers the formation of CCFs remains unknown (Fig. 3) [82].

Application and treatment strategies

Mitochondria: a novel anticancer drug target

Mitochondria have attracted considerable attention as targets for developing new anticancer drugs. Mitochondrial-targeted therapies exhibit selective antiproliferative and cytotoxic effects on cancer cells [83]. Mitochondrial drug targets include the ETC(Electron transport chain is a series of protein complexes and mobile electron

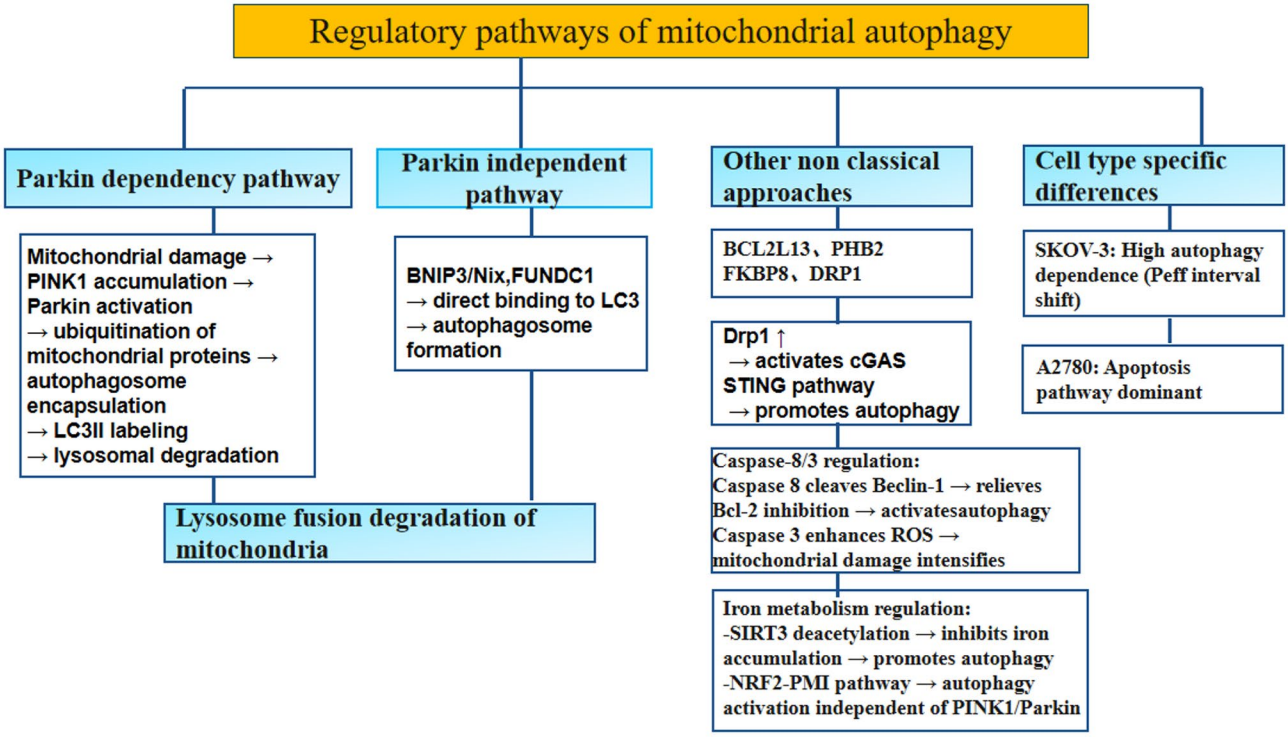

Fig. 3 Flowchart 1: Regulatory pathways of mitochondrial autophagy

Table 1 Application and therapeutic strategies of mitochondria in tumor and inflammation

