INTRODUCTION

Despite considerable advances over the past 50 years, cardiovascular disease (CVD) remains the major cause of global mortality. The etiology and pathophysiology of CVDs are complex, but the major risk factors include unhealthy lifestyle and behaviors coupled with a multifactorial complex interaction between environmental and genetic factors (McCord, 2004). Growing evidence suggests that highly reactive oxygen species (ROS) of endogenous or environmental origin play a cognitive role in the genesis and progression of various CVDs. The primary cause of CVD is atherosclerosis, which is characterized by thickening of the walls of the arteries. Atherosclerosis is a chronic inflammatory disease that progresses slowly during a lifetime and typically begins before adulthood. Among the initiating causes of atherosclerosis, the oxidative modification hypothesis has been confirmed in numerous studies and especially, ROS stimulate oxidation of low density lipoprotein (LDL), cholesterol, cholesterol derived species, and protein modifications which can lead to foam cell formation and atherosclerotic plaques (Sauer et al., 2010).

The production and effect of ROS depend on the expression and proper function of enzymes involved in ROS regulation in vascular cells. Moreover, cells contain numerous antioxidant defenses that detoxify ROS or reduce their effects. The site of ROS generators and distribution of antioxidant enzymes are highly localized within the cell. The imbalance between ROS generator and eliminator occurs due to the change of overall redox balance and modification of target molecules (Fig. 1) (Day, 2004). Allopurinol, xanthine oxidase inhibitor, as a potential antioxidant reverses endothelial dysfunction in heavy smokers, type-2 diabetics with mild hypertension, and in patients of chronic heart failure. Moreover, no deleterious effects were observed with this therapy, thereby clearly indicating that antioxidants decrease atherosclerotic progression (Traber and Atkinson, 2007).

In this article, we review current and potential approaches targeting antioxidant enzyme that could be employed to suppress atherosclerotic cardiovascular disease.
Other sources of superoxide include enzymes involved in the metabolism of arachidonic acid and the mitochondrial electron transport chain.

**NADPH oxidase**

The prototype of NADPH oxidase complex (NOX) contains membrane subunits (p22phox, gp91phox/Nox2), cytosolic regulatory subunits (p47phox, p67phox) and G protein Rac. Nox catalytic subunits possess flavin- and heme-binding regions and generate $O_2^{•−}$ via one electron transfer from NADH or NADPH to oxygen. Of the various Nox isoforms, Nox1, Nox2 and Nox4 are the most important in vascular cells (Table 1) (Lambeth, 2004). With the exception of Nox5 all the Nox isoforms require p22phox as a docking subunit. Nox4 functions constitutively and does not require cytosolic subunits. Interestingly, Nox isoforms can be differentially associated with various vascular disease phenotypes. Nox1 expression directly alters cell proliferation (Suh et al., 1999) and treatment of vascular smooth muscle cells (VSMCs) with platelet-derived growth factor (PDGF) upregulates Nox1, at the same time downregulating Nox4 (Lassegue et al., 2001). Expression of Nox2 and p22phox is greatly increased with the progression of human atherosclerosis (Guzik et al., 2006), whereas Nox4 is increased in early lesions but rather decreased in severe lesions (Sorescu et al., 2002).

**Xanthine oxidase**

Xanthine oxidase (XO) can be an additional source of vascular superoxide. Various stimuli, such as hypoxia and reoxygenation, cytokines, and oscillatory shear-stress, increase endothelial XO activity (Griendling, 2005). In CVD patients, the
**Table 1. NOX isoenzymes in mammalian cells**

| Type     | Domain structure                  | Distribution               | Regulatory factors                          | Functions                  |
|----------|-----------------------------------|-----------------------------|---------------------------------------------|----------------------------|
| Nox1     | Inducible, Flavo-protein, transmembrane cluster | Colon, VSMC, prostate       | NOXO, NOXA, and p22phox                       | Proliferation response     |
| Nox2     | Flavo-protein, transmembrane cluster | Phagocyte                   | P47phox, p67phox, p40phox, Rac1/2           | Host defense               |
| Nox3     | Flavo-protein, transmembrane cluster | Fetal kidney                | Not determined                              | Unclear                    |
| Nox4     | Flavo-protein, transmembrane cluster | Kidney, osteoclasts, ovary, eye, widespread | Not determined                              | Oxygen sensing, iron transport, host defense |
| Nox5     | EF hands, Flavo-protein, transmembrane cluster | Lymph nodes, testis, mammary gland, cerebrum | Calcium                                     | Fertilization              |
| Duox1, Duox2 (p138Tox) | Peroxidase, EF hands, Flavo-protein, transmembrane cluster | Thyroid, cerebellum, colon, lung, prostate, pancreatic islets | Calcium | Hormone synthesis |

