

Cardiovascular physiology at the bench for application in the clinic

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exercise, surgical interventions and drugs can be considered to combat these diseases in a clinical setting.

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Abstract

Our research focuses on microphysiological aspects of the cardiovascular system, with an emphasis on what is occurring in heart tissues, to learn more about how various diseases arise and how they can be avoided or cured. These diseases include atherosclerosis, diabetes, myocardial infarction, obesity and ischemia/reperfusion (I/R). We use animal models, particularly mice, to aid us in these studies. A key feature of our work centers on dissection of coronary arterioles and examining their functionality using drugs, electrophysiology, fluoroscopy, genomics, proteomics, and standard chemical analyses to determine their physiological status, and compare it with other treated animals. My laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, the roles of sodium salicylate, exercise and resveratrol in type 2 diabetes, I/R injury, obesity, and atherosclerosis. Recently, we began investigations of the effects of stem cells and gastric bypass surgery on vascular dysfunction in obesity and diabetes. Our work identifies how diet,

INTRODUCTION AND EDUCATIONAL EXPERIENCE

Dr. Cuihua Zhang received her medical degree in 1985 from Jin Zhou Medical College (Liaoning, China) and her PhD in 1995 from the Chinese Academy of Medical Science and Peking Union Medical College (Beijing, China), where she studied endothelium-derived relaxation factor and nitric oxide in hypertension^[1,2]. Dr. Cuihua did her postdoctoral work beginning with a research fellowship in Dr. Benedito Machado's laboratory in the Department of Physiology School of Medicine of Ribeirão Preto University, São Paulo, Brazil. She investigated the roles of blockade of neurokinin-1 receptors in the nucleus tractus solitarius of awake rats in the cardiovascular responses to chemoreflex activation^[3]. She continued with postdoctoral work in Dr. Lih Kuo's laboratory in the Department of Medical Physiology in the Medical College at Texas A&M

University (TAMU)^[4-12] (Figure 1, Mentor Dr. Lih Kuo and Cuihua Zhang), then accepted appointments in the Departments of Anesthesiology, Surgery, and Physiology in the School of Medicine at Louisiana State University Health Sciences Center in New Orleans as an Assistant Professor (Figure 2, 1st Zhang Laboratory), and then returned to TAMU as an Assistant Professor in Veterinary Physiology and Pharmacology, and affiliated with the Michael E. DeBakey Institute and the Cardiovascular Research Institute in the College of Medicine Health Science Center at TAMU, until coming to the University of Missouri-Columbia in January 2008. She currently is an Associate Professor of Medicine, Medical Pharmacology and Physiology, and Nutrition and Exercise Physiology in the Division of Cardiovascular Medicine in the University of Missouri-Columbia (Figure 3).

ACADEMIC STRATEGY AND GOALS

During the past decade, Dr. Cuihua has developed a successful independent research program conducting basic research in coronary microcirculation, which is aimed at understanding the underlying mechanisms responsible for the pathophysiological manifestations of ischemic heart disease. Specifically, her laboratory primarily studies natural and genetically modified murine strains to understand the role of specific genes in the pathophysiological sequelae of cardiovascular disease, i.e. atherosclerosis, hypertension, ischemia/reperfusion (I/R) injury, and diabetes at the molecular, cellular and intact tissue levels. Dr. Cuihua serves on the American Heart Association and National Institutes of Health study sections, editorial boards (*American Journal of Physiology-Heart and Circulatory Physiology*, *Basic Research in Cardiology*, *Circulation Research*, *Frontiers in Vascular Physiology* and *World Journal of Cardiology*), and organizes and moderates sessions in professional meetings (Experimental Biology Meetings, American Heart Association Scientific Sessions, Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference and World Congress for Microcirculation). Her research has resulted in the publication of approximately 70 peer-reviewed publications and has generated more than \$4 million in grant support. Progress has been made in finding therapeutic remedies for the above-mentioned diseases as a result of her work.

