

## **CDK5-MEDIATED HYPERPHOSPHORYLATION CONTRIBUTES TO THE LOSS-OF-SIRT1 FUNCTION DURING THE DEVELOPMENT OF ENDOTHELIAL SENESCENCE**

***B. Bai<sup>1</sup>, Y. Liang<sup>1</sup>, C. Xu<sup>1</sup>, M.Y.K. Lee<sup>1</sup>, A.M. Xu<sup>1</sup>, D.H. Wu<sup>2</sup>, P.M. Vanhoutte<sup>1</sup>, Y. Wang<sup>1</sup>***

1. Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong
2. Key Laboratory of Regenerative Biology, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

**BACKGROUND:** During vascular aging, endothelial cells lying on the inner surface of the blood vessels present a senescent phenotype, triggering and accelerating atherosclerosis development. The anti-aging activity of SIRT1, a NAD-dependent deacetylase, is lost during the occurrence of endothelial senescence (Cir Res 2010;106:1384-93). The present study aims to investigate the molecular mechanisms underlying the loss-of-SIRT1 function in senescent endothelial cells.

**METHODS AND RESULTS:** In senescent primary porcine aortic endothelial cells (PAECs), the phosphorylation of SIRT1 at serine 47 (S47) was significantly enhanced. Phosphorylation at S47 was stimulated by agents promoting senescence, attenuated by drugs with anti-senescence properties, and critically involved in regulating the intracellular localization of SIRT1. Cyclin-dependent kinase 5 (CDK5) was responsible for modulating the phosphorylation of SIRT1 at S47. Knocking down or inhibition of CDK5 alleviated endothelial senescence and attenuated the expression of inflammatory genes in PAECs. Chronic treatment with roscovitine (a CDK5 inhibitor) blocked the development of cellular senescence and atherosclerosis in aortae of hypercholesterolemic apolipoprotein E deficient mice.

**CONCLUSION:** CDK5-mediated hyperphosphorylation of SIRT1 facilitates the development of endothelial senescence and atherosclerosis.