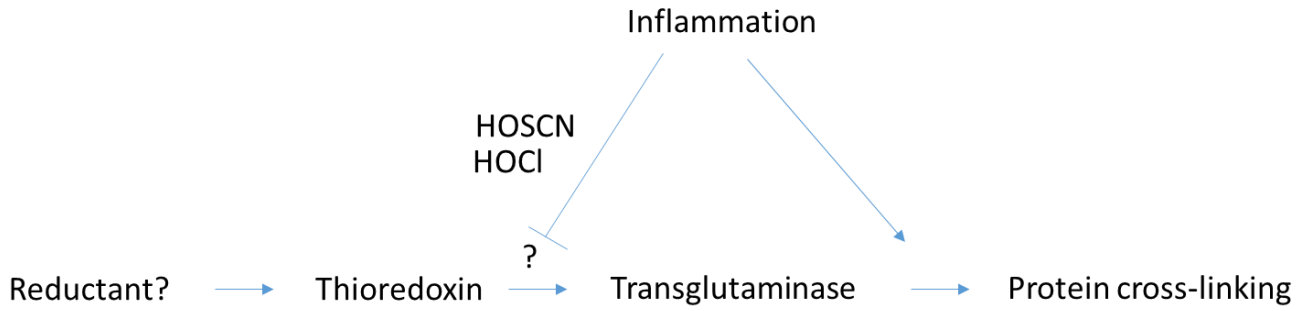
Impact of oxidants on thioredoxin – a redox regulator of extracellular matrix cross-linking in response to inflammatory disease?

Background: The protein thioredoxin (Trx) is a ubiquitous disulfide reductase that maintains cellular thiol groups in a reduced state and plays a key role as an electron donor for various enzymes such as ribonucleotide reductase and methionine sulfoxide reductase. The reducing power for these processes is provided by the NADPH-dependent flavoenzyme thioredoxin reductase. Recently, it has been reported that Trx is released from cells through an unknown mechanism, and can act as an activator of transglutaminase, an enzyme that forms non-reducible cross-links which stabilize proteins such as fibronectin in the extracellular matrix during inflammation and injury. Under such conditions increased levels of oxidants such as hypochlorous acid (HOCl) and hypothiocyanous acid (HOSCN) are produced by peroxidase enzymes released from activated immune cells (e.g. neutrophils, monocytes and some tissue macrophages). These oxidants may potentially cause reversible or irreversible damage to Trx and thereby affect its ability to reduce disulfidesin target proteins, such as transglutaminase.

We **hypothesize** that inflammation-induced damage to Trx will therefore have significant effects on the assembly and integrity of the extracellular matrices of tissues subject to inflammation.



The overall **aim** of this project is to gain novel insights into how Trx and its redox partners influence redox reactions involved in extracellular matrix synthesis and integrity. More specifically we will investigate how inflammatory oxidants such as HOCl and HOSCN impact on the structure and function of Trx. This project will provide important information regarding mechanisms involved in damage to the extracellular matrix during chronic inflammatory disorders such as atherosclerosis, the major cause of cardiovascular disease. The project involves the use of a range of state-of-the-art bioanalytical techniques in protein chemistry including mass spectrometry, chromatography, spectrophotometry and electrophoresis.

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