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Review article
Pregledni članak

MYELOPEROXIDASE: NEW ROLES FOR AN OLD MOLECULE

MIJELOPEROKSIDAZA: NOVE ULOGE STAROG MOLEKULA

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Summary: Myeloperoxidase (MPO) is a member of the heme peroxidase–cyclooxygenase superfamily. It is abundantly expressed in neutrophils and monocytes. During inflammation MPO is released from leukocytes and catalyzes the formation of several reactive species and tissue damage. In this article we present state of the art knowledge on the general properties, biosynthesis and processing and trafficking of MPO. The basic functions of MPO in inflammation and oxidative stress are discussed in detail. This article also summarizes the studies that investigated the relationship between MPO and cardiovascular disease. An overview of the assays for determination of MPO, the sample type and preanalytical procedures is given. Future studies are needed before this marker is introduced into routine clinical practice.

Keywords: acute coronary syndrome, chest pain, inflammation, myeloperoxidase

Kratak sadržaj: Mijeloperoksidaza (MPO) član je superfamilije hem peroksidaza–ciklooksigenaza. Većinom je eksprimirana u neutrofilima i monocitima. Tokom zapaljenja MPO se oslobađa iz leukocita i katalizuje formiranje nekoliko reaktivnih vrsta i oštećenje tkiva. U ovom radu prikazane su osnovne karakteristike MPO, biosinteza, obrada i transport MPO. Osnovne funkcije MPO u zapaljenju i oksidativnom stresu su detaljno opisane. Ovaj rad sumira rezultate epidemioloških studija koje su ispitivale povezanost MPO i kardiovaskularnih bolesti. Takođe su prikazane metode određivanja MPO, vrste biološkog materijala u kojima se može određivati, kao i preanalitički postupci. Dodatne studije su neophodne pre nego što se otpočne sa rutinskom primenom ovog markera u praksi.

Ključne reči: akutni koronarni sindrom, bol u grudima, zapaljenje, mijeloperoksidaza

Introduction

Myeloperoxidase (MPO, donor, hydrogen peroxide oxidoreductase, EC 1.11.1.7) belongs to the family of mammalian peroxidases, which also includes lactoperoxidase, eosinophil peroxidase, and thyroid peroxidase. It was discovered by Agner (1) in 1941 and described as a green colored iron-containing protein with peroxidase activity in the purulent fluid of patients with tuberculous empyema. Agner named it verdoperoxidase. Later it was renamed into myeloperoxidase, as its distribution was limited to myeloid cell lines.

MPO is one of the most abundant proteins (5%) in human polymorphonuclear neutrophils (PMNs) and to a lesser extent it is related to monocytes and tissue macrophages (2, 3). MPO is stored in the azurophilic granules of PMNs and monocytes. MPO synthesis occurs during myeloid differentiation in bone marrow. Only promyelocytes and promyelomonocytes actively synthesize MPO. Its synthesis begins in the endoplasmic reticulum from precursor preproMPO (80 kDa). PreproMPO consists of a propeptide, a large subunit (55–64 kDA, 466 amino acids) and a small subunit (10–15 kDa, 108 amino acids). After the cleavage of the signal peptide incorporation of high mannose oligosaccharide side chains yields 90 kDa apoproMPO (90 kDa). It associates with molecular chaperones CRT, and after that with CLN and heme forming enzymatically active proMPO which is competent for export into the Golgi. After exiting the

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Golgi the propeptide is removed from proMPO. Final proteolytic processing takes place in the azurophilic granules, resulting in the formation of a symmetric MPO homodimer (144 kDa) linked by a disulfide bond (4). MPO is a highly cationic protein and the reaction optimum of MPO is at pH 5.5, but the enzyme remains active over a wide range of pH.

MPO is encoded by a single gene located on the long arm of chromosome 17 (17q23.1), spanning 14 kb. It has 12 exons and 11 introns. A number of polymorphisms have been identified in the promoter of the MPO gene as well as in the coding regions (5). Serum MPO concentrations are related to the – 129 G>A polymorphism (rs34097845) (6). The – 463 G>A polymorphism (rs2333227) was associated with coronary artery disease (CAD), with the A allele reducing the risk (7). Genotypes – 463 A/A and A/G were associated with larger areas of fibrotic and calcified atherosclerotic lesions in the aorta in an autopsy study (8). GG genotype compared to AA/AG genotypes is a significant predictor of CAD, ischemic events and endothelial dysfunction (7–10). Wainstein et al. demonstrated that, in 118 stable CAD patients, there was no association between the MPO promoter polymorphism and angiographic severity of coronary atherosclerosis, although a relationship was observed between plasma MPO levels and the extent of CAD (11).

