世界华人消化杂志®
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世界华人消化杂志 2008年9月18日; 16(26): 2959-2963
ISSN 1009-3079 CN 14-1260/R

文献综述 REVIEW

枯否细胞在肝纤维化中的作用

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收稿日期: 2008-07-02 修回日期: 2008-08-02
接受日期: 2008-08-19 在线出版日期: 2008-09-18

Role of Kupffer cells in hepatic fibrosis

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Received: 2008-07-02 Revised: 2008-08-02
Accepted: 2008-08-19 Published online: 2008-09-18

Abstract
Kupffer cells (KC), a kind of nonparenchymal cells and defenders in the liver, release various chemical mediators to induce liver injury, and play an important role in many pathologic changes of the liver. Hepatic fibrosis is the common pathologic process of varied chronic liver diseases, and it is also a "transfer station" for many chronic liver diseases lapsing to cirrhosis. As important influencing factors, cytokines secreted by KC are involved in the occurrence and progression of hepatic fibrosis. Therefore, lucubrating the role and mechanism of KC in the progression of hepatic fibrosis, and investigating the KC-related therapeutic strategies of anti-fibrosis have practical significances for the prevention and treatment of liver injury and the raise of patients' survival rates in clinical practice.

Key Words: Kupffer cells; Hepatic fibrosis; Cytokine

Zhao C, Dai CL. Role of Kupffer cells in hepatic fibrosis. Shijie Huaren Xiaohua Zazhi 2008; 16(26): 2959-2963

摘要
枯否细胞(Kupffer cells, KC)是肝脏内一种重要的非实质细胞, 其在发挥防御作用的同时, 可释放多种化学介质介导肝脏损伤, 在诸多肝脏病理性改变中起重要作用. 肝纤维化(hepatic fibrosis, HF)是诸多慢性肝病共同的病理过程, 也是各种慢性肝病向肝硬化转归的中转站. KC分泌的细胞因子作为重要的影响因素, 参与HF的发生与发展. 因此, 深入研究KC在HF发生与发展中的作用和机制, 并研究与KC相关的抗纤维化治疗策略及方法, 对于临床工作中防治肝脏损伤, 提高患者生存率具有实际意义.

关键词: 枯否细胞; 肝纤维化; 细胞因子

赵闯, 戴朝六. 枯否细胞在肝纤维化中的作用. 世界华人消化杂志 2008; 16(26): 2959-2963
http://www.wjgnet.com/1009-3079/16/2959.asp

■背景资料
肝纤维化是诸多慢性肝病共同的病理过程, 也是各种慢性肝病向肝硬化转归的中转站. 近年来关于肝纤维化机制及对其防治的研究已成为国内外医学界研究的热点课题之一. 枯否细胞作为肝脏内一种重要的非实质细胞, 在肝纤维化的发生发展过程中起着重要作用. 本文就枯否细胞在肝纤维化中的作用和机制以及与枯否细胞相关的肝纤维化防治策略作一综述.

0 引言
枯否细胞(Kupffer cells, KC)是肝脏内重要的非实质细胞, 虽仅占肝脏体积的2%, 却承担着机体单核吞噬细胞系统功能的80%-90%, 在维持机体内环境恒定上起重要作用[1]. 肝纤维化(hepatic fibrosis, HF)是肝脏常见的病理改变, 关于HF机制及对其防治的研究近年来已成为国内外生物学、医学研究的热点课题之一[2-4]. KC分泌的细胞因子作为重要的影响因素, 参与HF的发生与发展[5-6]. 因此, 本文就KC在HF中的作用和机制及与其相关的纤维化防治策略作一综述.

1 KC概述
1.1 KC形态 KC形态不规则, 其细胞外衣较厚, 表面伸出许多板状或丝状伪足, 并有许多微绒毛或皱襞, 与识别和捕捉异物有关. KC表面还有许多特异性受体和结合位点, 如IgGFc受体、C_3受体和低密度脂蛋白、去脂蛋白质残基、甘露糖、半乳糖以及一些内分泌激素的结合位点. KC胞核较大, 胞质内溶酶体发达.

1.2 KC功能 KC的主要功能有: (1)识别和清除异物: KC通过吞噬及吞饮作用不断内吞机体内的多种异物及衰退的内源性物质, 还可通过Fc

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■研发前沿
本文涉及研究领域的热点问题为: KC在肝纤维化的各个阶段的不同作用机制; 基因治疗已取代传统方法成为肝纤维化防治的研究重点; KC相关的肝纤维化基因治疗策略.

