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Mitochondria pleiotropism in stem cell senescence: Mechanisms and therapeutic approaches

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ABSTRACT

Aging is a complex biological process characterized by a progressive decline in cellular and tissue function, ultimately leading to organismal aging. Stem cells, with their regenerative potential, play a crucial role in maintaining tissue homeostasis and repair throughout an organism's lifespan. Mitochondria, the powerhouses of the cell, have emerged as key players in the aging process, impacting stem cell function and contributing to age-related tissue dysfunction. Here are discuss the mechanisms through which mitochondria influence stem cell fate decisions, including energy production, metabolic regulation, ROS signalling, and epigenetic modifications. Therefore, this review highlights the role of mitochondria in driving stem cell senescence and the subsequent impact on tissue function, leading to overall organismal aging and age-related diseases. Finally, we explore potential anti-aging therapies targeting mitochondrial health and discuss their implications for promoting healthy aging. This comprehensive review sheds light on the critical interplay between mitochondrial function, stem cell senescence, and organismal aging, offering insights into potential strategies for attenuating age-related decline and promoting healthy longevity.

1. Introduction

Aging is a complex and inevitable process that affects all multicellular organisms. It is characterized by the progressive decline in tissue and organ function, leading to an increased susceptibility to diseases and ultimately, death. Stem cells play a critical role in maintaining tissue homeostasis and regeneration throughout life. Therefore, accumulating evidence suggests that stem cell aging contributes to the overall process of organismal aging [1,2].

Stem cells are a unique type of undifferentiated cells that can self-renew and differentiate into various specialized cell types. Self-renewal allows stem cells to generate identical copies of themselves, ensuring a constant pool of stem cells in each tissue. Their pluripotency refers to the ability of stem cells to differentiate into multiple cell types, serving as the building blocks for the development and renewal of tissues and organs, contributing to the restoration of injured or damaged tissues. Thus, stem cells play a crucial role in tissue regeneration, repair, and maintenance throughout the lifespan of an organism. A hallmark of stem cell aging is the alteration in stem cell populations within tissues niches. For instance, the number and quality of mostly all stem cell types decreases [3–5], with the exception of hematopoietic stem cells (HSC) which number increases but their function decreases with age [6]. New advanced methodologies, such as single-cell transcriptomics, lineage tracing and clonal analysis, have enabled a more quantitative measurement of stem cell populations within niches during aging [7]. The reduced number and quality of stem cell pools has significant consequences for tissue homeostasis and regenerative capacity. With advancing age, stem cells accumulate several damages (e.g.: somatic mutations) leading to increased cell death, cell senescence, reduced self-renewal capacity and reduced ability to produce a committed progeny [8,9]. Indeed, old stem cells may enter a state of senescence [10], or become excessively activated [11], or may undergo aberrant differentiation [12–14]. All these changes promote stem cell exhaustion leading to impaired regenerative potential in aged tissues [15,16]. Moreover, the balance between quiescent and actively dividing stem cells is disrupted. Quiescent stem cells, which normally serve as a reserve population ready for activation during tissue injury, become less responsive to regenerative signals and exhibit reduced proliferative capacity [7,17]. Taken together, these alterations impede the timely and effective repair of damaged tissues, leading to compromised tissue homeostasis.

Cellular senescence is a state of irreversible growth arrest that occurs

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in cells as a response to various stressors, including DNA damage, telomere shortening, oxidative stress, and oncogene activation [18]. This phenomenon plays a crucial role in stem cell aging and has significant implications for their functionality and regeneration capacity. As stem cells age, they become more prone to entering a senescent state, which is characterized by morphological alterations, such as flattening, vacuolization and accumulation of stress granules [19–21], increased activity of senescence-associated β-galactosidase (SA-β-Gal) and overexpressed $p16^{INK4a}$ levels [22,23], as well as an unusual pattern of heterochromatin that is present in discrete nuclear subdomains, known as senescence-associated heterochromatic foci (SAHFs), which are associated with S-phase- promoting gene loci, such as E2F target genes [24]. Senescent stem cells also display a secretion pattern consisting of inflammatory cytokines and other signalling molecules — including interleukin-1 (IL-1), IL-6, IL-8, vascular endothelial growth factor A (VEGFA) and matrix metalloproteinases (MMPs), known as the senescence-associated secretory phenotype (SASP). The SASP includes the release of pro-inflammatory cytokines, but also growth factors and extracellular matrix remodelling enzymes, which can have detrimental effects on the tissue microenvironment and neighbouring cells [25]. The SASP's original function is to act as a call for immune clearance of their parental cell so it can be replaced by a new cell. However, with advancing aging, the immune system is usually compromised and misses a total clearance of senescent cells, which in turn tend to accumulate. The accumulation of senescent stem cells within tissues can disrupt the normal balance between cell renewal and tissue repair, leading to a decline in organ function [26]. Additionally, the accumulation of senescent stem cells promotes a chronic inflammation status and contributes to the development of age-related diseases [27].

Mitochondria are essential cellular organelles often referred to as the "powerhouses" of the cell. Beyond their role in energy production, mitochondria play a critical role in various cellular processes, including metabolism, apoptosis, calcium homeostasis, and reactive oxygen species (ROS) regulation [28]. Mitochondrial dysfunction has been increasingly recognized as a central player in the aging process. According to the mitochondrial free radical theory of aging, ROS are considered to be unwanted toxic by-products of aerobic metabolism that induce oxidative damage to various macromolecules (lipids, proteins, and nucleic acids) due to their high chemical reactivity [29]. This mitochondrial theory of aging is based on the fact that mitochondrial function declines with aging leading to ROS overproduction and the activity of several ROS-scavenging enzymes also declines with age. Further supporting this theory, it has been reported that mutations of mitochondrial DNA (mtDNA) accumulate during aging. Mutations of mtDNA may arise as a consequence of unrepaired DNA damage, such as damage caused by ROS, or by replication errors during normal mtDNA synthesis [30]. Interestingly, mtDNA mutations have been proposed as a driving force in aging, as demonstrated by the mutator mice displaying an accelerated aging phenotype [31]. Finally, the link between mitochondrial function and signalling pathways has been reported to regulate longevity since aging-associated phenotypes have been associated to altered mitochondrial function, biogenesis and metabolism [28]. The role of mitochondria in cellular aging extends to stem cells [32], which rely heavily on mitochondrial activity for their proper functioning. Indeed, mitochondrial dysfunction in stem cells can manifest in various ways, including impaired ATP production, increased ROS production, compromised mitochondrial dynamics, and altered mitochondrial DNA integrity [33]. These mitochondrial changes can have detrimental effects on stem cell function, leading to reduced self-renewal capacity, impaired differentiation potential, and diminished regenerative capacity.

In this review, we focus on how mitochondrial dysfunction can lead to cellular senescence, and the subsequent consequences on tissue dysfunction and the ultimate organismal aging. Finally, we explore potential anti-aging therapies targeting mitochondrial health and discuss their implications for promoting healthy aging.

2. The role of mitochondria in stem cell fate

Mitochondria are double-membrane organelles found in most eukaryotic cells. They play a central role in cellular energy production, metabolism, and various other essential cellular processes, including calcium signalling, apoptosis regulation, and reactive oxygen species (ROS) metabolism.

Mitochondria consist of an outer membrane, an inner membrane, an intermembrane space, and a matrix. The inner mitochondrial membrane is highly folded, forming structures called cristae. Within these cristae, there are electron transport chain (ETC) complexes responsible for oxidative phosphorylation (OXPHOS). During this process, electrons derived from the breakdown of fuel sources, such as glucose and fatty acids, are transferred through the ETC complexes, leading to the generation of a proton gradient across the inner mitochondrial membrane. The flow of protons back into the matrix through ATP synthase drives the synthesis of ATP.

With aging, mitochondrial function is hampered as a consequence of an accumulation of mtDNA mutations, deficient proteostasis leading to the destabilization of the respiratory chain complexes, and changes in mitochondrial dynamics [1,2]. Altogether, mitochondrial function is compromised and ultimately cellular bioenergetics, which may trigger accidental permeabilization of mitochondrial membranes causing inflammation and cell death [34].

