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Review

Vascular-derived reactive oxygen species for homeostasis and diseases

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ABSTRACT

Numerous basic and clinical studies have clearly identified that reactive oxygen species (ROS, i.e., H_2O_2, O_2^-, and $^{\bullet}OH$) has a major role in the development of cardiovascular diseases. However, we still have no strong therapeutic strategy for clinical benefits of antioxidant administration. One potential reason for those could be a crucial role of ROS for intracellular signaling pathways that is important for vascular functions in a very low concentration. ROS contributes to the physiology and pathology of vasculature, but precise molecular regulations remain elusive. The mechanism how excessive ROS (oxidative stress) deteriorate vascular function and promote vascular diseases has not been clearly elucidated. Cyclophilin A (CyPA) has been studied as a multifunctional protein that is upregulated in a variety of inflammatory conditions, such as rheumatoid arthritis, autoimmune disease, and cancer. CyPA has been classified as an immunophilins and has a variety of intracellular functions including intracellular signaling, protein trafficking, and the regulating other proteins. Besides intracellular functions, we revealed that CyPA is a secreted molecule that has a pathological role in the cardiovascular system. CyPA has emerged as a potential biomarker and mediator of cardiovascular disease.

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Introduction

Oxidative stress, generated by excessive reactive oxygen species (ROS) promotes cardiovascular disease. However, the precise mechanism how ROS (i.e., H_2O_2, O_2^-, and $^{\bullet}OH$) deteriorate vascular function and promote vascular remodeling has not been clearly elucidated. Moreover, H_2O_2 also plays a crucial role as a signaling molecule under physiological conditions [1]. Our recent study revealed that H_2O_2 is one of the endothelium-derived hyperpolarizing factor (EDHF) that contributes as a signaling molecule in the vasculature.

Endothelial cells (EC) and vascular smooth muscle cells (VSMC) secrete a variety of vasoactive substances which contribute to the vascular remodeling [2,3]. Growth factors secreted from VSMC have been studied as important mechanisms that mediate varying cellular responses in vascular remodeling [4–6]. Many other stimuli that modulate VSMC function including ROS promote VSMC growth by inducing auto/paracrine growth mechanisms [7]. It has been shown that ROS increase cell proliferation, hypertrophy

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Table 1
Roles of CyPA in vivo and in vitro.

Species	Diseases	Phenotype	Authors	Years
Human	Human immunodeficiency virus (HIV)-1 infection	Cyclophilin A is important for HIV-1 infection in vitro	Thali et al. [68], Franke et al. [69]	1994
Human	Rheumatoid arthritis	Cyclophilin A levels are increased in the sera and synovial fluids of rheumatoid arthritis (RA) patients	Billich et al. [70]	1997
Human	Non-small cell lung cancer	Cyclophilin A is increased in non-small cell lung cancer	Campa et al. [71]	2003
Mouse	Cerebral infarction	Cyclophilin A regulates the nuclear translocation of apoptosis-inducing factor in neurons after cerebral hypoxia–ischemia	Zhu et al. [18]	2007
Mouse	Vascular stenosis	Cyclophilin A promotes intimal thickness in mice	Satoh et al. [46]	2008
Mouse/Human	Abdominal aortic aneurysm	Cyclophilin A activates MMPs and promotes aortic aneurysm formation and rupture	Satoh et al. [40]	2009
Mouse	Atherosclerosis	Cyclophilin A reduces endothelial eNOS expression and promotes atherosclerosis	Nigro et al. [61]	2011
Mouse	Cardiac hypertrophy	Cyclophilin A promotes cardiac hypertrophy and fibrosis	Satoh et al. [72]	2011

in a concentration-dependent manner [8]. Although production of intracellular ROS has been implicated in the pathogenesis of cardiovascular disease [9–11], specific molecular target has been remained to be elucidated.

