行政院國家科學委員會專題研究計畫 成果報告

低氧誘導因子-1α 與環孢靈誘發牙齦增生關係之探討(第 3 年)
研究成果報告(完整版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 97-2314-B-040-020-MY3
執 行 期 間 ：99 年 08 月 01 日至 100 年 07 月 31 日
執 行 單 位 ：中山醫學大學口腔科學研究所

計 畫 主 持 人：張育超

計畫參與人員：碩士級-專任助理人員：劉秀瑜

報 告 附 件 ：出席國際會議研究心得報告及發表論文

處 理 方 式 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 100 年 10 月 28 日

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

低氧誘導因子-1α 與環孢靈誘發牙齦增生關係之探討

計畫類別：■個別型計畫　□整合型計畫
計畫編號：NSC 97－2314－B－040－020－MY3
執行期間： 97 年 8 月 1 日至 100 年 7 月 31 日

執行機構及系所：中山醫學大學牙醫學系

計畫主持人：張育超
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計畫參與人員：

成果報告類型(依經費核定清單規定繳交)：□精簡報告　■完整報告

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中　華　民　國　100 年 10 月 27 日

Abstract

Aim: The prominent side effect of immunosuppressive drug cyclosporine A (CsA) is gingival overgrowth. Hypoxia-inducible factor (HIF)-1α regulates a wide variety of profibrogenic genes, which are closely associated with tissue fibrosis. The aim of this study was to compare HIF-1α expression in normal gingival tissues and CsA-induced gingival overgrowth specimens and further explore the potential mechanisms that may lead to induction of HIF-1α expression.

Materials and Methods: Fifteen CsA-induced gingival overgrowth specimens and five normal gingival tissues were examined by immunohistochemistry. Western blot was used to investigate the effects of CsA on the expression of HIF-1α in cultured human gingival fibroblasts. The effects of CsA on plasminogen activator inhibitor (PAI)-1 expression were evaluated in environmental hypoxia.

Results: HIF-1α staining in gingival tissue was stronger in CsA-induced gingival overgrowth group than normal gingival group ($p<0.05$). The expression of HIF-1α was significantly higher in CsA-induced gingival overgrowth specimens with higher levels of inflammatory infiltrates ($p=0.041$). CsA was found to upregulate HIF-1α protein in a dose-dependent manner ($p<0.05$). Hypoxia increased CsA-induced PAI-1 protein expression than normoxic conditions ($p<0.05$).

Conclusions: These results suggest that HIF-1α expression is significantly upregulated in CsA-induced gingival overgrowth specimens. The activation of HIF-1α may promote fibrogenesis by PAI-1 increasing expression of extracellular matrix in gingival tissues.

Keywords: cyclosporine A, gingival fibroblasts, gingival overgrowth, hypoxia-inducible factor-1α, plasminogen activator inhibitor-1

中文摘要

目的：

免疫抑制劑環孢靈最主要的副作用是造成牙齦增生，低氧誘導因子-1α(hypoxia-inducible factor -1α, HIF-1α)會調控許多纖維化基因，並與多種組織纖維化症有關。本研究的目的在比較 HIF-1α 在正常牙齦組織中與環孢靈誘發牙齦增生組織的表達情形；並進一步探討，造成 HIF-1α 表達的可能的機轉。

材料與方法:

利用免疫化學組織染色法檢查 15 個環孢靈誘發牙齦增生的組織及五個正常的牙齦組織。並利用西方墨點法來檢驗環孢靈是否會誘發正常人類牙齦造纖維母細胞表達 HIF-1α。並在厭氧環境下探討環孢靈是否會誘發正常人類牙齦造纖維母細胞表達第一型胞漿素原活化抑制劑(plasminogen activator inhibitor-1, PAI-1)。

實驗結果發現:

環孢靈誘發牙齦增生的組織比正常的牙齦組織有較高的 HIF-1α 表達，且具有統計學上的意義 $p<0.05$ 。環孢靈誘發牙齦增生組織中 HIF-1α 表達的強弱與發炎的程度具有正相關 $p<0.05$。環孢靈會誘發 HIF-1α 的表達並隨著劑量的增加而增加 $p<0.05$。在厭氧環境中環孢靈誘發 PAI-1 蛋白的程度比正常環境高，並具有統計學上意義 $p<0.05$

