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REVIEW

Redox regulation of vascular remodeling

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Abstract Vascular remodeling is a dynamic process of structural and functional changes in response to biochemical and biomechanical signals in a complex in vivo milieu. While inherently adaptive, dysregulation leads to maladaptive remodeling. Reactive oxygen species participate in homeostatic cell signaling in tightly regulated- and compartmentalized cellular circuits. It is well established that perturbations in oxidation–reduction (redox) homeostasis can lead to a state of oxidative-, and more recently, reductive stress. We provide an overview of the redox signaling in the vasculature and review the role of oxidative- and reductive stress in maladaptive vascular remodeling. Particular emphasis has been placed on essential processes that determine phenotype modulation, migration and fate of the main cell types in the vessel wall. Recent advances in systems biology and the translational opportunities they may provide to specifically target the redox pathways driving pathological vascular remodeling are discussed.

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Keywords Vascular remodeling · Reactive oxygen species · Redox stress · Signal transduction

Abbreviations

AngII	Angiotensin II
AP1	Activator protein 1
AT1R	Angiotensin II type 1 receptor
BH_4	Tetrahydrobiopterin
Cys	Cysteine
Cys-SH	Cysteinyl thiolates
Cys-S-SH	Cysteinyl persulfide
EC	Endothelial cell
ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthase
FAK	Focal adhesion kinase
GCHI	Guanosine triphosphate cyclohydrolase I
GSS	S-Glutathiolation
GTP	Guanosine triphosphate
Hic5	H_2O_2-inducible clone-5
HSP27	Heat shock protein 27
Nox	NADPH oxidase
Keap1	Kelch-like ECH-associated protein 1
LMW-PTP	Low molecular weight protein tyrosine phosphatase
MAPKAPK2	Mitogen-activated protein kinase-activated protein kinase 2
MEF2	Myocyte-enhanced factor 2
MLC	Myosin light chain
MLCP	Myosin light chain phosphatase
MRTF-A	Myocardin-related transcription factor A
NF-κB	Nuclear factor κB
Nrf2	Nuclear factor erythroid 2-related factor 2
p38 MAPK	p38 mitogen-activated protein kinase

PDGFβ	Platelet-derived growth factor β
PDGFR	Platelet-derived growth factor receptor
PI3K	Phosphoinositol 3-kinase
PIP3	Phosphatidylinositol 3,4,5 trisphosphate
PKCζ	Protein kinase Cζ
Poldip2	Polymerase [DNA-directed] delta-interacting protein 2
PTEN	Phosphatase and tensin homolog
ROCK	Rho-kinase
ROS	Reactive oxygen species
SMC	Smooth muscle cell
SOD	Superoxide dismutase
SRF	Serum response factor
SSH1L	Slingshot1L phosphatase,
TAT3	Signal transducer and activator of transcription 3
TGFβ	Transforming growth factor β
TXNIP	Thioredoxin-interacting protein
VEGF	Vascular endothelial growth factor
VEGF-R	Vascular endothelial growth factor receptor
WSS	Wall shear stress

Vascular remodeling

The vessel wall is a dynamic and integrated organ composed of endothelial cells (ECs), smooth muscle cells (SMCs), fibroblasts and perivascular tissue that interact with each other and the circulatory cells in a complex autocrine/paracrine manner [1]. The vasculature can sense changes within its milieu and integrate these signals to transduce intra- and intercellular communication that drive structural and functional changes in a process called vascular remodeling [1, 2]. Dynamic vascular remodeling involves alterations in many cellular processes including growth and proliferation, adhesion and migration, phenotypic changes, survival and death, as well as production or degradation of extracellular matrix (ECM). Remodeling is usually an adaptive process that occurs in response to long-term changes in hemodynamic conditions, but it may subsequently contribute to the pathophysiology of vascular diseases such as systemic- and pulmonary hypertension, atherosclerosis, restenosis following revascularization by balloon angioplasty and stenting (BAS) or venous bypass grafts [1, 2]. Complex interactions between growth factors, inflammatory cytokines, vasoactive substances and hemodynamic stimuli in the vessel wall determine physiologic- and pathophysiologic remodeling. Oxido-reductive or "redox" signaling via reactive oxygen species (ROS) plays an integral part in cellular effects of these stimuli and a key role in all aspects of the remodeling process [3].

Redox signaling in the vasculature

Cells are continuously exposed to ROS generated endogenously in what could be considered as a trade off for utilizing O_2 for metabolism [4]. Several ROS including superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), peroxynitrite ($OONO^-$), and the hydroxyl radical ($HO^{\cdot}$) are generated in biological systems [3]. To counter the damaging effects of ROS, a complex web of antioxidants, such as the abundant low molecular weight protein glutathione (GSH) and enzymatic antioxidant systems with specific subcellular distribution and reactivity maintain intracellular redox homeostasis [5]. In contrast to the historical view of ROS as purely harmful, extensive data indicate that some ROS, i.e. $O_2^{\cdot-}$ and H_2O_2, are generated as a regulated physiological process and function as signaling molecules in control of cell and tissue homeostasis [6]. Other ROS, such as $OONO^-$ and $HO^{\cdot}$, are not considered as signaling molecules because of their very reactive nature [3]. In the vasculature, ROS are produced by all cell types including ECs, SMCs, and adventitial cells. Another biologically generated free radical nitric oxide (NO) has many important effects in vessels, directly or via interaction with ROS. NO and ROS are generated by the membrane-bound NADPH-dependent enzymes, nitric oxide synthase (NOS) and NADPH oxidases (Nox), the expression of which is tightly controlled, compartmentalized and tissue-specific [6]. Other sources of ROS that are relevant to the vascular system are the mitochondrial respiration chain, xanthine oxidase, lipoxygensae and myeloperoxidase [3]. We provide an overview of the two NADPH-dependent sources of ROS/NO in the vasculature. It is important to note that ROS generation from each of these sources can lead to ROS release from other sources [3].

In addition to NO, hydrogen sulfide (H_2S) is another gaseous signaling molecule [7] that is enzymatically generated in ECs and mediates vasorelaxation [8]. As an electron donor [9], H_2S is a reductant [10] and can exert antioxidant effects via both direct- and indirect actions. The direct effect of H_2S involves sulfhydration of target proteins, which is the conversion of cysteinyl thiolates (Cys-SH) to cysteinyl persulfide (Cys-S-SH) by the addition of H_2S-derived sulfur [11]. Moreover, as shown in non-vascular tissues, H_2S donors can protect against oxidative stress indirectly by increasing GSH levels [12] or directly by sulfhydration of two Cys residues in kelch-like ECH-associated protein 1 (Keap1), the cystoplasmic adaptor that represses the "master regulator" nuclear factor erythroid 2-related factor 2 (Nrf2), thus promoting Nrf2 localization to the nucleus and inducing the expression of multiple cellular antioxidants [13, 14]. As will be pointed out, emerging data indicate that H_2S-induced redox

signaling participates in EC fate processes that can determine vascular remodeling, a role that is the subject of ongoing basic- and clinical research [15].

