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Forum Editorial

Redox Control of Protein Trafficking

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LOCALIZATION OF PROTEINS in discrete cellular compartments is an important factor in cell regulation, and is controlled by intrinsic localization signals and by extra- or intracellular signals. Reactive oxygen species (ROS) and the intracellular redox state have emerged as important factors in the signaling network. Changes in the redox state of the cell affect the interactions and activities of proteins. These changes regulate cellular phenotypes, such as morphology, motility, and cell–cell interactions, and elicit numerous signaling pathways and transcriptional activities. Although oxidants possess the capacity to act in a destructive fashion, growing evidence suggests that the production of ROS is closely regulated, and their downstream targets have positive functions in the regulation of cellular phenotypes. A key example of one of the many diverse redox-regulated phenotypic changes is the regulation of intracellular protein localization. How intracellular localization of proteins is regulated by changes in redox state is an important issue in biology that includes both redox-regulated interactions and modifications of proteins. *S*-Glutathionylation is a critical step for redox-based modifications as reviewed by Shelton *et al.* (32). Some progress has been made in identifying specific intracellular targets of oxidant signaling that are involved in protein trafficking. This Forum issue focuses on recent molecular based studies of protein trafficking regulated by ROS and changes in redox state.

FROM CYTOPLASM TO MEMBRANE

Numerous cellular stimuli lead to increased ROS production. These stimuli included growth factors such as serum (33), tumor necrosis factor-α (TNFα) (31), interleukin-1 (20), transforming growth factor β (25, 34), platelet-derived growth factor (30), lipopolysaccharides (7), and phorbol esters (19). Recent work has shown that NAD(P)H oxidases are major sources of superoxide in nonphagocytic cells, and that the NAD(P)H oxidases are essential for physiological responses of these cells, including growth, migration, and modification of the extracellular matrix (10, 17). It is not fully understood how these ROS-generating systems are regulated by extracellular stumuli, but they seem to display reciprocal dynamism in cellular signalings.

Van Buul *et al.* (43) describe expression and localization of catalytic subunits of NADP(H) oxidase, NOX2 and NOX4, in endothelial cells. NOX4 has been identified as a major subunit of NADP(H) oxidase in nonphagocytic cells, and mainly localized to an intracellular compartment that was costained with a marker for the endoplasmic reticulum. The regulatory subunit of NADPH oxidase, $p47^{phox}$, is associated with the actin cytoskeleton, and is translocated to the cell periphery by TNFα. The use of green fluorescent protein fusion proteins revealed that TNFα–induced changes are suppressed by ROS scavengers. Recruitment of subunits to the membrane may constitute one pathway of activation of ROS-generating systems. In addition, $p47^{phox}$ was shown to be important for vascular ROS production, redox-modulated signaling, and gene expression in the vascular smooth muscle cells of mice from experiments using gene knock-out (4).

Integrin-mediated reorganization of cell shape induces an altered cellular phenotype and redistribution of the actin cytoskeleton. This was found to be initiated by the binding of soluble antibody to α5β1 integrin and subsequent up-regulation of the collagenase-1 gene. Activation of the GTP-binding protein Rac1, which is a downstream effector of integrins, is necessary for this process, and expression of activated Rac1 is sufficient to increase expression of collagenase-1. These results indicate that Rac1 and oxygen radicals participate in the up-regulation of collagenase-1 expression as induced by cellular shape change in rabbit synovial fibroblasts (13). It was previously reported that Rac1 activation generated ROS that were essential for nuclear factor-kB (NFκB) activation (38).

During phagocytosis of particles by fibroblasts, integrin clustering and subsequent activation of RhoA are induced. RhoA is translocated from the cytoplasm to the membrane in early stages following integrin clustering as reported by Werner (45). A transient rise in hydrogen peroxide (H_2O_2)

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levels was observed after integrin clustering, and ROS scavengers such as Tiron and 1-pyrrolidinecarbodithioic acid down-regulated expression of the collagenase-1 gene that was induced by integrin clustering, whereas an inhibitor of NADPH oxidase, diphenyleneiodinium, did not alter expression of the collagenase-1 gene, suggesting that the source of ROS is not NADPH oxidase. From these results, it is expected that membrane dynamism affects ROS production and that ROS regulate subcellular localization of various proteins involved in signaling pathways and participate in the regulation of cellular phenotypes.

