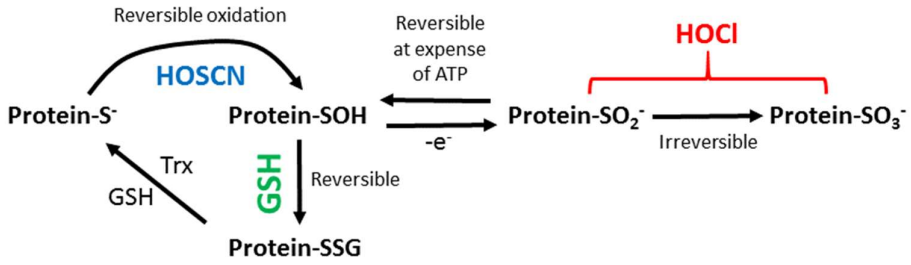
Investigating the effect of thiocyanate (SCN^-) in modulating oxidative damage in atherosclerosis

Background

Peroxidase enzymes are vital components of the human immune system, and are responsible for the production of chemical oxidants that kill bacteria and other invading pathogens. However, the immune cells that release peroxidase enzymes, particularly myeloperoxidase, also infiltrate tissue during inflammation. This results in an overproduction of chemical oxidants that can damage host cells and tissue and contribute to the development of numerous inflammatory diseases, including atherosclerosis – the major cause of heart disease. The main oxidant produced by myeloperoxidase during inflammation is the powerful bleaching agent hypochlorous acid (HOCl). HOCl reacts rapidly with almost all biological molecules, causing extensive, irreversible tissue damage and cell death, which is strongly correlated with disease progression. The anion thiocyanate (SCN^-) is present in the diet and decreases the production of HOCl by shifting the enzyme to produce a different chemical species, termed hypothiocyanous acid (HOSCN). HOSCN has a different pattern of reactivity compared to HOCl – it is selective for thiol (R-SH) groups and can react in a reversible manner (see Figure). This means that supplementation with SCN^- may be useful therapeutically to reduce HOCl-induced damage that is prevalent in atherosclerosis and other inflammatory diseases.



Scheme to show HOCl- and HOSCN-induced thiol modifications. Modification by HOSCN forms reversible oxidation products that can be repaired by cellular antioxidant enzymes (glutathione and reductase enzymes e.g. thioredoxin).

Overview of Studies

This project will build on our previous studies that show that exposure of cells to HOSCN can activate adaptive signaling pathways that boost antioxidant defenses and hence facilitate repair of damage (Love *et al*, 2016). We will assess whether supplementation with SCN^- can reduce oxidative damage and improve function in different inflammatory models. The approaches that will be employed to achieve this goal include use of different primary cell culture models and various analytical, biochemical and molecular biology methodologies to assess oxidative modifications, cellular viability, metabolic function, and alterations in protein and gene expression. This project will provide key mechanistic data on how SCN^- promotes repair and adaptation in cells subject to stress, which is necessary to understand how this anion provides protection at sites of acute and chronic inflammation and whether it can be used in a therapeutic setting to reduce the severity and development of inflammatory diseases.

Relevant Publications

- 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.
- Morgen *et al.* Thiocyanate supplementation decreases atherosclerotic plaque in mice expressing human myeloperoxidase. *Free Radic. Res.,* **49:** 743-749; 2015.

For more information contact:

Prof. Clare Hawkins, clare.hawkins@sund.ku.dk