

Review

Pathological Roles of Mitochondrial Oxidative Stress and Mitochondrial Dynamics in Cardiac Microvascular Ischemia/Reperfusion Injury

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Abstract: Mitochondria are key regulators of cell fate through controlling ATP generation and releasing pro-apoptotic factors. Cardiac ischemia/reperfusion (I/R) injury to the coronary microcirculation has manifestations ranging in severity from reversible edema to interstitial hemorrhage. A number of mechanisms have been proposed to explain the cardiac microvascular I/R injury including edema, impaired vasomotion, coronary microembolization, and capillary destruction. In contrast to their role in cell types with higher energy demands, mitochondria in endothelial cells primarily function in signaling cellular responses to environmental cues. It is clear that abnormal mitochondrial signatures, including mitochondrial oxidative stress, mitochondrial fission, mitochondrial fusion, and mitophagy, play a substantial role in endothelial cell function. While the pathogenic role of each of these mitochondrial alterations in the endothelial cells I/R injury remains complex, profiling of mitochondrial oxidative stress and mitochondrial dynamics in endothelial cell dysfunction may offer promising potential targets in the search for novel diagnostics and therapeutics in cardiac microvascular I/R injury. The objective of this review is to discuss the role of mitochondrial oxidative stress on cardiac microvascular endothelial cells dysfunction. Mitochondrial dynamics, including mitochondrial fission and fusion, are critically discussed to understand their roles in endothelial cell survival. Finally, mitophagy, as a degradative mechanism for damaged mitochondria, is summarized to figure out its contribution to the progression of microvascular I/R injury.

Keywords: microvascular I/R injury; endothelial cells; mROS; mitochondrial dynamics

1. Introduction

Acute myocardial infarction (AMI) is caused by blockage of one or more of the coronary arteries that supply the heart [1,2]. The sudden cessation of fresh blood flow will extensively result in tissue hypoxia or anoxia and, eventually, cell death through apoptosis or necrosis [3,4]. It has been widely accepted that re-introduction of blood flow through reperfusion strategies is necessary and fruitful to salvage damaged myocardium. Paradoxically, reperfusion also causes cardiomyocyte or endothelial cell death through inducing oxidative stress, calcium overload, and tissue inflammation response [5,6]. Of note, the clinical reality of ischemia-reperfusion (I/R) injury becomes apparent with the advent of thrombolytic and interventional reperfusion [7,8].

The cardiac circulation is not only the culprit of acute myocardial infarction through coronary occlusion due to the formation of thrombus after plaque erosion or rupture but also a victim of reperfusion treatment after myocardial ischemia [9,10]. Structurally, endothelial cells constitute a layer between blood and extravascular cells and are responsible for maintaining the structure and regulating

the function of blood vessels [11,12]. In addition to regulating the vascular tone, a series of dilators (such as bradykinin and nitric oxide) and constrictors (like endothelin) are generated, released, or regulated by endothelial cells, in order to prevent platelet aggregation and blood clot formation [13,14]. In the heart, endothelial cells sense the alterations of micro-environment and then release of a number of cell signaling transmitters to maintain hemostasis in the vessel and heart tissue [15,16]. Under normal conditions, no adhesion molecules or thrombogenic factors are expressed on the surface of endothelial cells; however, when blood vessels are damaged, vascular endothelial growth factor (VEGF) and adhesion molecule are expressed on the surface of endothelial cells and contribute to the pro-inflammation cells accumulation [17,18]. This effect may aggravate microvascular stenosis, especially at the stage of reperfusion [19,20]. From a clinical point of view, no-reflow phenomenon with severe capillary damage occurs in 25–50% of patients that received reperfusion strategies including percutaneous transluminal coronary intervention or coronary artery bypass grafting surgery [21,22]. More importantly, no-reflow phenomenon negatively affects the clinical outcome in patients with AMI and is highly correlated with arrhythmias, left ventricular remodeling, and death in the short, medium, and long term [23,24]. In addition, no-reflow phenomenon, mainly caused by cardiac microvascular I/R injury, has been used as an independent predictor of mortality at 5 years [25,26]. Unfortunately, although many studies have been performed to understand the molecular mechanisms underlying cardiomyocyte I/R injury, cardiovascular microvascular I/R injury is a so far neglected target of cardioprotection [27,28].

Mitochondria have historically been viewed as the battery of the cell through consuming oxygen and producing ATP with the help of citric acid cycle [29,30]. A host of cellular stress responses are under the control of mitochondria in addition to their necessary role in bioenergetics [29,31]. Unlike cardiomyocytes or skeletal muscle, mitochondria-dependent energy production is relatively low in vascular endothelium, which primarily uses glycolysis to produce ATP [32,33]. It is now accepted that mitochondria in endothelial cells mainly play a prominent role in signaling cellular responses to environmental cues [34,35]. More importantly, mitochondrial content in endothelial cells is relatively low (2–6% of cytoplasm volume) compared with other cell types such as cardiomyocytes (~32%) [36]. The low mitochondrial content in endothelial cells further validates a non-canonical function played by mitochondria in regulating signaling responses rather than in glucose metabolism [37]. In response to stress, reactive oxygen species (ROS) are produced by mitochondria and employed as a second messenger to transduce extracellular signal [38,39]. Mitochondrial fusion [40] and fission [41,42], together with mitophagy (removal of defected mitochondria), are also involved in the regulation of cell homeostasis through affecting the mitochondrial quality control [43,44]. Here, we summarize and discuss the main regulatory aspects of mitochondrial oxidative stress and mitochondrial dynamics in cardiac microvascular I/R injury (Figure 1).

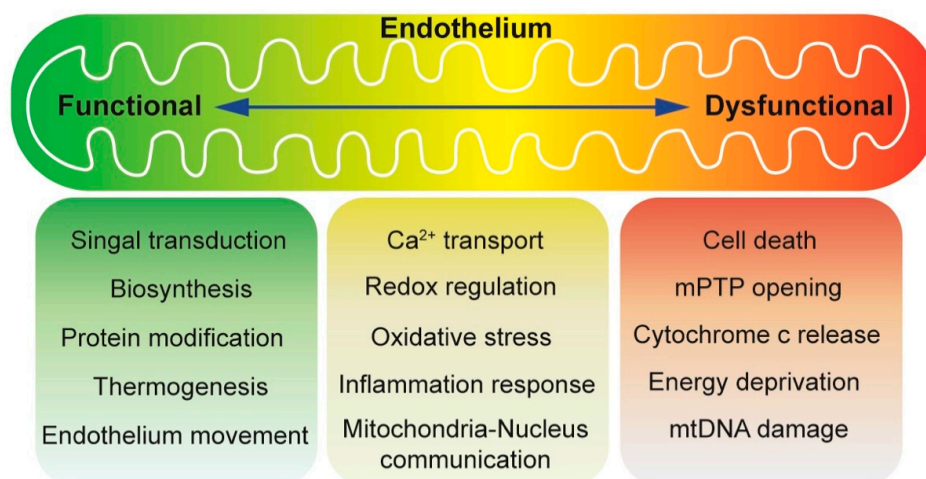


Figure 1. An overview of mitochondrial function in endothelium homeostasis. Mitochondria are

known as the powerhouse of the cell. Under normal conditions, mitochondria-dependent energy production is relatively low in vascular endothelium, which primarily uses glycolysis to produce ATP. It is now accepted that mitochondria in endothelial cells mainly play a prominent role in signaling cellular responses to environmental cues. Intermediate metabolism in the mitochondria produces metabolites for biosynthesis, protein modification, and thermogenesis. In addition, endothelial mobilization is under the control of mitochondria. Oxidative phosphorylation is coupled with generation of reactive oxygen species (ROS), which can either serve as molecular signals or cause cell damage and cell death. Mitochondrial metabolism is stimulated by calcium, but under pathological conditions, calcium overload can trigger the opening of the mitochondrial permeability transition pore (mPTP). The release of mitochondrial content, such as cytochrome c, induces apoptosis, or the loss of membrane potential (a consequence of prolonged mPTP opening), causes ATP deprivation and necrosis.

2. Mitochondrial Oxidative Stress

Oxygen is carried in from circulating blood transfers to perivascular tissues through endothelial cells. Of note, endothelial cells consume a slight amount of oxygen to produce ATP in order to transfer most of the oxygen to myocardium [45,46]. In vitro data suggest superoxide generated by mitochondria accounts for 0.2–2% of cellular oxygen consumption [47,48]. It has been found that endothelial cell dysfunction affects the diffusion rate of oxygen across the arteriolar vessel wall [49,50]; however, these observations require further discussion. In endothelial cells, due in larger part to the unique nature of endothelium's limited metabolic demands, mtROS primarily play a prominent role as cell-signaling molecules [51,52]. Vascular endothelial cells overwhelmingly rely on glycolysis rather than the TCA cycle for cellular ATP needs [53,54]. This allows endothelial cells the freedom to leverage the products of the electron transport chain (ETC) for cell signaling purposes. Jensen first observed the formation of ROS in the respiration chain [55,56]. This point has been further validated by later studies that confirm mtROS production mainly takes place at the electron transport chain localized on the inner mitochondrial membrane during the process of oxidative phosphorylation [57,58]. Mechanistically, the primary sites of superoxide anion production and release are Complex I (NADH-ubiquinone oxidoreductase), Complex II (succinate dehydrogenase, SDH), and Complex III (ubiquinol-cytochrome c oxidoreductase) [59]. Complexes I and II accept electrons from NADH + H⁺ and FADH₂, respectively, which are transferred to Complex III and finally to Complex IV (cytochrome c oxidase), where the final electron acceptor is oxygen and the final product is water [60]. In the ETC, Complex I and Complex III are primarily responsible for producing superoxide anions (O₂⁻). Complex I produces O₂⁻ in the process of oxidizing NADH into NAD and pumping a proton from the mitochondrial matrix into the intermembrane space [53]. Complex III produces O₂⁻ as it oxidizes CoQ to reduce cyt-c and pumps a proton into the intermembrane space [61,62]. Molecules of O₂⁻ are potent oxidants and, therefore, need to be reduced and “detoxified”.

NADPH oxidase (NOX) is another source of mtROS production in endothelial cells. NOX are membrane-bound enzyme complexes and NOX subunits gp91^{phox}, p22^{phox}, p67^{phox}, and p47^{phox} were first identified in cultured HUVEC by Jones and colleagues [63]. These NOX isoforms expressed in the vasculature differ in their subcellular localization, yet all function through electron transfer from cytosolic NOX to mitochondrial oxygen, thereby producing superoxide or hydrogen peroxide [64,65]. Although ample evidence in various endothelial cell lines has indicated mitochondrial ETC as the main source of I/R-related ROS, there is a possibility of cross-talk between NOX isoforms and mitochondria [66]. Of note, NOX4 is localized along the inner mitochondrial membrane, and the potential interaction between these two sources of ROS may be significant determinants of the total mtROS in the endothelium [67,68].

In addition to mitochondria and NOX, ROS in endothelial cells are also generated by xanthine oxidase and neutrophils, especially at the stage of I/R injury [69]. Xanthine oxidase, the conversion product of oxidative damage to xanthine dehydrogenase, produces superoxide and hydrogen

peroxide during purine metabolism [70,71]. This process is more prominent in endothelial cells [72]. First, xanthine oxidase is abundant in endothelial cells [64]. Second, xanthine oxidase-mediated ROS formation is a byproduct of ATP metabolism independent of mitochondria-related oxidative phosphorylation [73,74]. Third, xanthine oxidase is primarily activated by reperfusion after ischemia—hypoxia breaks down ATP and then forms a lot of AMP/hypoxanthine, which is utilized to generate ROS once oxygen is re-introduced [75]. These ROS recruit neutrophils to the blood-endothelial cell interface, thereby initiating migration into the surrounding tissues. Neutrophils then produce a greater amount ROS, further precipitating the effects of I/R injury [56,76]. In the normal physiological state, multiple antioxidant mechanisms exist to counteract the effect of mtROS: Superoxide dismutase (SOD), glutathione, and catalase [77,78]. Oxidative stress in endothelial cells is the result of increased ROS production and depressed antioxidant system [72]. The predominant ROS in the endothelial cells are superoxide and hydroxyl radicals. Their cellular toxicity comes from lipid peroxidation and its associated membrane damage [79,80]. DNA damage, oxidative post-transcriptional modification of cysteine residues in protein, and signal transduction are also governed by mtROS [81,82]. Due to the instability of free radical species, free radical scavengers have been utilized to directly prove the detrimental effects of mtROS in cardiac microvascular I/R injury.

In the mitochondrial matrix, superoxide dismutase (SOD) 2 reduces O_2^- into H_2O_2 , a less toxic ROS [83]. Then, glutathione peroxidase (GPX) catalyzes the reduction of H_2O_2 into H_2O through the oxidation of reduced glutathione (GSH) into its oxidized form (GSSG) [84,85]. Catalase in the mitochondrial matrix can also convert H_2O_2 into water and molecular oxygen [86,87]. Glutathione biosynthesis is catalyzed by glutathione reductase using the oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) into NADP and is crucial in antioxidant activities in the mitochondria [88,89]. In the intermembrane space, copper and zinc-containing SOD1 reduces O_2^- into H_2O_2 , and GPX reduces H_2O_2 into H_2O [90,91].