ACADEMIC ACHIEVEMENTS

Dr. Cuihua's research focuses on basic investigations in vascular biology, especially in coronary microcirculation and cardiovascular physiology (Figure 4, vasculature image). Heart malfunctions are at the root of many diseases and include risk factors such as atherosclerosis, I/R injury, and diabetes. Obtaining detailed knowledge of the mechanisms that lead to heart dysfunction can: (1) identify therapeutic targets for new and more effective drugs; (2) provide new protocols to reduce risks associated with surgical procedures; (3) suggest improvements in diet and exercise therapies; and (4) aid in discovering new remedies



Figure 1 Dr. Cuihua Zhang and her postdoctoral mentor Dr. Lih Kuo in 2003 at an Experimental Biology meeting.



Figure 2 The team at Louisiana State University Health Sciences Center, New Orleans. Front Row: Souad Belmadani, Cuihua Zhang, Marta Focardi, Jin-jiang Peng, Xue Gao. Back Row: Eric T Guilbeau, Andrea Picchi, Xiangbin Xu.



Figure 3 Cuihua Zhang, MD, PhD, FAHA, Division of Cardiovascular Medicine in the Departments of Internal Medicine, Medical Pharmacology and Physiology, Nutrition and Exercise Physiology, Dalton Cardiovascular Research Center, University of Missouri-Columbia, 134 Research Park Drive, Columbia, MO 65211, United States.

for cardiovascular disease. Her ongoing projects in the laboratory include studying the role of inflammatory cytokines in vascular dysfunction in type 2 diabetes. Another research interest is aimed at understanding a contributing factor to the pathophysiological manifestations of ischemic heart disease by assessing a potential role of the

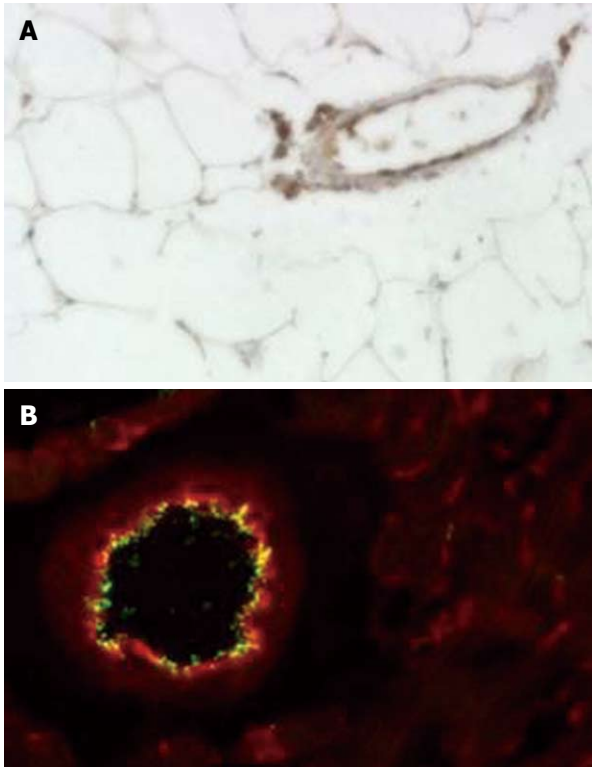


Figure 4 The magic of blood vessels in “A” shows that Mac3 positive macrophages infiltrate the adventitia of small vessels in the mesenteric adipose tissue of diabetic mice. The magic of blood vessels in “B” shows adiponectin is co-localized with endothelial layers of a small artery in the heart tissue of mice with genetic detection of tumor necrosis factor.

inflammatory cytokine, tumor necrosis factor (TNF)- α in I/R injury. A murine genetic model (TNF over-expression, TNF $^{++/++}$ mice) is used for these studies. The TNF $^{++/++}$ transgenic model offers a unique approach that allows assessment of the role played by TNF in many cardiovascular diseases. This work is supported by National Institutes of Health (NIH) funding (RO1) of the program. This was recognized with the 2007 Werner Risau New Investigator Award in Vascular Biology^[13] by American Heart Association Journal, stemming from the Zhang Laboratory 2006 publication in *Arteriosclerosis, Thrombosis, and Vascular Biology*.

