Department of Biomedical Sciences
香港城市大學
City University of Hong Kong

MAY THE FORCE BE WITH YOU: MECHANICAL SIGNALING IN THE CIRCULATORY SYSTEM

Jie Xu, Ph.D.
Principal Investigator
Institute of Precision Medicine
First Affiliated Hospital of Sun Yat-sen University
Guangzhou, China

DATE: 21 February 2025 (Friday)
TIME: 14:00 - 15:00
VENUE: B5-311, 5/F, Yeung Kin Man Acad Building

BIOGRAPHY

Dr. Jie Xu is a Principal Investigator in the Institute of Precision Medicine at the First Affiliated Hospital of Sun Yat-sen University. He received his postdoctoral training with Nobel Laureate Dr. Ardem Patapoutian at Scripps Research Institute. He designed the world's first high-throughput fluid shear stress screening device, and successfully discovered GPR68 as a mechanosensitive GPCR that senses blood flow and regulates the pathophysiology of blood vessels. In addition, Dr. Xu and colleagues characterized the physiological functions of mechanically-sensitive ion channel Piezo1 in the context of vasculature development. Dr. Xu was also the lead investigator of a 2.3-million compound screen resulting in a novel Piezo1 agonist Yoda1. Before joining FAH, Dr. Xu was a Principal Investigator at Novartis Pharmaceuticals and worked on translating novel biology into therapies for fibrosis diseases.

Currently, Dr. Xu's research focuses on the role of mechanical forces in physiology and pathology. His group is working on the role of shear stress sensor GPR68 in ischemic diseases, aiming to improve patient outcome via accelerating collateral circulation, by mimicking the mechanical effect of blood flow using small molecule modulators of GPR68. His group also developed the first 384-well format high-throughput cell stretch system and is in the forefront of hunting for novel sensor of mechanical force. Recently, his group identified a transmembrane protein that is critical regulator of plasma membrane rupture under mechanical tension and is currently elucidating its roles in programmed cell death.

ABSTRACT

Mechanical force play a critical role in biology, especially in the circulatory system, where the dynamics, development, remodeling and repair of the vessels are all influenced by mechanical stimuli. However, the molecular mechanisms have not been well understood, and discoveries in this area have been slow. We aim to accelerate discovery through development of novel technology. We designed and constructed a novel high-throughput, 384-well format shear stress stimulation system, and identified GPR68 as a sensor of fluid shear stress in endothelial cells through unbiased genetic screening. GPR68 is essential for both acute flow-mediated dilation and chronic outward remodeling. In a hindlimb ischemia model, Gpr68 KO mice exhibited significantly impaired collateral vessel growth and slower recovery of perfusion. These mice also showed worse cardiac function during the acute phase of myocardial infarction (MI). Notably, a small molecule GPR68 agonist improved blood flow recovery in peripheral ischemia and preserved cardiac function in acute MI. Additionally, we found that mechanical forces regulate plasma membrane integrity in circulating immune cells during inflammatory cell death. By conducting an unbiased screening using a 384-well cellular stretch system developed in-house, we identified NINJ1 as a key regulator of mechanical force-induced plasma membrane rupture, DAMP release, and inflammation. Our work highlights how mechanical forces intricately regulate physiological and pathological processes in the circulatory system.

Enquiries:
vivian.woo@cityu.edu.hk
3442-4985

ALL ARE WELCOME!