

Review

The relevance of organelle interactions in cellular senescence

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Abstract

Organelles are tiny structures with specific functions in eukaryotic cells. Since they are covered with membranes, different organelles can perform biological processes that are incompatible. Organelles can also actively communicate with each other to maintain cellular homeostasis via the vesicular trafficking pathways and membrane contact sites (MCSs), which allow the exchange of metabolites and other information required for normal cellular physiology. An imbalance in organelle interactions may result in multiple pathological processes. Growing evidence shows that abnormal organelle communication contributes to cellular senescence and is associated with organ aging. However, the key role of organelle interactions in aging has not yet been broadly reviewed and fully investigated. In this review, we summarize the role of organelle interactions in cellular senescence, and highlight their relevance for cellular calcium homeostasis, protein and lipid homeostasis, and mitochondrial quality control. Our review reveals important mechanisms of organelle interactions in cellular senescence and provides important clues for intervention strategies from a new perspective.

Key words: organelle; interaction; communication; MCSs; cellular senescence

1. Introduction

Organelles, including the endoplasmic reticulum (ER), mitochondria, and endosomes, possess membranes that allow organelles to perform incompatible biological processes [1-3]. However, organelles also communicate and cooperate to accomplish information exchange and specific functions [1, 2]. Organelle interactions can be mediated by vesicle transmission and non-vesicular mechanisms [1, 4]. In this study, we focus on the latter. Membrane contact sites (MCSs) are formed by the close contact between two organelle membranes [5]. They are a major pathway for organelle interactions and act as hubs for signaling interactions [1, 6]. In addition to facilitating ion, lipid, and protein

exchange, MCSs also play an important role in organelle dynamics [1, 6]. For example, lysosomes and ER both play a role in mitochondrial division through the MCSs [1, 3, 6]. MCSs are tethered by the parallel protein-protein or protein-lipid interactions, with a typical distance of 10-30 nm between organelles. MCS tethers are enriched with specific proteins or lipids that affect organelle function [5-8]. MCSs are often composed of several tethers, but they are dynamically expressed and regulated by modifications [6].

Cellular senescence can be defined as permanent cell cycle arrest. It plays a key role in embryogenesis, host immunity, tissue homeostasis [9, 10],

inflammation, and malignancy [11]. Cellular senescence independently contributes to aging and age-related diseases, such as Alzheimer's disease and renal fibrosis [9, 10, 12, 13]. Organelle interactions are extensively involved in mitochondrial dysfunction and cellular calcium imbalance, which are the underlying mechanisms of cellular senescence. However, the relevance of organelle interactions in cellular senescence has not yet been elucidated. In this review, we discuss the key role of organelle interactions in cellular senescence and highlight their relevance in cellular energy metabolism. We also comment on intervention strategies to retard cellular senescence by modulating organelle interactions.

2. Organelle interactions

Organelle interactions occur across multiple organelles, including the ER, mitochondria, Golgi apparatus, peroxisomes, lipid droplets (LDs), endosomes, and lysosomes. As one of the largest organelles in eukaryotic cells, the ER plays a major role in synthesis, folding, modification, structural maturation, and targeted deployment of cellular proteomes [14, 15], and serves as a central hub of lipid metabolism [14]. Mitochondria are the master controllers of energy metabolism [16]. They possess two layers of plasma membranes [17], and their own circular genome, referred to as mitochondrial DNA (mtDNA) [17]. The Golgi apparatus, located adjacent to the nucleus, is a central membrane-bound organelle for trafficking, processing, and sorting of membrane proteins, secretory proteins, and lipids [18]. Peroxisomes have variable functions in different cells [19], ranging from fatty acid β -oxidation and hydrogen peroxide degradation to glycerol metabolism and maintenance of cellular integrity [19]. LDs store neutral lipids for energy or membrane synthesis and are primarily located in the cytoplasm [20]. There are two types of endosomes: early and late. Early endosomes are the cargo originating from the uptake of extracellular material by the plasma membrane (PM), which can be transported into the PM, ER, or late endosomes. Late endosomes go into lysosomes either *via* direct acidification or fusion with existing lysosomes [21]. Lysosomes digest extracellular or cell-surface cargos obtained *via* endocytosis or degrade intracellular components *via* autophagy [21]. Both endosomes and lysosomes play an important role in endocytosis and degradation, thereby forming an endolysosomal system [22, 23].

2.1 ER network

With extensive reticular structures [14], ER membranes can form abundant physical connections with the PM [24] and nearly all membrane-bound

organelles [7, 25], such as mitochondria [26, 27], endosomes/lysosomes, phagosomes [28–32], Golgi apparatus [33], peroxisomes [34], and LDs [35]. The ER provides structural support for the transport of membrane-bound organelles [8], but is also connected with membraneless organelles [25, 36], thereby forming an intracellular network hub (Fig.1).

The stability of MCS requires tethering proteins, such as vesicle-associated membrane protein-associated proteins (VAPs), which play a key role in maintaining ER stability [6, 8, 37]. VAPs are highly conserved type II integral ER membrane proteins that can bind various intracellular proteins containing phenylalanine–phenylalanine acidic tract (FFAT) motifs [6, 38, 39].

Proteins containing FFAT motifs also have domains that can bind to lipids and other proteins [6]. For example, the oxysterol-binding protein-related protein family (ORPs) contains FFAT motifs and can be found in endosomes and the Golgi apparatus [39, 40]. VAPs can also bind to other proteins containing FFAT motifs, such as phosphatidylinositol transfer protein membrane associated 1 (PITPNM1, as known as Nir2) and ceramide-transfer protein (CERT) in the Golgi apparatus [41, 42], steroidogenic acute regulatory protein-related lipid transfer domain-3 (STARD3) and oxysterol-binding protein-related protein 1 (ORP1L) in endosomes [8, 43, 44], and acyl-CoA binding domain protein 5 (ACBD5) in peroxisomes [45]. The orthologues of VAPs in plants and yeast have similar effects [39, 46].

2.1.1 ER–PM interaction

2.1.1.1 ER–PM MCSs and lipid transport

Most lipids are synthesized in the ER and then are distributed to other membranes [47]. In mammalian cells, the ER and the PM form extensive MCSs, occupying approximately 2–5% of the cytoplasmic surface area [8]. It has been found that the extended synaptotagmin-like proteins (E-Syts), VAPs, transmembrane (TMEM) family, ORP5, and ORP8 contribute to ER–PM tethering [2, 8] and non-vesicular lipid transport between the ER and the PM [8, 48]. Notably, the absence of ER–PM tethers slows cell growth and reduces lipid content [47].

ER–PM MCSs play a key role in lipid transport. For example, ORP5 and ORP8 in the ER tether the ER to the PM through interactions with phosphatidylinositol 4-phosphate (PI(4)P) in the PM, thereby forming ER–PM MCSs to deliver PI(4)P to the ER for degradation and to deliver phosphatidylserine (PS) from the ER to the PM, to control PI(4)P levels and enrich PS in PM [8, 48, 49]. The E-Syts SMP domain can dimerize to form a long hydrophobic tunnel, allowing phospholipids to move between the

2.1.2 ER–mitochondria interaction

2.1.2.1 ER–mitochondria MCSs and lipid transport

The ER and the mitochondria can also form extensive MCSs, with a distance of approximately 10–25 nm, occupying approximately 2–5% of the mitochondrial surface area [8, 27]. Mitofusin 2 (Mfn2) is a major contributor in the formation of ER–mitochondria MCSs. ER–mitochondria MCSs are reduced by 40% when cells lack Mfn2 [27]. There are many protein interactions in ER–mitochondria MCSs, including ORP, tetrameric inositol 1,4,5-triphosphate receptor (IP3R), and B-cell receptor-associated protein 31 (BAP31) in the ER, protein tyrosine phosphatase interacting protein 51 (PTPIP51), voltage-dependent anion-selective channel protein (VDAC), and mitochondrial fission 1 (FIS1) in the mitochondria, and glucose-regulated protein 75 (GRP75) in the cytoplasm [48, 57].

Bidirectional lipid transfer between the mitochondria and the ER plays an important role in maintaining the defined lipid composition of mitochondrial membranes [57]. Since the mitochondria cannot synthesize PS, it must be imported from the ER [57]. PS is transferred from the ER to the mitochondria by ORP5 and ORP8 interaction with PTPIP51 in ER–mitochondria MCSs [48]. After PS is converted into phosphatidylethanolamine (PE) in the mitochondria, PE is transferred from the mitochondria to the ER [57–59]. However, the role of ER–mitochondria MCSs in PE export from the mitochondria is unclear [58].

