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REVIEW

Emerging roles of mitochondrial functions and epigenetic changes in the modulation of stem cell fate

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Abstract

Mitochondria serve as essential organelles that play a key role in regulating stem cell fate. Mitochondrial dysfunction and stem cell exhaustion are two of the nine distinct hallmarks of aging. Emerging research suggests that epigenetic modification of mitochondria-encoded genes and the regulation of epigenetics by mitochondrial metabolites have an impact on stem cell aging or differentiation. Here, we review how key mitochondrial metabolites and behaviors regulate stem cell fate through an epigenetic approach. Gaining insight into how mitochondria regulate stem cell fate will help us manufacture and preserve clinical-grade stem cells under strict quality control standards, contributing to the development of aging-associated organ dysfunction and disease.

Keywords Mitochondria · Stem cell fate · Epigenetic modifications · Mitochondria metabolites · Senescence

Introduction

It is now clear that epigenetic changes are one of the primary causes of aging in mammals, and restoring epigenome integrity can reverse signs of aging [1]. Epigenetic regulation of mitochondrial DNA (mtDNA) is an emerging and rapidly growing field of research. The generation and modification of epigenetic marks in the nucleus require metabolites provided by the mitochondria, and subsequently, these epigenetic marks modulate the expression of proteins within the mitochondria [2]. It is currently believed that mitochondrial epigenetics is regulated in four main ways: (1) epigenetic mechanisms that regulate nuclear-encoded mitochondrial genes affect mitochondria; (2) cell-specific mtDNA content and mitochondrial activity determine the level of methylation of nuclear genes; (3) mtDNA variation affects the pattern of nuclear gene expression and the degree of methylation of nuclear DNA; and (4) mtDNA itself is subjected to epigenetic modifications [3, 4]. In recent years, numerous studies have validated the crucial function of mitochondria in controlling the destiny of stem cells [5–7]. An increasing number of studies are concentrating on the epigenetic mechanisms by which mitochondria sustain stem cell proliferation, renewal, differentiation, and lifespan.

The impact of epigenetic dysregulation on adult stem cell function varies widely, ranging from nonsignificant to significant, depending on the tissue type and the specific epigenetic regulator affected [8]. Self-renewal and pluripotency are two key properties of stem cells [9]. Stem cell therapy is currently one of the most popular fields in regenerative medicine [10]. The basic idea is to plant selected stem cells into the patient's body through specific methods to promote regeneration of pathological tissues for therapeutic purposes [11]. Precise regulation of these two properties is the basis for ensuring healthy cell development and tissue homeostasis in stem cell therapy. The network of transcription factors regulating stem cell stemness and differentiation has been thoroughly studied [12–14]. Other aspects of regulation, such as miRNAs and epigenetic modification, have also been extensively studied [15–19]. Although posttranslational

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regulatory mechanisms have been poorly studied, recent studies have shown that protein quality control (PQC) is closely related to stem cell function [20–23].

Here, we focus on the influence of mitochondria and their metabolites on the fate of stem cells. In this rereview, we overview how the metabolites of the tricarboxylic acid cycle (TCA) in mitochondria support the survival and growth of stem cells. Additionally, we highlight the signaling function of mitochondria, which alters epigenetic remodeling through the mitochondrial stress response and mitochondrial dynamics during cell fate determination.

Mitochondrial metabolites are the material basis of epigenetic influence on stem cell senescence

Mitochondrial metabolites are important components of epigenetic pathways. It is increasingly recognized that metabolic signals originating from mitochondria initiate epigenetic modifications in the nucleus through nonmetabolic mechanisms [24]. Recent studies have found that mitochondrial metabolites regulate the epigenetic landscape that determines cell identity and function [25]. In particular, there is evidence to suggest that mitochondrial metabolites are involved in the regulation of epigenetic modifications, including chromatin structure regulation, DNA methylation, histone modification and noncoding RNA regulation. Moreover, it has been demonstrated that mitochondrial metabolism plays important roles in modulating gene transcription, DNA damage levels, and long-term developmental pathways in stem cells [26, 27]. Therefore, mitochondrial metabolites offer essential regulation of stem cell fate when properly harnessed. Overall, these studies underscore the significance of mitochondrial metabolites in governing the progression and sustenance of stem cells while also highlighting their prospective applications in regenerative medicine.

Stem cell identity and function are largely determined by gene expression profiles. In eukaryotic cells, gene transcription is regulated by the interaction between transcription factors and chromatin remodeling and modification factors [28]. The methylation of DNA and histones generally promotes the self-renewal of adult stem cells, while demethylation leads to stem cell activation, proliferation, and differentiation [29]. Furthermore, different metabolites of the TCA cycle are utilized as substrates by chromatin-modifying enzymes, which control gene expression by altering chromatin modification [30]. Acetyl-coenzyme A (acetyl-CoA) and alpha-ketoglutarate (α-KG) have been extensively studied for their role in modulating the fate of mammalian embryonic stem cells and adult stem cells [6, 31].

In this section, we will discuss several mitochondrial metabolites, including acetyl-CoA, α-KG, nicotinamide adenine dinucleotide (NAD^+), and S-adenosylmethionine (SAM), as potential cell regulatory factors and how changes in their abundance influence the epigenomes and the aging process in different organisms (Fig. 1).

Acetyl-CoA

Acetyl-CoA, which is necessary for histone acetylation, is produced in the cytoplasm by ATP citrate lyase (ACLY) and ACSS2, a member of the acyl-CoA synthetase short-chain family, using citrate and acetate as substrates, respectively [28]. Under conditions of nutrient restriction, ACSS2, a cytosolic enzyme belonging to the short-chain family of acyl-CoA synthases 2, plays a crucial role in generating acetyl-CoA by utilizing acetate as a substrate [32, 33]. Subsequently, acetyl-CoA is utilized in the mitochondria to generate citric acid and oxaloacetic acid via the TCA cycle [24]. In addition to its roles in metabolism and biosynthesis, acetyl-CoA provides acetyl groups for protein acetylation, such as histone acetylation, which is catalyzed by histone acetyltransferases (HATS) [34]. Acetylation neutralizes the positive charge on lysine residues, resulting in the opening of chromatin structures, which allows for the entry of transcription factors and impacts gene expression [34]. Therefore, acetyl coactivators serve as substrates for acetylation and regulate the nuclear epigenome of stem cells.

Hematopoietic stem cells (HSCs) primarily rely on anaerobic glycolysis to generate energy and remain stationary and undifferentiated, while their mitochondria remain active. As glycolysis and the TCA cycle are not directly linked in HSCs, they use other nutritional pathways, such as amino acid and fatty acid metabolism, to produce acetyl-CoA to fuel the TCA cycle. Recent studies have further revealed a connection between acetyl-CoA metabolism and histone acetylation in HSCs during hematopoietic recovery after bone marrow ablation [35].

Mouse and human pluripotent stem cells (PSCs) possess an open chromatin structure characterized by DNA hypomethylation, abundant active histone modifications (e.g., H3 and H4 acetylation, H3K4 trimethylation, etc.), and low heterochromatin [36]. To maintain this unique chromatin state, PSCs have specific metabolic requirements, such as high levels of acetyl-CoA [37]. Treatment with acetyl-CoA precursor acetate increased H3K9/K27 acetylation labeling and delayed the early differentiation of hPSCs and mouse embryonic stem cells (mESCs), suggesting that decreased acetyl-CoA levels drive the differentiation of PSCs, possibly by reducing histone acetylation labeling and, thus, making chromatin more inaccessible [38]. A similar phenomenon

