Myeloperoxidase: A New Twist to an Old Tale

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Traditionally, the enzyme myeloperoxidase (MPO) was almost exclusively associated with the phenomenon of innate immunity. For almost a century, most of the studies that were carried out on this enzyme were directed towards elucidating the intricate biochemical mechanisms involved in bacterial killing [1]. The unique ability of this enzyme to generate the hypochlorite ion by utilizing hydrogen peroxide, which is produced copiously in activated neutrophils, and chloride ions which is also always available in plenty, was elegantly demonstrated in several studies [2]. This was followed by an era in which the focus shifted to the deleterious effects of the same reaction on the host tissues; the acute inflammatory reaction that sets in and the downstream reactions which inevitably follow, causing damage to membrane lipids, proteins and even nucleic acids [3]. In recent times MPO is being implicated in diseases associated with chronic non-microbial pathological processes, which have no direct link with infection, and, in which oxidative stress and inflammation play dominant roles. This article seeks to provide a bird's eye view of these two aspects of the action of MPO, namely its protective action against micro-organisms and its role in chronic diseases associated with inflammation.

MPO is an oxidoreductase (EC No. 1.11.1.7) which is stored in the azurophilic granules of polymorphonuclear neutrophils [4]. It is a strongly cationic hemoprotein with a molecular mass of 114 kDa. It consists of two identical 72 kDa monomers linked by a disulphide bridge. Each monomer is composed of a light chain and a heavy chain

which is glycosylated and also contains the heme lodged in a deep cleft [5]. In the native form the heme iron is in the ferric state.

The enzymatic reaction catalyzed by MPO has been shown below

This simple reaction however does not completely represent the cascade of effects that are initiated by the catalytic action of MPO. Hypochlorous acid further reacts with H_2O_2 and nitrates to form reactive oxygen and nitrogen species ([6], see Fig 1).

The highly reactive nature of these products ensures destruction of the invading pathogen and is almost invariably associated with a certain degree of damage to the host tissue. While these reactions are primarily meant to take place within the confines of the phagosomes, not infrequently they are discharged outside the cell and this could bring about destruction of biomolecules in the surrounding tissue. Although MPO is crucial for the protection against invading pathogens, inappropriate activity of this enzyme could lead to host tissue damage. Increased activity of this enzyme is now being implicated in a wide variety of pathological conditions such as cardiovascular disease, cancer, renal disease, lung injury and Alzheimer's disease [2].

MPO and Cardiovascular Disease

In recent years several epidemiologic studies have shown that higher levels of MPO are associated with increased risk of cardio-vascular disease and also that this was independent of the hitherto established classical risk factors [7]. MPO levels were found to be higher in patients with angiographically proven coronary artery disease [8].

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Fig. 1 MPO activity triggers the production of several highly reactive and deleterious products

Several studies have suggested that measurement of MPO in patients presenting with acute chest pain provided clinically useful information of prognostic significance. In patients presenting with acute chest pain, it has been proved that, a single initial measurement of plasma myeloperoxidase independently predicts the early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30-day and six-month periods [9].

MPO serves not only as a marker of acute coronary syndromes but is also intimately involved in the process of atherosclerosis; it potentially acts as a mechanistic bridge between inflammation and cardio-vascular disease. MPO-dependant processes are involved in the etiopathogenesis of atherosclerosis through multiple mechanisms which include, foam cell formation, endothelial dysfunction, development of vulnerable plaque and ventricular remodeling following acute myocardial infarction [10]. The oxidative stress created by the down-stream products of increased MPO activity can bring about conversion of native LDL into the oxidized LDL, rendering it more atherogenic [11]. MPO decreases the protective potential of HDL by inducing alterations in apolipoprotein associated with it. Apo A-1 shows a hundred fold increase in the levels of 3-nitrotyrosine and 3-chlorotyrosine when exposed to the pro-inflammatory state produced by higher MPO activity [12]. Hazen and Heinecke reported that 3-chlorotyrosine was sixfold higher in human advanced atherosclerotic lesions compared with normal aortic tissue [13]. When subjects were classified into tertiles based upon the 3-chlorotyrosine content of HDL it was shown that the risk of developing CVD was 16-fold higher in the last tertile as compared with the first tertile.

