

Myeloperoxidase as an Active Disease Biomarker: Its Recent Biochemical and Pathological Perspectives

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Abstract

Myeloperoxidase (MPO) belong to the family of heme containing peroxidases, produced mostly from polymorphonuclear neutrophils. The active enzyme (150 kD) is the product of *MPO gene* located on long arm of chromosome 17. The primary gene product undergoes several modifications like removal of introns and signal peptide and leads to the formation of enzymatically inactive glycosylated apoproMPO which complexes with chaperons, producing active proMPO by the insertion of heme moiety. The active enzyme is a homodimer of heavy and light chain protomers. This enzyme is released into extracellular fluid after oxidative stress and different inflammatory responses. MPO is the only type of peroxidase using H₂O₂ to oxidize several halides and pseudohalides to form different hypohalous acids. So the antibacterial activities of MPO involve the production of reactive oxygen and reactive nitrogen species. Controlled MPO release at the site of infection is of prime importance for its efficient activities. Any uncontrolled degranulation exaggerates the inflammation that can also lead to tissue damage even in absence of inflammation. Several types of tissue injuries and pathogenesis of several other major chronic diseases like rheumatoid arthritis, cardiovascular diseases, liver diseases, diabetes and cancer have been reported to be linked with myeloperoxidase derived oxidants. So the enhanced level of MPO activity is one of the best diagnostic tool of inflammatory and oxidative stress biomarkers among these commonly occurring diseases.

Keywords: myeloperoxidase, leukocytes, inflammation, oxidative stress, chronic diseases, disease biomarker

1. Introduction

Myeloperoxidase (MPO) (EC 1.11.1.7) is a member of subfamily of peroxidases, most abundantly expressed in immune cells such as neutrophilic polymorphonuclear leukocytes (neutrophils) and lymphocytes [1,2], monocytes and macrophages [3] and also produced from other body cells. MPO is stored in cytoplasmic membrane bound azurophilic granules and during stimulation; these granules are secreted out to extracellular space by degranulation or exocytosis

[4,5]. The complete biochemical mechanism of neutrophil degranulation is not yet clear, but oxidative stress plays a key role for the release of MPO from these cells [6,7].

Neutrophils are well known WBCs playing a pivotal role in innate immunity and frontline defense against microbial attacks [8]. In addition to MPO, antimicrobial properties of neutrophils are also expressed by different proteins or enzymes e.g., defensins, serine proteases, cathepsin G, alkaline phosphatase, lysozyme, NADPH oxidase, collagenase, lactoferrin, cathepsin and gelatinase etc. [9]. Among all these antimicrobial agents, MPO is the most abundant and constitutes 5% dry weight of neutrophils and 25% of the azurophilic granular proteins [10].

Normally, the neutrophils degranulate at the infection site to combat different types of microbial activities and help to cure the diseases. But any unusual expression and release of MPO from activated neutrophils intensify the inflammation and tissue damage and may result in several other diseases, even in the absence of infection [8,11].

This review article mainly focusses on the recent advances in the biochemical and the pathological aspects of myeloperoxidase and its significance as a disease biomarker in some commonly occurring chronic diseases.

2. Biochemistry of MPO

MPO gene is located on long arm, segment q12-24 of chromosome 17 and the primary transcriptional product of this gene consists of 11 introns and 12 exons [12,13]. After some modifications like signal peptide removal and glycosylation with mannose-rich side chains, it produces apopromMPO [14]. This protein product is enzymatically inactive and further forms complex with some chaperons like calreticulin and calnexin in endoplasmic reticulum [15,16]. Enzymatically active, promMPO is formed from apopromMPO by the insertion of heme moiety [17]. Furthermore, removal of some N-terminal amino acids results in production of 72-75 kD protein which undergoes further cleavage to produce α and β subunits. The α -subunit is heavy, 57 kD and consists of 467 amino acids, while the β -subunit is light, 12 kD and consist of 112 amino acids (Fig. 1)

