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Review

# Mitochondrial Dynamics in Cellular Senescence: Mechanisms, Context Dependence, and Therapeutic Potential

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**ABSTRACT: Mitochondria function as the primary energy centers of cells, and the dynamic equilibrium between their fission and fusion is essential for preserving cellular functional integrity and metabolic homeostasis. As research in cell biology has advanced, an imbalance in mitochondrial dynamics is tightly and bidirectionally linked to cellular aging. It not only contributes to aging-related functional decline but is also exacerbated by the senescent state itself, creating a vicious cycle that impacts key biological processes. Recent studies have demonstrated that the disruption of mitochondrial fission and fusion during aging, through mechanisms such as impaired cellular energy metabolism, increased oxidative stress, compromised mitophagy, and the induction of senescence-associated secretory phenotypes, collectively accelerates the functional decline of cells and organs. Nonetheless, many questions remain regarding the specific regulatory network of mitochondrial dynamics and its variations across different stages of aging. The aim of this review is to systematically elucidate the fundamental role of imbalances in mitochondrial dynamics in the context of cellular aging, along with its underlying molecular mechanisms. This review summarizes various intervention strategies targeting this process, including targeted therapies, small molecule regulators, stem cell therapy, lifestyle modifications, and innovative mitochondrial transplantation technology, whereas these approaches are still in experimental or early-stage development, and their translational potential requires further validation. The ultimate objective is to offer novel theoretical insights and potential therapeutic approaches for mitigating aging and associated diseases.**

***Keywords:*** mitochondrial dynamics, mitochondria, cellular senescence, therapeutic strategies

## 1. Introduction

As energy supply centers in cells, mitochondria not only produce ATP through oxidative phosphorylation but also participate in a variety of important biological processes, such as calcium homeostasis regulation, oxidative stress response, and apoptosis. Therefore, maintaining the integrity of mitochondrial function is essential for cell homeostasis and function [1]. Mitochondrial dynamics, the process through which mitochondria continuously remodel their morphology and network structure through fission and fusion, is a central mechanism for maintaining mitochondrial mass, distribution, and function to adapt to the metabolic demands of different cell types and environmental changes [2]. For example, the unique dynamic characteristics of mitochondria in mature cardiomyocytes, which exhibit a spherical structure arranged end-to-end and are restricted in movement, are closely related to the occurrence and development of heart diseases [3]. Mitochondrial dynamics not only regulate the number, distribution and metabolic function of mitochondria but also ensure mitochondrial quality

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control by removing damaged mitochondria through autophagy (especially selective autophagy, mitophagy), which is key for cell adaptation to stress and for the maintenance of stable energy metabolism [4, 5].

Cellular senescence is an irreversible process of cell cycle arrest, which is accompanied by multifaceted changes in cell function, including increased oxidative stress levels, mitochondrial dysfunction, cellular metabolic imbalance, and an enhanced inflammatory response [6, 7]. Upon entering senescence, cells undergo profound remodeling of their intracellular environment, which destabilizes mitochondrial dynamics, which disrupt mitochondrial dynamics by impairing the coordinated balance between fusion and fission. These changes compromise key quality control mechanisms, notably mitophagy, and ultimately culminate in mitochondrial fragmentation, progressive bioenergetic failure, and eventual loss of functional mitochondria [8]. Critically, mitochondrial dysfunction extends beyond energy depletion: it amplifies reactive oxygen species (ROS) production, triggering oxidative damage and activating proinflammatory signaling cascades that drive the senescence-associated secretory phenotype (SASP). This SASP-mediated inflammatory feedback loop exacerbates both local tissue inflammation and systemic low-grade inflammation, thereby accelerating the onset and progression of multiple age-related pathologies [9].

In recent years, studies have shown that imbalances in mitochondrial dynamics are not only associated with disorders of energy metabolism but also contribute to cellular aging by regulating key processes such as oxidative stress, apoptosis, and the inflammatory response [10, 11]. For example, dysregulation of the mitochondrial fusion proteins MFN1 (mitofusin 1), MFN2 (mitofusin 2) and OPA1 (optic atrophy 1) can lead to abnormal mitochondrial morphology, promote intracellular accumulation of ROS, and activate apoptotic signals [12]. Moreover, abnormal activity of the mitochondrial fission protein Dynamin-related protein 1 (DRP1) is closely related to a variety of aging-related diseases, such as cardiovascular diseases and neurodegenerative diseases [13]. Studies have also shown that regulating the balance of mitochondrial dynamics and restoring mitochondrial function may delay cellular senescence and improve aging-related pathological states, such as by regulating the expression of fusion or fission proteins via antisense oligonucleotides, remodeling mitochondrial morphology and improving mitochondrial respiratory function [14]. In addition, mitophagy is a key quality control pathway responsible for removing damaged mitochondria. Dysfunction of this process can lead to the accumulation of mitochondria in senescent cells, further exacerbating the aging phenotype [15]. The stimulation of mitophagy has been shown to help improve senescent cell function and reduce tissue degeneration [16]. Thus, the relationship between imbalanced mitochondrial dynamics and cellular senescence is not a unidirectional regulatory relationship. Disruption of the balance between mitochondrial fission and fusion may be associated with the induction of cellular senescence, while cells that have entered a senescent state may also exhibit an imbalance in mitochondrial dynamics. Mitochondrial dynamics involve multiple interrelated processes, such as fusion, fission and mitophagy. These processes cooperate to maintain mitochondrial quality control and the homeostasis of energy metabolism, which is important for cells to resist aging and related diseases. Conversely, during cellular senescence, mitochondrial dysfunction and dynamic imbalance not only result from but also actively exacerbate energy deficits, oxidative stress, and inflammatory signals. This establishes a self-reinforcing, bidirectional crosstalk that propels the progression of age-related pathologies. In-depth studies on the regulatory mechanisms of mitochondrial dynamics will provide new insights into the cellular and molecular mechanisms of aging and lay the foundation for the development of targeted strategies to delay aging and treat aging-related diseases [17]. In this review, we synthesize evidence from multiple research domains. However, it is important to distinguish between direct evidence from physiological aging models (e.g., naturally aged animals, replicative senescent primary cells) and supportive or extrapolative evidence from age-related disease models, stress-induced senescence, or cancer biology. While these distinct contexts share common mechanistic themes, they also possess unique features that limit direct generalization. Therefore, throughout this review, evidence from distinct experimental contexts is explicitly distinguished to enable a nuanced and transparent synthesis of mitochondrial dynamics and cellular senescence, avoiding a unified but potentially misleading narrative.

## 2. Overview of mitochondrial dynamics

### 2.1 Mitochondrial fusion

Mitochondrial fusion is a key dynamic process that maintains the integrity and function of the mitochondrial network and is mediated mainly by three core proteins: the outer membrane fusion proteins MFN1 and MFN2 and the inner membrane fusion protein OPA1. MFN1 and MFN2 are located in the outer mitochondrial membrane and are responsible for regulating the binding and fusion of the outer membrane, whereas OPA1 is located in the inner membrane and mediates the fusion process of the inner membrane (Fig. 1A, B). This coordinated fusion of the inner and outer membranes ensures the dynamic

balance of mitochondrial morphology and the maintenance of mitochondrial function [18, 19].

