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Forum Review

Regulation of Novel Superoxide-Producing NAD(P)H Oxidases

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ABSTRACT

Deliberate production of reactive oxygen species (ROS) are catalyzed by enzymes that belong to the NAD(P)H oxidase (Nox) family. The human genome contains seven members of the Nox family: the superoxide-producing enzymes Nox1 through Nox5 and the dual oxidases Duox1 and Duox2 that release hydrogen peroxide but not superoxide. Among them, the classical member gp91*phox*/Nox2 functions as the phagocyte NADPH oxidase, playing a crucial role in host defense. Although Nox2, heterodimerized with its membrane-spanning partner p22*phox*, is inactive in resting cells, during phagocytosis it forms an active complex with soluble regulatory proteins such as the organizer p47*phox*, the activator p67*phox*, and the small GTPase Rac. Here the authors describe how the novel superoxide-producing Nox oxidases (Nox1, 3, 4, and 5) with different functions are regulated by p22*phox*, the Nox organizers, the Nox activators, and Rac, and how their expression is controlled at the transcriptional level. *Antioxid. Redox Signal.* 8, 1523–1532.

INTRODUCTION

Although reactive oxygen species (ROS) are considered to be mainly generated as by-products in aerobic metabolism, there exist enzymes specialized for ROS production, such as the phagocyte NADPH oxidase. The catalytic subunit of the phagocyte oxidase (*phox*) is gp91*phox*, a membrane-integrated glycoprotein that contains the entire transmembrane redox machinery: the N-terminal half comprises six transmembrane α-helices, to which two hemes are coordinated; and the FAD- and NADPH-binding sites reside in the C-terminal cytoplasmic domain (Fig. 1). Recently expanded information in genome databases has allowed identification of a family of gp91*phox*-related proteins, known as the NAD(P)H oxidase (Nox) (8, 32, 37, 52, 75, 78). The human genome contains seven members: Nox1 through Nox5, and the dual oxidases Duox1 and Duox2: Nox oxidases 1–5 produce superoxide from molecular oxygen in conjunction with oxidation of NAD(P)H, whereas Duox enzymes are known to release hydrogen peroxide without forming a detectable amount of superoxide (Fig. 1) (75).

The classical Nox enzyme gp91*phox*, also termed Nox2, is predominantly expressed in professional phagocytes. Although gp91*phox*/Nox2 is dormant in resting cells, it becomes activated during phagocytosis to produce superoxide, a precursor of microbicidal ROS, thereby playing a crucial role in host defense (19, 37, 60, 69). Nox1 is abundantly expressed in colon epithelial cells (12, 74) and is considered to play a role in host defense at the colon (30, 45). This nonphagocytic oxidase is also present in vascular smooth muscle cells (6, 74) and seems to be involved in angiotensin II (Ang II)-mediated hypertension (23, 28, 58). Nox3, the closest gp91*phox* homologue, exists in the inner ear of rodents (11, 64), which is essential for formation of otoconia, tiny mineralized structures that are required for perception of balance and gravity (64). The kidney oxidase Nox4, with unknown functions, is highly expressed in epithelial cells of renal tubules (29, 72) and also in vascular endothelial cells (2, 50, 85). Although Nox5, most distantly related to Nox2 among the other four Nox oxidases, is predominantly expressed in the testis and spleen (13), its biological role is also unknown at present.

The phagocyte oxidase gp91*phox*/Nox2 forms an active complex with its membrane-spanning partner p22*phox*, soluble regulatory proteins such as the Nox organizers and Nox activators, and the small GTPase Rac. Here we describe how these proteins function in the regulation of novel superoxide-

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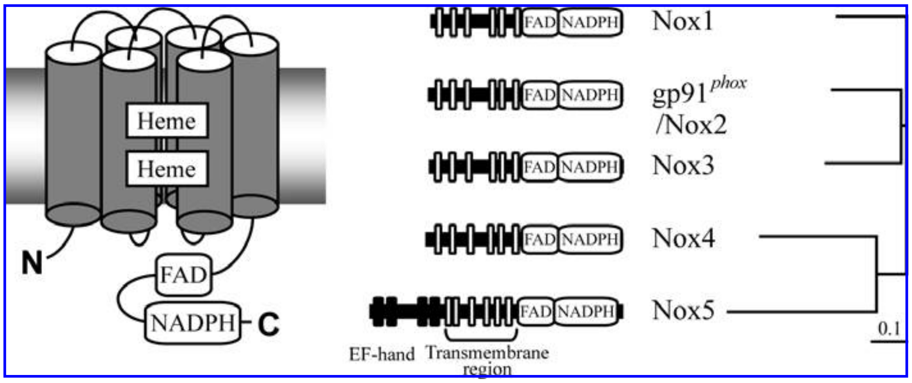

