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综 述

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转录因子 CCAAT 增强子结合蛋白 β(C/EBP β)的研究进展

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摘要: CCAAT 增强子结合蛋白 β(CCAAT enhancer binding protein, C/EBP β)是 CCAAT 增强子结合蛋白家族的一员。该家族是碱性亮氨酸拉链大家族的一个亚家族, 在细胞分化、能量代谢、生长发育等多个进程中发挥作用。文章就 C/EBP β 的结构、表达调控和生物学功能做一综述, 并对研究应用进行了展望。

关键词: CCAAT 增强子结合蛋白; 结构; 表达调控; 生物学功能

Progress of transcription factor CCAAT enhancer binding protein β

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Abstract: CCAAT enhancer binding protein β (C/EBP β) belongs to CCAAT enhancer binding protein (C/EBP) family, which is a subfamily of basic leucine zipper (bZIP) protein family. C/EBP family plays important roles in many processes such as cell differentiation, metabolism, and development. In this paper, the structure, expression regulation, and function of C/EBP β were reviewed.

Keywords: CCAAT enhancer protein; structure; regulation of expression; function

CCAAT 增强子结合蛋白(CCAAT enhancer binding protein, C/EBP)家族是碱性亮氨酸拉链蛋白家族的一个亚家族。迄今, 不同的实验室发现并命名了多个成员[1~9]。Cao 等[10]建议采用系统命名法对这一家族进行命名: 用 C/EBP 作为家族名, 后面加上一个希腊字母作为成员名, 并且希腊字母的顺序代表这一成员被发现的顺序。按这一命名法 C/EBP 家族成员包括 C/EBP α、C/EBP β、C/EBP γ、C/EBP δ、C/EBP ε 和 C/EBP ζ 等蛋白[11]。C/EBP 家族成员的共同特征是其蛋白质分子包括 3 个相似的结构组分: C 末端的亮氨酸拉链, N 末端的转录激活域, 中间的 DNA 结合域[12~17]。C/EBP 家族有多种生物学功能, 涉及到能量代谢、肝脏再生、细胞周期、炎症反应及多种疾病的病理。本文就这一家族中 C/EBP β 的结构、表达调控及生物学功能进行综述。

1 C/EBP β 的结构

C/EBP β 是由 Akria 等[2]首次发现, 并命名为 NF-IL6。C/EBP β 结合到 IL6 和与之相似的细胞因子启动子的 IL1 应答元件上, 此元件是一个 14 bp 的回文序列(ACATTGCACAATCT)[2]。C/EBP β 与其他 C/EBP 蛋白具有高度同源的羧基端(C 端)碱性亮氨

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酸拉链区, 可与其他蛋白形成二聚体, 行使 DNA 结合功能; 其氨基端(N 端)具有激活功能域和抑制功能域[18]。在 C/EBP β 的转录激活域和 DNA 结合域之间有两个负调控域(RD1, RD2)。RD1 位于临近 N 末端转录激活域的部分, 主要调控转录激活活性; RD2 位于碱性亮氨酸拉链的上游, 与 C/EBP β 活性的细胞特异性有关[19]。C/EBP β 的 mRNA 通过选择性剪切可生成 4 种异型体蛋白: 全长的 38 kDa 的 C/EBP β (LAP*)、35 kDa 的 LAP(Liver-enriched transcriptional activator protein)、21 kDa LIP (Liver-enriched transcriptional inhibitory protein)和一个 14 kDa 的蛋白[20, 21], 其中 LAP 和 LIP 是主要的剪切体, 而 LAP* 很少[22]。LAP 包含激活域和碱性亮氨酸拉链域, 具有全部的活性。而 LIP 仅有碱性亮氨酸拉链域, 但是可以和其他家族成员形成无活性的异源二聚体, 起到一种负调控作用。C/EBP β 在细胞内形成多种同源和异源二聚体, 从而大大增加了其靶基因的多样性[23~27]。

