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Aging and Senescence Associated Mitochondrial Dysfunction: A Target against Cardiovascular Disorders of the Elderly Individuals

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Abstract

The expansion of the world`s elderly population requires the identification of complex mechanisms beyond the continuous decline in cellular functions associated with aging and senescence. Both are risk factors that gradually impede health homeostasis and promote the incidence of cardiovascular, metabolic, neurodegenerative, and immune diseases in elderly people. The review aims to update and discuss the role of mitochondrial dysfunction in cardiovascular aging and senescence. The focus is targeted on molecular mechanisms beyond mitochondrial dysfunction occurring in (i) cardiac aging, (ii) vasculature aging, and (iii) cellular senescence. In line with the ongoing basic cardiovascular research, the review uncovers the promising strategies directed towards alleviating dysregulated and interrelated pathways of mitochondrial dysfunction by (iv) anti-aging therapies, and (v) anti-senescence treatments. Ultimately, the open questions and the perspectives of this domain (vi) are underlined. One can safely state that the recent translation of preclinical endeavors and interventions into clinical conduits helps to prevent/delay cardiovascular mitochondrial-dysfunction, and is of benefit to aged people.

Keywords: Cardiomyocytes; Blood vessels; Anti-aging therapy; Anti-senescence therapy

Introduction

Biological aging starts with the intracellular occurrence of molecular damages, followed by their gradual and irreversible accumulation. These changes result in the progressive loss of normal cellular functions, dysfunction of intracellular signaling, and altered intercellular communication. Next, such defects expand to the systemic decline of tissues and organs' operation and ultimately trigger organismal death. Aging is not a disease, but it significantly increases the susceptibility to the occurrence of a variety of age-related diseases, including cardiovascular, neurodegenerative, musculoskeletal, and metabolic diseases, macular degeneration, cancer, and many other disabilities with a poor prognosis for the elderly individuals [1-7]. A series of complex and interlinked processes are known as "hallmarks of aging". These involve (i) systemic alterations (such as deregulated nutrient sensing), (ii) specific cellular hallmarks (cellular senescence, exhaustion of stem cells, and altered intercellular communication), and (iii) molecular hallmarks, such as genomic instability, shortening of telomeres (repetitive DNA sequences found at the terminal loops of linear eukaryotic chromosomes), epigenetic alterations, loss of protein homeostasis ("proteostasis"), metabolome adjustments, low-grade chronic inflammation, compromised autophagy, and mitochondrial dysfunction [4, 8-10].

In cardiovascular aging, the decline of mitochondrial function (known as "mitochondrial dysfunction") is characterized by reduced ATP generation, impaired oxidative phosphorylation (OXPHOS), diminished mitochondrial biogenesis, depletion of NAD^+, overproduction of mitochondrial reactive oxygen species (mROS) correlated with increased oxidative stress, amplified mitochondrial DNA (mtDNA) mutation rate, telomere shortening, compromised quality control processes, and inefficient mitophagy.

These traits of mitochondrial dysfunction are implied in the development and progress of cellular dysfunction [4, 11-16].

Senescence is a pleiotropic process [17]: acute senescence appears to be a normal physiological activity with beneficial roles in embryogenesis, tissue remodeling, and wound healing [18, 19], while the chronic senescence has detrimental effects because the gradual accumulation of senescent cells during aging and age-related diseases leads to progressive tissular dysfunction [18, 20]. Here, the focus is on chronic age-related senescence (referred to further as "cellular senescence"). This is an adaptative response of cells facing the damage of severe stresses, leading to the irreversible loss of their proliferative potential and the long-term and stable cell cycle arrest. Meanwhile, the up-regulation of the anti-apoptotic pathways imposes cells to remain metabolically active [21]. Senescence is not identical to aging, as cells may become senescent irrespective of organismal age [22]. It should not be confused with quiescence, a condition of reversible proliferative arrest [23, 24]. The cell-cycle arrest pathways are different: activation of cell death inductor p53 and mammalian Target of Rapamycin (mTOR) causes cellular senescence, whereas p53 activation and mTOR inhibition trigger quiescence [25, 26]. Moreover, dependent on the diversity of cells and stressors, the attainment of cell senescence takes longer compared with some other cellular activities (replication, differentiation, apoptosis, or necrosis) [12]. The biomarkers of cellular senescence comprise alteration of morphology (cells become flat and enlarged), augmented reactivity of senescence-associated β-galactosidase, expression of Senescence-Associated Secretory Phenotype (SASP, a collection of factors with pro-inflammatory, proteolytic, extracellular matrix-degrading, complement-activating and pro-coagulating roles), intensified activity of Cyclin-Dependent Kinase (CDK) inhibitors, and modifications of chromatin and mtDNA [2, 18, 22, 27-31].

Mitochondrial dysfunction plays a key role in the initiation and progression of cellular senescence. The main promoters are excessive mROS generation, the conversion of metabolism from OXPHOS to glycolysis, impaired ATP generation, reduced mitochondrial membrane potential ($\Delta\Psi m$), diminished NAD^+/NADH ratio, and antioxidant capability. Moreover, released from the ER stores, Ca^{2+} triggers mitochondria overload and opening of the mitochondrial permeability transition pores (mPTP) located at the inner mitochondrial membrane (IMM). In cellular senescence, the dysfunctional mitochondria accumulate and are not efficiently cleared from the affected cells [13].

