New Horizons for the Roles and Association of APE1/Ref-1 and ABCA1 in Atherosclerosis

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Abstract: Atherosclerosis is the leading cause of death worldwide. APE1/Ref-1 and ABCA1 play key roles in the progression of atherosclerosis. APE1/Ref-1 suppresses atherosclerosis via multiple mechanisms, including reducing the IL-6-, TNF- α -, and IL-1 β -mediated proinflammatory responses, suppressing ROS-mediated oxidant activity and Bax/Bcl-2-mediated vascular calcification and apoptosis, and reducing LOX-1-mediated cholesterol uptake. However, APE1/Ref-1 also promotes atherosclerosis by increasing the activity of the NK- κ B and S1PR1 pathways. APE1/Ref-1 localizes to the nucleus, cytoplasm, and mitochondria and can be secreted from the cell. APE1/Ref-1 localization is dynamically regulated by the disease state and may be responsible for its proatherogenic and antiatherogenic effects. ABCA1 promotes cholesterol efflux and anti-inflammatory responses by binding to apoA-I and regulates apoptotic cell clearance and HSPC proliferation to protect against inflammatory responses. Interestingly, in addition to mediating these functions, ABCA1 promotes the secretion of acetylated APE1/Ref-1 (AcAPE1/Ref-1), a therapeutic target, which protects against atherosclerosis development. The APE1/Ref-1 inhibitor APX3330 is being evaluated in a phase II clinical trial. The LXR agonist LXR-623 (WAY-252623) is an agonist of ABCA1 and the first LXR-targeting compound to be evaluated in clinical trials. In this article, we review the roles of ABCA1 and APE1/Ref-1 in atherosclerosis and focus on new insights into the ABCA1-APE1/Ref-1 axis and its potential as a novel therapeutic target in atherosclerosis.

Keywords: atherosclerosis, inflammatory, APE1/Ref-1, ABCA1, cholesterol efflux

Introduction

Myocardial infarction (MI) due to coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Atherosclerosis is the main cause of CAD and MI.^{1–3} The major characteristic of the underlying pathology of atherosclerosis is a bidirectional interaction between lipids and inflammation. Atherosclerosis occurs during foam cell generation, a process regulated by balancing the lipid uptake and efflux rates.⁴ Lipid efflux is mainly controlled by ATP-binding cassette transporter A1 (ABCA1).^{5,6} Previous studies from our laboratory and others have shown that ABCA1 promotes cholesterol efflux and anti-inflammatory responses by binding to apolipoprotein A-I (apoA-I), suggesting that ABCA1 may be a therapeutic target for atherosclerosis.^{7–11}

Apurinic (apyrimidinic) endonuclease-1/redox factor-1 (APE1/APE1/Ref-1), a 37-kDa protein, is a ubiquitously expressed bifunctional protein involved in the oxidative stress response, DNA damage repair, and facilitation of the DNA-binding activities of many redox-sensitive transcription factors, including activator protein-

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1 (AP-1) and nuclear factor κ B (NF- κ B). APE1/Ref-1 is known to participate in a variety of redox-mediated events that regulate cell growth, differentiation, survival, and death.^{12,13} Many studies have shown that APE1/Ref-1 is a therapeutic target for vascular inflammation and a serological biomarker of CAD.¹⁴ Interestingly, in addition to mediating cholesterol efflux, ABCA1 promotes the secretion of acetylated APE1/Ref-1 (AcAPE1/Ref-1) and forms the ABCA1-APE1/Ref-1 axis.^{15,16} Accumulating evidence has shown that APE1/Ref-1 plays dual roles in atherosclerosis, as it can have both proatherogenic and antiatherogenic effects.^{17,18} However, AcAPE1/Ref-1 secretion may protect against the development of atherosclerosis, suggesting that ABCA1 promotes AcAPE1/Ref-1 secretion and protects against atherosclerosis development.¹⁹ Although ABCA1 mediates the release of AcAPE1/Ref-1, the effect of this function on atherosclerosis is not clear. In this article, we review the roles of APE1/Ref-1 and ABCA1 in atherosclerosis and focus on new insight into the ABCA1-APE1/Ref-1 axis and drugs targeting its components.