2.1.2.2 ER–mitochondria MCSs and Ca²⁺ regulation

ER–mitochondria MCSs can transfer Ca²⁺ from the ER lumen to the mitochondrial matrix [8, 60, 61]. The IP3R-GRP75-VDAC-mitochondrial calcium uniporter (MCU) complex is required in this process (a more detailed description is provided in Section 3.1.1) [62]. Other proteins are also important for ER–mitochondria MCSs. For instance, PDZ domain-containing protein 8 (PDZD8), a protein found concentrated in ER–mitochondria MCSs, is necessary for ER–mitochondria MCS formation in mammalian cells and is required for Ca²⁺ uptake by the mitochondria after calcium release from the ER [63]. Mfn2 ablation leads to the absence of ER–mitochondria MCSs, which reduces the efficiency of mitochondrial Ca²⁺ uptake [27, 64]. PTPIP51 also plays an important role in Ca²⁺ uptake of the mitochondria from the ER, by binding to vesicle-associated membrane protein-associated protein B (VAPB) [65]. Moreover, it has been shown that Ca²⁺ transfer from the mitochondria to the ER occurs via an unidentified Na⁺/Ca²⁺ exchanger [66].

2.1.2.3 ER–mitochondria MCSs and mitochondrial dynamics

Mitochondria are dynamic organelles that maintain proper function, quality, and distribution through continuous fission and fusion [8, 67]. The regulatory mechanisms of the ER involved in mitochondrial dynamics *via* ER–mitochondria MCSs are described in detail in Section 3.3.2.

2.1.2.4 ER stress and unfolded protein response (UPR)

A more detailed description of ER stress and UPR is provided in Section 3.2.1.

2.1.2.5 Autophagosome formation

A more detailed description of autophagosome formation is provided in Section 3.2.2.

2.1.3 ER–Golgi apparatus interaction

The bidirectional vesicular trafficking between the ER and the Golgi apparatus is not the only mechanism of interaction between the two organelles. Previous studies have reported that non-vesicular transport, which mainly involves the transfer of lipids, also plays an important role in the interaction between the two organelles [33]. Vesicular trafficking mainly occurs on the nuclear side of the Golgi apparatus, while ER–Golgi apparatus MCSs are mainly located on the cytomembrane side of the Golgi apparatus, with a distance of approximately 10–20 nm between the ER and the Golgi apparatus [33].

In the ER–Golgi apparatus MCSs, ER protein VAPs bind to Nir2, CERT, and oxysterol-binding protein (OSBP) in the Golgi apparatus, all of which have FFAT motifs and play an important role in lipid transfer between the ER and the Golgi apparatus [8]. Nir2 transfers PI from the ER to the Golgi apparatus, decreasing PI concentration in the ER. Furthermore, PI is converted into PI(4)P, recruiting CERT and OSBP to ER–Golgi MCSs by binding to their PH domains [41]. CERT is responsible for the transport of ceramide between the ER (the site of its synthesis) and the Golgi apparatus (the site of its conversion to sphingomyelin) [33]. In addition, OSBP plays a significant role in the exchange of PI(4)P for cholesterol. In ER–Golgi apparatus MCSs, PI(4)P levels are low because of the ER phosphatase Sac1, which converts PI(4)P into PI. PI(4)P is transferred from the ER to the Golgi apparatus to form a concentration gradient which drives cholesterol transport [8, 33, 68, 69].

2.1.4 ER–peroxisomes interaction

Peroxisomes, originating from the division of existing peroxisomes or from the ER [1, 70, 71], play an essential role in lipid synthesis, breakdown and detoxification of fatty acids, and detoxification of reactive oxygen species (ROS) [8, 72]. To mediate

these functions, peroxisomes interact with other organelles *via* vesicular trafficking or MCSs [72]. The interaction between peroxisomes and the ER is important for the biosynthesis of sterols, unsaturated fatty acids, and ether-phospholipids [72]. For instance, the synthesis of ether-linked phospholipids is initiated in peroxisomes, but is completed in the ER [8].

Peroxisomes lack an appropriate enzyme inventory for autonomous lipid synthesis. Phospholipids essential for the growth and division of peroxisomes are provided by the ER [8, 73]. Lipid transfer between peroxisomes and the ER depends on ER–peroxisome MCSs rather than on vesicles [73]. Notably, the interaction between ACBD5 in peroxisomes and VAPs in the ER plays an important role in maintaining the ER–peroxisome MCSs and lipid transfer [74]. The overexpression of VAPs or ACBD5 increases the number and surface area of ER–peroxisome MCSs [8]. Moreover, the interaction between phosphatidylinositol-4, 5-bisphosphate (PI(4,5)P₂) in peroxisomes and E-Syts in the ER plays an important role in cholesterol transfer from peroxisomes to the ER [75]. In addition, ER–peroxisome MCSs play a role in peroxisome mobility and distribution. The disruption of ER–peroxisome MCSs has been shown to increase the number and displacement of moving peroxisomes [8, 73].

2.1.5 ER–LD interaction

A more detailed description is provided in Section 3.4.

2.1.6 ER–endolysosomal organelle interaction

Both endosomes and lysosomes play an important role in the degradation of the cargo of cellular endocytosis, thereby forming an endolysosomal system [22, 23]. The ER–endolysosomal organelle MCSs regulate certain processes in these organelles [23]. The numbers of contacts between endosomes and the ER increase as the endosome matures. Approximately 50% of early endosomes and more than 99% of late endosomes are in contact with the ER, and their MCSs occupy approximately 5% of the endosome surface area.

Intracellular cholesterol mainly originates from endocytosis of low-density lipoprotein (LDL). LDL in early endosomes is delivered to the late endosomes/lysosomes and then hydrolyzed and transported by vesicular or non-vesicular mechanisms to downstream organelles, including the PM, ER, and mitochondria, to perform its functions [76]. Approximately 30% of LDLs from endosomes reach the ER *via* MCSs [23, 76]. VAPs and endosome-localized proteins, STARD3, ORP1L, and OSBP, play

key roles in maintaining ER–endosome MCSs and regulating lipid transport. The interaction between VAPs and the late endosome cholesterol-binding protein ORP1L promotes cholesterol transport from the late endosomes to the ER. However, STARD3, which can bind cholesterol and transfer it between membranes, plays the opposite role [23]. VAP–OSBP interaction contributes to phospholipid homeostasis in ER–endosome MCSs by recruiting PI(4)P-phosphatase Sac1 to MCSs to further decrease PI(4)P level in endosomes [8, 23, 77]. A previous report has shown that high levels of PI(4)P block cargo trafficking from endosomes to the Golgi apparatus [8].

ER–endolysosomal organelle MCSs also play an important role in endolysosomal fission and positioning [23]. It has been reported that endosomal tubule fission occurs at ER–endosome MCSs in approximately 80% of cases [78]. The interaction between endosome-located IST1 factor associated with the endosomal sorting complex required for transport-III (IST1) and ER-located spastin links endosomes to the ER and regulates endosome fission [78]. Loss of spastin leads to impaired endosomal tubule fission and abnormal lysosomal morphology [23]. In addition, when cholesterol levels are high, ORP1L promotes endosome trafficking to the cell center, where they can fuse with lysosomes. However, when cholesterol levels are low, ORP1L leads to the accumulation of late endosomes at the cell periphery [23]. It has also been found that ER–endolysosomal organelle MCSs result in Ca²⁺ uptake from the ER. For example, IP3Rs have been found to be clustered at ER–lysosome MCSs and deliver Ca²⁺ to lysosomes [23].

2.2 Mitochondrion network

Mitochondria are the primary sites of ATP production. Therefore, mitochondrial homeostasis plays a crucial role in a variety of biological processes [79]. Mitochondria interact with other organelles to maintain cellular homeostasis. Mitochondria have extensive contact with PM [80] and other organelles [31, 57], such as the LDs [81], Golgi apparatus [82], lysosomes [83–85], and peroxisomes [86]. As a result, these organelles form a secondary intracellular reticulum network that acts as an important cellular signaling platform [31, 86].

2.2.1 Mitochondria–PM interaction

PM–mitochondria MCSs are better studied in the processes involved in mitochondrial fission and Ca²⁺ uptake [31]. Almost 10% of the PM is adjacent to mitochondria in animal cells [87]. Notably, PM–mitochondria MCSs also play a role in the distribution of the mitochondria during cell division [80, 87].

Subplasmalemmal mitochondria relay Ca^{2+} to the ER by modulating the activity of Ca^{2+} -ATPases in the PM [88].

2.2.2 Mitochondria–lysosome interaction

Mitochondria and lysosomes are critical organelles involved in cellular homeostasis. Studies have shown that mitochondrial respiration dysfunction leads to lysosomal defects [89]. Lysosomes can regulate mitochondrial functions in a peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α)-independent manner through the biosynthesis of transcription factor EB (TFEB). Moreover, the dysfunction of lysosomal acidification leads to decreased mitochondrial respiration [85]. Mitochondria and lysosomes can also directly interact under stress conditions *via* mitochondrial-derived vesicles (MDVs) and mitophagy [85].

