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Toll样受体在代谢相关脂肪性肝病中的基础研究

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摘　要

代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD)是目前世界上最主要的肝脏疾病，对该病发病机制进行分析，能够看出其之所以会出现肝病，并非是由于酒精引起的肝损伤而是因为肝内过度沉积脂肪产生的一种临床病理综合征。流行病学研究的结果表明超重和胰岛素抵抗是MAFLD发展的关键风险因素，而临床和实验研究结果也表明，肠道微生物群组成和肠道屏障的改变可能有助于疾病的发生和发展。随着社会的逐渐发展，目前社会居民的生活质量得到显著改善，饮食习惯也发生极大变化，该病的发病率每年都在快速增长，构成了全世界肝脏纤维化的主要原因，逐渐对人体健康构成威胁，并已成为世界范围内的一大卫生问题。近年来，许多学者已经确认了固有免疫系统的活化对MAFLD的发展起到了重要的作用，Toll样受体(Toll-like receptor, TLR)途径是其中关键一环。TLR在各种肝病中均表现为异常，其作用机制是通过调节TNF-α、IL-1β的表达，从而加剧肝组织的炎症反应。

关键词

代谢相关脂肪性肝病(MAFLD)，非酒精性脂肪性肝炎(NASH)，肠道微生物群，高脂肪饮食，Toll样受体(TLR)

Basic Research on Toll-Like Receptors in Metabolism-Related Fatty Liver Disease

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Abstract

Metabolic associated fatty liver disease (MAFLD) is currently the world's leading liver disease. By analysis of the pathogenesis of the disease, it can be seen that the reason for liver disease is not due to liver damage caused by alcohol, but because of a clinicopathological syndrome produced by excessive deposition of fat in the liver. The results of epidemiological studies suggest that overweight and insulin resistance are key risk factors for the development of MAFLD, while clinical and experimental studies have also suggested that alterations in gut microbiota composition and intestinal barrier may contribute to the onset and progression of the disease. With the gradual development of society, the quality of life of social residents has been significantly improved, eating habits have also undergone great changes, the incidence of the disease is growing rapidly every year, constituting the main cause of liver fibrosis in the world, gradually posing a threat to human health, and has become a major health problem worldwide. In recent years, many scholars have confirmed that the activation of the innate immune system plays an important role in the development of MAFLD, and the Toll-like receptor (TLR) pathway is a key part of this. TLR is abnormal in various liver diseases, and its mechanism of action is to increase the inflammatory response of liver tissue by regulating the expression of TNF-α and IL-1β.

Keywords

Metabolism-Related Fatty Liver Disease (MAFLD), Nonalcoholic Steatohepatitis (NASH), Gut Microbiota, High-Fat Diet, Toll-Like Receptor (TLR)

1. 引言

2020 年 30 位来自全球的专家共同发表了一项重要的共识[1]，表示当前非酒精性脂肪性肝病被代谢性脂肪性肝病(MAFLD)所取代。MAFLD 是一种与新陈代谢有关的应急性肝损害，与胰岛素抵抗(IR)和基因遗传易感性息息相关，如果 MAFLD 的病理过程不能及时缓解，可能会演变为肝纤维化或肝细胞癌[2]。MAFLD 的发病机制复杂，基于近几年研究成果能够发现二次打击学说被得到进一步丰富与补充，此外随着相关研究的逐渐深入，当前也提出了多重打击学说，并且逐渐受到相关研究者的认可。另外，越来越多的研究表明 MAFLD 的发病机制还与胰岛素抵抗(IR)、脂肪酸和脂肪因子、炎症反应、表观遗传学、肠道菌群以及遗传多态性均具有一定联系。在欧美等发达国家，成人 MAFLD 的患病率在 20%~33%之间，是引起肝酶异常和慢性肝病的主要病因[3]。美国联合器官共享网络(UNOS)的最新数据表明，目前 MAFLD 是所有肝脏移植(LT)的第二大适应症，并迅速成为因肝细胞癌而被列入 LT 的首要适应症[4] [5]。近年来，许多研究已经确认了固有免疫系统激活对 MAFLD 的影响，而 TLR 通路是 MAFLD 发展的重要环节。目前关于外周血细胞中 TLR 表达及其与肠道微生物群和 MAFLD 发展的关系的知识有限。尽管 TLR 参与一系列炎症反应，但其在非酒精性脂肪性肝病及其并发症中的作用还没有被完全解释清楚。