Nox and "uncoupled" eNOS- major vascular sources of ROS

The Nox family is composed of 7 catalytic subunits termed Nox1-5, Duox1 and Duox2 (for Dual Oxidase) [16]. Several protein components form the classic NADPH oxidase complex, consisting of $p22^{phox}$ and $gp91^{phox}$ (the membrane-bound subunit, crucial for the activity) and $p47^{phox}$, $p67^{phox}$ (regulatory cytosolic proteins) and the low-molecular weight G protein Rac. Nox1, 2, 4 and 5 isoenzymes are expressed in vascular tissues and regulate such diverse functions as differentiation, proliferation, apoptosis, senescence, inflammatory responses and O_2 sensing [17]. The activity and expression of Nox can be regulated by cytokines [tumor necrosis factor-α (TNFα, transforming growth factor β (TGFβ), platelet-derived growth factor (PDGF)] and agonists like angiotensin II (AngII) and thrombin [18]. AngII is a potent stimulus of both Nox activity and expression, contributing to the association between activation of the renin–angiotensin system and ROS production in several vascular pathologies. When upregulated, Noxs have been implicated in diabetes-induced vascular disease, hypertension and atherosclerosis, but upregulation can be physiologically advantageous, as in angiogenesis and collateral formation [17].

eNOS, the predominant isoform of NOS in the vasculature, is critical in the regulation of vascular function and generates NO [19–21]. Under normal conditions, in the presence of Ca^{2+}/calmodulin, eNOS catalyzes the generation of NO from L-arginine (L-Arg) by means of electron transfer from NADPH through a flavin-containing reductase domain to oxygen bound at the heme of an oxygenase domain, which also contains binding sites for tetrahydrobiopterin (BH_4) and L-Arg [19, 21]. The oxidation of NADPH is tightly coupled to the production of NO by eNOS. However, when the oxidation of NADPH is uncoupled from the production of NO, eNOS generates $O_2^{\cdot-}$ and secondary ROS, in what is widely known as eNOS "uncoupling" [19]. eNOS uncoupling has been associated with many pathophysiologic conditions, such as hypertension, atherosclerosis and diabetes [21]. BH_4 is crucial for eNOS function and is involved in stabilizing NOS protein structure and eNOS is uncoupled when BH_4 is limiting. $O_2^{\cdot-}$ can oxidize the NOS-bound BH_4 [22]. The in vivo source of the ROS that may lead to BH_4 depletion has been attributed to pathways including Nox, xanthine oxidase and the mitochondrial electron transfer chain [23, 24]. $ONOO^-$ does rapidly oxidize BH_4. However, it can also irreversibly inactivate the NOS enzymes, likely by a direct reaction with the NOS heme, producing an inactive enzyme rather than an uncoupled enzyme [20].

"Oxidative" and "reductive" stress

An extensive network of signaling cascades and effector proteins regulates elimination of ROS. Increased generation of ROS can disrupt the homeostasis in thiol-dependent redox circuits by changing the redox state of the GSH pool and thioredoxin (Trx) enzyme family that act as the critical control nodes in the cellular redox network, thus leading to a state of "oxidative stress" [25]. Oxidative stress results in changes in signaling, structural and regulatory proteins and in DNA damage that lead to altered cell growth, proliferation, differentiation and death. In addition to the control of redox potential by GSH and Trx redox circuits, antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Gpx), catalyze rapid break down of ROS to less reactive or nonreactive products, and are key in preventing damage from oxidative stress [3].

Although oxidative stress is the established paradigm delineating an excess of ROS vis-à-vis the antioxidant capacity, "reductive stress" is also increasingly gaining recognition [26, 27]. A supra-physiological increase in the GSH pool can conceivably increase the reductive flux into the cellular thiol circuits and affect the redox-sensitive thiol elements, predominantly through formation of disulfide bonds with Cys residues in a reversible process called S-glutathiolation. For example, we have shown that reductive stress following vascular injury inflicted by BAS promotes S-glutathiolation of a regulatory protein to determine vascular remodeling [27]. In addition to thiol disulfide exchange, S-glutathiolation is promoted by ROS via thyil radical formation on numerous targets proteins, thus affecting virtually all aspects of the cellular processes (gene expression, cytoskeletal dynamics, signaling, ion channels and transporters function, cell death and survival) [28]—central processes in vascular remodeling in response to injury.

Effector cell types in redox-mediated vascular remodeling

Endothelial cells (ECs)

Redox signaling and endothelial dysfunction

ECs constitute the inner most layer of the vessel wall. Acting as the interface between blood circulation and multiple tissues, ECs are constantly exposed and are adapting to numerous biochemical and biomechanical stimuli. ECs have a remarkable ability for migration and

proliferation from a quiescent state that is key in angiogenesis. It is therefore not surprising that perturbations in these critical EC functions are at the crux of several vascular pathologies [29].

Redox signaling plays major regulatory roles in the maintenance of cellular homeostasis and in physiological adaptive responses in ECs. To this end, maintenance of a tight balance between NO- and ROS-dependent signaling is critical (Fig. 1). Endothelial dysfunction in the context of atherosclerosis [30] and diabetes [31] is characterized by a pathological decrease in NO- and an increase in redox-dependent signaling. eNOS-derived NO mediates endothelium-dependent vasodilation, required for normal vascular homeostasis, and it inhibits critical atherogenesis pathways such as platelet aggregation, SMC proliferation and migration and leukocyte adhesion [29]. eNOS uncoupling from NO- to ROS generation via BH_4 depletion is an important pathobiological step in endothelial dysfunction. De novo biosynthesis of BH_4 from guanosine triphosphate (GTP) is dependent on the rate limiting enzyme GTP cyclohydrolase (GCH) I (Fig. 1), and EC-specific knockout of this enzyme causes a loss of NO bioactivity and increase in $O_2^{\cdot-}$ production in ECs [32]. EC-targeted overexpression of GCH on the other hand increases BH_4 and NO bioavailability, and reduces neointimal hyperplasia in vein grafts of atherosclerotic mice via accelerated EC repopulation and growth [33] and decreased inflammation [34]. Direct oxidation of eNOS via S-glutathiolation of specific Cys residues also mediates eNOS uncoupling [20], which is distinct from BH_4 deficiency. Nonetheless, BH_4 depletion and S-glutathiolation interact and exacerbate eNOS uncoupling [35]. Moreover, there is an intricate signaling cross-talk between various sources of ROS in ECs that promotes endothelial pathology. For instance, AngII-induced Nox2-derived $O_2^{\cdot-}$ induces ROS release from mitochondria and contributes to hypertension [16]. Furthermore, AngII-induced Nox-dependent $O_2^{\cdot-}$ generation is amplified by S-glutathiolation-mediated uncoupling of eNOS, akin to "kindling a bonfire", and causes endothelial dysfunction [36] (Fig. 1).

