Hypertension is a complex, multifactorial, and multisystem disorder as originally described by Irvine Paige in his mosaic theory when he proposed that high blood pressure involves interplay among many elements, including genetic, environmental, anatomic, adaptive, neural, endocrine, humoral, and hemodynamic factors. Since then, there has been enormous progress in discovering the molecular and cellular processes that connect the numerous components underlying hypertension. In 2013, David Harrison revisited Paige’s mosaic theory, highlighting common molecular mechanisms, specifically oxidative stress and inflammation, as major drivers coordinating diverse cellular events and organ systems in hypertension.

Oxidative stress is characterized by excessive production of reactive oxygen species (ROS) and altered oxidation-reduction (redox) state. These molecular events induce protein oxidation and dysregulated cell signalling, leading to inflammation, proliferation, apoptosis, migration, and fibrosis, which are important processes contributing to impaired vascular function, cardiovascular remodelling, renal dysfunction, immune cell activation, and sympathetic nervous system excitation in hypertension.

A major source of cardiovascular ROS is a family of nonphagocytic NADPH oxidases (Nox1, Nox2, and Nox4 in rodents and Nox1, Nox2, Nox4, and Nox5 in humans). Expression and activation of Nox isoforms are increased in hypertension and are a likely cause of oxidative stress in cardiovascular, renal, and immune cells in hypertension-associated target organ damage. Other enzymatic sources of ROS include mitochondrial oxidases, xanthine oxidase, endoplasmic reticular oxidases, and uncoupled nitric oxide synthase (NOS).

Whereas the ROS-generating role of non-NADPH oxidases in cardiovascular cells seems to be minor in physiologic conditions, growing evidence suggests that ROS generated in mitochondria and the endoplasmic reticulum (ER) may contribute to oxidative stress in hypertension. This likely involves cross-talk between Noxs and mitochondria/ER. In particular, the concept of ROS-induced ROS release (RIRR) may be important, whereby ROS formed in one region activates ROS in another region (Fig. 1). A number of pharmacologic strategies have been developed to lower cross-talk between Noxs and mitochondria/ER. Mitochondrial oxidative stress—induced endothelial dysfunction in hypertension has been attributed to reduced sirtuin 3 (SIRT3)—mediated superoxide dismutase 2 (SOD2) signalling. These processes were ameliorated by restoration of SIRT3, suggesting that SIRT3 influences the mitochondrial redox state by regulating mitochondrial antioxidant systems.

Moreover, recent studies in
oxidants and antioxidants in favour of the oxidants that leads to a
disruption of oxidation-reduction (redox) signalling and control and
molecular damage. Physiologically, reactive oxygen species (ROS) act
as signalling molecules and influence cell function through highly
regulated redox-sensitive signal transduction. In hypertension, oxidative
stress promotes posttranslational modification (oxidation and
phosphorylation) of proteins and aberrant signalling with consequent
cell and tissue damage. Many enzymatic systems generate ROS, but
NADPH oxidases (Nox) are the major sources in cells of the heart,
vessels, kidneys, and immune system. Expression and activity of Nox
are increased in hypertension and are the major systems responsible
for oxidative stress in cardiovascular disease. Here we provide a uni-
ifying concept where oxidative stress is a common mediator underlying
pathophysiologic processes in hypertension. We focus on some novel
concepts whereby ROS influence vascular function, aldosterone/
mineralocorticotid actions, and immunoinflammation, all important
processes contributing to the development of hypertension.

humans showed that chronic supplementation with a mito-
chondrial antioxidant (MitoQ) improves vascular function in
aged individuals. Mitochondrial dysfunction and ROS
generation in the brain seem to be especially important in
neurogenic hypertension, where neural mitochondrial
biogenesis and bioenergetics influence sympathetic outflow to
the cardiovascular system. The ER has also been implicated in oxidative stress in
hypertension. We demonstrated that vascular hyper-
contractility in stroke-prone spontaneously hypertensive
rats (SHR-SPs) involves oxidative and ER stress through
Nox4-dependent processes. Inhibition of ER stress with
the use of 4-phenylbutyric acid (4-PBA) and STF083010
(an IRE1-XBP1 disruptor) ameliorated vascular dysfunction
in SHR-SPs. Treatment of SHR with 4-PBA reduced blood pressure and improved vascular function
and structure by ameliorating ER stress. Although ER-
and mitochondria-derived ROS may contribute in part to
oxidative stress in hypertension, the upstream driving fac-
tor appears to be Nox activation.

Oxidative stress and altered redox signalling are emerging
as major pathogenic factors in cardiovascular disease. This
review examines the role of cellular oxidants in the cardio-
vascular system and focuses on oxidative stress as a common
molecular process in some pathophysiologic events underlying
hypertension. In particular, we discuss some novel concepts
related to the central role of ROS in vascular function,
hyperlaldosteronism, and inflammation in hypertension. ROS
also influence many other systems involved in hypertension,
and the reader is referred to recent papers for further details.

**Reactive Oxygen Species, Oxidative Stress, and
Redox Signalling in Hypertension**

In physiologic conditions, ROS are intimately involved in
and required for normal biological function, in large part
through tightly controlled redox regulation, redox signaling
and redox sensing. In pathological conditions, uncontrolled
ROS production leads to oxidative stress defined as “an
imbalance between oxidants and antioxidants in favor of the
oxidants, leading to a disruption of redox signaling and con-
trol and/or molecular damage.” The most important ROS are superoxide anion (O2−),
hydrogen peroxide (H2O2), nitric oxide (NO), and perox-
nitrite (ONOO−). Although O2− is highly unstable and
cell membrane impermeable, H2O2 is cell membrane
permeable, is stable, and has a longer half-life than O2−,
making it an efficient signalling molecule. NO, produced
enzymatically by NOS, is the prototype endothelial-derived
vasodilator. When NO reacts with O2−, it forms
the prototype endothelial-derived
vasodilator. When NO reacts with O2−, it forms
ONOO−, a strong oxidant that is highly unstable. When
protonated (HOONO), peoxynitrite is cell membrane
permeable. The interplay between O2− and NO, together with
disregulated production of O2− and H2O2, contributes to
altered cellular redox status and oxidative damage of cells and
tissues.

ROS influence cell function by modifying proteins
through posttranslational modifications, such as oxidation,
sulfenylation, nitrosylation, glutathionylation, and carbamoy-
lization and phosphorylation. Proteins that are redox
sensitive include ion transporters, receptors, signalling mole-
cules, transcription factors, cytoskeletal structural proteins,
and matrix metallopeptases, all of which are involved in
regulating vascular, cardiac, and renal functions. ROS are
key signalling molecules through which vasoactive agents such
as angiotensin II (Ang II), endothelin-1 (ET-1), aldosterone,
and prostanooids mediate cellular effects, and they regulate
intracellular calcium homeostasis, which is important in
triggering and maintaining vasoconstriction and cardiac
contraction. ROS activate all 3 members of the mitogen-
activated protein kinase (MAPK) family, including ERK1/2,
p38MAPK, and JNK, which control cardiac and vascular cell
Evidence Supporting a Role for ROS and Oxidative Stress in Hypertension

