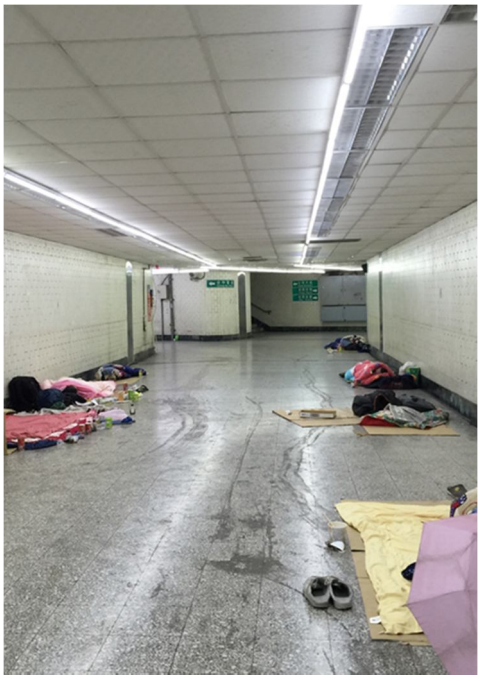
澳亞醫學科學研究學會台灣分會 電子報

第三期 (2016/02)

人文分享~~

劉青山醫師：台中市火車站地下道的朋友

我們常常有一些難過的事，有一些疑惑的事，有一些痛苦的事，但永遠難忘，早上坐火車上班，上帝帶我看一些朋友，住在火車站地下道，寒流讓他們聚在一起，幾乎是六十歲以上的老人，他們都有一個非常難過的故事（我腦海中假設），但他們的臉部並無太多表情，或許有經過許多的挫折失敗，離開自己溫暖的家，外界的看法對他已經不是重要，他們對世界似乎沒有任何的影響力，但對於他人而言，每個人一定都有一些深刻或美好的回憶。



信心，忍耐，再來就是堅持到成功！

聖經分享：晨耕 2016-1-25 信心與智慧

聖經 雅各書 1:2-8

「我的弟兄們，你們落在百般試煉中，都要以爲大喜樂； 因爲知道你們的信心經過試驗，就生忍耐。 但忍耐也當成功，使你們成全、完備，毫無缺欠。 你們中間若有缺少智慧的，應當求那厚賜與眾人、也不斥責人的神， 主 就必賜給他。只要憑 信心求，一點不疑惑；因爲那疑惑的人，就像海中的波浪，被風吹動翻騰。 這樣的人不要想從主那裏得甚麼。心懷二意的人，在他一切所行的路上都沒有定見。

http://bible.com/46/jas.1.2-8.cunp-神 3

願主賜福給大家

劉青山醫師 2016.02.05

研究成果

恭喜合作夥伴中興大學生命科學系蘇鴻麟教授論文獲得 Cell Transplant. 期刊接受，感謝血管暨基因體研究中心主任劉青山醫師與副主任張瑞芝研究員協助。

Cell Transplant. 2015 Nov 6. [Epub ahead of print] **Transferring Xenogenic Mitochondria Provides Neural Protection against Ischemic Stress in Ischemic Rat Brains.** Huang PJ, Kuo CC, Lee HC, Shen CI, Cheng FC, Wu SF, Chang JC, Pan HC, Lin SZ, Liu CS, Su HL.

Abstract

Transferring exogenous mitochondria has therapeutic effects on damaged heart, liver and lung tissues. Whether this protective effect requires the symbiosis of exogenous mitochondria in host cells remains unknown. Here, xenogenic mitochondria derived from a hamster cell line were applied to ischemic rat brains and rat primary cortical neurons. Isolated hamster mitochondria, either through local intracerebral or systemic intra-arterial injection, significantly restored the motor performance of brain-ischemic rats. The brain infarct area and neuronal cell death were both attenuated by the exogenous mitochondria. Although internalized mitochondria could be observed in neurons and astrocytes, the low efficacy of mitochondrial internalization could not completely account for the high rate of rescue of the treated neural cells. We further illustrated that disrupting electron transport or ATPase synthase in mitochondria significantly attenuated the protective effect, suggesting that intact respiratory activity is essential for the mitochondrial potency on neural protection. These results emphasize that nonsymbiotic extracellular mitochondria can provide an effective cell defense against acute injurious ischemic stress in the central nervous system.PMID:26555763

最新消息

「2016 彰基第 10 屆國際基因體醫學研討會&第 4 屆澳亞醫學科學研究研討會&2016 台灣粒線體醫學暨研究學會學術研討會暨年會」將於 2016 年 09 月 23-25 日於彰基舉辦。

第 15 屆亞澳肌肉醫學年會暨第 20 屆小兒神經醫學會學術演講會(AOMC 2016)將於 2016/05/26-29 於新竹國立交通大學電資大樓國際會議廳舉辦。詳情請參閱 http://www.aomc2016.org/edm1/edm.html

如對本中心或發行之電子報有任何疑問，或欲分享您專業領域之科學新知。歡迎電郵至 d4609@cch.org.tw.

