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BIOGRAPHICAL SKETCH

NAME: Yue, Hong

POSITION TITLE: Research Assistant Professor

eRA COMMONS USER NAME: YUEHONG

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
China Medical University, Liaoning, China	M.D.	07/1992	Clinical medicine
University of Fukui School of Medical Sciences, Fukui, Japan	Ph.D.	03/2003	Biochemistry
Cleveland Clinic, Ohio, USA	Postdoctoral	01/2010	Molecular cardiology

A. Personal Statement

I earned my MD from China Medical University in China, where I received training in both basic and clinical science. I practiced as a physician in Internal Medicine for 5 years. I earned my PhD from University of Fukui School of Medical Sciences in Japan, where I received further training primarily in biochemistry and cardiology. I started my postdoctoral training from 2005 in Lerner Research Institute, Cleveland Clinic, and was promoted to Research Associate in 2010. As a Principal Investigator, my study was supported by an American Heart Association Postdoctoral Fellowship grant. I moved to Case Western Reserve University in 2011 as a Senior Research Associate. In 2017, I joined my long-term collaborator - Dr. Wei Li's laboratory at Marshall University as a Research Assistant Professor, to develop our long-term collaborated project – exploring the role of thymidine phosphorylase in cardiovascular disease.

I have a broad background in cardiovascular and cancer immunity research, with specific training and expertise in biochemistry, cell biology, and molecular biology. As principal investigator on AHA-funded or co-Investigator on NIH-funded grants, I laid the groundwork for the proposed research, led to success on all the projects and produced many peer-reviewed publications from each project. The major publications generated recently in cardiovascular system or related with thymidine phosphorylase are as documented below.

1. Li W, Yue H. Thymidine Phosphorylase Is Increased in COVOD-19 Patients in an Acuity-Dependent Manner. ***Front Med*** 2021 Mar 22;8:653773. PMID: 33829029
2. Belcher A, Zulfiker AHM, Li OQ, Yue H, Gupta AS, Li W. Targeting Thymidine Phosphorylase With Tipiracil Hydrochloride Attenuates Thrombosis Without Increasing Risk of Bleeding in Mice. ***Arterioscler Thromb Vasc Biol.*** 2020 Dec 10:ATVBAHA120315109. PMID: 33297751
3. Yue H, Febbraio M, Klenotic PA, Kennedy DJ, Wu Y, Chen S, Gohara AF, Li O, Belcher A, Kuang B, McIntyre TM, Silverstein RL, Li W. CD36 Enhances Vascular Smooth Muscle Cell Proliferation and Development of Neointimal Hyperplasia. ***Arterioscler Thromb Vasc Biol.*** 2019;39:263-275. PMID: 30567481
4. Li W, Yue H. Thymidine phosphorylase: A potential new target for treating cardiovascular disease. ***Trends Cardiovasc Med.*** 2018;28:157-171. PMID: 29108898
5. Li W, Gigante A, Perez-Perez MJ, Yue H, Hirano M, McIntyre TM, Silverstein RL. Thymidine phosphorylase participates in platelet signaling and promotes thrombosis. ***Circ Res.*** 2014;115:997-1006. PMID: 25287063
6. Yue H, Tanaka K, Furukawa T, Karnik SS, Li W. Thymidine phosphorylase inhibits vascular smooth muscle cell proliferation via upregulation of STAT3. ***Biochim Biophys Acta.*** 2012;1823:1316-23. PMID: 22668509
7. Yue H, Li W, Desnoyer R, Karnik SS. Role of nuclear unphosphorylated STAT3 in angiotensin II type 1 receptor-induced cardiac hypertrophy. ***Cardiovasc Res***. 2010;85:90-9. PMID: 19696070

B. Positions and Honors

Positions/Employment:

1992–1997 Physician, Internal Medicine, Benxi Iron and Steel Co. General Hospital, Liaoning, China
1997-1999 Research Fellow, First Department of Internal Medicine, University of Fukui School of Medical Sciences, Fukui, Japan
2003–2005 Foreign Research fellow, First Department of Internal Medicine, University of Fukui School of Medical Sciences, Fukui, Japan
2005–2010 Postdoctoral Research Fellow, Department of Molecular Cardiology, Lerner Research Institute, the Cleveland Clinic, Ohio, USA
2010–2011 Research Associate, Department of Molecular Cardiology, Lerner Research Institute, the Cleveland Clinic, Ohio, USA
2011–2017 Senior Research Associate**,** Department of Biological Sciences, School of Dental Medicine, Case Western Reserve University, Ohio, USA
2017–Present Research Assistant Professor, Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, WV, USA