Oxidative stress has been causally linked to increased blood pressure in various experimental models of hypertension, including genetic hypertension (spontaneously hypertensive rats [SHRs], stroke-prone SHRs [SHR-SPs]), endocrine-induced hypertension [Ang II, aldosterone, deoxycorticosterone acetate (DOCA)], surgically induced hypertension (2-kidney 1-clip [2K1C], aortic banding), diet-induced hypertension (salt, fat, zinc), neurogenic hypertension, pulmonary hypertension, and preeclampsia. Biomarkers of oxidative stress, including plasma and urinary thiobarbituric acid—reactive substances (TBARS) and F$_2$-isoprostanes, tissue concentrations of O$_2^-$ and H$_2$O$_2$, and activation of Noxes and xanthine oxidase, are increased, whereas levels of NO and antioxidant enzymes are reduced in experimental hypertension. Further supporting a role for oxidative stress in the pathophysiology of hypertension are studies demonstrating blood pressure—lowering effects of antioxidants, ROS scavengers, and Nox inhibitors. Treatment with antioxidant vitamins (vitamins C and E), SOD mimetics (tempol [4-hydroxy-2,2,6,6-tetramethyl piperidinoxyl]), free radical scavengers (N-acetyl-l-cysteine), tetrahydrobiopterin, nonspecific Nox inhibitors (apocynin, diphenylene iodonium), and specific Nox inhibitors (gp91dstat, GKT compounds) reduce oxidative stress and ameliorate or prevent development of hypertension and associated target-organ damage.

Although experimental data support an etiologic role for oxidative stress in the development of hypertension, there is still no confirmation that oxidative stress is a primary cause of hypertension in humans. Reasons for this are complex, as we have previously highlighted, and relate in large part to 1) lack of sensitive and specific assays that can accurately assess redox state in the clinical setting, 2) paucity of mechanistic studies in disease-appropriate human tissue, and 3) absence of pharmacologic agents that specifically target Nox isoforms or ROS that could be used in patients. Nevertheless, there is clear evidence that ROS production is increased in patients with essential hypertension, renovascular hypertension, malignant hypertension, salt-sensitive hypertension, cyclosporine-induced hypertension, and preeclampsia. Population-based observational studies reported an inverse relationship between plasma antioxidants and blood pressure, and clinical studies have shown that systolic and diastolic blood pressures correlate positively with biomarkers of oxidative stress (plasma TBARS and 8-epi-isoprostanes) and negatively with antioxidant levels in patients with hypertension. Plasma levels of asymmetric dimethylarginine (endothelial NOS inhibitor) and the lipid peroxidation product of linoleic acid, 13-hydroxyoctadecadienoic acid, a marker of ROS production, were inversely correlated with blood pressures in hypertensive patients. Further supporting a role for oxidative stress in the pathophysiology of hypertension are studies in disease-appropriate human tissue, and 3) absence of pharmacologic agents that specifically target Nox isoforms or ROS that could be used in patients. Moreover, genome-wide association study data from more than 450,000 individuals identified Nox4 and Nox5 as novel blood pressure markers.
pressure–related genes. Although oxidative stress is likely not the sole cause of hypertension, it amplifies blood pressure elevation in the presence of other prohypertensive factors, such as Ang II, ET-1, aldosterone, and salt.

**Oxidative Stress, Sex, and Hypertension**

It is well known that premenopausal women are protected from hypertension relative to age-matched men and that this protection is lost with menopause. Although the biological basis for these sex-related differences in hypertension remain unclear, sex hormones, Y chromosome, Ang II, aldosterone, and sex hormone–related signalling play a critical role. In addition, growing evidence suggests that oxidative stress may be important in the sexual dimorphism in hypertension. Both clinical and preclinical studies have demonstrated that biomarkers of oxidative stress are higher in men than in women. In nonhuman male animals, blood pressure decreases in response to antioxidants such as tempol and apocynin, whereas female animals are nonresponsive. Oxidative stress is involved in the development and maintenance of hypertension in male rats but seems to be important only in the initial development of hypertension in female rats. In Ang II–induced hypertension in mice, plasma levels of TBARS were increased in male but not in female mice. Moreover, Ang II induced a significant increase in O$_2^-$ and H$_2$O$_2$ production in isolated arteries from male but not female mice. These differences have been attributed to increased activation of Noxs in males and increased antioxidant capacity in females. It has also been shown that estradiol reduces expression and activity of Noxs and increases expression of antioxidant enzymes superoxide dismutase and glutathione peroxidase. Accordingly, the blunted oxidative stress–mediated increase in blood pressure in females may be due to increased activation of antioxidant systems and down-regulation of prooxidant systems. Taken together, the current data suggest that oxidative stress may be more important in blood pressure elevation in males than in females.

**Oxidative Stress: A Unifying Mechanism in the Hypertension Mosaic**

Because ROS are key players in regulating cardiovascular function, it is not surprising that abnormal ROS regulation and oxidative stress play an important role in the pathophysiology of hypertension. Moreover, because oxidative stress influences myriad signalling molecules and pathways in multiple cells, tissues, organs, and systems, it represents a common molecular mechanism unifying the multifactorial mosaic (Fig. 1) that underlies hypertension. Here we focus on some new concepts relating to the central role of oxidative stress in Figure 1. Oxidative stress as a unifying factor in hypertension. Prohypertensive factors, eg, angiotensin II (Ang II), endothelin-1 (ET-1), aldosterone (Aldo), and salt (Na$^+$), induce activation of NADPH oxidases (Noxs) that generate reactive oxygen species (ROS), which influence multiple systems involved in the pathophysiology of hypertension. AT1R, angiotensin II type 1 receptor; ER, endoplasmic reticulum; ETAR, endothelin-1 type A receptor; MR, mineralocorticoid receptor; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor.
the regulation of vascular function by vasoactive agents and
growth factors, aldosterone and signalling through mineralo-
corticoid receptors, and inflammation and the immune
system.

**Vasoactive Factors, Oxidative Stress, and the
Vasculature**

Impaired endothelium-dependent vasorelaxation, increased
vasoconstriction, vascular remodelling and inflammation,
reduced distensibility, and increased stiffness are characteristic
features of small and large arteries in hypertension and
constitute the vascular phenotype, or “vasculopathy,” of
hypertension. Some of these vascular changes occur with
physiologic aging, but in hypertension and diabetes the pro-
cesses are accelerated, leading to “premature vascular aging,” a
process that is highly redox sensitive. These phenomena
are dynamic and involve functional (contraction-relaxation)
and structural changes (remodelling) that occur at different
phases during development of hypertension. They are defined
by complex interactions between vascular cells (endothelium,
VSMCs, adventitial fibroblasts) and circulating elements,
including vasoactive agents, (Ang II, ET-1, aldosterone,
dopamine, catecholamines, prostanoids), growth factors
(epidermal growth factor [EGF], insulin-like growth factor 1
[IGF-1], platelet-derived growth factor [PDGF]), sex hor-
mones, microRNAs, exosomes, and endothelial progenitor
cells. In addition, risk factors such as salt and fine particulate
matter (air pollutants) can induce vascular dysfunction and
inflammation in hypertension. Common to many of these
processes is oxidative stress and activation of redox-
sensitive signalling pathways.

