BRITISH SOCIETY FOR HAEMOSTASIS AND THROMBOSIS

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P & J Live, Aberdeen

Emerging Fellows presentation summary + biography

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Danger-associated molecular patterns S100 A8/A9 and heme as novel targets in thrombo-inflammation

Dr Julie Rayes
Birmingham

Hyperactive platelets and platelet-leukocyte aggregates are hallmarks of acute and chronic thrombo-inflammatory diseases such as SARS-CoV-2 infection, myocardial infarction and sickle cell disease. Under these conditions, danger-associated molecular patterns (DAMPs) are released from damaged cells as well as immune cells and can contribute to the thrombo-inflammatory environment. We investigate the effect of 2 DAMPs, heme and S100A8/A9, which are increased during haemolysis and ischemic events, on platelet activation and thrombosis.

We found that these 2 DAMPs trigger non-classical thrombosis, through different receptors, and these mechanisms are resistant to classical anti-platelet drugs. Heme induces platelet activation through CLEC-2. Platelet activation by heme triggers potent NETosis, which is reversed by blocking Src and Syk and by the anti-malarial drug hydroxychloroquine. However, inhibition of CLEC-2 or hydroxychloroquine did not alter ROS generation in platelets. Treatment of haemolysed blood with hydroxychloroquine reduces platelet adhesion on heme-activated endothelial cells. In vivo, hydroxychloroquine significantly reduces ferric chloride-induced thrombosis in the carotid but had no effect in *laser injury-induced thrombosis* in the cremaster arteriole, showing the efficacy of hydroxychloroquine in limiting thrombosis under oxidative stress conditions associated with heme release. In parallel, S100A8/A9 induces procoagulant platelets through GPIbα, with low capacity to aggregate. S100A8/A9 supports fibrin generation and the propagation of thrombosis, leading to fibrin-rich clots, independent of S100A8/A9 classical receptors.

In conclusion, we show that heme and S100A8/A9 act as prothrombotic DAMPs inducing non-classical platelet activation and thrombosis. Heme and S100A8/A9 emerge as novel targets to limit thrombosis in acute and chronic thrombo-inflammatory diseases.

Dr Julie Rayes
PhD, Lecturer in Cardiovascular Sciences, Institute of Cardiovascular Sciences, University of Birmingham

Julie Rayes holds a PhD in thrombosis and haemostasis from the University of Denis Diderot-Paris VII in France. During her post-doctoral fellowships, she focused on studying novel crosstalks between the haemostatic and innate and adaptive immunity. Since, 2019, she was appointed as Lecturer in Cardiovascular Sciences at the University of Birmingham and recently received a BHF intermediate Fellowship. Her research group focuses on understanding novel mechanisms of thrombo-inflammation induced by danger associated molecular patterns, which will be the focus of her talk.

Pathophysiology underlying the increased risk of thrombosis in overweight and obese pregnant women

Dr Susan McNeill
Glasgow

Venous thromboembolism (VTE) remains the leading direct cause of maternal mortality despite the implementation of risk-stratified thromboprophylaxis guidelines. Obesity was over-represented in the 2018 UK-MBRRACE maternal mortality report, with 73% of VTE-related deaths occurring in women who were either overweight or obese. With pregnancy already recognised as a prothrombotic state, the concurrent effects of obesity appear to further increase the risk of thrombosis with several population-based studies demonstrating a 2-5 fold increased risk of VTE for pregnant women with a BMI≥ 30. As a result, the Royal College of Obstetricians and Gynaecologists took a pragmatic approach to advise an increased dose of LMWH in pregnant women of higher body weight. However, the evidence base for this strategy is very weak and deaths still occur due to VTE during pregnancy.

Despite the epidemiological evidence, the pathophysiology underlying the increased thrombotic risk in overweight and obese pregnant women is poorly understood. In the non-pregnant obese population, a chronic inflammatory state associated with obesity, abnormal cytokine release from adipocytes and adipose tissue distribution are thought to contribute to the prothrombotic state. More research is required in the pregnant population.

In this study we aimed to characterize the prothrombotic state in obese pregnancy by assessing inflammatory cytokines, adipokines and adipose tissue distribution and correlating these measures with thrombin generation and BMI. By gaining a more thorough understanding of the prothrombotic state in obese pregnancy, it provides an opportunity for further strategies to reduce this risk to be developed.

Dr Susan McNeill
MBChB, MRCP, FRCPath
Clinical Research Fellow in Haematology
University of Glasgow
Haemostasis Department at Glasgow Royal Infirmary

Susan graduated from medical school at the University of Edinburgh in 2009, moving west to Glasgow for medical training and Haematology Specialty Training. She always had an interest in Haemostasis and Thrombosis and was fortunate to be awarded a BHF Clinical Training Fellowship in 2019. She is completing an MD investigating the prothrombotic state of obesity during pregnancy with supervisors Dr Catherine Bagot (Glasgow Royal Infirmary) and Dr Dilys Freeman (University of Glasgow).