Roles of APE1/Ref-1 and ABCA1 in Atherosclerosis

Dual Roles of APE1/Ref-1 in Atherosclerosis

APE1/Ref-1 was shown to be upregulated in human atherosclerotic plaques.²⁰ Moreover, hypercholesterolemia has been associated with the increased expression of the base excision repair (BER)-specific DNA repair enzyme APE1/Ref-1. A high-fat diet further increased total APE1/Ref-1 protein expression in apoE^{-/-} mice.²¹ Thus, APE1/Ref-1 has been shown to be associated with the development of atherosclerosis. However, the role of APE1/Ref-1 in atherosclerosis is twofold. APE1/Ref-1 accelerates the progression of atherosclerosis by promoting the secretion of M1 macrophage-mediated proinflammatory cytokines and suppresses the development of atherosclerosis by reducing inflammation and promoting tissue repair.

APE1/Ref-1 as an Antiatherogenic Factor

APE1/Ref-1 is involved in DNA damage repair.²² Oxidative tissue injury is aggravated during plaque formation, and increased reactive oxygen species (ROS) production and DNA damage in monocytes are biomarkers of aging and atherosclerosis.^{23,24} APE1/Ref-1 is present throughout the entire plaque.²⁰ APE1/Ref-1 is upregulated

in plaques in carotid arteries, suggesting that APE1/Ref-1 protects against atherosclerosis by repairing DNA damage and oxidative tissue injury. Vascular calcification is linked to plaque instability and contributes to increased cardiovascular mortality and poor cardiovascular outcomes for patients.^{25,26} APE1/Ref-1 was reported to inhibit vascular calcification in vascular smooth muscle cells (VSMCs) and in rat aortas cultured *ex vivo*.¹⁸ Moreover, APE1/Ref-1 was shown to reduce vascular calcification, antioxidant activity, and antiapoptotic activity by suppressing ROS production and reducing the Bax/Bcl-2 ratio. However, the APE1/Ref-1 redox mutant did not reduce calcification, suggesting that APE/Ref-1-mediated redox activity protects against vascular calcification and atherosclerosis development.¹⁸ In particular, APE1/Ref-1 reduces intracellular ROS production.^{27,28} APE1/Ref-1 suppressed monocyte adhesion by reducing vascular cell adhesion molecule-1 (VCAM-1) expression in a manner dependent on the inhibition of superoxide production and p38 MAPK activation in tumor necrosis factor α (TNF- α)-stimulated human umbilical vein endothelial cells (HUVECs).²⁹ APE1/Ref-1 was shown to exert anti-inflammatory effects by reducing the activity of thiol-disulfide exchanges¹⁹ and to suppress hypoxia-induced EC apoptosis.³⁰ Furthermore, APE1/Ref-1 suppressed balloon injury-induced neointimal formation in rats,³¹ suggesting that APE1/Ref-1 exhibits anti-inflammatory functions in the vascular endothelium. APE1/Ref-1 $\pm$ mice exhibit cardiovascular diseases such as hypertension. APE1/Ref-1 decreased ox-LDL-induced inflammatory molecules, including interleukin (IL)-6, TNF- α and IL-1 β , in macrophages.³² In addition, APE1/Ref-1 reduced ox-LDL uptake and foam cell formation from macrophages by hindering binding of the transcription factor OCT1 to the LOX-1 promoter.³² Thus, APE1/Ref-1 protects against atherosclerosis by prohibiting inflammation, reducing vascular calcification and cholesterol uptake, and repairing DNA damage and oxidative tissue injury.

APE1/Ref-1 as a Proatherogenic Factor

Angiotensin II (Ang II) is a major mediator of inflammation and VSMC migration and proliferation.³³ Chronic or long-term exposure to Ang II may accelerate the development of atherosclerosis.^{34,35} Interestingly, Ang II caused the translocation of APE1/Ref-1 from the cytoplasm to the nucleus in rat aortic smooth muscle cells (RASMCs).¹⁷ Ang II also stimulated migration and sphingosine-1-phosphate receptor (S1PR1) expression by increasing the

