Extracellular and Intracellular Cyclophilin A, Native and Post-Translationally Modified, Show Diverse and Specific Pathological Roles in Diseases

Chao Xue, Mark P. Sowden, Bradford C. Berk

Abstract—CypA (cyclophilin A) is a ubiquitous and highly conserved protein with peptidyl prolyl isomerase activity. Because of its highly abundant level in the cytoplasm, most studies have focused on the roles of CypA as an intracellular protein. However, emerging evidence suggests an important role for extracellular CypA in the pathogenesis of several diseases through receptor (CD147 or other)-mediated autocrine and paracrine signaling pathways. In this review, we will discuss the shared and unique pathological roles of extracellular and intracellular CypA in human cardiovascular diseases. In addition, the evolving role of post-translational modifications of CypA in the pathogenesis of disease is discussed. Finally, recent studies with drugs specific for extracellular CypA show its importance in disease pathogenesis in several animal models and make extracellular CypA a new therapeutic target.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38: 986-993. DOI: 10.1161/ATVBAHA.117.310661.)**

Key Words: cardiovascular diseases ■ cytoplasm ■ endothelial cells ■ inflammation ■ paracrine communication

Cyclophilins are a family of ubiquitous and highly conserved proteins with peptidyl prolyl isomerase (PPIase) activity, which catalyzes the *cis–trans* isomerization of peptide bonds at proline residues.[1,2] CypA (cyclophilin A) is the most abundantly expressed and first identified cyclophilin among the 18 known human cyclophilins.[3] It was first identified as the cytosolic binding partner of the immunosuppressive drug cyclosporin A (CsA).[4] The formation of CypA–CsA complex inhibits the transcription of immune response–related genes and prevents proliferation of T cells.[5]

CypA was initially believed to function as an intracellular protein because of its highly abundant level in the nucleus and cytoplasm of many cell types and its lack of signal export sequence.[3,6,7] Indeed, intracellular CypA (iCypA), with its catalytic and chaperone activity of PPIase, has been shown to influence major pathways, such as protein folding, trafficking, and function. As a consequence of these interactions, it regulates cell function, such as T cell subtype differentiation, platelet activation, and cytokinesis. CypA has been reported to participate in both de novo protein folding and refolding processes via its PPIase activity.[7–10] Several studies have suggested that CypA participated in protein trafficking in cells.[11,12] Our laboratory also reported that iCypA enhanced angiotensin II–induced reactive oxygen species (ROS) production in vascular smooth muscle cell (VSMC) by promoting translocation of NADPH oxidase cytosolic subunit p47phox to the caveolae through its interaction with p47phox and cell cytoskeleton.[13] CypA was reported to interact with YY1, a zinc finger transcription factor and alter its transcriptional activity.[14] In terms of T cell signaling, Colgan et al[15] reported that CypA inhibits CD4$^+$ T cell Th2 differentiation through the interaction with Itk via its PPIase active site, causing a favored shift to Th1 (T-helper cells) profile. Wang et al[16] reported that iCypA promoted platelet activation by inducing calcium influx and facilitating the interaction between αIIbβ3 and cytoskeleton. Recently, it was suggested that iCypA was a centrosome protein that undergoes cell cycle–dependent relocation to the midzone and midbody and was required for the completion of cytokinesis.[17]

Recent evidence shows an important role for secreted CypA, or extracellular CypA (eCypA), which participates in both autocrine and paracrine signaling pathways.[18,19] Reports from Billich et al[20] showed high levels of CypA in the synovial fluids from patients with rheumatoid arthritis. Our group was the first to show oxidative stress–induced CypA secretion from VSMC. We found that the secretion of CypA from VSMC was a highly regulated process of vesicle transport, docking, and fusion at the plasma membrane,[21] similar to neurotransmitters in the synaptic gap. Substantial evidence showed that many cell types other than VSMC, such as endothelial cells (EC), macrophages, and fibroblast-like synoviocytes, were sources of secreted CypA.[18,22,23]

eCypA has cellular functions similar to iCypA, such as inflammation and proliferation, but also unique properties, such as apoptosis, migration, matrix degradation, and generation of ROS.[19,24–27] Furthermore, a receptor for eCypA, CD147, also known as Basigin or EMMPRIN, plays a role in signal transduction by eCypA.[28] eCypA is a proinflammatory cytokine that promotes inflammation in many cell types. Specifically, it has a

Received on: December 24, 2017; final version accepted on: March 20, 2018.

From the Department of Medicine, Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, NY.

Correspondence to Bradford C. Berk, MD, PhD, Department of Medicine, Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, Box CVRI, Rochester, NY 14642. E-mail bradford_berk@urmc.rochester.edu

chemotactic effect on leukocytes and induces production of cytokines, such as IL (interleukin)-1β, IL-6, and IL-8 in macrophages and monocytes.[29,30] It promotes the proliferation and migration of VSMC, as well as the activation of matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9, in VSMC.[19,27,31] It stimulates the apoptosis of EC as well as the expression of adhesion molecules, such as VCAM1 (vascular cell adhesion molecule 1) and ICAM1 (intercellular adhesion molecule 1), in EC[24,25] (Figure). It enhances platelet adhesion and thrombus formation.[32] Activation of ERK1/2 (extracellular signal-regulated kinases 1 and 2), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), Akt, JNK (c-Jun N-terminal kinases), and p38 MAPK (mitogen-activated protein kinases) pathways were observed in different cell types after stimulation with eCypA.[24,28,33]

The mechanisms by which eCypA mediates proinflammatory functions remain elusive. CD147 was demonstrated as a cell surface receptor for eCypA and has been proposed to mediate most of its signaling.[34] This was supported by targeting CD147 using anti-CD147 antibody caused abrogation of certain functions, such as neutrophil chemotaxis in response to eCypA.[35] The importance of eCypA interaction with CD147 has been demonstrated in several in vivo situations, such as rheumatoid arthritis, pulmonary arterial hypertension (PAH), and myocardial ischemia.[36–38] However, the signal transduction mechanism by which CD147 mediates eCypA signaling remains unclear. In particular, CD147 does not dimerize, increase tyrosine phosphorylation, resemble a G-protein–coupled receptor, and has no enzymatic activity (Berk, unpublished data, 2016, and database searches). Nuclear magnetic resonance study suggested an overlap between CD147-binding site on CypA and its PPIase active site, as well as the isomerization of certain peptide bonds of CD147 catalyzed by eCypA.[39] Yurchenko et al[28] reported that PPIase activity of eCypA was crucial for CD147-mediated ERK1/2 activation in CD147 overexpressed Chinese hamster ovary cells. However, it was also reported that eCypA could induce leukocyte chemotaxis via direct binding to CD147 without the involvement of its PPIase activity.[40] Interestingly, it was reported that induction of IL-8 expression by eCypA in U937 cell was unaffected by knockdown of CD147 using siRNA (small interfering RNA).[41] In addition, Gwinn et al[42] reported that eosinophils expressing CD147 were not chemotactic to eCypA. Furthermore, Pushkarsky et al[43] reported that CD147 stimulated HIV-1 infection in a signal-independent fashion. We have unpublished data that knockdown of CD147 did not affect multiple signals activated by eCypA in VSMC and EC. Therefore, the existence of CypA receptors other than CD147 that are responsible for certain activities of eCypA requires further investigation (Table 1).