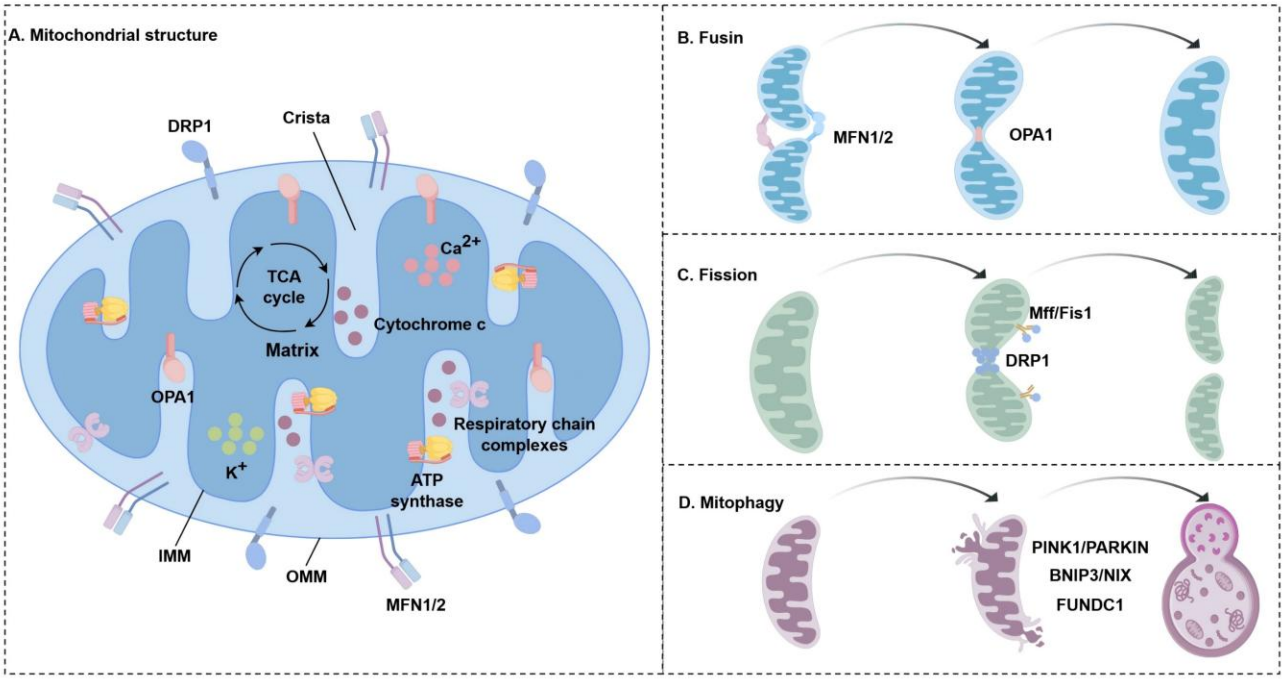



**Figure 1. Mitochondrial structure and dynamics. (A)** Mitochondrial structure, the mitochondrial matrix is surrounded by the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), and the tricarboxylic acid cycle (TCA cycle) takes place in the mitochondrial matrix. **(B)** Mitochondrial fusion is realized via the dynamic integration of membrane structures, which is mediated by specific proteins located in the outer and inner mitochondrial membranes. This process is facilitated by the cooperation of outer-membrane fusion proteins (MFN1/MFN2) and inner-membrane fusion proteins (OPA1), resulting in the formation of a continuous mitochondrial network to guarantee energy metabolism and the integrity of genetic material. **(C)** Mitochondrial fission is mediated by proteins like DRP1, and it contributes to the regulation of energy metabolism and quality control by modifying mitochondrial morphology. **(D)** Mitophagy is primarily mediated by pathways such as the PINK1/PARKIN pathway and receptors such as BNIP3 and BNIP3L (NIX) or FUNDC1. It initiates the engulfment of damaged mitochondria by autophagosomes by detecting changes in mitochondrial membrane potential and ultimately fuses with lysosomes for degradation.

Specifically, MFN1 and MFN2 possess highly conserved GTPase domains that drive outer membrane tethering and fusion through GTP hydrolysis. In addition, MFN2 is involved in the regulation of mitochondrial contact with the endoplasmic reticulum, which participates in calcium signaling and lipid metabolism and has multiple functions in the regulation of cellular metabolism [20-22]. OPA1 relies on its multiple splice isoforms to form a complex on the inner membrane, which regulates membrane fusion and mitochondrial cristae structural stability. The function of OPA1 is regulated by a variety of posttranslational modifications, such as protease cleavage and phosphorylation, to ensure that inner membrane fusion occurs under appropriate conditions [23, 24].

Mitochondrial fusion not only maintains mitochondrial morphology but also promotes the homogenization and repair of mitochondrial DNA (mtDNA), prevents the accumulation of mutations, and ensures the stability of mitochondrial function. The fusion process promotes the exchange of proteins, lipids, and genomic contents between mitochondria, optimizes energy metabolism, and enhances the ability of cells to adapt to environmental changes [25, 26]. In addition, the fusion process has positive effects on cellular energy production, oxidative phosphorylation efficiency, and antioxidant capacity. For example, upregulation of MFN2 improves mitochondrial function and alleviates disease-related pathological changes in Alzheimer's disease models [27].

### 2.2 Mitochondrial fission

DRP1 is the core regulator of mitochondrial fission, which is important for maintaining mitochondrial function and cell homeostasis. DRP1 is a GTPase that exists mainly in the cytoplasm. After being regulated by various signals, it is recruited to the outer mitochondrial membrane and assembles into a helical structure on the membrane. Through GTP hydrolysis, it drives the mechanical constriction of mitochondria and facilitates completion of the fission process [28]. In addition, multiple adaptors on

the mitochondrial outer membrane, such as mitochondrial fission factor (MFF), mitochondrial dynamics protein 49 (MiD49) and 51 (MiD51), and mitochondrial fission protein 1 (FIS1), cooperate in the localization and activation of DRP1 to form a fission complex [28] (Fig. 1C). Recent studies have revealed that intracellular mechanical tension and the actin-myosin system affect the function of DRP1 by regulating its phosphorylation status, thereby regulating mitochondrial fission [29].

Mitochondrial fission plays a key role in maintaining mitochondrial quality control. Through fission, damaged or dysfunctional mitochondrial fragments can be sequestered and removed by selective autophagy (i.e., mitophagy), thereby safeguarding the health of the mitochondrial population and the energy supply of the cell [30]. In cardiovascular disease, specifically in hypertension-induced heart failure models, PINK1 (PTEN-induced kinase 1) activates DRP1 by phosphorylating DRP1 at a specific site (S616), promoting mitochondrial fission, removing damaged mitochondria, and attenuating disease progression [31]. However, excessive activation of mitochondrial fission can lead to mitochondrial fragmentation, destroy the integrity of the mitochondrial network, and trigger mitochondrial dysfunction and the disorders of cellular energy metabolism, thereby promoting cellular aging and dysfunction [32]. In addition, multiple post-translational modifications of DRP1, such as phosphorylation and methylation, also regulate its activity and maintain the homeostasis of mitochondrial fission. Arginine methyltransferase 1 (CARM1)-mediated methylation of DRP1 promotes its interaction with MFF, thereby increasing mitochondrial fission and inducing cellular senescence, thus revealing a vicious cycle involving ROS generation, DRP1 modification, and cellular senescence [33].

### 2.3 Mitochondrial biogenesis and mitophagy

The quality and quantity of mitochondria are tightly regulated through two mutually balanced and coordinated mechanisms, mitochondrial biogenesis and mitophagy, to meet cellular energy demand and respond to various cellular and environmental stresses.

Mitochondrial biogenesis is regulated by multiple factors, among which PPARγ coactivator 1α (PGC-1α) and the deacetylase SIRT3 (sirtuin 3) play central roles. As a transcriptional coactivator, PGC-1α promotes mitochondrial biogenesis and function through the regulatation of mitochondrial gene expression. SIRT3 supports the generation and functional maintenance of new mitochondria by regulating the level of mitochondrial protein acetylation and preserving mitochondrial function and antioxidant capacity [34].

Mitophagy is an important process that selectively removes damaged mitochondria and prevents cellular damage caused by excessive accumulation of ROS. This process relies mainly on the PINK1/PARKIN-mediated ubiquitination pathway and receptor-mediated pathways involving BNIP3 and FUNDC1, which collectively identify and mark damaged mitochondria for subsequent degradation via the autophagy-lysosomal system [35] (Fig. 1D). Also, mitophagy not only maintains mitochondrial quality but also participates in cellular adaptive response to stress and pathological conditions. For example, enhanced mitophagy helps eliminate dysfunctional mitochondria and protect cells from oxidative damage such as hepatotoxicity, myocardial injury, and cell differentiation [36, 37].

### 2.4 Physiological functions of mitochondrial dynamics

Mitochondria are multifunctional and highly dynamic organelles. Under the regulation of mitochondrial dynamics, mitochondria can adjust their morphology and function according to the metabolic demand of cells, thereby ensuring the adaptability of the cellular energy supply [38]. For example, the fusion process contributes to the formation and functional enhancement of mitochondrial networks, increases the efficiency of ATP production, and promotes the stabilization and repair of mitochondrial DNA. In contrast, the fission process facilitates the removal of damaged mitochondria, maintain mitochondrial quality, and promote the renewal and distribution of mitochondria [26]. This dynamic balance is particularly important in energy-demanding cells such as neurons, skeletal muscle cells, and renal cells, where any imbalance can lead to cellular dysfunction and disease [39].

Mitochondrial dynamics also influence cellular stress responses and signaling [40]. Mitochondrial fusion and fission not only regulate metabolic adaptation and cell survival but also modulate intracellular ROS levels and calcium signaling and, together with mitophagy, maintain cellular homeostasis [41, 42]. In addition, mitochondrial dynamics are involved in cell migration, differentiation, and fate determination [43]. For example, in cancer cells, mitochondrial dynamics promote proliferation and metastasis by regulating metabolic reprogramming and ROS levels. Consequently, pharmacological intervention targeting mitochondrial homeostasis has emerged as a novel strategy for cancer treatment [44, 45].

## 3. Cellular senescence and mitochondrial dysfunction: indivisible markers of aging

### 3.1 Definition and causes of cellular senescence

Cellular senescence is a cellular state characterized by permanent cell cycle arrest while remaining metabolic activity [46]. Its phenotypic features include increased cell size, morphological flattening, cytoskeletal remodeling, and alterations of the cell surface, accompanied by enhanced β-galactosidase activity, which is widely used as a traditional marker of cellular senescence [47-49]. Although senescent cells no longer divide, they remain metabolically active and exhibit a distinctive senescence-associated secretory phenotype, comprising various proinflammatory cytokines, chemokines and proteases. This SASP participates in regulating the cellular microenvironment, it may facilitate tissue repair but can also promote chronic inflammation and tumor progression [50, 51].