Treatment strategies	Specific methods/drugs	Mechanism of Action	Clinical/Ex-perimental Results	notes	References
Mitochondrial Transcription Inhibitors (IMT)	Human mitochondrial RNA polymerase specific inhibitor	Interrupting mtDNA transcription, dose-dependent inhibition of mtDNA expression and OXPHOS	Good tolerance and strong anti-tumor response in mouse models	No OXPHOS dysfunction or toxicity to normal tissues	[77]
OXPHOS inhibitor	Compound I inhibitors: Metformin BAY 87–2243 、IACS–010759、 Fenofibrate VLX600 Compound II inhibitors: Lonidamide, VLX600, alpha tocopherol succinate Compound III inhibitor: Atorvastatin Complex IV inhibitors: arsenic trioxide VLX600 Mitochondrial protein synthesis inhibitors: tigecycline, doxycycline Mitochondrial transfer inhibitors: NOX2 and CD38 inhibitors	Directly or indirectly inhibit OXPHOS and reduce OCR (oxygen consumption rate)	Metformin reduces OCR by 10–20%; Atorvastatin reduces OCR by over 80%	Multiple drugs have entered the clinical trial stage	[78–80]
BCL2 family protein targeting	Venetoclax	Imitate the activity of BCL2 protein family members to trigger RCD (regulatory cell death)	FDA approved for chronic lymphocytic leukemia; Combination therapy with acetazolamide has a good response to AML	Combination with glycolysis or glutamine degradation inhibitors can kill cancer cells in vitro	[81]
Metabolic pathway reprogramming	BACH1 depletion or shRNA mediated degradation of heme	Increase cell sensitivity to ETC inhibitors (such as metformin)	Inhibiting the growth of triple negative breast cancer	Enhancing the inhibitory ability of metabolic inhibitors for cancer with limited treatment options	[82,83]
SIRT3 targeting	Specific inhibition of SIRT3	Stabilize mitochondrial LONP1 and promote primary tumor growth	The highly acetylated mutant K145Q enhances OXPHOS and accelerates tumor growth; Deacetylation mutant K145R inhibits tumor development	SIRT3 is involved in almost all aspects of mitochondrial metabolism and homeostasis	[22]
mitochondrial transplantation	Microinjection, incubation of fully purified mitochondria, cell attachment mediated by tunnel nanotubes or gap junction channels, direct transfer from donor cells (such as mesenchymal stem cells)	Inhibit oxidative stress, restore bioenergy, and promote the recovery of damaged tissues or organs	Emerging treatment strategies, customized personalized treatment plans	Equivalent to replacing a new 'energy factory' and restoring normal metabolic function	[84]
Mitochondrial targeted polymer micelles	OPDEA-PDCA	Inhibiting PDHK1, inducing mitochondrial oxidative stress, leading to immunogenic cell pyroptosis	Combined with anti-PD-L1 monoclonal antibody, it significantly inhibits the proliferation of osteosarcoma cells and prolongs T cell activation time	Propose a strategy of initiating cell pyroptosis by targeting mitochondria	[85]
Nano medical preparations	Carboxylate iron (III) metal organic framework as shell, upconversion nanoparticles as core	Synergistic enhancement of mitochondrial oxidative stress and calcium overload triggered by near-infrared light	Displaying therapeutic efficacy in tumor xenograft models derived from cells and patients in vivo	The therapeutic effect of nanomedicine based on mitochondrial damage has been validated	[86]
Iron copper NPs	Ferritic copper NPs	Inducing oxidative stress and cell death through the mitochondrial pathway	Induces oxidative stress and cell death in human breast cancer (MCF–7) cells	Demonstrated the rationality of mitochondria as a new anti-tumor target	[81]

carriers located on the inner mitochondrial membrane. Its core function is to transfer electrons through redox reactions, and use the released energy to establish proton gradients, ultimately driving ATP synthesis. ETC is a key step of oxidative phosphorylation and is responsible for about 90% of ATP production in cells.)mitochondrial permeability transition, Bcl-2 family proteins, and mtDNA. Göran Larsson and colleagues identified an inhibitor of mitochondrial transcription (IMT) specific to human mitochondrial RNA polymerase. IMTs can effectively disrupt mtDNA transcription, resulting in the dose-dependent inhibition of mtDNA expression and OXPHOS in cell lines. Four weeks of oral IMT treatment in mice inoculated with human cancer cells resulted in good tolerance and a strong antitumor response.

