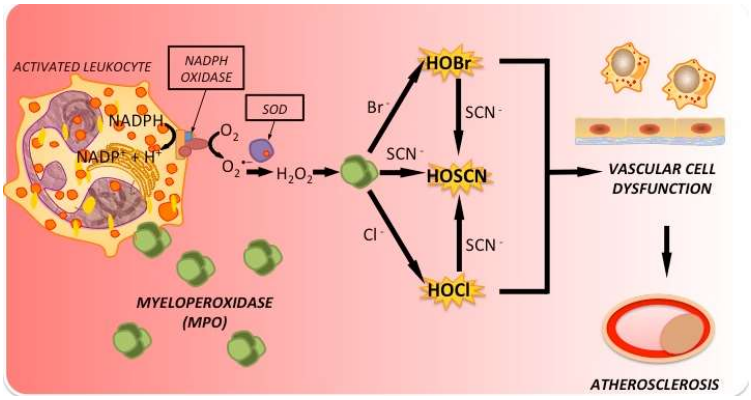
Investigating the molecular mechanisms involved in vascular cell damage and death, within the setting of atherosclerosis

Background

There is epidemiological, clinical, and experimental evidence that cellular stress and excessive inflammation are causally linked to various pathological conditions including atherosclerosis (hardening of the arteries). Macrophage infiltration and the resultant oxidant formation within atherosclerotic lesions in the vascular wall leads to oxidative stress, damage and ultimately death to cells of the vasculature. This accelerates lesion formation and can also result in the destabilisation of lesions, which is a major pathway to thrombosis and heart attacks. This project will focus on delineating the precise intracellular mechanisms and pathways that result from exposure to neutrophil and macrophage-derived oxidants to better inform the development of novel therapies for atherosclerosis.

Overview of Studies

This project will examine the pathways involved in vascular cell damage, with a focus on understanding how inflammatory oxidants produced by the enzyme myeloperoxidase (see Figure) modulate apoptosis, the oxidative stress response, and transcriptional regulation in various vascular cell types. The techniques that will be employed to achieve this goal include using endothelial, vascular smooth muscle and macrophage cell culture models, various biochemical assays, gene analysis by quantitative real-time PCR, protein expression analysis by Western blotting, and flow cytometry to analyse cellular dysfunction and death. The detailed knowledge relating to the biochemical mechanisms of vascular cell damage during inflammation is important for the design of new therapeutic agents to modulate inflammation and slow the progression of atherosclerosis.



Relevant Publications from our Group

- Love *et al*, Cellular targets of the myeloperoxidase-derived oxidant hypothiocyanous acid (HOSCN) and its role in the inhibition of glycolysis in macrophages. *Free Radic. Biol. Med.*, **94:** 88-98, 2016.
- Rayner *et al*., Comparative reactivity of myeloperoxidase-derived oxidants with mammalian cells. *Free Radic. Biol. Med.* **71:** 240-255; 2014.
- Lloyd *et al.,* Comparative reactivity of the myeloperoxidase-derived oxidants hypochlorous acid and hypothiocyanous acid with human coronary artery endothelial cells. *Free Radic. Biol. Med.* **65:** 1352-1362; 2013.

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