Myeloperoxidase and Cardiovascular Disease

Stephen J. Nicholls, Stanley L. Hazen

Abstract—Myeloperoxidase (MPO) is a leukocyte-derived enzyme that catalyzes the formation of a number of reactive oxidant species. In addition to being an integral component of the innate immune response, evidence has emerged that MPO-derived oxidants contribute to tissue damage during inflammation. MPO-catalyzed reactions have been attributed to potentially proatherogenic biological activities throughout the evolution of cardiovascular disease, including during initiation, propagation, and acute complication phases of the atherosclerotic process. As a result, MPO and its downstream inflammatory pathways represent attractive targets for both prognostication and therapeutic intervention in the prophylaxis of atherosclerotic cardiovascular disease. (Arterioscler Thromb Vasc Biol. 2005;25:1102-1111.)

Key Words: atherosclerosis • free radical • heart failure • high-density lipoprotein • low-density lipoprotein • myeloperoxidase • nitric oxide • scavenger receptor • vulnerable plaque

Inflammatory events have been implicated at all stages in the evolution of atherosclerotic plaque, from the early development of endothelial dysfunction, through to formation of the mature atheroma and its subsequent rupture. Elucidation of the factors that coordinate this complex cascade has assumed increasing importance in the search to identify accurate predictors of cardiovascular risk and targets for therapeutic intervention.

Myeloperoxidase (MPO) has emerged as a potential participant in the promotion and/or propagation of atherosclerosis. A member of the heme peroxidase superfamily, MPO generates numerous reactive oxidants and diffusible radical species that are capable of both initiating lipid peroxidation and promoting an array of post-translational modifications to target proteins, including halogenation, nitration, and oxidative cross-linking. MPO, the most abundant component of azurophilic granules of leukocytes, is secreted on leukocyte activation, contributing to innate host defenses. Found predominantly in neutrophils, monocytes, and some subtypes of tissue macrophages, MPO amplifies the oxidative potential of its cosubstrate hydrogen peroxide, forming potent oxidants capable of chlorinating and nitrating phenolic compounds. The hydrogen peroxide substrate may be derived from a number of sources in vivo, including leukocyte NADPH oxidases, xanthine oxidase, uncoupled nitric oxide synthase (NOS), and various Nox isoenzymes. MPO is unique in its ability to generate reactive chlorinating species such as hypochlorous acid (HOCl), the active component of bleach, which possesses potent bactericidal and viricidal activities. In addition, HOCl reacts with electron-rich moieties of a large range of biomolecules.

The essential role of MPO as a component of the innate immune response to foreign invasion was first recognized nearly 4 decades ago. The past decade has witnessed a resurgence in research efforts focusing on this unique heme protein. Spurred initially by the recognition that MPO is enriched within human atheroma, both MPO and its reactive oxidants have been implicated as participants in tissue injury...
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Myeloperoxidase (MPO) has been implicated in atherosclerotic disease process. MPO is a heme-containing enzyme that catalyzes the production of hypochlorous acid (HOCl) from hydrogen peroxide (H₂O₂) and chloride ions (Cl⁻). This reaction is catalyzed by the Fenton reaction, which is initiated by the enzymatic oxidation of heme by oxygen to ferrihemin. The HOCl generated is then oxidized by oxygen to form hypochlorite (OCl⁻). These reactive oxygen species (ROS) can interact with lipids, proteins, and DNA, leading to oxidative stress and cell damage. MPO is expressed by neutrophils, monocytes, macrophages, and some endothelial cells, and its expression is upregulated in response to inflammation and oxidative stress.

In cardiovascular disease (CVD), MPO plays a role in atherogenesis, the initiation, progression, and stabilization of atherosclerotic plaques. MPO expression is increased in the atherosclerotic lesions of patients with CVD, and MPO activity is associated with the severity of atherosclerotic lesions. MPO may contribute to the formation of advanced plaques, which are more prone to rupture and lead to acute cardiovascular events. MPO-mediated oxidation of low-density lipoprotein (LDL) can promote the formation of modified LDL, which is more atherogenic.