Prim Care Diabetes. 2015 Oct 19. pii: S1751-9918(15)00125-4. doi: 10.1016/j.pcd.2015.09.005. **High diabetes mellitus prevalence with increasing trend among newly-diagnosed tuberculosis patients in an Asian population: A nationwide population-based study.**
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Huang CH, Chang CC, Kuo C, Huang CS, Lin CS, Liu CS.
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U-shaped relationship between uric acid and residual renal function decline in continuous ambulatory peritoneal dialysis patients.
Hsieh YP, Yang Y, **Chang CC**, Kor CT, Wen YK, Chiu PF, Lin CC.
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Interferon gamma-induced protein 10 is associated with insulin resistance and incident diabetes in patients with nonalcoholic fatty liver disease.
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Kao HW, **Lee KW**, **Chen WL**, Kuo CL, Huang CS, Tseng WM, Liu CS, Lin CP.
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Efficiency of three-dimensional Doppler ultrasonography in assessing nodal metastasis of head and neck cancer.
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The therapeutic efficiency of extracorporeal magnetic innervation treatment in women with urinary tract dysfunction following radical hysterectomy.
Sun MJ, Sun R, Chen LJ.
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Cell transplantation. 2015, in press
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Allo-/xenogeneic transplantation of peptide-labelled mitochondria in Parkinson's disease: restoration of mitochondria functions and attenuation of 6-OHDA-induced neurotoxicity.
Jui-Chih Chang, Shey-lin Wu, Ko-Hung Liu, Ya-Hui Chen, Chieh-Sen Chuang, Fu-Chou Cheng, Hong-Lin Su, Yau-Huei Wei, Shou-Jen Kuo and **Chin-San Liu** 2015, in press

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The mitochondrial dynamism-mitophagy-cell death interactome: multiple roles performed by members of a mitochondrial molecular ensemble.

Dorn GW 2nd[1], Kitsis RN[2].

Author information

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[2]From the Department of Internal Medicine, Center for Pharmacogenomics, Washington University School of Medicine, St. Louis, MO (G.W.D.); and Departments of Medicine (Cardiology) and Cell Biology and Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, Bronx, NY (R.N.K.).

Abstract

Mitochondrial research is experiencing a renaissance, in part, because of the recognition that these endosymbiotic descendants of primordial protobacteria seem to be pursuing their own biological agendas. Not only is mitochondrial metabolism required to produce most of the biochemical energy that supports their eukaryotic hosts (us) but mitochondria can actively (through apoptosis and programmed necrosis) or passively (through reactive oxygen species toxicity) drive cellular dysfunction or demise. The cellular mitochondrial collective autoregulates its population through biogenic renewal and mitophagic culling; mitochondrial fission and fusion, 2 components of mitochondrial dynamism, are increasingly recognized as playing central roles as orchestrators of these processes. Mitochondrial dynamism is rare in striated muscle cells, so cardiac-specific genetic manipulation of mitochondrial fission and fusion factors has proven useful for revealing noncanonical functions of mitochondrial dynamics proteins. Here, we review newly described functions of mitochondrial fusion/fission proteins in cardiac mitochondrial quality control, cell death, calcium signaling, and cardiac development. A mechanistic conceptual paradigm is proposed in which cell death and selective organelle culling are not distinct processes, but are components of a unified and integrated quality control mechanism that exerts different effects when invoked to different degrees, depending on pathophysiological context. This offers a plausible explanation for seemingly paradoxical expression of mitochondrial dynamics and death factors in cardiomyocytes wherein mitochondrial morphometric remodeling does not normally occur and the ability to recover from cell suicide is severely limited.