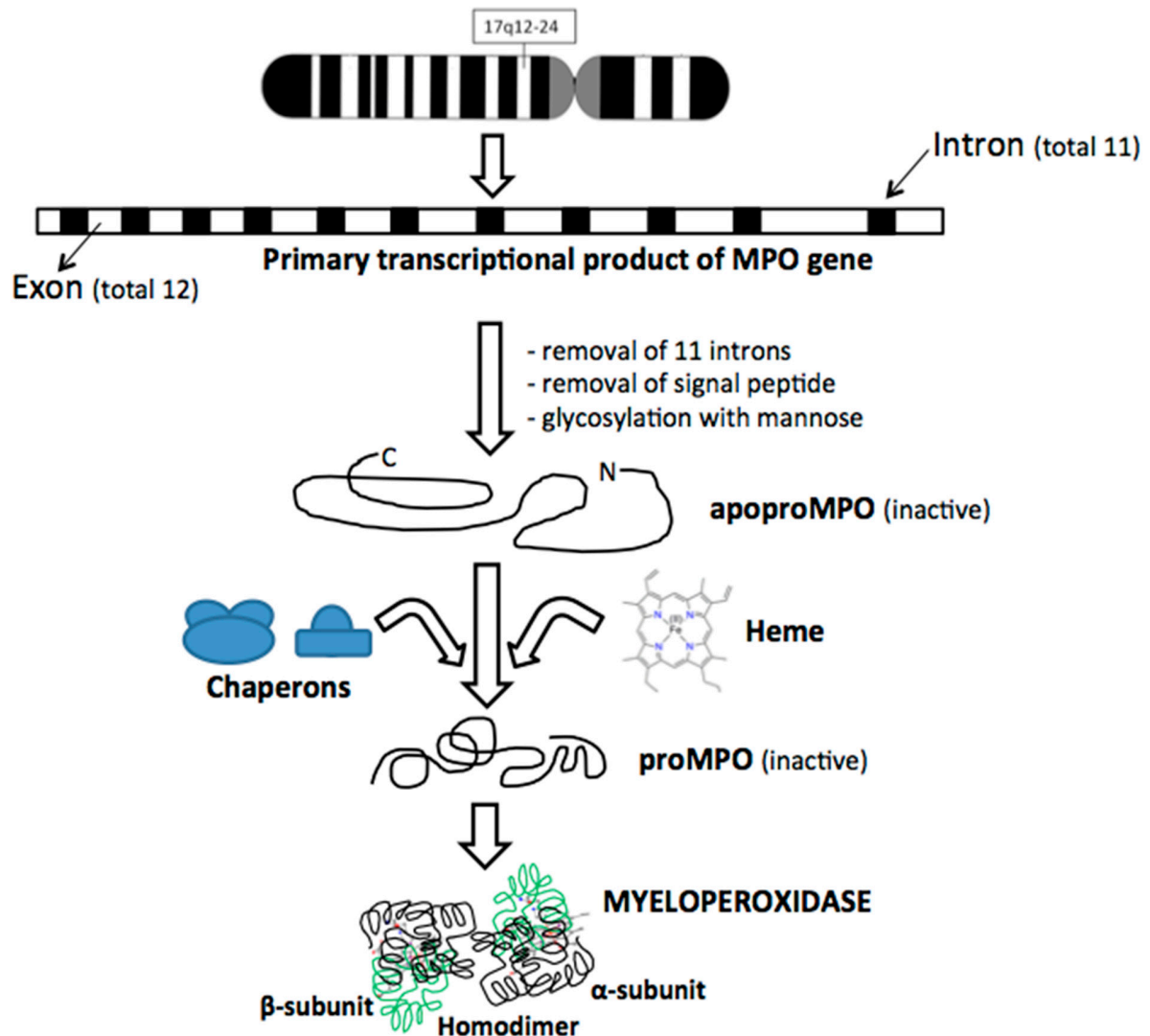


Figure 1: Sequential steps involved in the synthesis of myeloperoxidase

Mature MPO consist of a cationic homodimer heavy-light chain protomers and is about 150 kD by weight. Each heavy subunit of mature MPO is covalently linked with a heme group and a mannose rich moiety [18,19]. On the basis of the size of heavy chains in MPO, three isoforms have been observed as MPO I, MPO II, and MPO III [20]. MPO also contains a calcium-binding site, which is important for active site structure [21].

2.1. Activation and release of MPO by neutrophils

Although the coordination of MPO release by the degranulation of neutrophils is not fully

understood, evidences support that increased levels of oxidative stress by reactive oxygen species (ROS) and the activation of Src and p38MAP kinase signaling pathway performs a prominent role [22].

