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Mini Review

Redox Control of Growth Factor Signaling: Recent Advances in Cardiovascular Medicine

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ABSTRACT

Growth factors play vital roles in the regulation of various biologic processes, including those in cardiovascular and respiratory systems. Accumulating evidence suggests that reactive oxygen species mediate growth factor signal transduction. The discovery of reactive oxygen species production by angiotensin II in vascular smooth muscle cells via the activation of NAD(P)H oxidase promoted studies of redox control of growth factor signaling. In the past few years, there have been further advances in this field. In addition to established roles of reactive oxygen species in vascular smooth muscle growth, these species have been demonstrated to serve as second messengers for cardiac hypertrophy induced by angiotensin II. NAD(P)H oxidase also produces reactive oxygen species in response to endothelin-1 in vascular smooth muscle and cardiac muscle cells. These results suggest that inhibiting NAD(P)H oxidase might be a useful therapeutic strategy. In fact, adenovirus-mediated gene transfer appears to be an effective approach to prevent vascular hypertrophy in rodent models. Growth factors also induce survival signaling in cardiac and smooth muscle cells, and redox control may play a role in such events. It is likely that studies reporting the mechanisms of redox control of growth factor signaling will rapidly emerge in the next several years, and understanding of such regulation should help in the development of therapeutic strategies against heart and lung diseases. *Antioxid. Redox Signal.* 7, 829–834.

INTRODUCTION

THE DISCOVERY OF SUPEROXIDE PRODUCTION by angiotensin II (Ang II) via the activation of NAD(P)H oxidase (16) promoted the idea that reactive oxygen species (ROS) might serve as second messengers for vascular smooth muscle cell growth. During the past 10 years, evidence has accumulated in the literature to support such a concept. Recently, the Forum on Redox Control of Growth Factor Signaling in Heart, Lung, and Circulation (45), which was published in *Antioxidants & Redox Signaling* in 2003, compiled original contribution and review articles, which address more recent advances in the field of redox control of growth factor signaling and oxidant-mediated signal transduction in cardiovascular and pulmonary systems. As indicated in these articles, the roles of NAD(P)H oxidase and ROS in vascular smooth muscle cell regulation are the major thrust for the advances in this field (3, 5, 15, 18, 54). Further, redox signaling events also occur in cardiac myocytes (4, 39, 43, 44, 47) and endothelial cells (6, 12, 36, 51). Since then, there already has been rapid progress in this field. In this article, we summarize the recent advances in the field of redox signaling in heart, lung, and circulation, while particular attention is taken to address if components of the redox control of growth factor signaling can be used as therapeutic targets against cardiovascular diseases. In 2003 and 2004, there appear to have been significant advances in the understanding of the roles of ROS in cardiac and smooth muscle hypertrophy, as well as in strategies for gene transfer of redox molecules in order to suppress cardiovascular pathology, providing strong rationale for the research in understanding the mechanisms of redox signaling.

ROLES OF ROS IN SIGNALING FOR CARDIAC HYPERTROPHY

As numerous reports point to important roles of NAD(P)H oxidase and ROS in vascular smooth muscle cell hypertrophy,

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it is of interest to explore the roles of these species in cardiac muscle cell hypertrophy. Initial evidence supporting such a hypothesis has been reviewed by Sabri *et al.* (39) and Takano *et al.* (47) in the Forum on Redox Control of Growth Factor Signaling (45). More recently, rapidly accumulating reports further suggest the importance of redox control of signal transduction for cardiac hypertrophy. Nakagami *et al.* (35) demonstrated that Ang II produced superoxide in neonatal rat cardiac myocytes and that polyethylene glycol (PEG)-superoxide dismutase, but not PEG-catalase, attenuated Ang II-induced hypertrophy. Kakishita *et al.* (22) similarly showed the role of ROS in Ang II-induced cardiac hypertrophy in mice, but in these studies, the administration of Ang II produced hydroxyl radicals. Byrne *et al.* (7) studied the role of $gp91^{phox}$-containing NADPH oxidase in cardiac hypertrophy using knockout mice. They found that $gp91^{phox}$ suppression inhibited cardiac hypertrophy induced by Ang II, but not by pressure overload. Ang II-induced cardiac hypertrophy was also inhibited by heme oxygenase-1 overexpression (19). Similarly, Maytin *et al.* (32) reported that pressure overload-induced myocardial hypertrophy in mice does not require $gp91^{phox}$. In isolated cardiomyocytes, hypoxia/reoxygenation induces hypertrophic signaling via ROS (14). These results indicate that ROS can induce cardiac hypertrophy and are involved in signal transduction pathways for cardiac hypertrophy induced by stimuli such as Ang II. However, as $gp91^{phox}$ suppression does not influence pressure overload-induced hypertrophy, it is not yet clear whether antioxidants and inhibitors of ROS-generating molecules are useful therapeutic agents against cardiac hypertrophy and failure.