Mitochondria–lysosome MCSs are abundant and can be identified by electron microscopy in healthy cells [84]. Unlike MDVs fusing with lysosomes or mitophagy, mitochondria–lysosome MCSs do not result in bulk transfer of mitochondrial luminal content or mitochondrial degradation [84]. Mitochondria–lysosome MCSs have an average distance of 10 nm between the membranes and play an important role in modulating the dynamics of both organelles and ensuring Ca^{2+} transfer. Rab7, a GTPase, is an important protein that modulates the dynamics of mitochondria–lysosome MCS tethering and untethering [85]. Rab7 exhibits an active GTP-bound state under normal conditions, but shows an inactive GDP-bound state upon GTP hydrolysis [84]. The interaction between GTP-Rab7 in lysosomes and Rab7 effectors in the mitochondria plays a central role in maintaining the stabilization of mitochondria–lysosome MCSs. However, FIS1, the outer mitochondrial membrane (OMM) protein, recruits cytosolic TBC domain family member 15 (TBC1D15) to drive GTP-bound Rab7 hydrolysis to a GDP-bound state, thereby leading to untethering of MCSs [85].

Mitochondria can also modulate lysosomal retrograde and anterograde microtubule transport and coordinate lysosome dynamics *via* mitochondria–lysosome MCSs [84, 85]. These MCSs can also regulate mitochondrial dynamics (details are provided in Section 3.2.2). Mitochondria–lysosome MCSs also play a role in Ca^{2+} uptake by the mitochondria. The lysosomal channel transient receptor potential mucolipin 1 (TRPML1)-VDAC-MCU complex plays a significant role in the direct transfer of calcium from lysosomes to the mitochondria *via* mitochondria–lysosome MCSs [90]. The activation of TRPML1, a calcium-releasing channel on the lysosomal membrane, can increase the concentration of Ca^{2+} in

mitochondria–lysosome MCSs [85, 90]. Furthermore, Ca^{2+} enters the mitochondrial matrix *via* the VDAC channel in the OMM and MCU channels in the inner mitochondrial membrane (IMM) [90]. TRPML1 activity is increased due to increased ROS [85].

2.2.3 Mitochondria–peroxisome interaction

Both mitochondria and peroxisomes play important roles in lipid and ROS metabolism [86], suggesting that there may be an interaction between these two organelles to balance this process. Peroxisomes and mitochondria exhibit a close functional interaction, including metabolic cooperation in regulating fatty acid β -oxidation and maintaining ROS homeostasis, sharing a redox-sensitive relationship, and cooperation in viral combat [91]. Mitochondria and peroxisomes interact with each other *via* MCSs, vesicular traffic, and biological messengers, such as ROS, lipids, and other metabolites [86, 91]. In yeast, Pex11p is required for mitochondria–peroxisome MCS formation [31]. Peroxisome-located acyl-CoA binding domain protein 2 (ACBD2) and mitochondria-located enoyl-CoA- δ isomerase 2 (ECI2) play an important role in the formation of mitochondria–peroxisome MCSs and steroids in mammals [92]. These two organelles also share key components of their division machinery in MCSs, including dynamin-related protein-1 (DRP1), fission factor 1, mitochondrial fission factor, and ganglioside-induced differentiation-associated protein 1 [91].

Mitochondrial function is impaired in senescent cells, and this can be compensated by peroxisomes *via* the mitochondrial retrograde (RTG) signaling pathway [93]. Following the increasing transcription of mitochondrial and peroxisomal genes related to carbohydrate and nitrogen metabolism, peroxisome proliferation is activated and fatty acids are converted into acetyl-CoA to replenish the tricarboxylic acid (TCA) cycle in mitochondria [93, 94].

2.2.4 Mitochondria–LD interaction

A more detailed description is provided in Section 3.4.

2.3 Other organelle interactions

There are other organelle interactions, including peroxisome–lysosome [95, 96] and peroxisome–LD interactions [97]. Although the interactions of peroxisomes with lysosomes appears to be less frequent than their interaction with the ER or the mitochondria, peroxisome–lysosome interactions are still found in approximately 15% to 20% of the total peroxisomes in mammalian cells [73]. The lysosome–peroxisome MCSs are the principal pathway for cholesterol transfer from the lysosome to the

peroxisome [76]. Synaptotagmin-7 (Syt7), on lysosomes, and PI(4,5)P₂, on peroxisomes, form peroxisome-lysosome MCSs, which play an important role in cholesterol transport [34, 73, 76]. When cholesterol reaches peroxisomes, it participates in peroxisome biogenesis [76]. The disruption of lysosome-peroxisome MCSs decreases cholesterol levels in the PM and impairs cholesterol transport to the ER, suggesting that lysosome-peroxisome MCSs may be associated with cholesterol transport to other organelles [76]. MCSs may also regulate other functions of lysosomes and peroxisomes, such as autophagy and peroxisome biogenesis [76]. A more detailed description of LD-peroxisome interactions is provided in Section 3.4.

3. The role of organelle interaction in cellular senescence

Cellular senescence is a permanent cell cycle arrest induced by a series of stress factors, including telomere attrition, DNA damage, oxidative stress, oncogene activation, and organelle stress. Cellular senescence is characterized by chromatin remodeling, metabolic reprogramming, and senescence-associated secretory phenotype (SASP) [10, 98-101]. Senescent cells accumulate in organs during aging and secrete SASP molecules, including proinflammatory and fibrogenic molecules, to further promote a variety of age-related diseases [101, 102]. Senescence can be classified into the following types: replicative, DNA-damage-induced, stress-induced, and oncogene-induced [103].

3.1 Cellular calcium homeostasis and senescence

3.1.1 ER and mitochondrial calcium homeostasis

The ER is a dynamic calcium reservoir that maintains cellular calcium homeostasis [104]. In senescent cells, calcium is released from the ER to increase intracellular calcium levels [105]. Mitochondria and lysosomes also play crucial roles in cellular calcium homeostasis [85]. Hence, cellular calcium buffering is controlled by the interplay between ER, mitochondria, and lysosomes [106]. Studies have shown that an imbalance in ER calcium homeostasis not only induces the production of SASP molecules, but also causes cell cycle arrest by influencing mitochondrial calcium homeostasis [105]. In particular, appropriate calcium transfer from the ER to the mitochondria requires the correct distance between the two organelles [107] and accurate organelle interaction. ER-mitochondria MCS dysfunction can be found in senescent cells, which further leads to an imbalance in calcium control

[108-110]. ER-mitochondria MCSs play an important role in Ca²⁺ homeostasis *via* the IP3R-GRP75-VDAC-MCU complex. Ca²⁺ is released through the IP3R channel in the ER, which then enters the mitochondrial matrix *via* the VDAC channel in the OMM and MCU channels in the IMM [8, 111]. The VDAC channel is crucial for mitochondrial Ca²⁺ uptake [90], and the MCU channel is considered to be the major transporter of Ca²⁺ into the mitochondrial matrix [90]. Notably, GRP75 plays a role in linking IP3R and VDAC to shorten the distance between the ER and the mitochondria [62]. In cellular senescence, IP3R-mediated calcium release from the ER is activated and the expression of MCU increases [105, 112], leading to the accumulation of mitochondrial calcium and contributing to a decrease in mitochondrial membrane potential and increased ROS production [105]. Excess ROS can induce DNA damage and lead to single-strand breaks in telomere regions, resulting in accelerated telomere shortening, both of which can activate the DNA damage response (DDR) pathway [100, 109, 113, 114]. Consequently, DDR performs cell cycle checkpoint functions and blocks cell cycle progression. After DNA damage, DDR factors accumulate at the sites of DNA damage and cause chromatin modifications, such as the phosphorylation of histone H2AX. Persistent DNA damage causes a prolonged DDR signaling pathway. It induces the activation of the tumor suppressor p53, contributing to the expression of the cyclin-dependent kinase inhibitor p21, to cooperatively induce cellular senescence [100]. It has been shown that IP3R knockdown can attenuate cellular senescence by reducing the number of ER-mitochondria MCSs and ER calcium release [115, 116]. Moreover, MCU knockdown can also prevent cellular senescence by attenuating mitochondrial calcium intake [117] (Fig.2).

3.1.2 Lysosomal calcium homeostasis

Lysosomal calcium homeostasis plays an important role in maintaining lysosomal function. In senescent cells, the activated IP3R in the ER leads to increased ER calcium release [105] *via* ER-lysosome MCSs, resulting in lysosomal calcium accumulation. The imbalance of lysosomal calcium homeostasis induces disorders related to lysosomal acidification [118], which are associated with lysosomal proteolytic activity [119]. Furthermore, impaired proteolytic activity of lysosomes negatively affects the lysosome-mediated autophagy proteolytic system and causes cellular senescence [102, 120-123].

