The Nox Family of NAD(P)H Oxidases: Host Defense and Beyond*

NAD(P)H Oxidase 1 (Nox1)

Nox1, the first recognized homologue of gp91phox, now termed Nox2, is detected in abundance in the colon and at lower levels in uterus, prostate, and vascular smooth muscle cells (4). The 564-amino acid protein is 50% identical to gp91phox and contains the essential features of its phagocytic counterpart, including six transmembrane segments and several conserved motifs considered important for binding of NADPH, FAD, and two heme molecules. Two variants of the full-length isoform have been described. Bánfi et al. (10) isolated a short mRNA product of the Nox1 gene encoding a proton-conductive channel, called NOH-1S (10). They suggested that a unique intraexonic splicing process gives rise to the NOH-1S product, which lacks the entire exon 11 (residues 433–482) and does not encode a functional oxidase2 (10).

In early work exploring the function of Nox1, heterologous overexpression of Nox1 in NIH-3T3 cells was associated with increased cell proliferation and resulted in tumor formation when these cells were injected into nude mice (4). Subsequent reports proposed that hydrogen peroxide (H2O2) formation in these Nox1-expressing cells is responsible for the increased mitogenesis (11). These findings were enthusiastically received because enhanced cellular ROS generation has been linked to the enhanced growth triggered by growth factor stimulation or tumorigenesis (12–14). Cells overexpressing Nox1 also showed increased vascular endothelial growth factor expression, suggesting that ROS produced by Nox1 also stimulates angiogenesis in these tumors (15). Further studies revealed, however, that these Nox1-transfected NIH-3T3 cell lines also carry a mutant form of Ras that can account for the enhanced proliferation and transformation (16). Observations in colon-derived epithelial cells, which naturally express Nox1, do not support the proposed role of Nox1 as a mitogenic oxidase. In HT29 colon cancer cells, the suppression of Nox1 levels does not affect cell proliferation (17). Furthermore, significantly higher Nox1 expression occurs when HT29 or CaCo2 cells are induced to differentiate by interferon-γ or by calcitriol (17). Finally, a survey of various human cancerous tissues showed Nox1 expression is limited to colon tumors and the highest Nox1 expression occurs in more differentiated tumors (17). Together, these findings suggest that Nox1 serves some other specialized function in differentiated colon epithelium unrelated to mitogenesis.

Several observations suggest that Nox1 could serve as a host defense oxidase. Nox1 induction, along with increased ROS release, was detected in guinea pig gastric pit cells primed with Helicobacter pylori lipopolysaccharides (LPS) (18). Kawahara et al. (19) proposed that LPS from pathogenic H. pylori strains potently stimulates ROS production through a toll-like receptor 4 (TLR4) pathway. In contrast, colon epithelial cells, which lack TLR4 receptors and do not respond to LPS, exhibit high Nox1-mediated ROS production in response to flagellin from Salmonella enteritides, acting through TLR5-dependent pathways (19). A role for Nox1 in innate immunity was also suggested by experiments showing that Nox1 could replace Nox2 (gp91phox) in the regulated production of superoxide, thereby partially rescuing the deficiency in superoxide production observed in chronic granulomatous disease neutrophils (17). Together, these findings demonstrate that Nox1 is functionally similar to gp91phox/Nox2. Whether Nox1 has a primary role in maintaining colon epithelial integrity or in host defense will require further investigation.

Although few reports have explored the role of Nox1 in the colon, where it is most abundant, several groups have examined the possible involvement of Nox1 in ROS production in vascular tissue. Nox1 expression in cultured smooth muscle cells was described by Suh et al. (4), and several other groups confirmed these findings (reviewed in Ref. 20). Several agonists, including platelet-derived growth factor, angiotensin II, and prostaglandins F2α, appear to up-regulate Nox1 mRNA levels in cultured smooth muscle cells (4, 21, 22), whereas suppression of Nox1 expression by antisense techniques inhibited superoxide production (4). Thus, production of ROS by Nox1 in these cells could have roles in angiogenesis and growth factor-induced cell hypertrophy or proliferation. Future studies on knock-out and other transgenic animals should provide better insight into the role of Nox1 in vascular tissue.

NAD(P)H Oxidase 3 (Nox3)

Nox3, a 568-amino acid protein, also has close similarities to gp91phox/Nox2 (58% sequence identity) (23). Nox3 mRNA was not detected in adult or in fetal tissues by Northern blotting; however, reverse transcription-PCR experiments detected Nox3 mRNA in nearly as abundant as the full-length transcript. This transcript lacks the entire exon 11 (residues 433–482) and does not encode a functional oxidase2 (10).