Cellular senescence is a state induced by various endogenous and exogenous stresses, including DNA damage, telomere shortening, oxidative stress, and metabolic disorders [6]. These stresses lead to irreversible cell cycle arrest and senescence through the activation of the p53/p21 and p16INK4a/pRb signaling pathways [52]. For instance, DNA damage (e.g., induced by replication stress or chemotherapeutic agents) activates the p53 pathway, upregulates p21 expression and inhibits cyclin-dependent kinases (CDKs). In contrast, p16INK4a represses cell cycle progression by inhibiting Rb phosphorylation [53, 54]. Under oxidative stress, ROS and reactive nitrogen species (RNS) can damage proteins, lipid and DNA, thereby promoting senescence [55]. Metabolic disorders, such as abnormal cholesterol metabolism, can activate p53-dependent senescence programs by inducing mitochondrial dysfunction and ROS production [56]. In addition, chronic inflammation promotes the formation of the SASP and exacerbates tissue functional decline through the continuous secretion of inflammatory factors [57] (Fig. 2).

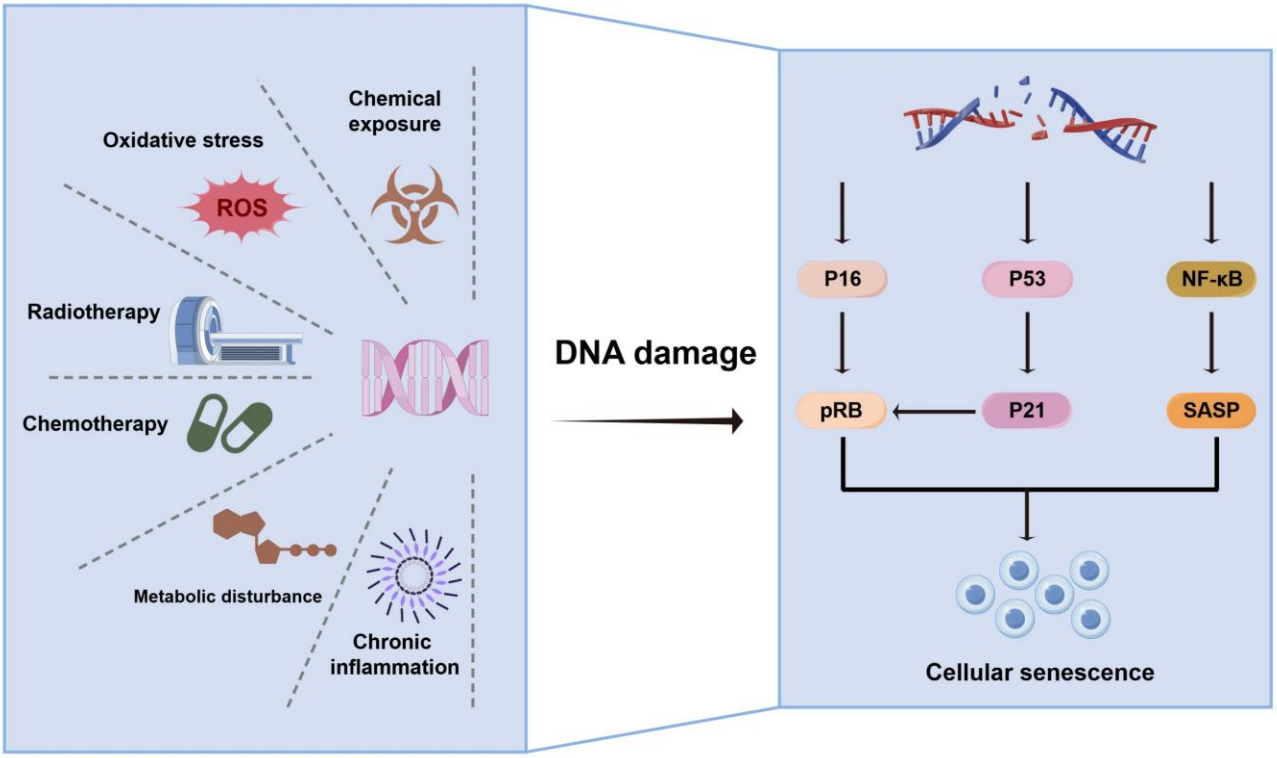



**Figure 2. Causes of DNA damage and molecular mechanisms of cellular senescence.** Multiple factors can lead to DNA damage, such as chemical exposure, oxidative stress, radiotherapy, chemotherapy, metabolic disturbance and chronic inflammation. The persistent DNA damage response (DDR) can activate both p53- and Rb-dependent pathways while also triggering the NF-κB signaling pathway, promoting the secretion of inflammatory factors related to the SASP and further reinforcing cellular senescence.

### 3.2 Formation and regulation of the SASP

The SASP is an important feature of cellular senescence, characterized by the continuous secretion of various inflammatory factors (such as IL-6, IL-8, and TNF-α), chemokines (such as CCL2 and CCL5), proteases (such as MMPs), and cytokines from senescent cells [58]. These secreted factors are not merely markers but also functional mediators that affect senescent cells themselves and, through paracrine effects, significantly alter the

microenvironment of surrounding cells and tissues, thereby producing complex bidirectional regulation on tissue repair, chronic inflammation, and the tumor microenvironment [59, 60]. For, example, p16INK4a in senescent macrophages increases the expression of inflammatory factors such as IL-1α, TNF-α, and MMP9 and promotes foam cell formation, thereby exacerbating atherosclerosis [61].

The formation and regulation of the SASP involve multiple signaling pathways, among which the NF-κB pathway is widely recognized as the primary driver of SASP expression. It induces the transcription of various proinflammatory factors and proteases, thereby eliciting a robust inflammatory response [62]. In arterial endothelial cells, the GATA4 protein activates NF-κB transcription and promotes the expression of SASP factors such as IL-6 and IL-8, accelerating vascular aging and the progression of atherosclerosis [63]. In addition, JAK-STAT signaling participates in SASP regulation. In the blind mole rat, upregulation of the JAK-STAT pathway and its related cytokines during aging is considered a key factor in maintaining SASP balance and regulating chronic inflammation [64].The SASP is central to the functional diversity of senescent cells and serves as a key regulator of the tissue microenvironment, contributing to both chronic inflammation and tissue remodeling. As such, it represents an important target for interventions aimed at cellular senescence and the treatment of multiple age-related diseases.

### 3.3 Age-related mitochondrial dysfunction

Mitochondrial dysfunction is a core feature of cellular senescence. Studies have shown that senescent cells exhibit significantly reduced mitochondrial membrane and decreasedATP production capacity, accompanied by excessive ROS accumulation, which leads to oxidative damage and a decrease in cellular function [65]. These changes collectively underlie the disturbed energy metabolism in senescent cells. As the energy factories of the cell, mitochondria directly influence energy supply, and their dysfunction consequently disrupts cellular homeostasis. Notably, excessive ROS accumulation not only damages mitochondrial membrane lipids, proteins, and DNA but also exacerbates cellular damage through oxidative stress response [66]. This vicious cycle is considered a key mechanism driving the senescence process.

The accumulation of mutations and damage to mitochondrial DNA (mtDNA) is particularly prominent during senescence. Owing to the lack of histone protection and efficient DNA repair mechanisms, and its location within the mitochondrial matrix, mtDNA is directly exposed to the ROS-generating environment and is therefore more susceptible to mutations [67]. Over time, accumulated mtDNA mutations lead to dysfunction of the mitochondrial respiratory chain complex, further exacerbating impaired ATP production and increased ROS production [68]. In addition, mtDNA mutations affect the function of mitochondrial transcription factor A (TFAM) and impair mitochondrial gene expression, resulting in a senescence-associated mitochondrial dysfunction phenotype [69]. In studies on cardiac aging, mitochondria from aged mouse cardiomyocytes exhibit reduced oxygen consumption, reduced ATP production, and elevated ROS production, which highly associated with functional defects in mitochondrial complexes I and II [70].

Dysregulation of the mitochondrial quality control (MQC) system is another key contributor to senescence-associated mitochondrial dysfunction. The MQC system encompasses mitochondrial dynamics (fusion/fission), mitophagy, and the mitochondrial unfolded protein response (UPRmt) [65]. During senescence, the expression levels of mitochondrial fusion proteins (such as MFN1/2 and OPA1) and fission proteins (such as DRP1) become imbalanced, leading to structural abnormalities in the mitochondrial network [71]. Moreover, mitophagy activity is decreased, resulting in the inability of functionally impaired mitochondria and further exacerbation of mitochondrial dysfunction [72]. Studies have shown that p53 inhibits the mitochondrial translocation of DRP1 through the protein kinase A (PKA) pathway, leading to excessive mitochondrial elongation, which in turn causes mitochondrial dysfunction and cellular senescence [71]. These findings highlight the important role of mitochondrial dynamics regulation in the senescence process.

## 4. Mitochondrial dynamics imbalance: Important regulatory factors and characteristics of cellular senescence

A dynamic mitochondrial balance is essential for maintaining mitochondrial structural and functional homeostasis. Its imbalance is a hallmark feature of the cellular senescence process and an important contributor to senescence-associated pathophysiological changes. During senescence, disorders of the mitochondrial fusion/fission regulatory network are associated with mitochondrial fragmentation and functional loss, further promoting the establishment and maintenance of cellular senescence by the activating multiple pathways, including oxidative stress, chronic inflammation, metabolic reprogramming and cell cycle arrest (Fig. 3). In this review, we summarize the functions of key regulators and their changes associated with dysregulation, as detailed in Table 1.

