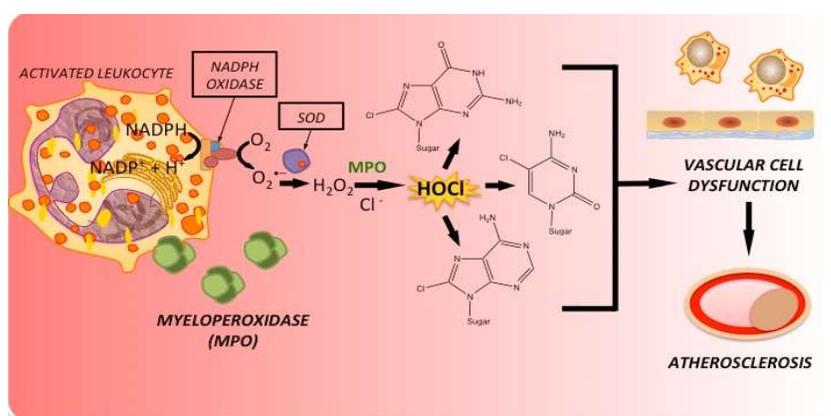


Investigating the role of nucleic acid modification in inflammatory disease

Background

Chlorine is a potent disinfectant, which is mainly present in aqueous solution as hypochlorous acid (HOCl), and molecular chlorine (Cl₂). Hypochlorous acid is used widely to kill harmful bacteria in both drinking water and swimming pools. This disinfectant is also produced in the body by activated leukocytes (white blood cells) via the myeloperoxidase-catalysed reaction of hydrogen peroxide (H₂O₂) with chloride (Cl⁻) ions (See Figure). The chemistry of HOCl in biological systems has attracted considerable attention, as excessive or misplaced production of this chemical during prolonged inflammation, where there is an infiltration of leukocytes, damages host tissue, which contributes to the development of disease. HOCl modifies the nucleoside building blocks of RNA and DNA, resulting in the formation of both oxidised and chlorinated products, which are present in inflammatory fluids and diseased tissue. Currently it is not known whether these modified nucleosides play a role in disease pathology.



Overview of Studies

This project will build on our preliminary data showing that different chlorinated nucleosides become incorporated into cellular RNA and DNA, and alter cellular function by the activation of stress-related signalling cascades that perturb protein and gene expression within the cells. These cellular changes can trigger the activation of cell death pathways, and lead to the release of pro-inflammatory molecules that are known to exacerbate disease. This may have toxicological significance for chlorinated drinking water supplies, in addition to providing novel insights into inflammation-induced disease. We will use a mass spectrometry approach to assess the uptake and turnover of modified nucleosides by different cell types and a molecular biology approach to define the cellular consequences of exposure to these agents. This project will provide training in primary cell culture, analytical techniques including HPLC and LC-MS, together with real-time RT-PCR (gene expression), Western blotting and ELISA (protein expression) and flow cytometry (cell function / death). This project will provide important data relating to the fundamental biochemical pathways involved in the propagation of inflammation, which is required for the development of new treatments for a range of diseases, including atherosclerosis and cancer.

For more information contact:

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