**Fig. 2.** Cellular antioxidant enzymes system. Superoxide anion can be converted to H$_2$O$_2$ by the reaction of SOD. Catalase is a H$_2$O$_2$ dismutase that contains a heme group and is exclusively present in the peroxisome. GPx catalyzes the reduction of the hydroperoxides by utilizing the electrons transferred from NADPH via glutathione reductase (GR) and glutathione (GSH). 2-Cys Prx reduces hydroperoxides to water by utilizing electrons transferred from NADPH via thioredoxin (Trx) and thioredoxin reductase (TR).

endothelial level of XO is increased and correlates with the degree of endothelial vasodilatation (Landmesser et al., 2002).

**Endothelial NO synthase**

In the absence of its cofactor (BH$_4$) or its substrate (L-arginine), the endothelial NO synthase (eNOS) generates O$_2$•− instead of NO. BH$_4$ plays a role in stabilizing the dimeric conformation of eNOS, crucial for NO production (Alp and Channon, 2004). BH$_4$ oxidation and NOS uncoupling has been demonstrated in hypertension and hypercholesterolemia (Landmesser et al., 2003).

**CELLULAR ANTIOXIDANT ENZYMES IN MAMMALIAN SYSTEM**

**Superoxide dismutases**

Cells constantly produce O$_2$•− as a by-product of normal aerobic metabolism. Superoxide dismutase (SOD) is the main defense against O$_2$•−, catalyzing its dismutation to H$_2$O$_2$ and O$_2$ (Fig. 2) (Abreu and Cabelli, 2010). Based on the metal cofactor they harbor, human SODs can be classified into four groups: copper-zinc SOD (Cu/ZnSOD), manganese SOD (MnSOD), and extracellular SOD (EC-SOD). MnSOD is the SOD typically found in mitochondria and peroxisomes, whereas Cu/ZnSOD is usually the most abundant SOD in the cytosol. The EC-SOD is the secreted form of Cu/ZnSOD (Table 2). These enzymes are thus fairly ubiquitous in aerobic organisms (Reddi et al., 2009).

**Glutathione peroxidases**

Glutathione peroxidases (GPxs) were the first selenocysteine-containing proteins discovered in mammals. The “classical” glutathione peroxidase, now called GPx1, was first described as an erythrocyte enzyme that specifically reduces H$_2$O$_2$ by GSH, but later shown to reduce a broad scope of organic hydroperoxides (Toppo et al., 2009). In mammals, up to eight distinct GPxs have been detected. Most of them are selenoproteins (mammalian GPx1, GPx2, GPx3, GPx4 and, depending on species, GPx6), while in the remaining two or three variants the active site selenocysteine residue is replaced by cysteines. Only GPx1, 3 and 4 have been functionally characterized to some extent (Table 3).

**Catalase**

Catalases are enzymes that catalyse the conversion of H$_2$O$_2$ to water and oxygen using either an iron or manganese cofactor with high catalytic rate. Catalase is encoded by a single gene, which is highly conserved among species. Mammals, including humans and mice, express catalase in all tissues, and a high concentration of catalase can be found in the liver, kidneys and erythrocytes. A study of catalase activity in mice reported high catalase activity in the liver (66,100 units/g tissue), lung (2,390 units/g tissue) and erythrocytes (6,340 units/ml blood) (Nishikawa et al., 2002). The expression is regulated at the transcription, post-transcription and post-translation levels. High catalase activity is detected in peroxisomes. Catalase is also found in the cytosol in erythrocytes (Nishikawa et al., 2009). The crystal structure of tetrameric human erythro-
Heme oxygenase
Humans and rodents have two heme oxygenase (HO) isoenzymes, HO-1 and HO-2 encoded by the HMOX-1 and HMOX-2 genes, respectively. HO-1 expression is induced ubiquitously in response to oxidative stress whereas HO-2 is constitutively expressed. HO are evolutionarily conserved enzymes that catabolize hemes, iron (Fe) protoporphyrin (IX), into equimolar amounts of labile Fe, carbon monoxide (CO), and biliverdin (Gozzelino et al., 2010).