Nitric oxide, a biomolecule which brings about vasodilatation, is rapidly inactivated by products of the MPO reaction causing endothelial dysfunction [14]. MPO also has a role in destabilization of stable coronary plaques by

promoting the degradation of the collagen layer which prevents abrupt rupture. Plaque destabilization and rupture are thought to be essential processes in inducing acute cardiovascular

events. These authors also found a higher incidence of unstable plaques in patients with AMI.

MPO may play a role in plaque destabilization by activating metalloproteinases, thereby weakening the fibrous cap [15]. The studies that have been quoted above form a small number in comparison with the large number of publications which link MPO, inflammation and cardiovascular disease.

MPO and Lung Injury

Studies carried out in experimental animals and humans have shown that MPO has a role to play in the induction of lung injury. Severe acute lung injury has been produced in rats by the simultaneous intratracheal infusion of glucose oxidase which served as a source of H₂O₂ and MPO [16]. Patients with idiopathic pulmonary fibrosis have increased levels of MPO in the alveolar epithelial lining fluid [17]. Tracheal aspirates of premature infants who developed chronic lung disease had elevated levels of 3-chlorotyrosine, which is considered to be a marker of protein damage by the MPO system [18].

Infiltration of lungs by neutrophils, a condition referred to as neutrophilia, is a common feature in a variety of lung diseases such as acute respiratory distress syndrome, idiopathic pulmonary fibrosis, asbestosis and chronic obstructive pulmonary disease [19]. Studies conducted by Haegens and coworkers have demonstrated that MPO promotes the development of lung neutrophilia and indirectly influences subsequent chemokine and cytokine production in the lung. Increased levels of MPO, a marker of active neutrophilia, have been found in the broncho-alveolar lavage of patients with COPD and MPO [20].

MPO and Alzheimer's Disease

MPO has been detected in microglia adjacent to senile clots in the cerebral cortex of patients with Alzheimer's disease [21]. Apo-E which is also found in senile clots of these patients is highly susceptible to oxidation by MPO [22].

MPO and Kidney Disease

MPO has been shown to be an important pathogenic factor in glomerular and tubulo-interstitial diseases. Several studies have shown the presence of MPO-containing cells

as well as MPO activity in a variety of renal disorders. When neutrophils adhere to glomeruli, they generate oxidants through MPO-catalysed reactions, causing degradation of the glomerular basement membrane. Renal perfusion experiments with MPO followed by its substrates, namely, H_2O_2 and chloride ions, resulted in glomerular morphologic changes, endothelial and mesangial cell injury, activation of platelets, and subsequent proliferative responses mimicking inflammatory and proliferative glomerular nephritis in humans.

MPO has been implicated in the pathogenesis of various types of renal diseases [23]. Studies carried out using experimental models of nephritis show considerable evidence for the role of neutrophil-mediated glomerular injury as evidenced by proteinuria. In experiments conducted by infusing MPO into the renal artery of the rat, the binding of this enzyme to the glomerular basement membrane was demonstrated by electron microscopy. MPO is a highly cationic protein and, therefore it could easily bind to the negatively charged sialo-glycoproteins and heparin sulphate proteoglycans of the glomerular basement proteins. Our studies have shown a steady decline in plasma MPO levels with advancing stages of chronic kidney disease [24]. The inhibitory effect of the uremic environment could have contributed to this. In another study conducted on patients with end-stage-renal disease, we observed that the process of hemodialysis itself resulted in a significant rise in plasma MPO levels [25].

There are always two sides to a coin as is true of the story of MPO. Although the destructive force of this enzyme is crucial for survival, given the constant encounters with deadly foreign organisms; on the flip side, it's slow and steady misguided relentless onslaught against passive bystanders leaves behind some bruised and battered tissues.

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