

The Role of Myeloperoxidase in the Pathogenesis of Coronary Artery Disease

Stephen J. Nicholls^{1,2} and Stanley L. Hazen^{1,2,3,4*}

¹Department of Cardiovascular Medicine, ²Center for Cardiovascular Diagnostics and Prevention, ³Department of Cell Biology, Cleveland Clinic Foundation and ⁴Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA

SUMMARY: A growing body of evidence continues to emerge implicating the role of myeloperoxidase (MPO) and its oxidant products in the promotion of atherogenesis. A major mechanism by which MPO impacts the arterial wall is through its modification of net cellular cholesterol flux. MPO promotes lipid peroxidation and conversion of LDL to an atherogenic form, where it is taken up by macrophages, a critical step in foam cell formation. Emerging evidence suggests that HDL can also be modified by MPO derived oxidants, resulting in an impairment of cholesterol efflux. In addition, modified HDL appears to be a strong predictor of clinical risk. These features highlight MPO and its products as potential predictive markers and targets in atheroprotection.

It has become increasingly recognized that atherosclerosis is a chronic inflammatory process, characterized by the accumulation of lipid, inflammatory cells and necrotic material within the arterial wall. As a result, there is great interest to identify the key factors promoting this process. A substantial body of evidence has emerged to implicate the role of the leukocyte derived enzyme myeloperoxidase (MPO) in atherogenesis. In particular, recent studies have highlighted the potential role that MPO plays in the regulation of cholesterol flux into the arterial wall.

Association between MPO and atherosclerosis: MPO, a member of the heme peroxidase superfamily, generates reactive oxygen species and diffusible radical species. It performs a physiological role as part of the innate immune system. However, MPO also can apparently exert a deleterious impact on the arterial wall. Immunohistochemical studies demonstrate the presence of MPO, its oxidant products, and their colocalization with macrophages, in human atheroma. Genetic studies support a protective role of MPO deficiency. MPO-deficient individuals have less coronary artery disease (CAD). In addition, a functional polymorphism in the promoter of the MPO gene, resulting in decreased enzyme expression, was associated with a decreased risk of CAD. Furthermore, systemic

levels of MPO and its oxidant products are associated with the prevalence of atherosclerotic disease. Systemic levels of MPO predict the presence and extent of angiographic disease (1). Moreover, levels predict the risk of clinical events in both subjects presenting with chest pain (2) or acute coronary syndromes (3).

MPO promotes atherogenesis via a range of mechanisms: It appears that MPO, through the generation of nitric oxide (NO)-derived oxidants, promotes numerous pathological events in the atherogenic cascade. In addition to generating potentially proatherogenic species, MPO utilises the atheroprotective NO as a substrate. These factors have been implicated in the development of endothelial dysfunction, accumulation of foam cells in the arterial wall and the promotion of plaque vulnerability (4). In particular, substantial evidence suggests that MPO derived oxidants influence the net flux of cellular cholesterol, via both an increase in its cellular uptake and a reduction in its removal.

MPO promotes cellular accumulation of cholesterol: Oxidative modification of low density lipoprotein (LDL) is a key early event in the promotion of atherogenesis. Modification of LDL to a high uptake form allows for its internalisation by macrophages, which undergo morphological changes to become foam cells, a major cellular component of the developing plaque. Evidence suggests that MPO-generated reactive nitrogen species convert LDL into a high uptake form, which is readily internalised by macrophages

*Corresponding author: E-mail: hazens@ccf.org

by a scavenger receptor mediated process. In addition to protein modification, MPO rapidly promotes the peroxidation of lipids. These modified lipids become attractive targets for uptake by macrophages and, in addition, promote the elaboration of proinflammatory factors, including adhesion molecules and chemokines. Furthermore, MPO-generated nitrating species promote the synthesis of cholesteryl esters and lipid loading of macrophages, resulting in the microscopic appearance of foam cells.

MPO impairs cholesterol efflux role of high density lipoproteins: It also appears that MPO promotes the oxidative modification of high density lipoproteins (HDL), influencing its ability to promote cholesterol efflux. Apolipoprotein A-I (apo A-I) modified by MPO-generated HOCl *in vitro* is less effective at promoting cholesterol efflux and more readily degraded by macrophages (5). It is possible that this chlorination impedes the interaction between apo A-I and the scavenger receptor SR-BI, which promotes cellular cholesterol flux (6). We recently identified apo A-I as a selective target for MPO catalyzed nitration and halogenation *in vivo*, with accompanying functional impairment *in vivo* (7). MPO facilitated modification of either HDL or apo A-I reduced their ability to promote ABCA1 dependent cholesterol efflux from cholesterol-laden macrophages. Serum Apo A-I demonstrated ~100-fold higher levels of nitrotyrosine and chlorotyrosine compared to total serum proteins, and apoA-I isolated from patients with CAD contained increased levels of nitrotyrosine and chlorotyrosine compared to healthy controls (7). The greatest content of these species was found in apo A-I isolated from human atheroma, suggesting that this oxidative modification occurs preferentially in the arterial wall. In addition, MPO was found to directly associate with both intact HDL and apo A-I, with a specific contact site on the lipoprotein for interaction with MPO noted. These results provide a structural basis for the colocalization noted between epitopes specific for proteins exposed to HOCl and apo A-I within human atheroma (8).

CONCLUSION

In summary, substantial evidence supports the concept that MPO and its oxidant products play a key role in the promotion of atherogenesis. A major mechanistic link appears to involve its influence on the net flux of cellular cholesterol. MPO promotes the conver-

sion of LDL and phospholipids to an atherogenic form, whilst at the same time reduces the protective ability of HDL to promote cholesterol efflux. These findings highlight the importance of MPO derived oxidants as both markers for risk prediction and targets for atheroprotection.

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