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ROLE OF APE1/REF-1 IN CARDIOVASCULAR DISEASES

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Abstract: Apurinic/apyrimidinic endonuclease 1/redox effector factor-1 (APE1/Ref-1) is a multifunctional protein involved in the DNA base excision repair pathway, redox regulation, inflammation, and survival pathways. APE1/Ref-1 could inhibit the production of reactive oxygen species (ROS). Excessive ROS production could lead to DNA damage and cell apoptosis, which is viewed as the cause of cardiovascular diseases. Recent advances of molecular studies have demonstrated that APE1/Ref-1 is involved in the pathogenesis of cardiovascular diseases. In this review, we will introduce the multifunctional role of APE1/Ref-1 and its potential usefulness as a therapeutic target in cardiovascular diseases.

Keywords: APE1/Ref-1, cardiovascular diseases, base excision repair, redox regulation

INTRODUCTION

Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is a multifunctional enzyme in base excision repair (BER) pathway [1-3]. APE1/Ref-1 responds to DNA damage and participates in the redox regulation of many transcriptional factors (TFs) [4-6]. Interestingly, these two kinds of functionalities are conducted by two distinct regions of APE1/Ref-1 protein: N-terminal region encodes the reductive activation function and the C-terminal region encodes the repair function [7]. Sequence analysis has revealed that the human APE1/Ref-1 shows high homology with other mammals, indicating that its functions are conservative in different species [8].

The excessive generation of reactive oxygen species (ROS), also referred as oxidative stress, can result in irreversible damage to cell membrane, DNA, other lipids and proteins [3]. Oxidative stress and DNA damage play a crucial rule in the pathogenesis of many human diseases, especially cardiovascular diseases [9, 10]. The role in both BER pathway and regulating redox status means that APE1/Ref-1 has a close relationship with many human pathologies [11]. In this review, we summarize how APE1/Ref-1 involves in cardiovascular diseases and suggest future directions of cardiovascular diseases treatment associated with APE1/Ref-1.

CELLULAR FUNCTIONS OF APE1/REF-1

APE1/Ref-1 is expressed ubiquitously in humans and is a relatively abundant protein with a long half-life [6]. Its DNA repair function has well understood. The apurinic/apyrimidinic (AP) endonuclease activity requires three residues (Phe266, Trp280 and Leu282) located at C-terminal domain [12]. These residues form a hydrophobic pocket that recognizes and captures the AP site [13]. The redox regulation function is on the other hand located at N-terminus [4, 12, 14, and 15]. The activity of several TFs such as activator protein-1 (AP-1), nuclear factor kappa B (NF- B), p53 and the cAMP response element binding protein (CREB) are regulated by APE1/Ref-1[5, 16]. Oxidative damage to both DNA and RNA have been associated with cardiovascular disease [9, 17, and 18]. Therefore, the DNA repair and redox activities of APE1/Ref-1 indicate that its potential use in future cardiovascular diseases therapies.

APE1/REF-1 AS A DNA REPAIRMAN

Oxidative DNA lesions have been reported as occurring at an estimated rate of 1.5×10^5 residues/cell/day [19]. Almost all the repair of oxidative DNA base lesions is dependent on the BER pathway [20]. In short patch BER, APE1/Ref-1 functions as an AP endonuclease initiated by monofunctional DNA glycosylase (DG) [10, 21]. APE1/Ref-1 hydrolyzes the phosphodiester backbone immediately 5' to the generated AP site to produce a 3' OH group and a 5' deoxyribose-5-phosphate blocking group [2]. In long-patch BER, a bifunctional DG with additional AP lyase activity generates 3' phosph -unsaturated aldehyde and 3' phosphate termini via elimination reaction at the site of strand cleavage [10]. The 3' phosphodiesterase activity of APE1/ Ref-1 helps to remove the - unsaturated aldehyde and 3' termini phosphate. Both the short-patch and long-patch BER need APE1/Ref-1 to produce 3' OH termini while different enzymes are required for subsequent completion procedure of DNA repair [2, 18, and 22]. Therefore, APE1/Ref-1 is the common path in both BER pathways and indispensable for DNA repair. The Cell is extremely likely to start apoptosis process if the repair was not in time [2, 3]. Hence, APE1/Ref-1 is necessary in protecting cell from both endogenous and exogenous DNA damage and is essential for cell viability and genomic stability.