Pathological Roles of Extracellular and Intracellular CypA in Cardiovascular Diseases

Vascular Diseases

It is clear that eCypA contributes to the pathogenesis of vascular disease. Common pathogenic signals induced by eCypA include expression of inflammatory mediators by EC, apoptosis of EC, proliferation and migration of VSMC, and degradation of extracellular matrix because of increased MMP-2 and MMP-9 expression. Below we will discuss 5 examples (carotid intima–media thickness, coronary artery disease, peripheral artery disease, PAH, and blood–brain barrier dysfunction) where CypA plays an important role. In some examples, we can separate the role of eCypA versus total CypA while in others total CypA was studied. Future studies will be required to use eCypA-specific inhibitors to show conclusively the role of eCypA.

Carotid Intima–Media Thickness

Intimal and medial hyperplasia after carotid ligation in CypA knockout mice was significantly less than in wild-type littermates. Specifically, global CypA knockout mice showed less VSMC migration and proliferation, as well as less inflammatory cell accumulation in ligated arteries. Bone marrow transplantation showed that tissue resident CypA played a more important role than bone marrow–derived CypA in vascular remodeling.[31] ROS was revealed as the key in vascular remodeling because of its stimulation of VSMC growth and proinflammatory effects

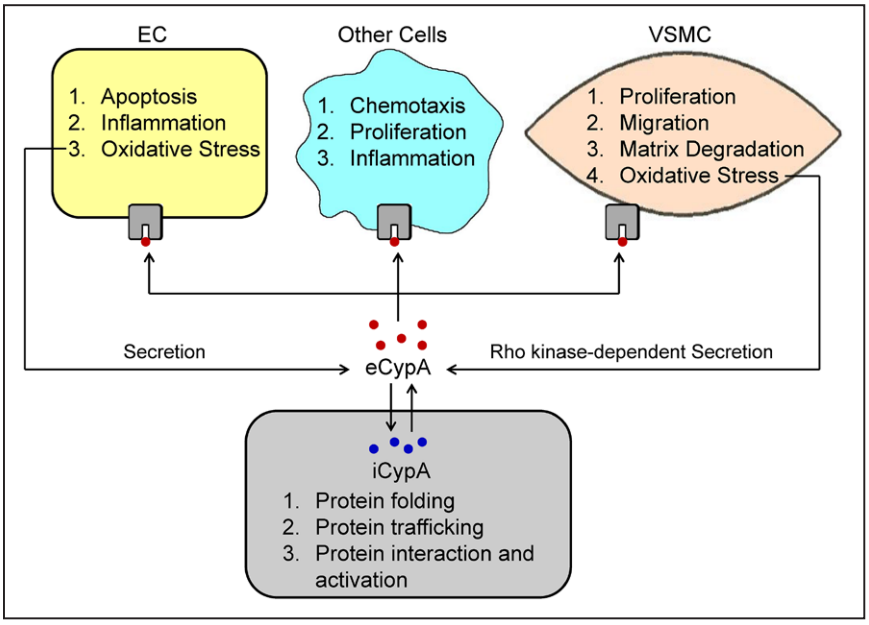

Figure. Cell-specific effects of extracellular CypA (cyclophilin A) on different cell types and the function of intracellular CypA. EC indicates endothelial cell; eCypA, extracellular cyclophilin A; iCypA, intracellular cyclophilin A; and VSMC, vascular smooth muscle cell.

Table 1. Major Extracellular CypA Functions and Potential Signaling Receptors Assayed In Vitro

Effects of Extracellular CypA	CD147	Unknown Receptor
Apoptosis (EC)		√
Chemotaxis (leukocytes)	√	
IL-8 production (U937)		√
Inflammation (EC, VSMC, etc)	√	√
MMP activation (macrophage, glial cell, etc)	√	
Proliferation and migration (cancer cell, VSMC, etc)	√	

CypA indicates cyclophilin A; EC, endothelial cell; IL, interleukin; MMP, matrix metalloproteinase; and VSMC, vascular smooth muscle cell.

on various cell types.[44,45] We have reported that agents that stimulate oxidative stress, such as angiotensin II and LY83583, could stimulate CypA secretion from EC and VSMC while secreted CypA in turn stimulated generation of ROS in these cell types, suggesting the existence of a positive feedback loop between extracellular CypA and ROS in the pathogenesis of vascular remodeling.[25,46] Also mice that overexpressed CypA in VSMC showed greater eCypA by immunohistochemistry that correlated with greater intima–media thickness.[31]

Coronary Artery Disease (CAD)

Substantial evidence has suggested eCypA as a novel biomarker with high diagnostic and prognostic value for CAD. Yan et al[47] reported that plasma CypA level in patients with unstable angina (n=60) and acute myocardial infarction (n=90) were higher than those with stable angina (n=60) and normal controls (n=50), suggesting eCypA as a predictor of the severity of acute coronary syndromes, possibly because of its correlation with increased MMP-3, MMP-9, and C-reactive protein concentrations. Satoh et al[48] reported a positive correlation between plasma CypA levels and the severity of CAD. They found plasma CypA levels increased in accordance with the number of atherosclerotic risk factors, suggesting eCypA as a novel biomarker of CAD (n=320). Their group also indicated that plasma CypA levels had prognostic value in patients with CAD (n=511) when combined with other traditional biomarkers, such as high-sensitivity C-reactive protein and brain natriuretic peptide.[49] Interestingly, a recent study by Seizer et al[50] showed that in patients with stable CAD (n=204), platelet-bound CypA was associated with hypertension and hypercholesterolemia. In patients with acute myocardial infarction (n=108), platelet-bound CyPA was significantly decreased. In all clinical studies, the significance was high ($P<0.05$) despite the small number of patients enrolled. These findings suggest that dynamic changes in platelet-bound CypA may have prognostic as well as pathological importance.