FIG. 1. Schematic structures and the phylogenetic tree of human members of the Nox family NAD(P)H oxidases. Schematic structures of the gp91^{phox}-related domain (*left*), and the phylogenetic tree constructed on the basis of the gp91^{phox}-related domains of human Nox1–5 (*right*). Evolutionary distances from a common ancestor sequence are represented as a *bar*, meaning 0.1 nucleotide substitutions per site.

producing Nox oxidases, and how the expression of the oxidases is controlled at the transcriptional level.

THE MEMBRANE NOX PARTNER p22^{phox}

The membrane-spanning glycoprotein gp91^{phox}/Nox2 in phagocytes forms a mutually stabilizing complex with p22^{phox}, a nonglycosylated membrane protein; the dimer is known as flavocytochrome b_{558}. In contrast to phagocyte-specific expression of gp91^{phox}/Nox2, it has been shown that the mRNA for p22^{phox} is expressed in a variety of tissues (76), suggesting that p22^{phox} associates with other Nox enzymes. Recent studies indeed have shown that nonphagocytic Nox oxidases also function by forming a heterodimer with p22^{phox}.

Formation of the Nox1–p22^{phox} complex is indicated by the following findings: Nox1-dependent superoxide production is markedly enhanced by ectopic expression of p22^{phox} in CHO cells, which scarcely express endogenous mRNA for p22^{phox} (79); Nox1 probably makes a direct contact with p22^{phox} (5, 38); and expression of Nox1 stabilizes p22^{phox} at the protein level, and *vice versa* (5). Nox3 also appears to be complexed with p22^{phox}, because p22^{phox} can be co-immunoprecipitated with Nox3 and the presence of Nox3 leads to stabilization of p22^{phox} protein (81). Indeed superoxide production by Nox3 in CHO cells requires co-expression of p22^{phox} (81). Although Nox4 can generate a small but significant amount of superoxide in a constitutive manner (29, 72), expression of p22^{phox} seems to facilitate the Nox4-dependent ROS production (5) and depletion of endogenous p22^{phox} by RNA interference results in a reduced Nox4 activity (56). In addition, Nox4 physically interacts with p22^{phox} and stabilizes this protein (5, 50, 56). Thus, Nox4 probably functions by forming a complex with p22^{phox}.

In addition to the role for stabilization of Nox enzymes, p22^{phox} participates in Nox regulation: the C-terminal cytoplasmic tail of p22^{phox} contains a proline-rich region (PRR), that serves as an essential target site for cytosolic proteins involved in formation of the active complex of Nox1 and Nox3 as well as Nox2 (79, 81). On the other hand, regulation of Nox5 is independent of p22^{phox} (46). Instead, the superoxide-producing activity of Nox5 is directly regulated by the intracellular concentration of Ca^{2+}: this ion directly binds to EF-hands in an N-terminal cytoplasmic extension unique to Nox5, which binding induces a conformational change leading to superoxide production (14).

ORGANIZERS AND ACTIVATORS INVOLVED IN NOX REGULATION

The classical organizer p47^{phox} and the classical activator p67^{phox}

Activation of the classical oxidase gp91^{phox}/Nox2 requires membrane recruitment of the two specialized cytosolic proteins p47^{phox} and p67^{phox}, as well as the small GTPase Rac (Fig. 2) (19, 37, 60, 69, 75). Although p47^{phox} and p67^{phox} are both required for the superoxide-producing activity of Nox2 in intact cells, p47^{phox} is dispensable for cell-free activation of Nox2 under the conditions where p67^{phox} and Rac are present at extremely high concentrations (27, 33, 49); p67^{phox} is an absolute requisite for Nox2 activation even in the cell-free system. Thus, p67^{phox} is considered to serve as an "activator", while p47^{phox} is regarded as an "organizer".