Peroxiredoxins
Peroxiredoxins (Prx) are a group of ubiquitous peroxidase enzymes in which redox-active cysteine residues participate in the reduction of \( \text{H}_2\text{O}_2 \) (Kang et al., 2005). Based on their catalytic mechanism, Prxs have been separated into three classes: typical 2-Cys, atypical 2-Cys, and 1-Cys Prxs. Typical 2-Cys Prxs are the largest subfamily of Prxs and contain two catalytic cysteine residues. This group includes Prxl, PrxII, PrxIII, and PrxIV (Table 4). The peroxidatic cysteine is oxidized directly by \( \text{H}_2\text{O}_2 \), generating a sulfenic derivative that is stabilized by the formation of a disulfide bond with the other resolving cysteine in a neighboring Prx molecule (Wood et al., 2003). The atypical 2-Cys Prxs including PrxV are functionally monomeric and both the peroxidatic cysteine and its corresponding resolving cysteine are contained within the same polypeptide. The 1-Cys Prxs including PrxVI conserve only the peroxidatic cysteine and do not contain the resolving cysteine (Choi et al., 1998).

**THERAPEUTIC USE OF ANTIOXIDANT ENZYMES IN ATHEROSCLEROTIC VASCULAR DISEASE**

An increased amount of superoxide radicals was reported in the arteries of spontaneously hypertensive rats (Fig. 3) (Chu et al., 2003). In this case, genetic transfer of EC-SOD amelio-

---

**Table 2. SOD isoenzymes in mammalian cells**

| Type | Structure | Distribution | Function |
|------|-----------|--------------|----------|
| SOD1 (Cu, Zn SOD) | Homodimer; non-disulfide linked | Cytosol | Familial amyotrophic lateral sclerosis (ALS) by mutated SOD1 (Zhang et al., 2007) |
| SOD2 (MnSOD) | Tetramer, contains a Mn ion bound to one aspartate and three histidine residues | Mitochondria | Protect mitochondria from ROS damage (Kokoszka et al., 2001) |
| SOD3 (extracellular SOD, EC-SOD) | Tetramer composed of two disulfide-linked dimers | Extracellular space, ~10 fold higher in the intima wall than in other tissues | Regulating the vascular redox state in extracellular space (van Deel et al., 2008) |

**Table 3. GPx isoenzymes in mammalian cells**

| Type | Structure | Distribution | Function |
|------|-----------|--------------|----------|
| GPx1 (cytosolic GPx; cGPx) | Homotetramer; contains a single selenocysteine residue in each of four identical subunits | Abundant in cytosol of erythrocytes, kidney, liver or lung | Selenium-dependent, ubiquitously distributed (Chu et al., 2004) |
| GPx2 (gastrointestinal GPx; GI-GPx) | Homotetramer; selenocysteine at active site 40 of the protein sequence | Abundant in the epithelium of the whole gastrointestinal tract | Selenium-dependent (Yan and Chen, 2006) |
| GPx3 (plasma/extracellular GPx; pGPx) | A glycosylated homotetramer of 23 kDa subunits | The only extracellular isoform of GPxs; a secreted protein into blood plasma; also expressed in the kidney, lung, heart, placenta | Selenium-dependent, extracellular peroxidase (Olson et al., 2010) |
| GPx4 (phospholipid hydroperoxide GPx; PHGPx) | Monomer; selenocysteine at active site 73 | In most tissue both in cytosol and associated with membranes | Selenium-dependent, protect phospholipid, inactive structural capsule of epididymal spermatozoa (Imai and Nakagawa, 2003) |
| GPx5 (epididymal androgerelated protein or secretory GPx) | 221 amino acids | In epididymis; secreted protein | Selenium-independent (Vernet et al., 1999) |
rated endothelium function and decreased the arterial pressure. The involvement of SOD in atherosclerosis has been suggested indirectly by the observation that the activity and content of EC-SOD are increased in the aorta of ApoE<sup>−/−</sup> mice compared with control mice (Fukai et al., 1998). However, neither the absence nor overexpression of EC-SOD did affect atherosclerosis in ApoE<sup>−/−</sup> and LDLR<sup>−/−</sup> mouse (Laukkanen et al., 2001; Sentman et al., 2001) and SOD1 overexpression had no effect on progression of atherosclerosis in ApoE<sup>−/−</sup> mice (Yang et al., 2004). Therefore, we must need a more careful investigation for the role of SOD in atherosclerosis. Increased catalase activity has been identified in foam cells from rabbit aortic lesions (Chen et al., 2012). Overexpression of catalase was reported to retard atherosclerosis progression and to decrease the aortic content of F2-isoprostanes in ApoE<sup>−/−</sup> mice (Yang et al., 2004). However, the underlying mechanisms for this protective effect remain to be established unambiguously. Despite its apparent importance in H<sub>2</sub>O<sub>2</sub> removal, humans with inherent deficiency of catalase called “acatalasemia” or catalase KO mice suffer few ill effects (Bliznakov, 1999). Overexpression of catalase or catalase together with SOD-1 in ApoE<sup>−/−</sup> mice inhibited development of atherosclerosis in this model (Yang et al., 2004). The synthetic compound mimicking both SOD and catalase activities via selenium and manganese, EUK-8 protects against remodeling of the left ventricle and cardiac decompensation in mice model developing heart failure (van Empel et al., 2006).