結論:

實驗結果顯示: HIF-1α 在環孢靈誘發牙齦增生的組織中，有明顯的表達。激發 HIF-1α 的表達可促進纖維化的產生，並藉由 PAI-1 來增加細胞外間質在牙齦組織的沉積。

關鍵字：環孢靈、造牙齦纖維母細胞、牙齦增生、低氧誘導因子-1α、第一型胞漿素原活化抑制劑

Introduction

Cyclosporine A (CsA) is a cyclic polypeptide used as an immunosuppressive drug. It is widely used to prevent organ transplant rejection and to treat various immunological diseases. Gingival overgrowth is a prominent side effect associated with the systemic use of CsA (Faulds et al. 1993). Gingival overgrowth as a clinical outcome presents as an increased gingival volume, including an increased number of cells and a higher level of extracellular matrix (ECM) production (Hassell & Hefti 1993). Despite extensive research, the precise mechanism underlying the pathogenesis of CsA-induced gingival outgrowth is still unclear.

A key mediator of cellular responses to low oxygen is hypoxia inducible factor-1 (HIF-1), a heterodimeric transcription factor consisting of a constitutively expressed β subunit (also known as aryl hydrocarbon receptor nuclear translocator) and an O_2-regulated α subunit. In normoxia, the HIF-1α subunit is a short-lived polypeptide that undergoes rapid oxygen-dependent hydroxylation on specific proline and asparagine residues by prolyl hydroxylases. In the presence of oxygen, prolyl hydroxylase domain (PHD) enzymes hydroxylate HIF-1α and enable interaction with von Hippel-Lindau protein (pVHL), which results in its ubiquitylation and subsequent proteasomal degradation (Schofield & Ratcliffe 2004). HIF-1 also induces expression of profibrogenic genes like tissue inhibitor of metalloproteinase-1, connective tissue growth factor, and plasminogen activator inhibitor (PAI)-1 (Kietzmann et al. 1999, Norman et al. 2000, Higgins et al. 2004). It is thus likely that by upregulating these profibrogenic factors, HIF-1 accelerates tissue fibrosis. In addition, HIF-1α is consistently and dramatically upregulated in a variety of fibrotic diseases, such as keloid (Zhang et al. 2003), renal fibrosis (Kimura et al. 2008), and oral submucous fibrosis (Tilakaratne et al. 2008).

Recently, HIF-1α was found to express in healthy and diseased periodontal tissues (Ng et al. 2011). However, little is known about the correlation between HIF-1α and CsA-induced gingival overgrowth. The present work was undertaken to identify the *in situ* localization of HIF-1α expression in normal gingival tissues and CsA-induced gingival overgrowth specimens. In addition, Western blot was used to determine the effects of CsA on the expression of HIF-1α in cultured human gingival fibroblasts (HGFs) in vitro. Previous findings have suggested that hypoxia, through HIF-1, could enhance fibrogenesis *via* factors involved in ECM modification, such as plasminogen activator inhibitor-1 (PAI-1) (Li et al. 2005). Recently, our study has shown that PAI-1 expression is significantly upregulated in CsA-induced gingival overgrowth specimens (Lin et al. 2007). To address the mechanisms underlying the hypoxic regulation of PAI-1 expression, the effects of

CsA on HGFs were performed in hypoxia chamber.

Materials and methods

Tissue Collection

Normal gingival tissue samples were obtained from five healthy individuals undergoing routine surgical crown lengthening, with little if any evidence of inflammation and no systemic medication. Fifteen redundant hyperplasic gingival biopsy materials were obtained from ten renal transplant patients receiving CsA therapy. These patients had been taken CsA for more than 1 year and the dose had been adjusted to maintain stable serum levels of about 200 ng/ml. No sign of graft rejection was detected in these renal transplant patients. The samples were obtained during surgical removal of diseased gingival as part of their routine clinical management, which also included intensive plaque control. Institutional Review Board permission at the Chung Shan Medical University Hospital was obtained for the use of discarded human tissue.

