Regulation of Vascular Function and Inflammation via Cross Talk of Reactive Oxygen and Nitrogen Species from Mitochondria or NADPH Oxidase—Implications for Diabetes Progression

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Abstract: Oxidative stress plays a key role for the development of cardiovascular, metabolic, and neurodegenerative disease. This concept has been proven by using the approach of genetic deletion of reactive oxygen and nitrogen species (RONS) producing, pro-oxidant enzymes as well as by the overexpression of RONS detoxifying, antioxidant enzymes leading to an amelioration of the severity of diseases. Vice versa, the development and progression of cardiovascular diseases is aggravated by overexpression of RONS producing enzymes as well as deletion of RONS detoxifying enzymes. We have previously identified cross talk mechanisms between different sources of RONS, which can amplify the oxidative stress-mediated damage. Here, the pathways and potential mechanisms leading to this cross talk are analyzed in detail and highlighted by selected examples from the current literature and own data including hypoxia, angiotensin II (AT-II)-induced hypertension, nitrate tolerance, aging, and others. The general concept of redox-based activation of RONS sources via “kindling radicals” and enzyme-specific “redox switches” as well as the interaction with redox-sensitive inflammatory pathways are discussed. Here, we present evidence for the existence of such cross talk mechanisms in the setting of diabetes and critically assess their contribution to the severity of diabetic complications.

Keywords: redox cross talk; mitochondria; NADPH oxidase; kindling radicals; oxidative stress; endothelial dysfunction; eNOS uncoupling; low-grade inflammation

1. Introduction

1.1. Reactive Oxygen and Nitrogen Species in the Organism

A molecular proof of the existence of superoxide anion radical (O₂•⁻) formation in the organism was based on the discovery of superoxide dismutases (SODs, mitochondrial Mn-SOD, and cytosolic/extracellular Cu, Zn-SOD) in living organisms by Fridovich and coworkers in the 1960s [1]. The existence of SODs in biological systems also suggests that O₂•⁻ is a harmful species involved in pathophysiological processes and that the expression of SODs is mandatory to protect the organism from oxidative damage by superoxide. Although the degradation product of O₂•⁻, hydrogen peroxide
(H$_2$O$_2$), may confer redox signaling by oxidation of protein thiol groups and act as an important second messenger that is essentially involved in fundamental cellular processes such as eustress [2,3] or cell differentiation/proliferation [4]. Its concentrations need to be tightly controlled by catalase and glutathione peroxidases (GPx) to prevent oxidative stress conditions and exaggerated oxidative damage of cellular structures [5]. Other important physiological functions of hydrogen peroxide comprise the formation of disulfide bonds during “oxidative” protein folding in the endoplasmic reticulum [6,7] and providing the “peroxide tone” for enzymes such as cyclooxygenases [8]. Redox signals by hydrogen peroxide are either directly mediated by sulfoxidation and S-glutathionylation of thiol-dependent enzymes or via modulation of the oxidation state of thiols in peroxiredoxins, thioredoxins, and glutaredoxins that are all interconnected and coupled to their reductases using NAD(P)H as an electron-providing cofactor [9,10]. More examples on hydrogen peroxide-dependent redox signaling are provided in the position paper by the EU-ROS COST Action [11]. The beneficial effects of ROS may also represent the reason why most large-scale clinical trials on antioxidants failed or even turned out negative [12], indicating that unspecific systemic inhibition of ROS formation may inhibit these physiological, beneficial functions of ROS and thereby promote adverse health effects.

In contrast, O$_2^•$− seems to be more harmful than H$_2$O$_2$ since genetic deficiency in Mn-SOD is lethal at the embryonic stage or shortly after birth due to heart failure and neurological disorders [13,14]. The only “real” physiological role of superoxide potentially comprises its role in host defense as Nox2$^{−/−}$ mice [15] and patients with chronic granulomatous disease (Nox gene mutations) [16] are more susceptible to infections. The harmful or antibacterial properties of O$_2^•$− may be explained not only by the high reactivity of O$_2^•$− towards transition metal complexes (e.g., iron–sulfur clusters in mitochondrial proteins of the respiratory chain or the central phosphatase calcineurin) but also by its fast reaction with nitric oxide (•NO) [17,18]. After two decades of intensive research (1970s and 1980s) •NO was identified as the “endothelium-derived relaxing factor” (EDRF), a potent vasodilator by its activation of soluble guanylyl cyclase (sGC) in the smooth muscle, which was a joint effort by the Noble Prize recipients Murad, Ignarro, und Furchgott [19–21]. This discovery changed the negative picture that scientists had of free radicals in biology and helped to understand that these species can also confer cellular redox signaling and thereby act as highly important physiological messenger molecules. The physiological role of •NO as a vasodilator and as a neurotransmitter was extensively reviewed [22–25]. In the 1990s, it became evident that O$_2^•$− reacts with •NO with almost diffusion-controlled kinetics leading to the formation of peroxynitrite (ONOO$^−$) [26], which leaves its footprints in vivo by nitration of protein-bound tyrosine residues [27–29] that can be detected by specific antibodies against 3-nitrotyrosine-positive proteins, e.g., in atherosclerotic plaques [30–32]. The formation of hydroxyl radicals (HO$^•$) is a driving force of the oxidative potential of ONOO$^−$ [33] and its nitrating potential is enhanced in the presence of carbon monoxide [34] or transition metal centers, e.g., of manganese, heme, or heme-thiolate (P450) enzymes [35–40].

In many aspects, O$_2^•$− can be regarded as direct antagonist of •NO [41–43], a concept that was already proven in 1986 by demonstrating that SOD prevents the loss of vasodilatory effects of •NO, formerly known as EDRF, in denuded vessels (Figure 1) [44]. The oxidative degradation of •NO by O$_2^•$− directly contributes to endothelial dysfunction by removal of a potent vasodilator. In addition, the formation of ONOO$^−$ causes oxidative damage of important vascular proteins, e.g., endothelial nitric oxide synthase (eNOS) [45,46], sGC [47], and prostacyclin synthase (PGIS) [48] and thereby contributes to endothelial (vascular) dysfunction [49,50]. Endothelial (vascular) dysfunction of the micro- and macrovascular system also represents a major health risk of diabetic patients [51–53]. The interplay and steady-state levels of O$_2^•$−, •NO, and their reaction product ONOO$^−$ as well as their tight control by antioxidant enzymes largely determine cellular redox state and whether RONS at low concentrations act as messengers in redox signaling or at high concentrations cause oxidative stress and damage of biomolecules (Figure 2) [11].
**Figure 1.** Overview on the simplified model of redox biology in the vascular system. $O_2^{•-}$ was identified as an antagonist of the EDRF (see red inhibitory bar), far before EDRF was widely accepted to be $•NO$ by the famous experiment of Gryglewski, Palmer, and Moncada based on the transfer of the perfusate from bradykinin-stimulated endothelial cell culture to an organ bath with denuded (endothelium-devoid) aortic ring segments [44]. The vasodilatory potency of EDRF coming from the cell culture was increased by addition of SOD to the buffer on the cells conferring dismutation of $O_2^{•-}$ (see green inhibitory bar), supporting the break-down of EDRF by $O_2^{•-}$. From previous work, we know today that $•NO$ and $O_2^{•-}$ react in a diffusion-controlled reaction to form ONOO$^{-}$ [30,31]. Without this reaction, $O_2^{•-}$ is dismutated either by SODs or undergoes spontaneous self-dismutation to form $H_2O_2$, which is largely involved in redox signaling pathways via oxidation of specific thiol residues, or inactivated by catalases (Cat), GPx, or peroxiredoxins (Prx). ONOO$^{-}$ can cause widespread oxidative damage in proteins (tyrosine nitration [3-NT] and methionine sulfoxidation [oxMet]) but also lipids and DNA molecules [54]. Scheme is modified from [41] with permission.
zymatic activities (e.g. Fe^{2+}, M^{2+}, M^{3+}), are NOX, Red. al sources.

High levels (Oxidative stress) lead to the Fenton reaction and hydroxyl radicals with a similar oxidative damage profile as observed for the Fenton reaction. Scheme is significantly modified from [55].

Protonated, ONOO can be degraded by spontaneous isomerization to nitrate or can be activated by xanthine oxidase (XO), an uncoupled NOS (ucNOS), and P450 enzyme side reactions. H_2O_2 homolysis to form the HO• radical (HO•) yields ONOO• (the Haber–Weiss cycle). Hydroxyl radicals cause severe oxidative damage at the protein, lipid, and DNA level. Biological •NO sources are neuronal, endothelial, or inducible NOS as well as the reduction of nitrite from nutritional sources. The diffusion-controlled reaction of •NO with O_2• yields ONOO• anion and is fast enough to even outcompete the extremely fast breakdown of O_2• by SOD.

Kinetic considerations support the formation of ONOO• under physiological and, especially, under pathophysiological conditions. The reported inactivation of SOD isozymes (via nitration/dityrosine formation in SOD2 and damage of the Cu,Zn-complex in SOD1/3) lead to a further increase in O_2• levels in a positive-feedback fashion. The redox signaling mechanisms by ONOO• are similar to those mediated by H_2O_2, but ONOO• (or its conjugated acid) has 100–1000-fold higher reactivity. Once protonated, ONOOH can be degraded by spontaneous isomerization to nitrate or can be activated by homolysis to form the HO• and the nitrogen dioxide (•NO_2) radicals with a similar oxidative damage profile as observed for the Fenton reaction. Scheme is significantly modified from [55].

Figure 2. The major pathways of vascular oxidative stress and redox signaling. Redox signaling is mainly based on H_2O_2 that is formed by breakdown of O_2• via self-dismutation or catalyzed by SODs. Biological O_2• sources are NADPH oxidases (NOX), the mitochondrial respiratory chain (Mito), xanthine oxidase (XO), an uncoupled NOS (ucNOS), and P450 enzyme side reactions. H_2O_2 modulates the thiol/disulfide equilibrium and thereby modifies enzymatic activities (e.g., in zinc-finger-motifs as found in transcription factors). Reaction with thiol groups is also a major route of detoxification for H_2O_2 via peroxiredoxins (Prx), glutaredoxins (Grx), and thioredoxins (Trx) or the low-molecular-weight thiol glutathione (GSH) that may be coupled to the faster reacting selenol in GPx—these systems require energy-consuming recycling by NAD(P)H-coupled reductases, are highly interconnected, and form a complex redox network that also affects thiol groups [9,10]. Decomposition of H_2O_2 is also catalyzed by catalase. Accumulation of H_2O_2 leads to the Fenton reaction and hydroxyl radical (HO•) formation, which is based on the reaction of H_2O_2 with ferrous iron (Fe^{2+}), yielding ferric iron (Fe^{3+}) that is reduced back to ferrous form by O_2• (the sum of these reactions is called the Haber–Weiss cycle). Hydroxyl radicals cause severe oxidative damage at the protein, lipid, and DNA level. Biological •NO sources are neuronal, endothelial, or inducible NOS as well as the reduction of nitrite from nutritional sources. The diffusion-controlled reaction of •NO with O_2• yields ONOO• anion and is fast enough to even outcompete the extremely fast breakdown of O_2• by SOD.

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1.2. Sources of Reactive Oxygen and Nitrogen Species

$O_2^{•−}$ can be formed from different sources such as xanthine oxidase (XO), NOX, ucNOS, and the mitochondrial respiratory chain as well as $H_2O_2$ by specific mitochondrial enzymes such as monoamine oxidase (MAO) or p66$^{Shc}$/cytochrome c complex. As all of these $O_2^{•−}$ sources were extensively reviewed in the past [56], their function and isoforms are only briefly summarized here. XO is a molybdenum/iron enzyme that transfers electrons from hypoxanthine or xanthine (also other substrates, e.g., acetaldehyde) to molecular oxygen to produce $O_2^{•−}$. Two meta-analyses of clinical studies concluded that XO inhibition may be cardioprotective [57,58]. NOX exist in different isoforms NOX1-5 and dual oxidase (DUOX)1-2. They are multiprotein complexes with transmembrane-spanning domains. The catalytic heme subunit transfers electrons from NADPH to molecular oxygen to produce $O_2^{•−}$. Most prominent isoforms are: NOX2, the phagocytic NOX, that is highly regulated by cytokines as well as AT-II via protein kinase C (PKC) and that has a role in inflammation; NOX1 that is highly expressed in the vasculature and regulated comparable to NOX2; and NOX4, the constitutive NOX that produces low levels of $H_2O_2$ for maintenance of essential cellular functions. NOX represent the only source of $O_2^{•−}$ that has no other biological function but to produce $O_2^{•−}$. Therefore, NOX attracted pharmacological interest and provides the basis for therapeutic targeting [56,59], but so far, none of these compounds reached application in the clinics. NOSs exist in different isoforms NOS1-3 (neuronal, inducible, and endothelial NOS). They usually produce •NO by conversion of the substrate L-arginine to L-citrulline by electron transfer from NADPH and reaction of molecular oxygen with the help of the heme-iron and the cofactor tetrahydrobiopterin (BH4). ucNOS isoforms produce $O_2^{•−}$ instead of •NO by electron transfer from NADPH to molecular oxygen, e.g., upon depletion of BH4 or in the absence of L-arginine [49,60]. There is no drug in clinical use for recoupling of NOS but therapeutic targeting of uncoupled eNOS is highly beneficial in various animal models of cardiovascular and metabolic diseases [61]. Based on estimations, up to 1% of the electrons, which are involved in mitochondrial respiration, are transferred to molecular oxygen [62] $O_2^{•−}$ is mainly formed at complex I as well as III [63] and potentially at complex II by reverse electron transport [64]. Mitochondria are a rich source of $O_2^{•−}$, which is also supported by lethality of Mn-SOD deficiency [13,14], and mitochondrial $O_2^{•−}$ formation plays a central role for ischemia/reperfusion damage (e.g., during myocardial infarction (MI) and stroke) [65,66]. Therefore, mitochondria-targeted antioxidants are currently investigated for a number of different diseases, including cardiovascular, neurodegenerative diseases, and diabetes [67–69]. MAO-A/B isoforms are flavoenzymes that catalyze the oxidative deamination of both endogenous and exogenous amines, including neurotransmitters and several drugs [70]. They are located at the outer mitochondrial membrane, produce $H_2O_2$ as a byproduct during normal enzymatic function, and have been investigated for therapy of neuronal disease and myocardial injury [56]. Upon activation and association with cytochrome c, p66$^{Shc}$ represents an important source of $H_2O_2$ in myocardial ischemia/reperfusion but may also contribute to vascular abnormalities associated with diabetes and aging [71]. Of note, although genetic p66$^{Shc}$ deletion mostly conferred antioxidant protective effects, it also plays a role in insulin signaling (which partly depends on a basal physiological reactive oxygen species (ROS) level) and is potentially involved in eustress [71], an endogenous protective preconditioning by mild oxidative stress as introduced above. It is well established that these RONS sources are also activated in the diabetic setting (see Section 3 for experimental and clinical evidence), suggesting that RONS contribute to diabetic cardiovascular and, potentially, other adverse health effects.