Peripheral Artery Disease

Our group demonstrated that in mice with severe atherosclerosis because of ApoE (apolipoprotein E) knockout, the development of atherosclerotic aortic aneurysms in response to angiotensin II infusion was completely prevented in the CypA knockout mouse.[27] We found both VSMC-derived iCypA and eCypA were required for the ROS generation and MMP-2 activation and subsequent inflammatory cytokine expression, elastic lamina degradation, and aortic expansion. In terms of atherogenesis, Seizer et al[51] reported that eCypA promoted the differentiation of $CD34^+$ progenitor cells into foam cells via CD147, thereby contributing to the progression of atherosclerosis. Likewise, Ramachandran et al[52] reported that eCypA enhanced macrophage lipid uptake and foam cell formation. In addition, Liu et al[53] reported in human patients that high plasma CypA was correlated with progressive peripheral arterial occlusion disease (n=68) and impaired renal function in chronic renal disease. Furthermore, Ramachandran et al[52] found higher circulating CypA level in patients with type 2 diabetes mellitus (n=313), possibly reflecting an increased oxidative stress and proinflammatory status compared with controls (n=122), suggesting a strong association of higher level of eCypA with diabetes mellitus and its related peripheral vascular disease.[54]

Pulmonary Arterial Hypertension

Oxidative stress has been implicated as a mediator of PAH. Considering the positive feedback loop between eCypA and oxidative stress, we studied the role of CypA in PAH. Our group observed a PAH phenotype in an EC-specific CypA overexpression mouse model with elevated levels of eCypA and showed an essential role for eCypA in promoting pulmonary EC apoptosis, inflammation, and ROS generation.[25] Satoh et al[37] demonstrated high plasma CypA level in patients with PAH (n=76) and CD147 knockout ameliorated experimental hypoxia-induced pulmonary hypertension in mice, indicating an essential role of eCypA in the pathogenesis of arteriole remodeling of PAH.

Blood–Brain Barrier Dysfunction

The blood–brain barrier is formed by brain EC lining the cerebral microvasculature and is an important mechanism for protecting the brain from harmful circulating agents, such as neurotransmitters and xenobiotics.[55] It has been proposed that dysfunction of the blood–brain barrier may contribute to neurodegenerative diseases, such as Alzheimer disease.[56] Several studies implicate CypA as a mediator of the ApoE4 pathway that predisposes to Alzheimer disease. Zlokovic and our group showed that elevated iCypA concentrations in pericytes caused nuclear translocation of NF-κB and increased activation of MMP-9.[57] The intracellular CypA–NF-κB–MMP9 pathway in pericytes was associated with degradation of EC tight junctions and basement membrane, resulting in blood–brain barrier dysfunction and the extravascular accumulation of neurotoxic molecules. Furthermore, Halliday et al's[58] group showed that older cognitively normal APOE4 carriers (n=5) had increased cerebrospinal fluid levels of eCypA by 190% and 95% compared with cognitively normal younger APOE4 carriers (n=5) or age-matched APOE4 noncarriers (n=16), respectively.

Cardiac Diseases

The role of CypA in cardiac diseases has not been well studied. Our group showed that cardiac hypertrophy induced by angiotensin II in the ApoE knockout, CypA wild-type mouse was

attenuated in the ApoE knock out, CypA knockout mouse. This was associated with significant decreases in Ang II–induced ROS production, cardiac fibroblast proliferation, and migration. Bone marrow cell transplantation showed that CypA in cells intrinsic to the heart played an important role in the cardiac hypertrophic response.[59] The relative roles of eCypA versus iCypA could not be fully determined, but in this study, we found eCypA directly induced protein synthesis of cultured myocytes and migration and proliferation of cultured cardiac fibroblasts, leading to cardiac hypertrophy.[59] In addition, Zuern et al[60] has proposed that CypA is an independent predictor for clinical outcomes of patients with congestive heart failure (n=227). Of all clinical, laboratory, and immunohistological parameters they tested, only CypA was identified as an independent predictor for the composite end point, as well as for all-cause death and heart transplantation alone, suggesting the high prognostic value of CypA for these patients.

Post-Translational Modification of Extracellular and Intracellular CypA

Both extracellular and intracellular CypA undergo post-translational modification. In HEK293 (human embryonic kidney) cells, serine/threonine residues of iCypA undergo phosphorylation in response to activation of chemokine receptor CXCR4 (C-X-C chemokine receptor type 4).[61] Phosphorylated CypA may then play a role in CXCR4 signaling. Glutathionylation of iCypA is observed in T-cells and hepatocytes under oxidative stress.[62] Recently, it has become clear that oxidative stress promotes the acetylation of CypA.[46] Several lysine residues are critical for acetylation of CypA and its biological functions[63–67] (Table 2). A correlation between phosphorylated and acetylated CypA and oxidative stress is indicated by proteomic analysis of spinal cord homogenates from presymptomatic amyotrophic lateral sclerosis G93A SOD1 mice.[68] Angiotensin II induced iCypA acetylation and acetylated CypA secretion in VSMC.[46] Importantly, substantial evidence indicates that extracellular acetylated CypA is a more potent agonist for EC and VSMC activation than nonacetylated CypA.[25] In addition, acetylation has been shown to interfere with the binding ability of iCypA to HIV-1 caspids, thus reducing the viral infectivity.[63] The emerging critical role of extracellular and intracellular acetylated CypA in disease pathology makes it a novel target for therapy.

Drugs That Block Extracellular and Intracellular CypA

Several drugs have been developed to study the function of CypA; most of these inhibit CypA PPIase activity. CsA is a cell permeable compound that is the best studied inhibitor of CypA PPIase activity. The binding of CsA to iCypA inhibits calcineurin and prevents the translocation of transcription factor nuclear factor of activated T-cells into the nucleus, thereby inhibiting the production of cytokines.[5] CsA is now broadly used as an immunosuppressant because of its inhibitory effect on T cell responses. However, its potent immunosuppressive activity prevents CsA from being widely used in the treatment of cardiovascular and inflammatory diseases. Because of this, nonimmunosuppressive CsA derivatives, such as N-methyl-4-isoleucine cyclosporin (NIM811) and alisporivir, were developed. It was reported that both NIM811 and alisporivir inhibited viral replication of HIV-1 and HCV (hepatitis C virus).[69–72] Seizer et al[73] reported that NIM811 inhibited myocardial fibrosis and inflammatory lesions in murine coxsackievirus B3–induced myocarditis. Stemmy et al[74] reported a reduction of leukocyte influx into the airways in a murine model of chronic asthma after application of NIM811. Recently, Ahmed-Belkacem et al[75] reported a fragment-based selection approach to generate a new family of nonpeptidic, small-molecule cyclophilin inhibitors, unrelated to CsA, with potent in vitro PPIase inhibitory activity and antiviral activity against HIV and HCV.