This review surveys and updates the molecular mechanisms of mitochondrial dysfunction in (i) cardiac aging, (ii) blood vessel aging, (iii) cardiovascular senescence, (iv) the current anti-aging, and (v) anti-senescence therapies targeting cardiovascular mitochondrial dysfunction. The open questions and the perspectives of this age-related essential topic conclude the review.

Mitochondrial dysfunction in cardiac aging

Mitochondria are abundant in the cardiomyocytes. They occupy 30-40% of the cell volume and generate ~90% of the ATP necessary for the normal contractile function [24, 32]. Noteworthy, cardiomyocytes contain spatially and morphologically distinct mitochondrial subpopulations with specific tasks: (i) the subsarcolemmal mitochondria (SSL, 0.4-3.0 μm in length) provide the ATP used in the transport of electrolytes and metabolites across the sarcolemma, (ii) the interfibrillar mitochondria (IF, ~1.5-2.0 μm in length) supply the ATP used in contraction, and (iii) the perinuclear mitochondria (PN, smaller in size, compared to SSL and IF) are relatively mobile during organelle`s fusion/fission dynamics [33-35].

Dysfunctional mitochondria are recognized as central contributors to heart aging, a process that harms the IF electron transport chain (ETC) [36]. Interestingly, an early event linked to cardiac aging is the acute ER stress (sustained by calpain I activation) that occurs earlier than mitochondrial dysfunction [35]. ER stress affects also the mitochondria-endoplasmic reticulum (ER) interacting zones (MERCs or Mitochondria Associated Membranes, MAMs); these function as signaling centers implied in lipid and calcium transfer, mitochondrial dynamics, and autophagy associated with the aging process [37-39].

The prominent features of the aging heart are hypertrophy, diastolic dysfunction, augmented fibrosis of the myocardium, and valvular calcification [32]. Recent knowledge highlights the main triggers of mitochondrial dysfunction in cardiac aging:

(i) Of the utmost importance is oxidative stress, defined as an imbalance between excessive ROS production and reduced scavenging capacity [16, 32, 40, 41]. Chemically, ROS are the superoxide anions ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). mROS are generated as by-products of OXPHOS and are viewed nowadays not only as inductors of oxidative stress but also as signaling molecules [42]. In physiological conditions, the low/moderate ROS levels contribute to cell homeostasis, as ROS are cleared by the cell`s antioxidant defense scavengers, including mitochondrial superoxide dismutase (SOD2 or Mn-SOD), peroxiredoxin 3, glutathione peroxidase (located in the cytosol, mitochondria, and peroxysomes), and the peroxisomal catalase. Excess of ROS levels suppresses the scavengers` activity, causees oxidative damage to mtDNA, proteins, and lipids, and ultimately activates the apoptotic pathways that induce cell death [1, 36, 41].

The abnormal accumulation of dicarbonyls in the aged myocardium (caused by the reduced efficiency of the glyoxalase detoxification pathway) was reported recently as an inductor of oxidative stress. The dicarbonyls are α-oxaldehydes (methylglyoxal, glyoxal, 3-deoxyglucosone), intermediates of glycolysis, gluconeogenesis, and lipid metabolism that favor ROS generation [43]. Moreover, excess dicarbonyls alter the formation and assembly of FoF1-ATP synthase monomers, which conduct to aberrant cristae formation, less efficient OXPHOS, and augmented energy dissipation through the opening of the mPTP. The glycation in the 5 subunits of FoF1-ATP synthase favors the opening of the mPTP [41,44]. Notable, the partial mPTP opening releases mtROS and Ca^{2+}

that activate nucleus-associated protective mechanisms such as the nuclear transcription factor E2-related factor (Nrf2) (with antioxidant function) and PGC-1α (implied in mitochondrial biogenesis). When mPTP opening is prolonged, the cytoplasm flows into mitochondria and causes extensive swelling of the IMM; subsequently, the outer mitochondrial membrane (OMM) becomes damaged, cytochrome c is released, and cell apoptosis ocurrs. mPTP opening can be normally stopped by the removal of dysfunctional mitochondria by mitophagy. In aging conditions, two situations may arise: (a) in case of massive mitophagy, the cell will be depleted of mitochondria leading to its death [16], and (b) in case of full opening of mPTP, the matrix metabolites (OXPHOS substrates, mROS, Ca^{2+}, NAD^{+}, and glutathione) will be released and an increased "proton (H^{+}) leak" through the mitochondrial inner membrane Adenine Nucleotide Transporter 1 will be stimulated [45]. In health conditions, a part of protons is pumped from the matrix to the mitochondrial intermembrane space, but some leak back to the matrix and generate ATP via ATP synthase. In the aged heart, the returned protons do not yield ATP, a condition known as "proton leak" [45]. The augmented proton leak is considered the primary bioenergetic change in aged heart mitochondria [46]. This is another example of a pleiotropic process: the mild proton leak occurs in the young heart, mimics caloric restriction, and confers protection against the damaging effects of ROS and oxidative stress, while in the aged heart, the excessive proton leak is detrimental, decreasing the respiratory efficiency [3].

