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締脂素與非酒精性脂肪肝疾病

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摘　要

現已知非酒精性脂肪肝疾病 (nonalcoholic fatty liver disease, NAFLD) 與肥胖、第二型糖尿病、胰島素抗性等病徵在流行病學上有極高相關性，且非酒精性脂肪肝疾病也被認爲是代謝症候群的肝臟病理表現。最近的研究指出締脂素 (adiponectin) 除原本已知與胰島素抗性的產生有顯著關聯之外，締脂素在非酒精性肝疾病甚至是進一步演變成非酒精性肝炎的致病機轉上，也扮演重要的角色；因此我們相信若再進一步釐清締脂素與非酒精性脂肪肝炎產生之間的因果關係，在未來對非酒精性脂肪肝炎的預防和治療上將有很大的助益。

關鍵詞：非酒精性脂肪肝疾病 (Nonalcoholic fatty liver disease, NAFLD)
非酒精性脂肪肝炎 (Nonalcoholic fatty liver steatohepatitis, NASH)
胰島素抗性 (Insulin resistance)
締脂素 (Adiponectin)

前言

脂肪肝依其成因大致可分爲：非酒精性脂肪肝疾病 (nonalcoholic fatty liver disease, NAFLD) 與酒精性脂肪肝疾病 (alcoholic fatty liver disease, AFLD)；在西方國家NAFLD已是除了病毒感染所致肝炎之外造成慢性肝炎的主因[1,2]，其更與肥胖[3,4]、第二型糖尿病[4,5,6,7]、高血脂[6,7,8,9]及胰島素阻抗性[10]等典型的代謝症候群特徵有極高相關連性，非酒精性脂肪肝疾病也因此被認爲是代謝症候群的典型肝臟表現[11]。體內脂肪細胞所分泌的荷爾蒙---締脂素 (adiponectin)，現已是用來評估代謝症候群與胰島素阻抗的生化指標[12,13]，最近的研究指出締脂素與NAFLD所導致肝臟受損的成因有關。本文中就整理回顧最近有關締脂素在非酒精性脂肪肝病變的形成中所扮演的角色的相關文獻，希望能提供臨床相關診斷和治療的參考。

非酒精性脂肪肝疾病與非酒精性肝炎

在臨床上，NAFLD 其範圍可從非演進性的單純脂肪肝[14]到演進性的非酒精性脂肪肝炎 (nonalcoholic fatty liver steatohepatitis, NASH)，而後者最終會演變爲肝硬化、肝衰竭或是肝腫瘤[15,16]。在西方國家中，NAFLD 的發生率約是 20%，而NASH 爲2-3%[17,18]。

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我們要先排除其它可能造成肝炎的因素，如：酗酒、病毒感染或是其它代謝疾病之後，再加上肝臟組織學切片的証實後，才可診斷爲NASH；而在顯微鏡下其典型的病理學特徵，包括有大囊泡狀脂肪變性、急慢性發炎細胞混合侵潤及出現麥格氏小體(Mallory body)，而大部份檢體有程度不一由第三肝區發展而來的中央—門脈及門脈--門脈橋樑樣的纖維化[19]，Matteon等學者更明確將NAFLD分成4種型式：第一型爲單純的脂肪變性、第二型爲脂肪變性加上發炎反應、第三型爲脂肪變性加上空泡樣退化、第四型則爲脂肪肝加上纖維化或併有麥格氏小體，而第三型與第四型可視爲NASH，在這二型中其相關死亡率有增加現象[20]。由NAFLD演進爲NASH的確切致病機轉現今還不是很明確，最被接受的是與胰島素抗性相關[21]由Day和Janes等學者所提出的”二次打擊假說”[22]。

第一擊：由於體內產生胰島素抗性，使得週邊組織脂解作用增加，合併有肝內脂肪聚積與脂肪變性，在許多NAFLD的病人中，過多的脂肪堆積起因於細胞內粒腺的β氧化作用受損與極低密度脂蛋白合成減少所致[23]，以致無法有效清除肝內所堆積的脂肪。

