ANTIOXIDANTS & REDOX SIGNALING
Volume 5, Number 6, 2003

Forum Review

Oxidants in Receptor Tyrosine Kinase Signal Transduction Pathways

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ABSTRACT

The accumulation of oxygen in the atmosphere created an evolutionary stress for organisms to survive because oxygen, while the by-product of photosynthesis and an important substrate in oxidative metabolism, can also be partially reduced to form toxic products. These forms of oxygen, reduced by one electron or two electrons, yield superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), respectively. Recent studies suggest that reactive oxygen species (ROS) such as $O_2^{\bullet -}$ and H_2O_2 function as mitogenic mediators of activated growth-factor receptor signaling. Reported data imply that growth factor-stimulated ROS generation can mediate intracellular signaling pathways by activating protein tyrosine kinases, inhibiting protein tyrosine phosphatase, and regulating redox-sensitive gene expression. This review examines the mechanisms of growth factor-induced generation of ROS and their roles in specific receptor tyrosine kinase signaling pathways. *Antioxid. Redox Signal.* 5, 781–788.

REACTIVE OXYGEN AND NITROGEN SPECIES

REACTIVE OXYGEN SPECIES (ROS) and nitrogen species are organic or inorganic molecules that have an odd number of electrons. These molecules are formed *in vivo* via oxidation–reduction reactions; they are highly reactive and thus very short-lived. Superoxide is the primary free radical formed within the cell by the reduction of molecular oxygen. The spontaneous or enzyme-catalyzed dismutation of superoxide anion ($O_2^{\bullet -}$) generates H_2O_2, which can undergo further reactions yielding hydroxyl radical ($OH^{\bullet}$) (21). Nitric oxide ($^{\bullet}NO$), an endogenously synthesized free radical, can be identified in numerous cell types, including vascular endothelium, macrophages, neutrophils, and hepatocytes (43). The production of $^{\bullet}NO$ by endothelial nitric oxide synthase promotes vessel relaxation and inhibits platelet aggregation and adhesion. Superoxide accelerates the destruction of $^{\bullet}NO$ via the facile radical reaction of these species to form the potent oxidant peroxynitrite ($ONOO^-$) and its conjugate acid peroxynitrous acid (p*K*a = 6.8). The rate constant for this reaction (2×10^{10} $M^{-1}s^{-1}$) is faster than the superoxide dismutase-catalyzed enzymatic dismutation of superoxide (9). $ONOO^-$ is a potent oxidant with a half-life of about 1.6 s at neutral pH (9). Peroxynitrous acid reacts by two pathways, with the first pathway yielding nitrate without forming strong oxidant intermediates. The second pathway forms $OH^{\bullet}$ and nitrogen dioxide, a potent oxidant that can initiate fatty acid oxidation and nitration of aromatic amino acids (51). Once reactive species are formed they can interact with lipids, proteins, and DNA to promote irreversible oxidative damage. Cellular free radical defense mechanisms have evolved to lower intracellular free radical concentrations and protect the organism against oxidative injury. Disease states can overwhelm these protective mechanisms and provoke oxidant-induced cytotoxicity.

SOURCES OF ROS

The mechanism of $O_2^{\bullet -}$ and H_2O_2 generation has been studied extensively in neutrophils and macrophages. In these phagocytic cells $O_2^{\bullet -}$ production results from the activation

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of a multicomponent NADPH oxidase system, which consists of two membrane components, a 22-kDa subunit (p22phox) and a 90–110-kDa glycoprotein subunit (gp91-phox), two cytosolic components, p47phox and p67phox, and the small-molecular-weight GTP binding protein, rac-2 (4). Recent studies suggest the presence of a nonphagocytic NADPH oxidase system that is structurally and genetically distinct from that in phagocytic cells. Fibroblasts have been reported to contain all or only the gp91-phox, p22phox, and p47phox components of the NADPH oxidase (24, 42, 46), while endothelial cells have been reported to contain all the phox proteins (8). p22phox and p47phox have been demonstrated in vascular smooth muscle cells (VSMCs) (48), but p67phox and gp91-phox proteins have not been identified. Instead, VSMCs express a nonphagocytic oxidase, nox-1, which is a gp91-phox homolog (55).