1.3. Preclinical/Molecular Proof of a Role of Oxidative Stress for Cardiometabolic Diseases

First evidence for a role of oxidative stress for cardiovascular complications in an experimental model of hypercholesterolemia is based on reports by Harrison and Ohara [72,73]. Later, genetic manipulations (e.g., knockout mice or transgenic overexpressing mice) provided a molecular proof of the involvement of ROS producing or detoxifying enzymes in the onset and progression of these
cardiometabolic diseases (for review see [74]). We here just mention some prominent examples. Genetic deletion of the p47phox (a subunit of NOX2) improved vascular •NO bioavailability in mice with MI, normalized ROS formation, and improved heart function (ejection fraction) as well as mortality after MI by 20% [75]. The cardiovascular complications in an AT-II-induced hypertension model, e.g., increased blood pressure and vascular ROS formation as well as impaired endothelial function, were largely absent in mice with p47phox or Nox1 deficiency [76,77]. In contrast, transgenic mice overexpressing Nox1 [78] and mice with deletion of antioxidant enzymes, e.g., by heterozygous Mm-SOD deficiency (Sod2+/−) [79,80], showed aggravated cardiovascular complications, especially with additional stress conditions. Deletion of the Gpx1 in atherosclerosis-prone apolipoprotein E-deficient (ApoE−/−) mice caused accelerated atherosclerotic plaque formation and enhanced vascular oxidative stress [81], whereas Gpx1 deficiency in wildtype mice resulted in more pronounced aging-associated complications [82]. Transgenic overexpression of GTP-cyclohydrolase-1, the enzyme that is responsible for de novo synthesis of BH4, is associated with improvement of cardiovascular complications in animal models of atherosclerosis [83], hypertension [84], and diabetes [85] by normalizing the coupling state and function of eNOS [86]. Genetic endothelial- or myelomonocytic-specific deficiency of the AMP-activated protein kinase (AMPKfl/flTekcre or LysMcre mice) resulted in endothelial dysfunction, vascular oxidative stress, and inflammation in AT-II-induced hypertension [87,88]. The contribution of oxidative stress to diabetic complications is substantial as demonstrated by the beneficial effects of antioxidant interventions, targeting mitochondrial O2•− formation in diabetic animals that largely prevented the adverse effects of hyperglycemia [89]. These data provide a molecular proof of the crucial role of oxidative stress in causing cardiovascular disease in animals (for review and more examples see [55,74,90–92]).

1.4. Clinical Evidence for a Role of Oxidative Stress in Cardiovascular and Metabolic Diseases

Oxidative stress is a hallmark of all cardiovascular diseases, confers activation of endothelial cells, and thereby facilitates adhesion/infiltration/activation of immune cells [55]. Oxidative stress is known to induce endothelial dysfunction [93] and to accelerate the progression of atherosclerosis [94]. The link between oxidative stress and cardiovascular prognosis is widely accepted and supported by data from large clinical trials. A positive correlation between levels of GPx-1 and cardiovascular event-free survival was reported by a large clinical study (636 subjects) [95]. Additionally, the serum levels of D-ROM (derivatives of reactive oxygen metabolites) that are indicative of ROS formation and the total thiol levels (representative of the total redox state) were strongly and independently associated with all-cause and cardiovascular mortality (10,622 subjects) [96]. The levels of 8-hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage, were increased in patients with cardiovascular disease according to the data of a meta-analysis (1900 subjects) [97]. Additionally, a number of small cohort clinical studies support the concept that endothelial function (measured by flow-mediated dilation (FMD)), which represents a subclinical marker of atherosclerosis and early predictor for cardiovascular events [49,50], correlates with the oxidative stress burden as assessed by vitamin C responsiveness [93], reduced circulating glutathione levels [98], SOD activity or oxidized low-density lipoprotein (oxLDL, oxidative stress marker, and initiator of atherosclerosis), as well as malondialdehyde (MDA) or 8-oxo-deoxyguanosine levels [99]. A detailed review on the impact of oxidative stress on cardiovascular disease development and progression with a detailed list of clinical studies can be found in references [61,74,100,101].

The contribution of oxidative stress to the cardiovascular complications in diabetes is widely accepted [102,103]. A meta-analysis of 33 studies revealed that administration of vitamin D significantly reduced the serum levels of high-sensitivity C-reactive protein (hs-CRP) and MDA levels in diabetic patients, whereas vitamin D treatment increased •NO bioavailability and the levels of reduced glutathione [104]. Although vitamin D is not a classical low-molecular-weight antioxidant compound, its beneficial effects on oxidative stress are more and more recognized [105–108]. A meta-analysis of 12 studies revealed that supplementation with vitamin E was associated with reduced blood glucose and glycated hemoglobin and administration of vitamins C as well as E were associated
with lower MDA levels and higher GPx as well as SOD activity [109]. The ADVANCE Trial revealed that 8-oxo-2’-deoxyguanosine levels were correlated with all-cause and cardiovascular mortality in adults with type 2 diabetes mellitus (T2DM) \( (n = 3766) \) [110]. Likewise, an independent prospective cohort study revealed a correlation of RNA oxidation with all-cause and cardiovascular mortality risk in patients with T2DM [111]. Dapagliflozin therapy conferred better glycemic control, endothelial function, which was associated with lower 8-oxo-2’-deoxyguanosine urine levels in T2DM patients [112]. Oxidative degradation of BH4, the essential eNOS cofactor, was observed in diabetic patients and points to an uncoupled/dysfunctional eNOS, all of which was corrected by acute BH4 infusion [113]. In addition, treatment with the antioxidants lipoic acid or vitamin C normalized endothelial function in diabetic subjects [114]. A population-based study (631 subjects) revealed an association between T2DM and endothelial dysfunction as well as low-grade inflammation providing an explanation for a 43% higher cardiovascular mortality risk for diabetic subjects [115].

Despite the large body of evidence for a role of oxidative stress in disease development and progression, almost all large clinical trials for nonselective antioxidant therapy (mainly vitamins C and E, chronic high dose oral administration) failed to show any health benefit for the treatment of cardiovascular disease [12,116]. Only a few exceptions are published such as the European Prospective Investigation into Cancer (EPIC)-Norfolk study with measurement of vitamin C plasma levels of all participants [117] and small-cohort studies using acute high-dose administration (mainly infusion) of vitamins (reviewed in [49,118]). Additionally, the quite expensive development of the synthetic antioxidant NXY-059 is not an exception and failed to prove benefits in clinical studies with stroke patients [119]. The most likely explanations for the rather disappointing outcome of clinical antioxidant trials so far, previously discussed in very detail but comprise among others, were the limited up-take of classic oral antioxidants in tissues undergoing oxidative stress, access to intracellular sites of ROS production, the limited reactivity towards specific ROS (e.g., H_2O_2 or O_2•¯), and most importantly, interference with essential physiological ROS signaling [12,49,91].

2. Cross talk between Different Sources of RONS

2.1. Interaction of Different RONS Sources—the Concept of “ROS-Triggered ROS Formation”

The concept of “ROS-triggered ROS formation” was first reported for self-amplified mitochondrial ROS formation envisaged by waves of enhanced ROS levels along mitochondrial networks (dysfunctional mitochondria release ROS that stimulate ROS release by neighbored mitochondria) [120]. This concept was extensively reviewed with all mechanistic details by Zorov and colleagues [121]. Later, this concept was extended not only to interaction of NOX and mitochondria in AT-II-mediated preconditioning [122] as well as adverse effects [64] but also to other disease settings and redox processes [92]. Kimura et al. established that AT-II-stimulated NOX-dependent ROS formation in the myocardium confers ischemic preconditioning [122]. These protective effects were blocked by the NOX inhibitor apocynin and blockade of the mitochondrial ATP-sensitive potassium channels (mtK_ATP) in cardiac myocytes by 5-hydroxydecanoate (5-HD). In an editorial to this original paper, Brandes proposed that cytosolic ROS generated by NOX can stimulate mitochondrial ROS formation [123]. The mechanism could be based on activation of mtK_ATP in the mitochondrial membrane by NOX-derived cytosolic ROS with subsequent opening of the permeability transition pore (mPTP, in the figure termed MPT) (Figure 3) [124]. In general, the concept of “kindling radicals” (or also “bonfire” hypothesis) is known for long time [125] and provides an attractive explanation for the activation of secondary ROS sources and functional damage of redox-regulated enzymes such as eNOS [55,126]. In summary, initial formation of ROS (most likely from NADPH oxidases or mitochondria) leads to further oxidative damage of key enzymes such as eNOS via different uncoupling mechanisms (see “redox switches” in Figure 4) [127,128]. The ROS-induced ROS production concept can be extended to almost any kind of source of RONS as almost all of these sources contain “redox switches.” For hypertension, it has been repeatedly shown that genetic deficiency in NADPH oxidase subunits, especially knockout of the phagocytic isoform NOX2 eliminating the superoxide formation from phagocytes, prevents eNOS
uncoupling and endothelial dysfunction [129]. Similar observations on eNOS uncoupling were made in cultured endothelial cells upon challenges with typical biological oxidants such as peroxynitrite or hypochlorous acid as well as in Nox2−/− mice [130]. Accordingly, NOX2 is a likely candidate for the generation of the “kindling radicals.”

The entire process was blocked by the specific mtKATP inhibitor 5-hydroxydecanoate (5-HD). This concept provides an amplification mechanism for AT-II-induced oxidative stress and contribute to AT-II-mediated preconditioning via P38 mitogen-activated protein kinases (p38 MAPK) and c-Jun N-terminal kinase (JNK) pathway. AT1R, angiotensin II type 1 receptor. Modified from [123] and adapted from [92] with permission.

The concept of the interaction (cross talk) of different ROS sources was developed to explain the observation that pharmacological inhibition or genetic deletion of one specific ROS source is in many disease models enough to confer a complete normalization of the disease phenotype (see numerous examples for hypertension and myocardial infarction (MI) in reference [127]). The reports on a complete normalization of hypertensive complications (including higher cardiovascular ROS formation) upon genetic deletion of Nox1, Nox2, or Nox4 as well as pharmacological inhibition of mitochondrial or XO-derived ROS either mean that some of these reports are not correct or that all ROS sources interact in a cross talk fashion and activate each other, with the logical conclusion that inhibition of only one of these sources is enough to prevent oxidative damage and normalize the overall ROS formation [127]. However, the cross talk between different ROS sources was also suggested to play a role in vascular cellular redox signaling, especially when substantial local ROS accumulation is required for redox-triggered processes [135]. The mechanism behind this concept is that each ROS source has so-called “redox switches” that confer activation upon oxidation [90,92,136] (Figure 4).
Although this redox cross talk was initially demonstrated for the NOX2/mitochondrial axis in the setting of hypertension [137-139], nitrate tolerance [140], and aging [79,82,139], it can be extended to other ROS-producing enzymes such as uncoupled eNOS [90,139] and xanthine dehydrogenase/oxidase conversion [64,90] (Figure 4) as well as to other disease settings. Especially, the role of cyclophilin D (CypD), a small redox-sensitive regulator of the mPTP, in the cross talk of mitochondrial ROS and NOX2-dependent ROS formation is meanwhile well established in AT-II-induced hypertension, by prevention of most adverse effects in CypD knockout mice [139,141]. Cysteine 203 in CypD determines the activity of the mPTP regulator CypD, and therefore, represents a redox switch of mPTP which confers higher opening probability of the pore under oxidative stress conditions [142]. In contrast, S-nitrosylation of cysteine 203 prevented H2O2-induced mPTP opening identifying nitric oxide as an antagonist of ROS in this redox process.

Figure 4. Cross talk between different sources of RONS (mitochondria, NOX, XO, and uncoupled NOS). XO originates from oxidative stress-mediated conversion of the xanthine dehydrogenase via oxidation of critical thiols in cysteine535/992 [143,144]. NOS (mainly eNOS) are uncoupled upon oxidative depletion of BH4 [129], S-glutathionylation (-SSG) [145], adverse phosphorylation by PKC [146] or protein tyrosine kinase-2 [147], and other redox switches (reviewed in [90]). Mitochondrial O2**/H2O2 formation is triggered by oxidative stress from all ROS sources (including other damaged/activated mitochondria) via redox-activation of PKC, mitogen-activated protein kinases (MAPK), other kinase pathways, and potential involvement of redox-sensitive mPKC with subsequent p66Hsc, MAO, respiratory complex activation, or impairment of mitochondrial antioxidant defense (reviewed in [127]). Mitochondrial O2**/H2O2 is released to the cytosol via mitochondrial pores and channels (e.g., redox-sensitive mPTP, inner membrane anion channel (IMAC) or aquaporins) or by diffusion due to increased mitochondrial permeability under pro-inflammatory conditions (reviewed in [127]). In the cytosol, these species (along with released calcium) cause activation of redox-sensitive PKC and tyrosine kinases (cSrc) with subsequent activation of NOX and amplification of the cellular oxidative stress [139]. Adapted from [127] with permission.

Ischemia/reperfusion damage is based on mitochondrial ROS formation as a central pathophysiological mechanism [148-150]. Rathore et al. reported a mechanism by which mitochondrial ROS activate PKCe (prevented by chelerythrine and PKCe deletion) with subsequent increase in NOX activity (prevented by apocynin and p47phox deletion) in the setting of hypoxia as a model of ischemia/reperfusion damage (e.g., as observed in myocardial infarction (MI) or stroke) [151]. The authors show that hypoxia activates most likely NOX1 isoform in pulmonary arteries as documented by translocation of p47phox to the plasma membrane. The involvement of mitochondrial ROS formation in this process was proven by lower NADPH activity in Gpx1 overexpressing mice and higher NADPH activity in Gpx1 knockout mice. A cross talk between mitochondria and NOX1 or NOX2 was also shown for cellular starvation [152], nitrate tolerance [140], the aging process [79,82,139,153], AGE/RAGE signaling [154], endotoxemia as a model of sepsis [155], dyspeptic patients with uremic lung injury [156], AsO3 toxicity [157], idiopathic pulmonary fibrosis [158], and tumorigenesis [159]. Even a triple cross

![Diagram](image-url)
talk between NOX4, NOX2, and mitochondria as well as ROS-induced ROS release was described in vascular endothelial growth factor (VEGF) signaling and angiogenesis [160]. Oxidative stress in general and this cross talk in particular have also large impact on cellular calcium homeostasis and mitochondrial function in the diabetic heart [161], similar to the Ca\(^{2+}\)/ROS cross talk previously described in cancer development and progression [162] and cellular function per se [163]. Of note, similar cross talk mechanisms are likely in the setting of diabetes as all major RONS sources are activated under hyperglycemic conditions as reviewed in [92,127] and discussed in detail in Section 3 of the present work.

2.2. Cross Talk of Oxidative Stress and Inflammation

The link between vascular dysfunction and cardiovascular diseases such as arterial hypertension, hypercholesterolemia, and coronary artery disease can be best explained by inflammation [100,128]. Recent data support this tight association between redox regulatory pathways and inflammation via redox activation of immune cells by mitochondrial O\(_2^-\)/H\(_2\)O\(_2\) and the subsequent activation of the phagocytic NOX2 [139,164]. NOX2 is efficiently activated by mitochondrial O\(_2^-\)/H\(_2\)O\(_2\) formation via the before described redox cross talk [90,127], a process that is key to the activation, recruitment, and infiltration of myelomonocytic cells [165,166] and T cells [167]. Likewise, blood pressure in hypertensive humanized mice was normalized when infiltration of immune cells was prevented [168], supporting the concept that inflammatory processes and NOX2 in immune cells are driving vascular dysfunction. This assumption is in accordance with previous observations that the cellular redox state controls the activity and inflammatory potential of macrophages [169,170]. Mitochondrial ROS formation can cause opening of the mPTP, which chronically causes disruption of mitochondria with subsequent unspecific release of (oxidized) mtDNA, a damage-associated molecular pattern (DAMP), leading to “sterile inflammation” [128,171]. Other examples for the redox regulation of inflammatory pathways are redox modifications of mediators of inflammation (e.g., high-mobility group protein 1 (HMGB1), S100 proteins, and damage-associated molecular patterns (DAMPs)) and modulation of transcription factors related to inflammation (e.g., nuclear factor erythroid 2-related factor 2 (NRF2), activator protein 1 (AP-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and hypoxia-inducible factor 1-alpha (HIF-1α)) [128]. A molecular basis for this cross talk between oxidative stress and inflammation was provided by identification of substantial redox regulation of the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome that controls the release of cytokines [172–177], the central organizer of inflammation high-mobility group box 1 (HMGB1) [178–182] and the antibacterial process of neutrophil extracellular traps (NETs) formation [183–188] as well as other processes reviewed in [128]. Another molecular proof of the large impact of oxidative stress on inflammation comes from animal models with genetic knockout of antioxidant defense enzymes, all of which displaying an inflammatory phenotype [100]. The link between (mitochondrial) ROS formation and inflammation [189] also disproved the previous opinion that ROS produced in the mitochondria are only unwanted by-products of oxidative metabolism and put-forward the concept that mitochondrial ROS represent a nexus of cellular homeostasis [184]. An aggravated cross talk between oxidative stress and inflammation may also be expected in the setting of diabetes as oxidative stress is increased and inflammatory markers are upregulated under hyperglycemic conditions as reviewed in [103].

