·综述·

库普弗细胞在非酒精性脂肪性肝病发病机制中的作用

朱　明　赵　蕾　龚建平

摘要：库普弗细胞(KC)是门脉系统的第一道屏障，也是机体固有免疫系统的重要组成部分，能分泌大量的炎性介质等物质，参与多种肝脏疾病的发生发展。非酒精性脂肪性肝病是指除乙醇等明确的损伤因素外，以弥漫性肝细胞大泡性脂肪变为病理特征的临床综合征，是仅次于病毒性肝炎的常见肝病。近年来研究发现KC与该病的发病全过程密切相关。

关键词：库普弗细胞；非酒精性肝病；机制

库普弗细胞(KC)是肝脏内固有巨噬细胞，长期以来人们一致认为它是清除门脉系统特定物质如内毒素等的主要细胞。然而，近年来越来越多的证据提示KC还参与了多种肝脏疾病的发生、发展，如：病毒性肝炎、酒精性肝病、肝内胆石症、脂肪肝、肝纤维化、以及激活或抑制肝移植中的排斥反应等。本文对近年来KC在非酒精性脂肪性肝病(NAFLD)发病机制中的作用研究进展作一综述。

1　KC概述

作为机体固有免疫系统的重要组成部分，KC可以是直接发挥效应的细胞，也可以作为抗原提呈细胞或多种细胞因子的重要来源，发挥它在机体固有免疫、抗感染等多方面的作用。同时，KC是胃肠道吸收物质入血后面临的第一道屏障，能清除微生物、内毒素、免疫复合物、老化细胞和毒素(如乙醇等)，同时由于KC分布位置的重要性，它还可作为抗原提呈细胞参与肝脏的再生与肿瘤发生。KC还能分泌大量的可溶性炎性介质，在机体固有免疫和机体防御功能中起关键作用。现有大量证据表明：KC与脂多糖(LPS)的相互作用是多种疾病中导致肝细胞损害的始动因素[1]，在多种肝脏损伤如：内毒素血症、缺血再灌注损伤、病毒感染、酒精性肝病和NAFLD的过程中都起到了重要的作用。

2　KC与NAFLD

NAFLD是指除乙醇和其他明确的肝损伤因素外，以弥漫性肝细胞大泡性脂肪变为病理特征的临床综合征，包括单纯性脂肪肝(SFL)以及由其演变的脂肪性肝炎(NASH)和肝硬化(FLC)三种类型，是仅次于病毒性肝炎的常见肝病。大多数NAFLD病例发生于肥胖、高脂血症、糖尿病患者，胰岛素抵抗、氧应激、细胞因子可能是其发病环节中的核心因素。近来研究还发现KC与非酒精性肝脏脂肪变性、肝炎、肝硬化的发病全过程密切相关。

2.1　KC与肝细胞脂肪变性

2.1.1　NAFLD与胰岛素抵抗　现有研究表明，几乎所有的NAFLD患者都存在肝脏和脂肪组织的胰岛素抵抗(IR)，IR的严重程度与NAFLD的病情进展呈正相关。IR使血清中游离脂肪酸(FFA)增多，当过量的FFA超出肝脏的代谢能力时，就会导致肝细胞脂肪变性。目前已基本公认NAFLD是代谢综合征(IR综合征)的表现之一[2-4]。

2.1.2　KC与NAFLD胰岛素抵抗　研究发现炎性反应可增加IR[2]。作为肠道吸收物质入血后的第一道屏障，KC可被LPS、饱和脂肪酸、高糖等多种物质激活，引发肝脏局部甚至全身的炎性反应，参与IR。

实验表明，KC是机体特别是肝脏局部TNF-α的主要来源[5]，而TNF-α是调节胰岛素敏感性的重要细胞因子。研究发现，在NASH患者的脂肪组织和肝组织内TNF-α mRNA表达明显上调。一方面，TNF-α能直接抑制调节脂肪酸代谢的蛋白表达如脂肪酸结合蛋白aP5、葡萄糖转运子4(GLUT4)，从而影响胰岛素发挥正常生物学功能，或者直接磷酸化胰岛素受体底物1(IRS-1)的丝氨酸位点，并将IRS-1转化为胰岛素受体酪氨酸激酶的抑制剂，从而减少胰岛素受体的酪氨酸激酶活性[6]，影响胰岛素信号转导；另一方面，TNF-α能通过下调过氧化物酶体增殖物活化受体，间接降低胰岛素敏感性，促进IR。

2.2　KC引起NASH的发病机制

根据NAFLD发病机制的“二次打击”学说，第一次打击是脂肪贮积或IR，第二次打击则是氧化应激和异常细胞因子作用导致肝脏坏死性炎性反应

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和纤维化。从脂肪肝到脂肪性肝炎的进展过程是前炎性因子与抗炎性因子失平衡，触发氧化应激和脂质过氧化反应的结果。