Low levels of both GPx1 and GPx3 are associated with the development of vascular disease. For example, in the Athero Gene study of patients with a history of CVD, those with low erythrocyte GPx1 activities had increased recurrent events (Blankenberg et al., 2003). Individuals with both low high density lipoprotein cholesterol and GPx3 activity are at markedly increased risk for death from CVD. In animal study, GPx1 deficiency resulted in impaired endothelium-dependent vasodilation and an increase in the aortic content of F2-isoprostanes in ApoE<sup>−/−</sup> mice (Park et al., 2011).

Table 4. Prx isoenzymes in mammalian cells

| Type   | Structure | Distribution                  | Functions                                                                 |
|--------|-----------|-------------------------------|---------------------------------------------------------------------------|
| Prxl   | (2-Cys)   | Dimer                         | Cytosol, nucleus                                                          | Signal regulation (c-Abl, c-Myc, GDE2, p38, etc) (Rhee et al., 2012) |
| PrxII  | (2-Cys)   | Decamer (Basic unit: dimer)   | Cytosol, nucleus                                                          | Signal regulation (PDGF, VEGF, LPS, etc) (Choi et al., 2005)      |
| PrxIII | (2-Cys)   | Dimer                         | Mitochondria                                                             | Apoptosis (Chang et al., 2004)                                   |
| PrxIV  | (2-Cys)   | Dimer                         | ER, extracellular                                                        | ER foldase, Epididymal spermatozoa (Nguyen et al., 2011)          |
| PrxV   | (atypical 2-Cys) | Dimer                        | Mainly peroxisome, some in cytosol and mitochondria                     | Unclear (Wood et al., 2003)                                       |
| PrxVI  | (1-Cys)   | Monomer                       | Cytosol                                                                  | Unclear (lung phospholipid metabolism and cellular invasive/metastatic potential) (Wood et al., 2003) |

Fig. 3. Involvement of cellular antioxidant enzymes in cardiovascular diseases. The positive and negative effects are indicated by red and blue arrowheads, respectively. The related references are also indicated in parentheses.
prostanoids, indicative of increased lipid oxidation in the vessel wall of these animals (Forgione et al., 2002). The size of atherosclerotic lesions in the aortic sinus decreased significantly after 20 weeks of high-fat feeding in mice lacking GPx1 as compared with control mice (Stocker and Kearney, 2004).

The role of HO-1 was shown to include protection against cellular oxidative stress and pathological conditions, including atherosclerosis and other CVDs (Ryter et al., 2006). In endothelial cells, expression of HO-1 has been suggested to protect against HOCl-mediated mitochondrial dysfunction, caspase-3 activation, and cell death via enzymatic activity and the generation of biliverdin and CO (Wei et al., 2009). HO-1 induction is thought to contribute to the efficacy of pharmacological agents used in the treatment of CVDs, including statins, ramipril, aspirin, and probucol (Li et al., 2007).