2.3. Glucotoxicity and AGE/RAGE Signaling

Hyperglycemia causes modifications of proteins by nonenzymatic glycosylation, leading to the formation of advanced glycation end products (AGEs) [190], which contribute to endothelial dysfunction [191]. AGE/RAGE signaling in diabetic rats also triggers vascular complications via NOX-induced oxidative stress [192], mitochondrial ROS formation [154], and inflammation with atherosclerosis [193]. Macrophages from gp91phox (Nox2) null mice responded less efficiently to AGE stimulation, whereas cultured endothelial cells showed inflammatory activation by AGE envisaged by vascular cell adhesion molecule 1 (VCAM-1) upregulation [192]. Multiple-antioxidant therapy
prevented higher expression of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and ROS-producing enzymes in a type 1 diabetes mellitus (T1DM) model [194], clearly supporting an association of oxidative stress, inflammation, and diabetic complications. Cardiovascular complications of diabetes are most probably initiated by AGE/RAGE signaling and diacylglycerol (DAG) formation due to higher AT-II levels (reviewed in [195]). Besides these mechanisms, enhanced PKC activity, hexosamine metabolism, and sorbitol production by the polyol pathway most likely contribute to the diabetic phenotype, which is also characterized by increased expression of inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1) [196]. We established correlations between oxidative stress, AGE/RAGE signaling, inflammation, and endothelial function in a model of T2DM (ZDF rats) with empagliflozin (SGLT2 inhibitor) therapy [197], pointing towards vital cross talk between these parameters.

2.4. Other Redox Switches—Link between Oxidative stress, Inflammation, and Vascular Function

The endogenous eNOS inhibitor asymmetric dimethyl arginine (ADMA) activates neutrophils and release of myeloperoxidase (MPO) leading to inhibition of dimethylaminohydrolases (DDAH), the enzyme catalyzing the breakdown of asymmetric dimethyl arginine (ADMA), and endothelial dysfunction [198]. Inhibition of sGC leads to decreased cGMP levels and loss of its anti-inflammatory effects [199,200]. Overall, the redox control of transcription factors of central importance represents a global redox switch that can affect almost all cellular pathways [201]. The sympathetic nervous system is activated under oxidative stress conditions leading to the release of vasoconstrictors (e.g., catecholamines) as demonstrated in different models of hypertension [202–204]. Likewise, the renin–angiotensin–aldosterone system (RAAS) is activated by ROS formation in different models of hypertension [165,205–207] and endothelin-1 generation by oxidative stabilization of its promoter [208]. Prostacyclin synthase (PGIS) is oxidatively inhibited via nitration of tyrosine 430 by ONOO−, whereas peroxide-driven activation of cyclooxygenase-1/2 (COX-1/2) leads to higher prostaglandin endoperoxide (PGH2) levels and cyclooxygenase-2 (COX-2) is oxidatively inhibited via tyrosine nitration, all of which contributes to redox regulation of prostanoid synthesis and vascular tone with relevance for atherosclerosis, diabetes, nitrate tolerance, and sepsis [8,49,209–215]. Additionally, sGC is redox regulated via thiol oxidation and S-nitrosylation, whereas oxidative activation and upregulation of phosphodiesterases lead to enhanced break-down of cGMP, all of which contribute to modulation of the NO/cGMP signaling cascade [47,49,216–220]. There are many prominent examples of well-established S-nitrosation-regulated enzymes such as caspase activity and initiation of apoptosis [221] as well as other examples reviewed elsewhere [222,223]. S-nitrosation per se is highly redox regulated as it requires the interaction of •NO and O2•− [224], and the optimal nitrosative conditions require tight control of the •NO/O2•− ratio (should be 3:1) to generate the potent nitrosating species N2O3 [225]. However, some evidence suggests that S-nitrosylation plays not a central role in redox regulation [226]. There are multiple other redox switches in the cardiovascular system regulating the glycocalyx, thrombosis and coagulation, inflammation, vasoconstrictors such as endothelin-1, fibrosis, calcification, and smooth muscle cell proliferation that are all important for cardiovascular health and disease. It would be beyond the scope of this review to list them all since they are summarized in a previous review [74]. Importantly, many of these alternative redox switches are dysregulated in the setting of diabetes as exemplified by enhanced degradation of the glycocalyx [227], activation of the RAAS as supported by successful medication of diabetic patients with cardiovascular complications with angiotensin-converting enzyme inhibitors or AT1-receptor blockers [228,229], and higher endothelin-1 plasma levels in diabetic patients [230].

3. Evidence for a Cross Talk between Different Sources of ROS in the Setting of Diabetes

There is evidence for activation of multiple ROS sources in the setting of diabetes. Increased NOX1 but not NOX4 expression in the aorta of T1DM rats (streptozotocin (STZ) model) go hand in hand with enhanced eNOS uncoupling, XO activity, and mitochondrial ROS formation [231]. Cardiac
NOX and serum XO activity are increased and NOX1/2 expression as well as eNOS uncoupling (measured by S-glutathionylation) are enhanced in T1DM rats (STZ model), which was partially normalized by treatment with an antioxidant organic nitrate (pentaerythritol tetranitrate, PETN) via nuclear factor erythroid 2-related factor 2 (NRF2) activation [232]. Histone deacetylases HDAC1/2 interact with promoters of Nox isoforms and play a role for NOX upregulation in experimental diabetes, which was prevented by a pan-HDAC inhibitor and aggravated by histone deacetylases 2 (HDAC2) overexpression [233]. NOX activity and expression of subunits p22phox, p67phox, and p47phox were increased in bypass vascular tissues of diabetic patients [234]. T2DM rats display higher NOX activity in leukocytes with increasing hyperglycemia (higher glycated hemoglobin (HbA1c) levels), which was associated with more pronounced mitochondrial oxidative stress (decreased aldehyde dehydrogenase 2 (ALDH-2) activity) and systemic inflammation as well as AGE/RAGE signaling (markers such as C-reactive protein (CRP) and methylglyoxal), all of which was normalized by glucosuria therapy (sodium/glucose cotransporter 2 (SGLT2) inhibition) [197]. Similar observations were also made in a T1DM with sodium/glucose cotransporter 2 (SGLT2) inhibition [235]. Enhanced mitochondrial O$_2^•−$ formation, NADPH oxidase activity in leukocytes (oxidative burst), and inflammatory markers interleukin-6 as well as 3-nitrotyrosine (probably from inducible NOS (iNOS) and ONOO$^−$ formation) were also recently reported (Figure 5) [236].

**Figure 5.** Detection of mitochondria and NOX-derived ROS formation as well as inflammation and

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**A** Superoxide formation in rat heart mitochondria by HPLC

**B** Whole blood oxidative burst with zymosan A stimulus

**C** IL-6 protein in plasma [\% of CTR]
nitro-oxidative stress markers in T1DM rats. (A) The yield of the superoxide-specific mitoSOX oxidation product triphenylphosphonium 2-hydroxy ethidium (2-OH-mito-E⁺) in mitochondrial preparations of diabetic (STZ) and respective control animals. Representative chromatograms are shown for the HPLC-based quantification of 2-OH-mito-E⁺. (B) Detection of ROS formation during oxidative burst in whole blood from diabetic rats. Quantification of ROS formation by L-012 (100 µM) ECL in response to stimulus by zymosan A. Representative kinetic traces are shown for 1 animal per group upon zymosan A (Ctr vs. STZ) stimulation with four technical replicates per data point. (C) Biomarkers of inflammation (IL-6) and oxidative stress by tyrosine nitration (3-NT) were increased in plasma of diabetic rats as compared to control animals. Each data point in the bar graphs represents one animal. * means p < 0.05 versus control. Adapted from [236] with permission under the Creative Commons Attribution License agreement.

T1DM is associated with enhanced Nox1 and Nox2 expression and activity as well as eNOS uncoupling, all of which was prevented by angiotensin-1 receptor blockade [237]. In accordance to our cross talk concept in the setting of diabetes, NADPH oxidases produce the “kindling radicals” leading to uncoupling of eNOS via the above described “redox switches” (e.g., BH4 depletion and S-glutathionylation) and may also contribute to direct dysfunction of eNOS by PKC-dependent phosphorylation of eNOS at Thr495 [55]. Albuminuria, kidney damage, and other major diabetic complications are initiated by NOX- and mitochondria-derived ROS formation with adverse signaling of down-stream kinases, caspases, and redox-sensitive transcription factors [238]. Initial evidence for a cross talk between different sources of ROS in the setting of diabetes comes from the observation that diabetic complications are prevented by specific inhibitors of single ROS sources (Table 1). Unfortunately, targeting the mPTP by CypD knockout in the setting of diabetes did not prevent diabetic renal damage [239], representing a drawback for the hypothesis that we have put forward above. Finally, also a cross talk between oxidative stress and inflammation may be expected in the setting of diabetes, as markers of inflammation are increased in diabetic patients [240,241]. Markers of inflammation and oxidative stress were also substantially decreased by SGLT2 inhibitor therapy in T1DM and T2DM animal models [197,235]. This may be also related to the fact that inflammation and oxidative stress are interconnected by AGE/RAGE signaling [100].

Table 1. Contribution of different ROS sources to the severity of diabetic complications.

| Studies and Major Outcomes | Ref. |
|---------------------------|-----|
| T1DM rats (STZ model) show sevenfold increase in gp91phox (Nox2) mRNA and uncoupled eNOS—diabetic complications were partially normalized by inhibition of PKC by chelerythrine | [242] |
| Genetic deletion of NoxO1 or p47phox reduced blood pressure and prevented diabetes-induced vascular dysfunction | [243] |
| Combined NOX1/4 inhibition with GKT137831 in mice provides dose-dependent reno- and atheroprotection even in established micro- and macrovascular disease | [244] |
| Nox1 deficiency normalized diabetic glomerular DNA damage | [245] |
| NOX1 plays a key role in diabetes mellitus-accelerated atherosclerosis, which can be prevented by siRNA against Nox1 and GKT137831 therapy | [246] |
| Critical role for NOX2 in insulin resistance-related endothelial cell dysfunction as demonstrated by genetic deletion of Nox2 | [247] |
| Nox2 deficiency protects against STZ-induced beta-cell destruction and development of diabetes in mice | [248] |
| Normalization of mitochondrial ROS formation prevents several diabetic complications (glucose-induced activation of protein kinase C, formation of AGEs, sorbitol accumulation, and NFkB activation) | [89] |
| Blocking mitochondrial ROS formation with mitoTEMPO prevented diabetic cardiomyopathy | [249] |
Table 1. Cont.

| Studies and Major Outcomes                                                                 | Ref.   |
|------------------------------------------------------------------------------------------|--------|
| The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by       | [250]  |
| mitophagy in diabetic kidney disease via NRF2/PINK1                                        |        |
| Deletion of p66Shc longevity gene protects against experimental diabetic glomerulopathy by | [251]  |
| preventing diabetes-induced oxidative stress                                              |        |
| Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66Shc gene | [252]  |
| Mammalian life-span determinant p66ShcA mediates obesity-induced insulin resistance        | [253]  |
| MAO-dependent endoplasmic reticulum-mitochondria dysfunction and mast cell degranulation lead to adverse cardiac remodeling in diabetes, which was supported by protective effects of MAO inhibito rparglyline | [254]  |
| Emerging role of MAO as a therapeutic target for cardiovascular disease including treatment of diabetes | [255]  |
| XO is activated in human and experimental T1DM, and the XO inhibitor allopurinol normalizes major diabetic complications | [256]  |
| Atrial remodeling was prevented by allopurinol in diabetic rabbits (alloxan model)         | [257]  |
| XO inhibitor febuxostat exerts an anti-inflammatory action and protects against diabetic nephropathy development in KK-Ay obese diabetic mice | [258]  |
| eNOS gene therapy exacerbates hepatic ischemia-reperfusion injury in diabetes, which was normalized by BH4 or the BH4 precursor sepiapterin providing evidence for eNOS uncoupling | [259]  |
| Oxidation of the zinc–thiolate complex and uncoupling of eNOS by ONOO⁻ as an explanation for endothelial dysfunction in the setting of diabetes | [260]  |
| Overexpression of the BH4-generating enzyme GTP-cyclohydrolase-1 rescues eNOS function in diabetic mice indicating oxidative BH4 depletion in this model | [85]   |

4. Conclusions

With the present review, we want to highlight redox signaling in physiology and disease emphasizing the cross talk of different ROS sources. NOX and mitochondria obviously represent a redox tandem playing a central role in many diseases [92,127]. Redox signaling may become an attractive target for drug development in the future, but its complexity warrants in-depth mechanistic understanding and careful fine-tuning since ROS not only are by-products causing damage but also fulfill essential physiological signaling functions [11]. Especially, the fact that this cross talk is not limited to the interplay of different ROS sources but can be extended to interactions of ROS with inflammatory pathways, AGE/RAGE signaling, vasoconstrictor synthesis, thrombosis/coagulation, and very clearly endothelial function (Figure 6), makes therapeutic targeting complicated. Mitochondria-targeted antioxidants and specific NOX isoform inhibitors constitute promising present and future approaches. Control of mitochondrial channels such as the mPTP or the mtKATP seems to be an attractive therapeutic strategy [65,131], as also considered for treatment of brain disorders [261] and combatting diabetic complications [262]. In addition, the interplay of (mitochondrial) ROS and the NLRP3 inflammasome represents an attractive therapeutic target that needs to be investigated for exploitation in more detail [189]. A number of antioxidant treatments was suggested for the mitochondria/NOX cross talk underlying the complications of idiopathic pulmonary fibrosis, but further evaluation by translational approaches is necessary [158]. Of note, also interfering with the redox cross talk between mitochondria and NOX most likely requires careful fine-tuning since ROS-induced ROS release via this cross talk is also implicated in physiological processes such as flow-mediated dilation (FMD) of microvessels [263].
Figure 6. Extension of the cross talk concept from ROS sources to pathways initiated by hyperglycemia and glucotoxicity (fructose and sorbitol overproduction) such as inflammation (typical diabetic markers in the blue elliptic box), AGE/RAGE signaling (typical AGE members: precursor methylglyoxal and protein adduct N²-(carboxylethyl)-l-lysine), synthesis of vasoconstrictors, regulation of thrombosis, calcification, and vascular function. Typical diabetic ROS and oxidative damage markers are shown in the red elliptic boxes. The major therapeutic targets of current antidiabetic and cardiovascular therapies are reflected by green text boxes. NETs, neutrophil extracellular traps; NLRP3, NLR Family Pyrin Domain Containing 3 inflammasome; HMGB1, high-mobility group box 1; VCAM-1, vascular cell adhesion molecule-1; IL, interleukin; TNF-α, tumor necrosis factor alpha; CD68, cluster of differentiation 68 (macrosialin); 8-isoPG, 8-isoprostane; 8-oxoG, 8-oxoguanine; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; ET-1, endothelin-1; mtROS, mitochondrial ROS; DAMPs, damage-associated molecular patterns; PGs, prostaglandins; ALDH-2, mitochondrial aldehyde dehydrogenase; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; ACE, angiotensin-converting enzyme; AT₁-receptor, angiotensin II type 1 receptor. Significantly modified from [197] under the terms and conditions of the Creative Commons Attribution License.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AGEs | Advanced glycation end products |
| AT-II | Angiotensin II |
| BH4 | Tetrahydrobiopterin |
| CRP | C-reactive protein |
| CypD | Cyclophilin D |
| EDRF | Endothelium-derived relaxing factor |
| eNOS | Endothelial nitric oxide synthase |
| GPx | Glutathione peroxidases |
| H2O2 | Hydrogen peroxide |
| HO• | Hydroxyl radical |
| MDA | Malondialdehyde |
| MAO | Monoamine oxidase |
| MI | Myocardial infarction |
| Mn-SOD | Mitochondrial superoxide dismutase |
| mPTP | Mitochondrial permeability transition pore |
| mtKATP NOX | Mitochondrial ATP-sensitive potassium channels |
| •NO | NADPH oxidases Nitric oxide |
| NOS | Nitric oxide synthase |
| NLRP3 | NLR Family Pyrin Domain Containing 3 |
| O2•− | Superoxide anion radical, superoxide |
| PKC | Protein kinase C |
| RONS | Reactive oxygen and nitrogen species |
| ROS | Reactive oxygen species |
| sGC | Soluble guanylyl cyclase |
| SOD | Superoxide dismutase |
| STZ | Streptozotocin |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| ucNOS | Uncoupled nitric oxide synthase |
| XO | Xanthine oxidase |