**Ang II and ET-1**

Among the many circulating vasoactive factors involved in
the pathophysiology of hypertension, Ang II and ET-1 are
especially important. They are potent vasoconstrictor,
mitogenic, and proinflammatory peptides that are critically
involved in regulating the cardiovascular system. Activation of
their respective vascular G protein–coupled receptors results in
Nox activation and increased generation of ROS, which if
uncontrolled leads to oxidative stress and stimulation of
vascular signalling pathways such as MAPK, PKC, phospho-
lipase C, cellular Src, and Rho kinase (Fig. 2). Increased
vascular ROS bioavailability induced by Ang II, ET-1, and
other vasoactive peptides also cause activation of Ca$^{2+}$
channels, leading to accumulation of intracellular Ca$^{2+}$ which in
turn activates Ca$^{2+}$-sensitive Nox isoforms in the vasculature,
specifically Nox5, promoting a feedforward system amplifying
oxidative signalling and vascular damage. Many of these sys-
tems are up-regulated in hypertension. We recently identified
transient receptor potential melastatin 2 cation channel as an
important Ca$^{2+}$ channel that acts as a link between Ca$^{2+}$ and
redox signalling, a phenomenon that is increased in VSMCs in
hypertension. Vascular oxidative stress is also associated with
altered phosphatase activity that further amplifies kinase sig-
nalling and thus contributes to vascular damage in
hypertension.

In Ang II–induced hypertension in mice and rats,
expression of Nox subunits, activity of Noxs, ROS genera-
tion, and oxidation of signalling molecules are increased.
These processes cause oxidative damage of cells and tissues
with consequent endothelial dysfunction, renal injury, and
cardiovascular remodelling, processes that are attenuated by
angiotensin-converting enzyme inhibitors, ROS scavengers,
and Nox inhibitors. Moreover, in mice deficient in Nox2
and p47phox, the blood pressure–elevating effect of Ang II
is blunted. These findings confirm the central role of
ROS in Ang II–mediated vascular dysfunction and
hypertension.

In addition to influencing Ang II vascular effects, ROS are
important mediators of ET-1–induced cardiovascular
dysfunction and hypertension. In mice overexpressing ET-1
in an endothelial-specific manner, blood pressure was
increased in an ET type A receptor (ETAR)–dependent
manner. This was associated with reduced renal artery flow,
mesenteric small artery stiffening, endothelial dysfunction,
vascular inflammation, and oxidative stress. In mice with
pressure overload and left ventricular hypertrophy induced by
transverse aortic coarctation, cardiac and coronary microvas-
cular dysfunction were causally linked to enhanced ET-1–
induced vasoconstriction, Rho kinase activation, and oxidative
stress. In sunitinib-induced hypertension, we showed that
endothelial dysfunction and arterial remodelling involved ET-
1/ETAR–mediated Nox activation and vascular oxidative
stress. Although ET-1 influences cardiovascular function
through ROS generation, ROS themselves regulate the
endothelin system. In Fischer 344 rats infused with a super-
oxide dismutase mimetic (AEOl 10150), plasma oxidative
stress markers and levels of ET-1 were reduced in a dose-
dependent manner. Clinically, serum ET-1 levels corre-
lated with biomarkers of oxidative stress in patients with
hypertension.

**Growth factors**

Many of the cardiovascular effects of Ang II and ET-1 are
amplified by growth factors in hypertension. Growth factors
such as EGF, IGF-1, and PDGF, which signal through their
cognate receptor tyrosine kinases, induce activation of mito-
genic pathways through ROS-dependent events. These
processes are also stimulated by Ang II and ET-1, which
transactivate growth factor receptors through various mecha-
nisms, including A disintegrin and metalloproteinase 17
(ADAM17)–dependent shedding of growth factors, tyrosine
kinase phosphorylation, and ROS107 (Fig. 2). Vascular
smooth muscle cells from SHRs exhibit increased cell prolif-
eration through Ang II/Ang II type 1 receptor (AT1R)–
and ET-1/ETAR–mediated transactivation of EGFR. These
processes involve increased Nox activity, oxidative stress,
activation of cellular Src, and EGF-mediated activation of
MAPKs. Ang II also transactivates the IGF-1 receptor and
PDGF receptor in VSMCs through ROS generation and
activation of PI3K, p38MAPK, and ERK5 pathways, leading
to vascular hypertrophy and fibrosis. The cross-talk
between G protein–coupled receptor and GFR signal-
ing is up-regulated in hypertension and is influenced by ROS
both upstream and downstream of receptor tyrosine kinase
signaling. Accordingly, oxidative stress may be a common
mechanism driving the amplified hypertrophic, fibrotic, and
inflammatory responses induced by Ang II, ET-1, and growth
factors in hypertension.
Aldosterone, Oxidative Stress, and Hypertension

An important component of the renin-angiotensin system in blood pressure regulation is Ang II stimulation of adrenal cortical cells to produce aldosterone, which signals through renal mineralocorticoid receptors (MRs) to regulate body electrolyte and fluid homeostasis. Aldosterone also signals through extrarenal MRs that influence vascular tone, adipose tissue function, cardiac contraction, and cardiovascular fibrosis. High levels of aldosterone are associated with hypertension, obesity, and increased risk of cardiovascular and cardiometabolic disease. Primary hyperaldosteronism accounts for 5%-15% of patients with hypertension. Experimental models of MR-dependent hypertension (deoxycorticosterone acetate/salt and aldosterone/salt rodents) exhibit oxidative stress as evidenced by increased Nox expression/activity, increased vascular ROS production, and elevated levels of TBARS, effects that are ameliorated by treatment with MR antagonists.

Aldosterone signals through its MRs through genomic and nongenomic pathways, with increasing evidence indicating a critical role for ROS in these processes. It increases ROS production in cultured VSMCs and endothelial cells. In VSMCs, aldosterone increases O$_2^-$ production primarily through up-regulation of Nox1, whereas in endothelial cells Nox4 seems to be more important. Nongenomic Nox-induced ROS generation by aldosterone/MR involves cellular Src and Rac-1, as we demonstrated in VSMCs from SHRs. In addition, there is tight interplay between Ang II and aldosterone redox signalling. Blockade of MRs inhibits Ang II–induced ROS production in vascular tissue, and AT1R is required for MR-induced endothelial dysfunction, vascular remodelling, inflammation, and oxidative stress in hypertension. In cardiomyocytes, interactions between MRs and AT1Rs participate in aldosterone-induced ROS generation through G protein–coupled receptor kinase 2–regulated Nox4.

Aldosterone is a potent profibrotic hormone involved in cardiac and vascular fibrosis and remodelling in hypertension. These effects are Nox1-ROS dependent and involve nongenomic and genomic signalling through increased expression/activity of adhesion molecules (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1]), osteopontin, plasminogen activator inhibitor 1 (PAI-1), and growth factors. Further supporting a role for ROS in aldosterone-mediated actions are in vitro studies showing that MR antagonists decrease expression of Nox isoforms and subunits and attenuate oxidative stress. Moreover, in vivo studies showed that antioxidants blunt blood pressure-elevating effects of aldosterone and, in mice overexpressing MR, that hypertension is associated with oxidative stress, effects that are absent when MR is knocked out.