(ii) The modification of Zn^{2+} transporters (in charge of Zn^{2+} distribution among cytosol and intracellular organelles) results in mitochondrial Zn^{2+} overload associated with increased ROS production and dysfunction of aged cardiomyocytes [40]. Earlier, it has been reported that Zn^{2+} originates from the lysosomes, after permeabilization of their membrane by Ca^{2+} that entered through the Transient Receptor Potential Melastatin 2 (TRPM2) channel; subsequently, the released Zn^{2+} stimulates the mitochondrial recruitment of Dynamin-related protein 1 (Drp-1) that triggers the aging-associated mitochondrial fission [47].

(iii) Another feature of mitochondrial dysfunction consists in the low levels of Coenzyme Q10 which transfers electrons from complexes I and II to complex III in the electron transport chain [48, 49].

(iv) The modifications of mTOR complex 1 and 2 signaling pathways occur in age-related cardiac dysfunction and heart failure [50]. It is known that the mTOR pathway regulates both cardiac homeostasis and aging through the adjustment of protein synthesis, autophagy, and mitochondrial function [51].

The recent reports bring evidence that mitochondrial dysfunction is a common attribute shared by both aged cardiomyocytes and blood vessels. The common traits consist in:

(a) the augmented production of ROS and the altered expression of proteins that regulate the redox balance; among the up-regulated proteins are the NADPH oxidase 4 (NOX4), the Src homologous-collagen homolog adaptor (p66Shc), and Arginase II (Arg-II). Opposed, are proteins down-regulated by aging, such as the Silent Information Regulator 1 (SIRT1), the antioxidant Nrf2, and the Nrf2 regulator, Klotho [32],

(b) the failure of the mitochondrial quality control caused by the offset of fission/fusion balance, and by the inefficient mitophagy conduct to the diminishment of endogenous antioxidant defenses. To compensate for the reduced functionality, mitochondrial morphology is affected. The malfunctioning mitochondria split by fission ("hyperfission") to remove the defective fragments and generate novel robust mitochondria aiming at the covering of energy requirements for growth and division (Figure 1),