References

1. McCord, J.M.; Keele, B.B., Jr.; Fridovich, I. An enzyme-based theory of obligate anaerobiosis: The physiological function of superoxide dismutase. Proc. Natl. Acad. Sci. USA 1971, 68, 1024–1027. [CrossRef] [PubMed]
2. Sies, H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. Redox Biol. 2017, 11, 613–619. [CrossRef] [PubMed]
3. Sies, H.; Berndt, C.; Jones, D.P. Oxidative stress. Annu. Rev. Biochem. 2017, 86, 715–748. [CrossRef] [PubMed]
4. Schroder, K.; Wandzioch, K.; Helmcke, I.; Brandes, R.P. Nox4 acts as a switch between differentiation and proliferation in preadipocytes. Arterioscler. Thromb. Vasc. Biol. 2009, 29, 239–245. [CrossRef] [PubMed]
5. Sies, H. Oxidative stress: A concept in redox biology and medicine. Redox Biol. 2015, 4, 180–183. [CrossRef]
6. Kakihana, T.; Nagata, K.; Sitia, R. Peroxides and peroxidases in the endoplasmic reticulum: Integrating redox homeostasis and oxidative folding. Antioxid. Redox Signal. 2012, 16, 763–771. [CrossRef]
7. Zito, E. ERO1: A protein disulfide oxidase and H2O2 producer. Free Radic. Biol. Med. 2015, 83, 299–304. [CrossRef]
8. Schildknecht, S.; Bachschmid, M.; Ullrich, V. Peroxynitrite provides the peroxide tone for PGHS-2-dependent prostacyclin synthesis in vascular smooth muscle cells. FASEB J. 2005, 19, 1169–1171. [CrossRef]
9. Ahsan, M.K.; Lekli, I.; Ray, D.; Yodoi, J.; Das, D.K. Redox regulation of cell survival by the thioredoxin superfamily: An implication of redox gene therapy in the heart. Antioxid. Redox Signal. 2009, 11, 2741–2758. [CrossRef]
10. Lu, J.; Holmgren, A. The thioredoxin antioxidant system. Free Radic. Biol. Med. 2014, 66, 75–87. [CrossRef]
11. Egea, J.; Fabregat, I.; Frapart, Y.M.; Ghezzi, P.; Gorlach, A.; Kietzmann, T.; Kubaikhuk, K.; Knaus, U.G.; Lopez, M.G.; Olaso-Gonzalez, G.; et al. European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS). Redox Biol. 2017, 13, 94–162. [CrossRef] [PubMed]
12. Schmidt, H.H.; Stocker, R.; Vollbracht, C.; Paulsen, G.; Riley, D.; Daiber, A.; Cuadrado, A. Antioxidants in translational medicine. Antioxid. Redox Signal. 2015, 23, 1130–1143. [CrossRef] [PubMed]
13. Lebovitz, R.M.; Zhang, H.; Vogel, H.; Cartwright, J., Jr.; Dionne, L.; Lu, N.; Huang, S.; Matzuk, M.M. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proc. Natl. Acad. Sci. USA 1996, 93, 9782–9787. [CrossRef] [PubMed]
14. Li, Y.; Huang, T.T.; Carlson, E.J.; Olson, J.L.; Noble, L.J.; Yoshimura, M.P.; Berger, C.; Chan, P.H.; et al. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nat. Genet. 1995, 11, 376–381. [CrossRef] [PubMed]
15. Gao, X.P.; Standiford, T.J.; Rahman, A.; Newstead, M.; Holland, S.M.; Dinauer, M.C.; Liu, Q.H.; Malik, A.B. Role of NADPH oxidase in the mechanism of lung neutrophil sequestration and microvesSEL injury induced by Gram-negative sepsis: Studies in p47phox− and gp91phox−/− mice. J. Immunol. 2002, 168, 3974–3982. [CrossRef]
16. Quie, P.G.; White, J.G.; Holmes, B.; Good, R.A. In vitro bactericidal capacity of human polymorphonuclear leukocytes: Diminished activity in chronic granulomatous disease of childhood. J. Clin. Investig. 1967, 46, 668–679. [CrossRef]
17. Namgaladze, D.; Shcherbyna, I.; Kienhofer, J.; Hofer, H.W.; Ullrich, V. Superoxide targets calcineurin signaling in vascular endothelium. Biochem. Biophys. Res. Commun. 2005, 334, 1061–1067. [CrossRef]
18. Ullrich, V.; Kissner, R. Redox signaling: Bioinorganic chemistry at its best. Nat. Genet. 1995, 11, 376–381. [CrossRef] [PubMed]
19. Furchgott, R.F.; Zawadzki, J.V. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980, 288, 373–376. [CrossRef]
20. Ignarro, L.J.; Buga, G.M.; Wood, K.S.; Byrns, R.E.; Chaudhuri, G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc. Natl. Acad. Sci. USA 1987, 84, 9265–9269. [CrossRef]
21. Arnold, W.P.; Mittal, C.K.; Katsumi, S.; Murad, F. Nitric oxide activates guanylate cyclase and increases guanosine 3′,5′-cyclic monophosphate levels in various tissue preparations. Proc. Natl. Acad. Sci. USA 1977, 74, 3203–3207. [CrossRef] [PubMed]
22. Forstermann, U.; Schmidt, H.H.; Pollock, J.S.; Sheng, H.; Mitchell, J.A.; Warner, T.D.; Nakane, M.; Murad, F. Isoforms of nitric oxide synthase. Characterization and purification from different cell types. Biochem. Pharmacol. 1991, 42, 1849–1857. [CrossRef]
23. Bian, K.; Murad, F. Nitric oxide (NO)—Biogeneration, regulation, and relevance to human diseases. Front. Biosci. J. Virtual Libr. 2003, 8, d264-78. [CrossRef] [PubMed]
24. Ignarro, L.J. Nitric oxide: A unique endogenous signaling molecule in vascular biology. Biosci. Rep. 1999, 19, 51–71. [CrossRef]
25. Ignarro, L.J. Nitric oxide as a unique signaling molecule in the vascular system: A historical overview. J. Physiol. Pharmacol. 2002, 53, 503–514.
26. Kissner, R.; Nauser, T.; Bugnon, P.; Lye, P.G.; Koppenol, W.H. Formation and properties of peroxynitrite as studied by laser flash photolysis, high-pressure stopped-flow technique, and pulse radiolysis. Chem. Res. Toxicol. 1997, 10, 1285–1292. [CrossRef]
27. Crow, J.P.; Beckman, J.S. Reaction between nitric oxide, superoxide, and peroxynitrite: Footprints of peroxynitrite in vivo. Adv. Pharmacol. 1995, 35, 17–43.
28. Radi, R. Nitric oxide, oxidants, and protein tyrosine nitration. Proc. Natl. Acad. Sci. USA 2004, 101, 4003–4008. [CrossRef]
29. Ischiropoulos, H.; Zhu, L.; Chen, J.; Tsai, M.; Martin, J.C.; Smith, C.D.; Beckman, J.S. Peroxynitrite-mediated tyrosine nitration catalyzed by superoxide dismutase. Arch. Biochem. Biophys. 1992, 298, 431–437. [CrossRef]
30. Beckmann, J.S.; Ye, Y.Z.; Anderson, P.G.; Chen, J.; Accavitti, M.A.; Tarpey, M.M.; White, C.R. Extensive nitration of protein tyrosines in human atherosclerosis detected by immunohistochemistry. *Biol. Chem. Hoppe Seyler* 1994, 375, 81–88. [CrossRef]

31. White, C.R.; Brock, T.A.; Chang, L.Y.; Crapo, J.; Briscoe, P.; Ku, D.; Bradley, W.A.; Gianturco, S.H.; Gore, J.; Freeman, B.A.; et al. Superoxide and peroxynitrite in atherosclerosis. *Proc. Natl. Acad. Sci. USA* 1994, 91, 1044–1048. [CrossRef] [PubMed]

32. Zou, M.H.; Leist, M.; Ullrich, V. Selective nitration of prostacyclin synthase and defective vasorelaxation in atherosclerotic bovine coronary arteries. *Am. J. Pathol.* 1999, 154, 1359–1365. [CrossRef]

33. Beckman, J.S.; Beckman, T.W.; Chen, J.; Marshall, P.A.; Freeman, B.A. Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxide. *Proc. Natl. Acad. Sci. USA* 1990, 87, 1620–1624. [CrossRef] [PubMed]

34. Demiconi, A.; Freeman, B.A.; Trujillo, M.; Radi, R. Peroxynitrite reaction with carbon dioxide/bicarbonate: Kinetics and influence on peroxynitrite-mediated oxidations. *Arch. Biochem. Biophys.* 1996, 333, 49–58. [CrossRef]

35. Daiber, A.; Herold, S.; Schoneich, C.; Namgaladze, D.; Peterson, J.A.; Ullrich, V. Nitration and inactivation of cytochrome P450BM-3 by peroxynitrite. Stopped-flow measurements prove ferryl intermediates. *Eur. J. Biochem.* FEBS 2000, 267, 6729–6739. [CrossRef]

36. Daiber, A.; Schoneich, C.; Schmidt, P.; Jung, C.; Ullrich, V. Autocatalytic nitration of P450CAM by peroxynitrite. *J. Inorg. Biochem.* 2000, 81, 213–220. [CrossRef]

37. Daiber, A.; Bachschmid, M.; Beckman, J.S.; Munzel, T.; Ullrich, V. The impact of metal catalysis on protein tyrosine nitration by peroxynitrite. *Biochem. Biophys. Res. Commun.* 2004, 317, 873–881. [CrossRef]

38. MacMillan-Crow, L.A.; Crow, J.P.; Kerby, J.D.; Beckman, J.S.; Thompson, J.A. Nitration and inactivation of manganese superoxide dismutase in chronic rejection of human renal allografts. *Proc. Natl. Acad. Sci. USA* 1996, 93, 11853–11858. [CrossRef]

39. Quijano, C.; Hernandez-Saavedra, D.; Castro, L.; McCord, J.M.; Freeman, B.A.; Radi, R. Reaction of peroxynitrite with Mn-superoxide dismutase. Role of the metal center in decomposition kinetics and nitration. *J. Biol. Chem.* 2001, 276, 11631–11638. [CrossRef]

40. Zou, M.; Yesilkaya, A.; Ullrich, V. Peroxynitrite inactivates prostacyclin synthase by heme-thiolate-catalyzed tyrosine nitration. *Drug Metab. Rev.* 1999, 31, 343–349. [CrossRef]

41. Daiber, A.; Oelze, M.; Steven, S.; Kroller-Schon, S.; Munzel, T. Taking up the cudgels for the traditional idea of tyrosine nitration. *Biochem. Biophys. Res. Commun.* 2001, 276, 11631–11638. [CrossRef]

42. Zou, M.H.; Leist, M.; Ullrich, V. Selective nitration of prostacyclin synthase and defective vasorelaxation in atherosclerotic bovine coronary arteries. *Am. J. Pathol.* 1999, 154, 1359–1365. [CrossRef]

43. Bachschmid, M.; Schildknecht, S.; Ullrich, V. Redox regulation of vascular prostanoid synthesis by the nitric oxide-superoxide system. *Eur. J. Biochem.* FEBS Lett. 1992, 333, 49–58. [CrossRef]

44. Gryglewski, R.J.; Palmer, R.M.; Moncada, S. Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. *Nature* 1986, 320, 454–456. [CrossRef]

45. Munzel, T.; Daiber, A.; Ullrich, V.; Mulsch, A. Vascular consequences of endothelial nitric oxide synthase uncoupling for the activity and expression of the soluble guanylyl cyclase and the cGMP-dependent protein kinase. *Arterioscler. Thromb. Vasc. Biol.* 2005, 25, 1551–1557. [CrossRef] [PubMed]

46. Kuzkaya, N.; Weissmann, N.; Harrison, D.G.; Dikalov, S. Interactions of peroxynitrite, tetrahydrobiopterin, ascorbic acid, and thiols: Implications for uncoupling endothelial nitric-oxide synthase. *J. Biol. Chem.* 2003, 278, 22546–22554. [CrossRef]

47. Weber, M.; Lauer, N.; Mulsch, A.; Kojda, G. The effect of peroxynitrite on the catalytic activity of soluble guanylyl cyclase. *Free Radic. Biol. Med.* 2001, 31, 1360–1367. [CrossRef]

48. Zou, M.H.; Ullrich, V. Peroxynitrite formed by simultaneous generation of nitric oxide and superoxide selectively inhibits bovine aortic prostacyclin synthase. *FEBS Lett.* 1996, 382, 101–104. [CrossRef]

49. Daiber, A.; Steven, S.; Weber, A.; Shuvaev, V.V.; Muzykantov, V.R.; Lamer, I.; Li, H.; Lamas, S.; Munzel, T. Targeting vascular (endothelial) dysfunction. *Br. J. Pharmacol.* 2017, 174, 1591–1619. [CrossRef]

50. Munzel, T.; Sinning, C.; Post, F.; Warnholz, A.; Schulz, E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann. Med.* 2008, 40, 180–196. [CrossRef]
51. Kimura, F.; Hasegawa, G.; Obayashi, H.; Adachi, T.; Hara, H.; Ohta, M.; Fukui, M.; Kitagawa, Y.; Park, H.; Nakamura, N.; et al. Serum extracellular superoxide dismutase in patients with type 2 diabetes: Relationship to the development of micro- and macrovascular complications. *Diabetes Care* 2003, 26, 1246–1250. [CrossRef] [PubMed]

52. Bailey, C.J. Metformin: Effects on micro and macrovascular complications in type 2 diabetes. *Cardiovasc. Drugs Ther.* 2008, 22, 215–224. [CrossRef] [PubMed]

53. Folli, F.; Corradi, D.; Fanti, P.; Davalli, A.; Paez, A.; Giaccari, A.; Perego, C.; Muscogiuri, G. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: Avenues for a mechanistic-based therapeutic approach. *Curr. Diabetes Rev.* 2011, 7, 313–324. [CrossRef] [PubMed]

54. Radi, R. Peroxynitrite, a stealthy biological oxidant. *J. Biol. Chem.* 2013, 288, 26464–26472. [CrossRef]

55. Daiber, A.; Oelze, M.; Daub, S.; Steven, S.; Schuff, A.; Kroller-Schön, S.; Hausding, M.; Wenzel, P.; Schulz, E.; Gori, T.; et al. Vascular redox signaling, redox switches in endothelial nitric oxide synthase and endothelial dysfunction. In *Systems Biology of Free Radicals and Antioxidants*; Laher, I., Ed.; Springer: Berlin/Heidelberg, Germany, 2014; pp. 1177–1211.

