行政院國家科學委員會專題研究計畫 期末報告

第二型轉麩胺醯和自體免疫疾病之研究(第 3 年)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 99-2314-B-040-006-MY3
執 行 期 間 ：101 年 08 月 01 日至 102 年 09 月 04 日
執 行 單 位 ：中山醫學大學微生物免疫研究所

計 畫 主 持 人：蔡嘉哲
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公 開 資 訊 ：本計畫可公開查詢

中 華 民 國 102 年 12 月 26 日

中 文 摘 要 ： 近年來研究第二型轉麩胺酶(Transglutaminase 2)與疾病的關係越來越密切，
包括，在自體免疫疾病之角色，例如紅斑性狼瘡(SLE)和麩質過敏症(celiac
disease)，癌症，如乳癌(Breast cancer)和前列腺癌(Prostate cancer)，血液凝聚 Factor
XIII 疾病有關，神經性疾病，如 Huntington’s disease 和慢性腎炎。TG2 具有轉
麩胺酶活性能聚合(cross-linking)蛋白質受質的穀胺醯胺(glytamine)和離胺酸
(lysine)殘基，具有 G 蛋白的功能，也可與細胞外基質的 integrin 和 fibronection
作用。過去我們研究結果顯示，TG2 會促進細胞凋亡，此機轉是透過一種 guanidine
nucleotide exchange factor (RAP1GDS1 或 GDS1)之聚合而調節內質網和粒線體的
鈣離子變化產生，而吞噬凋亡細胞產生之 Retinoid acid，會促使凋亡的胸腺細胞
有 TG2 之表現。這些結果顯示 TG2 透過 GDS1，而使內質網鈣離子進入粒線體
而產生凋亡，而 retinoid acid 也幫助吞噬凋亡細胞之功能，這些研究更讓我們了
解 TG2 在自體免疫疾病致病機轉之角色，我們將再進一步研究 GDS1 蛋白在發
炎之角色，並研究 TG2、GDS1 和細胞激素(cytokines)產生的關係。另外，多環
芳香烴受器(Aryl Hydrocarbon Receptor, Ahr)已知與抽菸、類風濕性關節炎
(Rheumatoid arthritis, RA)與肺癌之產生有關係，1. 2013 Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin S&aacute；ndor, Angela Bononi, Paolo Pinton, L&aacute；szl&oacute； Tretter, Zsuzsa Szondy and Gregory J. Tsay*. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca2+ homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).

中文關鍵詞： 關鍵詞 第二型轉麩胺酶、自體免疫疾病、細胞凋亡、鈣離子平衡

英 文 摘 要 ： Tissue or type 2 transglutaminase (TG2, EC 2.3.2.13) has been implicated in

multiple disease states, including autoimmune disease (SLE, celiac disease)；Cancers (Breast cancer and prostate cancer)，neurodegenerated disease (Alzheimer’s disease, Huntingtion’s disease) and Renal disease. It is a multifunctional enzyme belonging to the transglutaminase family. It catalyses Ca2+ dependent reaction and results in the post-translational modification of proteins at the level of glutamine and lysine residues. It acts as a GTP-binding protein (G脉h) in transmembrane signaling and a cell surface adhesion mediator as well. Recently, we found TG2 might contribute to apoptosis by acting as a Ca2+ sensor in the mitochondria to amplify ER-Derived Ca2+ signal via cross-linking RAP1GDS1. We also found that Retinoids produced by macrophages engulfing apoptotic cells contribute to the appearance of TG2 in apoptotic thymocytes. These results indicated a more general role of TG2 in the regulation of Calcium homeostasis, efferocytosis and the pathogenesis in autoimmune diseases. We will further to study the role of TG2 and RAP1GDS1 in inflammation process and cytokine production. Since it has been reported that the association of Aryl hydrocarbon receptor (Ahr) and pathogenesis of diseases, including Rheumatoid arthritis (RA) and lung cancer, We also published the paper:2013 Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin S&aacute；ndor, Angela Bononi, Paolo Pinton, L&aacute；szl&oacute； Tretter, Zsuzsa Szondy and Gregory J. Tsay*. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca2+ homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).