**Table 1**. Major mitochondrial-dynamics-related regulators discussed in senescence and aging.

| Regulator / pathway | Main function | Direction | Model System | Evidence Type | Aging type | Reference |
|---|---|---|---|---|---|---|
| **MFN1 / MFN2** | Outer-membrane fusion; network connectivity; ER-mitochondria contacts (especially MFN2) | Reduced | APP-expressing Neuro-2a cells, HFD-fed mice | Both in vitro and vivo | Replicative senescence, stress-induced senescence | [12, 22] |
| **OPA1** | Inner-membrane fusion; cristae integrity; mtDNA maintenance | Reduced | Retinal pigment epithelial cells (aged mice), intervertebral disc cells (aged mice), muscle tissue (aged mice), HFD-fed mice | Both in vitro and vivo | Replicative senescence, stress-induced senescence | [11, 12, 73, 103, 106] |
| **DRP1** | Mitochondrial fission and segregation of damaged organelle segments | Increased | Huvecs (high glucose), Drosophila, mice | Both in vitro and vivo | Replicative senescence, stress-induced senescence | [73, 104, 127] |
| **MFF / FIS1** | Recruitment and positioning of DRP1 at fission sites | Increased | Late-passage cells (IMR-90 cells, yeast cells) | In vitro | Replicative senescence | [19, 28] |
| **MiD49** | Recruitment and positioning of DRP1 at fission sites | Increased | Hela cells (etoposide) | In vitro | Stress-induced senescence | [19, 26] |
| **MiD51** | Recruitment and positioning of DRP1 at fission sites | Increased | HFD-fed mice | In vivo | Stress-induced senescence | [19, 39] |
| **PINK1-PARKIN / BNIP3 / FUNDC1** | Mitophagy-mediated removal of dysfunctional mitochondria | Reduced | Late-passage cells (MSC, Human Fibroblasts), ovariectomized mice, aged mice | Both in vitro and vivo | Replicative senescence, stress-induced senescence | [18, 34, 120, 121] |
| **PGC-1α / SIRT3** | Biogenesis, metabolic adaptation, antioxidant defense, protein deacetylation | Reduced | Late-passage cells (Human Fibroblasts), MPTP-induced mouse model of Parkinson's disease, HFD-fed mice | Both in vitro and vivo | Replicative senescence, stress-induced senescence | [21, 83, 107] |

### 4.1 Imbalances in fusion and fission disrupt mitochondrial quality control

Direct evidence from physiological aging models supports a link between mitochondrial dynamic imbalance and cellular senescence. In a physiological aging model, multiple tissues of aged mice exhibit enhanced mitochondrial fission and blocked fusion, leading to mitochondrial fragmentation and functional loss. These findings further reinforce the association between the two [73-75]. Supporting evidence from age-related disease models further implicates dynamic imbalance, though with context-specific nuances. In mouse obesity models, the expression and activity of the mitochondrial fission protein DRP1 are markedly increased in senescent adipocytes, whereas the expression of the fusion proteins MFN2 and OPA1 is significantly decreased [76]. This imbalance in fission-fusion leads to fragmentation of the mitochondrial network and the formation of numerous small, functionally defective mitochondrial fragments that fail to maintain normal energy metabolism and calcium homeostasis [77]. In addition, mitochondrial fragmentation can impair the integrity of mitochondrial DNA and promote mutation accumulation, thereby further exacerbating mitochondrial dysfunction [78]. Similar molecular changes have also been observed in diabetes models [81]. However, it should be noted that these disease models involve chronic hyperglycemia, dyslipidemia, and inflammation-factors that may amplify or modify dynamic changes beyond those observed in normal aging. Therefore, while evidence provides valuable mechanistic clues, its findings should not be directly extrapolated to physiological aging without caution.

Mechanistic intervention studies support a causal potential role for dynamic imbalance. Targeted

modulation of mitochondrial dynamics has emerged as a potential strategy to intervene in cellular aging. For instance, inhibiting excessive fission (such as by using the DRP1 inhibitor Mdivi-1) or promoting fusion (such as by overexpressing MFN2) has been shown to improve mitochondrial network integrity and delay cellular senescence [32]. In addition, $NAD^+$ precursors (such as NMN) can restore mitochondrial protein deacetylation by activating SIRT3, thereby promoting the mitochondrial dynamic balance [79]. These findings indicate potential avenues for development of anti-aging therapies, but further studies on tissue-specific regulatory strategies and long-term safety are warranted [80]. Notably, the relationship is bidirectional. Abnormal mitochondrial dynamics also trigger impaired mitochondrial quality control systems. Under physiological conditions, mitochondria compensate for each other's defects through fusion and isolate damaged portions via fission for subsequent clearance. However, during physiological aging, this quality control mechanism becomes dysregulated, leading to the accumulation of functionally impaired mitochondria [81]. Moreover, mitochondrial dysfunction can reduce the $NAD^+$/NADH ratio and inhibit the activity of deacetylases such as SIRT3, further exacerbating protein acetylation accumulation and cellular senescence [82, 83]. Similar molecular alterations have also been observed in diabetes model [79]. Mitochondrial dysfunction-associated senescence (MiDAS) is a distinct senescent state characterized by chronic oxidative stress and energy insufficiency resulting from impaired mitochondrial function. This state leads to autophagic resistance, hyperfusion, and the accumulation of dysfunctional mitochondria, ultimately rendering MiDAS chronic and potentially irreversible [84]. Cell-type and stage dependency is a critical consideration. For example, transient DRP1 activation may be protective by facilitating mitophagy, whereas chronic hyperactivation drives pathology. In post-mitotic neurons, moderate fission is essential for removing damaged mitochondrial fragments, while excessive fusion may be detrimental under certain contexts. Collectively, although the bidirectional relationship between dynamic imbalance and cellular senescence is well-supported, the strength and directionality of this relationship vary by biological context.

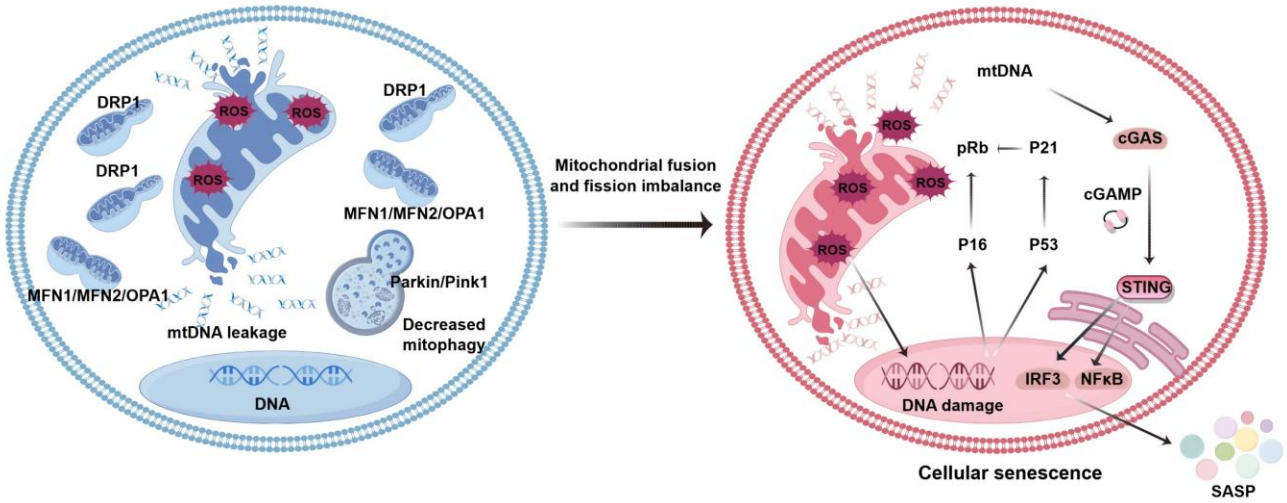



**Figure 3. Mitochondrial dynamics imbalance: a central driving force and hallmark of cellular senescence.** Schematic illustration depicting the molecular cascade linking mitochondrial dysfunction to cellular senescence. In the initial stage (left), mitochondrial dynamics imbalance (characterized by decreased fusion due to downregulated MFN1/MFN2/OPA1 and excessive fission mediated by DRP1) is associated with impaired mitophagy (reduced Parkin/PINK1 activity) to induce mitochondrial structural and functional damage. This pathological state triggers mtDNA leakage into the cytoplasm and excessive ROS generation. Sustained ROS overproduction causes nuclear DNA damage, whereas mtDNA leakage activates the cGAS-cGAMP-STING signaling pathway. These events converge to upregulate core senescence regulators (p16, p21, p53, and pRb) and activate proinflammatory transcription factors (IRF3 and NF-κB), ultimately promoting the secretion of the senescence-associated secretory phenotype and establishing the cellular senescence program (right).