Fibrin(ogen), a double-edged sword in thrombosis and wound healing

Dr Fraser Macrae
Leeds

Fibrinogen, one of the most abundant plasma proteins, plays a key role in blood clot formation when it is converted to fibrin upon activation of the coagulation cascade. Fibrin polymerises to form long fibres that have a positive impact on haemostasis by stabilising the platelet plug contributing to the prevention of blood loss. Fibrin also plays a further positive role in wound healing following secondary haemostasis where it acts as a provisional matrix proving a 3D scaffold for the influx of cells involved in the tissue repair process. It is well established that changes in the structure of the fibrin network can also have a negative impact contributing to an increase in thrombosis risk. It is also known that failure to remove fibrin from a wound can stall the tissue repair process. During this presentation I will give an overview on my research into some of the positive and negative impacts fibrinogen has or may have on thrombosis and wound healing. This will include exploring the role of newly discovered fibrin films in thrombosis and wound healing, the role of fibrinogen splice variant γ′ in clot formation under flow and the influence of clot structure on wound healing and how diabetes induced changes in clot structure may be impacting on the tissue repair process.

Dr Fraser Macrae
PhD
University Academic Fellow and Sir Henry Wellcome Fellow
University of Leeds, Discovery & Translational Science Department, Leeds Institute of Cardiovascular & Metabolic Medicine

Fraser completed his undergraduate medical sciences degree at Leeds University in 2011. He began working for Professor Robert Ariëns in 2012 as a research assistant before undertaking a PhD focussing on the role of fibrin clots in cardiovascular disease and infection.

In 2019 Fraaser was awarded a Sir Henry Wellcome Fellowship to explore fibrin films in infection and wound healing.

In 2020 he was promoted to University Academic Fellow to continue exploring the multifaceted role of fibrin(ogen) in thrombosis and tissue repair.

Non-invasive in vivo coronary artery thrombus imaging

Dr Evangelos Tzolos
MD, Research Fellow and Cardiology Registrar, University of Edinburgh

Background: The diagnosis and management of myocardial infarction is increasingly complex and establishing whether intracoronary thrombosis has occurred has major implications for both its classification and treatment. Using a novel glycoprotein IIb/IIIa-receptor radiotracer, ^{18}F-GP1, we investigated whether positron emission tomography and computed tomography could non-invasively detect *in vivo* thrombus formation in human coronary arteries.

Methods: Specificity and selectivity of ^{18}F-GP1 binding was assessed using micro-positron emission tomography and autoradiography of freshly generated human thrombus and coronary thrombectomy specimens. In a single centre case-control study, patients with or without acute myocardial infarction underwent coronary ^{18}F-GP1 PET-CT angiography. Coronary artery ^{18}F-GP1 uptake was assessed visually and quantified using maximum target-to-background ratios.

Results: ^{18}F-GP1 demonstrated highly specific and selective binding to platelet-rich regions of fresh human and coronary thrombus. ^{18}F-GP1 PET-CT angiography was performed in 49 patients with, and 50 patients without, acute myocardial infarction (61±9 years, 75% male). In those with acute myocardial infarction, 49 vessels had an angiographic culprit lesion and 39 (80%) had coronary ^{18}F-GP1 uptake. There was no ^{18}F-GP1 uptake in the non-culprit coronary arteries or in any coronary artery of those without myocardial infarction giving a specificity of 100% and sensitivity of 80%. False negative scans appeared to relate to time delays to scan conduct and low thrombus burden in small calibre distal arteries. On multivariable regression analysis, culprit vessel status was the only independent variable associated with higher ^{18}F-GP1 uptake. Extra-coronary ^{18}F-GP1 uptake identified cases of myocardial haemorrhage and microvascular obstruction (35%) and left ventricular (8%) or left atrial (2%) thrombus.

Conclusions: Coronary ^{18}F-GP1 PET-CT angiography is the first specific and accurate non-invasive test to identify *in vivo* coronary thrombosis in patients with acute myocardial infarction. It further defines the role and location of thrombosis within the heart that has the potential to inform the diagnosis, management and treatment of patients with acute myocardial infarction.

Dr Evangelos Tzolos
MD, Research Fellow and Cardiology Registrar, University of Edinburgh

Cardiology research fellow at the University of Edinburgh, Edinburgh Heart Centre and Cardiology Registrar in NHS Lothian. Prior Imaging fellow of Cedars-Sinai Medical Centre, Los Angeles. Fellow of the Royal College of Physicians/London. Intended future career in interventional cardiology with an interest in coronary physiology, cardiac CT and structural heart disease.