Cyclophilin A (CyPA) has been identified as the main target for the immunosuppressive drug cyclosporine A [12–15]. Cyclophilins are a family of highly conserved and ubiquitous proteins termed immunophilins [16]. The most abundant cyclophilin is CyPA, which is widely distributed in almost all tissues [17]. Due to its enzymatic properties, cellular localization, and role in protein folding, CyPA belongs to a diverse set of proteins which are termed molecular chaperones. Since CyPA catalyses the cis–trans isomerization of peptidyl–prolyl bonds of certain proteins (PPIase activity), CyPA acts as acceleration factor in protein folding and assembly. In addition to the role for protein folding, the PPIase activity of CyPA has recently been demonstrated to have a variety of roles including intracellular trafficking, signal transduction, and transcription regulation [18,19]. In addition, we have reported that CyPA is secreted from VSMC in response to ROS, and the secreted extracellular CyPA stimulates VSMC proliferation and inflammatory cell migration in vitro and in vivo. ROS-induced secreted CyPA contributed to several cardiovascular diseases in vivo. By using the CyPA knockout mouse and the CyPA overexpressing mouse (VSMC-Tg), we revealed that CyPA mediates a variety of cardiovascular diseases including vascular stenosis, atherosclerosis, and abdominal aortic aneurysms (AAA) (Table 1).

Vascular-derived ROS as protectors for vascular functions

EC-dependent relaxation is mediated primarily by prostacyclin, nitric oxide, and EDHF. The existence of EDHF was first described by Vanhoutte in 1988 [20]. We have recently elucidated that H_2O_2 plays an important role as an EDHF and contributes to the vascular homeostasis [21]. Vascular EC contains various superoxide-producing oxidases including eNOS, cyclooxygenase, lipoxygenase, P-450 monooxygenase, and NAD(P)H oxidases [22]. Superoxide attenuates EC-dependent relaxation and promotes the contraction in the VSMC through formation of hydroxyl radicals [23,24]. Superoxide is changed to H_2O_2 spontaneously or through superoxide dismutase (SOD)-dependent dismutation. H_2O_2 is known to have a direct relaxing effect on the VSMC [25,26] as well as hyperpolarizing effect. H_2O_2 is catalyzed by endogenous peroxidases into H_2O and O_2 or converted to hydroxyl radical. Hydroxyl radical causes endothelium-dependent contractions through activation of vasoconstrictor prostanoids in VSMC [27]. Thus, the mechanism of $H_2O_2^-$ induced hyperpolarization is complex and varies on the type of blood vessel. As mentioned above, we have elucidated that vascular EC produce a small amount of superoxide and H_2O_2 [21,28,29]. The H_2O_2 theory may open a new research field regarding the importance and complexity of EC-derived relaxing factors. Further studies are needed to clarify the processes involved in EC production of H_2O_2, vasodilator mechanism of the ROS, and the physiological and pathological role of H_2O_2 as an EDHF in vascular homeostasis.

Vascular-derived ROS as promoters for vascular diseases

Controlled ROS levels (physiological levels) are important to regulate cell functions and cell fate. We have shown that H_2O_2 is important for EC function and vascular relaxation in a very low concentration [21,29]. In contrast, the excess amount of ROS (pathological levels) is hazardous to cells and their content. In the vascular wall, ROS are generated by several mechanisms, including NADPH oxidases [30]. Vascular ROS formation can be stimulated by mechanical stretch, pressure, shear stress, hypoxia, and secreted factors [31]. We have demonstrated that ROS stimulate ERK1/2 biphasic-activation in VSMC [11,32]. One explanation for the delayed ERK1/2 activation was the response to the secreted oxidative stress-induced factors (SOXF). We analyzed the proteins released into the medium in response to ROS and finally found that CyPA is one of the major SOXF [33]. Human recombinant CyPA stimulated ERK1/2 activity and DNA synthesis in VSMC in a concentration dependent manner [34]. Thus, extracellular CyPA is a novel VSMC growth factor which contributes to the growth promoting activity of ROS in VSMC (Fig. 1).

Extracellular CyPA receptor(s) have not been clearly elucidated. Despite the accumulating evidence that CyPA serve multiple intracellular and extracellular functions, surprisingly little is known regarding the effect on specific receptors. Further knowledge of

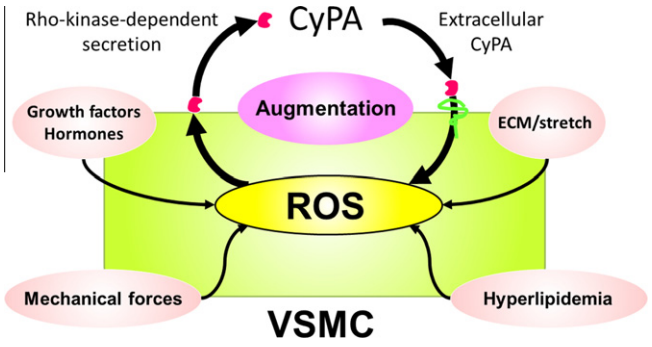

Fig. 1. Cyclophilin A augments ROS production. ROS inducer such as angiotensin II (AngII), mechanical stress, and hyperlipidemia, promotes cyclophilin A (CyPA) secretion from vascular smooth muscle cells (VSMC). Secreted CyPA activates ERK1/2 and promotes ROS production, contributing to the augmentation of ROS production.