Another example of translocation of an enzyme from the cytoplasm to the membrane is presented by Takahashi *et al.* (39). They describe some critical roles of lipoxygenases in low-density lipoprotein (LDL) oxidation. Oxidative modification of LDL is critical for development of atherosclerosis, and LDL receptor-related protein is involved in this process. A change in subcellular localization of 12/15-lipoxygenase from the cytoplasm to the membrane was induced by its binding to the LDL receptor protein, but the mechanism for this trafficking is unknown at present.

INVOLVEMENT OF THE CYTOSKELETON

One of the machineries for redox-based regulation of intracellular localization of proteins is the cytoskeleton. It was demonstrated that H_2O_2, in concentrations that induce severe fragmentation of F-actin in fibroblasts, also induces a reorganization of F-actin in primary cultures of human umbilical vein endothelial cells as characterized by the accumulation of stress fibers, recruitment of vinculin to focal adhesions, and loss of membrane ruffles. H_2O_2 also induces a strong activation of the p38 mitogen-activated protein (MAP) kinase in these cells, which results in activation of MAP kinase–activated protein kinase-2/3 and consequently phosphorylation of the F-actin polymerization modulator, heat shock protein 27 (HSP27) (11).

Arrigo *et al.* (2) demonstrated that HSP27 is present in the cytosol under normal conditions, but is concentrated in the membrane fraction of the nucleus after heat shock. Oxidative stress induces release of HSP27 from the membrane into the cytosol. HSP27 and its homologue, αB-crystallin, up-regulate the total glutathione level and decrease the basal level of intracellular ROS. This effect is mediated by an increase in glucose-6-phosphate dehydrogenase, glutathione reductase, and glutathione transferase.

The transient accumulation of HSP27 in the form of large oligomers probably induces the presentation of irreversibly oxidized protein to the ubiquitin-independent 20S proteasome. The intracellular burst of ROS induces the formation of large oligomers of HSP27. Parcellier *et al.* (27) discuss the roles of HSP27 and αB-crystallin as chaperones in the cell death pathway. In contrast to other main heat shock proteins, the main chaperone function of HSP27 and αB-crystallin was independent of ATP, and they function to prevent intracellular protein aggregation. They show a protective effect against apoptosis by interacting with and inhibiting components of apoptotic pathways, possibly by stabilizing actin microfilaments. HSP27 also exhibits an antioxidant effect by decreasing ROS levels. Oligomerization seems to be required for these effects. Other heat shock proteins may also have protective effects on oxidative stress as chaperons, but redox regulation of intracellular trafficking of these proteins has not been reported.

FROM THE CYTOPLASM TO THE NUCLEUS

The shuttling of proteins between points of focal adhesion and the nucleus can be a reasonable way for signal transduction from the cell surface to gene expression, as reviewed previously (1). There are many examples of proteins that shuttle between the cell surface and the nucleus. It was reported that H_2O_2 induces nuclear translocation of a transcription factor STAT3 (signal transducer and activator of transcription 3) to form a sequence-specific DNA-bound complex in human lymphocytes, in which endogenous catalase has been exhausted (5). Several signal transducers, including MAP and *abl* kinases, as well as regulatory molecules of transcription such as JAK/STAT, Smads, and JAB1, have also been shown to translocate from the cytoplasm to the nucleus and thereby transmit signals into the nucleus. These processes may be regulated by changes in redox state, but so far there has been no direct evidence to support this.

One of the most examined transcription factors whose activity is redox-regulated is NFκB. Kabe *et al.* (12) stated that redox regulation of NFκB activation is critical in the genetic regulation of inflammatory processes. Activation pathways for NFκB are well documented, and translocation from the cytoplasm to the nucleus, as well as transcriptional activity, is both positively and negatively regulated by change in redox state. Phosphorylation of IκBα permits nuclear translocation of p50/p65, and this process is activated by ROS. Tyrosine phosphorylation of IκB has been shown to increase in cells treated with ROS, whereas TNF-α and interleukin-1 induced serine phosphorylation. DNA-binding activity of NFκB is regulated by Cys62 of the p50 subunit, and glutaredoxin or thioredoxin and Ref-1 seem to be involved in this regulation.

