Regulatory Mechanism of 17β-estradiol and/or Estrogen Receptor β on Hypoxia-induced BNIP3 Autophagic and Apoptotic Pathways in H9c2 Cardiomyoblast Cells

Yi-Ping Lai[1, #], Wei-Wen Kuo[2] and Chih-Yang Huang[1, 3, *]

[1]*Graduate Institute of Basic Medical Science, China Medical University, Taichung*

[2]*Department of Biological Science and Technology, China Medical University, Taichung*

[3]*Graduate Institute of Chinese Medical Science, China Medical University, Taichung*

aping4903@hotmail.com

Myocardial infarction (MI) causes cardiomyocyte apoptosis, ventricular remodeling, leading to a dilated heart. Hypoxia is one of the causes involved in MI damage, but cardiac hypoxia results in two opposite effects: cell survival or death. In hearts, autophagy functions predominantly as a balance to maintain homeostasis during cellular stress by removing protein aggregation and damaged organelles, protecting the heart against famine and ischemia. However, when severely triggered, the autophagic machinery may lead to cell death. BNIP3 is a hypoxia-inducible marker and a sensor to increase both autophagy and apoptosis. BNIP3-docked organelles, mitochondria, also determine cell ongoing autophagy or apoptosis. Recent reports discussed ablating BNIP3 can restrain cardiomyocytes apoptosis and post-infarction remodeling. Therefore, BNIP3 is a crucial therapeutic target that connects several regulatory pathways. 17β-estradiol (E2)/estrogen receptor (ER) β exert cardiac protection to against reperfusion arrhythmias (RAs) in myocardial ischemia rats. The aim of the study is to uncover the regulatory mechanism of ER β on hypoxia-induced BNIP3-depedent effects. Heart-derived H9c2 cells were incubated in a normoxic or hypoxic (<1% oxygen) condition for 24 h after transient transfection of ER β. Our result showed the hypoxia caused the hypoxia-inducible factor (HIF)-1α expression highly increase, activated downstream BNIP3 and IGFBP3, further activated autophagic and apoptotic pathway. However, all phenomena recovered in E2/ER β overexpression cells. E2/ER β overexpression even further promoted the cardiac survival pathway related proteins, p-IGF1R and p-Akt activation. We hypothesized that ER β exerts the protective effect through repressed hypoxia-inducible BNIP3 protein levels to restrain the BNIP3-induced autophagy and apoptosis effects in H9c2 cardiomyoblast cells. Detail protective mechanisms will be further identified in the near future.