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1 The abbreviations used are: ROS, reactive oxygen species; phox, phagocyte oxidase; Nox, NADPH oxidase; LPS, lipopolysaccharide; TLR, toll-like receptor; Noxo1, NADPH oxidase organizer 1; Noxa1, NADPH oxidase activator 1; EPO, erythropoietin.

2 Geiszt, M., Lekstrom, K., and Leto, T. (2004) 279, 51661–51668.
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NAD(P)/H Oxidase 5 (Nox5)

NADPH oxidase 5 (Nox5) is more distantly related to the other Nox proteins, with an overall homology to gp91phox of 27% (9). The protein consists of 737 amino acids and contains an additional N-terminal extension comprising four calcium-binding EF-hand motifs that appear to render the enzyme directly responsive to calcium. Superoxide production by Nox5-expressing cells is induced by the calcium ionophore ionomycin (9). Recent work demonstrated that the EF-hands engage in direct, calcium-dependent interactions with the C-terminal domain of Nox5 (38). In testis, Nox5 mRNA was detected in pachytene spermatocytes (9), raising the possibility that it may function in mature spermatzoa, such as in oxidative changes associated with human sperm capacitation or the acrosome reaction (39). In the spleen, Nox5 message localizes to the mantle zone surrounding germinal centers (areas rich in B cells) and to periarterial lymphoid sheaths (where mostly T cells are present) (9). T and B lymphocytes produce ROS when stimulated by some receptor agonists (40, 41). A role for Nox5 in cell proliferation was suggested by Brar et al. (42), who demonstrated that antisense oligonucleotide-mediated down-regulation of Nox5 expression in DU 145 prostate cancer cells inhibits cell proliferation.

Dual Oxidases (Duox1 and Duox2)

Dual oxidases, originally designated thyroid oxidases (thIOX or tox), were cloned from human and porcine thyroid glands and proposed to serve in iodide organification during thyroxine synthesis (6, 7). The Duox (dual oxidase) nomenclature was suggested (43) as these proteins contain an N-terminal extracellular peroxidase-like domain and a gp91phox-like oxidase portion (6, 7, 43). Human Duox1 and Duox2 proteins contain 1551 and 1548 amino acids, respectively, and show 83% sequence similarity. Separating the peroxidase-like domain and the NADPH oxidase portion are an additional transmembrane segment and two EF-hand motifs (Fig. 1). The peroxidase-like domains of Duox proteins are unusual in that they lack conserved histidine residues found in all other peroxidases, considered essential for heme binding (44). The presence of several findings. The phagocyte cell homologue of Nox4, gp91phox/Nox2, was described as an oxygen sensor in the lung (26). In the kidney, EPO synthesis also occurs in proximal tubules (27), and ROS are implicated as negative feedback signals regulating EPO synthesis (28). Although the hypoxia-inducible factor-1α, which regulates EPO synthesis, is regulated by proline hydroxylases (29), other hypoxia-inducible factor-1α-independent transcription factors, such as GATA-2, are direct H_{2}O_{2}-sensitive targets that suppress EPO expression (30). Finally, recent knock-out studies indicate that superoxide dismutase 3, which is also expressed in renal proximal tubules, has a role in erythroid responses to hypoxia (31). These observations along with the high constitutive activity of Nox4 (5, 8) are consistent with a role for Nox4 in oxygen sensing.

A distinct possibility related to high renal Nox4 expression is that it serves as a p53-like antimicrobial system by releasing ROS into the glomerular filtrate; this might explain significant (i.e. 100 μM) urinary hydrogen peroxide levels (32). Other possible functions of the renal oxidase include roles in oxidation or detoxification of urine wastes or in renal pH or electrolyte homeostasis, based on the proton-generating and electrogenic activities of all NADPH oxidases. Finally, Gorin et al. (33) suggested that a Nox4-based oxidase is stimulated in response to angiotsin II in mesangial cells.

Several groups have also explored possible extra-renal functions of Nox4. According to Yang et al. (34), Nox4 and gp91phox (Nox2) are present in murine osteoclasts, where they may provide an oxidative basis for bone resorption. Low Nox4 expression is detected in vascular smooth muscle cells, where it appears to be down-regulated by agonists that increase Nox1 expression (21). Although the relative contribution of Nox4 to vascular ROS production remains unclear, Nox4 was also suggested as the major component of an endothelial NAD(P)H oxidase (35). In several cell lines, growth factor or insulin receptor stimulation increases ROS production, which has an enhancing effect on tyrosine phosphorylation in part through inhibition of protein-tyrosine phosphatases (36). A recent study indicates that Nox4 mediates insulin-stimulated ROS production in 3T3-L1 adipocytes (37). Further studies in gene-targeted animals may confirm roles for Nox4 in insulin signaling.

