科技部補助專題研究計畫成果報告
期末報告

OSGIN1蛋白及脂筏在n-3、n-6多元不飽和脂肪酸調控人類乳癌細胞生長、轉移及自噬作用扮演之角色及其分子機制

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中 文 摘 要 ： 乳癌是全球中最常見的女性癌症，目前雖然有標把藥物、放射性治療、手術切除等多種治療方法，卻無法有效降低因乳癌再復發所造成的死亡。Oxidative stress-induced growth inhibitor 1 (OSGIN1)被認為是一種抑癌蛋白，其大量表現可促進癌細胞凋亡。截至目前對於飲食因子調控OSGIN1基因及蛋白表現之相關研究甚少，是否可藉由飲食因子上調OSGIN1基因及蛋白表現，達到抑制癌細胞發展值得進一步探討。先前計畫研究結果得知在n-3、n-6 PUFAs中，僅DHA顯著誘發MCF-7細胞OSGIN1蛋白質表現。然而本計畫重點在探討DHA所誘發OSGIN1的表現是否抑制DHA乳癌細胞轉移、促進癌細胞自噬作用、凋亡。實驗結果發現，DHA相較於其他PUFAs可顯著上調LC3B蛋白質及下調mTOR的蛋白質活性，此表現呈劑量關係，並顯著誘發自噬作用。而DHA所誘發的OSGIN1蛋白質會參與調控這些訊號路徑，透過轉染OSGIN1 small interfering RNA或OSGIN1 DNA的過度表達質體兩個方法加以證實OSGIN1推動自噬作用進行。OSGIN1會影響AMPK，mTOR兩大系統訊號路徑，透過活化AMPK/Raptor，下調mTOR/ULK Ser757的活性，進而增加LC3B的活化並增加自噬作用。此外，結果也顯示，處理DHA或給予OSGIN1 DNA過度表達質體可誘導產生前期凋亡蛋白BAX表現並降低Bcl-2表現、cytochrome c由粒線體中釋放。透過流式細胞儀分析細胞死亡比例上升，也證實OSGIN1的誘發會促進乳癌細胞凋亡。本研究證實OSGIN1的表現在DHA促進乳癌細胞細胞自噬及凋亡中扮演重要角色。

中 文 關 鍵 詞 ： OSGIN1、自噬作用、mTOR、乳癌、凋亡

英 文 摘 要 ： Breast cancer has been known the most common female cancer in the world. Although multiple therapeutic approaches, such as target-drug, radiation therapy and surgery, are therapeutic for breast cancer patients, the breast cancer mortality is not decline; so far, these therapeutic approaches have been not enough effective for breast cancer patient. Our Study is committed to research Oxidative stress-induced growth inhibitor 1 (OSGIN1), identified as a tumor suppressor gene. Previous experiment data showed that within n-3 and n-6 PUFAs, only DHA significantly induced OSGIN1 protein expression. However, the effect of OSGIN1 on DHA inhibition of breast cell migration and induction of apoptosis and autophagy is not fully clarified. Our results that DHA is more up-regulated LC3B expression and down-regulated mTOR activation than other PUFAs, showed in dose dependent, and induced autophagy. OSGIN1, which is induced by DHA, was involved in these signaling pathways, we demonstrated that OSGIN1 promoted autophagy by transfection OSGIN1 small interfering RNA or OSGIN1 plasmid DNA. OSGIN1 influenced both of AMPK and mTOR signaling pathways, OSGIN1 activated LC3B by activation AMPK/Raptor and inactivation mTOR/ULK ser757 to induce autophagy. Therefore, our data also demonstrated that MCF-7 expressed high BAX levels, low Bcl-2 levels and cytochrome c released from mitochondria

with DHA treatment or transfection OSGIN1 plasmid DNA. And the proportion of cell death increased in flow cytometer, so OSGIN1 also promoted apoptosis in breast cancer cells. In our current study, we confirmed that the performance of OSGIN1 played an important role on DHA induction apoptosis and autophagy in breast cancer cells.

