Sepsis and septic shock

Wei Chao (wchao@anes.umm.edu):

Dr. Chao studies molecular, cellular, and physiological changes under various pathological conditions using multimodal animal studies. His laboratory has identified the critical role of the innate immunity, in particular Toll-like receptors (TLRs) and complement factor B, in cardiomyocyte death, myocardial inflammation, and cardiac dysfunction during sepsis or ischemia-reperfusion (I/R) injury. His recent work has focused on endogenous danger molecules that are released during sepsis and cardiac I/R and may function as molecular drivers in innate immunity and inflammation. His lab was among the first to identify the essential role of cellular RNA in myocardial injury and innate immune activation and has established a critical link between extracellular RNA/miRNAs, both released from the host cells in sepsis and cardiac I/R, and activation of innate immune responses via TLR7 signaling.

Highlighted Publications:

1. Zou L, Feng Y, Li Y, Zhang M, Chen C, Cai JY, Gong Y, Wang L, Thurman J, Wu X, Atkinson JP, Chao W. Complement factor B is the downstream effector of Toll-like receptors and plays an important role in a mouse model of severe sepsis. *J Immunol*. 2013; 191:5625-35. PMID: 24154627

2. Li Y, Feng Y, Chen H, Zou L, Si R, Wang E, Zhang M, Warren S, Sosnovik D, Chao W. Myocardial ischemia induces a rapid activation of innate immune signaling *via* cardiac heat-shock protein 60 and Toll-like receptor 4. *J Biol Chem.* 2011; 286:31308-19. PMID: 21775438

3. Chen C, Feng Y, Zou L, Chen HH, Cai JY, Xu JM, Sosnovik DE, Chao W. Role of extracellular RNA and TLR3-Trif signaling in myocardial ischemia-reperfusion injury. *J Am Heart Assoc.* 2014 Jan 3; 3(1): e000683. PMID: 24390148

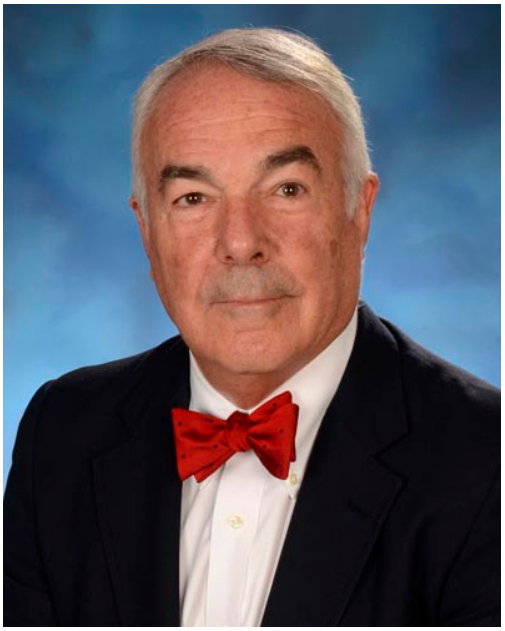
4. Feng Y, Chen H, Cai J, Zou L, Yan D, Xu G, Li D, Chao W. Cardiac RNA induces inflammatory responses in cardiomyocytes and immune cells via Toll-like receptor 7 signaling. *J Biol Chem.* 2015; 290: 26688-98. PMID: 26363072.

5. Zou L, Feng Y, Xu G, Jian W, Chao W. Splenic RNA and microRNA mimics promote complement factor B production and alternative pathway activation via innate immune signaling. *J Immunol.* 2016; 196: 2788-98. PMID: 26889043.

6. Feng Y, Zou L, Yan D, Chen H, Xu G, Jian W, Cui P, Chao W. Extracellular microRNAs induce potent innate immune responses via TLR7/MyD88-dependent mechanisms. *J Immunol.* 2017; 199: 2106-17. PMID: 28768728.

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Chao-Wei/
PubMed Publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1F3awzaP7DBkx/bibliography/47345926/public/?sort=date&direction=descending

Alan Cross (across@som.umaryland.edu)**:**



Dr. Cross' research focuses on the study of sepsis, including: (1) development of vaccines to prevent sepsis including development of multivalent vaccines for *P. aeruginosa, Klebsiella* and *E. coli* that progressed to phase 1 testing in human subjects; (2) study of glycobiology and sialic acid turnover as a druggable mechanism in innate host response and sepsis; (3) mechanisms of anthrax infection; (4) targeting the CD28/B7 axis to treat sepsis; and (5) mechanisms of Gram-negative bacterial sepsis.