As mentioned above, plasma levels of CypA have been found to correlate with disease progression and severity in many diseases. These findings suggest that eCypA may be more important than iCypA as a pathogenic mediator of disease. Because CsA and derivatives, such as NIM811, inhibit both extracellular and intracellular CypA, drugs have been developed to study the function of eCypA. Specifically, scientists have modified the chemical groups of CsA that affect

Table 2. Critical Lysine Residues and Their Biological Functions in Acetylation of CypA

Lysine Residues	Conservation	Location	Function When Not Acetylated	Function When Acetylated
K28	Not conserved	Inside		
K44	Conserved in all species	Inside		
K82	Conserved in most species	Surface	Calcineurin and CsA–CypA complex binding	1. EC apoptosis 2. EC inflammation 3. VSMC proliferation
K125	Conserved in most species	Surface	Calcineurin and CsA–CypA complex binding	1. PPIase inhibition 2.CsA–CypA complex binding inhibition 3. EC apoptosis 4. EC inflammation 5. VSMC proliferation 6. HIV-1-CypA interaction alteration
K131	Not conserved	Inside		

CsA indicates cyclosporin A; CypA, cyclophilin A; EC, endothelial cell; PPIase, peptidyl prolyl isomerase; and VSMC, vascular smooth muscle cell.

permeability, making the analogs impermeable. Because of this cell-impermeable property, the new derivatives can selectively inhibit eCypA without interfering the normal physiological functions of iCypA. MM218, as one of the recently synthesized cell-impermeable CsA derivatives, contains a highly charged moiety that prevents its passage through the plasma membrane, thereby making it a specific eCypA inhibitor.[76] Balsley et al[77] showed that MM218 effectively reduced inflammatory responses in a mouse model of allergic lung inflammation by blocking leukocyte recruitment mediated by extracellular cyclophilins. Pasetto et al[78] reported MM218 rescued motor neurons and extended survival of an amyotrophic lateral sclerosis mouse model by blocking eCypA. MM284 is another selective eCypA inhibitor similar to MM218. It has been reported that MM284 reduced myocardial inflammation and remodeling in a mouse model of myocarditis.[79] Seizer et al[32] showed that ADP-induced platelet aggregation was attenuated by MM284. A recent study indicated that MM284 inhibited SMAD activation and inflammation in an experimental biliary atresia model, ameliorating disease symptoms.[80]

Clinical Relevance of Extracellular CypA

The inflammatory hypothesis as a medidator of atherosclerosis received strong support from the recent Canakinumab Antiinflammatory Thrombosis Outcome Study conducted by Ridker et al.[81] They used a monoclonal antibody targeting interleukin-1β in patients with CAD (n=10 061) and showed a significantly lower rate of recurrent cardiovascular events for a median of 3.7 years.[81] There are many similarities in the proinflammatory effects of extracellular interleukin-1β and extracellular CypA on cells in the cardiovascular system. Our laboratory has identified eCypA as a pathological mediator of atherosclerosis, aneurysm, and PAH because of its proinflammatory effects.[27,31,82] The positive results of antibody to interleukin-1β suggest that preclinical data from the CypA relevant animal models mentioned above may have relevance to human cardiovascular diseases (Table 3). A clinical trial by Cung et al[83] tested the effect of CsA on clinical outcome and left ventricular remodeling in patients undergoing percutaneous coronary intervention for an acute myocardial infarction within 12 hours (n=970). There was no benefit of CsA. It should be noted that CsA may not be a good drug because of its broad immunosuppressive effects and its inhibition of iCypA and eCypA. Future studies will be necessary to determine the prognostic value of circulating eCypA and post-translational modified CypA for different cardiovascular diseases. Also, PPIase inhibitors targeting eCypA, such as MM284, may be effective in high-risk populations, like the Canakinumab Antiinflammatory Thrombosis Outcome Study population, or in the acute myocardial infarction setting because of its effects on platelets, immune cells, and cells of the vessel wall. In addition, CypA may potentially be an excellent marker because it could be a pathogenic marker both causative and predictive of disease. This is possible because it represents the combination of multiple atherosclerotic mechanisms. Specifically, it combines ROS, inflammation, and matrix degradation. It also involves paracrine stimulation as a secreted protein, and modification by acetylation seems to make it a more potent mediator, potentially representing a metabolomic indicator. Understanding the life cycle of CypA during cardiovascular disease will be necessary to find how to use it as a biomarker.

Table 3. Cardiovascular Diseases With Clear Evidence That Extracellular CypA Plays a Role in Pathogenesis

Cardiovascular Diseases	eCypA	Total CypA	References
Carotid intima–media thickness		√	31,44,45
Coronary artery disease	√		47,48,49
Hypertension	√		50
Hypercholesterolemia	√		50
Atherosclerotic aortic aneurysm		√	27
Atherosclerosis	√		51,52
Peripheral arterial occlusion	√		53
Pulmonary arterial hypertension	√		25,37
Cardiac hypertrophy		√	59

The only human data are for coronary artery disease, peripheral arterial occulusion, and pulmonary arterial hypertension where plasma CypA correlated with disease progression and severity; and hypertension and hypercholesterolemia where platelet-bound CypA correlated with. Other studies are in mouse. The right column stands for disease in which total CypA is studied, thus we cannot tell the effects of eCypA from iCypA. CypA indicates cyclophilin A; eCypA, extracellular CypA; and iCypA, intracellular CypA.

Summary

Both extracellular and intracellular CypA have been shown to play pathological roles in animal models of many diseases. Recent data in humans show that the level of plasma CypA correlates with disease progression and severity. Cardiovascular diseases in which CypA plays a potential pathogenic role include carotid intima–media thickness, coronary artery disease, peripheral artery disease, PAH, and blood–brain barrier dysfunction. This diversity of diseases supports the concept that extracellular CypA is a pathogenic mediator of cardiovascular disease. This concept is further strengthened by promising results with extracellular CypA inhibitors in several mouse models of human disease. Based on the evolving pathogenic role of circulating CypA, drugs that specifically inhibit extracellular CypA may be effective in multiple diseases.

