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Contributions of Myeloperoxidase to Proinflammatory Events: More Than an Antimicrobial System

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Abstract

Optimal oxygen-dependent antimicrobial activity of circulating polymorphonuclear leukocytes reflects the synergistic effects of the myeloperoxidase (MPO)–hydrogen peroxide–halide system. Delivered from its storage compartment to the phagolysosome during fusion of the azurophilic granules, MPO catalyzes the oxidation of chloride in the presence of H_2O_2, chemistry unique to MPO, and thereby generates an array of highly reactive oxidants. Recent investigations of a wide range of inflammatory disorders have identified biochemical markers of MPO-dependent reactions, thus indirectly implicating MPO in their pathogenesis, progression, or perpetuation. The implied involvement of MPO-dependent events in diseases such as atherosclerosis forces reexamination of several fundamental tenets about MPO that are derived from studies of myeloid cells, most notably factors important in the regulated expression of MPO gene transcription. The evidence supporting a role for MPO in the pathogenesis of atherosclerosis, demyelinating diseases of the central nervous system, and specific cancers is reviewed and some of the new questions raised by these studies are discussed. Lastly, an appreciation for the existence of a broad family of proteins structurally related to MPO and the functional diversity implied by the corresponding structures may provide insights into novel ways in which MPO can function as more than an important antimicrobial component. *Int J Hematol.* 2001;74:125-133.

Key words: Myeloperoxidase; Atherosclerosis; Myeloperoxidase deficiency; Inflammation

1. The MPO-H_2O_2-Halide System

Agner first described the peroxidase present in the pus of infected canine uteri as verdoperoxidase [1], reflecting the intense green color of the purified enzyme. Subsequent work revealed that the enzyme was exclusively in circulating leukocytes, specifically polymorphonuclear neutrophils (PMNs) and monocytes, thus the protein was renamed myeloperoxidase (MPO) to reflect its cellular distribution [2]. In the early 1970s, Klebanoff made the seminal observation that MPO represented a major component of the PMNs' oxygen-dependent microbicidal activity [3]. Upon stimulation, PMNs assemble and activate the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase, thus generating hydrogen peroxide from molecular oxygen, and degranulate, thereby releasing the azurophilic granule protein MPO into the phagolysosome. These concomitant events create an intraphagosomal environment that presents a complex mixture of a variety of toxic agents to the ingested microbe or particle. Among reactive oxygen-derived species generated by activation of the NADPH oxidase are superoxide anion, the proximal product of the oxidase, hydrogen peroxide, hydroxyl radical, singlet oxygen, HOCl, and chloramines, as well as byproducts of interactions with NO, including peroxynitrite. The relative representation of these various agents within the phagosome reflects the influences of multiple variables, including the pH, ionic composition, and the presence of competing substrates [4].

Among these noxious agents is HOCl, the product of the unique property of MPO to catalyze the 2-electron peroxidation of Cl^- in the presence of H_2O_2 [5-7]. The precise

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amounts of intraphagosomal HOCl generated are not known. Hampton et al [4] have modeled the intraphagosomal environment and estimate that the ingestion of bacteria by PMNs stimulates the generation of 5 to 10 mmols/L per second of superoxide anion with concentrations of MPO in the range of 1 to 2 mmol/L. The amount of HOCl produced under these conditions is variable, reflecting the local pH, chloride concentration, amount of H_2O_2, the presence and concentrations of competing substrates, and the complex biochemistry of MPO itself (see [4] for a lucid review of this complicated chemistry). Nonetheless, there is direct evidence for the generation of highly reactive HOCl within the phagosomes of human PMNs [8-10].

HOCl is a membrane-permeant potent oxidant with a broad range of potential targets, including thiols, phenols, and iron centers [11]. Furthermore, HOCl can react with amines to generate chloramines and thereby spawn a wave of toxic species that have relatively long half-lives and can propagate additional tissue damage [6,12]. Several lines of evidence support the importance of the MPO-H_2O_2-Cl^- system in oxygen-dependent microbicidal activity against a wide spectrum of organisms, including viruses, bacteria, fungi, protozoa, and tumor cells [6]. In cases of organisms too large for the PMN to ingest, the secreted MPO adheres to the surface of the organism, likely reflecting the cationic nature and mannosylated sidechains of native MPO [6].

