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文献综述 REVIEW

肝卵圆细胞在肝脏疾病中的研究现状

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Hepatic oval cells and liver diseases

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Abstract

In recent years, hepatic oval cells (HOC) have gradually become a research hotspot, and their participation in the reconstruction of liver structure and function has been preliminarily confirmed. This provides a new direction for the study of the pathogenesis and treatment of liver injury, hepatitis, liver fibrosis, cirrhosis, liver neoplasms and other liver diseases. This paper will discuss the relationship between hepatic oval cells and liver diseases.

Key Words: Hepatic oval cells; Liver diseases; Cell transplantation

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摘要

近年来, 肝卵圆细胞(hepatic oval cells, HOC)逐渐成为研究热点, 其参与肝脏结构与功能重建已得到初步证实, 这为探讨肝损伤、肝炎、肝纤维化、肝硬化、肝癌等肝脏疾病的发生、发展机制及防治方法提供了新方向和突破点, 但其分子机制仍有待深入研究.

关键词: 肝卵圆细胞; 肝脏疾病; 细胞移植

核心提示: 本文对肝卵圆细胞(hepatic oval cells, HOC)在肝脏疾病的治疗中的作用进行了综述, 认为HOC的研究目前仍停留在基础实验研究, 要较为成熟地用于临床治疗, 还有许多问题亟待解决. 但越来越多动物实验研究及临床尝试成功的报道亦向世人展示了HOC应用于临床的良好前景.

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背景资料
肝是体内以代谢与解毒功能为主的一个重要器官, 担负着重要而复杂的生理功能, 目前还没有人工器官或装置能够模拟肝脏所有功能, 而我国是肝脏疾病发病率较高的国家, 各种原因所致的肝脏疾病严重危害着我国人民的健康. 肝卵圆细胞(hepatic oval cells, HOC)是具有多分化潜能的肝干细胞, 在一定条件下可被激活向肝细胞和胆管细胞甚至其他组织细胞分化, 其参与肝脏结构与功能的重建已得到初步证实, 表现出其临床应用价值, 但也有研究表明HOC与肝硬化和肝癌的发生关系密切, 其发生的分子水平方面的机制仍有待于深入的研究.

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研发前沿

HOC的研究已经在动物模型和临床研究中取得了部分成功, 为最终治愈肝病开辟了新的研究方向. 目前HOC移植大多仅限于动物实验研究,若能应用于临床, 将为肝细胞移植和生物型人工肝提供重要的细胞来源, 可以缓解受体需求较多与供体肝脏严重缺乏之间的矛盾, 但其操作性仍需进一步确定.

0 引言

肝是人体内最大的实质性脏器, 是体内以代谢与解毒功能为主的一个重要器官, 担负着重要而复杂的生理功能[1], 目前还没有人工器官或装置能够模拟肝脏所有功能, 而我国是各型病毒性肝炎发病率较高的国家[2], 各种原因所致肝损伤、肝炎、肝纤维化、肝硬化、肝癌等肝脏疾病严重危害着我国人民的健康. 肝卵圆细胞(hepatic oval cells, HOC)是具有多分化潜能的肝干细胞, 可被激活向肝细胞和胆管细胞甚至其他组织细胞分化[3], 其参与肝脏结构与功能的重建已得到初步证实, 表现出其临床应用价值, 但也有研究表明HOC与肝硬化和肝癌的发生关系密切[4], 其发生的分子水平方面的机制仍有待于深入的研究. 现对HOC在肝脏疾病中的研究现状进行综述.

1 HOC

HOC最初是1944年由Opie在大鼠诱发肝癌的研究过程中发现的[5]. 1956年Farber首次将其命名为HOC[6]. 其形态学特点为: 体积小, 卵圆形, 核浆比例大, 核呈卵圆形, 胞浆嗜碱性且浅染. 有证据[7]表明HOC是存在于赫林管(Hering管)及门静脉周围的双电位肝干细胞. 也有部分研究发现HOC不仅位于门脉周围, 也分散在整个肝小叶, 存在于肝实质内. 正常情况下, HOC处于静止状态, 不能在正常的成体肝内检测到, 当肝实质严重受损或细胞增殖能力降低时, 或在化学因素引发的肝细胞癌早期, 可被激活, 并进一步增殖分化成肝实质细胞, 从而完成肝脏结构和功能的重建, 修复受损肝脏.