Mechano-sensitive redox pathways in ECs

Pulsatility of blood pressure and flow exposes the vessel wall to hemodynamic forces in the form of shear stress and cyclic stretch. The cytoskeleton and the integrins, transmembrane receptors that act as bridge between cell cytoskeleton and ECM [37], are the key structural framework for EC to transmit mechanical forces from its luminal, abluminal and junctional surfaces to its interior. ECs convert these mechanical stimuli into numerous intracellular signals that regulate a broad range of critical EC functions including migration, proliferation, permeability and apoptosis [38]. The response of ECs to physiologic levels of wall shear stress (WSS) serves a number of regulatory functions including modulation of hemostasis and thrombosis, control of inflammation through expression of chemotactic and adhesion molecules on the cell surface, and vascular SMC contraction through the release of vasoconstrictors and vasodilators [38]. Pulsatile flow induces WSS that varies temporally and spatially along the vascular bed [39]. In the straight part of the vessel, blood flow is undisturbed as opposed to disturbed blood flow on bends and bifurcations with very high WSS. Disruption or unsteady blood flow through these "atherosclerosis-prone" areas of the vessel can impair the physiological functions mentioned above leading to proatherogenic and/or prothrombotic states.

ROS have central role in physiological and pathophysiological WSS-induced vascular remodeling (Fig. 2). With normal pulsatile laminar flow, WSS-mediated generation of ROS at low levels by Nox regulates normal cell growth, proliferation and differentiation [40]. Several antioxidant pathways are induced and maintained by normal laminar WSS. Expression and activity of eNOS is enhanced by normal WSS through multiple mechanisms [39]. Normal WSS also activates Nrf2, a "master regulator" of numerous antioxidant enzymes, by releasing it from its cytoplasmic repressor Keap1, and it activates critical molecules involved in limiting inflammation [39]. Shear stress causes dissociation of cytoplasmic Nrf2 from Keap1 and Nrf2 translocation into the nucleus in a phosphoinositol 3-kinase (PI3K)/Akt-dependent pathway [41]. A mechano-sensitive switch has also been identified in the form of Trx-interacting protein, a scaffold protein that inactivates Trx [39]. By down-regulating Trx-interacting protein (TXNIP) expression hence activating Trx, physiological WSS inhibits pro-inflammatory signaling in ECs [42].

Acute cessation of the laminar flow [43] or presence of oscillatory flow on the other hand acutely increases cellular ROS formation [44], which subsequently remains elevated for the duration of WSS exposure [45] (Fig. 2). Nox2 and Nox4 isoforms of NADPH oxidase generate ROS in ECs, with Nox2 more abundantly expressed [46]. Although these Nox isoforms exist in differential subcellular compartments in ECs and their response to stimuli such as AngII differs, expression of both isoforms is upregulated by oscillatory flow and downregulated by pulsatile laminar flow in vitro [39]. Although contribution of Nox2-derived ROS in atherogenesis is shown [47], the exact role of Nox4 remains controversial. The shear responsive protein kinase Cζ (PKCζ) negatively regulates WSS-induced eNOS expression [48], induces Nox-mediated ROS generation [49] and is highly activated in atheroprone vascular regions [50]. Finally, abnormal WSS can induce activation of nuclear factor κB (NF-κB), the prototypical transcription

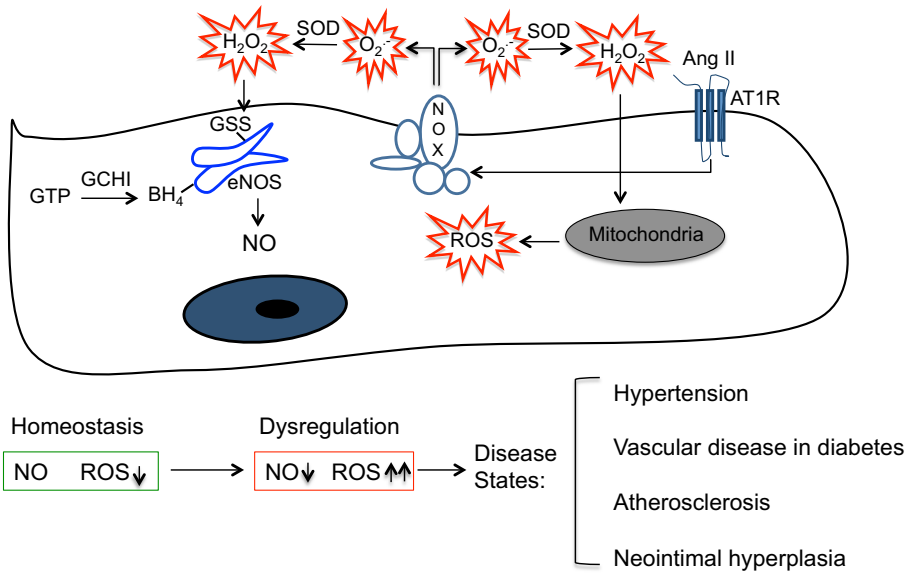

Fig. 1 Redox signaling and endothelial dysfunction. *AngII* angiotensin II, *AT1R* angiotensin II type 1 receptor, *SOD* superoxide dismutase, *Nox* NADPH oxidase, *eNOS* endothelial nitric oxide synthase, *GSS* S-glutathiolation, BH_4 tetrahydrobiopterin, *GTP* guanosine triphosphate, *GCHI* guanosine triphosphate cyclohydrolase I, *NO* nitric oxide, *ROS* reactive oxygen species