英文關鍵詞：OSGIN1, autophagy, mTOR, breast cancer, apoptosis

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中文摘要

乳癌是全球中最常見的女性癌症，目前雖然有標把藥物、放射性治療、手術切除等多種治療方法，卻無法有效降低因乳癌再復發所造成的死亡。Oxidative stress-induced growth inhibitor 1 (OSGIN1)被認為是一種抑癌蛋白，其大量表現可促進癌細胞凋亡。截至目前對於飲食因子調控 OSGIN1 基因及蛋白表現之相關研究甚少，是否可藉由飲食因子上調 OSGIN1 基因及蛋白表現，達到抑制癌細胞發展值得進一步探討。先前計畫研究結果得知在 n-3、n-6 PUFAs 中，僅 DHA 顯著誘發 MCF-7 細胞 OSGIN1 蛋白質表現。然而本計畫重點在探討 DHA 所誘發 OSGIN1 的表現是否抑制 DHA 乳癌細胞轉移、促進癌細胞自噬作用、凋亡。實驗結果發現，DHA 相較於其他 PUFAs 可顯著上調 LC3B 蛋白質及下調 mTOR 的蛋白質活性，此表現呈劑量關係，並顯著誘發自噬作用。而 DHA 所誘發的 OSGIN1 蛋白質會參與調控這些訊號路徑，透過轉染 OSGIN1 small interfering RNA 或 OSGIN1 DNA 的過度表達質體兩個方法加以證實 OSGIN1 推動自噬作用進行。OSGIN1 會影響 AMPK，mTOR 兩大系統訊號路徑，透過活化 AMPK/Raptor，下調 mTOR/ULK Ser757 的活性，進而增加 LC3B 的活化並增加自噬作用。此外，結果也顯示，處理 DHA 或給予 OSGIN1 DNA 過度表達質體可誘導產生前期凋亡蛋白 BAX 表現並降低 Bcl-2 表現、cytochrome c 由粒線體中釋放。透過流式細胞儀分析細胞死亡比例上升，也證實 OSGIN1 的誘發會促進乳癌細胞凋亡。本研究證實 OSGIN1 的表現在 DHA 促進乳癌細胞細胞自噬及凋亡中扮演重要角色。

關鍵詞: OSGIN1、自噬作用 、mTOR、乳癌、凋亡

Abstract

Breast cancer has been known the most common female cancer in the world. Although multiple therapeutic approaches, such as target-drug, radiation therapy and surgery, are therapeutic for breast cancer patients, the breast cancer mortality is not decline; so far, these therapeutic approaches have been not enough effective for breast cancer patient. Our Study is committed to research Oxidative stress-induced growth inhibitor 1 (OSGIN1), identified as a tumor suppressor gene. Previous experiment data showed that within n-3 and n-6 PUFAs, only DHA significantly induced OSGIN1 protein expression. However, the effect of OSGIN1 on DHA inhibition of breast cell migration and induction of apoptosis and autophagy is not fully clarified. Our results that DHA is more up-regulated LC3B expression and down-regulated mTOR activation than other PUFAs, showed in dose dependent, and induced autophagy. OSGIN1, which is induced by DHA, was involved in these signaling pathways, we demonstrated that OSGIN1 promoted autophagy by transfection OSGIN1 small interfering RNA or OSGIN1 plasmid DNA. OSGIN1 influenced both of AMPK and mTOR signaling pathways, OSGIN1 activated LC3B by activation AMPK/Raptor and inactivation mTOR/ULK ser757 to induce autophagy. Therefore, our data also demonstrated that MCF-7 expressed high BAX levels, low Bcl-2 levels and cytochrome c released from mitochondria with DHA treatment or transfection OSGIN1 plasmid DNA. And the proportion of cell death increased in flow cytometer, so OSGIN1 also promoted apoptosis in breast cancer cells. In our current study, we confirmed that the performance of OSGIN1 played an important role on DHA induction apoptosis and autophagy in breast cancer cells.