Tarlow等[8]的研究表明, 肝源性HOC主要来源于肝实质细胞与终末胆管上皮细胞相结合部及附近, 即Hering管. 另有学者[9,10]认为, HOC可能存在非肝源性来源, 如来源于骨髓干细胞、胚胎干细胞. 但目前非肝源性理论还存在较大争议, 绝大多数研究结果表明HOC主要来源于肝内.

现在尚未发现HOC的确切性标志物, 目前常用的HOC标志物有: 肝细胞标记蛋白: 白蛋白(albumin, Alb)、HepParl、G-6-P、甲胎蛋白(α-fetoprotein, AFP)等; 胆管细胞标记蛋白OV-6、CK7、CK8、CK19、α-GTP等; 造血干细胞标志物C-kit、CD34[11]、Thy-1[12]、CD45、fit-3R、干细胞因子(stem cell factor, SCF)、c-kit等. HOC还可表达CK43、CK18、CK14、CD29、CD38、CD43、CD69、c-met、EpCAM、CAM 5.2[13]、波形蛋白等. 随着研究深入, 人们又不断从发现了新的HOC分子标志物: 如类Delta蛋白、Oct3/4[14]、CD49f、CD133[15]、CD109[16]、CD24[17]、Sca-1[18]等. 这些标志物可能是未来进行研究的有用工具, 将有利于在体内和在体外的HOC细胞分选研究.

HOC增殖分化是多因素作用的结果, 有学者[19]将其分为细胞内调控和细胞外调控. 其中细胞外调控包括细胞因子的调控及细胞外基质(extracellular matrix, ECM)的调控. 参与调控HOC的细胞因子包括肿瘤坏死因子(tumor necrosis factor, TNF)[20], 白介素(白介素-15家族、白介素-6家族[21,22]等)、干扰素(interferon, IFN)(如IFN-γ)[23-25]、生长因子[包括肝细胞生长因子(hepatocyte growth factor, HGF)、表皮细胞生长因子(epidermal growth factor, EGF)、转化生长因子(transforming growth factor, TGF)[26]、结缔组织生长因子(connective tissue growth factor, CTGF)和酸性成纤维细胞生长因子(acidic fibroblast growth factor, aFGF)]、趋化因子、SCF[27]、尿激酶纤溶酶原活化因子(urokinase type plasminogen activator, uPA)、白血病抑制因子(leukemia inhibitory factor, LIF)、溶血磷脂酸(lysophosphatidic acid, LPA)、淋巴毒素(lymphotoxin, LT)-β与基质细胞衍生因子-1(stromal cell-derived factor-1, SDF-1)[28]等. 肝组织局部微环境(皮下组织微环境和肝内微环境)对于促进HOC的增殖、分化、肝的定植亦有重要作用, 并可加速HOC介导的肝再生[29]. 细胞内调控包括基因[30-33]、转录因子的调控[34,35]及生物钟对细胞周期的调控.

HOC的分离和纯化方法很多, 荧光活化细胞分离法(fluorescence-activated cell sorting, FACS)、两步胶原酶灌流消化法、两步胶原酶法加Percoll密度梯度离心法、免疫磁珠细胞筛选法[11]和单克隆抗体法等近年来已成功地从大鼠胎肝、成年肝脏及骨髓中分离或定向诱导分化出肝干细胞, 并可用放射性同位素或基因标记技术准确直观的跟踪HOC在体内的演变、分布、分化. 目前Y染色体特异性聚合酶链反应(PCR)技术亦会用来追踪HOC[29,36].

