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Inflammation, lipid metabolism dysfunction, and hypertension: Active research fields in atherosclerosis-related cardiovascular disease in China

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Atherosclerosis-related cardiovascular disease is one of the leading causes of death in China [1]. With advances in our understanding of the molecular mechanisms of atherosclerosis vascular inflammation, lipid metabolism dysfunction, and hypertension are regarded as the main pathogenetic pathways of both early atherogenesis and advanced plaque rupture [2,3]. Currently, much attention is being paid to the control of these pathways, which offers the potential for development of novel therapeutic approaches in the treatment of cardiovascular disease in China.

In the past few decades, considerable evidence has underscored that atherosclerosis is a chronic inflammatory disease of the arterial wall, where numerous molecular inflammatory components such as organophosphate and lipopolysaccharide (LPS) play crucial roles in the development of atherosclerosis [4,5]. ATP-binding cassette transporter A1 (ABCA1), a cytomembrane transporter first cloned in 1994, has been identified as playing a key role in cholesterol reverse transport (RCT), which is regarded as anti-atherosclerotic. Evidence from many recent studies indicates that inflammation impairs RCT, and many atherogenic-related mediators play distinct regulatory roles in ABCA1 expression [2]. Liu and colleagues [6] (South Central University) investigated the effect of paraoxon, an active metabolite of organophosphorus insecticide that increases cholesterol retention in macrophages [4], on ABCA1 expression and ABCA1-dependent cholesterol efflux in RAW 264.7 macrophage-derived foam cells, and found that paraoxon significantly downregulated ABCA1 expression and reduced ABCA1-dependent cholesterol efflux through cyclic AMP signaling pathway. Our group [7,8] (University of South China) found that LPS and interferon (IFN)-γ can downregulate expression of ABCA1 and promote accumulation of lipid and decrease cellular cholesterol efflux in THP-1 macrophage-derived foam cells.

Vascular endothelial dysfunction is known as the primary step in vascular inflammation and atherogenesis. Liu and colleagues [9] (Peking Union Medical College and Chinese Academy of Medical Sciences) discovered that human paraoxonase gene cluster transgenic overexpression represses atherogenesis and promotes atherosclerotic plaque stability in apoE-null mice. They also found that endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apoE-deficient mice [10]. Liu *et al.* [11] (Central South University) found that treatment with paraoxon resulted in significant inhibition of endothelium-dependent relaxation (EDR) in rabbits as well as a significant decrease of endothelial nitric oxide synthase (eNOS) activity in isolated aorta. These findings suggest that subchronic exposure to environmentally relevant matter such as LPS and organophosphate, even at low concentrations, potentiates inflammation, cholesterol retention, and

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athero-sclerosis.

It is worth noting that some Chinese traditional medicine and nutritive material from food may be useful for preventing and treating endothelial dysfunction and inflammatory response. Wen *et al*. [12] (Hebei Medical University) investigated the effects of 1,6-*O*,*O*-acetylbritannilactone (ABLO2), an extract of *Inula britannica* L., on activation of endothelial cells and its interaction with macrophages treated with LPS, and found that ABLO2 inhibited adhesion between endothelial cells and macrophages by decreasing expression of vascular cell adhesion molecules via inhibiting NF-κB activation by blocking IκB kinase (IKK) activation. Ma and colleagues [13] (Hebei Medical University) investigated the effects of eicosapentaenoic acid (EPA) on the release of inflammatory cytokines in human endothelial cells stimulated by LPS, and found that EPA inhibits LPS-induced production of inflammatory cytokines such as VEGF, IL-1α, and IL-6 in cultured HUVECs via suppressing activation of NF-κB.

A crucial feature of vulnerable plaques is the necrotic core, which contributes to inflammation, thrombosis, and proteolytic plaque breakdown [3]. Necrotic cores arise partly from apoptosis of advanced lesional macrophages. Although the significance of apoptosis in atherosclerosis depends on the stage of the plaque, sustained induction of apoptosis in advanced lesions seems to favor arterial wall inflammation and enhances recruitment of monocytes, leading to increased plaque burden [14]. Recently, many lipid metabolism-related genes have been found to play special roles in regulation of apoptosis. Proprotein convertase subtilisin/kexin 9 (Pcsk9), a central player in the regulation of levels of the LDL receptor, was recently identified to play a special role in macrophages apoptosis. Liu *et al*. [15] (University of South China) found that apoptosis of THP-1-derived macrophages induced by oxLDL could be effectively suppressed by pcsk9 siRNA, suggesting a novel role for pcsk9 in the development of inflammation and atherosclerosis. As a multifunctional regulator in cholesterol metabolism of mammal cells, Daxx has been suggested to play a special role in the function of macrophages, although the exact mechanisms remain to be elucidated [16]. Liao *et al*. [17] (Hunan University of Chinese Medicine) reported that Daxx mediates oxLDL-induced macrophages apoptosis by upregulating expression of caveolin-1.