ROS IN ENDOTHELIN-1 SIGNAL TRANSDUCTION

Wedgwood and Black (54) reviewed early evidence for the role of ROS in endothelin-1 (ET-1)-induced smooth muscle cell growth. For the last 2 years, this concept has been further supported by a number of reports in smooth muscle, cardiac muscle, and fibroblasts.

In deoxycorticosterone acetate (DOCA)-salt hypertensive rat model, Li *et al.* (26) reported that both superoxide and ET-1 levels were elevated in carotid arteries. ET-1 was found to stimulate superoxide production in isolated carotid artery preparations. This increase in arterial superoxide production in ET-1-treated or DOCA-salt rats was blocked by the inhibition of NADPH oxidase. Further, in DOCA-salt rats, ET_A-receptor blockade lowered the venous superoxide level and blood pressure (27), as well as vascular cell adhesion molecule-1 expression (28). Similarly, Callera *et al.* (8) reported the increase in superoxide production in DOCA-salt rats, which was blocked by vitamin E or an ET_A-receptor antagonist. Hypertension induced by the ET-1 infusion was inhibited by an antioxidant, Tempol, in rats (42), providing evidence for the roles of ROS in ET-1 signaling in vascular smooth muscle.

In the heart, ET-1 signal transduction events have also been shown to involve the generation of ROS. In isolated rat atria, a cell-permeable superoxide dismutase and catalase mimetic reduced the positive inotropic effect induced by endothelin receptor stimulation (41). In neonatal rat cardiac myocytes, Xu *et al.* (57) proposed that the ET-1–ET_A receptor–ROS pathway may be involved in cardiomyocyte hypertrophy induced by leptin.

Mechanisms of ROS-mediated ET-1 signal transduction were also investigated recently. In cardiac fibroblasts, ET-1 was found to induce ET-1 gene transcription via the activation of ROS production, extracellular signal-regulated kinase (ERK), and activator protein-1 transcription factor (9). Touyz *et al.* (50) concluded that, in human vascular smooth muscle cells, ET-1 stimulates mitogen-activated protein kinases via redox-sensitive processes that involve ROS derived from mitochondria, rather than NAD(P)H oxidase. In pulmonary artery smooth muscle cells, the ET-1–ROS–ERK–GATA-4 pathway was proposed (46), and superoxide dismutase/catalase mimetics attenuated cell growth (55). In A-10 vascular smooth muscle cells, ET-1-induced activation of ERK, Akt, and Pyk2 was attenuated by NAD(P)H oxidase blockade (11). Thus, accumulating evidence suggests that the ET-1 production of ROS mediates cardiac and smooth muscle cell hypertrophy via a yet undefined mechanism (Fig. 1).

GENE TRANSFER OF NAD(P)H OXIDASE INHIBITORS

Studies of NAD(P)H oxidase in smooth muscle and cardiac muscle suggest that this enzyme might be a useful therapeutic target against vascular and cardiac hypertrophy. Pagano and co-workers have shown that a small 9-amino acid peptide with a sequence from a region of the $gp91^{phox}$ molecule that is involved in the binding of $gp91^{phox}$ to $p47^{phox}$ is an effective way to suppress vascular growth. In the studies of Jacobson *et al.* (21), the infusion of this peptide, named gp91ds (gp91 docking sequence), suppressed balloon injury-induced superoxide production and neointimal hyperplasia in rats. In these studies, gp91ds was linked to another 9-amino acid peptide of human immunodeficiency virus (HIV) viral coats (HIV-tat), which can be internalized by the cells. The infusion of gp91ds linked to HIV-tat was also found to suppress Ang II-induced vascular macrophase infiltration and medial hypertrophy (29).