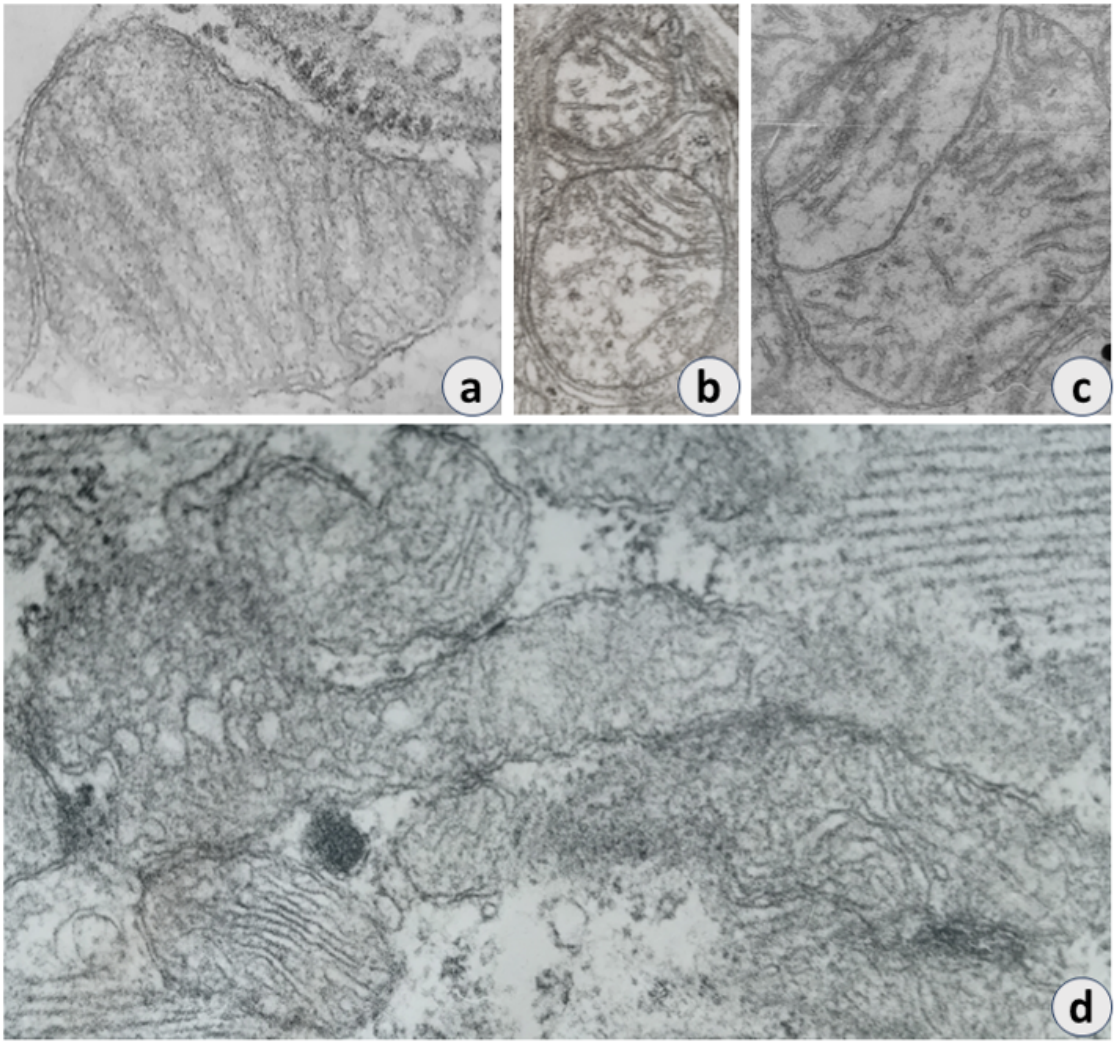

Figure 1: Electron microscopic ultrastructure of cardiomyocyte mitochondria in health (a), in aging: (b) smaller mitochondria generated by fission exposing defective cristae, (c) apoptotic mitochondria with a disorganized morphology, and in senescence: (d) fused, elongated mitochondria.

Magnifications: (a, c, d)- 54,600x; (b) 36,450x;

(c) other common traits of mitochondrial dysfunction in aged hearts and vasculature are reduced mitochondrial biogenesis, defective mitochondrial Ca^{2+} cycling, and impaired autophagy; the latter is caused by the reduced activation of AMP-activated protein kinase (AMPK) and E3 ubiquitin ligase Parkin, along with the involvement of Rho-associated coiled-coil-containing protein kinase (ROCK)1 and ROCK2 [11, 32, 52, 53],

(d) the malfunction of telomeres leads to mitochondrial dysfunction by the downregulation of transformation-related protein 53(TRP53)-dependent of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) and PGC-1β [54, 55],

(e) myocardial and blood vessels aging show activation of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome, stimulation of the Toll-like receptor 4 (TLR4), of inflammatory cytokines production, and NF-κB signaling [32]; thus, aging is associated with a low-grade, chronic inflammation that augments the local generation of ROS and amplifies the inflammatory response [9, 56-59]. The process was coined "inflammaging" by Franceschi et al. in 2000 and now is generally recognized as a risk factor for cardiovascular diseases [59,60].

The above-dysregulated and interrelated pathways of mitochondrial dysfunction in aged cardiomyocytes and blood vessels [61, 62] are accompanied by specific features developed in aged arteries and microvasculature (discussed in the next section).

Mitochondrial dysfunction in blood vessels aging

The data so far established that all cellular components within the vascular wall of large arteries (aorta), coronary arteries, atherosclerotic arteries, and microvasculature (capillaries included) are affected by age-related mitochondrial dysfunction. The elastic arteries (aorta and carotid artery) remodel in aging their wall; the lamellae become partially split and replaced by collagen, and the endothelial cells (ECs) lose the angiogenic ability and ECs-dependent vasodilation (to acetylcholine) [62, 63, 64]. Previously, it was demonstrated that in rat-aged aortas, the $O2^{\bullet-}$ reacts with the vasorelaxant nitric oxide (NO), forms peroxinitrite and nitrosylates mitochondrial manganese superoxide dismutase (MnSOD) [65]. Within the aged aorta, the enhanced Interleukin-6 (IL-6) levels increase mitochondrial dysfunction, and augment mitophagy and Parkin levels; these changes assist atherogenesis development in hyperlipidemia [66].

The high incidence of abdominal aortic aneurysm (AAA) in the aged population attracted attention to mitochondrial dysfunction`s role in this degenerative disease [67]. Recently, Navas-Madroñal et al. [68] showed the involvement of harmful mitochondrial oxidative stress in AAA and discovered the positive effects of mitochondria-targeted tetrapeptide Szeto-Schiller 31 that reduced the occurrence and gravity of AAA. Other studies showed that thoracic aortic aneurysm modified the vessel proteome both quantitatively and qualitatively [69].

Within the aged coronaries, mitochondrial dysfunction is promoted by acyl-coenzyme A: lysocardiolipin acyltransferase-1 (ALCAT-1) involved in cardiolipin remodeling [70]. Additionally, aging is associated with coronaries hyperconstriction, an event in which dysregulated mitochondrial redox homeostasis and the imbalanced fission/fusion dynamics play a role; the consequences consist of impaired physiological perfusion and the installment of several heart pathologies [71]. Such alterations are intensified by the mROS levels exceeding the cell's antioxidant buffering capacity [72]. Advanced aging produces modifications of the bioenergetic profile of coronary artery ECs and vascular smooth muscle cells (VSMCs) that express in aging lower resting OXPHOS levels, and reduced reserve capacity [73].