2. TLR 简介

1997 年 Medzhitov 等[6]首先对人类 Toll 蛋白进行了氨基酸序列分析，发现该蛋白结构和果蝇 Toll

蛋白具有极高相似度，因此将其命名为 Toll 样受体。TLR 主要是借助识别 PAMP，从而诱导机体对必需的炎症反应进行防御，然后经由机体中的多个信号传导过程刺激机体激活适应性免疫[7]。通过对代谢性脂肪性肝病患者进行分析，能够看出其机体中存在较多炎症细胞因子会诱发机体处于慢性低度炎症反应状态，此外随着特异性免疫系统被激活，其免疫状态会得到一定上调[8]。

在哺乳动物体内，其固有免疫系统主要发挥检测病原微生物以及诱导保护性炎性反应的过程，而上述过程实际上大部分是借助对 PAMP 进行识别达成的[9]。PAMP 之所以能够促使机体发出炎症信号，主要是借助识别受体达成的，在这一过程中 TLR 发挥重要作用。TLRs 家族中存在损伤模式识别受体以及病原模式识别受体，不仅能识别细菌脂多糖(LPS)、病毒 RNA 等具有高度保守性的微生物结构，同时还能够促使机体抗微生物感染，信号通路被激活，使免疫系统发挥相应作用[10]。在人体中，有 10 种 TLR 表达，所有的 TLR 均已在肝组织中检测到[11]。TLR3，7，8，9，10 则大部分在核内体中存在，能够对与内化微生物有关的核酸进行识别与分析，而位于哺乳动物细胞表面的 TLR1，2，4，5，6 能够检测到细菌、真菌和原生动物微生物的外膜成分[9] [12] [13] [14] [15]。TLRs 所具有的细胞定位功能往往和其感知病原体的能力具有高度相关性[16]。

3. TLR 与非酒精性脂肪性肝病

据报道，肠道微生物组及其衍生的代谢物在非酒精性脂肪肝的发展、进展和恢复中起着至关重要的作用[17]。肠道菌群在维持机体内环境稳态方面发挥重要作用，一旦其平衡失调，将会影响肠道通透性，从而促进 PAMP、损伤相关分子模式(DAMP)和 LPS 共同运转到门静脉循环，通过 TLR4 信号传导导致 NLRP3 的激活和肝脏炎症。TLR4 活化过程可以激活髓样分化因子 88 (MyD88)及下游的 MyD88 依赖性信号通路激活核转录因子 κB (NF-κB)，从而导致促炎症细胞因子如肿瘤坏死因子 α (TNF-α)、IL-6、IL-8 和 IL-12 及单核细胞趋化蛋白 1 (MCP-1)的表达，加剧炎症发展[18]。

目前研究较多的与 MAFLD 发病相关的 Toll 样受体为 TLR2、TLR4 与 TLR9 [19] [20] [21] [22] [23]。值得一提的是，Anja Baumann 等人[24]通过检测 37 例 MAFLD 患者和 15 名年龄匹配的健康对照者血液中肠通透性标志物和外周血单个核细胞中 TLRmRNA 表达，发现在 NAFLD 患者中只有 TLR1 mRNA 的表达增加，与霍尔德曼菌属的患病率显著正相关，提出了 TLR1 可能成为非酒精性脂肪性肝病的靶点这一观点，但仍需要进一步的研究来确定是否有临床意义。