Keyword: OSGIN1, autophagy, mTOR, breast cancer, apoptosis

前言

乳癌好發於女性，為美國女性癌症死亡的第二大原因，2008年流行病學研究調查即指出，在所有因癌症死亡的美國女性中，高達15%是死於乳癌(Marian and Roberts, 2009)。乳癌的高致死率主要來自於乳癌細胞的高度轉移能力，使癌細胞易擴散並侵犯鄰近組織、器官所致。一般而言，女性乳癌好發年齡在四十五至六十五歲間，但隨著飲食及生活習慣的改變。在台灣，惡性腫瘤為十大死因的榜首，而乳癌為癌症死亡第四名，女性癌症死亡第一名，近年來，台灣女性乳癌好發年齡已有逐年下降的趨勢。然而，對於如何提升乳癌細胞已發生轉移的乳癌患者之存活率，至今仍無顯著的改善。因此，在施以手術或化療、放射療等治療方式後，如何進一步有效抑制癌細胞復發及轉移，即成為防患乳癌死亡率增加的重要課題。由於不少研究指出乳癌之發生與飲食油脂有密切關係，因此，本實驗室致力於探討n-3多元不飽和脂肪酸(polyunsaturated fatty acid, PUFA)，α-linolenic acid (LNA)、Eicosapentaenoic acid (EPA)、docosahexaenoic acid (DHA)對降低乳癌死亡率相關癌細胞增生與轉移之作用及其分子作用機制，同時比較其它n-6 PUFAs，arachidonic acid (AA)、linoleic acid (LA)、γ-linolenic acid (GLA)在調控癌細胞增生與轉移所扮演的角色，期盼可藉由釐清脂肪酸調控乳癌細胞增生和轉移之機制，達到降低乳癌預後再復發及癌細胞遠端轉移的情形。

研究目的

越來越多研究證實，癌細胞的生長、存活與轉移也受到細胞自噬作用(autophagy)、細胞凋亡(apoptosis)的調控，故計畫除了延續探討n-3、n-6 PUFAs對乳癌細胞轉移外，也將探討OSGIN1蛋白在n-3、n-6 PUFAs對調控乳癌細胞autophagy、apoptosis之影響及其相關機制。

文獻探討

飲食油脂與癌症的相關性研究並不少見，長久以來，富含於魚油中的EPA與DHA等n-3 PUFAs被認為是可以預防癌症發生的飲食因子之一。針對乳癌而言，流行病學研究發現，飲食中多攝取魚肉(每周至少兩份)或補充較多的DHA有助於降低乳癌的罹患率。動物實驗也證實，飲食中添加魚油不但可以降低化學物所誘發的癌細胞生長(Braden et al., 1986)，也可提高動物對化學治療(chemotherapy)的敏感性，並可降低乳癌細胞的骨轉移。細胞實驗則證實預處理DHA 可顯著抑制MDA-MB 231人類乳癌細胞的增生，並誘發其凋亡。最近研究則發現，DHA抑制肺癌、前列腺癌等癌細胞增生並促使凋亡與DHA啟動自噬作用有關(Yao et al., 2014)。

OSGIN1基因之蛋白產物在抑制癌細胞生長扮演重要角色(Hu et al., 2012)，也因此被視為新的癌症治療標的基因。早期所發現的OSGIN1又稱為OKL38，由人類骨髓漿細胞(Bone marrow stromal cell; BMSC)分離出的蛋白，具有抑制細胞生長的功能(Wang et al., 2005)。OSGIN1屬於一種壓力反應蛋白，其基因表現會受到環境壓力所誘發，包括DNA damaging reagents或氧化壓力(Li et al., 2007; Romanoski et al., 2011)。Hammad (2009)等人發現給予oxidized LDL (oxLDL)處理人類U937單核球細胞可顯著誘發OSGIN1基因表現，而OSGIN1的基因表達可能與Nrf2轉錄因子的調控有關(Li et al., 2007)。根據Cancer profiling array (CPA)分析結果則發現，惡性度較高乳癌、腎癌、肝癌組織OSGIN1 mRNA及蛋白表現量顯著低於鄰近癌細胞之正常乳腺上皮細胞、腎細胞和肝臟實質細胞(Ong et al., 2004; Ong et al., 2007)。一旦給予可過度表達OSGIN1蛋白的基因載體，可抑制腎癌細胞生長並促使其細胞凋亡(Ong et al., 2004)。最新研究發現，OSGIN1等位基因發生變異的肝臟實質細胞容易形成肝細胞癌(Hepatocellular carcinoma, HCC)，此變異所造成OSGIN1功能缺失導致病患預後狀況較差(Liu et al., 2014b)。由上述研究結果得知，OSGIN1的表現在調控癌細胞死亡及降低癌細胞生長過程應扮演重要角色。然而，到目前為止只有OSGIN1對抑制增生促進凋亡的研究，並無透過飲食因子給予來誘發OSGIN1及誘發的OSGIN1調控癌細胞自噬作用的相關研究，本實驗室繼去年發現DHA可顯著誘發MCF-7、Hs578t乳癌細胞OSGIN1表現後，將繼續探討DHA如何調控OSGIN1表現，以及n-3、n-6 PUFAs是否可藉由調控OSGIN1表現影響乳癌細胞的自噬作用並探討OSGIN1透過何種機制調控癌細胞的自噬作用。