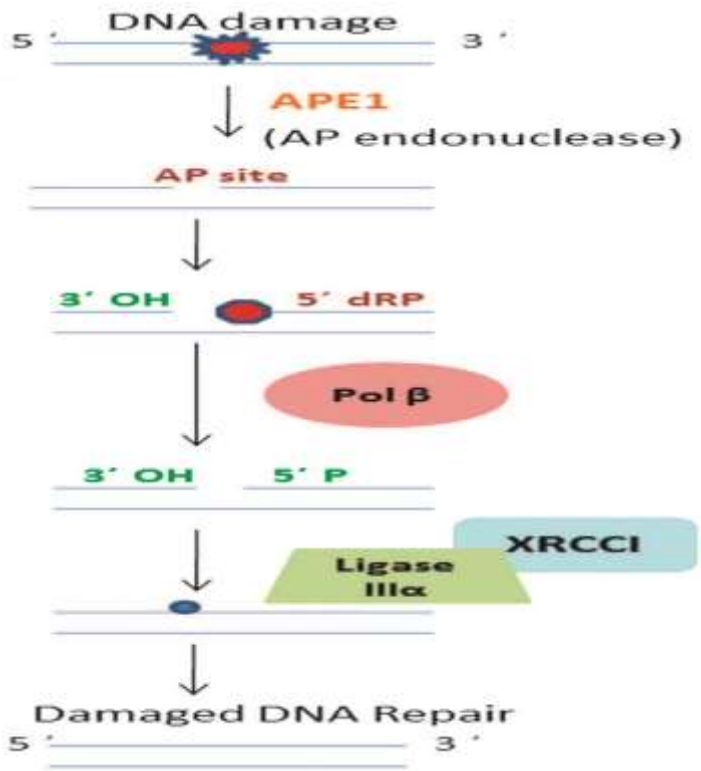

Fig. 1 Schematic representation of the mechanism of the base excision repair (BER) in mammalian cells. apurinic/apyrimidinic endonuclease 1 (APE1) functions as an AP endonuclease, initiated by monofunctional DNA glycosylase (DG). Pol β, X-ray repair cross-complementing protein 1 (XRCC1) and ligase III are required for BER repair.

APE1/REF-1 AS A REDOX REGULATOR

It has been shown that gene expressions could be controlled by redox through regulating the DNA-binding activities of TFs [4]. The specific mechanisms of APE1/Ref-1 in redox regulation of the DNA-binding activities of TFs are still under active investigation. The current view is that a thiol exchange reaction is involved in the reductive activation of a TF by reduced APE1/Ref-1. The oxidized form of APE1/Ref-1 is then reduced by thioredoxin (TRX). The Cys residues in APE1/Ref-1 are considered to be critical for its redox function [16, 23, and 24].

The DNA-binding activity of NF- B, a major TF that participates in immune and inflammatory signaling pathways, could be triggered by APE1/Ref-1. Loss of APE1/Ref-
1 decreases NF-kB activity in endothelial cells resulting in increasing cellular susceptibility to apoptosis [25]. APE1/Ref-1 contributes to maintain cellular homeostasis through balancing the redox status [18, 26, and 27]. It has been demonstrated that ROS activates APE1/Ref-1 expression, and elevated-APE1/Ref-1 confers resistance to the oxidative stress through inducing activation of some critical DNA-binding TFs. For example, activation of tumor-suppressor protein p53 could be enhanced by APE1/Ref- 1[28-31]. Activated p53 binds DNA and activates expression of several genes including microRNA miR-34a, WAF1/CIP1 encoding for p21 and hundreds of other down-stream genes, which contributes to the response to oxidative stress [6]. In summary, APE1/Ref- 1 is an essential enzyme in redox regulation of various DNA-binding TFs and is responsible for the maintenance of cellular homeostasis.