binding of APE1/Ref-1 to the S1PR1 promoter in RASMCs and rats.¹⁷ S1PR1 activation is responsible for VSMC migration, apoptosis, and proliferation, resulting in vascular restenosis and neointima formation,^{36,37} suggesting that APE1/Ref-1 contributes to the advancement of neointima plaque formation and atherosclerosis development by binding the S1PR1 promoter. Dai et al found that homocysteine (Hcy) increased ROS production by upregulating NADPH oxidase-mediated APE1/Ref-1 expression; moreover, they showed that APE1/Ref-1 increased NF- κ B activity and monocyte chemoattractant protein-1 (MCP-1) secretion by binding to the promoter in mouse and human macrophages, thereby accelerating atherosclerosis development in apoE^{-/-} mice.³⁸ Consistently, hyperhomocysteinemia (HHcy) has been shown to be an independent risk factor for atherosclerosis, suggesting that Hcy accelerates atherosclerosis development by increasing APE1/Ref-1 expression.^{38,39} Chen et al found that thioredoxin 1 (Trx1) decreases the expression and secretion of MCP-1 by suppressing APE1/Ref-1 in vascular endothelial cells (ECs).⁴⁰ Hadri et al reported that Trx-1 reduces the expression of proinflammatory M1 macrophage markers, such as TNF- α and MCP-1, in human monocyte-derived macrophages and murine peritoneal macrophages by reducing APE1/Ref-1 expression.⁴¹ M1 macrophages are oriented to produce proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α . M2 macrophages mostly resolve inflammation and promote tissue remodeling through the expression of factors such as arginase-1 (Arg-1), transforming growth factor (TGF)- β , and IL-10.^{42,43} Trx1 decelerates the progression of atherosclerosis by blunting M1 macrophage polarization and proinflammatory factor expression,^{44–46} suggesting that Trx1 antagonizes atherosclerosis by reducing APE1/Ref-1 expression. Taken together, these results suggest that APE1/Ref-1 accelerates atherosclerosis development by stimulating NF- κ B expression and M1 macrophage polarization (Figure 1).

Potential Roles of AcAPE1/Ref-1 in Atherosclerosis

Acetylation, a type of posttranslational modification, regulates the function of multiple cytoplasmic proteins involved in cell survival, proliferation, and death as well as disease-related signaling.^{47,48} APE1/Ref-1 acetylation controls multiple biological functions.⁴⁹ Apurinic/apyrimidinic (AP) sites are the most common forms of genomic DNA damage, and many studies have shown that AP sites are repaired by APE1/Ref-1.⁵⁰ In the absence of APE1/Ref-1 acetylation, AP sites accumulate in the

genome, evoking increased cellular sensitivity to DNA-damaging agents, suggesting that APE1/Ref-1 acetylation plays a key role in cell survival and/or proliferation in response to genotoxic stress.^{51,52} Extracellularly secreted APE1/Ref-1 inhibits TNF- α -stimulated endothelial inflammation and lipopolysaccharide (LPS)-induced cytokine production in response to intracellular acetylation.⁵³ An anti-APE1/Ref-1 antibody was shown to rapidly prevent APE1/Ref-1 acetylation-mediated anti-inflammatory signals.¹⁹ Importantly, AcAPE1/Ref-1 is a cancer therapeutic target.⁵⁴ These results suggest that AcAPE1/Ref-1 secretion protects against atherosclerosis development via anti-inflammatory and DNA damage repair mechanisms.

APE1/Ref-1 is a Potential CAD Biomarker

Increasing evidence indicates that APE1/Ref-1 is a potential biomarker of CAD. In animal experiments, APE1/Ref-1 was increased in the aorta and blood of apoE^{-/-} mice fed a Western diet (WD).⁵⁵ Interestingly, APE1/Ref-1 expression in aortic tissue was significantly positively correlated with VCAM-1, a vascular inflammation marker, and galectin-3, a macrophage marker, in apoE^{-/-} mice. Plasma APE1/Ref-1 levels were also shown to be significantly positively correlated with the neutrophil/lymphocyte ratio (NLR) ($r=0.79$), a marker of systemic inflammation. The cutoff value for APE1/Ref-1 to predict atherosclerotic inflammation was 4.903 ng/mL, with 100% sensitivity and 91% specificity, suggesting that APE1/Ref-1 is a potential biomarker of atherosclerotic inflammation.⁵⁵ In clinical studies, APE1/Ref-1 was shown to be increased in human atherosclerotic plaques. Serum APE1/Ref-1 levels were higher in 303 CAD patients than in 57 control patients (0.63 ± 0.07 vs 0.12 ± 0.07 ng/100 μ L, respectively; $p<0.01$). Moreover, serum APE1/Ref-1 levels were higher in 175 MI patients than in 128 angina patients (0.81 ± 0.10 vs 0.38 ± 0.11 ng/100 μ L, respectively; $p<0.01$).¹⁴ Correlation analysis revealed that the serum levels of APE1/Ref-1 were positively correlated with other cardiovascular biomarkers, including troponin I ($r=0.222$; $p<0.0001$) and N-terminal pro-B type natriuretic peptide (NT-proBNP, $r=0.217$; $p<0.0001$) but were not highly sensitive to C-reactive protein (CRP). APE1/Ref-1 levels were also shown to be negatively correlated with the ejection fraction (EF, $r=-0.221$; $p=0.002$).¹⁴ Nevertheless, the P -value of the APE1/Ref-1 single nucleotide polymorphism (SNP) rs1878703 in 1624 patients with MI compared with 4087 age- and sex-matched controls was