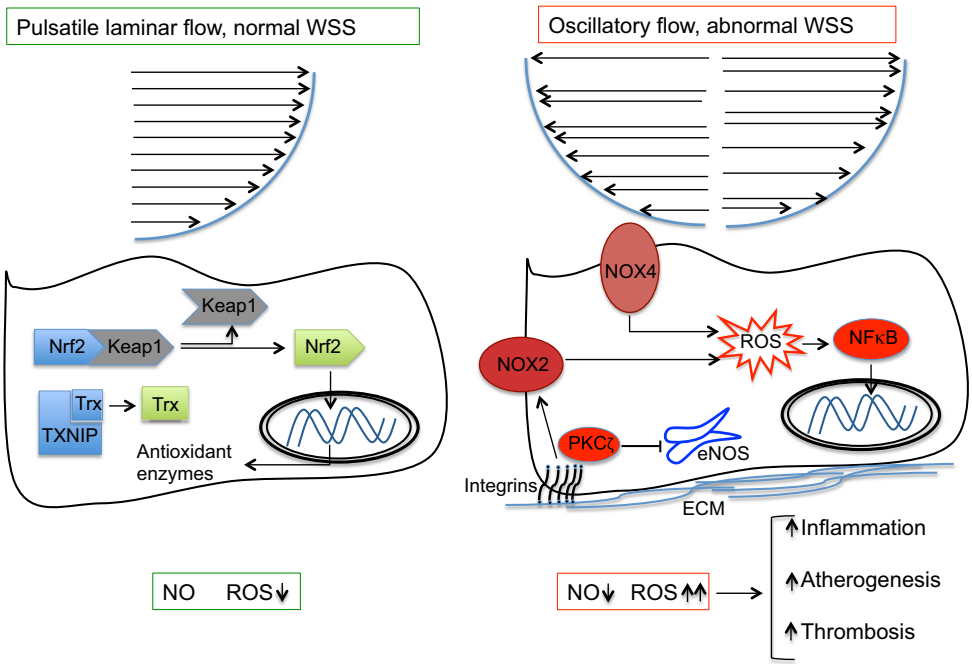

Fig. 2 Biomechanical stimuli and redox signaling in endothelial cells. *WSS* wall shear stress, *Nrf2* nuclear factor erythroid 2-related factor 2, *Keap1* kelch-like ECH-associated protein 1, *TXNIP* thioredoxin-interacting protein, *ROS* reactive oxygen species, *eNOS* endothelial nitric oxide synthase, *PKCζ* protein kinase Cζ, *NF-κB* nuclear factor κB, *ECM* extracellular matrix

factor for pro-inflammatory pathways, through integrin-mediated signaling in a process that is also dependent on Rac1-induced ROS generation [51] (Fig. 2).

Redox signaling in EC growth, proliferation and migration

In ECs, ROS modulate many processes determining cell fate (e.g. growth, proliferation and survival), cytoskeletal reorganization and inflammatory responses that are central in EC-mediated vascular remodeling [52]. EC growth and survival are dependent on several factors, such as vascular endothelial growth factor (VEGF), which are coupled to the intracellular production of ROS [53] (Fig. 3). While the physiological ROS-dependent signaling is critical for induction of proliferative pathways in ECs [54], dysregulated generation of ROS impairs EC proliferation and promotes apoptosis [54] and induces vascular hypertrophy when ROS diffuse into the subjacent SMCs [55].

Migration of ECs is essential for morphogenesis, wound healing and angiogenesis [56]. The migratory process primarily involves sensing a gradient by ECs and establishing polarity. The dynamic, integrated, cyclic process that

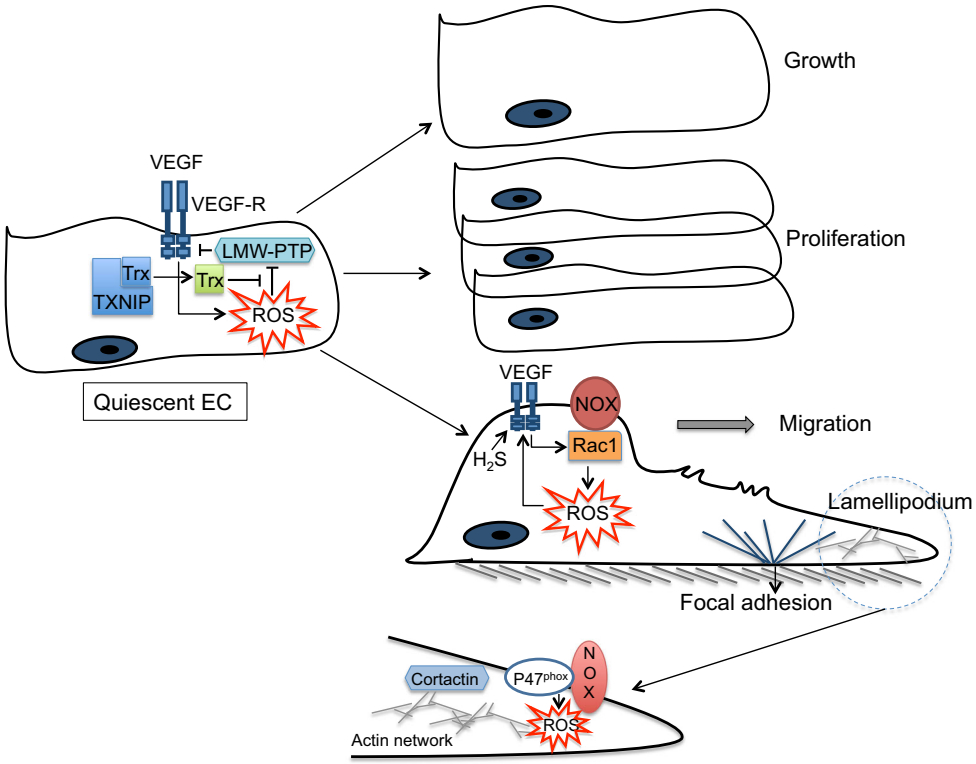

Fig. 3 Redox signaling and cell fate in endothelial cells. *VEGF* vascular endothelial growth factor, *VEGF-R* vascular endothelial growth factor receptor, *Trx* thioredoxin, *TXNIP* thioredoxin-interacting protein, *LMW-PTP* low molecular weight protein tyrosine phosphatase, *EC* endothelial cell, *ROS* reactive oxygen species

ensues is facilitated by highly coordinated cytoskeletal changes and includes extracellular adhesion, plasma membrane protrusion at the leading edge ("lamellipodia" formation), formation of new adhesion sites under the protrusion called focal adhesions (FAs), disruption of the older adhesions at the rear of the cell, followed by cell body contraction that draws the cell forward [56]. ROS play a key role in multiple steps of this process (Fig. 3). The amount and location of ROS generation are critical since successful migration is dependent on several biomolecules the actions of which are spatiotemporally regulated in subcellular compartments in front and rear of migrating ECs. The effects of VEGF in initiating EC migration are mediated by Nox-derived ROS production in a Rac1-dependent mechanism [57]. Similarly, a role for Nox2- and Nox4-derived ROS in EC migration has been demonstrated [58]. VEGF-induced EC migration is suppressed by overexpressing mitochondrial catalase or mitochondrial DNA depletion [59], implicating a role for mitochondria-derived ROS in promoting EC migration. The lamellipodia are characterized by a dense network of short, branched actin and cortactin filaments [60]. These cytoskeletal proteins play a role in activation of Nox [61], and cortactin co-localization with $p47^{phox}$ subunit of Nox is important in the assembly of Nox components with the actin cytoskeleton during agonists-induced ROS generation in ECs [62]. Targeting Nox components to focal complexes in lamellipodia may therefore facilitate ROS generation at specialized sites in the leading edge of migrating ECs, a requirement for stimulus-induced migration [63]. Accordingly, a role for recruitment of cortactin, Rac1 and $p47^{phox}$ Nox subunit and localized ROS production in the formation of the lamellipodia in pulmonary ECs has recently been shown [64].

