Editorial

MPO (Myeloperoxidase) Caused Endothelial Dysfunction

Not So Positive It Is About the Bleach, It May Be a Fatal Attraction

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MPO (myeloperoxidase) was first described as a highly abundant protein in neutrophils in 1941.[1] In 1958, MPO was purified,[2] but the function remained unknown. Over the next decade, studies revealed the mechanisms of degranulation[3] and reactive oxygen species production[4] by neutrophils during phagocytosis. A series of pivotal studies in 1967 and 1968 by Klebanoff[5–7] proposed the classical role of MPO in phagocytosis, suggesting that the MPO-halide-H_2O_2 system is a powerful antimicrobial mechanism. Highly reactive products of this system, including HOCl, are short-lived and react rapidly with any oxidizable group to kill pathogens during phagocytosis. Less reactive products, including H_2O_2 and some chloramines, can travel to be toxic at a distant site. Because MPO is a strongly basic protein and can bind to surface of a negatively charged cell, this potentially allows for continuous propagation of the antimicrobial response.

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In contrast to the classical role of MPO, there has been significant evidence that MPO can damage host tissue and contribute to human disease, specifically those that involve damage to the endothelium in the vasculature. Leukocyte-endothelial interactions are critically regulated to maintain macro- and microvascular health. Leukocyte MPO traditionally has been considered as a robust oxidation system that potentially has deleterious effects at the blood-endothelial interface, as well as the subendothelial space. Leukocyte interaction with the endothelium first involves an encounter with the endothelial glycocalyx. MPO has been shown to be released at or near the glycocalyx, accumulate along the endothelium, and be transported across endothelial cells.[8] MPO targets extracellular matrix proteins,[9] reduces NO availability,[10,11] and mediates neutrophil recruitment and activation[12,13] (Figure). MPO plays a role in renal disease,[14] sickle cell disease,[15] ischemia/reperfusion injury,[16] atherosclerosis,[17] and sepsis.[18,19]

In this issue of *ATVB*, Manchanda et al[20] reveal yet another deleterious role of MPO on the endothelium. Their cell culture and in vivo mouse studies elegantly demonstrate that MPO leads to the collapse of the endothelial glycocalyx. The authors revealed a novel mechanism in which MPO forms a physical interaction with glycocalyx heparan sulfate glycosaminoglycan residues leading to glycocalyx collapse, independent of the classic catalytic function of MPO. The cationic charge of MPO destabilizes the negatively charged endothelial glycocalyx, allowing for neutrophil recruitment and subsequent activation. Furthermore, MPO also stimulated the shedding of syndecan-1, a marker of endothelial glycocalyx breakdown. This is significant because these studies uncover another deleterious role of MPO on the endothelium.

Although this report by Manchanda et al[20] reveals a novel function of MPO, it also raises multiple questions. The exact mechanism by which MPO binds to heparan sulfate remains to be elucidated. Does MPO have specific binding sites or rather is MPO binding nonspecific for heparan sulfate? Heparan sulfate binds to proteins using a small number of cationic surface amino acids. The authors suggest that the binding is nonspecific because MPO has >70 of these cationic amino acids. Positive control experiments also showed positively charged polylysine binds to the glycocalyx reducing its negative charge. It is also important to note that neutrophil primary granules contain other cationic proteins, and these results do not exclude the possibility of their impact on the endothelial glycocalyx.

Overall, it is clear that MPO has many roles in changes in the endothelium. Studies examining the impact of MPO on altering endothelial function traditionally have focused on downstream products and actions of MPO catalytic activity, including tyrosine chlorination,[21] HOCl production,[22] MMP (matrix metalloproteinase) activation by cysteine oxidation,[23] and chlorinated lipid production.[19] The current study by Manchanda et al[20] provides an important new mechanism for MPO elicited endothelial dysfunction. This is potentially an important and novel paradigm, but as is with all new models, important questions remain to be answered to further elucidate this model. Future studies should establish the role of the noncatalytic function of MPO in glycocalyx alterations in human disease.

Sources of Funding

This work was supported (in part) by research funding from the National Institutes of Health R01 GM-115553 to D.A. Ford.

Disclosures

None.

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Arterioscler Thromb Vasc Biol*. 2018;38:1676-1677. DOI: 10.1161/ATVBAHA.118.311427.)

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***Arterioscler Thromb Vasc Biol* is available at https://www.ahajournals.org/journal/atvb**
DOI: 10.1161/ATVBAHA.118.311427

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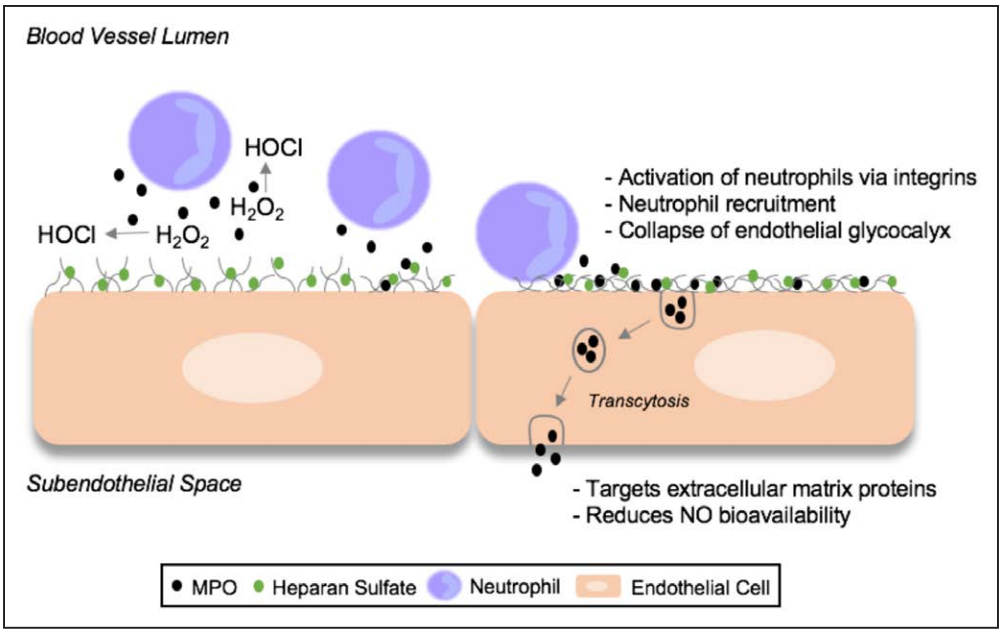

Figure. The impact of MPO (myeloperoxidase) on the endothelium. Classically, MPO produces HOCl near the neutrophil-endothelial interface. Apart from the catalytic activity, MPO can also recruit and activate neutrophils. This novel article demonstrates a physical interaction between MPO and heparan sulfate, leading to glycocalyx collapse. After transcytosis into the subendothelial space, MPO can also target extracellular matrix proteins and reduce NO bioavailability.

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Key Words: Editorials ■ atherosclerosis ■ glycocalyx ■ phagocytosis ■ sepsis ■ vascular disease

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