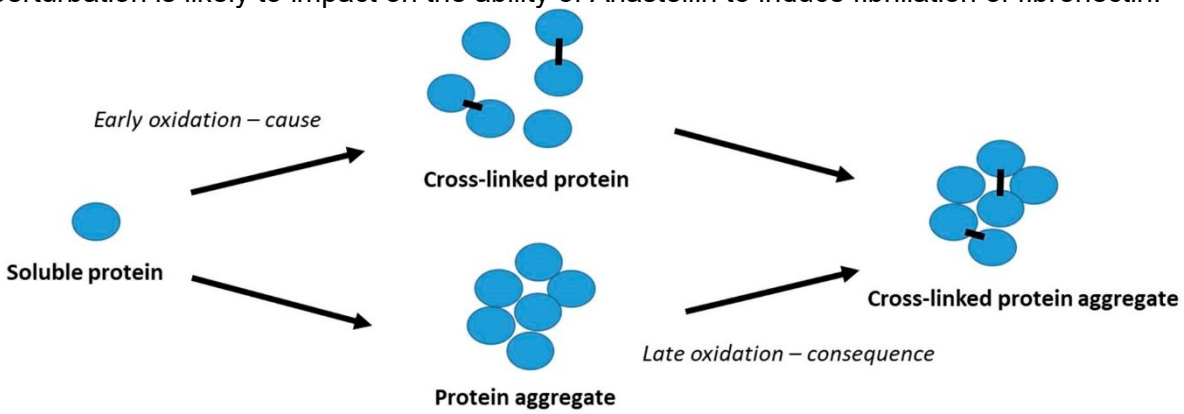
Is protein cross-linking a consequence or a cause of protein aggregation?

Pathologies such as Alzheimers, Parkinsons and cataract are associated with formation and accumulation of protein aggregates that play an important role in disease development. It is also well established that these diseases are linked to formation of oxidative protein modifications including non-reducible protein cross-links, such as dityrosine. It is however not known whether such cross-links are a consequence or cause of protein aggregation. Further insight into the mechanisms of cross-link formation is important for a better understanding of the mechanisms of disease development and may facilitate identification of biomarkers. As a model system to study protein aggregation and fibrillation we employ Anastellin, a fragment of the first type III domain in fibronectin, that can induce formation of superfibronectin, a polymerized form which resembles the native fibrillar form of fibronectin in the extracellular matrix.
Anastellin contains several aromatic residues which are potential targets of inflammatory oxidants such as peroxynitrous acid (ONOOH) or those generated by the leukocyte-derived heme enzyme myeloperoxidase that may induce formation of cross-links. Such structural perturbation is likely to impact on the ability of Anastellin to induce fibrillation of fibronectin.



We hypothesize that inflammatory oxidants will induce cross-links in Anastellin that may impact the ability of this protein to induce formation of protein fibrils and aggregates.
The overall aim of this project is determine the extent and nature of cross-links in aggregated and monomeric species of proteins exposed to oxidants. This data will provide important information regarding mechanisms of protein aggregation related to disease development. A range of state-of-the-art bioanalytical techniques will be applied including mass spectrometry, chromatography, spectrophotometry and electrophoresis.

Contact:

Per Hägglund (pmh@sund.ku.dk); Michael Davies (davies@sund.ku.dk)