受体和C_3受体识别和吞噬抗原物质和免疫复合物[7]. (2)分泌功能: 活化的KC可通过分泌多种细胞因子来影响肝细胞的结构和功能, 如转化生长因子(transforming growth factor, TGF)、肿瘤坏死因子(tumor necrosis factor, TNF)、血管内皮细胞生长因子(vascular endothelial cell growth factor, VEGF)、血小板激活因子(platelet activating factor, PAF)、血小板衍生生长因子(platelet-derived growth factor, PDGF)、白三烯(leukotriene, LT)、白介素(interleukin, IL)、内皮素(endothelin, ET)等[8]. (3)免疫功能: KC具有抗原功能, 能诱导T淋巴细胞反应, 通过肿瘤特异性受体杀伤肿瘤细胞[9]. (4)参与胆红素、铁、脂蛋白和胆固醇的代谢过程[10].

2 KC与HF

HF是各种慢性肝病发展为肝硬化的必经病理过程, 他以细胞外基质(extracellular matrix, ECM)在肝脏窦周间隙的过量沉积为特征[11]. ECM主要由肝脏星形细胞(hepatic stelate cell, HSC)产生合成, ECM的降解则主要由基质金属蛋白酶(matrix metalloproteinases, MMPs)以及金属蛋白酶组织抑制因子(tissue inhibitor of metalloproteinases, TIMP)参与调节[12-13]. 此外, 炎症反应也参与HF过程[14]. 研究表明, KC在HF形成的各个环节均有重要作用[15].

2.1 KC与HSC活化、ECM合成 HSC是合成ECM的主要细胞, 在HF发生发展中起关键作用[16]. 在各种实验性HF模型中, KC的浸润总是先于HSC的激活, 无论从正常大鼠还是从HF大鼠中分离出来的KC的条件培养液, 都能刺激胶原合成及HSC的活化和增殖[17]. KC通过释放如PDGF、VEGF、TGF-β和ET等旁分泌因子, 并活化如核因子-κB(NF-κB)、激活蛋白-1(AP-1)等核转录因子来激活HSC[18-20]. 活化的HSC基因和表型发生改变, 成为肌成纤维细胞样细胞, 产生大量ECM, 最终导致HF. 因此KC所产生的细胞因子是HSC“激活”的启动点. KC分泌的活化HSC的主要细胞因子为TGF-β和PDGF.

2.1.1 TGF-β: 研究证实, 细胞因子中只有TGF-β能刺激HSC合成胶原纤维, 而其他细胞因子则只刺激HSC增殖[21]. 在人肝组织中有3种异构体; TGF-β1、TGF-β2、TGF-β3, 其中TGF-β1最为重要. 一般情况下, TGF-β1以一种不能结合受体的、无活性的“潜在型TGF-β1”形式存在. HF形成过程中KC通过自分泌或旁分泌的方式产生大量的TGF-β, 并通过自身调节机制形成级联放大效应[22]. TGF-β具有强烈的促HSC合成ECM 的作用, 其可促进基质蛋白的合成, 抑制胶原酶和蛋白酶的产生, 促进组织抑制因子的分泌, 减少胶原的降解进而加重ECM沉积[23]. Wang *et al*[24]研究发现TGF-β1 mRNA的表达与Ⅰ型前胶原mRNA、血清Ⅲ型前胶原及组织损伤程度成正比. Verrecchia *et al*[25]研究结果表明TGF-β1还可通过活化Smad信号途径诱导ECM基因的表达上调以刺激ECM的合成, 从而加速HF进程. Murawaki *et al*[26]通过临床实验也证实慢性病毒性肝炎和丙肝患者血清TGF-β水平升高, 且与肝组织Knodell积分、血清前胶原Ⅲ、7S片段及Ⅳ型胶原水平呈正相关.

2.1.2 PDGF: PDGF是已知最强的促HSC增殖、分化的细胞因子[27]. PDGF是由A链、B链组成的二聚体, 分子质量为30 kDa, 有PDGF-AA、BB、AB等3种异构体, 其中以-BB作用最强, 且肝脏中表达以-BB为主. HSC激活早期的重要标志就是PDGF表达的增加. PDGF刺激HSC活化、分裂、增殖, 并转化为肝纤维样母细胞, 合成大量ECM沉积于肝细胞间质, 促进纤维化发生[28-30]. 阻断PDGF的信号转导途径, 则可有效抑制HSC的增殖[31].