Figure 2. Transactivation of growth factor receptors (GFRs) by angiotensin II (Ang II) and endothelin-1 (ET-1), through their G protein–coupled receptors (GPCRs), stimulate NADPH oxidase (Nox)–derived reactive oxygen species (ROS) production and activation of ROS-signalling pathways that influence cardiovascular processes leading to hypertension-associated target-organ damage.
out in an endothelial-specific manner. In addition, cardiomyocyte-specific overexpression of human MR induces severe coronary endothelial dysfunction with decreased NO-mediated relaxing responses to acetylcholine in coronary arteries (but not in peripheral arteries), effects prevented by MR antagonists, vitamin E/vitamin C, or a Nox inhibitor.137

Beyond its renal and cardiovascular effects, aldosterone influences immune cells and adipocytes, which also affect cardiovascular fibrosis and inflammation in hypertension. MRs are expressed in macrophages and T cells, where they function as a transcriptional regulator of cellular phenotype and function. The relationship between immune cells, MRs, and oxidative stress in hypertension was clearly demonstrated in aldosterone/salt–treated mice, which exhibited increased H2O2 production, up-regulation of oxidative stress–inducible tyrosine phosphatase and manganese-dependent SOD genes, and increased 3-nitrotyrosine expression in lymphocytes together with CD4+ inflammatory cells invading intramural coronary arteries. Some of the proinflammatory cardiovascular effects of aldosterone have been attributed to activation of macrophage MRs and adipocyte MRs. In adipocytes, aldosterone-induced MR activation causes Nox2 activation, ROS production, and activation of inflammatory pathways. In adipocytes, aldosterone/MR stimulates production of proinflammatory adipokines and ROS, which are especially important in vascular dysfunction in obesity-associated hypertension. Oxidative stress in different cell types, including VSMCs, endothelial cells, cardiomyocytes, renal cells, immune cells, and adipocytes emerges as an important player contributing to aldosterone/MR–induced cardiovascular dysfunction and damage associated with hyperaldosteronism. Accordingly, it may be possible that some of the vasoprotective and antihypertensive effects of MR antagonists, such as eplerenone and spironolactone, may be mediated, at least in part, by inhibiting aldosterone/MR–induced oxidative stress.

Oxidative Stress and Inflammation in Hypertension

The importance of inflammation in cardiovascular disease was first suggested by Ross in the 1990s, who showed that excessive inflammatory-fibroproliferative responses to various forms of insult to the endothelium and smooth muscle of the artery wall are critically involved in atherogenesis. There is now extensive experimental and clinical evidence indicating that hypertension is associated with inflammation, fibrosis, and activation of immune cells, processes that are driven in large part by oxidative stress. Tissue expression of adhesion molecules (VCAM-1, ICAM-1), production of inflammatory mediators (monocyte chemotactic peptide 1, tumour necrosis factor, interleukin [IL] 1, IL-6, IL-17), activation of proinflammatory signalling pathways (MAPK, STAT) and transcription factors (NF-kB, AP-1, HIF-1), and circulating levels of inflammatory biomarkers (C-reactive protein, PAI-1, ILs) are increased in hypertension. Although it still remains unclear whether inflammation is a cause or an effect of hypertension, it is clear that the immune system and ROS are important players.

Immunoinflammation, Oxidative Stress, and Hypertension

The importance of the immune system in the pathophysiology of hypertension relates primarily to its effects on inflammation, which is involved in the initiation, progression, and exacerbation of cardiovascular tissue damage and remodelling. Once activated, immune cells generate high levels of ROS through Nox-dependent mechanisms, leading to cytokine production and infiltration of immune cells into the vascular wall, kidney, and heart, causing tissue damage in hypertension. The damaging effects of immune cell activation is the consequence of a shift in balance between proinflammatory and antiinflammatory cytokines and mediators and involve cells of both the adaptive (CD8+ T cells, CD4+ T cells [T11, T12, T117, Treg cells], B cells] and innate immune systems (macrophages, monocytes, microglia, dendritic cells). As part of the innate immune system, inflammasomes seem to be especially important in inflammation, with increasing evidence suggesting a role for ROS-induced regulation of inflammasomes in hypertension. The NLRP3 inflammasome platform may play a key role in coordinating inflammatory responses in hypertension, especially in the context of caspase-1–, IL-1β–, and IL-18–mediated reactions. Activation of NLRP3 inflammasome through redox-dependent processes has been shown in Ang II–mediated and DOCA/salt hypertension and in pre-eclampsia, pulmonary hypertension, and hypertension-associated kidney dysfunction.

The importance of the immune system and oxidative stress in hypertension has been studied in various immunodeficient mouse models. The adaptive immune system in the pathophysiology of hypertension was first demonstrated in Rag1–/– mice, which lack B and T lymphocytes. In these immunodeficient mice, development of hypertension and generation of ROS induced by Ang II and DOCA/salt were blunted, effects that were reversed with adoptive transfer of T but not with B cells. Similar blood pressure responses were observed in mice deficient in macrophage colony–stimulating factor (op/op–/– mice). These mice, which lack macrophages, are resistant to Ang II–induced hypertension and have reduced ROS generation and vascular inflammation compared with macrophage-intact mice. In monocyte-deficient mice, pressor effects and vascular dysfunction induced by Ang II infusion were blunted, responses that were restored with adoptive transfer of wild-type monocytes. Together, these studies, among many, clearly indicate an important role for the adaptive and innate immune systems and oxidative stress in hypertension. Multiple factors have been implicated in the activation and regulation of immune cells in hypertension, including catecholamines, Ang II, salt, ROS, and neoantigens, as discussed in detail in the current issue of this journal.

Conclusion

There has been enormous progress in the understanding of cardiovascular, renal, and neural mechanisms involved in the pathophysiology of hypertension. Over the past decade, many new systems and factors have been identified as being important in the development of hypertension and hypertension-associated target-organ damage, including the
immune system, inflammation, sex hormones, microRNAs, interstitial sodium, the microbiome, and environmental stressors. Common to these processes is oxidative stress with associated abnormal redox status and altered redox signalling. Here we have provided a unifying paradigm whereby oxidative stress acts as a common mediator of cell injury and inflammation in multiple systems that influence blood pressure regulation. Although the exact causes of oxidative stress in hypertension remain unclear, dysregulation of Noxs in cardiovascular, renal, immune, and neural cells seems to be important. The most significant consequence of oxidative stress is increased posttranslational oxidation of proteins and perturbed redox-dependent signalling. To fully understand the functional impact of oxidative stress in health and disease, it will be essential to know how proteins are differentially oxidised and activated. This will demand high-fidelity redox proteomics, which we believe is the next frontier in the unravelling of mechanism-specific targets in hypertension.