2 HOC与肝脏疾病的关系

2.1 HOC与肝损伤及修复的关系 肝脏具有很

强的再生能力, 动物实验证明将正常肝切除70%-80%, 仍可维持正常的生理功能, 且能在约6 wk后修复生长到将近原来的重量[1], 肝脏轻度损伤时主要由肝实质细胞增殖修复损伤, 而肝脏受到严重损害, 肝细胞大量坏死或其分裂增殖受到抑制时, HOC表现出较高的可塑性和持久的增殖活性[37], 大量增殖并分化为肝细胞和胆管上皮细胞[38], 但其所表达的分子标志与成熟肝细胞及胆管上皮细胞都有不尽相同之处.

HOC增生的研究大多来自动物模型, 即应用致癌物来抑制肝细胞增殖而使HOC增生[39], 致癌物包括2-乙酰氨基芴(2-acetylamino-fluorene, 2-AAF)、胆碱缺乏乙硫氨酸饮食(choline-deficient/ethionine-supplemented diet, CDE)、D-半乳糖胺或呋喃妥因等. 在人类慢性肝病如慢性肝炎、肝硬化、胆道闭锁、酒精性肝病、血色病及肝肿瘤等的肝组织中均有HOC存在, 增生的HOC主要位于胆管区, HOC增生程度与肝病的炎症程度呈正相关, 故可认为HOC的生长和增殖可作为预测预后的一项重要指标. 有数据[40]表明, HOC可分化为肝细胞, 协助胆管不典型增生, 生产出化生上皮黏蛋白, 使损伤的肝脏再生. 由于损伤因素的不同, HOC所高表达的分子标志也有所不同, 从而决定了HOC的分化方向及趋势. HOC的演变和分化, 可用于治疗多种肝脏疾病. HOC的研究已经在动物模型和临床研究中取得了部分成功, 为最终治愈肝病开辟了新的研究方向.

2.1.1 HOC与脂肪肝的关系 在脂肪肝病患者的肝组织中, 脂肪变性的肝细胞DNA氧化损伤, 再生能力明显减弱, 此时HOC代偿性增生, 向中间型肝细胞样细胞分化修复损伤, 限制了损伤的扩大. 现已有学者[41]发现, 诱导HOC的损伤修复机制来替换损坏的肝细胞, 对限制脂肪肝的发展有重要意义. 但亦有研究[42]表明, 卵圆细胞的增殖并没有显著提高脂肪肝的再生.

2.1.2 HOC与肝炎的关系 Haybaeck等[43]的研究表明卵圆细胞参与了乙型肝炎病毒和丙型肝炎病毒引起的慢性肝炎和肝细胞癌. 另有Sobaniec-Lotowska等[44]的研究发现慢性乙型肝炎患者的卵圆细胞(肝前体细胞和肝细胞样细胞)和肝纤维化分期之间存在明显的关系. Hines等[45]的研究证实, T细胞介导肝切除术后早期肝炎改变的细胞因子反应, 减少肝细胞的再生, 诱导对NK细胞敏感的卵圆细胞和造血细胞扩增, 对抗炎症反应. Ma等[46]发现HOC在人类肝脏慢性病毒性肝炎经常被检测到, 间接表明在该状态下HOC增殖与肝再生相关联. 而在严重的肝毒性损伤时, HOC高水平表达的ABC转运蛋白基因可能有细胞保护功能[47].

2.1.3 HOC与肝纤维化的关系 有研究[48,49]显示减少卵圆细胞的活化与预防纤维化进展密切相关. Pi等[50,51]的研究表明, CTGF和整合素αvβ6是潜在的可用于控制胆管反应和肝纤维化相关肝脏疾病的治疗靶点. 另有Tsolaki等[52]的数据表明, 普乐沙福和粒细胞集落刺激因子(granulocyte colony stimulating factor, G-CSF)的差异作用在伤口愈合过程中, 诱导肝干细胞的增殖和降低的肝脏炎症, 发挥了有效的抗纤维化作用.