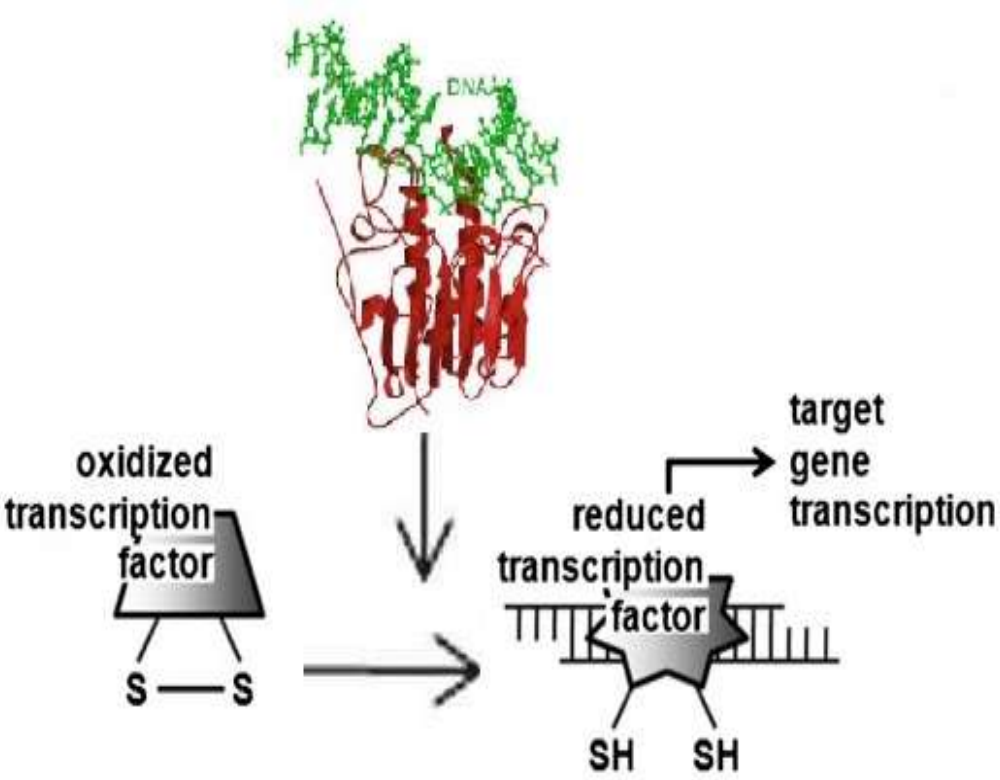

Fig. 2 Schematic representation of APE1 redox activities. APE1 is responsible for the reduction of oxidized cysteines within DNA-binding domain of a number of transcription factors.