第二擊：有了脂肪堆積及變性後，若再加上遺傳因子，鐵過量，粒腺體功能不佳與營養中元素缺乏等因素，使脂質氧化及過氧化作用增加，進而使氧化應力增強，就會造成肝臟發炎、老化、硬化等結果。

脂肪組織與NASH之關聯

人體內的脂肪組織，除可以儲存脂肪之外，現也被視爲是一種內分泌器官。隨著體內脂肪組織量的增加與脂肪細胞的分化，脂肪細胞也產生多種激素，如瘦體素(leptin)[24,25,26]、抗胰島素激素(resistin)[27,28,29,30]、血管張力素(angiotensin)[31,32]、腫瘤壞死因子α(tumor necrosis factor α, TNF-α)[33,34,35]與游離脂肪酸(free fatty acid)[36,37]等，但相反的，脂肪組織中締脂素的分泌卻是減少。

在NAFLD的病人，人體血中leptin濃度是增加的[24]，leptin與後續肝臟的纖維化有關聯[25]。而在有胰島素抗性時，血中resistin濃度也會上升[27,28,29,30]，但這二種激素的作用是否經由產生胰島素抗性進而影響NAFLD病程仍是未知。此外，以第二型血管張力素拮抗劑治療同時患有高血壓與NASH的病人，除可以降低血液中轉化生長素-β1(transforming growth factor-β1, TGF-β1)濃度，也可以改善NASH病人的肝指數與肝臟纖維化的程度，但血管張力素與NASH形成機轉中所扮演的角色仍需進一步釐清[32]。研究報告亦指出血液中腫瘤壞死因子α的濃度在NASH病人體內是增加的，腫瘤壞死因子α與胰島素抗性的產生[38,39]，粒腺體的細胞通透度及功能的改變[40,41,42]，促使細胞凋亡等有關[43]。在肥胖與NAFLD病人體內，其血液中締脂素濃度有明顯降低的情形[44,45]，最近的研究發現締脂素可以增加肝臟脂肪分解作用與清除率，改善全身胰島素抗性[46]，抑制肝臟葡萄糖新生作用[47]，而在動物實驗中外源性的補充締脂素可明顯改善脂肪肝情形[48]，這些結果皆指出締脂素在NAFLD與NASH可能扮演重要角色。

締脂素及其生理作用

締脂素是由體內脂肪細胞所分泌30-kDa大小的荷爾蒙[49,50]。部份剛分泌的整段締脂素在經體內水解作用之後，所形成球型小單位的締脂素就進入血液之中，進而到達其作用處。直到2004年，兩種不同結構的締脂素接受器才被進一步分離出來[51]。第一型締脂素接受器是對球型小單位的締脂素有較高的親和度，但對完整整段締脂素親和度較弱，但第二型締脂素接受器對此二型締脂素皆只有中等的親和度，而第一型締脂素接受器主要表現於骨骼肌，而第二型締脂素接受器主要分佈於肝臟。