Effects of aging on microvasculature implied in-depth studies on coronaries and brain microcirculation. Recently, the group of Mengozzi et al. [56] advanced the idea that microvascular dysfunction might represent a noticeable marker of aging compared to chronological age; this conclusion resulted from the study of age-associated mitochondrial and ECs dysfunction correlated with the irreversible modification in microvascular wall structure, low-grade inflammation, and oxidative stress. Furthermore, in ECs, the mitochondrial Sirtuin 3 (SIRT3) levels progressively decline with aging, the SIRT3-related ECs metabolism is impaired, and these modifications conduct in the rarefaction of coronary microvasculature [74]. Remarkably, vascular alterations occur earlier in individuals at risk for cardiovascular disease development [64]. Brain microvasculature restrains in aging a decreased number of mitochondria and a reduced efficiency of the remaining ones [75, 76]; the latter trait contributes the impaired OXPHOS, lower ATP generation, diminished glycolysis, and increased glutamine utilization as an energy source [56].

Nowadays, it is established that by affecting blood vessels, mitochondrial dysfunction has a key role in the morbidity and mortality of older individuals [29]. The input of mitochondrial dysfunction on cardiovascular senescence is discussed below.

Mitochondrial dysfunction in cardiovascular senescence

In response to aging and stressors, the cardiomyocytes (terminally differentiated post-mitotic cells) develop a senescent phenotype and accumulate within the myocardium, contributing to the risk of age-related cardiovascular pathologies, such as heart failure, diastolic dysfunction, myocardial infarction, cardiac arrhythmias, and atherosclerosis [24, 77-81].

Cardiomyocyte senescence is induced by various factors: mitochondrial dysfunction, oxidative stress, activation of the hexosamine biosynthetic pathway, and epigenetic regulation [82, 83]. Several processes explain mitochondrial dysfunction associated with cardiomyocyte senescence: the oxidative stress (counting for 90% of age-related ROS) [26], the overexpression of mitochondrial-membrane flavoenzyme Monoamine Oxidase-A (MAO-A) (another source for elevated ROS levels), downregulation of genes encoding subunits of mitochondrial ETC complexes, defects in mitochondrial dynamics and quality control [84], and the inefficient removal of damaged mitochondria by mitophagy (as a consequence of Parkin-mediated mitophagy inhibition by cytosolic p53) [85-89]. To assist the replenishment of damaged mitochondrial DNA, extensive mitochondrial fusion takes place, resulting in elongated mitochondria (Figure 1); this process is coordinated by the mitochondrial fusion proteins: Mitofusin 1(Mfn1), Mitofusin 2 (Mfn2), and optic atrophy 1 (OPA1) [90-92]. The cellular senescence is induced also by the clinical doses of chemotherapy that cause cardiotoxicity [93, 94].

The hallmarks of cardiomyocyte senescence are genomic instability, mitochondrial dysfunction, ER stress, contractile dysfunction, hypertrophic growth, β-galactosidase expression, and increased production of pro-inflammatory, pro-fibrotic and pro-hypertrophic SASP factors [24, 77, 79, 95, 96]. The latter is facilitated by minor permeabilization of the OMM (miMOMP) that permits the release of mtDNA into the cytosol (via BAX and BAK macropores), activates the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, and conducts to the increased expression of inflammatory molecules and of SASP [97]. The SASP generation in aged cardiomyocytes is also stimulated by the length-independent telomere damage that activates the classical senescence-inducing pathways p21CIP and p16 INK4a [77].

Within the myocardial "microenvironment" and under stress conditions, the senescence of resident cardiomyocytes and ECs (representing ~60% of heart noncardiomyocytes) is modulated by paracrine signaling factors released by these two types of cells: (i) the dysfunctional cardiomyocytes secrete angiogenic factors implied in the induction of ECs senescence; examples are the Vascular Endothelial Growth Factor A (VEGF A), angiopoietin-1, Lipoprotein Lipase (LPL, in diabetes), SASP, and extracellular vesicles (EV) [26, 98, 99]; (ii) the malfunctioning cardiac ECs secrete pro-inflammatory factors, such as Transforming Growth Factor- β (TGF-β), Interleukin-6 (IL-6), IL-33, Endothelin-1 (ET-1), Angiotensin II (Ang II), and EV, recognized as players in cardiomyocytes senescence [26, 96].

Among the consequences of cardiomyocyte senescence, studies uncover the increased risk of ventricular arrhythmias [100], the development of cardiomyopathy [101], and telomere dysfunction; ATP deficiency, excessive ROS generation, and chronic inflammation are potential therapeutic targets to improve the associated mitochondrial dysfunction [102]. The senescence of cardiac ECs may lead to reduced vasodilation and atrial fibrillation associated with the expression of senescence effector pathways, p53, and p16 [103]. Aortic stiffness, enhanced inflammation, and dysregulated vascular tone have been acknowledged among the features of senescent vascular ECs [104].