Besides, IMTs do not lead to OXPHOS dysfunction or toxicity in normal tissues [84]. Moreover, various antimitochondrial drugs that directly or indirectly inhibit OXPHOS have been explored as anticancer therapeutic agents. These include mitochondrial complex I inhibitors such as metformin (including phenacetin), BAY 87-2243, IACS-010759, fenofibrate, and VLX600; complex II inhibitors such as lonidamine, VLX600, and α-tocopherol succinate; complex III inhibitors such as atovaquone; the composite IV inhibitor arsenic trioxide and VLX600; mitochondrial protein synthesis inhibitors such as tigecycline and doxycycline; mitochondrial transfer inhibitors such as NOX2 and CD38 inhibitors [85]. Metformin drugs, such as metformin, can decrease the OCR by 10–20% (current approaches to address tumor hypoxia have focused on reducing oxygen consumption to decrease the oxygen demand of tumor cells). However, the antiparasitic drug atorvaquinone has a more profound inhibitory effect on OXPHOS, as it can reduce the OCR by more than 80% [86, 87]. Venetoclax triggers RCD by mimicking the activity of BCL2 protein family members. It has been approved by the FDA for use in patients with chronic lymphocytic leukemia. Research has identified that venetoclax combined with glycolysis or glutamine degradation inhibitors can kill cancer cells in vitro. Patients with AML responded well to a combination therapy consisting of venetoclax and the epigenetic modifier azacytidine. This example illustrates the possibility of indirect inhibition of OXPHOS [88]. Multiple clinical trials have tested the effectiveness of mitochondrial metabolism inhibition as a new cancer treatment method. Reprogramming of metabolic pathways can enhance the ability of metabolic inhibitors to inhibit cancer with limited treatment options. For instance, BACH1 depletion or hemin degradation by shRNA can increase cell sensitivity to ETC inhibitors (such as metformin), thus inhibiting the growth of triple-negative breast cancer [89, 90]. SIRT3 is involved in almost all aspects of mitochondrial metabolism and homeostasis to protect the mitochondria from various types of damage. Research has depicted that specific inhibition of SIRT3 by intestinal epithelial cells can promote the growth of primary tumors by stabilizing mitochondrial LONP1. SIRT3 deacetylates the N-terminal residue of the human oncogene LONP1 and lysine 145 (K145). The highly acetylated mutant K145Q of LONP1 enhances OXPHOS, thereby accelerating tumor growth, while the deacetylated mutant K145R produces a phenotype similar to heat restriction, inhibiting tumor development [22]. Mitochondrial transplantation, a new method of intercellular communication, can inhibit oxidative stress, restore bioenergy, and promote the recovery of damaged tissues or organs. Mitochondrial transplantation is an emerging therapeutic strategy that mainly includes microinjection, incubation of intact purified mitochondria, cell attachment mediated by tunnel nanotubes or gap junction channels, and direct transfer from donor cells (such as mesenchymal stem cells). This method is equivalent to replacing a new "energy factory," restoring normal metabolic function, and customizing treatment plans based on individual mitochondrial conditions [91].