The pivotal position of MPO in oxygen-dependent microbicidal activity makes the apparently benign clinical consequences of MPO deficiency a paradox [13], although several caveats should accompany such a conclusion. First, the MPO-H_2O_2-Cl^- system represents only 1 component contributing to the complex biology in the phagosolysosome, where overall microbicidal activity reflects synergy among these various elements. It is difficult to assess the relative potency of the intraphagosomal environment with and without MPO in the absence of a better understanding of the various interactions among granule products and reactive oxygen and nitrogen species. Second, the end point of phagocytosis likely extends beyond simply killing the ingested organism and includes the complete degradation of microbial products. Residual bacterial proteins and/or lipids may be important elements in chronic inflammation and in granuloma formation. Determinants of complete resolution of infection and the clinical implications of their shortcomings have not been fully evaluated. Lastly, the clinical sequelae of MPO deficiency need not be manifested as defective host defense against infection but may reflect the important role of MPO in the promotion or termination of inflammatory events independent of microbial invasion. Recent studies have described far-reaching roles for MPO in the biology of many seemingly disparate events [14-21].

2. Beyond Microbicidal Activity

The general reaction of peroxidases with H_2O_2 represents a chemical paradigm with widespread application in biology. For example, an ovoperoxidase consumes H_2O_2 generated by the NADPH-dependent respiratory-burst oxidase of fertilization to crosslink surface proteins in order to protect the early embryo after fertilization of sea urchin eggs [22,23]. A peroxidase also figures prominently in an extraordinary symbiotic relationship between squid and a species of luminescent bacteria. A halide peroxidase with significant structural homology with MPO is expressed exclusively in the light organ of *Euprymna scolopes*, where luminescence is dependent on its colonization by *Vibrio fischeri* [24-26]. The precise function served by such localized expression of the halide peroxidase and its relationship to the presence of *V. fischeri* have not been defined but may represent a specialized application of the antimicrobial properties of an MPO-like protein to modulate the local flora colonizing the light organ. These examples simply demonstrate how wide peroxidase-H_2O_2–dependent posttranslational modifications of biologically important substrates may extend.

In mammalian biology, MPO has been implicated in biological events not directly related to infection. Indirect evidence suggests that the MPO-H_2O_2 system may contribute to termination of the NADPH oxidase activity in stimulated PMNs [27-29]. Early studies of the superoxide-generating particles recovered from stimulated PMNs suggested that MPO-dependent events might contribute to oxidase inactivation [27]. Several independent studies have supported that suggestion and reported that PMNs from MPO-deficient subjects exhibit prolonged oxidase activity, with overall production of more reactive oxygen species in response to a given agonist [28,29]. This more exuberant oxidase activity can be mimicked in normal PMNs by treatment with sodium azide, potassium cyanide, or 3-aminotriazole, all inhibitors of MPO activity [29]. It is conceivable that products of the MPO-H_2O_2-halide system may irreversibly modify sites in flavocytochrome b_{558}, thereby changing the conformation and/or binding sites critical for oxidase assembly, or modifying p47*phox*, p67*phox*, or rac2 to release them from the oxidase complex. Although the mechanism(s) is not elucidated, a role for MPO in termination of the PMN respiratory burst illustrates its participation as an anti-inflammatory element in PMN biology.

The activated MPO-H_2O_2-halide system can modify a variety of bacterial toxins [30,31] and other potential substrates released as part of the inflammatory response [32,33]. Products of the MPO-H_2O_2-halide system can oxidize and inactivate granule components secreted during stimulated exocytosis [34], chemotactic factors that serve to recruit activated PMNs into an inflammatory site [35-38], model membranes [39] as well as eukaryotic cells [40-45], and soluble proteins such as α1-antiprotease [46-48] and transferrin [49]. Taken together, the potency of the products generated by this system and the wide range of potential substrates provide an extraordinary range of possible means both to advance and to defuse the inflammatory response.