In senescent cells, damaged mitochondria accumulate [124]. Dysfunctional mitochondrial respiratory chain impairs lysosomal calcium

homeostasis by repressing the lysosomal calcium-releasing channel mucolin 1 (MCOLN1, also known as TRPML1) [125], plays an important role in regulating lysosomal biogenesis, exocytosis, and autophagy *via* the regulation of lysosomal calcium release [126]. The impairment of the function of TRPML1 leads to enlarged lysosomes, lysosomal calcium accumulation, and increased pH, which further contributes to lysosomal malfunction and cellular senescence [119, 126]. It has been reported that mitochondrial ROS can activate TRPML1, inducing lysosomal calcium release [85], further inducing autophagy and lysosomal biogenesis [127] and delaying cellular senescence. However, excess ROS levels in the mitochondria have the opposite effect, leading to lysosomal dysfunction and cellular senescence [126, 127].

Transmembrane BAX inhibitor motif containing 6 (TMBIM6), a calcium channel-like protein integral to the intracellular membranes of the ER, can also regulate lysosomal calcium [128]. Specifically, it increases lysosomal calcium release under stress conditions to restore cellular homeostasis by

enhancing lysosomal calcium release-induced autophagy [128], thereby retarding cellular senescence [129].

3.2 Cellular protein homeostasis and senescence

Cellular protein homeostasis is crucial for maintaining cellular function. Dysregulation of cellular protein homeostasis contributes to cellular senescence and aging [130-134]. It has been shown that cellular proteostasis is decreased in senescent cells [135]. The imbalance of cellular protein homeostasis plays an important role in senescence-related pathologies [102], while improved proteostasis can delay aging [133]. Under persistent stress, cellular proteins are damaged, aggregated, misfolded, or no longer needed. The three primary pathways that are used by senescent cells to maintain cellular protein homeostasis are as follows: utilizing molecular chaperones, the proteasome proteolytic system, and the lysosome-autophagy proteolytic system [130, 133, 134, 136].

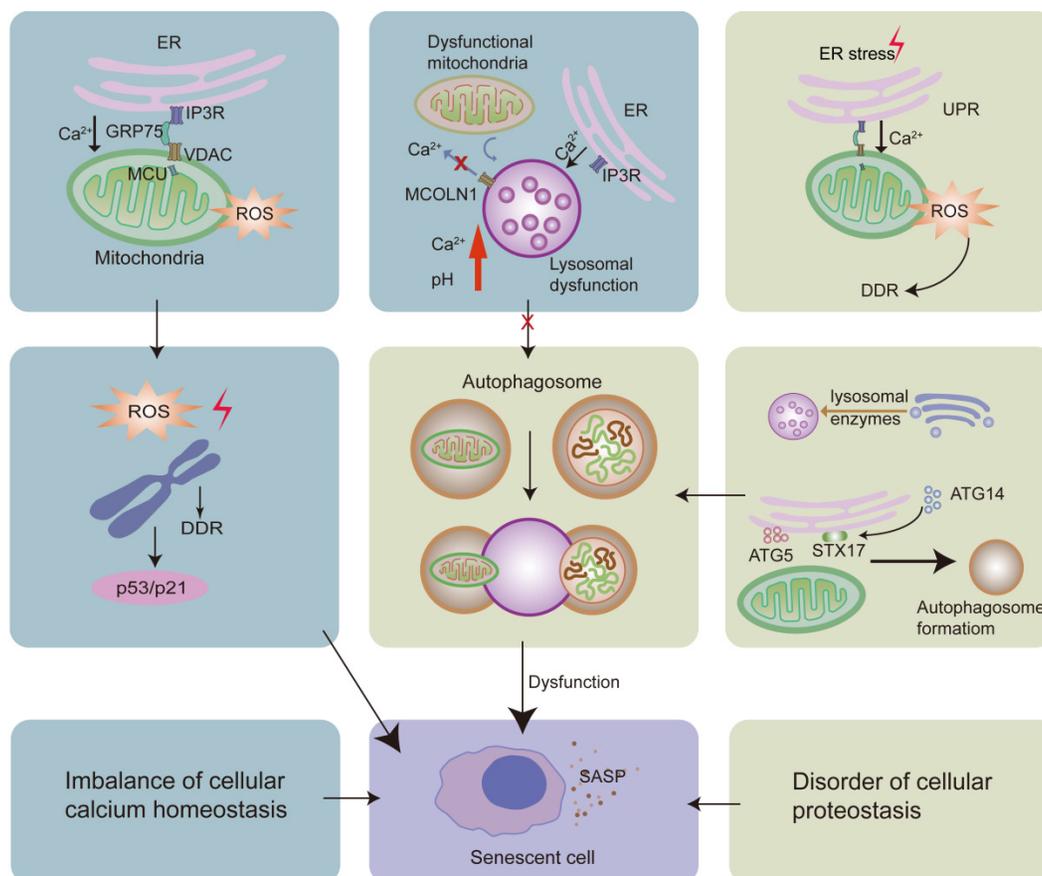


Figure 2. The increased calcium released from the ER can be transferred to the mitochondria *via* the IP3R-GRP75-VDAC-MCU complex. This leads to the increased levels of ROS in the mitochondria, contributing to DNA damage and DDR, activating the p53/p21 pathway, and causing cellular senescence. Moreover, while the UPR is consistently activated, it also leads to calcium accumulation in the mitochondria, causing cellular senescence. On the one hand, dysfunctional mitochondria can repress the lysosomal calcium-releasing channel MCOLN1; on the other hand, there is increased calcium release from the ER *via* IP3R. Both these processes lead to calcium accumulation and an increase in pH in the lysosomes, resulting in dysfunction of the lysosome-autophagy proteolytic system and contributing to cellular senescence. Lysosomes can originate from the direct acidification of late endosomes. The Golgi apparatus deliver lysosomal enzymes to endosomes. Moreover, ER-mitochondria MCSs promote the formation of autophagosomes. Impaired autophagosomal formation and lysosomal function leads to the dysfunctional autophagy, thereby causing cellular senescence.

3.2.1 UPR and cellular senescence

Most secretory proteins in eukaryotic cells undergo chaperone-assisted folding in the ER to acquire an appropriate spatial structure [137]. When cells are under stress, unfolded or misfolded proteins accumulate in the ER lumen, contributing to ER stress [137]. To maintain ER function and cellular protein homeostasis, the UPR is activated by the ER-localized transmembrane stress sensors, namely inositol requiring enzyme 1 alpha (IRE1 α), RNA-dependent protein kinase-like ER kinase (PERK), and activating transcription factor 6 alpha (ATF6 α) [66, 137]. Both IRE1 α and ATF6 α play important roles in enhancing the degradation of misfolded proteins. Under ER stress, full-length ATF6 in the ER translocates to the Golgi apparatus, where it is cleaved into ATF6p50; then, it transitions into the nucleus to induce gene expression. PERK can induce a transient decrease in protein synthesis to relieve ER stress through the attenuated influx of newly synthesized proteins into the ER lumen [137].

During the early phases of ER stress, the UPR boosts pro-survival signaling [66], which increases and tightens the ER-mitochondria MCSs and increases mitochondrial Ca²⁺ uptake, thereby driving adaptive mitochondrial metabolic boost and ATP production to establish the metabolic basis for recovering cell homeostasis [57, 107, 138]. However, when stress is not resolved, the UPR leads to excess intake of mitochondrial Ca²⁺, causing cellular senescence or even cell death [99, 139, 140]. UPR activation occurs in almost all types of senescence [99]. The UPR is not only a consequence of cellular senescence, but also its driver [99]. However, the mechanism by which UPR induces senescence remains poorly understood.

It has been reported that a variety of ER chaperones involved in protein folding are enriched in ER-mitochondria MCSs [141], such as PERK and IRE1 α [137]. PERK can facilitate the tethering of the ER to the mitochondria, leading to increased mitochondrial calcium intake and ROS production under ER stress [137]. Sustained ER stress leads to excess release of Ca²⁺ from the ER *via* IP3R. Calcium is enriched in ER-mitochondria MCSs and is taken up by the mitochondria *via* calcium uniporter. Large calcium influx leads to the loss of the mitochondrial membrane potential. Furthermore, cytochrome c translocates into the ER-mitochondria MCSs and binds to IP3R, which abolishes the calcium-mediated inhibition of IP3-associated calcium release and results in a feed-forward amplification of ER calcium release [66]. Finally, this causes an imbalance in mitochondrial Ca²⁺ homeostasis [139, 140] and

increases ROS production [105, 142], thereby resulting in cellular senescence [109, 143].