研究方法

Cell culture and treatments
Human breast cancer MCF-7 cell was purchased from American Type Cell Culture Collection (Rockville, MD, USA) and maintained in DMEM medium (pH 7.2) supplemented with 10% FBS, 1.5 g/l $NaHCO_3$ and 100 μg/ml penicillin-streptomycin in a humidified 5% CO_2 atmosphere at 37℃. The culture medium was changed every other day. MCF-7 cells was grown to 70–80% confluence and then were treated with various concentrations of 25–400 μM DHA for 24 h in medium with 10% FBS for the times indicated.

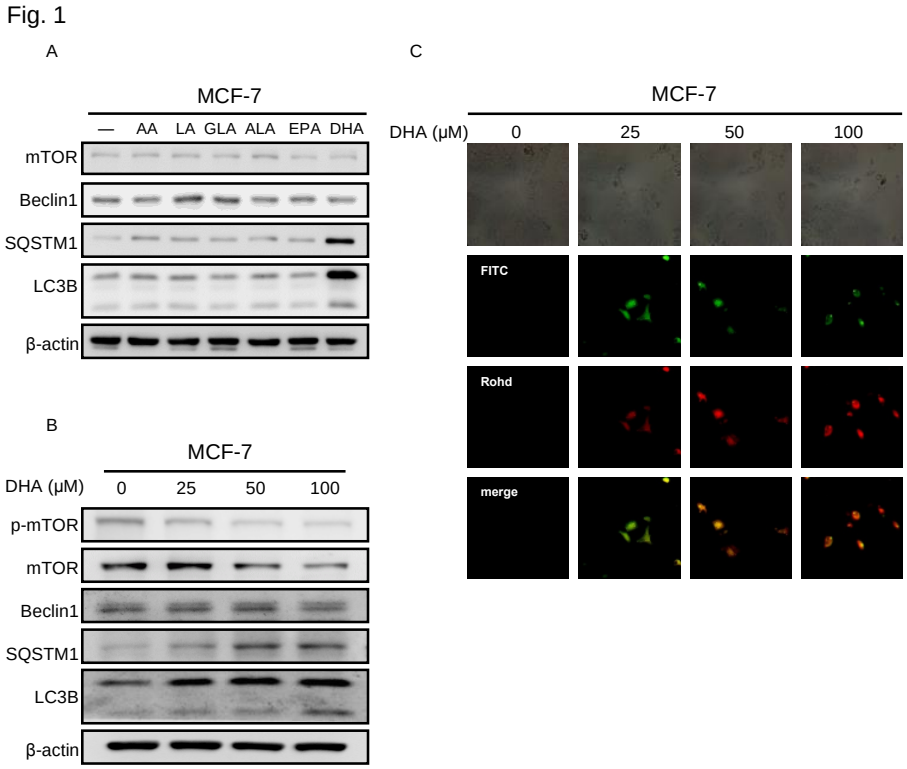
Fatty acid preparation
DHA was mixed with BSA at 6:1 molar ratio before being added to the culture medium with 0.1% butylated hydroxytoluene and 20 μM α-tocopheryl succinate that prevent DHA-induced lipid peroxidation.