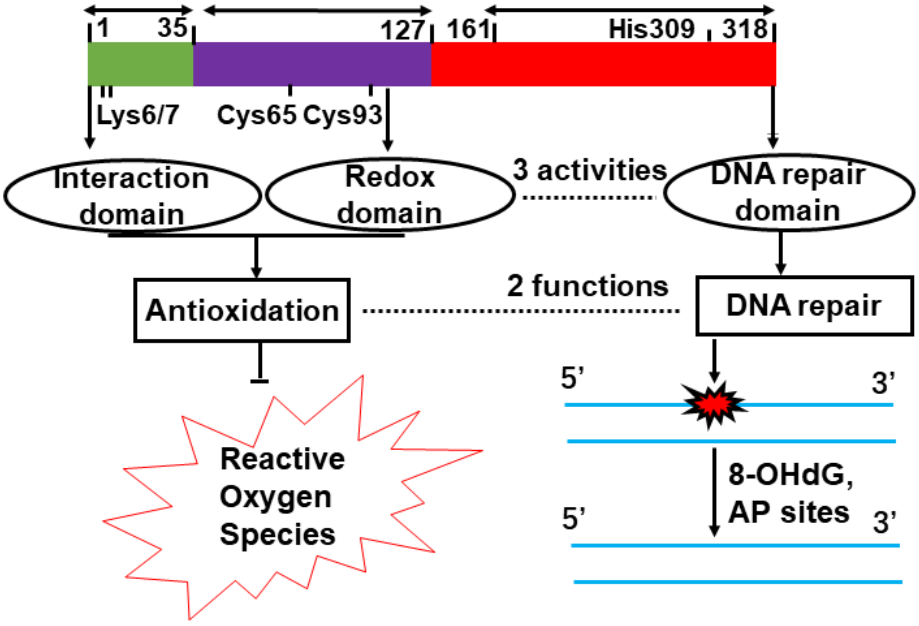

Fig. 3 Structure and function of APE1. The bifunctional protein APE1 has three domains, corresponding to three kinds of activities in the cells, it mainly manifested in anti-oxidative stress and repair of DNA damage, and inhibited the production of ROS and 8-OHdG and AP sites of DNA oxidative damage products.

APE1/REF-1 PARTICIPATES IN CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) are the leading cause of death worldwide [32].

Major categories of CVD include coronary artery disease (CAD), hypertensive heart disease, peripheral heart diseases, rheumatic heart disease and stroke [33]. Acute and chronic excessive intracellular increase of reactive oxygen species (ROS) is involved in the development and progression of CVDs [33, 34]. APE1/Ref-1, as a redox status modulator, is surely involved in the pathologies of CVDs.

CORONARY ARTERY DISEASE (CAD)

One of the most common CADs is ischemic cardiomyopathy. Cardiac cell therapy serves as a promising cure for hundreds of millions of patients with severe heart failure or ischemic cardiomyopathy [35]. A recent study has demonstrated that APE1/Ref-1 overexpression inhibited cardiac progenitor cell (CPC) apoptosis with activation of transforming growth factor -activated kinase 1 (TAK1) and NF- B. Furthermore, APE1/Ref-1 CPC grafts that effectively survived in the ischemic heart restored cardiac function and attenuated inflammation and fibrosis [36]. These findings suggest that APE1/Ref-1 overexpression in CPCs may be a novel strategy to reinforce cardiac cell therapy.

DNA damage plays an important role in the pathogenesis of CAD, and alterations in APE1/Ref-1 can occur in CAD. Another study found that the levels of serum APE1/Ref- 1 were elevated in CAD, and were higher in myocardial infarction (MI) than in angina [37]. APE1/Ref-1 has the potential to be a biomarker for the early diagnosis and prognostic evaluation of serum APE1/Ref-1 in CAD.

GAPDH interaction with APE1/Ref-1 is critical for GAPDH-mediated cell survival [38, 39]. A recent study has revealed that GAPDH regenerates APE1/Ref-1 activity by up- regulating APE1/Ref-1 expression and forming a nuclear GAPDH/APE1/Ref-1 complex. Their results suggest that both nuclear GAPDH/APE1/Ref-1 interaction and APE1/Ref-1 protein up-regulation protect DNA integrity and prevent apoptosis of vascular smooth muscle cell (SMC) [40]. Their findings provide a novel and potentially beneficial strategy to increase atherosclerotic plaque stability and prevent acute coronary events.

HYPERTENSIVE DISEASE

Impaired endothelium-dependent vascular relaxation is a prominent feature of highly prevalent vascular diseases such as hypertension [41-43]. APE1/Ref-$1^{+/-}$ mice have impaired endothelium-dependent vasorelaxation, reduced vascular NO levels, and are hypertensive. APE1/Ref-1 upregulates H-ras expression and leads to H-ras–mediated, phosphoinositide-3 kinase/Akt kinase–dependent calcium sensitization of endothelial NO synthase (eNOS), stimulating NO production [44]. Song et.al suggested that APE1/Ref-1 expression was increased in aortic coarctation-induced hypertensive rats [45]. A haplotype-Based Case–Control Study on Human APE1/Ref-1 gene showed that the G-T-T haplotype appeared to be a genetic marker and the APE1/Ref-1 gene appeared to be a susceptibility gene for essential hypertension [46]. Also, another group demonstrated that APE1/Ref-1 was involved in calcium-mediated repression of renin gene, and thereby in blood pressure maintenance [47].