Another important source of ROS in the re-perfused heart are the two isoforms of monoamine oxidases (MAO), MAO-A and MAO-B, which are located on the outer mitochondrial membrane [92]. It has been demonstrated that MAO-A activity is enhanced by I/R injury and is responsible for the precipitation of hydrogen peroxide and the progression towards left ventricle hypertrophy and cardiac remodeling [93]. Increased influx of mitochondrial iron stimulates the formation of more potent and deleterious hydroxyl radical groups from hydrogen peroxide [94,95]. Although the continuous release of ROS from mitochondria during normal conditions appears to play a necessary role in the maintenance of basal cellular function, transiently elevated ROS levels can promote selective protein synthesis, preconditioning, and changes in vascular tone [96,97]. However, even modest, acutely elevated mitochondrial ROS production can lead to cellular dysfunction.

Under I/R injury, endothelial cell proliferation is delayed due to excessive mtROS production [98]. Endothelial cell migration and tube formation are also impaired, an effect that is accompanied with a decrease in the expression of VEGF, VE-cadherin, and MMP2 [98,99], suggesting that oxidative stress affects the angiogenesis and regenerative capacity of micro-vessels in reperfused myocardium. Mechanistically, mtROS overproduction seems to be associated with a decrease in the levels of total antioxidant capacity and SOD [100]. Of note, the increase in mtROS in endothelial cells under I/R injury may also result from excessive inflammation response because myeloperoxidase (MPO) expression, a neutrophil infiltration marker, is upregulated in reperfused heart [101,102]. Increased thioredoxin-interacting protein (TXNIP) and a noticeable decline in the levels of thioredoxin 1 (Trx-1), thioredoxin reductase (TrxR), glutathione (GSH), catalase (CAT), and glutathione peroxidase (GPx) may also contribute to endothelial oxidative stress [103]. In order to attenuate oxidative stress in endothelial cells under I/R injury, several drugs or approaches have been developed. Ginkgolide A (GA) [104] and liraglutide [105] have anti-oxidative properties and could reduce endothelial oxidative stress, attenuating microvascular damage induced by reperfusion. Peroxisome proliferator-activated receptor γ (PPAR- γ) agonist inhibits vascular complications in I/R injury through modulation of oxidative stress and endoplasmic reticulum stress [106]. A histone deacetylase 7-derived peptide maintains

endothelium integrity and promotes angiogenesis in hindlimb ischemia partly through regulation of oxidative stress [107]. Propylene glycol alginate sodium sulfate (PSS) as heparinoid drug has many biological activities. A novel PSS-loaded nanoparticle has been found to normalize oxidative stress and thus reverse coronary microcirculation dysfunction [108,109].

Of note, oxidative stress is associated with altered expression of mitochondrial and nuclear proteins. For instance, it has been demonstrated that oxidative stress increases the activity of COUP-TFII transcription factor, which induces the expression of nuclear-encoded mitochondrial enzymes, favoring mitochondrial fragmentation [110]. Similarly, ROS downregulate the activity of ETC complexes and decrease oxygen consumption in patients with metabolic syndrome, which results in left ventricular hypertrophy and heart failure [111]. Lastly, ROS provoke structural changes in mitochondrial proteins, such as an imbalance between mitochondrial tyrosine kinase Src and phosphatase SPH2, which decreases tyrosine phosphorylation at the active region of many mitochondrial enzymes [112]. In cardiac microvascular I/R injury, inhibition of ROS generation has been found to reverse the transcription and expression of survivin [113], an anti-apoptotic protein.

Last but not least, the deterioration of mtROS is responsible for triggering cell death/loss during cardiac I/R. It is reported that biphasic mtROS dynamics may occur, which include gradual mtROS increase followed by mtROS flash. Of note, baseline mtROS increase and accumulation could be an activation signal for mtROS flash, which has been defined as a well-known and important phenomenon of ROS-induced ROS-release, first described by Zorov et al. in cardiomyocytes [114]. However, this point has not been validated in cardiac microvascular I/R injury. In addition, the molecular mechanism underlying baseline mtROS elevation and accumulation remains unknown.

3. Mitochondrial Fission

Mitochondria are dynamic organelles, not static entities. Mitochondria can undergo replication, fission, and fusion; move from one location to another within cells; and form networks with other mitochondria or cellular structures to increase efficiency of ATP production as well as providing for intracellular signaling in response to physiological and pathological stimuli [115,116]. Increased fusion or reduced fission promotes the formation of elongated mitochondrial networks, whereas increased fission or reduced fusion causes mitochondrial fragmentation [117]. Cells that primarily use mitochondria metabolism to generate ATP, such as cardiomyocytes, have more fusion and more elongated mitochondrial networks [118], whereas the mitochondria in cells that are more glycolytic and less reliant on mitochondria-mediated ATP synthesis, such as microvascular endothelial cells, appear more punctate [119]. Mechanistically, mitochondria undergo membrane remodeling through dynamin-related protein 1 (Drp1) [120]. Drp1 is widely and diffusely disturbed throughout the cytosol under normal condition and translocates to the outer mitochondria membrane when activated via posttranslational modifications (predominantly phosphorylation/dephosphorylation) [121]. Once positioned on the outer mitochondrial membrane, Drp1 interacts with four mitochondrial-bound proteins that serve as Drp1 receptors (mitochondrial dynamic proteins of 49 and 51 kDa (Mid49 and Mid51), mitochondrial fission protein 1 (Fis1), and mitochondrial fission factor (Mff), where it constricts and cleaves the mitochondria [122] (Figure 2).

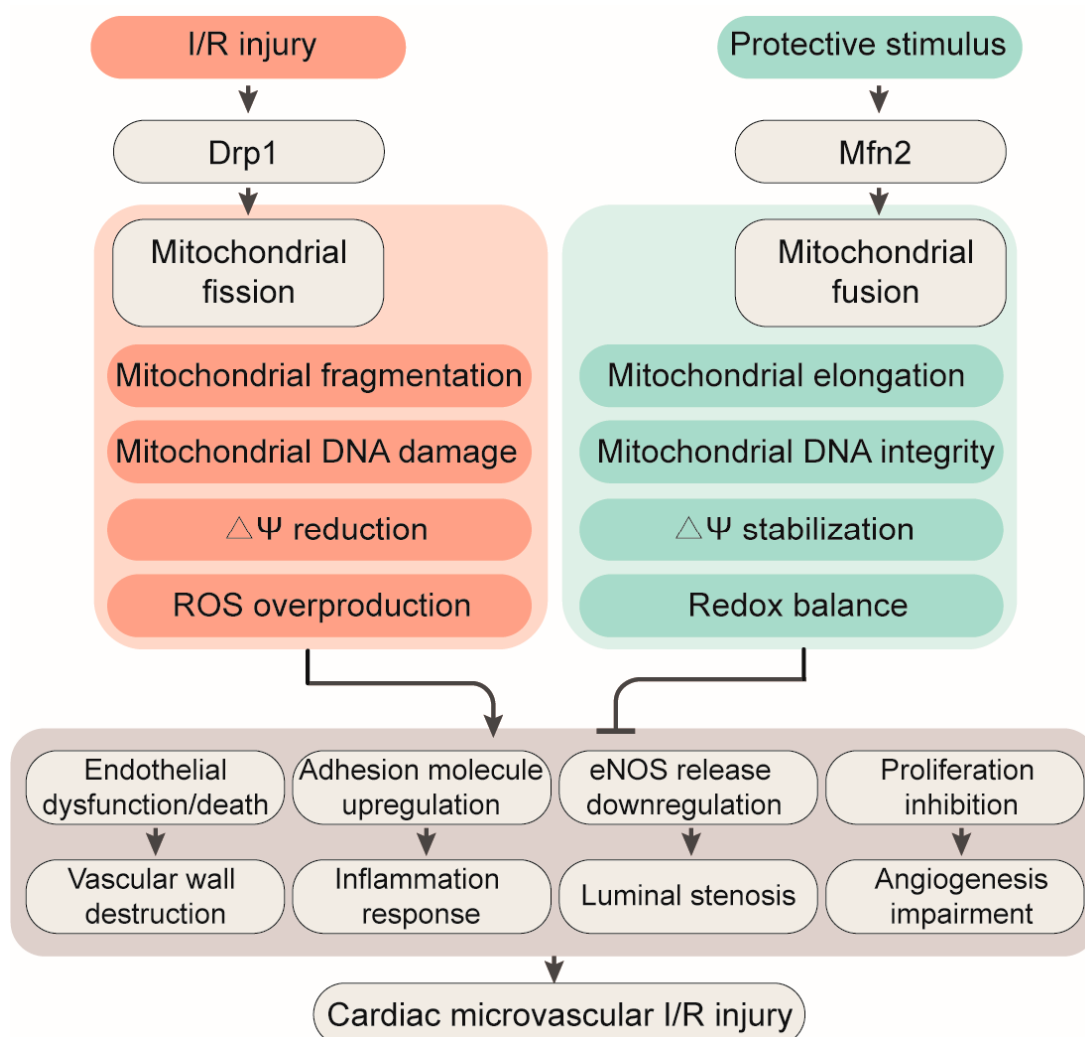


Figure 2. Role of mitochondrial fission and fusion in cardiac microvascular ischemia/reperfusion (I/R) injury. Increased mitochondrial fission is followed by mitochondrial damage, proliferation inhibition, apoptosis, and vascular inflammation. In contrast, mitochondrial fusion increases the resistance of cardiac microcirculation against I/R injury.

Under physiological condition, fission is required for cell division and movement of mitochondria within the cell and is involved in the elimination of senescent mitochondria. Fission is also an adaptive response to cellular stress that facilitates the isolation and removal of damaged mitochondrial components by mitophagy [123,124]. Finally, mitochondrial fission occurs concomitantly with outer membrane permeabilization and release of cytochrome c during apoptosis, although it remains controversial whether fission is a necessary step in mitochondria-dependent apoptosis [125,126]. Under I/R injury, Drp1 is primarily phosphorylated at Ser616 and dephosphorylated at Ser637 [127], resulting in Drp1 accumulation around mitochondria outer membrane to form a potential contractile ring. Although the role of mitochondrial fission in cardiomyocyte I/R injury has been widely explored [128–130], the regulatory mechanisms and functional contributions of fission in endothelial I/R injury remain unclear. Based on recent studies [127,131–136], mitochondrial fission affects endothelial cell fate possibly through three mechanisms. First, excessive mitochondrial fission causes mitochondrial DNA damage, as evidenced by mitochondrial DNA double strand breakage. This effect may blunt mitochondrial DNA copying and transcription. Due to an indispensable role played by mitochondrial DNA in regulating the expression and activity of mitochondrial respiratory complex, mitochondrial DNA damage is associated with mitochondrial respiration dysfunction, leading to

proton leak and ROS formation. Second, the accumulation of mtROS induces mitochondrial lipid oxidation, especially cardiolipin. Peroxidized cardiolipin loses its affinity to cyt-c, resulting in cyt-c detachment from mitochondrial inner membrane, an early marker of cell apoptosis. Third, abnormal mitochondrial fission induces mitochondrial fragmentation, and this effect mediates voltage-dependent anion-selective channel 1 (VDAC1) multimerization, a prerequisite for mPTP opening, which is a feature of mitochondria-initiated cell necrosis or necroptosis. Likely through the above three mechanisms, mitochondrial fission exacerbates endothelial cells' oxidative stress, induces mitochondrial DNA damage, and activates mitochondria-related cell death. Later studies have further found that mitochondrial fission in endothelial cells is activated or inhibited by nuclear receptor subfamily 4 group A member 1 (NR4A1) [135] or Bax inhibitor-1 (BI-1) [131,136], respectively. NR4A1 induces Mff phosphorylation and enhances Drp1 recruitment onto mitochondria [135], leading to mitochondrial fragmentation. In contrast, BI-1 interrupts the ROS-mediated mitochondrial damage and partly blocks mitochondrial fission-induced endothelial cell death [131,136]. However, the relationship between mitochondrial fission and oxidative stress and the threshold of physiological mitosis shift to fatal mitochondrial fission require further investigation.

4. Mitochondrial Fusion

Mitochondria may be separate or found in a network, where permanent dynamic fission and fusion can occur [137]. I/R injury or endothelial oxidative stress may alter mitochondrial shape, movement, and cellular interactions [138]. Mitochondria form a dynamic interconnected intracellular network, changing cellular location through cytoskeletal motors and altering size and shape in response to the metabolic needs of the cells. Fusion is mediated by three different GTPases: Optic atrophy 1 (Opa1), mitofusin 1 (Mfn1), and mitofusin 2 (Mfn2) [139,140] (Figure 2). Both Mfn1 and Mfn2 mediate fusion of the outer mitochondrial membranes [141], while Opa1 mediates the fusion of the inner mitochondrial membrane [142]. Mechanistically, mitofusins interact and form a hemifusion stalk to initiate the joining of two mitochondrial membranes [143]. The stalk then grows and creates a lipidic hole as well as a hemifusion diaphragm to reestablish membrane continuity [144]. Finally, a fusion pore is made for inner membrane fusion via the lipid binding domain in Opa1 that is specific for cardiolipin. Fusion of the inner and outer mitochondrial membrane is regulated through proteolytic cleavage and ubiquitination, respectively [145]. Opa1 consists of eight different isoforms generated by alternative splicing of three of the 30 Opa1 exons. Membrane-bound long Opa1 (L-Opa1) could be processed via two proteolytic cleavage sites (S1 and S2), generating short forms (S-Opa1) [146,147]. Proteolytic processing is carried out predominantly through two intermembrane space AAA proteases (ATPases associated with diverse cellular activities): (i) overlapping with m-AAA (OMA1) cleaving at the S1 site and (ii) yeast mitochondrial DNA escape 1-like (YME1L) cleaving at the S2 site [148–150]. Under normal physiological conditions, S1 and S2 are constitutively cleaved to produce a 50:50 ratio of L-Opa1 and S-Opa1 [151,152]. However, after exposure to stressful conditions, such as mitochondrial membrane depolarization, low levels of ATP, or oxidative stress, the balance is tipped and most L-Opa1 are cleaved by Oma1 resulting in mitochondrial fragmentation [153,154]. With respect to ubiquitin, mitofusins are primarily regulated by ubiquitin-mediated degradation, specifically through the PTEN-induced kinase (PINK1) and Parkin-mediated ubiquitination pathway [155]. This pathway is closely associated with mitophagy and is discussed later in further detail.

