Publications

1. **Wang Q,** Liu Z, Ren J, Morgan S, Assa C, Liu B. Receptor-interacting Protein Kinase 3 Contributes to Abdominal Aortic Aneurysms via Smooth Muscle Cell Necrosis and Inflammation. ***Circulation Research*****.** 2015 Feb 13;116(4):600-11.

2. **Wang Q**, Liu Z, Ren J, Morgan S, Assa C, Kent C, Liu B. Inhibition of Receptor-Interacting Protein Kinase 1 with Necrostatin-1 or -1s ameliorates aneurysm progression in the elastase-induced mouse model of abdominal aortic aneurysms (AAAs). Under Review.

3. **Wang Q,** Ren J, Morgan S, Liu Z, Dou C, Liu B. Monocyte chemoattractant protein-1 (mcp-1) regulates macrophage cytotoxicity in abdominal aortic aneurysm. ***PLoS One*****.** 2014;9:e92053

4. Liu Z*, **Wang Q***, Ren J, Assa CR, Morgan S, Giles J, Han Q, Liu B. Murine abdominal aortic aneurysm model by orthotopic allograft transplantation of elastase-treated abdominal aorta**. *J Vasc Surg*.** 2014 Jun 26. pii: S0741-5214(14)01000-3. ***: Co-First Authorship**

5. Lengfeld J*, **Wang Q***, Zohlman A, Salvarezza S, Morgan S, Ren J, Kato K, Rodriguez-Boulan E, Liu B. Protein kinase C δ regulates the release of collagen type I from vascular smooth muscle cells via regulation of Cdc42. ***Mol Biol Cell*****.** 2012 May; 23(10):1955-63. ***: Co-First Authorship**

6. Ren J, **Wang Q**, Morgan S, Si Y, Ravichander A, Dou C, Kent KC, Liu B. Protein kinase C-δ (PKCδ) regulates proinflammatory chemokine expression through cytosolic interaction with the NF-κB subunit p65 in vascular smooth muscle cells. ***J Biol Chem.*** 2014 Mar 28;289(13):9013-26.

7. Ren J, Liu Z, **Wang Q**, Giles J, Greenberg J, Sheibani N, Kent C, Liu B. Andrographolide Ameliorates Abdominal Aortic Aneurysm Progression by Inhibiting Inflammatory Cell Infiltration through Downregulation of Cytokine and Integrin Expression**. *Journal of Pharmacology and Experimental Therapeutics*.** 2015. In Press.

8. Liu Z, Morgan S, Ren J, **Wang Q**, Annis DS, Mosher DF, Zhang J, Sorenson CM, Sheibani N, Liu B. Thrombospondin-1 (TSP1) Contributes to the Development of Vascular Inflammation by Regulating Monocytic Cell Motility in Mouse Models of Abdominal Aortic Aneurysm**. *Circulation Research*.** 2015 Jul 3;117(2):129-41.

9. Morgan S, Yamanouchi D, Harberg C, **Wang Q**, Keller M, Si Y, Burlingham W, Seedial S, Lengfeld J, Liu B. Elevated protein kinase C-δ contributes to aneurysm pathogenesis through stimulation of apoptosis and inflammatory signaling. ***Arterioscler Thromb Vasc Biol.*** 2012 Oct; 32(10):2493-502.

10. Algharabil J, Kintner DB, **Wang Q**, Begum G, Clark PA, Yang SS, Lin SH, Kahle KT, Kuo JS, Sun D. Inhibition of Na(+)-K(+)-2Cl(-) cotransporter isoform 1 accelerates temozolomide-mediated apoptosis in glioblastoma cancer cells. ***Cell Physiol Biochem*****.** 2012; 30(1):33-48.

11. Xiao S, **Wang Q**, Gao J, Wang L, He Z, Mo D, Liu X, Chen Y. Inhibition of highly pathogenic PRRSV replication in MARC-145 cells by artificial microRNAs. ***Virol J*****.** 2011 Nov 1; 8:491.

12. Xiao S, Mo D, **Wang Q**, Jia J, Qin L, Yu X, Niu Y, Zhao X, Liu X, Chen Y. Aberrant host immune response induced by highly virulent PRRSV identified by digital gene expression tag profiling. ***BMC Genomics.*** 2010 Oct 7; 11:544.

13. Xiao S, Jia J, Mo D, **Wang Q**, Qin L, He Z, Zhao X, Huang Y, Li A, Yu J, Niu Y, Liu X, Chen Y. Understanding PRRSV infection in porcine lung based on genome-wide transcriptome response identified by deep sequencing. ***PLoS One.*** 2010 Jun 29; 5(6):e11377.

14. Xiao S*, **Wang Q***, Jia J, Cong P, Mo D, Yu X, Qin L, Li A, Niu Y, Zhu K, Wang X, Liu X, Chen Y. Proteome changes of lungs artificially infected with H-PRRSV and N-PRRSV by two-dimensional fluorescence difference gel electrophoresis. ***Virol J*****.** 2010 May 26; 7:107**: Co-First Authorship**

15. Qin L, Chen Y, Niu Y, Chen W, **Wang Q**, Xiao S, Li A, Xie Y, Li J, Zhao X, He Z, Mo D. A deep investigation into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis by modulating the canonical Wnt/beta-catenin signaling pathway. ***BMC Genomics*****.** 2010 May 23; 11:320.