3.2.2 Lysosome-autophagy proteolytic system and cellular senescence

Autophagy is a process of self-degradation of organelles and misfolded proteins by autophagosomes, which are then delivered to lysosomes [144]. The lysosome-autophagy proteolytic system plays a significant role in maintaining cellular protein homeostasis, and its imbalance contributes to cellular senescence [134, 145]. It has been reported that autophagy activation can prevent cellular senescence by downregulating p53 phosphorylation and p21 levels [146]. There are three main types of autophagy in mammalian cells that maintain the homeostasis of proteins and organelles: microautophagy, macroautophagy, and chaperone-mediated autophagy [145]. Lysosomal-mediated autophagosomal degradation plays an important role in maintaining cellular homeostasis under stress conditions [119, 128, 131]. Damaged proteins and organelles can induce cellular senescence [147]. Notably, autophagy plays a significant role in their degradation, providing adequate amino acids and maintaining energy levels to support cells [147-149]. Autophagy inhibition and insufficiency lead to cellular senescence [145], while increased autophagy delays aging [123, 150].

The formation of autophagosomes is the first step in the macroautophagy [148]. ER-mitochondria MCSs are the origins of autophagosomes [151]. When autophagy signals initiate, autophagosome formation-related proteins accumulate on the ER side of the ER-mitochondria MCSs [57, 152]. Autophagy-related gene 14 (ATG14), the pre-autophagosome marker, and autophagy-related gene 5 (ATG5), the autophagosome-formation marker, are enriched in ER-mitochondria MCSs after starvation. ATG14 is recruited to ER-mitochondria MCSs by syntaxin 17 (STX17), an ER-resident protein [151]. Mitochondria also supply membranes for autophagosome biogenesis [153].

Lysosomes play an important role in the final step of the lysosome-autophagy proteolytic system by fusing with autophagosomes. Lysosomal function affects the lysosome-autophagy proteolytic system. In senescent cells, lipofuscin accumulates in lysosomes, leading to diminished lysosomal activity [154]. In contrast, the activation of lysosomes restores the stemness of senescent stem cells [155]. Lysosomes can originate from the direct acidification of late endosomes [21]. In this process, lysosomal enzymes are transported from the Golgi apparatus to endosomes [156]. Previous studies have shown that

IST1–spastin interaction in ER–endosome MCSs plays an important role in endosomal tubule fission and in the transfer of lysosomal enzymes from the Golgi apparatus to endosomes [78]. Lack of spastin or IST1 leads to lysosomal defects and abnormalities [78].

3.3 Mitochondrial quality control (MQC) and senescence

Mitochondrial dysfunction plays a crucial role in cellular senescence [109, 157]. Cellular senescence accelerates mitochondrial dysfunction and, conjointly, mitochondrial dysfunction is also a cause of cellular senescence [124, 158, 159]. Increased mitochondrial ROS production induces DNA damage, activates DDR, and contributes to cellular senescence. Furthermore, decreased NAD⁺/NADH ratio in dysfunctional mitochondria leads to the persistent activation of the energy sensor AMP-activated protein kinase (AMPK), which induces cellular senescence by phosphorylating p53 and stabilizing p16^{INK4a} mRNA [159, 160].

MQC is an elaborate mechanism that maintains normal mitochondrial function. It includes two opposite processes: mitochondrial biogenesis and the removal of impaired mitochondria or their components [161]. Dysregulation of MQC induces the accumulation of damaged mitochondria, leading to cellular senescence [102]. Damaged proteins can be transported into lysosomes or peroxisomes in the form of mitochondrial-derived vesicles (MDVs) as the first defense against mitochondrial damage [102, 162]. The cargo delivered to lysosomes is ultimately degraded, however, the fate of the cargo delivered to peroxisomes is unclear [162]. When mitochondria are depolarized or dysfunctional, they are removed by mitophagy [102]. Cells can release damaged mitochondria into the extracellular space to maintain mitochondrial homeostasis [163, 164]. In addition, cells can acquire mitochondria *via* mitochondrial fission or by receiving extracellular healthy mitochondria [161, 165] (Fig.3).

3.3.1 MDVs and mitophagy

Lysosomes play an important role in the final degradation of damaged proteins in MDVs and dysfunctional mitochondria during mitophagy [166]. Mitochondria–lysosome interactions play an important role in MQC [166]. Mitophagy plays a role in the removal of dysfunctional mitochondria. The removed mitochondria are eventually replenished *via* biogenesis [166]. Damaged mitochondrial components can also be degraded in the form of MDVs [166]. Dysregulation of mitophagy leads to the accumulation of damaged mitochondria, thus contributing to cellular senescence [166].

However, in senescent cells, dysfunctional mitochondria produce high levels of ROS, which contribute to the accumulation of lipofuscin in lysosomes and lysosomal dysfunction [154]. Moreover, damaged mitochondria also impair the calcium release of lysosomes, which further contributes to lysosomal dysfunction. Dysfunctional lysosomes cause impaired mitophagy and the function of degrading damaged mitochondrial proteins, leading to further mitochondrial malfunction. This feedback loop aggravates cellular senescence [154].

3.3.2 Mitochondrial dynamics

Mitochondria can preserve homeostasis *via* continuous fusion and fission cycles [166]. However, this process is impaired in senescent cells [109]. It has been reported that mitochondrial dynamics involve the interaction of multiple organelles, including the Golgi apparatus, ER, and lysosomes.

ER–mitochondria MCSs have been shown to play an important role in mitochondrial fission and fusion by providing a series of enzyme-like nodes [39, 57, 167]. Active mtDNA synthesis occurs at ER–mitochondria MCSs, and constriction of IMM is a priming event [67, 168]. This suggests that the initial mitochondrial fission signal comes from the mitochondrial matrix, which then recruits the ER [8]. During mitochondrial fission, ER tubules physically wrap around the mitochondria and lead to mitochondria constriction, facilitating the recruitment and assembly of DRP1, the main driver of mitochondrial fission [169]. DRP1 then moves from the cytoplasm to the OMM at MCSs, constricting mitochondria down to less than 50 nm, and finally, Dnm2, a dynamin protein, is recruited to MCSs to induce fission [8, 57, 169–171]. Furthermore, multiple studies have shown that Golgi-derived PI(4)P-containing vesicles are recruited to mitochondria–ER MCSs and can activate DRP1-mediated mitochondrial division. Disruption of PI(4)P production leads to the prevention of mitochondrial fission, and mitochondrial morphological defects [172]. Mitochondria–lysosome MCSs also play a significant role in mitochondrial fission. It has been shown that more than 80% of mitochondrial fission events are marked by the lysosomal markers lysosomal associated membrane protein 1 (LAMP1)-positive vesicles [84, 85, 173]. A study has also found that mitochondria–lysosome contacts play a role in ER-mediated mitochondrial fission [84]. ER–mitochondria MCSs play an important role in mitochondrial fusion [57, 174], but the underlying mechanism is still unclear. Mfn2 may play a significant role in this process, as Mfn2 not only plays

a critical role in mitochondrial fusion, but also in the maintenance of ER-mitochondria MCSs [64, 174, 175].

3.3.3 Mitochondrial transfer

A novel MQC pathway involves the transfer of damaged mitochondria into the extracellular space for degradation [163]. For example, the mitochondria released from neurons can be degraded by lysosomes of neighboring glial cells [176]. This pathway is independent of mitophagy, and is activated by mitochondrial stress. When mitophagy is compromised, more mitochondria are released to compensate for the accumulation of damaged mitochondria [163].

Furthermore, intercellular mitochondrial transfer is a significant part of the MQC to rescue mitochondrial defects [163, 165]. It has been reported that donor cells, especially stem cells, can transfer healthy mitochondria into recipient cells, leading to the improvement of mitochondrial bioenergetics and

reduction of mitochondrial ROS [165, 177]. There are four main methods for intercellular mitochondrial transfer, including utilizing tunneling nanotubes (TNTs), dendrites and microvesicles, and extrusion and internalization [165].

It has been shown that the mitochondrial transfer between osteocytes relies on the ER-mitochondria interaction [165]. The inhibition of ER-mitochondria tethering significantly inhibits the transfer of the mitochondria between osteocytes [178]. It has been hypothesized that the mitochondria are transferred along with the ER tuber into the terminus of osteocyte dendrites, where the ER contacts the PM. The arrival of mitochondria changes the lipid metabolism of the PM, which enables the ER of the donor to fuse with the ER extension of the recipient. Mitochondria are then transferred to the recipient along the fusing ER tubular network [178].

