BIOGRAPHICAL SKETCH

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NAME Li, Xiang-An	POSITION TITLE Professor
eRA COMMONS USER NAME xiang-an.li	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Shandong University, China	B.S.	1978-1982	Chemistry
Shandong University, China	M.S.	1982-1985	Microbiology
Osaka University School of Medicine, Japan	Ph.D.	1991-1994	Biochemistry
National Cardiovascular Center, Japan.	Postdoc	1998-2000	Molecular Biology
University of Kentucky College of Medicine, Kentucky	Postdoc	2000-2000	Molecular/Cell Biology

A. Personal Statement

I study HDL and HDL receptor scavenger receptor BI (SR-BI), focusing on understating the mechanisms of how the HDL/SR-BI regulates adrenal stress response, and how adrenal stress response modulates host response in sepsis and in cardiovascular disease.

Sepsis research: My research in sepsis began from a serendipitous discovery 15 years ago. I utilized an endotoxemia animal model to assess the mechanism of how SR-BI protects against nitric oxide-induced cytotoxicity. I unexpectedly observed that lipopolysaccharide (LPS) induces 90% fatality in SR-BI null mice versus 0% in wild-type controls. With this finding, I started my research career to study sepsis in 2006. I spent the first several years delineating the roles of SR-BI in sepsis and found that SR-BI protects against sepsis through multiple mechanisms, including prevention of nitro oxide-induced cytotoxicity, promotion of LPS clearance in liver, suppression of inflammatory signaling in macrophages, and regulation of adrenal stress response.

In the past 5 years, I have shifted my research efforts from basic science to translational study, searching for a new approach to clinical sepsis therapy. Given the challenges of sepsis therapy and the complexity of septic patients, I have been calling for an endotype-based precision medicine approach to sepsis therapy. I translated my finding that SR-BI is a key regulator of adrenal stress response (iGC production) to target relative adrenal insufficiency (**RAI**), a common phenotype in septic patients. I established SR-BI null mice as the first RAI animal model, and demonstrated that RAI is an endotype and risk factor for adverse outcomes in sepsis. I showed that glucocorticoid (GC) treatment benefits septic mice with RAI, but harms septic mice without RAI. Thus, I provided convincing experimental evidence to support a precision medicine approach for sepsis treatment - namely, that GC therapy may be selectively used for septic patients with RAI.

In addition to studying the role of SR-BI in sepsis, I have investigated the role of HDL, the ligand of SR-BI, in sepsis. In a collaboration with Drs. Schwendeman and Standiford at the University of Michigan, we showed that HDL level is significantly decreased in septic patients, which is associated with a significant increase in mortality rate. Using ApoA1 null mice as a HDL deficiency model, we demonstrated that low HDL is a risk factor for adverse outcomes in sepsis. We propose the strategy of using synthetic HDL (sHDL) to increase HDL level as a potential therapy for sepsis. We have developed several new sHDLs for sepsis therapy.

Cardiovascular research: While most people focus on the role of HDL/SR-BI in reverse cholesterol transportation, I am interested in the role of HDL/SR-BI in regulating adrenal stress response and how its dysregulation contributes to cardiovascular disease.

Mentoring: As faculty of the University of KY, I have mentored 3 master's degree students, 8 PhD students, 4 postdoctoral fellows and served as thesis advisor for dozens of PhD students.

B. Positions and Honors:

Positions

1985-1986	Research fellow, Department of Biochemistry, Taishan Medical College, China
1987-1991	Assistant Professor, Department of Biochemistry, Taishan Medical College, China
1994-1997	Professor, Department of Biochemistry, Taishan Medical College, China
2000-2004	Research associate, Department of Pediatrics, University of Kentucky College of Medicine
2004-2005	Research assistant professor, Department of Pediatrics, University of Kentucky College of Medicine
2006-2011	Assistant Professor, Department of Pediatrics, University of Kentucky College of Medicine
2008 -	Full member, Nutritional Sciences Center, University of Kentucky College of Medicine
2013 -	Core member, Saha Cardiovascular Research Center, University of Kentucky College of Medicine
2011-2016	Associate Professor, Department of Pediatrics, University of Kentucky College of Medicine
2016 - 2017	Professor, Department of Pediatrics and Saha Cardiovascular Research Center, University of Kentucky College of Medicine
2017 -	Professor, Department of Physiology and Saha Cardiovascular Research Center, University of Kentucky College of Medicine
2017 -	Director, HDL Receptor Laboratory, Saha Cardiovascular Research Center, University of Kentucky College of Medicine

Professional Memberships

2000-2010	Member, American Heart Association (AHA)
2010-present	Fellow, AHA (FAHA)
2001-present	Member, American Society of Cell Biology
2009-present	Member, Society of Critical Care Medicine
2011-present	Member, Society for Leukocyte Biology
2014-present	Member, Shock Society