Under physiological conditions, fusion and fission are balanced, and mitochondrial networks are present. Fusion facilitates distribution of metabolites, proteins, and mtDNA and helps maintain electrical and biochemical connectivity [156–158]. However, there is little evidence available to describe the precise role played by mitochondrial fusion in microvascular I/R injury. In hyperhomocysteinemia-treated endothelial cells, mitochondrial fission is increased whereas fusion is inhibited, leading to ROS overproduction and endothelial cell death [159]. After ablation of toll-like receptor 4, reverse mitochondrial fusion thus reduces endothelial dysfunction during hyperhomocysteinemia [160]. Fluid mechanical forces have been found to regulate mitochondrial

fusion activity in a manner dependent on intracellular calcium concentration [161]. Considering that fluid shear stress may take place at the initial stage of reperfusion, it is of interest to explore the influence of fluid shear stress on mitochondrial fusion. In a mouse model of type-1 diabetes, the levels of Opa1 are downregulated, indicative of mitochondrial fusion inactivation. Interestingly, administration of ROS scavenger TEMPOL leads to a significant decrease in mitochondrial fragmentation without altering the levels of Opa1 [162]. These results indicate that mitochondrial fusion may play a protective role in regulating endothelial cell function. Further works are required to figure out the primary adaptors underlying mitochondrial fusion regulation in endothelial cells under I/R injury.

5. Mitophagy

Mitochondrial dysfunction causes cell/organ injury through several mechanisms, including diminished cellular energy status (low cellular ATP level, energy stress) and enhanced production of reactive oxygen species (ROS). Furthermore, mitochondrial damage is associated with the release of several apoptosis-activated factors, leading to programmed cell death [163]. Disturbances in ionic balance, particularly an increase in mitochondrial and cytoplasmic Ca^{2+} , stimulates mitochondrial permeability transition (PT) accompanied by the opening of non-selective channels known as the PT pores (PTP) that allow free movement of ions and other solutes with a molecular mass <1.5 kDa across the inner mitochondria membrane (IMM) [4]. As a result, mPTP opening enhances colloid-osmotic pressure in the matrix, leading to mitochondrial swelling associated with the activation of proteases and lipases that eventually lead to cell death [164] (Figure 3).

Mitophagy is the selective degradation of damaged mitochondria by autophagy. In this process, mitochondria are sequestered in autophagosomes and delivered to lysosomes for hydrolytic degradation [165]. Physiologically, mitophagy plays essential roles in development, including the complete removal of damaged mitochondria to keep mitochondrial network homeostasis [166]. Abnormal mitophagy exacerbates mitochondrial damage and cell death through inducing ATP depletion and mitophagy-dependent necrosis or mitophagic cell death [167,168]. Like autophagy, mitophagy shares the core molecular machinery with autophagy, which is initiated by the nucleation of an isolation membrane, and then the isolation membrane elongates and closes to form an autophagosome [169]. The origin of autophagosome membranes still remains controversial whereas autophagosome formation is regulated by two ubiquitin-like conjugation systems [170–172], Atg12-Atg5 and Atg8-PE. However, in contrast to mitophagy, autophagy is considered as a nonselective bulk degradative process where the autophagosomes randomly engulf contents in the cytosol [173,174]. Mitophagy induction and regulation are regulated by receptor-dependent or -independent pathways.

The most recognized mitophagy pathway in mammalian cells is mediated by PINK1 and Parkin, a receptor-independent pathway [175]. PINK1, a serine/threonine kinase, is constitutively imported to the inner membrane through its mitochondrial target sequence. Under normal condition, PINK1 is primarily cleaved by the inner membrane presenilin-associated rhomboid-like protease PARL and ultimately proteolytically degraded [176]. Upon mitochondria damage, such as mitochondrial membrane potential depolarization, PINK1 degradation is suppressed, and thus the full length of PINK1 is accumulated on the mitochondrial outer membrane [177]. Subsequently, PINK1 recruits Parkin from the cytosol to mitochondria [178]. Upon localization onto mitochondria, Parkin ubiquitinates mitochondrial membrane proteins such as mitofusins [179]. p62 is also recruited by Parkin to ubiquitinated mitochondria to promote the delivery of ubiquitinated mitochondria to autophagosome via the binding to LC3. Of note, Parkin can also interact directly with autophagy-regulating proteins such as Ambra1 to facilitate mitophagy [180].

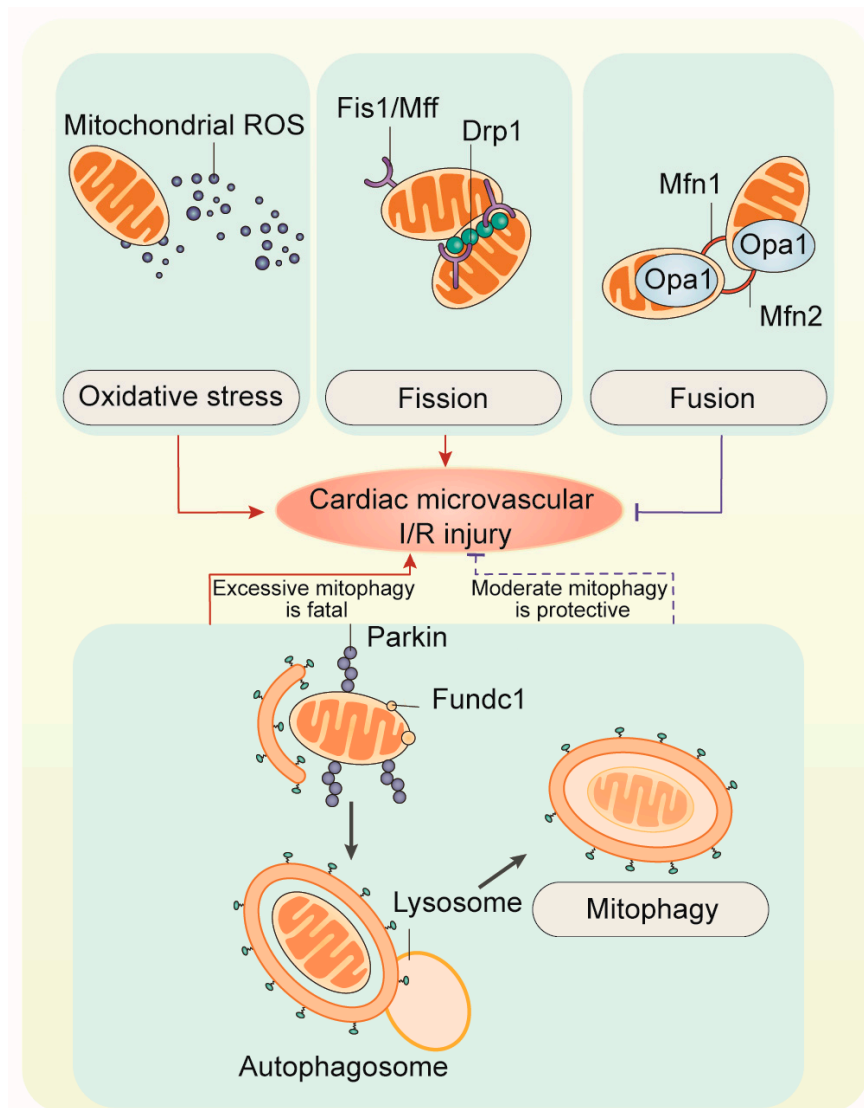


Figure 3. Overview of mitochondrial oxidative stress and mitochondrial dynamics in cardiac microvascular I/R injury. The mitochondrial network is constantly reshaped by the antagonistic activity of proteins that mediate fission, such as mitochondrial fission factor (Mff), mitochondrial fission 1 protein (Fis1), and dynamin 1-like protein (Drp1), and proteins that promote fusion, such as mitofusin 1 (Mfn), Mfn2, and optic atrophy protein 1 (Opa1). One of the essential roles of fission is to segregate dysfunctional mitochondria, thereby enabling their uptake by the autophagic machinery and consequent degradation in lysosomes. Parkin, parkin RBR E3 ubiquitin protein ligase; PINK1, PTEN-induced putative kinase protein 1; Fundc1, Fun14 domain-containing protein 1.

In addition to PINK1/Parkin-mediated mitophagy, receptor-dependent pathways for mitophagy induction include Bnip1, Nix, and Fundc1 [181]. BCL2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3L or Nix) are Bcl2 family proteins with an atypical BH3 domain [182]. Fun14 domain-containing protein 1 (Fundc1) is a mitochondrial outer membrane protein containing a conserved LC3 interaction region (LIR) with a W/Y/FxxL/I/V motif [183]. BNIP3 and Nix were initially identified as pro-death proteins and were recently identified as mitophagy activators in specific conditions. Nix seems indispensable for the complete mitochondrial elimination during reticulocyte maturation [184]. In Nix-deficient mice, mitochondrial clearance in reticulocytes was dramatically inhibited or retarded [184]. Several studies also revealed that Nix deficiency inhibits mitochondrial depolarization, and treatment with uncoupling chemicals (e.g., CCCP) or a BH3 mimetic (e.g., ABT-737) is able to induce mitochondrial depolarization and then restore the

sequestration of mitochondria into autophagosomes in Nix-deficient erythroid cells, suggesting that one mechanism for Nix induced-mitophagy is inducing mitochondrial depolarization [185]. Unlike Nix, BNIP3 and Fundc1 have also been implicated in hypoxia-induced mitophagy [130,135]. Under hypoxia conditions, BNIP3 expression is increased along with translocation onto the surface of mitochondria [130], whereas Fundc1 is primarily dephosphorylated at different sites including Ser13, Ser18, and Tyr17 [41,186–188]. Interestingly, BNIP3-mediated mitophagy is always followed by cell death [130], whereas Fundc1-related mitophagy mitigates cell death through preventing ROS overproduction and mitochondrial depolarization [1,35].

In endothelial cells under I/R injury, mitophagy seems to be modulated by Sirt3 in a manner dependent on PINK1-Parkin pathway [189]. Loss of Sirt3 facilitates angiotensin II-induced aberrant PINK1/Parkin acetylation and impairs mitophagy, and then excessive mtROS generation limits angiogenic capacity in primary mouse cardiac microvascular endothelial cells [189]. Of note, endothelial mitophagy during hypoxia is primarily regulated by endothelial uncoupling protein 2 (Ucp2). Unlike Sirt3, Ucp2 endothelial knockout mice lead to excessive PINK1/Parkin-related mitophagy, inadequate mitochondrial biosynthesis, and increased apoptosis in endothelium [190], suggesting that PINK1/Parkin mitophagy is connected with cell death. Similarly, in cardiac microvascular I/R injury [127], PINK1/Parkin mitophagy is elevated as a result of excessive mitochondrial fission. However, inhibition of fission could alleviate PINK1/Parkin mitophagy and thus promote endothelial cells survival [127]. A parallel study verifies the endothelial protective action exerted by Fundc1-induced mitophagy [135]. Post-transcriptional dephosphorylation of Ser13 could activate Fundc1 mitophagy and enhance the resistance of endothelial cells to reperfusion injury [135]. Taken together, PINK1/Parkin and receptor-dependent mitophagy may have different roles in regulating endothelial cell response to I/R injury through undefined mechanisms. Further studies are necessary to figure out the crosstalk between PINK1/Parkin and Fundc1 in regulating mitophagy activity in cardiac microvascular I/R injury.

6. Conclusion and Future Perspectives

The entire vascular system, from the heart to the smallest capillary, is lined by endothelial cells. A primary purpose of the microcirculation unit is to couple heart metabolic demand with glucose and oxygen delivery through the blood in a manner dependent on the endothelial-dependent vasodilation [191,192]. Of note, endothelial cells in the heart also adjust vascular resistance appropriately to systemic influences, such as blood gases, pH alterations, circulating hormones, blood pressure fluctuation, and shear stress [193,194]. It is now increasingly appreciated that mitochondria serve as the sentinel organelles that are not only capable of detecting insult signals but also orchestrating inflammation responses [195,196]. Mitochondria play an important role in regulating endothelial cell function (Figure 3). Last but not least, when we think about mitochondrial health and disease, the mitochondrial unfolded protein response (UPR^{mt}) has become a hot subject. Although UPR^{mt} is proven to be the downstream event of mitochondrial ROS-mediated oxidative stress including ETC defect and mtDNA damage/mutation, a few studies are available to demonstrate the potential role of UPR^{mt} in endothelial function. Additional investigations are required to describe the molecular mechanism underlying UPR^{mt} in cardiac microvascular I/R injury. The scientific information obtained from mitochondrial dynamics alteration and mitochondrial oxidative stress can be useful for basic and clinically oriented studies, as well as for the development of new diagnostic approaches and tests for cardioprotection strategies.