Immunohistochemistry

The surgically removed gingival tissues were fixed with 10 % buffered formalin overnight, the specimens were dehydrated in an ascending series of graded alcohols and embedded in paraffin. Five μm sections were stained with the monoclonal anti- HIF-1α (sc-10790) antibody (Santa Cruz Biotechnology, CA, USA) (1:100 dilution) using a standard avidin-biotin-peroxidase complex method (Tsai et al. 2009a, Lee et al. 2010). 3-amino-9-ethylcarbazole (AEC, DAKO, Carpinteria, CA, USA) was then used as the substrate for localizing the antibody binding. Negative controls included serial sections from which either the primary or secondary antibodies were excluded. The preparations were counterstained with hematoxylin, mounted with Permount (Merck, Darmstadt, Germany) and examined by light microscopy.

One section from each CsA-induced gingival overgrowth specimen was stained with hematoxylin and eosin to evaluate the magnitude of inflammation at the histological level. Most of the inflammatory cells present in the infiltrates represented in these specimens were lymphocytes. Each specimen was graded at 200x magnification as: grade low, inflammatory cells less than 50 % per field and grade high, inflammatory cells higher than 50 % per field. Grading of each specimen was based on the average inflammatory condition in three consecutive microscopic fields starting from the epithelial-connective tissue border and proceeding gradually deeper into lamina propria.

Processed immunohistochemically for HIF-1α expression, sections graded as "low" were represented by positive stained cells less than 50 %; sections graded "high" exhibited positive stained cells over 50 % on 3 sections/tissue at 400x magnification.

Cell culture

HGFs were cultured by using an explant technique. Three healthy individuals were selected from the crown lengthening procedure for this study. The normal gingival tissue samples were minced using sterile techniques and washed twice in phosphate buffer saline (PBS) supplemented with antibiotics (100 U/ml penicillin, 100 µg/ml streptomycin and 0.25 µg/ml of fungizone). Explants were placed into 60 mm Petri dishes and maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco Laboratories, Grand Island, NY, USA) supplemented with 10 % fetal calf serum (FCS) (Gibco Laboratories, Grand Island, NY, USA) and antibiotics as described above. Cell cultures between the third and eighth passages were used in this study.

Effect of CsA on HIF-1α expression in HGFs by Western blot

Cells arrested in G_0 by serum deprivation (0.5 % fetal calf serum; 48 h) were used in the experiments. Nearly confluent monolayers of HGFs were washed with serum-free Dulbecco's modified Eagle's medium and immediately thereafter exposed to various concentrations (0, 100, 200, and 500 ng/mL) of CsA (Sigma, St Louis, MO, USA) after 24 h incubation period. Cultures without FCS were used as negative controls. Cells were solubilized with sodium dodecyl sulfate-solubilization buffer (5 mM EDTA, 1 mM $MgCl_2$, 50 mM Tris–HCl, pH 7.5 and 0.5 % Trition X-100, 2 mM phenylmethylsulfonyl fluoride, and 1 mM *N*-ethylmaleimide) for 30 min on ice. Then, cell lysates were centrifuged at 12,000 *g* at 4 °C and the protein concentrations determined with Bradford reagent using bovine serum albumin as standards. Equivalent amounts of total protein per sample of cell extracts were run on a 10 % sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immediately transferred to nitrocellulose membranes. The membranes were blocked with phosphate-buffered saline containing 3 % bovine serum albumin for 2 h, rinsed, and then incubated with primary antibodies anti-HIF-1α (1:500) in phosphate-buffered saline containing 0.05 % Tween 20 for 2 h. After three washes with Tween 20 for 10 min, the membranes were incubated for 1 h with biotinylated secondary antibody diluted 1:1000 in the same buffer, washed again as described above and treated with 1:1000 streptavidin-peroxidase solution for 30 min. After a series of washing steps, protein

expression was detected by chemiluminescence using an ECL detection kit (Amersham Biosciences UK Limited, England), and relative photographic density was quantitated by scanning the photographic negatives on a gel documentation and analysis system (AlphaImager 2000, Alpha Innotech Corp., San Leandro, CA). Each densitometric value was expressed as the mean ± standard deviation (SD).