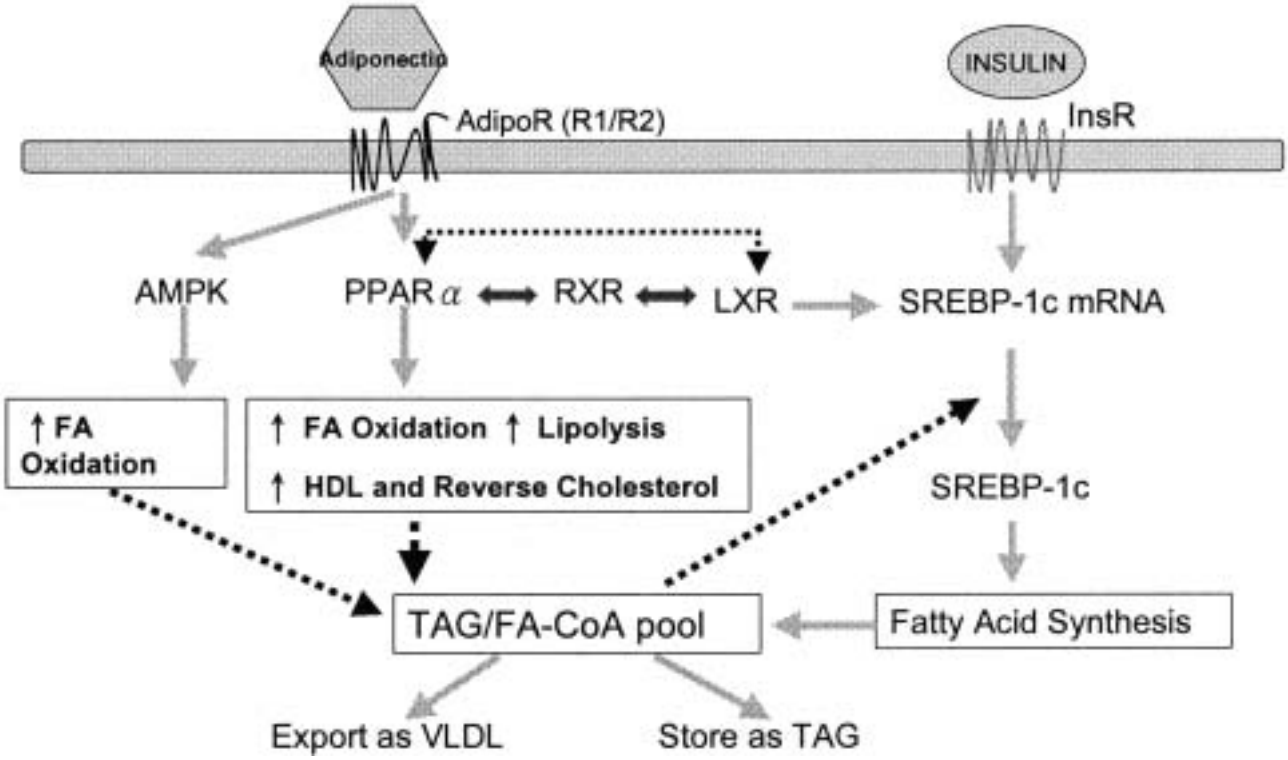
締脂素與腫瘤壞死因子α(tumor necrosis factor α, TNF-α)有類似的分子結構，但其在體內的生理學作用卻是完全不同的。無論在離體或是活體研究都指出，在某些特定的組織，締脂素與腫瘤死因子α在功能上是互相拮抗的[52]。舉例而言，腫瘤死因子α可導致胰島素阻抗可與血管粥狀硬化的形成[53]，但締脂素卻可以改善組織胰島素的敏感性[28]並有抗血管粥狀硬化特性[54,55]。而在肌肉細胞更可以發現兩者之間有明顯且直接

的對抗作用，彼此間會影響對方在肌肉細胞內醣類與脂質代謝的作用[28]。締脂素非但可抑制巨噬細胞功能[56]，也可藉由活化環磷酸腺蛋白酶(cyclic adenosine monophosphate dependent protein kinase, AMPK)與細胞核因子-κB (nuclear factor-κB, NF-κB)等不同路徑而產生抗發炎的作用[57]。

締脂素與NASH

近年來許多研究皆在探討NASH的發炎過程中，各種發炎介質所扮演的角色。Cai等學者以特種轉殖的蒼鼠作研究後，證實過量脂質堆積在肝臟後，的確產生亞急性的肝臟發炎反應，其機轉主要在於活化細胞內細胞核因子-κB及進而產生多種後續如介白質-6(IL-6)，介白質-IB(IL-1B)與腫瘤壞死因子α等發炎介質所致。此種發炎反應進而會產生肝臟與全身性胰島素抗性[58]。而Hui在分析臨床上109位NAFLD的病人後發現，NASH的病人與單純脂肪肝病人相較，其體內胰島素抗性明顯較高，但血液中締脂素濃度反而明顯偏低[48]。若再進一步比較NASH，單純脂肪肝與控制組三組病人，其各組病人體內締脂素皆有顯著差異；因此，學者們就推論除了先前認爲的胰島素抗性之外，低締脂素血症(hypoadiponectinemia)與NASH的形成有關。