全文詳見 http://circres.ahajournals.org/cgi/pmidlookup?view=long&pmid=25323859

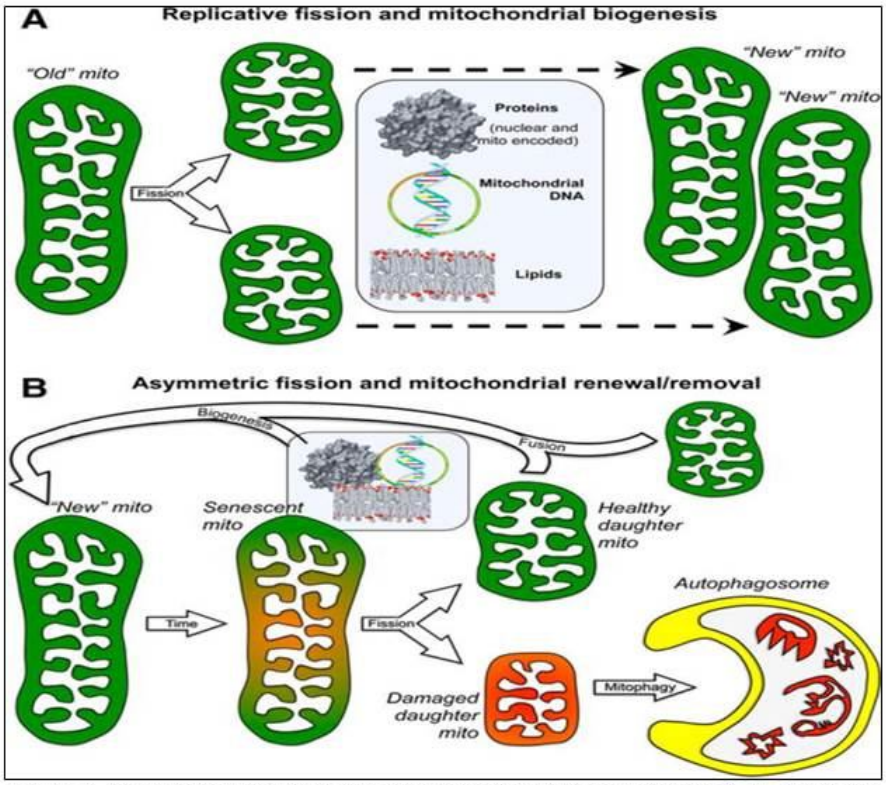


Figure 1. Consequences of replicative vs asymmetrical mitochondrial fission. A, Replicative fission of one healthy old parent mitochondrion produces 2 small healthy daughter organelles that incorporate biogenically produced protein, DNA, and lipids (central rectangle) to grow into new mitochondria. B, Asymmetrical fission of a damaged or senescent mitochondrion produces 1 healthy daughter organelle that fuses with other healthy organelles to regenerate the collective, and 1 severely damaged/depolarized (red) daughter organelle that is rapidly eliminated by autophagosomal engulfment, thereby protecting the cell from mitotoxicity and providing new recycled components for biogenic repair.

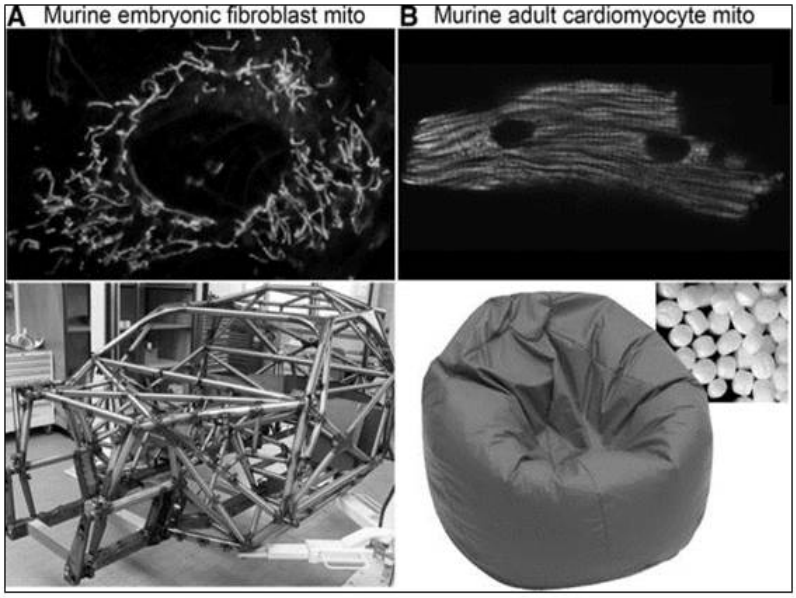


Figure 2. Structural differences between mouse fibroblast and adult cardiomyocyte mitochondria. A, Top, is MitoTracker Green stained filamentous, interconnected mitochondria of a cultured murine embryonic fibroblast; bottom, roll cage of a NASCAR racing car, specifically designed to withstand compressive forces. B, Top, Distinct individual rounded green fluorescent protein–labeled mitochondria on an isolated adult mouse cardiomyocyte; bottom, bean bag (inset shows bean structure), specifically designed to be readily and reversibly deformable.

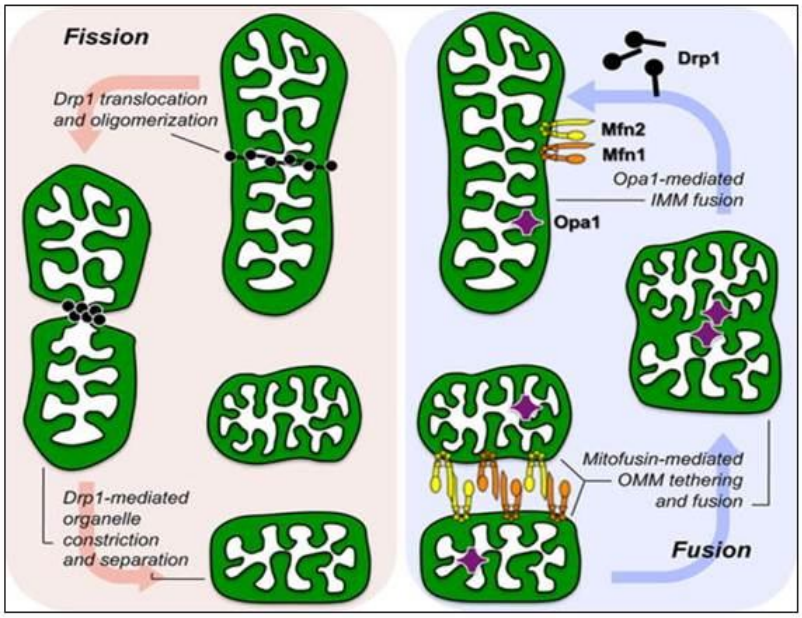


Figure 3. Molecular mechanism of mitochondrial fission and fusion. The 3 molecular drivers of fission and fusion are schematically depicted as they would be associated with a normal mitochondrion. Replicative fission (left) is initiated by recruitment of cytosolic dynamin-related protein 1 (Drp1) to the organelle, Drp1 oligomerization, and constriction of the parent into 2 daughters. Asymmetrical fission uses the same mechanism. Fusion (right) requires initial mitofusin 1 (Mfn1)/Mfn2-mediated outer membrane tethering followed by fusion, and finally optic atrophy 1 (Opa1)–mediated inner membrane fusion.