3. Myeloperoxidase Chemistry

Because the complex biochemistry of peroxidases in general and myeloperoxidase in particular has been the subject of extensive study and described in detail elsewhere [4-6,50-52], an overview here will summarize the reactions prerequisite to understanding the biological processes described later. In general, the overall reactivity of the MPO system reflects not only the structural determinants of the potential

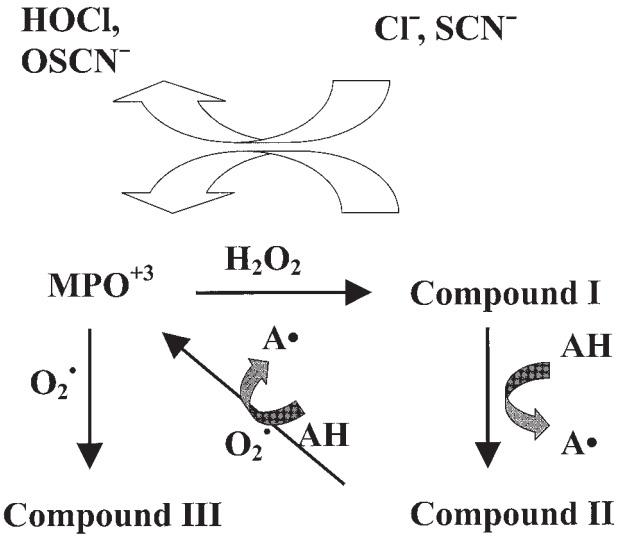

Figure 1. The peroxidase cycle of myeloperoxidase (MPO).

substrates but also local variables including pH, availability of intermediate substrates that may quench or amplify the potency of the system, and the concentration of available H_2O_2. Like all peroxidases, MPO oxidizes substrates by the classical peroxidase cycle, mediated by sequential single electron transfers by compound I and compound II [50] (Figure 1). The reaction of H_2O_2 with the ferric form of MPO yields the potent oxidant compound I that converts halides (except fluoride) and the pseudohalide thiocyanate to hypohalous acid at concentrations of H_2O_2 less than or equal to the concentration of MPO. This rapid reaction ($k = 5 \times 10^6$ $M^{-1}\cdot s^{-1}$ [53]) generates both HOCl and HOSCN in the extracellular space at physiologic concentrations of halides and thiocyanate [54]. In the presence of higher concentrations of H_2O_2, compound I is converted to the inactive compound II, which in turn can be reduced back to the active form of MPO by reaction with a variety of reducing agents, most notably superoxide anion [55]. Superoxide, the most proximal product of the phagocyte NADPH oxidase, likewise reacts with the ferric form of MPO ($k = 2 \times 10^6$ $M^{-1}\cdot s^{-1}$ [56]) to form compound III, a reaction of physiologic importance in the context of phagocytosis and HOCl generation [57].

For ease of presentation, 4 general enzymatic activities of MPO will be discussed: halogenation, tyrosyl radical generation, lipid peroxidation, and reactions involving nitric oxide. MPO is unique among animal peroxidases in its capacity to catalyze the 2-electron oxidation of chloride ion to generate OCl^- [5,50,58,59]. Although HOCl exists in equilibrium with OCl^- at pH 7.4, HOCl and Cl_2 predominate at the acidic pH within the phagosome [9,58]. Furthermore, these 3 products are potent oxidants that in some circumstances can directly oxidize lipoproteins [60-65], as well as generate additional reactive species. For example, when free tyrosines are the target, an unstable monochloramine is generated that undergoes decarboxylation to produce the amphipathic aldehyde, p-hydroxyphenylacetaldehyde (pHA) [66,67], the potential biological significance of which will be discussed later. The deamination and decarboxylation of chloramines can form other aldehydes that propagate additional cytotoxicity of susceptible targets [68]. On the other hand, tyrosine residues in proteins can be chlorinated to generate chlorotyrosine, a stable product that provides a reliable and specific marker for the presence of enzymatically active MPO [9,64].