Sources of Funding

This work was supported by National Institutes of Health RO1 HL049192 to B.C. Berk.

Disclosures

None.

References

1. Fischer G, Wittmann-Liebold B, Lang K, Kiefhaber T, Schmid FX. Cyclophilin and peptidyl-prolyl cis-trans isomerase are probably identical proteins. *Nature*. 1989;337:476–478. doi: 10.1038/337476a0.

2. Takahashi N, Hayano T, Suzuki M. Peptidyl-prolyl cis-trans isomerase is the cyclosporin A-binding protein cyclophilin. *Nature*. 1989;337:473–475. doi: 10.1038/337473a0.
3. Hoffmann H, Schiene-Fischer C. Functional aspects of extracellular cyclophilins. *Biol Chem*. 2014;395:721–735. doi: 10.1515/hsz-2014-0125.
4. Handschumacher RE, Harding MW, Rice J, Drugge RJ, Speicher DW. Cyclophilin: a specific cytosolic binding protein for cyclosporin A. *Science*. 1984;226:544–547.
5. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology*. 2000;47:119–125.
6. Koletsky AJ, Harding MW, Handschumacher RE. Cyclophilin: distribution and variant properties in normal and neoplastic tissues. *J Immunol*. 1986;137:1054–1059.
7. Wang P, Heitman J. The cyclophilins. *Genome Biol*. 2005;6:226. doi: 10.1186/gb-2005-6-7-226.
8. Helekar SA, Char D, Neff S, Patrick J. Prolyl isomerase requirement for the expression of functional homo-oligomeric ligand-gated ion channels. *Neuron*. 1994;12:179–189.
9. Göthel SF, Marahiel MA. Peptidyl-prolyl cis-trans isomerases, a superfamily of ubiquitous folding catalysts. *Cell Mol Life Sci*. 1999;55:423–436. doi: 10.1007/s000180050299.
10. Matouschek A, Rospert S, Schmid K, Glick BS, Schatz G. Cyclophilin catalyzes protein folding in yeast mitochondria. *Proc Natl Acad Sci USA*. 1995;92:6319–6323.
11. Ansari H, Greco G, Luban J. Cyclophilin A peptidyl-prolyl isomerase activity promotes ZPR1 nuclear export. *Mol Cell Biol*. 2002;22:6993–7003.
12. Brown CR, Cui DY, Hung GG, Chiang HL. Cyclophilin A mediates Vid22p function in the import of fructose-1,6-bisphosphatase into Vid vesicles. *J Biol Chem*. 2001;276:48017–48026. doi: 10.1074/jbc.M109222200.
13. Soe NN, Sowden M, Baskaran P, Smolock EM, Kim Y, Nigro P, Berk BC. Cyclophilin A is required for angiotensin II-induced p47phox translocation to caveolae in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2013;33:2147–2153. doi: 10.1161/ATVBAHA.113.301894.
14. Yang WM, Inouye CJ, Seto E. Cyclophilin A and FKBP12 interact with YY1 and alter its transcriptional activity. *J Biol Chem*. 1995;270:15187–15193.
15. Colgan J, Asmal M, Neagu M, Yu B, Schneidkraut J, Lee Y, Sokolskaja E, Andreotti A, Luban J. Cyclophilin A regulates TCR signal strength in CD4+ T cells via a proline-directed conformational switch in Itk. *Immunity*. 2004;21:189–201. doi: 10.1016/j.immuni.2004.07.005.
16. Wang L, Soe NN, Sowden M, Xu Y, Modjeski K, Baskaran P, Kim Y, Smolock EM, Morrell CN, Berk BC. Cyclophilin A is an important mediator of platelet function by regulating integrin αIIbβ3 bidirectional signalling. *Thromb Haemost*. 2014;111:873–882. doi: 10.1160/TH13-09-0738.
17. Bannon JH, O'Donovan DS, Kennelly SM, Mc Gee MM. The peptidyl prolyl isomerase cyclophilin A localizes at the centrosome and the midbody and is required for cytokinesis. *Cell Cycle*. 2012;11:1340–1353. doi: 10.4161/cc.19711.
18. Sherry B, Yarlett N, Strupp A, Cerami A. Identification of cyclophilin as a proinflammatory secretory product of lipopolysaccharide-activated macrophages. *Proc Natl Acad Sci USA*. 1992;89:3511–3515.
19. Jin ZG, Melaragno MG, Liao DF, Yan C, Haendeler J, Suh YA, Lambeth JD, Berk BC. Cyclophilin A is a secreted growth factor induced by oxidative stress. *Circ Res*. 2000;87:789–796.
20. Billich A, Winkler G, Aschauer H, Rot A, Peichl P. Presence of cyclophilin A in synovial fluids of patients with rheumatoid arthritis. *J Exp Med*. 1997;185:975–980.
21. Suzuki J, Jin ZG, Meoli DF, Matoba T, Berk BC. Cyclophilin A is secreted by a vesicular pathway in vascular smooth muscle cells. *Circ Res*. 2006;98:811–817. doi: 10.1161/01.RES.0000216405.85080.a6.
22. Nishioku T, Dohgu S, Koga M, Machida T, Watanabe T, Miura T, Tsumagari K, Terasawa M, Yamauchi A, Kataoka Y. Cyclophilin A secreted from fibroblast-like synoviocytes is involved in the induction of CD147 expression in macrophages of mice with collagen-induced arthritis. *J Inflamm (Lond)*. 2012;9:44. doi: 10.1186/1476-9255-9-44.
23. Kim SH, Lessner SM, Sakurai Y, Galis ZS. Cyclophilin A as a novel biphasic mediator of endothelial activation and dysfunction. *Am J Pathol*. 2004;164:1567–1574. doi: 10.1016/S0002-9440(10)63715-7.
24. Jin ZG, Lungu AO, Xie L, Wang M, Wong C, Berk BC. Cyclophilin A is a proinflammatory cytokine that activates endothelial cells. *Arterioscler Thromb Vasc Biol*. 2004;24:1186–1191. doi: 10.1161/01.ATV.0000130664.51010.28.