In addition to NADPH oxidase, it is important to note that autoxidation of mitochondrial respiratory chain components and other oxidases, like xanthine oxidase, prostaglandin endoperoxide synthase, lipooxygenase, and cytochrome P-450, can also serve as critical sources of oxygen radical production in various cell types (3).

ROS AND RECEPTOR TYROSINE KINASE SIGNALING PATHWAYS

Recent studies suggest that ROS such as $O_2^{\cdot -}$ and H_2O_2 function as mitogenic mediators of activated growth factor receptor signaling. Growth factors bind to extracellular domains of cell surface receptors and signal through receptor tyrosine kinases (RPTKs), which notably include fibroblast growth factor (FGF) receptor, vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, epidermal growth factor (EGF) receptor (EGFR), macrophage colony-stimulating factor receptor, hepatocyte growth factor receptor, insulin receptor, insulin-like growth factor receptor, nerve growth factor receptor, and ephrine receptors (57). General characteristics of RTKs are that they cross the membrane with a single transmembrane pass, they have a ligand-binding extracellular domain, and they all have a cytoplasmic catalytic domain that upon activation transfers a phosphate group from ATP to selected tyrosine residues (57). These tyrosine side chains are located on both the receptor proteins themselves and on the intracellular signaling proteins that interact with phosphorylated RPTKs.

EGF SIGNALING

The EGF signaling system is known to have four different receptors, ErbB1, ErbB2, ErbB3, and ErbB4, which share up to 50% homology at the protein level (11). The EGFR is a monomer containing a glycosylated extracellular domain, which is characterized by two cysteine-rich clusters, and an intercellular domain, consisting of a juxtamembrane and tyrosine kinase domain. When the receptor binds to its ligand, it is autophosphorylated and forms dimers or oligomers with itself or other members of the ErbB family (11). The activated RPTK then triggers intracellular signaling by recruitment of receptor-bound protein 2 (Grb2) and son of sevenless nucleotide exchange factor (SOS). The recruitment of Grb2 and SOS promotes the activation of Ras and the mitogen-activated protein kinase (MAPK) cascade (11). The EGFR signaling pathway functions in many cellular processes, including proliferation, cell migration, and apoptosis.

ROS in EGF signaling

EGF stimulation of A431 human epidermoid carcinoma cells induces an increase in cellular ROS production, which is measured by the oxidation of the fluorescent probe 2′,7/-dichlorofluorescein diacetate (5). The reported increase in 2′,7′-dichlorofluorescein diacetate fluorescence is completely inhibited in the presence of catalase and thus attributed to EGF-induced generation of H_2O_2. The reported study further demonstrates that the CD-126 mutant receptor, which lacks four of the five autophosphorylation sites, is as effective as the wild-type in generating H_2O_2. Thus, it is suggested that EGF-induced intracellular H_2O_2 generation requires the receptor kinase activity but not the autophosphorylation sites. Detailed experiments with phospholipase C-γ (PLC-γ)1 indicate that an increase in H_2O_2 is necessary but not sufficient for the increase in the steady-state level of protein tyrosine phosphorylation and that inhibition of protein tyrosine phosphatase activity by H_2O_2 may be required for EGF-induced tyrosine phosphorylation to be observed (5). Indeed, it has been demonstrated that H_2O_2 causes the oxidation of a sulfhydryl group at the active site of protein tyrosine phosphatase and that this inhibition is reversed in the presence of a reducing agent, dithiothreitol (30). However, it is important to note that the single remaining autophosphorylation site in the CD-126 mutant may serve as the binding site for a signaling molecule that serves as an effector molecule in the generation of H_2O_2 (5).

ROS in angiotensin II (Ang II)-induced EGF transactivation

Ang II is a bioactive peptide that is produced in the renin–angiotensin system from angiotensin I via an Ang II converting enzyme. Ang II exerts its effect mainly through angiotensin 1 and 2 receptors (AT1 and AT2, respectively) (10). Activation of AT1 causes vasoconstriction and cellular proliferation, while the stimulation of AT2 induces vasodilation and inhibits cellular proliferation (10). AT1 is a seven-transmembrane heterotrimeric G protein-coupled receptor, and once bound to Ang II, the heterotrimeric G protein subunits $G_{q/11}$, $G_{12/13}$, and $G_{\beta\gamma}$ become activated, which in turn induces the activation of PLC-γ (60). The catalytic activity of PLC-γ leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3), which stimulates the release of Ca^{2+} from the endoplasmic reticulum, which leads to the activation of protein kinase C (PKC) (28).

