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Betatrophin 在非酒精性脂肪性肝病发病中的研究进展

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[摘 要] 非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)是肝功能障碍最常见的原因之一，与肥胖和代谢紊乱高度相关。然而肝脂肪变性的发病机制十分复杂，尤其是肝细胞和肝细胞因子之间的相互作用尚未完全阐明。促代谢因子或者血管紧张素蛋白8(又称Betatrophin)作为新型的肝细胞因子，其通过调节三酰甘油(TG)代谢、胰岛素抵抗(insulin resistance，IR)和炎症，参与NAFLD的形成。

[关键词] 非酒精性脂肪性肝病；Betatrophin；肝细胞因子

Novel insights into the betatrophin in pathogenesis of non-alcoholic fatty liver disease

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Abstract Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent causes of hepatic dysfunction and is highly correlated with obesity and metabolic disturbance. The complex pathogenesis of NAFLD, especially the interaction between hepatocytes and hepatokines has not been fully elucidated. Betatrophin, as a novel hepatokines, are likely to be involved in the pathogenesis of NAFLD via modulating triglyceride metabolism, insulin resistance and inflammation.

Keywords non-alcoholic fatty liver disease; betatrophin; hepatokines

非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)是一种以超过5%的肝细胞中异位脂肪[主要是三酰甘油(triglyceride，TG)]的积累为主要病理改变的临床综合征[1]。随着肥胖的流行，NAFLD患病率显著增加，已成为世界公共卫生难题。然而NAFLD具体的发病机制仍不清楚，对NAFLD发病机制及防治策略的研究具有重要的理论和现实意义。因此，本文就新型的肝细胞因子Betatrophin与NAFLD的关系作一综述。

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1 Betatrophin 概述

促代谢因子或者血管紧张素蛋白8(又称Betatrophin)是一种受营养状态调节并主要由肝分泌的可溶性蛋白[2-4]。Betatrophin因其能促进胰岛β细胞的增殖而得名[5]。尽管后续研究[6]发现Betatrophin并不能改善小鼠胰腺β细胞功能和糖耐量，但在体外实验[3,7]中，Betatrophin仍被证明受胰岛素调节并可以增强肝细胞的胰岛素敏感性。Betatrophin因其缺乏纤维蛋白原样结构域，且只具有N端卷曲螺旋结构域，成为血管紧张素家族ANGPTL的特殊成员并影响TG代谢[8-10]。Betatrophin在棕榈酸处理的HepG2细胞、db/db小鼠和高脂饮食小鼠的肝组织中高表达[11]。然而缺乏Betatrophin的小鼠由于脂蛋白水解酶(lipoprotein lipase，LPL)活性增加导致血浆TG清除率增加，因此表现出较低的TG水平[12-13]，说明Betatrophin是调节小鼠肝糖脂代谢的重要代谢性因子。

大部分的临床研究[14-18]显示：NAFLD及患者的血清Betatrophin水平增加，且与胰岛素抵抗(insulin resistance，IR)和肝TG蓄积程度相关[11,15]。Cengiz等[19]研究发现血清Betatrophin水平在肝脂肪变性、甚至纤维化程度更严重的NAFLD和非酒精性脂肪性肝炎(non-alcoholic steatohepatitis，NASH)患者中下降。在这种情况下，大量炎性细胞因子释放，导致Betatrophin的低表达。考虑到TG升高和IR都能引起Betatrophin升高，因此有2个疑问：增加Betatrophin水平究竟是由肝脂肪积累引起的，还是继发于NAFLD中胰岛素敏感性的降低；Betatrophin是作为一种致病因子促进NAFLD的形成，还是作为保护性因子增强胰岛素敏感性，继而阻止NAFLD的进展。

2 Betatrophin 作为 NAFLD 的恶化因素

2.1 Betatrophin 促进肝脂肪变性

在NAFLD的早期阶段的特征是肝细胞内过量的TG沉积，而肝TG的积聚是合成与分解失衡的结果。在HepG2细胞中，下调Betatrophin表达可以减轻肝细胞TG沉积[20]。类似的，Betatrophin缺陷小鼠可以抵抗高脂饮食诱导的肝脂肪变性[21]。Betatrophin促进TG在肝蓄积主要通过3个方面：1)减少餐后血清TG清除；2)促进TG的合成；3)抑制TG分解。Betatrophin可以和ANPTL3的N-末端形成复合物，协同抑制心脏、骨骼肌餐后LPL活性，阻止TG向脂肪组织运输[22]。另一方面，Betatrophin还可以通过上调肝脂肪酸合成及摄取相关基因的表达[23]，下调脂质分解代谢基因ATGL的表达[24]，加重肝TG积累。