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References

1. Heusch, G. 25 years of remote ischemic conditioning: From laboratory curiosity to clinical outcome. *Basic Res. Cardiol.* **2018**, *113*, 15. [[CrossRef](#)] [[PubMed](#)]
2. Amanakis, G.; Kleinbongard, P.; Heusch, G.; Skyschally, A. Attenuation of ST-segment elevation after ischemic conditioning maneuvers reflects cardioprotection online. *Basic Res. Cardiol.* **2019**, *114*, 22. [[CrossRef](#)]
3. Deussen, A. Mechanisms underlying coronary autoregulation continue to await clarification. *Basic Res. Cardiol.* **2018**, *113*, 34. [[CrossRef](#)] [[PubMed](#)]
4. Xu, T.; Ding, W.; Ao, X.; Chu, X.; Wan, Q.; Wang, Y.; Xiao, D.; Yu, W.; Li, M.; Yu, F.; et al. ARC regulates programmed necrosis and myocardial ischemia/reperfusion injury through the inhibition of mPTP opening. *Redox Biol.* **2019**, *20*, 414–426. [[CrossRef](#)] [[PubMed](#)]
5. Chen, C.; Zou, L.X.; Lin, Q.Y.; Yan, X.; Bi, H.L.; Xie, X.; Wang, S.; Wang, Q.S.; Zhang, Y.L.; Li, H.H. Resveratrol as a new inhibitor of immunoproteasome prevents PTEN degradation and attenuates cardiac hypertrophy after pressure overload. *Redox Biol.* **2019**, *20*, 390–401. [[CrossRef](#)] [[PubMed](#)]
6. Wu, D.; Hu, Q.; Tan, B.; Rose, P.; Zhu, D.; Zhu, Y.Z. Amelioration of mitochondrial dysfunction in heart failure through S-sulphydration of Ca(2+)/calmodulin-dependent protein kinase II. *Redox Biol.* **2018**, *19*, 250–262. [[CrossRef](#)]
7. Hadebe, N.; Cour, M.; Lecour, S. The SAFE pathway for cardioprotection: Is this a promising target? *Basic Res. Cardiol.* **2018**, *113*, 9. [[CrossRef](#)]
8. Botker, H.E. The changing face after acute myocardial infarction. *Basic Res. Cardiol.* **2019**, *115*, 5. [[CrossRef](#)]
9. Heusch, G. Coronary microvascular obstruction: The new frontier in cardioprotection. *Basic Res. Cardiol.* **2019**, *114*, 45. [[CrossRef](#)]
10. Dassanayaka, S.; Brittian, K.R.; Jurkovic, A.; Higgins, L.A.; Audam, T.N.; Long, B.W.; Harrison, L.T.; Militello, G.; Riggs, D.W.; Chitre, M.G.; et al. E2f1 deletion attenuates infarct-induced ventricular remodeling without affecting O-GlcNAcylation. *Basic Res. Cardiol.* **2019**, *114*, 28. [[CrossRef](#)]
11. Kluge, M.A.; Fetterman, J.L.; Vita, J.A. Mitochondria and endothelial function. *Circ. Res.* **2013**, *112*, 1171–1188. [[CrossRef](#)] [[PubMed](#)]
12. DeLeon-Pennell, K.Y.; Mouton, A.J.; Ero, O.K.; Ma, Y.; Iyer, R.P.; Flynn, E.R.; Espinoza, I.; Musani, S.K.; Vasan, R.S.; Hall, M.E.; et al. LXR/RXR signaling and neutrophil phenotype following myocardial infarction classify sex differences in remodeling. *Basic Res. Cardiol.* **2018**, *113*, 40. [[CrossRef](#)] [[PubMed](#)]
13. Faraci, F.M.; Didion, S.P. Vascular protection: Superoxide dismutase isoforms in the vessel wall. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 1367–1373. [[CrossRef](#)] [[PubMed](#)]
14. Wu, L.; Tan, J.L.; Chen, Z.Y.; Huang, G. Cardioprotection of post-ischemic moderate ROS against ischemia/reperfusion via STAT3-induced the inhibition of MCU opening. *Basic Res. Cardiol.* **2019**, *114*, 39. [[CrossRef](#)]
15. Bateman, R.M.; Sharpe, M.D.; Ellis, C.G. Bench-to-bedside review: Microvascular dysfunction in sepsis-hemodynamics, oxygen transport, and nitric oxide. *Crit. Care* **2003**, *7*, 359–373. [[CrossRef](#)]
16. Wang, J.; Dai, M.; Cao, Q.; Yu, Q.; Luo, Q.; Shu, L.; Zhang, Y.; Bao, M. Carotid baroreceptor stimulation suppresses ventricular fibrillation in canines with chronic heart failure. *Basic Res. Cardiol.* **2019**, *114*, 41. [[CrossRef](#)]
17. Zhang, D.X.; Gutterman, D.D. Mitochondrial reactive oxygen species-mediated signaling in endothelial cells. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *292*, H2023–H2031. [[CrossRef](#)]
18. Bochaton, T.; Claeys, M.J.; Garcia-Dorado, D.; Mewton, N.; Bergerot, C.; Jossan, C.; Amaz, C.; Boussaha, I.; Thibault, H.; Ovize, M. Importance of infarct size versus other variables for clinical outcomes after PPCI in STEMI patients. *Basic Res. Cardiol.* **2019**, *115*, 4. [[CrossRef](#)]
19. Botker, H.E.; Hausenloy, D.; Andreadou, I.; Antonucci, S.; Boengler, K.; Davidson, S.M.; Deshwal, S.; Devaux, Y.; Di Lisa, F.; Di Sante, M.; et al. Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. *Basic Res. Cardiol.* **2018**, *113*, 39. [[CrossRef](#)]

20. Coverstone, E.D.; Bach, R.G.; Chen, L.; Bierut, L.J.; Li, A.Y.; Lenzini, P.A.; O'Neill, H.C.; Spertus, J.A.; Sucharov, C.C.; Stitzel, J.A.; et al. A novel genetic marker of decreased inflammation and improved survival after acute myocardial infarction. *Basic Res. Cardiol.* **2018**, *113*, 38. [[CrossRef](#)]
21. Gaspar, A.; Lourenco, A.P.; Pereira, M.A.; Azevedo, P.; Roncon-Albuquerque, R.J.; Marques, J.; Leite-Moreira, A.F. Randomized controlled trial of remote ischaemic conditioning in ST-elevation myocardial infarction as adjuvant to primary angioplasty (RIC-STEMI). *Basic Res. Cardiol.* **2018**, *113*, 14. [[CrossRef](#)] [[PubMed](#)]
22. Mendieta, G.; Ben-Aicha, S.; Casani, L.; Badimon, L.; Sabate, M.; Vilahur, G. Molecular pathways involved in the cardioprotective effects of intravenous statin administration during ischemia. *Basic Res. Cardiol.* **2019**, *115*, 2. [[CrossRef](#)]
23. Resnic, F.S.; Wainstein, M.; Lee, M.K.; Behrendt, D.; Wainstein, R.V.; Ohno-Machado, L.; Kirshenbaum, J.M.; Rogers, C.D.; Popma, J.J.; Piana, R. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. *Am. Heart J.* **2003**, *145*, 42–46. [[CrossRef](#)] [[PubMed](#)]
24. Audia, J.P.; Yang, X.M.; Crockett, E.S.; Housley, N.; Haq, E.U.; O'Donnell, K.; Cohen, M.V.; Downey, J.M.; Alvarez, D.F. Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y₁₂ receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. *Basic Res. Cardiol.* **2018**, *113*, 32. [[CrossRef](#)]
25. Ndrepepa, G.; Tiroch, K.; Fusaro, M.; Keta, D.; Seyfarth, M.; Byrne, R.A.; Pache, J.; Alger, P.; Mehilli, J.; Schomig, A.; et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J. Am. Coll. Cardiol.* **2010**, *55*, 2383–2389. [[CrossRef](#)] [[PubMed](#)]
26. Bacmeister, L.; Schwarzl, M.; Warnke, S.; Stoffers, B.; Blankenberg, S.; Westermann, D.; Lindner, D. Inflammation and fibrosis in murine models of heart failure. *Basic Res. Cardiol.* **2019**, *114*, 19. [[CrossRef](#)]
27. Davidson, S.M.; Arjun, S.; Basalay, M.V.; Bell, R.M.; Bromage, D.I.; Botker, H.E.; Carr, R.D.; Cunningham, J.; Ghosh, A.K.; Heusch, G.; et al. The 10th Biennial Hatter Cardiovascular Institute workshop: Cellular protection-evaluating new directions in the setting of myocardial infarction, ischaemic stroke, and cardio-oncology. *Basic Res. Cardiol.* **2018**, *113*, 43. [[CrossRef](#)]
28. Cao, T.; Fan, S.; Zheng, D.; Wang, G.; Yu, Y.; Chen, R.; Song, L.S.; Fan, G.C.; Zhang, Z.; Peng, T. Increased calpain-1 in mitochondria induces dilated heart failure in mice: Role of mitochondrial superoxide anion. *Basic Res. Cardiol.* **2019**, *114*, 17. [[CrossRef](#)]
29. Kalyanaraman, B.; Cheng, G.; Hardy, M.; Ouari, O.; Lopez, M.; Joseph, J.; Zielonka, J.; Dwinell, M.B. A review of the basics of mitochondrial bioenergetics, metabolism, and related signaling pathways in cancer cells: Therapeutic targeting of tumor mitochondria with lipophilic cationic compounds. *Redox. Biol.* **2018**, *14*, 316–327. [[CrossRef](#)]
30. Vico, T.A.; Marchini, T.; Ginart, S.; Lorenzetti, M.A.; Adan Arean, J.S.; Calabro, V.; Garces, M.; Ferrero, M.C.; Mazo, T.; D'Annunzio, V.; et al. Mitochondrial bioenergetics links inflammation and cardiac contractility in endotoxemia. *Basic Res. Cardiol.* **2019**, *114*, 38. [[CrossRef](#)]
31. Hao, L.; Sun, Q.; Zhong, W.; Zhang, W.; Sun, X.; Zhou, Z. Mitochondria-targeted ubiquinone (MitoQ) enhances acetaldehyde clearance by reversing alcohol-induced posttranslational modification of aldehyde dehydrogenase 2: A molecular mechanism of protection against alcoholic liver disease. *Redox. Biol.* **2018**, *14*, 626–636. [[CrossRef](#)] [[PubMed](#)]
32. Davidson, S.M. Endothelial mitochondria and heart disease. *Cardiovasc. Res.* **2010**, *88*, 58–66. [[CrossRef](#)] [[PubMed](#)]
33. Edwards, K.S.; Ashraf, S.; Lomax, T.M.; Wiseman, J.M.; Hall, M.E.; Gava, F.N.; Hall, J.E.; Hosler, J.P.; Harmancey, R. Uncoupling protein 3 deficiency impairs myocardial fatty acid oxidation and contractile recovery following ischemia/reperfusion. *Basic Res. Cardiol.* **2018**, *113*, 47. [[CrossRef](#)] [[PubMed](#)]
34. Shen, G.X. Oxidative stress and diabetic cardiovascular disorders: Roles of mitochondria and NADPH oxidase. *Can. J. Physiol. Pharmacol.* **2010**, *88*, 241–248. [[CrossRef](#)]
35. Eid, R.A.; Alkhateeb, M.A.; Eleawa, S.; Al-Hashem, F.H.; Al-Shraim, M.; El-Kott, A.F.; Zaki, M.S.A.; Dallak, M.A.; Aldera, H. Cardioprotective effect of ghrelin against myocardial infarction-induced left ventricular injury via inhibition of SOCS3 and activation of JAK2/STAT3 signaling. *Basic Res. Cardiol.* **2018**, *113*, 13. [[CrossRef](#)]
36. Groschner, L.N.; Waldeck-Weiermair, M.; Malli, R.; Graier, W.F. Endothelial mitochondria-less respiration, more integration. *Pflugers Arch.* **2012**, *464*, 63–76. [[CrossRef](#)]