Establishment of hypoxic condition for PAI-1 expression

Cells growing to about 80 % confluence were transferred to a hypoxic chamber with auto purge airlock (NexBiOxy, Unimed Healthcare Inc., Taipei, Taiwan). Environmental hypoxic conditions (1 %) were achieved in an airtight humidified chamber and continuously flushed with a gas mixture containing 5 % CO_2 and 95 % N_2. Maintenance of the desired O_2 concentration was constantly monitored during incubation using a microprocessor-based oxygen controller. Normoxic conditions were defined as 20 % O_2, 5 % CO_2 at 37 °C. The culture period and Western blot by using anti-PAI-1 antibody (Santa Cruz Biotechnology, CA, USA) were described previously.

Statistical analysis

Three replicates of each experiment were performed for each test. All assays were repeated three times to ensure reproducibility. For testing of differences in the HIF-1α between normal healthy gingival tissues and CsA-induced gingival overgrowth specimens, Fisher's exact test was applied for the statistical analysis of the results. The significance of the results obtained from control and CsA-treated HGFs was statistically analyzed by Kruskal-Wallis test. Tests of differences of the treatments were analyzed by Duncan's test. A *p*-value of < 0.05 was considered to be statistically significant.

Results

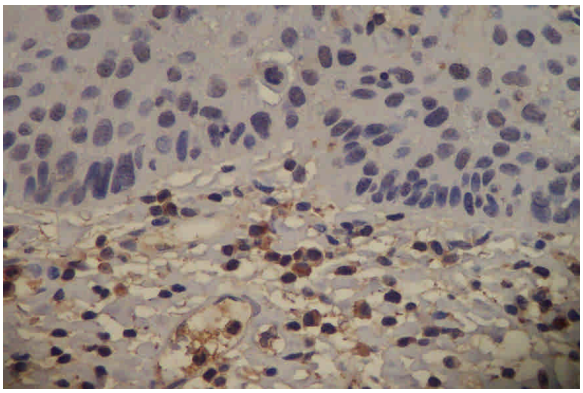

Fig. 1 Very faint immunoreactivity of HIF-1α was observed in normal human gingival tissues (400x).

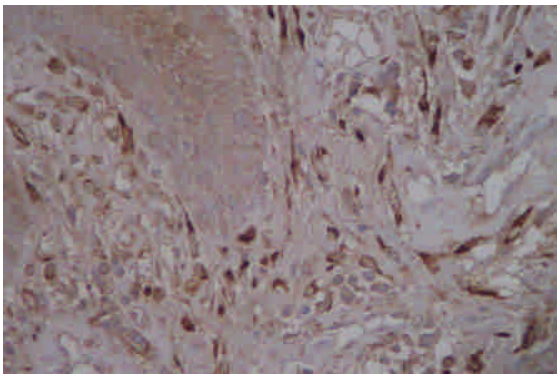

Fig. 2 Strong immunostaining for HIF-1α was noted in the CsA-induced gingival overgrowth specimens. HIF-1α was evident as intensive redbrown color in the cytoplasm of fibroblasts, epithelial cells and inflammatory cells. (400x)

Table The results of HIF-1α expression and the grade of inflammation in CsA-induced gingival overgrowth tissues

	Inflammation high	Inflammation low
HIF-1α high	7	1
HIF-1α low	2	5

A significantly greater HIF-1α expression was noted in CsA-induced gingival overgrowth tissues with high levels of inflammation as compared to tissues with low levels of inflammatory cell infiltrates by Fisher's exact test (p=0.041)

