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文献综述 REVIEW

肝卵圆细胞分子标志物的研究进展

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■背景资料
肝卵圆细胞来源于肝门管区有一些增生的小细胞. 增殖的卵圆细胞最终能分化为成熟的肝细胞及胆管细胞. 这类细胞通常能够参与肝细胞再生和肝脏损伤修复.

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Progress in research of molecular markers for hepatic oval cells

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Abstract
Hepatic stem cells have the capacity of self-renewal, proliferation and differentiation and can produce progeny cells that have the same phenotypes and genotype as parental cells. The cells originate from the foregut endoderm and exist in the form of hepatic cells in embryonic liver, and small oval cells (OCs) with a large nuclear/cytoplasmic ratio and special cell markers in the adult liver. Hepatic stem cells are normally in the dormant state and divide at a very slow rate. The cells begin to be activated to proliferate quickly and transit from quiescent phase to proliferative phase when the liver is resected by operation or injured by drugs. In recent years, numerous studies have confirmed that hepatic OCs are hepatic stem cells that have the bipotential capability of differentiation into mature hepatocytes and biliary epithelial cells when hepatocyte proliferation is inhibited and liver regeneration compromised. The research of the role of hepatic OCs in the management of acute and chronic liver dysfunction, advanced cirrhosis, other liver diseases, and diabetes caused by pancreatic lesions has attracted wide attention. Great efforts have been made to find and isolate hepatic OCs. This review discusses the progress in research of molecular markers for hepatic OCs.

Key Words: Hepatic oval cells; Molecular markers; Hepatic stem cells

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摘要
肝干细胞是一类具有自我更新与增殖分化能力的细胞, 能产生表现型与基因型和自己完全相同的子细胞. 起源于前肠内胚层, 在胚胎发育过程中以肝细胞的形式存在, 在成年哺乳动物肝中以小卵圆细胞存在, 表现为核大而胞质小并具有特殊的细胞标记. 正常情况下这类细胞处于静止期, 增生分裂非常慢. 当切除或药物损伤后, 这类细胞开始活化增生, 迅速从静止期进入增殖期. 近年来的研究已经证实, 肝卵圆细胞在肝细胞严重受损和分裂增生受抑制时呈现出向肝细胞和胆管上皮细胞双向分化的潜能, 是一种肝脏的干细胞, 目前已经成为热点. 肝卵圆细胞不仅在急慢性肝功能不良、晚期肝硬化等肝脏病变, 在胰腺病变引起的糖尿病等疾病研究中也开始引起兴趣. 但如何发现和获得肝卵圆细胞始终是解决此类问题的关键. 本文就肝卵圆细胞的分子标志物的研究进展作一综述.

关键词: 肝卵圆细胞; 分子标志物; 肝干细胞

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0 引言
临床上, 进行肝干细胞移植治疗各类型终末期慢性肝病已被深切关注. 肝卵圆细胞(hepatic

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oval cells, HOC)作为肝脏干细胞的观点已被广泛接受. 肝卵圆细胞于1937年由Kinosita首次发现, 其细胞形态体积较小, 核呈椭圆或圆型, 细胞质浅染. Farber等[1]在研究肝癌的病理变化中, 观察到肝卵圆细胞来源于肝门管区有一些增生的小细胞. Wilson和Leduc在研究肝损伤的修复机制中, 证实增殖的卵圆细胞最终能分化为成熟的肝细胞及胆管细胞, 首先指出这类细胞为肝脏内原始肝干细胞[2]. 这类细胞通常能够参与肝细胞再生和肝脏损伤修复. 当肝脏受到药物刺激, 或其他原因造成的严重损伤或者肝功能受到严重损害时, 这类细胞被激活并增殖、分化为肝实质细胞和胆管上皮细胞, 使得肝功能得以重建.

1 肝卵圆细胞的分子标志物

近年来随着对肝卵圆细胞研究的不断深入, 已经确立了一些肝卵圆细胞高度表达的分子标志物. 依据其表达于细胞部位的不同, 将其分为3类: 细胞膜类-表达于细胞膜表面的分子标志物类、细胞胞质类-表达于细胞胞质的分子标志物类、细胞胞核类-表达于细胞胞核的分子标志物类.

