EXPERT REVIEWS

Highlights from the 2010 BAS/BSCR spring meeting: New Frontiers in Cardiovascular Research

Expert Rev. Proteomics 7(6), 811–813 (2010)

Mélanie Abonnenc[1*], Christin Stegemann[1*] and Manuel Mayr[†1]

[1]*King's BHF Centre, King's College London, 125 Coldharbour Lane, London, SE5 9NU, UK*
[†]*Author for correspondence:*
Tel.: +44 207 848 5238
Fax: +44 207 848 5296
manuel.mayr@kcl.ac.uk

**Both authors contributed equally to this work*

2010 BAS/BSCR spring meeting
Manchester, UK, 7–8 June 2010

The British Atherosclerosis Society (BAS)/British Society for Cardiovascular Research (BSCR) spring meeting was held in Manchester, UK, on 7–8 June 2010. Experts in the field of systems biology, proteomics, metabolomics and miRNAs presented how these techniques can be used to discover 'New Frontiers in Cardiovascular Research'. The conference was attended by over 150 participants, mainly from the UK. A total of 2 days of presentations and a poster session with 55 posters provided the possibility to discuss the latest research results and showed the opportunities that new techniques can offer in cardiovascular research.

The British Atherosclerosis Society (BAS)/British Society for Cardiovascular Research (BSCR) spring meeting, 'New Frontiers in Cardiovascular Research' was held in Manchester, UK, on 7–8 June 2010. For the first time, a joint conference was organized, in conjunction with the British Cardiovascular Society (BCS). The British Heart Foundation (BHF) provided financial support to facilitate this interaction between the leading cardiovascular societies in the UK.

The scientific program started on Monday, with the first session focusing on systems biology and proteomics in cardiovascular research. This session was sponsored by the British Society for Proteome Research (BSPR). Systems biology aims to identify complex systems and to model their dynamic interactions. Jake Lusis (University of California, Los Angeles, CA, USA) discussed the four steps involved in a systems-based approach: to define the system to be examined; to identify the components of the system; to determine, experimentally or based on published work, how the components interact with each other; and finally, to model the dynamics of the network mathematically in order to determine changes over time or responses to perturbations [1]. This approach was successfully used to model inflammatory networks associated with atherosclerosis. Jake Lusis identified the cation transport regulator-like protein 1 (*CHAC1*), a novel gene regulated by oxidized 1-palmitoyl-2-arachidonyl-*sn*-3-glycero-phosphorylcholine (ox-PAPC) as a novel component of the activating transcription factor 4 and 3 - C/EBP homologous protein (ATF4–ATF3–CHOP) signaling pathway. Peter Kohl (University of Oxford, UK) defined a model as:

> *"…a simplified version of reality. It has to be simple enough to be understandable but complex enough to answer a biological question"* [2].

They used a systems-based approach combining experimental findings and simulations to model the heart. This approach provides a better understanding of cardiac mechanisms, such as calcium feedback, and how forces on the heart affect electrical activity.

The state-of-the-art in proteomics and its relevance in cardiovascular research were reviewed by Jennifer Van Eyk (Johns Hopkins University Proteomics Centre, MD, USA). She presented a study of the overall effect of preconditioning on the myocardial proteome using a gel-based proteomic approach [3]. Of interest, the majority of the altered proteins were involved in mitochondrial energetics. ATP synthase was shown

 10.1586/EPR.10.94 ISSN 1478-9450

to be implicated in several cardiac phenotypes and preconditioning. Phosphorylation of this enzyme upon preconditioning was demonstrated by mass spectrometry (MS) and revealed five novel phosphorylation sites. Finally, Andrew Pitt (University of Glasgow, UK) presented the urinary proteomics as a noninvasive tool for the diagnosis and monitoring of a variety of human diseases, such as coronary artery disease (CAD). Urine was analyzed with capillary electrophoresis online coupled to electrospray ionization time-of-flight (ESI-TOF) MS in order to identify a panel of polypeptide biomarkers as a signature of CAD [4]. A total of 15 peptides were part of a signature for CAD showing a sensitivity of 98 and 83% specificity. It remains to be seen whether these characteristic urinary peptides originate from the vasculature and have the potential to be used for early diagnosis and to monitor therapeutic interventions.