Recently, Douglas E. Biancur and colleagues developed a mitochondrial-targeting polymer micelle (OPDEA-PDCA) and found that the micelle induces mitochondrial oxidative stress by inhibiting PDHK1 and leads to immunogenic cell pyroptosis in osteosarcoma cell lines. Additionally, OPDEA-PDCA could induce the secretion of soluble programmed cell death ligand 1 (PD-L1) molecules. Accordingly, combining OPDEA-PDCA and anti-PD-L1 monoclonal antibodies can significantly inhibit OS cell proliferation and prolong the activation time of T cells. This study offers a strategy for initiating cellular pyroptosis by targeting mitochondria [92]. Another study reported a core-shell nanomedicine formulation using carboxylic iron (III) metal-organic frameworks as the shell and upconversion nanoparticles as the core, enabling near-infrared light-triggered synergistic enhancement of mitochondrial oxidative stress and calcium overload. The therapeutic efficacy of nanomedicines based on mitochondrial damage has been demonstrated in in vivo cell and patient-derived tumor xenograft models [93]. Ferritic copper NPs have been exhibited to induce oxidative stress and cell death in human breast cancer (MCF-7) cells through the mitochondrial pathway [88]. Consequently, it is reasonable to select mitochondria(Mc) as a new target for antitumor strategies. However, most drugs or nanocarriers currently on the market do not have a Mc-targeting function. Owing to the complexity of the tumor tissue environment, many obstacles must be overcome before reaching the tumor tissue, cells, and Mc. The concept of Mc positioning may seem simple in theory, but it has various subtle differences in practice [1].(Table 1).

Mitochondria: a novel anti-inflammatory target

Inflammatory disorders are associated with numerous human diseases, not only infectious and autoimmune diseases but also neurological, cardiovascular, renal, liver, and tumor diseases [22]. Conversely, disproportionate, unwarranted, or unresolved inflammation can be a true driver of diseases such as chronic inflammatory bowel disease. However, unchecked inflammatory responses may exacerbate the progression of noninflammatory conditions such as myocardial infarction. These examples underscore the critical requirements for regulating inflammatory responses in bodily development and homeostasis. Cyclosporin A, a PPIF-targeting agent with MPT inhibitory activity, has also been approved for human use. Cyclosporin A is frequently used as an immunosuppressive drug to treat autoimmune diseases and method transplant rejection, primarily because it binds to the PPIF-like cytoplasmic protein PPIA, ultimately inhibiting lymphocytes by blocking calcineurin. However, the partial immunosuppressive effects of cyclosporine A may be attributed to MPT inhibition and subsequent suppression of inflammatory responses driven by permeable mitochondria, a possibility that has yet to be definitively resolved [94, 95].

Metformin is the most frequently used antidiabetic medication. It ameliorates chronic inflammation by enhancing metabolic parameters and exerts direct anti-inflammatory effects. Besides, metformin plays a crucial role in mitochondrial function and cellular homeostasis, such as autophagy, given its vital role in maintaining cellular health. Mitochondrial dysregulation and failure in the autophagy pathway (leading to functional impairment or excessive clearance of organelles) can severely affect cellular health and potentially trigger the onset of age-related and metabolic diseases. Immune cells are the foundational cell types that regulate health. Therefore, dysfunctions in autophagy or mitochondria within immune cells significantly affect susceptibility to infections, vaccine responses, tumor development, and progression of inflammatory and autoimmune conditions [96, 97]. Multifunctional protein voltage-dependent anion channel 1 (VDAC1) is located on the outer membrane of the mitochondria. It is a critical protein for maintaining mitochondrial function and powering cellular activities through energy production. VDAC1 dysfunction has been linked to mitochondrial diseases that affect inflammatory responses, leading to heightened defensive responses to stress stimuli in the body [98]. VDAC1 overexpression may promote ulcerative colitis, and new interaction targets based on VDAC1 are being developed to treat inflammation and autoimmune diseases. Moreover, studies have exhibited that VDAC1 is associated with cardiovascular and cerebrovascular diseases [99]. This indicates that VDAC1 is a potential target for developing next-generation therapeutic drugs (Tables 1 and 2).