Honors

1995	National Outstanding Young Investigator Award, Department of Education of China
2005 - 2020	Wethington Award for Excellence in Research, University of Kentucky
2009	Finalist of Irvine H. Page Young Investigator Award, Council of Arteriosclerosis, Thrombosis and Vascular Biology, American Heart Association (AHA)
2013	Mid-Career Investigator Award, Council of Peripheral Vascular Disease, AHA

C. Contributions to Science

1. Identify SR-BI as a novel protective factor in sepsis - I am a pioneer in the study of the roles of SR-BI in sepsis. SR-BI is a well-established HDL receptor. It mediates intracellular cholesterol uptake from HDL, which plays a key role in reducing cholesterol levels in circulation. Using endotoxemia and cecal ligation and puncture (CLP) sepsis models, my laboratory first identified SR-BI as a protective factor in sepsis. We further demonstrated that SR-BI protects against sepsis through multiple mechanisms, including preventing nitric oxide-induced toxicity, promoting LPS clearance in the liver, modulating LPS-TLR4 signaling in macrophages, and regulating glucocorticoid production in the adrenal gland.

a. **Li XA***, Guo L, Asmis R, Nikolova-Karakashian M, Smart EJ: Scavenger receptor BI prevents nitric oxide-induced cytotoxicity and endotoxin-induced death. *Circ Res* 2006, 98:e60-5.

b. Guo L, Song Z, Li M, Wu Q, Wang D, Feng H, Bernard P, Daugherty A, Huang B, **Li XA***: Scavenger Receptor BI Protects against Septic Death through Its Role in Modulating Inflammatory Response. *J Biol Chem* 2009, 284:19826-34. PMC2740408

c. Guo L, Zheng Z, Ai J, Deborah AH, Mittelstadt PR, Thacker S, Daugherty A, Ashwell JD, Remaley A and **Li XA***. Scavenger receptor BI and HDL regulate thymocyte apoptosis in sepsis. *Arterioscler Thromb Vasc Biol* 2014; 34: 966-975. PMC4010389

d. Guo L, Zheng Z, Ai J, Huang B and **Li XA***. Hepatic scavenger receptor BI protects against polymicrobial-induced sepsis through promoting LPS clearance in mice. *J Biol Chem* 2014; 289: 14666-14673. PMC4031522.

2. Establish SR-BI null mice as the first RAI animal model and call for an endotype-based precision medicine approach to sepsis therapy - Prior therapeutic efforts have shown a limited survival benefit in sepsis. A limitation is that these therapies were applied to all septic patients nonselectively. However, septic patients have heterogeneous clinical subtypes. Thus, I have been calling for a precision medicine approach based on endotypes of sepsis. When I explored the mechanisms underlying SR-BI protection against sepsis, I found that SR-BI is a key regulator of adrenal stress response (iGC production). I translated this finding to target relative adrenal insufficiency (**RAI**), a common phenotype in septic patients. I established SR-BI null mice as the first RAI animal model, and demonstrated that RAI is a risk factor for adverse outcomes and a unique endotype of sepsis; further experimental work in my lab demonstrated that GC therapy benefits septic mice with RAI but harms septic mice without RAI. Our study provides a "proof of concept" that a precision medicine approach can help guide GC therapy for septic patients - specifically, that selective GC therapy for septic patients with RAI may improve survival.

a. Ai J, Guo L, Zheng Z, Wang SX, Huang B and **Li XA*.** Corticosteroid therapy benefits septic mice with adrenal insufficiency but harms septic mice without adrenal insufficiency. *Critical Care Medicine* 2015; 43:e490-8.

b. Guo L, Ye X and **Li XA***. Glucocorticoid only benefits septic mice with adrenal insufficiency: a precision medicine approach. *Critical Care Medicine*. 2016; 44:447

c. Wu C-H, Guo L, Wang, Q, Ye X, Mineo C, Shaul PW and **Li XA***. Relative adrenal insufficiency is a risk factor and an endotype of sepsis - A proof of concept study to support a precision medicine approach for glucocorticoid sepsis therapy. *BioRxiv* 2020; https://doi.org/10.1101/2020.04.16.043976

3. Demonstrate low HDL as a risk factor for sepsis and develop synthetic HDL for sepsis therapy - I am a leading investigator of the role of HDL in sepsis. Septic patients have low HDL levels, which is associated with poor prognosis. However, whether low HDL is a cause of septic death or simply a marker of sepsis severity remains unclear. Using ApoA-I knockout mice as a HDL-deficient animal model, we demonstrated that a deficiency of ApoA1 leads to a significant decrease in survival in CLP-induced sepsis. We further demonstrated that HDL has multiple protective roles in CLP-induced sepsis: in addition to its well-established role in neutralization of LPS, HDL exerts its protective effects in sepsis by promoting LPS clearance, modulating corticosterone production and leukocyte recruitment, and regulating thymocyte apoptosis. Combined with the earlier clinical findings, our work demonstrates that low HDL is a poor prognostic risk factor in sepsis. We have proposed to raise HDL levels using synthetic HDL (sHDL) as a therapeutic approach for sepsis. We have developed several new sHDLs for sepsis therapy.

