Lipoproteins as a window on cardiovascular health.

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Lipoproteins in blood, for example those often referred to as “bad cholesterol” (Low Density Lipoprotein, LDL) and “good cholesterol” (High density lipoprotein, HDL), have for many years been identified as risk factors or beneficial factors for disease. Much attention has simply focused on the levels of the major lipid species carried by the lipoproteins, such as cholesterol and triglycerides, but in fact these parameters do not correlate very well with disease. The lipoproteins are known to be complex, containing the carrier proteins (ApoB100 for LDL and ApoA-I and ApoA-II for HDL) and an extensive collection of lipids in addition to those above, such as phospholipids, glycolipids, fatty acids and ceramides. Recently, we investigated the lipidomics of LDL in detail and found that in healthy volunteers in contained more than 350 different lipid species [1] and that changes in the lipidome occur in chronic kidney disease [2]

It is also well established that inflammation causes oxidative and other modifications of both lipid and protein molecules in lipoproteins, which have inflammatory effects and play an important role in diseases such as atherosclerosis. Phospholipid oxidation generates several reactive products that can attack the protein in a process called lipoxidation, and antibody-based assays for these modifications have shown that they are increased in cardiovascular disease. However, it is only recently that the molecular detail of the modifications have started to be elucidated in detail. We recently demonstrated the locations of a wide variety of modifications on Apo B-100, including oxidation, nitration and glycosylation, using novel mass spectrometry approaches [3]. These more informative approaches to detecting changes in lipoproteins are expected to lead to a better understanding on lipoprotein pathology, which will give information on the health of the cardiovascular system and may have value in diagnosis.

The aim of this project is to build on the techniques and approaches developed in our group to carry out advanced proteomic and lipdomic characterisation of the different modifications of apolipoproteins in healthy and disease samples. Aston University has extensive expertise in diabetes and neurodegeneration, so the initial stages of the project will focus on these conditions. Different lipoproteins will be separated by density gradient centrifugation, and then subjected to lipid extraction. After sample preparation, liquid chromatography mass spectrometry will be used to identify the modifications to both phospholipids and proteins. These will be mapped to different lipoproteins and principle component analysis will be used to investigate their relationship with disease. An important part of the project will also be to develop novel miniaturisation methods to allow analysis from small blood samples. Overall, the project will provide training in advanced mass spectrometry and omics technologies, as well as its application to pathology and clinical diagnostics.

References

[1]. http://www.ncbi.nlm.nih.gov/pubmed/23670529
[2]. http://www.ncbi.nlm.nih.gov/pubmed/25424003
[3]. http://www.ncbi.nlm.nih.gov/pubmed/23534669