Western blotting
Cells were washed with cold PBS twice and were harvested in 200 μl of 20 mM potassium phosphate buffer (pH 7.0). Cell homogenates were centrifuged at 15000 × rpm for 30 min at 4℃. The protein content of the supernatant was measured by using the Coomassie Plus Protein Assay Reagent kit (Pierce, Rockford, IL). Equal amounts of cellular proteins were electrophoresed in a sodium dodecyl sulfate (SDS)–polyacrylamide gel, and proteins were transferred to polyvinylidene fluoride membranes (Millipore, Bedford, MA). The nonspecific binding sites in the membranes were blocked with 5% nonfat dry milk in 15 mM Tris–150 mM NaCl buffer (pH 7.4) at room temperature for 2 h. After blocking, the membranes were incubated with antibodies against OSGIN1 (1:1000), SQSTM1 (1:1000), Beclin1 (1:1000), LC3B (1:1000), mTOR (1:1000), phosphor-mTOR (1:1000),AMPKα (1:1000), phospho-AMPKα (1:1000) and Actin (1:4000) at 4°C overnight. The next day, the membranes were incubated with the secondary peroxidase-conjugated anti-rabbit (1:6000) or anti- mouse IgG (1:5000) at room temperature for 1 h, and the immune-reactive bands were developed by use of the Western Lightning Plus- ECL Kit (PerkinElmer, Waltham, MA) and were scanned by a luminescence image analyzer (Fuji Film LAS-4000, Japan). The bands were quantitated with Image-J software.

Small interfering RNA of OSGIN1
Small interfering RNAs (siRNAs) for OSGIN1 was synthesized by MDbio Inc. (Taipei, Taiwan). MCF-7 cells were grown to 50–60% confluence in 6cm dish and was transfected with OSGIN1 siRNA or non-targeting siRNA (negative control) by using Lipofectamine RNAi MAX Transfection Reagent (Thermo Fisher Scientific, MA, USA). OSGIN1 siRNA or negative siRNA were added in 200ul Opti- MEM medium (Thermo Fisher Scientific, MA, USA), and mixed with 1.5 μl of transfection reagent; after incubation for 20 minutes at room temperature, the mixture was added to 1300 μl of Opti- MEM medium and applied to the cells. Total siRNA concentration is 25 nM. After 12 h of transfection, discard transfection reagent and added DMEM medium with 10% FBS for another 12 h, then the cells were treated as indicated in the experimental design.

Construction and transfection of OSGIN1 plasmid DNA
The plasmid DNA of OSGIN1 obtained from transOMIC technologies (Huntsville, AL, USA), it's sequencing primer: Forward, GTACGGTGGGAGGTCTATAT; Reverse, TAGAAGGCACAGTCGAGG, the product was ligated into pTCN expression vector. The MCF-7 cells were transfected with the pTCN-OSGIN1 plasmid or pTCN control vector by using TransIT® -2020 transfection reagent (Mirus Bio, Inc., Madison, WI, USA). Mixed pTCN-OSGIN1 plasmid or pTCN control vector 2.5ug and TransIT® -2020 transfection reagent 7.5ul in 200 μl of Opti- MEM medium gently; after incubating for 20 minutes at room temperature, the mixture was added to 2.2ml of Opti- MEM medium and applied to the cells.

Autophagy Immunofluorescence Detection
This experiment is detected by Premo™ Autophagy Tandem Sensor RFP-GFP-LC3B Kit from Thermo Fisher Scientific (Waltham, MA, USA). MCF-7 was plated in EZ slide (Millipore, Billerica, MA, USA) with the RFP-GFP-LC3B (Component A) 2 ul per well in medium, then the cells incubated overnight in a humidified 5% CO2 at 37℃. The next day, after being treated as indicated in the experimental design, detected by a up right fluorescence microscope.