2.2 KC与ECM降解 正常体内存在多种参与ECM降解的酶类, MMPs是最重要的一类, MMPs及其抑制因子TIMP表达的平衡统一是维持正常肝组织中ECM合成与降解动态平衡的关键[32]. HF早期, MMPs mRNA表达轻度升高, 至HF发展为肝硬化后降到很低的水平, 而在肝硬化逆转过程中, 其表达水平复又升高[33]. Sakaida *et al*[34]应用三氯化钆($GdCl_3$)清除KC, 证实可通过ERK及SAPK/JNK-P38旁路增强MMP-13和MMP-9 mRNA的表达水平, 促进ECM降解从而减轻HF程度. HF过程中, KC分泌TIMP增加, 同时KC分泌的的TGF-β亦可增加TIMP的生物学活性, 从而抑制MMPs mRNA的表达和活性, 减少ECM降解. Jiang *et al*[35]将反义TIMP-1重组质粒转染入大鼠, 能显著抑制TIMP-1表达, 使胶原酶活性增加, 从而促进Ⅰ、Ⅲ型胶原的降解, 起到抗纤维化的作用.

2.3 KC与HF中炎症反应 炎症反应在HF中起重要作用, 中性粒细胞的浸润与HF的严重程度正相关. KC分泌的细胞因子介导炎症级联反应, 导致组织重塑和纤维化[36].

2.3.1 KC与促炎因子: KC分泌的促炎因子主要

有TNF-α和IL-1. TNF-α是介导肝损伤的主要和终末介质. TNF-α与HF有关的功能主要包括(1)诱导急性炎症过程; (2)加强HSC的趋化性; (3)刺激间质细胞的有丝分裂; (4)诱导蛋白多糖的合成. Tomita *et al*[37]对比研究发现, 经8 wk低胆碱饮食后, TNF受体基因缺陷型大鼠HF程度较正常野生型大鼠减轻, 肝实质中活化的KC数量减少, TNF-α水平亦显著降低, 提示TNF/TNF-R介导的KC自分泌和旁分泌在HF中发挥重要作用. IL-1含量与肝纤维化严重程度呈高度正相关. IL-1通过成纤维细胞的自分泌和KC的旁分泌作用在肝组织重塑中起作用, 并可调节MMPs表达[38].

2.3.2 KC与抑炎因子: KC同样分泌抑炎因子, 其中作用已公认的的为干扰素-γ(interferon-γ, IFN-γ)和IL-10. INF-γ已较广泛的应用于临床和动物试验. 其抗肝纤维化机制主要是影响Ⅰ、Ⅲ型胶原的合成[39]. IFN-γ与ECM呈相反关系: 当IFN-γ减少时, 肝内Ⅰ、Ⅲ型胶原增加, 汇管区及肉芽肿周围开始有胶原纤维沉积, 导致汇管区及小叶间纤维化; 当其含量增加时, 则能显著减少汇管区及小叶间纤维化. IL-10是抑制间质炎症反应的重要因子. IL-10可通过抑制炎症反应、抑制MMP-2和TIMP-1的表达同时促进Ⅰ型和Ⅲ型胶原的降解而发挥逆转HF作用的[40].

当然在HF过程中, KC分泌的促炎因子和抑炎因子是不平衡的, 促炎因子的分泌量远远多于抑炎因子, 这可能与KC中NF-κB被激活上调促炎因子的表达有关[41].

3 与KC相关的抗HF策略

近年来, 基因治疗取代传统方法成为肝纤维化防治研究热点. 利用各种载体系统将KC相关的调控HSC活化或ECM合成与降解的外源基因, 分别导入细胞或HF动物模型体内, 可在一定程度上缓解HF.