A fine coordination is necessary between different biochemical pathways like neutrophil activation, production of ROS by superoxide generating NADPH oxidase and MPO release by exocytosis. All these organized reactions lead to eliminate the bacterial invasion. Invading bacteria initiate enhanced production of H_2O_2 by superoxide dismutase (SOD), which is utilized by MPO for the production of chloramine and hypochlorite. Both of these products are highly toxic for the invading bacteria [8,23]. This biochemical phenomenon is also termed as respiratory burst. A clear illustration of the role of MPO is also observed in MPO knockout mice, which are highly susceptible for infections by *Klebsiella* and *Candida* and show persistent inflammation [24,25].

Various pro-inflammatory factors also trigger the release of MPO and ROS from neutrophils. During bacterial infection, one of the important mediators for this cascade is formylated peptide, which also work as chemoattractants. Neutrophils get activated via formyl peptide receptor (fPR), a G-protein coupled receptor [26]. Some more proteins involved in antibacterial activities include phospholipases, protein kinases as; mitogen-activated protein kinases (MAPK), protein kinase C (PKC) [27-29]. During different pathological situations or by the influence of several drugs, this signaling cascade gets impaired and finally leads to neutrophil dysfunction. These aberrations can be detrimental to host-defense against several diseases or disease causing microorganisms [26,30,31].

2.2. Reaction mechanism of MPO

Activated neutrophils, monocytes and some tissue macrophages release MPO at the sites of inflammation, using hydrogen peroxide (H_2O_2) to oxidize several substrates like halides (Cl^- , Br^- and pseudohalides (thiocyanate, SCN^-) to form hypohalous acid, hypochlorous acid (HOCl), hypobromous acid (HOBr), and hypothiocyanous acid (HOSCN) [32]. MPO is able to interact with diverse ionic, atomic and molecular entities via interface with H_2O_2 , including HOCl, hydroxyl radicals, singlet oxygen, ozone, chloramines and aldehydes [33-35]. These species are potent oxidants, which under normal and controlled circumstances are toxic to several microorganisms and play an important role in immune system [36-38]. However, any excessive or

unregulated production of these oxidants can even lead to damage of host cells and result in several diseases.

MPO produces the reactive oxidants and free radicals through its peroxidase and chlorinating activities. It is the only type of peroxidase, which facilitates the oxidation of chloride to HOCl by consuming H₂O₂. During its reaction cycles, MPO is converted to many transitional forms with different half-lives. MPO contains ferric heme (MPO-Fe(III)) in its resting state. During peroxidase cycle, compound I is formed by the reaction with H₂O₂ [39]. In absence of Cl⁻, this intermediate, [MPO-Fe(IV)=O] in presence of peroxide, is reduced back to ferric state in two sequential steps. The first step leads to the formation of Compound II. This compound is reduced to compound III by second equivalent AH₂ [40,41]. During the halogenation cycle, MPO-compound I exclusively oxidize Cl⁻ to HOCl and no further intermediates are formed in this reaction, as compound I directly gets converted to its native form (Fig. 2).

The fate of H₂O₂ as a substrate of MPO via peroxidation or chlorination reaction depends upon the concentration of chloride and the reducing substrates. A number of sources like NADPH oxidase, xanthine oxidase and NO synthase are the sources of H₂O₂ for the MPO reaction, which also enhances the oxidative potential of H₂O₂ [42].

A strong antimicrobial cascade of reactions (respiratory burst), takes place in presence of NADPH oxidase [43]. The initial products of this reaction are superoxide anion (O₂⁻) produced as, $\text{NADPH} + \text{O}_2 \longrightarrow \text{O}_2^- + \text{NADP}^+ + \text{H}^+$.