英文關鍵詞： Type II transglutaminase, autoimmune disease, apoptosis and calcium homeostasis

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/■期末報告）

第二型轉麩胺酶和自體免疫疾病之研究

計畫類別：■個別型計畫　□整合型計畫

計畫編號：NSC　99－2314－B－040－006－MY3

執行期間：　2010 年 8 月　1 日至 2013　年 12 月 4　日

執行機構及系所：中山醫學大學微生物免疫學研究所

計畫主持人：蔡嘉哲

共同主持人：劉光耀

計畫參與人員：謝雨帆

本計畫除繳交成果報告外，另含下列出國報告，共 ___ 份：

□執行國際合作與移地研究心得報告

□出席國際學術會議心得報告

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中　華　民　國 102　年 12　月　26　日

（一） 計畫中文摘要。（五百字以內）

近年來研究第二型轉麩胺酶(Transglutaminase 2)與疾病的關係越來越密切，包括，在自體免疫疾病之角色，例如紅斑性狼瘡(SLE)和麩質過敏症(celiac disease)，癌症，如乳癌(Breast cancer)和前列腺癌(Prostate cancer)，血液凝聚Factor XIII 疾病有關，神經性疾病，如Huntington’s disease 和慢性腎炎。TG2 具有轉麩胺酶活性能聚合(cross-linking)蛋白質受質的穀胺醯胺(glytamine)和離胺酸(lysine)殘基，具有G 蛋白的功能，也可與細胞外基質的integrin 和fibronection 作用。過去我們研究結果顯示，TG2 會促進細胞凋亡，此機轉是透過一種guanidine nucleotide exchange factor (RAP1GDS1 或GDS1)之聚合而調節內質網和粒線體的鈣離子變化產生，而吞噬凋亡細胞產生之Retinoid acid，會促使凋亡的胸腺細胞有TG2 之表現。這些結果顯示TG2 透過GDS1，而使內質網鈣離子進入粒線體而產生凋亡，而retinoid acid 也幫助吞噬凋亡細胞之功能，這些研究更讓我們了解TG2 在自體免疫疾病致病機轉之角色，我們將再進一步研究GDS1 蛋白在發炎之角色，並研究TG2、GDS1 和細胞激素(cytokines)產生的關係。另外，多環芳香烴受器(Aryl Hydrocarbon Receptor, Ahr)已知與抽菸、類風濕性關節炎(Rheumatoid arthritis, RA)與肺癌之產生有關係，我們將進一步研究Ahr 與TG2 及GDS1 在自體免疫疾病及特定關節炎如痛風或退化性關節炎等之關係。

三年計劃如下:第一年: 研究TG2 在退化性關節炎、類風濕性關節炎與痛風之角色。第二年: 研究TG2 和GDS1 與細胞激素分泌及吞噬作用之角色。

第三年: 研究TG2 及Ahr 在疾病，如類風溼性關節炎或慢性腸發炎疾病(Inflammatory bowel disease, IBD)，之關係。關鍵詞 第二型轉麩胺酶、自體免疫疾病、細胞凋亡、鈣離子平衡

（一） 計畫英文摘要。（五百字以內）

Tissue or type 2 transglutaminase (TG2, EC 2.3.2.13) has been implicated in multiple disease states, including autoimmune disease (SLE, celiac disease)；Cancers (Breast cancer and prostate cancer)，neurodegenerated disease (Alzheimer’ s disease, Huntingtion’ s disease) and Renal disease. It is a multifunctional enzyme belonging to the transglutaminase family. It catalyses Ca^{2+} dependent reaction and results in the post-translational modification of proteins at the level of glutamine and lysine residues. It acts as a GTP-binding protein (Gαh) in transmembrane signaling and a cell surface adhesion mediator as well. Recently, we found TG2 might contribute to apoptosis by acting as a Ca2+ sensor in the mitochondria to amplify ER-Derived Ca2+ signal via cross-linking RAP1GDS1. We also found that Retinoids produced by macrophages engulfing apoptotic cells contribute to the appearance of TG2 in apoptotic thymocytes. These results indicated a more general role of TG2 in the regulation of Calcium homeostasis, efferocytosis and the pathogenesis in autoimmune diseases. We will further to study the role of TG2 and RAP1GDS1 in inflammation process and cytokine production. Since it has been reported that the association of Aryl hydrocarbon receptor (Ahr) and pathogenesis of diseases, including Rheumatoid arthritis (RA) and lung cancer, we will investigate the relationship between Ahr, TG2 and RAP1GDS1 in autoimmune disease and other arthritis such as gout and osteoarthritis (OA).

