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Themed Section: Targeting Inflammation to Reduce Cardiovascular Disease Risk

EDITORIAL

Targeting inflammation to reduce cardiovascular disease risk

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This joint themed section of the *British Journal of Pharmacology* and the *British Journal of Clinical Pharmacology* stems from a joint British Pharmacological Society – Italian Society of Pharmacology symposium held at the 37th National Congress of the Italian Society of Pharmacology in Naples (Italy) from 27 to 30 October 2015.

LINKED ARTICLES

This article is part of a themed section on Targeting Inflammation to Reduce Cardiovascular Disease Risk. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.22/issuetoc and http://onlinelibrary.wiley.com/doi/10.1111/bcp.v82.4/issuetoc

Abbreviations

AT, adipose tissue; ATL, aspirin-triggered lipoxin A4; CVDs, cardiovascular diseases

Cardiovascular diseases (CVDs) are the major cause of morbidity and mortality in Western society and, in the near future, are expected to be the main cause of death globally (WHO, 2011). Basic research data strongly support a crucial role played by inflammatory and immune mechanisms in CVD, and studies in animal models have shown that specific immune-inflammatory pathways could be targeted for therapeutic utility. However, the translation of this scientific knowledge to the treatment of human CVDs is still in the early stages (Welsh *et al.*, 2017).

New and selective immune therapies are already in use for the treatment of autoimmune diseases, and large clinical trials have just been published or are currently evaluating the effect of several of these treatments on atherosclerosis and related pathologies. The outcome of these studies is likely to lead to new approaches in the management of vascular inflammation.

This joint themed section of the *British Journal of Pharmacology* and the *British Journal of Clinical Pharmacology* has brought together scientists studying cardiovascular inflammation over a broad range of topics. The aim is to provide an up-to-date overview of the current understanding of inflammatory and immune mechanisms in CVD, to summarize the current clinical picture regarding the use of anti-inflammatory drugs in cardiovascular medicine and to discuss future directions towards more specific immune therapies.

The themed section is introduced by Welsh *et al.* (2017). These authors provide an overview of the key therapeutic targets in the treatment of vascular inflammation, placing basic research in a wider clinical perspective. Following the publication of the review article, data from the Phase III **Canakinumab** Anti-inflammatory Thrombosis Outcomes Study (https://clinicaltrials.gov/ct2/show/NCT01327846) have been published, showing that canakinumab – a monoclonal antibody against **IL-1β** – in combination with standard therapy reduces recurrent cardiovascular events in patients with a prior myocardial infarction and high levels

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of circulating C-reactive protein (Ridker *et al.*, 2017). This is the first demonstration in a large, randomized, double-blind, placebo-controlled phase III study that using anti-cytokine-based therapies may be a viable approach for secondary prevention of atherosclerosis-related CVD. This is particularly relevant given that the use of traditional non-steroidal anti-inflammatory drugs and coxibs alike is limited by cardiovascular toxicity, as comprehensively discussed by Patrono (2016). He provides an overview of the cardiovascular effects of **COX**-2 inhibitors, with a focus on the mechanisms contributing to the clinical readouts of COX-2 inhibition.

Several other key immune-mediated mechanisms in CVD could represent future options for therapeutic targeting and are discussed in detail in this issue. T-cell-mediated immune responses play a key role in ischaemic heart disease and in acute viral myocarditis (Stephenson *et al.*, 2017). The authors propose that the development of novel-specific diagnostic biomarkers could help to identify at an early stage patients who may benefit from immunomodulatory therapies. Sage and Mallat (2017) discuss therapeutic strategies to target adaptive immunity to reduce atherosclerosis progression, such as regulatory T-cell enhancing therapies, B-cell depletion and vaccine-based approaches. Their work is complemented by the review from Foks and Kuiper (2017), where the authors discuss the therapeutic potential to control atherosclerosis through targeting a large variety of co-stimulatory and inhibitory immune checkpoint proteins. In addition, the role of cytotoxic lymphocytes such as NK cells, $CD8^+$ T-cells, NK T-cells, γδ T-cells and human $CD4^+CD28^-$ T-cells in the development of atherosclerosis and unstable atheromas is reviewed (Kyaw *et al.*, 2017).