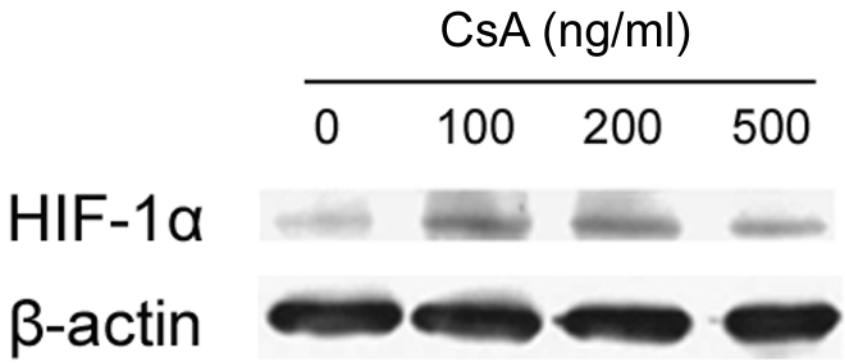

Fig. 3 Expression of HIF-1α protein by HGFs in the presence of 0, 100, 200 and 500 ng/ml CsA. Cells were exposed to CsA for a 24 h incubation period. β-actin was performed in order to monitor equal protein loading.

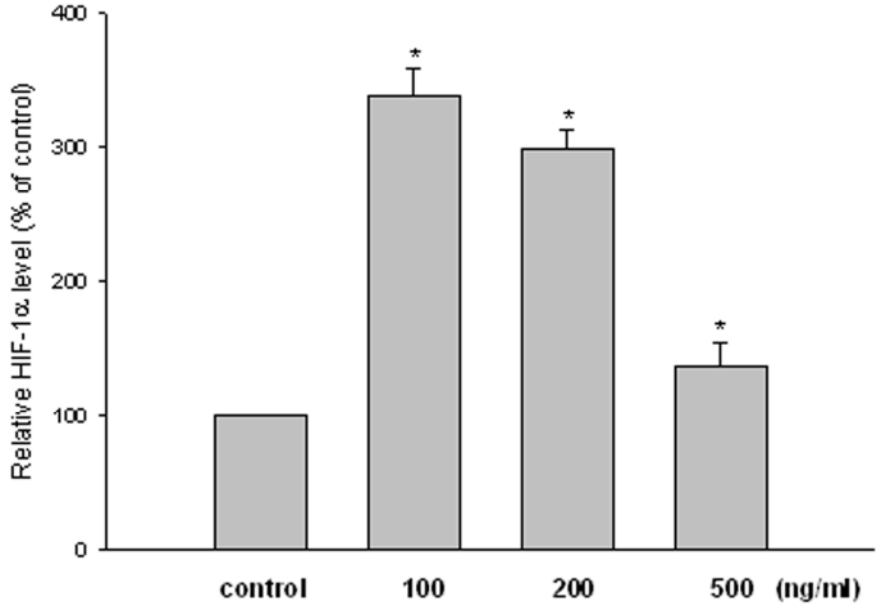

Fig. 4 Levels of HIF-1α protein treated with CsA were measured by AlphaImager 2000. The relative level of HIF-1α protein expression for each sample was normalized against β-actin signal and the control was set as 1.0. Optical density values represent the means of three different HGF strains ± standard deviations. Triplicate experiments were performed. * represents significant difference from control values with $p<0.05$.

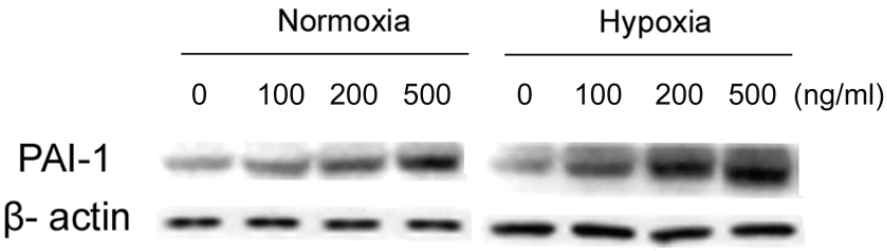

Fig.5 Effects of CsA on PAI-1 protein expression in HGFs under normoxic and hypoxia conditions.