56. Casas, A.I.; Dao, V.T.; Daiber, A.; Maghzal, G.J.; Di Lisa, F.; Kaludercic, N.; Leach, S.; Cuadrado, A.; Jaquet, V.; Seredena, T.; et al. Reactive oxygen-related diseases: Therapeutic targets and emerging clinical indications. *Antioxid. Redox Signal.* 2015, 23, 1171–1185. [CrossRef]

57. Higgins, P.; Dawson, J.; Lees, K.R.; McArthur, K.; Quinn, T.J.; Walters, M.R. Xanthine oxidase inhibition for the treatment of cardiovascular disease: A systematic review and meta-analysis. *Cardiovasc. Ther.* 2012, 30, 217–226. [CrossRef]

58. Bredemeier, M.; Lopes, L.M.; Eisenreich, M.A.; Hickmann, S.; 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]

59. Altenhofer, S.; Radermacher, K.A.; Kleikers, P.W.; Wingler, K.; Schmidt, H.H. Evolution of NADPH oxidase inhibitors: Selectivity and mechanisms for target engagement. *Antioxid. Redox Signal.* 2014, 23, 406–427. [CrossRef] [PubMed]

60. Forstermann, U.; Munzel, T. Endothelial nitric oxide synthase in vascular disease: From marvel to menace. *Circulation* 2006, 113, 1708–1714. [CrossRef]

61. Daiber, A.; Xia, N.; Steven, S.; Oelze, M.; Hanf, A.; Kroller-Schön, S.; Munzel, T.; Li, H. New therapeutic implications of endothelial nitric oxide synthase (eNOS) function/dysfunction in cardiovascular disease. *Int. J. Mol. Sci.* 2019, 20, 187. [CrossRef]

62. Robinson, B.H. The role of manganese superoxide dismutase in health and disease. *J. Inherit. Metab. Dis.* 1998, 21, 598–603. [CrossRef] [PubMed]

63. Drose, S.; Brandt, U. The mechanism of mitochondrial superoxide production by the cytochrome bc1 complex. *J. Biol. Chem.* 2008, 283, 21649–21654. [CrossRef] [PubMed]

64. Dikalov, S. Cross talk between mitochondria and NADPH oxidases. *Free Radic. Biol. Med.* 2011, 51, 1289–1301. [CrossRef] [PubMed]

65. Di Lisa, F.; Bernardi, P. Mitochondria and ischemia-reperfusion injury of the heart: Fixing a hole. *Cardiovasc. Res.* 2006, 70, 191–199. [CrossRef]

66. Schinzel, A.C.; Takeuchi, O.; Huang, Z.; Fisher, J.K.; Zhou, Z.; Rubens, J.; Hetz, C.; Danial, N.N.; Moskovitz, M.A.; Korsmeyer, S.J. Cyclophilin D is a component of mitochondrial permeability transition and mediates neuronal cell death after focal cerebral ischemia. *Proc. Natl. Acad. Sci. USA* 2005, 102, 12005–12010. [CrossRef]

67. Szeto, H.H. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. *Antioxid. Redox Signal.* 2007, 10, 601–620. [CrossRef]

68. Smith, R.A.; Hartley, R.C.; Murphy, M.P. Mitochondria-targeted small molecule therapeutics and probes. *Antioxid. Redox Signal.* 2011, 15, 3021–3038. [CrossRef]

69. Jin, H.; Kanthasamy, A.; Ghosh, A.; Anantharam, V.; Kalyanaraman, B.; Kanthasamy, A.G. Mitochondria-targeted antioxidants for treatment of Parkinson’s disease: Preclinical and clinical outcomes. *Biochim. Biophys. Acta* 2014, 1842, 1282–1294. [CrossRef]
70. Kaludercic, N.; Mialet-Perez, J.; Paolocci, N.; Parini, A.; Di Lisa, F. Monoamine oxidases as sources of oxidants in the heart. *J. Mol. Cell Cardiol.* 2014, 73C, 34–42. [CrossRef]

71. Di Lisa, F.; Giorgio, M.; Ferdinandy, P.; Schulz, R. New aspects of p66Shc in ischaemia reperfusion injury and other cardiovascular diseases. *Br. J. Pharmacol.* 2017, 174, 1690–1703. [CrossRef]

72. Ohara, Y.; Peterson, T.E.; Harrison, D.G. Hypercholesterolemia increases endothelial superoxide anion production. *J. Clin. Investig.* 1993, 91, 2546–2551. [CrossRef] [PubMed]

73. Harrison, D.G.; Ohara, Y. Physiologic consequences of increased vascular oxidant stresses in hypercholesterolemia and atherosclerosis: Implications for impaired vasomotion. *Am. J. Cardiol.* 1995, 75, 75B–81B. [CrossRef]

74. Daiber, A.; Chlopicki, S. Revisiting pharmacology of oxidative stress and endothelial dysfunction in cardiovascular disease: Evidence for redox-based therapies. *Free Radic. Biol. Med.* 2020. [CrossRef] [PubMed]

75. Doerries, C.; Grote, K.; Hilfiker-Kleiner, D.; Luchtefeld, M.; Schaefer, A.; Holland, S.M.; Sorrentino, S.; Manes, C.; SchIEffer, B.; DrexlER, H.; et al. Critical role of the NAD(P)H oxidase subunit p47phox for left ventricular remodeling/dysfunction and survival after myocardial infarction. *Circ. Res.* 2007, 100, 894–903. [CrossRef]

76. Landmesser, U.; Cai, H.; Dikalov, S.; McCann, L.; Hwang, J.; Ho, H.; Holland, S.M.; Harrison, D.G. Role of p47(phox) in vascular oxidative stress and endothelial dysfunction caused by angiotensin II. *Hypertension 2002*, 40, 511–515. [CrossRef]

77. Matsuno, K.; Yamada, H.; Iwata, K.; Jin, D.; Katsuyama, M.; Matsuki, M.; Takai, S.; Yamanishi, K.; Miyazaki, M.; Matsubara, H.; et al. Nox1 is involved in angiotensin II-mediated hypertension: A study in Nox1-deficient mice. *Circulation* 2005, 112, 2677–2685. [CrossRef]

78. Dikalova, A.; Clempus, R.; Lassegue, B.; Cheng, G.; McCoy, J.; Dikalov, S.; San Martin, A.; Lyle, A.; Weber, D.S.; Weiss, D.; et al. Nox1 overexpression potentiates angiotensin II-induced hypertension and vascular smooth muscle hypertrophy in transgenic mice. *Circulation* 2005, 112, 2668–2676. [CrossRef]

79. Wenzel, P.; Schuhmacher, S.; Kienhofer, J.; Muller, J.; Hortmann, M.; Oelze, M.; Schulz, E.; Treiber, N.; Kawamoto, T.; SchIEffetter-Kochanek, K.; et al. Manganese superoxide dismutase and aldehyde dehydrogenase deficiency increase mitochondrial oxidative stress and aggravate age-dependent vascular dysfunction. *Cardiovasc. Res.* 2008, 80, 280–289. [CrossRef]

80. Oelze, M.; Kroller-Schon, S.; Steven, S.; Lubos, E.; Coldewey, M.; Schulz, E.; Treiber, N.; Hink, U.; Mulsch, A.; SchIEffetter-Kochanek, K.; Munzel, T. Heterozygous deficiency of manganese superoxide dismutase in mice (Mn-SOD+/-): A novel approach to assess the role of oxidative stress for the development of nitrate tolerance. *Mol. Pharmacol.* 2005, 68, 579–588. [CrossRef]

81. Torzewski, M.; Ochsenhirt, V.; Kleschyov, A.L.; Oelze, M.; Daiber, A.; Li, H.; Rossmann, H.; Tsimikas, S.; Reifenberg, K.; Cheng, F.; et al. Deficiency of glutathione peroxidase-1 accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 2007, 27, 850–857. [CrossRef] [PubMed]

82. Alp, N.J.; Cai, H.; Channon, K.M. Increased endothelial tetrahydrobiopterin synthesis by targeted transgenic GTP-cyclohydrolase I overexpression reduces endothelial dysfunction and atherosclerosis in ApoE-knockout mice. *Arterioscler. Thromb. Vasc. Biol.* 2004, 24, 445–450. [CrossRef] [PubMed]

83. Alp, N.J.; McAteer, M.A.; Khoo, J.; Choudhury, R.P.; Channon, K.M. Increased endothelial tetrahydrobiopterin synthesis by targeted transgenic GTP-cyclohydrolase I overexpression reduces endothelial dysfunction and atherosclerosis in ApoE-knockout mice. *Arterioscler. Thromb. Vasc. Biol.* 2004, 24, 445–450. [CrossRef] [PubMed]

84. Du, Y.H.; Guan, Y.Y.; Alp, N.J.; Channon, K.M.; Chen, A.F. Endothelium-specific GTP cyclohydrolase I overexpression attenuates blood pressure progression in salt-sensitive low-renin hypertension. *Circulation* 2008, 117, 1045–1054. [CrossRef]

85. Alp, N.J.; Mussa, S.; Khoo, J.; Cai, S.; Guzik, T.; Jefferson, A.; Goh, N.; Rockett, K.A.; Channon, K.M. Tetrahydrobiopterin-dependent preservation of nitric oxide-mediated endothelial function in diabetes by targeted transgenic GTP-cyclohydrolase I overexpression. *J. Clin. Investig.* 2003, 112, 725–735. [CrossRef]
86. Bendall, J.K.; Alp, N.J.; Warrick, N.; Cai, S.; Adlam, D.; Rockett, K.; Yokoyama, M.; Kawashima, S.; Channon, K.M. Stoichiometric relationships between endothelial tetrahydrobiopterin, endothelial NO synthase (eNOS) activity, and eNOS coupling in vivo: Insights from transgenic mice with endothelial-targeted GTP cyclohydrolase 1 and eNOS overexpression. *Circ. Res.* 2005, 97, 864–871. [CrossRef] [PubMed]

87. Jansen, T.; Kroller-Schon, S.; Schonfelder, T.; Foretz, M.; Viollet, B.; Daiber, A.; Oelze, M.; Brandt, M.; Steven, S.; Kvandova, M.; et al. α1AMPK deletion in myelomonocytic cells induces a pro-inflammatory phenotype and enhances angiotensin II-induced vascular dysfunction. *Cardiovasc. Res.* 2018, 114, 1883–1893. [CrossRef]

88. Kroller-Schon, S.; Jansen, T.; Tran, T.L.P.; Kvandova, M.; Kalinovic, S.; Oelze, M.; Keaney, J.F., Jr.; Foretz, M.; Viollet, B.; Daiber, A.; et al. Endothelial alpha1AMPK modulates angiotensin II-mediated vascular inflammation and dysfunction. *Basic Res. Cardiol.* 2019, 114, 8. [CrossRef]

89. Nishikawa, T.; Edelstein, D.; Du, X.L.; Yamagishi, S.; Matsumura, T.; Kaneda, Y.; Yorek, M.A.; Beebe, D.; Oates, P.J.; Hammers, H.P.; et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000, 404, 787–790. [CrossRef]

90. Schulz, E.; Wenzel, P.; Munzel, T.; Daiber, A. Mitochondrial redox signaling: Interaction of mitochondrial reactive oxygen species with other sources of oxidative stress. *Antioxid. Redox Signal.* 2012, 20, 308–324. [CrossRef]

91. Chen, A.F.; Chen, D.D.; Daiber, A.; Faraci, F.M.; Li, H.; Rembold, C.M.; Laher, I. Free radical biology of the cardiovascular system. *Clin. Sci.* 2012, 123, 73–91. [CrossRef]

92. Daiber, A. Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species. *Biochim. Biophys. Acta* 2010, 1797, 897–906. [CrossRef] [PubMed]

93. Heitzer, T.; Schlinzig, T.; Krohn, K.; Meinertz, T.; Munzel, T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001, 104, 2673–2678. [CrossRef] [PubMed]

94. Harrison, D.; Griendling, K.K.; Landmesser, U.; Hornig, B.; Drexler, H. Role of oxidative stress in atherosclerosis. *Am. J. Cardiol.* 2003, 91, 7A–11A. [CrossRef]

95. Blankenberg, S.; Rupprecht, H.J.; Bickel, C.; Torzewski, M.; Hafner, G.; Tietz, L.; Smiejka, M.; Cambien, F.; Meyer, J.; Lackner, K.J. Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. *N. Engl. J. Med.* 2003, 349, 1605–1613. [CrossRef]

96. Schottker, B.; Brenner, H.; Jansen, E.H.; Gardiner, J.; Peasey, A.; Kubinova, R.; Pajak, A.; Topor-Madry, R.; Tamosiunas, A.; Saum, K.U.; et al. Evidence for the free radical/oxidative stress theory of ageing from the CHANCES consortium: A meta-analysis of individual participant data. *BMC Med.* 2015, 13, 300. [CrossRef]

97. Di Minno, A.; Turnu, L.; Porro, B.; Squellerio, I.; Cavalca, V.; Tremoli, E.; Di Minno, M.N. 8-hydroxy-2-deoxyguanosine levels and cardiovascular disease: A systematic review and meta-analysis of the literature. *Antioxid. Redox Signal.* 2016, 24, 548–555. [CrossRef]

98. Fratta Pasini, A.; Albiero, A.; Stranieri, C.; Cominacini, M.; Pasini, A.; Mozzini, C.; Vallerio, P.; Cominacini, L.; Garbin, U. Serum oxidative stress-induced repression of Nrf2 and GSH depletion: A mechanism potentially involved in endothelial dysfunction of young smokers. *PLoS ONE* 2012, 7, e30291. [CrossRef]

99. Jurado-Gamez, B.; Fernandez-Marin, M.C.; Gomez-Chaparro, J.L.; Munoz-Cabrera, L.; Lopez-Barea, J.; Perez-Jimenez, F.; Lopez-Miranda, J. Relationship of oxidative stress and endothelial dysfunction in sleep apnoea. *Eur. Respir. J.* 2011, 37, 873–879. [CrossRef]

100. Steven, S.; Frenis, K.; Oelze, M.; Kalinovic, S.; Kuntic, M.; Bayo Jimenez, M.T.; Vujacic-Mirski, K.; Helmsadder, J.; Kroller-Schon, S.; Munzel, T.; et al. Vascular inflammation and oxidative stress: Major triggers for cardiovascular disease. *Oxidative Med. Cell. Longev.* 2019, 2019, 7092151. [CrossRef]

101. Mikhed, Y.; Daiber, A.; Steven, S. Mitochondrial Oxidative Stress, Mitochondrial DNA Damage and Their Role in Age-Related Vascular Dysfunction. *Int. J. Mol. Sci.* 2015, 16, 15918–15953. [CrossRef]

102. Jay, D.; Hitomi, H.; Griendling, K.K. Oxidative stress and diabetic cardiovascular complications. *Free Radic. Biol. Med.* 2006, 40, 183–192. [CrossRef] [PubMed]

103. Steven, S.; Frenis, K.; Oelze, M.; Vujacic-Mirski, K.; Bayo Jimenez, M.T.; Kalinovic, S.; Kroller-Schon, S.; Munzel, T.; Daiber, A. SGLT2 inhibitors, diabetes and oxidative stress. In *Diabetes—Oxidative Stress and Dietary Antioxidants*, 2nd ed.; Preedy, V., Ed.; Academic Press: Cambridge, MA, USA, 2020; pp. 1–12.
118. Steven, S.; Munzel, T.; Daiber, A. Exploiting the pleiotropic antioxidant e

115. De Jager, J.; Dekker, J.M.; Kooy, A.; Kostense, P.J.; Nijpels, G.; Heine, R.J.; Bouter, L.M.; Stehouwer, C.D.

105. Haas, M.J.; Jafri, M.; Wehmeier, K.R.; Onstead-Haas, L.M.; Mooradian, A.D. Inhibition of endoplasmic

104. Mansournia, M.A.; Ostadmohammadi, V.; Doosti-Irani, A.; Ghayour-Mobarhan, M.; Ferns, G.; Akbari, H.;

117. Khaw, K.T.; Bingham, S.; Welch, A.; Luben, R.; Wareham, N.; Oakes, S.; Day, N. Relation between plasma

116. Munzel, T.; Gori, T.; Bruno, R.M.; Taddei, S. Is oxidative stress a therapeutic target in cardiovascular disease?

114. Heitzer, T.; Finckh, B.; Albers, S.; Krohn, K.; Kohlschutter, A.; Meier, T. Tetrahydrobiopterin improves endothelium-dependent