Potential Mechanisms for Myeloperoxidase

Myeloperoxidase Converts LDL Into an Atherogenic Form

Population studies have consistently demonstrated that the incidence of CVD correlates directly with circulating concentrations of LDL. Similarly, therapeutic interventions that reduce systemic levels of LDL are associated with a marked atheroprotective benefit. Although reduction in MPO expression appears cardioprotected, with markedly reduced angiographic evidence of coronary artery disease, nonfatal myocardial infarction, and cardiac death. Increasing systemic levels of MPO have also been demonstrated to predict the presence of angiographic coronary artery disease. Individuals who possess MPO levels in the highest quartile among sequential subjects undergoing diagnostic cardiac catheterization at a tertiary referral center were 15- to 20-fold more likely to demonstrate abnormal coronary angiograms (defined as >50% stenosis in one or more major coronary arteries) compared with subjects in the lowest quartile. This relationship remained significant after statistical adjustments for Framingham risk score and C-reactive protein. In addition, plasma and serum levels of MPO have been shown to predict risks of subsequent major adverse cardiac events (nonfatal myocardial infarction, death, and need for revascularization) in patients presenting with either chest pain or acute coronary syndromes. Thus, numerous biochemical and genetic studies in humans demonstrate strong and independent relationships between MPO and CVD risks.

Potential Mechanisms for Myeloperoxidase

Contributing to the Promotion of Vascular Disease

A role for MPO throughout the evolution of the atherosclerotic process has been supported by numerous investigations. As described herein, mechanistic links exist between MPO and the generation of atherogenic lipoproteins, consumption of nitric oxide (NO) and development of endothelial dysfunction, initiation and propagation of the mature atheroma and its subsequent complications of plaque rupture, thrombosis, and ventricular remodeling.

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A role for MPO is also evident in the setting of acute myocardial infarction, as discussed. MPO is a key player in the inflammatory response to ischemia-reperfusion injury. MPO-mediated oxidation of LDL and other lipids is involved in the formation of atherosclerotic plaques. Moreover, MPO can promote the activation of macrophages and the production of proinflammatory cytokines, which can contribute to the progression of atherosclerosis.

Myeloperoxidase as a Therapeutic Target

The therapeutic potential of targeting MPO in the prevention and treatment of atherosclerosis is an area of active research. Anti-MPO antibodies have been shown to reduce atherosclerotic lesion size in animal models. Moreover, inhibition of MPO activity by pharmacological agents has been associated with reduced atherosclerosis in animal models. Despite these promising results, further research is needed to fully understand the role of MPO in atherogenesis and to develop effective therapeutic strategies.
its derived oxidants in the conversion of LDL into an atherogenic form within human atheroma. Mass spectrometry and immunohistochemical studies demonstrate that MPO is catalytically active within human atheroma because chlorotyrosine, a specific product of protein modification by MPO-generated halogenating oxidants, is enriched within human atherosclerotic lesions compared to normal arterial intima. More recent studies demonstrate marked enrichment of bioactive chlorinated lipid oxidation products within human atheroma as well. Additionally, alternative oxidation products which may be generated by MPO, as well as other pathways, such as nitrotyrosine (a post-translational modification generated by reactive nitrogen species) and dityrosine (an oxidative crosslink formed by tyrosyl radical–mediated pathways), are similarly enriched within human atheroma. In addition, LDL isolated from human atheroma contains greater amounts of these products than circulating LDL from healthy controls. Thus, multiple lines of evidence confirm a role for MPO as a catalyst for oxidant generation within the artery wall in CVD subjects.

Multiple lines of evidence suggest that proatherogenic biological consequences may be triggered by oxidative modification of targets in the artery wall by MPO-generated reactive species. Lipid oxidation products of plasmalogens generated by the MPO-derived oxidant HOCl are both enriched within human atheroma and possess potent leukocyte chemotactic activity. Incubation of HOCl and LDL results in oxidation of lysine residues in apolipoprotein B-100, the predominant protein of LDL. Increasing anionic surface charge, as well as HOCl-induced lipoprotein aggregation, both convert LDL into a high-uptake form, and appear to occur within human atheroma. Under physiological conditions, activated human monocytes also use MPO-generated reactive nitrogen species to render LDL atherogenic, converting it into a high-uptake form for macrophages, while simultaneously promoting both apolipoprotein B-100 protein nitration and initiation of LDL lipid peroxidation (Figure 2). The oxidized form of LDL generated, termed “NO2-LDL,” has since been demonstrated to be selectively recognized by the scavenger receptor CD36, a major participant in fatty streak and atherosclerotic lesion development. Detailed subsequent studies using biochemical, mass spectrometry and chemical synthesis have identified a novel family of oxidized phospholipids that serve as high affinity ligands for the macrophage scavenger receptor CD36 on both NO2-LDL and other forms of oxidized LDL, as well as documented their enrichment within atherosclerotic lesions (Figure 2).