It has been suggested that mitochondrial dysfunction is also a feature of cellular senescence. The first link between mitochondria and the senescent phenotype was discovered as an attempt to find environmental strategies to extend the lifespan of cell cultures *in vitro*. Success came nearly two decades after Hayflick's initial report [35], when it was observed that simply reducing the ambient oxygen concentration in which the cells were cultured resulted in a significant extension in population doublings [36,37]. This observation suggested a relationship between oxygen availability, mitochondrial ROS, and senescence induction [38].

Correia-Melo et al. experiment demonstrated the effects of removing mitochondria in different models of cellular senescence [39]. In particular, these mitochondrial-deficient senescent cells were growth arrested but failed to exhibit an enlarged cell size, increased senescent associated β-galactosidase activity, heterochromatin foci formation, or augmented p21 and $p16^{INK4a}$ expression, all of them being currently observed in senescent cells. It is important to mention that this reduction in the overall senescent phenotype was not related to impaired levels of ATP, which remained unaltered in these senescent cells lacking mitochondria. Although, as expected, a marked compensatory increase in glycolysis was observed in these mitochondria-deficient senescent cells. Together, these observations suggest that mitochondria are required for the induction and maintenance of the senescent state.

Supporting this idea, cumulative evidence indicates that senescent cells exhibit mitochondria with a variety of changes in their structure, dynamics, and function [40]. It has been shown that senescent fibroblasts display an increase in mitochondrial mass and number [41,42]. Even though mitochondria are more abundant in senescent cells, they are less functional as they display a decreased mitochondrial membrane potential, increased proton leak, and increased generation of ROS [43,44].

Proper mitochondrial function is essential for maintaining the balance between self-renewal and differentiation in stem cells [45]. Therefore, dysfunctional mitochondria can disrupt the delicate balance of metabolic pathways and signalling networks, leading to skewed differentiation outcomes. The following sections provide an in-depth explanation of how dysfunctional mitochondria can act as drivers of cellular senescence, thereby promoting impaired stem cell function and compromised tissue repair (Fig. 1).

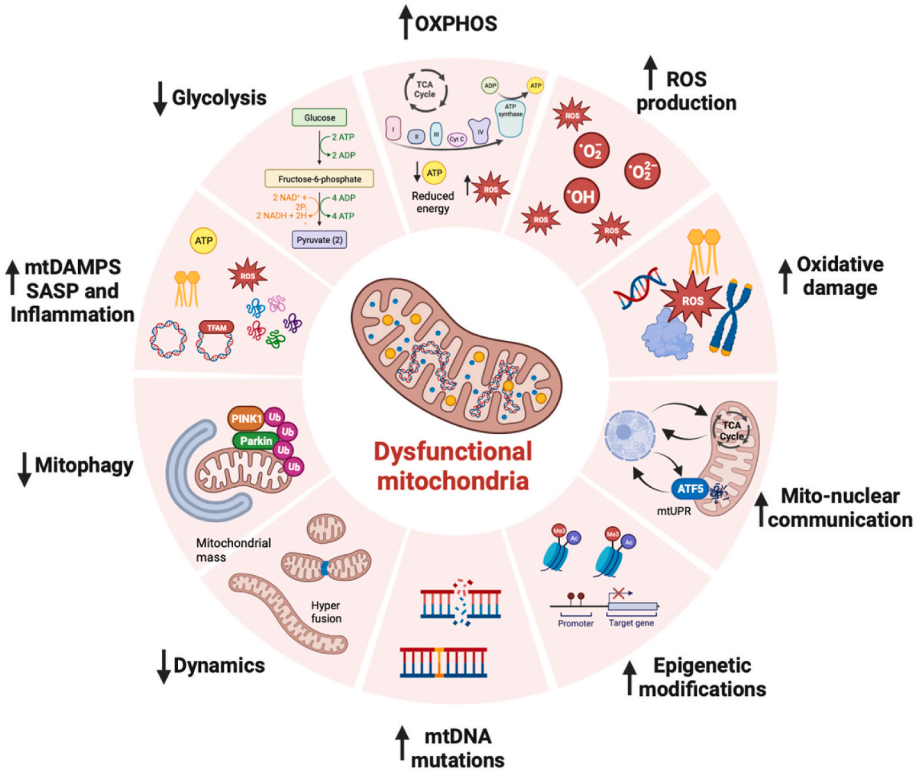

Fig. 1. Pleiotropism of dysfunctional mitochondria in stem cell senescence.

2.1. Energetic metabolism and ROS production

Mitochondria are highly dynamic organelles capable of adapting their metabolic function to meet cellular demands. They can switch between OXPHOS and glycolysis based on nutrient availability and cellular requirements [46]. This metabolic flexibility is particularly important for stem cells, which need to balance self-renewal and differentiation.

The importance of mitochondria in mediating stem cell activity has been largely neglected owing to the little presence of mitochondria in many types of stem cells [47]. Moreover, different types of stem cells have different metabolic profiles; however, reported data describe stem cells mostly as glycolytic [48]. Consistent with a tendency towards glycolysis over OXPHOS, human hematopoietic stem cells (HSCs) [49], mesenchymal stem cells (MSCs) [50] and embryonic stem cells (ESCs) [51] have few mitochondria. For instance, anaerobic metabolism in

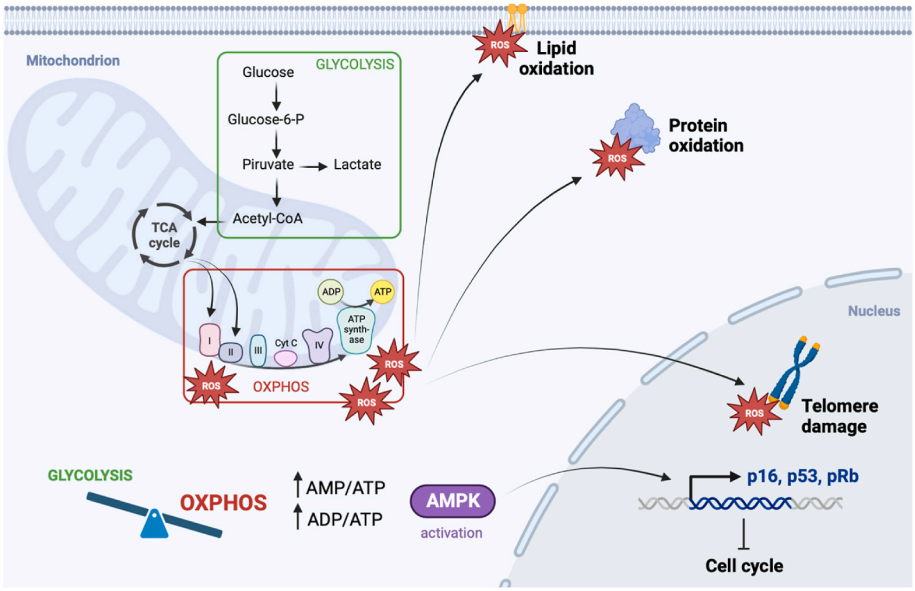

Fig. 2. Mitochondrial OXPHOS metabolism and ROS production in stem cell senescence. Damaged mitochondria display aberrant OXPHOS that produces excessive amounts of ROS that damage lipids, proteins and DNA, specially telomeric regions. The imbalance between OXPHOS and glycolysis reduces ATP production which activates AMPK leading to cell cycle arrest and senescence induction. Tricarboxylic acid cycle (TCA), Oxidative phosphorylation (OXPHOS), AMP-activated protein kinase (AMPK), Reactive Oxygen Species (ROS), Retinoblastoma protein (pRb).

stem cells may reflect an evolutionary adaption to their low-oxygen niche. Also, the glycolytic metabolism is more efficient in providing the necessary intermediates required for anabolic pathways that are essential during self-renewal and differentiation. Lastly, anaerobic metabolism avoids excessive oxidative damage derived from mitochondria-generated ROS.

When stem cells enter senescence, they display a switch of their mitochondrial bioenergetics from glycolysis towards OXPHOS [52]. This bioenergetic imbalance has been characterized by an increase in AMP/ATP and ADP/ATP ratios [53,54]. This drop in ATP production in senescent cells is associated with an inefficient OXPHOS and a reduction of the mitochondrial membrane potential [55]. The increase of these ratios leads to the activation of the AMP-activated protein kinase (AMPK). In turn, AMPK activation can lead to the direct phosphorylation and activation of p53 [56,57], upregulation of p16 expression [58,59], and reduction of retinoblastoma protein (pRb) phosphorylation, all of which have been shown to contribute to cell cycle arrest and senescence induction [60] (Fig. 2).