109. Balbi, M.E.; Tonin, F.S.; Mendes, A.M.; Borba, H.H.; Wiens, A.; Fernandez-Llimos, F.; Pontarolo, R. Antioxidant

108. Dai, Y.; Zhang, J.; Xiang, J.; Li, Y.; Wu, D.; Xu, J. Calcitriol inhibits ROS-NLRP3-IL-1beta signaling axis via

106. Di Domenico, F.; Barone, E.; Perluigi, M.; Butterfield, D.A. Strategy to reduce free radical species in

107. Chaiprasongsuk, A.; Janjetovic, Z.; Kim, T.K.; Jarrett, S.G.; D’Orazio, J.A.; Holick, M.F.; Tang, E.K.Y.;

113. Heitzer, T.; Krohn, K.; Albers, S.; Meinertz, T. Tetrahydrobiopterin improves endothelium-dependent

103. Mansournia, M.A.; Ostadmohammadi, V.; Doosti-Irani, A.; Ghayour-Mobarhan, M.; Ferns, G.; Akbari, H.;

101. Thomas, M.C.; Woodward, M.; Li, Q.; Pickering, R.; Tikellis, C.; Poulter, N.; Cooper, M.E.; Marre, M.;

110. Thomas, M.C.; Woodward, M.; Li, Q.; Pickering, R.; Tikellis, C.; Poulter, N.; Cooper, M.E.; Marre, M.;

102. Chaiprasongsuk, A.; Janjetovic, Z.; Kim, T.K.; Jarrett, S.G.; D’Orazio, J.A.; Holick, M.F.; Tang, E.K.Y.;

119. Shuaib, A.; Lees, K.R.; Lyden, P.; Grotta, J.; Davalos, A.; Davis, S.M.; Diener, H.C.; Ashwood, T.;

112. Shigiyama, F.; Kumashiro, N.; Miyagi, M.; Ikehara, K.; Kanda, E.; Uchino, H.; Hirose, T. E...
120. 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]

121. Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol. Rev.* 2014, 94, 909–950. [CrossRef]

122. Kimura, S.; Zhang, G.X.; Nishiyama, A.; Shokoji, T.; Yao, L.; Fan, Y.Y.; Rahman, M.; Abe, Y. Mitochondria-derived reactive oxygen species and vascular MAP kinases: Comparison of angiotensin II and dioxyzide. *Hypertension* 2005, 45, 438–444. [CrossRef]

123. Brandes, R.P. Triggering mitochondrial radical release: A new function for NADPH oxidases. *Hypertension* 2005, 45, 847–848. [CrossRef] [PubMed]

124. Zhang, D.X.; Chen, Y.F.; Campbell, W.B.; Zou, A.P.; Gross, G.J.; Li, P.L. Characteristics and superoxide-induced activation of reconstituted myocardial mitochondrial ATP-sensitive potassium channels. *Circ. Res.* 2001, 89, 1177–1183. [CrossRef] [PubMed]

125. Vanhoutte, P.M. Cardiovascular pharmacology: Endothelial control. *Adv. Pharmacol.* 2010, 60, 13–14.

126. Karbach, S.; Wenzel, P.; Waisman, A.; Munzel, T.; Daiber, A. eNOS uncoupling in cardiovascular diseases—The role of oxidative stress and inflammation. *Curr. Pharm. Des.* 2014, 20, 3579–3594. [CrossRef]

127. Daiber, A.; Di Lisa, F.; Oelze, M.; Kroller-Schon, S.; Steven, S.; Schulz, E.; Munzel, T. Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function. *Br. J. Pharmacol.* 2017, 174, 1670–1689. [CrossRef]

128. Wenzel, P.; Kossmann, S.; Munzel, T.; Daiber, A. Redox regulation of cardiovascular inflammation—Immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. *Free Radic. Biol. Med.* 2017, 109, 48–60. [CrossRef]

129. Landmesser, U.; Dikalov, S.; Price, S.R.; McCann, L.; Fukai, T.; Holland, S.M.; Mitch, W.E.; Harrison, D.G. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. *J. Clin. Invest.* 2003, 111, 1201–1209. [CrossRef]

130. Xu, J.; Xie, Z.; Reece, R.; Pimental, D.; Zou, M.H. Uncoupling of endothelial nitric oxidase synthase by hypochlorous acid: Role of NAD(P)H oxidase-derived superoxide and peroxynitrite. *Arter. Thromb. Vasc. Biol.* 2006, 26, 2688–2695. [CrossRef]

131. Di Lisa, F.; Canton, M.; Menabo, R.; Kaludercic, N.; Bernardi, P. Mitochondria and cardioprotection. *Heart Fail. Rev.* 2007, 12, 249–260. [CrossRef] [PubMed]

132. Andrukhiv, A.; Costa, A.D.; West, I.C.; Garlid, K.D. Opening mitoK_{ATP} increases superoxide generation from complex I of the electron transport chain. *Am. J. Physiol. Heart Circ. Physiol.* 2006, 291, H2067–H2074. [CrossRef] [PubMed]

133. Heinzel, F.R.; Luo, Y.; Li, X.; Boengler, K.; Buechert, A.; Garcia-Dorado, D.; Di Lisa, F.; Schulz, R.; Heusch, G. Impairment of diazoxide-induced formation of reactive oxygen species and loss of cardioprotection in connexin 43 deficient mice. *Circ. Res.* 2008, 102, 488–496. [CrossRef] [PubMed]

134. Pain, T.; Yang, X.M.; Critz, S.D.; Yue, Y.; Nakano, A.; Liu, G.S.; Heusch, G.; Cohen, M.V.; Downey, J.M. Opening of mitochondrial K(ATP) channels triggers the preconditioned state by generating free radicals. *Circ. Res.* 2000, 87, 460–466. [CrossRef] [PubMed]

135. Zinkevich, N.S.; Gutterman, D.D. ROS-induced ROS release in vascular biology: Redox-redox signaling. *Am. J. Physiol. Heart Circ. Physiol.* 2011, 301, H647–H653. [CrossRef] [PubMed]

136. Wosniak, J., Jr.; Santos, C.X.; Kowaltowski, A.J.; Laurindo, F.R. Cross-talk between mitochondria and NADPH oxidase: Effects of mild mitochondrial dysfunction on angiotensin II-mediated increase in Nox isoform expression and activity in vascular smooth muscle cells. *Antioxid. Redox Signal.* 2009, 11, 1265–1278. [CrossRef]

137. Doughan, A.K.; Harrison, D.G.; Dikalov, S.I. Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: Linking mitochondrial oxidative damage and vascular endothelial dysfunction. *Circ. Res.* 2008, 102, 488–496. [CrossRef] [PubMed]
139. Kroller-Schon, S.; Steven, S.; Kossmann, S.; Scholz, A.; Daub, S.; Oelze, M.; Xia, N.; Hausding, M.; Mikhe, Y.; Zinssius, E.; et al. Molecular mechanisms of the crosstalk between mitochondria and NADPH oxidase through reactive oxygen species-studies in white blood cells and in animal models. *Antioxid. Redox Signal.* 2014, 20, 247–266. [CrossRef]

140. Wenzel, P.; Mollnau, H.; Oelze, M.; Schulz, E.; Wickramanayake, J.M.; Muller, J.; Schuhmacher, S.; Hortmann, M.; Baldus, S.; Gori, T.; et al. First evidence for a crosstalk between mitochondrial and NADPH oxidase-derived reactive oxygen species in nitroglycerin-triggered vascular dysfunction. *Antioxid. Redox Signal.* 2008, 10, 1435–1447. [CrossRef]

141. Itani, H.A.; Dikalova, A.E.; McMaster, W.G.; Nazarewicz, R.R.; Bikineyeva, A.T.; Harrison, D.G.; Dikalov, S.I. Mitochondrial cyclophilin D in vascular oxidative stress and hypertension. *Hypertension* 2016, 67, 1218–1227. [CrossRef]

142. Nguyen, T.T.; Stevens, M.V.; Kohr, M.; Steenbergen, C.; Sac, M.N.; Murphy, E. Cysteine 203 of cyclophilin D is critical for cyclophilin D activation of the mitochondrial permeability transition pore. *J. Biol. Chem.* 2011, 286, 40184–40192. [CrossRef] [PubMed]

143. Nishino, T. The conversion from the dehydrogenase type to the oxidase type of rat liver xanthine dehydrogenase by modification of cysteine residues with fluorodinitrobenzene. *J. Biol. Chem.* 1997, 272, 29859–29864. [CrossRef] [PubMed]

144. Ryan, M.G.; Balendran, A.; Harrison, R.; Wolstenholme, A.; Bulkley, G.B. Xanthine oxidoreductase: Dehydrogenase to oxidase conversion. *Biochem. Soc. Trans.* 1997, 25, 5305. [CrossRef] [PubMed]

145. Chen, C.A.; Wang, T.Y.; Varadharaj, S.; Reyes, L.A.; Hemann, C.; Talukder, M.A.; Chen, Y.R.; Druhan, L.J.; Zweier, J.L. S-glutathionylation uncouples eNOS and regulates its cellular and vascular function. *Nature* 2010, 468, 1115–1118. [CrossRef] [PubMed]

146. Fleming, I.; Fisslthaler, B.; Dimmerl, S.; Kemp, B.E.; Busse, R. Phosphorylation of Thr195 regulates Ca2+/calmodulin-dependent endothelial nitric oxide synthase activity. *Circ. Res.* 2001, 88, e68–e75. [CrossRef] [PubMed]

147. Loot, A.E.; Schreiber, J.G.; Fisslthaler, B.; Fleming, I. Angiotensin II impairs endothelial function via tyrosine phosphorylation of the endothelial nitric oxide synthase. *J. Exp. Med.* 2009, 206, 2889–2896. [CrossRef] [PubMed]

148. Archer, S.L.; Gomberg-Maitland, M.; Maitland, M.L.; Rich, S.; Garcia, J.G.; Weir, E.K. Mitochondrial metabolism, redox signaling, and fusion: A mitochondria-ROS-HIF-1α-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer. *Am. J. Physiol. Heart Circ. Physiol.* 2008, 294, H570–H578. [CrossRef]

149. Giordano, F.J. Oxygen, oxidative stress, hypoxia, and heart failure. *J. Clin. Investig.* 2005, 115, 500–508. [CrossRef]

150. Powell, C.S.; Jackson, R.M. Mitochondrial complex I, aconitase, and succinate dehydrogenase during hypoxia-reoxygenation: Modulation of enzyme activities by MnSOD. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2003, 285, L189–L198. [CrossRef]

151. Rathore, R.; Zheng, Y.M.; Niu, C.F.; Liu, Q.H.; Korde, A.; Ho, Y.S.; Wang, Y.X. Hypoxia activates NADPH oxidase 1 isozyme for the sustained production of reactive oxygen species and cell death. *J. Biol. Chem.* 2006, 281, 36228–36235. [CrossRef]

152. Lee, S.B.; Bae, I.H.; Bae, Y.S.; Um, H.D. Link between mitochondria and NADPH oxidase 1 isozyme for reactive oxygen species formation for age-induced vascular dysfunction. In *Aging and Age-Related Reactive Oxygen Species Formation for Age-Induced Vascular Dysfunction*; Bondy, S.C., Maiese, K., Eds.; Oxidative Stress in Applied Basic Research and Clinical Practice; Springer (Humana Press): Totowa, NJ, USA, 2010; pp. 237–257. [CrossRef]

153. Itani, H.A.; Dikalova, A.E.; McMaster, W.G.; Nazarewicz, R.R.; Bikineyeva, A.T.; Harrison, D.G.; Dikalov, S.I. Mitochondrial cyclophilin D in vascular oxidative stress and hypertension. *Hypertension* 2016, 67, 1218–1227. [CrossRef] [PubMed]
156. Chang, J.F.; Liang, S.S.; Thanasekaran, P.; Chang, H.W.; Wen, L.L.; Chen, C.H.; Liou, J.C.; Yeh, J.C.; Liu, S.H.; Dai, H.M.; et al. Translational medicine in pulmonary-renal crosstalk: Therapeutic targeting of p-cresyl sulfate triggered nonspecific ROS and chemoattractants in dyspneic patients with uremic lung injury. *J. Clin. Med.* 2018, 7, 266. [CrossRef] [PubMed]

157. Srivastava, R.K.; Li, C.; Ahmad, A.; Abrams, O.; Gorbatyuk, M.S.; Harrold, K.S.; Wek, R.C.; Afaq, F.; Athar, M. ATF4 regulates arsenic trioxide-mediated NADPH oxidase, ER-mitochondrial crosstalk and apoptosis. *Arch. Biochem. Biophys.* 2016, 609, 39–50. [CrossRef] [PubMed]

158. Veith, C.; Boots, A.W.; Idris, M.; van Schooten, F.J.; van der Vliet, A. Redox imbalance in idiopathic pulmonary fibrosis: A role for oxidant cross-talk between NADPH oxidase enzymes and mitochondria. *Antioxid. Redox Signal.* 2019, 31, 1092–1115. [CrossRef] [PubMed]

159. Desouki, M.M.; Kulawiec, M.; Bansal, S.; Das, G.M.; Singh, K.K. Cross talk between mitochondria and superoxide generating NADPH oxidase in breast and ovarian tumors. *Cancer Biol. Ther.* 2005, 4, 1367–1373. [CrossRef]

160. Kim, Y.M.; Kim, S.J.; Tatsunami, R.; Yamamura, H.; Fukai, T.; Ushio-Fukai, M. ROS-induced ROS release orchestrated by Nox4, Nox2, and mitochondria in VEGF signaling and angiogenesis. *Am. J. Physiol. Cell Physiol.* 2017, 312, C749–C764. [CrossRef]

161. Da Silva, M.F.; Natali, A.J.; da Silva, E.; Gomes, G.J.; Teodoro, B.G.; Cunha, D.N.; Drummond, L.R.; Drummond, F.R.; Moura, A.G.; Belfort, F.G.; et al. Attenuation of Ca$^{2+}$ homeostasis, oxidative stress, and mitochondrial dysfunctions in diabetic rat heart: Insulin therapy or aerobic exercise? *J. Appl. Physiol.* 2015, 119, 148–156. [CrossRef]

162. Hempel, N.; Trebak, M. Crosstalk between calcium and reactive oxygen species signaling in cancer. *Cell Calcium* 2017, 63, 70–96. [CrossRef]

163. Gorlach, A.; Bertram, K.; Hudecova, S.; Krizanova, O. Calcium and ROS: A mutual interplay. *Redox Biol.* 2015, 6, 260–271. [CrossRef]

164. Dikalov, S.I.; Li, W.; Doughan, A.K.; Blanco, R.R.; Zafari, A.M. Mitochondrial reactive oxygen species and calcium uptake regulate activation of phagocytic NADPH oxidase. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2012, 302, R1134–R1142. [CrossRef] [PubMed]

165. Wenzel, P.; Knorr, M.; Kossmann, S.; Stratmann, J.; Hausding, M.; Schuhmacher, S.; Karbach, S.H.; Schmidgen, M.I.; Brandt, M.; Knorr, M.; Hu, H.; Kroller-Schon, S.; Schonfelder, T.; et al. Angiotensin II-induced vascular dysfunction depends on interferon-gamma-driven immune cell recruitment and mutual activation of monocytes and NK-cells. *Arterioscler. Thromb. Vasc. Biol.* 2013, 33, 1313–1319. [CrossRef]

166. Guzik, T.J.; Hoch, N.E.; Brown, K.A.; McCann, L.A.; Rahman, A.; Dikalov, S.; Goronzy, J.; Weyand, C.; Harrison, D.G. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J. Exp. Med.* 2007, 204, 2449–2460. [CrossRef]

167. Itani, H.A.; McMaster, W.G., Jr.; Saleh, M.A.; Nazarewicz, R.R.; Mikolajczyk, T.P.; Kaszuba, A.M.; Konior, A.; Prejblisz, A.; Januszewicz, A.; Norlander, A.E.; et al. Activation of human T cells in hypertension: Studies of humanized mice and hypertensive humans. *Hypertension* 2016, 68, 123–132. [CrossRef]

168. Qiao, M.; Zhao, Q.; Lee, C.F.; Tannock, L.R.; Smart, E.J.; LeBron, R.G.; Phelix, C.F.; Rangel, Y.; Asmis, R. Thiol oxidative stress induced by metabolic disorders amplifies macrophage chemotactic responses and accelerates atherogenesis and kidney injury in LDL receptor-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 2009, 29, 1779–1786. [CrossRef]

169. Tavakoli, S.; Asmis, R. Reactive oxygen species and thiol redox signaling in the macrophage biology of atherosclerosis. *Antioxid Redox Signal.* 2012, 17, 1785–1795. [CrossRef]