Masaki等學者發現，原本在KK-Ay小鼠體內注入內毒素會引起肝臟發炎受損的情形，會因爲給予締脂素前處理獲得改善，其原因在於締脂素會降低肝臟內腫瘤壞死因子α的表現與作用[59]。Xu等學者以肥胖ob/ob小鼠作爲研究對象，結果發現在給予外源性締脂素後，小鼠肝內所產生腫瘤壞死因子α與多種發炎介質，濃度皆受到明顯抑制，而小鼠體內的肝臟腫大，脂肪肝與高肝指數等症狀皆有明顯改善[49]。Kamada等學者以締脂素基因剔除的小鼠和其對照組作比較，二者在皆給予四氯化碳所產生的肝臟發炎及纖維



圖一：肝臟肝細胞內脂肪代謝圖。胰島素與細胞膜上接受器結合後會藉由轉錄因子SREBP-1c促使肝臟內脂肪合成，LXR與RXR結合後也可促使脂肪合成。締脂素與細胞膜上接受器結合後會活化胞內AMPK與PPAR-α路徑，後者另會與RXR結合，調控核內轉錄步驟，進而氧化分解與清除肝臟內的脂肪酸。→ 代表促進作用，⇢ 代表抑制作用。(縮寫: AMPK, cyclic adenosine monophosphate dependent protein kinase; LXR, liver X receptor; PPAR-α, peroxisome proliferation activated receptor - α; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element binding protein-1c)

化情形，前者明顯較爲嚴重，但可在利用腺病毒(adenovirus)轉殖締脂素基因治療後獲得改善，其原因在於肝臟內主司發炎的星狀細胞所釋出的發炎介質與活性都受到抑制[60]。由這些研究結果，學者們推論締脂素可藉由抑制發炎介質如腫瘤壞死因子α或是其它的方式減少肝臟發炎與纖維化的情形，後續許多的研究也支持此一論點。

另已知肝臟中脂質的代謝，主要受兩種位於細胞核上接受器-肝臟X型接受器(liver X receptor, LXR)與過氧化物酶增殖體啓動受體(peroxisome proliferation activated receptors, PPARs)影響調控，而二者間也有互相拮抗作用[61]。前者活化後會藉由影響細胞核內轉錄因子－固醇調節區域結合蛋白-1c(sterol regulatory element binding protein-1c, SREBP-1c)與碳水化合物反應元素結合蛋白質(carbohydrate response element binding protein, ChREBP)，增加與脂質合成相關(fatty acid synthase, FAS)與(acetyl CoA carboxylase)的基因表現[62,63,64]。近來的研究結果指出，締脂素也可藉由活化PPARs及依賴於cAMP的蛋白激酶A(cyclic adenosine monophosphate dependent protein kinase, AMPK)來調控肝臟內脂質的代謝與發炎反應[51,65]。PPAR-α主要分佈於肝臟，這些接受器在活化後，會與細胞核中的視網酸接受器X(retinoid X receptor, RXR)結合，調控核內轉錄步驟[66]，調控肝臟內脂肪結合蛋白(liver fatty acid binding protein)、肝臟乙醯輔酶A羧化酶、細胞色素P450(cytochrome P450)、微粒體內三酸甘油脂移轉蛋白(microsomal triglyceride transfer protein)、脂蛋白B100(apolipoprotein B100)等蛋白質，進而氧化分解與清除肝臟內的脂肪酸[67,68,69,70,71](如圖一)。現已知有PPAR-α，PPAR-γ與PPAR-δ(先前命名爲PPAR-β)三種不同接受器。而PPAR-γ主要分佈於身體的脂肪組織，其可以促進週邊脂肪組織內脂肪酸的合成，脂肪細胞的分化與改善胰島素抗性[72]。