Constanza Emanueli (Bristol University, UK) received the Michael Davies Early Career Award 2009 for her work on 'novel molecular mechanisms of diabetes-induced endothelial damage: focus on $p75^{NTR}$ and microRNAs'. Her group has shown that the atypical neurotrophin receptor $p75^{NTR}$ mediates diabetes-determined impairment of reparative neovascularization. Going further into the understanding of the molecular mechanisms involving this receptor, they studied whether $p75^{NTR}$ modulates the expression of miRNAs. miRNA-503 was then demonstrated to have a role in diabetes-induced microangiopathy and impaired angiogenesis.

From those submitted, the six top-graded abstracts were chosen to compete for the Young Investigator Award. Simon Cuhlmann, a student in Paul Evans' laboratory (Imperial College London, UK), won the award. He showed that c-Jun N-terminal kinase promotes endothelial activation at atherosclerosis-susceptible sites by enhancing expression of nuclear factor-κB transcription factors. Besides oral sessions, 55 abstracts were presented as posters during the following poster session.

The scientific program finished with the BAS John French Lecture given by Manuel Mayr (King's College London, UK). His talk aimed to show how different 'omics' technologies, including proteomics, miRNA-omics and lipidomics, can be used in combination to advance our understanding of cardiovascular disease (CVD) and to find potential new biomarkers. In his first example, he showed results from a proteomic analysis of endothelial progenitor cells, revealing that this common culture assay does not result in the outgrowth of genuine endothelial stem cells but in macrophages contaminated with platelet proteins. The uptake of 'endothelial markers' such as CD31 (platelet endothelial adhesion molecule 1), which are abundant platelet proteins, has led to a misinterpretation of this assay [5]. These findings demonstrate the advantage of an unbiased proteomic approach to assess cellular phenotypes. In a second example, he presented a newly developed three-step protein extraction method for the proteomic analysis of extracellular matrix proteins, which resulted in the identification of 103 extracellular proteins, of which a third have never been reported in the proteomic literature of vascular tissues thus far [6]. The next part of the talk gave an insight into the complexity of lipids extracted from human atherosclerotic plaques. The group used shotgun lipidomics on a triple quadrupole (QqQ) MS to identify and quantify lipids extracted from different human plaques. A total of 28 plaque-specific lipids and an unanticipated lipid signature of vulnerable and stable plaque areas were identified. Last but not least, the potential of plasma miRNAs as biomarkers of CVDs was shown. In the first population-based study on plasma miRNAs, a miRNA signature for Type 2 diabetes was identified that included endothelial miRNA-126 [7].

The program of the second day included a session focused on metabolomics in cardiovascular research. Talks were given by Rob Gerszten (Massachusetts General Hospital, MA, USA) and Jules Griffin (University of Cambridge, UK). The first presentation focused on a metabolic platform developed to analyze changes in the human metabolome. Rob Gerszten's group developed a liquid chromatography (LC)-MS/MS-based platform that combines three different LC-columns with a triple quadrupole MS to analyze nucleotides, amino acids, organic acids, carbohydrates and recently implemented lipids. Within this targeted metabolomic approach, each metabolite is characterized by one specific transition, which is then used in multiple reaction monitoring measurements. This powerful approach covers most areas of the known human metabolome by scanning for one to two metabolites per metabolic pathway. The technology offers insights into the full complexity of disease phenotypes, such as CVD. One study focused on the identification of new biomarkers of myocardial injury [8]. This presentation demonstrated the potential of LC-MS for biomarker research in CVD. The second talk given by Jules Griffin gave an example of how NMR, which beside MS is a common technique for metabolomics, can be used for metabolome analysis. Urine and plasma from low-density lipoprotein receptor knockout mice fed on a high-fat diet and control mice fed on a standard diet were analyzed by ^{1}H NMR [9]. Multivariate statistical analysis of the metabolomic data showed that the high-fat diet and low-density lipoprotein receptor gene deficiency caused a significant metabolic perturbation in the metabolome of urine or plasma. Furthermore, the study shows that the detected metabolic changes are comparable with those detected in ApoE knockout mice fed the same high-fat diet and, therefore, offers a possibility to monitor the onset of atherosclerosis in animal models.