Myeloperoxidase in inflammation and oxidative stress

MPO is connected with inflammation and oxidative stress. In a state of inflammation it is released from the azurophilic granules of activated leukocytes (mostly neutrophils and monocytes). Release of MPO and formation of reactive species may be induced by the following mechanisms: inflammation induces recruitment and leukocytes activation, minimally modified low-density lipoprotein (LDL) particles in the intima may trigger the influx of monocytes that mature in resident macrophages (some of them express MPO), and neutrophils in circulation are attracted and bound to the sites of endothelial damage.

MPO is the only human enzyme that catalyses the reaction of generating hypochlorous acid (HOCl) and other reactive species with antimicrobial activity. Also, it promotes oxidative damage of tissues that impacts the development of atherosclerosis, endothelial dysfunction, plaque destabilization, etc.

MPO is also a catalyst for the oxidative modification of lipoproteins. It is well known that LDL modified particularly by an oxidative reaction promotes cholesterol uptake by the macrophages' scavenger receptor and triggers atherosclerosis. Macrophages use reactive oxygen species for killing pathogens. They use NADPH oxidase to produce superoxide that can dismutate and form hydrogen peroxide (H_2O_2). MPO uses H_2O_2 to generate HOCl that damages host tissue. HOCl converts free and protein-bound tyrosine residues to 3-chlorotyrosine (12, 13). Nitrite (NO_2^-) forms in the reaction of nitric oxide (NO) oxidation. Nitrite with H_2O_2 in a reaction catalyzed by MPO converts to a nitrogen dioxide radical ($NO_2^{\bullet}$). Nitrogen dioxide radical nitrates tyrosine residues generating 3-nitrotyrosine (14, 15). High levels of 3-chlorotyrosine and 3-nitrotyrosine in LDL were detected in human atherosclerotic tissue (16, 17). MPO is capable of oxidizing and nitrating LDL *in vivo*, making LDL a very potent ligand for the macrophage scavenger receptor. The system MPO–hydrogen peroxide–nitrite (MPO–H_2O_2–NO_2^-) was identified as a preferential mechanism for converting LDL into a high-uptake form (NO_2^-LDL) for macrophages and the scavenger receptor CD36 and foam cell formation (18). These data suggest that MPO is involved in the oxidative modification of LDL in the vascular intima, resulting in the conversion of LDL into an atherogenic form.

Except LDL, high-density lipoprotein (HDL) is also susceptible to oxidative modification which generates dysfunctional HDL in humans. HOCl generated in a reaction catalyzed by MPO modifies specific Tyr (Tyr192) and Met residues in apolipoprotein (apo) A-I by nitration or halogenation. Oxidation of apoA-I by MPO inhibits two steps of reverse cholesterol transport: oxidation of lipid-free apoA-I by MPO inhibits cholesterol efflux by the ABCA1 pathway and oxidation of lipid-associated apoA-I by MPO impairs lecithin-cholesterol acyltransferase activation. Impairment of cholesterol removal can promote foam cell formation and atherogenesis (19).

The MPO level is also connected with endothelial dysfunction. NO is the main factor involved in the antiatherosclerotic properties of the endothelium. NO interferes with monocyte and leukocyte adhesion to the endothelium and the platelet–vessel wall interaction, decreases endothelial permeability and reduces vessel tone, decreases flux of lipoproteins into the vessel wall, and inhibits vascular smooth muscle cell proliferation and migration. MPO consumes NO under physiological conditions (20). MPO also produces oxidizing substrates that inhibit NO synthase activity or reducing cofactors like NADPH. It causes impaired vasodilatation, platelet aggregation, recruitment and leukocyte activation and endothelial dysfunction (21).

MPO activates matrix metalloproteinases. Matrix metalloproteinases affect the remodeling and stability of atherosclerotic plaque. HClO produced by MPO promote degradation of the extracellular matrix of the fibrous layer by degrading collagen and proteoglycans (22). MPO can mediate the degradation of proteoglycans and it is associated with the decrease of endothelial cell adhesiveness to the subendothelial

extracellular matrix, and promotes superficial erosion, which may cause acute coronary syndrome, especially in the case of fibrous plaques (23). MPO inactivates protease inhibitors such as α_1-antitrypsin, tissue inhibitors of metalloproteases and plasminogen activator inhibitor-1.

Because MPO is a strongly basic protein, it can attach to the negatively charged glycosaminoglycans of extracellular matrix and endothelial cell surfaces (24). This contributes to the accumulation of MPO in the plaque. On the other hand, administration of heparin and heparin-related products can release the bound MPO.

MPO is linked to the activation of proapoptotic or oncotic cell-death pathways. MPO increases thrombogenicity, inducing activation and platelet aggregation, and intracoronary thrombus generation (25).