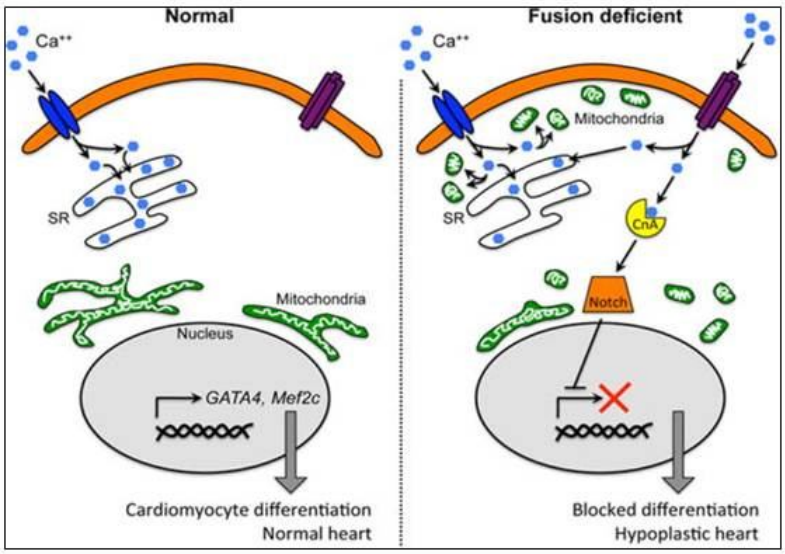


Figure 4 . Mitochondrial fusion and control of cardiomyocyte differentiation/heart development. Functional interactions between L-type calcium channels (LCC; blue), store-operated calcium channels (purple), mitochondria (green), calcineurin A (yellow), Notch (orange), and developmental gene expression as conceived in cardiomyocyte progenitor cells. Left, Normal stem cell with fused perinuclear mitochondria in which LCC calcium signaling is normal and capacitative calcium entry is low. Right, How mitochondrial fragmentation and subsarcollemmal redistribution disturbs LCC signaling through mitochondrial calcium uptake (sponge), invoking capacitative calcium entry that activates calcineurin and downstream Notch, repressing developmental gene expression.

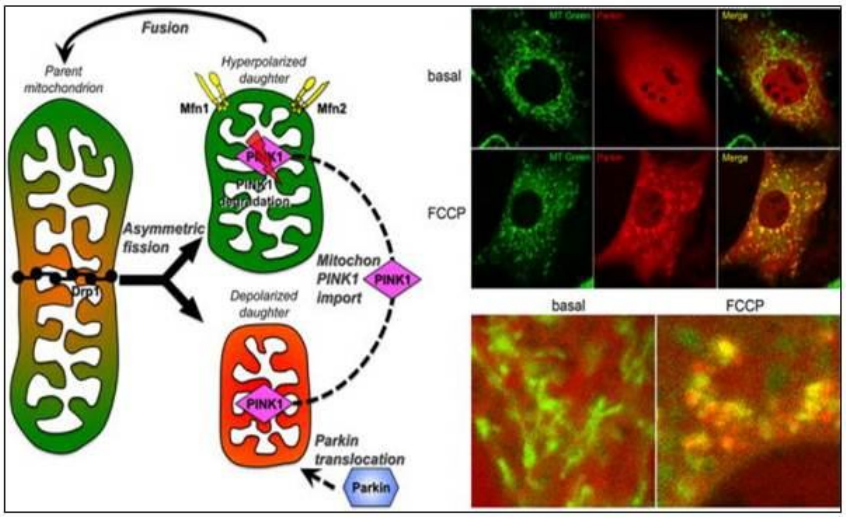


Figure 5 . The (PTEN)-induced putative kinase 1 (PINK1)-Parkin mechanism of mitophagy. Left, Schematic diagram of PINK1-Parkin initiation of mitophagy signaling after asymmetrical mitochondrial fission. Right, Confocal fluorescent images showing mcherryParkin (red) translocation from cytosol to mitochondria (MitoTracker green) after mitochondrial depolarization with the uncoupling agent FCCP. Parkin-containing mitochondria appear yellow in the merged image.