37. Schoenfeld, J.D.; Sibenaller, Z.A.; Mapuskar, K.A.; Bradley, M.D.; Wagner, B.A.; Buettner, G.R.; Monga, V.; Milhem, M.; Spitz, D.R.; Allen, B.G. Redox active metals and H₂O₂ mediate the increased efficacy of pharmacological ascorbate in combination with gemcitabine or radiation in pre-clinical sarcoma models. *Redox Biol.* **2018**, *14*, 417–422. [[CrossRef](#)]
38. Tai, Y.; Cao, F.; Li, M.; Li, P.; Xu, T.; Wang, X.; Yu, Y.; Gu, B.; Yu, X.; Cai, X.; et al. Enhanced mitochondrial pyruvate transport elicits a robust ROS production to sensitize the antitumor efficacy of interferon-gamma in colon cancer. *Redox Biol.* **2019**, *20*, 451–457. [[CrossRef](#)]
39. Eiringhaus, J.; Herting, J.; Schatter, F.; Nikolaev, V.O.; Sprenger, J.; Wang, Y.; Kohn, M.; Zabel, M.; El-Armouche, A.; Hasenfuss, G.; et al. Protein kinase/phosphatase balance mediates the effects of increased late sodium current on ventricular calcium cycling. *Basic Res. Cardiol.* **2019**, *114*, 13. [[CrossRef](#)]
40. Zhou, H.; Wang, S.; Hu, S.; Chen, Y.; Ren, J. ER-mitochondria microdomains in cardiac ischemia-reperfusion injury: A fresh perspective. *Front. Physiol.* **2018**, *9*, 755. [[CrossRef](#)]
41. Zhou, H.; Ma, Q.; Zhu, P.; Ren, J.; Reiter, R.J.; Chen, Y. Protective role of melatonin in cardiac ischemia-reperfusion injury: From pathogenesis to targeted therapy. *J. Pineal Res.* **2018**, *64*. [[CrossRef](#)] [[PubMed](#)]
42. Zheng, H.; Tie, Y.; Fang, Z.; Wu, X.; Yi, T.; Huang, S.; Liang, X.; Qian, Y.; Wang, X.; Pi, R.; et al. Jumonji domain-containing 6 (JMJD6) identified as a potential therapeutic target in ovarian cancer. *Signal Transduct. Target. Ther.* **2019**, *4*, 24. [[CrossRef](#)] [[PubMed](#)]
43. Gebhard, C.; Maafi, F.; Stahl, B.E.; Dang, J.; Nachar, W.; de Oliveira Moraes, A.B.; Kernalguen, A.E.; Lavoie, V.; Mecteau, M.; Mihalache-Avram, T.; et al. Apolipoprotein A-I proteolysis in aortic valve stenosis: Role of cathepsin S. *Basic Res. Cardiol.* **2018**, *113*, 30. [[CrossRef](#)] [[PubMed](#)]
44. Hofmann, F. A concise discussion of the regulatory role of cGMP kinase I in cardiac physiology and pathology. *Basic Res. Cardiol.* **2018**, *113*, 31. [[CrossRef](#)] [[PubMed](#)]
45. Nanadikar, M.S.; Vergel Leon, A.M.; Borowik, S.; Hillemann, A.; Zieseniss, A.; Belousov, V.V.; Bogeski, I.; Rehling, P.; Dudek, J.; Katschinski, D.M. O₂ affects mitochondrial functionality ex vivo. *Redox Biol.* **2019**, *22*, 101152. [[CrossRef](#)] [[PubMed](#)]
46. Kim, Y.R.; Baek, J.I.; Kim, S.H.; Kim, M.A.; Lee, B.; Ryu, N.; Kim, K.H.; Choi, D.G.; Kim, H.M.; Murphy, M.P.; et al. Therapeutic potential of the mitochondria-targeted antioxidant MitoQ in mitochondrial-ROS induced sensorineural hearing loss caused by Idh2 deficiency. *Redox Biol.* **2019**, *20*, 544–555. [[CrossRef](#)]
47. Alvarez, S.; Valdez, L.B.; Zaobornyj, T.; Boveris, A. Oxygen dependence of mitochondrial nitric oxide synthase activity. *Biochem. Biophys. Res. Commun.* **2003**, *305*, 771–775. [[CrossRef](#)]
48. Ekim Kocabey, A.; Kost, L.; Gehlhar, M.; Rodel, G.; Gey, U. Mitochondrial sco proteins are involved in oxidative stress defense. *Redox Biol.* **2019**, *21*, 101079. [[CrossRef](#)]
49. Tsai, A.G.; Friesenecker, B.; Mazzoni, M.C.; Kerger, H.; Buerk, D.G.; Johnson, P.C.; Intaglietta, M. Microvascular and tissue oxygen gradients in the rat mesentery. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6590–6595. [[CrossRef](#)]
50. Tsai, A.G.; Johnson, P.C.; Intaglietta, M. Oxygen gradients in the microcirculation. *Physiol. Rev.* **2003**, *83*, 933–963. [[CrossRef](#)]
51. Pung, Y.F.; Sam, W.J.; Hardwick, J.P.; Yin, L.; Ohanyan, V.; Logan, S.; Di Vincenzo, L.; Chilian, W.M. The role of mitochondrial bioenergetics and reactive oxygen species in coronary collateral growth. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *305*, H1275–H1280. [[CrossRef](#)] [[PubMed](#)]
52. Kowaltowski, A.J. Strategies to detect mitochondrial oxidants. *Redox Biol.* **2019**, *21*, 101065. [[CrossRef](#)] [[PubMed](#)]
53. Bereiter-Hahn, J.; Voth, M.; Mai, S.; Jendrach, M. Structural implications of mitochondrial dynamics. *Biotechnol. J.* **2008**, *3*, 765–780. [[CrossRef](#)] [[PubMed](#)]
54. Kleinbongard, P.; Skyschally, A.; Gent, S.; Pesch, M.; Heusch, G. STAT3 as a common signal of ischemic conditioning: A lesson on “rigor and reproducibility” in preclinical studies on cardioprotection. *Basic Res. Cardiol.* **2018**, *113*, 3. [[CrossRef](#)]
55. Jensen, P.K. Antimycin-insensitive oxidation of succinate and reduced nicotinamide-adenine dinucleotide in electron-transport particles. I. pH dependency and hydrogen peroxide formation. *Biochim. Biophys. Acta* **1966**, *122*, 157–166. [[CrossRef](#)]
56. Rossello, X.; Yellon, D.M. The RISK pathway and beyond. *Basic Res. Cardiol.* **2018**, *113*, 2. [[CrossRef](#)] [[PubMed](#)]

57. Thomas, S.R.; Witting, P.K.; Drummond, G.R. Redox control of endothelial function and dysfunction: Molecular mechanisms and therapeutic opportunities. *Antioxid. Redox Signal* **2008**, *10*, 1713–1765. [[CrossRef](#)]
58. Schulz, R.; Agg, B.; Ferdinandy, P. Survival pathways in cardiac conditioning: Individual data vs. meta-analyses. What do we learn? *Basic Res. Cardiol.* **2018**, *113*, 4. [[CrossRef](#)]
59. Karwi, Q.G.; Bice, J.S.; Baxter, G.F. Pre- and postconditioning the heart with hydrogen sulfide (H₂S) against ischemia/reperfusion injury in vivo: A systematic review and meta-analysis. *Basic Res. Cardiol.* **2018**, *113*, 6. [[CrossRef](#)]
60. De Bock, K.; Georgiadou, M.; Carmeliet, P. Role of endothelial cell metabolism in vessel sprouting. *Cell Metab.* **2013**, *18*, 634–647. [[CrossRef](#)]
61. Szewczyk, A.; Jarmuszkiewicz, W.; Koziel, A.; Sobieraj, I.; Nobik, W.; Lukasiak, A.; Skup, A.; Bednarczyk, P.; Drabarek, B.; Dymkowska, D.; et al. Mitochondrial mechanisms of endothelial dysfunction. *Pharmacol. Rep.* **2015**, *67*, 704–710. [[CrossRef](#)] [[PubMed](#)]
62. Ye, C.; Brand, D.; Zheng, S.G. Targeting IL-2: An unexpected effect in treating immunological diseases. *Signal Transduct. Target. Ther.* **2018**, *3*, 2. [[CrossRef](#)] [[PubMed](#)]
63. Jones, S.A.; O'Donnell, V.B.; Wood, J.D.; Broughton, J.P.; Hughes, E.J.; Jones, O.T. Expression of phagocyte NADPH oxidase components in human endothelial cells. *Am. J. Physiol.* **1996**, *271*, H1626–H1634. [[CrossRef](#)] [[PubMed](#)]
64. Pichavaram, P.; Mani, A.M.; Singh, N.K.; Rao, G.N. Cholesterol crystals promote endothelial cell and monocyte interactions via H₂O₂-mediated PP2A inhibition, NFκappaB activation and ICAM1 and VCAM1 expression. *Redox Biol.* **2019**, *24*, 101180. [[CrossRef](#)]
65. Li, Y.; Cifuentes-Pagano, E.; DeVallance, E.R.; de Jesus, D.S.; Sahoo, S.; Meijles, D.N.; Koes, D.; Camacho, C.J.; Ross, M.; St Croix, C.; et al. NADPH oxidase 2 inhibitors CPP11G and CPP11H attenuate endothelial cell inflammation & vessel dysfunction and restore mouse hind-limb flow. *Redox Biol.* **2019**, *22*, 101143. [[CrossRef](#)]
66. Graham, N.A.; Tahmasian, M.; Kohli, B.; Komisopoulou, E.; Zhu, M.; Vivanco, I.; Teitell, M.A.; Wu, H.; Ribas, A.; Lo, R.S.; et al. Glucose deprivation activates a metabolic and signaling amplification loop leading to cell death. *Mol. Syst. Biol.* **2012**, *8*, 589. [[CrossRef](#)]
67. Tang, V.; Fu, S.; Rayner, B.S.; Hawkins, C.L. 8-Chloroadenosine induces apoptosis in human coronary artery endothelial cells through the activation of the unfolded protein response. *Redox Biol.* **2019**, *26*, 101274. [[CrossRef](#)]
68. Wu, B.; Pan, X.; Chen, X.; Chen, M.; Shi, K.; Xu, J.; Zheng, J.; Niu, T.; Chen, C.; Shuai, X.; et al. Epigenetic drug library screening identified an LSD1 inhibitor to target UTX-deficient cells for differentiation therapy. *Signal Transduct. Target. Ther.* **2019**, *4*, 11. [[CrossRef](#)]
69. Panieri, E.; Santoro, M.M. ROS signaling and redox biology in endothelial cells. *Cell Mol. Life Sci.* **2015**, *72*, 3281–3303. [[CrossRef](#)]
70. de Jesus, D.S.; DeVallance, E.; Li, Y.; Falabella, M.; Guimaraes, D.; Shiva, S.; Kaufman, B.A.; Gladwin, M.T.; Pagano, P.J. Nox1/Ref-1-mediated activation of CREB promotes Gremlin1-driven endothelial cell proliferation and migration. *Redox Biol.* **2019**, *22*, 101138. [[CrossRef](#)]
71. Butts, B.; Calhoun, D.A.; Denney, T.S., Jr.; Lloyd, S.G.; Gupta, H.; Gaddam, K.K.; Aban, I.; Oparil, S.; Sanders, P.W.; Patel, R.; et al. Plasma xanthine oxidase activity is related to increased sodium and left ventricular hypertrophy in resistant hypertension. *Free Radic. Biol. Medi.* **2019**, *134*, 343–349. [[CrossRef](#)] [[PubMed](#)]
72. Cortese-Krott, M.M.; Mergia, E.; Kramer, C.M.; Luckstadt, W.; Yang, J.; Wolff, G.; Panknin, C.; Bracht, T.; Sitek, B.; Pernow, J.; et al. Identification of a soluble guanylate cyclase in RBCs: Preserved activity in patients with coronary artery disease. *Redox Biol.* **2018**, *14*, 328–337. [[CrossRef](#)] [[PubMed](#)]
73. Ribon-Demars, A.; Pialoux, V.; Boreau, A.; Marcouiller, F.; Lariviere, R.; Bairam, A.; Joseph, V. Protective roles of estradiol against vascular oxidative stress in ovariectomized female rats exposed to normoxia or intermittent hypoxia. *Acta Physiol. (Oxf.)* **2019**, *225*, e13159. [[CrossRef](#)] [[PubMed](#)]
74. Riehle, C.; Bauersachs, J. Of mice and men: Models and mechanisms of diabetic cardiomyopathy. *Basic Res. Cardiol.* **2018**, *114*, 2. [[CrossRef](#)] [[PubMed](#)]