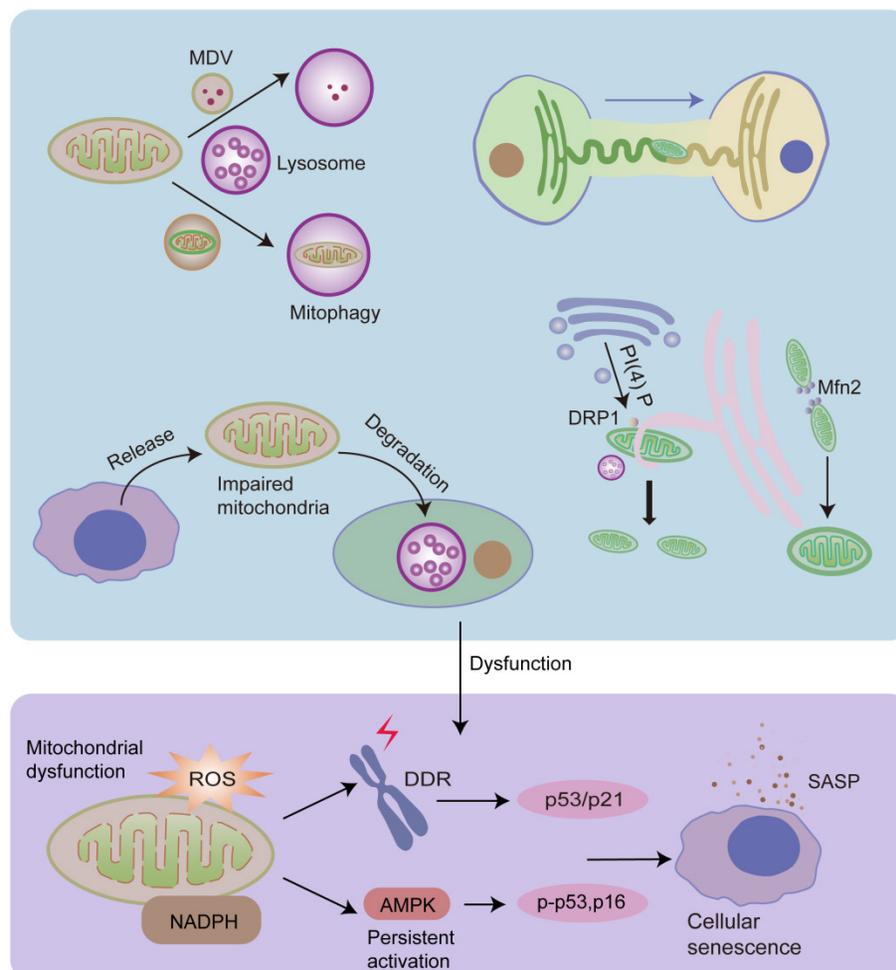


Figure 3. Mitochondrial fission and fusion, mitophagy, MDVs, and mitochondrial transfer play important roles in MQC, and they are regulated by organelle interactions. Damaged mitochondrial proteins can be transported into lysosomes in the form of MDVs, and dysfunctional mitochondria can be degraded by lysosomes *via* mitophagy. Mitochondria can preserve shape and reduce damage *via* continuous fusion and fission cycles. ER tubules physically wrap around and constrict the mitochondria, promoting mitochondrial fission. Moreover, Golgi-derived vesicles containing PI(4)P are necessary for this process. Mitochondria-lysosome interactions also play an important role in mitochondrial fission. In addition, ER regulates mitochondrial fusion, and Mfn2 plays a significant role in this process. Dysfunctional mitochondria can also be released from cells and degraded by lysosomes of other cells. Furthermore, healthy cells can transfer healthy mitochondria into other cells *via* the ER tuber. Dysfunctional MQC leads to the accumulation of impaired mitochondria, leading to increased ROS levels and decreased NAD⁺/NADH ratios, both of which contribute to cellular senescence.

3.4 Lipid homeostasis and senescence

LDs play important roles in the maintenance of lipid homeostasis by coordinating lipid synthesis, storage, and secretion and lipolysis [179]. Under fed conditions, free fatty acids are converted into neutral lipids by ER, and then deposited in LDs [93, 180]. These neutral lipids include, but are not limited to, triacylglycerol, sterol esters, and esterified ceramides [179]. Under the stress conditions or energy insufficiency, lipases on the surface of LDs can convert triglycerides into fatty acids, which are then imported into the mitochondria for β -oxidation to satisfy energy demands [31, 81, 181, 182].

Lipotoxicity is caused by the accumulation of lipids, particularly fatty acids [179]. When cellular fatty acids exceed the requirements of synthesis and catabolism, they can be stored in the form of triacylglycerol in LDs to avoid lipotoxicity [179]. However, the capacity of triacylglycerol buffering is limited [179, 183]. When the limited triacylglycerol buffering capacity is saturated, accumulated lipids react with ROS, especially mitochondrial ROS, thereby producing large quantities of lipid peroxides. Interestingly, continuous production and accumulation of lipid peroxides cause serious lipid toxicity-related damage to mitochondrial structure and function, and induce a rapid increase in ROS levels, thereby contributing to cellular senescence [184]. Moreover, continuous production and accumulation of lipid peroxides can induce ER stress [179, 182], which also contributes to cellular senescence. It has been shown that triacylglycerol accumulates in replicative senescent cells. This is a cellular mechanism that prevents lipotoxicity in senescent cells [185]. As LDs play primary roles in lipid storage and homeostasis [179], the biogenesis and expansion of LDs, which are regulated by organelle interactions, play significant roles in cellular senescence. It has been shown that LD contact sites play an important role in fatty acid synthesis, storage, release, and breakdown [186]. Inhibition of LD biogenesis during rapid fatty acid release leads to fatty acid-mediated mitochondrial depolarization [81], which increases the release of mitochondrial ROS [187], and leads to cellular senescence (Fig.4).

LDs originate from ER [182]. Most neutral lipid and phosphatidylcholine (PC) synthesizing enzymes are absent in LDs, while they exist in the ER, implying that the interaction between LDs and the ER is essential for lipid metabolism [35]. LDs widely interact with the ER *via* membrane bridges and MCSs. The ER-localized protein ORP5 plays an important role in the transfer of PC from the ER to LDs in ER-LD MCSs [188]. The tether proteins of ER-LD MCSs

include ER-localized fatty acid transport protein 1 (FATP1) and LD-localized diacylglycerol acyltransferase 2 (DGAT2), the ER-associated NAG-RINT1-ZW10 (NRZ) tethering complex and their associated SNAREs (Syntaxin18, Use1, BNIP1), and LD-localized Rab18 [8, 35, 189]. Rab18 is associated with lipolysis and lipogenesis, and its overexpression induces a close apposition of the ER and LDs. It has been shown that the Rab18-NRZ-SNARE interaction facilitates LD growth and maturation by regulating the synthesis of triglycerides in the ER [35, 189]. The FATP1 and DGAT2 complexes maintain the ER-LD MCSs and facilitate LD expansion by coupling the synthesis and deposition of triglycerides into LDs [35, 190].

Except for ER-LD MCSs, there are membrane bridges where the LD monolayer appears to be directly continuous with the ER bilayer, playing a significant role in maintaining the structure and biogenesis of LDs and facilitating the incorporation of neutral lipids and membrane proteins into LDs [8, 35]. Notably, triacylglycerol synthesis enzymes are required for LD growth and expansion, and they can be transferred from the ER into LDs *via* membrane bridges [180]. Moreover, the ER protein seipin plays an important role in protein transfer from the ER to LDs, LD biogenesis, and the regulation of the local lipid environment [1, 35, 191].

The interactions between the mitochondria and LDs also play an important role in maintaining lipid homeostasis. In the presence of excess fatty acids in the cell, LD coat proteins perilipin5, and DGAT2, which catalyze the final step in triglyceride synthesis [192], recruit mitochondria to LDs to provide ATP to promote the expansion of LDs, thereby protecting against lipotoxic insult [81, 193].

It has been shown that 10% of LDs form contacts with peroxisomes [73]. The peroxisome-LD MCSs may link LD-mediated lipolysis to fatty acid β -oxidation in peroxisomes. LDs protein M1 spastin interacts with ATP binding cassette subfamily D member 1 (ABCD1), a peroxisome protein, to promote peroxisome-LD MCS formation and facilitate direct channeling of fatty acids across the boundaries of organelles to protect against lipotoxic insult [93, 97].

4. A strategy for delaying senescence based on organelle interaction

4.1 Maintaining calcium homeostasis

Mitochondrial calcium homeostasis plays an important role in maintaining mitochondrial function. Abnormal organelle interactions lead to excessive calcium intake into the mitochondria, thereby leading to cellular senescence. Thus, maintaining

mitochondrial calcium homeostasis may be a reasonable way to retard cellular senescence. Notably, knockdown of MCU can prevent cellular senescence [115]. Furthermore, IP₃-induced IP₃R activation induces premature senescence [117], whereas IP₃R absence decreases the progression of aging [115] (Fig.5).

Mitochondrial calcium homeostasis can be regulated through ER-mitochondria MCSs. The increased number and area of ER-mitochondria MCSs leads to enhanced calcium transfer from the ER to the mitochondria. It has been shown that the downregulation of phosphofurin acidic cluster sorting protein 2 (PACS-2), a key regulator of ER-mitochondria MCSs, retards mitochondrial calcium accumulation [194]. While an increase in the ER-

mitochondria contact leads to cellular senescence [116], the ablation of ER-mitochondria MCS tethers delays cellular senescence [116].