The first year: To study the role of TG2 in inflammatory disease, including osteoarthritis, rheumatoid arthritis and gout arthritis

The second year: To investigate the role of TG2 and RAP1GDS1 in cytokines production during inflammation and efferocytosis

The third year: To evaluate the correlation of Ahr, TG2 and RAP1GDS1 in diseases, such as rheumatoid arthritis and inflammatory bowel disease (IBD)

Key word: Type II transglutaminase, autoimmune disease, apoptosis and calcium homeostasis

報告內容:

（一）前言

細胞凋亡是一種細胞內驅動自殺的方式,是一種生命的基本現象(1),在發育過程中調控生物體器官形成過程，能維持免疫的耐受性，當細胞受到感染、DNA發生突變或損傷時,細胞凋亡能調控組織更新、清除無用、衰老或病變的細胞,能維持生物體內細胞數目的恆定,控制細胞生長與死亡之間的平衡,因此是一個非常重要的生理現象(2)。倘若此機制出現問題時,會造成疾病的發生。受損的細胞無法進行凋亡，產生不正常的修復或突變，會導致細胞癌化形成腫瘤;當人類免疫系統發生教育錯誤，無法辨識自我或非自我的細胞存活，或者死亡的細胞未能及時被清除，將會導致自體免疫疾病(3)。

（二）研究目的

本研究目的主要在說明TG2在細胞凋亡與疾病致病機轉的相關性和重要性， TG2的功能是如何參與T細胞的凋亡及細胞內鈣離子調控。

（三）文獻探討

第二型轉麩胺酶

文獻報導指出，第二型轉麩胺酶為轉麩胺酶家族中的一員，分子量約為80 kDa左右，廣泛地分布於生物體內的各個組織(4)。TG2主要分布於細胞質中，部分TG2分布於細胞核或細胞膜上，或是透過尚未清楚的機制分泌到細胞外。TG2是一個具多重功能的酵素(5)，參與多項細胞的重要功能，如細胞分化、細胞凋亡(6)、細胞移動、發炎反應、傷口癒合及吞噬能力等等(7)。

第二型轉麩胺酶與細胞凋亡

TG2被認為是參與細胞凋亡過程和凋亡小體形成的潛在因子(8)，在細胞凋亡的過程中會大量誘導TG2蛋白質和酵素活性的表現(5, 9)。在誘導肝臟(liver)或是胸腺(thymus)產生細胞凋亡的過程中被發現會大量誘導活化TG2蛋白質和酵素活性產生，進而形成高度聚合的蛋白質聚合體(cross-linked protein polymers)(10, 11)。在MRL*lpr/lpr*老鼠(一種紅斑性狼瘡的動物模式)的淋巴組織堆積了大量不具有酵素活性的TG2蛋白質，可能與調控凋亡機制失常而導致自體免疫疾病產生有關(12-14)。在TG2-/-基因剔除(knock out)老鼠的研究中，誘導TG2-/-老鼠的胸線或肝臟產生細胞凋亡後，這些凋亡細胞被清除的速度有減緩的情形，同時伴隨著肝臟產生嚴重的發炎反應;而以正常巨噬細胞吞噬凋亡TG2-/-紅血球的速度也比清除正常凋亡紅血球來的緩慢(15)。這些結果皆說明TG2在細胞凋亡與疾病致病機轉的相關性和重要性。

細胞內之鈣離子調控與細胞凋亡

鈣離子在生物體內是很重要的訊息傳遞因子，其濃度的衡定與細胞週期、細胞增生及細胞凋亡有5

關(16)。正常的生理情況下，鈣離子參與多種功能，包括，肌肉收縮、神經物質的分泌、神經的傳導及參與體內酵素的活化等等(16-18)。鈣離子與細胞凋亡的關系首先是由Fleckenstein研究團隊所提出，說明過量的鈣離子進入心肌細胞(myocytes)會造成死亡，可能和缺血性心臟病有關，之後的研究也說明鈣離子在細胞凋亡扮演的重要角色(19-20)，當細胞受到生長激素減少或是投與藥物等不正常的刺激會引起細胞內鈣離子衡定失調，大量的鈣離子堆積在粒線體並且伴隨細胞凋亡的發生(21)。鈣離子可透過多種方式參與調節細胞凋亡的過程，鈣離子能透過活化calcineurin和NF-AT進而誘導與細胞凋亡相關基因的表現，如calpain；它能活化相關的蛋白酶(protease)或內切酶(endonuclease)，主要的內切酶如DNase I能切割DNA產生DNA片斷化的現象，其他的的蛋白酶則能降解lamins使之產生細胞凋亡的特徵；phosphatidylserine (PS)能外翻至凋亡小體的細胞膜與鈣離子調控PS-translocase有關；而鈣離子也參與粒線體凋亡路徑活化(16-21)。因此，調節鈣離子的驅動、平衡以及在細胞內的分佈對調控細胞凋亡是相當重要的。

