Myeloperoxidase, modified lipoproteins, and atherogenesis

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Abstract Numerous lines of evidence implicate a role for myeloperoxidase (MPO) in the pathogenesis of atherosclerosis. Enriched within vulnerable plaque, MPO serves as an enzymatic source of eicosanoids and bioactive lipids and generates atherogenic forms of both low- and high-density lipoproteins. These factors likely contribute to clinical studies demonstrating that increased systemic levels of MPO and its oxidation products predict increased cardiovascular risk. As a result, interest has focused on the potential to target MPO for the development of new risk markers, imaging, and therapies to prevent cardiovascular events.—Nicholls, S. J., and S. L. Hazen. Myeloperoxidase, modified lipoproteins, and atherogenesis. J. Lipid Res. 2009. 50: S346–S351.

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It has become increasingly established that inflammatory events contribute to all stages of atherosclerosis. However, the role of specific inflammatory mediators in the orchestration of these events remains to be defined. Accumulating evidence that myeloperoxidase (MPO) has effects on a range of factors that influence the arterial wall suggests that it plays a pivotal role in the natural history of atherosclerotic cardiovascular disease (CVD).

PHYSIOLOGIC ACTIVITY OF MPO AND ITS ROLE IN THE INNATE IMMUNE RESPONSE

MPO is a member of the mammalian heme peroxidase superfamily and is stored within the azurophilic granules of leukocytes (1). MPO is found within circulating neutrophils, monocytes, and some tissue macrophage populations (2). The catalytic activity of MPO results in the generation of various reactive oxidants and diffusible radical species (1). These products play an important role in killing invading parasites and pathogens. MPO-deficient humans and animals demonstrate heightened susceptibility to fungal and yeast infections (3). However, the ability of MPO-derived reactive oxidants to promote host tissue injury through lipid peroxidation (4) and posttranslational protein modifications (5) has resulted in MPO being thought as participating in a wide range of chronic inflammatory diseases (4–7).

During leukocyte activation, MPO amplifies the oxidative potential of the respiratory burst by using hydrogen peroxide as a cosubstrate to form more reactive oxidant species. This can result in the generation of a number of potent oxidant compounds capable of promoting oxidative modification of host tissues (8–12). Production of reactive chlorinating species, such as hypochlorous acid, is an activity specific to the MPO pathway (8). The antimicrobial activities of these products provide the rationale for the role of MPO in the innate immune response to foreign invasion (13). Generation of oxidized bioactive lipids provides additional mechanisms linking MPO and inflammatory pathways (4). Indeed, studies employing mice with functional deficiency in MPO reveal that the enzyme plays an important role in the formation of arachidonic acid oxidation products involved in the promotion of inflammatory cascades (4). While this provides evidence that MPO and its products are important homeostatic factors, evidence suggests that excessive activity of MPO can play a role in inflammatory tissue injury.

ROLE OF MPO IN THE GENERATION OF ATEROGENIC LDL SPECIES

MPO has emerged as one enzymatic catalyst for LDL oxidation in vivo via several chemical processes (Fig. 1) and conversion into more atherogenic forms within the artery wall. Enrichment of LDL with markers of chlorination, such as 3-chlorotyrosine, served to identify MPO as the first enzymatic catalyst of a specific oxidative pathway operative within human atherosclerotic plaque and modifying LDL.
in vivo (9). Subsequent studies have expanded the repertoire of oxidant generating pathways catalyzed by MPO in the artery wall, including formation of nitric-oxide-derived oxidants and consequent nitrated LDL (14). Exposure of LDL to activated monocytes via MPO-generated reactive nitrogen species facilitates lipid peroxidation and protein nitration and converts LDL into a high uptake form (14) that is avidly taken up by macrophages via the macrophage scavenger receptor CD36 (15). The physiologic nature of this pathway for initiating lipid peroxidation is supported by studies employing MPO-knockout mice, demonstrating reduction in lipid peroxidation products following leukocyte activation at sites of inflammation (4, 11) and the observation that neutrophils isolated from individuals with MPO deficiency do not initiate lipid peroxidation when activated ex vivo in plasma but regain this ability with exogenous addition of only catalytic levels of MPO (6).

