Diabetes, glycation and extracellular matrix damage in cardiovascular disease

Supervisor: Prof. Michael Davies, Panum Institute, Building 4.5
Email: davies@sund.ku.dk

Cardiovascular disease (CVD) accounts for *ca.* 75% of deaths of people with diabetes. People with diabetes manifest a range of risk factors, and there is convincing evidence that hyperglycaemia and glycation are major contributing factors, but the mechanism by which this occurs is however unclear. This program will investigate the links between hyperglycaemia and atherosclerosis, the underlying cause of most cardiovascular disease.

Hyperglycaemia results in increased non-enzymatic modification of proteins by glucose, and reactive aldehydes derived from glucose and other metabolic processes (e.g. triose phosphate metabolism). Reactive aldehydes are elevated in people with diabetes and correlate positively with disease duration and severity. These species give rise to modified proteins and advanced glycation end-products (AGEs) and it is well established that elevated levels of AGEs are present in plasma and atherosclerotic lesions from people with diabetes, and correlate with disease severity and extent.

The extracellular matrix of the artery wall, which consists of a compelx mixture of proteins, proteoglycans and glycosaminoglycans, plays a key role not only in providing structure and elasticity to blood vessels, but also plays a key in determining cell adhesion, proliferation and function. Due to the high abundance of matrix proteins and proteoglycans, and their relatively slow turn-over, these species have been postulated to accumulate high extents of glycation-induced damage and AGEs, and there is limited experimental evidence to support this hypothesis.

We have hypothesized that glycation may induce significant structural and functional changes to the extracellular matrix of the artery wall, and thereby modify the function of adherent cells. In recent studies we have shown that extracellular matrix molecules damaged by other protein modifying agents are present at elevated levels in people with atherosclerosis, and in vitro studies have shown that these changes may modulate both endothelial and smooth muscle cell cell function. Whether similar events are exacerbated by hyperglycaemia and diabetes is less well understood and will be examined in this project.

Key references

1. Kennett, E.C.; Chuang, C.Y.; Degendorfer, G.; Whitelock, J.M.; Davies, M.J. (2011) Mechanisms and consequence of oxidative damage to extracellular matrix, Biochem. Soc. Trans., 39, 1279-1287.
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.
3. Chuang, C.Y.; Degendorfer, G.; Davies, M.J. (2014) Oxidation and modification of extracellular matrix and its role in disease, Free Radical Res., 48, 970-989.
4. Morgan, P.E.; Sheahan, P.J.; Davies, M.J. (2014) Perturbation of human coronary artery endothelial cell redox state and NADPH generation by methylglyoxal, PloS One, 9, e86564