### 4.2 Mitochondrial dynamic imbalance triggers mitochondrial inflammation and activates the SASP

Evidence from physiologically aged tissues and senescent cell cultures indicates that mitochondrial dysfunction-particularly the leakage of mtDNA into the cytoplasm-is a consistent feature of senescence. This mtDNA leakage correlates with activation of the cGAS-STING signaling pathway, which in turn induces the expression of type I interferons and various inflammatory factors (such as IL-6 and IL-8). Through this mechanism, mitochondrial stress signals are effectively amplified from the cellular

level to a chronic inflammatory state affecting local and even systemic tissues, thereby establishing a key molecular basis for "inflammaging" [9].

Corroborating evidence from age-related disease models further implicates the mtDNA-cGAS-STING–SASP axis. In fibroblast-like synoviocytes from patients with rheumatoid arthritis, the TL1A/TNFR2 axis induces mitochondrial dysfunction and increased mitochondrial ROS production, which in turn amplifies the inflammatory response [85]. In heat stress-induced injury to mammary epithelial cells, mitochondrial dysfunction and ROS accumulation activate the NLRP3 inflammasome and promote the release of IL-1β [86]. Moreover, an imbalance in mitochondrial dynamics itself-such as excessive mitochondrial fission (fragmentation)-contributes to the assembly and activation of the NLRP3 inflammasome [87]. However, these disease and acute stress models involve inflammatory or physical stressors that may not fully recapitulate the chronic, low-grade, sterile inflammation of physiological aging. Therefore, while these studies illuminate possible mechanistic pathways, their direct applicability to normal physiological aging requires cautious interpretation.

Mechanistic studies have elucidated the molecular links between dynamic imbalance and inflammatory signaling. The continuous activation of these inflammatory signaling pathways resulting from an imbalance in mitochondrial dynamics drives senescent cells to secrete a wide array of inflammatory factors, chemokines and proteases, thereby generating the SASP.

Notably, the relationship is bidirectional and paracrine. SASP factors released by senescent cells, such as interleukins and chemokines, can also affect mitochondrial function in neighboring cells in a paracrine manner [88]. During the *in vitro* expansion of bone marrow mesenchymal stem cells (MSCs), IL-1α and IL-8 are secreted by late-passage senescent MSCs, which induce senescence in early-passage MSCs and may further impair their mitochondrial function by activating the NF-κB pathway [89]. In intervertebral disc degeneration, senescent nucleus pulposus cells recruit and activate proinflammatory macrophages via the SASP, collectively forming a pathological senescent microenvironment that exacerbates tissue degeneration [90]. Thus, an imbalance in mitochondrial dynamics not only results from senescence but, in turn, propagates it across cells, establishing a non-cell-autonomous amplification loop.

Cell-type and context dependency is prominent. The magnitude and consequence of cGAS-STING activation vary markedly by cell type. In macrophages, it amplifies pro-inflammatory cytokine production; in certain epithelial cells, it preferentially promotes senescence-associated growth arrest; and in neurons, it may trigger distinct degenerative programs without a classic SASP. An imbalance in mitochondrial dynamics activates inflammatory signaling pathways such as cGAS-STING and NLRP3 by releasing DAMPs and the production of ROS, thereby serving as a key link between cellular senescence and a chronic inflammatory.

### 4.3 Dysregulated mitochondrial dynamics cause metabolic changes that sustain cellular senescence

Evidence from physiological aging indicates that senescent cells often exhibit a metabolic shift toward glycolysis, accompanied by impaired oxidative phosphorylation [91]. In replicatively senescent human fibroblasts and aged rodent tissues, this metabolic shift is closely related to a dysregulated mitochondrial dynamics, with disruption of the balance between mitochondrial fusion and fission serving as key mechanisms [92]. For example, in models of ovarian aging, imbalances in mitochondrial dynamics (such as decreased fusion and increased fission) are associated with enhanced glycolysis and inhibition of oxidative phosphorylation, whereas treatment with recombinant follicle-stimulating hormone (FSH) and luteinizing hormone (LH) restores metabolic function by re-establishing mitochondrial fusion dynamics [93].

Metabolic alterations are not only regulated by mitochondrial dynamics but also feedback to affect mitochondrial morphology and function, thereby establishing a vicious cycle. For example, SIRT2 affects the activity of the mitochondrial fission protein DRP1 by regulating the MEK1-ERK-DRP1 and AKT1-DRP1 axes, thereby regulating the balance between glycolysis and oxidative phosphorylation [94]. In the tumor microenvironment, mitochondrial metabolic reprogramming (e.g., enhanced glycolysis and glutamine metabolism) further remodels mitochondrial morphology by altering metabolite signals (e.g., ATP/AMP levels and calcium flow), leading to either fragmentation or hyper-fusion of mitochondrial networks [95]. These findings should be considered hypothesis-generating rather than direct evidence for physiological aging, as cancer cells harbor oncogenic mutations and metabolic adaptations that may drive mitochondrial dynamics through distinct mechanisms. This interaction between metabolism and mitochondrial morphology has also been reported in pulmonary arterial hypertension. Excessive mitochondrial fusion promotes a glycolytic phenotype by increasing mitochondrial reactive oxygen species (mt-ROS) levels and inhibiting the activity of electron transport chain complexes [96].

Dysregulation of mitochondrial dynamics also exacerbates cellular senescence by affecting metabolic intermediates. For example, loss of nuclear myosin 1

(NM1) leads to hypoplasia of inner mitochondrial cristae and downregulation of oxidative phosphorylation genes, driving cells toward glycolysis for energy supply, a metabolic reprogramming closely related to tumorigenesis [97]. Stem cells and cancer cells can undergo metabolic reprogramming toward aerobic glycolysis (the Warburg effect); such cells frequently display aberrant expression of mitochondrial dynamic proteins, including OPA1 and DRP1, which alters the mitochondrial membrane potential and ATP production efficiency and further sustains the expression of glycolytic enzymes via transcription factors such as HIF-1α [98]. In immune cells, enhanced mitochondrial fusion promotes fatty acid oxidation through inhibition of HIF-1α expression, thereby regulating regulatory T-cell (Treg) differentiation and function [99].

These findings suggest that the crosstalk between mitochondrial dynamics and metabolic reprogramming represents an important mechanism in cellular senescence and related diseases, and that targeting this pathway may provide novel therapeutic strategies.

### 4.4 Disrupted mitochondrial dynamics accelerate cellular senescence by causing cell cycle arrest and affecting organelles

Mitochondrial dynamics play a key role in maintaining cell cycle arrest and senescence state by regulating the expression of cyclins and senescence markers (Fig. 3). Evidence from physiological aging models indicates that impaired mitochondria generate excessive ROS, which subsequently activate cellular senescence-related signaling pathways, including p53-p21 and p16-Rb [100]. ROS damage biological macromolecules through oxidative modifications of proteins, lipids, and nucleic acids, thereby initiating the DNA damage response (DDR). This activation involves upstream kinases such as ATM/ATR, which further stabilize and activate p53, leading to the initiation of downstream p21 expression. Consequently, this process inhibits cyclin-dependent kinases, ultimately resulting in permanent cell cycle arrest [101].

Tissue-specific studies have further elucidated context-dependent mechanisms. Loss of the mitochondrial fusion protein OPA1 causes muscle stem cells (MuSCs) to transition from deep quiescence to G-alert quiescence, leading to premature cell cycle activation and exhaustion. This process is accompanied by the activation of the glutathione (GSH) redox signaling pathway. The redox state promotes cell cycle progression and myogenic gene expression [102]. Similarly, in retinal pigment epithelial (RPE) cells, activation of the mitochondrial fission protein DRP1 impairs phagocytosis and delays the visual cycle, which may be associated with the pathogenesis of age-related macular degeneration (AMD) [103]. These findings illustrate that the functional consequences of mitochondrial dynamic imbalance are highly tissue-specific, reflecting the unique metabolic and functional demands of each cell type.

Importantly, the crosstalk between mitochondrial dynamics and cell cycle regulators is reciprocal. While ROS-induced p53 activation promotes cell cycle arrest, p53 itself directly modulates mitochondrial dynamics. Specifically, p53 inhibits DRP1 translocation to mitochondria through the PKA pathway, leading to excessive mitochondrial elongation under certain conditions [70]. In some contexts, this p53-mediated inhibition of fission may further impair mitochondrial quality control and reinforce the senescent state. Thus, p53 serves as a bidirectional node: it is both a downstream effector of mitochondrial stress and an upstream modulator of mitochondrial dynamics, thereby closing a regulatory loop.

Evidence from disease models provides additional mechanistic insights but requires careful extrapolation. In diabetic models of endothelial cell senescence, DRP1-mediated aberrant mitochondrial fission promotes VDAC1 oligomerization, leading to mtDNA release and activation of the cGAS-STING pathway, which exacerbated aging-related inflammatory responses [104]. Although this mechanism is plausible in physiological aging, direct evidence in non-diabetic aged endothelium remains limited. Similarly, CLIC1 promotes oxidative stress and mitochondrial fission by inhibiting the Nrf2/HO-1 pathway, thereby exacerbating endothelial cell senescence and dysfunction [105].