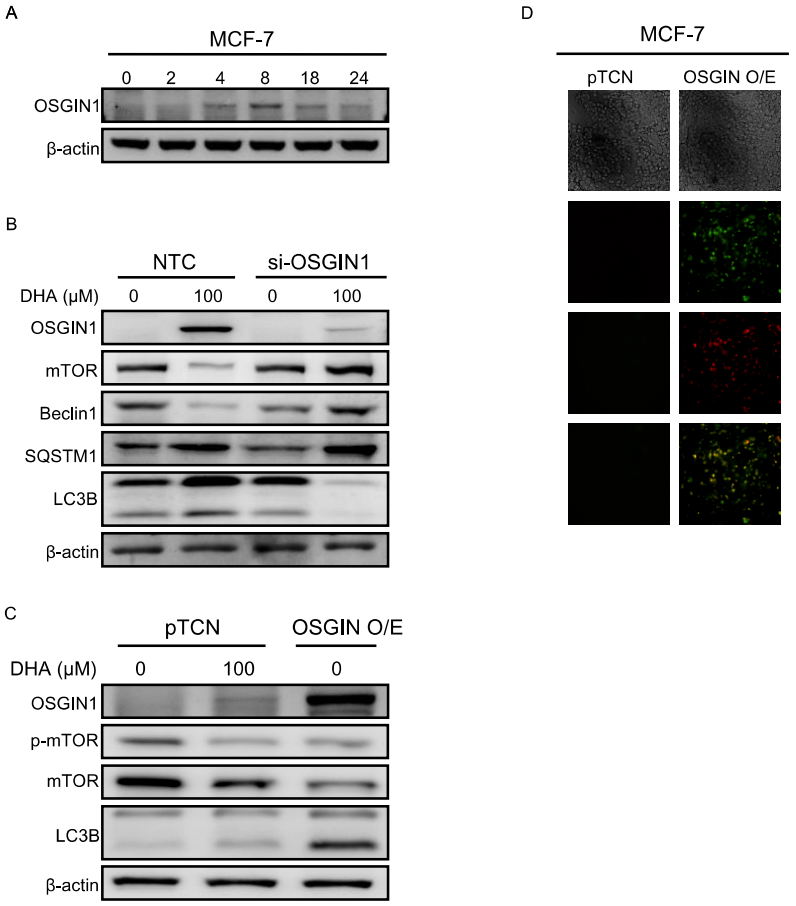
圖一

A. n-6、n-3 PUFAs對autophagy相關蛋白表現之影響

B. DHA 劑量關係對autophagy相關蛋白表現之影響

C. DHA 對 autophagy 指標蛋白 LC3-GFP-RFP 之螢光表現

Fig. 2

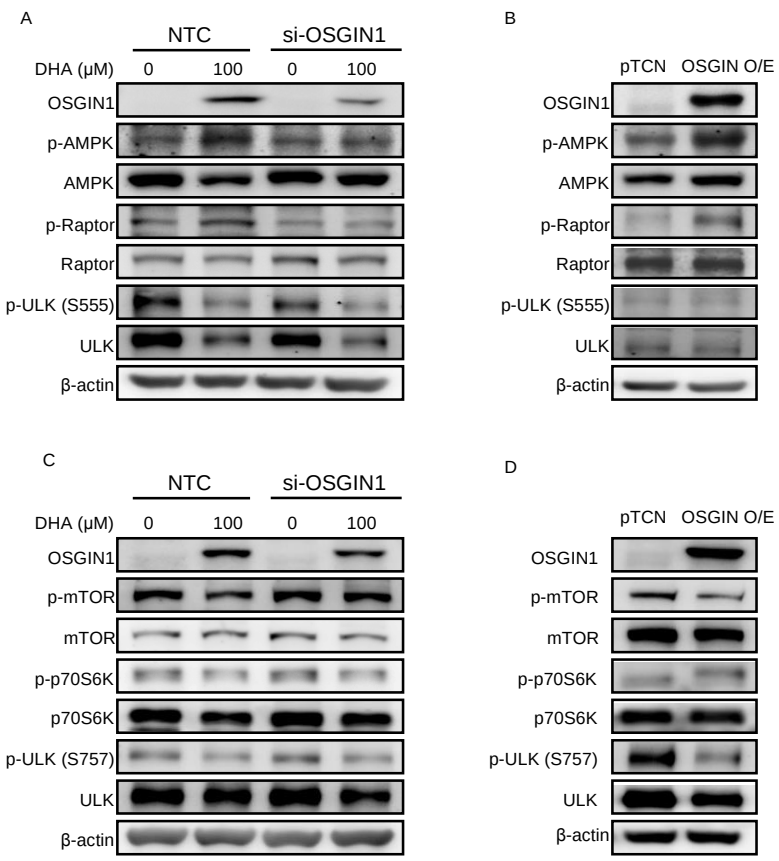


圖二

A. DHA 誘發 OSGIN1 在各時間點的表現