（四）研究方法

藉由基因重組技術，構築全長cDNA之wtTG2和TG2C277S質體分別於Tetracyclin inducible gene expression system (簡稱Tet system)的表達系統，於T細胞中大量表達TG2蛋白質。利用各種細胞胞器螢光染劑分別檢測細胞內細胞質、粒線體和內質網內鈣離子的變化。使用蛋白質體學鑑定大量表現TG2細胞株蛋白質的變化，找出可能參與細胞內鈣離子調控之分子。

（五）結果與討論

圖一是經由Doxycycline (50μM)處理60小時後，我們收集細胞經由酒精固定後以PI染劑染核酸，使用流式細胞儀分析sub-G1 phase的比例，結果發現，大量誘導TG2蛋白質表現會促使Tet-On wtTG2和Tet-On TG2C277S細胞株之sub-G1 phase比例增加，表示細胞凋亡的比例增加，經由統計結果顯示，其中Tet-On wtTG2 sub-G1和Tet-On TG2C277S sub-G1 phase比率分別為48%和32%，由此結果我們可以發現，大量誘導表現野生型TG2細胞株(Tet-On wtTG2)和突變型TG2(Tet-On TG2C277S)會加細胞凋亡的比率，其中，野生型TG2細胞株(Tet-On wtTG2)會增加sub-G1 phase的比例高於突變型的TG2細胞株(Tet-On TG2C277S)，表示表現野生型的TG2細胞株(Tet-On wtTG2)引起細胞凋亡能力較高，由於轉麩胺酶活性的存在與否是兩組細胞株的差別，因此，我們推測轉麩胺酶活性是影響細胞凋亡結果有所差異的可能原因。

圖二實驗分析大量誘導TG2蛋白表現是否對細胞內鈣離子的平衡，我們以Doxycycline (50μM)處理各細胞株表現大量TG2蛋白質18小時後，加入了抑制內質網鈣離子回收之通道SERCA pump抑制劑tapsigargin (tg)，tg是一個不可逆的抑制劑能排空內質網內的鈣離子，藉此檢測確認細胞內鈣離子是否受到大量TG2蛋白質影響堆積於粒線體。結果發現，加入tg後短時間即可偵測粒線體鈣離子螢光強度增加，特別是Tet-On wtTG2細胞株的粒線體鈣離子強度增加幅度大於Tet-On TG2C277S，統計分析後發現，特別是Tet-On wtTG2細胞株的粒線體鈣離子受tg誘發後，其粒線體鈣離子在偵測時間內累積的總合 (AUC)比其他細胞株高，說明了大量表現野生型TG2蛋白質的情況下，所排空的內質網的鈣離子會流向粒線體。而當加入tg後，大量表現wtTG2蛋白質能增加tg誘導內質網鈣離子釋放的程度，6

而所釋放的內質網鈣離子比例比Tet-On vector和Tet-On TG2C277S高。在大量表現野生型TG2蛋白質的情況下，會增加粒線體鈣離子的堆積和內質網鈣離子釋放的程度，而細胞質的鈣離子濃度並無明顯的變化。

為了瞭解TG2蛋白質對細胞內鈣離子變化的影響，我們使用TG2缺陷的老鼠胚胎纖維母細胞(mouse embryonic fibrioblast，MEF)進行實驗(圖三)。我們首先觀察到，若未經處理之兩株MEF細胞株粒線體和細胞質內鈣離子的濃度沒有顯著的差異，但是，TG2缺陷的MEF細胞的內質網鈣離子濃度比WT MEF細胞株高。倘若加入tg處理細胞可見，缺乏TG2表現之MEF細胞粒線體鈣離子累積吸收的情形明顯低於野生型MEF細胞，然而，我們分析內質網鈣離子的濃度時發現，當加入Tg處理TG2 KO MEF細胞株時則發現，缺乏TG2蛋白質會使內質網鈣離子排空的情形降低。而tg所誘導的細胞質鈣離子變化沒有明顯的差別。實驗結果可以說明，缺乏TG2蛋白質的MEF細胞株，在未受刺激的情況下有較高的內質網鈣離子濃度，而當受tg誘導時缺乏TG2蛋白質則會降低粒線體鈣離子的吸收和內質網鈣離子的釋放。