In addition, mitochondrial dynamics also regulates the interaction network of multiple organelles, adding another layer of complexity. OPA1 not only regulates mitochondrial morphology but also affects the structure of various organelles, including peroxisomes, early endosomes, and the cis-Golgi apparatus, and its loss leads to dysregulated autophagy [106].

Intervention strategies targeting mitochondrial dynamics have shown anti-aging potential, albeit with varying evidence levels. Adipose-derived stem cells (ADSCs) can increase mitochondrial membrane potential and ATP production in senescent HFF-1 cells and alleviate senescence-associated cell cycle arrest, apoptosis, and inflammation by regulating mitochondrial dynamics (promoting fusion/inhibiting fission) [32]. In diabetic vascular lesions, flavonoids such as homoplantaginin delay vascular endothelial cells senescence by inhibiting the DRP1-mediated mitochondrial fission-VDAC1 axis and blocking the mtDNA-cGAS-STING pathway [104]. These findings suggest potential avenues for developing senotherapeutic therapies targeting mitochondrial dynamics; however,

distinguishing between evidence from physiological senescence models and that from disease or acute stress models is essential for accurate translational expectations.

## 5. Anti-aging strategies targeting mitochondrial dynamics

Mitochondrial dysfunction can result in an inadequate supply of cellular energy and accumulation of reactive oxygen species, leading to cellular damage, senescence, and ultimately organismal aging. This condition is closely associated with numerous age-related diseases, including neurodegenerative diseases, cardiovascular diseases, and metabolic syndrome. Consequently, interventions targeting mitochondrial dynamics have become a focus of intensive research. However, it is important to recognize that the majority of these strategies remain at preclinical or early exploratory stages, and their translational readiness varies substantially. Below, the major emerging modalities are critically evaluated emphasis on the maturity of the evidence base and existing limitations (Fig. 4, Table 2).

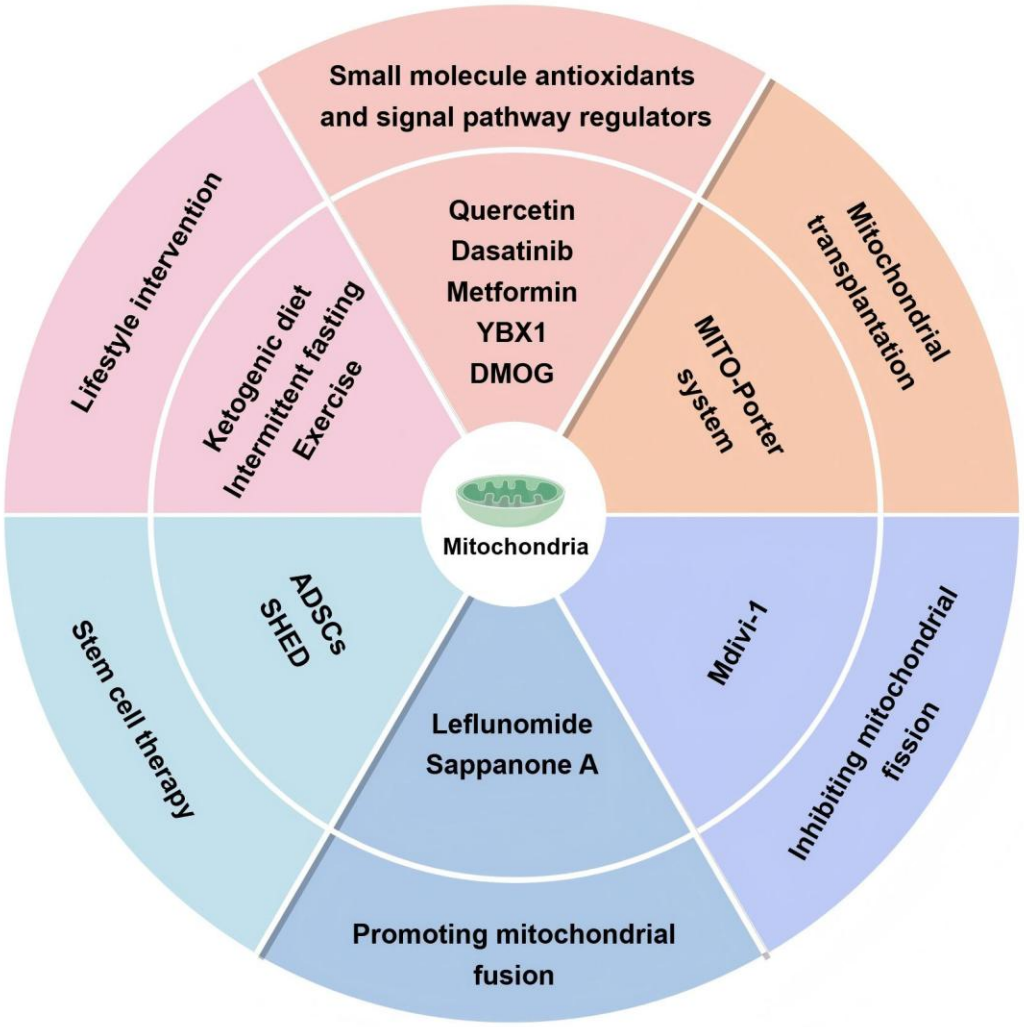



**Figure 4. Anti-aging strategies targeting mitochondrial dynamics.** These strategies fall into the following main categories: promoting mitochondrial fusion, inhibiting mitochondrial fission, small-molecule antioxidants and signaling pathway modulators, stem cell therapy, mitochondrial transplantation, and lifestyle intervention.

### 5.1 Pharmacological interventions targeting mitochondrial fusion/fission proteins

Mitochondrial dynamics maintain normal mitochondrial function and cellular homeostasis by regulating the balance between mitochondrial fusion and fission. Disruption of this dynamic balance is a key factor leading to mitochondrial dysfunction, ROS accumulation, and apoptosis during cellular senescence. Pharmacological intervention targeting mitochondrial fusion and fission proteins has emerged as potential strategies to delay cellular senescence and ameliorate related diseases.

**Table 2.** Anti-aging clinical trials targeting mitochondrial dynamics.

| Therapeutic class/strategy | Representative intervention | ClinicalTrials.gov ID | Translational stage | Condition / population | Mechanistic category | Main limitations / safety concerns |
|---|---|---|---|---|---|---|
| Senolytic | Dasatinib (D) and Quercetin (Q) | NCT04063124 | T1/T2 (Phase 1/2) | Early AD / older adults | Broad-acting (senescence-modifying) | Off-target effects on non-senescent cells; not mitochondria-specific |
| Metabolic / senomorphic | Metformin | NCT02432287 | T3 (Phase 4) | Aging-biology study | Broad-acting (metabolism-modifying) | Indirect mechanism (AMPK); benefits context-dependent |
| Mitophagy | Urolithin A | NCT03283462 | T2 (Phase 2) | Older adults / muscle | Broad-acting (metabolism-modifying) | Mitophagy biomarkers not yet validated as surrogates for clinical benefit |
| NAD+ replenishment | Nicotinamide Riboside（NR） | NCT03432871 | T1/T2 (Phase 1/2) | Mito biogenesis / energy | Broad-acting (metabolism-modifying) | Inconsistent functional improvements across trials; long-term data limited |
| Mito antioxidant | Mitoquinone（MitoQ） | NCT02597023 | T2 (Phase 2) | Middle-aged / older adults | Broad-acting (metabolism-modifying) | Indirect antioxidant mechanism; modest and variable clinical benefits |
| Bioenergetic support | Elamipretide | NCT02367014 | T1/T2 (Phase 1/2) | Mito myopathy | Broad-acting (metabolism-modifying) | Efficacy mainly in disease-specific populations |
| mTOR modulation | Rapamycin | NCT02874924 | T2 (Phase 2) | Older persons 70-95 y | Broad-acting (senescence-/metabolism-modifying) | Safety concerns (glucose intolerance, immunosuppression); indirect mTOR-mediated effects |
| Stem cell therapy | Allogeneic hMSC | NCT02065245 | T1/T2 (Phase 1/2) | Frailty | Broad-acting (stem cell-based, indirect) | Product heterogeneity (donor/source variation); durability of effects unclear |
| Stem cell therapy | UC-MSC (UMC119-06-05) | NCT06501066 | T1/T2 (Phase 1/2) | Frailty syndrome | Broad-acting (stem cell-based, indirect) | Uncertain in vivo persistence; reproducibility concerns across batches |
| Mito transfer | MNV-BM-BLD | NCT03384420 | T1/T2 (Phase 1/2) | Pearson syndrome | Direct (mitochondrial transfer) | Evidence limited to rare mitochondrial diseases; not validated for general aging |
| Mito transfer (repro) | ASC mitochondria | NCT07066267 | T1 (First-in-human/ early feasibility) | ART / oocyte competence | Direct (mitochondrial transfer) | Currently tested only in reproductive aging ; not applicable to systemic aging |

Translational stages (T0–T4) correspond to clinical trial phases as follows: T0: Basic research / Preclinical, T1: Phase 1 (first-in-human, safety), T2: Phase 2 (efficacy, proof-of-concept), T3: Phase 3 (confirmation, large-scale) or Phase 4 (post-marketing), T4: Population-level outcomes / Implementation.