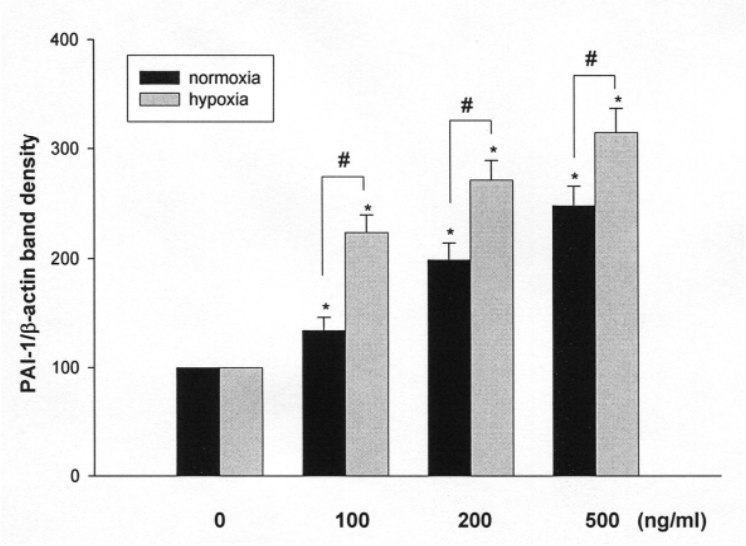

Fig.6 The relative level of PAI-1 protein expression for each sample was normalized against β-actin signal and the control was set as 1.0. Optical density values represent the means of three different HGF strains ± standard deviations. Triplicate experiments were performed. * represents significant difference from control values with $p<0.05$. # represents statistically significant between normoxic and hypoxia conditions; $p < 0.05$.

Conclusions

As far as we known, this is the first systematic attempt to evaluate the role of HIF-1α expression in CsA-induced gingival overgrowth in human at both in vivo and in vitro. We have demonstrated that HIF-1α is elevated in CsA-induced gingival overgrowth than normal gingival tissues. Data from our in vitro experiments showed that CsA was capable of stimulating HIF-1α expression in HGFs. Hypoxia through HIF-1α may promote fibrogenesis *via* stimulation of PAI-1 that promotes ECM accumulation in gingival connective tissues (Fig. 7).

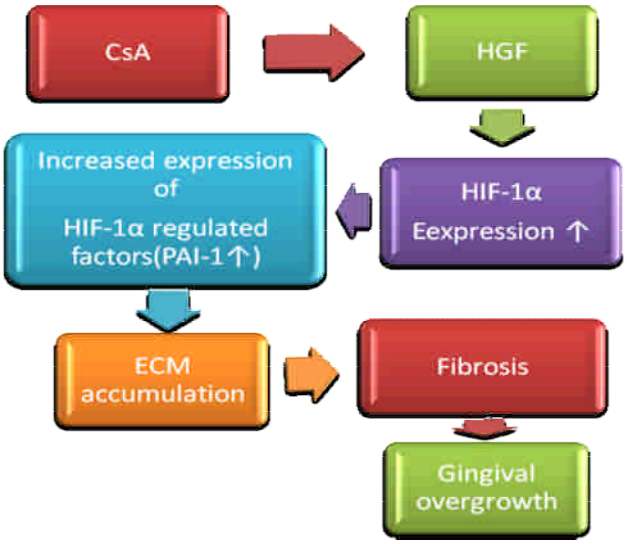

Fig. 7 Model proposing a role for HIF-1α/PAI-1 in the progression of CsA-induced gingival overgrowth. Gingival tissue inflammation could generate hypoxic stress and CsA increase HIF-1α expression. As a consequence of hypoxia in HGFs HIF-1α is stabilized, resulting in increased expression of PAI-1, thus promoting the accumulation of ECM.

References

Chang, T. Y., Tsai, C. H. & Chang, Y. C. (2010) The upregulation of heat shock protein 47 in human gingival fibroblasts stimulated with cyclosporin A. *Journal of Periodontal Research* 45, 317-322.

Faulds, D., Goa, K. L & Benfield, P. (1993) Cyclosporin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. *Drugs* 45, 953-1040.

Fine, L. G., Bandyopadhay, D. & Norman, J. T. (2000) Is there a common mechanism for the progression of different types of renal diseases other than proteinuria? Towards the unifying theme of chronic hypoxia. *Kidney International* 75, S22-S26.

Hassell, T. & Hefti, A. F. (1991) Drug-induced gingival overgrowth: Old problem, new problem. *Critical Review of Oral Biology & Medicine* 2, 103-137.