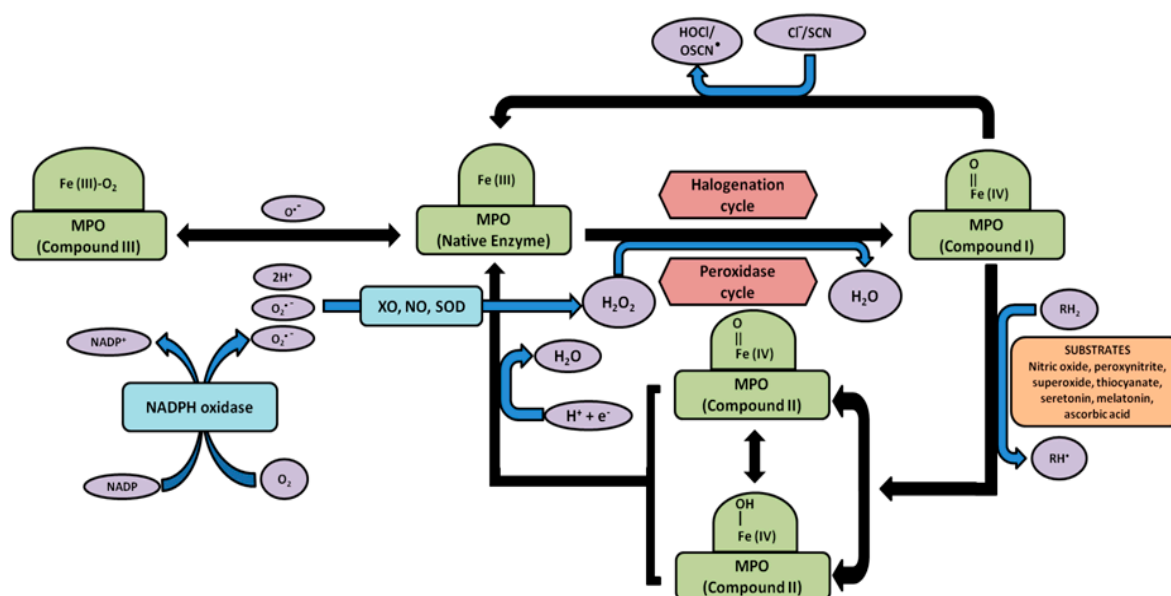


Figure 2: Reaction mechanism of Myeloperoxidase in presence of different substrates

2.3. Inhibitors and activators of MPO

Even though a strong correlation has been found between atherosclerosis, inflammatory diseases and the MPO release, little work has been done to inhibit MPO to suppress these diseases. Several naturally occurring compounds possess the inhibitory activities against MPO, which include polyphenols, melatonin, flavonoids etc. [44].

Like other peroxidases, MPO is inhibited by benzoic acid hydrazide-containing compounds, but the proper mechanism of its inhibition is still unknown [45]. MPO reaction is also inhibited by general peroxidase inhibitors like azide and there are some specific inhibitors of MPO as well like 4-amino benzoic acid hydrazide (4-ABH) [46]. Ceruloplasmin, an acute phase plasma protein, produced from hepatocytes and activated macrophages, is a physiologic inhibitor of MPO [47]. Niacin can also inhibit cellular ROS production and the MPO release through some complex signaling mechanisms [48].

In addition to the above compounds, some naturally occurring anti-inflammatory, antioxidants, antihistaminic compounds possess inhibitory activities against MPO which includes: nonsteroidal anti-inflammatory drugs (NSAIDs), e.g. diclofenac, ferulic acid, caffeic acid, resveratrol, indomethacin, flufenamic acid, chalcones, and gallic acid [49-51].

As compared to inhibitors, little is known about the activators of MPO. MPO is present as inactive or partially active form in resting granulocytes. Activation of MPO occurs by different factors. Granulocyte macrophage colony stimulating factor (GM-CSF), enhances the MPO activity. In addition to this, N-formyl-methionyl-leucyl-phenylalanine (fMLP), a chemo-attractant, has been observed to activate MPO from neutrophils [52].

2.4. Biochemical functions of Myeloperoxidase

During normal conditions, the antibacterial activities of MPO involve the production of different reactive oxygen and nitrogen species (ROS and RNS), These ROS and RNS can also cause lipid peroxidation, protein nitration and protein carbonylations. MPO plays role in oxidative and chemical modifications of different lipoproteins as well. MPO also mediates protein nitrosylation and dityrosine crosslinking and 3-chlorotyrosine formation [53,54].

MPO also oxidize tyrosine to tyrosyl radical with the help of H₂O₂. Neutrophils use tyrosyl radicals and hypochlorous acid (HOCl) as cytotoxic agents against different types of bacteria and other pathogens [55]. As a signaling molecule, HOCl can activate several pathways, which later induces cellular senescence or apoptosis [56].