Senescent cells usually display an OXPHOS energetic metabolism that produces excessive amounts of ROS, including superoxide, hydrogen peroxide, and hydroxyl radicals, all of them being natural by-products of mitochondrial metabolism. It has been reported that ROS can induce cellular senescence. Indeed, hydrogen peroxide is a potent inducer of cellular senescence [61]. ROS overproduction is associated with the induction of replicative senescence, oncogene-induced senescence, and $p16^{INK4a}$-induced senescence [43,62–65]. The common underlying mechanism is a positive feedback loop involving mitochondrial damage, ROS overproduction, and the activation of the DNA damage response (DDR) through the $p53/p21^{CIP1}$ pathway, which ultimately leads to the establishment of the growth arrest phenotype of cellular senescence [66].

During aging, accumulated damage to the mitochondrial ETC promotes mitochondrial stress, which causes cellular senescence. Experimental inhibition of complex I by rotenone, of complex II by 2-thenoyltriflu-oroacetone (TFFA) and of complex III by antimycin A induces cell proliferation arrest and premature senescence [41,67,68]. These evidences support the idea that defective mitochondrial ETC could be a trigger to establish cellular senescence. However, the specific mechanism linking defective ETC and growth arrest is still unclear [69]. A possible explanation could be that impaired ETC can increase ROS production and promote molecular damage to proteins, lipids, and DNA, which then results in cellular senescence [37,44]. Importantly, mitochondrial ROS can accelerate telomere-induced senescence, since high levels of ROS can induce both single- and double-stranded breaks in the genome, particularly at telomere regions [70] leading to premature cell cycle arrest (Fig. 2).

2.2. Mito-nuclear communication and epigenetic modifications

The mitochondrial-nuclear communication is known to be bidirectional [71]. Mitochondrial function is controlled by nuclear-encoded genes through anterograde signalling (nuclear-to-mitochondrial), which promotes mitochondrial biogenesis or enhances mitochondrial activity to adapt to cellular demands. This regulation mainly depends on mitochondrial transcription factor (TFAM), peroxisome proliferator-activated receptor γ co-activator 1α (PCG1α) and Nuclear respiratory factor 1 (Nrf1), which induce the expression of mitochondrial DNA-encoded genes [72,73]. However, with aging, nuclear genome is subjected to cumulative damage, leading to epigenetic modifications that can influence the accessibility of DNA to transcription factors and other regulatory molecules, thereby impacting gene expression patterns. Indeed, signal transduction of p53, Ataxia-Telangiectasia Mutated (ATM) and Poly (ADP-Ribose) Polymerase 1 (PARP1) genes is altered during aging, which leads to mitochondrial dysfunction and cellular senescence [74]. Thus, nuclear DNA damage play a crucial role in mitochondrial function as they can directly affect the expression of genes involved in mitochondrial biogenesis and function (Fig. 3).

On the other hand, retrograde signalling (mitochondrial-to-nuclear) is transmitted from mitochondria to the nucleus in response to perturbations within mitochondria [75]. This signalling is mediated by mitochondrial metabolites derived from the tricarboxylic acid (TCA) cycle, including acetyl-CoA, α-ketoglutarate (α-KG), citrate, succinate, fumarate, and 2-hydroxyglutarate (2-HG), which are involved in epigenetic modifications and chromatin remodelling. In particular, these metabolites control key regulators of epigenetic enzymes involved in histone acetylation and methylation, as well as DNA methylation [76–79]. Indeed, these TCA metabolites have been identified as drivers of senescence (Fig. 3).

Of note, several histone-related epigenetic modifications in adult stem cell aging have been reported [80]. According to the literature, a global increase in histone acetylation (H4K16ac) is observed in aged stem cells [81]. Reduced acetyl-CoA levels promote H4K16ac, leading to telomere silencing and accelerated stem cell aging [82]. Similarly, both histone repressive methylations (H3K9me3 and H3K27me3) and histone permissive methylations (H3K4me3) have been reported in old stem cells [83]. α-KG ameliorates the senescent phenotype of bone marrow mesenchymal stem cells (BM-MSCs) obtained from aged mice, as well as promoting their proliferation, colony formation, migration, and osteogenic potential, by decreasing the accumulation of H3K9me3 and H3K27me3 [84]. Also, a high amount of DNA methylation changes is detected in stem cells during the aging process [85–87]. Succinate and fumarate inhibit 2-oxoglutarate-dependent dioxygenases (2-OGDO) enzymes, thus consequently increasing DNA methylation and promoting senescence [88] (Fig. 3).

2.3. Mitochondrial DNA mutations

Aging promotes mitochondrial perturbations, including mitochondrial DNA (mtDNA) mutations. Various factors contribute to the accumulation of mtDNA mutations over time, including oxidative damage, replication errors, and inadequate repair mechanisms. mtDNA is strongly impacted by age-associated mutations and deletions due to its high replicative index, the limited efficiency of its repair mechanisms, its oxidative microenvironment within the mitochondria, and the lack of protective histones [2]. mtDNA mutations can result in dysfunctional ETC complexes, leading to decreased ATP production and increased production of ROS. This oxidative stress can further damage mtDNA, creating a vicious cycle of mitochondrial dysfunction and mutation accumulation. The accumulation of mtDNA mutations can in turn lead to impaired mitochondrial function and compromised energy production. In stem cells, which rely heavily on mitochondrial function for their self-renewal and differentiation processes, mtDNA mutations can impair their regenerative capacity (Fig. 4).

mtDNA mutations have been pointed out as a driving force behind the aging phenomenon. This hypothesis was supported by the creation of a transgenic mouse expressing a proof-reading deficient Polγ which displayed an accelerated aging phenotype. This mouse, named “mutator mouse”, accumulates mutations in the mitochondrial genome of stem cells, leading to tissue dysfunction at a higher rate than wild-type animals [31]. The authors reported that tissue dysfunction was not homogenous, as it seems that different stem cell types respond in different ways to mtDNA mutations. For instance, hematopoietic stem cell (HSC) differentiation potential was affected, but HSCs quiescence and self-renewal remained unaltered [89]. Conversely, neural stem cells (NSCs) were functionally compromised due to a reduction in the number of quiescent NSCs and to a reduced self-renewal capacity [90]. Moreover, homozygous mutator mice also show a 2-fold mutation rate increment, although no relevant pro-aging phenotype was observed, suggesting a relatively high tolerance to mtDNA mutations [91]. The establishment of a tolerance threshold might not be possible. mtDNA mutation sites, accumulation rate and impact on stem cell function

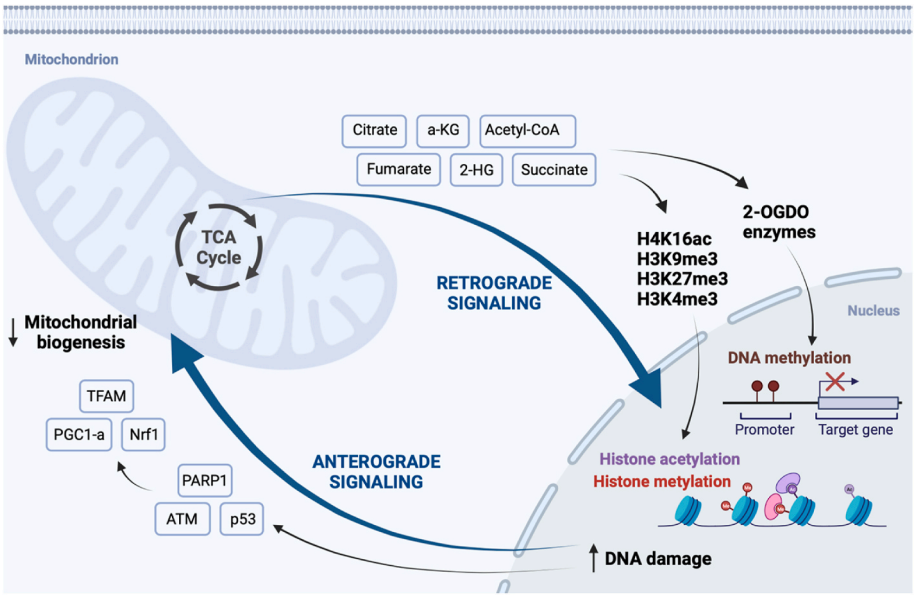

Fig. 3. Mito-nuclear communication in stem cell senescence. Mitochondria and nucleus accumulate damages during aging, and they communicate their damages through anterograde and retrograde signalling, creating a vicious cycle that leads to epigenetic modifications and dysfunctional mitochondria, thereby accelerating cellular senescence. Tricarboxylic acid cycle (TCA), α-ketoglutarate (α-KG), 2-hydroxyglutarate (2-HG), 2-oxoglutarate-dependent dioxygenases (2-OGDO), Ataxia-telangiectasia mutated (ATM), Poly (ADP-ribose) polymerase 1 (PARP1), peroxisome proliferator-activated receptor γ co-activator 1α (PGC1-α), Nuclear respiratory factor 1 (Nrf1), mitochondrial transcription factor (TFAM).