MPO and H_2O_2 oxidize tyrosine residues to generate tyrosyl radicals [69,70] that can catalyze protein crosslinking [71] and lipid peroxidation [72]. In this way the MPO-dependent system can modify both protein and lipid targets not only by generating chlorhydrins and chlorinated sterols but also in the absence of halogenation reactions. Such modifications of lipoproteins have been linked in vitro to augmentation of the atherogenic potential [14].

In addition, recent studies have revealed an extraordinarily complex chemistry of interactions between MPO and N-centered biomolecules including nitric oxide and nitrite. Nitric oxide directly binds to the ferrous form of MPO [73], likely inhibiting its activity, but also regenerates the ferric form of MPO from compound III [74]. Stimulated PMNs can convert nitrite into the inflammatory oxidants NO_2Cl and $\cdot NO_2$ in an MPO-dependent fashion [75-77], providing a mechanism for conversion of tyrosine residues to 3-nitrotyrosine [78]. Posttranslational modification of proteins in this fashion can have striking functional consequences, as seen after nitrotyrosinolation of α-tubulin [79]. The generation of ·NO-derived oxidants is favored at low rates of ·NO generation [80], as might be anticipated if derived from endothelial cells, as would most likely be the case in humans. MPO-generated nitrating intermediates can mediate lipid peroxidation [81], providing another potential link between MPO-dependent biochemistry and atherogenesis. ·NO not only can serve as a substrate for MPO [82], independent of the presence or concentration of Cl^- [82], but also directly modulates its catalytic activity [83].

It is important to keep in mind that not all chemistry that is possible occurs in vivo. For example, there is ample evidence for multiple reactions in which nitrate and superoxide, in the presence of MPO, modify a wide range of substrates. Using a fluoresceinated particle to probe the intraphagosomal environs of activated PMNs, Hurst demonstrated that chlorination is the strongly favored reaction and found no evidence for nitration by reactive nitrogen intermediates within the phagosome [8,10]. In contrast, the MPO-H_2O_2 system supports both chlorination and nitration reactions in the extracellular space. Thus, conclusions implicating the participation of MPO-derived species in biological events should be supported by in vivo evidence of its contribution.

4. Role of MPO in Atherosclerosis

From the earlier discussion, it is clear that the MPO-H_2O_2-Cl^- and MPO-H_2O_2-NO_2^- systems each have the capacity to modify lipids. Not only does MPO bind to LDL [84] but the MPO-H_2O_2 system oxidizes LDL [85] and catalyzes the modification of its lysine residues by derivatization by pHA, a reactive aldehyde generated by HOCl-dependent oxidation of tyrosine [67]. This modification causes aggregation and conversion of LDL to a form avidly taken up by tissue macrophages [86,87]. In vitro, pHA-modified VLDL also

is rapidly ingested by cultured murine macrophages and internalized by a mechanism independent of the type A scavenger receptor [15]. The immunochemical and biochemical evidence for MPO-H_2O_2-halide–mediated modifications of lipoproteins in atheromata provides in vivo support for the proposed role of MPO in the initiation and/or propagation of atherosclerosis. Alternatively, the MPO-dependent generation of reactive nitrogen species can modify LDL into a more atherogenic form [14]. The MPO-H_2O_2-NO_2^- system nitrates both proteins and lipids in LDL [14] and macrophages ingest the NO_2-LDL via CD36, the type A scavenger receptor [62], although its participation in vivo remains unproven. Thus, using either Cl^- or NO_2^-, the MPO-H_2O_2 system can convert lipids to a more atherogenic form. The relative contribution of these alternative pathways to the conversion of lipoproteins into more atherogenic forms is not known but there is ample biochemical evidence for the presence of products of both in atheromata [61].