170. Pittman, K.; Kubes, P. Damage-associated molecular patterns control neutrophil recruitment. *J. Innate Immun.* 2013, 5, 315–323. [CrossRef]

171. Bulua, A.C.; Simon, A.; Maddipati, R.; Pelletier, M.; Park, H.; Kim, K.Y.; Sakc, M.N.; Kastner, D.L.; Siegel, R.M. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFRI-associated periodic syndrome (TRAPS). *J. Exp. Med.* 2011, 208, 519–533. [CrossRef]
173. West, A.P.; Brodsky, I.E.; Rahner, C.; Woo, D.K.; Erdjument-Bromage, H.; Tempst, P.; Walsh, M.C.; Choi, Y.; Shadel, G.S.; Ghosh, S. TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. *Nature* 2011, 472, 476–480. [CrossRef]

174. Boeck, C.; Koenig, A.M.; Schury, K.; Geiger, M.L.; Karabatsiakis, A.; Wilker, S.; Waller, C.; Gundel, H.; Fegert, J.M.; Calzia, E.; et al. Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. *Mitochondrion* 2016, 30, 197–207. [CrossRef][PubMed]

175. Zhou, R.; Yazdi, A.S.; Menu, P.; Tschopp, J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* 2011, 469, 221–225. [CrossRef][PubMed]

176. Abais, J.M.; Xia, M.; Zhang, Y.; Boini, K.M.; Li, P.L. Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? *Antioxid. Redox Signal.* 2015, 22, 1111–1129. [CrossRef]

177. Bae, J.Y.; Park, H.H. Crystal structure of NALP3 protein pyrin domain (PYD) and its implications in inflammasome assembly. *J. Biol. Chem.* 2011, 286, 39528–39536. [CrossRef][PubMed]

178. Stark, K.; Philippi, V.; Stockhausen, S.; Busse, J.; Antonelli, A.; Miller, M.; Schubert, I.; Hoseinpour, P.; Maugeri, N.; Rovere-Querini, P.; Baldini, M.; Baldissera, E.; Sabbadini, M.G.; Bianchi, M.E.; Manfredi, A.A. Redox regulation of inflammation: Old elements, new story. *Med. Res. Rev.* 2015, 35, 306–340. [CrossRef]

179. Janko, C.; Filipovic, M.; Munoz, L.E.; Schorn, C.; Schett, G.; Ivanovic-Burmazovic, I.; Herrmann, M. Redox modulation of HMGB1-related signaling. *Antioxid. Redox Signal.* 2014, 20, 1075–1085. [CrossRef]

180. Venereau, E.; Casalgrandi, M.; Schiraldi, M.; Antoine, D.J.; Cattaneo, A.; De Marchis, F.; Liu, J.; Antonelli, A.; Preti, A.; Raeli, L.; et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J. Exp. Med.* 2012, 209, 1519–1528. [CrossRef]

181. Azevedo, E.P.; Rochael, N.C.; Guimaraes-Costa, A.B.; de Souza-Vieira, T.S.; Ganilho, J.; Saraiva, E.M.; Janko, C.; Filipovic, M.; Munoz, L.E.; Schorn, C.; Schett, G.; Ivanovic-Burmazovic, I.; Herrmann, M. Redox regulation of inflammation: Old elements, new story. *Med. Res. Rev.* 2015, 35, 306–340. [CrossRef]

182. Lei, Y.; Wang, K.; Deng, L.; Chen, Y.; Nice, E.C.; Huang, C. Redox regulation of inflammation: Old elements, a new story. *Med. Res. Rev.* 2015, 35, 306–340. [CrossRef]

183. Dan Dunn, J.; Alvarez, L.A.; Zhang, X.; Soldati, T. Reactive oxygen species and mitochondria: A nexus of cellular homeostasis. *Redox Biol.* 2015, 6, 472–485. [CrossRef][PubMed]

184. Douda, D.N.; Khan, M.A.; Grasemann, H.; Palaniyar, N. SK3 channel and mitochondrial ROS mediate NADPH oxidase-independent NETosis induced by calcium influx. *Proc. Natl. Acad. Sci. USA* 2015, 112, 2817–2822. [CrossRef][PubMed]

185. Lood, C.; Blanco, L.P.; Furmala, M.M.; Carmona-Rivera, C.; De Ravin, S.S.; Smith, C.K.; Malech, H.L.; Ledbetter, J.A.; Elkon, K.B.; Kaplan, M.J. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat. Med.* 2016, 22, 146–153. [CrossRef][PubMed]

186. Venereau, E.; Casalgrandi, M.; Schiraldi, M.; Antoine, D.J.; Cattaneo, A.; De Marchis, F.; Liu, J.; Antonelli, A.; Preti, A.; Raeli, L.; et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J. Exp. Med.* 2012, 209, 1519–1528. [CrossRef]

187. Maugeri, N.; Rovere-Querini, P.; Baldini, M.; Baldissera, E.; Sabbadini, M.G.; Bianchi, M.E.; Manfredi, A.A. Redox regulation of inflammation: Old elements, new story. *Med. Res. Rev.* 2015, 35, 306–340. [CrossRef]

188. Kirchner, T.; Moller, S.; Klinger, M.; Solbach, W.; Laskay, T.; Behnen, M. The impact of various reactive oxygen species on the formation of neutrophil extracellular traps. *Mediat. Inflamm.* 2012, 2012, 849136. [CrossRef]

189. Rovira-Llopis, S.; Apostolova, N.; Banuls, C.; Muntane, J.; Rocha, M.; Victor, V.M. Mitochondria, the NLRP3 inflammasome, and sirtuins in type 2 diabetes: New therapeutic targets. *Antioxid. Redox Signal.* 2018, 29, 749–791. [CrossRef]

190. Preti, A.; Raeli, L.; et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J. Exp. Med.* 2012, 209, 1519–1528. [CrossRef]

191. Fegert, J.M.; Calzia, E.; et al. Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. *Mitochondrion* 2016, 30, 197–207. [CrossRef][PubMed]

192. Eggel, A.; Kaufmann, T.; et al. NADPH oxidase-independent formation of extracellular DNA traps by basophils. *J. Immunol.* 2014, 192, 5314–5323. [CrossRef]

193. Kirchner, T.; Moller, S.; Klinger, M.; Solbach, W.; Laskay, T.; Behnen, M. The impact of various reactive oxygen species on the formation of neutrophil extracellular traps. *Mediat. Inflamm.* 2012, 2012, 849136. [CrossRef]

194. Rovira-Llopis, S.; Apostolova, N.; Banuls, C.; Muntane, J.; Rocha, M.; Victor, V.M. Mitochondria, the NLRP3 inflammasome, and sirtuins in type 2 diabetes: New therapeutic targets. *Antioxid. Redox Signal.* 2018, 29, 749–791. [CrossRef]

195. Uitto, J.; Perejda, A.I.; Grant, G.A.; Rowold, E.A.; Kilo, C.; Williamson, J.R. Glycosylation of human glomerular basement membrane collagen: Increased content of hexose in ketoamine linkage and unaltered hydroxylysine-O-glycosides in patients with diabetes. *Connect. Tissue Res.* 1982, 10, 287–296. [CrossRef]

196. Bucala, R.; Tracey, K.J.; Cerami, A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J. Clin. Investig.* 1991, 87, 432–438. [CrossRef]
192. Wautier, M.P.; Chappey, O.; Corda, S.; Stern, D.M.; Schmidt, A.M.; Wautier, J.L. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am. J. Physiol. Endocrinol. Metab 2001, 280, E685–E694. [CrossRef]

193. Bucciarelli, L.G.; Wendt, T.; Qu, W.; Lu, Y.; Lalla, E.; Rong, L.L.; Goova, M.T.; Moser, B.; Kislinger, T.; Lee, D.C.; et al. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation 2002, 106, 2827–2835. [CrossRef]

194. Kumar, S.; Prasad, S.; Sitasawad, S.L. Multiple antioxidants improve cardiac complications and inhibit cardiac cell death in streptozotocin-induced diabetic rats. PLoS ONE 2013, 8, e67009. [CrossRef] [PubMed]

195. Oelze, M.; Schuhmacher, S.; Daiber, A. Organic nitrates and nitrate resistance in diabetes: The role of vascular dysfunction and oxidative stress with emphasis on antioxidant properties of pentaerithritol tetranitrate. Exp. Diabetes Res. 2010, 2010, 213176. [CrossRef] [PubMed]

196. Brownlee, M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001, 414, 813–820. [CrossRef] [PubMed]

197. Steven, S.; Oelze, M.; Hanf, A.; Kroller-Schon, S.; Kashani, F.; Roohani, S.; Welschof, P.; Kopp, M.; Godtel-Armbrust, U.; Xia, N.; et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. Redox Biol. 2017, 13, 370–385. [CrossRef]

198. Von Leitner, E.C.; Klinke, A.; Atzler, D.; Slocum, J.L.; Lund, N.; Kielstein, J.T.; Maas, R.; Schmidt-Haupt, R.; Steven, S.; Oelze, M.; Hanf, A.; Kroller-Schon, S.; Kashani, F.; Roohani, S.; Welschof, P.; Kopp, M.; Paul, M.; Meinertz, T.; Emmerson, A.; Trevelin, S.C.; Mongue-Din, H.; Becker, P.D.; Ortiz, C.; Smyth, L.A.; Peng, Q.; Elgueta, R.; Rajamohan, S.B.; Raghuraman, G.; Prabhakar, N.R.; Kumar, G.K. NADPH oxidase-derived H

199. Stasch, J.P.; Schlossmann, J.; Hocher, B. Renal effects of soluble guanylate cyclase stimulators and activators: A review of the preclinical evidence. Curr. Opin. Pharmacol. 2015, 21, 95–104. [CrossRef]

200. Bonan, C.; Parnaudeau, E.; Coudert, F.; Tissier, B.; Boutevin, B.; Battini, S.; Mennesson, S.; Chauveau, J.P.; Murer, H.; Boucher, L.; Kiesewetter, M.; Boudry, G.; Bataille, M.; Faivre, V.; Pernot, L.; Chenevert, E.; Boulanger, C.; Galland, M.; Brivi, F.; Cliche, C.; Douard, M.; Grimaldi, R.; Morigi, R.; Jeannin, P.; Puech, M.; Lazdunski, M.; Pin, J.P.; Roudier, F.; Zappe, O. Nucleotide receptor agonists act on aldosterone synthesis and release in adrenal tissue. J. Clin. Endocrinol. Metab. 2001, 86, 2998–3006. [CrossRef]

201. Mikhed, Y.; Gorlach, A.; Knaus, U.G.; Daiber, A. Redox regulation of genome stability by effector molecules of the oxidant response. Antioxid. Redox Signal. 2015, 22, 1225–1241. [CrossRef] [PubMed]

202. Ye, S.; Zhong, H.; Yanamadala, S.; Campese, R.M. Oxidative stress mediates the stimulation of sympathetic nerve activity in the phenol renal injury model of hypertension. Hypertension 2006, 48, 309–315. [CrossRef]

203. Campos, R.R.; Oliveira-Sales, E.B.; Nishi, E.E.; Paton, J.F.; Bergamaschi, C.T. Mechanisms of renal sympathetic activation in renovascular hypertension. Exp. Physiol. 2015, 100, 496–501. [CrossRef]

204. Oliveira-Sales, E.B.; Nishi, E.E.; Carillo, B.A.; Boim, M.A.; Dolnikoff, M.S.; Bergamaschi, C.T.; Campos, R.R. Oxidative stress in the sympathetic premotor neurons contributes to sympathetic activation in renovascular hypertension. Am. J. Hypertens. 2009, 22, 484–492. [CrossRef]

205. Rajamohan, S.B.; Raghuraman, G.; Prabhakar, N.R.; Kumar, G.K. NADPH oxidase-derived H2O2 contributes to angiotensin II-induced aldosterone synthesis in human and rat adrenal cortical cells. Antioxid. Redox Signal. 2012, 17, 445–459. [CrossRef]

206. Keidar, S.; Kaplan, M.; Pavlotzky, E.; Coleman, R.; Hayek, T.; Hamoud, S.; Aviram, M. Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: A possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone. Circulation 2004, 109, 2213–2220. [CrossRef]

207. Emmerson, A.; Trevelin, S.C.; Mongue-Din, H.; Becker, P.D.; Ortiz, C.; Smyth, L.A.; Peng, Q.; Elgueta, R.; Sawyer, G.; Ivetic, A.; et al. Nox2 in regulatory T cells promotes angiotensin II-induced cardiovascular remodeling. J. Clin. Investig. 2018, 128, 3088–3101. [CrossRef]

208. Kahler, J.; Mendel, S.; Weckmuller, J.; Orzechowski, H.D.; Mittmann, C.; Koster, R.; Paul, M.; Meinertz, T.; Munzel, T. Oxidative stress increases synthesis of big endothelin-1 by activation of the endothelin-1 promoter. J. Mol. Cell Cardiol. 2000, 32, 1429–1437. [CrossRef]

209. Hink, U.; Oelze, M.; Kolb, P.; Bachschmid, M.; Zou, M.H.; Daiber, A.; Mollnau, H.; August, M.; Baldus, S.; Tsilimingas, N.; et al. Role for peroxynitrite in the inhibition of prostacyclin synthase in nitrate tolerance. J. Am. Coll. Cardiol. 2003, 42, 1826–1834. [CrossRef]

210. Schmidt, P.; Youhnovski, N.; Daiber, A.; Balan, A.; Arsich, M.; Bachschmid, M.; Przybyski, M.; Ullrich, V. Specific nitration at tyrosine 430 revealed by high resolution mass spectrometry as basis for redox regulation of bovine prostacyclin synthase. J. Biol. Chem. 2003, 278, 12813–12819. [CrossRef]
211. Bachschmid, M.; Thurau, S.; Zou, M.H.; Ullrich, V. Endothelial cell activation by endotoxin involves superoxide/NO-mediated nitration of prostacyclin synthase and thromboxane receptor stimulation. *FASEB J.* 2003, 17, 914–916. [CrossRef]

212. Schildknecht, S.; Karrer, C.; Daiber, A.; Zhao, C.; Hamacher, J.; Perlman, D.; Jung, B.; van der Loor, B.; O’Connor, P.; Leist, M.; et al. Autocatalytic nitration of prostaglandin endoperoxide synthase-2 by nitrite inhibits prostanooid formation in rat alveolar macrophages. *Antioxid. Redox Signal.* 2012, 17, 1393–1406. [CrossRef]

213. Zou, M.H.; Martin, C.; Ullrich, V. Tyrosine nitration as a mechanism of selective inactivation of prostacyclin synthase by peroxynitrite. *Biol. Chem.* 1997, 378, 707–713. [CrossRef]

214. Zou, M.H.; Bachschmid, M. Hypoxia-reoxygenation triggers coronary vasospasm in isolated bovine coronary arteries via tyrosine nitration of prostacyclin synthase. *J. Exp. Med.* 1999, 190, 135–139. [CrossRef]

215. Zou, M.H.; Shi, C.; Cohen, R.A. High glucose via peroxynitrite causes tyrosine nitration and inactivation of prostacyclin synthase that is associated with thromboxane/prostaglandin H2 receptor-mediated apoptosis and adhesion molecule expression in cultured human aortic endothelial cells. *Diabetes* 2002, 51, 198–203. [CrossRef]

216. Brune, B.; Schmidt, K.U.; Ullrich, V. Activation of soluble guanylate cyclase by carbon monoxide and inhibition by superoxide anion. *Eur. J. Biochem.* Feb 1990, 192, 683–688. [CrossRef]

217. Riego, J.A.; Broniowska, K.A.; Kettenhofen, N.J.; Hogg, N. Activation and inhibition of soluble guanylyl cyclase by S-nitrosocysteine: Involvement of amino acid transport system L. *Free Radic. Biol. Med.* 2009, 47, 269–274. [CrossRef]

218. Crassous, P.A.; Couloubaly, S.; Huang, C.; Zhou, Z.; Baskaran, P.; Papapetropoulos, A.; Fioramonti, X.; Duran, W.N.; Beuve, A. Soluble guanylyl cyclase is a target of angiotensin II-induced nitrosative stress in a hypertensive rat model. *Am. J. Physiol. Heart Circ. Physiol.* 2012, 303, H597–H604. [CrossRef]

219. Beuve, A. Thiol-based redox modulation of soluble guanylyl cyclase, the nitric oxide receptor. *Antioxid. Redox Signal.* 2017, 26, 137–149. [CrossRef]

220. Radhakrishnan, T.S.; Savithri, H.S.; Rao, N.A.; Venkitasubramanian, T.A. Temperature and thiol-induced desensitization of a Ca$^{2+}$-sensitive cyclic-3',5'-nucleotide phosphodiesterase from sheep lung. *Biochem. Int.* 1988, 17, 927–933.

