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Themed Section: Chinese Innovation in Cardiovascular Drug Discovery

EDITORIAL

Chinese innovation in cardiovascular drug discovery

Xin Wang[1], Yong Ji[2] and Baofeng Yang[3]

[1]*Faculty of Life Sciences, The University of Manchester, Manchester, UK,* [2]*Atherosclerosis Research Centre, Nanjing Medical University, Nanjing, China, and* [3]*Department of Pharmacology, Harbin Medical University, Harbin, China*

Correspondence
Xin Wang, Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, UK. E-mail: xin.wang@manchester.ac.uk

LINKED ARTICLES

This article is part of a themed section on Chinese Innovation in Cardiovascular Drug Discovery. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-23

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GPCRs[a]	**Enzymes**[f]
β_1-adrenoceptor	CaMKII
β_2-adrenoceptor	CBR1
M_3 receptor	ERK1
Ligand-gated ion channels[b]	ERK2
ENaC	JNK
Ion channels[c]	MEK
KCNQ1/KCNE1	MKK4
TRPV1	NOS
Nuclear hormone receptors[d]	p38
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Catalytic receptors[e]	
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LIGANDS	
ACh	Cisapride
Adenosine	Genistein
Amiodarone	Nitric oxide (NO)
Aspirin	Oestrogen
BMP-4	RGS5
Choline	Spironolactone

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d,e,,f]Alexander *et al.*, 2013a,b,c,d,e,f).

Recent epidemiological data highlight the prevalence of cardiovascular disease (CVD) in China. One in five Chinese adults is suffering from CVD and this number is expected to double within the next decade. Approximately 3.5 million Chinese adults die of CVD annually, which accounts for 41% of total deaths, placing CVD as the leading cause of death in China. Facing this increasingly serious medical concern and economic burden, the Chinese government, academics and pharmaceutical industries have been making great endeavours in both basic and translational research aiming to identify and validate new drug targets and in subsequent new drug development. Here, Gao *et al*. (2015) is giving an overview on the current status of cardiovascular research in China, focusing on drug discovery and development that have been achieved since the last decade, and the challenges China will be facing down the road.

Although protein-coding genes as determinants for the pathogenesis of CVD are a generally accepted dogma, recent studies have added the non-protein-coding genes microRNAs (miRNAs) as new players in CVD. Over the past few years, Chinese researchers have contributed greatly to this research field. In this issue, Pan *et al*. (2015) summarize the current status of miRNA research in China with an emphasis on cardiac arrhythmia, myocardial ischaemia, cardiac hypertrophy and heart failure. They also describe the potential of miRNAs as novel diagnostic biomarkers and therapeutic targets.

GPCRs are the largest and most diverse group of membrane receptors in eukaryotes, and represent the largest class of drug targets. Upon ligand binding, GPCRs undergo a conformational rearrangement, followed by interactions with effector proteins, including the cognate G-proteins and the multifunctional adaptor proteins, like β-arrestins. These effector proteins fulfil one or several functions by initiating distinct signal transduction pathways. Recently, the notion of ligand-directed GPCR signalling, also called functional selectivity or biased agonism, has been proposed to explain the phenomenon that chemically varied ligands exert different efficacies through distinct signalling pathways. Many studies have demonstrated that ligand-specific GPCR conformations are the basis of ligand-directed signalling. In this issue, Woo *et al*. (2015a) highlight the recent advances in techniques used in the study of functionally-selective GPCR conformations with a particular focus on the β_2-adrenoceptor.