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**References**

1. Oparil S, Acelajado MC, Bakris GL, et al. Hypertension. Nat Rev Dis Primers 2018;4:18014-20.
2. Harrison DG. The mosaic theory revisited: common molecular mechanisms coordinating diverse organ and cellular events in hypertension. J Am Soc Hypertens 2013;7:68-74.
3. Harvey A, Montezano AC, Touyz RM. Vascular biology of ageing—implications in hypertension. J Mol Cell Cardiol 2015;8:112-21.
4. Stanley CP, Maghzal GJ, Ayer A, et al. Singlet molecular oxygen regulates vascular tone and blood pressure in inflammation. Nature 2019;5:548-52.
5. Knock GA. NADPH oxidase in the vasculature: expression, regulation and signalling pathways: role in normal cardiovascular physiology and its dysregulation in hypertension. Free Radic Biol Med 2019;1:385-427.
6. Lassegue B, Clempus RE. Vascular NAD(P)H oxidases: specific features, expression, and regulation. Am J Physiol Regul Integr Comp Physiol 2003;2:R277-97.
7. Montezano AC, Burger D, Ceravolo GS, et al. Novel Nox homologues in the vasculature: focusing on Nox4 and Nox5. Clin Sci (Lond) 2011;1:131-41.
8. Touyz RM, Schiffrin EL. Increased generation of superoxide by angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients: role of phospholipase D—dependent NAD(P)H oxidase—sensitive pathways. J Hypertens 2001;1:1245-54.
9. Zhang Y, Murugesan P, Huang K, Cai H. NADPH oxidases and oxidase crosstalk in cardiovascular diseases: novel therapeutic targets. Nat Rev Cardiol 2020;17:170-94.
10. Dikalova AE, Bikineyeva AT, Budzyn K. Therapeutic targeting of mitochondrial superoxide in hypertension. Circ 2010;1:106-16.
11. Dikalov RR, Nazarewicz A, Bikineyeva AT. Nox2—induced production of mitochondrial superoxide in angiotensin II—mediated endothelial oxidant stress and hypertension. Antioxid Redox Signal 2014;2:281-9.
12. Carlile RE, Werner KE, Yum V, et al. Endoplasmic reticulum stress inhibition reduces hypertension through the preservation of resistance blood vessel structure and function. J Hypertens 2016;3:1556-69.
13. Zinkevich NS, Guterman DD. ROS—induced ROS release in vascular biology: redox—redox signalling. Am J Physiol 2011;3:647-53.
14. Koja N, Taleb A, Zhou J, et al. Pharmacological strategies to lower crosstalk between nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondria. Biomed Pharmacother 2019;1:1478-98.
15. He J, Liu X, Su C, et al. Inhibition of mitochondrial oxidative damage improves reendothelialization capacity of endothelial progenitor cells via SIRT3 (Sirtuin 3)—enhanced SOD2 (superoxide dismutase 2) deacetylation in hypertension. Arterioscler Thromb Vasc Biol 2019;3:1682-98.
16. Rosman MJ, Santos-Parker JR, Steward CAC, et al. Chronic supplementation with a mitochondrial antioxidant (MitoQ) improves vascular function in healthy older adults. Hypertension 2018;7:1056-63.
17. Chan SHH, Chan JYH. Mitochondria and reactive oxygen species contribute to neurogenic hypertension. Physiology (Bethesda) 2017;3:308-21.
18. Camargo LL, Harvey AP, Rios FJ, et al. Vascular Nox (NADPH oxidase) compartmentalization, protein hyperoxidation, and endoplasmic reticulum stress response in hypertension. Hypertension 2018;7:235-46.
19. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Chem Biol Interact 2014;2:164-75.
20. Sies H, Berndt C, Jones DP. Oxidative stress. Annu Rev Biochem 2017;8:715-48.
21. Lichtenberg D, Pinchuk I. Oxidative stress, the term and the concept. Biochem Biophys Res Commun 2015;4:441-4.
22. Sies H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: oxidative eustress. Redox Biol 2017;1:613-9.
23. Sies H. On the history of oxidative stress: concept and some aspects of current development. Curr Opin Toxicol 2018;7:122-6.
24. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;2:373-6.
25. Ignarro LJ, Byrns RE, Buga GM, Wood KS, Chaudhuri G. Pharmacological evidence that endothelium-derived relaxing factor is nitric oxide: use of pyrogallol and superoxide dismutase to study endothelium-dependent and nitric oxide—elicited vascular smooth muscle relaxation. J Pharmacol Exp Ther 1988;2:181-9.
26. Ferrer-Sueta G, Campolo N, Trujillo M, et al. Biochemistry of peroxynitrite and protein tyrosine nitration. Chem Rev 2018;1:1338-408.
27. Incalza MA, d’Oria R, Natalicchio A, et al. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol 2018;1:1-19.
28. Baba SP, Bhatnagar A. Role of thiols in oxidative stress. Curr Opin Toxicol 2018;7:133-9.
29. Hawkins CL, Davies MJ. Detection, identification, and quantification of oxidative protein modifications. J Biol Chem 2019;2:19683-708.

30. Griendling KK, Touyz RM, Zweier JL, et al. Measurement of reactive oxygen species, reactive nitrogen species, and redox-dependent signaling in the cardiovascular system: a scientific statement from the American Heart Association. Circ Res 2016;1:39-75.

31. Skoko JJ, Attaran S, Neumann CA. Signals getting crossed in the entanglement of redox and phosphorylation pathways: phosphorylation of peroxiredoxin proteins sparks cell signaling. Antioxidants (Basel) 2019;8:29.

32. Wenzel P, Kossmann S, Müinz T, Daiber A. Redox regulation of cardiovascular inflammation—inmunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. Free Radic Biol Med 2017;1:48-60.

33. Hood KY, Montezano AC, Harvey AP, et al. Nicotinamide adenine dinucleotide phosphate oxidase-mediated redox signaling and vascular remodeling by 16α-hydroxyestrone in human arterial cells: implications in pulmonary arterial hypertension. Hypertension 2016;6:796-808.

34. Vukelic S, Griendling KK. Angiotensin II, from vasoconstrictor to therapeutic target for chronic diseases: a systems medicine approach. Pharmacol Rev 2018;7:348-83.

35. Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal 2012;2:981-90.

36. García-Redondo AB, Briones AM, Martínez-Revelles S, et al. c-Src, ERK1/2 and Rho kinase mediate hydrogen peroxide-induced vascular contraction in hypertension: role of TXA2, NAD(P)H oxidase and mitochondria. J Hypertens 2015;3:7-87.

37. Wei Z, Salmon RM, Upton PD, Morrell NW, Li W. Regulation of bone morphogenetic protein 9 (BMP9) by redox-dependent proteolysis. J Biol Chem 2014;2:31150-9.

38. Tabet F, Schiffrin EL, Touyz RM. Mitogen-activated protein kinase activation by hydrogen peroxide is mediated through tyrosine kinase C-dependent, protein kinase C-independent pathways in vascular smooth muscle cells: upregulation in spontaneously hypertensive rats. J Hypertens 2005;2:2005-12.

39. Go YM, Jones DP. Cysteine/cystine redox signaling in cardiovascular disease. Free Radic Biol Med 2011;5:495-509.

40. Cuello F, Wittig I, Lorenz K, Eaton P. Oxidation of cardiac myofilament proteins: priming for dysfunction? Mol Aspects Med 2018;6:47-58.

41. Paravicini TM, Touyz RM. Redox signaling in hypertension. Cardiovasc Res 2006;7:247-58.

42. Cuadrado A, Manda G, Hassan A, et al. Transcription factor NRF2 as a therapeutic target for chronic diseases: a systems medicine approach. Pharmacol Rev 2018;7:348-83.

43. Brautigan DL, Shenolikar S. Protein serine/threonine phosphatases: keys to unlocking regulators and substrates. Annu Rev Biochem 2018;8:921-64.

44. Tabet F, Schiffrin EL, Callera GE, et al. Redox-sensitive signaling by angiotensin II involves oxidative inactivation and blunted phosphorylation of protein tyrosine phosphatase SHP-2 in vascular smooth muscle cells from SHR. Circ Res 2008;1:149-58.

45. Tejero J, Shiva S, Gladwin MT. Sources of vascular nitric oxide and reactive oxygen species and their regulation. Physiol Rev 2019;9:311-79.

46. Freed JK, Guterman DD. Communication is key: mechanisms of intercellular signaling in vasodilation. J Cardiovasc Pharmacol 2017;6:264-72.

47. Feehley M, Akaide T, Griffiths K, et al. Long-lasting blood pressure lowering effects of nitrite are NO-independent and mediated by hydrogen peroxide, peroxides, and oxidation of protein kinase Giβ2 redox signalling. Cardiovasc Res 2020;1:51-62.

48. Friederich-Person M, Nguyen Dinh Cat A, Person P, Montezano AC, Touyz RM. Brown adipose tissue regulates small artery function through NADPH oxidase 4-derived hydrogen peroxide and redox-sensitive protein kinase G-1α. Arterioscler Thromb Vasc Biol 2017;3:455-65.

