行政院國家科學委員會專題研究計畫　成果報告

β1 型轉化生長因子於腎肥大過程中肝細胞生長因子失調之角色

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中文摘要

我們將 25 天大之大白鼠右腎切除研究其左腎於術後 6 小時、12 小時、24 小時、48 小時、72 小時及 7 天之腎臟生長及肝細胞生長因子(HGF)，β1 型轉化生長因子(TGF-β1)、C-met 蛋白及 TGF-β1 mRNA 之變化情形。結果發現腎中 HGF/TGF-β1 比值於術後 12 小時實驗組有意義高於控制組，而 TGF-β1 mRNA 則於 12-24 小時達到最低，C-met 蛋白則在 6~24 小時明顯增加，而顯著的腎肥大(腎臟重量增加)則發生在術後 7 天之實驗組。

關鍵詞：肝細胞生長因子、β1 型轉化生長因子、腎切除後代償性腎肥大。

英文摘要

Kidney growth and growth factors change were observed after unilateral nephrectomy in the 25-day-old rats. Renal HGF/TGF-β1 ratio was found significantly higher at 12 hours after nephrectomy. C-met receptor protein was remarkably increased at the first 24 hours associated with low renal TGF-β1 and TGF-β1 mRNA at least at the 12~24 hours after nephrectomy. Kidney weight was increased at 7 days after nephrectomy, but not in the first 72 hours.

Keywords：hepatocyte growth factor, transforming growth factor β1, postnephrectomy compensatory renal growth

Introduction

We have recently reported an entirely new finding not only nephromegaly in children with biliary atresia, but also a correlation between nephromegaly and elevated plasma HGF in these patients (1). However, our animal experiment using low-to-medium dose of HGF injection to rats for a short duration couldn't induce high plasma HGF condition. Our more recent data on infants with subacute or chronic liver injury revealed the extent of nephromegaly correlated positively with plasma HGF but negatively with plasma TGF-β1 (2). The reciprocal relationship of plasma HGF and TGF-β1 in this situation may reduce anti proliferative effect of TGF-β1 and thus potentiate proliferative effect of HGF resulting in nephromegaly. We thus created an animal model of chronic liver injury using ligation of common bile duct in rats to observe the nephromegaly (3), and found that plasma HGF was significantly decreased at one week and plasma TGF-β1 was persistently low through one and two weeks after surgery in experimental rats. Renal HGF/TGF-β1 started rising since first week and reached a significantly higher level than sham controls at 2nd week postoperatively. This was followed by a higher kidney weight/body weight ratio and an elevated protein/DNA ratio (suggesting renal hypertrophy) at 3rd week in CBD ligation rats. From human (2) and our rat model, the low TGF-β1 after liver injury may be the most important factor to result in renal hypertrophy in this situation. We thus plan to examine the role of TGF-β1 in another situation, postnephrectomy compensatory renal growth (4,5).

Methods

Wistar rats, 25-day-old, were performed right nephrectomy. They were sacrificed at 6h, 12h, 24h, 48h, 72h and 7 days after surgery. Blood was collected and kidneys were removed after saline perfusion during sacrifice. Kidneys were homogenized with TRI reagent and extracted for tissue lysate. Renal tissue HGF and TGF-β1, TGF-β1 mRNA, and c-met protein were than measured using various specific EIA kits, northern blots and western blots. The initial changes of renal HGF/TGF-β1, c-met protein and TGF-β1 mRNA were evaluated at each timepoint compared with sham control using student t test for statistical analysis.

Results

Renal HGF/TGF-β1 ratio was elevated at 12h after nephrectomy when compared with sham controls (Table). C-met (HGF receptor) protein was also increased in the first 24h as indicated on western blots (not shown here). TGF-β1 mRNA expression was diminished at 12~24h after nephrectomy as shown on northern blots. Single kidney weight was increased at 7 days after nephrectomy, but not in

the first 72hr.

Discussion

To examine the role of TGF-β1 in postnephrectomy compensatory renal hypertrophy, we first found elevated renal HGF/TGF-β1 ratio in 12h after nephrectomy. Similar to our previous liver injury model, renal hypertrophy (detectable increased kidney weight) occurred at 7d after surgery. C-met receptor portein increased in the first 24h suggesting HGF involvement in the hypertrophy process (5). However the main factor of elevated renal HGF/TGF-β1 ratio in compensatory renal hypertrophy depends on a decrease of renal TGF-β1 in the first day. This is further supported by the decreased TGF-β1 mRNA at 12~24h after nephrectomy. Interestingly, elevated renal HGF/TGF-β1 ratio, either resulted from increased HGF (possibly in liver injury model) or decreased TGF-β1 (evidence from present study for compensatory renal growth), all proceeds to renal hypertrophy apparently about one week later. The reciprocal relation of HGF and TGF-β1 for growth control is interesting, and the detailed mechanism of these factors in the hypertrophy process needs further explored.

計劃成果自評：

如同肝傷害模型腎肥大一樣，本計劃證實另一種腎切除後代償性腎肥大亦與腎中 HGF/TGF-β1 比值增高有關連，前者可能受血中生長因子變化影響，而本研究則與腎中之 TGF-β1 mRNA 降低有關，這些結果均是新的發現，以前並沒有報告過，因此對腎臟生長的了解應有很大的價值。

Reference

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Table Changes in kidney growth and growth factors after unilateral nephrectomy in 25-day-old rats

	Time after nephrectomy					
	6h	12h	24h	48h	72h	7d
Kidney weight (g)						
nephrectomy	0.39±0.06	0.43±0.05	0.44±0.02	0.57±0.09	0.51±0.09	0.91±0.13*
sham control	0.38±0.03	0.42±0.04	0.42±0.05	0.49±0.06	0.47±0.07	0.61±0.08
Renal HGF/TGF-β1 (ng/ng)						
nephrectomy	25.6±21.5	34.7±10.4#	28.3±23.0	19.4±12.2	24.0±23.3	15.2±5.9
sham control	22.7±22.5	18.7±12.1	22.3±15.4	14.7±11.6	25.7±18.3	17.7±14.4
C-met receptor protein						
nephrectomy	increased	increased	increased			
TGF-β1 mRNA						
nephrectomy		decreased	decreased			

* $P<0.001$ # $P<0.05$