大多数饮食(高脂饮食[25]、果糖饮食、蛋氨酸/胆碱缺乏(MCD)饮食[26]和胆碱缺乏氨基酸[27]饮食)诱导的 MAFLD 动物模型，皆出现严重变性或脂肪性肝炎，循环 LPS 水平皆有所升高。Sawada 等人高脂诱导小鼠 NASH 模型，并对肝组织 Toll 样受体进行检测，研究发现相较于对照组而言，NASH 小鼠肝组织中 TLR2、TLR4、TLR9 表达水平明显升高[28]。相比于野生型小鼠，TLR4 基因敲除小鼠在相同饲养环境血清 LPS 水平无明显差异，而发生脂肪变性、脂肪性肝炎的程度较低。同样，对 MCD 饮食诱导肝损伤小鼠进行腹腔 LPS 注射，其损伤程度明显加重[14]。由此可见，LPS-TLR4 是 MAFLD 进展的关键途径。

TLR9 是一个与新陈代谢和炎症事件密切相关的受体，是 NASH 的一个关键驱动因素[29]。Miura 等人采用 CDAA 饲喂 WT、TLR9-/-、IL-1R-/-和 MyD88-/-小鼠，处理 22 周之后评估小鼠脂肪性肝炎、纤维化和胰岛素抵抗[30]。研究结果显示：与 WT 小鼠比较，TLR9-/-、IL-IR-/-和 MyD88-/-的脂肪性肝炎、肝纤维化程度较低。其作用机制可能为，细菌 DNA 与 Kupffer 细胞上的 TLR9 结合，活化 Kupffer 细胞，使其产生大量的 IL-1β，引起肝脏细胞内脂质的积累和细胞的死亡[31]。

TLR2 在 MAFLD 中的作用尚未得到深入研究。但有研究证明阻断 TLR2 信号传导可以预防高脂喂养导致的小鼠胰岛素抵抗[32]。另外，已有研究表明高脂饮食组 WT 小鼠的血糖值、IL-6、TNF-α 炎性因子

水平均显著增高，IL-10 抗炎因子水平明显下降，TLR2 基因缺失增强了高脂喂养小鼠的葡萄糖耐量和胰岛素敏感性[33]。

4. TLR 信号通路启动因素

血清中游离脂肪酸(FFA)水平升高是脂肪代谢异常的典型表现，也是肥胖引起的 IR 的主要因素之一。目前的研究表明 FFA 致 IR 的机制包括了氧化应激、炎症作用、调亡、线粒体功能障碍、内质网应激等，涉及的分子主要包括 JNK (Jurn N-尾激酶)、ROS (活性氧)、PKC8 (蛋白激酶 C-8)、NLRP3 (核昔酸结合寡聚化结构域样受体蛋白 3)等[34]。已有研究报道，游离脂肪酸的表达水平在非酒精性脂肪性肝病患者中异常升高，游离 FA 一般借助 TLR4 作用调节 MAFLD [35]。进一步研究发现，游离脂肪酸的组成成分棕榈酸与硬脂酸是 TLR4 的潜在受体，能够促使 Kupffer 细胞中的 TLR4 活化，从而分泌更多炎症因子[36]。Yamamoto 等人研究显示，棕榈酸有可能会使得 TLR2 和配体结合之后产生的生理效应被增强，激活 Kupffer 细胞诱发炎症反应[37]。亦有相关研究采用 RNA 干扰术抑制机体表达 C2CL2 肌细胞 TLR2 与 MyD88，从而缓解棕榈酸诱导的 IR 程度与 IL-6 表达水平[38]。Sawada 团队探究了棕榈酸在引发 MAFLD 促炎状态发展中的作用，结果显示高脂饮食的 NASH 小鼠肝组织中 TLR2、TLR4、TLR5、TLR9 的表达量明显高于正常饮食组，同样用棕榈酸处理的原代肝细胞、Kupffer 细胞的 TLR 表达量也有所增加[39]。由此可见，棕榈酸有可能刺激 MAFLD 形成前期 TLR2。LPS 被认为是 TLR4 配体，进一步研究发现，LPS 中的脂质组分中所含的链脂肪酸、月桂酸有可能激活巨噬细胞中 TLR4 [40]。Schaeffler 等人研究了脂肪酸对脂肪细胞 3T3-L1 脂肪细胞分泌脂肪因子的影响及 TLR4/核因子 kappaB [12]途径的参与，结果显示，TLR4 在脂肪细胞分化过程中被诱导，脂肪酸刺激后其表达增强；硬脂酸和棕榈酸对 MCP-1 分泌的刺激作用通过 TLR4、NF-kB 介导的；脂肪酸不能直接与 TLR-4/MD-2 结合，因此其介导的效应是由内源性配体引起的[13]。对活化态 TLR4 而言，其会受到机体调节作用而被动被募集到脂质筏中，基于此可以确定细胞膜中局部区域含有的胆固醇或者鞘脂等可能会激活 TLR4。内皮细胞主要依靠 TLR4 与 CD14 识别 MM-LDL，并导致趋化因子 IL-8 的分泌[14]。