The organizer p47^{phox} of 390 amino acids contains tandem SH3 domains that are normally masked via an intramolecular association with the C-terminal autoinhibitory region (AIR) (Fig. 2) (4, 36, 86). During phagocytosis, p47^{phox} undergoes phosphorylation at several serine residues in the AIR (26). The cell stimulant-dependent phosphorylation of p47^{phox} induces a conformational change to render the two SH3 domains in a state accessible to the C-terminal PRR of p22^{phox}, an event that is required for both membrane translation of p47^{phox} and activation of Nox2 (4, 63, 73). p47^{phox} also has a PX domain in the N-terminus (Fig. 2): the domain can bind to phosphoinositides, which binding is negatively regulated in resting cells (3). The phosphorylation-induced conformational change of p47^{phox} also allows the PX domain to bind to membrane phosphoinositides, which is crucial for Nox2 activation (3, 42).

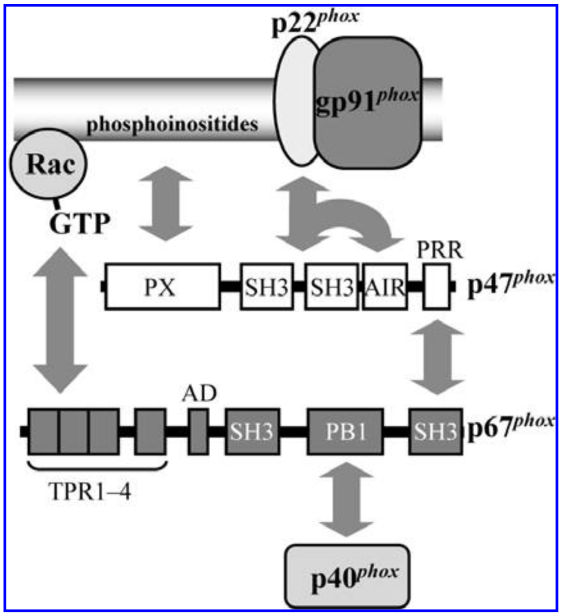

FIG. 2. Structure of the classical organizer p47^{phox} and the classical activator p67^{phox}, and interactions involved in activation of the phagocyte oxidase gp91^{phox}. AD, activation domain; PRR, proline-rich region; AIR, autoinhibitory region; TPR, tetratricopeptide repeat.

The activator p67^{phox} translocates during phagocytosis to the membrane in a manner dependent on p47^{phox}, whereas p47^{phox} is recruited to the membrane by itself (40). p67^{phox} associates with p47^{phox} via the interaction between the p67^{phox} C-terminal SH3 domain and the p47^{phox} C-terminus (Fig. 2) (41), which plays a crucial role in both p67^{phox} translocation and Nox2 activation (59). In this interaction, the p67^{phox} SH3 domain simultaneously makes direct contacts with the p47^{phox} PRR (amino acids 360–369) and its C-terminal region (amino acids 372–386) (41, 59). Phosphorylation of p47^{phox} at Ser-379 in the latter region likely weakens the interaction with p67^{phox} (57, 59), thereby regulating Nox2 activity negatively (59). The membrane-targeted p67^{phox} binds to Rac via the N-terminal tetratricopeptide repeat (TPR) domain (48, 53), which may allow direct interaction of p67^{phox} with Nox2, leading to superoxide production (70).

The novel organizer Noxo1 and the novel activator Noxa1

Nox1, as well as gp91^{phox}/Nox2, is inactive in the absence of p47^{phox} and p67^{phox}; on the other hand, these regulatory proteins exhibit only a marginal effect on Nox1 activation. The activation mechanism for Nox1 has been uncovered by discovery of the p47^{phox} homologue Noxo1 (Nox organizer 1) and the p67^{phox} homologue Noxa1 (Nox activator 1) (Fig. 3) (10, 31, 78). Endogenous Nox1 in the colon epithelial adenocarcinoma Caco2 cells spontaneously generates superoxide without cell stimulants, when Noxo1 and Noxa1 are co-expressed (31). Nox1 expressed ectopically in COS-7 or HEK293 cells is also constitutively active when a pair of Noxo1 and Noxa1 is co-expressed (10, 79). In contrast to Nox1, Nox2 is only slightly activated by Noxo1 and Noxa1 (31, 78).