Literature data shows that elevated serum MPO levels independently predicted future risk of CAD (nonfatal acute myocardial infarction (AMI) or hospitalization) in apparently healthy individuals during an 8-year follow-up (26). Recent data suggest that higher MPO concentrations may predict the development of coronary events in healthy people with evidence of subclinical atherosclerotic plaque (27).

Myeloperoxidase in patients with chest pain

Elevation of MPO levels may occur in the early stages of ACS, even prior to evidence of myonecrosis, possibly reflecting atherosclerotic plaque instability. It was shown that MPO concentrations have a good prognostic value in the setting of chest pain.

Brennan et al. analyzed 604 plasma samples drawn from patients with chest pain but no increase in cardiac troponin T levels, and the predictive power of MPO was not related to traditional risk factors and CRP (28). The clinical value of MPO to predict AMI and adverse events after 30 days and 6 months of follow-up in patients with acute chest pain was assessed by Brennan and coworkers (28). MPO was higher in patients with established AMI than in those without established AMI at presentation. Patients initially negative for troponin T but subsequently positive for troponin T had higher MPO concentrations than patients with no increase in troponin T. Patients with high MPO (upper vs lower quartile) were more likely to have a major cardiac event at 30 days (OR 4.7, 95% CI, 2.8–7.7) and 6 months (OR 4.7, 95% CI, 2.9–7.7) of follow-up. Rudolph et al. (29) evaluated the prognostic information of MPO prospectively and in consecutive measurements in 274 patients with chest pain admitted to the emergency room. They confirmed the role of MPO as a diagnostic marker in acute coronary disease only in patients presenting in the early phase of symptom onset. In contrast, Apple et al. (30) showed that in 457 patients presenting with symptoms suggestive of ACS, increased MPO (99^{th} percentile) was not a predictor of two cardiac endpoints: all cause mortality (including cardiac death) and cardiac events which included cardiac death, MI, percutaneous coronary intervention and coronary artery bypass grafting. The next study by Apple et al. found that MPO has no additional diagnostic value compared to troponin I in patients with confirmed ACS (31). A study of Cheng et al. showed that MPO had a higher diagnostic sensitivity and specificity in identifying patients with AMI than the total white blood cell count and 3-chlorotyrosine (32). In 140 patients presenting with acute chest pain and a non-ST elevation ECG high MPO levels upon admission to the hospital were an important tool to predict in-hospital adverse events (33).

Myeloperoxidase and acute coronary syndrome

According to the literature data, the first study to report the potential role of MPO as a marker for the diagnosis of atherosclerosis and risk assessment was the study by Zhang et al. (34). They demonstrated the association between elevated MPO activity in neutrophils/blood and the prevalence of angiographically documented CAD in 175 patients and 158 controls. Two years later, investigators of the CAPTURE study (35) examined the association of short-term (6 months) prognostic value of the serum MPO level in 1090 patients with ACS. They found that patients with increased MPO (upper vs lower tertile) had a 2.25-fold (95% CI, 1.32–3.82) increased risk of reinfarction or death.

Exner et al. (36) in 2006 examined the progression of internal carotid artery stenosis in 1019 asymptomatic CAD patients with a follow-up of 7.5 months. Patients with progressive stenosis had significantly higher serum MPO concentrations compared with patients with the stable form of disease. An MPO concentration higher than median was associated with a 2.6-fold risk (95% CI, 1.4–4.8) of disease progression in patients with low HDL cholesterol (lower than median). The first study that linked increased baseline MPO level to long-term adverse clinical outcome was the study of Cavusoglu et al. (37). They investigated the ability of the baseline plasma MPO level to independently predict the development of myocardial infarction (MI) in 193 men with ACS during 2 years of follow-up. They found a significant independent association with MI (OR 1.60, 95% CI, 1.09–2.36). Mocatta et al. (38) who examined the association of long-term (5 years) prognostic value of EDTA plasma MPO in 512 patients with MI observed 1.81-fold (95% CI, 1.07–3.05) greater adjusted risk of death in patients with MPO values above the median. Khan et al. (39) investigated the role of EDTA plasma MPO as a predictor of a combined end point

