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VALVULAR INTERSTITIAL CELL INNATE IMMUNITY IN THE PATHOBIOLOGY OF CALCIFIC AORTIC VALVE DISEASE

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Calcific aortic valve disease (CAVD) is one of the most prevalent cardiovascular diseases in the elderly and is becoming an increasingly important health issue with the emerging longevity. Chronic inflammation and progressive calcification of the aortic valve leaflets cause valvular dysfunction and heart failure. Currently, pharmacological intervention of CAVD progression is unavailable and the interaction between the pro-inflammatory and pro-osteogenic mechanisms in aortic valve calcification is poorly understood. Aortic valve interstitial cells (AVICs) are actively involved in valvular calcification. Our studies found that human AVICs express osteogenic proteins (including BMP-2 and TGF-β1) in response to stimulation of Toll-like receptor (TLR) 2, 3 or 4. Further, the TLR-mediated osteogenic response in human AVICs leads to pro-osteogenic reprogramming characterized by the expression of Runx2 and alkaline phosphatase, and formation of calcium deposits. These studies uncovered a novel mechanistic role of the AVIC innate immunity in aortic valve calcification. Our recent work identified several endogenous factors that can elicit the osteogenic responses in human AVICs through TLRs, including oxidized low-density lipoprotein, biglycan and matrilin 2. While these endogenous factors utilize distinct TLRs, they induce the osteogenic responses through common signalling pathways, mainly the NF-κB and ERK1/2 pathways. Our findings demonstrate that damage-associated molecular patterns are capable of inducing the osteogenic responses in human AVICs and that the innate immune receptors have novel functions in modulating the osteogenic responses in human aortic valve cells. These findings suggest that AVIC TLRs may play an important role in the pathogenesis of CAVD and that modulation of the common signalling pathways utilized by TLRs may have therapeutic potential for suppression of CAVD progression.

Biography

Xianzhong Meng has been graduated from Harbin Medical University, Harbin, China in 1978. He received MS in 1981 and PhD in 1985 from the same university. He then received Postdoctoral training at Cleveland Clinic, Cleveland, USA. He became an Investigator in the Cardiothoracic Inflammtion Research Laboratory, Department of Surgery, University of Colorado Denver in 1990. He is currently a Tenured Professor in the Department of Surgery and the Director of Cardiothoracic Inflammation Research Program at University of Colorado Denver. His current research focusses on the impact of aging on myocardial ischemia/reperfusion injury and the molecular mechanism of heart valve calcification. His research is supported continuously by NIH grants. He is the author/co-author of over 160 papers published in peer-reviewed journals, and he has given over 100 presentations, invited lectures and seminars in universities, professional societies, and international conferences.

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