中文題目：Cilostazol 經由 AMP 活化激酶路徑改善人類內皮前驅細胞和內皮細胞的功能進而促進血管新生

英文題目：Cilostazol improves high glucose-induced impaired angiogenesis in human endothelial progenitor cells and vascular endothelial cells as well as enhances vasculo-angiogenesis in hyperglycemic mice mediated by AMP-activated protein kinase pathway

作者：曾詩雅 [1,2] 卓忠隆 [1] 趙庭興 [2]

服務單位: 中山大學生物科學系 [1] 成大醫院內科 [2]

Background：Cilostazol is an antiplatelet agent with vasodilatory effects that works by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP). This study aimed to investigate the effects of cilostazol in preventing high glucose (HG)-induced impaired angiogenesis, and to examine the potential mechanisms involving activation of AMP-activated protein kinase (AMPK).

Methods：Assays for colony formation, adhesion, proliferation, migration and vascular tube formation were used to determine the effect of cilostazol in HG-treated endothelial progenitor cells (EPCs) or human umbilical vein endothelial cells (HUVECs). Animal-based assays were performed in hyperglycemic ICR mice undergoing hindlimb ischemia. An immnunoblotting assay was used to identify the expression and activation of signaling molecules in vitro and in vivo.

Results： Cilostazol treatment significantly restored endothelial function in EPCs and HUVECs through activation of AMPK/acetyl-coenzyme A carboxylase (ACC) - and cAMP/protein kinase A (PKA)-dependent pathways. Recovery of blood flow in the ischemic hindlimb and the population of circulating $CD34^+$ cells were significantly improved in cilostazol-treated mice, and these effects were abolished by local AMPK knockdown. Cilostazol increased the phosphorylation of AMPK/ACC and Akt/endothelial nitric oxide synthase signaling molecules, either in parallel with or

downstream of cAMP/PKA-dependent signaling pathway in vitro and in vivo.

Conclusions： Cilostazol prevents HG-induced endothelial dysfunction in EPCs and HUVECs, and enhances angiogenesis in hyperglycemic mice by interactions with a broad signaling network, including activation of AMPK/ACC and probably cAMP/PKA pathways.