Increases in protein phosphorylation levels are controlled by both increased kinase activity and decreased protein phosphatase activity. As effector molecules, ROS generally induce an increase in tyrosine phosphorylation. One possible mediator in ROS-mediated effects is alteration of the tyrosine kinase/phosphatase balance (8). Protein tyrosine phosphatases (PTPs) are particularly credible candidates as they contain reactive cysteine residues within their active sites. Such reactive cysteine residues are easily oxidized by even mild oxidants, such as H_2O_2. Several recent reports have demonstrated that exogenous oxidants or oxidants generated by peptide growth factor binding can reversibly oxidize and hence inactivate PTPs (3, 21, 29).

Transcription factor NF-E2 related factor 1 (Nrf1) plays an important role in the regulation of antioxidant proteins and phase 2 detoxifying enzymes (14). It remains in the cytoplasm through binding to Kelch-like ECH associating protein 1 (Keap1). ROS, as well as phase 2 inducers, induce dissociation of this complex and permit nuclear translocation of Nrf2. Keap1 is an actin binding protein and remains on the cy-

toskeleton in unactivated cells. Nrf2 forms a heterodimer with a small Maf protein and binds to target DNA sequences. This binding is competitively regulated by the transcriptional repressors Bach1 and Bach2. Oxidative stress induces the nuclear accumulation of Bach2 and decreases transcriptional activity.

Tell *et al.* (40) describe the characteristics of apurinic/apyrimidinic endonuclease-1/redox effector factor-1 (APE1/Ref-1), a transcriptional coactivator for several transcription factors, regulated by both redox-dependent and -independent mechanisms. APE1/Ref-1 also functions as an apurinic/apyrimidinic endonuclease during DNA base excision repair. It is localized mainly in the nucleus, but also in the cytoplasm within the endoplasmic reticulum. Shuttling of APE1/Ref-1 between these compartments seems to be a regulated process, and intracellular localization has been shown to be altered by prooxidant injuries, direct ROS exposure, and other stimuli. The mechanism of APE1/Lef-1 shuttling is unclear at present, but posttranslational modifications, such as phosphorylation within a nuclear localization sequence (NLS) that a contains casein kinase II phosphorylation site, seem to be responsible. It may be that dephosphorylation is required for nuclear localization of APE1/Ref-1, as in the case of the NF-AT transcription factor.

Yap/Pap family members are transcription factors involved in the oxidative stress response of yeast. They accumulate in the nucleus upon exposure to oxidants and thereby regulate gene transcription (15, 16, 42). Okazaki *et al.* (26) showed that Tsa1, a thioredoxin peroxidase (peroxiredoxin), is critical for redox-regulated nuclear translocation of yeast transcription factor, Yap1. Nuclear export of Yap1 is inhibited by formation of a disulfide bond that results in nuclear localization. Glutathione peroxidase-like protein, Gpx3, is required for disulfide formation in Yap1.

Movement of macromolecules between cytoplasmic and nuclear compartments is primarily mediated by the nuclear pore complex, importin/exportin family members, and Ran GTPase (9). Importin β recognizes a NLS consisting of basic residues within the cargo protein and complexes with importin α. Export from the nucleus is mediated by exportin molecules such as chromosomal region maintenance protein (Crm) 1, which recognizes leucine-rich nuclear export signals and forms a complex with Ran-GTP to mediate transport to the cytoplasm. Recruitment of subunits into importin or exportin complexes before transport is influenced by anchor proteins in each compartment that mask transport signals within the signaling molecule (6).