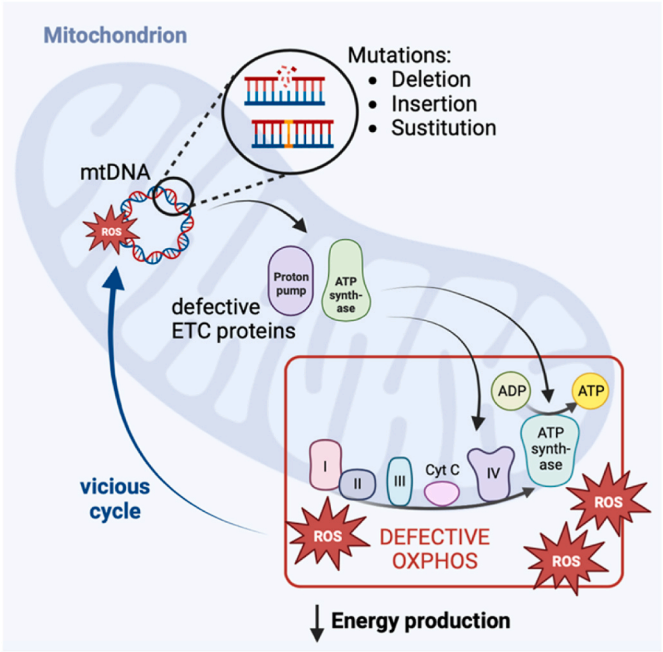

Fig. 4. Mitochondrial DNA mutations in stem cell senescence. During aging, mitochondria accumulate mtDNA mutations resulting in aberrant ETC complexes and defective OXPHOS. As a result, mitochondria produce insufficient ATP and excessive ROS, which in turn damage mtDNA creating a vicious cycle. Electron Transport Chain (ETC), Cytochrome *c* (Cyc c), Oxidative phosphorylation (OXPHOS), Reactive Oxygen Species (ROS).

differently affect each tissue type [92].

2.4. Mitochondria quality control

Mitochondrial quality control refers to a set of cellular mechanisms that ensure the maintenance and proper functioning of mitochondria. Given the critical role of mitochondria in cellular energy production and metabolism, it is essential to preserve their integrity and prevent the accumulation of damaged or dysfunctional mitochondria. Mitochondrial quality control involves several interconnected processes, including mitochondrial biogenesis, fusion and fission dynamics, and the removal of damaged or unnecessary mitochondria through mitophagy. These processes work together to maintain a healthy mitochondrial population within cells.

Maintaining a delicate equilibrium between mitochondrial fission and fusion processes is crucial for sustaining essential cellular functions such as the cell cycle [93]. Numerous studies indicate that cellular senescence is associated with altered mitochondrial behaviour [70,94]. The fusion of damaged and undamaged mitochondria can serve as a protective mechanism by diluting the damage, while fission facilitates the segregation and subsequent degradation of damaged mitochondria through mitophagy. Thus, to ensure proper cellular function, precise regulation of the balance between fission and fusion is necessary [95]. Data suggest that senescence is linked to impaired mitochondrial dynamics, leading to elongated, enlarged, and hyperfused mitochondria [96]. This hyperfusion has been associated with reduced expression of the Mitochondrial fission protein 1 (Fis1), which is involved in mitochondrial fission by recruiting Dynamin-related protein 1 (Drp1) to the mitochondria [97,98]. Moreover, the hyperfused mitochondrial network observed during senescence has been proposed as a protective mechanism contributing to apoptosis resistance [99] (Fig. 5).

Mitochondrial fission-fusion processes crosstalk with mitophagy. Mitophagy is a specific form of autophagy that specifically targets and eliminates impaired or surplus mitochondria. It involves the sequestration of damaged mitochondria into autophagosomes, which then fuse with lysosomes for degradation. Mitophagy is regulated by various signalling pathways and involves key players such as PTEN-induced putative kinase 1 (PINK1) and Parkin. PINK1 is a mitochondrial kinase that accumulates on the outer mitochondrial membrane of damaged mitochondria, while Parkin is an E3 ubiquitin ligase that is recruited to damaged mitochondria by PINK1. This recruitment leads to the ubiquitination of mitochondrial proteins and subsequent recognition by autophagic machinery [100] (Fig. 5).

For effective mitophagy to occur, mitochondria must undergo

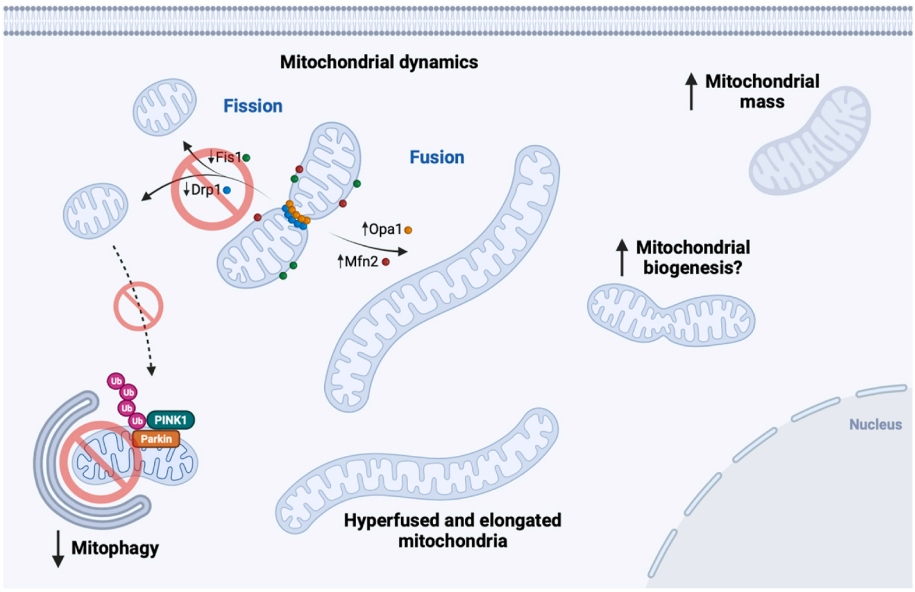

Fig. 5. Mitochondrial dynamics in stem cell senescence. Mitochondrial quality control impairment during aging stands for altered dynamics (promoting fusion over fission) and reduced mitophagy. Asa a consequence, senescent cells display an increased mitochondrial mass and mitochondria with an hyperfused and elongated morphology. Mitochondrial fission protein 1 (Fis1), Dynamin-related protein 1 (Drp1), Mitofusin 2 (Mfn2), Optic atrophy 1 (Opa1), PTEN-induced putative kinase 1 (PINK), Ubiquitination (Ub).

fission, enabling their isolation. Nevertheless, as previously mentioned, research has revealed that senescent cells possess an elongated and hyperfused mitochondrial network. This suggests that reduced fission could contribute to impaired mitophagy during senescence, resulting in increased mitochondrial mass, which is another common feature of senescent cells [101]. Numerous studies indicate that senescent cells experience compromised mitophagy, and importantly, that defects in mitophagy may contribute to the induction of cellular senescence [102, 103]. Moreover, it has been reported that improved mitophagy drives mitochondrial rejuvenation and influences stem cell decisions to retain stemness or to undergo differentiation for tissue regeneration in aging [104].

2.5. Mitochondrial unfolded protein response (mtUPR)

The mitochondrial unfolded protein response (mtUPR) is a subcellular mechanism that monitors and responds to stress. When mitochondria experience problems such as protein misfolding or accumulation of damaged proteins within the mitochondrial matrix, the mtUPR is activated to restore mitochondrial health [105].