Highlighted Publications:
1. Cross AS, Karreman HJ, Zhang L, Rosenberg Z, Opal SM, Lees A. Immunization of cows with novel core glycolipid vaccine induces anti-endotoxin antibodies in bovine colostrum. Vaccine 2014; 32(46):6107-14. PMID: 25242628.

2. Feng C, Stamatos NM, Dragan A, Medvedev A, Whitford M, Zhang L, Song C, Rallabhandi, P, Nhu Q, Vogel SN, Geddes C, Cross AS. Sialyl residues modulate LPS-mediated signaling through the Toll-like receptor 4 complex. PLoS One 2012;7:e32359

3. Feng C, Zhang L, Almulki L, Faez S, Whitford M, Hafezi-Moghadam A, Cross AS. Endogenous PMN sialidase activity exposes activation epitope on CD11b/CD18 which enhances its binding interaction with ICAM-1. J. Leukoc. Biol. 2011;90:313-321

4. Ramachandran G, Tulapurkar ME2, Harris KM, Arad G, Shirvan A, Shemesh R, DeTolla LJ, Benazzi C, Opal SM, Kaempfer R, Cross AS. A peptide antagonist of CD28 signaling attenuates toxic shock and necrotizing soft tissue infection induced by Streptococcus pyogenes J. Infect Dis. 2013;207:1869-77. Epub 2013Mar14. PMID23493729

Links: Faculty webpage: http://www.medschool.umaryland.edu/profiles/Cross-Alan/
PubMed publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/alan.cross.1/bibliography/41139315/public/?sort=date&direction=ascending

Jeffrey Hasday (jhasday@som.umaryland.edu)**:**

The Hasday lab has focused on how febrile-range hyperthermia and hypothermia modify biological processes relevant to disease pathogenesis with emphasis on acute lung injury/ARDS and fibrosis. Using approaches that span structural biology, gene and protein expression, cell culture, animal models and human trials, the Hasday laboratory has shown that hyperthermia worsens and hypothermia improves lung injury by modifying endothelial permeability, neutrophil recruitment, epithelial injury, and cytokine and heat shock protein expression. Dr. Hasday is expanding on his open-label trial of therapeutic hypothermia in ARDS by currently conducting a randomized clinical trial of hypothermia vs. standard temperature management in patients with

ARDS. The p38 MAP kinase pathway appears to be a major contributor to the temperature-dependence of endothelial barrier function and expression of pro- inflammatory cytokines. The Hasday laboratory is following up on exciting data showing that the structure and function of p38alpha, the proinflammatory p38 family member, but not p38beta is temperature-dependent in the 33° to 39°C range. Finally, the Hasday laboratory in collaboration with Dr. Paul Shapiro in the School of Pharmacy is designing novel p38alpha inhibitors that target the substrate binding domain rather than the catalytic domain of p38alpha. These novel compounds modify rather than inactivate its downstream signaling, are superior to conventional catalytic p38 inhibitors in preclinical testing, and are being developed into potential new drugs to treat ARDS and other inflammatory diseases. Dr. Hasday also directs the University of Maryland Cytokine Core Laboratory (www.cytokines.com).

Highlighted Publications:

1. Shah NG, Tulapurkar ME, Ramarathnam A, Brophy A, Martinez R 3rd, Hom K, Hodges, T, Samadani R, Singh IS, MacKerell AD Jr, Shapiro P, Hasday JD. Novel Noncatalytic Substrate-Selective p38α-Specific MAPK Inhibitors with Endothelial-Stabilizing and Anti-Inflammatory Activity. J Immunol. 2017; 198(8):3296-3306. Pubmed PMID: 28298524.

2. Slack DF, Corwin DS, Shah NG, Shanholtz CB, Verceles AC, Netzer G, Jones KM, Brown CH, Terrin ML, Hasday JD. Pilot Feasibility Study of Therapeutic Hypothermia for Moderate to Severe Acute Respiratory Distress Syndrome. Crit Care Med. 2017 45:1152-59;PubMed PMID: 28406814.

