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在线投稿: http://www.baishideng.com/wcjd/ch/index.aspx
帮助平台: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.11569/wcjd.v23.i13.2071

世界华人消化杂志 2015年5月8日; 23(13): 2071-2076
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

Kupffer细胞与肝脏脂质代谢紊乱的研究进展

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国家自然科学基金资助项目, No. 31370753
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收稿日期: 2015-02-10 修回日期: 2015-03-16
接受日期: 2015-03-18 在线出版日期: 2015-05-08

Kupffer cells and hepatic lipid metabolism disorder

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Received: 2015-02-10 Revised: 2015-03-16
Accepted: 2015-03-18 Published online: 2015-05-08

Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disorder of our times in both developed and developing countries, which is associated with insulin resistance and genetic susceptibility. Simple steatosis, a seemingly innocent manifestation of early stage NAFLD, may progress into steatohepatitis and cirrhosis, which may even progress into hepatocellular carcinoma. Kupffer cells (KCs) constitute the first firewall of the liver, representing 80%-90% of all tissue macrophages in the body and taking part in various acute and chronic inflammatory reactions. It is deemed that the genesis and development of NAFLD are closely related to the chronic metabolic inflammation induced by KCs. KCs could be activated by lipids accumulated in the liver, and activated KCs participate in metabolic inflammation through releasing pro-inflammatory factors. In this review, we focus on recently uncovered aspects of the biochemical, immunological and molecular events that are responsible for the development and progression of this highly prevalent and potentially serious disease, and summarize the role of KCs in the pathogenesis of NAFLD.

Key Words: Kupffer cell; Non-alcoholic fatty liver disease; Insulin resistance

Zhou TZ, He K, Gong JP. Kupffer cells and hepatic lipid metabolism disorder. Shijie Huaren Xiaohua Zazhi 2015; 23(13): 2071-2076 URL: http://www.wjgnet.com/1009-3079/23/2071.asp DOI: http://dx.doi.org/10.11569/wcjd.v23.i13.2071

摘要

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)目前已成为发达国家及发展中国家最常见的慢性肝病之一, 是一种与胰岛素抵抗和遗传易感密切相关的代

背景资料
非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)目前已成为发达国家及发展中国家最常见的慢性肝病之一, 是一种与胰岛素抵抗和遗传易感密切相关的代谢性肝脏疾病, 该病发展的初期为单纯性脂肪肝, 其危害较小, 但有可能进一步发展为脂肪性肝炎及脂肪性肝硬化, 后者甚至有可能发展为肝细胞肝癌.

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研发前沿
目前关于单纯性脂肪肝到脂肪性肝炎的发病机制的研究为NAFLD研究的热点, 目前认为Kupffer细胞(Kupffer cells, KCs)参与的慢性代谢性炎症与NAFLD的发生发展密切相关, 但具体机制尚不清楚.

谢性肝脏疾病, 该病发展的初期为单纯性脂肪肝, 其危害较小, 但有可能进一步发展为脂肪性肝炎及脂肪性肝硬化, 甚至发展为肝细胞肝癌. Kupffer细胞(Kupffer cells, KCs)为聚集于肝内的巨噬细胞, 占全身巨噬细胞的80%-90%, 是肝脏的第一道防御屏障. 目前认为KCs参与的慢性代谢性炎症与NAFLD的发生发展密切相关, 肝脏蓄积脂质激活的KCs通过释放促炎因子参与代谢性炎症的发生, 但具体机制尚不清楚. 本综述结合国内外最新相关文献, 总结KCs在NAFLD中发挥的重要作用.

关键词: Kupffer细胞; 非酒精性脂肪性肝病; 胰岛素抵抗

核心提示: 随着非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)患病率逐年上升, 对于Kupffer细胞(Kupffer cells, KCs)参与脂肪性肝炎的分子机制的研究已成为肝脏脂质代谢研究领域的热点, 发现了KCs中许多潜在的在NAFLD发生发展过程中发挥重要作用的信号通路, 今后还应将各种信号通路整合起来, 进行更为系统的研究.