B. si-OSGIN1對 DHA誘發 autophagy相關蛋白表現之影響

C. OSGIN1 plasmid DNA 過度表達對 autophagy 相關蛋白表現之影響
D. OSGIN1 plasmid DNA 過度表達對 autophagy 指標蛋白 LC3-GFP-RFP 之螢光表現

Fig. 3



圖三

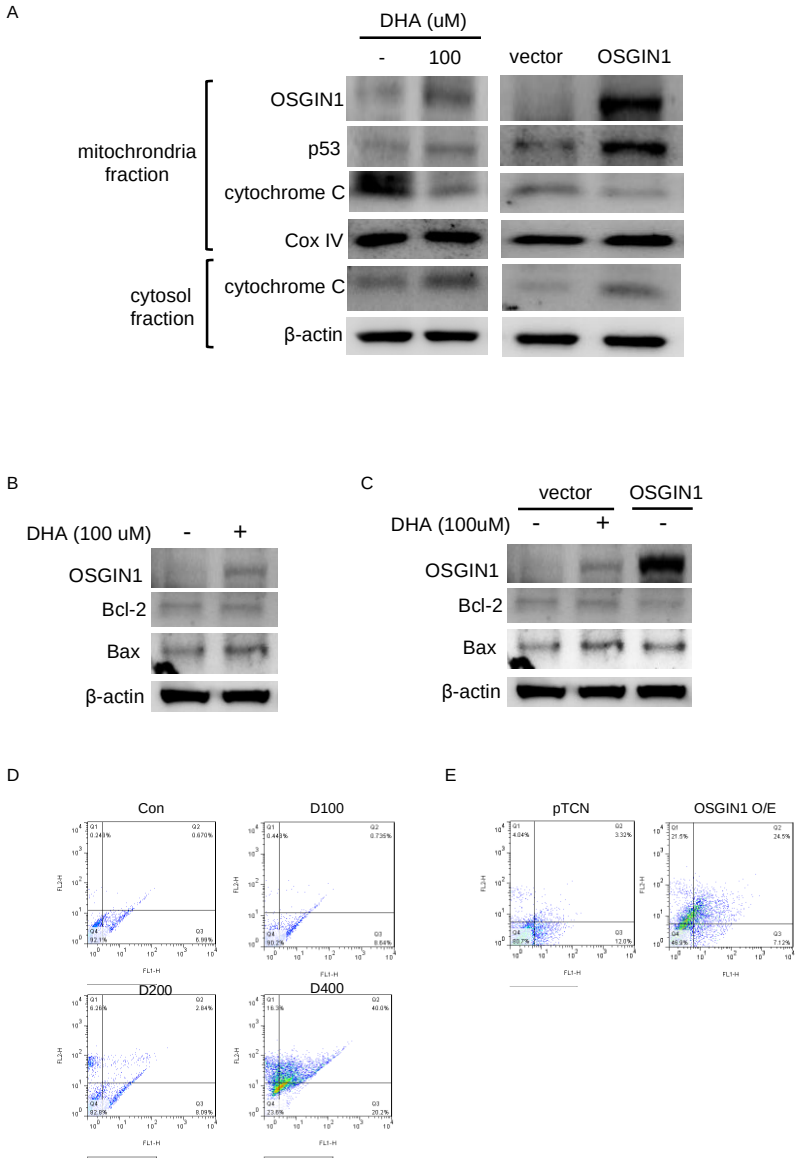
A. si-OSGIN1 對 DHA 誘發 AMPK 相關蛋白訊號路徑表現之影響

