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文献综述 REVIEW

肝型脂肪酸结合蛋白研究进展

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Advance in liver-type fatty acid binding protein

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Abstract

Liver-type fatty acid binding protein (L-FABP) is an important member of FABP family, and mainly expressed in liver, intestine and kidney. In the past, it was found that L-FABP was related to the absorption, translocation and redistribution of long-chain fatty acid in intestine and cell compartments. Recent studtes indicated L-FABP is one pivotal signal molecular related to alcoholic or non-alcoholic fatty liver, kidney parenchymal injury, diabetes, ischemia injury and so on. In regard to its small molecular weight and membrane infiltration ability, L-FABP may be a high-sensitive marker of liver or kidney injury. Here, we review the research progress in the physical function, regulation mechanism and clinical application of L-FABP.

Key Words: Liver-type fatty acid binding protein; Regulation mechanism; Tissue injury

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摘要

肝型脂肪酸结合蛋白(liver type fatty acid binding protein, L-FABP)是脂肪酸结合蛋白家族的重要成员, 主要在肝脏、小肠及肾脏表达. 既往研究其主要与机体脂肪酸的吸收及转运、细胞内的长链脂肪酸的转运及细胞器内的再分布等密切相关. 近年发现肝型脂肪酸结合蛋白具有信号转导分子的功能, 是机体能量代谢的重要环节, 进一步的研究证明与酒精性、非酒精性脂肪肝损伤、肾间质损害、糖尿病、器官缺血损伤等密切相关. 鉴于其小的分子量及良好的细胞膜通透性, 有望成为较好的肝、肾组织损伤的敏感指标. 本文就近年肝型脂肪酸结合蛋白的生理功能、调控机制以及临床应用进展作一综述.

关键词: 肝型脂肪酸结合蛋白; 调控机制; 组织损伤

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0 引言

自1971年脂肪酸结合蛋白(fatty acid binding protein, FABP)被发现以来, 陆续分离并鉴定了9种不同类型的脂肪酸结合蛋白: 肝脏型(L-FABP)、小肠型(I-FABP)、心肌型(H-FABP)、脂肪细胞型(A-FABP)、表皮型(E-FABP)、回肠型(IL-FABP)、脑细胞型(B-FABP)、周围神经髓磷脂型(M-FABP)和睾丸型(T-FABP)[1]. 其中L-FABP得到最为广泛、深入的研究, 已被阐明的基本功能包括参与小肠脂肪酸的吸收及转运、细胞内长链脂肪酸的转运及细胞器内再分布利用、胆汁酸、胆固醇等物质的代谢等[2-6]. 随着转基因及基因敲除动物模型、蛋白结构解析技术和蛋白质组学技术等应用于L-FABP的研究, 人们对

■背景资料
L-FABP主要在肝细胞、小肠黏膜细胞和肾小管上皮细胞表达, 其基本功能包括参与机体脂肪酸的吸收、细胞内的长链脂肪酸转运及细胞器内的再分布等. 近年研究证实L-FABP与脂肪肝、肾间质损害、糖尿病、器官缺血损伤等密切相关. 因而L-FABP有望成为治疗脂肪肝、减轻器官氧化损伤等的药物作用靶点.

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■研发前沿
L-FABP的表达受基因和药物两种作用途径控制, 鉴于其转运和促进脂肪酸代谢以及抗氧化的生理功能, 开发有效的调控药物是当前研究的热点与难点. 有关其抗氧化的机制以及抗氧化损伤的临床意义有待进一步更深入的研究.

L-FABP的分子结构、分布定位、生物功能、表达调控以及与疾病的关系等都有了更为全面的了解.

1 L–FABP的分子特点

1.1 L-FABP的基因结构 不同种属L-FABP基因的定位不同, 如人源L-FABP位于2p11, 小鼠位于6C1, 褐鼠则在4q33. 其基因结构高度保守, 由4个外显子和3个内含子组成. 来源于鼠类肝细胞的L-FABP基因, 在其启动子上游132位与下游21位处存在正向和反向的顺式作用元件, 包含了肝细胞核因子-1(hepatocyte nuclear factor-1, HNF-1)与TATA、CCAAT盒子. 不同器官、组织L-FABP的表达受其基因上的抑制子与增强子调控, 如抑制和增强回肠和结肠表达L-FABP的序列分别位于启动子上游1600-4000位点与351-597位点, 而抑制肾脏表达L-FABP的序列位于启动子上游133-186位点[7].