The novel organizer Noxo1, like p47^{phox}, has one PX and two SH3 domains and a PRR (Fig. 3). Noxo1 binds to the PRR of p22^{phox} via the SH3 domains (79), which is required for Nox activation (81). On the other hand, Noxo1 lacks a region homologous to the p47^{phox} AIR that prevents the p47^{phox} SH3 domains from binding to p22^{phox}. The absence of AIR in Noxo1 may allow its SH3 domains to become accessible to its target p22^{phox}, which can explain at least partially the constitutive activity of Nox1 (17, 79). The PX domain of Noxo1 is also involved in Nox1 activation: the R40Q substitution in the PX domain decreases both phosphoinositide-binding activity and the ability to activate Nox1 (16). Noxa1 associates with Noxo1 via binding of the Noxa1 SH3 domain to the Noxo1 PRR (79) (Fig. 3). Like p67^{phox}, Noxa1 binds to Rac in a GTP-bound state, via the N-terminal domain composed of four TPRs (79) (Fig. 3).

Splice variants of Noxo1 and Noxa1

The presence of spliced variants of human Noxo1 mRNA has been recognized during the course of its cDNA cloning (16, 31, 79). The combination of two types of alternative splicing, leading to one amino acid deletion or five amino acid insertions at distinct sites of the PX domain, results in formation of four forms of Noxo1, designated Noxo1α, β, γ, and δ (15). Noxo1β without any deletion or insertion is the major form in most organs, including the colon. Both Noxo1α and Noxo1δ lack Lys-50 of the PX domain, and exhibit a much weaker activity to activate Nox1. Noxo1γ, containing five additional amino acids in the PX domain, is expressed in the testis to the same extent as that of Noxo1β. Whereas Noxo1β localizes exclusively to the membranes of resting cells, Noxo1γ is present in the cytoplasm, which is likely due to a reduced affinity of the Noxo1γ PX domain for phosphoinositides *in vitro*; indeed, Noxo1γ supports Nox1 activation to a lesser extent than Noxo1β (78a). This finding

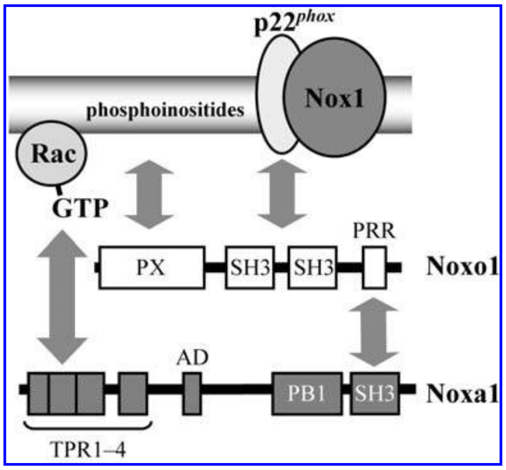

FIG. 3. Structure of the novel organizer Noxo1 and the novel activator Noxa1, and interactions involved in Nox1 activation. AD, activation domain; PRR, proline-rich region; TPR, tetratricopeptide repeat.

is inconsistent with the observation by others that Noxo1β and Noxo1γ seem to be equally active in Nox1 activation (15), the reason for which is presently unknown. In addition to Noxo1, there also exists spliced variants of the activator Noxa1, some of which can act as a dominant negative inhibitor (18). These findings raise the possibility that Nox-family oxidases may be distinctly regulated by various forms of Noxo1 and Noxa1.

Effect of combination of the organizers and activators on Nox regulation

The classical activator p67^{phox} can form a complex with p47^{phox} and with Noxa1 via the C-terminal SH3 domain; similarly, the novel activator Noxa1 can interact with both organizers (10, 31, 78). As expected from the cross interactions, Nox1 and gp91^{phox}/Nox2 can be activated by some combinations of the classical or novel organizers and activators in transfected HEK293 or Cos-7 cells (10, 31, 78). Among them, there is a favorable combination of activators and organizers for individual Nox oxidases, as described in previous parts of this review: Nox1 is preferentially activated by the combination of Noxo1 and Noxa1, while Nox2 prefers to the pair of p47^{phox} and p67^{phox} (10, 31, 78). These findings suggest that cytosolic factors interact not only with p22^{phox} but also with Nox itself. It has been reported that p47^{phox} and p67^{phox} can bind directly to Nox2 (1, 21, 22, 62) and that Noxo1 may make a direct contact with Nox1 (66).