2.2.1 KC与氧化应激 氧化应激在NAFLD中起重要作用，不断增强的氧应激及前炎性因子（如TNF-α）是导致NAFLD发病的"第二次打击"，导致肝脏坏死性炎性反应和纤维化。Koruk等[8]发现，NASH患者血清中的氧化应激产物丙二醛（MDA）、NO、还原型谷胱甘肽和FFA明显增加，而抗氧化酶如超氧化物歧化酶（SOD）减少。在NASH大鼠模型中也发现类似结果，而且肝内KC活化与肝脏组织脂质过氧化损伤程度呈正相关。还有学者发现用$GdCl_3$预处理小鼠、大鼠，能明显减轻对乙酰氨基酚的肝毒性，NO和超氧化物生成减少[9]。

此外，研究者在非酒精性脂肪肝患者的肝活组织切片中发现了一种壳质酶（CHIT）[10]，这种酶只在KC上表达，而且NAFLD患者的CHIT水平明显高于单纯性脂肪肝患者，CHIT的过度表达还可以激活肝星状细胞。

2.2.2 KC与内毒素及β细胞因子 目前已有几项临床研究显示NASH可被抗生素逆转，Wigg等[11]进一步证实NASH患者存在着小肠内细菌过繁殖，可能在NASH的发病机制中发挥一定的作用。内毒素使KC激活，产生大量中间产物如前列腺素、活性氧、细胞因子（如TGF-β、TNF-α、IL-8）、NO及各种蛋白酶，从而诱导一系列类似于酒精性肝病的表现。

2.2.3 KC与内源性乙醇 Cope等[12]在NASH动物模型中发现胃肠源性乙醇，因此小肠内微生物可能通过产生乙醇发挥效应，其作用机制类似酒精性肝炎和慢性酒精性肝脏疾病。研究表明，急性或慢性乙醇注射都可以增加KC数量并激活KC，引起CD14表达上调，炎性介质IL-1、TNF-α分泌增加，氧自由基产生增加。用$GdCl_3$特异性阻断KC后，可以逆转乙醇引起的肝脏炎性反应和肝细胞坏死。最近的研究还表明，慢性乙醇注射能降低KC细胞内cAMP水平并增强LPS对KC细胞NF-κB通路的活化作用，引起TNF-α生成增加[13]。

2.2.4 KC与铁超负荷 1994年，Bacon首次发现许多NAFLD患者存在血清铁升高、铁超负荷（iron overload）现象，但具体机制不清。近年来在高脂饮食诱导的兔NASH模型上发现，肝内转化生长因子-1（TGF-β1）、TNF-α、IL-8和胶原α增加，红细胞脆性增加，细胞膜表面磷脂酰丝氨酸（PS）改变，使红细胞聚集，易在血流缓慢的肝窦内停滞，更易被KC吞噬降解，红细胞血红蛋白中的铁导致肝脏内铁沉积[14]。同时，铁超负荷又可以催化羟自由基产生、激活KC，激活NF-κB和TNF-α表达，诱导氧应激和脂质过氧化[15]。

2.3 KC与NAFLD肝纤维化的发生机制

KC在NAFLD肝纤维化中的主要作用是在其激活后分泌细胞因子、产生氧化应激和/或促使星状细胞转化为成纤维细胞[16-18]。肝星状细胞（HSC）是肝纤维化发展过程中的关键细胞。激活HSC的主要因素有氧应激、转化生长因子-1（TGF-β1）、结缔组织生长因子（CTGF）等。

研究比较NASH患者与单纯性脂肪肝患者的血清TGF-β1水平后发现，TGF-β1与纤维化发病机制关系密切。激活的KC可以分泌大量TGF-β1，它是HSC和纤维母细胞的生长因子，而且是促使HSC活化的最强有力因子。CTGF在TGF-β1的诱导下由HSC、成纤维细胞等间质细胞产生，有介导TGF-β1对HSC促进其增生及细胞外基质合成的作用。研究观察到CTGF在NASH患者的肝组织内过表达，并与纤维化严重度相关。另一项研究发现TNF-α能诱导HSC中CTGF的表达。最近还有试验指出：与正常小鼠相比，TNF受体1（TNFR1）和2（TNFR2）基因双敲除小鼠给予不含蛋氨酸和胆酸的饮食后，肝内活化KC减少，TNF-α含量降低，金属基质蛋白1（TIMP1）、细胞间黏附分子-1（ICAM-1）、血管细胞黏附分子-1（VCAM-1）都减少[18-19]。

3 结语

随着生活水平的提高，肥胖群体的迅速扩增，我国NAFLD尤其是儿童及青少年NAFLD、NASH的发病率呈快速递增趋势，并有部分发生肝硬化[20]。当前NAFLD缺乏特定有效的治疗方案，因此通过对NAFLD发病机制进一步的研究有助于防治NAFLD。既往许多研究已表明IR、细胞因子、氧应激与NAFLD关系密切，然而其详细的作用机制以及KC在其中的具体作用机制都需要进一步研究。上述问题的解决，无疑将对NAFLD的防治发挥重要的推动作用。

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