A central role for MPO as a physiological catalyst for initiation of lipid peroxidation in vivo has been established using neutrophils isolated from humans with MPO deficiency versus normal subjects and subsequently activated within plasma. Studies with MPO knockout mice also confirm a dominant role for MPO in the initiation of lipid peroxidation at sites of acute
ligands for CD36 on oxidized forms of LDL, including NO2LDL. Tethered glycerophospholipids have been identified as high-affinity sources of these lipid hydroperoxides, however, is unknown. In vitro studies of HDL oxidation have been reported to have either neutral,67 or detrimental68–72 impact on the atheroprotective properties of the lipoprotein particle, and the precise oxidative pathways that modify HDL within the diseased artery wall. Recent evidence has emerged to identify HDL as a target for site-specific modification by MPO-derived oxidants in the artery wall with concomitant functional impairment.73 As a role for MPO in the oxidative modification of HDL in vivo, Myeloperoxidase and Vascular Disease

Figure 2. MPO-generated reactive nitrogen species render LDL atherogenic. Human monocytes use the MPO-H2O2-nitrite (NO2−) system to form nitrogen dioxide (NO2), an NO-derived oxidant, which promotes protein nitration, lipid peroxidation, and conversion of LDL into a high-uptake form of oxidized LDL (oxLDL), NO2LDL, for the scavenger receptor CD36. CD36 plays a critical role in formation of foam cells, fatty streaks, and atherosclerotic plaque in vivo. A novel family of α,β unsaturated γ-hydroxy (or oxo)-sn-2 tethered glycerophospholipids have been identified as high-affinity ligands for CD36 on oxidized forms of LDL, including NO2LDL. Adapted from references 4 and 57 to 60. Reprinted with permission from J Biol Chem, October 11, 2002.

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Myeloperoxidase Selectively Modifies Apolipoprotein A-I, Generating Dysfunctional High-Density Lipoprotein

High-density lipoprotein (HDL) particles are the major carriers of lipid hydroperoxides in circulating plasma.64 The enzymatic source of these lipid hydroperoxides, however, is unknown. In vitro studies of HDL oxidation have been reported to have either a beneficial,65,66 neutral,67 or detrimental68–72 impact on the ability of HDL to promote cellular cholesterol efflux. However, it remained to be determined whether physiologically relevant oxidative modifications of HDL influence the atheroprotective properties of the lipoprotein particle, and the precise oxidative pathways that modify HDL within the diseased artery wall. Recent evidence has emerged to identify HDL as a target for site-specific modification by MPO-derived oxidants in the artery wall with concomitant functional impairment.

A role for MPO in the oxidative modification of HDL in vivo, with consequent functional inactivation, has been supported by results from several groups. HDL isolated from atherosclerotic lesions contain numerous MPO-derived peptides, including site-specific oxidative modifications by reactive chlorinating and nitrating species.73,74 Moreover, HDL isolated from human atheroma contains MPO, consistent with the recent finding that MPO selectively binds to apolipoprotein A-I within plasma via a specific region on helix 8 of the lipoprotein.73 Analysis of apolipoprotein A-I isolated from plasma of subjects with CVD versus that from healthy controls reveals that a greater content of nitrotyrosine (NO2Tyr) and chlorotyrosine (ClTyr) per apolipoprotein A-I particle are observed within subjects with CVD.73,75 The degree of this modification was found to correlate with the frequency of coronary artery disease and CVD,73 findings that have now been independently confirmed.75,76 Examination of nearly 100 sequential subjects to an outpatient preventive cardiology clinic revealed that patients harboring the highest tertile of apolipoprotein A-I NO2Tyr and ClTyr content were 6- and 16-fold more likely to have CVD than those in the respective lowest tertile.73 Moreover, apolipoprotein A-I isolated from atherosclerotic plaque demonstrates a much greater degree of modification (by several orders of magnitude) than a typical protein within plasma or atherosclerotic plaque, with up to 1 of every 2 HDL particles recovered from human atherosclerotic lesions bearing a ClTyr or NO2Tyr modification in some subjects.73 These results suggest that MPO-catalyzed oxidation of apolipoprotein A-I preferentially occurs in the arterial wall. Consistent with this finding, immunohistochemical analysis of human atheroma specimens reveals MPO- and HOCl-modified proteins colocalize with apolipoprotein A-I in the region of macrophages.67,77