Higgins, D. F., Biju, M. P., Akai, Y., Wutz, A., Johnson, R. S. & Haase, V. H. (2004) Hypoxic induction of Ctgf is directly mediated by Hif-1. *American Journal of Physiolology Renal Physiology* 287, F1223-1232.

Ho, Y. C., Lin, H. J., Tsai, C. H. & Chang, Y. C. (2010) Regulation of type I plasminogen activator inhibitor in human gingival fibroblasts with cyclosporine A. *Oral Diseases* 16, 396-401.

Kietzmann, T., Roth, U. & Jungermann, K. (1999) Induction of the plasminogen activator inhibitor-1 gene expression by mild hypoxia *via* a hypoxia response element binding the hypoxia-inducible factor-1 in rat hepatocytes. *Blood* 94, 4177-4185.

Kimura, K., Iwano, M., Higgins, D. F., Yamaguchi, Y., Nakatani, K., Harada, K., Kubo, A., Akai, Y., Rankin, E. B., Neilson, E. G., Haase, V. H. & Saito, Y. (2008) Stable expression of HIF-1α in tubular epithelial cells promotes interstitial fibrosis. *American Journal of Physiolology Renal Physiology* 295, F1023-F1029.

Lee, S. S., Tsai, C. H., Yang, S. F., Ho, Y. C. & Chang, Y. C. (2010) Hypoxia inducible facto-1α expression in areca quid chewing-associated oral squamous cell carcinomas. *Oral Diseases* 16, 696-701.

Lewis, J. S., Lee, J. A., Underwood, J. C., Harris, A. L. & Lewis, C. E. (1999) Macrophage responses to hypoxia: relevance to disease mechanisms. *Journal of Leukocyte Biology* 66, 889-900.

Li, X., Kimura, H., Hirota, K., Kasuno, K., Torii, K., Okada, T., Kurooka, H., Yokota, Y. & Yoshida, H. (2005) Synergistic effect of hypoxia and TNF-α on production of PAI-1in human proximal renal tubular cells. *Kidney International* 68, 569-583.

Lin, H. J., Tsai, C. H., Huang, F. M. & Chang, Y. C. (2007) The upregulation of type I plasminogen activator inhibitor in human gingival fibroblasts stimulated with cyclosporin A. *Journal Periodontal Research* 42, 39-44.

Ng, K. T., Li, J. P., Ng, K. M., Tipoe, G. L., Leung, W. K. & Fung, M. L. (2011) Expression of hypoxia-inducible factor-1α in human periodontal tissue. *Journal of Periodontology* 82, 136-141.

Norman, J. T., Clark, I. M. & Garcia, P. L. (2000) Hypoxia promotes fibrogenesis in human renal fibroblasts. *Kidney International* 58, 2351-2366.

Schofield, C. J. & Ratcliffe, P. J. (2004) Oxygen sensing by HIF hydroxylases. *Nature Reviews Molecular Cell Biology* 5, 343-354.

Tilakaratne, W. M., Iqbal, Z., Teh, M. T., Ariyawardana, A., Pitiyage, G., Cruchley, A., Stewart, J. E., Hagi-Pavli, E., Lalli, A., Waseem, A., Parkinso, E. K. & Fortune, F. (2008) Upregulation of HIF-1α in malignant transformation of oral submucous fibrosis. *Journal of Oral Pathology & Medicine* 37, 372-377.

Tsai, C. H., Chen, Y. J., Huang, F. M., Su, Y. F., Chang, Y. C. (2005) The upregulation of matrix metalloproteinase-9 in inflamed human dental pulps. *Journal of Endodontics* 31, 860-862.

Tsai, C. H., Chang, T. Y. & Chang, Y. C. (2009a) Upregulation of lysyl oxidase expression in cyclosporin A-induced gingival overgrowth. *Journal of Dental Sciences* 4, 13-17.

Tsai, C. H., Yang, S. F., Huang, F. M. & Chang, Y. C. (2009b) The upregulation of cystatin C in human gingival fibroblasts stimulated with cyclosporin A. *Journal of Periodontal Research* 44, 459-464.