ER is the major storage compartment for intercellular calcium [107]. ER calcium homeostasis is closely related to mitochondrial calcium homeostasis [195]. There is an inverse relationship between calcium storage in the ER and the mitochondria [195]. Notably, a large amount of calcium is buffered by calcium-binding proteins, such as calsequestrin or calreticulin, in the ER [196]. It has been shown that decreased expression of calreticulin is related to aging [197], while overexpression of calreticulin enhances ER calcium storage and inhibits the activity of IP₃R, thereby regulating mitochondrial calcium homeostasis [195].

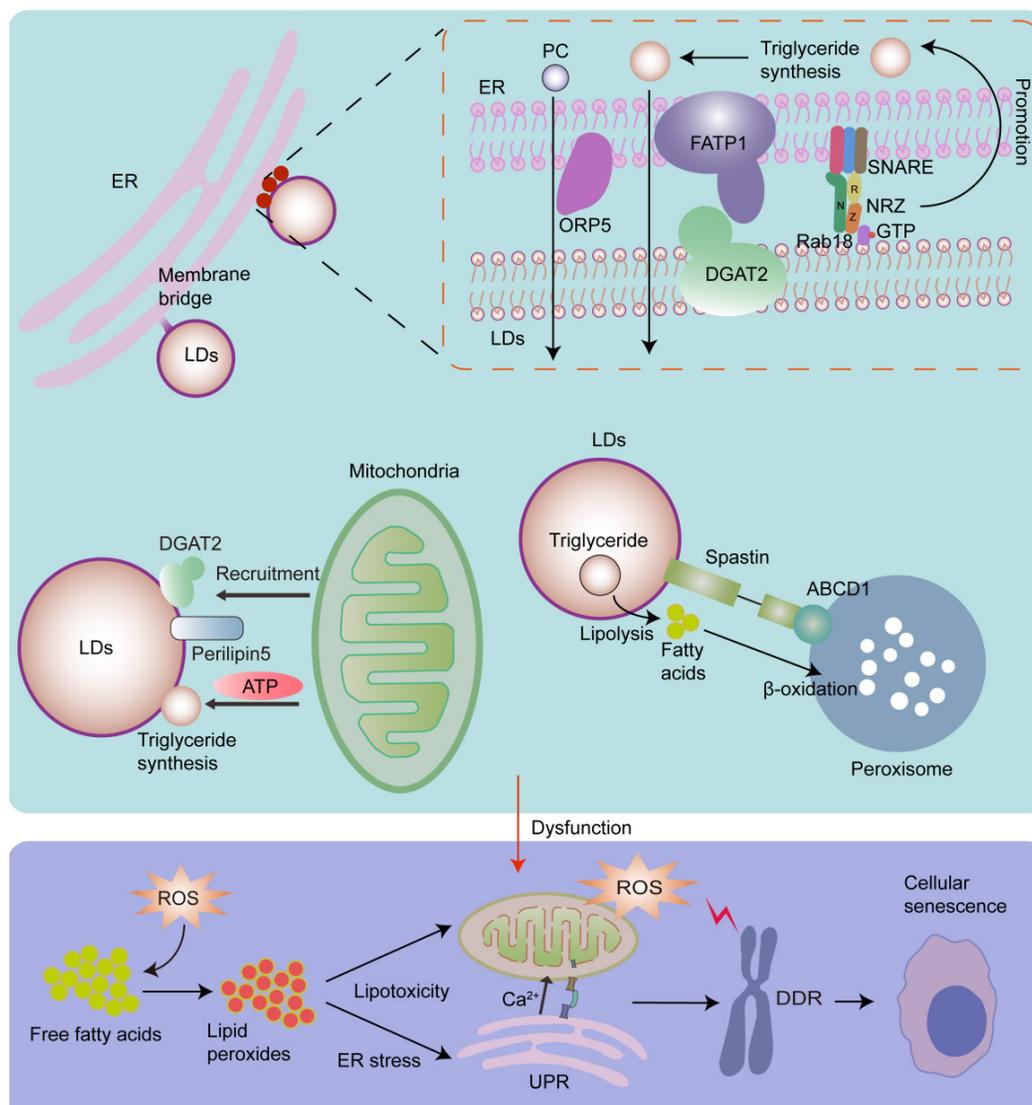


Figure 4. LDs originate from the ER, and the ER can transport triacylglycerol synthesis enzymes required for LD growth and expansion via membrane bridges. Rab18-NRZ-SNARE interaction facilitates LD growth and maturation by regulating the synthesis of triglycerides in the ER. Moreover, FATP1 and DGAT2 complex maintain the ER-LD MCSs and facilitates LD expansion by coupling the synthesis and deposition of triglycerides into LDs. ORP5 plays an important role in transferring PC from the ER to LDs via ER-LD MCSs. Mitochondria-LD interactions also play an important role in maintaining lipid homeostasis. Perilipin5 and DGAT2 in LDs recruit the mitochondria to promote the expansion of LDs by providing ATP for triglyceride synthesis. In addition, the interaction of M1 spastin on LDs with ABCD1 on peroxisomes promotes fatty acid transfer from LDs to peroxisomes for β -oxidation. Dysfunctional growth and expansion of LDs leads to the accumulation of fatty acids, which then react with ROS and produce lipid peroxides, thereby resulting in ER stress, increased mitochondrial ROS, and cellular senescence.

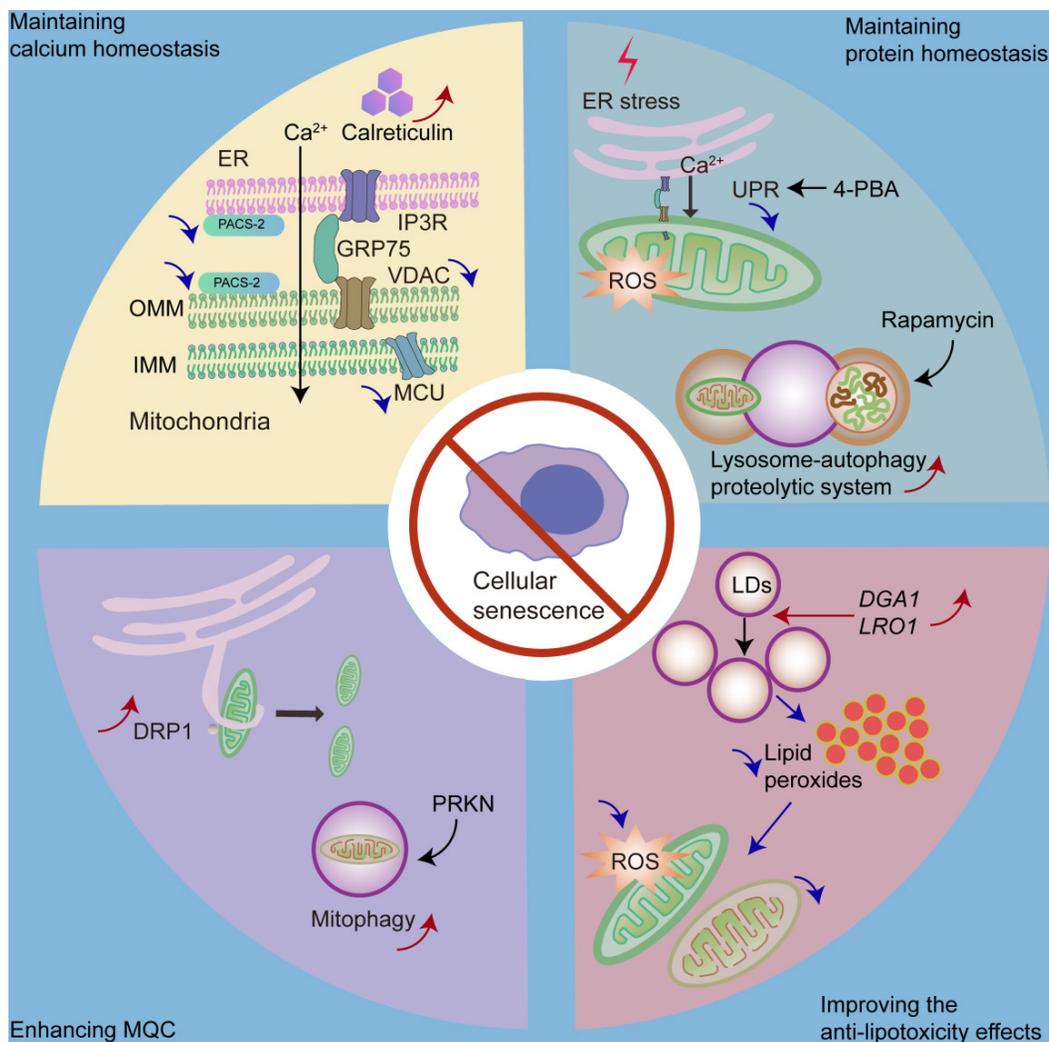


Figure 5. There are some strategies for delaying senescence with respect to organelle interaction, including maintaining calcium homeostasis, maintaining protein homeostasis, enhancing MQC, and improving anti-lipotoxicity effects. We can decrease mitochondrial calcium intake by repressing the expression of IP3R, MCU or PACS-2, and increasing the expression of calreticulin. Moreover, we can inhibit the overactivated UPR by 4-PBA to delay cellular senescence. Promoting lysosome-mediated autophagy by rapamycin is also effective. Furthermore, we can increase mitochondrial fission or mitophagy via DRP1 or PRKN, respectively, to enhance MQC. Moreover, by overexpressing DGA1 (encodes DGAT homologue in yeast) and LRO1 (encodes phospholipid:diacylglycerol O-acyltransferase in yeast), we can increase the number of LDs to decrease mitochondrial ROS and mitochondrial fragmentation caused by high amounts of fatty acids.