Duox1 and Duox2: Peroxidase Homology

Fig. 1. Topology of Nox family NAD(P)H oxidase with respect to the membrane. All members share features in common with those originally characterized in the core component of the phagocytic oxidase, gp91phox or Nox2 (reviewed in Refs. 1–3); these include six hydrophobic, membrane-spanning segments and several conserved motifs involved in binding NAD(P)H, FAD, and two heme moieties. Nox5 has an additional four calcium-binding EF-hands, whereas the dual oxidases (Duox1 and -2) have two EF-hands and an extracellular peroxidase homology domain.

several fetal tissues, including kidney, liver, lung, and spleen (23, 24). Recently, a unique role for this oxidase within the inner ear was revealed by positional cloning studies that mapped genetic lesions causing the head tilt (het) phenotype in mice (25). Mice with Nox3 mutations exhibit impaired otoconial morphogenesis and defects in perception of gravity and balance. It was proposed that this oxidase mediates ROS-dependent conformation changes in otocin-90 involved in the nucleation of calcite crystal formation during the development of otoconia.

**NAD(P)/H Oxidase 4 (Nox4)**

Nox4, a 578-amino acid protein with 39% sequence identity to gp91phox/Nox2, was originally described as a renal oxidase (Renox) because its expression at high levels is limited to the kidney (5, 8). However, the specific intrarenal distribution of Nox4 mRNA differs significantly in mice and humans. In situ hybridization in mouse kidney sections demonstrated the highest levels in proximal tubules (5), whereas immunohistochemical and in situ hybridization studies on human kidneys detected Nox4 expression in distal portions of the nephron (8). When overexpressed in NIH-3T3 fibroblasts, Nox4 increased superoxide production and induced a cellular senescence phenotype (5, 8). Expression of antisense Nox4 mRNA in HEK293 cells, which contain endogenous Nox4, resulted in a decreased NADH- and NADPH-dependent superoxide production in vitro (8). The expression pattern of Nox4 is consistent with several renal-specific functions. One proposed role in oxygen sensing and regulation of erythropoietin (EPO) synthesis (5, 8) is based on several findings. The phagocyte cell homologue of Nox4, gp91phox/Nox2, was described as an oxygen sensor in the lung (26). In the kidney, EPO synthesis also occurs in proximal tubules (27), and ROS are implicated as negative feedback signals regulating EPO synthesis (28). Although the hypoxia-inducible factor-1α, which regulates EPO synthesis, is regulated by proline hydroxylases (29), other hypoxia-inducible factor-1α-independent transcription factors, such as GATA-2, are direct H_{2}O_{2}-sensitive targets that suppress EPO expression (30). Finally, recent knock-out studies indicate that superoxide dismutase 3, which is also expressed in renal proximal tubules, has a role in erythroid responses to hypoxia (31). These observations along with the high constitutive activity of Nox4 (5, 8) are consistent with a role for Nox4 in oxygen sensing.

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3 M. Geiszt and T. Leito, unpublished observations.
zymes were proposed to serve as sources of H$_2$O$_2$ supporting the (43). It appears to catalyze cross-linking of tyrosine residues. Duox2 is clearly essential for thyroxine biosynthesis because Duox2 mutations result in congenital hypothyroidism, even in heterozygotes (47). The role of Duox1 in thyroid tissue has not been clarified. Duox proteins are also encoded by the genomes of lower species, such as Caenorhabditis elegans (43). Defective cuticle formation was observed during C. elegans development following inhibition of Duox expression by RNA interference (43). It was proposed that Duox provides the ROS for oxidative cross-linking of extracellular matrix tyrosine residues in a reaction thought to involve the extracellular peroxidase-like domain. The isolated C. elegans peroxidase-like domain produced in Escherichia coli appears to catalyze cross-linking of tyrosine residues in vitro (43).

Novel roles for Duox enzymes in host defense were recently proposed in several non-thyroid tissues (48). Based on the high level of Duox in epithelial cells of salivary gland ducts and along mucosal surfaces of colon, rectum, and major airways, these enzymes were proposed to serve as sources of H$_2$O$_2$ supporting the anti-microbial activity of lactoperoxidase. Lactoperoxidase, abundant in milk, saliva, tears, and mucosal secretions, uses H$_2$O$_2$ to oxidize thiocyanate to hypothiocyanite, an oxidant effective against both Gram-negative and Gram-positive bacterial species (49). Thus, the dual oxidases may represent "missing links" that complete an oxidant-dependant microbialidical system that has been long recognized in many body fluids.