Discovery of a new paradigm for vascular inflammation in I/R injury

The basic factors leading to microvascular dysfunction in the pathophysiology of I/R injury involve a series of events that begin with ischemia, characterized by reduction of blood flow, inadequate oxygen supply, reduction in cellular energy stores, and accumulation of noxious metabolites. These conditions begin to improve when blood flow is restored, but reperfusion injury occurs when blood flow carries reactive oxygen species (ROS), including peroxynitrite, which is derived from reactions between nitric oxide (NO) and superoxide anions, into the affected tissue. Differentiation of the contributions of ischemia from those of reperfusion to microvascular dysfunction

is difficult, and the current focus is on documentation of the degree and manner in which reperfusion exacerbates cellular damage that is initiated during ischemia. The reason for this focus is that ischemia is usually a pre-existing condition that the patient presents to the clinician, and the quickest remedy is for the clinician to induce reperfusion. If we understand the exact process of damage that accompanies reperfusion, then useful remedies can be developed and applied by the clinician when reperfusion is induced.

The formation of oxygen-derived free radicals depends on the generation of superoxide anions through endothelium- and leukocyte-stimulated biochemical reactions. This understanding is based on the facts that endothelial cells contain xanthine oxidase, whereas leukocytes feature membrane-bound NADPH oxidase. Although leukocyte-endothelium interactions are nearly universally established in inflammatory processes and in the increased microvascular permeability to macromolecules in I/R^[14-16], the results of Zhang *et al*^[14] and Gao *et al*^[15,16] have demonstrated that their activation is not a relevant mechanism of action for TNF-induced derangement of vasodilation. We have shown that TNF enhances generation of superoxide, and the same deleterious microcirculatory effects in control and leukopenic animals; an observation that supports an important direct action of TNF on microvascular cells, which leads to the generation of ROS and a decrease in the vasodilatory capacity of coronary arterioles. We also hypothesize that neutralization of TNF at the time of reperfusion exerts a beneficial effect on endothelial function and reduces the production of ROS. We have employed a murine model of myocardial I/R (30 min/90 min) and administered TNF-neutralizing antibodies at the time of reperfusion. I/R elevated TNF expression (mRNA and protein), whereas administration of anti-TNF prior to reperfusion attenuated TNF expression. We have detected TNF expression in vascular smooth muscle cells, mast cells and macrophages, but not in endothelial cells. I/R induces endothelial dysfunction and superoxide production. Administration of anti-TNF at the onset of reperfusion partially restores NO-mediated coronary arteriolar dilation and reduces superoxide production. I/R increases the activity of NADPH oxidase and xanthine oxidase, and enhances the formation of nitrotyrosine residues in untreated mice compared to sham-treated animals. Administration of anti-TNF prior to reperfusion blocks the increase in activity of these enzymes. Inhibition of xanthine oxidase (allopurinol) or NADPH oxidase (apocynin) improves endothelium-dependent dilation and reduces superoxide production in isolated coronary arterioles following I/R. I/R enhances superoxide generation and reduces endothelial function in neutropenic animals, and in mice treated with a neutrophil NADPH oxidase inhibitor, which indicates that the effects of TNF are not through neutrophil activation. We conclude that myocardial ischemia initiates TNF expression, which induces vascular oxidative stress, independent of neutrophil activation, and leads to coronary endothelial dysfunction.

Molecular mechanisms and therapies in diabetic microvasculopathy

Recent evidence suggests that inflammation plays a role in the development of insulin resistance, and predicts the development of type 2 diabetes mellitus. Type 2 diabetes mellitus is often anticipated by the development of the metabolic syndrome, which is a clustering of atherosclerotic cardiovascular risk factors characterized by visceral adiposity, insulin resistance, low high-density lipoprotein cholesterol, and a systemic proinflammatory state. The diagnosis of the metabolic syndrome appears to identify substantial additional risks beyond the individual risk factors. Inflammation is a condition that underscores much cardiovascular pathology, including endothelial dysfunction, but no link has yet been established between the vascular pathology of the metabolic syndrome and a particular inflammatory cytokine. We hypothesized that impairments in coronary endothelial function in obesity, the prediabetic metabolic syndrome, is caused by TNF overexpression. Our results have demonstrated that endothelial dysfunction in obesity is the result of effects of the inflammatory cytokine TNF and subsequent production of superoxide. Our work is supported by an AHA award (SDG) to our program, and some results were published in *Circulation Research* in 2006^[17], and have been reported at national and international meetings.