Cellular and Molecular Pathology Graduate Program, Joanne Thornton, 3170−10K MFCB, 1685 Highland Avenue, Madison, WI 53705

CMP Cellular and Molecular Pathology

Qiwei Wang

Program of the Dissertation Defense Seminar
for the Degree of Doctor of Philosophy
in Cellular and Molecular Pathology

"The Role of Smooth Muscle Cell Death in Vascular Inflammation and Abdominal Aortic Aneurysm"

Wisconsin Institutes for Medical Research

Tuesday, November 10, 2015

10:00 AM Room 5001A

Research conducted in the lab of
Bo Liu, PhD
Department of Surgery

UNIVERSITY OF WISCONSIN − MADISON

Qiwei Wang

Education

University of Wisconsin-Madison
PhD in Cellular and Molecular Pathology

Sun Yat-sen University, 2010
MS, Biotechnology

Research Experience

University of Wisconsin – Madison (Vascular Biology)
September 2011 – present
Graduate Research Assistant (Advisor: Bo Liu, PhD)
January 2014 – present
American Heart Association Predoctoral Fellowship

- Studied novel molecular and cellular mechanisms of abdominal aortic aneurysm.
- Major findings
  - Receptor-Interacting Protein Kinase 3 Contributes to Abdominal Aortic Aneurysms via Smooth Muscle Cell Necroptosis and Inflammation.
  - Inhibition of Receptor-Interacting Protein Kinase 1 with Necrostatin-1 or -1s ameliorates aneurysm progression in the elastase-induced mouse model of abdominal aortic aneurysm.
  - Monocyte chemoattractant protein-1 regulates macrophage cytotoxicity in abdominal aortic aneurysm.
  - Protein kinase C δ regulates the release of collagen type I from vascular smooth muscle cells via regulation of Cdc42.

University of Wisconsin – Madison (Neuroscience)
September 2010 – August 2011
Graduate Research Assistant (Advisor: Dandan Sun, PhD)
Studied the role of Na(+)-K(+)-2Cl(-) cotransporter isoform 1 in the apoptosis of glioblastoma cancer cells.

Sun Yat-sen University, China (Molecular Virology)
September 2007 – August 2010
Master of Science (Advisor: Yaosheng Chen, PhD)
Studied molecular virology and host pathogenesis of porcine reproductive and respiratory disease virus (PRRSV)

DISSERTATION ABSTRACT

Necroptosis is a newly discovered type of regulated cell death that favors proinflammatory signaling. The primary objectives of my thesis work are: (1) to study the significance and mechanisms of necroptosis in abdominal aortic aneurysm (AAA), a common and potentially lethal vascular disease; (2) to explore necroptosis as a novel target for the treatment of small aneurysms in mice.

AAA is an age-related vascular disease characterized by progressive aortic dilation. Currently, there is no effective pharmacological treatment available for AAA patients. Proteolysis of elastin and collagen, inflammation and smooth muscle cell (SMC) loss with thinning of the media are thought to be key processes contributing to AAA formation and progression. To therapeutically target AAAs, there is an urgent need to study how these pathophysiological processes are interconnected at a cellular and molecular level.

In my thesis work, I first tested the significance of necroptosis in vascular inflammation and aneurysm pathogenesis. Using *Rip*3-deficient mice and an aorta transplant model, we demonstrate for the first time that enhanced RIP3 signaling in arterial wall is a critical pathological process during aneurysm progression. Mechanistic studies demonstrate a critical role for RIP3 in mediating pro-inflammatory SMC necroptosis, as well as NFκB-mediated inflammatory response in SMCs, which is independent of pro-necroptosis function of RIP3. Little is known about the upstream regulators of RIP3. Interestingly, we found in SMCs that PKCδ is necessary for RIP3 expression and necroptosis. Of note, this role for PKCδ is cell-type specific.

To further test whether necroptosis may serve as a novel therapeutic target for AAA, we examined the effects of necroptosis inhibitors on the progression of established small aneurysms in mice. We demonstrate that targeting necroptosis with RIP1 inhibitors stabilizes pre-existing aneurysms and reduces vascular inflammation during the progression of aneurysms.

Next, we identified non-toxic necroptosis inhibitors capable of concurrently targeting both RIP1 and RIP3 kinases *in vitro*. Our data warrant further *in vivo* studies testing the efficacies of these novel inhibitors in disease models.

Finally, we explored the interactions between inflammation and apoptosis in the pathogenesis of AAA by examining the pro-apoptotic role of infiltrated macrophages. We showed that MCP-1-primed macrophages induce apoptosis of aortic SMCs through a FasL/Fas-Caspase8-RIP1 mediated mechanism.

In conclusion, my work, along with data produced by other lab members suggests a positive feedback loop between cell death and vascular inflammation in the pathogenesis of AAA. This paradigm conceptually shifts the conventional thinking of vascular cell death as only a byproduct or consequence of aneurysmal tissue degeneration. Furthermore, the investigation of the underlying mechanisms involved in the development and progression of AAA may shed some light on potential “druggable” targets for treatment of human AAA.