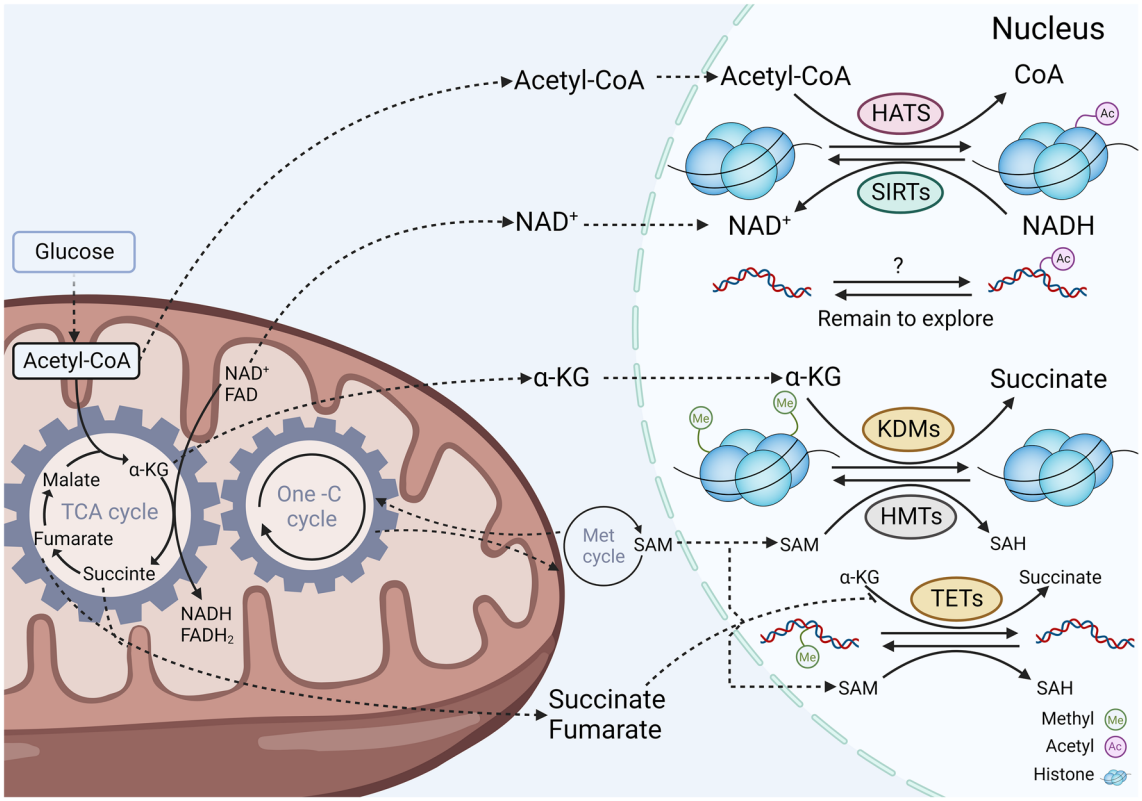

Fig. 1 Mitochondrial metabolites regulate the epigenetic landscape to determine stem cell fate. Historically, mitochondrial metabolism has been linked to the production of ATP and tricarboxylic acid cycle (TCA) metabolites to support stem cell survival and growth, respectively. However, it is now clear that beyond these canonical roles, mitochondria, as signaling organelles, dictate stem cell fate and function through TCA cycle metabolite production, NAD+/NADH ratio modulation, and epigenetic regulation. Metabolites generated by the TCA cycle and one-carbon cycle act as substrates or cofactors to control epigenetic modification of stem cells, especially histone acetylation and methylation as well as DNA methylation. These metabolic cycles interact with each other like a gear, making the mitochondria a high-speed organelle that controls various life processes of stem cells. An imbalance in the ratio of mitochondrial metabolites can disrupt the normal function of stem cells. For example, an imbalance in the α-KG/succinic acid ratio or the NAD^+/NADH ratio can lead to changes in stem cell fate and function. *α-KG* alpha-ketoglutarate, *NAD^+* nicotinamide adenine dinucleotide, *NADH* NAD^+ hydrogen, *SAM* S-adenosylmethionine, *TCA* tricarboxylic acid

has been observed in muscle stem cells (MuSCs), where glucose-derived acetyl-CoA also influences their differentiation through histone acetylation [39].

In mesenchymal stem cells (MSCs), an unexpected age-dependent change in the localization of acetyl-lysine signaling was observed, shifting from the nucleus to the mitochondria during senescence [40]. Due to reduced levels of citrate carriers, acetyl-lysine was trapped within senescent MSC mitochondria, resulting in reduced histone acetylation and age-dependent chromatin tightening. Expression of exogenous citrate carriers or supplementation with acetate restores cell membrane acetyl-CoA levels, remodels the chromatin landscape and rejuvenates MSCs [40]. The findings of this study underscore the impact of communication between mitochondria and the nucleus on the process of stem cell senescence. Additionally, during the differentiation of neural stem cells (NSCs), the antiapoptotic gene TP53-inducible glycolysis and apoptosis regulator (TIGAR) specifically modulates H3K9 acetylation by regulating the level of acetyl-CoA in cells and mitochondria, which determines the differentiation process of neural cells [41].

Recently, the emergence of non-histone acetylation has sparked a great deal of interest among biomedical researchers. Numerous studies have shown that non-histone protein acetylation plays a central role in various cellular processes related to physiology and disease [42]. However, the epigenetic regulation of stem cells is mainly focused on histone acetylation, with little attention given to the effects of non-histone acetylation. Therefore, further research is warranted to investigate this area.

Alpha-ketoglutarate

α-KG is a crucial intermediate in the TCA cycle, also known as the Krebs cycle, located between isocitrate and

succinyl-CoA. Remarkably, recent studies have highlighted the crucial role of α-KG in preserving the pluripotency of ESCs [43] and its potential application in anti-aging therapies [44]. Indeed, administering α-KG in a dose-dependent manner has been shown to extend the lifespan and delay the diminish of rapid, coordinated body movements in worms [44]. Wang and colleagues demonstrated that α-KG administration improved bone health in aged mice by increasing bone mass, reducing age-related bone loss, and accelerating bone regeneration. Additionally, α-KG treatment ameliorated the senescence-associated phenotypes of bone MSCs derived from aged mice while also enhancing their proliferation, colony formation, migration, and osteogenic potential [45]. The mechanism underlying the beneficial effects of α-KG on bone health involved a decrease in the accumulation of H3K9me3 and H3K27me3, which in turn led to an upregulation of bone morphogenetic protein (BMP) signaling and Nanog expression [45]. These findings shed light on the rejuvenating role of α-KG in MSCs and its potential for ameliorating age-related osteoporosis, highlighting its promising therapeutic potential for age-related diseases.

Ten–eleven translocation (TET) proteins play a key role in the demethylation of ESCs [46], and their absence leads to a decrease in pluripotency gene expression and an increase in the methylation level of their promoters, resulting in reduced cell pluripotency and cell differentiation [47]. Furthermore, overexpression of TET1 and TET2 has been shown to significantly improve induced pluripotent stem cell (iPSC) reprogramming in a catalytic-dependent manner. In these cells, α-KG maintains cellular pluripotency by controlling the level of histone K3K27me3 and TET-dependent DNA demethylation [43].

Studies have revealed that phosphoserine aminotransferase 1 (Psat1) plays a key role in maintaining intracellular α-KG levels in mESCs. The levels of Psat1 and a-KG have a direct impact on the timing of differentiation. By modulating a-KG levels at the onset of differentiation, an epigenetic landscape is created that is conducive to differentiation [48]. When ESCs are grown in the presence of signaling inhibitors to mitogen-activated protein kinase and glycogen synthase kinase, they utilize both glucose and glutamine in the medium to preserve high levels of α-KG to alter chromatin modifications [43, 49]. Compared with more differentiated cells, naïve ESCs utilize glucose and glutamine catabolism to maintain high intracellular levels of α-KG. When Psat1 levels are lowered, mESCs start to differentiate more quickly [50]. The study also found that α-KG levels decline during differentiation and that the dysregulation of α-KG impedes differentiation. In vitro, supplementation with cell-permeable α-KG directly supports ESC self-renewal. Importantly, treatment with cell-permeable dimethyl α-KG (DMKG) reverses the increases in the H3K27 and H4K20 trimethylation marks in the mESCs, confirming that the increases in trimethylations are caused by a decline in α-KG levels in the cells [43]. Nevertheless, the enzymes that control α-KG production and how α-KG fine-tunes the fate of mESCs remain unclear. For NSCs, different levels of oxygen pressure and durations of hypoxic exposure determine the developmental process. The hydroxylation response activity of hypoxia-inducible factor (HIF) is controlled by a-KG [51].

Succinate and fumarate

In addition, succinate and fumarate, which are structurally similar to α-KG, competitively inhibit TETs and Histone lysine demethylases (KDMs), leading to the regulation of gene expression [52–54]. It was reported that in naïve embryonic stem cells, glutamine-derived α-KG helps sustain a high α-KG-to-succinate ratio, which is important for promoting histone/DNA demethylation and maintaining a highly accessible genome [50, 55]. Furthermore, succinate accumulation and, thereby, a decrease in the α-KG/succinate ratio induced by pharmacological inhibition or genetic knockdown of succinate dehydrogenase A (SDHA) delay primed hPSCs differentiation [56]. This effect can be rescued by DMKG treatment, which increases the α-KG/succinate ratio. An increase or decrease in the αKG/succinate ratio also appears to regulate primed PSC fate by activating or inhibiting TET and KDM enzymes, respectively [56]. Recently, activation of succinate receptors on neural stem cells was shown to enhance their anti-inflammatory activity in an experimental model of autoimmune encephalomyelitis [57]. Interestingly, succinate may indirectly impact hematopoiesis in individuals with diabetes, as osteoclasts, which function as negative regulators of HSCs [58], may be influenced by succinate levels. In contrast, osteoblasts, which support lymphoid progenitors, may be less affected by succinate [59, 60]. Further research is necessary to confirm and expand upon these hypotheses.