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相关报道
体型肥胖尤其是躯干性肥胖、高脂血症、胰岛素抵抗等仍是NAFLD发病的重要危险因素. 由于肝脏有强大的代偿功能, 肝损害的临床表现并不能准确反映肝脏内的炎症及纤维化程度, 在肝功能失代偿征象显现之前, 只有肝组织病理检查才能准确区分脂肪性肝炎或肝硬化等进展期肝病. 由于肝活检病理检查不仅能排除其他原因导致的肝功能异常及明确脂肪肝诊断, 还可对肝组织标本进行分级分期, 这对于NAFLD合并进展性肝纤维化或肝硬化患者的早期干预治疗具有指导作用.

0 引言

肝脏固有免疫系统的激活在维持稳态、肝细胞再生及各种肝脏疾病的发病机制中发挥重要的作用[1]. 目前认为在肝脏固有免疫中占有重要的地位Kupffer细胞(Kupffer cells, KCs)的激活与非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)的发生发展密切相关. NAFLD是一种与胰岛素抵抗(insulin resistance, IR)和遗传易感密切相关的代谢性肝脏疾病, 疾病谱包括单纯性脂肪肝(non-alcoholic fatty liver, NAFL)、脂肪性肝炎(steatohepatitis, NASH)、脂肪性肝硬化, 部分患者甚至有可能最终发展为肝细胞肝癌(hepatocellular carcinoma, HCC). 目前认为NAFL属于良性病变, 具有自限性, 对身体危害较小; 然而, 一旦发展为NASH, 就有可能进一步进展为脂肪性肝硬化甚至肝癌[2,3].

NAFLD的发生机制尚不清楚, Day等[4]于1998年提出了“二次打击”学说, 认为在第一次打击(肝细胞脂肪变)的基础上, 各种炎症刺激参与了第二次打击, 促使由NAFL向NASH的转变. 目前认为NAFLD的产生与发展与代谢性炎症密切相关, 后者是一种低度的慢性炎症, 是NAFLD发生发展的一个重要节点[5,6], 我们的研究[7]也已证实用鼠γ疱疹病毒68感染小鼠可促进小鼠脂肪肝及IR的形成. 因此, 理解这种代谢性炎症的发生机制对于阐明NAFLD的发病机制及改进NAFLD的治疗手段具有重要的意义.

1 肝脏脂质蓄积可激活KCs, 改变KCs的生物学活性

肝细胞脂质聚集是NAFL的一个重要的形态学特点, 也是NAFLD发展初期肝脏的主要病理学改变[8]. 脂肪肝肝组织中脂质的量与构成的改变可通过以下机制控制KCs的生物学活性: (1)脂肪病变肝细胞的“间隙占据”效应可导致肝血窦灌注障碍, 聚集于狭窄间隙的中性粒细胞可吸引KCs参与微循环的炎症反应; (2)KCs与游离脂肪酸(free fatty acid, FFA)的过度接触可通过与细胞表面的受体发生反应调控炎症及IR; (3)肝细胞的异常脂质积聚可被KCs视为有害物质, 对其进行吞噬破坏, 进一步促进肝细胞的损伤[9]. KCs在NAFLD的发病过程中发挥的作用具有一定的争议. 有研究[9]报道在用蛋氨酸与胆碱缺乏的饲料(MCD饲料)喂养的小鼠体内注射脂质体包裹的氯膦酸盐剔除KCs后, 小鼠肝脏脂肪变的严重程度较未注射氯膦酸盐的小鼠明显减轻; 另有研究[10]报道用脂质体包裹的氯膦酸盐剔除小鼠肝脏中的KCs可促进小鼠脂肪肝的发生, 该研究认为KCs是抗炎因子白介素-10(interleukin-10, IL-10)的主要来源, 可能与剔除KCs后导致IL-10分泌减少有关.

2 激活的KCs促进NAFLD的进展

2.1 KCs促进肝脏IR的发生 已有研究[11]表明, 几乎所有的NAFLD患者的肝脏与脂肪组织都存在IR, IR的严重程度与NAFLD的病情进展呈正相关. IR通过脂肪分解, 释放FFA增加, 一方面激活线粒体反应性氧体系致不饱和脂

肪酸氧化, 引起脂质过氧化后活化核因子-κB (nuclear factor kappa B, NF-κB)激酶亚基β途径导致NAFL的发生; 另一方面FFA增加可加重IR, 引起高胰岛素血症, 影响甘油三酯及胆固醇代谢, 致甘油三酯在肝细胞内积聚[12,13]. NF-κB信号通路下游的细胞因子肿瘤坏死因子α(tumor necrosis factor alpha, TNF-α)可导致肝脏及全身组织的IR, 而这个过程与KCs的激活密切相关. Tomita等[14]在小鼠的NASH模型中发现, 通过激活KCs的TNF-α信号通路, 可导致NASH的进展, 而在这一过程中, KCs为TNF-α的主要来源. 由此可见, KCs与NAFLD中IR的发生有密切的关系.