Other Experience and Professional Memberships

Professional Member of International/American Association of Dental Research
Professional Member of American Heart Association
Professional Member of Japanese Circulation Society

Editorial board of Frontier in Medicine (review editor) (from 2021)

Ad Hoc Reviewer for: PLOS ONE; J Mol Cell Cardiol; Hypertension.

Honors:

Grant: American Heart Association Postdoctoral Fellowship Award (7/1/2008 ~ 6/30/2010),
Title: Role of Unphosphorylated STAT3 in Angiotensin II Type 1 Receptor Induced Heart Failure
Role: PI
Direct: $ 88,000.

Awards:
The Bernadine Healy Award, The Department of Molecular cardiology, Lerner Research Institute, Cleveland Clinic (2010 ~ 2011)
Yoneyama Doctor Course Scholarship from Rotary Yoneyama Memorial Foundation, Japan (2002 ~ 2003)
Young Investigator's Award of 26th International Congress of Internal Medicine (2002)
Honors Scholarships from Heiwa Nakajima Foundation, Japan (2000 ~ 2002)
Scholarships from Fukui International Association Foundation, Japan (1999 ~ 2000)

C. Contribution to Science

1. Role of extracellular matrix metalloproteinases in vascular as well as cardiac diseases

My early research during my PhD training addressed the mechanistic role of magnesium as well as calcium channel blockers (CCBs) on cardiovascular disease via studying extracellular matrix metalloproteinases (MMP) in cultured rat vascular smooth muscle cells as well as cardiac fibroblasts. Magnesium has been implicated in the negative correlation between cardiovascular disease and hardness of drinking water. Dietary deficiency of magnesium augments atherogenesis markedly in experimental animals fed a high cholesterol diet, while oral supplementation of magnesium to similar animals lowers serum lipids and attenuates the atherosclerotic process. Our data suggest that the beneficial effect of magnesium supplementation on vascular disease processes as well as cardiac disease such as heart failure may be due to the inhibitory effect of magnesium on the production of MMP-2 in VSMCs and in cardiac fibroblasts, respectively, via a protein tyrosine kinase mediated pathway. However, the 3 distinct classes of CCBs used clinically in the treatment of hypertension and angina pectoris, exerted different effects on MMP-2 expression in cardiac fibroblasts via different

mechanism, indicated that the various effects of CCBs on ventricular remodeling or heart failure might be related to the different effects of CCBs on MMP-2 expression in cardiac fibroblasts. These studies suggested that how and when to use the different CCBs beneficially according to their different characters on MMP-2 is important.

a. Yue H, Lee JD, Shimizu H, Uzui H, Mitsuke Y, Ueda T. Effects of magnesium on the production of extracellular matrix metalloproteinases in cultured rat vascular smooth muscle cells. ***Atherosclerosis.*** 2003;166:271-7. PMID:12535739

b. Yue H, Uzui H, Lee JD, Shimizu H, Ueda T. Effects of magnesium on matrix metalloproteinase-2 production in cultured rat cardiac fibroblasts. ***Basic Res Cardiol.*** 2004;99:257-63. PMID:15221343

c. Yue H, Uzui H, Shimizu H, Nakano A, Mitsuke Y, Ueda T, Lee JD. Different effects of calcium channel blockers on matrix metalloproteinase-2 expression in cultured rat cardiac fibroblasts. ***J Cardiovasc Pharmacol.*** 2004;44:223-30. PMID: 15243304

2. Role of STAT3 in Angiotensin II type I receptor – induced cardiac hypertrophy and in vascular smooth muscle cells

I joined Dr. Karnik's lab at Cleveland Clinic in 2005, during which I made a significant progression in understating the role of rennin-angiotensin system on cardiac hypertrophy and remodeling. We have found that a novel unphosphorylated Signal Transducer and Activator of Transcription 3 (U-STAT3) signaling mechanism linked to heart failure induced by angiotensin II type 1 receptor. Despite significant therapeutic advances, morbidity and mortality in heart failure remain unacceptably high. This finding addresses a potentially novel molecular pathway underlying heart failure, which might provide a new insight into the molecular basis of heart failure. Meanwhile, I have also found that Connective Tissue Growth Factor, a known hypertrophic factor in cardiac myocytes, is differentially regulated by STAT3 and Angiotensin II, which might be a posttranscriptional mechanism mediated by microRNA (Unpublished data). This finding was further developed into another project, in which I have built up a vascular smooth cells system with my expertise developed from my PhD training, and led to a publication.