It has been reported that Ang II causes VSMC hypertrophy through EGFR transactivation (Fig. 1). The mechanism by which Ang II transactivates the EGFR signaling cascade is not clear, but a possible mechanism is thought to be through

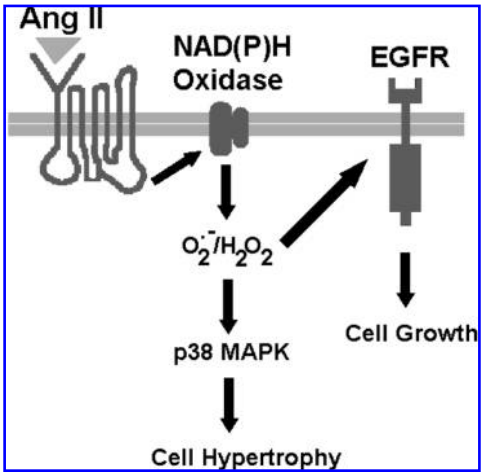

FIG. 1. Redox-sensitive signaling pathways activated by Ang II in VSMCs. Ang II activates an NAD(P)H oxidase, which in turn stimulates the production of ROS, leading to p38 MAPK and EGFR activation.

the formation of ROS (44, 66). Ang II has been shown to increase $O_2^{\cdot-}$ production in VSMCs through an NAD(P)H oxidase system. The reported Ang II-stimulated $O_2^{\cdot-}$ formation is inhibited by diphenylene iodonium (DPI), an inhibitor of flavin oxidases, tiron, an $O_2^{\cdot-}$ scavenger, *N*-acetylcysteine (NAC), which increases intracellular glutathione pools, and superoxide dismutase (25, 36, 61, 66). The mechanism of Ang II-induced NAD(P)H oxidase activation is not clearly identified, but it has been demonstrated that antisense p22phox transfection into VSMCs results in a 50% decrease in Ang II-stimulated NAD(P)H oxidase activity (58).

Redox-sensitive transactivation of the EGFR is thought to occur through a proximal tyrosine kinase, c-Src (32), which is shown to be activated by oxidative stress in cultured cardiac myocytes (2). c-Src is known to be an essential component for Ang-II-induced Ras/ERK activation in VSMCs (33).

Other key molecules that mediate Ang II-induced growth and cell proliferation are MAPKs, including p38 MAPKs, c-Jun N-terminal kinases, and the ERKs ERK1/2 (59, 62). While Ang II activation of p38 MAPK and c-Jun N-terminal kinase is found to be redox-sensitive, the sensitivity of ERK1/2 to oxidative stress is not certain (35). In a study done to determine the relative redox sensitivity of p38 MAPK and ERK1/2, it was found that p38 MAPK was the major redox-sensitive MAPK that was activated by Ang II. It was shown that Ang II stimulation of H_2O_2 generation caused a rapid phosphorylation of p38 MAPK, which was inhibited by DPI, antisense p22phox, and catalase overexpression (59).

PDGF SIGNALING

PDGF is a homo- or heterodimeric protein composed of A or B chains assembled in different combinations creating three isoforms, PDGF-AA, PDGF-AB, or PDGF-BB (14). The PDGF isoforms bind to two structurally similar RPTKs, PDGF-α and PDGF-β receptors (15, 26, 39). The PDGF receptor is a transmembrane protein containing five extracellular immunoglobulin (Ig)-like domains and an intercellular domain consisting of a juxtamembrane, tyrosine kinase, and C-terminal domains (14). PDGF receptors are widely expressed in many cell types, while PDGF isoforms are synthesized in megakaryocytes and other normal cell types (14). Once bound to the ligand, the receptor molecules undergo dimerizaton, which is coupled to kinase activation and transphosphorylation of receptor molecules. Seven autophosphorylation sites have been identified in the PDGF-β receptor, which have been characterized as specific binding sites for the Src family of protein kinases, phosphoinositide 3-kinase (PI3K), the GTPase-activating protein Ras, Src homology 2 phosphatase 2 (SHP2), and PLC-γ (14). The early response to PDGF receptor activation is intracellular Ca^{2+} fluxes and cytoplasmic pH changes, while long-term effects include migration, proliferation, and differentiation (14).

