NCKUES SEMINAR & mPAM LECTURE SERIES

MAY 30, 2019

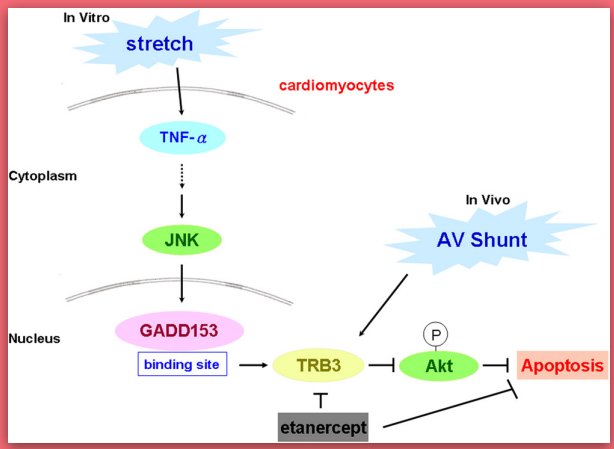
The effect of mechanical stress on cardiovascular cell death

PLACE: 工科系大樓地下一樓越生講堂

TIME: 14:10-15:30

Abstract

Cardiovascular diseases (CVDs) are major cause of death worldwide. CVDs, such as hypertrophy, myocardial infarction, heart failure and atherosclerosis, are often accompanied by cell death and inflammatory reactions. Cardiac hypertrophy is often accompanied by cardiac remodeling characterized by cardiomyocytes death and increases the risk of heart failure. Atherosclerosis is a chronic inflammatory disease involved in vascular smooth muscle cells (VSMCs) death. Cells die primarily by autophagy, necrosis and apoptosis. Apoptosis is regulated by sequential activation of caspases cascade and does not trigger immune responses. Endoplasmic reticulum (ER) stress has recently been identified as another major pathway involved in the initiation of apoptosis. Growth arrest and DNA damage inducible gene 153 (GADD153), p53-up-regulated modulator of apoptosis (PUMA), and tribbles 3 (TRB3) are the major component of the ER stress-mediated apoptotic pathway. In contrast, necrosis was traditionally regarded as passive and unregulated. Recent studies accumulated over the past decade demonstrate that necrosis is also programmed and should be considered as programmed necrosis or necroptosis. The expression of receptor-interacting protein 1 (RIP1) and receptor-interacting protein 3 (RIP3) are increases during necroptosis. Mechanical force volume overload (resulted from aorta-caval shunt, also termed AV-shunt) is able to induce inflammation, hypertrophy and heart failure. Using a cyclic stretch system on cultured cells subjects them to repetitive stretching and relaxation at rates comparable to dynamic stretch overload in vivo. This system has been applied widely in studying the molecular mechanisms of gene expression and signal transduction in cardiovascular cells. Our results indicate that GADD153, PUMA and TRB3 play an important role in mechanical stress-induced cardiovascular cell apoptosis. We also demonstrate necroptosis related gene RIP1 and RIP3 are involved in cardiovascular cells under mechanical stress.



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鄭文斌博士的研究方向

以分子心臟學為主軸，探討心血管疾病相關基因表現的變化及其分子調控路徑。主要研究方式為利用活體外(in vitro)的機械性周期展延(mechanical cyclic stretch)和缺氧模式(hypoxia)，搭配包含急性心肌梗塞(acute myocardial infarction)、動靜脈廔管(AV-shunt)所引起的容積過度負荷(volume overload)和banding所誘發的壓力過度負荷(pressure overload)等活體內(in vivo)疾病動物模式(animal model)，探討包含心臟細胞(cardiomyocytes)、血管平滑肌細胞(vascular smooth muscle cells)與內皮細胞(endothelial cells)等心血管相關細胞中的基因表現。相關發表如下

- **利用細胞體外cyclic stretch與AV-shunt，探討內質網壓力相關細胞凋亡基因對心血管系統的影響：**

(1) Cheng WP, Wang BW, Lo HM, Shyu KG. Mechanical Stretch Induces Apoptosis Regulator TRB3 in Cultured Cardiomyocytes and Volume-Overloaded Heart. PLoS One. 2015; 10(4):e0123235.