75. Bredemeier, M.; Lopes, L.M.; Eisenreich, M.A.; Hickmann, S.; Bongiorno, G.K.; d'Avila, R.; Morsch, A.L.B.; da Silva Stein, F.; Campos, G.G.D. Xanthine oxidase inhibitors for prevention of cardiovascular events: A systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc. Disord.* **2018**, *18*, 24. [[CrossRef](#)]
76. Daseke, M.J., 2nd; Valerio, F.M.; Kalusche, W.J.; Ma, Y.; DeLeon-Pennell, K.Y.; Lindsey, M.L. Neutrophil proteome shifts over the myocardial infarction time continuum. *Basic Res. Cardiol.* **2019**, *114*, 37. [[CrossRef](#)] [[PubMed](#)]
77. Espinosa-Diez, C.; Miguel, V.; Vallejo, S.; Sanchez, F.J.; Sandoval, E.; Blanco, E.; Cannata, P.; Peiro, C.; Sanchez-Ferrer, C.F.; Lamas, S. Role of glutathione biosynthesis in endothelial dysfunction and fibrosis. *Redox Biol.* **2018**, *14*, 88–99. [[CrossRef](#)]
78. Bernhart, E.; Kogelnik, N.; Prash, J.; Gottschalk, B.; Goeritzer, M.; Depaoli, M.R.; Reicher, H.; Nusshold, C.; Plastira, I.; Hammer, A.; et al. 2-Chlorohexadecanoic acid induces ER stress and mitochondrial dysfunction in brain microvascular endothelial cells. *Redox Biol.* **2018**, *15*, 441–451. [[CrossRef](#)]
79. Jia, Y.; Wang, F.; Guo, Q.; Li, M.; Wang, L.; Zhang, Z.; Jiang, S.; Jin, H.; Chen, A.; Tan, S.; et al. Curcumin induces RIPK1/RIPK3 complex-dependent necroptosis via JNK1/2-ROS signaling in hepatic stellate cells. *Redox Biol.* **2018**, *19*, 375–387. [[CrossRef](#)]
80. Ter Horst, E.N.; Krijnen, P.A.J.; Hakimzadeh, N.; Robbers, L.; Hirsch, A.; Nijveldt, R.; Lommerse, I.; Fontijn, R.D.; Meinster, E.; Delewi, R.; et al. Elevated monocyte-specific type I interferon signalling correlates positively with cardiac healing in myocardial infarct patients but interferon alpha application deteriorates myocardial healing in rats. *Basic Res. Cardiol.* **2018**, *114*, 1. [[CrossRef](#)]
81. Yang, J.; Chen, Z.; Liu, N.; Chen, Y. Ribosomal protein L10 in mitochondria serves as a regulator for ROS level in pancreatic cancer cells. *Redox Biol.* **2018**, *19*, 158–165. [[CrossRef](#)] [[PubMed](#)]
82. Robinson, A.R.; Yousefzadeh, M.J.; Rozgaja, T.A.; Wang, J.; Li, X.; Tilstra, J.S.; Feldman, C.H.; Gregg, S.Q.; Johnson, C.H.; Skoda, E.M.; et al. Spontaneous DNA damage to the nuclear genome promotes senescence, redox imbalance and aging. *Redox Biol.* **2018**, *17*, 259–273. [[CrossRef](#)] [[PubMed](#)]
83. Tymko, M.M.; Tremblay, J.C.; Bailey, D.M.; Green, D.J.; Ainslie, P.N. The impact of hypoxaemia on vascular function in lowlanders and high altitude indigenous populations. *J. Physiol.* **2019**, *597*, 5759–5776. [[CrossRef](#)] [[PubMed](#)]
84. Sultan, C.S.; Saackel, A.; Stank, A.; Fleming, T.; Fedorova, M.; Hoffmann, R.; Wade, R.C.; Hecker, M.; Wagner, A.H. Impact of carbonylation on glutathione peroxidase-1 activity in human hyperglycemic endothelial cells. *Redox Biol.* **2018**, *16*, 113–122. [[CrossRef](#)] [[PubMed](#)]
85. Morell, M.; Burgos, J.I.; Gonano, L.A.; Vila Petroff, M. AMPK-dependent nitric oxide release provides contractile support during hyperosmotic stress. *Basic Res. Cardiol.* **2018**, *113*, 7. [[CrossRef](#)] [[PubMed](#)]
86. Engineer, A.; Saiyin, T.; Greco, E.R.; Feng, Q. Say NO to ROS: Their roles in embryonic heart development and pathogenesis of congenital heart defects in maternal diabetes. *Antioxidants* **2019**, *8*, 436. [[CrossRef](#)]
87. Trieb, M.; Kornej, J.; Knuplez, E.; Hindricks, G.; Thiele, H.; Sommer, P.; Scharnagl, H.; Dages, N.; Dinov, B.; Bollmann, A.; et al. Atrial fibrillation is associated with alterations in HDL function, metabolism, and particle number. *Basic Res. Cardiol.* **2019**, *114*, 27. [[CrossRef](#)]
88. Prasai, P.K.; Shrestha, B.; Orr, A.W.; Pattillo, C.B. Decreases in GSH:GSSG activate vascular endothelial growth factor receptor 2 (VEGFR2) in human aortic endothelial cells. *Redox Biol.* **2018**, *19*, 22–27. [[CrossRef](#)]
89. Malekmohammad, K.; Sewell, R.D.E.; Rafieian-Kopaei, M. Antioxidants and atherosclerosis: Mechanistic aspects. *Biomolecules* **2019**, *9*, 301. [[CrossRef](#)]
90. Munoz, M.; Martinez, M.P.; Lopez-Oliva, M.E.; Rodriguez, C.; Corbacho, C.; Carballido, J.; Garcia-Sacristan, A.; Hernandez, M.; Rivera, L.; Saenz-Medina, J.; et al. Hydrogen peroxide derived from NADPH oxidase 4- and 2 contributes to the endothelium-dependent vasodilatation of intrarenal arteries. *Redox Biol.* **2018**, *19*, 92–104. [[CrossRef](#)]
91. Yellon, D.M.; He, Z.; Khambata, R.; Ahluwalia, A.; Davidson, S.M. The GTN patch: A simple and effective new approach to cardioprotection? *Basic Res. Cardiol.* **2018**, *113*, 20. [[CrossRef](#)] [[PubMed](#)]
92. Tarantini, S.; Valcarcel-Ares, M.N.; Toth, P.; Yabluchanskiy, A.; Tucsek, Z.; Kiss, T.; Hertelendy, P.; Kinter, M.; Ballabh, P.; Sule, Z.; et al. Nicotinamide mononucleotide (NMN) supplementation rescues cerebrovascular endothelial function and neurovascular coupling responses and improves cognitive function in aged mice. *Redox Biol.* **2019**, *24*, 101192. [[CrossRef](#)] [[PubMed](#)]

93. Santin, Y.; Fazal, L.; Sainte-Marie, Y.; Sicard, P.; Maggiorani, D.; Tortosa, F.; Yucel, Y.Y.; Teyssedre, L.; Rouquette, J.; Marcellin, M.; et al. Mitochondrial 4-HNE derived from MAO-A promotes mitoCa(2+) overload in chronic postischemic cardiac remodeling. *Cell Death Differ.* **2019**. [[CrossRef](#)] [[PubMed](#)]
94. Chang, H.C.; Wu, R.; Shang, M.; Sato, T.; Chen, C.; Shapiro, J.S.; Liu, T.; Thakur, A.; Sawicki, K.T.; Prasad, S.V.; et al. Reduction in mitochondrial iron alleviates cardiac damage during injury. *EMBO Mol. Med.* **2016**, *8*, 247–267. [[CrossRef](#)]
95. Trindade, F.; Vitorino, R.; Leite-Moreira, A.; Falcao-Pires, I. Pericardial fluid: An underrated molecular library of heart conditions and a potential vehicle for cardiac therapy. *Basic Res. Cardiol.* **2019**, *114*, 10. [[CrossRef](#)]
96. MacKinney, A.; Woska, E.; Spasojevic, I.; Batinic-Haberle, I.; Zennadi, R. Disrupting the vicious cycle created by NOX activation in sickle erythrocytes exposed to hypoxia/reoxygenation prevents adhesion and vasoocclusion. *Redox Biol.* **2019**, *25*, 101097. [[CrossRef](#)]
97. Gianazza, E.; Brioschi, M.; Fernandez, A.M.; Banfi, C. Lipoxidation in cardiovascular diseases. *Redox Biol.* **2019**, *23*, 101119. [[CrossRef](#)] [[PubMed](#)]
98. Liang, S.; Ren, K.; Li, B.; Li, F.; Liang, Z.; Hu, J.; Xu, B.; Zhang, A. LncRNA SNHG1 alleviates hypoxia-reoxygenation-induced vascular endothelial cell injury as a competing endogenous RNA through the HIF-1alpha/VEGF signal pathway. *Mol. Cell Biochem.* **2019**. [[CrossRef](#)]
99. Zhang, H.F.; Wang, Y.L.; Tan, Y.Z.; Wang, H.J.; Tao, P.; Zhou, P. Enhancement of cardiac lymphangiogenesis by transplantation of CD34(+)VEGFR-3(+) endothelial progenitor cells and sustained release of VEGF-C. *Basic Res. Cardiol.* **2019**, *114*, 43. [[CrossRef](#)]
100. Abdelzaher, W.Y.; Rofaail, R.R.; Ali, D.M.E.; Attya, M.E. Protective effect of dipeptidyl peptidase-4 inhibitors in testicular torsion/detorsion in rats: A possible role of HIF-1alpha and nitric oxide. *Naunyn Schmiedebergs Arch. Pharmacol.* **2019**. [[CrossRef](#)]
101. Abd Al Haleem, E.N.; Ahmed, S.F.; Temraz, A.; El-Tantawy, W.H. Evaluation of the cardioprotective effect of casuarina suberosa extract in rats. *Drug Chem. Toxicol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
102. Nepstad, I.; Hatfield, K.J.; Gronningsaeter, I.S.; Aasebo, E.; Hernandez-Valladares, M.; Hagen, K.M.; Rye, K.P.; Berven, F.S.; Selheim, F.; Reikvam, H.; et al. Effects of insulin and pathway inhibitors on the PI3K-Akt-mTOR phosphorylation profile in acute myeloid leukemia cells. *Signal Transduct. Target. Ther.* **2019**, *4*, 20. [[CrossRef](#)] [[PubMed](#)]
103. Abdel-Magied, N.; Shedid, S.M. Impact of zinc oxide nanoparticles on thioredoxin-interacting protein and asymmetric dimethylarginine as biochemical indicators of cardiovascular disorders in gamma-irradiated rats. *Environ. Toxicol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
104. You, W.; Wu, Z.; Ye, F.; Wu, X. Ginkgolide A protects adverse cardiac remodeling through enhancing antioxidation and nitric oxide utilization in mice with pressure overload. *Pharmazie* **2019**, *74*, 698–702. [[CrossRef](#)] [[PubMed](#)]
105. Helmstadter, J.; Frenis, K.; Filippou, K.; Grill, A.; Dib, M.; Kalinovic, S.; Pawelke, F.; Kus, K.; Kroller-Schon, S.; Oelze, M.; et al. Endothelial GLP-1 (Glucagon-Like Peptide 1) receptor mediates cardiovascular protection by liraglutide in mice with experimental arterial hypertension. *Arterioscler. Thromb. Vasc. Biol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
106. Soliman, E.; Behairy, S.F.; El-Maraghy, N.N.; Elshazly, S.M. PPAR-gamma agonist, pioglitazone, reduced oxidative and endoplasmic reticulum stress associated with L-NAME-induced hypertension in rats. *Life Sci.* **2019**, *239*, 117047. [[CrossRef](#)]
107. Yang, J.; Moraga, A.; Xu, J.; Zhao, Y.; Luo, P.; Lao, K.H.; Margariti, A.; Zhao, Q.; Ding, W.; Wang, G.; et al. A histone deacetylase 7-derived peptide promotes vascular regeneration via facilitating 14-3-3gamma phosphorylation. *Stem Cell Res. Ther.* **2019**. [[CrossRef](#)]
108. Mao, Y.; Hu, Y.; Feng, W.; Yu, L.; Li, P.; Cai, B.; Li, C.; Guan, H. Effects and mechanisms of PSS-loaded nanoparticles on coronary microcirculation dysfunction in streptozotocin-induced diabetic cardiomyopathy rats. *Biomed. Pharmacother.* **2020**, *121*, 109280. [[CrossRef](#)]
109. Rozengurt, E.; Sinnott-Smith, J.; Eibl, G. Yes-associated protein (YAP) in pancreatic cancer: At the epicenter of a targetable signaling network associated with patient survival. *Signal Transduct. Target. Ther.* **2018**, *3*, 11. [[CrossRef](#)]
110. Wu, S.P.; Kao, C.Y.; Wang, L.; Creighton, C.J.; Yang, J.; Donti, T.R.; Harmancey, R.; Vasquez, H.G.; Graham, B.H.; Bellen, H.J.; et al. Increased COUP-TFII expression in adult hearts induces mitochondrial dysfunction resulting in heart failure. *Nat. Commun.* **2015**, *6*, 8245. [[CrossRef](#)]