Figure 1 The mechanism of APE1/Ref-1 in atherosclerosis. APE1/Ref-1 has both proatherogenic and antiatherogenic effects. APE1/Ref-1 suppresses atherosclerosis via multiple mechanisms. APE1/Ref-1 reduces the proinflammatory response by increasing thiol–disulfide exchanges and suppressing the expression of IL-6, TNF- α , and IL-1 β . APE1/Ref-1 reduces oxidant activity by suppressing ROS levels and decreases vascular calcification and apoptosis by suppressing the Bax/Bcl-2 ratio. APE1/Ref-1 reduces cholesterol uptake by binding OCT1 to inhibit activation of the LOX-1 promoter. APE1/Ref-1 decreases monocyte adhesion by suppressing superoxide production and p38 MAPK expression to restrain VCAM-1. APE1/Ref-1 reduces DNA damage and oxidative tissue injury. APE1/Ref-1 promotes atherosclerosis via multiple mechanisms. APE1/Ref-1 increases the proinflammatory response by increasing NF- κ B pathway signaling and TNF- α and MCP-1 expression. APE1/Ref-1 promotes VSMC migration, apoptosis, and proliferation by binding the S1PR1 promoter.

0.09 ($p > 0.05$), suggesting that this APE1/Ref-1 SNP is not associated with the risk of MI ($p = 0.09$).⁵⁶ In addition, APE1/Ref-1 serum levels were not correlated with the severity of myocardial injury, unlike the correlations with peak troponin I and peak CK-MB expression.¹⁴ However, serum APE1/Ref-1 levels were positively correlated with the degree of inflammation and myocarditis score in the heart of mice infected with the CVB3 virus ($r = 0.750$, $p < 0.01$), suggesting that serum APE1/Ref-1 levels can be used to assess myocardial injury in the context of viral myocarditis.⁵⁷ Therefore, APE1/Ref-1 is a potential biomarker of CAD and is, at the very least, a potential biomarker of vessel damage. However, despite numerous

studies on this biomarker, its value in clinical translation is still being investigated.

Role of ABCA1 in Atherosclerosis

ABCA1 is a key mediator of intracellular cholesterol efflux to apoA-I for the generation of high-density lipoprotein (HDL), which protects against atherosclerotic vascular diseases by transferring cholesterol from peripheral cells to the liver for biliary excretion, constituting the process of reverse cholesterol transport (RCT).^{58–60} Previous studies by our laboratory and others have demonstrated that ABCA1 plays a critical role in preventing cholesterol accumulation in macrophages,

while deficiency or mutation of this transporter lead to defects in cholesterol efflux and an increased risk of atherosclerosis.^{10,11,15,61–65} Several studies have shown that ABCA1 reduces inflammatory responses by inhibiting the NF- κ B signaling pathway via the removal of ROS.^{8,66} High cholesterol and inflammatory signals promote HSPC proliferation and preferential differentiation to enhance vascular inflammation and atherosclerosis progression.⁶⁷ ABCA1 suppressed HSPC proliferation and extramedullary hematopoiesis by reducing the expression of the common β subunit of the receptor for granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-3,⁶⁸ suggesting a mechanism by which ABCA1 suppresses vascular inflammation.

Previous studies by our laboratory and others have also demonstrated that ABCA1 complexed with apoA-I plays a critical role in anti-inflammatory activities.^{8,61,62,69,70} ABCA1 also regulates the secretion of various proteins, such as macrophage migration inhibitory factor (MIF),⁷¹ IL-1 β ,⁷² apoE,⁷³ and annexin A1 (ANXA1),⁷⁴ the latter of which is associated with anti-inflammatory responses. We found that ABCA1 and ANXA1 may form a feedback loop and regulate each other.⁷⁴ However, the crosstalk between ABCA1 and ANXA1 in atherosclerosis has not been investigated. ApoA-I and apoE decreased the development of atherosclerosis by enhancing cholesterol efflux and anti-inflammatory effects in macrophage cultures and in vivo. Importantly, ABCA1 is a key regulator of apoA-I⁷⁵ and apoE lipidation.⁷⁶ Furthermore, ABCA1, apoA-I, and apoE are coexpressed in macrophages, implying that ABCA1 also protects against atherosclerosis by enhancing apoA-I- and apoE-mediated antiatherogenic effects. ABCA1 also mediates microparticle^{77–79} and exosome secretion.^{79,80} Microparticles, which encompass exosomes, nanoparticles, and shedding vesicles, are not only prognostic markers of atherosclerosis acceleration but also a clinical manifestation of familial hypercholesterolemia.^{81–83} Therefore, ABCA1 may regulate atherosclerosis development by mediating the secretion of exosomes and microparticles.