The mtUPR general mechanism starts by sensing the stress, such as an accumulation of unfolded or misfolded proteins within the mitochondria. Upon detection of mitochondrial stress, specific signalling pathways are activated. One key regulator of the mtUPR is the activating transcription factor 5 (ATF5), which helps initiate the response. The activated signalling pathways communicate with the cell's nucleus to change gene expression. Genes involved in mitochondrial quality control, such as chaperone proteins (e.g., HSP60 and HSP10) and proteases (Lon protease), as well as mtDnaJ and ClpP, which are responsible for mitochondrial maintenance and quality control, are upregulated [106]. This upregulation helps in refolding or degrading damaged proteins and maintaining mitochondrial function. The mtUPR may also stimulate the generation of new mitochondria by promoting mitochondrial biogenesis.

A research investigation compared gene expression data sets of muscle stem cells between young and aged mice. Their findings revealed an increase in senescence-related pathways and a decrease in cell cycle pathways with advancing age. Notably, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) pathways were prominently downregulated in aging muscle stem cells. The authors highlighted that a decrease in nicotinamide adenine dinucleotide (NAD+) levels, a phenomenon associated with aging, impairs the quantity and functionality of muscle stem cells, consequently slowing down muscle regeneration following cardiotoxin-induced damage. Additionally, the depletion of NAD+ was linked to heightened senescence markers in muscle stem cells. This study underscores the significance of mitochondrial oxidative respiration in maintaining the functionality of muscle stem cells during the aging process. In essence, the decline in cellular NAD + pools inhibits the adaptive mtUPR pathway, ultimately disrupting mitochondrial equilibrium and reducing the population and self-renewal capabilities of muscle stem cells [107].

Disruption of the maintenance of mitochondrial proteins, referred to as mitochondrial proteostasis, is a type of stress that activates the mtUPR. It has been documented that stress related to the folding of mitochondrial proteins (mtPFS) serves as a trigger for a metabolic checkpoint, which controls the quiescence of HSCs and contributes to the aging of HSCs through dysregulation of the mtUPR. SIRT7, an enzyme responsible for removing acetyl groups from histones, suppresses the activity of nuclear respiratory factor 1 (NRF1). This suppression results in reduced expression of the machinery responsible for translating mitochondrial proteins and helps alleviate mtPFS [108]. Recent research has reported analogous outcomes in the context of neural stem cells (NSCs). Increasing mitochondrial protein folding stress resulted in compromised NSC maintenance and neurogenesis, neural hyperactivity and cognitive decline. Conversely, mitigating this stress related to mitochondrial protein folding in older animals enhanced neurogenesis and cognitive function. These discoveries underscore the role of mtPFS in regulating the aging of NSCs and neural hyperactivity within the hippocampus, which contributes to cognitive decline. These findings align with previous observations indicating that activating the mtUPR can slow down cellular senescence and delay aging of stem cells while extending lifespan [109].

2.6. Mitochondria and the SASP

Aging is associated with increased senescent cell burden that leads to chronic, low-grade, sterile inflammation [110,111]. Increased levels of cytokines, including IL-6, IFN-γ, and TNF-α, contribute to the

pro-inflammatory secretome of senescent cells, known as the senescence-associated secretory phenotype or SASP [112]. As mentioned earlier, the study performed by Correia-Melo et al. proved the impact of mitochondria on cellular senescence. Importantly, the authors reported a dramatic reduction in the secretory phenotype in mitochondrial-depleted senescent cells, suggesting that the SASP is dependent on mitochondria [39].

Inflammation is generally initiated by the activation of pattern recognition receptors (PRRs) that are expressed by both immune and non-immune cells. Importantly, PRRs can be stimulated not only by viral and bacterial molecules associated with infection but also by intracellular molecules released by senescent cells, termed damage-associated molecular patterns (DAMPs) [113]. Moreover, DAMPs, increase with aging [114].

Mitochondrial dysfunction is accompanied by mtDNA release, which is a potent DAMP [115], that can activate both intracellular and extracellular immune signalling pathways. On the one hand, when released in the cytosol, mtDNA activates the NLRP3 inflammasome, causing interleukin (IL)-1β and IL-18 secretion. Additionally, cells can sense mtDNA in the cytosol through the cyclic GMP–AMP synthase (cGAS), which is stimulated by double-stranded DNA, leading to the production of cyclic GMP–AMP (cGAMP), which is an agonist of the stimulator of interferon genes (STING), thereby releasing IL-6, interferon (IFN)-β1 and tumour necrotic factor (TNF) [116,117]. On the other hand, mtDNA can also be released to the extracellular milieu. Indeed, senescent cells have been identified as a key source of circulating mtDNA [118]. Cell-free mtDNA can in turn stimulate immune responses through the activation of PRRs that are present in the membrane of several immune cells (Fig. 6).

Other mitochondrial DAMPs are also known to induce and promote inflammation in different ways. ATP, produced by the mitochondrial ETC, can be released to the extracellular milieu by damaged cells through lysosomal secretion and pannexin 1 (PANX1) channels. Cell-free ATP binds to purinergic receptors P2RX7 and P2RY2 on antigen-presenting cells (APCs), thereby promoting chemotaxis, phagocytosis, and immunostimulatory effects [119]. Mitochondrial protein translation starts with an N-formylated methionine. Upon mitochondrial dysfunction, the leakage of N-formylated peptides outside the mitochondria activates a specific family of PRRs, the formyl peptide receptors (FPR), which are present in neutrophils, thereby inducing the activation of the innate immune system [120]. mtDNA complexed with TFAM, which accumulates in the extracellular milieu upon cell apoptosis, also causes neutrophil activation via Toll-like receptor 9 (TLR9) or advanced glycosylation end product-specific receptor (AGER) [113]. Succinate, an intermediate of the TCA cycle, is also considered as an important signalling molecule. Cardiolipin is a phospholipid present in the mitochondrial inner membrane [121]. When released to the extracellular medium, cardiolipin can join the major histocompatibility complex II (MHC II)-like molecule CD1d of dendritic cells, which will in turn result in the activation of T cells. Lastly, mitochondrial dysfunction leading to ROS overproduction can activate a ROS-mediated JUN N-terminal kinase (JNK) retrograde signalling pathway, which drives the release of cytosolic chromatin fragments (CCFs). These CCFs, excluded from the