Unexpectedly, conclusive demonstration of a causal relationship between the presence of functional MPO in the subendothelial space and the generation of atheromatous changes may be relatively difficult to obtain. Two groups have independently created MPO-knockout mice in which the contribution of MPO-dependent events to various biological phenomena may be examined. Both animal models demonstrate increased susceptibility to infection with *Candida* [88-90], recapitulating the defect in host defenses that is seen in some humans with complete MPO deficiency. In vitro, activated neutrophils from wild-type mice oxidize LDL by a mechanism that is increased by the presence of tyrosine, whereas neutrophils from MPO-knockout mice oxidize LDL to a lesser extent, independent of added tyrosine [91]. To test the hypothesis that MPO contributes to the proinflammatory events in the initiation and/or propagation of atherosclerosis, Brennan et al [90] studied the consequences of hypercholesterolemia in a double-knockout mouse that lacked both MPO and the LDL receptor. The latter is a recognized murine model for human hypercholesterolemia [92] and atherosclerosis [93,94]. Unexpectedly the mice deficient in both MPO and the LDL receptor had more, rather than less, severe vascular disease, a finding that, at first blush, seems to disprove the hypothesis. More unsettling however was the absence of MPO in the atheromata from the LDL receptor–deficient mice that had normal levels of MPO. This finding undermines the validity of the model for human atherosclerosis, if one accepts the presence of MPO in vascular lesions as an integral feature of the disease. It would appear then that the best system in which to test the hypothesis that the MPO-H_2O_2 system contributes to atherogenesis might come from the study of the prevalence of atherosclerosis in large cohorts of MPO-deficient and healthy individuals. Alternatively, it may be feasible to obtain supportive evidence by correlating levels of functional MPO in circulating phagocytes with the risk for atherosclerosis, assuming that the allelic polymorphism in the MPO promoter [95] is reflected in quantitative differences in the amount of enzymatically active MPO produced (see below).

Despite the very compelling immunochemical evidence for the presence of MPO in atheromatous lesions and the colocalization of biochemical modifications specific for MPO-dependent changes, the origin of the MPO in the plaque remains unexplained. Neutrophils, the circulating blood cells with the bulk of MPO, are absent from atheromatous plaques, whereas monocytes and macrophages, expressing little and no MPO, respectively, predominate and later develop into foam cells [96]. It has been suggested [97] that the local cytokine environment within the atheromatous plaque might reinitiate transcription of the MPO gene, an activity normally restricted to the promyelocytic stage of myeloid development [98,99]. Support for this conjecture comes from a recent report that granulocyte-macrophage colony–stimulating factor (GM-CSF) may regulate MPO gene expression in advanced human atheroma, with evidence that GM-CSF selectively increases MPO expression and HOCl production by macrophages in vitro [100]. It is conceivable that the local combination of cytokines in other inflammatory diseases (see below) may also underlie the expression of enzymatically active MPO by cells not generally thought to retain that capacity.

5. Role for MPO in Other Clinical Disorders

There is substantial, albeit indirect, evidence for the participation of MPO in other disorders with inflammatory features. As mentioned earlier, there is an allelic polymorphism at nucleotide –463 in the MPO promoter, whereby –463G provides a binding site for the SP1 transcription factor but –463A creates a binding site for an estrogen receptor [95]. Accordingly, the –463G promoter is approximately 25-fold more active in transcription assays using a reporter gene [95] and is associated with greater MPO expression in myeloid leukemia cells [101]. In the general population, most individuals possess the GG genotype (61%); 33% have GA and only 6% have AA. In 2 independent studies, the prevalence of the AA genotype has been associated with a decreased lung cancer risk among Caucasians [102,103], although in 1 study the 72% protective effect was sex specific and limited to men [102]. Given evidence that MPO mediates the biotransformation of intermediate products of tobacco smoke into more potently carcinogenic species [104,105], one would predict that less MPO activity, the result of lower transcription rates in the AA genotype, would result in less carcinogenic reactants generated. Subsequent studies to examine the amount of MPO correlating with the specific genotypes should directly test this hypothesis, as well as possibly explain the basis for the sex differences seen.