2.2 Betatrophin 促进肝胰岛素抵抗

IR依然是NAFLD发病机制的中心环节，同时也是促发NAFLD向NASH进展的始动因素。此外，NAFLD本身又可能诱发及加重IR，引起恶性循环[1]。Betatrophin可以损害胰岛素敏感性。IR的诱导剂S961可以显著上调Betatrophin的表达[3]。然而，二甲双胍可以激活AMPK信号通路，从而减少Betatrophin的蛋白及mRNA表达水平[25]，改善胰岛素敏感性。利用第2代反义寡核苷酸(ASO)技术拮抗成年小鼠Betatrophin表达可以增强胰岛素敏感并改善糖耐量[21]。在IR状态下，Betatrophin既可以调节自噬过程加强TG分解代谢[26]，还可以上调脂肪组织FATP4和ATGL的表达直接促进游离脂肪酸的分泌及TG动员[23]。增强的TG分解导致升高的游离脂肪酸及DAG水平，从而激活PKCε损害肝胰岛素信号转导。

3 Betatrophin 作为 NAFLD 的保护因素

3.1 Betatrophin 改善脂肪组织 IR

尽管多数研究表明Betatrophin可以加重IR，但也有一些与之相悖的研究。在脂肪组织中，侵入脂肪组织中的巨噬细胞和肥胖组织分泌的炎症因子可严重干扰胰岛素信号传递导致IR，最终引起NAFLD。最近有研究[27]表明：通过给肥胖小鼠尾静脉注射Betatrophin过表达病毒，可以减轻脂肪组织炎症因子的释放并促进抗炎型巨噬细胞的表达，从而改善小鼠血糖水平。除通过减轻脂肪炎症改善IR外，Betatrophin还可以通过直接促进胰岛素受体底物-1的磷酸化，促进糖原合成和抑制糖异生等途径增强胰岛素敏感性[28]。

3.2 Betatrophin 减轻脂肪组织炎症

NAFLD的进展涉及“多重打击学说”，例如氧化应激诱导的线粒体功能障碍，内质网应激，内毒素诱导，TLR4依赖性炎性细胞因子释放和铁超负荷等。这些有害因素导致许多信号级联的触发，导致炎症通路的激活[1]。研究[11,24]表明：内质网应激诱导剂衣霉素，组氨酸缺乏诱导的应激反应，以及LPS诱导的TLR受体的激活都可以显著促进肝细胞内Betatrophin的表达。这些损伤导致炎症因子TNF-α浓度升高进一步促进Betatrophin表达，

然而升高的Betatrophin通过抑制NF-κB炎症信号通路减少炎症因子的释放[29]。说明Betatrophin可能通过减轻肝脏炎症，阻止肝脂肪变性向脂肪性肝炎进展。

4 Betatrophin 在肝关键的调节通路

4.1 Insulin/LXRα/SREBP-1c 通路

肝X受体α(LXRα)是介导肝脂肪生成，活化的主要代谢性核受体，其在餐后状态可以由胰岛素激活，并进一步诱导下游甾醇调节元件结合蛋白-1c(SREBP-1c)转录因子表达，从而促进肝TG生成。据研究[2]报道：Betatrophin和LXRα有相似的表达模式，都可以被高浓度的胰岛素、游离脂肪酸和葡萄糖诱导。不仅如此，胰岛素还可通过特异性激活LXRα促进肝细胞Betatrophin的表达[25]，从而调节餐后LPL活性。因此，Betatrophin对餐后TG的调控作用可能依赖Insulin/LXRα/SREBP-1c信号通路。

4.2 维生素 D 受体通路

虽然肥胖和糖尿病是众所周知的NAFLD代谢风险因素，25-羟基维生素D3缺乏也被报道与NAFLD进展相关。25-羟基维生素D3可以激活肝细胞维生素D受体(VD receptor，VDR)，促进NAFLD早期的TG积累[30]。研究[20]发现：Betatrophin和VDR都在NASH患者中表达升高，激活的VDR上调Betatrophin表达，导致人肝细胞中TG的积累。因此，VDR信号通路可能介导了Betatrophin在NAFLD中的作用。

4.3 Ras/Raf/MAPK 通路

ERK1/2信号通路是最早发现的MAPK家族成员，主要参与细胞的增殖、分化、凋亡等过程。在IR及应激等条件下，蛋白激酶C或Ras被激活，从而诱导Raf的磷酸化，最终导致磷酸化的ERK1/2激活。研究[24]显示：在应激状态下，激动的RAS/RAF/MAPK通路可以诱导Betatrophin的产生；同时Betatrophin可以上调表皮生长转录因子Egr1，后者反过来抑制ATGL的活性。

5 结语

Betatrophin作为NAFLD发病中的争议性因子，当Betatrophin作为NAFLD的致病因素时，高卡路里饮食和高浓度的25-羟基维生素D3可以持续激活insulin/LXR/SREBP1-c和VDR信号通路，导致高Betatrophin血症，继而其通过调节TG代谢和加重IR导致NAFLD的发生。当升高的Betatrophin作为NAFLD的保护性因子时，高循环胰岛素和代谢性应激反应都可诱导Betatrophin代偿性表达增加，通过抑制炎信号通路和增强胰岛素信号转导阻止NAFLD的进展。需要进一步的实验探索Betatrophin激活的方式，以及其对的内质网应激、氧化应激的作用，以明确Betatrophin与NAFLD的关系。

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