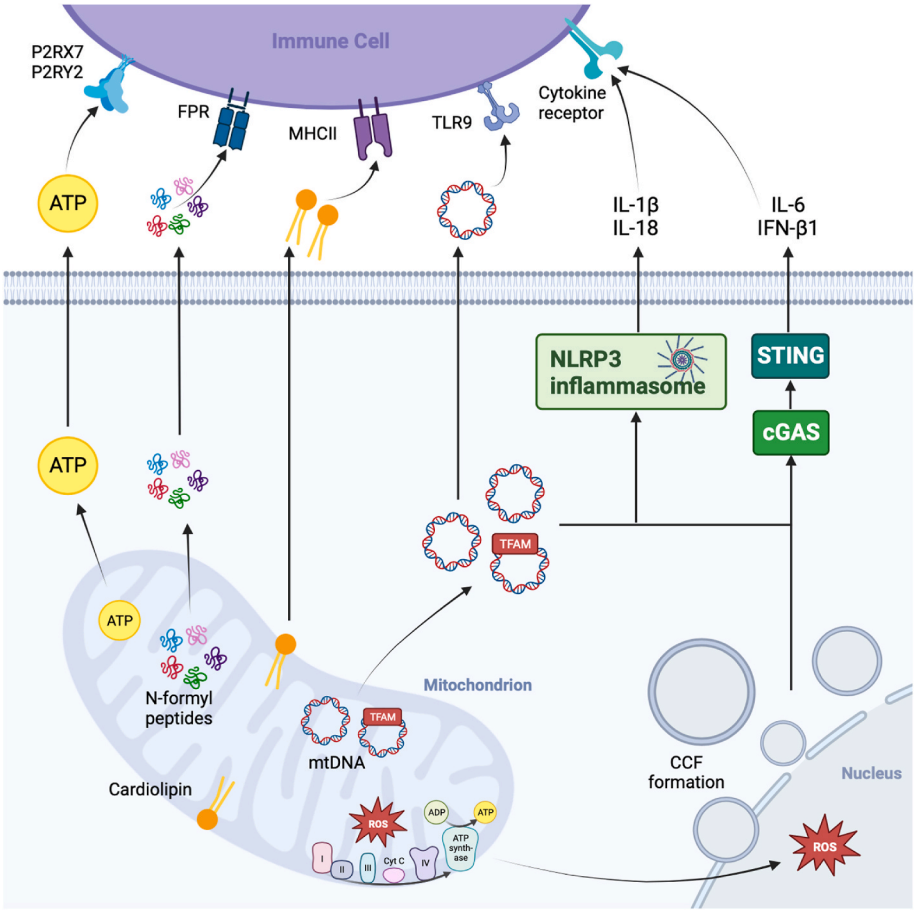

Fig. 6. Mitochondrial DAMPS in stem cell senescence. Damaged mitochondria release DAMPs, including free ATP, N-formyl peptides, free cardioliìn, mtDNA with or without TFAM, and ROS. These mtDAMPs are part of the SASP and will in turn activate inflammatory responses inside the cell and when released to the extracellular medium, they will activate specific receptors in immune cells to promote a pro-inflammatory ambient. Cyclic GMP–AMP synthase (cGAS), Stimulator of interferon genes (STING), mitochondrial transcription factor (TFAM), Purinergic receptors (P2RX7 and P2RY2), Formyl peptide receptors (FPR), major histocompatibility complex II (MHC II), Toll-like receptor 9 (TLR9), Interleukin (IL), Interferon (IFN), Cytosolic Chromatin Fragments (CCFs), Reactive Oxygen Species (ROS).

nucleus of senescent cells, activate the cGAS-STING pathway [122], thereby promoting the release of proinflammatory components [123] (Fig. 6).

In summary, mitochondrial dysfunction can trigger stem cell senescence through increased ROS production, defective energetic metabolism, accumulation of epigenetic mutations and damaged proteins, impaired mitophagy, and SASP modulation. Understanding the interplay between mitochondria and stem cells across aging is crucial for advancing regenerative medicine approaches and developing interventions to promote health.

3. Mito-therapy: targeting mitochondria to prevent stem cell senescence

Targeting mitochondrial dysfunction represents a promising tool to prevent stem cell senescence, thereby delaying aging and age-related pathologies. Several molecules and compounds have been tested to improve mitochondrial health by reducing ROS production, promoting mitochondrial function, increasing mitochondrial biogenesis, enhancing mitochondrial dynamics, and removing damaged mitochondria. Also, mitochondria replacement therapies as well as senolytic and senomorphic treatments are currently being tested. However, very few of these strategies have been performed specifically in stem cells (Table 1).

Table 1
Mito-therapies to rejuvenate senescent stem cells.

Mito-therapy	Compound	Stem cell type	Ref.
Decreasing mitochondrial ROS production	GSH and melatonin	ADSCs	[124]
	MitoQ	HSCs	[125, 126]
Improving mitochondrial function and energetic metabolism (NAD + boosters)	NR	Muscle SCs and NPSCs	[107, 127]
		HSCs	[128]
	NAM	BM-MSCs	[129]
	NMN	BM-MSCs	[130]
	NMNAT3	BM-MSCs	[131]
	NAMPT	BM-MSCs, NPSCs	[132, 133]
Improving mitochondrial dynamics	P110	Primary cardiomyocytes	[134]
	MDIVI-1	NPSCs, ADSCs	[135, 136]
	AICAR	BM-MSCs, ADSCs	[137, 138]
	Rapamycin	Glioblastoma cells	[139]
	NAC and AAP	ADSCs	[140]
	Icariin	BM-MSCs	[141]
	Leptin	CPCs	[142]
		BM-MSCs	[143, 144]
	Haemin	BM-MSCs	[145]
Removing damaged mitochondria	Melatonin	BM-MSCs	[146]
	Genistein	BM-MSCs	[147]
	Urolithin A	TM-SCs	[148, 149]
		Muscle SCs	
Promoting mitochondrial biogenesis	Resveratrol	mESCs	[150]
	Rosiglitazone	NPSCs	[151]
Mitochondria-targeted senomorphics	Aspirin & H-151	MSCs-derived organoids	[152]

Abbreviations: Mitochondrially-targeted coenzyme Q (MitoQ), Nicotinamide riboside (NR), Nicotinamide (NAM), Nicotinamide mononucleotide (NMN), Nicotinamide mononucleotide adenylyl transferase 3 (NMNAT3), Nicotinamide phosphoribosyl transferase (NAMPT), glutathione (GSH), N-acetylcysteine (NAC), Ascorbic acid 2-phosphate (AAP), adipose-derived stem cells (ADSCs), hematopoietic stem cells (HSCs), Muscle stem cells (Muscle SCs), neural progenitor stem cells (NPSCs), bone marrow mesenchymal stem cells (BM-MSCs), chondrogenic progenitor cells (CPCs), T memory stem cells (TM-SCs), mouse embryonic stem cells (mESCs).

3.1. Decreasing mitochondrial ROS production

Due to the central role of mitochondrial ROS in driving stem cell senescence, mitochondrial-targeted antioxidant therapies have been explored as potential treatments [153].

Supplementation with antioxidants such as vitamins E, C, and D [154–158], overexpression of SOD2 and catalases through sirtuins [159], treatment with chemical and natural compounds with described antioxidants properties (for example, coenzyme Q [160], fisetin [161] and curcumin [162]), and many other compounds have all been used to reduce oxidative stress, and inhibit cellular senescence in different cell types [163].

Focusing on stem cells, glutathione, and melatonin supplementation have proved to reduce intracellular ROS levels and prevent replicative senescence in adipose-derived stem cells (ADSCs) [124]. Recently, mitochondrially-targeted coenzyme Q (MitoQ), one of the best-characterized mitochondrially targeted antioxidants, has been shown to protect against oxidative stress [125] *in vitro*. Furthermore, MitoQ has been shown to improve old HSCs engraftment and lineage kinetics upon transplantation, as well as to revert and prevent the onset of the hematopoietic aging phenotype [126]. In humans, MitoQ improves vascular aging in middle-aged and older adults (aged 60–79 years) [164].

It is worth noting that although the impact of ROS on cellular senescence is extensively studied, there are certain challenges associated with targeting ROS for senoprevention. This is due to the crucial roles that ROS play in numerous intracellular signalling pathways essential for normal cellular functioning.

3.2. Improving mitochondrial function and metabolism

Aging is associated with a decline in the oxidized form of nicotinamide adenine dinucleotide (NAD+). Likewise, low NAD + promotes cellular senescence and mitochondrial metabolism disorders, while high NAD + improves mitochondrial function. Thus, agents that increase NAD + levels are thought to inhibit cellular senescence.

One such molecule is the NAD + precursor nicotinamide riboside (NR), which activates SIRT1 to rejuvenate muscle stem cells, neural stem cells and melanocyte stem cells in aged mice and prevent these cells from becoming senescent [107]. Another study performed with HSCs concluded that NR restores youthful metabolic capacity by modifying mitochondrial function. The metabolic restoration was accompanied by a shift of the aged transcriptome towards a more youthful bone marrow cellular composition and an improved regenerative capacity in a transplant setting [128].

Other compounds involved in NAD + biosynthesis such as nicotinamide (NAM) and nicotinamide mononucleotide (NMN) have also demonstrated to rescue mesenchymal stem cells from becoming senescent. Treatment with NAM increases the intracellular NAD + levels and re-balances the NAD+/NADH ratio, via the NAD + -SIRT1 axis in MSCs at high passage, which partially restores mitochondrial fitness and rejuvenates senescent MSCs [129]. Similarly, NMN supplementation leads to a significant increase in intracellular NAD + levels, NAD+/NADH ratio, but in this case via the NAD + -SIRT3 axis, which ameliorated mitochondrial function and rescued senescent MSCs [130]. Another study confirmed that overexpression of nicotinamide mononucleotide adenylyl transferase 3 (NMNAT3), another NAD + precursor, improves mitochondrial function, enhances antioxidative stress and promotes resistance to stress-induced apoptosis in MSCs. The underlying mechanism was the activation of the NMNAT3-NAD + -SIRT3 axis [131]. Lastly, it has also been reported that overexpression of nicotinamide phosphoribosyl transferase (NAMPT), the rate-limiting enzyme in mammalian NAD + biosynthesis, ameliorates senescence-associated phenotypic features in late passage MSCs via mediating NAD + -SIRT1 signalling [132]. Parallel results were observed in Neural stem/progenitor cells (NSPCs), where NAMPT ablation resulted in reduced NSPCs

proliferation and defective differentiation [133].