Using tandem mass spectrometric techniques, specific sites on apolipoprotein A-I have been identified as the preferred targets for modification by MPO-derived oxidants, with associated functional impairment of the lipoprotein.74 Residues on helix 8 (eg, Tyr 192) appear to be the predominant site of MPO-catalyzed oxidation in vitro and within human atheroma and colocalize with the MPO-binding site identified on apolipoprotein A-I within HDL.73,74 Remarkably, the degree of site-specific modification of apolipoprotein A-I and enrichment of apolipoprotein A-I with NO2Tyr and ClTyr are each associated with a reduction in the ability of apolipoprotein A-I to promote ABCA-1–dependent cholesterol efflux in vitro and in vivo (Figure 3).73,74 Findings which have been independently confirmed.75 In vitro studies also demonstrate

Figure 3. MPO-catalyzed site-specific apolipoprotein A-I chlorination and the impairment of ABCA-1–mediated reverse cholesterol transport activity. Exposure of HDL to either the MPO/H2O2/Cl− system or HOCl results in dose-dependent loss of ABCA-1–dependent reverse cholesterol efflux activity of HDL (A). Parallel site-specific quantitation of apolipoprotein A-I chlorination using LC/ESI/MS/MS reveals comparable dose-dependent losses of the MPO-binding peptides (B). Mass spectrometry studies demonstrate the same sites are modified in apolipoprotein A-I recovered from human plaque. Reprinted with permission from Zheng et al.74

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that HDL exposed to the MPO-generated oxidant HOCl competes with unmodified HDL as a ligand for the scavenger receptor BI, suggesting that MPO-generated oxidants may interfere with the normal interaction of apolipoprotein A-I with scavenger receptor BI, a key step in the promotion of cholesterol efflux.82

A major determinant of plaque progression or regression rate is the balance between cholesterol uptake versus efflux pathways. These results suggest that MPO may adversely impact on both processes, fostering the net deposition and accumulation of cholesterol within cells of the artery wall. The correlation between MPO levels and angiographic evidence of atherosclerotic plaque,31 as well as the apparent atheroprotective effects of genetic deficiencies of MPO,26–30 are consistent with the hypothesis that MPO participates in the initiation and/or propagation of CVD (Figure 1). Studies directly assessing systemic levels of MPO in parallel to quantitative indices of human atherosclerotic plaque volume will be both informative and of potential prognostic relevance.

**Myeloperoxidase Promotes Endothelial Dysfunction**

Dysfunction of the endothelial cell layer is one of the earliest changes of atherogenesis.1 This state is characterized by the development of abnormal vascular reactivity and expression of various proinflammatory and prothrombotic factors. A key factor promoting endothelial dysfunction involves a reduced bioavailability of NO.78,79 Abnormal vascular reactivity has been demonstrated in patients with both cardiovascular risk factors80 and with established coronary heart disease.91 Furthermore, numerous therapeutic interventions with a proven atheroprotective benefit have been demonstrated to improve vascular reactivity.82

Recent studies strongly suggest a direct role for MPO as a participant in the development of endothelial dysfunction through limitation in NO bioavailability. Although a potential role of NO as a cosubstrate for prostaglandin H synthase had been suggested,83 it had yet be investigated as a potential substrate for leukocyte heme peroxidases like MPO until the first report by Abu-Soud and Hazen.84 Given the colocalization of MPO within atherosclerotic plaque, a direct role for the enzyme in promoting endothelial dysfunction via consumption of NO has subsequently been explored by several groups. MPO-generated oxidants have been reported capable of inhibiting the activity of NOS. Chlorination of arginine following reaction with HOCl reduces its substrate availability and directly inhibits enzymatic activity of NOS, reducing the in vitro formation of NO metabolites by endothelial cells, and subsequent acetylcholine-induced relaxation of rat aortic ring segments.85,86 Reactive nitrogen species such as those generated by MPO have also been shown to uncouple NOS.87 NO synthesis is further inhibited by HDL modified by a MPO-generated chlorinating system, which results in delocalization of endothelial NOS from its normal plasma membrane location.88 Further, MPO and HOCl both reduce the availability of NADPH, an essential NOS cofactor.89 A combination of both direct catalytic consumption, radical–radical scavenging effects, and modulation of NOS activity through oxidation of its substrates and cofactors all likely contribute to the observations that MPO inhibits NO-dependent dilatation of preconstricted arterial37,86 and tracheal segments.90