2　C/EBP β 的表达调控

C/EBP β 具有广谱表达的特性, 但是在肝脏、小肠、肺、脂肪组织、脾脏、肾脏和髓单核细胞中有较高的表达量[2~5, 10, 14, 28]。C/EBP β 的 4 种异型体蛋白的表达模式不同, 其中 LAP 和 LIP 在多种细胞中表达, 而 LAP*主要在肝脏中表达, 但是这 4 种异型体蛋白都是由同一个 mRNA 转录而来, 分别由 4 个 AUG 启始[29]。在 C/EBP β mRNA 的第一个和第二个 AUG 密码子之间有两个并联的 CUG 结合蛋白 1(CUGBP1)结合位点。CUGBP1 结合到 *C/EBP β* 5′区可促进小分子量的 C/EBP β 异型体蛋白的翻译[30]。C/EBP β mRNA 内的 GCN 重复形成 SL 结构, 钙网蛋白可以结合到这种 SL 结构上, 导致 C/EBP β mRNA 翻译抑制。删除或者突变消除 SL 结构, 钙网蛋白不能结合从而解除抑制作用[31]。在 *C/EBP β* 的启动子区有 3 个蛋白因子结合原件: UF1(–376~–325)、UF2(–254~–223)和 UF3(–220~–190); 两个 Sp1 基序(–309~–227 和–264~–241)。在急性应答阶段, C/EBP β 可以结合到 UF1 和 UF2 位点进行自我调控[32]。在 *C/EBP β* 翻译起始位点上游 TATA box 附近有两个 CREB 的结合位点, 这两个位点对维持 C/EBP β 启动子活性很重要。WB 和转录实验证实, 在大鼠肝脏再生中 CREB 磷酸化和 C/EBP β mRNA 转录有相互作用[33]。在缺氧时, 缺氧诱导因子 1α(HIF-1 alpha)诱导 p27 稳定表达, 从而抑制眼癌蛋白(Rp)的磷酸化, 封锁 G1/S 的转化, 破坏 C/EBP β 的 DNA 结合能力[34]。同时, ETO/MTG8 和 SMAT 可以抑制 C/EBP β 的表达[35, 36]。在表观遗传上, C/EBP β 是 MicroRNA155 的直接靶基因, miR-155 沉默可以解除 C/EBP β 异构体的阻遏作用[37]。

3　C/EBP β 的生物学功能

3.1　C/EBP β 调控细胞分化

作为一个重要的调控因子, C/EBP β 参与了脂肪细胞, 乳腺细胞等多种细胞的增殖和分化进程。

3.1.1　调控前脂肪细胞分化

在脂肪细胞分化过程中, C/EBP β 能够激活 C/EBP α、PPAR γ 等细胞因子, 促进脂肪细胞分化[38, 39]。在脂肪细胞分化早期 C/EBP β 就有表达, 它首先启动有丝分裂克隆扩增(Mitotic clonal expansion, MCE)[40~43], 使前脂肪细胞进入细胞增殖周期, 约两轮有丝分裂后退出细胞增殖周期, 进入细胞分化期。此时, C/EBP β 激活 C/EBP α、PPAR γ 等因子[44~51]。ETO/MTG8 在早期脂肪生成中作为 C/EBP β 的抑制剂, 可调控早期脂肪细胞分化[35]。用 *C/EBP β* 替代 *C/EBP α*, 产生 β/β 型小鼠。这种小鼠消瘦, 在脂肪细胞中有显著低的脂肪沉积, 没有高血脂和脂肪肝症状, 而且有较长的寿命, 高的能量消耗和白色脂肪线粒体活性[52~54]。β/β 等位基因主要是通过 G 蛋白 a 刺激物亚基(Gs)发挥作用[55]。C/EBP β 还能使非脂肪细胞定向分化为脂肪细胞。在激素诱导下, C/EBP β 异位表达能激活 PPAR γ, 使 NIH- 3T3 成纤维细胞定向分化为前体脂肪细胞[56]。C/EBP β 或 C/EBP δ 缺失的胚胎成纤维细胞, 其生脂能力略微降低, 但二者同时缺失时细胞分化严重受阻[57]。而 PRDM16-C/EBP β 复合物则能够起始成肌细胞前体向棕色脂肪的转化[58]。

3.1.2　调节乳腺细胞分化

C/EBP β 可以调控乳腺分化。C/EBP β 对乳腺表皮细胞的发育、分化和增殖都是十分重要的[59~62]; C/EBP β 还影响乳汁中的蛋白含量如 β 酪蛋白、乳