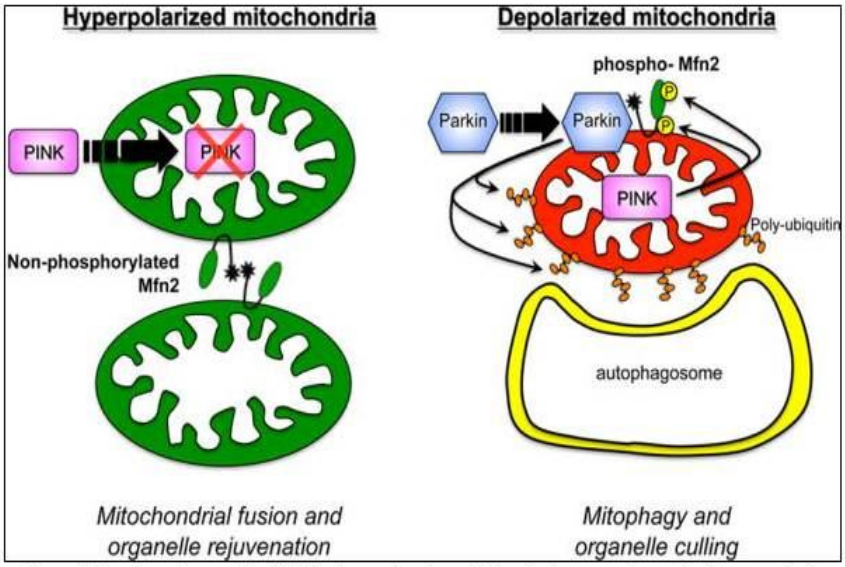


Figure6.Dual roles of Mfn2 in mitochondrial fusion and mitophagy. Left, Nonphosphorylated Mfn2 provokes tethering and fusion of normal (hyperpolarized) mitochondria. Right, PTEN-induced putative kinase 1 (PINK1)-phosphorylated Mfn2 acts as a receptor that attracts Parkin to depolarized mitochondria (in which PINK1 protein is stabilized), initiating ubiquitylation of mitochondrial outer membrane proteins that recruits autophagosomes.

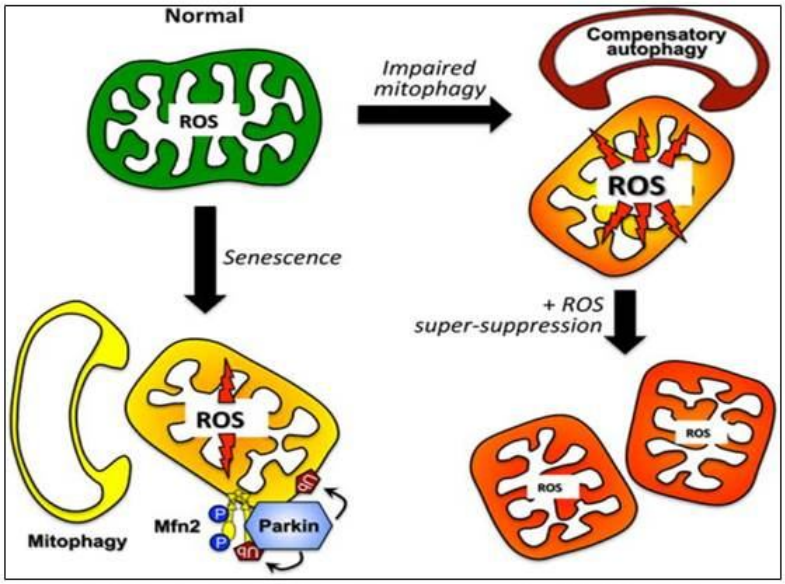


Figure 7 . Role of mitochondrial reactive oxygen species (ROS) in mitochondrial autophagy signaling. The primary mechanism for culling damaged or senescent mitochondria normally is Parkin-mediated mitophagy (left). When mitophagy is impaired, increased mitochondrial ROS acts as a signal to stimulate compensatory macroautophagy, resulting in Parkin-independent mitochondrial autophagy (right top). Supersuppression of mitochondrial ROS, as with highly expressed mitochondrial catalase, suppresses the ROS signal and compensatory mitochondrial autophagy, provoking further deterioration of the cell mitochondrial collective.