Our work also examines the mechanisms underlying the endothelial dysfunction of the coronary artery in pathological conditions such as coronary artery disease and other cardiovascular-related health problems of particular importance in the United States. We utilize genetic models for obesity and type 2 diabetes (*Lepr^{db}* mouse), the heterozygote lean controls (*m Lepr^{db}*), and *Lepr^{db}* mice null for TNF (*db^{TNF-/-}/db^{TNF-/-}*)^[18]. We have chosen to focus on TNF because this cytokine is one of the key inflammatory mediators that are expressed during a variety of inflammatory conditions. Furthermore, TNF initiates the expression of an entire spectrum of inflammatory cytokines ranging from many interleukins to interferon. Our hypothesis regarding diabetes diverges when considering the enzyme system responsible for this pathophysiological disease. Diabetes is one of the leading risk factors for the development of coronary artery and peripheral vascular diseases. Before vascular disease develops in diabetes, endothelial dysfunction occurs. In fact, endothelial dysfunction appears to be a hallmark that underlies many vascular diseases with differing etiology. We believe that understanding endothelial dysfunction is crucial because the progression of vascular disease may be halted if endothelial dysfunction is rectified. Our goal has been to delineate a potential cause of endothelial dysfunction by testing the hypothesis that TNF induces the inflammation that is responsible for endothelial dysfunction in type 2 diabetes. Our data have revealed that endothelial function is normal in diabetic mice that lack TNF (TNF knockout in the *Lepr^{db}* diabetic mouse). Moreover, we have observed that diabetic mice have elevated expression of TNF, which suggests that this inflammatory cytokine produces, or at least contributes

to, endothelial dysfunction in diabetes^[19-26]. We also have found that the endothelial dysfunction induced by TNF in diabetes is related to excess production of the free radical, superoxide. Finally, we have observed that advanced glycosylation end products (AGEs) and their receptors (RAGEs) seem to amplify TNF expression in diabetes; thus, TNF and AGE/RAGE signaling play pivotal roles in endothelial dysfunction in type 2 diabetes. The work is supported by an NIH grant (RO1) to our program, and some results have been published in *Circulation*^[18] and *American Journal of Physiology - Heart and Circulatory Physiology*^[27]. Our current studies on the role of lectin-like oxidized low-density lipoprotein receptor (LOX)-1 in atherosclerosis have documented the first direct evidence that endothelial dysfunction in atherosclerosis is mediated, at least in part, *via* the interaction of oxidized low-density lipoprotein (Ox-LDL) with its receptor, LOX-1, which in turn stimulates endothelial generation of superoxide radicals by activation of NADPH oxidase. The results of this study may contribute to the development of novel adjunctive therapies using anti-Ox-LDL and/or anti-LOX-1 antibodies or soluble receptors to prevent endothelial dysfunction following atherosclerosis^[28].

Basic factors in vascular dysfunction

We have experience with measuring transmural differences in coronary arteriolar dilation in response to adenosine^[6]; pathophysiological disturbances in hypertension^[11] and I/R^[7]; endothelial regulation of vascular function; heterogeneous coronary arteriolar dilation in response to β_2 -adrenergic receptor activation^[5], and the role of NO and K-ATP channels^[4]; divergent roles of angiotensin II AT1 and AT2 receptors^[8] in modulating coronary microvascular function, and the effect of TNF-induced production of superoxide on endothelium-dependent, NO-mediated dilation of coronary arterioles; and the role of ceramide signaling and xanthine oxidase^[29]. This experience combined with newly available murine genetic models has allowed rapid progress in understanding cardiovascular pathophysiology in our laboratory.