Many studies have demonstrated that the impaired clearance of apoptotic cells promotes the development of atherosclerosis. Apoptotic cell clearance is also termed programmed cell removal (PrCR) or efferocytosis and mainly involves the following stages: (1) “find me”, (2) “eat me”, (3) and endocytosis.^{84,85} ABCA1 also promotes the apoptotic cell clearance process.⁸⁶ ABCA1 promotes efferocytosis by regulating the release of “find me”

ligands, including LPC, and the exposure, release, and expression of “eat me” ligands, including phosphatidylserine (PtdSer), ANXA1, ANXA5, multiple EGF-like domains 10 (MEGF10), and engulfment adaptor phosphotyrosine-binding domain (PTB) domain containing 1 (GULP1).^{74,87,88} ABCA1 engages a pathway similar to that of transglutaminase 2 (TG2), an “eat me” ligand.⁸⁹ Interestingly, apoptotic cell clearance increases ABCA1 expression, but the mechanism is unclear. ABCA1 can form several regulatory feedback axes with ANXA1, MEGF10, and GULP1, suggesting that apoptotic cell clearance increases ABCA1 expression by enhancing the expression of ANXA1, MEGF10, and GULP1. However, further studies are needed to clearly elucidate these axes. Taken together, these results suggest that ABCA1 protects against atherosclerosis by enhancing cholesterol efflux, anti-inflammatory effects, autophagy, apoptotic cell clearance, and microparticle and exosome secretion (Figure 2).

The ABCA1-APE1/Ref-1 Axis: New Insight into Atherosclerosis

The ABCA1-APE1/Ref-1 Axis: ABCA1 Promotes APE1/Ref-1 Secretion

Recently, ABCA1 was shown to promote APE1/Ref-1 secretion.¹⁶ The histone deacetylase (HDAC) inhibitor trichostatin A (TSA) did not regulate APE1/Ref-1 secretion. However, glyburide, which inhibits the expression of ABC transporters, including ABCA1, ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC8, and ABCC9, inhibited butyrate-induced APE1/Ref-1 secretion.^{16,90} Butyrate also increased ABCA1 expression,^{65,91} suggesting that butyrate promotes APE1/Ref-1 secretion by inducing ABCA1 expression and that glyburide suppresses butyrate-induced APE1/Ref-1 secretion by reducing ABCA1 expression. Specific knockdown of ABCA1 without affecting the expression of other ABC transporters, including ABCB1, ABCC1, ABCC2, and ABCC8, significantly inhibited APE1/Ref-1 secretion. Importantly, knockdown of other ABC transporters, including ABCB1, ABCC1, ABCC2, and ABCC8, did not regulate APE1/Ref-1 secretion, suggesting that ABCA1 plays a central role in APE1/Ref-1 secretion. Mutating the acetylation sites in APE1/Ref-1 (K6/K7R) has been shown to reduce colocalization with ABCA1. ABCA1 promotes APE1/Ref-1 secretion by binding to acetylated regions of APE1/Ref-1, suggesting that the extracellular secretion of APE1/Ref-1 depends on its acetylation.¹⁶ Taken together, the evidence suggests that

Reduces atherosclerosis

Figure 2 The mechanism of ABCA1 in atherosclerosis. ABCA1 promotes cholesterol efflux by binding to apoA-I and enhancing apoE secretion and lipidation. ABCA1 suppresses the proinflammatory response via multiple mechanisms, including promoting microparticle and exosome secretion; binding to apoA-I to reduce the NF-κB pathway; promoting LPC, PtdSer, ANXA1, ANXA5, MEGF10, GULP1, and TG2 expression to enhance apoptotic cell clearance; suppressing ROS levels; and reducing the common β subunit of GM-CSF and IL-3 receptor-mediated HSPC proliferation and extramedullary hematopoiesis. ABCA1 can form several regulatory feedback axes with ANXA1, MEGF10, and GULP1. Apoptotic cell clearance increases cholesterol efflux and anti-inflammatory activities by enhancing ABCA1 expression.

AcAPE1/Ref1 secretion mainly depends on the ABCA1 transporter, which promotes APE1/Ref-1 secretion and forms the ABCA1-APE1/Ref-1 axis.

