

Protein damage in cardiovascular disease

Supervisor:

Prof. Michael Davies, Panum Institute, Building 4.5

Email: davies@sund.ku.dk

Activated white cells play a central role in the immune response to invading pathogens. These cells generate large fluxes of reactive species via an oxidative burst that gives rise to the killing of pathogens. Inappropriate or misdirected stimulation of this system can however damage host tissues and inflammation-induced damage has been linked to multiple human pathologies including atherosclerosis, asthma, arthritis and some cancers.

A major source of these reactive oxidants is the heme enzyme myeloperoxidase (MPO) that is released by activated phagocytes. This enzyme catalyses the reaction of hydrogen peroxide (H_2O_2 , generated by the NADPH oxidase system of activated leukocytes) with halide (Cl^- and Br^-) and pseudo-halide (SCN^-) ions to form powerful oxidants, including hypochlorous acid (HOCl, the major component of household bleach), hypobromous acid (HOBr) and hypothiocyanous acid (HOSCN). Under physiological conditions, the major products formed are HOCl and HOSCN.

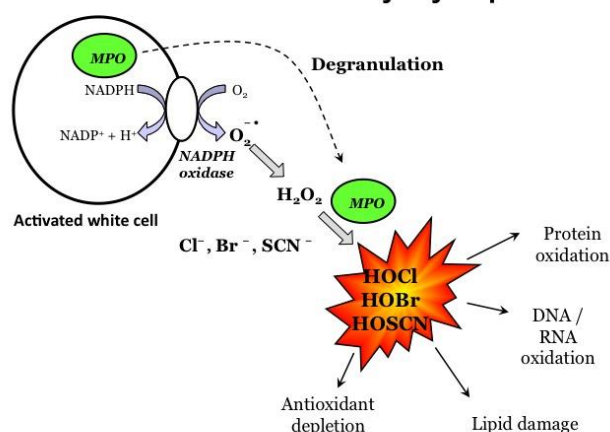
The reactions of HOSCN may be of particular importance in smokers, as smoking results in elevated plasma SCN^- levels, and hence greater concentrations of HOSCN, and such people suffer from an enhanced incidence, and a worse prognosis, for many inflammatory diseases.

The evidence for a role of MPO in cardiovascular disease is particularly compelling. Enzymatically active MPO and elevated levels of a biomarker generated by its oxidants (3-chlorotyrosine) are present in human atherosclerotic lesions. In addition, elevated MPO levels have been shown to be both a major risk factor for coronary artery disease, and a powerful predictor of health outcomes. However, the processes responsible for this elevated risk and detrimental outcomes remain unknown.

We have shown that MPO-derived oxidants have dramatic effects on human arterial endothelial cells and monocyte-derived macrophages, and can modulate multiple key proteins including tyrosine phosphatases (PTPs), kinases and nitric oxide synthases. This results in altered cell signalling, and a reduced availability of the key vasoactive molecule, nitric oxide.

In this project we will examine how these oxidants modulate the PTP / kinase balance in human coronary artery endothelial cells and how this might result in hyperphosphorylation and the induction of apoptosis. Such loss of endothelial cell function is one of the earlier markers of atherosclerosis and a key step in disease development.

Generation of oxidants by myeloperoxidase



Key references

1. Davies MJ et al, Mammalian heme peroxidases: from molecular mechanisms to health implications, *Antioxid. Redox Signalling*, 2008, 10, 1199-1234.
2. Lane AE et al, The myeloperoxidase-derived oxidant HOSCN inhibits protein tyrosine phosphatases and modulates cell signalling via the mitogen-activated protein kinase (MAPK) pathway in macrophages, *Biochem. J.*, 2010, 430, 161-169.