ROS mediate numerous effects in initiation and promotion of angiogenesis, another major function of ECs. Both physiological angiogenesis (wound healing, vessel damage and ischemic repair) and pathological angiogenesis (cancer, diabetic retinopathy and macular degeneration) involve the same initial signaling cascades, all of which involve ROS. VEGF plays a key role in EC activation from a quiescent state in a process that is, in part, ROS-dependent [65]. ROS upregulate VEGF expression and VEGF binding to VEGF receptor 2 (VEGFR2) induces ROS production that is critical for angiogenesis [66]. This is mediated by VEGFR2-induced localized ROS generation that promotes junctional detachment of the EC monolayer [67] and initiation of EC migration. During angiogenesis, ECs need to rapidly proliferate, and proliferating ECs have increased ROS production as compared with quiescent cells [68]. ROS generated by VEGF signaling induces S-glutathiolation-mediated inhibition of low-molecular weight protein tyrosine phosphatase (LMW-PTP), which dephosphorlyates and inhibits VEGFR2 signaling [69].

Downregulation of TXNIP results in deglutathiolation-mediated activation of LMW-PTP and thereby inhibition of VEGFR2 signaling [69] (Fig. 3). As discussed, EC proliferation in response to growth factors and activation of downstream kinases is ROS-dependent. Migration and proliferation of ECs result in tube formation, the earliest stage of new vessel formation. Autophagy, subcellular degradation that is critical for cell survival under nutrient-deprived conditions, plays a key role in phenotypic responses of ECs in tube formation in a process that is also driven by ROS generation [70]. Lastly, H_2S, at low physiological concentrations, has been shown to stimulate EC proliferation and migration [71, 72] and to participate in VEGF signaling through breaking an intrinsic inhibitory disulfide bond in VEGFR2 thus promoting EC migration (Fig. 3) [73]. H_2S exerts potent proangiogenic effect in ECs in the setting of chronic ischemia by activating extracellular kinase pathways that promote vessel growth [74].

Smooth muscle cells (SMCs)

Phenotypic plasticity of SMCs

Smooth muscle cells are highly plastic cell types that play key roles in normal vascular physiology and in pathophysiology. Biological responses in the SMCs are complex due to impressive ability of the SMCs to undergo phenotypic switching, heterogeneity of SMC origin in the vasculature, and the presence of SMC progenitor cells [75]. SMCs exist in different phenotypic states [76], with the switch from a quiescent contractile phenotype to a synthetic proliferative type playing an important role in pathologic vascular remodeling, particularly in atherosclerotic plaque progression and vascular injury-induced intimal proliferation [75, 76]. Due to the presence of SMC progenitor cells in the vessel wall and their potential contribution to vascular remodeling [77, 78], in vivo SMC lineage tracing studies are needed to elucidate the exact origin of the cell types that are found in intima lesions [75, 78]. This is further complicated by the diverse developmental origins of SMCs in the vascular system [79]. Although phenotypic switching seems to occur in all SMCs regardless of their origin, the responses of these SMCs to different stimuli vary [79].

Redox signaling and phenotypic modulation in SMCs

Intracellular regulation of SMC phenotype depends on several kinases and downstream transcription regulation of contractile proteins and proteins that are associated with the cytoskeleton [75]. ROS play an essential role in this process (Fig. 4). Specificity of the intracellular ROS-mediated effects is dependent on subcellular compartmentalization. For instance, Nox1 and Nox4 isoforms of NADPH oxidase have differential signaling roles in phenotypic regulation of SMCs, which correlate with their differential compartmentalization in the membrane and leading edge of migratory SMCs [3]. Nox4 mainly produces H_2O_2 and Nox4 expression and activity is critical in the maintenance of the differentiated phenotype of SMCs isolated from aorta in vitro [80]. Nox4 modulates effects of TGFβ in aortic SMCs via p38 mitogen-activated protein kinase (MAPK)-dependent regulation of several transcription factors that mediate gene transcription elicited by diverse signaling pathways (e.g. serum response factor (SRF) and myocardin-related transcription factor A (MRTF-A) [81]). In contrast to the homeostatic role in systemic arteries, Nox4 mediates hypoxia-induced proliferation of SMCs in the pulmonary artery [82]. Unlike Nox4, Nox1 expression and activity are associated with a reduction in differentiation markers and increase in migratory, synthetic and proliferative SMC type. Through these modulations, Nox1 plays a key role in neointima formation after vascular injury [83]. Of direct relevance, cyclophilin A, a secreted growth factor from SMCs under oxidative stress, induces Nox activation by translocation of the cytosolic $p47^{phox}$ subunit to membrane lipid rafts or caveolae [84] and promotes neointima formation [85].

Redox signaling also regulates numerous aspects of cytoskeletal dynamics [86] and thereby modulates SMC differentiation. For example, carbonylation and subsequent degradation of annexin A1, a member of the annexin family of proteins that bind or "annex" to phospholipid membranes, promotes the growth of pulmonary artery SMCs [87]. In the nucleus, oxidation of actin by the oxidoreductase MICAL-2, an atypical actin regulatory protein, promotes actin disassembly and increases nuclear retention of MRTF-A and subsequent activation of SRF/MRTF-A-dependent gene transcription [88]. Finally, biomechanical forces can also modulate the SMC phenotype via redox-dependent mechanisms. Mechanical stretch for instance potentiates Nox1-mediated ROS production that causes vascular SMC switch to synthetic phenotype via myocyte-enhanced factor 2 (MEF2), a transcription factor that plays a key role in cell fate in response to extracellular signals [89].

Redox signaling and SMC adhesion and migration

In vascular remodeling associated with disease, a phenotypic switch in the SMCs to a synthetic type enables them to migrate and proliferate in response to a variety of extracellular stimuli. Migratory steps in the SMCs are similar to ECs, with ROS regulating multiple phases in the process (Fig. 5).