Although a limited number of studies have suggested an involvement of Prxs in atherosclerosis, some of the evidence is interesting. For example, Prx II was shown to suppress the proliferation and migration of smooth muscle cells (SMCs) with the site-selective phosphorylation of the PDGF receptor and increased the neointimal thickness of SMCs in a balloon-injured carotid artery (Choi et al., 2005). Deficiency of Prx II in the ApoE−/− background mice fed a high-cholesterol diet accelerated plaque formation through increased expression of adhesion molecules, leading to increased immune cell adhesion and infiltration into the aortic intima (Park et al., 2011). Prx IV overexpression suppressed the development of atherosclerosis in ApoE−/− mice fed a high-cholesterol diet (Guo et al., 2012). Increased expression of the Prx I has been reported in advanced lesions in ApoE−/− mice (Mayr et al., 2005), and the lack of Prx I in ApoE−/− mice has been associated with increases in both lesion size and endothelial expression of the adhesion molecule P-selectin (Kisucka et al., 2008).

Although numerous experimental studies have indicated that antioxidants and scavenging ROS could prevent pathological events leading to atherosclerosis, translating this concept into the treatment of human disease has been problematic. ROS have important signaling properties, and the nonselective approach of scavenging all ROS could have deleterious effects. Distinguishing between pathologic radical and signaling ROS is currently difficult. It is generally accepted that the profound changes of ROS are observed in advanced stages of CVD. However, in the early stages that involve the initiation of disease, the alteration in the ROS level may be a highly localized event within individual cellular compartments or even by individual antioxidant enzymes without affecting overall cellular redox status. Such local changes of ROS by certain antioxidant enzyme systems result in the disturbance of redox signaling leading to the pathological consequences. Therapeutic interventions on the level of global redox status inside cells might not be sufficient to correct these disturbances. Novel strategies should instead target a specific cellular antioxidant enzyme by either inhibiting or mimicking the activity following an in-depth study for selective function of each antioxidant enzyme.

ACKNOWLEDGMENTS

This study was supported by Bio & Medical Development Program (2011-0019696) and the Research Center for Cellular Homeostasis (2012R1A5A1048236) of the National Research Foundation funded by the Korean government (MEST). D.H. Kang was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the MEST (2012R1A6A01015674).

REFERENCES

Abreu, I. A. and Cabelli, D. E. (2010) Superoxide dismutases-a review of the metal-associated mechanistic variations. Biochim. Biophys. Acta 1804, 263-274.

Alp, N. J. and Channon, K. M. (2004) Regulation of endothelial nitric oxide synthase by tetrahydrobiopterin in vascular disease. Arterioscler. Thromb. Vasc. Biol. 24, 413-420.

Bedart, K. and Krause, K. H. (2007) The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol. Rev. 87, 245-313.

Blankenpen, S., Rupprecht, H. J., Bickel, C., Torzewski, M., Hafner, G., Tietz, L., Smieja, M., Cambien, F., Meyer, J. and Lackner, K. J. (2003) Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. N. Engl. J. Med. 349, 1605-1613.

Bilznakov, E. G. (1999) Cardiovascular diseases, oxidative stress and antioxidants: the decisive role of coenzyme Q10. Cardiovasc. Res. 43, 248-249.

Chang, T., Cho, C. Park, S., Yu, S. and Kang, S. W. (2004) Peroxiredoxin III, amilothionin-specific peroxidase, regulates apoptotic signaling by mitochon. J. Biol. Chem. 279, 41975-41984.

Chen, H., Yu, M., Li, M., Zhao, R., Zhu, Q., Zhou, W., Lu, M., Lu, Y., Zheng, T., Jiang, J., Zhao, W., Xiang, K., Jia, W. and Liu, L. (2012) Polymeric variations in manganese superoxide dismutase (Mn-SOD), glutathione peroxidase 1 (GPX1), and catalase (CAT) contribute to elevated plasma triglyceride levels in Chinese patients with type 2 diabetes or diabetic cardiovascular disease. Mol. Cell. Biochem. 363, 85-91.

Choi, H. J., Kang, S. W., Yang, C. H., Rhee, S. G. and Ryu, S. E. (1998) Crystal structure of a novel human peroxidase enzyme at 2.0 A resolution. Nat. Struct. Biol. 5, 400-406.

Choi, M. H., Lee, I. K., Kim, G. W., Kim, B. U., Han, Y. H., Yu, D. Y., Park, H. S., Kim, K. Y., Lee, J. S., Choi, C., Bae, Y. S., Lee, B. I., Rhe, S. G. and Kang, S. W. (2005) Regulation of PDGF signaling and vascular remodelling by peroxiredoxin II. Nature 435, 347-353.