3. Tulapurkar ME, Ramarathnam A, Hasday JD, Singh IS. Bacterial lipopolysaccharide augments febrile-range hyperthermia-induced heat shock protein 70 expression and extracellular release in human THP1 cells. PLoS One. 2015;10(2):e0118010. PubMed PMID: 25659128; PubMed Central PMCID: PMC4320107.

4. Gupta A, Cooper ZA, Tulapurkar ME, Potla R, Maity T, Hasday JD, Singh IS. Toll-like receptor agonists and febrile range hyperthermia synergize to induce heat shock protein 70 expression and extracellular release. J Biol Chem. 2013 Jan 25;288(4):2756-66. PubMed PMID: 23212905; PubMed Central PMCID: PMC3554941.

5. Tulapurkar ME, Almutairy EA, Shah NG, He JR, Puche AC, Shapiro P, Singh IS, Hasday JD. Febrile-range hyperthermia modifies endothelial and neutrophilic functions to promote extravasation. Am J Respir Cell Mol Biol. 2012 Jun;46(6):807-14. PubMed PMID: 22281986; PubMed Central PMCID: PMC3380289.

6. Shah NG, Tulapurkar ME, Damarla M, Singh IS, Goldblum SE, Shapiro P, Hasday JD. Febrile-range hyperthermia augments reversible TNF-α-induced hyperpermeability in human microvascular lung endothelial cells. Int J Hyperthermia. 2012;28(7):627-35. PubMed PMID: 22834633.

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Hasday-Jeffrey/
PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40776367/?sort=date&direction=ascending

Rosemary Kozar (RKozar@som.umaryland.edu):

Dr. Kozar's research focuses on the pathogenesis of shock and include (1) mechanisms of syndecan-1 shedding after hemorrhagic shock and its contribution to shock pathogenesis and improved resuscitation strategies; (2) the contribution of intestinal ischemia/reperfusion injury to shock and its modification by modulation of enteral nutrients; (3) the gut-protective and immunomodulatory effects of glutamine.

Highlighted Publications:

1. Ban K, Peng Z, Lin W, Kozar RA. Arginine decreases peroxisome proliferator-activated receptor-γ activity via c-Jun. Mol Cell Biochem. 2012 Mar;362(1-2):7-13. PubMed PMID: 22038625; PubMed Central PMCID: PMC3270150.

2. Peng Z, Ban K, Wawrose RA, Gover AG, Kozar RA. Protection by enteral glutamine is mediated by intestinal epithelial cell peroxisome proliferator-activated receptor-γ during intestinal ischemia/reperfusion. Shock. 2015 Apr;43(4):327-33. PubMed PMID: 25394240; PubMed Central PMCID: PMC4359662.

3. Peng Z, Ban K, LeBlanc A, Kozar RA. Intraluminal tranexamic acid inhibits intestinal sheddases and mitigates gut and lung injury and inflammation in a rodent model of hemorrhagic shock. J Trauma Acute Care Surg. 2016 Aug;81(2):358-65. PubMed PMID: 27027557; PubMed Central PMCID: PMC5308205.

4. Ban K, Peng Z, Kozar RA. Inhibition of ERK1/2 worsens intestinal ischemia/reperfusion injury. PLoS One. 2013;8(9):e76790. PubMed PMID: 24073294; PubMed Central PMCID: PMC3779170.

5. Kozar RA, Pati S. Syndecan-1 restitution by plasma after hemorrhagic shock. J Trauma Acute Care Surg. 2015 Jun;78(6 Suppl 1):S83-6. PubMed PMID: 26002270; PubMed Central PMCID: PMC4841450.

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Kozar-Rosemary/
PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/rosemary.kozar.1/bibliography/47390535/public/

Carl Shanholtz (Cshanhol@som.umaryland.edu):

Dr. Shanholtz has had a longstanding interest in improving management of critically ill patients and has a long and successful record of clinical research in critical illness in general, and acute respiratory distress syndrome specifically. Together Dr. Roy Brower, Dr. Shanholtz conducted the phase II clinical trial of low tidal volume ventilation in ARDS on which the ARDSNet ALVEOLI study was based and he has been site director for ARDSnet-I and II. Dr. Shanholtz also studies pain management/sedation pathways and pain assessment in critically ill patients, methods to reduce fluid administration to critically ill patients, and is a co-investigator on Dr. Hasday's clinical trial of therapeutic hypothermia in ARDS patients.