1.1 细胞膜类 依据细胞膜类分子标志物类型的不同, 将其分为CD分子类、受体类及膜蛋白类.

1.1.1 CD分子类: CD分子为细胞分化分子, 在细胞分化、增殖、迁移中发挥着重要的作用. Yovchev等[3]在肝卵圆细胞增殖模型中, 研究发现大量增殖的肝卵圆细胞表面表达多种CD分子: CD24、CD44、CD90、CD133. CD24是一种高度糖基化蛋白质分子, 与细胞黏附有关, CD24的表达参与了细胞的迁移, 并调节细胞生长, 增殖. Nestl等[4]应用Northern杂交印迹和免疫组织化学方法对小鼠肿瘤细胞及人类肿瘤组织进行了研究, 证实CD24表达与肿瘤的转移表型相. Baumann等[5]用RNA干扰技术下调肿瘤细胞的CD24表达, 发现培养的肿瘤细胞数量明显减少, 提示CD24在肿瘤细胞生长过程中起重要作用. CD44是一种细胞膜表面糖基化蛋白质分子, 参与细胞异质性黏附, 研究表明CD44表达强度增加将有助于细胞迁移. Seiter等[6]在给接种有转移BSp73ASML细胞的大鼠, 从静脉注射识别CD44的单克隆抗体, 发现能明显抑制肿瘤细胞生长和转移. CD90和CDl33均为干细胞分子标志物[7,8], CD90又称Thy-1抗原, 是细胞黏附分子免疫球蛋白超家族中最小的成员, 与细胞增殖、分化等有重要关联[9]. CDl33是一种细胞表面抗原, 是干细胞独特的分子标志, 其显著特点就是: CDl33的表达会随着细胞的分化成熟而迅速下调[8], 常被用于干细胞分离和鉴定. 在D-半乳糖胺/2-乙酰氨基菊, 半肝切除构建鼠肝损伤模型, Yovchev等[10]进一步研究证实了增殖的肝卵圆细胞的确有分子CD44, CD24, CD133的表达. 同时发现CD44, CD24分子在胆管细胞中也有表达, CD133分子在成熟肝细胞中未表达; 肝卵圆细胞作为肝干细胞之一, CD44, CD24在肝卵圆细胞中持续表达或高表达, 提示肝卵圆细胞存在着正处在向胆管细胞分化的可能, CD133在肝卵圆细胞中低表达或者表达消失, 提示肝卵圆细胞正处在向成熟肝细胞分化的可能.

在研究胚胎肝卵圆细胞中, CD分子表达各有不同, Rao等[11]发现EpCAM阳性的肝卵圆细胞在增殖的过程中表达分子CD90, CD34, 在分化过程中表达CD45, 同时也有CD49f的表达. 其中, CD90, CD45, 分别被认为是肝前体细胞, 胆管上皮细胞, 造血干细胞的表面分子标志[12], CD49f则被认为是具有分化为肝细胞的潜能的原始内胚肝细胞的一种表面分子标志[13]; Nyamath等[14]研究发现CD34分子表达阳性的胚胎期肝卵圆细胞最终可表达AFP, ALB. CD45分子属于典型的受体型蛋白酪氨酸磷酸酶, 为Ⅰ型跨膜蛋白, 位于白细胞表面的白细胞共同抗原, 参与免疫细胞的分化, 发育等过程[15]. 在肝卵圆细胞中表达, 与肝卵圆细胞发育分化密切相关; CD49f属于整合素家族成员, 介导了细胞局部黏附和信号传导. 积极参与细胞的生长、分化、增殖的调控[16,17]. CD49f表达于肝卵圆细胞, 参与调控肝卵圆细胞的分化、增殖. CD34是一种相对分子质量为105-120 kDa的跨膜细胞表面磷酸糖蛋白, 为一种造血干/祖细胞的表面标志. 选择性地局限表达于造血干/祖细胞[18,19], 肝卵圆细胞中表达CD34, 提示肝卵圆细胞可能具有多分化潜能, 为肝卵圆细胞作为肝干细胞之一提供佐证. 另有研究发现CD34、CD90、CD133、CD49f在肝卵圆细胞膜上的表达则持有不同观点, Schmelzer等[20]用细胞免疫磁珠分选出的胚胎肝卵圆细胞表达分子发现造血干细胞分子标志物CD34、CD90未见表达; CD133可见表达; 而CD133、CD49f曾被视为2个独有的分子标志去分辨胚胎肝卵圆细胞[21,22]; Liu等[23]研究也证实了CD133、CD49f是2个高选择性的分子标志针对胚胎肝卵圆细胞, 这与Rountree等[24]进行肝干细胞筛选时, 证实肝卵圆细胞表达分子CD133、CD49f相一