1.2 L-FABP的蛋白结构 不同类型FABP的氨基酸序列高度同源(20%-70%), 三级结构也高度相似[8-9]. X线衍射晶体和核磁共振分析结果表明, L-FABP由10个反向平行的β链和2个短的α螺旋组成一个β折叠桶. 后者稳定性较强, 空间构型不易受到化学修饰、大分子荧光物质和基因诱变的影响. 空间大小可容纳2-3个脂肪酸分子, 上方的两个α螺旋构成入口结构. L-FABP可以结合2个长链脂肪酸分子, 而其他FABP只能结合1个. 产生这种差异的原因主要是不同的FABP在其入口α-Ⅱ螺旋与β折叠C和D结合处具有不同的结构形式[10].

2 L–FABP的分布定位

L-FABP是人体内表达最多的FABP, 主要分布于肝脏、小肠、肾脏与胰腺, 其中肝脏细胞和小肠刷状缘细胞中尤为丰富, 占细胞质蛋白总量3%-5%[11]. 在禁食条件下, L-FABP多表达于细胞靠近肠道内腔面的边缘部分; 给予进食或高脂饮食条件下, L-FABP则在细胞质内平均分布, 这与其吸收和转运饱和与非饱和长链脂肪酸的功能密切相关[12]. 由于过去只发现L-FABP具有结合和运输脂肪酸的简单功能, 因此认为L-FABP仅表达于细胞质. 后来Huang *et al*[13]发现在肝细胞胞核中也表达F-FABP, 甚至有人将F-FABP基因转染至细胞核研究L-FABP参与细胞信号转导的作用.

■相关报道
国外对L-FABP的基因序列及蛋白结构的研究已较为深入, 有关其参与机体脂肪代谢的研究较多. 将L-FABP基因转染至Chang Liver细胞并表达, 结果显示L-FABP可以减轻缺氧等所导致的氧化应激损伤.

3 L–FABP的生物功能

3.1 结合并转运脂肪酸 脂肪酸进入肠壁细胞、脂类物质由血液进入肝细胞转化代谢、脂肪酸在细胞器之间的运输等均需要L-FABP参与. L-FABP能转运多于^{14}C的饱和与非饱和脂肪酸, 并且有两个结合位点. 位于中心的是一个主要结合位点, 以羧基与精氨酸及两个丝氨酸残基相互结合; 另一个则靠近分子结构入口, 其羧基朝向入口并与分子周围的溶质相接触. 两个位点结合饱和脂肪酸具有相同的亲和力, 但中心位点结合非饱和脂肪酸的亲和力却是入口位点的10倍[10]. 新近研究发现, 入口位点结合脂肪酸依赖于中心位点与脂肪酸的首先结合以及细胞微环境的变化[14-15]. 此外, L-FABP还结合、运输血红素、维生素A及癌抗原等物质. 这体现了肝脏多样而复杂的生理功能.

3.2 参与细胞信号转导 尽管早已观察到L-FABP可在细胞核与细胞器内表达, 但对其生理功能并不清楚. 最近Hagan *et al*[16]通过人工细胞膜实验观察到L-FABP可与磷脂微囊结合, 并实现细胞器之间的再分布, 进入细胞核后可引起细胞质内非脂化脂肪酸浓度升高. 以前认为脂肪酸可导致过氧化物酶增殖体激活受体α(peroxisome proliferation activated receptor-α, PPAR-α)激动, 近来研究发现L-FABP也参与了该机制, 即L-FABP实际上起到了配体的作用[17]. Schachtrup *et al*[18]亦证实L-FABP基因启动子序列包含过氧化物增殖酶体增殖物受体反应元件. 此外有证据表明, L-FABP可与丝裂原物质以及癌抗原结合, 进入细胞核后引起细胞增殖, 促进细胞恶性转化, 因此认为其具有核转录因子的作用. 尽管目前尚缺乏L-FABP作为信号转导分子的直接证据, 但上述研究结果表明L-FABP可能不仅仅简单地作为载体蛋白, 其分子信号转导作用值得进一步研究.

