中文題目：Cilostazol經由Axl訊息傳遞路徑抑制由尿毒誘發之血管平滑肌功能異
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英文題目：Cilostazol inhibits uremic toxin–induced vascular smooth muscle cell
dysfunction through the Axl dependent signaling pathway
作　　者：李建興[1] 洪乙仁[1] 許育瑞[1] 林致源[2] 簡筑妍[3] 謝義興[4]
服務單位：三軍總醫院內科部[1] 三軍總醫院外科部[2] 國防醫學院醫學科學研究所[3]
三軍總醫院牙科部[4]

Background

Chronic kidney disease (CKD) is associated with increased cardiovascular mortality, and vascular smooth muscle cell (VSMC) dysfunction plays a pivotal role in uremic atherosclerosis. Axl signaling is involved in vascular injury and is highly expressed in VSMC. Recent reports have shown that cilostazol can regulate in various stages of the atherosclerotic process. However, the role of cilostazol in uremic vasculopathy remains unclear. This study aimed to identify the effect of cilostazol in VSMCs in the experimental CKD and to investigate whether the regulatory mechanism occurs through Axl signaling.

Methods

We investigated the effect of P-cresol and cilostazol on Axl signaling in A7r5 rat VSMCs and the rat and human CKD models.

Results

From the *in vivo* CKD rats and patients, aortic tissue exhibited significantly decreased Axl expression after cilostazol treatment. P-cresol increased Axl, PCNA, FAK and MMP-2 expressions, decreased caspase-3 expression, and was accompanied with increased cell viability and migration. Cilostazol significantly reversed P-cresol-induced Axl, downstream gene expressions and cell functions. Along with the increased Axl expression, P-cresol activated PLCγ, Akt and ERK phosphorylation and cilostazol significantly suppressed the effect of P-cresol. Axl knockdown significantly reversed the expressions of P-cresol-induced Axl related gene expression and cell functions. Cilostazol with Axl knockdown have additive changes in downstream gene expression and cell functions in P-cresol culture.

Conclusion

Both *in vitro* and *in vivo* experimental CKD models elucidate a new mechanism of cilostazol-mediated protection against uremic toxin related VSMCs dysfunction and highlight the involvement of the Axl signaling and downstream pathways.