Recent findings indicate that some LIM proteins, such as zyxin, lipoma-preferred partner, and thyroid receptor interacting protein-6 (Trip6), shuttle between focal adhesions and the nucleus in a Crm1/exportin-dependent manner (23, 24, 28, 44). Other components of cell–extracellular matrix or cell–cell adhesion complexes, such as ZO-1, ajuba, and zyxin, have been found to translocate into the nucleus and potentially transduce signals from sources to the nucleus directly. (1, 18). In the nucleus, these LIM proteins associate with either the nuclear matrix or other transcriptional machineries (35, 36, 47). The focal adhesion protein, Cas-interacting zinc finger protein, also holds the ability to translocate to the nucleus, where it regulates expression of matrix metalloproteinases (22). All of these proteins are predominantly localized at focal contacts, but also shuttle to the nucleus.

Hic-5 is a LIM protein with similarity to paxillin, being localized mostly at focal adhesions, but was reported to interact with the glucocorticoid receptor transactivation domain and function as a coactivator for this transcription factor (47). It was shown that oxidative stress induces nuclear translocation of Hic-5, and that this translocation participates in the transcriptional induction of c-*fos* gene (35). Paxillin itself has a putative nuclear export sequence (LSELDRLLL) and seems to traffic in and out of the nucleus (41, 46), but regulatory pathways for this nuclear shuttling are unclear at present. LIM domains in the C-terminus of Hic-5 are necessary for its accumulation in the nucleus, but no obvious NLS has been found in the region. From the experiments using individual mutations of each of the LIM domains, it was suggested that all four LIM domains cooperated as an unconventional NLS. This type of NLS was previously reported in zyxin and Trip6, both of which are LIM proteins related to Hic-5 and have no classical NLS. Their nuclear targeting capacity was found to be in the multiple LIM domains of their C-termini (24, 44). As for the nuclear exclusion signal (NES), the amino acid sequence of the LD3 motif of Hic-5 contains characteristic hydrophobic amino acids, including the leucine residues, which was proven critical for NES functioning. In addition to the NES, Hic-5 contains two cysteine residues in the LD2 domain that are not present in paxillin. Amino acid sequence surrounding the cysteine residues in the NES module of Hic-5 seems to have homology with the NESs of Yap1 and Pap1. A redox-sensitive functional NES was characterized in Pap1 and classified as a novel type of leucine-rich NES containing two or three cysteine residues besides a leucine-rich stretch (15). Shibanuma *et al.* (37) showed that several interacting proteins of Hic-5, such as PTP-PEST, negatively regulate the nuclear translocation of Hic-5, and the interaction between these proteins is sensitive to ROS. These results indicate that redox-sensitive interactions of Hic-5 and its partners regulate change in subcellular localization of Hic-5.

FUTURE PERSPECTIVES

As an intracellular signal, ROS seem rather nonspecific as they modify numerous cellular components, but they elicit discrete cellular responses at specific concentrations and localization. Protein trafficking among intracellular organelles is tightly regulated by specific localization signals and cargos that associate with target proteins. Although such associations are good targets for redox regulation, there have been few studies on this subject. Modifications of proteins, especially at cysteine residues, such as sulfenylation and *S*-glutathionylation can change the affinity of protein–protein interactions, thereby inducing changes in subcellular localizations leading to altered functions. Recent progress made using proteomic approaches such as cysteine-reactive fluorescent probes and a fluorescence resonance energy transfer technology can be successfully applied in identification of critical redox-regulated factors that participate in protein trafficking among intracellular compartments, including the cytoplasmic membrane, Golgi apparatus, microsome, mito-

chondria, cytoskeleton, and nucleus. Such developments will open a new window for research into ROS signalings.

ABBREVIATIONS

APE1/Ref-1, apurinic/apyrimidinic endonuclease1/redox effector factor-1; Crm-1, chromosomal region maintenance protein 1; H_2O_2, hydrogen peroxide; HSP, heat shock protein; Keap1, Kelch-like ECH associating protein 1; LDL, low-density lipoprotein; LIM, Lin-11, Isl-1, Mec-3; MAP, mitogen-activated protein; NES, nuclear exclusion signal; NFκB, nuclear factor-κB; NLS, nuclear localization signal; NOX, NADPH oxidase; Nrf2, NF-E2 related factor 2; PTP, protein tyrosine phosphatase; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-α; Trip6, thyroid receptor interacting protein 6; Yap1, yeast activator protein 1.

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