STROKE

APE1/Ref-1 expression is elevated after acute stroke [37, 48]. An animal study induced transient global cerebral ischemia in male Sprague-Dawley rats with the 4-vessel occlusion method and employed low-dose proton irradiation or transgenic overexpression to upregulate APE1/Ref-1. Results showed that upregulation of APE1 protected hippocampal CA1 neurons against cell loss, reduced AP sites, DNA fragmentation and restore behavior output [49, 50]. Another recent study created the first APE1/Ref-1 conditional knock-out (cKO) mouse line. They found that APE1/Ref-1 cKO mice dramatically enlarged infarct volume and impaired the recovery of sensorimotor and cognitive deficits [51]. Their findings provided evidence that endogenous APE1 protected against ischemic infarction in both gray

and white matter and facilitated the functional recovery of the central nervous system after mild stroke injury.

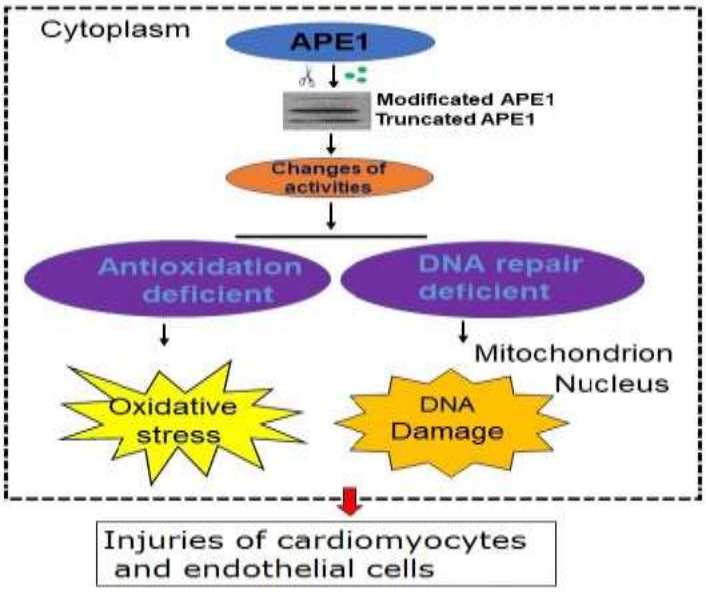

Fig. 4 the scientific hypothesis of this study. In abnormal environment, the level of APE1 protein in myocardium increased posttranslational modifications, such as cleavage, lead to changes in activity involved in oxidative stress and DNA repair function decline (loss), thus causing oxidative stress and DNA oxidative damage, leading to myocardial and endothelial damage, and then cardiovascular diseases.

CONCLUSIONS

APE1/Ref-1 is known as a multifunctional protein participating both DNA repair and redox regulation, as well as antioxidant activities. The results from tons of studies have confirmed that APE1/Ref-1's pleiotropic functions are crucial for promoting cell survival and maintaining cellular genomic integrity [52]. A continuously growing body of evidence shows that APE1/Ref-1 seems to be involved in the pathogenesis of several types of cardiovascular diseases. Overexpression of APE1/Ref-1 could increase the survival of cardiac progenitor cells, vascular smooth muscle cell or neuronal cell. APE1/Ref-1 also promotes endothelium-dependent vasorelaxation by stimulating NO production. APE1/Ref-1 knockout mouse shows deficits in the recovery of stroke. All these evidences conclude that APE1/Ref-1 is a promising candidate for the treatment of cardiovascular diseases.Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J 2003; 17 (10): 1195-214. eng.

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