Due to its polycationic protein nature, MPO binds to negatively charged surfaces of pathogens and by its enzymatic activity, cause cell membrane destructions, which ultimately leads to cell death [57]. MPO can even bind to the surfaces of epithelial cells [58], fibroblasts [59], endothelial cells [60,61], macrophages [62], platelets [63,64], neutrophils [60,65], LDL and VLDL lipoproteins in addition to pathogens [66]. Binding of MPO to the cell surface alters some functional properties, for example, MPO interaction with neutrophil integrins causes enhanced tyrosine phosphorylation of some proteins. This activates protein tyrosine kinase resulting in degranulation and also the respiratory burst [65]. Binding of MPO to platelets causes reorganization of platelet cytoskeleton and alters the aggregation activities [67]. MPO also oxidize a variety of aromatic compounds by a 1-electron mechanism to produce substrate radicals (R[•]) [68,69].

In addition to this, HOCl derived from MPO has high chemical reactivity as it diffuses across cell membrane and interacts with many cytoplasmic enzymes like creatine kinase, lactate

dehydrogenase, hexokinase, glyceraldehyde-3-phosphate dehydrogenase etc. and inactivates them [70].

Moreover, MPO is a major concern for some clinicians who are interested to use carbon nanotubes for drug delivery as it suddenly breaks down these drug delivery vehicles [46] so limits its applications.

3. Role of MPO in different diseases

Besides the antipathogenic or bactericidal role of MPO derived HOCl during normal conditions, under some pathological circumstances, overproduction of these oxidizing agents cause oxidative damage of proteins and DNA of the host cells as well. Several types of tissue injuries and pathogenesis of various chronic diseases like atherosclerosis, cancer, renal disease, lung injury, multiple sclerosis; Alzheimer's and Parkinson's disease have been reported to be directly/indirectly linked with MPO derived oxidants [8] (Table 1). So the enhanced level of MPO is one of the best inflammatory and oxidative stress markers among these commonly occurring diseases [71,72].

S. No.	Name of disease	Brief etiology and possible role of MPO	Reference
1.	CVD and Atherosclerosis	Raised level of MPO cause RBC deformability, accumulation of cholesterol and its esters, ruptures atherosclerotic plaque	[8], [67]
2.	Neurodegenerative diseases	Release of neurotoxic mediators by many factors spearheaded by MPO from neurons, astrocytes, microglia cells	[11]
3.	Cancer	MPO derived ROS/RNS react with major biomolecules causing mutagenesis, gene polymorphism, SNPs, acrolein-protein adduct formation	[73-75]
4.	Diabetes/Diabetic retinopathy	Neutrophil activation and release of MPO in vessels and retina, upregulation of leukocyte adhesion molecules, increased production of anti-MPO antibodies	[76,77]
5.	Renal diseases	MPO initiated HOCl-modified proteins in glomerular peripheral basement membranes	[78]
6.	Liver diseases	Neutrophil infiltration, hepatic fibrosis by activation of Kupffer cells cause production of oxidants, impaired signaling events	[79,80]
7.	Lung injury	Activation and expression of proinflammatory cytokines and mediators by MPO	[5]
8.	Cystic fibrosis	Bacterial infiltration especially <i>P. aeruginosa</i> and infiltrating neutrophils	[81]

9.	Multiple sclerosis	MPO generated ROS cause axonal damage by proteolytic enzymes and cytotoxic oxidants by activated immune cells and glia	[82]
10.	Alzheimer's disease	Increased production of oxidants like advanced glycation end products, o,o'-dityrosine, lipid oxidation products, protein carbonyls, oxidized DNA, and 3-nitrotyrosine in neuronal tissues proposed by increased expression of MPO.	[83]
11.	Parkinson's disease	Upregulation of MPO and its by-product, 3-chlorotyrosine in ventral midbrain	[84]
12.	Tuberculosis	Enhanced MPO expression along with TNF- α and IL-12 activation	[85]
13.	Asthma	Excessive MPO release from neutrophils in lower respiratory tract cells	[86]
14.	Rheumatoid arthritis	Inflamed synovium intervened by lymphocytes and neutrophils leads to release of proinflammatory mediators	[87,88];
15.	Chronic sinusitis	Enhanced level of MPO and IL-8 in sinuses	[89]
16.	Peptic ulcer	Free radicals formation initiated by MPO	[90]
17.	Ulcerative colitis	Neutrophil accumulation and enhanced expression of MPO in inflamed intestinal mucosa	[91]
18.	Chronic periodontitis	Increased MPO activity in gingival crevicular fluid	[92]

Table 1: Brief etiology and the direct/indirect involvement of MPO in different types of diseases

The description of some of the diseases through the perspective of MPO is reviewed here as under.