為了瞭解究竟大量誘導TG2蛋白質會影響何種蛋白質分子進而影響鈣離子平衡，我們使用蛋白質體學方法以二維電泳膠體分離純化及鑑定大量表現TG2後所誘導的蛋白質，比較分析控制組大量表現野生型Tet-on wtTG2 和突變型Tet-on TG2C277S (圖四)所誘導之蛋白質之差別。我們先將細胞株處理doxycycline誘導TG2蛋白質表現後，經二維電泳及coomassie blue染色解析後，由重覆實驗之膠圖中比較Tet-on wtTG2和Tet-on TG2C277S細胞株有差別表現量的蛋白質，揀選出十九個表現量有差別的蛋白質，再經由蛋白質質譜(LS-MS/MS)鑑定(表一)。

未來我們將進一步研究TG2是否可能透過調控其中的蛋白質而影響鈣離子的平衡和細胞凋亡情形。

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A. In the past five years we have been interesting on the study of transglutaminase 2 (TG2), apoptosis, calcium regulation and its possible relationship to the development of autoimmune disease. TG2 is a multi-function enzyme with diverse functions. TG2 knockout mice will develop lupus-like disease with deceased efferocytosis and the development of splenomegaly, autoantibodies, and immune complex glomerulonephritis. We found that TG2 contribute to apoptosis induction in Jurkat cT cells by modulating Calcium homeostasis via cross-linking RAP1GDS1 (Hsieh et al,PLOS ONE 8(12):e81516,2013).RAP1GDS1, GDP-GTP dissociation stimulator 1, is an unusual guanine exchange factor acting on small GTPase to promote the calcium release from ER and to enhance mitochondrial calcium uptake. So TG2 might act as a calcium sensor to amplify ER-derived Calcium signals to enhance mitochondrial calcium uptake.

Recently there are many interesting findings related to this field.

1. An increasing number of calcium channels and transporter have been described and these channels play a key role in the regulation of calcium homeostasis in T cell. The modulation of T-cell calcium homeostasis may become one of therapeutic strategies to combat immune-mediated disorders. The best known calcium channel in T cells is the Calcium-release-activated calcium (CRAC) channel, which is composed of Orai1 and STIM1 proteins. Mutations in Orail1 and STIM1 cause immune deficiency. Calcium signaling is essential for induction of the nuclear orphan receptor pathway to drive Th17 differentiation.
2. TG2 is involved in autophagy and autophagy is a novel pathway to regulate calcium mobilization in T cells.
3. SmgGDS promote the malignant lung cancer: SmgGDS Regulates Cell Proliferation, Migration, and NF-kappa B. So SmgGDS is an therapeutic target in lung cancer (NSCLC)
   These are related to our recent novel findings.

B. We have also been study the effects of IL-10 RNAi in the possible therapy for lupus. We found that virus-like particles (VLPs) packaged with IL-10 RNAi from the JC virus efficient to block IL-10 production in vivo and in vitro (Chou *et al.* 2010). In further, We also assessed that RNA interference targeting IL-10 is an effective strategy to silence the IL-10 pathway (Tsay *et al.* European J Immunology). Accordingly, they possesses a therapeutic potential that could be useful in the management of SLE and, possibly, other immune-mediated disorders.

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Scientific Production: selected the five published papers in the past five years.

1. 2013 Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin Sándor, Angela Bononi, Paolo Pinton, László Tretter, Zsuzsa Szondy and **Gregory J. Tsay***. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca^{2+} homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).

2. 2013 **Gregory J Tsay**, Yu-Fan Hsieh, Meilin Wang, Deching Chang, Jinghua Tsai Chang, and Moncef Zouali. Targeting the IL-10 pathway by RNA interference has beneficial effects on the development of experimental lupus. European Journal of Inflammation. 2013, 11(1): 43-53. (SCI) (IF

5.233; 22/139)

3. 2012 Ching-Bin Lin, Chun-Che Lin, and **Gregory J. Tsay*.** 6-Gingerol Inhibits Growth of Colon Cancer Cell LoVo via Induction of G2/M Arrest. **Evidence-Based Complementary and Alternative Medicine** Volume 2012, Article ID 326096. (SCI) (IF 4.774；1/22)