the extracellular CyPA receptors on vascular cell responses will contribute to the development of novel therapies for cardiovascular diseases [35–38]. On the other hand, we demonstrated that CyPA is secreted from VSMC through a process requiring ROS production and vesicle formation and Rho-kinase inhibitor reduced ROS-induced CyPA secretion [39,40].

CyPA promotes vascular intimal thickness

ROS have been implicated in the pathogenesis of neointima formation in part by promoting VSMC growth [11,32] as well as stimulating pro-inflammatory events [41,42]. We demonstrated that extracellular CyPA stimulates pro-inflammatory signals in EC [36]. In addition to the effects on vascular cells, CyPA promotes migration of inflammatory cells [43,44] and promotes matrix metalloproteinases (MMPs) activation [45]. Therefore, CyPA is a key mediator that affects EC, VSMC and inflammatory cell function under oxidative stress condition in vivo.

We found that CyPA expression is dramatically increased with a time course that paralleled neointima formation after carotids ligation, suggesting an important role for CyPA in the cell response to oxidative stress induced by vascular injury [46]. In parallel with CyPA expression, carotid ligation induced phosphorylation of ERK1/2 in wild-type carotids, which was significantly less in $CyPA^{-/-}$ carotids. Co-localization of CyPA, αSMA, and Masson-Trichrome staining revealed that CyPA expression was especially elevated in VSMC. VSMC-specific CyPA overexpression (VSMC-Tg mice) revealed increased medial and intimal area in ligated arteries, suggesting that VSMC-derived CyPA promotes the vascular restenosis. In addition, VSMC-Tg mice revealed enhanced accumulation of inflammatory cells in ligated carotids, supporting the important role for CyPA in mediating the recruitment of inflammatory cells [46]. This study revealed three important pathologic consequences of CyPA activity in vivo. First, VSMC-derived secreted CyPA is mitogenic by virtue of its ability to promote VSMC proliferation. Second, secreted extracellular CyPA is pro-inflammatory because it stimulates the recruitment of inflammatory cells. Third, secreted CyPA can further promote a pathological setting exacerbating the generation of intracellular ROS in VSMC derived from mouse aorta. Therefore, CyPA can be a potential biomarker for restenosis and is a target for the development of novel therapy in humans.

CyPA promotes aortic aneurysm formation and rupture

Abdominal aortic aneurysms (AAA) formation results from chronic inflammation of the aortic wall, associated with decreased medial VSMC, and progressive destruction of structural components, particularly the elastic lamina. Key mechanisms include VSMC senescence [47], oxidative stress [7,48], increased local production of proinflammatory cytokines [49] and increased activities of MMPs that degrade extracellular matrix [50,51]. CyPA plays a crucial role for MMP activation in patients with rheumatoid arthritis [43]. Genetic and pharmacological inhibition of ROS production and MMPs suppressed development of aneurysms [52–55]. Furthermore, treatment with an AT_1 receptor blocker significantly suppressed aneurysm formation in $ApoE^{-/-}$ mice [56]. Based on these reports, we hypothesized that AngII induces ROS and MMP activation via a CyPA-dependent pathway and promotes AAA formation.

As we expected, AAA formation in the AngII-induced $ApoE^{-/-}$ model was completely prevented in the $CyPA^{-/-}$ background [40]. CyPA was highly expressed in the aorta of patients with AAA, and co-localizes with active form of MMPs as assessed by DQ gelatin [40]. Our data suggest that extracellular CyPA and its signaling pathways are novel targets for AAA therapy and potentially other cardiovascular diseases associated with inflammation. Secreted CyPA, acting as a proinflammatory cytokine, synergistically augments AngII-mediated ROS production contributing to the onset of vascular inflammatory cell migration and AAA formation [52].