清蛋白等[63~65]。乳腺发育是在各种激素作用下分阶段进行的, C/EBP β 很可能是这些激素信号的识别和功能执行者, 如在 MCF-7 细胞系中, C/EBP β 就参与了雌激素受体(Estrogen receptor, ER)信号的应答[66, 67]。缺失 C/EBP β 的小鼠乳腺分化有缺陷, 不能排卵[68~70]。研究表明, 乳腺表皮细胞对 C/EBP β 的需求是细胞自治的, 在 C/EBP β 缺失的小鼠中, 雌性未成年小鼠的乳腺管变大但分支减少。把正常小鼠的卵巢移植到 C/EBP β 缺失的青春期小鼠中或者包埋含雌激素和孕激素的微管, 能部分的重建乳腺管的形态, 使小鼠可以怀孕, 但不能支持妊娠期的泌乳[68]。运用消减抑制杂交法分析 C/EBP β 缺失小鼠的乳腺, 发现多个差异表达的基因如孕激素受体(PR)、雌激素受体(ER)、催乳素受体(PrlR)和 IGF-Ⅱ等。这些基因缺失的小鼠和 C/EBP β 缺失有相似的表型[59], 表明 C/EBP β 很可能是在激素信号下, 通过调控这些差异表达的基因来调控乳腺细胞的分化。

3.1.3 参与其他细胞的分化

Cole 等[71]认为细胞周期蛋白 Rb 和 C/EBP β 之间的互作能使 C/EBP β 参与细胞周期调控, 进而调控细胞分化和增殖。在神经细胞中, 有多个信号通路可以激活 C/EBP β: 损伤再生有关的 MEK-ERK 途径[72]; 与感觉神经元轴突再生有关的 JAK-STAT 通路[73]; cAMP 级联通路[74]等。C/EBP β 在小鼠神经元细胞中广泛表达, 参与大鼠海马区突触可塑性, 在基因巩固中也有重要作用, 并且参与轴突受损后的再生[75, 76]。C/EBP β 可促进胚胎小鼠皮层中基础细胞分化成神经细胞[77], 在小鼠神经细胞瘤中过表达 C/EBP β 时, 能诱导神经元分化[78]。C/EBP α/β 偶联基质角化细胞增殖的停止从而诱导分化的起始。C/EBPs 在基质角化细胞中共表达, 并且在角化细胞出现基底层和进行最终分化时被上调, 缺失 C/EBPs 的小鼠角化细胞增殖增加而分化受损, 这导致角蛋白 14 和 σNp63 在基底层细胞中的异位表达, 降低多刺层和颗粒层蛋白的表达, 引起角化不全以及表皮防水功能缺陷。C/EBPs 基因敲入实验证实 C/EBP-E2F 互作对控制滤泡间表皮角化细胞增殖是必须的; C/EBP 的 DNA 结合作用对于 σ Np63 下调和 K1/K10 诱导则是必须的, 并最终导致表皮中 C/EBP α/β 诱导的干细胞基因表达痕迹消失。因此, C/EBP 通过 E2F 应答和 DNA 结合作用偶联基质角化细胞增殖终止进入分化, 而且可能抑制表皮干细胞区室化[79]。在 Myb 的协同作用下, C/EBP β 参与血液干细胞分化为颗粒细胞的调节, Myb 和 C/EBP β 突变可阻止分化过程, 导致白血病[80, 81]。*C/EBP β*$^{-/-}$小鼠表现出巨噬细胞分化受阻[82]、淋巴细胞增殖紊乱[83, 84]等症状。此外, C/EBP β 还参与了造血细胞[85~87]、骨细胞等的分化[88]。

3.2 C/EBP β 参与肝脏再生

C/EBP β 在向细胞核转运时, 受肝细胞生长因子(HGF)的调控。HGF 能结合到 C/EBP β 上游的 HGF 应答元件上, 加快 C/EBP β 向核内运转[89]。肝脏部分切除后, *C/EBP β*$^{-/-}$小鼠的 DNA 合成下降到正常小数的 25%, 而且肝脏再生时间延长。*C/EBP*$^{-/-}$小鼠和 *IL-6*$^{-/-}$小鼠肝脏中早期基因表达异常的特点不同, 在切除早期, 生长调节基因表达下降, 而细胞周期素 B、E 基因的表达量也显著下降, 但是细胞周期素 D1 的水平不变[90]。在肝脏切除后 1 h 内 C/EBP β mRNA 水平增加 4~5 倍, 而且在整个恢复期前仍不断增加, 直到 24 h 才回落到基础水平。C/EBP β 的磷酸化影响半光天冬酶 8 相关蛋白 Nu FLIPL 的活性, 从而调控星状细胞的存活, 对肝纤维形成来说这是很关键的一步, 如果用竞争抑制物阻断 C/EBP β 的这一作用, 可以预防肝纤维化[91]。在肝癌病例中, C/EBP β 在肝脏癌变区表达量下降, 并且癌变区 C/EBP β 表达量高的病人存活时间相对较长。