ROS in PDGF signaling pathway

PDGF-AB and PDGF-BB but not PDGF-AA have been reported to increase $O_2^{\cdot-}$ production in human aortic smooth muscle cells (38). In the presence of a flavoenzyme inhibitor, DPI, and a PI3K inhibitor, wortmannin, the generation of $O_2^{\cdot-}$ by PDGF-AB was attenuated. Allopurinol and nifedipine, a Ca^{2+} channel blocker, had no significant effect on PDGF-AB-induced $O_2^{\cdot-}$ release. Since ROS are shown to activate nuclear factor κB (NF-κB), mobility shift assays were performed with double-stranded oligonucleotides containing the sequence of the binding site for NF-κB. Subsequent to PDGF-AB stimulation, nuclear extracts showed an enhancement of binding of NF-κB that contained predominantly the p50/p65 heterodimer (38). In a separate study, PDGF-BB was also shown to generate $O_2^{\cdot-}$ in human lung fibroblasts (56). Cells treated with PDGF-BB demonstrated significant increases in $O_2^{\cdot-}$ production shortly after ligand binding, as determined by lucigenin-enhanced chemiluminescence. The reported increase in $O_2^{\cdot-}$ production was not accompanied by NADH oxidase activation and extracellular H_2O_2 production. When cells were infected with a viral vector encoding a mutant form of the GTP binding protein Ras, it was shown that cells overexpressing the mutant form of Ras failed to increase intracellular superoxide production in response to mitogenic stimuli. It was proposed that PDGF stimulated intracellular $O_2^{\cdot-}$ production in lung fibroblasts via a Ras-dependent activation of a $O_2^{\cdot-}$-generating oxidase/electron transferase and that this mechanism may be a common signaling pathway in a number of RPTKs (56). Similarly, PDGF treatment of bovine tracheal myocytes loaded with 2′7′-dichlorofluorescein diacetate caused oxidation of the fluorescence probe to dichlorofluorescein, indicating an increased production of ROS (47). In the reported study, the induction of ROS by PDGF was blocked by the glutathione peroxidase mimetic ebselen.

As stated previously, autophosphorylation of the PDGF receptor triggers intracellular signaling by recruitment of the Src family of protein kinases, PI3K, the GTPase-activating protein Ras, SHP2, and PLC-γ (14). The roles of these effectors on PDGF-induced generation of H_2O_2 have been investi-

gated in HepG2 cells expressing PDGF receptor mutants (6). Depending on the mutant tyrosine residue, these mutants are unable to bind GTPase-activating protein, SHP2, PI3K, and PLC-γ. It was shown that PDGF-induced H_2O_2 production only required the PI3K binding site and that H_2O_2 production was blocked by the PI3K inhibitors LY294002 and wortmannin. Overexpression of a negative dominant mutant of Rac1, an Rho family GTPase that constitutes a part of the NADPH oxidase complex, also blocked PDGF-induced H_2O_2 production (6).

FGF SIGNALING

To date, 20 different FGFs have been reported, and these proteins have been shown to have diverse effects on a variety of cell types (49). In order to achieve this kind of diversity, the FGF signaling system has four different FGF receptors (FGFR-1 through FGFR-4), which share between 55% to 72% homology at the protein level (34). The structure of the FGF receptor has been shown to be composed of three extracellular Ig-like domains (IgI, IgII, and IgIII), a transmembrane domain, and an intercellular tyrosine kinase domain (49). Once bound to the extracellular domain, FGF promotes receptor dimerization and induces receptor kinase activation, which in turn phosphorylates FGF receptor-stimulated 2 binding protein [FRS2 (SNT)]. The phosphorylated FRS2 (SNT) recruits Grb2, SOS, and SHP2. The recruitment of Grb2, SOS, and SHP2 promotes the activation of Ras and leads to signaling via the ERK pathway, which in turn leads to changes in gene transcription (23).