Nox3 appears to be partially active without an oxidase organizer or activator (81), which is in contrast to Nox1 and Nox2 (Fig.4). The superoxide-producing activity of Nox3, however, can be enhanced by either of the organizers p47^{phox} and Noxo1 via the SH3-mediated interaction with p22^{phox}, even in the absence of an activator protein (81). This suggests that, in Nox3 regulation, p47^{phox} and Noxo1 may act as an activator rather than as an organizer. The activator p67^{phox} by itself is also capable of facilitating the Nox3-dependent superoxide production (81), whereas the novel activator Noxa1 fails to facilitate Nox3 activation (17, 81). Under certain conditions, Noxa1 and p67^{phox} can act as negative regulators of Nox3: they suppress the Noxo1-enhanced Nox3 activity (81). On the other hand, Noxa1 and p67^{phox} can further enhance the p47^{phox}-supported Nox3 activity (Fig. 4) (81). Thus, all the organizers and activators have an ability to regulate the Nox3 activity. In the inner ear of mice, Noxo1 is likely essential for Nox3 function. A recent study has identified the Noxo1 gene as being responsible for *head slant* (*hslt*) mice, whose phenotype is similar to that of Nox3-deficient mice: a single nucleotide insertion occurs in the Noxo1 gene of *hslt* mice, leading to premature termination at codon 35 in the PX domain (47).

In contrast to Nox1–3, Nox4 does not seem to be regulated by the Nox organizers or activators (5, 56), although it forms a complex with p22^{phox}, a target of the organizers p47^{phox} and Noxo1.

Expression profiles of the Nox organizers and activators

Preferential organizer–activator combinations for gp91^{phox}/Nox2 and Nox1 (see above) are indeed observed in some types of cell; professional phagocytes, expressing large amounts of gp91^{phox}/Nox2, contain solely p47^{phox} and p67^{phox}, while colon epithelial cells, abundant in Nox1, exclusively express Noxo1 and Noxa1 (10, 31, 79). On the other hand, expression of p47^{phox} and p67^{phox} does not seem to be restricted to phagocytes, and Noxo1 and Noxa1 are expressed in a variety of tissues besides the colon (10, 31, 79). For understanding of Nox regulation, it is thus important to know expression profiles of the genes for the oxidase organizers and activators.

Figure 5 shows human gene expression profiles suggested by analysis of expressed sequence tag (EST) counts, which are calculated from the number of the interested gene-EST and the total number of ESTs from a pool of cDNA libraries from the same tissue, on the basis of data of NCBI's UniGene (http://www.ncbi.nlm.nih.gov/UniGene) (84) in March, 2006. In the kidney, where Nox1 as well as Nox4 is present, as suggested by a similar EST-based profiling, p47^{phox} is expressed as the sole organizer, whereas Noxa1 is the predominant activator (Fig. 5). Since p47^{phox}, together with Noxa1, can activate Nox1 (79), these proteins may be involved in activation of Nox1 in the kidney. All of human Nox3-EST deposited at present are derived from the bone marrow or testis. Since bone marrow contains p47^{phox}-EST and p67^{phox}-EST, Nox3 may be activated mainly by p47^{phox} and p67^{phox} in the bone marrow (Fig. 5). On the other hand, Noxo1-EST and p67^{phox}-EST are obtained from the testis. In the testis, Nox3 is possibly activated by Noxo1, which may be negatively regulated by p67^{phox} (see above; and Ref. 81) (Fig. 4C).

Co-expression of the two organizers p67^{phox} and Noxa1 is observed in several tissues such as the mammary gland and ovary (Fig.5). It remains, however, unclear whether classical and novel homologues function competitively or additively in Nox activation. Future studies are awaited for answering this question. In some cases, for example, in vascular smooth muscle cells, two or more Nox oxidases seem to be expressed in a single cell (9, 35, 54, 67). How Nox oxidases in a single cell are regulated remains an area for further investigation.