111. Sverdlov, A.L.; Elezaby, A.; Qin, F.; Behring, J.B.; Luptak, I.; Calamaras, T.D.; Siwik, D.A.; Miller, E.J.; Liesa, M.; Shirihai, O.S.; et al. Mitochondrial Reactive Oxygen Species Mediate Cardiac Structural, Functional, and Mitochondrial Consequences of Diet-Induced Metabolic Heart Disease. *J. Am. Heart Assoc.* **2016**, *5*. [[CrossRef](#)] [[PubMed](#)]
112. Yao, X.; Carlson, D.; Sun, Y.; Ma, L.; Wolf, S.E.; Minei, J.P.; Zang, Q.S. Mitochondrial ROS Induces cardiac Inflammation via a pathway through mtDNA damage in a pneumonia-related sepsis model. *PLoS ONE* **2015**, *10*, e0139416. [[CrossRef](#)] [[PubMed](#)]
113. Zhang, Y.; Zhou, H.; Wu, W.; Shi, C.; Hu, S.; Yin, T.; Ma, Q.; Han, T.; Zhang, Y.; Tian, F.; et al. Liraglutide protects cardiac microvascular endothelial cells against hypoxia/reoxygenation injury through the suppression of the SR-Ca(2+)-XO-ROS axis via activation of the GLP-1R/PI3K/Akt/survivin pathways. *Free Radic. Biol. Med.* **2016**, *95*, 278–292. [[CrossRef](#)] [[PubMed](#)]
114. Zorov, D.B.; Filburn, C.R.; Klotz, L.O.; Zweier, J.L.; Sollott, S.J. Reactive oxygen species (ROS)-induced ROS release: A new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. *J. Exp. Med.* **2000**, *192*, 1001–1014. [[CrossRef](#)] [[PubMed](#)]
115. Makrecka-Kuka, M.; Liepinsh, E.; Murray, A.J.; Lemieux, H.; Dambrova, M.; Tepp, K.; Puurand, M.; Kaambre, T.; Han, W.H.; de Goede, P.; et al. Altered mitochondrial metabolism in the insulin resistant heart. *Acta Physiol. (Oxf.)* **2019**, e13430. [[CrossRef](#)] [[PubMed](#)]
116. Shrum, S.; Rusch, N.J.; MacMillan-Crow, L.A. Specific BK channel activator NS11021 protects rat renal proximal tubular cells from cold storage-induced mitochondrial injury in vitro. *Biomolecules* **2019**, *9*, 825. [[CrossRef](#)]
117. Breda, C.N.S.; Davanzo, G.G.; Basso, P.J.; Saraiva Camara, N.O.; Moraes-Vieira, P.M.M. Mitochondria as central hub of the immune system. *Redox Biol.* **2019**, *26*, 101255. [[CrossRef](#)]
118. Tian, R.; Colucci, W.S.; Arany, Z.; Bachschmid, M.M.; Ballinger, S.W.; Boudina, S.; Bruce, J.E.; Busija, D.W.; Dikalov, S.; Dorn, G.W.; et al. Unlocking the secrets of mitochondria in the cardiovascular system: Path to a cure in heart failure—A report from the 2018 National Heart, Lung, and Blood Institute Workshop. *Circulation* **2019**, *140*, 1205–1216. [[CrossRef](#)]
119. Boyman, L.; Karbowski, M.; Lederer, W.J. Regulation of mitochondrial ATP production: Ca(2+) signaling and quality control. *Trends Mol. Med.* **2019**. [[CrossRef](#)] [[PubMed](#)]
120. Morales, P.E.; Arias-Duran, C.; Avalos-Guajardo, Y.; Aedo, G.; Verdejo, H.E.; Parra, V.; Lavandero, S. Emerging role of mitophagy in cardiovascular physiology and pathology. *Mol. Aspects Med.* **2019**. [[CrossRef](#)]
121. Ong, S.B.; Kwek, X.Y.; Katwadi, K.; Hernandez-Resendiz, S.; Crespo-Avilan, G.E.; Ismail, N.I.; Lin, Y.H.; Yap, E.P.; Lim, S.Y.; Ja, K.; et al. Targeting mitochondrial fission using mdivi-1 in a clinically relevant large animal model of acute myocardial infarction: A pilot study. *Int. J. Mol. Sci.* **2019**, *20*, 3972. [[CrossRef](#)]
122. Jhun, B.; Adaniya, S.; Cypress, M.; Yoon, Y. Adrenergic regulation of Drp1-Driven mitochondrial fission in cardiac physio-pathology. *Antioxidants* **2018**, *7*, 195. [[CrossRef](#)] [[PubMed](#)]
123. Zhou, X.L.; Wu, X.; Xu, Q.R.; Zhu, R.R.; Xu, H.; Li, Y.Y.; Liu, S.; Huang, H.; Xu, X.; Wan, L.; et al. Notch1 provides myocardial protection by improving mitochondrial quality control. *J. Cell Physiol.* **2019**, *234*, 11835–11841. [[CrossRef](#)] [[PubMed](#)]
124. Zhou, H.; Wang, S.; Zhu, P.; Hu, S.; Chen, Y.; Ren, J. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. *Redox Biol.* **2018**, *15*, 335–346. [[CrossRef](#)] [[PubMed](#)]
125. Tian, L.; Potus, F.; Wu, D.; Dasgupta, A.; Chen, K.H.; Mewburn, J.; Lima, P.; Archer, S.L. Increased Drp1-Mediated mitochondrial fission promotes proliferation and collagen production by right ventricular fibroblasts in experimental pulmonary arterial hypertension. *Front. Physiol.* **2018**, *9*, 828. [[CrossRef](#)] [[PubMed](#)]
126. Li, R.; Xin, T.; Li, D.; Wang, C.; Zhu, H.; Zhou, H. Therapeutic effect of Sirtuin 3 on ameliorating nonalcoholic fatty liver disease: The role of the ERK-CREB pathway and Bnip3-mediated mitophagy. *Redox Biol.* **2018**, *18*, 229–243. [[CrossRef](#)] [[PubMed](#)]
127. Zhou, H.; Zhang, Y.; Hu, S.; Shi, C.; Zhu, P.; Ma, Q.; Jin, Q.; Cao, F.; Tian, F.; Chen, Y. Melatonin protects cardiac microvasculature against ischemia/reperfusion injury via suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis. *J. Pineal Res.* **2017**, *63*. [[CrossRef](#)]

128. Alam, S.; Abdullah, C.S.; Aishwarya, R.; Miriyala, S.; Panchatcharam, M.; Peretik, J.M.; Orr, A.W.; James, J.; Robbins, J.; Bhuiyan, M.S. Aberrant mitochondrial fission is maladaptive in desmin mutation-induced cardiac proteotoxicity. *J. Am. Heart Assoc.* **2018**, *7*. [[CrossRef](#)]
129. Hoque, A.; Sivakumaran, P.; Bond, S.T.; Ling, N.X.Y.; Kong, A.M.; Scott, J.W.; Bandara, N.; Hernandez, D.; Liu, G.S.; Wong, R.C.B.; et al. Mitochondrial fission protein Drp1 inhibition promotes cardiac mesodermal differentiation of human pluripotent stem cells. *Cell Death Discov.* **2018**, *4*, 39. [[CrossRef](#)]
130. Jin, Q.; Li, R.; Hu, N.; Xin, T.; Zhu, P.; Hu, S.; Ma, S.; Zhu, H.; Ren, J.; Zhou, H. DUSP1 alleviates cardiac ischemia/reperfusion injury by suppressing the Mff-required mitochondrial fission and Bnip3-related mitophagy via the JNK pathways. *Redox Biol.* **2018**, *14*, 576–587. [[CrossRef](#)] [[PubMed](#)]
131. Zhou, H.; Wang, J.; Hu, S.; Zhu, H.; Toanc, S.; Ren, J. BI1 alleviates cardiac microvascular ischemia-reperfusion injury via modifying mitochondrial fission and inhibiting XO/ROS/F-actin pathways. *J. Cell Physiol.* **2019**, *234*, 5056–5069. [[CrossRef](#)] [[PubMed](#)]
132. Zhou, H.; Hu, S.; Jin, Q.; Shi, C.; Zhang, Y.; Zhu, P.; Ma, Q.; Tian, F.; Chen, Y. Mff-Dependent mitochondrial fission contributes to the pathogenesis of cardiac microvasculature Ischemia/Reperfusion injury via induction of mROS-mediated cardiolipin oxidation and HK2/VDAC1 Disassociation-Involved mPTP opening. *J. Am. Heart Assoc.* **2017**, *6*. [[CrossRef](#)] [[PubMed](#)]
133. Hu, S.Y.; Zhang, Y.; Zhu, P.J.; Zhou, H.; Chen, Y.D. Liraglutide directly protects cardiomyocytes against reperfusion injury possibly via modulation of intracellular calcium homeostasis. *J. Geriatr. Cardiol.* **2017**, *14*, 57–66. [[CrossRef](#)]
134. Zhu, H.; Jin, Q.; Li, Y.; Ma, Q.; Wang, J.; Li, D.; Zhou, H.; Chen, Y. Melatonin protected cardiac microvascular endothelial cells against oxidative stress injury via suppression of IP3R-[Ca(2+)]c/VDAC-[Ca(2+)]m axis by activation of MAPK/ERK signaling pathway. *Cell Stress Chaperones* **2018**, *23*, 101–113. [[CrossRef](#)] [[PubMed](#)]
135. Zhou, H.; Wang, J.; Zhu, P.; Zhu, H.; Toan, S.; Hu, S.; Ren, J.; Chen, Y. NR4A1 aggravates the cardiac microvascular ischemia reperfusion injury through suppressing FUNDC1-mediated mitophagy and promoting Mff-required mitochondrial fission by CK2alpha. *Basic Res. Cardiol.* **2018**, *113*, 23. [[CrossRef](#)]
136. Zhou, H.; Shi, C.; Hu, S.; Zhu, H.; Ren, J.; Chen, Y. BI1 is associated with microvascular protection in cardiac ischemia reperfusion injury via repressing Syk-Nox2-Drp1-mitochondrial fission pathways. *Angiogenesis* **2018**, *21*, 599–615. [[CrossRef](#)]
137. Gumeni, S.; Evangelakou, Z.; Tsakiri, E.N.; Scorrano, L.; Trougakos, I.P. Functional wiring of proteostatic and mitostatic modules ensures transient organismal survival during imbalanced mitochondrial dynamics. *Redox Biol.* **2019**, *24*, 101219. [[CrossRef](#)]
138. Marin-Garcia, J.; Akhmedov, A.T. Mitochondrial dynamics and cell death in heart failure. *Heart Fail. Rev.* **2016**, *21*, 123–136. [[CrossRef](#)]
139. Zhang, Y.; Wang, Y.; Xu, J.; Tian, F.; Hu, S.; Chen, Y.; Fu, Z. Melatonin attenuates myocardial ischemia-reperfusion injury via improving mitochondrial fusion/mitophagy and activating the AMPK-OPA1 signaling pathways. *J. Pineal Res.* **2019**, *66*, e12542. [[CrossRef](#)]
140. Eisner, V.; Cupo, R.R.; Gao, E.; Csordas, G.; Slovinsky, W.S.; Paillard, M.; Cheng, L.; Ibeti, J.; Chen, S.R.; Chuprun, J.K.; et al. Mitochondrial fusion dynamics is robust in the heart and depends on calcium oscillations and contractile activity. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E859–E868. [[CrossRef](#)]
141. Hu, L.; Ding, M.; Tang, D.; Gao, E.; Li, C.; Wang, K.; Qi, B.; Qiu, J.; Zhao, H.; Chang, P.; et al. Targeting mitochondrial dynamics by regulating Mfn2 for therapeutic intervention in diabetic cardiomyopathy. *Theranostics* **2019**, *9*, 3687–3706. [[CrossRef](#)] [[PubMed](#)]
142. Wang, Z.; Wang, S.P.; Shao, Q.; Li, P.F.; Sun, Y.; Luo, L.Z.; Yan, X.Q.; Fan, Z.Y.; Hu, J.; Zhao, J.; et al. Brain-derived neurotrophic factor mimetic, 7,8-dihydroxyflavone, protects against myocardial ischemia by rebalancing optic atrophy 1 processing. *Free Radic. Biol. Med.* **2019**, *145*, 187–197. [[CrossRef](#)] [[PubMed](#)]
143. Zhao, L.; Zhuang, J.; Wang, Y.; Zhou, D.; Zhao, D.; Zhu, S.; Pu, J.; Zhang, H.; Yin, M.; Zhao, W.; et al. Propofol ameliorates H9c2 cells apoptosis induced by oxygen glucose deprivation and reperfusion injury via inhibiting high levels of mitochondrial fusion and fission. *Front. Pharmacol.* **2019**, *10*, 61. [[CrossRef](#)] [[PubMed](#)]
144. Siasos, G.; Tsigkou, V.; Kosmopoulos, M.; Theodosiadis, D.; Simantiris, S.; Tagkou, N.M.; Tsimpiktsioglou, A.; Stampoulouglou, P.K.; Oikonomou, E.; Mourouzis, K.; et al. Mitochondria and cardiovascular diseases—from pathophysiology to treatment. *Ann. Transl. Med.* **2018**, *6*, 256. [[CrossRef](#)]

145. Yang, F.; Wu, R.; Jiang, Z.; Chen, J.; Nan, J.; Su, S.; Zhang, N.; Wang, C.; Zhao, J.; Ni, C.; et al. Leptin increases mitochondrial OPA1 via GSK3-mediated OMA1 ubiquitination to enhance therapeutic effects of mesenchymal stem cell transplantation. *Cell Death Dis.* **2018**, *9*, 556. [[CrossRef](#)]
146. Sprenger, H.G.; Langer, T. The good and the bad of mitochondrial breakups. *Trends Cell Biol.* **2019**, *29*, 888–900. [[CrossRef](#)]
147. Romanello, V.; Scalabrin, M.; Albiero, M.; Blaauw, B.; Scorrano, L.; Sandri, M. Inhibition of the Fission Machinery Mitigates OPA1 Impairment in Adult Skeletal Muscles. *Cells* **2019**, *8*, 597. [[CrossRef](#)]
148. Yin, W.; Li, R.; Feng, X.; James Kang, Y. The involvement of cytochrome c oxidase in mitochondrial fusion in primary cultures of neonatal rat cardiomyocytes. *Cardiovasc. Toxicol.* **2018**, *18*, 365–373. [[CrossRef](#)]
149. Anderson, C.J.; Kahl, A.; Fruitman, H.; Qian, L.; Zhou, P.; Manfredi, G.; Iadecola, C. Prohibitin levels regulate OMA1 activity and turnover in neurons. *Cell Death Differ.* **2019**. [[CrossRef](#)]
150. Schulman, J.J.; Szczesniak, L.M.; Bunker, E.N.; Nelson, H.A.; Roe, M.W.; Wagner, L.E., 2nd; Yule, D.I.; Wojcikiewicz, R.J.H. Bok regulates mitochondrial fusion and morphology. *Cell Death Differ.* **2019**, *26*, 2682–2694. [[CrossRef](#)]
151. Ding, M.; Liu, C.; Shi, R.; Yu, M.; Zeng, K.; Kang, J.; Fu, F.; Mi, M. Mitochondrial fusion promoter restores mitochondrial dynamics balance and ameliorates diabetic cardiomyopathy in an Opa1-dependent way. *Acta Physiol. (Oxf.)* **2019**, e13428. [[CrossRef](#)]
152. Hong, Y.; Tak, H.; Kim, C.; Kang, H.; Ji, E.; Ahn, S.; Jung, M.; Kim, H.L.; Lee, J.H.; Kim, W.; et al. RNA binding protein HuD contributes to beta-cell dysfunction by impairing mitochondria dynamics. *Cell Death Differ.* **2019**. [[CrossRef](#)] [[PubMed](#)]
153. Meyer, J.N.; Leuthner, T.C.; Luz, A.L. Mitochondrial fusion, fission, and mitochondrial toxicity. *Toxicology* **2017**, *391*, 42–53. [[CrossRef](#)] [[PubMed](#)]
154. Wu, W.; Zhao, D.; Shah, S.Z.A.; Zhang, X.; Lai, M.; Yang, D.; Wu, X.; Guan, Z.; Li, J.; Zhao, H.; et al. OPA1 overexpression ameliorates mitochondrial cristae remodeling, mitochondrial dysfunction, and neuronal apoptosis in prion diseases. *Cell Death Dis.* **2019**, *10*, 710. [[CrossRef](#)] [[PubMed](#)]
155. Westermann, B. Mitochondrial fusion and fission in cell life and death. *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 872–884. [[CrossRef](#)]
156. Niu, Y.J.; Zhou, W.; Nie, Z.W.; Shin, K.T.; Cui, X.S. Melatonin enhances mitochondrial biogenesis and protects against rotenone-induced mitochondrial deficiency in early porcine embryos. *J. Pineal Res.* **2019**, e12627. [[CrossRef](#)]
157. Boga, J.A.; Caballero, B.; Potes, Y.; Perez-Martinez, Z.; Reiter, R.J.; Vega-Naredo, I.; Coto-Montes, A. Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. *J. Pineal Res.* **2019**, *66*, e12534. [[CrossRef](#)]
158. Wang, Q.; Xu, J.; Li, X.; Liu, Z.; Han, Y.; Xu, X.; Li, X.; Tang, Y.; Liu, Y.; Yu, T.; et al. Sirt3 modulate renal ischemia-reperfusion injury through enhancing mitochondrial fusion and activating the ERK-OPA1 signaling pathway. *J. Cell Physiol.* **2019**, *234*, 23495–23506. [[CrossRef](#)]
159. Jeremic, N.; Weber, G.J.; Tyagi, S.C. Ablation of toll-like receptor 4 mitigates cardiac mitochondrial dysfunction in hyperhomocysteinemia. *Can. J. Physiol. Pharmacol.* **2017**, *95*, 1369–1375. [[CrossRef](#)]
160. Jeremic, N.; Weber, G.J.; Familteva, A.; Metreveli, N.; Tyagi, S.C. Ablation of Toll-like receptor 4 mitigates central blood pressure response during hyperhomocysteinemia. *J. Hypertens.* **2017**, *35*, 2226–2237. [[CrossRef](#)]
161. Scheitlin, C.G.; Nair, D.M.; Crestanello, J.A.; Zweier, J.L.; Alevriadou, B.R. Fluid mechanical forces and endothelial mitochondria: A bioengineering perspective. *Cell Mol. Bioeng.* **2014**, *7*, 483–496. [[CrossRef](#)] [[PubMed](#)]
162. Makino, A.; Scott, B.T.; Dillmann, W.H. Mitochondrial fragmentation and superoxide anion production in coronary endothelial cells from a mouse model of type 1 diabetes. *Diabetologia* **2010**, *53*, 1783–1794. [[CrossRef](#)] [[PubMed](#)]
163. Xie, L.; Huang, W.; Fang, Z.; Ding, F.; Zou, F.; Ma, X.; Tao, J.; Guo, J.; Xia, X.; Wang, H.; et al. CircERCC2 ameliorated intervertebral disc degeneration by regulating mitophagy and apoptosis through miR-182-5p/SIRT1 axis. *Cell Death Dis.* **2019**, *10*, 751. [[CrossRef](#)] [[PubMed](#)]
164. Fu, A.; Hou, Y.; Yu, Z.; Zhao, Z.; Liu, Z. Healthy mitochondria inhibit the metastatic melanoma in lungs. *Int. J. Biol. Sci.* **2019**, *15*, 2707–2718. [[CrossRef](#)]
165. Zhang, J.; Sun, X.; Wang, L.; Wong, Y.K.; Lee, Y.M.; Zhou, C.; Wu, G.; Zhao, T.; Yang, L.; Lu, L.; et al. Artesunate-induced mitophagy alters cellular redox status. *Redox Biol.* **2018**, *19*, 263–273. [[CrossRef](#)]