DRP1 inhibitors. Inhibitors targeting the fission protein DRP1, especially Mdivi-1, have been extensively investigated. DRP1 is a key GTPase that mediates mitochondrial fission, and its excessive activation can lead to mitochondrial fragmentation, increased ROS production and apoptosis. Mdivi-1 inhibits the GTPase activity of DRP1, thereby reducing mitochondrial fission and maintaining normal mitochondrial morphology and function. Multiple studies have shown that Mdivi-1 exerts protective effects in various disease models. For example, in a Parkinson's disease model, Mdivi-1 reduces neuronal damage by inhibiting excessive fission to promote PGC-1α-mediated mitochondrial biogenesis [107]. In myocardial ischemia–reperfusion injury, Mdivi-1 improves mitochondrial function and reduces apoptosis [108]. In addition, Mdivi-1 attenuates drug-induced cardiotoxicity, such as adriamycin-induced mitochondrial fission and myocardial injury [109]. However, the

specificity of Mdivi-1 as a DRP1 inhibitor has been questioned, and its effects should be interpreted with caution [110].

Promoting fusion. Enhancing mitochondrial fusion represents an alternative strategy. Decreased expression of MFN2 and OPA1 leads to impaired mitochondrial fusion and dysfunction, pharmacological or genetic approaches of these two proteins can help restore mitochondrial fusion, counteract oxidative stress, and protect cellular function [111]. For example, leflunomide, an FDA-approved immunosuppressive agent, has been found to directly activate MFN2 expression and partially promote OPA1 expression, although its protective effect was limited in models of neuronal ischemia [112]. Unfortunately, to date, no selective MFN2 or OPA1 activator has been developed specifically for senescence intervention. The reported agents exhibit pleiotropic effects, and their mechanisms are incompletely understood. Moreover, indiscriminate promotion of fusion could theoretically impede the clearance of damaged mitochondrial fragments. Consequently, these strategies remain strictly exploratory.

Pathway modulators. In addition to directly regulating the expression and activity of fusion and fission proteins, targeting related signaling pathways has also been considered a potential strategy. Among them, the p53-PKA-DRP1 pathway plays an important role in regulating mitochondrial fission. However, these strategies remain at an even earlier stage, with only proof-of-concept studies in cell lines. Upon p53 activation, the phosphorylation of DRP1 can be mediated by PKA, thereby affecting its mitochondrial localization and fission activity. Regulation of this pathway may inhibit abnormal mitochondrial fission and protect cells from oxidative stress and apoptotic damage [113]. In addition, CARM1 is involved in the cellular stress response and metabolic regulation by regulating the transcription of related genes and affecting the expression of mitochondrial fusion and fission proteins [114]. While these agents have generated important mechanistic insights, none of the currently available agents is ready for clinical anti-aging use. Major hurdles include off-target effects, lack of tissue specificity, and the absence of long-term safety data in aged organisms. Clinical trials specifically targeting aging (rather than acute diseases) are lacking.

### 5.2 Small-molecule antioxidants and signaling pathway modulators

Small-molecule antioxidants and signaling pathway modulators have demonstrated therapeutic potential in intervening in cellular senescence, especially by restoring mitochondrial function and regulating mitochondrial dynamics [115]. Small-molecule antioxidants. As a natural flavonoid with significant antioxidant and anti-inflammatory properties, quercetin can remove excess reactive oxygen species and protect mitochondria from oxidative damage. Preclinical studies reveal that the combined use of quercetin and dasatinib eliminate senescent cells and ameliorate aging-related physiological decline. These two compounds modulate senescence phenotypes and metabolic homeostasis and indirectly regulate mitochondrial function [116]. Moreover, signaling pathway modulators targeting oxidative stress, such as CLIC1 inhibitors, reduce oxidative damage and senescence of endothelial cells by activating the Nrf2/HO-1 antioxidant pathway, which holds promise for the anti-aging treatment of cardiovascular diseases [105]. Although certain small molecules, including quercetin and metformin, act on multiple targets, their regulatory mechanisms underlying mitochondrial dynamics (fission, fusion and mitophagy) remain poorly elucidated.

Signaling pathway modulators. As a prototype of broad metabolism-modifying interventions, metformin acts primarily through systemic pathways rather than direct mitochondrial targeting. Its anti-aging effects are largely attributed to AMPK activation and mTOR inhibition, which can be initiated partly by mild inhibition of mitochondrial complex I, ultimately contributing to delayed cellular senescence [117]. Similarly, interventions targeting the STAT3 signaling pathway, another broad senescence-modulating strategy, can alleviate cellular senescence secondarily by reducing oxidative stress and restoring mitochondrial function [118]. Pharmacological inhibitors of mTOR delay cellular senescence and improve tissue function, partly by inducing autophagy and mitochondrial renewal [119]. For instance, targeting the mTOR pathway by inhibiting its downstream effector YBX1 has demonstrated anti-aging and antitumor potential, as YBX1 knockdown induces cellular senescence in gastric cancer cells [120]. Although regulators targeting pivotal signaling pathways, such as JAK2/STAT3 and mTOR, exert favorable effects in restraining senescence-associated inflammation and ameliorating metabolic imbalance, these pharmacological interventions may also cause undesired side effects and interfere with physiological processes, including normal cell growth, host immune responses, and endogenous tissue repair capacity.

Activating mitophagy. Certain broad-acting natural products, such as the senolytic agent quercetin and the flavonoid kaempferol, protect cells from oxidative damage and delay senescence, partly through activation of mitophagy as a downstream effect. For instance, kaempferol restores bone marrow mesenchymal stem cell (BMSC) function and reduces osteoporosis-related cellular senescence by activating Sp1/FUNDC1 signaling

to promote mitophagy [121]. By contrast, small molecules such as dimethyloxalylglycine (DMOG) more specifically target the mitophagy machinery by activating the HIF-1α/BNIP3 signaling pathway, thereby improving mitochondrial function and metabolic reprogramming in MSCs to delay cellular senescence [122]. However, regardless of their mechanism, interventions that activate mitophagy carry inherent risks due to its dual role of this process. Insufficient mitophagy fails to eliminate damaged mitochondria, thereby exacerbating oxidative stress and cellular senescence. Conversely, excessive mitophagy may degrade healthy mitochondria, disrupt energy metabolism, and impair cell growth and stem cell function. Moreover, these agents may exert off-target effects or induce nonspecific activation/inhibition of other signaling pathways, potentially resulting in metabolic disorders or cytotoxicity.

### 5.3 Stem cell therapy

ADSCs have shown potential for improving cellular energy metabolism and delaying cellular senescence through the regulation of the dynamic balance of the dynamic balance between mitochondrial fusion and fission. In the $H_2O_2$-induced senescence model of HFF-1 cell, ADSC treatment significantly increased the mitochondrial membrane potential and ATP production while reducing levels of inflammatory factors (IL-6, IL-1β, TNF-α) and oxidative stress markers (MDA). This protective effect is closely related to the ability of ADSCs to promote the expression of mitochondrial fusion proteins (such as OPA1) and inhibit the activity of fission proteins (such as DRP1) [32]. In particular, the anti-senescence effect was more pronounced when ADSCs were combined with the mitochondrial fission inhibitor Mdivi-1, suggesting that precise regulation of the balance of mitochondrial dynamics balance is an important mechanism underlying the therapeutic effects of ADSCs [123]. However, despite their anti-senescence benefits, ADSCs and their derivatives may secrete proinflammatory factors that could contribute to the SASP, potentially aggravating chronic inflammation and tissue damage. Furthermore, aberrant differentiation of ADSCs also raises potential tumorigenic concerns.

Recent studies have shown that young sEVs derived from stem cells from human exfoliated deciduous teeth (SHEDs) can promote the translocation of DRP1 from the cytoplasm to mitochondria, thereby improving the mitochondrial network structure in replicative senescent bone marrow mesenchymal stem cells (BM-MSCs) [124]. These sEV-enriched miRNAs and other biologically active molecules may reverse stem cell functional decline by remodeling mitochondrial morphology and restoring mitochondrial membrane potential and ATP synthesis capacity [125]. Similarly, EVs from hypoxia-preconditioned gingival mesenchymal stem cell (GMSC)-derived extracellular vesicles (H-3D-EVs), the proliferation ability and differentiation potential of aged GMSCs can be improved by upregulating the expression of genes related to mitochondrial dynamics [126]. Although stem cell-derived EVs possess promising therapeutic potential, their composition and biological function are influenced by multiple factors, including donor age and disease state. Furthermore, their context-dependent characteristics often result in inconsistent and unstable therapeutic efficacy.

A bidirectional regulatory relationship exists between mitochondrial dynamics and stem cell fate decisions. On the one hand, the differentiation state of stem cells affects the morphology of mitochondria. Undifferentiated female germline stem cells (GSCs) exhibit predominantly fragmented mitochondria, whereas differentiated germ cells show more elongated mitochondria. On the other hand, artificially manipulation of mitochondrial dynamics can significantly affect stem cell function [127]. For example, inhibition of the mitochondrial fission protein DRP1 delays age-related loss of ovarian GSCs in Drosophila, whereas promotion of mitochondrial fusion enhances GSCs attachment to the niche [128]. In MSCs, metabolic syndrome (MetS) impairs three-dimensional mitochondrial structure, increases mitochondrial fission, and decreases mitochondrial fusion, accompanied by decreased membrane potential and ATP production. These changes are closely associated with a decline in stem cell function [129].