Chu, F. F., Esworthy, R. S., Chu, P. G., Longmate, J. A., Huycke, M. M., Wilczynski, S. and Doroshow, J. H. (2004) Bacteria-induced intestinal cancer in mice with disrupted gpx1 and gpx2 genes. Cancer Res. 64, 962-968.

Chu, Y., Iida, S., Lund, D. D., Weiss, R. M., DiBona, G. F., Watanabe, Y., Faraci, F. M. and Heistad, D. D. (2003) Gene transfer of extracellular superoxide dismutase reduces arterial pressure in spontaneously hypertensive rats: role of heparin-binding domain. Circ. Res. 92, 461-468.

Day, B. J. (2004). Catalytic antioxidants: a radical approach to new therapeutics. Drug Discov. Today 9, 557-566.

Forgione, M. A., Weiss, N., Heydrick, S., Cap, A., Kling, E. S., Bierl, C., Eberhardt, R. T., Farber, H. W. and Loscalzo, J. (2002) Cellular glutathione peroxidase deficiency and endothelial dysfunction. Am. J. Physiol. Heart Circ. Physiol. 282, H1255-1261.

Fukai, T., Galis, Z. S., Menge, X. P., Parthasarathy, S. and Harrison, D. G. (1998) Vascular expression of extracellular superoxide dismutase in atherosclerosis. J. Clin. Invest. 101, 2101-2111.

Gozzelinio, R., Jeney, V. and Soares, M. P. (2010) Mechanisms of cell protection by heme oxygenase-1. Annu. Rev. Pharmacol. Toxicol. 50, 323-354.

Grindling, K. K. (2005). ATVB in focus: redox mechanisms in blood vessels. Arterioscler. Thromb. Vasc. Biol. 25, 272-273.

Guo, X., Yamada, S., Tanimoto, A., Ding, Y., Wang, K. Y., Shimajiri, S., Murata, Y., Kimura, S., Tasaki, T., Nabeshima, A., Watanabe, T., Kohno, K. and Sasaguri, Y. (2012) Overexpression of peroxiredoxin 4 attenuates atherosclerosis in apolipoprotein E knockout mice. Antioxid. Redox Signal. 17, 1362-1375.

Guzik, T. J., Sadowski, J., Guzik, B., Jopek, A., Kapela, B., Przyby-
Kang and Kang. Antioxidant Enzymes as Therapeutic Targets

Nishikawa, M., Tamada, A., Kumai, H., Yamashita, F. and Hashida, M. (2002) Inhibition of experimental pulmonary metastasis by controlling biodistribution of catalase in mice. Int. J. Cancer 99, 474-479.

Ohara, Y., Peterson, T. E. and Harrison, D. G. (1993) Hypercholesterolemia increases endothelial superoxide anion production. J. Clin. Invest. 91, 2546-2551.

Olson, G. E., Whitlin, J. C., Hill, K. E., Winfrey, V. P., Motley, A. K., Austlin, L. M., Deal, J., Cohen, H. J. and Burk, R. F. (2010) Extracellular glutathione peroxidase(Gpx3) binds specifically to basement membranes of mouse renal cortex tubule cells. Am. J. Physiol. Renal Physiol. 298, F2144-1253.

Park, J. G., Yoo, J. Y., Jeong, S. J., Choi, J. H., Lee, M. R., Lee, M. N., Hwa, L. J., Kim, H. C., Jo, H., Yu, D. Y., Kang, S. W., Rhee, S. G., Lee, M. H. and Oh, G. T. (2011) Peroxiredoxin 2 deficiency exacerbates atherosclerosis in apolipoprotein E-deficient mice. Circ. Res. 109, 739-749.

Rajagopalan, S., Kurz, S., Munzel, T., Tarpey, M., Freeman, B. A., Griengl, K. K. and Harrison, D. G. (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J. Clin. Invest. 97, 1916-1923.

Reddi, A. R., Jensen, L. T., Narunaratrat, A., Rosenfeld, L., Leung, E., Shah, R. and Colotta, V. C. (2009) The overlapping roles of manganese and Cu/Zn SOD in oxidative stress protection. Free Radic. Biol. Med. 46, 154-162.

Rhee, S. G., Wu, H. A., Kil, I. S. and Bae, S. H. (2012) Peroxiredoxin functions as a peroxidase and a regulator and sensor of local peroxides. J. Biol. Chem. 287, 4403-4410.