166. Vistro, W.A.; Zhang, Y.; Bai, X.; Yang, P.; Huang, Y.; Qu, W.; Baloch, A.S.; Wu, R.; Tarique, I.; Chen, Q. In vivo autophagy up-regulation of small intestine enterocytes in chinese soft-shelled turtles during hibernation. *Biomolecules* **2019**, *9*, 682. [[CrossRef](#)]
167. Zhang, Y.; Zhang, M.; Zhu, W.; Yu, J.; Wang, Q.; Zhang, J.; Cui, Y.; Pan, X.; Gao, X.; Sun, H. Succinate accumulation induces mitochondrial reactive oxygen species generation and promotes status epilepticus in the kainic acid rat model. *Redox Biol.* **2020**, *28*, 101365. [[CrossRef](#)]
168. Vazquez-Calvo, C.; Suhm, T.; Buttner, S.; Ott, M. The basic machineries for mitochondrial protein quality control. *Mitochondrion* **2019**, *50*, 121–131. [[CrossRef](#)]
169. Rani, L.; Mondal, A.C. Emerging concepts of mitochondrial dysfunction in Parkinson's disease progression: Pathogenic and therapeutic implications. *Mitochondrion* **2019**, *50*, 25–34. [[CrossRef](#)]
170. Chakraborty, D.; Felzen, V.; Hiebel, C.; Sturner, E.; Perumal, N.; Manicam, C.; Sehn, E.; Grus, F.; Wolfrum, U.; Behl, C. Enhanced autophagic-lysosomal activity and increased BAG3-mediated selective macroautophagy as adaptive response of neuronal cells to chronic oxidative stress. *Redox Biol.* **2019**, *24*, 101181. [[CrossRef](#)]
171. Xiao, W.; Xiong, Z.; Xiong, W.; Yuan, C.; Xiao, H.; Ruan, H.; Song, Z.; Wang, C.; Bao, L.; Cao, Q.; et al. Melatonin/PGC1A/UCP1 promotes tumor slimming and represses tumor progression by initiating autophagy and lipid browning. *J. Pineal Res.* **2019**, *67*, e12607. [[CrossRef](#)] [[PubMed](#)]
172. Zhou, J.; Zhang, L.; Wang, M.; Zhou, L.; Feng, X.; Yu, L.; Lan, J.; Gao, W.; Zhang, C.; Bu, Y.; et al. CPX targeting DJ-1 triggers ROS-induced cell death and protective autophagy in colorectal cancer. *Theranostics* **2019**, *9*, 5577–5594. [[CrossRef](#)] [[PubMed](#)]
173. Vanzo, R.; Bartkova, J.; Merchut-Maya, J.M.; Hall, A.; Bouchal, J.; Dyrskjot, L.; Frankel, L.B.; Gorgoulis, V.; Maya-Mendoza, A.; Jaattela, M.; et al. Autophagy role(s) in response to oncogenes and DNA replication stress. *Cell Death Differ.* **2019**. [[CrossRef](#)] [[PubMed](#)]
174. Guerrero-Gomez, D.; Mora-Lorca, J.A.; Saenz-Narciso, B.; Naranjo-Galindo, F.J.; Munoz-Lobato, F.; Parrado-Fernandez, C.; Goikolea, J.; Cedazo-Minguez, A.; Link, C.D.; Neri, C.; et al. Loss of glutathione redox homeostasis impairs proteostasis by inhibiting autophagy-dependent protein degradation. *Cell Death Differ.* **2019**, *26*, 1545–1565. [[CrossRef](#)]
175. Praharaaj, P.P.; Naik, P.P.; Panigrahi, D.P.; Bhol, C.S.; Mahapatra, K.K.; Patra, S.; Sethi, G.; Bhutia, S.K. Intricate role of mitochondrial lipid in mitophagy and mitochondrial apoptosis: It is implication in cancer therapeutics. *Cell Mol. Life Sci.* **2019**, *76*, 1641–1652. [[CrossRef](#)]
176. Lin, Q.; Li, S.; Jiang, N.; Shao, X.; Zhang, M.; Jin, H.; Zhang, Z.; Shen, J.; Zhou, Y.; Zhou, W.; et al. PINK1-parkin pathway of mitophagy protects against contrast-induced acute kidney injury via decreasing mitochondrial ROS and NLRP3 inflammasome activation. *Redox Biol.* **2019**, *26*, 101254. [[CrossRef](#)]
177. Gustafsson, A.B.; Dorn, G.W., 2nd. Evolving and Expanding the Roles of Mitophagy as a Homeostatic and Pathogenic Process. *Physiol. Rev.* **2019**, *99*, 853–892. [[CrossRef](#)]
178. Yao, L.; Chen, H.; Wu, Q.; Xie, K. Hydrogen-rich saline alleviates inflammation and apoptosis in myocardial I/R injury via PINK-mediated autophagy. *Int. J. Mol. Med.* **2019**, *44*, 1048–1062. [[CrossRef](#)]
179. Bayne, A.N.; Trempe, J.F. Mechanisms of PINK1, ubiquitin and Parkin interactions in mitochondrial quality control and beyond. *Cell Mol. Life Sci.* **2019**, *76*, 4589–4611. [[CrossRef](#)]
180. Van Humbeeck, C.; Cornelissen, T.; Vandenbergh, W. Ambra1: A Parkin-binding protein involved in mitophagy. *Autophagy* **2011**, *7*, 1555–1556. [[CrossRef](#)]
181. Villa, E.; Marchetti, S.; Ricci, J.E. No Parkin Zone: Mitophagy without Parkin. *Trends Cell Biol.* **2018**, *28*, 882–895. [[CrossRef](#)]
182. Naik, P.P.; Birbrair, A.; Bhutia, S.K. Mitophagy-driven metabolic switch reprograms stem cell fate. *Cell Mol. Life Sci.* **2019**, *76*, 27–43. [[CrossRef](#)]
183. Zhou, H.; Zhu, P.; Wang, J.; Toan, S.; Ren, J. DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. *Signal Transduct. Target. Ther.* **2019**, *4*, 56. [[CrossRef](#)]
184. Zhang, J.; Ney, P.A. NIX induces mitochondrial autophagy in reticulocytes. *Autophagy* **2008**, *4*, 354–356. [[CrossRef](#)]
185. Sandoval, H.; Thiagarajan, P.; Dasgupta, S.K.; Schumacher, A.; Prchal, J.T.; Chen, M.; Wang, J. Essential role for Nix in autophagic maturation of erythroid cells. *Nature* **2008**, *454*, 232–235. [[CrossRef](#)]
186. Zhou, H.; Zhu, P.; Guo, J.; Hu, N.; Wang, S.; Li, D.; Hu, S.; Ren, J.; Cao, F.; Chen, Y. Ripk3 induces mitochondrial apoptosis via inhibition of FUNDC1 mitophagy in cardiac IR injury. *Redox Biol.* **2017**, *13*, 498–507. [[CrossRef](#)]

187. Zhou, H.; Du, W.; Li, Y.; Shi, C.; Hu, N.; Ma, S.; Wang, W.; Ren, J. Effects of melatonin on fatty liver disease: The role of NR4A1/DNA-PKcs/p53 pathway, mitochondrial fission, and mitophagy. *J. Pineal Res.* **2018**, *64*. [[CrossRef](#)]
188. Zhou, H.; Zhu, P.; Wang, J.; Zhu, H.; Ren, J.; Chen, Y. Pathogenesis of cardiac ischemia reperfusion injury is associated with CK2alpha-disturbed mitochondrial homeostasis via suppression of FUNDC1-related mitophagy. *Cell Death Differ.* **2018**, *25*, 1080–1093. [[CrossRef](#)]
189. Wei, T.; Huang, G.; Gao, J.; Huang, C.; Sun, M.; Wu, J.; Bu, J.; Shen, W. Sirtuin 3 Deficiency Accelerates Hypertensive Cardiac Remodeling by Impairing Angiogenesis. *J. Am. Heart Assoc.* **2017**, *6*. [[CrossRef](#)]
190. Haslip, M.; Dostanic, I.; Huang, Y.; Zhang, Y.; Russell, K.S.; Jurczak, M.J.; Mannam, P.; Giordano, F.; Erzurum, S.C.; Lee, P.J. Endothelial uncoupling protein 2 regulates mitophagy and pulmonary hypertension during intermittent hypoxia. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 1166–1178. [[CrossRef](#)]
191. Abukar, Y.; Ramchandra, R.; Hood, S.G.; McKinley, M.J.; Booth, L.C.; Yao, S.T.; May, C.N. Increased cardiac sympathetic nerve activity in ovine heart failure is reduced by lesion of the area postrema, but not lamina terminalis. *Basic Res. Cardiol.* **2018**, *113*, 35. [[CrossRef](#)]
192. Aluja, D.; Inserte, J.; Penela, P.; Ramos, P.; Ribas, C.; Iniguez, M.A.; Mayor, F., Jr.; Garcia-Dorado, D. Calcains mediate isoproterenol-induced hypertrophy through modulation of GRK2. *Basic Res. Cardiol.* **2019**, *114*, 21. [[CrossRef](#)]
193. Alvarez-Fernandez, M.; Sanz-Flores, M.; Sanz-Castillo, B.; Salazar-Roa, M.; Partida, D.; Zapatero-Solana, E.; Ali, H.R.; Manchado, E.; Lowe, S.; VanArsdale, T.; et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. *Cell Death Differ.* **2018**, *25*, 828–840. [[CrossRef](#)]
194. Anderton, H.; Bandala-Sanchez, E.; Simpson, D.S.; Rickard, J.A.; Ng, A.P.; Di Rago, L.; Hall, C.; Vince, J.E.; Silke, J.; Liccardi, G.; et al. RIPK1 prevents TRADD-driven, but TNFR1 independent, apoptosis during development. *Cell Death Differ.* **2019**, *26*, 877–889. [[CrossRef](#)]
195. Chen, Y.; Liu, K.; Shi, Y.; Shao, C. The tango of ROS and p53 in tissue stem cells. *Cell Death Differ.* **2018**, *25*, 637–639. [[CrossRef](#)]
196. Fu, L.; Zhang, L. Serotonylation: A novel histone H3 marker. *Signal Transduct. Target. Ther.* **2019**, *4*, 15. [[CrossRef](#)]



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