Senescence disturbs also the VSMCs that show increased β-galactosidase expression, short telomeres, up-regulated secretion of inflammatory cytokines, and enhanced DNA damage [105]. In cardiovascular pathophysiology, accumulation of senescent VSMCs increases with age, is regulated by Ang II [106], occurs within atherosclerotic plaques, throughout all stages of the disease [107], and is implicated in the calcification of old aortas, a process associated with the upregulation of transcriptional factor GATA6 [108]. Furthermore, the senescent VSMCs are involved in the activation of pro-ferroptotic signaling, a novel form of regulated cell death associated with arterial stiffness [109]; the secreted SASP factors contribute to the development of vascular diseases, such as atherosclerosis, aneurysm, and hypertension [110].

The knowledge described above allows the selection of the common and individual traits of mitochondrial dysfunction in cardiovascular aging and senescence. A brief synopsis is included in Figure 2.

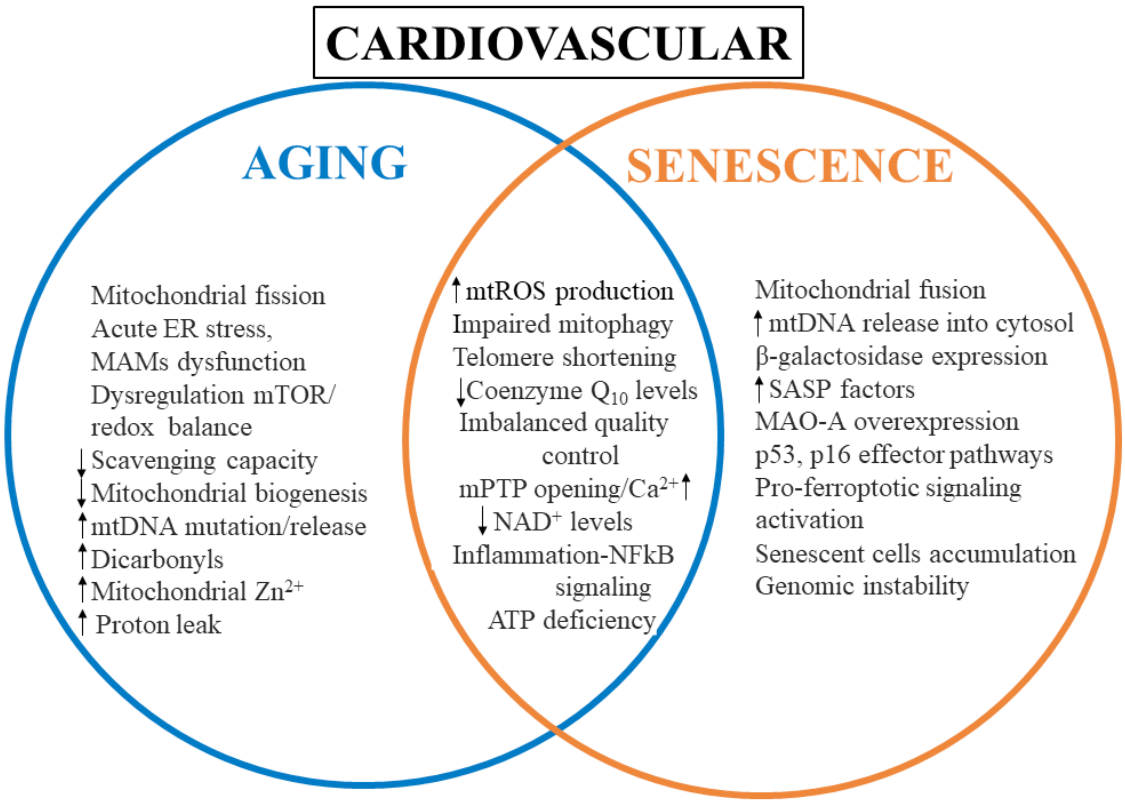

Figure 2: Mitochondrial dysfunction molecular mechanisms in cardiovascular aging and senescence: the common and the specific features.

The recent preclinical endeavors to alleviate cardiovascular consequences of aging and cellular senescence are discussed in the last part of this review.

Current anti-aging therapies targeting cardiovascular mitochondrial dysfunction

Preclinical studies acknowledge that alleviation of mitochondrial dysfunction in cardiovascular aging is produced by several natural compounds, antioxidants, peptides, pharmacological agents, and hormones; other recent promising approaches are nanomedicine drugs, gene therapy, mitochondrial transfer, and lifestyle changes (Table 1).