Potential Association Between ABCA1 and APE1/Ref-1 in Atherosclerosis

As mentioned above, the secretion of AcAPE1/Ref-1 protects against atherosclerosis development via anti-inflammatory and DNA damage repair mechanisms. ABCA1 controls the secretion of AcAPE1/Ref-1 and forms the ABCA1-APE1/Ref-1 axis. ABCA1 is also a therapeutic target in atherosclerosis. ABCA1 is expressed in macrophages and ECs and promotes cholesterol efflux to apoA-I. APE1/Ref-1 is also expressed in macrophages and ECs.⁵⁵ Thus, ABCA1 promotes the secretion of AcAPE1/Ref-1 and might protect against the development of atherosclerosis. However, the effect of these

activities on atherosclerosis is unclear, and more studies are needed.

The ABCA1-APE1/Ref-1 Axis as a Drug Target

Drugs Targeting ABCA1

DrugBank (<https://go.drugbank.com/drugs>) shows that ABCA1 is the target of drugs including ATP, glyburide, probucol, tocopherol, vitamin E, and tamoxifen. Drugs approved for cardiometabolic diseases, including metformin, atorvastatin and rosuvastatin, may affect ABCA1 function. Metformin promotes cholesterol efflux and attenuates atherosclerotic plaques by enhancing the FGF21-ABCA1/ABCG1 axis.⁹² Atorvastatin induces cholesterol efflux by regulating the RhoA-PPARγ/LXRα-ABCA1 axis,⁹³ and rosuvastatin promotes cholesterol efflux by regulating the miR-33b-5p-ABCA1 axis.⁹⁴ Moreover, LXR agonists,

including T0901317, GW3965, GW6340, IMB-808, 22(R)-hydroxycholesterol (22(R)-HC), and LXR-623, promote cholesterol efflux and protect against atherosclerosis by binding the LXR target gene ABCA1 (Table 1). The administration of T0901317 or GW3965, first-generation LXR agonists, reduces plaque formation in mice, but neither T0901317 nor GW3965 is clinically useful due to the

unwanted side effects of hepatic steatosis and hypertriglyceridemia.⁹⁵ GW6340, an intestine-specific LXR agonist, increased macrophage ABCA1 expression and RCT efficiency but did not increase plasma triglyceride (TG) levels.⁹⁶ IMB-808, a newly developed LXR agonist, promoted ABCA1 expression and cholesterol efflux and did not induce lipogenesis in HepG2 cells.⁹⁷ 22(R)-HC, an

Table 1 ABCA1 is a Therapeutic Drug Target

Type	Name	Structure	Drug Group	References
	ATP		Investigational, nutraceutical	DrugBank
	Glyburide		Approved	
	Probucol		Approved, investigational	
	Tocofersolan		Approved	
	Vitamin E		Approved, nutraceutical, vet-approved	
	Tamoxifen		Approved	[92]
Agonist	Metformin		Approved	

(Continued)

Table 1 (Continued).

Type	Name	Structure	Drug Group	References
	Atorvastatin		Approved	[93]
	Rosuvastatin		Approved	[94]
	T0901317		Animal studies	[95]
	GW3965			[95]

(Continued)

Table 1 (Continued).

Type	Name	Structure	Drug Group	References
	GW6340			[96]
	IMB-808			[97]
	22(R)-Hydroxycholesterol			[98]
	LXR-623		Investigational	[99]
Antagonist	TPHP		Animal studies	[100]

(Continued)

Table 1 (Continued).

Type	Name	Structure	Drug Group	References
	EHDPP			[100]
	SR9238			[101,102]
	SR9243			[103,104]

(Continued)

Table 1 (Continued).

Type	Name	Structure	Drug Group	References
	GSK2033			[104]

endogenous LXR agonist, increases ABCA1 expression and cholesterol efflux.⁹⁸ The LXR agonist LXR-623 (WAY-252623) increases ABCA1 expression and cholesterol efflux and does not change hepatic lipid metabolism. LXR-623 was the first LXR-targeting compound to be evaluated in clinical trials, and no deaths or serious adverse events were reported.⁹⁹ LXR antagonists, including SR9238, SR9243, GSK2033, triphenyl phosphate (TPHP), and 2-ethylhexyl diphenyl phosphate (EHDPP), inhibited cholesterol efflux and promoted atherosclerotic lesion formation in mice (Table 1). TPHP and EHDPP have been detected in indoor dust, especially TPHP, which is one of the most predominant pollutants with concentrations as high as 20,700 µg/g.¹⁰⁰ Therefore, we should be aware that indoor dust can be a cardiovascular hazard. Nevertheless, some LXR-targeting compounds are beneficial. For example, SR9238 reduced

hepatic lipogenesis in models of obesity and hepatic steatosis,^{101,102} and SR9243 suppressed intrahepatic inflammation and fibrosis in patients with nonalcoholic steatohepatitis.^{103,104} These beneficial compounds usually require liver specificity to avoid causing potential detrimental effects on RCT in peripheral tissues. These results suggest that ABCA1 is a therapeutic target of atherosclerosis.

