Kinetics and mechanisms of oxidative damage

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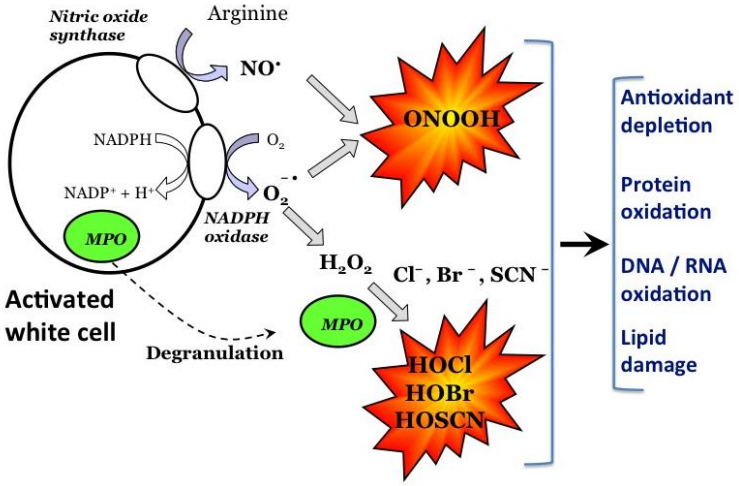
Activated white cells play a central role in the immune response to invading pathogens. These cells generate large fluxes of reactive species via an oxidative burst that gives rise to the killing of pathogens. Inappropriate or misdirected stimulation of this system can however damage host tissues and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

Rupture of the fibrous cap of atherosclerotic lesions is a major contributor to deaths arising from atherosclerosis. Rupture-prone lesions are known to have a thin fibrotic cap, have a decreased rate of matrix synthesis or an increased rate of degradation, contain oxidized matrix materials, and large numbers of activated macrophages that contain or release, enzymes that generate oxidants such as hypochlorous acid (HOCl, generated by the heme enzyme myeloperoxidase, MPO) and peroxynitrous acid (generated by the reaction of nitric oxide, generated by endothelial nitric oxide synthase with superoxide radicals).



Considerable evidence has been accumulated for a role for oxidants in cardiovascular disease. Enzymatically active MPO and elevated levels of biomarkers generated by released oxidants such as 3-chloro- and 3-nitrotyrosine have been detected in human atherosclerotic lesions. In addition, elevated levels of the enzymes that generate these species 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.

In the light of this data there is widespread interest in minimising damage induced by oxidants, either by preventing their formation, or by removal of these species once formed. In order to develop such compounds, it is imperative to understand the reactions of these oxidants and the damage they induce.

In this project state-of-the-art analytical methods (HPLC, UPLC and LC-MS/MS) will be used to characterise and quantify novel oxidation products generated by these oxidants with a particular emphasis on protein side chains that play a key role in stabilising protein structures and their functional activity.

Key References:

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2) Chuang, C.Y.; Degendorfer, G.; Hammer, A.; Whitelock, J.M.; Malle, E.; Davies, M.J. (2014) Oxidation modifies the structure and function of the extracellular matrix generated by human coronary artery endothelial cells, Biochem. J., 459, 313-322.
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