THE SMALL G-PROTEIN Rac IN NOX REGULATION

The small G-protein Rac is essential for a cell-free system for activation of the phagocyte NADPH oxidase gp91^{phox}/Nox2 (7, 60, 83). This is the first example that has demonstrated a crucial role of this small GTPase in biological system. In resting cells, Rac is likely complexed with RhoGDI in the cytoplasm. Upon cell stimulation, Rac, dissociated from RhoGDI, is recruited to the membrane, which occurs in a manner independent of p47^{phox} or p67^{phox} (Fig. 4) (39). At the membrane, GTP-bound Rac is considered to interact with p67^{phox}, which renders this protein in a active state, leading to superoxide production by Nox2 (70). Thus, Rac directly participates in Nox2 activation by binding to p67^{phox}.

Rac may be also involved in the activation of Nox1, because blockade of Rac activation decreases stimulant-induced superoxide production in Nox1-expressing cells (44, 65, 71). It has been, however, unclear whether Rac is directly involved

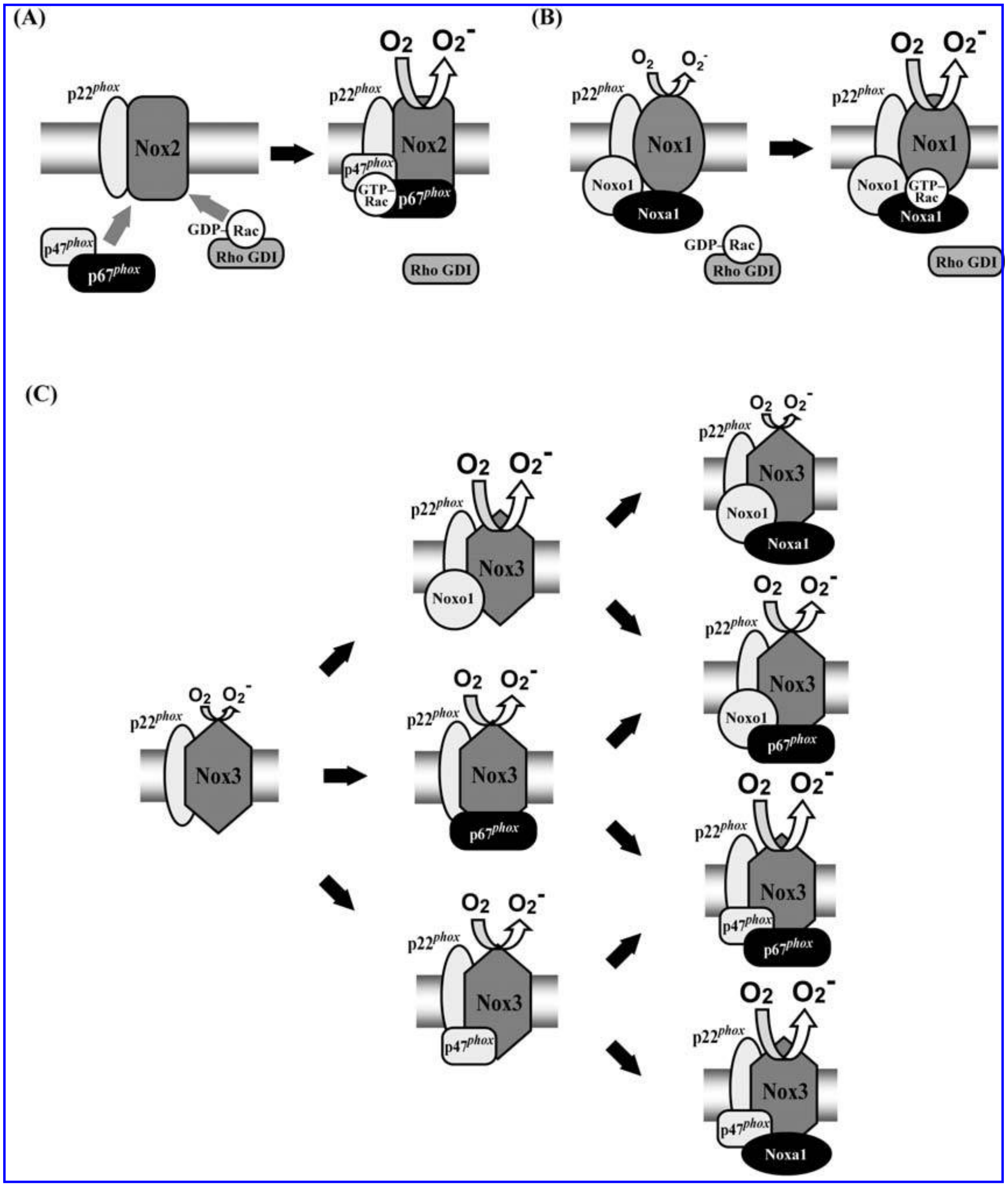

FIG. 4. Formation of active Nox complexes. Schematic structures of the assembled active complexes of gp91*phox*/Nox2 (**A**), Nox1 (**B**), and Nox3 (**C**).