2.2 KCs促进肝脏炎症发生 体内许多有害物质可作为危险相关分子模式(damage-associated molecular patterns, DAMPs)或病原相关分子模式(pathogen-associated molecular patterns, PAMPs)激活KCs, 导致后者发生炎症反应, 产生炎症因子, 导致NAFL发生炎症, 向NASH转变, 例如脂多糖(lipopolysaccharides, LPS)、FFA、细菌及胆固醇等[15-17].

LPS是一个重要的内生的有害分子[18-20]. 在大多数NAFLD动物实验模型中, 体循环中LPS的水平均明显增高, 并且肝脏对LPS非常敏感. Toll样受体4(Toll-like receptor 4, TLR4)是LPS的主要配体, 在KCs激活的过程中发挥着核心的作用, TLR4激活后可吸引下游分子髓样分化因子(myeloid differentiation factor 88, MyD88)与Toll/IL-1的接头蛋白(Toll-interleukin 1 receptor domain containing adaptor protein, TIRAP), 导致NF-κB及激活蛋白1(activator protein, AP-1)转录因子的激活, 促炎因子TNF-α及IL-6产生增多, 促进NAFLD的发生与发展[21-24]. 我们研究[25]发现S腺苷蛋氨酸(S-adenosyl methionine, SAM)可以明显改善内毒素血症小鼠的生存率和肝脏炎症, 并且证实这种效应至少有部分是通过下调KCs中TLR4的表达来完成的, 甘氨酸可能也是通过抑制KCs中TLR4/NF-κB信号通路的激活, 改善内毒素导致的肝脏炎症[26]; 另外我们发现过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma, PPAR-γ)可阻止NF-κB信号通路中的关键分子kappa B alpha抑制物(inhibitor of kappa B alpha, IκBα)的磷酸化降解, 阻止LPS激活巨噬细胞中NF-κB信号通路及促进巨噬细胞胆固醇的外流, 发挥抗炎作用[27]. 清道夫受体A(scavenger receptor A, SR-A)是位于脂筏结构域的跨膜蛋白, 具有清除及解毒LPS的功能, KCs表达高水平的SR-A, 后者对修饰的低密度脂蛋白(low-density lipoprotein, LDL)具有高亲和力, 并且可以摄取LPS[28,29]. 我们研究[30]证实用LPS刺激巨噬细胞株RAW264.7, 可以通过上调SR-A的表达及下调低密度脂蛋白受体(lower-density lipoprotein receptor, LDL-R)的表达促进KCs发生泡沫化, 产生炎症. 另有研究[31]发现由高脂、高糖及蛋氨酸及胆碱缺乏的饲料建立的小鼠NASH模型肝脏中TLR4及其附件分子髓样细胞分化蛋白2(myeloid differentiation protein-2, MD-2)与CD14的表达均有增加, 而TLR4$^{-/-}$小鼠肝脏损伤及炎症程度均明显减轻; 剔除NASH小鼠肝脏KCs后, 小鼠肝脏TLR4的表达水平较正常小鼠明显下降, 表明NASH中炎症的产生有部分是依赖KCs中TLR4信号通路的, 并且KCs中TLR4的表达占有非常大的比重.

IL-1β是一个重要的促炎因子, 在NAFLD的发展中扮演重要的角色. 我们前期研究[32]发现用促炎因子IL-1β刺激HepG2细胞后, 细胞内胆固醇水平明显增高, 证实了IL-1β可导致小鼠肝脏脂质代谢紊乱. 机体内IL-1β的生物学功能主要受两个信号通路的控制, 其中TLR4信号通路控制其在细胞内的转录及合成, 而NOD样受体蛋白3(NACHT, LRR and PYD domains-containing protein 3, NLRP3)炎症小体信号通路控制其成熟与分泌[33,34]. NLRP3炎症小体是一个巨大的蛋白复合体, 包括NLRP3、配体分子凋亡相关微粒蛋白(apoptosis-associated speck-like protein containing CARD, ASC)以及效应分子胱冬肽酶-1 pro-Caspase1; 刺激该小体激活后, pro-Caspase1变为有催化活性的Caspase1, 后者催化IL-1β的前体pro-IL-1β变为成熟的IL-1β, IL-1β释放到细胞外发挥炎症效应[35-38]. NLRP3炎症小体及IL-1β信号通路已被证实在NASH的形成过程中发挥重要的作用[39-43]. 有实验证实, FFA可作为DAMPs激活KCs中的NLRP3炎症小体, 导致KCs炎症的发生, 并且KCs是NASH小鼠血清及肝组织中IL-1β的主要来源, 用高脂饲料喂养NLRP3$^{-/-}$小鼠, 该小鼠肝脏脂肪变严重程度较正常小鼠明显减轻[44]. Baroja-Mazo等[45]的最新成果证