Therapeutic approach	Targeted mitochondrial dysfunction/Effects	References
NATURAL COMPOUNDS Flavonoids – Quercetin	Abnormal mitochondrial dynamics ↓mitochondrial superoxide Protects mitochondrial morphology	111-116
Phenols and polyphenols -Resveratrol (3,5,4'-trihydroxystilbene) Salvinoic acid D	AMPK-SIRT1-PGC-1α mitochondrial biogenesis pathway SIRT1 activation Sirt1/Sirt3-FoxO pathway activation mitophagy impediment, mPTP opening prevention restores mitochondrial morphology	115, 117-120
Metformin	↑ autophagy; alleviate aging-associated inflammation ↓ ROS generation; mitochondrial function modulation offsets aging and extend lifespan	121-123
ANTIOXIDANTS Coenzyme Q10 MitoQ (Mitoquinone) Vitamin E MitoTEMPO (2-(2,2,6,6-Tetramethylpiperidin-1-oxyl-4-ylamino)-2 -oxoethyl) triphenylphosphonium chloride monohydrate)	Antioxidant, mROS scavenger improves age-related endothelial dysfunction by ↓oxidized LDL, ↑ NO production and ↓mitochondrial oxidative stress ↓mROS prevents vascular reactivity alterations	117, 124-127
Zn^{2+}	Modulation of cardiomyocyte Zn^{2+}transporters	41
PEPTIDES Spermidine (1,8-Diamino-4-azaoctane, *N*-(3-Aminopropyl)-1,4-diaminobutane MOTS-c	Attenuates mitochondrial dysfunction, ↓IL-6 and Parkin Restores mitochondrial metabolic imbalance	66 128
PHARMACOLOGICAL AGENTS The SS-31 tetrapeptide (D-Arg-2',6'-dimethylTyr-Lys-Phe-NH2) (elamipretide or bendavia)	↓ mitochondrial proton leak & PTP opening, prevents mitochondrial proton leak	28, 47, 72
Rapamycin	mTOR inhibitor, improves cardiac systolic and diastolic function	129
GENE THERAPY	Overexpression of PGC-1α SIRT1, TFAM & Parkin	15, 130

NEUROENDOCRINE HORMONE Melatonin (N-acetyl-5-methoxytryptamine)	Antioxidant, anti-inflammatory ↓Drp1 expression; mitochondrial fission inhibition ↑mitochondrial fusion/mitophagy, activation of AMPK-OPA1 signalling pathways ↓ apoptosis mitochondrial membrane potential restauration ↑myocardial mitochondrial dynamics & Sirt3 expression protective in cardiovascular diseases	131-141
NANOMEDICINE DRUGS Nanocarriers, nanoparticles	Cyclosporin A nanoparticles conjugated with poly-lactic/glycolic acid or with SS-31	142
MITOCHONDRIAL TRANSFER	Re-establishes mitochondrial function	143
LIFE STYLE CHANGES Physical activity/Exercise Calorie restriction; calorie restriction mimetics	Improve the altered mitochondrial quality control mechanisms; nutritional strategy; the targets include mTOR, sirtuins, diminishment of mitochondrial dysfunction	2, 5, 33, 144-147

Table 1: Therapeutic targeting of mitochondrial dysfunction in cardiovascular aging.

The current knowledge ascertains that aging is a remarkably complex process, and mitochondrial dysfunction is only one of its hallmarks. Using experimental models (cell cultures and laboratory animals) a large diversity of compounds with anti-aging effects have been tested/discovered. Moreover, the last decade brought the fast transfer of several promising compounds from preclinical studies to human clinical trials. According to Guarente, Sinclair, and Kroemer [148], the beneficial compounds are metformin (a biguanidine known for its glucose-lowering effects), NAD^+ precursors, glucagon-like peptide-1 receptor agonists, TORC1 inhibitors, spermidine, senolytics, probiotics, and anti-inflammatory drugs. Large clinical trials are ongoing to check metformin`s effects on health-span extension and cardiovascular advantage [149, 150]. The potential use of peptides in anti-aging strategies is facilitated nowadays by the availability of a comprehensive peptide database ("AagingBase") [151]. Targeting aging genes is a fast-developing research area, and TERT and ApoE genes are now exploited in clinical trials [152]. In applying caloric restriction, attention is given now to alternative "antiaging "diets (intermittent fasting, protein restriction, ketogenic diets, etc.) [153].

From the survey of human anti-aging therapies, novel research directions emerged:

(i) geroscience (anti-aging medicine), as a strategy to improve health span free of disabled age-related pathologies [149, 154]; back in 2019, Campisi et al identified compounds currently tested in humans for their geroprotective potential: metformin, rapamycin analogs, sirtuin activators (resveratrol, SRT2) [2], nicotinamide riboside, nicotinamide mononucleotide (NAD^+ precursors), exercise, and senolytics (discussed in the next subchapter),

(ii) rejuvenating conduits to delay/reverse aging by epigenetic regulation reprograming [155], and

(iii) interventions targeting the (healthy) longevity pathways like MILES (Metformin in Longevity Study) [3, 5, 53, 123].

Current anti-senescence therapies targeting cardiovascular mitochondrial dysfunction

To challenge senescence, the link between mitochondrial dysfunction and cellular senescence is exploited by strategies that adequately adjust and reprogram the disturbed mitochondrial metabolism [153] (Table 2).