NAD^+/NADH

Nicotinamide adenine dinucleotide is a dietary compound essential for life and a coenzyme implicated in cellular redox reactions [61]. NAD^+ and its reduced form, NAD^+ hydrogen (NADH), are crucial for cellular function and genomic stability [61]. As a coenzyme for redox reactions, NAD^+ is essential for key metabolic pathways, including the TCA cycle, the mitochondrial electron transport chain (ETC), glycolysis, and fatty acid β-oxidation. Mitochondria, as critical regulators of the cellular NAD^+/NADH ratio, dictate the fate and function of different stem cells. Recent studies in yeast, worms, and mice have suggested that the activity of three different enzyme groups, namely, sirtuins (class III histone deacetylases), CD38 (cyclic ADP-ribose synthases),

and PARPs (poly ADP-ribose polymerases), are regulated by NAD + /NADH [62–64]. Supplementation with NAD^+ in a nematode Werner syndrome model improved mitotic cell numbers and proliferation capacity, promoting nematode health and longevity, indicating enhanced stem cell function [65]. Notably, studies of sirtuins have yielded many exciting findings in recent years.

Sirtuins are conserved protein NAD-dependent deacetylases, and their functions are intrinsically linked to stem cell differentiation and senescence. When NAD^+ is deficient in nasopharyngeal carcinomas, their ability to differentiate and self-renew is impaired. NAD^+ levels in the hippocampus of mice decline with age and are highly correlated with NSCs dysfunction [66]. Sirt1 and Sirt2 redundantly mediate neural stem/progenitor cell fate decisions into oligodendrocytes [67]. Moreover, Gomes et al. reported that reduced levels of NAD^+ contribute to the mitochondrial decay associated with skeletal muscle aging and that SIRT1 modulates this process [68]. In aged mice, a decrease in NAD^+ levels in MuSCs leads to cell senescence, and boosting NAD^+ levels with the dietary precursor nicotinamide riboside alleviates MuSCs senescence and extends mouse lifespan [69]. A comparable occurrence was noted in HSCs, where the process was mediated by SIRT3 and SIRT7. The expression of SIRT3 and SIRT7 declines with age and leads to HSC dysfunction [70, 71]. Furthermore, overexpression of SIRT3 reduces oxidative stress and rescues functional defects in aged HSCs [70]. Expression of SIRT2, another SIRT family member, also decreases with age, which leads to chromatin silencing [72]. Activation of SIRT2 regulates signaling for mitochondrial stress in HSC, inhibits activation of NLRP3 inflammatory vesicles, and reverses functional deterioration in aging hematopoietic stem cells [73].

The NAD + /NADH redox cycle, which plays a crucial role in energy production via glycolysis, the TCA cycle, and oxidative phosphorylation (OXPHOS), is also involved in regulating aging-related signaling pathways and functions [69, 74]. Human MSCs with damaged mitochondria exhibit depolarized mitochondrial membranes and low mitochondrial complex I function, which could compromise the ability to metabolize NADH and maintain NAD^+/NADH redox balance. This observation indicates that senescent hMSCs may shift toward a more reducing (or less oxidized) NAD^+/NADH cycle [75]. The ectopic expression of the single-subunit yeast alternative NADH dehydrogenase in Drosophila intestinal stem cells has been shown to delay the onset of intestinal aging and extend lifespan by modulating the NAD^+/NADH ratio in aged cells [76]. This suggests that the NAD^+/NADH ratio is a fundamental factor in cellular aging and lifespan. It is intriguing to investigate whether the role of NAD^+ and NADH dehydrogenases in age-related mitochondrial dysfunction is conserved in various tissues and stem cells of different species and whether strategies to manipulate the NAD^+/NADH ratio in humans could have therapeutic benefits.

SAM

S-Adenosyl methionine (SAM) is a cofactor for histone methyltransferases connecting histone methylation to one-carbon metabolism [36] and threonine (Thr) metabolism [77]. DNA and histone methylations are driven by SAM as the methyl donor. Hence, mitochondrial metabolic fluctuation-induced changes in SAM levels may exert an influence on histone and DNA methylation, which are critical for maintaining cellular homeostasis and regulating lifespan [78].

The metabolic state of mouse ESCs is highly dependent on Thr catabolism. Recently, it was reported that Thr metabolism regulates intracellular SAM and histone methylation such that depletion of Thr from the culture medium or knockdown of threonine dehydrogenase (Tdh) in mouse ESCs decreases SAM accumulation and trimethylation of histone H3 lysine 4 (H3K4me3), leading to slowed growth and increased differentiation. Studies have shown that Thr metabolism regulates intracellular SAM and histone methylation [79, 80]. Removal of Thr from the medium or knockdown of Tdh reduced SAM accumulation and trimethylation of H3K4me3, resulting in slower growth and increased differentiation [79].

Naïve hPSCs also control SAM levels to regulate H3K4 trimethylation, which acts as a recognized signature marker of active chromatin [81]. This process links the metabolic and epigenetic regulation of pluripotent hPSCs. In a subsequent study, methionine deprivation was simulated under conditions of zinc deficiency in the culture medium, leading to a reduction in intracellular SAM and, thus, leaving PCSs in a state of enhanced differentiation [82].

Stress signals affect epigenetic pathways in stem cell senescence

Environmental factors can easily impact the metabolic state of stem cells. Mitochondrial disruptions trigger stress signals and notify the nucleus of its functional state, resulting in adaptations. Various pathways are activated when mitochondrial function is impaired, including mitochondrial DNA (mtDNA) loss, mtDNA mutation accumulation, mitochondrial unfolded protein response (UPR^{mt}), and generation of ROS [83, 84] (Table 1). These stress-related changes can cause modifications to the epigenome and gene expression, leading to metabolic adaptation and increased lifespan of stem cells [85, 86] (Fig. 2). This section delves into how

Table 1 Mitochondrial stress response in stem cell proliferation, differentiation, and aging

Stressor	Stem cell type	Cell activity	Effects	References
MtDNA mutation	NSCs, HPCs	Dysfunction	Anemia and lymphopenia	[87]
	ISCs	Abnormal proliferation Senescence	Impair intestinal function Reduce nutrient absorption	[88]
MtDNA mutation	HSCs	Inhibit differentiation	Hematopoietic abnormalities Defects in lymphopoiesis Myelodysplastic syndromes	[89] [90]
MtDNA deletion	MuSCs	Dysfunction Increase senescence	Affect MuSCs pool Reduce regenerate and repair ability	[91]
ROS	HSCs	Regulate divisions Increase senescence	Regulate the differentiation Reduce the replicative potential	[92, 93]
			Affect FAO pathway Modulation cell divisions	[94]
			Maintain the quiescence and survival by FOXO proteins	[95]
	NSCs	Survival Proliferation	Increase Nrf2 expression and Transcription	[96]
			Regeneration of neurons	[97]
	MSCs	Inhibit proliferation Increase senescence	Affect sirtuins expression and activity	[98]
UPRmt	HSCs	Functional decline Maintain Proliferation	Downregulation of SIRT7 Increase mitochondrial protein Dysfunction	[71]
			UPRmt is activated during the Transition from quiescence to Proliferation	[99]
			SOD2 activates UPRmt	[100]
	MuSCs	Senescence	NR treatment can induce UPRmt Rejuvenate aged MuSCs	[101, 102]