The NAD+/sirtuin pathway regulates lifespan through the activation of the mtUPR and the FOXO signalling [165]. The NAD+/sirtuin regulation of stem cell aging has also been reported for SIRT2 [166], SIRT3 [167] and SIRT7 [108,109]. These studies provide promising results in reducing muscle SCs, HSCs and NSCs senescence and dysfunction by genetical overexpression of sirtuins. Using knock-out and knock-in mouse models, sirtuin regulation has proven to maintain tissue regeneration following acute and chronic damage, as well as expanding lifespan. Indeed, modulation of all sirtuins by NAD + boosters (NR, NAM, NMN, NMNAT3 and NAMPT) appears as a powerful tool to delay tissue malfunction and aging [127,168,169].

All these promising *in vitro* studies have been tested in animal models. In 22-month-old mice, NMN supplementation restored NAD + levels and several markers of mitochondrial dysfunction during aging [170], while increasing energetic metabolism and physical activity [171]. Moreover, NMN [172] and NR [173], increased mitochondrial function and improved glucose homeostasis in obese mice. Hence, augmenting NAD+ is perceived as a promising method to mitigate stem cell senescence.

3.3. Improving mitochondrial dynamics

During cellular senescence, there is an increase in mitochondrial fusion over fission events. While mitochondrial fusion can be a compensatory mechanism in response to stress, mitochondrial fission is needed for the removal of damaged mitochondrial components by lysosomal degradation. To date, several chemical probes and pharmacological compounds have been reported to be able to modulate mitochondrial dynamics [174–176], although few studies have been performed using stem cells.

P110 is an artificial compound that blocks Drp1/Fis1 interactions. It has been reported that P110 treatment can prevent ischemia/reperfusion-induced damage in mouse hearts, suggesting their therapeutic potential for stem cells under oxidative stress conditions [134]. MDIVI-1 is another compound that acts by preventing the polymerization of DRP1. A study examined the role of MDIVI-1 on the survival of cultured hippocampal NPSCs exposed to high palmitate concentrations. MDIVI-1 rescued NPSCs from palmitate-induced lipotoxicity by suppressing mitochondrial ROS production and by stabilizing mitochondrial transmembrane potential [135]. Moreover, the MDIVI-1 effect on the mitochondrial network has been explored in ADSCs subjected to a metabolic syndrome model. Treatment with MDIVI-1 rescued abnormal mitochondrial networks and reversed the senescence of ADSCs [136]. AICAR is a pharmaceutical agent that induces Drp1 phosphorylation, thereby promoting mitochondrial fission and preventing senescence in human BM-MSCs and ADSCs [137,138]. Moreover, AICAR, a direct AMPK activator, has been reported to improve memory and motor function in aged 23-month-old female mice [177]. Rapamycin induces the expression of genes involved in mitochondrial fission (FIS1, DRP1) and promotes mitophagy. Glioblastoma (GBM) cells feature mitochondrial alterations related to mTOR overexpression and autophagy suppression. Rapamycin treatment of GBM cells restored their mitochondrial status through mTOR inhibition [139]. A study analysed the effect of N-acetylcysteine (NAC) and ascorbic acid 2-phosphate (AAP) on ADSCs that were subjected to H_2O_2-induced oxidative stress. The combined treatment of NAC and AAP reduced ROS overproduction, stabilized mitochondrial membrane potential, and decreased mitochondrial fission/fragmentation through decreased activation of Drp1 [140]. Lastly, icariin is another compound able to promote mitochondrial fission protein FIS1 and fusion protein MFN2 expressions, and to increase DRP1. In a model of iron-induced senescence, icariin restored the osteogenic differentiation and proliferation of BM-MSCs. These effects were related to the modulation of mitochondrial fusion and fission dynamics, the activation of the PI3K/AKT/mTOR pathway, and the inhibition of ERK1/2 and JNK pathways [141].

Contrarily to the above-mentioned studies, other compounds promote mitochondrial fission over fusion. Such is the case of leptin, which promotes optic atrophy 1 (OPA1) dependent mitochondrial fusion. Indeed, it has been reported that leptin altered the differentiation fate and induced senescence in chondrogenic progenitor cells by activating the p53/p21 pathway and inhibiting the Sirt1 pathway (CPCs) [142]. However, leptin can also have beneficial effects since the enhanced leptin production associated with hypoxia preconditioning contributes to improved MSCs survival after myocardial infarction (MI). Indeed, leptin can regulate OPA1-dependent glycolysis to improve BM-MSC survival through sodium-glucose symporter 1 (SGLT1) activation. Hence, the leptin/OPA1/SGLT1 signalling pathway improves mitochondrial dynamic mediated glycolysis, thereby optimizing the therapeutic efficiency of BM-MSCs for cardiovascular diseases such as MI [143,144]. Similarly, haemin, a potent heme-oxygenase 1 (HO1) inducer, promoted enhanced mitochondrial fusion in a model of MSCs transplantation for MI, which consisted of BM-MSCs cultured under serum deprivation and hypoxia. In the *in vivo* study, haemin pre-treatment decreased cardiomyocytes apoptosis and enhances angiogenesis, suggesting leptin is a useful strategy for improving MSC-based therapy for MI [145].

3.4. Removing damaged mitochondria

Mitophagy, which relies on PINK1 and Parkin, efficiently eliminates unhealthy mitochondria through lysosomal degradation. Hence, a disruption in the PINK1–Parkin pathway impairs mitophagy, which leads to the accumulation of damaged mitochondria, causing cells to undergo senescence. Very few molecules have been tested to enhance mitophagy [178]. Some examples include 17β-estradiol, which enhances mitophagy in human umbilical vein endothelial cells submitted to H_2O_2-induced senescence [179] and in chondrocyte model of osteoarthritis via the SIRT1-Mediated AMPK/mTOR signalling pathway [180]. Spermidine also improves mitophagy in SY5Y cells exposed to the cytotoxic effects of the tau protein [181]. Tomatidine also promotes neuroprotection of SY5Y cells by boosting mitophagy [182]. More recently, the P62-mediated mitophagy inducer PMI has proven to stimulate mitophagy in MEFs and SH-SY5Y (SHY) cells independently of the PINK1/Parkin pathway [183].

Nonetheless, some other pharmacological compounds have been already tested in stem cells. For instance, Melatonin prevented senescence in BM-MSCs by increasing mitophagy through the upregulation of heat shock protein 1L (HSPA1L), a protein that enhances the translocation of Parkin to damaged mitochondria, and cellular prion protein (PrPC), a protein that binds to PINK1 [146]. Similarly, genistein, a major isoflavone in soy products, rescued the senescent phenotype of BM-MSCs obtained from postmenopausal women and ovariectomized rodents. Genistein improved ERRα-mediated mitochondrial biogenesis and enhanced mitophagy by increasing lysosome biogenesis and lysosomal metabolism [147].

Another better-studied compound is urolithin A. This molecule boosted T memory stem cells (TM-SCs) formation and proliferation through the modulation of PINK1-mediated mitophagy to promote mitochondrial health [148]. Also, the administration of urolithin A rescued mitophagy in Duchenne muscular dystrophy (DMD) worms and mice and in primary Muscle SCs from patients with DMD. The observable effect were an increased skeletal muscle respiratory capacity and an improved Muscle SCs' regenerative capacity, resulting in the muscle and increased survival of DMD mouse models [149]. Another *in vivo* study assessed urolithin A effects on premature senescent auditory cells. Urolithin A significantly decreased the expression of senescence-associated p53 and p21, and increased the expression of mitophagy-related proteins [184]. However, whether Urolithin A is specifically promoting mitophagy, rather than global macroautophagy has not been corroborated [185,186].

Taken together, it seems that mitophagy can be modulated

pharmacologically. However, direct therapeutic strategies are still limited and specificity might be an issue towards the use of these compounds to study mitophagy. Therefore, future studies are needed to identify specific modulators of mitophagy.