CONCLUSION

In summary, we believe that activation of inflammatory cytokines, especially TNF, leads to the interaction of AGEs/RAGEs and Ox-LDL/LOX-1, which causes progression of inflammatory disorders and initiates endothelial dysfunction, which culminates in coronary microcirculation in type 2 diabetes, I/R injury, obesity, and atherosclerosis. The excessive production of TNF^[30] has a deleterious downstream effect by augmentation of ROS production^[31] and limiting NO bioavailability in endothelial cells, which results in reducing NO-dependent vasodilation in vascular smooth muscle cells. Our laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, and the roles of sodium salicylate^[22], exercise and resveratrol^[24,25] in type 2 diabetes^[18,19,21-23,27], I/R injury^[13-16], obesity^[17] and atherosclerosis^[28,32]. Recently,

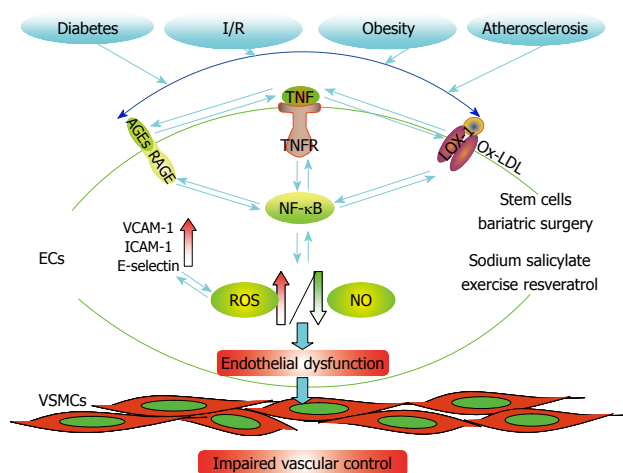


Figure 5 Activation of inflammatory cytokines leads to the interaction of advanced glycosylation end product and their receptor and oxidized low-density lipoprotein/lectin-like oxidized low-density lipoprotein receptor-1, which causes progression of inflammatory disorders which initiates endothelial dysfunction and culminates in coronary microcirculation in type 2 diabetes, ischemia/reperfusion injury, obesity, and atherosclerosis. The excessive production of tumor necrosis factor (TNF)- α has a deleterious downstream effect by augmentation of superoxide production and limiting nitric oxide (NO) bioavailability in endothelial cells, which results in reduction of NO-dependent vasodilation. My laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, and the roles of sodium salicylate, exercise and resveratrol in type 2 diabetes, ischemia/reperfusion (I/R) injury, obesity, and atherosclerosis. Recently, we have started looking at the effects of stem cells and bariatric surgery on vascular dysfunction in obesity and diabetes. ROS: Reactive oxygen species; NF- κ B: Nuclear factor κ B; Ox-LDL: Oxidized low-density lipoprotein; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1; AGEs: Advanced glycosylation end products; RAGE: Advanced glycosylation end products receptor; ECs: Endothelial cells; VSMCs: Vascular smooth muscle cells.

we have started looking at the effects of stem cells and gastric bypass surgery^[33] on vascular dysfunction in obesity and diabetes (Figure 5).

Dr. Cuihua credits her postdoctoral success to her many mentors that include training by Drs. Yongfeng Zheng, Benedito Machado, Lih Kuo, Michael Davis, and William Chilian; administrators in many institutions that had sufficient faith in her abilities to employ her; receptivity of funding agencies to her proposals; collaborators, postdoctoral workers and committed graduate students that have shared fresh ideas and added new approaches of mutual interest; dedicated technical personnel in the laboratory and administrative personnel at the institutional level whose hard work keeps projects on track; and opportunities for involvement with scientific organizations, where one can make the transition from education achieved by pursuing a formal degree to a lifetime of continuing education, which are supported by the meetings, publications and other activities that they support. A scientific career can be much more than a job, and it can, under the best of circumstances, become a way of life. Success, Dr. Cuihua believes, is not an individual accomplishment, but rather a collective outcome that results from the interactions that take place between the individual and other persons in their everyday lives. Alacrity is the best trait to

cultivate in oneself to have the best chance of success. Dr. Zhang has trained and interacted with > 10 postdoctoral fellows and > 5 graduate students in the past 8 years. It is a joy to see young scientists using their training and becoming successful.

Our future plans are to build and expand this research program along the lines outlined above for the next few years. We also expect new animal models, diagnostic techniques and therapeutic agents to be developed and delivered to reduce the risks and ravages of cardiovascular disease. I am excited that our laboratory can participate in that future to improve human health through science.

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The design in Figure 4 was created by Dr. Hanrui Zhang. I gratefully acknowledge Dr. Marvin K. Harris for technical assistance.

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