3.1. Inflammation

Inflammation results during the response of body's challenge for self-protection to remove harmful stimuli like damaged cells, irritants or pathogens. Vascular permeability is increased by the activation of various inflammatory mediators, which results in the influx of immunoglobulins and serum proteins at the site of inflammation [93,94]. This cascade of inflammatory process also motivates the migration of polymorphonuclear neutrophils which result in the release of MPO [95,96].

Inflammatory processes are triggered by lipid peroxidation and the synthesis of eicosanoids. Cytochrome P450, lipoxygenase and cyclooxygenase play a prominent role in these events. MPO generates reactive intermediates that stimulate lipid peroxidation. This oxido-

reductase can oxidize tyrosine and nitrite to form tyrosyl radical and nitrogen dioxide ($\cdot\text{NO}_2$), respectively. These reactive intermediate can oxidize lipids in plasma and cell membrane [97]. Lipoprotein phospholipid peroxidation of membrane is linked to their interference, leading to cellular dysfunctions. Lipid peroxidation can be normal physiological activity or a potential contributor to pathophysiological consequence of acute and chronic inflammatory diseases [98,99].

Tyrosyl radical, formed by MPO initiates lipid peroxidation and also forms phenolic cross-links on proteins. A typical molecular fingerprint, protein-bound dityrosine, is enhanced during atheroma and other sites of inflammation [100].

Lipid peroxidation also occurs by nitrogen dioxide ($\cdot\text{NO}_2$), which is formed by MPO enzymatic action. Post-translational modification of proteins, which results in the formation of nitrotyrosine, can also occur in the presence of $\cdot\text{NO}_2$ [101,102].

Some of the common examples of diseases and conditions with chronic inflammation are: tuberculosis, asthma, rheumatoid arthritis, chronic sinusitis, chronic hepatitis, peptic ulcer, ulcerative colitis and chronic periodontitis etc.

3.2. Rheumatoid arthritis

Chronically inflamed synovial joints with some destruction of cartilage and bones are a common characteristics of rheumatoid arthritis (RA) [103]. Several factors have been proposed for this disease among which oxidative stress is a leading hypothesis [104,105]. Inflamed synovium is often intervened by B and T lymphocytes, macrophages and neutrophils. Intrusion of these cells in synovium during RA leads to the release of multiple pro-inflammatory mediators. Degranulation of neutrophils leads to the release of enzymes and peptides, leading to respiratory burst and oxidative stress [106-109]. Overproduction of ROS are potential tissue damaging agents which are further formed by the cascades of reactions by HOCl produced from the activated neutrophils present in synovial fluid [110,88]. This has been verified from the inflamed cartilages of the patients suffering from RA [87]. Currently, a firm hypothesis is believed that the enhanced levels of MPO in inflamed cartilages of RA are causally associated in compelling the disease progression lifelong.

3.3. Cardiovascular diseases and Atherosclerosis

The alliance of coronary artery diseases (CAD) and MPO level was first reported in 2001 [111]. Since that time, MPO is considered as a circulating marker of such related diseases like acute coronary syndrome, CAD, and chronic heart failure [112-115]. Patients with coronary artery diseases, unstable angina and acute myocardial infarction have been observed with raised levels of circulating MPO [8,116-118]. Still, little is known about the clinical utility of anti MPO antibodies against some microvascular diseases.

In patients with combined ischemic heart disease and diabetes, a strong correlation has been observed between circulating MPO level and the RBCs rigidity index. Band-3 protein and glycophorins, many changes in the RBCs cellular morphology and biophysical properties like cell size, hemolysis sensitivity, cellular deformability, transmembrane potential, plasma membrane fluidity, intracellular Ca^{2+} [67].

Atherosclerosis is the major cause of cardiovascular diseases (CVD). Neutrophils and monocytes play a key role during atherosclerosis leading to chronic inflammatory problems. Different events and sequences occur during CVD, which include endothelial dysfunction besides formation and rupture of atherosclerotic plaque [119]. In arterial wall subendothelial region, all these stages occur during inflammation, which ultimately leads to accumulation and deposition of altered lipids [120].