Highlighted Publications:

1. Netzer G, Dowdy DW, Harrington T, Chandolu S, Dinglas VD, Shah NG, Colantuoni E, Mendez-Tellez PA, Shanholtz C, Hasday JD, Needham DM. Fever is associated with delayed ventilator liberation in acute lung injury. Ann Am Thorac Soc. 2013 Dec;10(6):608-15. PubMed PMID: 24024608; PubMed Central PMCID: PMC3960965.

2. Shah NG, Cowan MJ, Pickering E, Sareh H, Afshar M, Fox D, Marron J, Davis J, Herold K, Shanholtz CB, Hasday JD. Nonpharmacologic approach to minimizing shivering during surface

cooling: a proof of principle study. J Crit Care. 2012 Dec;27(6):746.e1-8. PubMed PMID: 22762936; PubMed Central PMCID: PMC3494806.

3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301-8. PubMed PMID: 10793162.

4. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999 Aug;27(8):1492-8. PubMed PMID: 10470755.

5. Slack DF, Corwin DS, Shah NG, Shanholtz CB, Verceles AC, Netzer G, Jones KM, Brown CH, Terrin ML, Hasday JD. Pilot Feasibility Study of Therapeutic Hypothermia for Moderate to Severe Acute Respiratory Distress Syndrome. Crit Care Med. 2017 45:1152-59;PubMed PMID: 28406814.

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Shanholtz-Carl/
PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47839782/?sort=date&direction=ascending

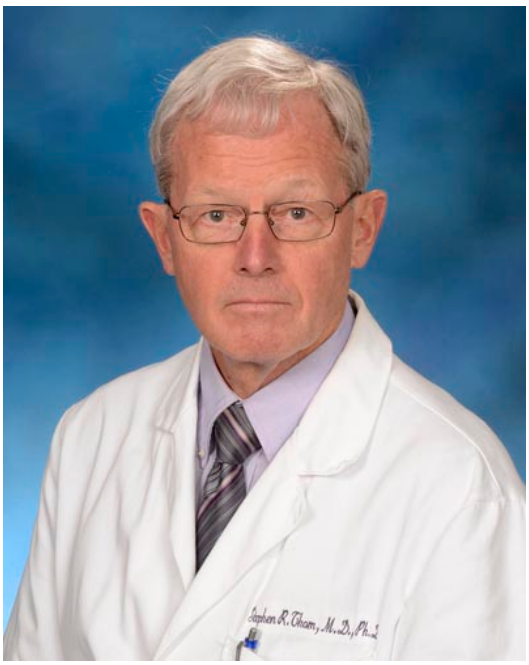
Kari Ann Shirey (kshirey@som.umaryland.edu):

Dr. Shirey's research focuses on the ability of pathogens, *e.g.*, *Francisella tularensis*, Respiratory Syncytial Virus (RSV), and influenza to modulate the host's innate immune response by altering macrophage differentiation (alternatively activated phenotype (M2)) and skewing toward a Th2-like phenotype (e.g., IL-4, IL-13, TSLP). A second aspect of Dr. Shirey's research focuses on host-oriented approaches as novel therapeutics for pathogens that induce acute lung injury by modifying expression of cytokines and endogenous danger-associated molecular pattern (DAMP) molecules. Working with Dr. Vogel, Dr. Shirey demonstrated that the TLR4 antagonist, Eritoran, blocks influenza-mediated acute lung injury even when given late in infection. More recently, this work has been followed up with other small molecule inhibitors or neutralizing antibodies that have effectively blocked viral-induced lethality in mice and cotton rats.

Highlighted Publications:
1. Shirey KA, Nhu QM, Yim, KC, Roberts ZJ, Teijaro JT, Farber DL, Blanco JC, and Vogel SN. (2011). The anti- tumor agent, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), induces IFN-□-mediated antiviral activity *in vitro* and *in vivo*. J Leuk Biol. 89:351-57. See accompanying editorial. PMC3040469
2. Shirey KA, Lai W, Scott AJ et al. (2013) The TLR4 antagonist, Eritoran, protects mice from lethal influenza infection. *Nature* 497:498-502. PMC3725830 See accompanying podcast interview.
3. K. A. Shirey, W. Lai, L. M. Pletneva et al. (2014) Agents that increase alternatively activated macrophage differentiation blunt Respiratory Syncytial Virus-mediated lung pathology. *J. Leukoc. Biol.* 96: 951-955. PMC4226793 See accompanying editorial.
4. Piao W, Shirey KA, Ru LW et al. (2015). A decoy peptide that disrupts TIRAP recruitment to TLRs protects mice in a murine model of influenza. *Cell Reports* 11: 1941-1952. PMC4490105
5. Shirey KA, Lai W, Patel MC et al. (2016). Novel strategies for targeting innate immune responses to influenza. *Mucosal Immunol*. 9:1173-82. PMC5125448