5. 炎症因素通过 TLR 参与 MAFLD 发生

大部分患有慢性肝脏疾病的病人都有细菌过度生长或者菌群失调导致的肠道通透性增高，MAFLD 患者也不例外。迄今为止，各种研究已经证明了肠道－肝脏轴[41]的重要性。来自葡聚糖硫酸钠(dextran sulfate sodium, DSS) + 高脂饮食模型的肝脏显示出 toll 样受体 TLR4 和 TLR9 的表达显著增加，它们特异性识别细菌/细菌成分，包括脂多糖(LPS)，也称内毒素[42]，并激活炎症相关基因的活性，促使肝脏慢性炎症的产生，从而导致 MAFLD 的发生发展。Tripathi 等发现增加的病原体相关分子模式(PAMPs)如 LPS、细菌 RNA 和病毒 RNA 从肠道转运通过肠道屏障进入肝脏，它们通过与 KCs 膜上的 TLR4 结合刺激免疫细胞，导致诱发肝脏炎症，并发展为肝损伤和疾病[43]。

通过动物实验，能够看出在 NASH 发病过程中，TLR4 以及肠源性内毒素在其中发挥关键性作用[44]。Ye 等通过高脂饲养方案对小鼠进行为期 12 周的饲养后，其肝脏表现出典型的 NASH 病理特点；但是 ApoE(-/-)/TLR4(mut)小鼠因为预先敲除对应基因，导致机体无法合成 TLR4，因此不会出现肝脏炎性损伤。ApoE(-/-)/TLR4/WT 小鼠的 x 盒结合蛋白(XBP)1 能够受到 HF-HC 的刺激作用而活化，但是 ApoE(-/-)/TLR4(mut)小鼠不会受到这一影响[45]。

6. 总结

在临床上，TLR2 为血管疾病治疗靶点的相关研究处于领先地位，阻断 TLR2 信号可降低炎症水平来缓解动脉粥样硬化的进展。但关于 TLRs 信号的治疗性仍存在一定的挑战，例如 TLRs 在宿主对病原体的

防御中发挥重要作用，阻断 TLRs 信号是否会增加患者的感染风险？TLRs 信号参与机体脂质堆积过程，而在其他关键方面(细胞凋亡、氧化应激)发挥什么作用？因此，进行 TLRs 信号阻断治疗需要适当的风险评估。另外，一项关于 MyD88 及其邻近信号蛋白白细胞介素-1 受体相关激酶-4 (IRAK-4)遗传缺陷[46]的患者感染性疾病易感性的研究发现，MyD88 缺陷儿童明显缺乏体外 MyD88 依赖的功能反应，这与 MyD88 缺陷小鼠的表现一致。MyD88 缺陷小鼠易被病原体侵袭，但 MyD88、IRAK-4 遗传缺陷儿童并没有出现严重的真菌、寄生虫、病毒感染，这表明 MyD88 依赖性反应在宿主防御中的作用可能更为精确，这一现象给 TLRs 及其信号选择性阻断治疗脂质代谢紊乱提供了一定的可行性。因此，关于 TLRs 在脂代谢紊乱中的作用值得进一步探究。

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