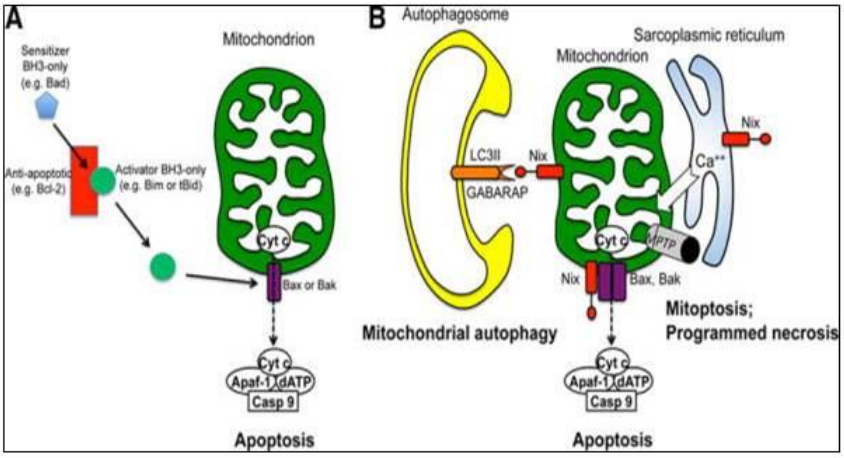


Figure 8 . Multiple roles of Bcl-2 proteins in selective mitochondrial destruction and generalized cell death. A, Bax and Bak permeabilize the outer mitochondrial membrane after they undergo conformational changes induced by the direct binding of activator BH3-only proteins Bim or tBid. Antiapoptotic Bcl-2 proteins, such as Bcl-2, sequester activator BH3-only proteins so that they are unavailable for binding to Bax or Bak. Sensitizer BH3-only proteins bind antiapoptotic Bcl-2 proteins and displace Bim and tBid. B, The conventional role of Nix as a proapoptotic BH3-only factor that facilitates Bax/Bak-mediated cytochrome c release and caspase-mediated apoptosis is shown at the bottom center. Right, SR-localized Nix increases SR calcium content and mitochondrial calcium cross talk, inducing mitochondrial permeability transition pore (MPTP) opening. When MPTP opening is selective, the result is mitoptosis, a nonmitophagic mechanism of mitochondrial culling. When MPTP opening is generalized, the cell dies from programmed necrosis. Left, Mitochondrial Nix is a receptor for autophagosomal proteins microtubule-associated protein 1A/1B-light chain 3 (LC3) and GABARAP, targeting Nix-associated mitochondria for mitochondrial autophagy.

內容：參加 2015 年 AAHRPP 芝加哥年會心得

活動日期：2015/05/19-21

活動名稱：美國人類研究保護計畫認證協會 (AAHRPP)

活動地點：美國芝加哥希爾頓飯店

彰基一直以來相當重視參與研究的受試者安全與權益，本院在研究倫理審查方面，很早就陸續通過了國內外的評鑑，但為了讓彰基的受試者保護機制更加完善，在院方的全力支持，與團隊的努力之下，彰基已於今年(2015 年)3 月順利獲得完全通過的認證(full accreditation)。

AAHRPP 今年的年會在芝加哥舉辦，長官指派人體試驗委員會蘇矢立醫師、黃淑萍藥師、陳書毓督導長與受試者保護辦公室陳彥宇醫師共四位代表彰基參與。與會的目的，除了代表彰基接受認證的通過，更能進一步了解人體研究受試者保護最新的訊息。此次參與年會的國內醫院代表還包括台大醫院何弘能副院長(現為台大醫院院長)、長庚醫院謝燦堂副院長、中國醫藥大學的林正介副校長等帶領的團隊、台北榮總、雙和醫院團隊及財團法人醫藥品查驗中心副執行長林志六醫師等，一行 25 人來自台灣，三天的時間彼此做了很好的交流與學習。

與往年一樣，三天的會議，第一天主要介紹 AAHRPP 的發展、目標、及評鑑的流程，雖然重點在如何準備評鑑，但提示的內容亦是人體受試者保護的核心價值。第二天與第三天的會議，內容涵蓋相當全面，特別強調的主題包括知情同意、順從性、社會與行為研究、人體受試者保護計畫之品質改善、利益衝突、生物資料庫、大數據研究、臨床試驗、兒童研究之爭議議題、受試者同意之免除或彈性，中間穿插 AAHRPP 評鑑要求的標準解讀及如何去達成這些要求的標準，會議中也列出了各個機構在評鑑各個階段與實地訪查時(site visit)常見的缺失，讓大家互相學習。內容有相當的深度，已有實務經驗的相關人員可從中得到不少收穫。

臨床醫學研究日新月異，進幾年進展相當的快速。但我們由過去全球的許多研究案例了解，受試者有可能在研究的過程中受到傷害，其發生的原因包括研究設計不當、易受傷害族群的保護不周、研究人員的利益衝突、研究人員的不遵從...等。臨床研究的目的為產生對人類有貢獻的知識，出發點多為良善，但為了保護參與研究的受試者，及確保研究的科學性與完善性，目前國際上已制定了許多的研究倫理準則與法規，規範涉及到人類受試者的生物醫學研究在進行之前，需要經過人體試驗委員會或倫理委員會的審查，以確保研究的科學性與倫理性、及受試者的保護是完善的。

鑑於現今研究的複雜性更勝以往，受試者的風險因而提高，加上資訊的發達、個人隱私的著重、種種繁複的法規，不論是研究人員或是審查委員，所面臨的挑戰日益加重。我們需要有一個完整的受試者保護計畫與政策，才能提供受試者完善的保障，並確保研究的完整性。唯有審查人員素質的不斷提升，才能避免不必要的過度審查所造成的曠日廢時及資源浪費。

圖一、人體試驗委員會行政中心蘇矢立主任代表彰基接受AAHRPP執行長Elyse I. Summers頒發全面認證通過證書

圖二、 AAHRPP全面認證通過證書

圖三、與AAHRPP執行長Elyse I. Summers合影

圖四、參加AAHRPP會議的彰基代表：由左而右依序為黃淑萍藥師（人體試驗委員會行政中心副主任）、陳彥宇醫師（受試者保護辦公室主任）、蘇矢立醫師（人體試驗委員會行政中心主任）、陳書毓督導長（彰基護理部）、黃睦升組長（鹿基復健科）