3.3 作为内源性抗氧化及解毒物质 将L-FABP基因转染至Chang Liver细胞表达, 结果L-FABP可以减轻双氧水、缺氧等所导致的氧化应激损伤[19]. 在肝脏胆道梗阻的动物模型研究中, 给予传统的抗高血脂药物氯贝丁脂可上调L-FABP的表达水平, 并减轻肝脏的胆汁淤滞性氧化损伤[20]. 在肝脏酒精损伤过程中, 如果给予PPAR-α激动剂提高L-FABP浓度, 则可减轻酒精所致的过氧化毒性作用[21-22]. L-FABP的抗氧化功能可能与蛋白结构中大量的半胱氨酸、甲硫氨酸残基有关. 这些残基可参与巯基的氧化还原, 提高还原性谷胱甘肽的生成率. 但Feng *et al*[23]发现, 在大鼠非酒精性脂肪肝形成过程中, L-FABP水平逐渐升高, 以后逐渐降低. 作者认为起初表现为适应反应, 后期失代偿则表现为肝脏损伤. 因此, 进一步研究L-FABP的

抗氧化及解毒机制, 将有助于阐明L-FABP在脂肪肝、肝脏缺血/再灌注损伤等临床常见病理过程中的作用.

4 L–FABP的表达调控

既往认为影响L-FABP表达的因素包括血液脂肪酸水平, 激素(尤其是类固醇激素)水平, 某些药物(如过氧化物增殖酶体受体激动剂)等. 近来又发现了多种调控途径.

已经证明, 环境的氧应激水平可影响细胞内L-FABP表达, 细胞微环境氧自由基浓度可以升高L-FABP水平[24]. 除了氯贝丁脂等降血脂药物外, 许多新提纯的植化药物也可激动过氧化物增殖酶体受体, 间接引起L-FABP水平升高, 进而对某些氧化损害产生保护作用. Kim *et al*[25]发现橘梗多苷可通过上调L-FABP水平减轻和延缓酒精所致的肝脏损伤和脂肪肝的形成. 其机制主要与该药物抑制了细胞色素P4502E1有关. 另有研究发现, 非诺贝特和罗西格列酮分别通过激动PPAR-α与PPAR-γ减轻非酒精性脂肪的损伤和病变程度. 其机制与上调促进脂肪转运和代谢的L-FABP及其他脂肪代谢酶系密切相关[26-27]. 不同性别个体之间L-FABP水平存在差异, 这与性激素水平有关. 类固醇激素(如地塞米松)可抑制肝细胞表达L-FABP, 加重肝细胞的氧应激损伤, 生长激素亦可以通过非依赖PPAR途径下调L-FABP, 减缓脂肪肝的形成[28-29]. 而食用富含维生素B及甲硫蛋氨酸的食物可有效降低酒精性肝损伤动物肝脏的L-FABP和炎症因子水平, 起到保护作用[30]. 最近一个重要的进展是证明了L-FABP与PPAR受体之间的相互作用, L-FABP可引起PPAR受体激动, 进而导致L-FABP合成增加. 两者构成了正反馈环状调节通路, 其机制和生理意义有待进一步研究[31-32].

基因调节途径则是近年来L-FABP表达调控机制的主要研究进展. 关键基因位点的干预比药物干预更加高效和准确. 例如, 锌指转录因子GATA-4、GATA-5和GATA-6可以结合L-FABP启动子上游128位点, 从而上调L-FABP表达[33-34]. 而用PPARα-视黄醇X受体与PGC1β联合转染肝细胞, 可抑制L-FABP与甘油三脂转运蛋白表达, 阻止脂肪肝形成, 并有效减轻酒精性肝损伤[35-36]. 在L-FABP基因敲除动物模型中, 脂肪酸β氧化功能减弱, 并且在禁食及喂饲高脂饮食条件下不易形成脂肪肝[37]. 另外还发现[38], L-FABP与脂膜形成脂蛋白微囊以出芽的形式输出脂蛋白是肝细胞内质网合成脂蛋白的重要限速步骤. 因此, L-FABP在脂蛋白合成方面具有重要功能.