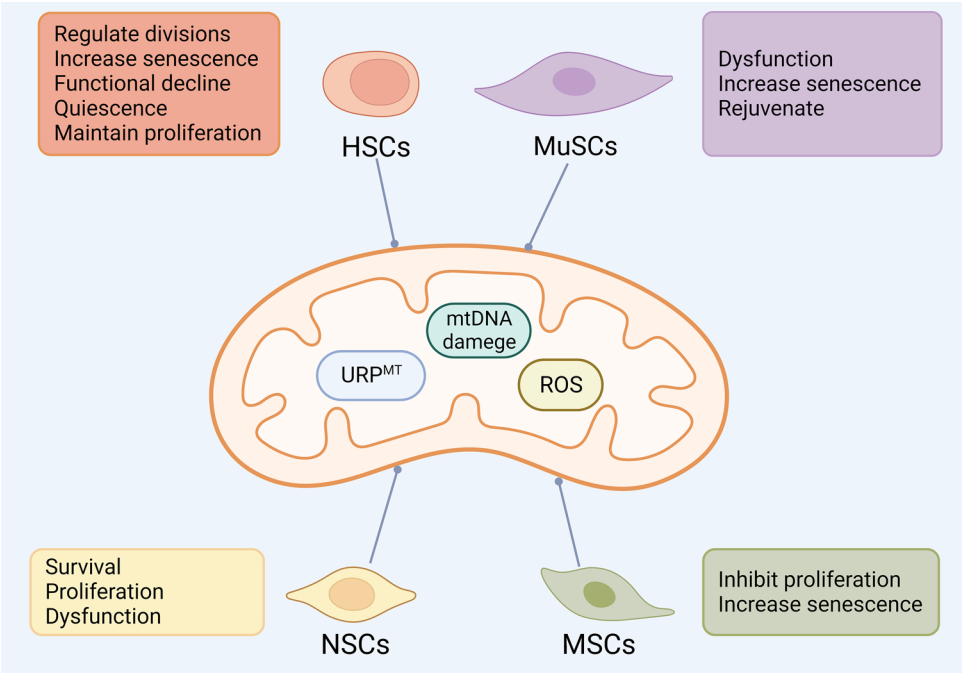

Fig. 2 Roles of mitochondrial stress signaling responses in stem cells. Mitochondrial stress signaling responses play important roles in stem cells and are regulated by several key players, including mtDNA, ROS, and the UPRmt. These stress-related changes result in modifications to the epigenome and gene expression, leading to metabolic adaptation and increased lifespan of stem cells [85, 86]. In a variety of stem cells, different mitochondrial stress responses are regulated to some extent by epigenetic changes. *mtDNA* mitochondrial DNA, *HSCs* hematopoietic stem cells, *MSCs* mesenchymal stem cells, *MuSCs* muscle stem cells, *NSCs* neural stem cells, *ROS* reactive oxygen species, *UPR^{mt}* mitochondrial unfolded protein response

mitochondrial stress signaling controls stem cell senescence through epigenetic regulation.

Mitochondrial DNA

Mitochondria possess multiple copies of their DNA. The 13 subunits of the mitochondrial respiratory chain enzymes as well as the 22 tRNAs and 2 rRNAs needed for the translation of these proteins are encoded by mtDNA [103].

The accumulation of damaged mitochondrial genomes is considered to be the underlying cause of age-related neurological and cardiovascular diseases, including Parkinson's disease and coronary artery disease [104–107]. Many studies have shown that altered mitochondrial DNA causes a reduction in stem cell populations and dysfunction, which is responsible for triggering aging and degenerative diseases. For instance, mtDNA polymerase gamma (POLG) mutant mice had NSC and hematopoietic progenitor cell (HPC) dysfunction from embryogenesis. HPCs showed abnormal lineage differentiation leading to anemia and lymphopenia [87]. Accelerated mitochondrial DNA mutations in stem cells of POLG mutant mice lead to impaired intestinal function and reduced nutrient absorption, which are important processes in aging [88]. In addition, the reprogramming ability of POLG mutant stem cells was significantly impaired during the generation of iPSCs [108]. McDonald et al. [109] showed that mtDNA mutations were present in stem cells of the normal human gastric epithelium and were passed on to differentiated progeny. Age-associated mitochondrial DNA mutations have also been reported to cause abnormal cell proliferation and apoptosis in human colonic crypts and inhibit the early differentiation of HSCs [89, 110]. In another mouse model of aging, systemic dysfunction of mitochondria due to mtDNA deletion affects the pool of muscle stem cells, thereby diminishing the muscle's capacity to regenerate and repair itself during the aging process [91]. Overall, these studies highlight the importance of mtDNA in controlling stem cell fate and function in a variety of contexts. Intact mitochondrial function is needed for appropriate multilineage stem cell differentiation. Notably, Norddahl et al. revealed that mitochondrial DNA mutations alone are not sufficient to cause age-related stem cell dysfunction [90].

Increasing evidence suggests that aberrant mtDNA modification plays an important role in disease development and progression [111–113]. Although mitochondria do not have histones, there are DNA−protein assemblies consisting of mtDNA [114]. A variety of nucleoid factors are involved in the maintenance and transcription of mtDNA, including mitochondrial transcription factor A (TFAM, the central mtDNA packaging factor), mitochondrial single-strand DNA binding protein (mtSSB), mitochondrial RNA polymerase (POLRMT), and Lon protease [115, 116]. Whether mtDNA is modified by methylation has been controversial [111, 117]. Because methylase cannot enter mitochondria and mtDNA does not bind to histones, the prevailing view is that mtDNA cannot be methylated [118]. One study found that mtDNA methylation does not occur in the oocytes and early embryos of mice [119]. Recently, Tian et al. demonstrated that the mitochondrial genome undergoes DNA de novo methylation similar to the nuclear genome, which can help embryonic and somatic cells combat mtDNA damage triggered by mitochondrial oxidative stress and maintain mitochondrial genome stability [120]. Recent studies have implied that methylation can occur on cytosine and adenine residues in mtDNA, which is associated with aging and age-related diseases [121–123]. However, the methylation status of mtDNA remains a topic of controversy due to limitations in current methods for detection, as both CpG and non-CpG sites are present in mtDNA [124–126]. Many of the available methods for detecting mtDNA methylation have significant drawbacks [127]. mtDNA methylation changes to different degrees during development, aging, and hypoxic stress [127, 128], but the regulatory mechanism remains to be studied. Likewise, methylation of mtDNA regulates the activities of mitochondrial transcription factors. Methylation of mtDNA attenuates the binding of TFAM to the genome, thereby altering its transcriptional activity. This process may indirectly regulate the activities of TFB2M (transcription factor B2, mitochondrial) and POLRMT through the recruitment mechanism of TFAM [129]. Although the physiological role of mtDNA methylation is unknown, it has been found that aging reduces mtDNA 5-hydroxymethylcytosine (5hmC) in the frontal cortex of mice. In the same tissue, the expression of mitochondrial-encoded genes is upregulated with aging [130], suggesting that epigenetic regulation of mtDNA transcription is also involved in the aging process. In contrast. mtDNA methylation was not observed in mouse oocytes and early embryos [119]. This idea needs to be supported by more research.

Mitochondrial ROS

ROS refers to oxygen-containing free radicals or compounds that are more reactive than molecular oxygen, including superoxide radical anion (O2 −), hydroxyl radical (·OH), hydrogen peroxide (H2O2), and lipid hydroperoxides (LOOH) [131]. Mitochondria are a major source of ROS and central modulators of redox homeostasis in stem cells, a consequence of their role in energy (i.e., ATP) production via OXPHOS. Murphy has elaborated in detail on the process of ROS production by mitochondria [132, 133].

Impairment of the mitochondrial respiratory chain and inefficient OXPHOS can enhance electron leakage, leading to increased ROS generation. This detrimental

cycle can cause progressive and irreversible damage to cells, ultimately contributing to the aging process [134]. Mitochondria alter the epigenetic landscape via ROS, which play a particularly relevant role in regulating stem cell fate [6, 7]. The regenerative potential of stem cells is closely related to intracellular reactive oxygen species levels and cellular redox homeostasis [135].

The majority of mitochondrial ROS are produced due to electron leakage from OXPHOS complexes I and III, leading to damage to various cellular components, such as DNA, lipids, and proteins [136]. Stem cells appear to be particularly sensitive to elevated ROS levels. Under normal conditions, ROS function as signaling molecules that regulate the differentiation of stem/progenitor cells, such as in Drosophila hematopoietic cells [92]. Nevertheless, ROS levels increase in HSCs with age, and prolonged treatment with the antioxidant N-acetyl-L-cysteine (NAC) increases the replicative potential of HSCs upon serial transplantation in irradiated mice [93]. Another study demonstrated that Bmi1-deficient cells exhibit compromised mitochondrial function, elevated levels of reactive oxygen species, and activation of the DNA damage response pathway. However, these effects were ameliorated through NAC treatment [137]. Ito et al. provided evidence that mitochondrial ROS generation in HSCs and progenitors could be influenced by the fatty acid β-oxidation (FAO) pathway, leading to the modulation of symmetric and asymmetric HSC division [94]. Furthermore, Forkhead box O (FOXO) proteins, crucial mediators in ROS signaling, play an important role in the response to oxidative stress and are involved in preserving the quiescence and survival of HSCs [95]. Neural stem cells can eliminate ROS by upregulating Nrf2 expression and transcription [96]. High ROS levels inhibit MSC proliferation and increase senescence. Modulating sirtuins expression and activity may reduce oxidative stress in MSCs [98]. Alterations in ROS levels may impact the expansion, depletion, and maintenance of stem cells.

Mitochondria altering the epigenetic landscape through ROS play a particularly pertinent role in regulating stem cell fate [138–140]. For instance, mitochondrial dysfunction induces histone hypermethylation by increasing the levels of ROS, which inhibits histone demethylases [2]. Neural stem cells exposed to the synthetic glucocorticoid dexamethasone or ROS have reduced overall DNA methylation and DNA methyltransferases, intimating the development of epigenetic alterations [141]. The generation of ROS is also associated with epigenetic chromatin modifications, including global DNA CpG hypomethylation and histone-3 phosphorylation, which promote cellular apoptosis and lead to hematopoietic catastrophe [142].