(2) Cheng WP, Wu GJ, Wang BW, Shyu KG. Regulation of PUMA induced by mechanical stress in rat cardiomyocytes. J Biomed Sci. 2012; 19:72.

(3) Cheng WP, Wang BW, Chen SC, Chang H, Shyu KG. Mechanical stretch induces the apoptosis regulator PUMA in vascular smooth muscle cells. Cardiovasc Res. 2012; 93(1):181-9.

(4) Cheng WP, Wang BW, Shyu KG. Regulation of GADD153 induced by mechanical stress in cardiomyocytes. Eur J Clin Invest. 2009; 39(11):960-71.

(5) Cheng WP, Hung HF, Wang BW, Shyu KG. The molecular regulation of GADD153 in apoptosis of cultured vascular smooth muscle cells by cyclic mechanical stretch. Cardiovasc Res. 2008; 77(3):551-9.

- **利用活體外cyclic stretch或hypoxia模式與活體內動物模式volume overload或AMI，探討hypertrophy相關基因muscle restricted coiled-coil protein (MURC)在心肌細胞中所扮演的角色：**

(1) Cheng WP, Lo HM, Wang BW, Chua SK, Shyu KG. Effect of atorvastatin on cardiomyocyte hypertrophy through suppressing MURC induced by volume overload and cyclic stretch. J Cell Mol Med. 2019; 23(2):1406-1414.

(2) Shyu KG, Cheng WP, Wang BW, Chang H. Hypoxia activates muscle-restricted coiled-coil protein (MURC) expression via transforming growth factor-β in cardiac myocytes. Clin Sci (Lond). 2014; 126(5):367-75.

- **利用活體外hypoxia與活體內動物模式AMI，探討內質網壓力相關細胞凋亡基因對心血管系統的影響：**

(1) Cheng WP, Lo HM, Wang BW, Chua SK, Lu MJ, Shyu KG. Atorvastatin alleviates cardiomyocyte apoptosis by suppressing TRB3 induced by acute myocardial infarction and hypoxia. J Formos Med Assoc. 2016; S0929-6646(16)30178-4.

- **利用stretch 和AMI探討MicroRNA-208a和-145在心血管細胞中的角色：**

(1) Shyu KG, Cheng WP, Wang BW. Angiotensin II Downregulates MicroRNA-145 to Regulate Kruppel-like Factor 4 and Myocardin Expression in Human Coronary Arterial Smooth Muscle Cells under High Glucose Conditions. Mol Med. 2015; 21(1):616-25.

(2) Shyu KG, Wang BW, Cheng WP, Lo HM. MicroRNA-208a Increases Myocardial Endoglin Expression and Myocardial Fibrosis in Acute Myocardial Infarction. Can J Cardiol. 2015; 31(5):679-90.

(3) Wang BW, Wu GJ, Cheng WP, Shyu KG. MicroRNA-208a increases myocardial fibrosis via endoglin in volume overloading heart. PLoS One. 2014; 9(1):e84188

(4) Wang BW, Wu GJ, Cheng WP, Shyu KG. Mechanical stretch via transforming growth factor-β1 activates microRNA-208a to regulate hypertrophy in cultured rat cardiac myocytes. J Formos Med Assoc. 2013; 112(10): 635-43.

Short CV

Education

Master (September 2001 – June 2004),
Ph.D. (September 2004 – June 2008)
Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan

Work Experience

Postdoctoral Research Fellow (October 2009 – July 2013)
Doctoral Research Fellow (August 2013 - Present)
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Grants

Project of Ministry of Science and Technology 2016-2019; 2014-2015

Research Interests

Hypertrophy and atherosclerosis
ER stress related apoptosis
Necroptosis
Pyroptosis