■研发前沿
近年来的研究已经证实, 肝卵圆细胞在肝细胞严重受损和分裂增生受抑制时呈现出向肝细胞和胆管上皮细胞双向分化的潜能, 是一种肝脏的干细胞, 目前已经成为热点.

■应用要点
肝卵圆细胞不仅在急慢性肝功能不良、晚期肝硬化等肝脏病变, 在胰腺病变引起的糖尿病等疾病研究中也开始引起兴趣.

致; 同时, Liu等[23]用流式细胞仪检测到胚胎肝卵圆细胞还表达分子CD117. CDl17又称C-kit受体, 属于Ⅲ型蛋白酪氨酸激酶受体超家族成员[25], 为Ⅰ型跨膜性糖蛋白. 正常情况下CD117的活化需要干细胞因子(SCF)的参与[26]. SCF是重要的造血生长因子, 与其他细胞因子协同作用可刺激造血干/祖细胞的增殖和分化. SCF-CD117相互作用可能是干细胞生存的关键因素. CDl17在肝卵圆细胞的表达, 参与调控肝卵圆细胞生长、增殖和分化.

CD分子在肝卵圆细胞不同分化阶段呈现不同表达, 具备多向性分化潜能, 提示肝卵圆细胞有着肝干细胞特质. 肝卵圆细胞是否具有防御性免疫功能, 与造血干细胞是否具有同源性有待进一步研究证实.

1.1.2 受体类: 在肝卵圆细胞增殖模型中, Yovchev等[3]研究指出, 肝卵圆细胞表面有多种受体的表达: Dmbt 1, Ednra Endothelin receptor type A, Ednrb Endothelin receptor type B, Sctr Secretin receptor, Gabrp (Gamma-aminobutyrate, type A receptor π), Fractalkine, Ddr1, Smo, Ros1, Integrinβ4, Integrin α6; Chiu等[27]应用2-乙酰氨基芴/四氯化碳构建鼠肝损伤模型, 在肝再生修复的过程中, 发现增殖的肝卵圆细胞表达多种受体: CTGF受体、HGF受体、SCF受体、IFN受体、FGF-1受体、jagged 1受体、pleiotrophin受体、IGFBP 1受体、TGF 2受体、secretin受体. 这些受体对肝卵圆细胞的增殖、迁移、分化起着重要作用. 其中, HGF受体与HGF结合, 可明显刺激肝卵圆细胞有丝分裂, 促进肝卵圆细胞增殖; Ednra Endothelin receptor type A, Ednrb Endothelin receptor type B, Sctr Secretin receptor, Fractalkine, Integrinβ4, Integrinα6这类受体与肝卵圆细胞迁移相关. Dmbt 1, Gabrp (Gamma-aminobutyrate, type A receptor π), Ddr1, Smo, Ros1, CTGF, SCF, IFN, FGF-1, jagged 1, pleiotrophin, IGFBP 1, TGF 2, secretin这类受体参与肝卵圆细胞的分化过程.