4. 2011 Hsien-Hua Liao**,** Yao-Chen Wang**,** Miles CHIH-MING Chen**,** Hsien-Yu Tsai**,** Johnson Lin**,** Shui-Tein Chen**, Gregory Tsay*** and Sun-Long Cheng**.** Down-regulation of granulocyte-macrophage colony-stimulating factor by 3C-like proteinase in transfected A549 human lung carcinoma cells. **BMC Immunol.** 2011 Feb 17;12(1):16. (correspondent)（SCI）（IF2.724；65/128）

5. 2010 Chou MI, Hsieh YF, Wang M, Chang JT, Chang D, Zouali M, **Tsay GJ***.
In vitro and in vivo targeted delivery of IL-10 interfering RNA by JC virus-like particles. **J Biomed Sci**. Jun 24;17:51（SCI）（IF 2.007；50/92）

We also submitted this paper to Molecular Immunology.

“Daidzein Enhances Efferocytosis via Transglutaminase 2 and Augmentation of Rac1 Activity ” by Jia-Hau Yen, Deng-Jye Yang, Meng-Chi Chen, Wu Yi-Ying, Yu-Fan Hsieh, Yueh-Mei Cheng, Wen-Nan Huang, Zsuzsa Szondy, Gregory J Tsay,

Abstract:

Defective efferocytosis is cumulatively recognized in autoimmune and chronic inflammatory diseases. Based on our previous finding, an ethanolic extract from *Glycine tomentella* Hayata (GTH) can enhance mouse macrophage Raw264.7 efferocytosis (clearance of apoptotic cells). We have previously demonstrated that the major components of GTH are daidzein, catechin, epicatechin and naringin. Here, we explore the potential of each component for modulating efferocytosis activity. For detecting the effect of daidzein, catechin, epicatechin and naringin on efferocytosis, RAW264.7 cells were cultured with CFDA-stained apoptotic cells and assayed by flow cytometry. We found that daidzein is the main component of GTH, and it can enhance Raw264.7 efferocytosis dose-dependently. Moreover, the increased effect of daidzein on macrophage efferocytosis activity is accompanied by TG2 at both the mRNA and protein levels. Conversely, TG2 knockdown attenuated the effect of daidzein on increased macrophage efferocytosis activity. After treatment with daidzein, increased phosphorylation was observed in Erk, but not P38 and JNK. Finally, we report that after daidzein treatment, Raw264.7 macrophages markedly increased Rac1 activity and decreased the mitochondrial membrane potential, which may contribute to efferocytosis. Taken together, these data suggest that daidzein enhancement of macrophage efferocytosis activity was mainly through up-regulation of TG2 expression and Rac1 activity. Daidzein may have the potential for treatment strategies for inflammatory diseases.

附件二

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（簡要敘述成果是否有嚴重損及公共利益之發現）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）Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin Sándor, Angela Bononi, Paolo Pinton, László Tretter, Zsuzsa Szondy and **Gregory J. Tsay***. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca^{2+} homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).

國科會補助計畫衍生研發成果推廣資料表

日期:2013/12/26

國科會補助計畫	計畫名稱: 第二型轉麩胺酶和自體免疫疾病之研究
	計畫主持人: 蔡嘉哲
	計畫編號: 99-2314-B-040-006-MY3　　學門領域: 血液科腫瘤科風濕免疫及感染

無研發成果推廣資料

99 年度專題研究計畫研究成果彙整表

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計畫名稱：第二型轉麩胺醯和自體免疫疾病之研究	

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	3	3	100%		Taiwan Rheumatology association annual meeting 2010, 2011, 2012
		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	1	1	100%	篇	1. 2013 Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin S&aacute ; ndor, Angela Bononi, Paolo Pinton, L&aacute ; szl&oacute ; Tretter, Zsuzsa Szondy and Gregory J. Tsay*. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca2+ homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).
		研究報告/技術報告	0	0	100%		

		研討會論文	0	0	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	0	0	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。)		train the Ph.D student					

	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	

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技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

Yu-Fan Hsieh, Guang-Yaw Liu, Yi-Ju Lee, Jiann-Jou Yang, Katalin S&aacute；ndor, Angela Bononi, Paolo Pinton, L&aacute；szl&oacute； Tretter, Zsuzsa Szondy and Gregory J. Tsay*. Transglutaminase 2 contributes to apoptosis induction in Jurkat T cells by modulating Ca2+ homeostasis via cross-linking RAP1GDS1. (PLOS ONE 8(12):e81516,2013).

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