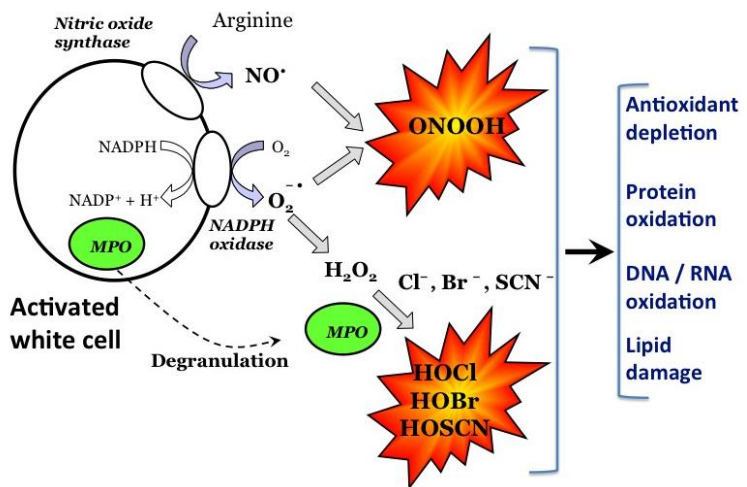


## Extracellular matrix damage in cardiovascular disease

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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 peroxyntrous acid (generated by the reaction of nitric oxide, generated by endothelial nitric oxide synthase with superoxide radicals). There is therefore considerable evidence that damage to matrix materials is a key event in this disease.



These data have led us to hypothesize that oxidants can damage the extracellular matrix and alter cellular function, and weaken the fibrous cap of lesions; this is believed to result in enhanced plaque rupture. The mechanism(s) by which such damage arises is not well defined. In particular there is a lack of information on the mechanisms and functional consequences of reaction of oxidants with the proteins, glycosaminoglycans (GAGs), and proteoglycans that make up the extracellular matrix of the artery wall.

In this project we will examine how these oxidants modulate the extracellular matrix generated by human coronary artery endothelial cells and human aortic smooth muscle cells and the functional consequences of these events. These events may play a key role in the development of cardiovascular disease.

### Key references

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