During my postdoctoral training period in Cleveland Clinic, I started collaboration with Dr. Li upon thymidine phosphorylase, and we found that gene transfection of human thymidine phosphorylase into vascular smooth muscle cells significantly increased STAT3 activation and production, which contribute to thymidine phosphorylase induced inhibition of VSMC proliferation. This part of work triggered my interests in thymidine phosphorylase, which led to my long-term collaboration with Dr. Li, as well as joining his laboratory to work on thymidine phosphorylase related projects.

a. Yue H, Li W, Desnoyer R, Karnik SS. Role of nuclear unphosphorylated STAT3 in angiotensin II type 1 receptor-induced cardiac hypertrophy. ***Cardiovasc Res.*** 2010;85:90-9. PMID:19696070

b. Kemp JR, Unal H, Desnoyer R, Yue H, Bhatnagar A, Karnik SS. Angiotensin II-regulated microRNA 483-3p directly targets multiple components of the renin-angiotensin system. ***J Mol Cell Cardiol***. 2014;75:25-39. PMID: 24976017

c. Yue H, Tanaka K, Furukawa T, Karnik SS, Li W. Thymidine phosphorylase inhibits vascular smooth muscle cell proliferation via upregulation of STAT3. ***Biochim Biophys Acta.*** 2012;1823:1316-23. PMID:22668509

3. Role of human beta-defensin 3 in HIV as well as cancer

From 2011, I joined Dr. Weinberg's and Dr. Jin's laboratory in Case Western Reserve University as a Senior Research Associate, to study HIV as well as cancer especially in association with human beta defensin-3 (hBD-3), a cationic, amphipathic peptides with antimicrobial and immunosurveillance properties. We found a differential modulation of myeloid and lymphoid Cells by hBD-3, through CXCR4, the coreceptor used by HIV-1 and CCR-2, a chemokine receptor mediated signal transduction pathway, respectively. We also found that hBD-3 induces head and neck cancer Epithelial-Mesenchymal transition, therefore might play an important role in cancer metastasis. Furthermore, human papillomavirus oncogenic E6 protein regulates hBD3 expression via the tumor suppressor protein p53; exosomes derived from HIV-1-infected cells promote growth and progression of cancer via HIV TAR RNA. These studies strengthened and widened my experiences and

knowledge in scientific research, and further lead to my promotion to a Research Assistant Professor in Dr. Li's laboratory.

a. Chen L, Feng Z, Yue H, Bazdar D, Mbonye U, Zender C, Harding CV, Bruggeman L, Karn J, Sieg SF, Wang B, Jin G. Exosomes derived from HIV-1-infected cells promote growth and progression of cancer via HIV TAR RNA. ***Nat Commun.*** 2018;9:4585. PMID: 30389917.

b. DasGupta T, Nweze EI, Yue H, Wang L, Jin J, Ghosh SK, Kawsar HI, Zender C, Androphy EJ, Weinberg A, McCormick TS, Jin G. Human papillomavirus oncogenic E6 protein regulates human β-defensin 3 (hBD3) expression via the tumor suppressor protein p53. ***Oncotarget.*** 2016;7:27430-44. PMID: 27034006

Complete List of Published Work in My Bibliography

https://www.ncbi.nlm.nih.gov/myncbi/1jOqkuD-QYbsj4/bibliography/public/

https://scholar.google.com/citations?hl=en&user=FCIAGVgAAAAJ&view_op=list_works&sortby=pubdate

Research Support

Completed Research Support

American Heart Association Postdoctoral Fellowship Award (7/1/2008 ~ 6/30/2010),
Title: Role of Unphosphorylated STAT3 in Angiotensin II Type 1 Receptor Induced Heart Failure
Role: PI
Direct: $ 88,000.