Although ROS are better known for their damaging properties, recent findings indicate that ROS may also be an integral physiological mediator of cellular signaling in primary cells [143]. Intriguingly, the effects of mitochondrial ROS on stem cell dysfunction and aging are not all negative. Long-lived species do not always demonstrate lower levels of ROS [144]. A rise in ROS even increases the lifespan of worms [145]. Similarly, an increase in ROS levels is accompanied by an increase in mitochondrial size and ATP levels to protect HSCs from irradiation-induced apoptosis [146]. ROS production is an important component of neural stem cell regulation. The regeneration of dopamine neurons also depends on ROS production [97]. ROS signaling is considered to be an emerging key regulator of multiple stem cell populations [147]. Metabolic analysis has demonstrated that oxidative phosphorylation stimulates p38 mitogen-activated protein kinase (p38-MAPK) activation by mitochondrial reactive oxygen species signaling, thereby establishing the mature crypt phenotype. Hye Jin Jin et al. observed that senescent UCB-MSCs release monocyte chemoattractant protein 1 (MCP-1), a prominent chemokine, which facilitates the transmission of senescence signaling through its receptor chemokine (c–c motif) receptor 2 (CCR2), thereby promoting senescence by elevating the levels of p53 and p21 proteins via ROS or p38-MAPK signaling. Additionally, the polycomb protein BMI1 was found to downregulate the expression of MCP-1 by binding to its regulatory elements. As UCB-MSCs undergo senescence and BMI1 levels decrease, the epigenetic profile of MCP-1 changes, leading to the loss of H2AK119Ub and ultimately causing the derepression of MCP-1 [148]. This suggests that ROS signaling plays a critical role in the differentiation of stem cells in the small intestine [149]. Nevertheless, the effects of mtROS on stem cell function and the specific mechanisms remain to be further investigated.

Mitogen-activated protein kinases allow cells to interpret and respond to a wide variety of signals, such as changes in osmolarity, oxidative stress, and heat shock [150, 151]. Activation of MAPKs is associated with the ability to differentiate multiple types of stem cells in humans and mice [152–154]. In particular, all four p38 identified isoforms (p38α, β, γ, and δ) serve as nexuses for signal transduction and play crucial roles in many biological processes [155, 156]. For stem cells, studies have indicated that the p38-MAPK pathway activated by ROS has a negative effect on the self-renewal and expansion of HSCs [155, 157]. SB203580 is a selective inhibitor of p38-MAPK. One possible mechanism is that SB203580 regulates the p38-MAPK signaling pathway by reducing the downstream phosphorylation of MAPKAPK2, HSP27, and ATF2 [158]. Administration of SB203580 helps HSCs recover the regenerative ability, maintain a static state, and promote expansion. [157, 159–161]. One recent study revealed that p38α differentially modulates HSC function between the early and late progression phases of chronological aging [162]. During the early progression phase of chronological

aging, p38-MAPK activity maintains HSC repopulation capacity and multipotency after transplantation, whereas in the late progression phase, it decreases HSC repopulation capacity after transplantation [162]. The p38 pathway is also one of the major controllers that determines the fate of muscle stem cells by inducing the expression of muscle-specific genes [163]. The p38-MAPK pathway is also a key player in MSC senescence [164]. Inhibition of p38-MAPK signaling leads to improved regenerative properties of MSCs and their ability to support HSCs, even abrogating aging phenotypes [165, 166]. Prakash et al. found that depleting SIRT3 increases p38 signaling and promotes MSC death during oxidative stress [167]. Notably, in a later study, inhibition of p38 by SB203580 significantly impairs the lipid differentiation potential of MSCs [168], which diverges from the results obtained in the above study. This may be due to the different response of varied types or sources of stem cells to SB203580. As the major source of cancer initiation, relapse, and drug resistance, research on cancer stem cells (CSCs) has increased in recent years. For most cancers, inhibition of p38 can reduce the expression of stemness factors in CSCs and attenuate the invasion and metastasis of circulating tumor cells [169]. Another study suggested that the p38 pathway inhibits cancer development by inhibiting cell proliferation and mediating cell senescence. Specifically, for non-small cell lung cancer cells, increased expression of WIP1 (wild-type p53-induced phosphatase) suppresses p38 activity and promotes CSCs properties by enhancing the expression of stemness-related transcription factors [170]. In a previous study, Shuhei Hattori demonstrated that the expression of EC-SOD (Extracellular-superoxide dismutase) in tubular-epithelial COS7 cells is downregulated through intracellular ROS signaling [171]. In line with this finding, treatment with $CoCl_2$ decreased the acetylation levels of histone H3 and H4 by activating intracellular ROS–p38-MAPK signaling. Additionally, luteolin effectively mitigated the reduction in EC-SOD caused by $CoCl_2$ by inhibiting ROS–p38-MAPK signaling and histone deacetylation [172]. Additionally, Arctigenin, a dietary phytoestrogen, has been identified as an inducer of apoptosis in MDA-MB-231 cells by activating the ROS/p38-MAPK pathway and regulating Bcl-2 through increased histone H3K9 trimethylation [173]. Nevertheless, further investigation is required to determine the potential involvement of $CoCl_2$ and Arctigenin in regulating the stem cells fate.

In summary, these studies reveal multifaceted functions of the p38-MAPK pathway in various contexts of multiple

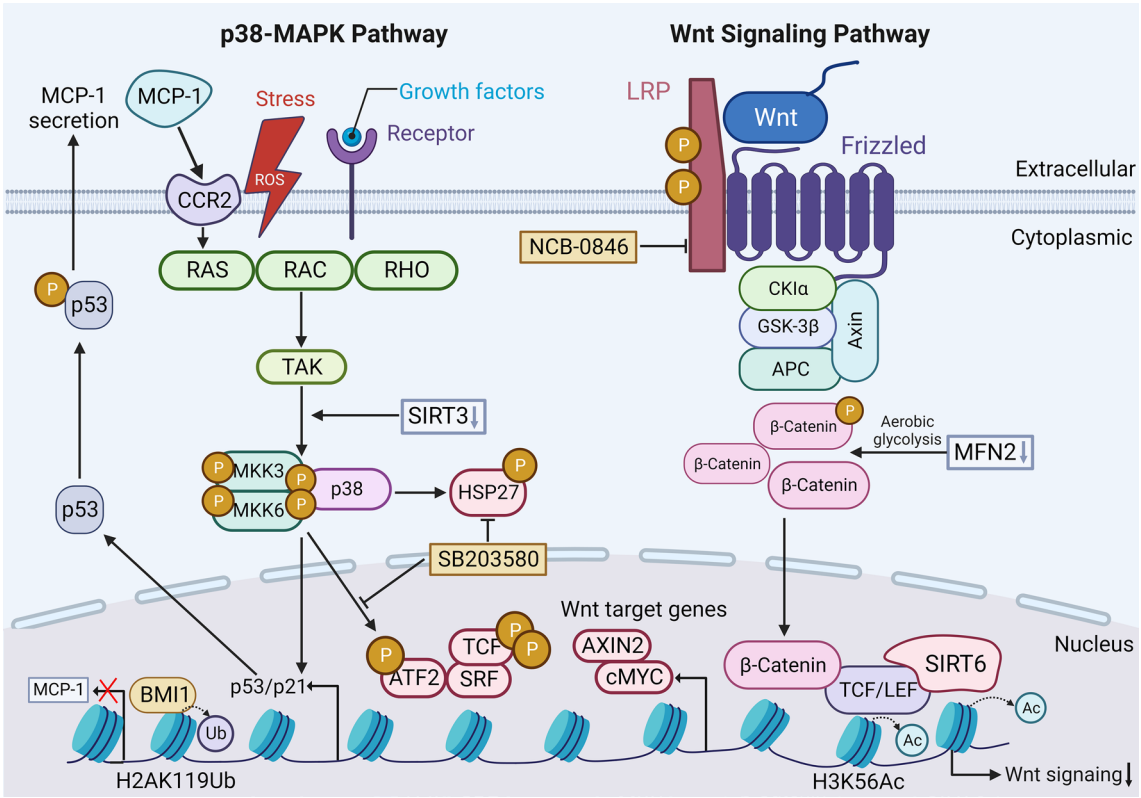

Fig. 3 Roles of mitochondrial stress signaling responses in stem cells. Some pathways activated by stress signals, such as p38-MAPK and Wnt, control whether stem cells express stemness factors and affect their differentiation and aging. This figure shows how related regulators (SIRT3/6, BMI1, SB203580, NCB-0846) influence these process through epigenetic pathways

stem cells (Fig. 3). Thus, regulating p38 might enable us to control the stem cell state and differentiation direction.