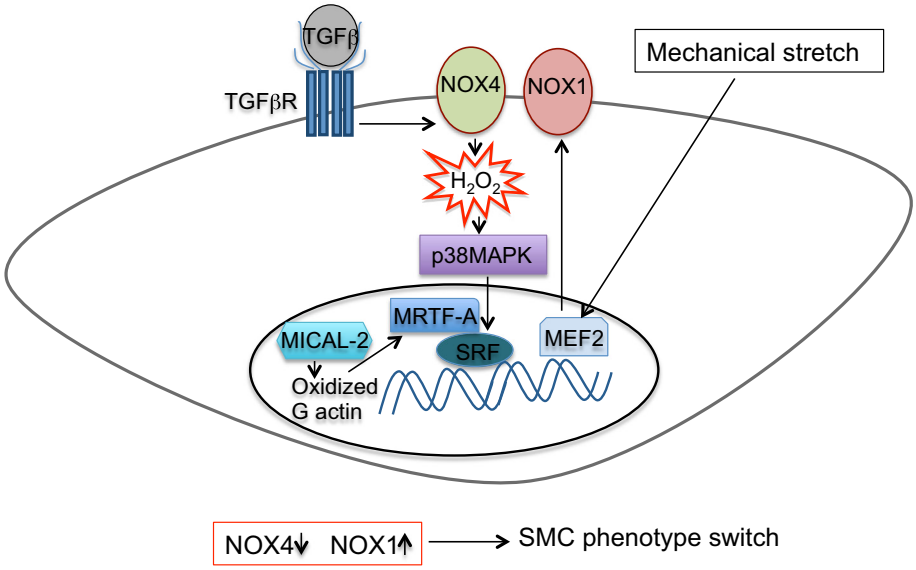

Fig. 4 Redox-dependent phenotype switch in smooth muscle cells. *TGFβ* transforming growth factor β, *p38 MAPK* p38 mitogen-activated protein kinase, *MRTA-F* myocardin-related transcription factor A, *SRF* serum response factor, *MEF2* myocyte-enhanced factor 2, *SMC* smooth muscle cell

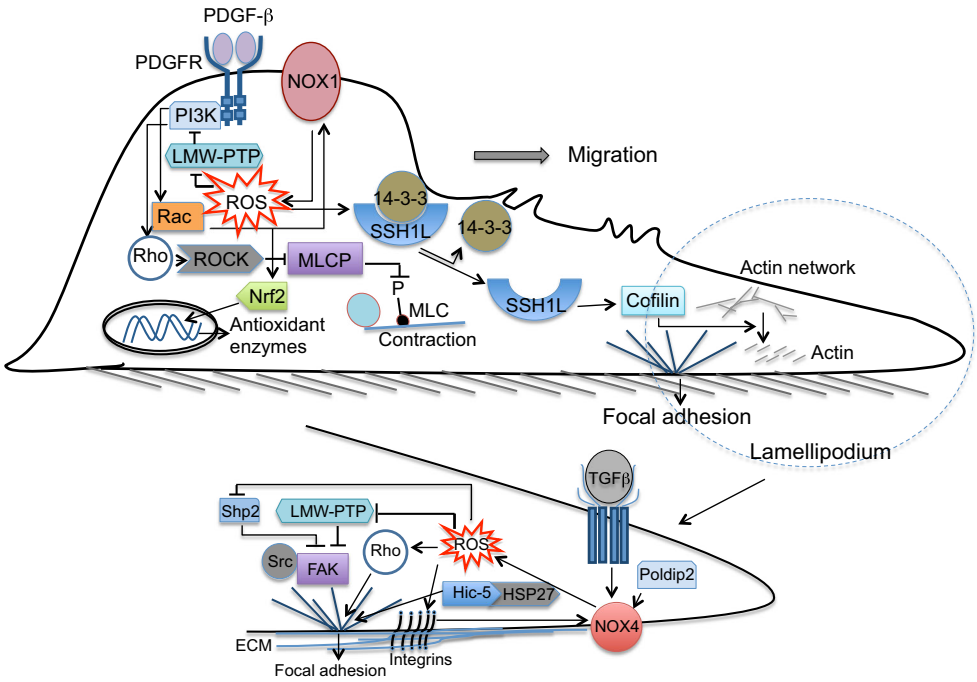

Fig. 5 Redox-mediated smooth muscle cell migration. *PDGFβ* platelet-derived growth factor β, *PDGFR* platelet-derived growth factor receptor, *PI3K* phosphoinositol 3-kinase, *LMW-PTP* low molecular weight protein tyrosine phosphatase, *ROS* reactive oxygen species, *ROCK* rho-kinase, *MLCP* myosin light chain phosphatase, *MLC* myosin light chain, *Nrf2* nuclear factor erythroid 2-related factor 2, *SSH1L* slingshot1L phosphatase, *TGFβ* transforming growth factor β, *FAK* focal adhesion kinase, *Hic5* H_2O_2-inducible clone-5, *HSP27* heat shock protein 27, *Poldip2* polymerase [DNA-directed] delta-interacting protein 2, *ECM* extracellular matrix

Vascular SMC migration is modulated by numerous stimuli, in particular PDGF is the major promigratory factor [90]. The effects of PDGF occur mainly via PDGF-β receptor activation [91]. Although the PDGF receptors have very low abundance in normal vessels, PDGF-β receptor expression is induced during initial response to injury or the phenotypic transformation of SMCs [90]. Since Nox inhibition blocks PDGF-induced PDGF-β-receptor phosphorylation [92], ROS may be involved as early as the initial activation of the receptor. LMW-PTP limits PDGF receptor activation and its activity is inhibited by ROS through formation of an inactivating disulfide bond between two vicinal Cys in its catalytic pocket [93]. Upon activation, PDGF receptor provides binding sites for phospholipase C, Src kinase and PI3K. PI3K activates Rhoguanine nucleotide exchange factors to stimulate Rho-GTPase family members (such as Rho, Rac and cdc42) [3]. Rac activates several Nox family members, mainly Nox1 and Nox2 [3], and increases ROS, which in turn induce generation of other pro-migratory factors and thus amplify the migratory cell response [90]. The redox-sensitive transcription factor Nrf2 limits PDGF-stimulated vascular

SMC migration by decreasing ROS, and is protective against neointimal hyperplasia after vascular injury [94] (Fig. 5). Mechano-responsive signaling can also initiate SMC migration, but the underlying mechanisms are not fully elucidated. It has recently been shown that cyclic mechanical stretch can induce Nox4-dependent activation of cofilin, which is required for cytoskeletal reorganization and SMC reorientation after mechanical stimulation [95]. Activation of cofilin increases depolymerization of actin filaments, a necessary step in the formation of new actin filaments, thereby playing an essential role in maintaining and protruding lamellipodia at the leading edge of migrating cells [90] (Fig. 5). In PDGF-stimulated SMCs, cofilin is activated through dephosphorylation by Slingshot1L (SSH1L) phosphatase via Nox1-dependent oxidation of 14-3-3, which results in disruption of its inhibitory association with SSH1L [96].