More recently, MPO has been identified as an enzymatic catalyst for promoting protein and lipoprotein carbamyla-

Fig. 1. Role of MPO-catalyzed pathways in the generation of atherogenic LDL and dysfunctional HDL particles. MPO-generated products promote lipid peroxidation, conversion of LDL to a high-uptake form, and impairment of the ability of apoA-I to promote cholesterol efflux. MPO-catalyzed carbamylation has recently been reported also to be involved in generation of high-uptake forms of LDL and impaired functional activities of HDL.

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ROLE OF MPO IN THE GENERATION OF DYSFUNCTIONAL HDL PARTICLES

Increasing interest has focused on the relative functionality of HDL in different subjects. This is highlighted by observations that cardiovascular events can occur even in the presence of high levels of HDL cholesterol, and upon isolation, HDL from subjects with CVD can show proinflammatory activities. The recent failure of HDL-raising agents has fueled speculation that novel therapies need to be evaluated to ensure they do not have an adverse effect on HDL functionality. While early studies suggested that in vitro oxidative modification of HDL particles can serve as one global mechanism for impairment in HDL functional properties, the potential pathways resulting in the generation of dysfunctional HDL particles in vivo remain to be elucidated. Recent observations suggest a potential role for an altered “HDL-associated proteome” and MPO-catalyzed site-specific modification of apolipoprotein A-I (apoA-I) as mechanisms resulting in functional impairment.

HDL isolated from plaque contains MPO and its oxidant products (17, 18), consistent with the observation that MPO binds to a specific region of helix 8 of apoA-I (17). ApoA-I isolated from plasma of subjects with coronary heart disease contains greater amounts of nitrotyrosine and chlorotyrosine than healthy controls (17, 19, 20). In a study of outpatient cardiology subjects, individuals with highest tertile levels of apoA-I nitrotyrosine and chlorotyrosine demonstrated a 6- and 16-fold greater likelihood of having CVD compared with subjects possessing lowest tertile levels of oxidized apoA-I (17). The finding that apoA-I enrichment in chlorotyrosine was 500-fold greater than other proteins in lesions and similarly enriched within apoA-I in plasma supports the concept that oxidative modification occurs preferentially on apoA-I in the artery wall (17). This is consistent with colocalization of apoA-I with MPO-catalyzed modification of apoA-I and carbamyllysine in plaque (21, 22). The finding that the degree of apoA-I modification correlates with impairment of HDL to promote ABCA1-dependent cholesterol efflux led to the search for a mechanism to promote ABCA1-dependent cholesterol efflux (Fig. 1) (17, 19, 20).

Mass spectrometry has identified specific sites on apoA-I as preferred targets for MPO-derived oxidative modification (17). In vitro studies demonstrate that oxidation occurs preferentially at residues on helix 8 (Tyr-192) in close spatial proximity with where MPO is mapped to bind apoA-I of HDL (17). Subsequent studies have revealed that MPO-induced modification of apoA-I has a detrimental impact on additional aspects of the reverse cholesterol transport pathway. For example, apoA-I Tyr-166, an abundant site-specific modification on apoA-I recovered from human atherosclerotic lesions via both nitrating and chlorinating pathways, has been shown to be an essential component of an apoA-I LCAT binding loop located on nascent HDL (23). MPO-catalyzed oxidation of a single methionine of apoA-I near the LCAT activation region (Met-148) is also reported to result in functional impairment of LCAT activity. MPO-catalyzed modifications to apoA-I that inhibit LCAT binding and activity are likely to interfere with reverse cholesterol transport. Recent studies by Podrez report that HDL exposed to the MPO-H$_2$O$_2$-Cl$^-$ system competes with native HDL as a ligand for the scavenger receptor BI, potentially interfering further with mobilization of cholesterol from peripheral tissues to the liver. Further studies are warranted on MPO-catalyzed oxidation of HDL and the effects on plaque development.