Zhang, Q. H., Wu, Y. D., Ann, D. K., Messadi, D. V., Tuan, T. L., Kelly, A. P., Bertolami, C. N. & Le, A. D. (2003) Mechanisms of hypoxic regulation of plasminogen activator inhibitor-1 gene expression in keloid fibroblasts. *Journal of Investigative Dermatolology* 121, 1005-1012.

國科會補助專題研究計畫項下出席國際學術會議心得報告

日期:100 年 7 月 20 日

計畫編號	NSC 97－2314－B－040－020－MY3		
計畫名稱	低氧誘導因子-1α 與環孢靈誘發牙齦增生關係之探討		
出國人員姓名	張育超	服務機構及職稱	中山醫學大學牙醫學系教授
會議時間	100 年 3 月 16 日 至 100 年 3 月 19 日	會議地點	美國加州聖地牙哥 Hall C (San Diego Convention Center)
會議名稱	(中文)第 89 屆國際牙醫研究學會年會 (英文) 89th General Session & Exhibition of the International Association for Dental Research		
發表論文題目	(中文)低氧誘導因子-1α 在環孢靈誘發牙齦增生之表達會增加 (英文) Increased hypoxia-inducible factor-1α expression in cyclosporine A-induced gingival overgrowth		

一、參加會議經過

今年的國際牙醫研究學會年會於美國加州聖地牙哥舉行，本屆年會盛況空前，其論文發表發表形式分為 oral presentation、poster presentation、poster discussion 三種。筆者今年報告的論文題目為" Increased hypoxia-inducible factor-1α expression in cyclosporine A-induced gingival overgrowth."屬於牙周病學組。

國際牙醫研究學會年會是當今牙醫界最大且地位最高的學術會議，目前共分為 Behavioral Sciences & Health Services Research、Cariology Research、Craniofacial Biology、Dental Materials、 Diagnostic Systems、Dental Anesthesiology Research、Education Research、Geriatric Oral Research、Implantology Research、Microbiology/Immunology、Mineralized Tissue、Neuroscience、Nutrition Research、Oral Health Research、Oral & Maxillofacial Surgery、Oral Medicine & Pathology、Periodontal Research、

Pharmacology/Therapeutics/Toxicology、Prosthodontics Research、Pulp Biology、Salivary Research 等 21 個組別。其官方出版的期刊 Journal of Dental Research 是牙科 5 year impact factor 最高之期刊。

二、與會心得

本次盛會收穫良多，吸取了許多寶貴的經驗及目前研究的新方向，對於往後的研究裨益良多，再此亦非常感激國科會予以經費補助參與此次國際牙醫研究學會年會。國際牙醫研究學會已受到政治的藉入，臺灣無法自己成立單獨的 division，目前歸在 South-East Asian Division，而中共加入即自成 China Division，政府應正視此一現象。

三、考察參觀活動(無是項活動者略)

四、建議

應盡量寬列出席國際之經費，鼓勵牙醫學相關領域之研究生參予此一盛會，與國際交流，擴大視野。

五、攜回資料名稱及內容

六、其他

國科會補助計畫衍生研發成果推廣資料表

日期:2011/10/20

國科會補助計畫	計畫名稱: 低氧誘導因子-1α與環孢靈誘發牙齦增生關係之探討
	計畫主持人: 張育超
	計畫編號: 97-2314-B-040-020-MY3　　學門領域: 牙醫學

無研發成果推廣資料

97 年度專題研究計畫研究成果彙整表

計畫主持人：張育超	計畫編號：97-2314-B-040-020-MY3
計畫名稱：低氧誘導因子-1α與環孢靈誘發牙齦增生關係之探討	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	1	1	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	1	1	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	無

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 ■未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

實驗結果顯示: HIF-1α在環孢靈誘發牙齦增生的組織中，有明顯的表達。激發 HIF-1α的表達可促進纖維化的產生，並藉由 PAI-1 來增加細胞外間質在牙齦組織的沉積。初步研究成果已於 100 年 3 月 16 至 19 日美國加州聖地牙哥第 89 屆國際牙醫研究學會年會中以貼式報告之方法呈現，題目為 Increased hypoxia-inducible factor-1α expression in cyclosporine A-induced gingival overgrowth。目前所有資料以整理好，撰寫初步文稿，目前投稿 SCI 期刊中。