研究課題

新規生理活性分子AcSDKPの腎疾患における病態生理学的意義の臨床的解析

課題番号
10671012

平成11年度科学研究費補助金（一般研究C）研究成果報告書

平成12年3月3日

研究代表者　伊藤克己
東京女子医科大学医学部教授

研究組織

研究代表者：伊藤克己（東京女子医科大学医学部教授）

研究分担者：吉岡俊正（東京女子医科大学医学部助教授）

研究分担者：白髪宏司（東京女子医科大学医学部助教授）

研究分担者：秋岡裕子（東京女子医科大学医学部助手）

研究経費

平成10年度　1000千円

平成11年度　　90千円

計　　1900千円

研究発表

ア　学会誌等

1. N. Iwamoto, H-J. Xiao, T. Yoshioka, H. Shiraga, K. Nitta,T. Muraki, and K. Ito. ：Acetyl-Seryl- Asparatyl-Lysyl-Proline is a novel natural cell cycle regulator of renal cells. Life Sciences, 66(15): PL221-226 2000.
2. M. Motojima, J. Kakuchi, T. Yoshioka. : Association of TGF-β signaling in angiotensin II-induced PAI-1 mRNA upregulation in mesangial cells : role of PKC. Biochemica et Biophysica Acta, 1449:217-226 1999.
3. T. Yoshioka et al. Antiinflammatory potency of dehydrocurdione, a zedoary-derived sesquiterpene. Inflamm. res. 47:476-481 1998.
4. T. Yoshioka, H. Shiraga, K. Ito, et al. :Deletion polymorphism of the angiotensin converting enzyme gene predicts persistent proteinuria in Henoch-Scholein purpura nephritis. : Archiv. Dis. child. 79(5):394-399 1998.
5. Y.Akioka, H. Shiraga, K. Ito, et al. :Cryosupernatant plasma exchange in the treatment of antiphospholipid antibody Syndrome with lupus nephritis. : Therapeutic Apheresis 2(3):236-239 1998.

イ　口頭発表

1. 岩本典子、吉岡俊正、白髪宏司、伊藤克己：新規生理活性ペプチド、AcSDKPの腎細胞増殖抑制作用とアンジオテンシン変換酵素阻害剤（ACEI）AcSDKPに関わる新たな分子薬理作用の解析。第33回小児腎臓病学会雑誌抄録集p141　1998年6月

2. 岩本典子、吉岡俊正、白髪宏司、伊藤克己：造血幹細胞抑制因子、N-acetyl-seryl-aspartyl-lysyl-prolineの腎細胞増殖抑制作用の検討。第8回腎とエリスロポエチン研究会　1999年11月
3. N. Iwamoto, H-J. Xiao, T. Yoshioka, H. Shiraga, H. Nagafuchi, K. Takahashi, Y. Akioka, K. Nitta, K. Irie, T. Muraki, and K. Ito. : AcSDKP AS A NEW MEDIATOR OF RENAL CELL PROLIFERATION AND A TARGET FOR THE MOLECULAR ACTION OF ACEI. The 11th Congress of the International Pediatric Nephrology association Pediatric Nephrology. Septenber 1998/London, England.
4. T. Yoshioka, N. Iwamoto, K. Nitta, K. Irie, H-J. Xiao,T. K. Ito and T. Muraki. : AcSDKP is a novel anti-proliferative peptide for renal fibroblasts. XIIIth international Congress of Pharmacology. 26-31/July 1998/Munchen, Germany.

ウ　出版物

1. 岩本典子、吉岡俊正、萬野純恵、高桑雄一、伊藤克己：生体での非NOS依存性一酸化窒素産生。腎とフリーラジカル第４集　東京医学社 p42-47、1998。
2. 秋岡裕子、角田由里、吉岡俊正、伊藤克己：小児特発性ネフローゼ症候群。Annual Review 腎臓1998　中外医学社、ｐ184-188、1998。
3. 伊藤克己、秋岡裕子：ソマトロピン（遺伝子組換え）。新しい治療薬のポイント1998前期　メデイカルレビュー社　８：51-85

研究成果

1. **Acetyl-seryl-asparatyl-lysyl-proline is a novel natural cell cycle regulator of renalcells.**

A natural tetrapeptide, acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is a physiological negative regulator of hematopoiesis. The precursor of AcSDKP, thymocin β4, is expressed in many tissues including kidney. The present study examined the antiproliferative effect of AcSDKP in two renal cell lines, namely, renal interstitial fibloblasts cell line (NRK 49F) and renal proximal tubular epitherial cells (LLC-PK1). An addition of AcSDKP for 48 hours in theses cells resulted in a concentration-dependent attenuation in the proliferation rate (significant difference to non-treated cells was observed at 10^{-9} to 10^{-5} M AcSDKP) determined by a colorimetry of alamer blue oxidation. The cell cycle analysis of NRK 49F cells treated with AcSDKP showed that AcSDKP significantly reduced the ratio of S-phase to G2/M-phases. Thus, physiological concentrations of AcSDKP is capable of altering cell cycle to inhibit the proliferation of renal cells.

2. **Regulation of renal cell proliferation by a natural tetrapeptide acetyl-seryl-aspartyl-lysyl-proline**

N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is a natural peptide that inhibits proliferation of hematopoietic stem cells. We tested if the peptide regulates proliferation of renal cells. AcSDKP concentration-dependently attenuated growth of NRK49F cells, a cell line of renal fibroblasts. Captopril which blocks the N- and C-terminals of angiotensin converting enzyme (ACE), augmented the antiproliferative activity of AcSDKP, while lisinopril which selectively blocks the C-terminal showed no effect. Treatment with AcSDKP and ACE inhibitors did not change mRNA expressions of ACE and the precursor of the peptide, thymosin β4. The antiproliferative activity of AcSDKP was also demonstrated in glomerular mesangial cells but not in U937 cells, a monocytic cell line. Thus, AcSDKP may be a novel regulatory factor of renal cell proliferation. An inhibition of AcSDKP degradation may constitute the anti-proliferative effect of ACE inhibitors that block the ACE N-terminal active site.

3. Other findihgs of the project

Reprint of published manuscripts are attached.