

## Immunity, Atherogenesis and Vascular Function

The session entitled *Immunity, Atherogenesis and Vascular Function* was presented as part of an ISN Forefronts Symposium, organized by the International Society of Nephrology (ISN) and held in Shenzhen, China, 22-25 October 2015. The goal of the symposium was to review, update, and exchange current knowledge and ideas on the pathophysiology of hypertension, vascular injury, atherogenesis, and immune regulation. The symposium brought together cardiovascular physiologists, nephrologists, and immunologists to promote exploration of new and innovative areas in research, as well as to encourage new and wider cross-disciplinary collaborations.

Dr Andrew Newby's review, based on his lecture at the ISN symposium, discusses how metalloproteinase from macrophages cause atherosclerotic plaque rupture and myocardial infarction (Newby *et al.* 2016). Macrophages are present at all stages of human and experimental atherosclerosis. Although widely assumed that the M1 pro-inflammatory state of macrophages can promote plaque rupture and lead to myocardial infarction, the evidence in support of this is only slowly accumulating. Moreover, the important mediators of macrophage activation are uncertain, which is a barrier to the development of appropriate treatments (Stoger *et al.* 2012). In his presentation and review, Dr Newby highlights that plaque rupture and myocardial infarction are most likely the result of a 'perfect storm' caused by the synergistic local effects of multiple inflammatory mediators acting together in a hypoxic environment combined with the loss of anti-inflammatory factors that are responsible for an excess of matrix metalloproteinase (MMPs) over tissue inhibitors of MMP (TIMPs) expression. Dr Newby goes on to critically appraise new data pointing to the relative importance of foam cell formation as a result of lipid accumulation, and the role of acquired and innate immunity, and discusses the limitations of identifying precise mediators in human atherosclerosis and in animal models. While MMP and TIMP are regulated divergently in human and mouse macrophages, production of matrix degrading enzymes is a key feature connecting macrophage activation to plaque instability. Inflammatory mediators work through activator protein-1 and nuclear factor- $\kappa$ B signalling pathways to regulate different MMP and TIMP expression levels. Dr Newby also reviews transcriptional and epigenetic regulation of protease production, together with recent evidence from population genetics that supports their importance. Furthermore, he addresses prospects for new therapies targeted at macrophage activation or its consequences to prevent strokes and myocardial infarctions.

Dr Zhiming Zhu provides an overview of the role of transient receptor potential (TRP) channels in the pathogenesis of hypertension and metabolic vascular damage (Zhu *et al.* 2016), also based on his ISN symposium lecture. It is well documented that intracellular  $\text{Ca}^{2+}$  ( $[\text{Ca}^{2+}]_i$ ) homeostasis is important for vascular function and blood pressure regulation, as well as for hormone secretion. Recently, TRP channels have gained attention in the field of hypertension and metabolic disorders research because of their unique roles in controlling  $[\text{Ca}^{2+}]_i$  concentration and vascular function. Mammalian TRP channels can be divided into six subfamilies, including TRP canonical (TRPC), TRP vanilloid (TRPV), TRP melastatin (TRPM), TRP mucolipin (TRPML), TRP ankyrin (TRPA) and TRP polycystin (TRPP). Dr Zhu and his colleagues found an increase in

TRPC3 and TRPC5 channel protein expression linked to an increase in the gadolinium/calcium-influx ratio through TRPC channel activities in the monocytes and the vasculature, which are important for an elevation in blood pressure. In contrast, activation of TRPV1 and TRPM8 cause vasodilatation and a lowered blood pressure (Zhu *et al.* 2011). Activation of TRPV1 by capsaicin elicits release of NO from endothelium and vasodilatation, which is inhibited by the TRPV1 antagonists. In addition, TRPM8 activation by menthol attenuates vasoconstriction and lowers blood pressure. These findings suggest a functional equilibrium among different TRP channels subtypes that play a critical role in maintaining vascular function and normal blood pressure control. Indeed, Dr Zhu propose's an imbalance in TRP channel function as a new underlying mechanism for hypertension (Liu *et al.* 2014), which may facilitate the design of new therapeutics for hypertension and associated vascular damage.

In conclusion, these review articles provide a useful and timely update in the field of applied vascular biology that should encourage further study on the wider interactions of immunity, atherogenesis, and vascular function.

Jie Sun, Xiaolin Zhang, Xiong Z. Ruan,

Email: [xiongzruan@gmail.com](mailto:xiongzruan@gmail.com) [x.ruan@ucl.ac.uk](mailto:x.ruan@ucl.ac.uk)

## References

- Liu D, Xiong S, Zhu Z (2014) Imbalance and dysfunction of transient receptor potential channels contribute to the pathogenesis of hypertension. *Sci China Life Sci* **57**, 818-825.
- Newby AC (2016) Metalloproteinase production from macrophages - a perfect storm leading to atherosclerotic plaque rupture and myocardial infarction. *Exp Physiol*. DOI: 10.1113/EP085567
- Stoger JL, Gijbels MJ, van der Velden S, Manca M, van der Loos CM, et al. (2012) Distribution of macrophage polarization markers in human atherosclerosis. *Atherosclerosis* **225**, 461-468.
- Zhu Z, Xiong S, Li Q (2016) The role of transient receptor potential channels in hypertension and metabolic vascular damage. *Exp Physiol*. DOI: 10.1113/EP085568
- Zhu Z, Luo Z, Ma S, Liu D (2011) TRP channels and their implications in metabolic diseases. *Pflug Arch Eur J Phy*. **461**, 211-223.