4.2 Maintaining protein homeostasis

Overactivation of the UPR is positively associated with senescence [99]. One possible mechanism could be that UPR leads to an imbalance in mitochondrial calcium homeostasis. UPR activation is associated with cellular protection; however, overactivation of the UPR is associated with pathological processes. UPR inhibition also shows therapeutic value [195]. It has been shown that the inhibition of UPR retards cellular senescence [99]. For example, the chemical chaperone 4-phenylbutyric acid (4-PBA), a UPR inhibitor, reduces the number of senescent cells in a premature tubular epithelial cell senescence model [198].

In addition, lysosome-mediated autophagy plays an important role in maintaining cellular protein homeostasis and preventing cellular

senescence; however, it is impaired in senescent cells [199]. Autophagy activation has been shown to inhibit stress-induced senescence [146, 200]. As a result, enhancing the function of lysosome-autophagy proteolytic system may be a strategy to delay senescence. It has been shown that restoring autophagy in stem cells can prevent cellular senescence and maintain stemness [144]. Furthermore, rapamycin, an autophagy inducer, can protect against oxidative stress-induced senescence [146].

4.3 Enhancing MQC

Mitochondrial dysfunction and MQC failure play significant roles in cellular senescence [166, 201]. Thus, enhancing MQC may be a therapeutic strategy against cellular senescence. Of note, DRP1 plays a significant role in mitochondrial fission by generating

a constriction ring around the mitochondria [166]. Increased p53 levels in senescent cells inhibit DRP1 translocation into the mitochondria [202], while a previous report has shown that the increased expression of DRP1 promotes mitochondrial fission and delays cellular senescence [203, 204]. In addition, Parkin RBR E3 ubiquitin protein ligase (PRKN) plays a crucial role in regulating mitophagy [205]; hence, overexpression of PRKN could prevent cellular senescence by increasing mitophagy [205].

4.4 Improving anti-lipototoxicity effects

Since LDs play important roles against lipotoxicity, increasing the number of LDs may be an appropriate way to ameliorate cellular senescence. The overexpression of DGA1 (encodes DGAT homologue in yeast) and LRO1 (encodes phospholipid:diacylglycerol O-acyltransferase in yeast) [206], both of which are associated with triacylglycerol synthesis, leads to an increased number of LDs and reduced mitochondrial fragmentation as well as mitochondrial ROS production, ultimately contributing to the alleviation of replicative senescence [207].

5. Conclusions

The essential reactions in eukaryotic cells are compartmentalized in membrane-bound organelles, which allow the segregation of incompatible biological processes with tailored microenvironments [1, 25]. However, the cell is a complicated biological system, and organelles are not isolated entities [86]; they need to actively communicate and interact with each other to maintain cell homeostasis [1, 208]. For example, peroxisomes convert glyoxylate and alanine into glycine and pyruvate; then, glycine is transported into the mitochondria for oxidation and the detoxification of glyoxylate [91]. The exchange of metabolites and information between organelles depends on vesicular trafficking pathways and MCSs [1].

Cellular senescence is a process of permanent cell-cycle arrest. It involves cellular calcium homeostasis, protein homeostasis, and MQC and is regulated by organelle interactions. In this review, we provide important clues to the intervention strategies for cellular senescence from a new perspective, including maintaining calcium homeostasis, maintaining the protein homeostasis, enhancing MQC, and improving anti-lipototoxicity effects.

Dysfunctional organelle interactions not only lead to cellular senescence, but also affect other important processes, such as the imbalance of cellular energy metabolism. Mitochondria are the main energy producers [209]. Their activities, especially

ATP production, are regulated by calcium signaling [209]. In particular, IP3R-mediated calcium transfer in ER-mitochondria MCSs plays an important role in maintaining basal mitochondrial metabolism [209], and the inhibition of IP3R activity leads to the impaired cellular energy metabolism under normal cellular conditions [209]. Peroxisomes and mitochondria act together in the degradation of fatty acids [91]. Dysfunctional mitochondria can replenish the TCA cycle *via* the RTG pathway, where peroxisomes convert fatty acids into acetyl-CoA [93, 94]. Defects in peroxisomes have an impact on mitochondrial pathology due to the impairment of fatty acid metabolism [210]. Thus, the organelles cooperatively form an interactive network to maintain cell homeostasis and accomplish a series of biological processes. Further understanding of the relevance of organelle interactions would certainly broaden our horizons for the understanding of mechanical and therapeutic exploration of complicated cell behavior. However, this is not limited to cellular senescence. Hence, our review provides important clues for a deeper understanding of cell function from a new perspective.

Abbreviation

ABCD1: ATP binding cassette subfamily D member 1; ACBD2: acyl-CoA binding domain protein 2; ACBD5: acyl-CoA binding domain protein 5; AMPK: AMP-activated protein kinase; ATF6 α : activating transcription factor 6 alpha; ATG5: autophagy-related gene 5; ATG14: autophagy-related gene 14; BAP31: B-cell receptor-associated protein 31; CERT: ceramide-transfer protein; CRAC: Ca²⁺ release-activated Ca²⁺; DDR: DNA damage response; DGAT2: diacylglycerol acyltransferase 2; DRP1: dynamin-related protein-1; ECI2: enoyl-CoA- δ isomerase 2; ER: endoplasmic reticulum; E-Syts: extended synaptotagmin-like proteins; FATP1: fatty acid transport protein 1; FFAT: phenylalanine-phenylalanine acidic tract; FIS1: mitochondrial fission 1; GRP75: glucose-regulated protein 75; IMM: inner mitochondrial membrane; IP3R: inositol 1,4,5-triphosphate receptor; IRE1 α : inositol requiring enzyme 1 alpha; IST1: IST1 factor associated with the endosomal sorting complex required for transport-III; LAMP1: lysosomal associated membrane protein 1; LDL: low-density lipoprotein; LDs: lipid droplets; MCOLN1: mucolipin 1; MCS: membrane contact site; MCU: mitochondrial calcium uniporter; MDV: mitochondrial-derived vesicle; Mfn2: mitofusin 2; MQC: mitochondrial quality control; mtDNA: mitochondrial DNA; NRZ: NAG-RINT1-ZW10; OMM: outer mitochondrial membrane; ORPs: oxysterol-binding protein-related protein family;

OSBP: oxysterol-binding protein; ORP1L: oxysterol-binding protein-related protein 1; PACS-2: phosphofurin acidic cluster sorting protein 2; PC: phosphatidylcholine; PDZD8: PDZ domain-containing protein 8; PE: phosphatidylethanolamine; PERK: RNA-dependent protein kinase-like ER kinase; PGC-1 α : proliferator-activated receptor gamma coactivator 1-alpha; PI: phosphatidylinositol; PIP1: phosphatidylinositol transfer protein membrane associated 1; PI(4)P: phosphatidylinositol 4-phosphate; PI(4,5)P₂: phosphatidylinositol-4,5-bisphosphate; PM: plasma membrane; PRKN: Parkin RBR E3 ubiquitin protein ligase; PS: phosphatidylserine; PTPIP51: protein tyrosine phosphatase interacting protein 51; ROS: reactive oxygen species; RTG: retrograde; RyR1: ryanodine receptor 1; SASP: senescence-associated secretory phenotype; SERCA: sarco/ER Ca²⁺-ATPase; STARD3: steroidogenic acute regulatory protein-related lipid transfer domain-3; STIM1: stromal interaction molecule 1; STX17: syntaxin 17; Syt7: Synaptotagmin-7; TBC1D15: TBC domain family member 15; TCA: tricarboxylic acid; TFEB: transcription factor EB; TM6SF2: transmembrane BAX inhibitor motif containing 6; TMEM: transmembrane; TNTs: tunneling nanotubes; TRPM1: transient receptor potential mucolipin 1; UPR: unfolded protein response; VAPB: vesicle-associated membrane protein-associated protein B; VAPs: vesicle-associated membrane protein-associated proteins; VDAC: voltage-dependent anion-selective channel protein; 4-PBA: 4-phenylbutyric acid.

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Competing Interests

The authors have declared that no competing interest exists.

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