in Nox1 regulation; Rac may indirectly activate Nox1 via acting in the upstream signaling pathway. The finding that GTP-bound Rac, but not GTP-bound Cdc42, binds to the N-terminal TPR domain of Noxa1 (79) has suggested a direct role of Rac in activation of Nox1, a Noxa1-dependent enzyme (Fig. 4). Indeed, we have recently shown that the R103E substitution in the third TPR of Noxa1 results not only in a loss of binding to Rac (79) but also in an impaired activation of Nox1; and a mutant Rac, defective in binding to Noxa1, fails to facilitate superoxide production by Nox1 (58a). A recent report has also indicated that Rac is directly involved in activation of Nox1 (82).

Although Nox3 can be controlled by the Nox activators p67*phox* and Noxa1 that bind directly to Rac, this G-protein does not seem to be involved in Nox3 regulation: expression of a dominant negative or a constitutively active form of Rac1 does not affect the superoxide-producing activity of Nox3 under the conditions where the gp91*phox*/Nox2 activity requires Rac activation (81). In addition, Rac binding to p67*phox* is not required for the p67*phox*-induced enhancement of Nox3

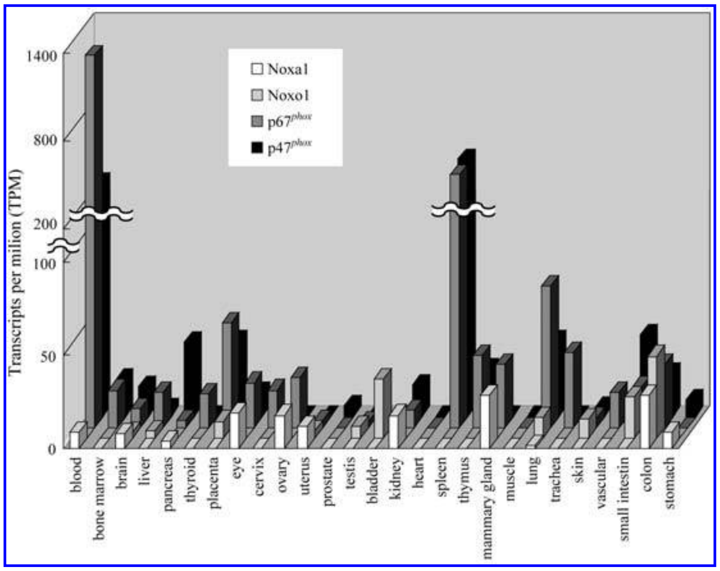

FIG. 5. Expression profiles of the Nox organizers and activators. The expression profiles presented are obtained by analysis of EST counts for human oxidase organizer and activator genes on the basis of data from NCBI's UniGene. Transcripts per million (TPM) are calculated from counts of the interested gene-EST and total number of ESTs in each tissue. The sample size of each tissue is normalized to 1,000,000 counts.

activity (81). It is also unlikely that Rac participates in regulation of Nox4 (56).

TRANSCRIPTIONAL REGULATION OF NOX OXIDASES

Although the classical oxidase gp91*phox*/Nox2 is strictly dependent upon agonists for activation, the oxidases Nox1, Nox3, and Nox4 are capable of constitutively producing superoxide. This indicates that superoxide production by these novel Nox members can be primarily controlled by expression of the oxidases.