While there is consensus in the field that MPO catalyzes oxidative modification of apoA-I and impairs its function, the precise modifications that result in impairment in different HDL functions requires further study. Structural studies have provided further insights to understand structure-function relationships of HDL and site-specific changes involved during oxidative modification of apoA-I. A refined structural model of HDL was recently generated by application of hydrogen-deuterium exchange mass spectrometry, a method for quantifying solvent accessibility through amide proton exchange throughout the polypeptide chain of apoA-I of nascent HDL (23). The so-called “solar flare model” found two apoA-I molecules arranged in an anti-parallel double belt structure with protruding solvent-exposed loops corresponding to amino acid residues 159 to 170, a region shown to be involved in LCAT docking and activation (23). This docking loop also contains one of the preferred targets for MPO oxidation observed in apoA-I recovered from human plaque, Tyr-166 (23). Recent studies suggest that tyrosine modification is not required for MPO-induced loss of ABCA1-dependent cholesterol efflux activity since apoA-I mutants lacking all tyrosine are susceptible to oxidative inactivation by MPO (24). However, mutation of Tyr-166 to Phe was shown to result in loss of the majority of LCAT activity (23). Investigation of the residues involved in oxidative inactivation of apoA-I-mediated ABCA1-dependent efflux activity has similarly recently been investigated. Proteomic analyses have identified all four tryptophan residues within apoA-I as targets for oxidation. Site-directed mutagenesis to substitute all four tryptophan residues to leucine resulted in a HDL particle lacking efflux activity; however, substitution of each of the four tryptophan residues to phenylalanine generated an apoA-I and HDL particle that showed normal cholesterol efflux and LCAT activities under native conditions and that was markedly resistant to oxidative inactivation, suggesting that tryptophan modification is an essential factor involved in loss of ABCA1-mediated efflux activity of HDL (25). Paradoxically, other investigators report no effect on efflux activity with tryptophan mutation and instead invoke a key role for tryptophan and methionine in oxidative inactivation, despite reports that apoA-I lacking all tryptophan or methionine retain complete efflux and LCAT activities and sensitivities to oxidative inactivation (25). Recent studies show that MPO-catalyzed carbamylation may also play an important role in atherosclerosis via mod-
iffication of HDL. Low levels of MPO-catalyzed carbamyla-
tion of HDL ablates its nonlipid transporting influence on
endothelial cell apoptosis and smooth muscle cell prolif-
eration (16). Given that MPO adversely influences LDL
atherogeneity and HDL functionality, it is possible that in-
hibiting MPO activity may provide a therapeutic approach
to management of both LDL and HDL. The finding that the
statins partially reduce MPO expression (26) and reduce
systemic levels of protein modification by MPO-catalyzed
pathways (27) suggests that perhaps some of the so-called
pleiotropic benefit of statins may be due in part to influ-
ence on MPO levels and activity.

**ANIMAL OBSERVATIONS OF MPO
AND ATHEROSCLEROSIS**

Investigation of the impact of MPO on lesion formation in
animal models of atherosclerosis has produced variable
results. Murine models have demonstrated the in vivo role
of MPO and its products in acute inflammation, lipid per-
oxidation, endothelial dysfunction, and adverse ventricu-
lar remodeling following myocardial infarction (4, 11, 28,
29). However, early studies found that genetic deletion of
MPO had no impact on lesion formation in apolipoprotein
E knockout mice (30), and infusion of bone marrow from
MPO-knockout mice into irradiated LDL receptor knock-
out mice demonstrated an unexpected modest increase in
lesion size (30). The subsequent observations that mouse
apoprotein lesions contained virtually no traces of MPO and its
products, in contrast with observations within human ather-
oma, coupled with the observations that murine leukocytes
contain 10- to 20-fold less MPO per cell than found in hu-
mans, indicates that many substantial species differences
exist (30, 31). Several groups have consequently sought to
generate “humanized” MPO/atherosclerosis models. Re-
cent reports from multiple groups with distinct mouse
strains have shown that human MPO transgenic mice have
accelerated atherosclerotic plaque development (16, 32,
33). As a result, there remains hope that humanized animal
models of atherosclerosis, such as those overexpressing the
human MPO transgene, may be of some use in evaluating
the impact of experimental MPO inhibitors on atheroscle-
rosis models where MPO is present and catalytically active.