有其它研究也指出締脂素可降低肝臟細胞上CD36的表現，進而減少脂肪酸運送至肝內。但總結迄今的相關臨床研究，仍無研究發現肝臟發炎與肝硬化的程度與血液中締脂素濃度間的關聯性，也無法排除在NASH病人體內的低締脂素血症是否儘是續發於肝臟發炎受損後的表現，這依賴進一步大規模的研究來釐清。

NASH的治療

現今最主要非藥物治療NASH的方式，仍是減少外源性脂質攝取，以及儘可能消耗肝內堆積的脂質。有計劃逐步式的減重，才可以改善肝臟組織學上的脂質堆積與降低生化檢查上的肝指數[73]，相反的，但過於快速的減輕體重，反而會產生肝臟纖維化、膽汁淤積與局部組織的壞死[74,75]。此外值得一提的是，低糖的飲食比低脂飲食更可以降BMI[76]。

至於藥物治療，現今仍無標準治療NASH的原則，臨床上許多有治療潛力的藥物如服用熊脫氧膽酸(Ursodeoxycholic acid, UDCA) 10-15 mg/kg/day可以改善NASH病人的肝指數[77,78,79]。也有較小規模研究指出若給予甜菜鹼(betain) 20 g/day的劑量治療持續1年，會因增加體內s-腺核甘甲硫胺酸(s-adenosylmethionine)的濃度進而改善組織學上肝臟發炎反應與較高肝指數的程度[80]。在實驗上維生素E(vitamin E)是極有潛力的抗氧化劑，尤其是在對抗細胞膜脂質的過氧化反應，因此有研究也試用維生素E 400~1200 IU/days的劑量治療，其結果也能改善血清中過高的肝指數[81]；而glutathione的前趨藥物乙醯半胱胺酸(N-acetylcysteine)，在臨床試驗時也的確可以保護肝臟對抗氧化反應並降低肝指數[82]。

現今臨床上已有使用PPAR-α agonist(如弗尼利脂寧，fenofibrate)來治療高血脂血症與PPAR-γ agonist(如愛妥糖，pioglitazone與梵帝雅, rosiglitazone)來治療第二型糖尿病病人，改善體內胰島素抗性。Harano等學者發現若以fenofibrate持續治療自發性脂肪肝動物實驗模式(fatty liver Shionogi mouse)十二天，可改善脂肪肝與肝臟內脂肪過氧化作用[83]。Tiikkaie等學者發現使用rosiglitazone治療十六週後，非但可以改善第二型糖尿病病人體內胰島素抗性與脂肪肝的情形，體內血清中締脂素的濃度也明顯上升[84]。Promrat等學者也證實以pioglitazone治療NASH病人48週後，發現這些病人非但胰島素抗性有改善，連同組織學與血清學上肝臟發炎情

形皆獲得改善[85]。可知補充PPARs agonist或是締脂素或許是日後治療NASH上的新選擇，但仍須日後進一步大型的研究來驗證。

結論

如何避免原本NAFLD的病人進一步演變爲NASH甚至肝硬化的產生是現今一個重大的健康問題[86]，在日後若仍更一步釐清血清中締脂素與NASH病人體內肝臟發炎的因果關係及相關致病機轉有進一步瞭解，或許日後締脂素及締脂素激動劑(adiponectin agonist)亦具有治療NAFLD與NASH病人的潛在開發價值。

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Adiponectin and Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is associated with obesity, type II diabetes mellitus, insulin resistance and is considered as hepatic manifestation of metabolic syndrome. A strong association exists between adiponectin and metabolic syndrome. Besides insulin resistance, adiponectin is linked with pathobiology of NAFLD and also plays an important role in the pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH). We believed that in the future, adiponectin may have potential roles in the diagnosis, follow-up or treatment of NASH.
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