It is noteworthy that the sex differences in genotypic linkage of the MPO allelic polymorphism are seen in several study populations. For example, the GG genotype is disproportionately represented among female patients with early onset multiple sclerosis (86%) [18]. Immunochemical detection of MPO in macrophages in the central nervous system lesions of patients with MS supports the implications of the genotypic linkage, suggesting that the local neurotoxicity seen in MS may reflect the consequences of excessive MPO–generated reactive species. In addition, a disproportionate number of women with Alzheimer's disease have the GG genotype (77%), again implicating a role for MPO in the risk for or severity of an inflammatory disease in the central nervous system [19]. However, in a genetically homogeneous

population in Finland [106] there was no difference in the distribution of any MPO genotype among women with Alzheimer's disease, although there was a statistical association of the coexistence of the MPO-A allele and the APOEε4 genotype with Alzheimer's among men. The mechanism(s) of the apparent synergy between the products of the MPO and APOE genes and the basis for the sex differences within this study and with findings from other studies are important unknowns awaiting more rigorous testing.

As with the studies of atherosclerosis, it is uncertain whether murine models will elucidate or further obfuscate some of these issues. Experimental autoimmune encephalomyelitis, an animal model for multiple sclerosis, is characterized histologically by extensive perivascular inflammation with infiltrating macrophages expressing MPO [107]. In MPO-knockout mice, the histological extent of inflammation and demyelination is the same as that seen in the experimental animals with normal levels of MPO. However, the appearance of complete hind limb paralysis, a phenotypic manifestation of extensive demyelination, was more common in the knockout mice [107], suggesting that the absence of MPO increased susceptibility to experimental autoimmune encephalomyelitis. This finding is directly opposite to that predicted if the proinflammatory activity of MPO significantly contributed to the development of demyelination. As with the study of atherosclerosis in the MPO-knockout mice [90], alternative animal systems that better mirror the activities of human phagocytes may be needed to unravel the contribution of MPO to demyelinating diseases.

6. Future Directions

No longer can the function of MPO be categorized only as a component of O_2-dependent antimicrobial defenses. The broad diversity of reactive products generated by the MPO-H_2O_2 system in the presence of Cl^- or NO_2^- and the implication of these products in a wide variety of clinical disorders provide an exciting challenge to those investigators wishing to tease apart the relative contributions of each component to the pathogenesis of a given disease. Furthermore, the identification of MPO protein or activity in tissues or cells not previously thought to possess MPO prompts reconsideration of the regulation of MPO gene transcription. Whether in the central nervous system or in the subendothelial space, local cytokine production may promote MPO production in cells not normally recognized for MPO synthesis. The form of the gene product, whether mature dimeric MPO, as found in neutrophil azurophilic granules, or enzymatically active, monomeric proMPO, as constitutively secreted by cultured promyelocytes [108], is unknown, as are the functional implications of the specific structural form made under different conditions.

In specialized niches, other members of the animal peroxidase protein family may be structurally modified to combine other biologically important functions with peroxidase activity. For example, peroxinectin, a homologue of MPO that participates in innate host defense in crayfish, is both an adhesive protein and active peroxidase [109,110]. Limited experimental evidence suggests a potential role for MPO in cell adhesion [111] but one can easily imagine important