After formation of lamellipodia, integrins mediate the formation of focal adhesions (FA). The FAs act as organizers of the SMC contractile proteins and incorporate and integrate multiple signaling molecules such as focal adhesion kinase (FAK), integrin-linked kinase and Src kinase [97]. These kinases link integrins to the actin cytoskeleton and coordinate the formation and strengthening of FAs in the lamellipodium, as well as their recycling from the rear of the cell [90]. ROS are critically involved in many aspects of FA formation and turnover in SMCs (Fig. 5). Integrin activity is modulated by oxidation of redox-sensitive motifs when cells attach to surface [98]. Integrin signaling itself involves ROS generation [45]. ROS production via this mechanism can inhibit LMW-PTP [99] that, in addition to modulating PDGFR activation discussed earlier, associates with and inactivates FAK [100]. Moreover, redox-mediated inhibition of the phosphatase Shp2 can lead to activation of FAK [101]. ROS are critically involved in FA turnover, which is key in successful cell motility. Rho mediates actin polymerization and FA formation and ROS can directly activate Rho by oxidation of a redox-sensitive motif [102]. Moreover, Nox4 is key in FA turnover and polymerase [DNA-directed] delta-interacting protein 2 (poldip2), an activator of Nox4-mediated ROS production in vascular SMCs, affects FA turnover and inhibits SMC migration in a RhoA/FAK-dependent manner [103]. Nox4 expression is increased by TGFβ and TGFβ in turn increases the number of FAs. Downstream mediators of TGFβ-induced Nox4-dependent FA formation have recently been shown to include the FA resident protein H_2O_2-inducible clone-5 (Hic-5) and its binding partner the heat shock protein 27 [104].

Following FA formation, cell body contraction generates the force that is needed to move the SMC forward. FAs are connected to actin and ROS can influence actin dynamics directly or indirectly during specific phases of migration [90]. Actin polymerization is affected by ROS, with the direction of effects depending on the type and amount of ROS that are generated [3]. Interaction of actin and myosin to generate contractile force is modulated by the redox-sensitive GTPase Rho [105]. Activation of the Rho/Rho-kinase (ROCK) pathway promotes myosin light chain phosphorylation by inhibiting the regulatory subunit of myosin light chain phosphatase (MLCP), thus promoting contraction in pulmonary SMCs [106]. Consistent with this, ROCK2 isoform of Rho-kinase promotes migratory and proliferative phenotype in pulmonary SMCs in mice, and its expression is increased in patients with PAH [107]. Further studies are needed to clarify the specific roles and functional differences between ROCK1 and ROCK2 isoforms [108].

Redox signaling and SMC hypertrophy and proliferation

SMC proliferation is an essential part of biological development and contributes to adaptive responses to injury—i.e. vascular repair. Similar to the migratory process, dysregulation of SMC proliferation perpetuates pathology (e.g. progression of atherosclerosis or neointima formation postBAS). Several migratory and proliferative pathways overlap in the SMCs and critical promigratory factors such as PDGF also promote proliferation [3]. AngII mainly mediates SMC hypertrophy [109] rather than migration or proliferation. SMC proliferation is tightly coupled with cellular redox state, and ROS have key regulatory roles by modulating the function of many growth factors and kinases that are essential in proliferative signaling cascades (Fig. 6), largely by oxidative modification of Cys residues [110]. These regulatory roles are perturbed under conditions associated with increased ROS. High levels of ROS generally inactivate downstream effectors of growth factor signaling [3]. For example, many signaling elements and effectors in growth factor-mediated PI3K signal transduction are redox-sensitive. While PI3K itself is susceptible to sulfenation [111], the functional significance of this modification or the presence of other oxidative Cys modifications is yet to be determined. Oxidative modification of one or two Cys on Src, depending on the context and cell type, leads to its activation [112], and Src in turn can activate PI3K. Growth factors potentiate the accumulation of phosphatidylinositol 3,4,5 trisphosphate (PIP_3), both through a PI3K-dependent increase in synthesis as well as oxidative inactivation of phosphatase and tensin homolog (PTEN) that catalyzes the removal of PIP_3 [113]. PIP_3 then activates the redox-sensitive Akt, activity of which is affected by sulfenation of a Cys residue [114]. Moreover, AngII-induced ROS generation promotes association of the redox-sensitive p38 mitogen-activated protein kinases (MAPK) and MAPK-activated protein

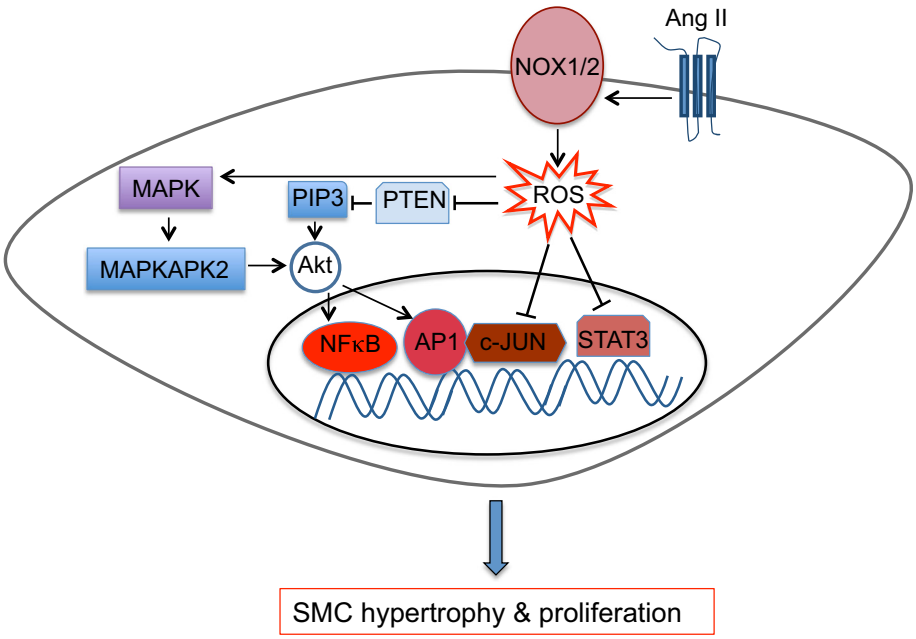

Fig. 6 Redox signaling and smooth muscle cell hypertrophy and proliferation. *PDGFβ* platelet-derived growth factor β, *PDGFR* platelet-derived growth factor receptor, *AngII* angiotensin II, *AT1R* angiotensin II type 1 receptor, *ROS* reactive oxygen species, *MAPK* mitogen-activated protein kinase, *MAPKAPK2* mitogen-activated protein kinase-activated protein kinase 2, *PIP3* phosphatidylinositol 3,4,5 trisphosphate, *PTEN* phosphatase and tensin homolog, *AP1* activator protein 1, *NF-κB* nuclear factor κB, *STAT3* signal transducer and activator of transcription 3

kinase-2 with Akt [115]. Akt activates the transcription factors activator protein 1 (AP1) and NF-κB to promote cell cycle progression [3]. Finally, many transcription factors in proliferative pathway are directly regulated by redox modifications, for instance signal transducer and activator of transcription 3 (STAT3) and c-Jun are both negatively regulated by S-glutathiolation [116, 117] (Fig. 6).