Ryter, S. W., Alam, J. and Choi, A. M. (2006) Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol. Rev. 86, 583-650.

Safo, M. K., Musayev, F. N., Wu, S. H., Abraham, D. J. and Ko, T. P. (2001) Structure of tetragonal crystals of human erythrocyte catalase. Acta Crystallogr. D. Biol. Crystallogr. 57, 1-7.

Sauer, H., Shah, A. M. and Laurindo, F. R. M. (2010) Studies on Cardiovascular Disorders, Oxidative Stress in Applied Basic Research and Clinical Practice. Humana Press, New York.

Sauer, H., Wartenberg, M. and Hescheler, J. (2001) Reactive oxygen species as intracellular messengers during cell growth and differentiation. Cell Physiol. Biochem. 11, 173-186.

Sentman, M. L., Brannstrom, T., Westerlund, S., Laukkanen, M. O., Yla-Herttuala, S. (2001) Gene transfer of extracellular superoxide dismutase to atherosclerotic mice. Antioxid. Redox Signal. 3, 397-402.

Lee, M. Y., Martin, A. S., Mehta, P. K., Dakalova, A. E., Garrido, A. M., Datla, S. R., Lyons E., Krause, K., Banfi, B., Lambeth J. D., Lassegure, B. and Griengl, K. K. (2009) Mechanism of vascular smooth muscle NADPH Oxidase 1 contribution to injury-induced neointimal formation. Arterioscler. Thromb. Vasc. Biol. 29, 480-487.

Li, C., Hossieny, P., Wu, B. J., Qawasmeh, A., Beck, K. and Stocker, R. (2007) Pharmacologic induction of heme oxygenase-1. Antioxid. Redox Signal. 9, 2227-2239.

Mayr, M., Chung, Y. L., Mayr, U., Yin, X., Ly, L., Frederick, S., Hui, Y., Griffiths, J. R. and Xu, Q. (2005) Proteomic and metabolomic analyses of atherosclerotic vessels from apolipoprotein E-deficient mice reveal alterations in inflammation, oxidative stress, and energy metabolism. Arterioscler. Thromb. Vasc. Biol. 25, 2135-2142.

McCord, J. M. (2004) Therapeutic control of free radicals. Drug Discov. Today 9, 781-782.

Milenkovic, M., De Deken, X., Jin, L., De Felice, M., Di Lauro, R. and Lambeth, J. D. (2010) Pharmacologic induction of heme oxygenase-1. Antioxid. Redox Signal. 9, 2227-2239.

Nishikawa, M., Hashida, M. and Takakura, Y. (2009) Catalase delivery for inhibiting ROS-mediated tissue injury and tumor metastasis. Adv. Drug Deliv. Rev. 61, 319-326.

Nishikawa, M., Tamada, A., Kumai, H., Yamashita, F. and Hashida, M. (2002) Inhibition of experimental pulmonary metastasis by controlling biodistribution of catalase in mice. Int. J. Cancer 99, 474-479.

Ohara, Y., Peterson, T. E. and Harrison, D. G. (1993) Hypercholesterolemia increases endothelial superoxide anion production. J. Clin. Invest. 91, 2546-2551.

Olson, G. E., Whitlin, J. C., Hill, K. E., Winfrey, V. P., Motley, A. K., Austlin, L. M., Deal, J., Cohen, H. J. and Burk, R. F. (2010) Extracellular glutathione peroxidase(Gpx3) binds specifically to basement membranes of mouse renal cortex tubule cells. Am. J. Physiol. Renal Physiol. 298, F2144-1253.

Park, J. G., Yoo, J. Y., Jeong, S. J., Choi, J. H., Lee, M. R., Lee, M. N., Hwa, L. J., Kim, H. C., Jo, H., Yu, D. Y., Kang, S. W., Rhee, S. G., Lee, M. H. and Oh, G. T. (2011) Peroxiredoxin 2 deficiency exacerbates atherosclerosis in apolipoprotein E-deficient mice. Circ. Res. 109, 739-749.

Rajagopalan, S., Kurz, S., Munzel, T., Tarpey, M., Freeman, B. A., Griengl, K. K. and Harrison, D. G. (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J. Clin. Invest. 97, 1916-1923.

Reddi, A. R., Jensen, L. T., Narunaratrat, A., Rosenfeld, L., Leung, E., Shah, R. and Colotta, V. C. (2009) The overlapping roles of manganese and Cu/Zn SOD in oxidative stress protection. Free Radic. Biol. Med. 46, 154-162.