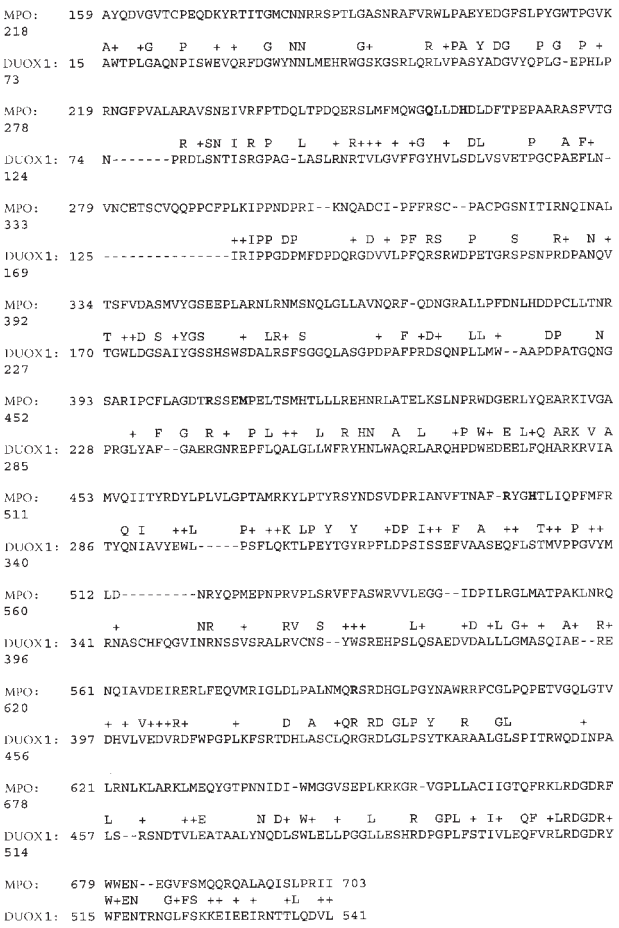

Figure 2. Comparison of amino acid sequences of myeloperoxidase (MPO) and dual oxidase 1 (DUOX 1).

functional consequences of enzymatically active MPO being secreted into the subendothelial space and remaining immobilized there by direct interaction with elements of the extracellular matrix. As the breadth of the myeloperoxidase family of proteins becomes better defined [112], the inclusion of members that are a mosaic for the peroxidase domain with additional functional motifs will expand our understanding of the biological activities possible in specialized settings.

Recent work on gp91*phox*, the heavy subunit of the heterodimeric flavocytochrome b_{558} essential for a functional phagocyte NADPH oxidase [113], has revealed the existence of several eukaryotic homologues [114]. Among these are relatively large proteins that include a C-terminal region that is homologous with gp91*phox* and an N-terminus that is homologous with animal peroxidases, including MPO [115]. Although human MPO and the human dual oxidase 1 (Genbank accession # XP 007654.1) share 26% identity at the amino acid level, several residues essential for MPO function are replaced in dual oxidase 1 (Figure 2). Several lines of evidence [9,116-119] implicate 5 residues in MPO in heme binding. (N.B. Because consideration here includes the propeptide of MPO, there are 166 more amino acid designations used [120] [for the 166 amino acids in the propeptide] than are used by Fenna [121,122].) Histidines at residues 261 and

502 represent the distal and proximal ligands to the heme iron, respectively, and heme is covalently bound to MPO through a methionyl sulfonium linkage with M409 and through ester linkages to E408 and D260 [116,122]. Although crystal structures of LPO and EPO have not yet been solved, models based on domain organization homologous with that of MPO [123,124] indicate that they have identical coordinating residues in the heme-binding pocket with 1 critical exception. Only MPO possesses the sulfonium linkage (M409) to the heme, a structural feature possibly underlying both its unique spectral properties and its relative facility in oxidizing Cl^- to form HOCl. In the case of dual oxidase 1, the proximal and distal ligands for the heme iron in MPO are replaced with serine residues and a glutamic acid is substituted for M409 (Figure 2). Within 7 Å of the heme iron are several residues (R405, R499, R590, and Q257) that form ionic interactions with the heme and are conserved among all members of the family of animal peroxidases. Although Q257 is replaced with tyrosine, the remaining residues are identical (R405, R590) or involve conservative substitution (Q) in dual oxidase 1. Additional data will be needed to clarify the functional consequences of this structural homology, although the relationship may already provide potentially important implications regarding the evolution of oxidase and peroxidase protein families.

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