3.5. Promoting mitochondrial biogenesis

Mitochondrial biogenesis plays a vital role in responding to stress by replenishing damaged mitochondria. This compensatory process is believed to replace impaired mitochondria during senescence, as senescent cells exhibit heightened mitochondrial biogenesis. Consequently, there is growing interest in increasing mitochondrial biogenesis to prevent cellular senescence and extend lifespan. However, while boosting mitochondrial biogenesis can compensate for the loss of healthy mitochondria resulting from mitochondrial stress, continuous stress experienced by mitochondria during cellular senescence may expose newly synthesized mitochondria to oxidative stress. This can create a positive feedback loop, leading to increased production of ROS and further mitochondrial damage [187]. Therefore, enhancing mitochondrial biogenesis as a strategy to prevent senescence would be more effective when combined with treatments that also limit the generation of mitochondrial ROS.

Resveratrol is a well-known compound that inhibits ROS production and inhibits senescence in BM-MSCs [188]. Resveratrol treatment of mouse embryonic stem cells (mESCs) correlated with upregulation of PGC1-α gene expression and indicated increased mitochondrial biogenesis [150]. Similar results were obtained in *in vivo* studies where resveratrol increased the expression of PGC-1α, Nrf1, and TFAM, and promoted PGC-1α nuclear translocation. Moreover, resveratrol scavenged excessive ROS and increased the activity of antioxidant enzymes in different models of brain injury [189]. Another compound, rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, stimulated mitochondrial biogenesis by activation of PGC1α and upregulated the antioxidant defense of NPSCs against Aβ-induced toxicity [151].

Identifying signalling pathways that enhance mitochondrial biogenesis and reduce mitochondrial ROS simultaneously would provide novel targets for senopreventive drugs.

3.6. Mitochondria-targeted senomorphics

Senomorphics aim to suppress SASP release by senescent cells. Thus, senomorphics hamper the senescence phenomenon, acting as SASP inhibitors without killing the cell. Potential senomorphic therapies are based on the targeting of pathways related to SASP expression, such as the p38MAPK, PI3k/Akt, mTOR, and JAK/STAT pathways, and transcription factors, such as NF-κB, C/EBP-β and STAT3 [190]. Little attention has been given to the possibility of modulating inflammation through mitochondria-targeted agents, which may reflect the novelty of research in this area.

Indeed, another approach is to act directly on the cGAS-STING pathway [191]. Genetic silencing of the cGAS-STING signalling pathway results in SASP inhibition and reduces tissue inflammation *in vivo* [122,192]. Given the tight correlation between cGAS-STING, inflammation and senescence, several inhibitors of cGAS and STING are being developed. Some examples include RU-521, Cu-32 and Cu-76, which prevent cGAS dimerization and subsequence activation [193,194], and additional small molecules identified through screenings such as G140/G150 [195] and PF-06928215 [196]. Also, antimalarial drugs are being considered since they can modulate the cGAS/SING signalling pathway [197].

To date, some of these new approaches have been tested *in vitro* and *in vivo*. A study reported the effect of treatment with the cGAS inhibitor aspirin [195,198] and the STING inhibitor H-151 [199] on human pluripotent stem cell-derived cortical brain organoids to study Ataxia-telangiectasia (A-T) neuropathology. The authors demonstrated that cGAS and STING inhibition effectively suppressed self-DNA-triggered SASP expression in A-T brain organoids, inhibited astrocyte senescence and neurodegeneration, and ameliorated A-T brain organoid neuropathology [152].

In conclusion, although mitochondria are clear master regulators of inflammation, additional research is needed. An improved understanding of the molecular mechanisms linking mitochondrial dysfunction to intracellular and extracellular DAMP signalling will ultimately unlock the development of specific mitochondria-targeting drugs for the control of senescence and inflammation.

3.7. Mitochondrial transfer

Several *in vitro* studies have demonstrated that stem cells donate healthy mitochondria to replace dysfunctional mitochondria in different types of recipient cells [200]. MSCs are shown to transfer their own mitochondria into cells with damaged mitochondria or mtDNA-depleted cells [201]. Existent data suggest that stem cell-derived mitochondria might improve the survival of recipient cells by rescuing aerobic respiration and energy metabolism, regulating mitophagy and mitochondrial biogenesis, optimizing mitochondrial dynamics, and decreasing the mtDNA mutation load, thus preventing cellular senescence [202].

Different routes have been found to participate in mitochondrial transmission from stem cells to recipient cells, which include tunnelling nanotube (TNT) formation, the release of extracellular vesicles, cellular fusion, and mitochondrial extrusion [202]. These exchange pathways occur naturally between cells when subjected to co-culture conditions. Of note, artificial transfer of mitochondria has also been reported. A study isolated mitochondria from UC-MSCs (donor cells) which were extrinsically transplanted into senescent ARPE-19 cells by co-incubation. Exogenous mitochondrial transplantation improved mitochondrial dysfunction and alleviated cellular senescence hallmarks. These results indicate that exogenous mitochondrial transplantation might help to modulate cellular senescence and may be considered a novel therapeutic strategy [203].

Co-culture of BM-MSCs and ischemic rat cardiomyocytes has been shown to increase mitochondrial membrane potential in the latter cells [204]. Similarly, mitochondrial transfer from BM-MSCs to human HUVECs also improved aerobic respiration and reduced apoptosis [205]. It has also been reported that MSCs transfer their healthy mitochondria to astrocytes cultured under oxidative stress conditions [206], which in turn recovered cellular aerobic respiration and proliferation. The stimulation of oxidative stress in transfer effectiveness has also been demonstrated in corneal epithelial cells [207].

Intriguingly, mitochondria are not confined to a unidirectional transfer from MSCs to injured cells. In co-culture of human BM-MSCs and coronary artery vascular smooth muscle cells (VSMCs), mitochondrial transfer has been demonstrated to be bidirectional with no preferential direction of movement [208]. Transfer from VSMCs to MSCs increased MSC proliferation, but not differentiation, and this effect was lost if VSMCs had dysfunctional mitochondria due to mtDNA defects. Further experiments showed that human cardiomyocytes and HUVECs challenged by hydrogen peroxide could donate mitochondria to MSCs as a warning signal [209].

Taken together, more studies are needed to provide an in-depth knowledge of the pros and cons of mitochondrial transfer on stem cell function and in the context of aging.

4. Conclusion

Studying stem cell aging and the role of mitochondria is of paramount importance in understanding the underlying mechanisms of tissue degeneration and age-related diseases. Stem cells play a crucial role in tissue regeneration and maintenance, and their decline with age contributes to the functional decline of organs and tissues. Mitochondria, the powerhouses of the cell, are much more than simple

powerhouses and play a central role in cellular metabolism, fate, signalling and homeostasis. Dysfunctional mitochondria have also been implicated in driving stem cell senescence and the loss of regenerative capacity. Therefore, investigating the interplay between stem cell aging and mitochondrial dysfunction provides valuable insights into the aging process and opens avenues for potential interventions.

Understanding stem cell aging and the impact of mitochondrial dysfunction in it has significant implications for regenerative medicine. With the aging population, the demand for effective therapies to combat age-related tissue degeneration and diseases is increasing. Unraveling the role of mitochondria in stem cell fate and senescence can guide the development of mitochondria-targeted therapies to rejuvenate aged stem cells and enhance their regenerative potential, which would improve overall tissue health and prevent age-related decline. This knowledge could inform the development of novel strategies for tissue engineering, organ transplantation, and regenerative therapies.

While significant progress has been made, there are still many areas that require further exploration. Future research should aim to elucidate the intricate molecular pathways involved in stem cell senescence and mitochondrial dysfunction. This includes a deeper understanding of the regulatory networks that govern mitochondrial dynamics, oxidative stress responses, and mitochondrial quality control mechanisms in stem cells. Moreover, the development of innovative therapeutic strategies to target mitochondrial enhancement and stem cell rejuvenation should be a priority. This entails the further exploration of pharmacological agents, gene-editing technologies, stem cell-based therapies and extracellular vesicle-based therapies that hold the potential for reversing or delaying the aging process. Preclinical and clinical studies are necessary to evaluate the safety, efficacy, and long-term effects of these interventions.

In conclusion, understanding the intricate relationship between mitochondrial function, stem cell senescence and aging is of utmost importance. The knowledge gained from such studies has the potential to revolutionize regenerative medicine and improve the quality of life for an aging population. Continued research efforts and interdisciplinary collaborations are crucial for unraveling the complexities of stem cell aging, developing targeted interventions, and ultimately achieving successful strategies for promoting stem cell rejuvenation and tissue regeneration.

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Supervisor's supporting statement

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Declaration of competing interest

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

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