Atherosclerosis leads to the accumulation of cholesterol and cholesteryl esters on arterial walls, which are derived from low density lipoproteins (LDL). Besides this, LDL retention on these walls triggers an immune response, resulting in cascade of production of oxidants and inflammation [121,122]. Plasma LDL interacts with circulating MPO, which has been reported to be higher from the patients suffering from atherosclerosis [123]. It has been reported that in some patients, undergoing hemodialysis, the HOCl reacts with LDL, which promotes atherogenesis [78,124]. Macrophage exposure to HOCl-LDL results in accumulation of cholesterol and its esters and the production of lipid-rich foam cells [125].

3.4. Neurodegenerative diseases

Oxidative stress is also proposed to be responsible for the release of neurotoxic mediators commanded by MPO derived from cells like neurons, astrocytes and activated microglia as well as peripheral inflammatory cells [11]. In brain, out of the different neurotoxic oxidants, HOCl is stable, highly reactive and predominant one. This acid is involved in a number of neurodegenerative diseases which includes stroke, epilepsy, multiple sclerosis, Parkinson's and Alzheimer's disease, multiple sclerosis etc. [126].

In addition to inflammation and oxidative stress, MPO is related to depression, which is an emotional disorder affecting a vast majority of population [127]. Furthermore, patients suffering from bipolar disorders, anti-inflammatory drugs such as lithium and valproate are used, indicating some links with MPO [128]. A complete mechanism for the role of myeloperoxidase biochemistry in neuronal diseases is still awaiting.

3.5. *Diabetes/Diabetic Retinopathy*

Diabetes mellitus and its complication, diabetic retinopathy (DR) is also known as a disease with subclinical inflammation measured by neutrophil activation [76]. During diabetic retinopathy, retinal structural and biochemical alterations cause activation of neutrophils [129]. Increased expression of various types of growth factors and cytokines including TNF α occurs due to biochemical modifications during DR. Inflammatory mediator priming causes MPO translocation and interaction with anti-MPO antibody.

In the vessels of diabetic retina, upregulation of leukocyte adhesion molecules occurs and leukocytes are also observed in the lumen of human microaneurysm. Furthermore, patients with DR, the vitreous samples show elevated levels of CD4/CD8 and T lymphocytes [77].

Chronic inflammation during diabetic retinopathy is sustained by cytokine-producing B-lymphocytes. There is a correlation between the activity of proliferative DR (PDR) and the increased lymphocyte infiltration [130]. Increased vascular permeability due to leukocytosis leads to retinal abnormalities, endothelial injury and capillary occlusion [131-133]. Neutrophils and monocytes can be activated by Proteinase-3 antineutrophilic cytoplasmic antibody (PR3-ANCA) and MPO antineutrophilic cytoplasmic antibody (MPO-ANCA), to release acute inflammatory mediators, which cause endothelial cell injuries [134,135]. Priming by proinflammatory factors

like cytokines, TNF α and microbial products like bacterial formyl peptides etc. triggers circulating neutrophils to express more ANCA antigens.

3.6. *Liver diseases*

Among several types of liver disease like fibrosis, necrosis, inflammation and steatosis respectively; alcoholic cirrhosis denotes a major cause of mortality with an estimated 3.8% of all worldwide deaths [136,137]. Cirrhosis is closely related with immune dysfunctions, thus inability of the host to protect against various infections [138]. In several types of liver injuries like alcoholic steatohepatitis in human beings or in animal models, neutrophils contribute to the pathogenesis of cirrhosis [139]. Infiltration of neutrophils in liver is good for predicting the forecast of the disease [80] as these cells increase the intracellular oxidative stress during liver injury [140]. In addition to this, the stellate macrophages or Kupffer cells, located in the liver, also synthesize MPO. Activation of these cells results in hepatic fibrosis which is proposed to be developed by the local release of oxidants and the cytokines [141,79].

Neutrophils employ their favorable effects through different factors like granulopoiesis (Eash et al, 2009) [142], production of hepatocyte growth factor [143], and collagen degradation. Granulocyte colony stimulating factor (G-CSF) therapy has been observed to be beneficial in cases with severe alcoholic hepatitis [144]. Patients with cirrhosis have impaired neutrophilic ROS production, phagocytotic and the microbicidal activities [145-147]. Post-hepatic cirrhosis has also been observed closely related to diminished ROS production in some recipients of liver transplant [148]. The mechanism of impaired signaling events of the neutrophils in relation with alcoholic cirrhosis is not fully understood. Several researchers have observed an erroneous MAPK-dependent phosphorylation of p47phox, an important component of NADPH oxidase [29].