49. Kim YM, Kim SJ, Tatsunami R, et al. ROS-induced ROS release orchestrated by Nox4, Nox2, and mitochondria in VEGF signaling and angiogenesis. Am J Physiol Cell Physiol 2017;3:4794-64.

50. Knock GA, Ward JP. Redox regulation of protein kinases as a modulator of vascular function. Antioxid Redox Signal 2011;1:1531-47.

51. Cameron JM, Gabrielsen M, Chinh YH, et al. Polarized cell motility induces hydrogen peroxide to inhibit collagen via cysteine oxidation. Curr Biol 2015;2:1520-5.

52. Dikalov SI, Ungvari Z. Role of mitochondrial oxidative stress in hypertension. Am J Physiol Heart Circ Physiol 2013;3:4147-27.

53. Araujo M, Wilcox CS. Oxidative stress in hypertension: role of the kidney. Antioxid Redox Signal 2014;2:74-101.

54. Callera GE, Tostes RC, Yogi A, Montezano AC, Touyz RM. Endothelin-1—induced oxidative stress in DOCA-salt hypertension involves NADPH-oxidase—dependent mechanisms. Clin Sci (Lond) 2006;1:243-53.

55. Vaka VR, Cunningham MW, Deer E, et al. Blockade of endogenous angiotensin II type I receptor agonist autoantibody activity improves mitochondrial reactive oxygen species and hypertension in a rat model of preeclampsia. Am J Physiol Regul Integr Comp Physiol 2020;3:R256-62.

56. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol 2014;5:372-6.

57. Lopes RA, Neves KB, Tostes RC, Montezano AC, Touyz RM. Downregulation of nuclear factor erythroid 2-related factor and associated antioxidant genes contributes to redox-sensitive vascular dysfunction in hypertension. Hypertension 2015;6:1240-50.

58. Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. Nat Rev Drug Discov 2011;1:453-7.

59. Cifuentes-Pagano E, Czanyi G, Pagano PJ. NADPH oxidase inhibitors: a decade of discovery from Nox2ds to HTS. Cell Mol Life Sci 2012;6:2315-25.

60. Maksimenko AV. Experimental antioxidant biotherapy for protection of the vascular wall by modified forms of superoxide dismutase and catalase. Curr Pharm Des 2005;1:2007-16.

61. Gomez-Guzman M, Jimenez R, Sanchez M. Epicatechin lowers blood pressure, restores endothelial function, and decreases oxidative stress and endothelin-1 and NADPH oxidase activity in DOCA-salt hypertension. Free Rad Biol Med 2012;5:70-9.

62. Touyz RM, Montezano AC, Ries F, Widlansky ME, Liang M. Redox stress defines the small artery vasculopathy of hypertension: how do we bridge the bench-to-bedside gap? Circ Res 2017;1:1721-3.
63. Montezano AC, Dulak-Li M, Tsiropoulou S, et al. Oxidative stress and human hypertension: vascular mechanisms, biomarkers, and novel therapies. Can J Cardiol 2015;3:631-41.

64. Ward NC, Hodgson JM, Puddey IB. Oxidative stress in human hypertension: association with antihypertensive treatment, gender, nutrition, and lifestyle. Free Radic Biol Med 2004;3:226-32.

65. Ghasemzadeh N, Patel RS, Eapen DJ, et al. Oxidative stress is associated with increased pulmonary artery systolic pressure in humans. Hypertension 2014;6:1270-5.

66. Verma MK, Jaiswal A, Sharma P, Kumar P, Singh AN. Oxidative stress and biomarker of TNF-α, MDA and FRAP in hypertension. J Med Life 2019;1:253-9.

67. Gkaliagkouni E, Gaviilik E, Triantafyllou A, et al. Asymmetric dimethylarginine levels are associated with augmentation index across untreated patients with different hypertension phenotypes. J Clin Hypertens (Greenwich) 2018;2:680-5.

68. Carrizzo A, Puca A, Damato A, et al. Resveratrol improves vascular function in patients with hypertension and dyslipidemia by modulating NO metabolism. Hypertension 2013;6:359-66.

69. González J, Valls N, Brío R, Rodríguez R. Essential hypertension and oxidative stress: new insights. World J Cardiol 2014;6:353-66.

70. Touyz RM, Yao G, Quinn MT, Pagano PJ, Schiffrin EL. p47phox associates with the cytoskeleton through contactin in human vascular smooth muscle cells: role in NADPH oxidase regulation by angiotensin II. Arterioscler Thromb Vasc Biol 2005;2:512-8.

71. Young CN. Endoplasmic reticulum stress in the pathogenesis of hypertension. Exp Physiol 2017;1:869-84.

72. Santos CX, Nabeelbacus AA, Shah AM, et al. Endoplasmic reticulum stress and Nox-mediated reactive oxygen species signaling in the peripheral vasculature: potential role in hypertension. Antioxid Redox Signal 2014;20:121-34.

73. Rodrigo R, Libuy M, Feliú F, Hasson D. Oxidative stress-related biomarkers in essential hypertension and ischemia-reperfusion myocardial damage. Dis Markers 2013;3:773-90.

74. Edami S, Sahbekar A, Glutathione-S-transferase M1 and T1 null genotypes are associated with hypertension risk: a systematic review and meta-analysis of 12 studies. Curr Hypertens Rep 2014;1:43-9.

75. Wyche KE, Wang SS, Griendling KK, et al. C242T CYBA polymorphism of the NADPH oxidase is associated with reduced respiratory burst in human neutrophils. Hypertension 2004;4:1246-51.

76. Rafiq A, Aslam K, Malik R, Afroze D. C242T polymorphism of the NADPH oxidase p22phox gene and its association with endothelial dysfunction in asymptomatic individuals with essential systemic hypertension. Mol Med Rep 2014;9:1857-62.

77. Kraja AT, Cook JP, Warren HR, et al. New blood pressure-associated loci identified in meta-analyses of 475,000 individuals. Circ Cardiovasc Genet 2017;10. pii: e001778.

78. Sylvester MA, Brooks HL. Sex-specific mechanisms in inflammation and hypertension. Curr Hypertens Rep 2019;2:53-9.

79. Ji H, Zheng W, Wu X, et al. Sex chromosome effects unmasked in Ang II–induced hypertension. Hypertension 2010;5:1275-82.

80. Khan SI, Andrews KL, Jennings GL, Sampson AK. Chin-Dusting JPF. Y chromosome, hypertension and cardiovascular disease: is inflammation the answer? Int J Mol Sci 2019;20:2892.

81. Ojeda NB, Intapad S, Alexander BT. Sex differences in the developmental programming of hypertension. Acta Physiol (Oxf) 2014;2:307-16.

82. Reckelhoff JF, Romero DG, Yanes Cardozo LL. Sex, oxidative stress, and hypertension: Insights from animal models. Physiology (Bethesda) 2019;3:178-88.

83. Ide T, Tsutsui H, Ohashi N, et al. Greater oxidative stress in healthy young men compared with premenopausal women. Arterioscler Thromb Vasc Biol 2002;2:1239-42.

84. Bhatia K, Elmarakby AA, El-Remessy AB, Sullivan JC. Oxidative stress contributes to sex differences in angiotensin II–mediated hypertension in spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol 2012;3:R274-82.

85. Ji H, Zheng W, Menini S, et al. Female protection in progressive renal disease is associated with estradiol attenuation of superoxide production. Gend Med 2007;4:56-71.