221. Rossig, L.; Fichtlscherer, B.; Breitschopf, K.; Haendeler, J.; Zeiher, A.M.; Mulsch, A.; Dimmeler, S. Nitric oxide inhibits caspase-3 by S-nitrosation in vivo. *J. Biol. Chem.* 1999, 274, 6823–6826. [CrossRef]

222. Benhar, M.; Stamler, J.S. A central role for S-nitrosoylation in apoptosis. *Nat. Cell Biol.* 2005, 7, 645–646. [CrossRef]

223. Chouchani, E.T.; Methner, C.; Nadtochiy, S.M.; Logan, A.; Pell, V.R.; Ding, S.; James, A.M.; Cocheme, H.M.; Reinhold, J.; Lilley, K.S.; et al. Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I. *Nat. Med.* 2013, 19, 753–759. [CrossRef]

224. Espey, M.G.; Miranda, K.M.; Thomas, D.D.; Xavier, S.; Citrin, D.; Vitek, M.P.; Wink, D.A. A chemical perspective on the interplay between NO, reactive oxygen species, and reactive nitrogen oxide species. *Ann. N. Y. Acad. Sci.* 2002, 962, 195–206. [CrossRef] [PubMed]

225. Daiber, A.; Schildknecht, S.; Muller, J.; Kamuf, J.; Bachschmid, M.M.; Ullrich, V. Chemical model systems for cellular nitrosylation reactions. *Free Radic. Biol. Med.* 2009, 47, 458–467. [CrossRef] [PubMed]

226. Wollhuter, K.; Whitwell, H.J.; Switzer, C.H.; Burgoyne, J.R.; Timms, J.F.; Eaton, P. Evidence against stable protein S-nitrosylation as a widespread mechanism of post-translational regulation. *Mol. Cell* 2018, 69, 438–450. [CrossRef]

227. Sieve, I.; Munster-Kuhnel, A.K.; Hilfiker-Kleiner, D. Regulation and function of endothelial glycocalyx layer in vascular diseases. *Vasc. Pharmacol.* 2018, 100, 26–33. [CrossRef]

228. Barnett, A.H.; Bain, S.C.; Bouter, P.; Karlberg, B.; Madsbad, S.; Jervell, J.; Mustonen, J. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N. Engl. J. Med.* 2004, 351, 1952–1961. [CrossRef]

229. Candido, R.; Allen, T.J.; Lassila, M.; Cao, Z.; Thallas, V.; Cooper, M.E.; Jandeleit-Dahm, K.A. Irbesartan but not amlodipine suppresses diabetes-associated atherosclerosis. *Circulation* 2004, 109, 1536–1542. [CrossRef]

230. Takahashi, K.; Ghati, M.A.; Lam, H.C.; O’Halloran, D.J.; Bloom, S.R. Elevated plasma endothelin in patients with diabetes mellitus. *Diabetologia* 1990, 33, 306–310. [CrossRef]
231. Wendt, M.C.; Daiber, A.; Kleschyov, A.L.; Mulsch, A.; Sydow, K.; Schulz, E.; Chen, K.; Keaney, J.F., Jr.; Lassegue, B.; Walter, U.; et al. Differential effects of diabetes on the expression of the gp91(phox) homologues nox1 and nox4. Free Radic. Biol. Med. 2005, 39, 381–391. [CrossRef]

232. Schuhmacher, S.; Oelze, M.; Bollmann, F.; Kleinert, H.; Otto, C.; Heeren, T.; Steven, S.; Hausding, M.; Knorr, M.; Pautz, A.; et al. Vascular dysfunction in experimental diabetes is improved by pentaerythritol tetranitrate but not isosorbide-5-mononitrate therapy. Diabetes 2011, 60, 2608–2616. [CrossRef]

233. Manea, S.A.; Antonescu, M.L.; Fenyo, I.M.; Raicu, M.; Simionescu, M.; Manea, A. Epigenetic regulation of vascular NADPH oxidase expression and reactive oxygen species production by histone deacetylase-dependent mechanisms in experimental diabetes. Redox Biol. 2018, 16, 332–343. [CrossRef]

234. Guzik, T.J.; Musa, S.; Gastaldi, D.; Sadowski, J.; Ratnatunga, C.; Pillai, R.; Channon, K.M. Mechanisms of increased vascular superoxide production in human diabetes mellitus: Role of NAD(P)H oxidase and endothelial nitric oxide synthase. Circulation 2002, 105, 1656–1662. [CrossRef]

235. Oelze, M.; Kroller-Schon, S.; Welschof, P.; Jansen, T.; Hausding, M.; Mikhey, P.; Stamm, P.; Mader, M.; Zinsius, E.; Agdauletova, S.; et al. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. PLoS ONE 2014, 9, e112394. [CrossRef]

236. Kalinovic, S.; Oelze, M.; Kroller-Schon, S.; Steven, S.; Vujacic-Mirski, K.; Kvandova, M.; Schmal, I.; Al Zuabi, A.; Munzel, T.; Daiber, A. Comparison of mitochondrial superoxide detection ex vivo/in vivo by mitoSOX HPLC method with classical assays in three different animal models of oxidative stress. Antioxidants 2019, 8, 514. [CrossRef]

237. Wenzel, P.; Schulz, E.; Oelze, M.; Muller, J.; Schuhmacher, S.; Alhamdani, M.S.; Debrezion, J.; Hortmann, M.; Reifenberg, K.; Fleming, I.; et al. AT1-receptor blockade by telmisartan upregulates GTP-cyclohydrolase I and protects eNOS in diabetic rats. Free Radic. Biol. Med. 2008, 45, 619–626. [CrossRef]

238. Fakhruddin, S.; Allanazi, W.; Jackson, K.E. Diabetes-induced reactive oxygen species: Mechanism of their generation and role in renal injury. J. Diabetes Res. 2017, 2017, 8379327. [CrossRef]

239. Lassegue, B.; Walter, U.; et al. Differential eNOS regulation of vascular NADPH oxidase expression and reactive oxygen species production by histone deacetylase-dependent mechanisms in experimental diabetes. Circ. Res. 2001, 88, E14–E22. [CrossRef]

240. Parrinello, C.M.; Lutsey, P.L.; Ballantyne, C.M.; Folsom, A.R.; Pankow, J.S.; Selvin, E. Six-year change in high-sensitivity C-reactive protein and risk of diabetes, cardiovascular disease, and mortality. Am. Heart J. 2013, 165, 298–305. [CrossRef]

241. Ofstad, A.P.; Gullestad, L.; Orvik, E.; Aakhus, S.; Endresen, K.; Ueland, T.; Aukrust, P.; Fagerland, M.W.; Munzel, T.; Daiber, A. Comparison of mitochondrial superoxide detection ex vivo/in vivo by mitoSOX HPLC method with classical assays in three different animal models of oxidative stress. Antioxidants 2019, 8, 514. [CrossRef]

242. Wendt, M.C.; Daiber, A.; Kleschyov, A.L.; Mulsch, A.; Sydow, K.; Schulz, E.; Chen, K.; Keaney, J.F., Jr.; Lassegue, B.; Walter, U.; et al. Differential effects of diabetes on the expression of the gp91(phox) homologues nox1 and nox4. Free Radic. Biol. Med. 2005, 39, 381–391. [CrossRef]

243. Rezende, F.; Moll, F.; Walter, M.; Helfinger, V.; Hahner, F.; Janetzko, P.; Ringel, C.; Weigert, A.; Fleming, I.; Weiswmann, N.; et al. The NADPH oxidase Nox1 and p47phox are both mediators of diabetes-induced vascular dysfunction in mice. Redox Biol. 2018, 15, 12–21. [CrossRef]

244. Gray, S.P.; Di Marco, E.; Okabe, J.; Szendralewicz, C.; Heitz, F.; Montezano, A.C.; de Haan, J.B.; Koulis, C.; El-Osta, A.; Andrews, K.L.; et al. NADPH oxidase 1 plays a key role in diabetes mellitus-accelerated atherosclerosis. Circulation 2013, 127, 1888–1902. [CrossRef]
Ranieri, S.C.; Fusco, S.; Panieri, E.; Labate, V.; Mele, M.; Tesori, V.; Ferrara, A.M.; Maulucci, G.; De Spirito, M.; Widlansky, M.E.; Hill, R.B. Mitochondrial regulation of diabetic vascular disease: An emerging opportunity.

Desco, M.C.; Asensi, M.; Marquez, R.; Martinez-Valls, J.; Vento, M.; Pallardo, F.V.; Sastre, J.; Vina, J. Xanthine oxidase synthase by peroxynitrite.

Deshwal, S.; Forkink, M.; Hu, C.H.; Buonincontri, G.; Antonucci, S.; Di Sante, M.; Murphy, M.P.; Paolocci, N.; Lettas, K.P.; et al. Monoamine oxidase-dependent endoplasmic reticulum-mitochondria dysfunction and mast cell degranulation lead to adverse cardiac remodeling in diabetes.

Rota, M.; LeCapitaine, N.; Hosoda, N.; Boni, A.; De Angelis, A.; Padin-Truegas, M.E.; Esposito, G.; Vitale, S.; Urbanek, K.; Casarsa, C.; et al. Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene.

Menini, S.; Amadio, L.; Oddi, G.; Ricci, C.; Pesce, C.; Pugliese, F.; Giorgio, M.; Migliaccio, E.; Pelicci, P.; Iacobini, C.; et al. Deletion of p66Shc longevity gene protects against experimental diabetic glomerulopathy by preventing diabetes-induced oxidative stress.

Rota, M.; LeCapitaine, N.; Hosoda, N.; Boni, A.; De Angelis, A.; Padin-Truegas, M.E.; Esposito, G.; Vitale, S.; Urbanek, K.; Casarsa, C.; et al. Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene.

Ranieri, S.C.; Fusco, S.; Panieri, E.; Labate, V.; Mele, M.; Tesori, V.; Ferrara, A.M.; Maulucci, G.; De Spirito, M.; Martorana, G.E.; et al. Mammalian life-span determinant p66shcA mediates obesity-induced insulin resistance.

Deswal, S.; Di Sante, M.; Di Lisa, F.; Kaludercic, N. Emerging role of monoamine oxidase as a therapeutic target for cardiovascular disease.

Deswal, S.; Di Sante, M.; Di Lisa, F.; Kaludercic, N. Emerging role of monoamine oxidase as a therapeutic target for cardiovascular disease.

Yang, Y.; Zhao, J.; Qiu, J.; Li, J.; Liang, X.; Zhang, Z.; Zhang, X.; Fu, H.; Korantzopoulos, P.; Lettas, K.P.; et al. Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes mellitus rabbits.

Mizuno, Y.; Yamamotoya, T.; Nakatsu, Y.; Ueda, K.; Matsunaga, Y.; Inoue, M.K.; Sakoda, H.; Fujishiro, M.; Ono, H.; Kikuchi, T.; et al. Xanthine oxidase inhibitor febuxostat exerts an anti-inflammatory action and protects against diabetic nephropathy development in KK-Ay obese diabetic mice.

Xiao, L.; Xu, X.; Zhang, F.; Wang, M.; Xu, Y.; Tang, D.; Wang, J.; Qin, Y.; Liu, Y.; Tang, C.; et al. The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via Nrf2/PINK1.

Xia, L.; Xu, X.; Zhang, F.; Wang, M.; Xu, Y.; Tang, D.; Wang, J.; Qin, Y.; Liu, Y.; Tang, C.; et al. The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via Nrf2/PINK1.

Menini, S.; Amadio, L.; Oddi, G.; Ricci, C.; Pesce, C.; Pugliese, F.; Giorgio, M.; Migliaccio, E.; Pelicci, P.; Iacobini, C.; et al. Deletion of p66Shc longevity gene protects against experimental diabetic glomerulopathy by preventing diabetes-induced oxidative stress.

Sukumar, P.; Viswambharan, H.; Imrie, H.; Cubbon, R.M.; Yuldasheva, N.; Gage, M.; Galloway, S.; Skromna, A.; Kandavelu, P.; Santos, C.X.; et al. Nox2 NADPH oxidase has a critical role in insulin resistance-related endothelial cell dysfunction.

Xiang, F.L.; Lu, X.; Strutt, B.; Hill, D.J.; Feng, Q. NOX2 deficiency protects against streptozotocin-induced beta-cell destruction and development of diabetes in mice.

Ni, R.; Cao, T.; Xiong, S.; Ma, J.; Fan, G.C.; Lacefield, J.C.; Lu, Y.; Le Tissier, S.; Peng, T. Therapeutic inhibition of mitochondrial reactive oxygen species with mito-TEMPO reduces diabetic cardiomyopathy.

Ono, H.; Kikuchi, T.; et al. Xanthine oxidase inhibitor febuxostat exerts an anti-inflammatory action and protects against diabetic nephropathy development in KK-Ay obese diabetic mice.

Uchino, H.; Elmer, E. Evaluation of putative inhibitors of mitochondrial permeability transition for brain disorders–specificity vs. toxicity.

Elrod, J.W.; Duranski, M.R.; Langston, W.; Greer, J.J.; Tao, L.; Dugas, T.R.; Kevil, C.G.; Champion, H.C.; Lefer, D.J. eNOS gene therapy exacerbates hepatic ischemia-reperfusion injury in diabetes: A role for eNOS uncoupling.

Zou, M.H.; Shi, C.; Cohen, R.A. Oxidation of the zinc-thiolate complex and uncoupling of endothelial nitric oxide synthase by peroxynitrite.

Morota, S.; Mansson, R.; Hansson, M.J.; Kasuya, K.; Shimazu, M.; Hasegawa, E.; Yanagi, S.; Omi, A.; Uchino, H.; Elmer, E. Evaluation of putative inhibitors of mitochondrial permeability transition for brain disorders–specificity vs. toxicity.

Mochly-Rosen, D.; Krieg, T.; et al. Monoamine oxidase-dependent endoplasmic reticulum-mitochondria dysfunction and mast cell degranulation lead to adverse cardiac remodeling in diabetes.

Xiang, F.L.; Lu, X.; Strutt, B.; Hill, D.J.; Feng, Q. NOX2 deficiency protects against streptozotocin-induced beta-cell destruction and development of diabetes in mice.

Zou, M.H.; Shi, C.; Cohen, R.A. Oxidation of the zinc-thiolate complex and uncoupling of endothelial nitric oxide synthase by peroxynitrite.

Biomed. 2016, 90, 12–23. [CrossRef] [PubMed]

Int. J. Mol. Sci. 2019, 20, 4680. [CrossRef] [PubMed]

Int. J. Mol. Sci. 2018, 99, 78–85. [CrossRef]

Proc. Natl. Acad. Sci. USA 2010, 107, 13420–13425. [CrossRef]

Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes mellitus rabbits. J. Am. Heart Assoc. 2018, 7, e008807. [CrossRef]

J. Clin. Investig. 2018, 123, e12380. [CrossRef]

Diabetes 2006, 55, 1642–1650. [CrossRef] [PubMed]

Diabetes 2013, 62, 2130–2134. [CrossRef] [PubMed]

Diabetes 2009, 58, 42–52. [CrossRef]

Diabetes 2013, 62, 297–311. [CrossRef] [PubMed]

Diabetes 2018, 107, 13420–13425. [CrossRef]

Diabetes 2009, 58, 42–52. [CrossRef]

Diabetes 2013, 62, 297–311. [CrossRef] [PubMed]

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