中文題目：發現微小核糖核酸 **146a-5p** 透過對介白素**-1** 受體相關激酶**-1** 的表現量調控來影響高糖刺激下的內皮細胞發炎反應

英文題目**: Identification of MicroRNA-146a-5p Mediates High Glucose-Induced Endothelial Inflammation via Targeting Interleukin-1 Receptor-Associated Kinase 1 Expression**

作者**:** 王黃舟[a]，羅婉瑜[b]

服務單位**:** [a]中國醫藥大學附設醫院內科部**,** [b]弘光科技大學生物科技系

Huang-Joe Wang[a], Wan-Yu Lo[b,*]

a. Division of Cardiovascular Medicine, Department of Medicine, China Medical University Hospital

b. Cardiovascular & Translational Medicine Laboratory, Department of Biotechnology, Hung Kuang University

ABSTRACT

Background: The hallmark of diabetes is hyperglycemia. The high glucose (HG) can lead to the chronic inflammation of the endothelium. Interleukin-1 receptor-associated kinase (IRAK-1) is a critical protein in mediating toll-like receptor-signaling and interleukin 1 receptor signaling. It is not clear whether the expression of IRAK-1 was altered in HG-stimulated endothelial cells. In addition, we investigated the potential involvement of the microRNAs (miR) in regulating the HG-induced endothelial inflammation by targeting IRAK-1.

Methods: Human aortic endothelial cells (HAECs) were treated with HG (25 mmol/L) for 24 h and 48 h. Real-time PCR, Western blot, THP-1 monocytic cell adhesion assay, bioinformatics prediction, TaqMan® Array screening, miR qPCR validation, miR-146a-5p mimic/inhibitor transfection, and siRNA IRAK-1 transfection were performed. The expression levels of miR-146a-5p and soluble ICAM-1 from human

serums of type I diabetic cases and control cases were examined by qPCR and ELISA, respectively. The institutional review board approved the human study.

Results: We showed that HG exerted a time-dependent increase in IRAK-1 mRNA and protein level in HAECs. Increased IRAK-1 expression was associated with an increase of VCAM-1/ICAM-1 gene expression and THP-1 adhesion to HAECs. Bioinformatics' miR analysis identified a total of 13 possible microRNAs possess homology between microRNAs and the 3'-UTR of the human IRAK-1 mRNA. Using TaqMan® Array and qPCR validation, we identified that miR-146a-5p, miR-339-5p and miR-874-3p were significantly downreguated in HG-treated HAECs, suggesting impaired feedback restraint of HG-induced endothelial inflammation via IRAK-1. However, only miR- 146a-5p mimic transfection attenuated HG-induced upregulation of IRAK-1 gene and protein expression. In contrast, miR-146a-5p inhibitor transfection caused an increase of HG-induced IRAK-1 gene expression. Furthermore, miR-146a-5p mimic transfection decreased the VCAM-1/ICAM-1 gene expression and THP-1 monocytic adhesion. Additional experiments with siRNA transfection against IRAK-1 identified the decrease of HG-induced IRAK-1 gene and protein expression, VCAM-1/ICAM-1 gene expression and THP-1 adhesion, indicating HG-induced endothelial inflammation partially mediated through IRAK-1. In vivo evidences showed that downregulation of miR-146a-5p and upregulation of soluble ICAM-1 in the human serum of type I diabetic patients.

Conclusion: we identified that microRNA-146a-5p is involved in the regulation of HG-induced endothelial inflammation via modulation of IRAK-1.