The interferon regulatory factor (IRF) family was first described as transcriptional regulators of the type I interferon system. Since 1988 when the first IRF was identified (Miyamoto *et al*., 1988), most studies on IRFs have focused on their functions in the immune system. However, recent clinical and experimental studies have unravelled the critical roles of IRFs in CVD, arising from their involvement in divergent molecular networks beyond the immune response. Zhang *et al*. (2015) review the current understanding of IRFs as novel stress sensors and mediators of CVD. The common consequence of heart disease is heart failure and the associated mortality and morbidity (Heidenreich *et al*., 2013). Cardiac hypertrophy is the cellular response to pathological stress characterized by the thickening of ventricular walls (Frey and Olson, 2003), which eventually leads to symptoms of heart failure (Kemp and Conte, 2012). Lang *et al*. (2015) demonstrated that capsaicin activates transient receptor potential vanilloid (subtype 1; TRPV1) channels through improvement of mitochondrial function, which represents a novel target for the management of early cardiac dysfunction. Qin *et al*. (2015) report that genistein markedly attenuates pressure overload-induced cardiac dysfunction, hypertrophy and fibrosis. The underlying mechanism may involve the regulation of the MTA3/TAK1/MKK4/JNK signalling pathway. Genistein may have the potential to prevent cardiac disorders associated with fibrosis. Meanwhile, Yin *et al*. (2015) report that isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate (IDHP), the main metabolite of Compound Danshen Dripping Pills in the heart, prevents cardiac fibrosis by inhibiting the NOX2/ROS/p38 pathway, suggesting that IDHP is a potential candidate drug to combat cardiac fibrosis.

Oestrogen has been well documented to inhibit cardiac hypertrophy and apoptosis. However, its detailed mechanisms of action are still unclear. Here, the study by Wang *et al*. (2015b) demonstrates that oestrogen treatment inhibits BMP4-induced BMP4 expression in cardiomyocytes through stimulating the ER-β and inhibiting JNK activation, uncovering a novel mechanism of oestrogen-mediated protection against cardiac hypertrophy. This study provides further evidence in support of oestrogen replacement therapy for heart diseases.

In recent years, clinical studies have indicated that aldosterone antagonists in combination with the standard therapies significantly decrease the risk of ventricular arrhythmias associated with heart failure. However, the antiarrhythmic mechanisms of these drugs are not fully understood. The study reported by Lv *et al*. (2015) sheds light on this aspect by showing that hyperaldosteronaemia lengthens the QT interval and action potential duration in an *in vivo* guinea pig model and *in vitro* cultured cardiomyocytes, and increases the incidence of early after depolarizations. They further clarified that aldosterone down-regulates *KCNQ1* and *KCNE1*, the genes encoding the K^+ channel subunits carrying the slow component of delayed-rectifier potassium current I_{Ks}, which probably accounts for the QT prolongation in hyperaldosteronaemia, as aldosterone has no effect on the rapid component of the delayed-rectifier potassium current I_{Kr}. Hyperaldosteronism-induced electrophysiological remodelling is fully prevented by co-administration of the aldosterone antagonist spironolactone. These results provide new insights into the mechanisms underlying potassium channel remodelling in the heart and enhance our understanding of the clinical benefits of aldosterone antagonists for treating heart failure associated with ventricular arrhythmias.

The role of autonomic imbalance in heart failure has been a focus of recent research. Autonomic imbalance, characterized by a reduction in vagal (parasympathetic) activity and an increase in the input from the sympathetic nervous system, correlates with various CVDs (Olshansky *et al*., 2008). On the one hand, dysregulation of β-adrenoceptor subtype signalling is a critical cause in the development of heart failure and, therefore, β-blocker treatment to suppress sympathetic overactivation has been the mainstay of heart failure therapy. Woo *et al*. (2015b) give an overview on this perspective and propose that the combination of a Gs-biased β_2-adrenoceptor agonist and a β_1-adrenoceptor antagonist may represent a novel therapeutic approach for better treatment of heart

failure. On the other hand, vagal modulation for correcting autonomic imbalance has been largely neglected for correcting autonomic imbalance. Here, He *et al*. (2015) give an overview of therapeutic strategies to improve autonomic imbalance through enhancing vagal tone, including direct vagal activation (electrical vagal stimulation, ACh administration and ACh receptor activation), pharmacological treatments (using adenosine, cholinesterase inhibitors and statins) or exercise training (He *et al*., 2015). In addition, they review the mechanisms underlying the benefit afforded by enhancing vagal activity, including anti-inflammatory pathways, modulation of NOS and NO signalling, regulation of the redox state, improvement of mitochondrial biogenesis and functions, as well as calcium regulation. Insights into these mechanisms may be of relevance to the development of novel therapeutic approaches for correcting autonomic imbalance.