**HUMAN STUDIES OF MPO AND CVD**

The past 5 years have witnessed dramatic growth in the
number of human clinical investigations exploring the role
of MPO in atherosclerosis. Early studies localized MPO
and its products as being enriched within human ather-
sclerotic plaques (2, 9, 34–36). Furthermore, individuals
with total or subtotal MPO deficiency (3) or loss-of-function
polymorphisms have more recently been associated with
protection from coronary heart disease. As illustrated be-
low, many studies now demonstrate associations between
increasing systemic MPO levels and risks of CVD through-
out the full spectrum of cardiovascular risk.

In a recent nested case-control analysis of >25,000 ap-
parently healthy middle-aged individuals (EPIC/Norfolk
study), the prospective risk of developing symptomatic cor-
onary heart disease over the ensuing 6-year period was
shown to increase in parallel with baseline MPO levels
(37). In patients with stable coronary artery disease symp-
toms, MPO levels have been shown to predict the preva-
lence and extent of coronary artery disease and future risk
of cardiovascular events. Case-control studies report the
relationship between increasing MPO levels and the preva-
lence and extent of obstructive disease on coronary angiog-
raphy (38, 39), consistent with the initial observations by
Zhang et al. (40), who observed correlations between the
content of MPO per leukocyte and angiographic evidence
of coronary stenosis >50%.

Multiple studies now link systemic MPO levels and ad-
verse cardiovascular outcomes in patients investigated in
the setting of acute ischemic syndromes. For example, in
a study of >600 patients presenting to the emergency
room for evaluation of acute chest pain, MPO plasma lev-
els were found to independently predict cardiovascular risk,
regardless of evidence of myocardial necrosis (41). Addi-
tional reports of associations between MPO levels and in-
cident adverse cardiovascular risks in patients with acute
coronary syndromes were observed from clinical trials of
antiplatelet therapies. These findings were even observed
in subjects with low systemic levels of markers of myocar-
dial necrosis or inflammation (42) and were found to have
the highest sensitivity to predict risk of recurrent ischemic
events when compared with a panel of current cardiovascu-
lar biomarkers (43). This relationship has also been demon-
strated in patients presenting with myocardial infarction,
regardless of levels of clinical risk (44, 45).

The past few years have also witnessed the extension of
the diagnostic and prognostic role of MPO to the setting of
stable, chronic heart failure (46). MPO levels predicted
functional class and adverse outcomes, regardless of brain
natriuretic protein levels and degree of systolic dysfunction
(46). In a community-based screen of apparently healthy
middle-aged subjects, MPO levels demonstrated the greatest
sensitivity for identifying subjects with occult left ventricular
dysfunction (47). The relationship between MPO and sys-
tolic heart failure is further supported by the observation
of increasing activation of polymorphonuclear leukocytes
in patients with impaired left ventricular systolic function
(48) and the role of MPO in impaired ventricular remodeling
in murine models of both chronic coronary artery liga-
tion and ischemia-reperfusion (29, 49).

**SUMMARY**

A large body of evidence demonstrates that MPO and its
reactive oxidant species play a role in the promotion of path-
ological events involved in all stages of atherosclerotic CVD.
More recent observations of associations between systemic
MPO levels and cardiovascular risks in humans suggest that
MPO testing may play a role in clinical risk prediction. New
developments with MPO functional imaging may permit
imaging of vulnerable plaque and myocardial injury (50). MPO represents a potential target for the development of new therapeutic agents to prevent or retard development of CVD.

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