1.1.3 膜蛋白类: 也有研究发现, 在肝卵圆细胞增殖, 分化, 迁移及信号传导过程中, 有膜蛋白的参与. DLK1(delta-like protein/preadipocyte factor 1)是一种跨膜蛋白, 其结构特征为蛋白的细胞外区域拥有6串在结构及氨基酸序列上与表皮生长因子高度同源的重复结构, 属于表皮生长因子家族的成员之一, 定位于人类染色体14q32, 是真正的祖细胞表面标志[28,29]. Huang等[30]研究发现肝卵圆细胞表达分子DLK1, 参与肝卵圆细胞的增殖分化过程; 磷脂酰肌醇蛋白聚糖-3(GPC3), 为硫酸肝素糖蛋白家族成员之一. GPC3通过糖基磷脂酰肌醇锚定于细胞膜上. GPC3 mRNA在胎肝中高表达, 在成人表达关闭[31]. Grozdanov等[32]应用D-半乳糖胺、2-乙酰氨基芴和半肝切除构建肝损伤模型, 在肝修复再生早期, 发现大量增殖的肝卵圆细胞高表达分子Gpc3, 这种分子可作为肝卵圆细胞一种新的标志物. 与肝卵圆细胞分化密切相关. Epiplakin为细胞支架结合蛋白, 锚定于细胞膜上, 参与细胞增殖、分化、迁移的过程, 属于细胞功能型膜蛋白. Matsuo等[33]在胆碱缺乏的乙硫氨酸补充(choline-deficient ethionine–supple-mented, CDE)饮食建立的肝损伤模型中, 发现肝再生过程中增殖的肝卵圆细胞表达Eppk1. 细胞黏附分子是一类细胞膜表面跨膜糖蛋白, 与细胞的信号传导、细胞迁移、分化密切相关, 在肝卵圆细胞表面也有表达. 上皮型钙黏蛋白(E-cadherin)为上皮细胞标志物, 神经型钙黏蛋白(N-cadherin)为间质细胞标志物, E-cadherin表达的下调和N-cadherin表达的上调被称为EMT现象, 这种现象表现为细胞骨架系统排列发生变化, 细胞黏附功能下降, 易于细胞迁移. Zhao等[34]研究肝卵圆细胞分化过程中发现了分子N-cadherin的表达; Tirnitz-Parker等[35]在胆碱缺乏的乙硫氨酸补充(choline-deficient ethionine-supple-mented, CDE)饮食诱导的卵圆细胞增殖模型中, 证实了增殖的肝卵圆细胞表达分子E-cadherin; EpCAM(Epithelial cell adhesion molecule, 上皮细胞黏附分子)作为细胞膜表面的一种跨膜糖蛋白, 主要介导同源细胞之间的黏附, 有促进细胞迁移的作用. Rao等[11]研究证实了EpCAM分子肝卵圆细胞膜上也有表达. Matrilin-2是近年新发现的非胶原型细胞外基质蛋白的新家族成员之一, 有4个呈现出大致相同结构的家族成员. 唯独不同的是, Matrilin-2包含1个位于第2个vWFA域和寡聚合反应域之间的片段. 在卵圆细胞增殖和分化过程中, 卵圆细胞与肝脏胞外基质成分Matrilin-2具有紧密的解剖学关系, 介导的肝再生发挥重要作用. Szabó等[36]在大鼠肝再生实验动物模型AAF/PH中发现Matrilin-2 mRNA只在增殖肝卵圆细胞中表达, 提示Matrilin-2可能是高分化增殖能力肝卵圆细胞的标记.

1.2 细胞胞质类 在D-半乳糖胺/2-乙酰氨基芴, 半肝切除构建鼠肝损伤模型中, Yovchev等[10]研

究发现, 在肝再生修复过程中, 大量增殖的肝卵圆细胞还表达分子: OV-1, 间质细胞分子标志物: 波形蛋白、内皮蛋白、成骨蛋白7; Dorrell等[37]应用DDC(1, 4二氢-3, 5吡啶二甲酸二乙酯)诱导的肝卵圆细胞增殖的模型中, 发现大量增殖的肝卵圆细胞表达分子OC2-1C6, OC2-2A6, OC2-6E10, 同时, 表达胆管上皮细胞分子标志物: MIC1-1C3, OC2-1D11, OC2-2F3; 这些在肝卵圆细胞的细胞质中表达的多类型细胞标志蛋白, 为肝卵圆细胞多向性分化提供依据.