3.7. *Cancer*

The knowledge about the precise biochemical relationship between the inflammatory response and specific malignancy is a vast field to be understood but a growing evidence links between the relationships of MPO, inflammation and cancer [149,75,150]. Cancer progression advances by the biochemical alterations of different biomolecules and genes by various oxidative species, ultimately produced through MPO.

DNA damage can be caused by the oxidants directly or indirectly produced by the MPO, which can lead to mutagenesis [73]. An abnormal MPO expression and greater risks of different forms of cancers are directly associated with MPO gene polymorphism [151]. In the promoter region of this peroxidase gene, single nucleotide polymorphisms (SNPs) can possibly affect the transcription and the protein level [152,74]. In addition to this, substitution of thymidine for cytosine in codon 569 cause substitution of amino acid from arginine to tryptophan, which may also cause some genetic defects of MPO [153].

In addition to gene polymorphism, MPO induces cancer through the activation of genotoxic intermediates and the procarcinogens through an indirect implication of MPO [154,155]. Metabolism of unsaturated fats and some amino acids like serine and threonine can form byproducts like acrolein, which in turn forms acrolein-protein adducts [156]. In humans, these new protein adducts can transform colon tumor from benign to malignant state [157]. Still, little information is available about such proteins which form adducts with the acrolein or their role in progression of tumor.

Several reports are available about the relationship between breast cancer and the increased serum MPO level as compared to the control groups. Promotion of this cancer is also enhanced by the inflammatory leukocytes, which produce ROS, chemo and cytokines, proteases, histamine and other mediators [158]. Various types of DNA damages and genomic instability occur by the MPO synthesized ROS [149,159]. So, in premenopausal women, suffering from breast cancer, MPO acts as one of the efficient markers [160]. So risks of the development of cancer are directly linked to the endogenous production of high MPO levels [161].

3.8. Cystic fibrosis

Cystic fibrosis (CF), a disease of the respiratory tract, is characterized by severe bacterial infections especially *P. aeruginosa* and huge numbers of infiltrating neutrophils [162]. Neutrophils are also thought to contribute the lung damage instead of eliminating bacteria from the respiratory tract [81]. CF patient's sputum contains high concentration of MPO and human neutrophil elastase (HNE) and these levels correlate with the severity of the lung disease [163,164]. The clear mechanism for the release of inflammatory mediators like HNE, extra cellular DNA and MPO from neutrophils during CF is not known. However, neutrophil extracellular traps gather a

potential mechanism for the release of these mediators [165].

4. Myeloperoxidase deficiency

Several studies have shown that in USA and Europe, the partial or complete MPO deficiency is relatively common among human population (affecting 1 in 2000 to 1 in 4000) [166,167]. But, there is a geographic heterogeneity between the frequencies of hereditary MPO deficiency in different populations as well reported 1 in 55000 in Japan [168-170]. Generally, the MPO deficiency results in modest increase of either inflammatory problems or infectious complications [171]. MPO deficient neutrophils exhibit impaired bactericidal and candidacidal activities against *S. aureus* and many species of *Candida* [172,173].

The deficiency of MPO is a hereditary problem that disposes to immune deficiency as well [174]. Several different types of autoantibodies have also been observed raised against MPO in various types of vasculitis. The three clinically most prominent vasculitis forms of this type are granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis. The autoantibodies against neutrophils also known as anti-neutrophil cytoplasmic antibodies (ANCA) have also been detected in perinuclear region staining [175].

5. Conclusion

MPO is a heme-containing homodimer of heavy-light chain protomers mostly present in the immune cells especially neutrophils. It is released from these cells by proinflammatory factors and during oxidative stress at the site of infection to combat different types of microbial activities. The antibacterial activities of MPO involve the production of different reactive oxygen and nitrogen species. MPO also plays role in chemical modifications of different lipoproteins, protein nitrosylation, tyrosyl radical formation and dityrosine crosslinking etc. Any unusual expression and release of MPO from activated neutrophils due to oxidative stress imbalance intensify the inflammation and tissue damage and may result in several diseases, even in the absence of infection. MPO is a well-known marker of several inflammatory diseases like rheumatoid arthritis, cardiovascular diseases, neurodegenerative diseases, diabetic retinopathy, liver diseases, cancer etc. Deficiency of MPO has also been reported in some human populations, which may result in modest increase either in inflammatory or infectious complications.

Conflicts of Interest: The authors declare no conflict of interest.

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