圖五、與參加AAHRPP會議的台灣各醫院代表合影

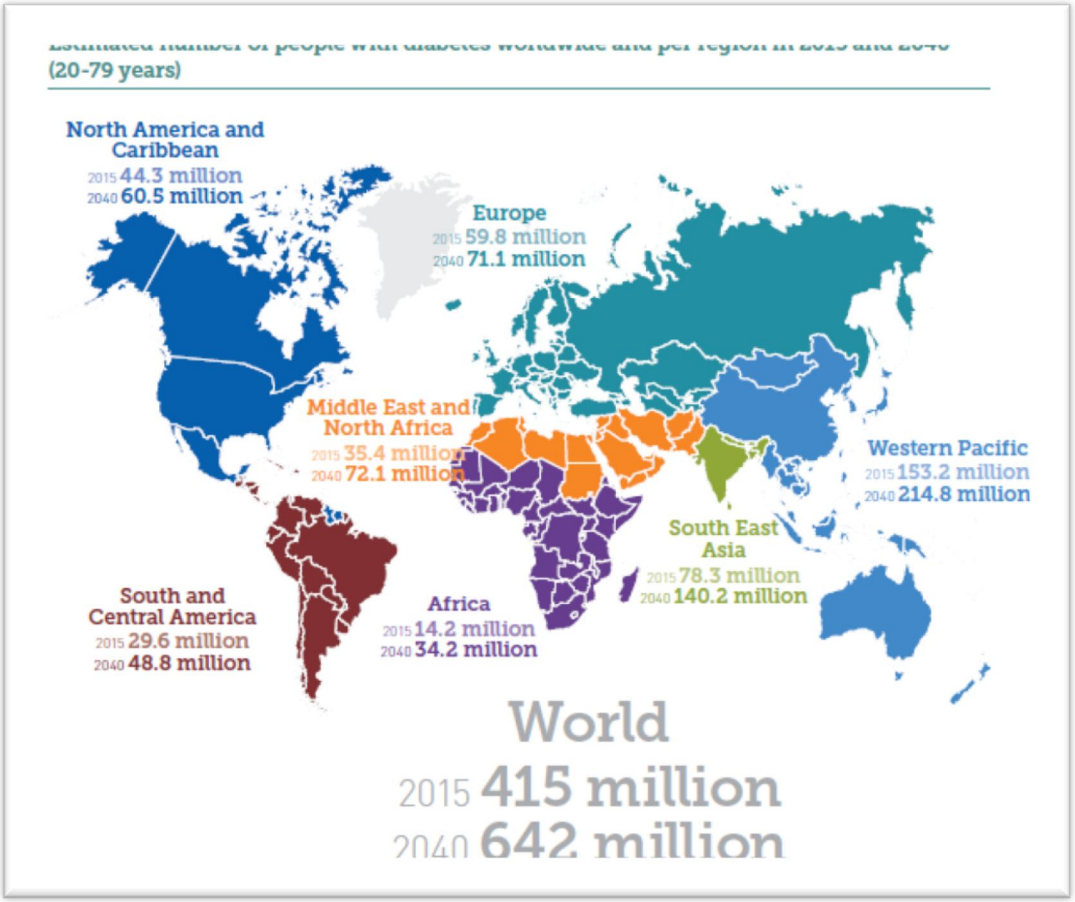
內容：參加 2015 年世界糖尿病聯盟會議分享

活動日期：2015/11/30-12/04

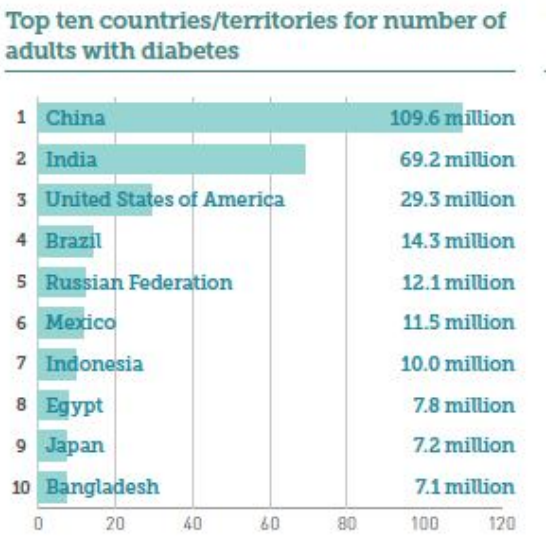
活動名稱：國際糖尿病聯盟(international diabetes federation)會議

活動地點：加拿大溫哥華

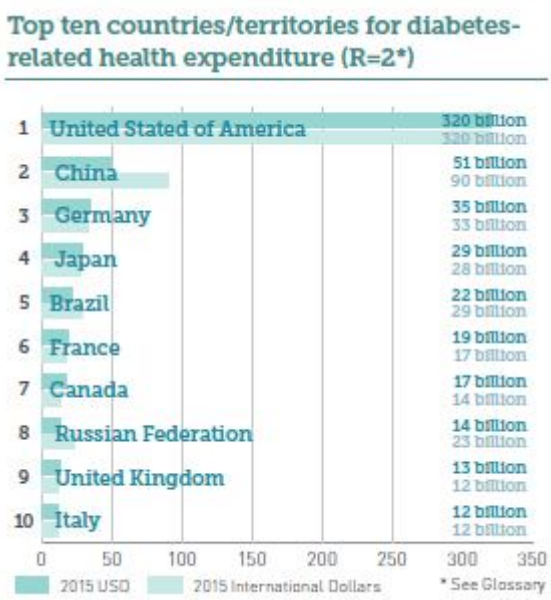
2015 年 11 月 30 日到 12 月 4 日在加拿大溫哥華舉辦的二年一次的國際糖尿病聯盟(international diabetes federation)會議，第一個重頭戲是發表全球最新的糖尿病狀態，依 IDF 糖尿病圖鑑(diabetes atlas) 第 7 版所述，2015 年全球每 11 人中就有 1 人罹病約 4.15 億人，預估到 2040 年會有 6.42 億人，換言之，每 10 人即有 1 人。更糟的是，被診斷出來的個案與未診斷的個案數預估是相同，質言之，上述的個案數需貿乘 2。