Direct in vivo support for MPO as a catalytic sink for NO is supported by studies in murine models. Arterial segment NO-dependent relaxation was shown to be reduced after endotoxin administration in wild-type relative to MPO knockout mice.37 The demonstrations that MPO avidly binds to endothelial cells and is subsequently transcytosed to the subendothelial space,99 the compartment where immunohistochemical studies localize both MPO and nitrotyrosine,91 further suggests that MPO is anatomically positioned between endothelial cells and their target smooth muscle cells to intercept NO and limit its bioavailability.

Experimental data implicating a role for MPO in the development of endothelial dysfunction have recently been extended to humans. Vita et al demonstrated that serum MPO levels independently predict the prevalence of endothelial dysfunction in a cohort of 298 subjects.92 A strong inverse correlation was observed between MPO levels and flow-mediated dilatation of the brachial artery. After adjusting for the presence of traditional cardiovascular risk factors, medications, and prevalent CVD, MPO remained a robust predictor of endothelial dysfunction, with individuals possessing fourth-quartile MPO levels remaining 6.4-fold more likely to demonstrate endothelial dysfunction compared with subjects with MPO levels in the lowest quartile. Similarly, MPO has recently been shown to enhance NO catabolism during myocardial ischemia and reperfusion.93 Myocardial tissues from patients presenting with acute myocardial infarction were shown to demonstrate intense recruitment of MPO-positive neutrophils localized along infarct-related vessels, as well as diffuse endothelial distribution of free MPO immunoreactivity. Parallel endothelium-dependent microvascular function studies demonstrated that forearm blood flow in patients with symptomatic coronary artery disease was strongly and inversely correlated with MPO plasma levels ($r=-0.75$, $P<0.005$). Thus, kinetic, cellular, animal model, and human clinical studies all point toward a role for MPO as a major enzymatic sink for NO within diseased coronary vessels.

**Myeloperoxidase and Development of Vulnerable Plaque**

The majority of clinical ischemic events result from the breakdown of the fibrous cap overlying the atherosclerotic plaque.94 Pathological studies have established that culprit lesions are typically macrophage rich atheroma containing large amounts of matrix metalloproteinases and prothrombotic material.95,96 These plaques are more likely to undergo thinning and subsequent breakdown of the overlying fibrous cap. This exposes circulating blood to the plaque’s thrombogenic core, resulting in thrombus formation, luminal compromise, and ischemia (Figure 1). Factors that promote the inflammatory cascade in atherosclerotic plaque are likely to be associated with the development of clinical ischemia.