Table 2 Research progress of mitochondria in tumor and inflammation

Research Area	Research Advances	Potential Applications	References
Mitochondrial Metabolism and Tumors	Mitochondrial metabolic reprogramming is a hallmark of cancer, maintaining tumor growth through a balance of OXPHOS and glycolysis.	Targeted therapies focusing on mitochondrial metabolism, such as metformin and lonidamine, have been explored for anticancer treatment.	[16] [17–21]
Mitochondrial Autophagy and Tumors	Mitophagy is crucial for mitochondrial quality control, affecting mitochondrial mass, dynamics, redox balance, and cell death signaling in cancer cells.	Therapeutic strategies targeting mitophagy pathways, such as PINK1/Parkin and FUNDC1, have been proposed for cancer therapy.	[34, 35] [37–40]
Mitochondria and Inflammation	Release of mtDNA into the cytoplasm activates PRRs and innate immune responses, leading to inflammation.	Inhibitors targeting the mtDNA-CGAS-STING pathway, such as ru.521, have shown potential in reducing inflammation in sepsis.	[3] [50–52]
Mitochondria and Aging	Mitochondrial dysfunction is associated with aging and chronic inflammation, which can promote tumor development.	Targeting mitochondrial function and autophagy may offer strategies for anti-aging therapy and cancer prevention.	[57–59] [60–73]
Mitochondrial-Targeted Therapy	Mitochondrial-targeted therapies, such as IMT and metformin, exhibit selective antiproliferative and cytotoxic effects on cancer cells.	Development of novel anticancer drugs, including IMT and nanotechnology-based treatments, is being explored to improve therapeutic outcomes.	[74–86]
Mitochondria in Inflammatory Diseases	Dysregulated mitochondrial dynamics and ROS production are implicated in inflammatory diseases.	Therapies targeting mitochondrial dysfunction, such as drp1 inhibitors and mitochondrial antioxidants like mitoq, are being investigated for inflammatory conditions.	[54–56]

Prospects

Mitochondrial dysfunction can promote cancer progression toward antiapoptotic and invasive phenotypes

through various mechanisms. During carcinogenesis and tumor progression, these changes in the mitochondria can activate cellular signaling pathways from the mitochondria to the nucleus, ultimately altering nuclear gene expression and leading to tumor transformation. However, it is currently unclear how specific mtDNA mutations regulate cancer formation and development. The detailed molecular mechanism of mitochondrial retrograde signaling needs further investigation [100]. Mitochondrial dysfunction has been recognized as a mechanism of chronic low-grade inflammation (i.e., inflammation) associated with aging. In particular, fragmentation and release of mtDNA are considered characteristic interactions between mitochondrial metabolic disorders and inflammation. Abnormal CpG methylation motifs in mtDNA enable these molecules to be recognized as "nonself," thus becoming inflammatory triggers. In many disease conditions, mtDNA and mitochondrial nucleoids can be replaced. However, the underlying mechanism is still not fully understood [101].

Mitochondria are a rich source of DAMPs, such as ATP, formyl peptides, and mtDNA, that effectively trigger the innate immune system. Mitochondrial DAMP (mtDAMP) is currently recognized as a potent trigger of innate immune responses during stress, infection, and injury. mtDAMP-sensitive PRRs play essential roles in inflammation and diseases induced by environmental exposure. However, further studies are required to determine the ligands, dynamics, and mechanisms underlying the link between mitochondrial dysfunction and mtDAMP release. More research is needed to identify therapeutic interventions to limit the progression of pathologies and diseases associated with environmental exposures [102]. One of the main challenges currently faced in treating mitochondrial diseases is the inconsistent relationship between phenotype and genotype found in patients with mitochondrial diseases, coupled with the unmet clinical needs for treating these patients. We believe that, in the near future, researchers will discover new small-molecule substances capable of improving cellular mitochondrial function through advances in gene therapy and the development of screening methods. These advancements, combined with innovative clinical trial design methods, including the development of wearable and virtual control technologies, may herald an era of innovative personalized therapies for patients with mitochondrial disease [103].

Author contributions

Hui Liu: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. Mengmeng Pan: Writing – original draft, Conceptualization. Yumeng Li: Writing – review & editing. Hanying Li, Chunlei Guo, Zhen Huang: Visualization. Chenguang Zhang: Writing – review & editing, Writing –original draft. Hui Wang: Writing – review & editing, Visualization, Supervision, Conceptualization. HL and MP conceived and designed the project. HW and ZY supervised this project. YL, ZH, HL and CG edited the manuscript. HL wrote the manuscript, and all authors discussed the results and proofread this paper.

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Data availability

No data was used for the research described in the article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have approved this manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

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