Vascular dysfunction is a key aetiology of many cardiovascular conditions, such as hypertension, atherosclerosis, diabetes and stroke (Brunner *et al*., 2005). Wang *et al*. (2015a) show that nuciferine, which is found within lotus leaves, elicits a vasorelaxant effect via both endothelium-dependent and -independent mechanisms. The activation of M_3 receptors by choline reduces cardiovascular risk. The article by Lu *et al*. (2015) suggests that inhibition of the ROS-mediated CaMKII pathway and modulation of Ca^{2+}-cycling proteins may present novel mechanisms underlying choline-induced vascular protection. These findings suggest the possibility of targeting M_3 receptors in the vasculature for the management of ischaemia/reperfusion (I/R)-induced vascular injury. High-salt intake is known to be a 'lifestyle' factor for hypertension; yet how salt causes hypertension remained poorly understood. To shed light on this issue, Liu *et al*. (2015a) investigated how endothelial epithelial sodium channel (ENaC) in Sprague-Dawley rats respond to high-salt challenge. Their results revealed that high-salt intake increased blood pressure, along with simultaneous enhancement of endothelium-dependent relaxation primarily due to high salt-induced down-regulation of ENaC expression and activity.

Low-dose aspirin is effective for the secondary prevention of heart attack and stroke, and for the primary prevention of non-fatal myocardial infarction (Marangoni and Poli, 2013; Gouya *et al*., 2014). However, patient responses to this therapy are extremely variable (Floyd and Ferro, 2014). The study by Gong *et al*. (2015) provides a potential solution for optimizing the efficacy of aspirin therapy; the authors report that co-administration of fish oil and low-dose aspirin can act synergistically to protect against thrombosis and injury-induced vascular remodelling in mice.

Hydrogen sulphide (H_2S), a member of the endogenous gasotransmitter family in addition to NO and CO, has recently been found to influence a wide range of physiological and pathological processes associated with vessel constriction and relaxation. Meng *et al*. (2015) review the current state of research on H_2S and its role in hypertension. A better understanding of the functions of H_2S may lead to the identification of novel strategies for the treatment of hypertension and related CVDs.

Atherosclerotic CVD is a leading cause of premature death worldwide (Libby *et al*., 2013). Liu *et al*. (2015b) report that cryptotanshinone from Danshen has anti-atherosclerotic effects through the inhibition of the lectin-like oxidized LDL receptor 1-mediated signalling pathway. The article by Cheng *et al*. (2015) explores the effect of regulator of G-protein signalling 5 (RGS5) on atherosclerosis and the underlying mechanisms. They report that RGS5 deletion accelerates the development of atherosclerosis and decreases the stability of atherosclerotic plaques partly through activating NF-κB and the MEK-ERK1/2 signalling pathways. In addition, cardiovascular effects of PPARs (Cheang *et al*., 2015) and class A1 Scavenger Receptor (Ben *et al*., 2015) are reviewed in this themed issue.

For drug development, predicting compound safety at an early stage is a challenge. The *in silico* prediction system offers a powerful platform for drug screening. Yuan *et al*. (2015) review recent progress in the development of mathematical modelling of drug–ion channel interactions. They propose a detailed biophysical computer model of the heart as a useful tool for studying drug–ion channel interactions during normal and disease conditions. They also present a case of assessing the pro-arrhythmic effects of cisapride and amiodarone by mathematical simulations. This review also discusses several challenges for further development of a virtual human heart for screening drug cardiotoxicity.

Although many natural products have been proven effective in CVD in China and other countries as well, their targeting and signalling mechanisms of action remain to be identified. Zhou *et al*. (2015) propose an approach of 'reverse pharmacokinetics' to aid the discovery of targets or mechanisms based on the pharmacokinetic profile of naturally existing compounds. Based on the pharmacokinetic data from multiple levels, they demonstrate that 23-hydroxybetulinic acid, a major active constituent isolated from *Pulsatilla chinensis*, inhibits doxorubicin metabolism and thus reduces its active metabolite doxorubicinol-induced cardiotoxicity via interaction with carbonyl reductase 1 (CBR1). This study provides a new pharmacokinetic-directed research model to elucidate the mechanism of drug action.

In conclusion, with 22 papers including 10 reviews and 12 original research articles, this themed issue highlights the state of cardiovascular research in China.

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