Rhee, S. G., Wu, H. A., Kil, I. S. and Bae, S. H. (2012) Peroxiredoxin functions as a peroxidase and a regulator and sensor of local peroxides. J. Biol. Chem. 287, 4403-4410.

Ryter, S. W., Alam, J. and Choi, A. M. (2006) Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol. Rev. 86, 583-650.

Safo, M. K., Musayev, F. N., Wu, S. H., Abraham, D. J. and Ko, T. P. (2001) Structure of tetragonal crystals of human erythrocyte catalase. Acta Crystallogr. D. Biol. Crystallogr. 57, 1-7.

Sauer, H., Shah, A. M. and Laurindo, F. R. M. (2010) Studies on Cardiovascular Disorders, Oxidative Stress in Applied Basic Research and Clinical Practice. Humana Press, New York.

Sauer, H., Wartenberg, M. and Hescheler, J. (2001) Reactive oxygen species as intracellular messengers during cell growth and differentiation. Cell Physiol. Biochem. 11, 173-186.

Sentman, M. L., Brannstrom, T., Westerlund, S., Laukkanen, M. O., Yla-Herttuala, S., Basu, S. and Marklund, S. L. (2001) Extracellular superoxide dismutase deficiency and atherosclerosis in mice. Arterioscler. Thromb. Vasc. Biol. 21, 1477-1482.

Sorescu, D., Weiss, D., Lassegue, B., Climpus, R. E., Szocs, K., Sorescu, G. P., Valpup, L., Quinn, M. T., Lambeth, J. D., Vega, J. D., Taylor, W. R. and Griengl, K. K. (2002) Superoxide production and expression of ox family proteins in human atherosclerotic tissue. Circulation 105, 1429-1435.

Stocker, R. and Kearney, J. F. R. (2004) Role of oxidative modifications in atherosclerosis. Physiol. Rev. 84, 1391-1478.

Suh, A. Y., Arnold, R. S., Lassegue, B., Shi, J., Xu, X., Sorescu, D., Chung, A. B., Griengl, K. K. and Lambeth, J. D. (1999) Cell transformation by the superoxide-generating oxidase Moxl. Nature 401, 79-82.

Toppo, S., Flohe, L., Ursini, F., Vanin, S. and MaIRRORNO, M. (2009) Catalytic mechanisms and specificities of glutathione peroxidases: variations of a basic scheme. Biochim. Biophys. Acta 1790, 1496-1500.

Traber, M. G. and Atkinson, J. (2007) Vitamin E, antioxidant and noth...
Gpxs in mice subjected to selenium deficiency. *Mol. Reprod. Dev.* **54**, 362-370.

Watts, G. F. and Staels, B. (2004) Regulation of endothelial nitric oxide synthase by PPAR agonists: molecular and clinical perspectives. *Arterioscler. Thromb. Vasc. Biol.* **24**, 619-621.

Wei, Y., Liu, X. M., Peyton, K. J., Wang, H., Johnson, F. K., Johnson, R. A. and Durante, W. (2009) Hypochlorous acid-induced heme oxygenase-1 gene expression promotes human endothelial cell survival. *Am. J. Physiol. Cell Physiol.* **297**, C907-915.

Wood, Z. A., Schroder, E., Robin Harris, J. and Poole, L. B. (2003) Structure, mechanism and regulation of peroxiredoxins. *Trends. Biochem. Sci.* **28**, 32-40.

Yan, W. and Chen, X. (2006) GPX2, a direct target of p63, inhibits oxidative stress-induced apoptosis in a p53-dependent manner. *J. Biol. Chem.* **281**, 7856-7862.

Yang, H., Roberts, L. J., Shi, M. J., Zhou, L. C., Ballard, B. R., Richardson, A. and Guo, Z. M. (2004) Retardation of atherosclerosis by overexpression of catalase or both Cu/Zn-superoxide dismutase and catalase in mice lacking apolipoprotein E. *Circ. Res.* **95**, 1075-1081.

Zhang, F., Strom, A., Fukada, K., Lee, S., Hayward, L. J. and Zhu, H. (2007) Interaction between Familial Amyotrophic Lateral Sclerosis (ALS)-linked SOD1 Mutants and the Dynein Complex. *J. Biol. Chem.* **282**, 16691-16699.