The UPRmt

During aging, mitochondria will decline in function as a result of several factors. In cases of mitochondrial dysfunction, cells initiate a transcriptional response mechanism known as UPRmt, which serves to regulate mitochondrial protein homeostasis [174]. UPR^{mt} was originally discovered in cultured mammalian cells where deletion of mtDNA or overexpression of mitochondrial targeting proteins triggered associated transcriptional responses, including mitochondrial molecular chaperones and quality control proteases [175, 176]. Studies in *C. elegans* have identified components in multiple subcellular compartments, providing insights into how cells detect mitochondrial dysfunction and communicate with the nucleus to adapt to transcription accordingly [177]. Importantly, this mitochondrial protein quality control mechanism is conserved among many species, including worms, mice, and humans [178–181]. However, the human UPR^{mt}, which is gaining relevance in a variety of physiological processes, remains not fully understood. The UPR^{mt} pathway not only triggers the transcription of chaperones and proteases to restore mitochondrial proteostasis but also renders cells more resistant to aging and metabolic stresses by inducing tolerance to mitochondrial stress [182, 183].

Following comprehensive research on the function and regulation of the UPR^{mt} in somatic cells, scientists have focused on exploring the regulatory mechanisms of the UPR^{mt} in stem cells. Mohrin et al. found that the reduction in *SIRT7* expression in aged HSCs leads to functional decline. The downregulation of *SIRT7* contributes to age-related functional degradation through an increase in mitochondrial protein dysfunction [71]. In line with this study, they further provide direct evidence that the mitochondrial UPR^{mt} is activated when hematopoietic stem cells transition from quiescence to proliferation [99]. This work has been recently extended into NSC aging. Wang et al. used single-cell RNA sequencing to analyze the dentate gyrus of young and aged mice and confirmed that mitochondrial protein folding stress is elevated as neural stem cells age. Among them, SIRT7 overexpression inhibited mitochondrial protein folding stress to protect neural stem cells [184]. In addition to *SIRT7*, UPR^{mt} activation by superoxide dismutase 2 (SOD2) is imperative for HSCs to maintain the integrity of the mitochondrial network [100]. The expression of UPR^{mt}-associated genes can be affected by the level of cellular NAD^+. NR (Nicotinamide riboside) treatment rejuvenated aged MuSCs by inducing the mitochondrial unfolded protein response and synthesis of prohibition proteins [101, 102]. Moreover, intestinal epithelial-specific heat shock protein 60 (HSP60) deficiency triggers the UPRmt pathway, which leads to the excessive proliferation of residual stem cells [185]. The findings indicate that the UPR^{mt} performs crucial functions in preserving adult stem cell populations in various tissues by ensuring metabolic robustness prior to committing to proliferation.

As a well-studied 'old pathway', Wnt signaling has been found to have a novel function in the UPR^{mt}. Highly conserved Wnt signaling is sufficiently required to mediate the involuntary activation of the UPR^{mt} in neuronal–intestinal cells [186]. Furthermore, there is a remarkable phenomenon wherein the UPR^{mt} induced by mitochondrial stress in neurons can be inherited by offspring [187]. Traditionally, the Wnt pathway is recognized as an important regulatory signaling axis that influences developmental processes in the embryo and regulates the maintenance, self-renewal, and differentiation of adult mammalian tissue stem cells [188]. In general, Wnt proteins act to maintain the undifferentiated state of stem cells [189]. Specifically, Wnt signaling regulates the metabolic requirements of neural crest-like stem cells through glycolysis and determines their differentiation [190]. There have been many advances in the epigenetic regulation of Wnt signaling in stem cells [191] (Fig. 3). For instance, the activation of the Wnt/β-catenin signaling pathway ensures normal DNA methylation of mESCs, which is essential for differentiation and proliferation [192]. SIRT6 is a histone deacetylase that maintains Wnt signaling at a low level in HSCs by two methods: (1) deacetylating H3K56ac at the promoters of Wnt target genes and thereby inhibiting transcription; and (2) limiting signaling specificity by interacting with Wnt signaling factor TCF/LEF1. [193]. In addition, when Wnt signaling is activated by p38β via LRP6 phosphorylation, this pathway maintains the self-renewal capacity of normal stem cells and cancer stem cells (CSCs) in many cell types [169]. A novel Wnt small molecule inhibitor NCB-0846 down-regulates the levels of LRP5 and LRP6 in colorectal cancer cells. NCB-0846 reduces the expression of Wnt downstream targets AXIN2 and cMYC and is expected to remove cancer stem cells [194]. What is more, the WNT protein is a critical cell reprogramming signaling molecule that can successfully reprogram fibroblasts or skin cells into induced pluripotent stem cells [195]. Given the important role of the Wnt/β-catenin pathway in the pluripotent differentiation and regeneration of stem cells, further exploration of how Wnt signaling pathway-mediated UPR^{mt} in stem cells prolongs their lifespan is a promising direction of research.

Mitochondrial quality control and stem cell senescence

Mitochondria have evolved multiple mechanisms to ensure mitochondrial quality. These programs are dysregulated during physiological aging, which contributes to the functional deterioration of stem cells, tissue degeneration, and shortened organismal lifespan. A decline in mitochondrial quality control pathways results in a multitude of cellular malfunctions, including genetic and epigenetic changes. For example, Katarzyna Kornicka and her colleagues identified that the regulation of mitochondrial dynamics and autophagy by 5-azacytydine and resveratrol can reverse senescence and aging in adipose stem cells [196]. Specifically, 5-azacytidine/resveratrol treatment rejuvenates adipose stem cells isolated from equine metabolic syndrome (EMS) horses through epigenetic alternations [196]. Currently, several genes involved in mitophagy and mitochondrial dynamics have been identified to regulate stem cell activation and differentiation (Table 2).

Mitochondrial dynamics: fusion and fission

In higher eukaryotes, the segregation of mtDNA within cells is regulated by continuous cycles of mitochondrial fission and fusion. These processes are highly dynamic, and their rates are finely tuned to meet the specific requirements of different cell types [217]. Mitochondrial dynamics is an important aspect of mitochondrial behavior that involves the processes of mitochondrial fission, fusion, tethering, and motility [218]. The balance between mitochondrial fission and fusion is critical for maintaining mitochondrial function and preventing cell death (Fig. 4) [219]. The alteration of mitochondrial dynamics leads to an increase in mitochondrial fission, which facilitates the process of mitophagy for the removal of damaged mitochondria and plays a role in driving cellular differentiation [220].

The use of mitochondria-specific probes, combined with fluorescence microscopy, has demonstrated that mitochondria are in the process of mitochondrial dynamics in mammalian cell lines and yeast [221]. The regulation of mitochondrial fusion is primarily achieved through three large proteins of GTPases situated on the mitochondrial membrane, namely, mitochondrial fusion proteins 1 and 2 (MFN1, MFN2) and optic nerve atrophy protein 1 (OPA1) [221, 222]. Conversely, the process of mitochondrial fission is controlled by a group of five proteins, which include dynamin-related protein 1 (DRP1), mitochondrial fission protein 1 (FIS1), mitochondrial fission factor (MFF), and mitochondrial elongation factors 1 and 2 (Mi49 and MiD51) [223]. Specifically, DRP1, which resides in the cytoplasm, plays an imperative role in the regulation of mitochondrial fission [224]. Upon receiving the fission signal, a

Table 2 Mitochondrial stress response in stem cell proliferation, differentiation, and aging

Dynamics	Key genes	Manipulation	Effect on stem cell	References
Fusion	OPA1, MFN1/2	Removal of MFN1 and MFN2	Impair NSC self-renewal	[197]
			Block asymmetric division of stem cells	[198]
			Improve reprogramming efficiency and pluripotency	[199]
		Gene trapping of MFN2 or OPA1	Impair ESC differentiation	[200]
		Removal of OPA1	Impair ISCs differentiation	[201]
		Overexpression of MFN2	promote ESC differentiation	[202]
			Promote hiPSCs differentiation	[203]
			Maintain HSCs stemness	[204]
Fission	DRP1 FIS1, MFF, Mi49/51	Downregulation of DRP1	Rescue ISC differentiation defect	[205]
			Reduces the reprogramming efficiency of IPSCs	[206]
			MSCs lost differentiation potential	[207]
			Loss stemness	[208]
		Upregulation of DRP1, FIS1	Improve reprogramming efficiency of iPSCs	[209]
			Impair developmental potential	[210]
			Influence MSCs' differentiation direction	[207]
Mitophagy	PINK1, PARKIN, FUNDC1, BNIP3 AMBRA1	Upregulation of PARKIN and PINK1	Maintain stemness and regenerative capacity	[211, 212]
			Induction of ISCs aging	[213]
		Upregulation of BNIP3	Lead to mitochondrial fragmentation and apoptosis	[214]
		Deficiency of PINK1	Increase spontaneous differentiation and decrease reprogramming efficiency of iPSCs	[215]
		Deficiency of SIRT1	Delay activation of muscle stem cells	[216]