5 L–FABP的临床应用

由于L-FABP分子质量较小(14.4 kDa), 在肝细胞、肾小管细胞受到损伤时, 细胞膜通透性变化可使其快速溢出, 因此L-FABP可作为一个敏感、特异的组织损伤标志物[39-40]. Pelsers *et al*[41]报道, 肝移植术后患者在发生排斥反应的当天, 所有患者血清L-FABP均明显增加(>50%), 而α谷胱甘肽S-转移酶升高者为91%, ALT升高者仅占40%. 并且L-FABP增加早于急性排斥反应, 甚至比α谷胱甘肽S-转移酶、ALT明显提前. 提前时间的中位数L-FABP为2 d, α谷胱甘肽S-转移酶为1 d, ALT则晚于2 d. 提示L-FABP是一个早期监测肝细胞损伤的有用生化标志. 后来的研究进一步表明, 应用L-FABP作为肝细胞损伤的标志物, 对于评估尸体供肝的缺血损害程度以及评估肝切除术中导致肝损害的关键因素等, 都具有较高的敏感性和特异性[42-43].

L-FABP最引人注目的临床应用进展是作为慢性和急性肾损伤的分子标志. L-FABP主要表达在近曲小管, 其功能尚不明了. 在肾脏疾病出现大量蛋白尿、缺血和毒性损害时, 推测L-FABP参与尿夜游离脂肪酸的重吸收, 促进β氧化供能, 从而减轻氧应激损伤. Kamijo *et al*[44]在研究慢性非糖尿病肾病时发现, 肾功能恶化患者的尿L-FABP水平显著升高. 其后进行的多中心队列研究进一步发现, 在预测慢性肾病进展方面, 尿L-FABP较尿蛋白有较高的敏感度(93.8% *vs* 68.8%), 但其特异性较差(62.5% *vs* 93.8%). 因此尿L-FABP对于筛检肾病恶化具有较大优势, 其敏感度高于尿蛋白及葡糖胺酶等常用指标[45]. 随着研究的逐步深入, 尿L-FABP在检测局灶性肾小球坏死[46]、糖尿病肾病、冠脉造影剂所致肾病[47]、心脏转流术后急性肾损伤[48]以及肾脏移植缺血再灌注损伤方面[49]均显示了较好的预测作用. 由于肝细胞含有大量的L-FABP, 在肝移植合并肾损伤或者伴有肝肾疾病时, L-FABP的检测特异性和敏感度受到限制. 但新近报道血清L-FABP的变化并不影响尿L-FABP的数值[50]. 因此尿L-FABP仍可作为一个较有应用前景的急慢性肾脏损伤分子标志.

6 结论

尽管目前对于L-FABP的细胞内外功能、调控因

■创新盘点

本文全面阐述了L-FABP的结构与生理功能、基因与药物调控的机制以及临床应用. 较为集中地阐明了L-FABP在脂肪肝、肝肾组织损伤等病理过程中的作用及意义.

■应用要点
由于L-FABP分子量较小(14.4 kDa), 在肝细胞、肾小管细胞受到损伤时, 细胞膜通透性变化可使其快速溢出, 因此L-FABP可作为一个敏感、特异的组织损伤标志物. 将来可与肝酶、肌酐等现有的化验指标联合应用, 成为临床有用的肝肾功能指标.

素以及与糖尿病、肥胖症、高脂血症以及某些肿瘤的关系尚未明了, 但现有的研究已显示出L-FABP有望成为治疗上述疾病的有效药物靶点. 因此, 加强对L-FABP功能与调控机制的研究, 开发以L-FABP为靶点的药物将是未来研究的重点内容.

7 参考文献

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■同行评价

本文在参阅多篇国内外参考文献的基础上, 对肝型脂肪酸结合蛋白的生理功能、调控机制以及临床应用进展作一综述, 撰写较为规范, 参考文献引用较新, 科学性、创新性和可读性能较好地反映我国有关肝型脂肪酸结合蛋白研究的先进水平.

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