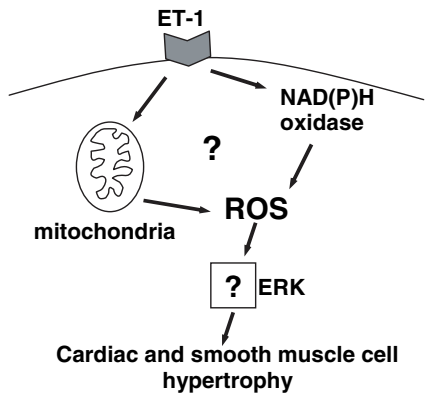

FIG. 1. Hypothetical model for the role of ROS in ET-1 signaling for cardiac and smooth muscle cell hypertrophy.

Adenovirus-mediated gene transfer is potentially a useful method for gene therapy against cardiovascular diseases. Although there are some concerns on toxicity and specific targeting that must be addressed, recent studies have provided some specific means to effectively target smooth muscle cells via adenovirus-mediated transfer. Appleby *et al.* (1) reported that the fusion of a fragment of smooth muscle myosin heavy chain promoter to the cytomegalovirus promoter increased transgene expression 90-fold in smooth muscle cells *in vitro* and 40-fold in coronary arteries. Further, the incorporation of a smooth muscle cell-specific peptide sequence into the HI loop of adenovirus fibers or the capsid protein of the adeno-associated virus-2 resulted in significant increases in gene expression specifically in smooth muscle cells (56). These methods might be useful for directly targeting the expression of inhibitors of NADPH oxidase in intimal and medial smooth muscle cells to attenuate vascular hypertrophy.

Pagano and co-workers constructed their adenovirus to specifically target the adventitia by expressing gp91ds under the control of platelet-derived growth factor-β receptor promoter, which gives selectivity of expression in proliferating fibroblasts (30). This approach allowed for perivascular gene transfer, and they showed that the application of this adenovirus expressing the NADPH oxidase inhibitor to mouse carotid adventitia resulted in significant reduction in the medial smooth muscle hypertrophy induced by Ang II. Similarly, in a rat model of angioplasty-induced neoitima formation in the carotid artery, the perivascular delivery of adenovirus expressing gp91ds suppressed the superoxide formation and neointimal hyperplasia (13).

These results indicate that targeting NADPH oxidase via adenovirus-mediated gene transfer might be useful to suppress vascular hypertrophy at least in rodent models. Such an approach to inhibit NADPH oxidase could also be applied for attenuating the development of cardiac hypertrophy.

ROLE OF NADH OXIDASE IN CARDIAC MUSCLE RYANODINE RECEPTOR REGULATION

Other advances in the redox regulation of the cardiovascular system include a discovery that NADH oxidase might regulate cardiac muscle ryanodine receptor (RyR), a Ca^{2+}-release channel of the sarcoplasmic reticulum. Ca^{2+} release from the sarcoplasmic reticulum via RyR plays a major role in the excitation–contraction coupling mechanisms in skeletal and cardiac muscle. RyR1 is the predominant isoform expressed in skeletal muscle, whereas RyR2 predominates in cardiac muscle. The RyR has been shown to be regulated by redox reactions, and *Antioxidants & Redox Signaling* has compiled a series of articles that describe the redox regulation of cardiac and skeletal sarcoplasmic reticulum (34). ROS produced in response to growth factors might alter the RyR activity, and it has been postulated that redox-regulated Ca^{2+} release from the sarcoplasmic reticulum might elicit growth signaling in cardiac myocytes (33).

Recently, Zima *et al.* (58) reported that NADH decreased the RyR2 activity in planar lipid bilayers, which was counteracted by NAD^+. Further, in studies of permeabilized rat ventricular myocytes, an increase of the cytoplasmic NADH/NAD^+ ratio depressed the Ca^{2+} release from the sarcoplasmic reticulum (59). Cherednichenko *et al.* (10) demonstrated an endogenous NADH oxidase activity in the cardiac sarcoplasmic reticulum that was inhibited by diphenyleneiodonium. Photo-affinity labeling identified a 23-kDa protein that resembles a subunit of NADH:ubiquinone oxidoreductase. As Ca^{2+} may play a role as a key second messenger in signal transduction pathways that control the growth of the heart (53), investigations on the role of NADH oxidase regulation of RyR2 might provide therapeutic targets against cardiac hypertrophy and failure.