86. Miller A, Drummond G, Mast A, Schmidt H, Sobey C. Effect of gender on NADPH-oxidase activity, expression and function in the cerebral circulation: role of estrogen. Stroke 2007;3:2142-9.

87. Borras C, Gambini J, Gomez-Cabrera M, et al. 17Beta-oestradiol up-regulates longevity-related, antioxidant enzyme expression via the ERK-1 and ERK2 (MAPK)/NFκB cascade. Aging Cell 2005;4:113-8.

88. Nguyen Dinh Cat A, Montezano AC, Burger D, Touyz RM. Angiotensin II, NADPH oxidase, and redox signaling in the vasculature. Antioxid Redox Signal 2013;1:1110-20.

89. Montezano AC, Nguyen Dinh Cat A, Rios FJ, Touyz RM. Angiotensin II and vascular injury. Curr Hypertens Rep 2014;1:431-40.

90. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. Hypertension 2017;7:660-7.

91. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol 2018;3:575-84.

92. Masi S, Uliana M, Virdis A. Angiotensin II and vascular damage in hypertension: Role of oxidative stress and sympathetic activation. Vasc Pharmacol 2019;1:13-7.

93. Mattson DL. Immune mechanisms of salt-sensitive hypertension and renal end-organ damage. Nat Rev Nephrol 2019;1:290-300.

94. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2018;7:2054-207.

95. Rautureau Y, Schiffrin EL. Endothelin in hypertension: an update. Curr Opin Nephrol Hypertens 2012;2:128-36.

96. Touyz RM, Alves-Lopes R, Rios FJ, et al. Vascular smooth muscle contraction in hypertension. Cardiovasc Res 2018;1:529-39.

97. Lopes R, Neves KB, Anagnostopoulou A, et al. Crouststalk between vascular redox and calcium signaling in hypertension involves TRPM2 (transient receptor potential melastatin 2) cation channel. Hypertension 2020;7:139-49.

98. Mihalj M, Tadzic R, Vivec A, Rusecic S, Drenjancevic I. Blood pressure reduction is associated with the changes in oxidative stress and endothelial activation in hypertension, regardless of antihypertensive therapy. Kidney Blood Press Res 2016;4:721-35.

99. Xu S, He Y, Vokurkova M, Touyz RM. Endothelial cells negatively modulate reactive oxygen species generation in vascular smooth muscle cells: role of thioredoxin. Hypertension 2009;5:427-33.
Dikalov SI, Nazarewicz RR, Bikineyeva A, et al. Nox2-induced production of mitochondrial superoxide in angiotensin II–mediated endothelial oxidative stress and hypertension. Antioxid Redox Signal 2014;2:281-94.

Coelho SC, Berillo O, Caillon A, et al. Three-month endothelial human endothelin-1 overexpression causes blood pressure elevation and vascular and kidney injury. Hypertension 2018;7:208-16.

Tsai SH, Lu G, Xu X, et al. Enhanced endothelin-1/Rho-kinase signaling and coronary microvascular dysfunction in hypertensive myocardial hypertrophy. Cardiovasc Res 2017;1:1329-37.

Colaella KM, Neves KB, Montezano AC, et al. Selective ETA versus dual ETA/B receptor blockade for the prevention of sunsitinib-induced hypertension and albuminuria in WKY rats [e-pub ahead of print]. Cardiovasc Res.

Ganesh D, Kumarathanas P, Thomson EM, et al. Impact of superoxide dismutase mimetic AEOL 10150 on the endothelin system of Fischer 344 rats. PLoS One 2016;1.e0151810.

du Ploooy CS, Martha Cornelia Mels C, Huisman HW, Kruger R. The association of endothelin-1 with markers of oxidative stress in a biracial South African cohort: the SABPA study. Hypertens Res 2017;4:189-95.

Fernandez-Patron C. Therapeutic potential of the epidermal growth factor receptor transactivation in hypertension: a convergent signaling pathway of vascular tone, oxidative stress, and hypertrophic growth downstream of vasoactive G-protein–coupled receptors? Can J Physiol Pharmacol 2007;8:97-104.

Forrester SJ, Booz GW, Sigmund CD, et al. Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. Physiol Rev 2018;9:1627-738.

Neves KB, Rios FJ, van der Mey L, et al. VEGFR (vascular endothelial growth factor receptor) inhibition induces cardiovascular damage via redox-sensitive processes. Hypertension 2018;7:638-47.

Li Y, Lévesque LO, Anand-Srivastava MB. Epidermal growth factor receptor transactivation by endogenous vasoactive peptides contributes to hyperproliferation of vascular smooth muscle cells of SHR. Am J Physiol Heart Circ Physiol 2010;2:H1959-67.

Cruzado MC, Risler NR, Miatello RM, et al. Vascular smooth muscle cell NAD(P)H oxidase activity during the development of hypertension: effect of angiotensin II and role of insulinlike growth factor-1 receptor transactivation. Am J Hypertens 2005;4:81-7.

Touyz RM, Cruzado M, Tabet F, et al. Redox-dependent MAP kinase signaling by Ang II in vascular smooth muscle cells: role of receptor tyrosine kinase transactivation. Can J Physiol Pharmacol 2003;8:159-67.

Touyz RM, Wu XH, He G, Salomon S, Schiffrin EL. Increased angiotensin II–mediated Src signaling via epidermal growth factor receptor transactivation is associated with decreased C-terminal Src kinase activity in vascular smooth muscle cells from spontaneously hypertensive rats. Hypertension 2002;3:479-85.

Dinh QN, Drummond GR, Kemp-Harper BK, et al. Pressor response to angiotensin II is enhanced in aged mice and associated with inflammation, vasoconstriction, oxidative stress. Aging (Albany NY) 2017;9:1595-606.

Zahradka P, Litchie B, Storie B, Helwer G. Transactivation of the insulin-like growth factor-I receptor by angiotensin II mediates downstream signaling from the angiotensin II type 1 receptor to phosphati-dylinositol 3-kinase. Endocrinology 2004;1:2978-87.

Montezano AC, Tsipoupolou S, Dukak-Liu M, et al. Redox signaling, Nox5 and vascular remodeling in hypertension. Curr Opin Nephrol Hypertens 2015;2:425-33.

Palandis P, Sideris M, Yiigimaa M, et al. The mechanisms of actions of aldosterone and its antagonists in cardiovascular disease. Curr Pharm Des 2018;2:5491-9.

Cannavo A, Bencivenga L, Liccardo D, et al. Aldosterone and mineralocorticoid receptor system in cardiovascular physiology and pathophysiology. Oxid Med Cell Longev 2018;20:1204598.

Chou CH, Hung CS, Liao CW, et al. IL-6 trans-signalling contributes to aldosterone-induced cardiac fibrosis. Cardiovasc Res 2018;1:690-702.

Rossi GP. Primary aldosteronism: JACC state-of-the-art review. J Am Coll Cardiol 2019;7:2799-811.

Kawarazaki W, Fujita T. The role of aldosterone in obesity-related hypertension. Am J Hypertens 2016;2:415-23.

Funder JW. Primary aldosteronism. Hypertension 2019;7:458-66.

Virdis A, Neves MF, Amiri F, et al. Spironolactone improves angiotensin-induced vascular changes and oxidative stress. Hypertension 2002;4:504-10.

Beswick RA, Dorrance AM, Leite R, Webb RC. NADH/NADPH oxidase and enhanced superoxide production in the mineralocorticoid hypertensive rat. Hypertension 2001;3:1107-11.

