行政院國家科學委員會補助專題研究計畫成果報告

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※ApM1/AdipoQ Gene 在X症候群及粥狀動脈硬化之角※
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計畫類別：■個別型計畫 □整合型計畫

計畫編號：NSC89－2314－B－002－449－

執行期間：89年8月1日至90年7月31日

計畫主持人：楊偉勛

共同主持人：

本成果報告包括以下應繳交之附件：

□赴國外出差或研習心得報告一份

□赴大陸地區出差或研習心得報告一份

□出席國際學術會議心得報告及發表之論文各一份

□國際合作研究計畫國外研究報告書一份

執行單位：臺大醫學院臨床醫學研究所

中 華 民 國90年10月20日

一、計畫中文摘要：請於五百字內就本計畫要點作一概述，並依本計畫性質自訂關鍵詞。

關鍵詞：AdipoQ, ApM1, adiponectin, 肥胖， 冠心病，X 症候群

肥胖長久以來已然被認定為冠狀動脈心臟病之重要危險因子。然而肥胖對粥狀動脈硬化的效應之生物機制至今仍然未明。近年來對脂肪細胞之生物學研究顯示脂肪組織不僅是能量儲存之油脂庫而且是一藉由荷爾蒙與細胞素與身體其他組織積極交互作用之"內分泌"器官。其分泌之物質中最佳的幾個例子是瘦素，纖維蛋白溶解酵素原活化物之抑制物-1 及甲型瘤壞死素，三者均具有極明顯之全身作用。

AdipoQ/apM1 蛋白大小約 28-30 Kd，在體內僅由脂肪組織所表達並分泌於血液中。其蛋白一次結構與膠原蛋白質,補體及哺乳類冬眠相關血漿蛋白質及其他蛋白質等有頗大之相似。此基因之生物功能大多仍然未明。然而有研究顯示其基因表現在 ob/ob 肥胖鼠中較低。在人類中，肥胖病人血漿 apM1 之濃度亦較正常控制組受試為低。近來亦有研究發現在細胞培養之系統中它可減低甲型瘤壞死素引起之單核球細胞附著於血管內皮細胞上並降低血管內皮細胞中某些黏著分子之基因表現。此外，在冠狀動脈心臟病之病人中，血漿 apM1 之濃度也較正常控制組受試為低。總結這些研究顯示 AdipoQ/ApM1 也許在肥胖及與其相關之病症，如 X 症候群及粥狀動脈硬化之病理生理中扮演一些角色。

過去一年中，吾等在人類研究中發現，血漿中之 apM1 (adiponectin) 濃度與 X 症候群之表現有密切相關，並與冠心病有關，同時也是肥胖與冠心病之遺傳因子，除此之外，吾等並發減重及以新型之糖尿病治療藥物有助提高血漿中之 apM1 (adiponectin) 濃度。是否有益病人之 X 症候群及粥狀動脈硬化之改善，則有待進一步之研究。同時吾等並發現其在培養細胞中與胰島素刺激血糖吸收有關。此一豐碩之成果並未獲心肺學門委員之青睞，至為惋惜。

二、計畫英文摘要：請於五百字內就本計畫要點作一概述，並依本計畫性質自訂關鍵詞。

Keywords：AdipoQ, ApM1, adiponectin, obesity, coronary heart disease, X syndrome

Obesity has long been well accepted as a major risk factor for coronary artery disease. However, the biological mechanisms mediating the effects of obesity on atherosclerosis remain obscure. Recent studies of the biology of adipocytes have shown that adipose tissue, rather than just a fat depot for energy storage, is an extremely active tissue constantly interacting with the other tissues by hormones and cytokines. The well-known examples of secreted products of adipose tissue are leptin, PAI-1 and TNFα, all of which have profound systemic effects.