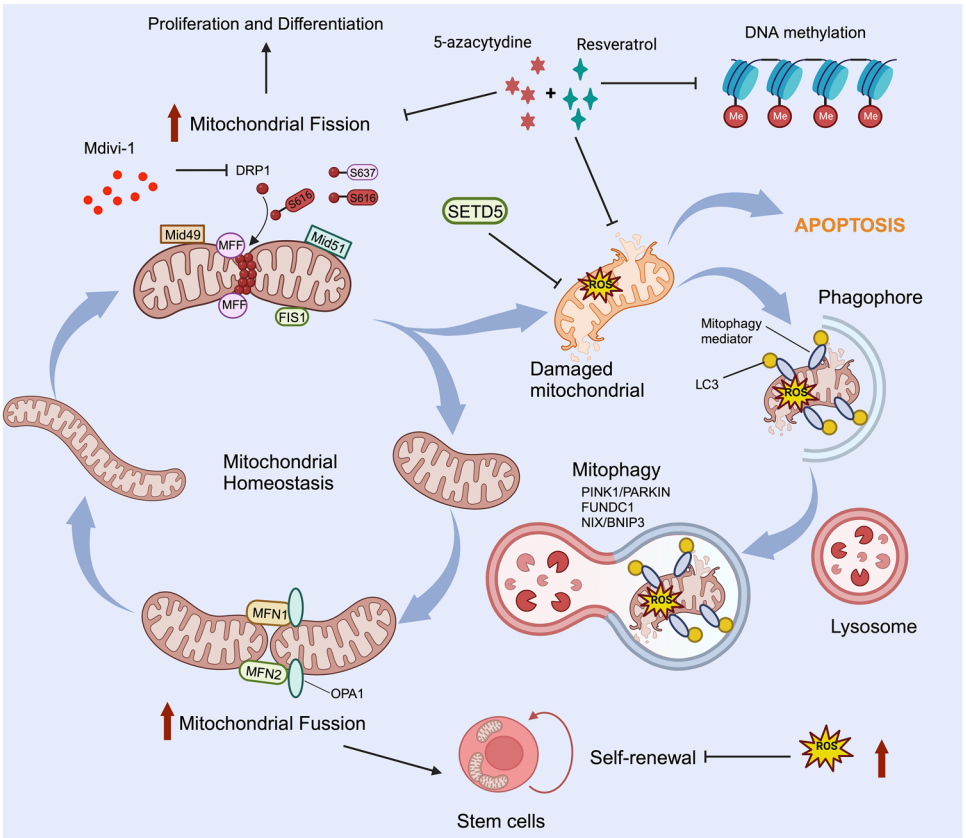

Fig. 4 Mitochondrial quality control in stem cells. The mitochondrial dynamic balance between fusion and fission maintains mitochondrial homeostasis, while damaged mitochondria are cleared via the mitophagy pathway or mitochondria-dependent apoptosis pathway. The alteration of mitochondrial dynamics leads to an increase in mitochondrial fission, which facilitates the process of mitophagy for the removal of damaged mitochondria and plays a role in driving cellular differentiation

considerable amount of DRP1 is transported to the outer membrane of mitochondria, where it interacts with FIS1, MFF, MiD49, and MiD51 to facilitate the process of mitochondrial fission [219]. Additionally, GDAP1 (Ganglioside Induced Differentiation Associated Protein 1), as a mitochondrial outer membrane protein, plays a role in certain types of Charcot–Marie–Tooth disease and is also responsible for regulating mitochondrial fission [225]. However, the specific mechanism through which it accomplishes these actions remains unclear.

Mitochondrial dynamics induce the differentiation potential of pluripotent stem cells. Chen and Chan suggested that there is a relationship between the shape and structure of mitochondria and the ability of stem cells to mature into specialized cell types. Specifically, high levels of mitochondrial fission are associated with resistance to differentiation in some stem cells [226]. Loss of some key proteins leads to severe respiratory chain function, which may be essential for cell differentiation. Mitochondrial dynamics affect NSCs by regulating their self-renewal and fate decisions through transcriptional programming. Manipulation of mitochondrial structure impairs NSC self-renewal, leading to age-dependent depletion, neurogenesis defects, and cognitive impairments. Removal of *MFN1* and *MFN2* causes age-dependent attrition, neurogenesis deficits, and cognitive impairment in NSCs [197]. Additionally, A recent study found that lower levels of SETD5 caused fragmentation in mitochondria and decreased mitochondrial membrane potential and ATP production in both neural precursors and neurons. And mutant neurons exhibited mislocalized mitochondria, with fewer organelles within neurites and synapses [227]. Gene trapping of *MFN2* or *OPA1* in mice arrested mouse heart development and impaired the differentiation of ESCs into cardiomyocytes [200]. MFN1 interacts with a cell polarity protein complex to direct asymmetric cell division, allowing stem cell progeny to inherit fused mitochondria with enhanced reactive oxygen species scavenging capacity to sustain the stem cell pool [198]. *MFN2* is specifically needed for the maintenance of HSCs with extensive lymphoid potential [204]. MFN2 also plays a role in inducing stem cell development. For example, knockdown of *MFN2* resulted in deficits in mitochondrial metabolism, whereas overexpression of *MFN2* enhanced mitochondrial bioenergetics and functions and promoted the differentiation of hiPSCs [203]. *MFN2*-induced mitochondrial elongation is sufficient to drive the exit of embryonic stem cells from initial pluripotency. This implies that *MFN2* plays a vital role in the transformation of mouse initial pluripotent cells to initiating pluripotent cells by promoting mitochondrial elongation [202]. The depletion of MFN1/2 facilitates the transition of cells into a pluripotent state and sustains pluripotency through the coordinated

integration of Wnt or p53 signaling [199, 228] (Fig. 3). Knockdown of *OPA1* blocked enterocyte differentiation in intestinal stem/progenitor cells [201].

As with mitochondrial fusion, loss of mitochondrial fission results in stem cell fate changes. Dysfunction of DRP1 leads to mitochondrial fragmentation and impaired mitochondrial quality control [229]. Specifically, the induction of pluripotency is associated with mitochondrial fragmentation via the regulation of DRP1 phosphorylation [205]. Inhibition of DRP1 using a small molecule called mdivi-1 leads to the formation of a fused mitochondrial network. This greatly reduces the efficiency of reprogramming, thereby inhibiting the reprogramming of somatic cells to induced pluripotent stem cells [206]. The upregulation of Fis1 expression during chondrogenesis implies that mitochondrial fragmentation plays a vital role in this differentiation process. The depletion of Drp1 and Fis1 resulted in a significant reduction in the differentiation potential of MSCs [207]. Drp1 also helps CSCs of nasopharyngeal carcinoma (NPC) maintain stemness [208]. The possibility of DRP1 improving the reprogramming efficiency of iPSCs cannot be ruled out; thus, further investigation is required to fully understand its potential involvement [209]. Zhong et al. showed that excessive mitochondrial division regulated by DRP1 is associated with impaired embryonic developmental potential of stem cells. This indicates that the balance between mitochondrial fission and fusion regulated by DRP1 and other proteins is essential for the pluripotency of stem cells [210].

In contrast, Wang and colleagues discovered that knockdown of Drp1 affected neither mitochondrial division and function nor ESC proliferation and pluripotency [230]. The defect in intestinal stem cell (ISC) differentiation could be rescued by concomitant inhibition of DRP1 [201]. Treatment with Drp1-specific inhibitors rescues mitochondrial function and apoptosis [231]. Downregulation of Drp1 negatively affects the eventual differentiation of stem cells, particularly in the neurogenesis profile in vitro and in vivo [230]. Consequently, significant controversies persist concerning the mechanism by which DRP1 modulates stem cell fate. As mentioned above, mitochondrial fusion is involved in the regulation of stem cell pluripotency. However, the exact mechanisms involved are still being explored. The relationship between these factors requires further research for a comprehensive understanding.

Mitophagy

The concept of mitochondrial autophagy was first formalized in 2005 by Lemasters, who observed that loss of mitochondrial membrane potential and the opening of mitochondrial permeability pores could cause mitochondrial autophagy [232]. Mitophagy, along with mitochondrial dynamics, plays a crucial role in maintaining a balance that preserves the quality control system of mitochondria.