B. OSGIN1 plasmid DNA過度表達對AMPK相關蛋白訊號路徑表現之影響

C. si-OSGIN1對 DHA誘發 mTOR相關蛋白訊號路徑表現之影響

D. OSGIN1 plasmid DNA過度表達對mTOR相關蛋白訊號路徑表現之影響

Fig. 4



圖四

A. DHA 及 OSGIN1 plasmid DNA 過度表達對粒線體及細胞質蛋白中 p53，Cytochrome C 蛋白表現影響

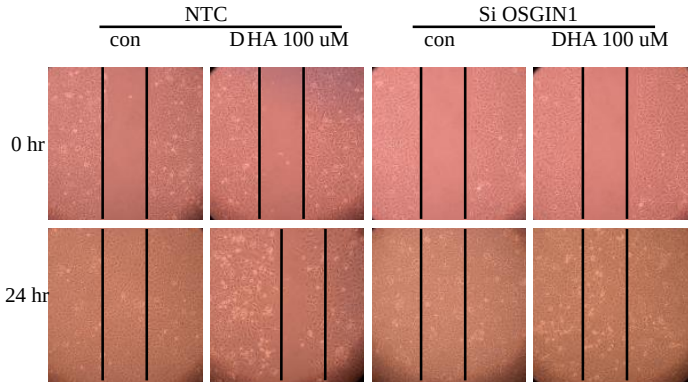
B. DHA對Bcl-2，BAX蛋白表現影響

C. OSGIN1 plasmid DNA過度表達對Bcl-2，BAX蛋白表現影響

D. DHA對細胞凋亡之影響

E. OSGIN1 plasmid DNA 過度表達對細胞凋亡之影響

Fig. 5



圖五

si-OSGIN1 對 DHA 抑制癌細胞移行之影響

結論:

These results suggest that DHA induces OSGIN1 expression, and then OSGIN1 promote autophagy through activation AMPK and inhibition mTOR and promote apoptosis by up-regulation BAX/Bcl-2 ratio and Cytochrome C release. All in all, induction of OSGIN1 involve in DHA's anti-cancer activity by promotion autophagy and apoptosis.

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科技部補助計畫衍生研發成果推廣資料表

日期:2016/10/25

科技部補助計畫	計畫名稱: OSGIN1蛋白及脂筏在n-3、n-6多元不飽和脂肪酸調控人類乳癌細胞生長、轉移及自噬作用扮演之角色及其分子機制
	計畫主持人: 李健群
	計畫編號: 104-2320-B-040-005- 學門領域: 營養保健

無研發成果推廣資料

104年度專題研究計畫成果彙整表

計畫主持人：李健群	**計畫編號：**104-2320-B-040-005-
計畫名稱：OSGIN1蛋白及脂筏在n-3、n-6多元不飽和脂肪酸調控人類乳癌細胞生長、轉移及自噬作用扮演之角色及其分子機制	

成果項目					量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			0	篇	
		研討會論文			0		
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			0	件	
		收入			0	千元	
國外	學術性論文	期刊論文			0	篇	
		研討會論文			1		Chien-Chun Li, (2015), Induction of oxidative stress-induced growth inhibitor by docosahexaenoic acid is mediated through the PI3K/Akt/Nrf2 pathway in MCF-7 breast cancer cells. 12th Asian Congress of Nutrition , 日本橫濱市(Yokohama, Japan).
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		

		商標權	0		
		營業秘密	0		
		積體電路電路布局權	0		
		著作權	0		
		品種權	0		
		其他	0		
	技術移轉	件數	0	件	
		收入	0	千元	
參與計畫人力	本國籍	大專生	0	人次	
		碩士生	0		
		博士生	1		蔡佳翰(博士班三年級)
		博士後研究員	0		
		專任助理	0		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
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。）					

科技部補助專題研究計畫成果自評表

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（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）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（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   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200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）
   了解其作用機制便可以建立研究平台，篩選相關飲食因子或針對機制作用進行藥物開發，機制的建立是往後更深入研究的基石。本研究結果證實DHA可透過PI3K/Akt訊號路徑誘發OSGIN1表現促進乳癌細胞自噬作用，進而誘導細胞凋亡。未來將進一步深入探討OSGIN1如何引發細胞自噬作用之機制，並釐清OSGIN1在DHA輔助癌症化療療效過程扮演之角色，期望能找出飲食因子對改善癌症預後的新方向。

4. 主要發現
   本研究具有政策應用參考價值：■否　□是，建議提供機關
   （勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
   本研究具影響公共利益之重大發現：■否　□是
   說明：（以150字為限）
   本研究使用的為保健食品魚油中富含的DHA，為生活中隨手的得的產品，透過本研究結果能更加確定魚油對於將的癌細胞發展的優勢，為來研究將探討魚油是否輔助化療藥物以減少用藥劑量、改善化療副作用進而降低復發風險，對於醫療具有很大幫助。