创新盘点

白介素(interleukin, IL)-1β是一个重要的促炎因子, 在NAFLD的发展中扮演重要的角色. 我们前期研究发现用促炎因子IL-1β刺激HepG2细胞后, 细胞内胆固醇水平明显增高, 证实了IL-1β可导致小鼠肝脏脂质代谢紊乱. 机体内IL-1β的生物学功能主要受两个信号通路的控制, 其中Toll样受体4(Toll-like receptor 4)信号通路控制其在细胞内的转录及合成, 而NOD样受体蛋白3(NACHT, LRR and PYD domains-containing protein 3, NLRP3)炎症小体信号通路控制其成熟与分泌.

应用要点

KCs在NAFLD发生发展中的重要性已得到全世界的认可, 且KCs在该病的发病过程中扮演的角色具有“两面性”, 在遇到外来有害物质时适度激活, 可发挥防御作用, 但过度激活又会释放许多炎症因子, 对细胞及组织造成损伤, 因此, 如何使KCs发挥防御效应的同时并控制其不被过度激活将成为下一步研究的重点.

实NLRP3炎症小体可以释放到细胞外, 进入血循环, 产生炎症放大效应. 目前我们通过构建硫氧还原蛋白反应蛋白(thioredoxin-interacting protein, TXNIP)与*NLRP3*基因敲除小鼠, 正在进一步研究FFA导致NAFLD形成的具体机制, 并在外周血中寻找NLRP3炎症小体释放的证据. KCs亦可通过依赖IL-1β的途径抑制过氧化物酶体增殖物激活受体α(peroxisome proliferator-activated receptor alpha, PPAR-α)的活性, 促进肝脏脂质蓄积, 从而导致PPAR-α靶基因表达及脂肪氧化下降[46].

肝脏X受体(liver X receptor, LXR)在胆固醇代谢及炎症信号通路中发挥重要的作用[47-49]. 有研究[50]证实使用LXR激动剂可以明显减轻LPS导致的肝脏炎症及NAFLD的发生.

3 结论

目前, KCs在NAFLD发生发展中的重要性已得到全世界的认可, 且KCs在该病的发病过程中扮演的角色具有“两面性”, 在遇到外来有害物质时适度激活, 可发挥防御作用, 但过度激活又会释放许多炎症因子, 对细胞及组织造成损伤, 因此, 如何使KCs发挥防御效应的同时并控制其不被过度激活将成为下一步研究的重点. 随着NAFLD患病率逐年上升, 在过去20年间, 对于KCs参与NAFL发展为NASH的分子机制的研究已成为肝脏脂质代谢研究领域的热点, 发现了KCs中许多潜在的在NAFLD发生发展过程中发挥重要作用的分子信号通路, 今后还应将各种信号通路整合起来, 进行更为系统的研究, 才能全面的理解NAFLD的发病机制及改进NAFLD的治疗手段.

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名词解释
NOD样受体蛋白3(NLRP3)炎症小体: 是一个巨大的蛋白复合体, 包括NLRP3、配体分子凋亡相关微粒蛋白以及效应分子胱冬肽酶-1pro-Caspase1; 刺激该小体激活后, pro-Caspase1变为有催化活性的Caspase1, 后者催化IL-1β的前体pro-IL-1β变为成熟的IL-1β.

同行评价

本文综述了KCs在NAFLD中发挥的重要作用. 文笔流畅, 内容反映了最新的进展. 对于了解KCs在代谢性肝病炎症反应有一定的作用.

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编辑: 韦元涛 电编: 都珍珍

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ISSN 1009-3079