Inflammation and hypercholesterolaemia are linked in a cycle where an excess of **cholesterol** accumulating in the vessel wall layers induces immune-inflammatory response(s), which in turn increase cholesterol deposition and accelerate pathology formation and development. Catapano *et al.* (2017) provide an overview of the crosstalk between inflammation and lipid metabolism, suggesting that the clinical impact of lipid-lowering drugs on inflammation is proportional to the reduction of LDL cholesterol levels. Concurrently, Iqbal *et al.* (2017) discuss the negative impact of systemic and vascular inflammation on the healthy metabolism and function of HDL cholesterol.

The contribution of perivascular adipose tissue (AT) to vascular inflammation has gained significant attention recently. Adipocytes, immune cells and fibroblasts within AT secrete a broad range of adipokines exerting endocrine or paracrine effects on the cardiovascular system. Among them, the role of **adiponectin** in cardiovascular pathogenesis, its capacity to regulate the crosstalk between AT and the cardiovascular system and its role as a biomarker in CVD is comprehensively discussed (Woodward *et al.*, 2017).

In the final review article, Cirino *et al.* (2017) discuss the role of gasotransmitters in vascular physiology and pathology. The authors summarize what is currently known on the interconnection between **NO** and **hydrogen sulfide**, pointing out that addressing the molecular mechanisms underlying the interaction of these two gaseous mediators may lead to the development of new therapeutic approaches.

The themed section ends with five original research contributions. The work by Roviezzo *et al.* (2017) analyses the effect of **proteinase-activated receptor 2** on aortic contraction in fibrotic tight-skin mice. Petri *et al.* (2017) investigated the effect of **aspirin-triggered lipoxin A4** (ATL) and its receptor **Fpr2** on atherosclerosis development and progression, showing anti-atherogenic effects of ATL in apolipoprotein E-deficient mice. The selective **Mas receptor** agonist AVE0991 was shown to exert anti-atherosclerotic effects by affecting monocyte/macrophage recruitment to the perivascular space in experimental atherosclerosis (Skiba *et al.*, 2017). Esposito *et al.* (2017) demonstrated that the **dipeptidyl peptidase 4** inhibitor **sitagliptin** preserved diastolic function in a rat model of heart failure with preserved ejection. Finally, the effect of inhibitors of COX-2 and microsomal **PGE synthase-1** enzyme, which catalyses the formation of **PGE_2** from COX-derived **PGH_2**, was compared *in vitro,* on human vascular tone (Ozen *et al.*, 2017).

In summary, this joint themed section of the *British Journal of Pharmacology* and the *British Journal of Clinical Pharmacology* will provide readers with a review of the key inflammatory and immune mechanisms in cardiovascular pathologies, the role of lipid and gas mediators in cardiovascular inflammation and the use of conventional anti-inflammatory drugs in cardiovascular medicine. In addition, the interplay between vascular inflammation and lipid metabolism, together with recent clinical trials targeting immune pathways for CVD prevention, is comprehensively discussed. Great advances have been made in our understanding of immune mechanisms underlying CVD. Translation of these findings in clinical practice has only just begun. However, promising recent results may pave the way for the design of novel tissue-specific and or disease-specific immunomodulatory approaches to tackle the challenge posed by CVD for public health.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015a,b,c).

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Conflict of interest

The authors wish to acknowledge that they are co-authors of the articles by Welsh *et al.* (2017), Cirino *et al.* (2017) and Roviezzo *et al.* (2017) in this issue. They have also co-authored papers with Andrew Sage, Ziad Mallat, Liberato Berrino, Francesco Rossi, Antonella De Angelis and Konrad Urbanek.

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