Similar to leptin, AdipoQ/ApM1 protein (28-30 Kd) is exclusively expressed in and secreted by adipose tissue into blood circulation. Analysis of its primary peptide sequence revealed striking homology to those of collagens, complement and mammalian hibernation-associated plasma protein and others. The biological function of its product is mostly unclear. It was demonstrated that the expression of AdipoQ is down regulated in ob/ob mice. In human, the plasma level of apM1 in obese subjects was significantly lower than that in normal controls. Recently, it was shown to reduced TNFα-induced monocyte adhesion to endothelial cells and gene expression of certain adhesion molecules in endothelial cells *in vitro*. In addition, the plasma level of apM1 in patients with coronary artery disease was significantly lower than that in the normal controls. Taken together, these studies suggest that AdipoQ/apM1 may play a role in the pathophysiology of obesity and obesity-related disease processes, such as syndrome X and atherosclerosis.

In the last one year, we found in human study that the plasma levels of apM1 (adiponectin) intimately correlated with variables of X syndrome and coronary artery disease. It is also a genetic contributor to obesity and coronary artery disease. In addition, we demonstrated that weight reduction and treatment with a new anti-diabetic drugs raised plasma apM1 levels. Whether these may benefit patients with X syndrome and coronary artery disease awaits further studies. In cultured cells, we also found that apM1 may improve insulin-stimulated glucose uptake. However, these fruitful results did not impress the division of cardiovascular and pulmonary medicine of NSC. It is a regret the project was not further granted after one year.

三、結果：

We found that in humans that the plasma apM1 levels were significantly lower in subjects with obesity, diabetes mellitus, dyslipidemia and hyperuricemia, but not in hypertension and hypercholesterolemia (table 1). The manuscript of these data is nuder final preparation.

Table 1. Mean plasma apM1 levels in subjects with or without selected characteristics

	mean+S.D. of apM1 (g/mL)		p=
phenotypes	**no (N)**	**yes (N)**	
obesity	6.24±2.40 (89)	4.94±1.81 (116)	0.0001
hypertension	5.52±2.26 (163)	5.44±1.85 (42)	0.85
diabetes mellitus	5.70±2.29 (144)	5.02±1.85 (61)	0.043
dyslipidemia	5.89±2.33 (146)	4.45±1.37 (59)	0.0001
hypercholesterolemia	5.46±2.15 (180)	5.84±2.46 (25)	0.41
hyperuricemia	5.96±2.16 (84)	5.18±2.15 (121)	0.012

Genotyping an SNP in exon 2 of apM1, we found that it is a genetic contributor to obesity and coronary heart disease in a genetic association study (tables 2 and 3). The manuscript is ready for submission.

Table 2. Adiponectin allele frequencies according to body mass index divided by the mean of the total among and odds ratio (OR) of having a "higher BMI" with adiponectin alleles.

BMI	**≥26.9**	**<26.9**	
	N (%)	**N (%)**	**OR (95% CI)**
Alleles			
G	48 (9.8%)	130 (26.5%)	0.65 (0.42-0.99
T	112 (22.9%)	200 (40.8%)	

Table 3. Adiponectin allele frequencies among CHD patients and controls; and odds ratio (OR) of having CHD with adiponectin alleles

	CHD	**controls**	
	N (%)	**N (%)**	**OR (95% CI)**
Alleles			
G	66 (25.8%)	178 (36.3%)	0.61 (0.43 - 0.86)
T	190 (74.2%)	312 (63.7%)	

We also found that weight reduction increased plasma adiponectin levels in patients receiving gastric partition surgery. This finding was published in reference 1. We also found the treatment with rosiglitazone in diabetic patients increased plasma adiponectin levels by two folds (table 4). This manuscript is in its final stage of review by journalists.

Table 4 Changes of selected characteristic from baseline to 6 months after treatment either ith rosiglitazone in 30 subjects or with placebo in 34 subjects.

	Rosiglitazone(N=30). (6-0) mons (mean+S.D)	**Placebo(N=34) (6-0) mons (mean+S.D)**	**p <**
variables			
apM1 (μg/mL)	7.45±6.38	0.33±1.37	0.0005

We also have data in human tissue and cell lines, which will not be detailed here.

References:

1 Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab. 2001 Aug;86(8):3815-9.