The biological functions of FGFs are diverse. Both FGF-1 and FGF-2 possess a nuclear localization motif and have been found to be associated with the nucleus (49). Like FGF-1, FGF-2 has potent growth and angiogenic activities and is thought to signal by autophosphorylating the tyrosine kinase domains of the receptor. Angiogenesis (20) and endothelial cell and fibroblast proliferation (41, 63) are among the well-characterized roles for FGF-1 and FGF-2, which play an important role in wound healing. The production of interleukin-2 during inflammation has also been shown to be stimulated by FGF-1, suggesting that FGFs may also play a role in the migration of inflammatory cells (12). FGF-3, -4, -5 and -8 have all been shown to function in embryonic development, with limb development being the most fully characterized function of these proteins (49).

ROS in FGF signaling pathway

It has been demonstrated that FGF-2 induces ROS production in chondrocytes and that this is a common signaling effect in the stimulation of c-*fos* gene expression (37). In the reported study, it was separately shown that FGF-2 and H_2O_2 increased c-fos mRNA levels in chondrocytes and that FGF-2 induced ROS production as detected by dihydrorhodamine-123 fluorescence. Pretreatment of chondrocytes with DPI, a potent inhibitor of flavinoid-containing enzymes such as NADPH oxidase and nitric oxide synthase, completely abolished both the induction of c-*fos* gene expression and ROS production. The antioxidants NAC and ascorbic acid also inhibited FGF-2-induced c-fos mRNA levels (37). It was concluded that FGF-2 production of ROS was through a flavinoid-containing enzyme and that this signaling effect could be inhibited by antioxidants. In a separate study, FGF-2 was shown to generate $O_2^{\bullet -}$ in human lung fibroblasts (56). Cells treated with FGF-2 demonstrated significant increases in $O_2^{\bullet -}$ production shortly after ligand binding, as determined by lucigenin-enhanced chemiluminescence. The reported increase in $O_2^{\bullet -}$ production was not accompanied by NADH oxidase activation and extracellular H_2O_2 production. When cells were infected with a viral vector encoding a mutant Ras protein, it was shown that cells overexpressing the mutant form of Ras failed to increase intracellular $O_2^{\bullet -}$ production in response to mitogenic stimuli. It was proposed that FGF-2 stimulated intracellular $O_2^{\bullet -}$ production in lung fibroblasts via Ras-dependent activation of a $O_2^{\bullet -}$-generating oxidase/electron transferase and that this mechanism may be a common signaling pathway in a number of RPTKs (56).

VEGF RECEPTOR SIGNALING

VEGFs are a family of dimeric glycoproteins that include VEGF-A, -B, -C, -D, and -E and placenta growth factor (40). The diverse VEGF isoforms interact with three structurally related receptor kinases denoted VEGFR-1, -2, and -3 (31, 40). Generally, VEGFR-1 and -2 are expressed on vascular endothelial cells, whereas VEGFR-3 is expressed on lymphatic endothelial cells (40). The structure of the VEGF receptor is that of a transmembrane protein containing seven extracellular Ig-like folds and an intercellular tyrosine kinase domain (53). Once bound to the extracellular domain, VEGF promotes receptor dimerization and induces receptor kinase activation, which in turn phosphorylates the receptor itself and several cytoplasmic signal transduction molecules. VEGF-A stimulation of endothelial cells has been reported to activate PI3K (22), Akt/protein kinase B (64), PLC-γ (65), the Src tyrosine kinases (17), Ras GTPase-activating protein kinase (27), focal adhesion kinase (1), ERK (16), and p38 MAPK (50). Activation of PI3K results in accumulation of PIP_3, which regulates membrane targeting and phosphorylation of Akt/protein kinase B. Activation of PLC-γ catalyzes the hydrolysis of PIP_2, leading to the formation of IP_3 and diacylglycerol, which stimulate the release of intracellular Ca^{2+} and activate PKC (40).

Biological angiogenetic functions of VEGF are mainly transmitted through VEGFR-2, which include differentiation, migration, survival of endothelial cells, and mediation of vascular permeability (18). The activation of VGFR-1, which is also expressed in monocytes, leads to chemotaxis and tissue factor production (19).