Therapeutic approach	Targeted mitochondrial dysfunction/Effects	References
Mitochondrial metabolic reprogramming for senescence alleviation	↑ OXPHOS efficiency, ↓mtROS	153
Glycolytic enzymes inhibition	Cellular glucose metabolism alterations → ECs senescence	156
Mitochondrial-derived peptides (Humanin, MOTS-c) administration	Mitochondrial function regulation, senolytic effects	157, 158
Senolytic drugs	Induce the selective apoptosis of senescent cells	30, 159, 160
Flavonoids – Quercetin combined with Dasatinib or with Fisetin (Senolytic cocktail)	Reduce inflammation, alleviates frailty in humans	80, 81, 161
Naringenin, hesperetin, hesperidin, fisetin, kaempferol, rutin, apigenin, luteolin, nobiletin, tangeretin, genistein, wogonin, epigallocatechin gallate (EGCG), theaflavin-3-gallate (TF2A), procyanidin C1	Modulate cellular senescence pathways/interact with molecular targets that regulate ageing-related processes.	162
Bcl-2 family protein inhibitor, Navitoclax (ABT-263)	Clearance of senescent cardiomyocytes, improves myocardial remodelling, diastolic function, and survival following myocardial infarction	163
Heat-Shock Protein 90 inhibitors	Reduces age-related symptoms in progeroid mice.	164
Polyphenols - Resveratrol (3,5,4'- trihydroxystilbene) with and without nanocarriers.	Senotherapeutics used in both preclinical and clinical settings.	165
NAD^+ precursors supplementation	CD38/NAD^+/SIRT1 axis for enhanced efficacy of geroprotectors	166
Senolytic vaccination	Reduces atherosclerosis in apolipoprotein E knockout mice on a high-fat diet.	167
Dietary restriction	Small adipocyte size and low DNA damage	168
Senomorphic drugs	Suppress SASP	30,159
mTOR inhibition	Associated with SGLT2, synergistic benefits on senescence pathways	169
JAK/STAT inhibition	Augments muscle function in myopathy.	170
NF-kB inhibition by avenanthramide C	SASP suppression	171
Activation of SIRT1 (a longevity modulator) by *Nephelium lappaceum* (rambutan) seeds	SASP selective inhibition	172
SIRT3 activation	Effects linked to exercise-induced adaptation	173
Rapamycin and its derivatives (rapalogs)	mTOR inhibitors, improve physiological parameters associated with ageing in cardiovascular system, including.	174
Kaempferol	Anti-inflammatory, antioxidant, and anti-apoptotic actions	175
Ruxolitinib	Reduces cytokine release and protects the endothelium from Ischemia/Reperfusion-mediated dysfunction.	176

Table 2: Senotherapeutic interventions targeting mitochondrial dysfunction.

Noteworthy, in the therapeutic alleviation of aging-related senescence two types of drugs are considered: the "senolytics" that selectively remove the senescent cells (diminishing their number), and the "senomorphics" that suppress the production/expression of secreted SASP factors (Table 2). Although the search for specific senescent senolytics and senomorphics is ongoing, these drugs have a series of impediments: they are not directed to a certain intracellular pathway and the dynamics of the senescence process across the lifespan make it impossible to use a single drug to target the diversity of senescent cells (the use of cocktails is preferable); the senotherapeutic-associated adverse effects should be also considered: as an example, the caloric restriction could increase the risk for osteoporosis, and is not be employed at people with body mass index less than 21 kg/m^2) [12, 81, 172, 178]. A current trend in senescence treatment is the identification of genes associated with this process (http://Senequest.net) along with the translation of preclinical endeavors on "mitochondrial transplantation" to clinical trials [179, 180].

Conclusions, Open Questions and Perspectives

This review provides an updated outlook on the molecular mechanisms of mitochondrial dysfunction in cardiovascular aging and senescence, and emphasizes the specific alleviation therapies. Based on the significant recent progress in this area, it was possible to delineate not only the common and the individual features of mitochondrial dysfunction in aged cardiomyocytes and blood vessels but also the evaluation of the attributes in aging vs. senescence.

It becomes apparent that several pertinent questions related to mitochondrial dysfunction during aging require fast answers. These are the following: (i) whether oxidative stress is a cause or a consequence of the elderly`s cardiovascular pathology, (ii) the uncovering of adequate aging models, (iii) the establishment of strategies for scavenging the dicarbonyl compounds, (iv) the prevention of aging-related mitochondrial proton leak, and (v) the identification of mechanisms involved in microvascular aging [4, 36, 45, 127, 143, 176]. The "geroscience" area needs reliable biomarkers to prevent/delay the aging process, and to assess the efficacy of anti-aging treatments [144, 181]. The ongoing endeavors are focused on the quantification of vascular aging, and on translational research (mitochondrial transfer included) to promote healthy aging and longevity [123, 143, 181, 182].

In the cellular senescence area, an urgent need is uncovering molecular mechanisms beyond the different types of senescence, and identifying phenotypes that "escape" senescence [18]. The recent literature acknowledged the lack of sensitive and specific markers for senescent cells [183]; the MAMs modulation [184], the metabolic reprogramming [185], and the genetic-related approaches, in terms of identification of senescence-related genes [186], and the genomic repair systems operating in this pathology [187, 188] are ongoing trends in this area. Taken together, the above directions at the horizon emphasize the complex interactions taking place in aging and cardiovascular senescence. Once deciphered, further translational research may pave the way toward people`s healthy aging and longer lives.

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