Accumulation of free cholesterol (FC) in the endoplasmic reticulum (ER) is also a cause of macrophage apoptosis. ABCA1 plays a key role in removing intracellular FC into vesicles that are translocated to the plasma membrane for exocytosis, suggesting a unique role for ABCA1 in protecting FC loading, ER stress, and oxidized lipids-mediated apoptosis [2]. Apoptosis of vascular smooth muscle cells (VSMCs) has also been identified as an important process in restenosis after percutaneous coronary intervention (PCI) [18]. Han and coworkers [19] (Fourth Military Medical University) revealed that E1A-stimulated genes (CREG), a recently described glycoprotein that plays a crucial role in cellular or tissue homeostasis, plays a key role in modulating VSMC apoptosis by p38/JNK signaling transduction pathway *in vitro*, suggesting a potential therapeutic target for attenuating the progression of atherosclerotic plaques and restenosis after PCI. This was the first study to show that CREG is involved in VSMC apoptosis.

Necrosis, another form of cell death, often results in more serious inflammation, organ failure, or mortality in atherosclerosis-related cardiovascular disease [20]. Lin *et al*. [21] (Nanjing University) investigated the cell death mode switch from necrosis to apoptosis in hydrogen peroxide-treated macrophages, and found that negative feedback between NF-κB and MAPKs is implicated in converting necrosis into apoptosis in macrophages exposed to hydrogen peroxide.

Essential hypertension (EH) is a complex disease caused by interaction of genetic and environmental factors, in which impairment of constriction and relaxation of vascular ring is the main pathophysiologic characteristic [22]. Chen *et al*. [23] (University of South China) reported that the diastolic reactivity of apelin-13, a G protein-coupled receptor APJ endogenous ligand, is reduced in *ex vivo* vascular rings of spontaneously hypertensive rat (SHR) via NO- and ERK1/2-dependent pathways. Gao *et al*. [24] (People's Liberation Army 323rd Hospital) also found that apelin-13 decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) in SHR. These results provide new insights for understanding the function of apelin in EH.

Endothelial lipase (EL) is an important determinant of high-density lipoprotein (HDL) metabolism and inflammation acting at the vessel wall. Liao *et al*. [25] (Hunan University of Chinese Medicine) investigated the effect of high hydrostatic pressure on expression of EL, and revealed that hydrostatic pressure increased mRNA and protein expression level of EL in human umbilical vein endothelial cells, which may be related to nuclear factor-κB signal pathways. Their findings suggest that EL may be a possible link between hypertension and vascular inflammation.

The roles for microRNAs (miRNAs) in cardiac hypertrophy and heart failure are well documented. However, little is known about the roles of miRNAs in EH. Recently, Xin and colleagues [26] (Capital Medical University) reported for the first time a circulating miRNA profile for hypertensive patients using microarray-based miRNA expression profiling, and found that 27 miRNAs including miR-296-5p, let-7e, and a human cytomegalovirus-encoded miRNA were differentially expressed between hypertensive patients and control subjects, suggesting that miRNA is a new frontier in EH research. The enzyme eNOS plays an important role in maintaining normal relaxation of coronary arteries. Ou *et al*. [27] (University of South China) revealed a new mechanism for eNOS expression, which was mediated by 27-nt miRNA located in intron 4 of eNOS gene. Their data further revealed that the expression of transcription

factors Sp-1 and Ap-1 was altered by 27-nt miRNA, suggesting that 27-nt miRNA may play a potential role in development of EH via regulating expression of eNOS. Globular actin has been reported to increase activity of eNOS. Ji *et al.* [28] (Nanjing Medical University) have shown that eNOS agonists such as adenosine and histamine can regulate eNOS activity through affecting its association with globular actin, providing a novel mechanism for regulating eNOS activity by eNOS agonists.