2.1.4 HOC与糖尿病的关系 糖尿病是丙型肝炎和肝细胞癌的独立危险因素, 脂肪肝是2型糖尿病(type 2 diabetes mellitus, T2DM)患者的一个明显伴随症状, 他可以发展为脂肪性肝炎、脂肪性肝纤维化或肝硬化. 并且T2DM患者的肝病(如酒精性脂肪肝疾病、慢性病毒性肝炎、血色素沉着症、酒精性肝病和肝硬化)患病率更高. 然而, 只有有限的证据表明确定肝脏疾病对糖尿病的发展之间的相关性[53]. 而Yechoor等[32]证实了转录因子Neurogenin3(Ngn3)的传递可以诱导细胞谱系从HOC转分化为胰岛谱系, 这一研究可以应用于治疗多种器官疾病, 是一种很有前途的糖尿病的新疗法. Li等[54]的研究也支持了Yechoor的观点.

2.2 HOC与终末期肝病的关系 HOC肝内移植可改善暴发性肝衰竭(fulminant hepatic failure, FHF)大鼠的肝功能并增加受体的存活率已得以证实. 对于终末期肝病的患者, 进行HOC植入, 亦可改善肝功能并提高生存率[55]. HOC移植也借鉴了肝细胞移植的方法, 在大鼠肝移植模型中发现植入的HOC与受体肝融合并分泌白蛋白, 表明HOC移植可以改善肝再生, 可以被开发作为治疗严重的肝损伤的方法[39,56]. HOC可分化为具有功能的成熟肝细胞, 这将为肝细胞移植和生物型人工肝提供重要的细胞来源, 有利于缓解供体肝脏严重缺乏的矛盾. 随着研究的不断深入, HOC不断在移植、生物

相关报道
Haybaeck等分析了在人类乙型肝炎病毒(hepatitis B virus, HBV)或HCV引起的慢性肝炎、肝癌或非病毒性肝癌的肝脏中淋巴毒素(lymphotoxin, LT)α, LTβ, LIGHT, 肿瘤坏死因子-α(tumor necrosis factor α, TNF-α), LTβR和TNFR1的转录水平, 并与健康的肝脏标本相对照, 表明HOC可能参与了乙型肝炎病毒和丙型肝炎病毒引起的慢性肝炎和肝细胞癌.

创新盘点
本文对HOC在肝脏疾病中的应用进行了较为全面、清晰的总结, 较为真实、客观的反映了目前HOC在肝脏疾病中的研究进展, 对后续的相关动物实验和临床研究有一定的指导意义.

人工肝、各种终末期肝病的治疗等方面开辟新的途径.但HOC的分化过程和机制非常复杂, 分化异常可能导致肝癌的发生.

2.3 HOC与肝癌的关系 大量研究结果已证明了HOC的可塑性, 而HOC的恶性转化参与了肝癌的发生发展, 而差异性表达的miRNA、局部微环境在HOC分化成为肝细胞癌(hepatocellular carcinoma, HCC)的过程中发挥重要作用[11,30,34,57-63]. Dong等[64]发现上皮-间质转变促进皮下植入HOC分化转移到间质肿瘤组织. 乙型肝炎病毒X蛋白(protein X from hepatitis B virus, HBx)似乎可以通过激活c-myc诱导HOC恶性转化, 在HCC的发展中起着至关重要的作用[65], 在HBx和黄曲霉素的共同作用下HOC可部分分化成肝细胞癌. Knight等[20]的研究结果表明TNF-1在肝癌的癌前阶段通过参与了HOC的增殖, 减少肿瘤形成的发生率. 有研究[66]运用免疫组织化学方法检测不同肝病组(检测对照组、肝血管瘤组、良性肝病合并肝硬化组、肝癌组、肝癌合并肝硬化组)肝脏组织中表达Ck7、Ck8/18、Ck19、C-kit、AFP的HOC数目, 结果显示肝癌组、肝癌合并肝硬化组间表达的C-kit阳性的HOC数有显著性差异(P<0.05), 说明HOC参与了原发性肝癌的生长、细胞分化调控. 同时, 也有学者认为HOC并未参与所有肝癌的发生、发展, 因为许多可激活癌前肝细胞增生和肝癌形成的肝肿瘤基因启动因子, 并不激活HOC增生. TNF信号参与卵圆细胞增殖、肝脏癌变的前期阶段, 故TNF的炎症通路可以作为用于预防性治疗肝癌的靶点[20]. 其他参与HOC增殖、分化调控的细胞因子、信号通路也可视为潜在的肝脏疾病的防治靶点[4].