### 5.4 Mitochondrial transfer technology and its application in senescent cells

As an emerging therapeutic strategy, mitochondrial transfer technology has shown significant potential for improving the mitochondrial function in senescent cells. This technology can slow or partially reverse cellular senescence by introducing exogenous healthy mitochondria into functionally impaired cells, thereby repairing mitochondrial dysfunction, improving cellular energy metabolism, and alleviating age-related phenotypes [130]. Studies have shown that mitochondrial transfer can deliver functional mitochondria from bone marrow mesenchymal stem cells to $CD8^+$ T cells through tunneling nanotube-mediated intercellular transfer mechanisms, significantly enhancing the metabolic adaptability and antitumor efficacy of T cells [131]. The generation of such "supercharged T cells" not only provides a novel technical platform for tumor immunotherapy but also offers an important reference for restoring mitochondrial function in senescent cells. In addition, mitochondrial transfer technology has been

shown to reestablish the metabolic function of diseased or damaged cells and has broad application prospects in the treatment of metabolic diseases [132].

Recent studies have demonstrated the efficacy of mitochondrial transfer technology in disease models such as age-related macular degeneration (AMD). Retinal pigment epithelial cells from AMD patients often exhibit mitochondrial dysfunction, the transfer of exogenous mitochondria can restore their energy metabolism, improve the functional state of retinal tissue, and delay disease progression [130]. In addition, mitochondrial transfer has been explored in a variety of fields, such as diabetic complications, cardiovascular diseases, and neurodegenerative diseases, and has shown broad application potential in the treatment of age-related diseases [133, 134].

Several challenges remain in the clinical application of mitochondrial transfer technology, such as the selection of optimal mitochondrial sources, enhancement of delivery efficiency, and long-term stability of transplanted mitochondria [135]. At present, the development of new delivery systems, such as tunneling nanotubes and extracellular vesicles, has made it possible to overcome these technical bottlenecks. As an innovative drug delivery platform, the MITO-Porter system has shown unique advantages in mitochondrial targeted therapy [136]. With continued technological advancement, mitochondrial transplantation is expected to become a transformative therapeutic strategy in cell- and organelle-specific medicine, offering new therapeutic avenues for age-related diseases.

Although mitochondrial transplantation therapy has shown promising potential in the field of anti-aging research, several challenges remain that limit its clinical translation. First, the selection of mitochondrial sources is problematic. Compared with native mitochondria, mitochondria from different origins, including allogeneic, xenogeneic and artificially synthesized sources, differ significantly in immunogenicity, functional activity and compatibility with recipient cells, and no unified evaluation criteria have been established. Second, the delivery efficiency requires further optimization. Current strategies rely mainly on natural routes such as tunneling nanotubes and extracellular vesicles, which exhibit low active delivery efficiency and cannot deliver healthy mitochondria to senescent cells or specific tissues in a targeted and scalable manner. Third, post-transplantation stability remains inadequate. After entering recipient cells, exogenous mitochondria are at risk of degradation, mitophagic degradation, or failure to integrate into the host mitochondrial network, the maintenance of long-term function remains unresolved. Fourth, safety evaluation systems are still evolving. Xenogeneic mitochondria may trigger unforeseen side effects such as immune rejection, genetic material transfer and cellular metabolic disorders, and long-term safety data are still lacking.

### 5.5 Lifestyle intervention

Lifestyle interventions, such as diet and exercise, have also been shown to improve cellular metabolism and function by affecting mitochondrial dynamics, thereby delaying cellular senescence. Regarding dietary interventions, the ketogenic diet (KD) has shown positive effects in various models of metabolic disease. In mouse models of type 2 diabetes, a ketogenic diet improved cardiac dysfunction by balancing mitochondrial dynamics and inhibiting apoptosis [137]. In mice with metabolic dysfunction-associated fatty liver disease, two weeks of ketogenic diet feeding partially improved hepatic lipid deposition, restored the balance of mitochondrial dynamics, and ameliorated mitochondrial dysfunction [138]. In addition, intermittent fasting has been shown to reduce the senescence phenotype of adipose stem cells and restore their adipogenic potential in the adipose tissue of aged mice. Moreover, it increases the number of eosinophils in adipose tissue, which helps to improve white adipose tissue homeostasis and immune function, thereby slowing age-related adipose tissue dysfunction [139]. Exercise, as an important lifestyle intervention, has been shown to enhance mitochondrial health. In aged mice, environmental enrichment (mimicking an active lifestyle) improved motor function and upregulated the expression of mitochondrial genes related to oxidative phosphorylation and the tricarboxylic acid cycle in skeletal muscle, suggesting that it may act by protecting mitochondrial function [140]. In a mouse model of spinal muscular atrophy, a single exercise stimulus increased citrate synthase expression and corrected autophagosome overassembly in skeletal muscle, suggesting that exercise can enhance mitochondrial health [141]. In human studies, higher levels of physical activity have been associated with significant reductions in circulating levels of various SASP proteins in older adults [142]. This evidence suggests that lifestyle interventions, such as diet and exercise, are associated with improved regulation mitochondrial dynamics and quality control and represent important non-pharmacological means to improve cellular metabolism, delay functional decline, and mitigate age-related decline.

## 6. Conclusion and future perspectives

As an important driver of cellular senescence, the mechanism and impacts of mitochondrial dynamics imbalance have become increasingly clear. Research in this field has progressed from the description of

phenomena to the elucidation of molecular mechanisms and is now moving toward clinical transformation. According to existing studies, multidimensional dynamic processes such as mitochondrial fusion, fission and mitophagy, collectively maintain the dynamic balance of mitochondrial function. Disruption of this balance is a fundamental causes mitochondrial dysfunction in senescent cells. This disruption not only significantly contributes to a crisis of cellular energy (ATP) production and excessive accumulation of reactive oxygen species but also profoundly disrupts the stability of the intracellular environment by interfering with calcium homeostasis and the release of proinflammatory signals, thereby driving cells into a persistent senescent state. This process underlies the comorbidities associated with multiple age-related diseases, such as neurodegenerative diseases, cardiovascular diseases and metabolic syndrome.

At present, some differences and controversies exist regarding the role of mitochondrial dynamics in cellular senescence. It is necessary to recognize that the regulation of mitochondrial dynamics is highly dependent on the cell type and environment. For example, a moderate enhancement of fission may promote the removal of damaged mitochondria, whereas excessive activation leads to functional fragmentation. Enhanced fusion maintains network integrity but may impede selective autophagy. Similarly, studies on the regulatory effects of upstream pathways, such as SIRT1, AMPK, and mTOR, may sometimes appear contradictory results; these discrepancies, however, reflect the complex and dynamic balance among energy sensing, stress response, and anabolism maintained by these pathways. Future studies should aim to clarify the physiological and pathological backgrounds of these regulatory events. This will require not only by conducting in-depth analyses of the molecular mechanisms underlying mitochondrial dynamics but also the integrating emerging high-resolution imaging techniques and single-cell analysis methods to reveal the heterogeneity of senescent cells and spatiotemporal dynamic changes in mitochondrial function.

In addition, although intervention strategies targeting key proteins and upstream regulatory genes of mitochondrial dynamics have yielded promising results in preclinical studies, substantial challenges remain. The main limitation lies in achieving spatiotemporal specificity and safety in therapeutic applications. Small-molecule inhibitors or activators may produce off-target effects. Exercise and nutritional interventions (e.g., caloric restriction mimics) are more systemic but less targeted in their effects. Mitochondrial transplantation and stem cell therapy face challenges related to delivery and long-term safety. Therefore, a key next step is the development of precision tools capable of targeting specific cell types (e.g., senescent cells), or specific organelle states(e.g., severely impaired mitochondria).

Mitochondrial dynamics is a central regulatory mechanism in the biology of aging. Related studies not only deepen our understanding of the nature of cellular senescence but also provide new insights and strategies for mitigating age-related decline and treating associated diseases. An imbalance in mitochondrial dynamics should not be viewed as an isolated target but rather as a hub of a network connecting cellular metabolism, stress resistance, protein homeostasis, and epigenetic regulation. By integrating multi-omics data, conducting multi-level and multi-dimensional in-depth analyses, and validating findings using organoid and gene-editing models, a more comprehensive regulatory network model of mitochondrial dynamics can be constructed. Furthermore, personalized and precise treatment strategies should be developed to the greatest extent possible, thereby facilitating the translation of basic research findings into clinical applications.

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## Author contributions

All the authors contributed to the conception and design of the review. Dan Wu, Shihao Jiang and Chenyang Li drafted the main text and designed the figures. Xianqi Wang, Yuexiang Ma and Peiwen Wang consulted related literature. Yanan Xu, Heliang Fu and Qianmei Wang synthesized the literature. Junjie Li, Rui Zheng and Kuo Shen supervised the work and provided expert revisions. All the authors participated in manuscript revisions, approved the final version, and agreed to be accountable for its content.

## Competing interests

The authors declare that they have no competing interests.

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