Dysfunction of lipid metabolism including hypertriacylglyceridemia and hypercholesterolemia is well established as an independent risk factor for atherosclerosis-related cardiovascular disease [29]. Liu and colleagues [30] (Beijing University Medical Center) have observed spontaneous atherosclerosis arising in aged lipoprotein lipase (a rate-limiting enzyme in hydrolysis of triacylglycerides in plasma VLDL)-deficient mice with severe hypertriacylglyceridemia on a normal chow diet, indicating a strong association between hypertriacylglyceridemia and coronary arteriosclerotic disease. Our group [31] (University of South China) has established that activation of liver X receptor, a crucial mediator in lipid metabolism, reduces atherosclerotic lesions in apoE-null mice by upregulating NPC1 expression and HDL levels. An early event leading to the genesis of atherosclerosis is accumulation of cholesterol and other lipids within the arterial wall, which were taken up by scavenger receptors such as scavenger receptor A. Deng *et al*. [32] (Beijing University of Aeronautics and Astronautics) found that accumulation of lipids within the arterial wall is positively correlated with concentration polarization of atherogenic lipids, and the integrity of the endothelium plays an important role in penetration and accumulation of atherogenic lipids in blood vessel walls.

Berberine, an alkaloid derived from Chinese goldthread, has been identified as lowering serum cholesterol levels. The effect of berberine on atherosclerosis development, however, remains to be determined. Liao and colleagues [33] (Shanghai Institute of Biological Sciences, Chinese Academy of Science) recently discovered that berberine promotes the development of atherosclerosis and foam cell formation by inducing scavenger receptor A expression in macrophages, suggesting that promotion of foam cell formation could counterbalance the beneficial effect of lowering serum cholesterol for berberine. Semen Cassiae (*Cassia* seed), a traditional Chinese herbal medicine, has been found to decrease serum cholesterol concentration. Li *et al*. [34] (South China Normal University) isolated a novel protein that exerts inhibitory effects on cholesterol biosynthesis from *Senna obtusifolia* seed by gel filtration and ion exchange chromatography. Their study may provide a novel treatment for regulation of hypolipidemic action.

Identification and quantification of lipids is of major importance for the diagnosis, prognosis, and understanding of the molecular mechanisms involved in atherosclerosis-related cardiovascular disease [35]. Lipidomics is systems-level analysis and characterization of lipids and their interacting moieties, which has been met by growing interest in the field of cardiovascular disorders, potentially leading to discovery of novel biomarkers and the development of new therapies [36]. There have been few studies on the application of lipidomics methods in cardiovascular disease research in China to date. However, Yang *et al*. [37] (Chinese Academy of Sciences) and Zhong *et al*. [38,39] (Chinese Academy of Agricultural Sciences) reviewed and summarized recent progress in this field of research including the present situation and future applications. They then introduced a direct-infusion, high-throughput analytical strategy, namely electrospray ionization tandem mass spectrometry (ESI-MS/MS), and provided an overview of application advances of this approach in lipidomics. These papers give explicit information on the development of lipidomics and a clear understanding of application in this newly emerging field.

Yuan *et al*. [40] (Tianjin University) recently profiled phospholipids in human endothelial cells under oxidative stress by a novel lipidomics approach combining liquid chromatography (LC)-ion trap MS and LC-tandem quadrupole MS. They thus identified the 28 most discriminant species in response to different levels of oxidative stress induced by hydrogen peroxide, which also induced phosphorylation of cytosolic phospholipase A(2) (cPLA[2]) via activation of ERK1/2, and increased production of some phospholipids. Their study provided a novel application for a combined lipidomics and signal transduction approach.

The underlying mechanisms by which atherosclerosis is initiated and progresses have attracted much attention all over the world, including in China. Atherosclerosis is a dynamic process wherein multiple risk factors form a complex network with systematic regulation. Future investigations should attempt to link how these factors might be integrated at a cellular level with other pathways such as lipoprotein oxidative stress. Here, we introduced some work mainly focusing on inflammation, lipid metabolism dysfunction, and hypertension related to atherosclerosis-related cardiovascular disease in China. Other important work in oxidative stress and immunology was beyond the scope of this review. As investigations continue, we believe that additionally meaningful results will be obtained in China.

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