ROS in VEGF signaling pathway

Transient heart ischemia has been demonstrated to increase VEGF gene expression (29). Although the mechanism of induction is undetermined, a ROS-dependent mechanism is suggested to play a role with regard to increased rates of reactive species production following myocardial ischemia/

TABLE 1. ROS FORMATION BY ACTIVATED GROWTH FACTOR RECEPTOR SIGNALING

Ligand	*ROS*	*Cell type*	*Inhibitor*	*Reference*
EGF	H_2O_2	A431 human epidermoid carcinoma	Catalase	5
PDGF	$O_2^{\bullet -}$	Human aortic Smooth muscle	DPI Wortmannin	38
PDGF	$O_2^{\bullet -}$	Human lung fibroblases	Overexpression of mutant Ras	56
PDGF	Unspecified	Bovine tracheal myocytes	Ebselsen	47
PDGF	H_2O_2	HepG2	Wortmannin Overexpression of mutant Rac1	6
FGF	H_2O_2	Chondrocytes	DPI NAC Ascorbic acid	37
FGF	$O_2^{\bullet -}$	Human lung fibroblasts	Overexpression of mutant Ras	56

reperfusion (7). Indeed, H_2O_2 was shown to stimulate VEGF gene expression in rat-derived endothelial cells (13). VEGF mRNA levels increased rapidly upon the addition of H_2O_2 and was abolished in the presence of a transcription inhibitor, actinomycin, indicating that *de novo* RNA synthesis was required for the observed induction. When H_2O_2 treatment was carried out in the presence of cycloheximide the observed increase in VEGF mRNA levels was higher than with H_2O_2 alone, showing that H_2O_2-mediated VEGF gene expression did not require *de novo* protein synthesis and that cycloheximide might be inhibiting the synthesis of either labile ribonucleases that are involved in degrading VEGF mRNA or repressor protein(s) involved in the regulation of VEGF gene expression. Electrophoretic mobility shift assays of nuclear extracts showed an H_2O_2-dependent enhancement of activator protein-1 (AP-1) and NF-κB binding to labeled oligomers containing either an AP-1 or an NF-κB binding site (13). The activation of NF-κB and AP-1 after oxidative stress (45, 52) and the presence of AP-1 and NF-κB binding sites on the promoters of human and mouse VEGF genes (54) suggest that H_2O_2-mediated VEGF gene expression occurs through an AP-1- and NF-κB-dependent mechanism. The reported study (13) also shows that the induction of VEGF mRNA levels could be blocked by NAC, a synthetic antioxidant that can replenish intracellular glutathione levels. H7, a PKC inhibitor, was also able to block the induction of VEGF mRNA, suggesting that the effect of H_2O_2 was also mediated by a PKC-dependent pathway.

CONCLUSIONS

Growth factor-stimulated ROS generation can mediate intracellular signaling pathways by activating protein tyrosine kinases, inhibiting protein tyrosine phosphatase, and regulating redox-sensitive gene expression (Table 1). The role of ROS in RPTK signaling pathways is supported by growth factor-mediated $O_2^{\bullet -}$ and H_2O_2 production and the inhibition of growth factor signaling effects by antioxidants. In many of the reported studies, growth factor-induced ROS generation is considered to be via the activation of NAD(P)H oxidase and is shown to be inhibited by DPI, a potent inhibitor of flavinoid-containing enzymes. The mechanism by which NAD(P)H oxidase activation takes place is not clearly identified, but it is important to note that the observed effect of DPI inhibition on ROS production may not be specifically related to NADPH oxidase and may also reflect the inhibition of other flavinoid-containing enzymes like xanthine oxidase. Although the reported data are consistent with a model in which ROS act as secondary signaling molecules, additional studies are necessary to clearly determine the molecular mechanisms through which the redox-based signaling events take place.

ABBREVIATIONS

Ang II, angiotensin II; AT1 and AT2, angiotensin 1 and 2 receptor, respectively; DPI, diphenylene iodonium; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FRS2 (SNT), FGF receptor-stimulated 2 binding protein; Grb2, receptor-bound protein 2; Ig, immunoglobulin; IP_3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; NAC, *N*-acetylcysteine; NF-κB, nuclear factor κB; $^{\bullet}NO$, nitric oxide; $O_2^{\bullet -}$, superoxide anion; $OH^{\bullet}$, hydroxyl radical; $ONOO^-$, peroxynitrite; PDGF, platelet-derived growth factor; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC-γ, phospholipase C-γ; ROS, reactive oxygen species; RPTK, receptor tyrosine kinase; SHP2, Src homology 2 phosphatase 2; SOS, son of sevenless nucleotide exchange factor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor kinase; VSMC, vascular smooth muscle cell.

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Received November 16, 2002; accepted August 1, 2003.

This article has been cited by:

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