Functional Partners of Nox Isoforms

In phagocytic cells, gp91$^{	ext{phox}}$ is the core catalytic component of a multi-component enzyme complex (1–3). However, p22$^{	ext{phox}}$, p47$^{	ext{phox}}$ and p67$^{	ext{phox}}$ are also essential for superoxide production, as is evident in chronic granulomatous disease, where defects or the absence of any one of these components result in oxidase deficiencies. p47$^{	ext{phox}}$, a classic adaptor protein, recruits p67$^{	ext{phox}}$ into the complex, whereas p67$^{	ext{phox}}$ and Rac appear to regulate catalysis (45, 51). An essential role for Rac in oxidase activation was well established in vitro (52) and was later confirmed in an oxidase-deficient patient who expressed mutant Rac2 (53) and in mice deficient in Rac2 (54).

The molecular architectures of the non-phagocytic oxidases are a subject of intense interest, as emerging evidence suggests that some of the closest homologues of gp91$^{	ext{phox}}$ also function as multi-component oxidases. Suh et al. (4) originally reported that Nox1 overexpression increases superoxide production although others could not detect superoxide when Nox1 alone was expressed in several hosts (17, 55–57). Interestingly, co-expression of p47$^{	ext{phox}}$ and p67$^{	ext{phox}}$ augments superoxide production in cells expressing Nox1 (17, 56). Searching sequence data bases, we identified p41$^{	ext{phox}}$, a protein with remarkable homology to p67$^{	ext{phox}}$, as a putative catalytic subunit of the non-phagocytic oxidase complex (1–3). The PX domain of Noxo1 also lacks the "P XX P" motif seen in p47$^{	ext{phox}}$, which is thought to mediate interaction with the flavocytochrome complex. Co-expression of Nox1 and Noxo1 in several Nox1-expressing hosts increases spontaneous (55) and phorbol 12-myristate 13-acetate-induced superoxide production (55, 57). The activity of this non-phagocytic oxidase is also enhanced by overexpression of p22$^{	ext{phox}}$, consistent with observations showing that Noxo1 and p22$^{	ext{phox}}$ interact (57). Together, these findings illustrate that the oxidase has close structural and functional similarities to the phagocytic enzyme (Fig. 2).

Nox3 activity is also enhanced in the presence of p47$^{	ext{phox}}$ and p67$^{	ext{phox}}$, Noxo1 and Noxo1, or Noxo1 alone (59). Consistent with this close homology to both gp91$^{	ext{phox}}$ and Nox1, however, the physiologically relevant partners of Nox3 have not been defined. Distinct roles for Nox1 as a regulator of other Nox/Duox isoforms are possible because its expression is detected in several tissues, notably thyroid and salivary glands, kidney, and pancreas (55, 57). The widespread expression of p22$^{	ext{phox}}$ may also be indicative of its involvement with other Nox isoforms, particularly Nox4 because this transcript is abundant in kidney (60). An association of p22$^{	ext{phox}}$ with Duox isoforms is unlikely, however, because p22$^{	ext{phox}}$-deficient chronic granulomatous disease patients have no problems in thyroid function. Furthermore, genes homologous to p22$^{	ext{phox}}$ are not detected in the genome of C. elegans, which encodes Duox genes. 3 Rac is another widely expressed candidate modulator of the novel Nox enzymes. Some of the earliest suggestions that NADPH oxidases function in non-myeloid cells were based on observation in cells overexpressing mutant Rac1 (12, 13); however, there is little evidence confirming that Rac proteins directly regulate the novel Nox enzymes (61). The best direct evidence linking Rac to the non-phagocytic Nox enzymes relates to recent demonstrations of Rac binding to Nox1 (56); thus, the Nox enzymes regulated by Nox1, or its homologue p67$^{	ext{phox}}$, are prime candidates for modulation by Rac.

FIG. 2. Homologous multicomponent Nox family oxidases of phagocytes and colon epithelium. Left, the phagocyte oxidase assemblies on newly forming phagosomes, following recruitment of Rac and phosphorylated cytosolic Phox proteins. Right, the Nox1-based oxidase of colon cells comprises some of the related or co-factors.

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Conclusion

With the recent discovery of new Nox/Dox family members it is clear that ROS production in many non-phagocytic cells can originate from multiple, related enzymatic sources. Novel signaling roles for these enzymes have been proposed in a variety of tissues where they are detected at low levels. However, their high levels at other sites, particularly terminally differentiated epithelial cells, suggest that they have other dedicated functions in addition to host defense, such as in hormone biosynthesis, fertilization, oxygen sensing, and extracellular matrix cross-linking. It is likely that ROS-based innate host defense processes are not restricted to phagocytes and that epithelial cells can also use this weapon against invading microbes, particularly along mucosal surfaces. Current challenges are to characterize better the molecular composition of these novel oxidases and to define their precise physiological roles. With recognition of these exciting new functions comes the possibility that these enzymes also have roles in a variety of disease processes related to inappropriate overproduction or underproduction of ROS.

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