Drugs Targeting APE1/Ref-1

DrugBank shows that APE1/Ref-1 is a target of numerous drugs, including lucanthone and the APE1/Ref-1 inhibitors APX3330 (E3330), APX2009, APX2014, gossypol, inhibitor III, endonuclease inhibitor (compound #3), RN7-60, RN8-51, RN10-52, MC043, MC047, MC042, MC019, compound 13, compound 21, compound 23, and compound 24 (Table 2). APX3330, a

Table 2 APE1/Ref-1 is a Therapeutic Drug Target

Type	Name	Structure	IC ₅₀ (µM)	Drug Group	References
	Lucanthone			Investigational	DrugBank

(Continued)

Table 2 (Continued).

Type	Name	Structure	IC ₅₀ (μM)	Drug Group	References
Antagonist	APX3330			Investigational	[105]
	APX2009			Animal studies	[91]
	APX2014				[91]
	Gossypol				[106]
	Inhibitor III		3		[107]
	Endonuclease inhibitor (Compound #3)				[108]

(Continued)

Table 2 (Continued).

Type	Name	Structure	IC ₅₀ (μM)	Drug Group	References
	RN7-60				[109]
	RN8-51				[109]
	RN10-52				[109]
	MC019		1.8		[110]
	MC042		1.2		[110]

(Continued)

Table 2 (Continued).

Type	Name	Structure	IC ₅₀ (μM)	Drug Group	References
	MC043		5.4		[110]
	MC047		2.5		[110]
	Compound 13		9.3		[110]
	Compound 21		2.7		[110]

(Continued)

Table 2 (Continued).

Type	Name	Structure	IC ₅₀ (μM)	Drug Group	References
	Compound 23		1.3		[110]
	Compound 24		2.5		[110]

potential inhibitor of solid tumors, is currently being investigated in a phase II clinical trial.¹⁰⁵ APX2009 and APX2014, which are currently under development, are potentially the most potent second-generation compounds.⁹¹ Gossypol in combination with docetaxel and cisplatin improved the efficacy of chemotherapy for advanced non-small-cell lung cancer (NSCLC).¹⁰⁶ Inhibitor III showed substantial antileukemic efficacy,¹⁰⁷ and compound #3 affected mitochondrial activity and suppressed colorectal cancer.¹⁰⁸ RN7-60 and RN10-52 had a greater effect than APX3330 on ovarian cancer cells, and RN8-51 had an effect similar to that of APX3330. However, unlike RN7-60 and RN10-52, APX3330 and RN8-51 did not induce the apoptosis of umbilical cord blood-derived erythroid-colony-forming cells (ECFCs), suggesting that RN8-51 has potential as a cancer therapeutic.¹⁰⁹ The IC₅₀ values of MC043, MC047, MC042, MC019, compound 13, compound 21, compound 23, and compound 24 were 5.4, 2.5, 1.2, 1.8, 9.3, 2.7, 1.3, and 2.5 μM, respectively, and the EC₅₀ values for all these compounds were > 100 μM.¹¹⁰ These results suggest that APE1/Ref-1 is a therapeutic target in cancer. However, the function of APE1/Ref-1 inhibitors in atherosclerosis is minimal, and more studies are needed.

The ABCA1-APE1/Ref-1 Axis: A Potential Therapeutic Target for Atherosclerosis

As mentioned above, ABCA1 is a therapeutic target in atherosclerosis that enhances cholesterol efflux, anti-inflammatory responses, and apoptotic cell clearance. AcAPE1/Ref-1 is a therapeutic target in cancer and decreases the development of atherosclerosis by enhancing anti-inflammatory effects and DNA damage repair.¹¹¹ ABCA1 controls the secretion of AcAPE1/Ref-1, and together, these proteins form the ABCA1-APE1/Ref-1 axis. Based on these results, we hypothesize that the ABCA1-APE1/Ref-1 axis is a potential therapeutic target for atherosclerosis. However, further studies are needed.