25. Xue C, Sowden M, Berk BC. Extracellular cyclophilin A, especially acetylated, causes pulmonary hypertension by stimulating endothelial apoptosis, redox stress, and inflammation. *Arterioscler Thromb Vasc Biol*. 2017;37:1138–1146. doi: 10.1161/ATVBAHA.117.309212.
26. Yang Y, Lu N, Zhou J, Chen ZN, Zhu P. Cyclophilin A up-regulates MMP-9 expression and adhesion of monocytes/macrophages via CD147 signalling pathway in rheumatoid arthritis. *Rheumatology (Oxford)*. 2008;47:1299–1310. doi: 10.1093/rheumatology/ken225.
27. Satoh K, Nigro P, Matoba T, O'Dell MR, Cui Z, Shi X, Mohan A, Yan C, Abe J, Illig KA, Berk BC. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. *Nat Med*. 2009;15:649–656. doi: 10.1038/nm.1958.
28. Yurchenko V, Zybarth G, O'Connor M, Dai WW, Franchin G, Hao T, Guo H, Hung HC, Toole B, Gallay P, Sherry B, Bukrinsky M. Active site residues of cyclophilin A are crucial for its signaling activity via CD147. *J Biol Chem*. 2002;277:22959–22965. doi: 10.1074/jbc.M201593200.
29. Kim H, Kim WJ, Jeon ST, Koh EM, Cha HS, Ahn KS, Lee WH. Cyclophilin A may contribute to the inflammatory processes in rheumatoid arthritis through induction of matrix degrading enzymes and inflammatory cytokines from macrophages. *Clin Immunol*. 2005;116:217–224. doi: 10.1016/j.clim.2005.05.004.
30. Yuan W, Ge H, He B. Pro-inflammatory activities induced by CyPA-EMMPRIN interaction in monocytes. *Atherosclerosis*. 2010;213:415–421. doi: 10.1016/j.atherosclerosis.2010.09.033.
31. Satoh K, Matoba T, Suzuki J, O'Dell MR, Nigro P, Cui Z, Mohan A, Pan S, Li L, Jin ZG, Yan C, Abe J, Berk BC. Cyclophilin A mediates vascular remodeling by promoting inflammation and vascular smooth muscle cell proliferation. *Circulation*. 2008;117:3088–3098. doi: 10.1161/CIRCULATIONAHA.107.756106.
32. Seizer P, Ungern-Sternberg SN, Schönberger T, Borst O, Münzer P, Schmidt EM, Mack AF, Heinzmann D, Chatterjee M, Langer H, Malešević M, Lang F, Gawaz M, Fischer G, May AE. Extracellular cyclophilin A activates platelets via EMMPRIN (CD147) and PI3K/Akt signaling, which promotes platelet adhesion and thrombus formation *in vitro* and in vivo. *Arterioscler Thromb Vasc Biol*. 2015;35:655–663. doi: 10.1161/ATVBAHA.114.305112.
33. Seko Y, Fujimura T, Taka H, Mineki R, Murayama K, Nagai R. Hypoxia followed by reoxygenation induces secretion of cyclophilin A from cultured rat cardiac myocytes. *Biochem Biophys Res Commun*. 2004;317:162–168. doi: 10.1016/j.bbrc.2004.03.021.
34. Muramatsu T, Miyauchi T. Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion. *Histol Histopathol*. 2003;18:981–987. doi: 10.14670/HH-18.981.
35. Arora K, Gwinn WM, Bower MA, Watson A, Okwumabua I, MacDonald HR, Bukrinsky MI, Constant SL. Extracellular cyclophilins contribute to the regulation of inflammatory responses. *J Immunol*. 2005;175:517–522.
36. Damsker JM, Okwumabua I, Pushkarsky T, Arora K, Bukrinsky MI, Constant SL. Targeting the chemotactic function of CD147 reduces collagen-induced arthritis. *Immunology*. 2009;126:55–62. doi: 10.1111/j.1365-2567.2008.02877.x.
37. Satoh K, Satoh T, Kikuchi N, et al. Basigin mediates pulmonary hypertension by promoting inflammation and vascular smooth muscle cell proliferation. *Circ Res*. 2014;115:738–750. doi: 10.1161/CIRCRESAHA.115.304563.
38. Seizer P, Ochmann C, Schönberger T, Zach S, Rose M, Borst O, Klingel K, Kandolf R, MacDonald HR, Nowak RA, Engelhardt S, Lang F, Gawaz M, May AE. Disrupting the EMMPRIN (CD147)-cyclophilin A interaction reduces infarct size and preserves systolic function after myocardial ischemia and reperfusion. *Arterioscler Thromb Vasc Biol*. 2011;31:1377–1386. doi: 10.1161/ATVBAHA.111.225771.
39. Schlegel J, Redzic JS, Porter CC, Yurchenko V, Bukrinsky M, Labeikovsky W, Armstrong GS, Zhang F, Isern NG, DeGregori J, Hodges R, Eisenmesser EZ. Solution characterization of the extracellular region of CD147 and its interaction with its enzyme ligand cyclophilin A. *J Mol Biol*. 2009;391:518–535. doi: 10.1016/j.jmb.2009.05.080.
40. Song F, Zhang X, Ren XB, Zhu P, Xu J, Wang L, Li YF, Zhong N, Ru Q, Zhang DW, Jiang JL, Xia B, Chen ZN. Cyclophilin A (CyPA) induces chemotaxis independent of its peptidylprolyl cis-trans isomerase activity: direct binding between CyPA and the ectodomain of CD147. *J Biol Chem*. 2011;286:8197–8203. doi: 10.1074/jbc.C110.181347.
41. Bahmed K, Henry C, Holliday M, Redzic J, Ciobanu M, Zhang F, Weekes C, Sclafani R, Degregori J, Eisenmesser E. Extracellular cyclophilin-A stimulates ERK1/2 phosphorylation in a cell-dependent manner but broadly stimulates nuclear factor kappa B. *Cancer Cell Int*. 2012;12:19. doi: 10.1186/1475-2867-12-19.
42. Gwinn WM, Damsker JM, Falahati R, Okwumabua I, Kelly-Welch A, Keegan AD, Vanpouille C, Lee JJ, Dent LA, Leitenberg D, Bukrinsky MI, Constant SL. Novel approach to inhibit asthma-mediated lung inflammation using anti-CD147 intervention. *J Immunol*. 2006;177:4870–4879.