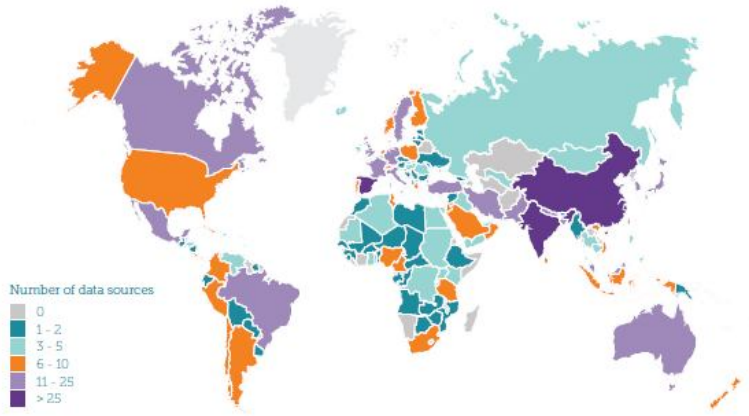
其中貢獻最多自然是擁有世界人口數較多的中國與印度，西太平洋區域的其他國家如印尼、日本也共襄盛舉。這二區的糖尿病數就佔了全球的一半，全球病患數的排名如下。



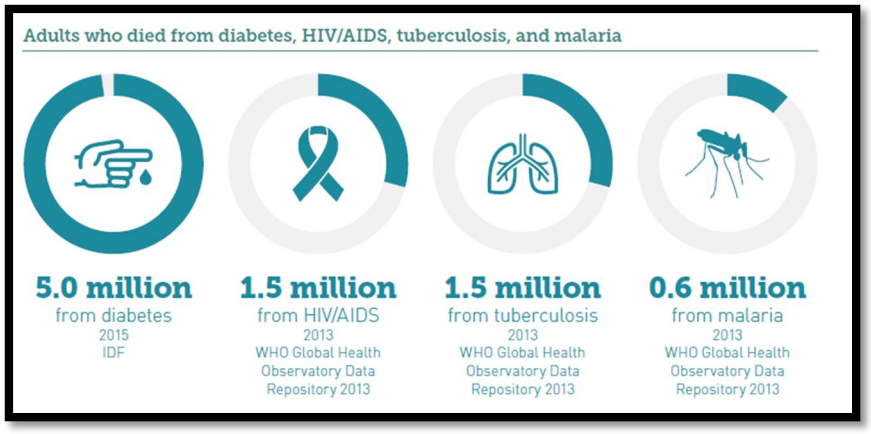
各國對抗糖尿病所投入的經濟總值排行則如下，約佔全球醫療支出的 12%。



有個比較新的呈現圖是將糖尿病及葡萄糖耐受性不良的盛行率合併計算的世界分佈圖。臺灣呈現的是較高的紫色系。



而 2015 年死於糖尿病的人數大約有 500 萬之眾，遠多於一些法定的傳染病，如愛滋、肺結核或瘧疾的死亡個數之總合。



有一個特別的主題為”糖尿病的精神醫學觀(psychological aspects of diabetes)”，值得我等加以慎思。

依據美國的統計大約有 1/3 的糖尿病患者有憂鬱症的困擾，相反的；憂鬱症患者得到糖尿病的機會是一般人的 2 倍。如同過去所知當有這二個共病在一起時，容易出現 1）治療的遵從性會降低，2)易高血糖，3)增加了醫療費用，4)增加了併發症，5)認知能力下降，6)死亡率增加等。造成社會家庭及個人很重的經濟及心理的負擔。

二者共病可能的原因有 1)人類年齡增長， 2)現代醫學進步，存活能力的改變，3)微弱的傳統人際關係，4)社會多元發展，造成輕忽，5)學習自失照料的能力減退，6)長期倦怠乏力。使得二種疾病交互影響造成臨床治療的難度增加，效益不彰，進而失去動力，陷入惡性循環裏。

自 2012 年起已有 50 多個國家加入了”糖尿病與憂鬱症的對話 (dialogues on depression and diabetes)”的計劃，透過填寫問卷調查、訓練專業人員、訂定治療準則...等方法，希望能有抑制的功效，歐美、亞洲及非洲的醫師、護理師、心理師及政府人員都參與了這樣的訓練課程，雖然台灣目前沒有參加此一計劃，但有志之士及相關的學會，需要及早的面對與處理。

如對本中心或發行之電子報 有任何疑問，或欲分享您專業領域之科學新知。
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