The afternoon started with a session entitled 'translational issues in cardiovascular research'. John Lepore (GlaxoSmithKline, UK) and Lars Sundstrom (Pharmnovo, UK) pointed out that collaboration between academia and pharmaceutical industry is necessary for successful drug development and there is a need to strike new paths of collaborations between both. David Crossman (University of Sheffield, UK) and Peter Weissberg (British Heart Foundation, London, UK) gave two very interesting talks about research funding, a topic as important as scientific presentations and discussions.

The meeting was closed with two plenary lectures given by Stefanie Dimmeler (Goethe University Frankfurt, Germany) and Guido RY De Meyer (University of Antwerp, Belgium), who both discussed new perspectives in cardiovascular research. Stephanie Dimmeler described the recent advances in the study of miRNAs in CVDs [10]. In endothelial cells, several specific miRNAs have

recently been identified to stimulate or inhibit angiogenesis *in vitro*. To name few, miRNA-126 was demonstrated to be highly enriched in endothelial cells and its expression appears essential for vascular development. Members of the miRNA-17–92 cluster were shown to modulate angiogenesis, while miRNA-143 and miRNA-145 were highly expressed in smooth muscle cells and alter smooth muscle cell maintenance. Understanding the complex network involving miRNAs and their targets will provide important insights for developing novel therapeutic strategies in CVDs. Dimmeler concluded by highlighting the need for complementary techniques such as proteomics to help in the understanding of miRNA targets and functions. The second lecture by Guido RY De Meyer stressed the role of autophagy in cardiovascular research [11]. Autophagy is a major cytoprotective pathway that eukaryotic cells use to degrade and recycle cytoplasmic contents. The role of autophagy in normal cardiovascular function and in CVDs was discussed along with the therapeutic potential of pharmacological approaches. Autophagy is now recognized as being involved in human disorders but the most fundamental question for autophagy in CVDs is whether its role is harmful or protective.

Overall, this joint meeting of the BAS/BSCR within the BCS was seen as a success and will be held again next year at the same venue.

Financial & competing interests disclosure

Manuel Mayr is a Senior Research Fellow of the British Heart Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Lusis AJ, Weiss JN. Cardiovascular networks: systems-based approaches to cardiovascular disease. *Circulation* 121(1), 157–170 (2010).

2 Kohl P, Crampin EJ, Quinn TA, Noble D. Systems biology: an approach. *Clin. Pharmacol. Ther.* 88(1), 25–33 (2010).

3 Arrell DK, Elliott ST, Kane LA *et al.* Proteomic analysis of pharmacological preconditioning: novel protein targets converge to mitochondrial metabolism pathways. *Circ. Res.* 99(7), 706–714 (2006).

4 Zimmerli LU, Schiffer E, Zürbig P *et al.* Urinary proteomic in coronary artery disease. *Mol. Cell. Proteomics* 7(2), 290–298 (2008).

5 Prokopi M, Pula G, Mayr U *et al.* Proteomic analysis reveals presence of platelet microparticles in endothelial progenitor cell cultures. *Blood* 114, 723–732 (2009).

6 Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M. Proteomic characterization of extracellular space components in the human aorta. *Mol. Cell. Proteomics* 9(9), 2048–2062 (2010).

7 Zampetaki A, Kiechl S, Drozdov I *et al.* Plasma microRNA profiling reveals loss of endothelial MiR-126 and other microRNAs in Type 2 diabetes. *Circ. Res.* 107, 810–817 (2010).

8 Lewis GD, Wei R, Liu E *et al.* Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. *J. Clin. Invest.* 118, 3503–3512 (2008).

9 Cheng KK, Benson GM, Grimsditch DC, Reid DG, Connor SC, Griffin JL. A metabolomic study of LDL receptor null mouse fed a high-fat diet reveals profound perturbations in choline metabolism that are shared with ApoE null mice. *Physiol. Genomics* 41, 224–231 (2010).

10 Urbich C, Kuehbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. *Cardiovasc. Res.* 79, 581–588 (2008).

11 Martinet W, Knaapen MW, Kockx MM, De Meyer GR. Autophagy in cardiovascular disease. *Trends Mol. Med.* 13(11), 482–491 (2007).