CyPA promotes endothelial apoptosis and atherosclerosis

Numerous basic and clinical studies have clearly identified that ROS has a major role in the endothelial damage and the development of atherosclerosis [57–59]. However, we still have no strong therapeutic strategy for clinical benefits of antioxidant administration. One potential reason for those could be a crucial role of ROS (especially H_2O_2) for intracellular signaling pathways that is also important for vascular functions in a very low concentration [21,28,29,60]. We demonstrated that CyPA (both intracellular and extracellular) contributes to atherosclerosis by promoting EC apoptosis and EC expression of leukocyte adhesion molecules, stimulating inflammatory cell migration, enhancing ROS production, increasing proliferation of macrophages and VSMC, and increasing pro-inflammatory signal transduction in VSMC [61]. In the context of atherosclerosis, CyPA will be regarded as a proinflammatory and proatherogenic molecule.

CyPA reduces endothelial eNOS expression

The athero-protection observed in the $ApoE^{-/-}CyPA^{-/-}$ mice was due to the decreased inflammation mediated by the absence of CyPA. The vascular endothelium has a large array of functions that are vital for the initiation of atherosclerosis. eNOS function is critical for vascular homeostasis via generation of nitric oxide (NO) and its loss is pro-atherogenic. Furthermore, the progression of atherosclerosis is associated with decreases in both eNOS expression and NO production. *En face* aortic staining revealed significantly higher eNOS expression in the $ApoE^{-/-}CyPA^{-/-}$ mice compared to $ApoE^{-/-}$ mice. Moreover, shear stress-induced eNOS expression was significantly increased by CyPA siRNA in HUVEC. Also, CyPA knock down in HUVEC increased eNOS promoter activity and eNOS mRNA levels. In contrast, overexpression of CyPA reduced eNOS at protein and mRNA levels. These findings illustrate a novel mechanism by which CyPA promotes atherosclerosis through suppression of eNOS transcription.

CyPA-mediated ROS production reduces eNOS expression

ROS production was significantly higher in HUVEC overexpressing CyPA compared to cell transfected with the vector control. These data suggest that CyPA plays a critical role in ROS generation in EC similar to our findings in VSMC [40]. To demonstrate that ROS are key determinants in CyPA-mediated inflammation, we evaluated whether CyPA decreases eNOS expression by a ROS-dependent mechanism. Both the anti-oxidants N-Acetyl-Cysteine (NAC) and Tiron reversed the CyPA-mediated inhibition of eNOS promoter activity [61]. These data demonstrated that CyPA induces inflammation through ROS-dependent mechanisms in EC as well as in VSMC [37]. Based on these results, we believe that CyPA, acting as a proinflammatory cytokine, synergistically augments ROS production, contributing to vascular inflammation and atherogenesis [38].

CyPA is highly expressed at sites with unstable atherosclerotic plaques, especially those associated with macrophages and foam cells. However, CyPA expression and its regulatory molecular mechanisms remain elusive during the process of plaque unstabilization in humans. Therefore, further research with regard to the

role of CyPA in the progression of atherosclerosis is necessary to identify potential CyPA-related therapeutic targets.

Conclusion

Numerous basic and clinical studies have clearly identified that ROS has a major role in the EC damage and the development of cardiovascular diseases [61]. However, we still have no strong therapeutic strategy for clinical benefits of antioxidant administration. One potential reason for those could be a crucial role of ROS for intracellular signaling pathways that is also important for vascular functions in a very low concentration [21,28,29].

In contrast, the identification of CyPA as a mediator of oxidative stress-induced tissue damage provides insight into the mechanisms of several therapies. For example, the Rho-kinase inhibitor Y27632, and simvastatin significantly reduced CyPA secretion from VSMC [39,40]. Rho-kinase is an important therapeutic target in cardiovascular disease [62] and Rho-kinase inhibition has been reported to reduce AngII-induced AAA formation [63], atherosclerosis, and cardiac hypertrophy [64]. Moreover, AT1a receptor blockers and ACE inhibitors have been shown to prevent cardiovascular diseases [56,65,66] and reduced CyPA secretion may partially contribute to the therapeutic effect of these drugs on AAA, atherosclerosis, and cardiac hypertrophy [40].

Therefore, it is logical to propose that agents which prevent CyPA binding to its receptors may have therapeutic potential (Fig. 1). By blocking this malignant cycle that augments ROS production through CyPA autocrine/paracrine signaling pathway, we may have a novel therapeutic tool for controlling cardiovascular diseases in the near future. However, CyPA expression and its regulatory molecular mechanisms remain elusive during the development of cardiovascular diseases. Therefore, further research with regard to the role of CyPA is needed to identify potential CyPA-related therapeutic targets [67].

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