a. Feng H, Guo L, Song Z, Wang D, Han J, Li Z, Huang H and **Li XA***. Caveolin-1 prevents sepsis through its role in modulating inflammatory response, alleviating bacterial burden and suppressing thymocyte apoptosis. *J Biol Chem* 2010; 285: 25154-25160. PMC2919077

b. Guo L, Ai J, Zheng Z, Deborah AH, Daugherty A, Huang B and **Li XA***. HDL protects against polymicrobial-induced sepsis in mice. *J Biol Chem* 2013; 288:17947-17953. PMC3689940.

c. Morin E, Guo L, Schwendeman A, and **Li XA***. HDL in sepsis - risk factor and therapeutic approach. *Front. Pharmacol.* 2015; 6: 244. doi:10.3389/fphar.2015.00244. PMC4616240

d. Morin E, **Li XA**, and Schwendeman A. High density lipoproteins in endocrine carcinomas: biomarker, drug carrier and potential therapeutic. *Front Endocrinol* 2018; https://doi.org/10.3389/fendo.2018.00715

4. Identify SR-BI as a novel regulator of autoimmune disease - My laboratory first reported that mice deficient in SR-BI have impaired T cell homeostasis. We further showed that the aged SR-BI null mice develop autoimmune disease.

a. Feng H, Guo L, Wang D, Gao H, Hou G, Zheng Z, Ai J, Forman O, Daugherty A and **Li XA*.** Impaired lymphocyte homeostasis and autoimmune disorder in mice deficient in HDL receptor SR-BI. *Arterioscler Thromb Vasc Biol* 2011; 31: 2543-2551. PMC3220294

b. Zheng Z, Ai J and **Li XA***. Scavenger receptor BI and immune dysfunctions. *Curr Opin Endocrinol Diabetes Obese* 2014; 21: 121-128. PMID: 24569553

c. Zheng Z, Ai J, Guo L, Ye X, Bondada S, Howatt D, Daugherty A, **Li XA***. SR-BI (Scavenger Receptor Class B Type 1) Is Critical in Maintaining Normal T-Cell Development and Enhancing Thymic Regeneration. *Arterioscler Thromb Vasc Biol*. 2018; 38: 2706-2717. PMC6209104.

5. Propose dysfunctional HDL and hypothesize that HDL is a stress responder and regulator – I proposed dysfunctional HDL and speculated that the quality of HDL may be more important than its quantitate in 2009. I am testing a new hypothesis that HDL is a stress responder and regulator and HDL/SR-BI-mediated adrenal stress response is an essential host response in regulating innate and adaptive immunity.

a. Feng H and **Li XA***. Dysfunctional HDL. Curr Opin Endocrinol Diabetes Obese 2009; 16:156-162. PMC3065374

b. Ito M, Ye X, Wang Q, Guo L, Hao D, Deborah H, Cai L, Temel R, Daugherty A and **Li XA***. Scavenger receptor BI, not LDL receptor, mediates adrenal stress response. *Arterioscler Thromb Vasc Biol* 2020 https://doi.org/10.1161/ATVBAHA.120.314506 PMCID: PMC7526689

***** Corresponding author

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/xiang-an.li.1/bibliography/41165489/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

1. NIH/NIGMS R01GM113832 Li (MPIs, Contact PI) 01/01/2015 – 04/30/2022
Synthetic HDL_a potential sepsis therapy
The goal of this grant is to understand mechanism(s) of sHDL vascular protection, and to tailor the sHDL composition and treatment regimen specifically for sepsis.
(No-cost extension)

2. NIH/NIGMS R01GM121796 Li (PI) 09/01/2017 – 08/31/2022
Mechanism of adrenal insufficiency as a risk factor for sepsis
The goal of this project is to elucidate the role of adrenal insufficiency in sepsis.

3. NIH/NHLBI R01HL142640 ZY Li (PI, XA Li Co-I) 04/01/2019 – 03/31/2023
Inflammasome activation triggers systemic coagulation in sepsis
The goal of this project is to assess the mechanism of how Inflammasome activation triggers systemic coagulation in sepsis.

4. VA merit 1I01BX004639 Li (PI) 10/2019 – 09/2023
HDL as a therapeutic target for sepsis
The goal of this project is to target HDL with a novel ApoE peptide-based sHDL (YGZL3) for sepsis therapy

5. NIH/NIGMS 1R35GM141478-01 Li (PI) 05/01/2021 – 04/30/2026
Relative adrenal insufficiency as a risk factor and an endotype for sepsis
The goals of this project are to understand the role of adrenal stress response in sepsis.