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Shirey-Kari-Ann/
PubMed publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1xQKiut_y7t5X/bibliography/48010950/public/?sort=date&direction=ascending

Steve Thom (SThom@som.umaryland.edu)**:**



The Thom lab is funded by the National Institutes of Health, Office of Naval Research and US Air Force to study the role of vasculogenic stem cells in neovascularization especially focused on diabetic wound healing; mechanisms of production and pathophysiology of circulating microparticles and exosomes in traumatic brain injury and decompression sickness; and cytoskeletal regulation of neutrophil β_2 adhesion molecules in innate immune responses.

Highlighted Publications:

1. Thom SR, Bennett M, Banham ND, Chin WW, Blake DF, Rosen A, Pollock NW, Madden D, Barak O, Marroni A, Balestra C, Germonpre P, Pieri M, Cialoni D, Le P-NJ, Logue C, Lambert DS, Hardy KR, Sward D, Yang M, Bhopale VM, and Dujic Z. Association of microparticles and neutrophil activation with decompression sickness. *J Appl Physiol* 119: 427-434, 2015.
2. Thom SR, Bhopale VM, Hu J, and Yang M. Inflammatory responses to acute elevations of carbon dioxide in mice. . *J Appl Physiol* 123: 297-302, 2017.
3. Thom SR, Bhopale VM, Yu K, Huang W, Kane MA, and Margolis DJ. Neutrophil microparticle production and inflammasome activation under hyperglycemia due to cytoskeletal instability. *J Biol Chem* 292: 18312-18324, 2017.
4. Thom SR, Hampton M, Troiano M, Mirza Z, Malay DS, Shannon S, Jennato N, Donohue C, Hoffstad O, Woltereck D, Yang M, Yu K, Bhopale V, and Margolis DJ. Measurements of CD34+/CD45-dim stem cells predict healing of diabetic neuropathic wounds. *Diabetes* 65: 486-497, 2016.

Links:
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Stefanie Vogel (svogel@som.umaryland.edu)**:**

Dr. Vogel's focuses on the innate immune response to infection, the mechanisms by which inflammatory responses are regulated, macrophage differentiation and disease outcome, and targeting TLR signaling pathways to blunt pathogen-mediated acute lung injury. Dr. Vogel's most recent work has identified novel strategies for treating influenza therapeutically by blocking Toll-like receptor 4 signaling, the role of metabolism in the differentiation of macrophages, the cross-talk between innate immune signaling pathways, and other related topics. Innate immune responses to respiratory infections

Highlighted Publications:

1. K. A. Shirey, W. Lai, A. J. Scott, M. Lipsky, P. Mistry, L. M. Pletneva, C. L. Karp, J. McAlees, T. L. Gioannini, J. Weiss, W. H. Chen, R, K. Ernst, D. P. Rossignol, F. Gusovsky, J. C. Blanco, and S. N. Vogel. The TLR4 antagonist, Eritoran, protects mice from lethal influenza infection. *Nature* 497:498-502 (2013) PMC3725830

2. K. A. Shirey, W. Lai, L. M. Pletneva, F. D. Finkelman, D. J. Feola, J. C. G. Blanco, and S. N. Vogel. Agents that increase alternatively activated macrophage differentiation blunt Respiratory Syncytial Virus-mediated lung pathology. *J. Leukoc. Biol.* 96: 951-955. PMC4226793. (2014). See accompanying editorial.