The ability of systemic MPO levels to predict the likelihood of clinical events suggests that MPO plays a role in the
transition of a mature atherosclerotic plaque to the vulnerable state. Brennan et al demonstrated the prognostic value of plasma MPO levels in a cohort of 604 sequential patients presenting to the emergency department with chest pain. Subjects in the highest MPO quartile had a 3.9-fold higher likelihood of having a myocardial infarction on presentation and were 4.7-fold more likely to have a major adverse cardiac event in the ensuing 30 days and 6 months. Remarkably, this relationship was observed both in the presence and absence of biochemical evidence of myocardial necrosis. The predictive value of MPO over the ensuing 6-month period exceeded that of other established biomarkers including troponin T, CK-MB, and C-reactive protein. In a similar fashion, Baldus et al found that serum MPO was an independent predictor of adverse cardiac outcomes at 30 days and 6 months in patients with acute coronary syndromes participating in the CAPTURE study. Patients with MPO levels in the top tertile were ~3 times more likely to experience death or nonfatal myocardial infarction within 72 hours of enrollment compared with patients in the lowest MPO tertile. The ability of serum MPO levels obtained at the time of subject randomization to predict adverse outcomes over the past 6 months was independent of other prognostic markers, including troponin, C-reactive protein, and soluble CD40 ligand. Acute coronary syndromes are characterized by evidence of leukocyte activation. Pathological studies have localized both a marked infiltration of neutrophils and colocalization of MPO- and HOCl-modified proteins with macrophages in culprit lesions associated with intracoronary thrombi. In addition, unstable angina is characterized by an increase in the expression of leukocyte activation markers, as well as the presence of a transcoronary reduction in intracellular leukocyte MPO staining, consistent with systemic leukocyte activation. Further studies have demonstrated potential mechanisms by which MPO may promote plaque instability. MPO-derived oxidants colocalize with macrophages and the latent form of matrix metalloproteinase-7 in atherosclerotic lesions. In vitro studies demonstrate that HOCl promotes the activation of latent matrix metalloproteinase-7 via oxygenation of a thiol residue in the enzyme’s cysteine switch. This molecular switch provides a mechanistic rationale for the demonstration 2 decades ago by Weiss et al that neutrophils release and activate gelatinase by a HOCl-dependent process. This process appears to be under dynamic control because oxidative modification of tryptophan and glycine residues in the catalytic domain of matrix metalloproteinase-7 serve as a potential mechanism for restraining proteolytic activity during inflammation. Libby et al recently reported that MPO-generated HOCl may contribute to intracoronary endothelial cell desquamation and the engenderment of a prothrombotic phenotype. Physiologically relevant levels of HOCl were shown to promote endothelial cell apoptosis and detachment of endothelial cells in vitro. MPO-triggered endothelial cell apoptosis has been suggested as a mechanism for development of superficial erosions, the apparent inciting event in intracoronary thrombus formation in more than one-quarter of acute coronary syndromes, with particular prevalence in women and smokers. Interestingly, MPO levels in women appear to exhibit a trend toward being a stronger predictor of clinical events, and estradiol has recently been identified as a potential endogenous substrate for MPO-catalyzed lipid peroxidation. Whether these observations provide a mechanistic link for the observation that superficial plaque erosions are more commonly observed in females, and are enriched with MPO, remains to be established.

Several lines of evidence suggest that MPO may also increase the propensity to thrombus formation in the setting of plaque instability. The appearance of detached apoptotic cells in the systemic circulation is a potential stimulus for platelet activation and aggregation. The ability of MPO to reduce NO bioavailability renders the normally antithrombotic endothelial surface thrombogenic via the expression of various prothrombotic and antifibrinolytic factors. In addition, MPO-derived lipid oxidation products enriched in atheroma activate endothelial cells, promoting the surface expression of P-selectin, favoring platelet adhesion. Incubation of endothelial cells with low doses of MPO, or MPO-expressing macrophages, results in increased expression and activity of tissue factor. Latent tissue factor pathway activity is also activated by lipid hydroperoxides, which are generated by the activity of MPO in vivo.
to have a significant increase in risk for infections, and only in the setting of concomitant factors that predispose to immunosuppression, such as diabetes. Moreover, whereas levels of MPO per leukocyte appear relatively stable in a given subject over time, there appears to be a wide range of MPO levels per leukocyte within populations of normal subjects, and thus a large potential therapeutic range may exist while maintaining MPO levels still within a functional range for host defenses. Finally, MPO stores within leukocytes may be relatively protected from inhibition because the enzyme is stored in a crystalline form within granules and only released into the phagolysosome compartment and extracellular space upon leukocyte activation. As a result, through use of more polar inhibitors, it may be possible to target extracellular MPO, such as enzyme trapped within the subendothelial space, and not to significantly impede leukocyte killing of phagocytosed pathogens. The development of MPO inhibitors awaits further investigation.

Summary

Generation of reactive oxidant species via MPO-catalyzed pathways may have a substantial impact on the promotion of inflammatory events that contribute not only to immune defenses but also to the tissue damage that results from a range of inflammatory conditions, including atherosclerosis. MPO appears to participate in a range of events involved in the initiation, propagation and subsequent complications of atherosclerotic plaque. As a result, the components of the MPO pathway represent attractive targets for the development of prognostic biomarkers and therapeutic interventions to prevent atherosclerotic cardiovascular disease.

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