3.1 针对TGF-β及其信号转导通路 TGF-β对肝成纤维作用已被广泛证实, 故如果阻断此信号通路, 是阻止HF进程的有效方法[42]. Arias *et al*[43]报道TGF-β1反义mRNA的腺病毒载体表达在胆管结扎的鼠可在基因转录、翻译水平阻止Ⅰ型胶原mRNA的表达, 预防HF. Nakamuta *et al*[44]将构建的可溶性TGF-βⅡ型受体通过骨骼肌转染二甲亚硝胺诱导的HF模型大鼠中, 以阻断TGF-β信号通路, 其结果表明此法能显著降低HF的发生率. 还有研究应用反义Smad4基因阻断TGF-β1通路, 也能抑制ECM的产生, 改善HF[45]. 但由于阻断TGF-β/Smad信号途径也影响生理上信号转导, 因此完全阻断其表达可能有很多难以预料的不良后果. 于是, Inagaki *et al*[46]尝试用既表达绿色荧光蛋白, 又表达TGF-β/Smad信号受体的重组腺病毒载体Y-盒-结合蛋白-1(YB-1)注射入实验小鼠体内, 在alpha-(Ⅰ)胶原基因(COL1A2)控制下, YB-1显著降低了COL1A2引物的活性进而抑制了HF的进程.

3.2 以PDGF为靶位 抑制PDGF的产生或对其作用进行拮抗是抗肝纤维化的重要途径. Schoemaker *et al*[47]应用重组腺病毒转染可溶性PDGF受体可以降低Ⅰ型胶原mRNA的表达, 抑制PDGF-BB mRNA产物的自分泌, 有效抑制KC对HSC的激活. Si *et al*[48]则研究一种新的蛋白激酶抑制剂, 取名A771726, 发现其可通过使PDGF受体磷酸化而抑制HSC的活化以及MAPK旁路活性, 以减轻HF程度.

3.3 IFN-γ IFN-γ是迄今发现的惟一具有确切抗肝纤维化作用的细胞因子, 在临床上也有应用, 美国肝病年会推荐IFN-γ为抗纤维化的首选药物. Hazra *et al*[49]体外重组鼠源IFN-γ腺病毒成功转染小鼠肝细胞株, 经脾移植给血吸虫感染16 wk的小鼠, 结果发现利用IFN-γ基因治疗4 wk后, 检测TGF-β1及TGF-βⅡ型受体mRNA表达水平平行下降, 并且能显著降低Ⅱ型胶原的合成与沉积, 减轻HF. IFN-γ治疗HF的临床实验也显示出了可靠的疗效[50].

3.4 IL-10 IL-10的抗炎特性为其抗HF奠定了基础, 其可减轻肝脏炎症反应从而间接影响HF进程. Hung *et al*[51]将IL-10表达质粒通过电穿孔方法转导入硫代乙酰胺诱导的HF大鼠体内, 经RT-PCR检测显示, 转导的IL-10质粒显著降低了肝组织中TNF-α、α胶原的表达, 同时使环氧化酶的激活作用显著减弱, 表明IL-10基因在治疗HF方面具有潜在的临床应用前景.

3.5 其他 Bahcecioglu *et al*[52]报道TNF-α单抗可通过减轻炎症坏死和纤维形成从而对CCL_4诱导的大鼠HF起防护作用; Roderfeld *et al*[53]应用IL-1特异性阻断剂, 发现其可减少TIMP-1基因表达以起到抗HF作用; Ide *et al*[54]则应用$GdCl_3$清除KC以抑制HSC的激活, 也可减轻HF的程度.

总之, KC参与HF各个机制与阶段, 在HF的病理改变过程中起着重要作用. 虽然对KC的某些具体作用机制尚存在争议和疑问, 这一方面体现了KC在HF病理改变中作用的复杂性, 另一

■创新盘点

本文以客观全面的角度向读者展示KC在肝纤维化发生发展过程中的作用和机制, 对与KC相关的最新抗肝纤维化基因治疗策略作一盘点. 阅读本文可以使读者对该方面的研究有较综合的认识.

■应用要点
KC参与肝纤维化发生发展的各个阶段, 以枯否细胞为靶点的治疗策略为抗纤维化治疗提供了新的思路和广阔的前景.

方面也向我们展示了众多有益的提示和新的研究方向. 因此, 以KC为靶点, 研制针对KC的HF防护措施, 不仅对基础性研究有价值, 更重要的是对于临床肝脏疾病的治疗发展具有重大的现实意义.

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■同行评价

本文综述了枯否细胞在肝纤维化中的作用, 有一定的新意, 对国内外相关领域的研究了解比较深入, 文笔流畅.

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