SIGNALING FOR CARDIOPROTECTION AGAINST OXIDATIVE STRESS

In addition to the role of ROS in signal transduction pathways induced by growth factors, growth factors can control cellular events modulated by ROS, conferring a new mode of redox regulation. For example, various growth factors, including insulin-like growth factor-1, hepatocyte growth factor, basic fibroblast growth factor, transforming growth factor, and ET-1, can attenuate apoptosis induced by oxidative stress as described by Suzuki (44) in a review article published in the Forum on Redox Control of Growth Factor Signaling. Several articles were published in 2003 and 2004 to address further the mechanism of growth factor-mediated control of oxidative stress-induced cardiac myocyte apoptosis.

Kawamura *et al.* (23) reported that the ET-1-mediated cell survival signaling mechanism involves calcineurin-dependent activation of NFAT (nuclear factor of activated T-cells) and association with a transcriptional coactivator p300 to promote gene transcription of Bcl-2. They found NFAT-binding sites in the *bcl-2* promoter. The ET-1-mediated antiapoptotic signaling mechanism appears to play an important role in nonmyocyte-directed protection of cardiac myocytes against doxorubicin (48). Suzuki (44) described the role of GATA-4 as an antiapoptotic factor of cardiac myocytes. GATA-4 might also be involved in NFAT-dependent cardiac myocyte survival mechanisms elicited by ET-1 and α-agonist (20). α_1-Adrenergic receptor agonists, such as norepinephrine and phenylephrine, are hypertrophic stimuli in the heart and can also exert a cardioprotective effect. Aries *et al.* (2) reported the role of GATA-4 in norepinephrine-mediated protection against cardiac myocyte apoptosis induced by anthracycline chemotherapeutic agents. Further, cardiotoxic effects induced by doxorubicin (2) or daunorubicin (24) were attenuated by ectopic expression of GATA-4. Anthracyclines also decreased gene expression of GATA-4 and Bcl-x_L, and the restoration of the GATA activity protected cardiac myocytes against apoptosis (2, 24). Two consensus GATA-binding sites are present in the promoter region of *bcl-x* gene, which regulates the expression of Bcl-x_L isoform (17, 38), and activators of GATA-4, such as hepatocyte growth factor, enhance Bcl-x_L gene expression via the MEK/ERK-dependent phosphorylation (25). Although some of the biologic actions of anthracyclines have been attributed to the production of ROS such as hydrogen peroxide (H_2O_2), *bcl-x* gene regulation appears to behave differently in cardiac myocytes

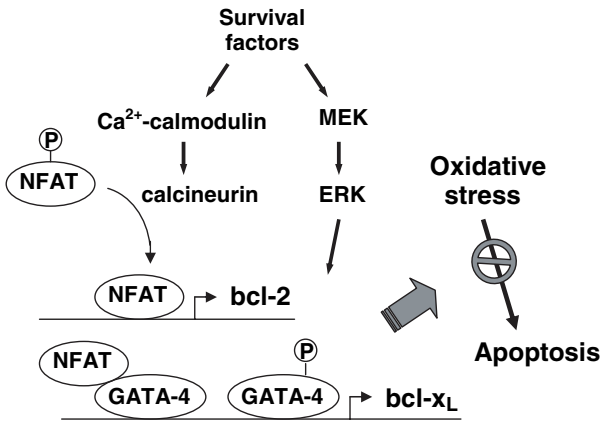

FIG. 2. Hypothetical model for a mechanism of signal transduction for cardiac muscle cell survival against oxidative stress.

under these stimuli, as Valks *et al.* (52) reported that H_2O_2 enhanced Bcl-x_L gene transcription. This is consistent with the findings that H_2O_2, unlike anthracyclines, failed to down-regulate GATA-4 in cardiac muscle cells (24). Figure 2 depicts a hypothetical model based on recent reports concerning signaling mechanisms for cardiac myocyte survival, which can be elicited by various growth factors. As described above, growth factor signaling can produce ROS; however, the role of ROS in growth factor-mediated cell survival has not been demonstrated. It is likely that ROS serve as signaling molecules for cardioprotection because there is evidence that ROS are mediators of ischemic preconditioning (31, 37, 40, 49).

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ABBREVIATIONS

Ang II, angiotensin II; DOCA, deoxycorticosterone acetate; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; gp^{91ds}, gp^{91} docking sequence; HIV, human immunodeficiency virus; H_2O_2, hydrogen peroxide; NFAT, nuclear factor of activated T-cells; PEG, polyethylene glycol; ROS, reactive oxygen species; RyR, ryanodine receptor.

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