行政院國家科學委員會專題研究計畫 期中進度報告

以新合成 的 TGF-beta 拮抗劑探討 TGF-beta 對腎臟纖維化

的角色(1/3)

<u>計畫類別</u>: 個別型計畫 <u>計畫編號</u>: NSC93-2314-B-002-146-<u>執行期間</u>: 93 年 08 月 01 日至 94 年 10 月 31 日 <u>執行單位</u>: 國立臺灣大學醫學院內科

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NSC93-2314-B002-146 期中報告

計畫名稱:The effects of a synthetic TGF-β1 pentacosapeptide (β1-(41-65)) on renal fibrogenesis **計畫名稱:**以新合成的 TGF-beta 拮抗劑探討 TGF-beta 對腎臟纖維化的角 色(1/3) (第一年期中報告)

In the present study, we hypothesize that this non-agonist TGF- β_1 pentacosapeptide (β_1 (41-65)) is capable of (1) blocking TGF- β -stimulated ECM production via downregulation of TGF- β 1-activated Smad and/or P42/44 MAPK pathways in cultured mesangial cells and interstitial fibroblasts (NRK49F), and inhibiting TGF- β -mediated tubular epithelial-myofibroblast transdifferentiation in cultured tubular cells (NRK52E); (2) suppressing the development mesangial hypercellularity and glomerulosclerosis in rat anti-Thy1 glomerulonephritis induced by a single injection of mouse anti-rat Thy1.1 antibody; and (3) preventing the progression of glomerulosclerosis and interstitial fibrosis in rat remnant kidney model induced by 5/6 nephrectomy.

In Year 1, we plan to investigate the modulatory effects of a non-agonist TGF- β_1 -mimetic (β_1 -(41-65)) on TGF- β_1 -activated fibrogenesis in cultured rat mesangial cells and interstitial fibroblasts (NRK49F), and to investigate the potential effects of TGF- β_1 (β_1 -(41-65) on transdifferentiation in NRK52E cells.proximal tubular cells (NRK52E). The mechanisms whereby TGF- β_1 (β_1 -(41-65) acts in all three types of cells, focusing on TGF- β_1 -activated MAPK (P42/44, P38, and JNK) and Smad (Smad 2/3 and 7) pathways, will also be studied

As of May 20 our mid-term results are as follows (Figures 1-4):

Figure 1. Time-course of TGF- β 1-induced extracellular matrix gene expression in rat mesangial cells. T5 and T10 denote TGF- β 1 at 5 ng/mL and 10 ng/mL, respectively.



Figure 2. Time-course of TGF-β1 (1 ng/mL)-activated phosphorylation of p42/44 MAPK (ERK1/2) and Smad2 proteins in rat mesangial cells.



Figure 3. TGF- β_1 pentacosapeptide (β_1 (41-65) blocks TGF- β_1 -induced matrix gene expression in rat mesangial cells. T10 represents TGF- β_1 at 1 ng/mL.



Figure 4. TGF- β_1 pentacosapeptide (β_1 (41-65) attenuates TGF- β_1 -induced phosphorylation of p42/44 MAPK (ERK1/2) and Smad2 proteins in rat mesangial cells. T1 represents TGF- β_1 at 1 ng/mL.



In summary, our results in cultured rat mesangial cells <u>so far</u> show that (1) TGF- β_1 activates phosphorylation of p42/44 MAPK and Smad2 pathways; (2) TGF- β_1 induces gene expression of extracellular matrix, including type 1 (α 1) collagen, type 3 (α 1) collagen, and fibronectin; (3) the non-agonist TGF- β_1 pentacosapeptide (β_1 (41-65)) is capable of suppressing TGF- β_1 -activated phosphorylation of Smad2; and (4) the non-agonist TGF- β_1 pentacosapeptide (β_1 (41-65)) is capable of inhibiting TGF- β_1 -pentacosapeptide (β_1 (41-65)) is capable of and fibronectin.