of death or readmission with non-fatal MI in 384 patients with ST-segment MI. They observed that patients with MPO values above the median had an almost 7-fold (HR 6.91, 95% CI, 1.79–26.73) increased risk of adverse outcomes. Morrow and coworkers (40) studied the predictive values of plasma MPO, soluble CD40 ligand, troponin I, and CRP in 1524 patients with non-ST elevation ACS in a tirofiban intervention trial for survival within 180 days. Patients with increased MPO levels (above the median) were at higher risk for nonfatal MI or rehospitalization for ACS at 30 days. Furthermore, MPO was associated with recurrent ischemic events (OR 2.10, 95%CI, 1.36–3.23), after adjustment for CRP, troponin I, soluble CD40 ligand, and other major CVD risk factors. Dominguez-Rodriguez et al. (41) examined the role of MPO as a predictor of in-hospital mortality in 38 patients with ST-segment MI presenting with cardiogenic shock and treated with primary percutaneous coronary intervention. Patients who died at coronary care unit admission had higher serum MPO levels compared with survivors. In these patients, baseline MPO was an independent predictor of in-hospital mortality (OR 3.9, 95% CI, 1.8–7.5). Only one study (42) examined the association of the serum MPO level and the response to thrombolytic treatment in 158 patients with ST-segment MI. MPO levels before thrombolysis were significantly lower in patients with successful reperfusion. Borges et al. (43) found that although the plasma MPO level decreases over time after ACS, it might remain elevated for up to 2 years of follow-up. Chang et al. (44) found that high serum MPO independently predicts the risk of 30-day composite occurrence of major adverse clinical events (reinfarction, repeat PCI, Killip classification ≥3) in 128 patients with ST-segment elevation AMI undergoing primary percutaneous coronary intervention. In 160 patients with ST-segment elevation AMI who had undergone percutaneous coronary stenting within 12 hours of symptom onset, MPO was an independent predictor of impaired myocardial microcirculation after reperfusion (45).

Roman et al. (46) found that elevated MPO levels were higher in patients with ACS than in patients with stable angina. Also, among patients with ACS, an elevated MPO level (higher than the median value) at admission to the emergency was a predictor of cardiovascular events (death, recurrent angina, congestive heart failure, severe arrhythmia) during hospital stay (OR 2.95, 95% CI, 1.1–8.2).

Stable coronary artery disease

The association between plasma MPO levels and stable CAD is controversial. Duzguncinar et al. (47) demonstrated that MPO was increased in 48 stable CAD patients with angiographically documented coronary lesions and correlated to the extent and severity of atherosclerosis of the coronary vessels. In a case-control study (48) in 680 patients, 382 patients with stable CAD and 194 controls with normal coronary angiograms, MPO was higher in the patients with CAD compared to controls. MPO has been shown to progress from stable CAD to non-ST elevation ACS, reaching the highest levels in patients with ST-elevation AMI. MPO concentrations were found to correlate with the presence of CAD (OR 2.08, 95% CI 1.54–2.81). Tang et al. found that the plasma MPO concentration predicts long-term risk (3-year follow-up) in stable patients with angiographically documented coronary artery stenosis (49).

Subsequent cross-sectional studies have failed to confirm the association of MPO with mortality or new CVD events. Stefanescu et al. (50) found that MPO did not predict mortality independently of other cardiovascular risk factors in 382 patients with stable CAD during 3.5 years of follow-up. One case-control study (51) showed that MPO in HIV infected patients was negatively associated with the cardiovascular endpoints of MI, myocardial ischemia and coronary revascularization during one year of follow-up. Another study in 557 clinically stable patients undergoing elective coronary angiography showed no significant differences in MPO levels for those with proven stable CAD compared to those without proven CAD (52).

Laboratory determination of myeloperoxidase

These studies indicate that the measurement of MPO in patients presenting with acute chest pain or ACS provides clinically relevant information. It should be noted that methodological issues associated with MPO measurement make comparisons between studies difficult. Between-study differences in the MPO cutoff values might have affected the diagnostic and prognostic value of MPO. The cut points are different because of various sample types (serum, plasma, leukocytes), and the preanalytical handling of specimens for MPO determination. Examination of different collection tube types showed a difference in MPO concentrations of 10–100%. MPO levels were higher in serum and heparinized plasma than in EDTA or citrate plasma. While heparin can induce MPO release from leukocytes, neutrophils are activated during the process of blood coagulation. A very important step in MPO determination is the storage of samples before centrifugation, because MPO could be artificially released from neutrophils in the sample. It is evident that the administration of unfractionated heparin increases the MPO levels. Recently, a diurnal variation in MPO concentrations in ST-segment elevation MI patients was noticed (53). Different principles and assays were used for MPO determination. Most of the published papers utilized commercially available enzyme-linked immunosorbent assays (ELISA) (for example Calbiochem (36), Assay Design (38), CardioMPOTM from PrognostiX, Inc. (41)), and a smaller number of

studies used the novel automated high throughput Abbott's chemiluminescent immunoassays that correlate very well with ELISA (54).

Conclusion

Within the last decade a broad range of biomarkers associated with an increased risk for death and cardiovascular endpoints have been identified. Epidemiological studies clearly indicate that MPO has the potential to become a useful clinical biomarker because it provides independent information in the diagnosis, and especially CVD risk stratification. In the future we can expect new drugs (MPO inhibitors) that will affect patient management. Together with assay standardization, further evaluation is needed before MPO can be routinely adopted in clinical practice for better risk stratification and therapeutic choice in patients with cardiovascular disease.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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