Summary

Atherosclerotic cardiovascular disease is the leading cause of death worldwide.^{112,113} APE1/Ref-1 plays dual roles in atherosclerosis and is a potential biomarker of CAD. However, biomarkers should be sensitive and specific for diagnosing the disease state. Additional larger studies are needed before APE1/Ref-1 can be clinically used as a novel biomarker for the early diagnosis and prognostic prediction of CAD. Notably, early studies and computer analysis via the GeneCards database

Figure 3 The subcellular localization of APE1/Ref-1 and ABCA1 is responsible for both cholesterol efflux and APE1/Ref-1 secretion. Computational analysis of the subcellular localization of human APE1/Ref-1 using GeneCards (<https://www.genecards.org/>). APE1/Ref-1 was detected in not only the nucleus but also other compartments, including the cytoskeleton, plasma membrane, etc. The extracellular secretion of APE1/Ref-1 depends on its acetylation. ABCA1 is responsible for both cholesterol efflux and acetylated APE1/Ref-1 secretion.

have shown that APE1/Ref-1 is localized in the nucleus, cytoplasm, and mitochondria and is even secreted from the cell (Figure 3). Under basal conditions, APE1/Ref-1 is localized in the nucleus; localization of this protein is dynamically regulated by the disease state, which can evoke cytoplasmic/mitochondrial translocation or extracellular secretion, potentially leading to the proatherogenic and antiatherogenic effects of APE1/Ref-1. Cell- or tissue-specific APE1/Ref-1 localization may also play dual roles in atherosclerosis.¹¹⁴ APE1/Ref-1 is highly expressed in the cells of patients with atherosclerosis to protect against hypoxic injury in tissues, and the secretion of AcAPE1/Ref-1 is a treatment target in

atherosclerosis. However, larger studies, such as those involving knockout experiments, GWAS and exome sequencing, are needed to determine whether APE1/Ref-1 is proatherogenic or antiatherogenic. In addition, ABCA1 is responsible for not only cholesterol efflux and anti-inflammatory effects but also the secretion of AcAPE1/Ref-1 (Figure 3). However, the effect of the ABCA1-APE1/Ref-1 axis on atherosclerosis is unclear, and more studies are needed. The APE1/Ref-1 inhibitor APX3330 is being evaluated in a phase II clinical trial, and the ABCA1/LXR agonist LXR-623 (WAY-252623) has been evaluated in clinical trials. We sincerely hope that more scientists will study the role of the ABCA1-

APE1/Ref-1 axis in atherosclerosis to identify potential biomarkers and novel therapeutic targets.

Abbreviations

MI, myocardial infarction; CAD, coronary artery disease; ABCA1, ATP-binding cassette transporter A1; apoA-I, apolipoprotein A-I; APE1/APE1/Ref-1, apurinic (apyrimidinic) endonuclease-1/redox factor-1; AP-1, activator protein-1; NF- κ B, nuclear factor κ B; BER, base excision repair; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells; VCAM-1, vascular cell adhesion molecule-1; TNF- α , tumor necrosis factor α ; HUVECs, human umbilical vein endothelial cells; IL-6, interleukin-6; Ang II, angiotensin II; RASMCs, rat aortic smooth muscle cells; S1PR1, sphingosine-1-phosphate receptor; Hcy, homocysteine; MCP-1, monocyte chemoattractant protein-1; HHcy, hyperhomocysteinemia; Trx1, thioredoxin 1; ECs, endothelial cells; Arg-1, arginase-1; TGF- β , transforming growth factor β ; AP, apurinic/aprimidinic; LPS, lipopolysaccharide; WD, Western diet; NLR, neutrophil/lymphocyte ratio; NT-proBNP, N-terminal pro-B type natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction; SNP, single nucleotide polymorphism; HDL, high-density lipoprotein; RCT, reverse cholesterol transport; GM-CSF, granulocyte macrophage colony-stimulating factor; MIF, migration inhibitory factor; IL-1 β , interleukin-1 beta; ANXA1, annexin A1; PrCR, programmed cell removal; PtdSer, phosphatidylserine; MEGF10, multiple EGF-like domains 10; GULP1, engulfment adaptor phosphotyrosine-binding domain (PTB) domain containing 1; TG2, transglutaminase 2; HDAC, histone deacetylase; TSA, trichostatin A; TPHP, triphenyl phosphate; EHDPP, 2-ethylhexyl diphenyl phosphate; ECFCs, erythroid-colony-forming cells.

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Disclosure

The authors declare no conflicts of interest associated with this paper.

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