McCurley A, Pires PW, Bender SB, et al. Direct regulation of blood pressure by smooth muscle cell mineralocorticoid receptors. Nat Med 2012;1:1429-33.

Briet M, Barhoumi T, Mian MOR, et al. Aldosterone-induced vascular remodeling and endothelial dysfunction require functional angiotensin type 1a receptors. Hypertension 2016;6:897-905.

Montezano AC, Callera GE, Yogi A, et al. Aldosterone and angiotensin II synergistically stimulate migration in vascular smooth muscle cells through c-Src–regulated redox-sensitive RhoA pathways. Arterioscler Thromb Vasc Biol 2008;2:1511-8.

Fan C, Kawai Y, Inaba S, et al. Synergy of aldosterone and high salt induces vascular smooth muscle hypertrophy through up-regulation of NOX1. J Steroid Biochem Mol Biol 2008;1:29-36.

Iwashima F, Yoshimoto T, Minami I, et al. Aldosterone induces superoxide generation via Rac1 activation in endothelial cells. Endocrinology 2008;1:1009-14.

Harvey AP, Montezano AC, Hood KY, et al. Vascular dysfunction and fibrosis in stroke-prone spontaneously hypertensive rats: the aldosterone–mineralocorticoid receptor–NOX1 axis. Life Sci 2017;1:110-9.

Hashikabe Y, Suzuki K, Jojima T, Uchida K, Hattori Y. Aldosterone impairs vascular endothelial cell function. J Cardiovasc Pharmacol 2006;4:609-13.

Callera GE, Montezano AC, Yogi A, et al. c-Src–dependent non-genomic signaling responses to aldosterone are increased in vascular myocytes from spontaneously hypertensive rats. Hypertension 2005;4:1032-8.

Raurureau Y, Paradis P, Schiffrin EL. Cross-talk between aldosterone and angiotensin signaling in vascular smooth muscle cells. Steroids 2011;7:834-9.

Cannavo A, Liccardo D, Eguchi A, et al. Myocardial pathology induced by aldosterone is dependent on noncanonical activities of G protein–coupled receptor kinases. Nat Commun 2016;7:10877-80.
134. Silva MA, Bruder-Nascimento T, Cau SB, et al. Spironolactone treatment attenuates vascular dysfunction in type 2 diabetic mice by decreasing oxidative stress and restoring NO/GC signaling. Front Physiol 2015;6:269-74.

135. Nakano S, Kobayashi N, Yoshida K, Ohno T, Matsuoka H. Cardioprotective mechanisms of spironolactone associated with the angiotensin-converting enzyme/epidermal growth factor receptor/extracellular signal-regulated kinases, NAD(P)H oxidase/lectin-like oxidized low-density lipoprotein receptor-1, and Rho-kinase pathways in aldosterone/salt-induced hypertensive rats. Hypertens Res 2005;2:36.

136. Nguyen Dinh Cat A, Griebl-Charbhili V, Loufrani L, et al. The endothelial mineralocorticoid receptor regulates vasoconstrictor tone and blood pressure. FASEB J 2010;2:2454-63.

137. Favre J, Gao J, Zhang AD, et al. Coronary endothelial dysfunction after myocardectomy-specific mineralocorticoid receptor overexpression. Am J Physiol Heart Circ Physiol 2011;341H55-43.

138. Ahokas RA, Warrington KJ, Gerling IC, et al. Aldosteronism and peripheral blood mononuclear cell activation: a neuroendocrine-immune interface. Circ Res 2003;93:124-35.

139. Bienvenu LA, Morgan J, Rickard AJ, et al. Macrophage mineralocorticoid receptor signaling plays a key role in aldosterone-independent cardiac fibrosis. Endocrinology 2012;1:3416-25.

140. Hirata A, Maeda N, Nakatsui H, et al. Contribution of glucocorticoid-mineralocorticoid receptor pathway on the obesity-related adipocyte dysfunction. Biochem Biophys Res Commun 2012;4:182-7.

141. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;3:801-9.

142. Barrows IR, Ramezani A, Raj DS. Inflammation, immunity, and oxidative stress in hypertension—partners in crime? Adv Chronic Kidney Dis 2012;9:122-30.

143. Tomiyama H, Shiina K, Matsumoto-Nakano C, et al. The contribution of inflammation to the development of hypertension mediated by increased arterial stiffness. J Am Heart Assoc 2017;6. e005729.

144. Carbone F, Elia E, Casula M, et al. Baseline hs-CRP predicts hypertension remission in metabolic syndrome. Eur J Clin Invest 2019;4:31328.

145. Schüller R, Efentakis P, Wild J, et al. T cell–derived IL-17A induces vascular dysfunction via perivascular fibrosis formation and dysregulation of NO/cGMP signaling. Oxid Med Cell Longev 2019;20:6721533.

146. Burger D, Montezano AC, Nishigaki N, et al. Endothelial microparticle formation by angiotensin II is mediated via Ang II receptor type I/NADPH oxidase/Rho kinase pathways targeted to lipid rafts. Arterioscler Thromb Vasc Biol 2011;34:1898-907.

147. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med 2018;2:21-33.

148. Schilling EL. Mechanisms of remodeling of small arteries, antihypertensive therapy and the immune system in hypertension. Clin Invest Med 2015;3:394-402.

149. Harijith A, Ebenezer DL, Natarajan V. Reactive oxygen species at the crossroads of inflammation and hypertension. Front Physiol 2014;5:352-36.

150. Pasqua T, Pagliaro P, Rocca C, Angelone T, Penna C. Role of NLRP3 inflammasome in hypertension: A potential therapeutic target. Curr Pharm Biotechnol 2018;20:708-14.

151. Zhang Z, Zhai Y, Liang S, et al. TRPM2 links oxidative stress to NLRP3 inflammasome activation. Nat Commun 2013;4:1611-5.

152. Zhang X, Hong S, Qi S, et al. NLRP3 inflammasome is involved in calcium-sensing receptor–induced aortic remodeling in SHRs. Mediators Inflamm 2019;20:6847087.

153. Villegas LR, Kluck D, Field C, et al. Superoxide dismutase mimetic, MnTe-2-PyP, attenuates chronic hypoxia-induced pulmonary hypertension, pulmonary vascular remodeling, and activation of the NALP3 inflammasome. Antioxid Redox Signal 2013;1:1753-64.

154. Ferreira NS, Bruder-Nascimento T, Pereira CA, et al. NLRP3 inflammasome and mineralocorticoid receptors are associated with vascular dysfunction in type 2 diabetes mellitus. Cells 2019;8:1595.

155. Guzik TJ, Hoch NE, Brown KA, et al. Role of the T cell in the genesis of angiotensin ii induced hypertension and vascular dysfunction. J Exp Med 2007;2:2449-60.

156. de Cuceis C, Amiri F, Brassard P, et al. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II–infused macrophage colony–stimulating factor–deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. Arterioscler Thromb Vasc Biol 2005;25:2106-13.

157. Wenzel P. Monocytes as immune targets in arterial hypertension. Br J Pharmacol 2019;1:1966-77.

158. Radi R. Oxygen radicals, nitric oxide, and peroxynitrite: redox pathways in molecular medicine. Proc Natl Acad Sci U S A 2018;1:5839-48.

159. Carracedo J, Ramírez-Carracedo R, Martínez de Toda I, et al. Protein carbamylation: a marker reflecting increased age-related cell oxidation. Int J Mol Sci 2018;19:1495.

160. Sheehan D, McDonagh B. The clinical potential of thiol redox proteomics. Expert Rev Proteomics 2019;2:1-8.