In contrast to growth factor signaling, functional effects of oxidative modification of phosphatases are varied. S-glutathiolation of a reactive Cys in protein tyrosine phosphatase 1B reversibly inhibits its activity and promotes proliferative signaling [110]. Similarly, reversible oxidation of Shp1/2 inhibits their function through a different mechanism. Of the critical Cys residues in the enzymes' active site, when the catalytic Cys is re-reduced, two conserved "backdoor" Cys form an intramolecular disulfide. Formation of this backdoor–backdoor disulfide is dependent on the presence of the active site Cys and can proceed via either active site Cys-backdoor Cys intermediate [118]. These two backdoor Cys are necessary and sufficient to ensure reversible oxidation of the Shps because removal of both Cys leads to irreversible oxidative inactivation [27, 118]. This regulatory mechanism has recently been shown to be critical in neointima formation postBAS [27].

Perivascular tissue

Perivascular tissue, in particular perivascular adipose tissue (PVAT) is increasingly recognized to play important physiological roles in vascular homeostasis [119]. PVAT generates numerous cytokines (pro-inflammatory such as IL6 and anti-inflammatory like adiponectin [120]) as well as ROS that affect the adjacent vascular layers in a paracrine manner and play an integral role in vascular remodeling [121]. PVAT actively participates in the inflammatory response to BAS [122]. Vessel injury downregulates the anti-inflammatory adiponectin in PVAT and promotes SMC growth [123] and PVAT-released leptin contributes on neointima formation after vascular injury [124]. PVAT also exerts effects on vascular remodeling via redox pathways. For example, 4-hydroxynonenal (4-HNE), a product of lipid peroxidation generated in the vascular wall, mediates paracrine activation of peroxisome proliferator-activated receptor-γ signaling in the PVAT, thus promoting the release of adiponectin, which exerts a paracrine effect back to the vascular wall to reduce Nox activity [120] and to promote eNOS coupling [125]. Moreover, a reduction in the activity of the anti-inflammatory mammalian target of rapamycin complex 2 (mTORC2) in the PVAT leads to inducible NOS-mediated increase in $ONOO^-$, which impairs endothelium-mediated vasorelaxation [126]. Further mechanistic studies are needed to elucidate the role of redox signaling in PAVT-mediated vascular remodeling, particularly in the context of obesity and metabolic syndrome.

Pericytes in the microvasculature

Pericytes are contractile cells on capillaries that may have a role in regulating local blood flow in addition to stabilizing

newly formed capillaries [127]. Pericytes can be constricted and dilated by signaling molecules in vitro and capillary blood flow heterogeneity might reflect differences in pericyte tone. These properties of pericytes are increasingly recognized in physiology and in remodeling of microvasculature in pathology. Pericyte contraction in response to ischemia–reperfusion contributes to "no-reflow" phenomenon in the brain that is mediated by oxidative-nitrosative stress [128], nonetheless, pericyte death in rigor, which majorly contributes to no-reflow phenomenon, does not change with ROS scavenging [127]. A role for pericytes in myocardial no-reflow has been implicated [129] but remains to be established. A marked increase in the capillary pericyte coverage and a switch in phenotype to contractile SMC have been shown to contribute to distal vascular remodeling in human PAH [130]. Since receptor tyrosine kinases have been shown to reduce pericyte density in solid tumor models, it is plausible that these agents might be useful in treatment of PAH. Given these recent studies, it is clear that the physiological regulatory role of pericytes in the microvasculature and putative involvement of redox-dependent mechanisms in these cell types require further elucidation.

Therapeutic implications and future directions

Like most biological processes, vascular remodeling and redox signaling are extremely complex. The complexity of the biology mandates sophisticated approaches to tackle dysregulation of biosystems. As can be seen from our overview, enormous efforts have been made for gaining in-depth insights into the pathobiology of vascular remodeling and the role that ROS play in this phenomenon. Bearing this in mind, it is no surprise that general antioxidants that primarily aimed to scavenge ROS failed to improve redox-dependent cardiovascular pathologies [131].

The advent of systems biology, with high dimensional "omics" tools, provides a unique opportunity for more sophisticated, unbiased understanding of the biological processes. This approach promises to provide most biologically relevant therapeutic targets. A relevant example of using this method in vascular remodeling is transcriptomic characterization of in-stent restenosis by our group. We performed near genome wide analysis in de novo atherosclerosis and in-stent restenosis in atherectomy samples from patients. Independently, we generated networks of gene–gene interactions using text mining of the entire abstracted literature. By overlaying gene expression from atherectomy tissue on these networks and scoring individual networks according to the average differential significance of network members, we found the network with Gpx1 as its hub to be the most significantly down-regulated of all gene networks in in-stent restenosis [27]. In mechanistic studies, we found that loss of Gpx1 leads to increased SMC proliferation, migration and apoptosis, and that this is attenuated by inhibition of the orphan receptor tyrosine kinase ROS1 through cell-fate regulation. Sustained ROS1 activation that triggered SMC proliferation and neointimal hyperplasia was mediated by the reductive stress associated with Gpx1 deficiency, which lead to inhibition of the regulatory phosphatase Shp2 by S-glutathiolation of 2 backdoor Cys residues. Importantly, we determined that pharmacological inhibition of ROS1 attenuated in-stent restenosis without affecting reendothelialization. This differential effect on SMCs and ECs is critical since the current anti-proliferative drugs used in stents, whilst very effective, indiscriminately affect ECs and SMCs leading to delayed reendothelialization [132] and higher risk of late stent thrombosis [133].

As our understanding of the mechanisms governing phenotype switching and cell fate in ECs and SMCs deepens, differential targeting of these cells will be more attainable. Similar to ROS1 inhibitors, targeting pyruvate dehydrogenase kinase isoform 2, which governs mitochondrial hyperpolarization in SMCs after BAS [134] or cytidine triphosphate synthase 1 that catalyzes generation of the energy-rich nucleotide cytidine triphosphate in proliferating SMCs after balloon injury [135], reduce neointima formation without affecting reendothelialization. It is high time for development of similarly tailored therapies that are directed at redox pathways to slow or halt pathological vascular remodeling.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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