1.3 细胞胞核类 Golding等[38]研究发现, 经D-半乳糖胺处理过的鼠肝在肝再生过程中, 增殖的肝卵圆细胞表达分子HNF1α, HNF4α, C/EBPα, β, δ, Foxa1, Foxa2. Shafritz等[39]在肝损伤修复过程中, 同样发现增殖的肝卵圆细胞高表达细胞分子HNF4α和HNF6. HNF1α, HNF4α, C/EBPα, β, δ, HNF6, Foxa1, Foxa2均属于HNF家族成员中的转录因子, 这些转录因子及其之间的相互作用构成的复杂调控网络, 精确地调控肝脏的发育和肝细胞增殖, 分化及其功能[40]. 基因分析证明了肝细胞分化中HNF4α、C/EBPα和HNF1α的作用. HNF1α和HNF4α主要控制葡萄糖代谢以及脂质和氨基酸代谢; HNF6控制一些生长因子的分泌, 如抑制糖皮质激素的活性; C/EBPα主要调节葡萄糖和糖原代谢以及脂质平衡. 但C/EBPα也可能抑制肝母细胞增殖和胆管发育, 并介导HGF诱导的肝内基因表达[41,42]. 近期研究指出Foxa1、Foxa2调控肝卵圆细胞定向分化胆管细胞及增殖水平, 开始发育的肝卵圆细胞中敲除FoxA1和FoxA2后, 突变体则因胆管细胞过度增殖而形成超常增生的胆管系统[43]. Suzuki等[44]证实了肝卵圆细胞分化阶段有转录调控分子Tbx3表达, 调控分子Hhex[45], Sall4[46]也有表达; Tbx(T-box)属发育调控相关转录因子家族, 表达产物作为真核生物的转录调控因子, 具有重要的发育调控功能, 在脊椎和非脊椎动物胚胎的形态和组织发生中发挥着重要作用[47]. Tbx3是T-box家族转录因子之一[48], 参与调节细胞分化, 正常表达量调控细胞定向分化, 过表达可导致细胞去分化, 恶变促发肿瘤形成. 造血细胞表达的同源异形框因子(hematopoietically expressed homeobox, Hhex)调控心源性区域内能决定肝细胞命运的腹侧内胚层的增殖和定位[49]. 缺失Hhex的小鼠胚胎虽然可以进行肝向特化(hepatic specification), 但是不能完成肝芽的形态学形成[50]. 在早期肝卵圆细胞内对Hhex基因进行条件性敲除后, 也不能分化成肝细胞[45]. Sall4促进胆管分化, 而Tbx3则抑制分化[44,46,51]. Tbx3敲除小鼠肝卵圆细胞增殖减弱而胆管分化增强. Sackett等[52]采用胆管结扎术致肝损伤来研究肝再生, 结果发现大量增殖肝卵圆细胞高表达分子Foxl1, Foxl1属于Fox基因家族成员, 是功能多样的转录因子, 含有“翼螺旋”的DNA结合区域[53,54], 参与转录调控和信号转导途径在细胞生长增殖、细胞分化、代谢、凋亡等方面发挥关键作用. 由此, 细胞核类分子标志物的表达与肝卵圆细胞信号传导, 调控肝卵圆细胞生长、增殖、分化密切相关.

2 结论

目前, 尚未找到肝卵圆细胞的特异性标志. 可能与其阶段性表达、多分化潜能或异质性有关. 尽管通过细胞膜、细胞质和细胞核等各部位的标志物已经基本达到标志、分离、纯化的目的, 但仍然缺乏一种简单有效准确的标志物, 相信在不久的将来, 随着肝卵圆细胞的进一步研究, 对其认识的不断深入, 终将会找到一种或几种理想的标志物, 为肝功能衰竭的有效治疗提供有力保障.

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■同行评价
本文主要综述了肝卵圆细胞相关分子标志物的研究进展, 内容丰富详实, 文献信息量大, 具有较好的参考意义.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.