43. Pushkarsky T, Yurchenko V, Laborico A, Bukrinsky M. CD147 stimulates HIV-1 infection in a signal-independent fashion. *Biochem Biophys Res Commun*. 2007;363:495–499. doi: 10.1016/j.bbrc.2007.08.192.
44. Satoh K, Nigro P, Berk BC. Oxidative stress and vascular smooth muscle cell growth: a mechanistic linkage by cyclophilin A. *Antioxid Redox Signal*. 2010;12:675–682. doi: 10.1089/ars.2009.2875.
45. Xu S, Touyz RM. Reactive oxygen species and vascular remodelling in hypertension: still alive. *Can J Cardiol*. 2006;22:947–951.
46. Soe NN, Sowden M, Baskaran P, Kim Y, Nigro P, Smolock EM, Berk BC. Acetylation of cyclophilin A is required for its secretion and vascular cell activation. *Cardiovasc Res*. 2014;101:444–453. doi: 10.1093/cvr/cvt268.
47. Yan J, Zang X, Chen R, Yuan W, Gong J, Wang C, Li Y. The clinical implications of increased cyclophilin A levels in patients with acute coronary syndromes. *Clin Chim Acta*. 2012;413:691–695. doi: 10.1016/j.cca.2011.12.009.
48. Satoh K, Fukumoto Y, Sugimura K, et al. Plasma cyclophilin A is a novel biomarker for coronary artery disease. *Circ J*. 2013;77:447–455.
49. Ohtsuki T, Satoh K, Omura J, Kikuchi N, Satoh T, Kurosawa R, Nogi M, Sunamura S, Yaoita N, Aoki T, Tatebe S, Sugimura K, Takahashi J, Miyata S, Shimokawa H. prognostic impacts of plasma levels of cyclophilin A in patients with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2017;37:685–693. doi: 10.1161/ATVBAHA.116.308986.
50. Seizer P, Fuchs C, Ungern-Sternberg SN, Heinzmann D, Langer H, Gawaz M, May AE, Geisler T. Platelet-bound cyclophilin A in patients with stable coronary artery disease and acute myocardial infarction. *Platelets*. 2016;27:155–158. doi: 10.3109/09537104.2015.1051466.
51. Seizer P, Schönberger T, Schött M, Lang MR, Langer HF, Bigalke B, Krämer BF, Borst O, Daub K, Heidenreich O, Schmidt R, Lindemann S, Herouy Y, Gawaz M, May AE. EMMPRIN and its ligand cyclophilin A regulate MT1-MMP, MMP-9 and M-CSF during foam cell formation. *Atherosclerosis*. 2010;209:51–57. doi: 10.1016/j.atherosclerosis.2009.08.029.
52. Ramachandran S, Vinitha A, Kartha CC. Cyclophilin A enhances macrophage differentiation and lipid uptake in high glucose conditions: a cellular mechanism for accelerated macro vascular disease in diabetes mellitus. *Cardiovasc Diabetol*. 2016;15:152. doi: 10.1186/s12933-016-0467-5.
53. Liu MC, Lee YW, Lee PT, Chang CS, Tai YL, Yu JR, Su XT, Hsu LW, Lin SH, Wu CH, Liu PY. Cyclophilin A is associated with peripheral artery disease and chronic kidney disease in geriatrics: the Tianliao Old People (TOP) study. *Sci Rep*. 2015;5:9937. doi: 10.1038/srep09937.
54. Ramachandran S, Venugopal A, Kutty VR, A V, G D, Chitrasree V, Mullassari A, Pratapchandran NS, Santosh KR, Pillai MR, Kartha CC. Plasma level of cyclophilin A is increased in patients with type 2 diabetes mellitus and suggests presence of vascular disease. *Cardiovasc Diabetol*. 2014;13:38. doi: 10.1186/1475-2840-13-38.
55. Abbott NJ. Astrocyte-endothelial interactions and blood-brain barrier permeability. *J Anat*. 2002;200:629–638.
56. Zenaro E, Piacentino G, Constantin G. The blood-brain barrier in Alzheimer's disease. *Neurobiol Dis*. 2017;107:41–56. doi: 10.1016/j.nbd.2016.07.007.
57. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature*. 2012;485:512–516. doi: 10.1038/nature11087.
58. Halliday MR, Pomara N, Sagare AP, Mack WJ, Frangione B, Zlokovic BV. Relationship between cyclophilin A levels and matrix metalloproteinase 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood-brain barrier breakdown. *JAMA Neurol*. 2013;70:1198–1200. doi: 10.1001/jamaneurol.2013.3841.
59. Satoh K, Nigro P, Zeidan A, Soe NN, Jaffré F, Oikawa M, O'Dell MR, Cui Z, Menon P, Lu Y, Mohan A, Yan C, Blaxall BC, Berk BC. Cyclophilin A promotes cardiac hypertrophy in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol*. 2011;31:1116–1123. doi: 10.1161/ATVBAHA.110.214601.
60. Zuern CS, Müller KA, Seizer P, Geisler T, Banya W, Klingel K, Kandolf R, Bauer A, Gawaz M, May AE. Cyclophilin A predicts clinical outcome in patients with congestive heart failure undergoing endomyocardial biopsy. *Eur J Heart Fail*. 2013;15:176–184. doi: 10.1093/eurjhf/hfs185.
61. Pan H, Luo C, Li R, Qiao A, Zhang L, Mines M, Nyanda AM, Zhang J, Fan GH. Cyclophilin A is required for CXCR4-mediated nuclear export of heterogeneous nuclear ribonucleoprotein A2, activation and nuclear translocation of ERK1/2, and chemotactic cell migration. *J Biol Chem*. 2008;283:623–637. doi: 10.1074/jbc.M704934200.
62. Ghezzi P, Casagrande S, Massignan T, Basso M, Bellacchio E, Mollica L, Biasini E, Tonelli R, Eberini I, Gianazza E, Dai WW, Fratelli M, Salmona M, Sherry B, Bonetto V. Redox regulation of cyclophilin A by glutathionylation. *Proteomics*. 2006;6:817–825. doi: 10.1002/pmic.200500177.
63. Lammers M, Neumann H, Chin JW, James LC. Acetylation regulates cyclophilin A catalysis, immunosuppression and HIV isomerization. *Nat Chem Biol*. 2010;6:331–337. doi: 10.1038/nchembio.342.
64. Massé K, Bhamra S, Haldin CE, Jones EA. Cloning and characterisation of the immunophilin X-CypA in Xenopus laevis. *Gene Expr Patterns*. 2004;5:51–60. doi: 10.1016/j.modgep.2004.06.007.
65. Ivery MT. A proposed molecular model for the interaction of calcineurin with the cyclosporin A-cyclophilin A complex. *Bioorg Med Chem*. 1999;7:1389–1402.
66. Mikol V, Kallen J, Walkinshaw MD. X-ray structure of a cyclophilin B/cyclosporin complex: comparison with cyclophilin A and delineation of its calcineurin-binding domain. *Proc Natl Acad Sci USA*. 1994;91:5183–5186.
67. Etzkorn FA, Chang ZY, Stolz LA, Walsh CT. Cyclophilin residues that affect noncompetitive inhibition of the protein serine phosphatase activity of calcineurin by the cyclophilin.cyclosporin A complex. *Biochemistry*. 1994;33:2380–2388.
68. Massignan T, Casoni F, Basso M, Stefanazzi P, Biasini E, Tortarolo M, Salmona M, Gianazza E, Bendotti C, Bonetto V. Proteomic analysis of spinal cord of presymptomatic amyotrophic lateral sclerosis G93A SOD1 mouse. *Biochem Biophys Res Commun*. 2007;353:719–725. doi: 10.1016/j.bbrc.2006.12.075.
69. Rosenwirth B, Billich A, Datema R, Donatsch P, Hammerschmid F, Harrison R, Hiestand P, Jaksche H, Mayer P, Peichl P. Inhibition of human immunodeficiency virus type 1 replication by SDZ NIM 811, a nonimmunosuppressive cyclosporine analog. *Antimicrob Agents Chemother*. 1994;38:1763–1772.
70. Ma S, Boerner JE, Tiong Yip C, Weidmann B, Ryder NS, Cooreman MP, Lin K. NIM811, a cyclophilin inhibitor, exhibits potent *in vitro* activity against hepatitis C virus alone or in combination with alpha interferon. *Antimicrob Agents Chemother*. 2006;50:2976–2982. doi: 10.1128/AAC.00310-06.
71. Gallay PA, Lin K. Profile of alisporivir and its potential in the treatment of hepatitis C. *Drug Des Devel Ther*. 2013;7:105–115. doi: 10.2147/DDDT.S30946.
72. Gallay PA, Ptak RG, Bobardt MD, Dumont JM, Vuagniaux G, Rosenwirth B. Correlation of naturally occurring HIV-1 resistance to DEB025 with capsid amino acid polymorphisms. *Viruses*. 2013;5:981–997. doi: 10.3390/v5030981.
73. Seizer P, Klingel K, Sauter M, Westermann D, Ochmann C, Schönberger T, Schleicher R, Stellos K, Schmidt EM, Borst O, Bigalke B, Kandolf R, Langer H, Gawaz M, May AE. Cyclophilin A affects inflammation, virus elimination and myocardial fibrosis in coxsackievirus B3-induced myocarditis. *J Mol Cell Cardiol*. 2012;53:6–14. doi: 10.1016/j.yjmcc.2012.03.004.
74. Stemmy EJ, Balsley MA, Jurjus RA, Damsker JM, Bukrinsky MI, Constant SL. Blocking cyclophilins in the chronic phase of asthma reduces the persistence of leukocytes and disease reactivation. *Am J Respir Cell Mol Biol*. 2011;45:991–998. doi: 10.1165/rcmb.2011-0007OC.
75. Ahmed-Belkacem A, Colliandre L, Ahnou N, Nevers Q, Gelin M, Bessin Y, Brillet R, Cala O, Douguet D, Bourguet W, Krimm I, Pawlotsky JM, Guichou JF. Fragment-based discovery of a new family of non-peptidic small-molecule cyclophilin inhibitors with potent antiviral activities. *Nat Commun*. 2016;7:12777. doi: 10.1038/ncomms12777.
76. Malesevic M, Kuhling J, Erdmann F, Balsley MA, Bukrinsky MI, Constant SL, Fischer G. A cyclosporin derivative discriminates between extracellular and intracellular cyclophilins. *Angew Chem Int Ed Engl*. 2010;49:213–215.
77. Balsley MA, Malesevic M, Stemmy EJ, Gigley J, Jurjus RA, Herzog D, Bukrinsky MI, Fischer G, Constant SL. A cell-impermeable cyclosporine A derivative reduces pathology in a mouse model of allergic lung inflammation. *J Immunol*. 2010;185:7663–7670. doi: 10.4049/jimmunol.1001707.
78. Pasetto L, Pozzi S, Castelnovo M, et al. Targeting extracellular cyclophilin A reduces neuroinflammation and extends survival in a mouse model of amyotrophic lateral sclerosis. *J Neurosci*. 2017;37:1413–1427. doi: 10.1523/JNEUROSCI.2462-16.2016.
79. Heinzmann D, Bangert A, Müller AM, et al. The novel extracellular cyclophilin A (CyPA) - inhibitor MM284 reduces myocardial inflammation and remodeling in a mouse model of troponin I-induced myocarditis. *PLoS One*. 2015;10:e0124606. doi: 10.1371/journal.pone.0124606.
80. Iordanskaia T, Malesevic M, Fischer G, Pushkarsky T, Bukrinsky M, Nadler E. Targeting extracellular cyclophilins ameliorates disease progression in experimental biliary atresia. *Mol Med*. 2015;21:657–664.

81. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914.
82. Nigro P, Satoh K, O'Dell MR, Soe NN, Cui Z, Mohan A, Abe J, Alexis JD, Sparks JD, Berk BC. Cyclophilin A is an inflammatory mediator that promotes atherosclerosis in apolipoprotein E-deficient mice. *J Exp Med*. 2011;208:53–66. doi: 10.1084/jem.20101174.
83. Cung TT, Morel O, Cayla G, et al. Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med*. 2015;373:1021–1031. doi: 10.1056/NEJMoa1505489.

Highlights

- Both extracellular and intracellular CypA (cyclophilin A) play important roles in cardiovascular disease pathogenesis through shared and unique mechanisms.
- Substantial evidence reveals extracellular CypA as a potent mediator of cardiovascular diseases through a specific receptor(CD147 or another)-mediated inflammation, matrix degradation, and reactive oxygen species generation.
- Post-translational modification of extracellular and intracellular CypA, especially acetylation, may strongly influence their biological functions.
- Increasing evidence shows a correlation between circulating extracellular CypA and cardiovascular disease severity, suggesting that extracellular CypA may not only be a good biomarker but also potentially a good therapeutic target for drug development.

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Extracellular and Intracellular Cyclophilin A, Native and Post-Translationally Modified, Show Diverse and Specific Pathological Roles in Diseases

Chao Xue, Mark P. Sowden and Bradford C. Berk

Arterioscler Thromb Vasc Biol. 2018;38:986-993; originally published online March 29, 2018;
doi: 10.1161/ATVBAHA.117.310661
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636