3 HOC移植的在肝脏疾病中的应用

3.1 HOC移植应用于肝脏疾病的潜能 肝移植作为目前治疗终末期肝病、肝癌等疾病的唯一有效手段, 由于费用昂贵、肝源稀缺及存在排异反应, 使得其大范围推广受到了限制, 故医务工作者开始考虑肝干细胞移植的可行性, 而HOC体积小、易获取、可分化为具有功能的成熟肝细胞, 若能应用于临床, 将为肝细胞移植和生物型人工肝提供重要的细胞来源, 可以缓解受体需求较多与供体肝脏严重缺乏之间的矛盾, 但其移植后有可能不重新填充正常肝脏,其操作性仍需进一步确定[67]. 目前在肝干细胞移植的基础研究和临床应用中, 采用的植入方式有门静脉、肝动脉、外周静脉、脾内植入等. 临床上用于临床移植尝试治疗肝病的干细胞多为骨髓造血干细胞, 并取得了较为可喜的结果[68].

3.2 HOC移植应用于肝脏疾病的争议 目前HOC移植大多仅限于动物实验研究, 研究人员已经建立过多种模型, 但研究发现HOC在不同的种属之间也有较大的差异性, 大鼠、小鼠模型的研究结果之间尚且存在较大差异, 而这些模型显然不太适合研究人类HOC, 故必要建立一个新的、有效的模型来研究人类的HOC[10]. 或可将HOC移植入肝损伤动物模型体内观察其分布、演变、再生及修复肝脏的潜能等方法进行鉴别, 但耗时长且花费较高, 可行性较差. 而HOC存在恶变可能, 虽然有研究[69]表明经过长时间的培养, HOC可保留祖细胞特性, 没有出现自发的恶变, 另有Bmil通路通过限制Ink4a/Arf位点, 可防止HOC往肿瘤方向发展[70], 但其运用于临床的安全性及长期有效性缺乏相关证据, 同时亦使研究者面临伦理学方面的挑战, 这将限制HOC的应用. 除此之外, 现尚未发现HOC的确切性标志物, 其体外提取、纯化、培养等技术相对低效, 且采用何种移植方式最为高效尚无科学定论. 研究者试图通过对某些细胞因子的调控使得HOC能够更加快速有效地修复受损肝脏, 体外诱导HOC定向分化后再植入体内治疗肝脏疾病, 但尚未找到较好的应用工具及方法.

4 结论

HOC在各种原因所致肝脏损伤、肝炎、肝纤维化、肝硬化、肝癌等肝脏疾病的治疗方面拥有广阔的应用前景. 但HOC的研究目前仍停留在基础实验研究, 离临床应用还有很远的距离. HOC要较为成熟地用于临床治疗, 还有许多问题亟待解决. 但越来越多动物实验研究及临床尝试成功的报道亦向世人展示了HOC应用于临床的良好前景.

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■应用要点

HOC要较为成熟地用于临床治疗，还有许多问题亟待解决，本文对HOC在多种肝脏疾病中的相关研究作综述，进一步指导动物实验和临床研究方向.

名词解释

终末期肝病(ESLD): 各种原因如肝炎、肝硬化、肝癌、药物性肝损伤和自身免疫肝病等所致肝功能极度减退甚至衰竭的一种病理状态.

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同行评价
本文综述了HOC在肝脏疾病中的研究现状, 参考文献较多, 有一定的临床意义.

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