Nox1 is expressed in both colon epithelial cells and vascular smooth muscle cells (6, 12, 74); however, the expression is distinctly regulated, depending on cell types. Nox1 in the colon is considered to function in local host defense (30, 45). Interferon γ (IFNγ) drastically induces the Nox1 mRNA in the colon epithelial carcinoma cell lines Caco2 and HT29 (30). The IFNγ-induced Nox1 transcription appears to be at least partially mediated via a γ–activated sequence (GAS) element that locates at -3818 to -3810 bp from the transcriptional initiation site (51). It is widely known that IFNγ also upregulates transcription of the gp91*phox*/Nox2 gene in myeloid cells via a PU.1/HAF-1-binding element (PU box) (24, 25, 61, 77); this element does not seem to be involved in IFNγ-triggered transcriptional activation of the Nox1 gene (51). A bacterial component, flagellin, stimulates Nox1 mRNA expression in human colon cancer T84 cells, probably through the toll-like receptor TLR5 (45). An NAD(P)H oxidase-like enzyme in guinea pig gastric mucosal cells produces superoxide in response to lipopolysaccharide (LPS) from *Helicobacter pylori* (80). This enzyme is presently considered to be Nox1, and the superoxide production is associated with LPS-induced expression of the Nox1 mRNA (44). Interestingly, the message for Noxo1 is also elevated by LPS treatment, in parallel with induction of superoxide production (44). Since Noxa1 is constitutively expressed in these cells, transcriptional activation of both Nox1 and Noxo1 likely plays a crucial role in LPS-induced superoxide production (44).

The first example for superoxide production by an NAD(P)H oxidase in the cardiovasculature has been shown in vascular smooth muscle cells stimulated with Ang II (34). Later studies have demonstrated that the responsible oxidase is Nox1, the mRNA of which is elevated by cell treatment with Ang II (55, 74, 85). Nox1 is presently considered to be involved in Ang II-mediated hypertension (23, 58). Nox1 expression in vascular smooth muscle cells is also induced by other vasoactive factors, such as platelet-derived growth factor (55) and prostaglandin $F_{2\alpha}$ (43). On the other hand, it has been reported that the Nox1 mRNA is markedly decreased by treatment of rat renal mesangial cells with the NO-releasing compound DETA-NO (68). The effect appears to be partially mediated by cGMP (68).

Little is known about mRNA expression of other Nox oxidases. Serum depletion has been shown to upregulate Nox4 transcription in rat aortic smooth muscle cells (55) and in rat aortic endothelial cells (2). The Nox4 mRNA level is elevated by Ang II in primary culture of rat aortic smooth muscle cells (55), but declined by the same agent in rat aortic smooth muscle cell line A7r5 (85). In cardiac fibroblasts, TGF-β1 dramatically upregulates the transcriptional activity of the Nox4 gene, whereas it downregulates that of the Nox5 gene (20).

CONCLUDING REMARKS

Superoxide generated by Nox-family oxidases serves as a precursor of other ROS, which are involved in a variety of physiological processes, including host defense, synthesis of bioactive compounds, and signal transduction (8, 32, 37, 52, 75); Duox oxidases are also known to be involved in synthesis of bioactive compounds such as thyroid hormone, which are not included in this review. It is hence important to understand mechanisms for regulation of the superoxide-producing

Nox oxidases. Activation of the classical oxidase gp91^{phox}/Nox2, complexed with p22^{phox}, requires the organizer p47^{phox}, the activator p67^{phox}, and the small GTPase Rac. Nox1 also forms a complex with p22^{phox}, and becomes active in the presence of the novel organizer Noxo1 and the novel activator Noxa1, in which Rac is involved as well. Nox3, being a heterodimer with p22^{phox}, can produce superoxide without an organizer or an activator, although it can be controlled by the classical and novel types of the Nox organizers and activators. Thus, recent studies have revealed that the three most related members of the Nox family are distinctly regulated. On the other hand, Nox5, an oxidase that does not involve p22^{phox}, seems to be regulated by the cytoplasmic concentration of Ca^{2+}. However, little is known about regulatory mechanism of Nox4. This should be addressed in future studies. It is possible that a here-to-fore unidentified factor is involved in Nox4 activation. In addition, further investigations are required for clarifying transcriptional regulation of the novel Nox oxidases and their activating proteins such as Noxo1 and Noxa1.

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ABBREVIATIONS

AIR, autoinhibitory region; Ang II, angiotensin II; EST, expressed sequence tag; GAS, γ–activated sequence; IFNγ, interferon γ; LPS, lipopolysaccharide; Nox, NAD(P)H oxidase; Noxa1, Nox activator 1; Noxo1, Nox organizer 1; *phox*, phagocyte oxidase; PRR, proline-rich region; PU box, PU.1/HAF-1-binding element; ROS, reactive oxygen species; TPR, tetratricopeptide repeat.

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