Rosiglitazone 透過 ERK-1/-2 信息傳遞路徑誘導腎臟環間膜細胞之分化

ERK-1/-2 Dependent Induction of Mesangial Cell Differentiation by Rosiglitazone

中文摘要

Rosiglitazone 是一種 peroxisome proliferator-activated receptor-gamma (PPAR-g agonist，在第二型糖尿病的實驗模式中被認爲能夠減少 mesangium 的過度增生。本研究中發現，在大鼠腎臟環間膜細胞中給予 PPAR-g agonist 時，會調控大鼠腎臟環間膜細胞增生。當以 rosiglitazone 刺激大鼠腎臟環間膜細胞時，發現會造成活細胞數目與 DNA 合成的減少，並使得 CDK 抑制劑--p21cip1 的表現增加，進而造成細胞生長停滯。此外，rosiglitazone 也會增加大鼠腎臟環間膜細胞 PDK-1、protein kinase B/Akt (PKB/Akt) Serine473 磷酸化與 Akt kinase 的活性。而這些反應會被 phosphatidylinositol 3-kinase (PI3-K)的抑制劑--LY294002 與 wortmannin 所抑制。而 rosiglitazone 會使腎臟環間膜細胞分化的指標-- smooth muscle a-actin (SMA) 的表現增加。由於 LY294002 與 wortmannin 並無法抑制 SMA 的表現，所以 SMA 表現可能不是經由 PI3-K 的信息傳遞路徑而來的。但是 SMA 表現可以被 protein tyrosine kinase 的抑制劑--genistein 與 MEK 的抑制劑--PD98059 所抑制。因此，推測 SMA 表現可能是透過 protein tyrosine kinase-MEK-mitogen-activated protein kinase 的信息傳遞路徑來調控大鼠腎臟環間膜細胞的分化。這些結果證明了 PPAR-g 透過 Erk 的傳遞路徑，扮演了調控腎臟環間膜細胞的分化的機制。

英文摘要

Rosiglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-g) agonist that has been shown to halt mesangium expansion in experimental models of type 2 diabetes mellitus. In the present study, rat mesangial cells were treated with rosiglitazone and its molecular mechanisms coupling growth arrest were examined. Treatment of rat mesangial cells with rosiglitazone resulted in reduction of viable cells and inhibition of [3H] thymidine incorporation. Treatment with rosiglitazone increased the expression of CDK inhibitor, p21CIP-1, which was associated with cell cycle arrest. Rosiglitazone increased PDK-1 and protein kinase B/Akt (PKB/Akt) Serine473 phosphorylation and Akt kinase activity in rat mesangial cells, and these responses were inhibited with the pharmacological inhibitor of phosphatidylinositol 3-kinase (PI3-K), LY294002 or wortmannin. Rosiglitazone increased the expression of smooth muscle a-actin (SMA), a differentiation marker for mesangial cells.

LY294002 or wortmannin pretreated cells failed to blocked SMA expression suggesting SMA expression is not mediated through PI3-K dependent pathway. The expression of SMA was inhibited by genistein (a protein tyrosine kinase inhibitor), by PD98059 (a MEK inhibitor), suggesting protein tyrosine kinase-MEK-mitogen-activated protein kinase pathway mediates the differentiation of renal glomerular mesangial cells. These data demonstrate a role for PPAR-g in mediating a molecular mechanism coupling growth arrest and mesangial cell differentiation.