3. K. A. Shirey, W. Lai, M. C. Patel, L. M. Pletneva, G. Pang, E. Kurt-Jones, M. Lipsky, T. Roger, T. Calandra, K. J. Tracey, Y. Al-Abed, A. G. Bowie, A. Fasano, C. A. Dinarello, F. Gusovsky, J. C. G. Blanco , S. N. Vogel. Novel strategies for targeting innate immune responses to influenza. *Mucosal Immunol*. 9: 1173-1182. (2016). PMC5125448

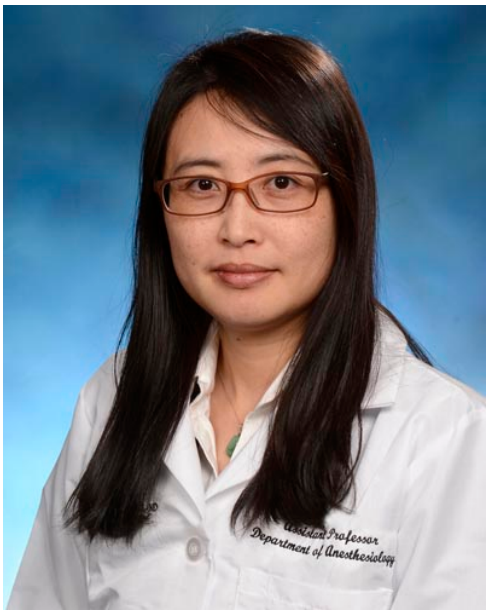
4. K. Richard, B. Mann, L. Stocker, A. Qin, E. M. Barry, R. K. Ernst, and S. N. Vogel. Monophosphoryl Lipid A enhances efficacy of a *Francisella tularensis* LVS-catanionic nanoparticle subunit vaccine against *F. tularensis* Schu S4 challenge by augmenting both humoral and cellular immunity. *Clin Vaccine Immunol*. 24: pii: 300574-16 (2017) PMC5339645

5. K. A. Shirey, W. Lai, L. M. Pletneva, C. L. Karp, S. Divanovic, J. C. G. Blanco, and S. N. Vogel. Role of the lipoxygenase pathway in RSV-induced alternatively activated macrophages leading to resolution of lung pathology. *Mucosal Immunol* 7: 549-557. (2013) PMC3965659.

6. A. A. Awomoyi, P. Rallabhandi, T. I. Pollin, E. Lorenz, M. B. Sztein, M. S. Boukhvalova, V. G. Hemming, J. C. G. Blanco, and S. N. Vogel. Association of TLR4 polymorphisms with symptomatic Respiratory Syncytial Virus infection in high-risk infants and young children. *J. Immunol*. 179: 3171-3177 (2007).

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Vogel-Stefanie/
PubMed publications:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40447249/?sort=date&direction=ascending

Lin Zou (lzou@som.umaryland.edu):



My research interest has been inflammation and organ injury in sepsis, specifically the role of innate immune signaling, such as Toll-like receptors (TLRs) and complement, in the development of cardiac and renal injury during sepsis. More recently, we demonstrated that extracellular RNAs/miRNAs are released during tissue ischemia or polymicrobial sepsis and are capable of activating TLR7-dependent cytokine/complement production in cardiac cells and macrophages. We are currently extending this work by studying the role of extracellular miRNA in sepsis induced acute lung injury.

Highlighted Publications:

1. Zou, L., Feng, Y., Chen, Y-J., Si, R., Shen, S., Zhou, Q., Ichinose, F., Scherrer-Crosbie, M., Chao, W. Toll-like receptor 2 plays a critical role in cardiac dysfunction during polymicrobial sepsis. Critical Care Med. 2010; 38:1335-1342. PMID: 20228680

2. Zou, L., Feng, Y., Li, Y., Zhang, M., Chen, C., Cai, JY., Gong, Y., Wang, L., Thurman, JM., Wu, XB., Atkinson, JP., Chao, W. Complement factor B is the downstream effector of TLRs and plays an important role in a mouse model of severe sepsis. J Immunol. 2013; 191:5625-5635.

3. Li D, Zou L, Feng Y, Xu G, Gong Y, Zhao G, Ouyang W, Thurman JM, Chao W. Complement factor B production in renal tubular cells and its role in sodium transporter expression during polymicrobial sepsis. Crit Care Med. 2016; 44 (5): e289-99.

4. Feng Y, Chen H, Cai J, Zou L, Yan D, Xu G, Li D, Chao W. Cardiac RNA induces inflammatory responses in cardiomyocytes and immune cells via Toll-like receptor 7 signaling. J Biol Chem. 2015; 290: 26688-98

Links:
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PubMed publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/lin.zou.1/bibliography/40653615/public/?sort=date&direction=descending