Mitophagy regulatory pathways are classified as ubiquitin-dependent or ubiquitin independent [233]. The most studied mitophagy pathway involves mitochondrial serine/threonine PTEN-inducible kinase 1 (PINK1) and the cytoplasmic E3-ligase PARKIN [234–236]. In situations where mitochondria become damaged, there is typically a decrease in mitochondrial membrane potential, which triggers the activation of Parkin and PINK1 [237]. Initially, PINK1 starts to accumulate on the outer mitochondrial membrane. Once activated, PINK1 phosphorylates ubiquitin proteins that are minimally associated with outer mitochondrial membrane proteins. This process leads to an increase in Parkin levels on the outer mitochondrial membrane, which results in the continual formation of clustered ubiquitin chains by Parkin on outer mitochondrial membrane proteins [238]. Ubiquitin chain-tagged damaged mitochondria are recognized by a set of ubiquitin-bound mitochondrial autophagy receptors, resulting in Parkin-mediated degradation of mitochondrial outer membrane proteins [238]. In addition to Parkin, other ubiquitin E3 ligases are involved in the regulation of mitochondrial autophagy, either joining or acting in parallel with the Parkin/PINK1-mediated mitophagy pathway in a dendritic branching model [239, 240]. Furthermore, alternative pathways for mitophagy exist, which typically involve the recruitment of receptor molecules for LC3 family members on the outer mitochondrial membrane to identify and eliminate damaged mitochondria [241, 242]. These mechanisms mainly involve FUNDC1 (a mitochondrial autophagy receptor) regulated by hypoxia-inducible factor-1 (HIF-1), the mitochondrial outer membrane receptor BNIP3L/NIX (a mitochondrial protein belonging to the BCL2 family), and autophagy and Beclin 1 regulator 1 (AMBRA1) [243–245]. Despite the identification of numerous participants in mitophagy, the overall understanding is further complicated by significant overlap between these pathways.

There is increasing evidence highlighting the significance of mitophagy in maintaining stem cell homeostasis and promoting rejuvenation. For instance, adult human stem cells require intact mitophagy pathways for self-renewal and differentiation. The level of autophagy is higher in certain types of stem cells, including HSCs and skin stem cells, than in the surrounding cells [246]. HSCs maintain stem cell potential during cell cycling due to high mitochondrial clearance through the upregulation of Parkin and Pink1 [211, 212]. Loss of PINK1-dependent mitophagy led to a decrease in the efficiency of iPSC reprogramming and an increase in spontaneous differentiation [215]. Similarly, the reduction of Pink1 or Parkin in intestinal stem cells (ISCs) appears to lead to the induction of senescence, which in turn inhibits age-related loss of tissue homeostasis [213].

Moreover, BNIP3L/NIX is involved in mitophagy that occurs during reprogramming, which is important for iPSCs and is not dependent on mitochondrial membrane potential dissipation [247]. During the differentiation of MSCs into adipocytes and osteoblasts, autophagosome-forming proteins were significantly upregulated, indicating increased levels of autophagy. Additionally, the lipogenic capacity of MSCs was reduced after treatment with autophagy inhibitors [248]. Inhibition of autophagy leads to an increase in ROS accumulation and DNA damage, resulting in the loss of stemness in MSCs [249]. The nutrient sensor SIRT1 also plays a crucial role in regulating autophagy in muscle stem cell progeny. SIRT1 deficiency results in a delay in MuSCs activation, which is partially rescued by exogenous pyruvate. The loss of SIRT1 also leads to hyperacetylation of ATG7, a protein involved in autophagy [216]. Increasing evidence suggests that abnormal mitophagy can lead to senescence of bone marrow mesenchymal stem cells (BMSCs) [250, 251]. Targeting BMSC senescence can ameliorate osteoporosis, highlighting their potential as effective therapeutic interventions [252]. Intriguingly, Sirtuin-3 (Sirt3) is a crucial enzyme involved in regulating mitochondrial metabolism and maintaining mitochondrial homeostasis [253]. Brown et al. reported that the inhibition of Sirt3-mediated mitochondrial homeostasis contributes to increased oxidative stress in aged stem cells [70]. Most importantly, recent evidence has indicated that Sirt3 plays a protective role in mitigating senescence and sarcopenic obesity (SOP) induced by AGEs in BMSCs. In addition, targeting Sirt3 to enhance mitophagy could serve as a promising therapeutic approach to attenuate age-related SOP [254]. Additionally, the decline in autophagy in geriatric satellite cells leads to a loss of proteostasis, increased mitochondrial dysfunction, and oxidative stress, resulting in a decline in the function and number of satellite cells. Nevertheless, reestablishment of autophagy reverses senescence and restores regenerative functions in geriatric satellite cells [255]. In general, mitophagy-driven mitochondrial rejuvenation is required to induce and maintain stem cell pluripotency.

Emerging evidence suggests that mitochondrial dynamics and mitophagy are integrated systems [256–258] (Fig. 4). For example, as a master regulator of mitochondrial fission, Drp1 may play a role beyond the regulation of fission itself and is also considered to be an integral part of mitophagy [256]. After being ubiquitinated by Parkin, Drp1 promotes autophagy in damaged mitochondria [259]. Another previous study demonstrated that overexpression of Drp1 in HeLa cells resulted in a 70% reduction in mitochondrial mass, suggesting a direct link between mitochondrial division and mitophagy. Considering the size of mitochondria, only fragmented mitochondria can enter the autophagosome [260]. In contrast, an article published in 2021 observes that mitochondrial fission in primary neuronal cells exposed to oxygen–glucose deprivation is a Drp1-dependent process, whereas mitochondrial clearance by mitophagy is not Drp1 dependent. A similar phenomenon has been observed in stem cells in recent years. Mitochondrial division promotes mitophagy in cancer stem cells [261]. Mitochondrial fission permits mitophagy in satellite cells during muscle regeneration [262]. However, the role of this relationship in other types of stem cells remains unclear.

Conclusions and perspectives

Mitochondria have evolved multiple mechanisms to ensure mitochondrial quality. These programs are dysregulated during physiological aging, which contributes to the functional deterioration of stem cells, tissue degeneration, and shortened organismal lifespan. A decline in mitochondrial quality control pathways results in a multitude of cellular malfunctions, including genetic and epigenetic changes. Currently, several genes involved in mitophagy and mitochondrial dynamics have been identified to regulate stem cell activation and differentiation (Table 2).

Mitochondria are essential organelles that play a crucial role in regulating stem cell fate. Both mitochondrial dysfunction and stem cell exhaustion have been the focus of considerable research in recent years. Evidence suggests that mitochondrial metabolites regulate various epigenetic changes that impact stem cell aging or differentiation by altering stress signaling levels or through quality control mechanisms. In this review, we elaborate on the crosstalk between mitochondrial and epigenetic changes in the modulation of stem cell fate. Understanding how mitochondria regulate stem cell fate is critical to the development of clinical-grade stem cells under strict quality control standards, contributing to the management of aging-associated organ dysfunction and disease.

Stem cells have promising applications in regenerative medicine and cell therapy. Researchers are dedicated to resolving how stem cells regulate their self-renewal, pluripotency, and plasticity. Maintaining stem cell stemness, controlling the direction of stem cell differentiation, preserving stem cell quality, and preventing their senescence are crucial aspects of stem cell research and its applications in regenerative medicine. Given the critical role of mitochondria in the induction and maintenance of stem cell pluripotency and cell differentiation, numerous researchers are striving to gain a comprehensive understanding of the mechanisms and roles of mitochondria in regulating the physiological functions of stem cells.

Despite the great progress that has been made, research in this field is still in the developmental stage. These relationships obtained thus far, like some threads, are insufficient to construct a mitochondrial network

that regulates the fate of stem cells. In particular, there are still overlaps and intersections between some relationships, and certain conclusions remain controversial and require further clarification [263]. This topic is also directly linked to several age-related diseases, such as Parkinson's disease, Alzheimer's disease, cancer, and other degenerative diseases. It is known that mitochondrial function decreases in several types of adult stem cells, but it remains unclear whether all types of stem cells, upon aging or differentiation, have similar mitochondrial and metabolic changes. Additionally, the identification of key regulators of the UPR^{mt}, mitophagy, and mitochondrial dynamics in different stem cells is one of the current research hotspots.

Modulating mitochondrial function or enhancing mitochondrial quality control may prove to be effective strategies for controlling stem cell amplification, stimulating stem cell activation for regenerative medicine, and combating stem cell dysfunction during the aging process. Notably, many aspects of mitochondrial regulation of stem cell function require additional research. Encouragingly, emerging tools of modern biology have made it easier to gain insight into this complex interaction. For example, simultaneous analysis of the genome, transcriptome, proteome, and metabolome to connect multiple levels of information has been successfully applied to the study of genetic reference populations. This multilayered study is also valuable for identifying the regulatory networks that govern stem cell function and fate decisions [264]. Another effective approach to study cellular diversity among stem cells is the use of emerging single-cell technologies such as single-cell RNA sequencing. This approach may be particularly relevant because of its high sensitivity and the limited availability of stem cells [265]. The application of these new technologies will undoubtedly provide stronger support in building mitochondrial regulatory networks and mapping stem cell epigenetic profiles.

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Data availability Please contact author for data requests.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate Not applicable.

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