3.3 C/EBP β 参与能量代谢

C/EBP β 控制脂类的代谢及由饮食诱导的肥胖的发生。在脂肪组织中, 胰岛素协调调控 C/EBP β 的上调和 C/EBP α 的下调和磷酸化, 这反过来又调控脂肪特异性基因的表达。包含 C/EBP β 的肝脏核复合物可以结合胰岛素样生长因子结合蛋白 1 的胰岛素应答序列, 从而调控胰岛素相关基因的表达[92, 93]。C/EBP β 缺失影响激素调控的信号传导, 引起动物饥饿时的低血糖和减少脂肪酸的动员。在饲喂高脂肪日粮(60%)12 周时, C/EBP β 缺失的小鼠全身脂肪量降低; 血液中甘油三酯、自由脂肪酸、胆固醇及肝脏甘油三酯的累积水平较低; 肝脏脂肪合成基因、乙酰辅酶 A 羰基裂解酶基因、脂肪酸合成酶基因表达量减少; 棕色脂肪中 β 氧化酶的表达量增加[94]。*C/EBP β*$^{-/-}$小鼠在窝产仔数及个体外形上和对照小鼠没有

明显的差别, 但是同型纯合子个体在围产期死亡。存活下来个体的皮下脂肪量显著下降; 在饥饿和糖尿病时, 这些小鼠有较低的糖异生和脂肪合成能力, 肝脏和脂肪组织中 cAMP 水平较低, 但对胰高血糖素耐受性高。C/EBP β 缺失的小鼠在 8 周时皮下脂肪组织减少 35%, 而且脂肪细胞不能累积脂滴, 但是脂肪细胞有正常的形态和大小, 编码主要脂肪分化因子的 mRNA 也没有变化。C/EBP β 的缺失并不影响磷酸烯醇式丙酮酸羧激酶(Phosphoenolpyruvate carboxykinase, PEPCK)的本底水平的表达, 在肝脏中, 胰岛素下调 C/EBP β 的表达时, 却能使 PEPCK 表达量减少。在 *C/EBP β*$^{-/-}$的链脲霉素-糖尿病小鼠中, PEPCK 和葡萄糖 6 磷酸酶的 mRNA 水平降低 35%~40%, 同时这种小鼠在饥饿时血清胰岛素、葡萄糖和自由脂肪酸的浓度较低, 但并不影响肝脏和脂肪组织中代谢和胰岛素应答相关基因的表达。在 C/EBP β 缺失小鼠的骨骼肌中, 胰岛素刺激的胰岛素受体、Akt 丝氨酸 ^{473} 磷酸化和 3-磷脂酰基醇激酶活性增强了 1.6~2.5 倍, 胰岛素受体亚基 1 蛋白水平增加 2 倍[95]。在 MIN6 小鼠胰岛素瘤细胞中, 过表达 C/EBP β, 可以降低 β 细胞的总量及血糖胰岛素的水平并可以引起糖尿病的发生。其原因在于 ER 压力可以诱导 C/EBP β 的表达, 引起 C/EBP β 在胰岛 β 细胞中的累积, 抑制了转录因子 ATP6α 的转录激活活性, 导致分子伴侣葡萄糖诱导蛋白 78 kDa 的丰度下降, 增强了 β 细胞对 ER 压力的敏感性, 从而引起胰岛 β 细胞的失活[96]。

3.4　C/EBP β 参与炎症反应

白介素 1 β(IL-1)可以诱导 11-β-羟基类固醇脱氢酶 1(11-beta-HSD1)的表达, 这一作用是通过 C/EBP β 介导的, 后者可以结合到 11-beta-HSD1 的启动子区域, 过表达 C/EBP β 时增强其表达水平, 而干扰抑制 C/EBP 表达时, 则显著消弱了 IL-1 的诱导作用[97]。内质网压力通过 PERK(Protein kinase-like ER kinase)和 IRE1(Inositol-requiring ER-to-nucleus signal kinase 1)通路介导的优先诱导 C/EBP β 的作用, 减弱了细胞因子触发的 NF-kappa-B 活性, 从而有助于抵制炎症[98]。

3.5　C/EBP β 参与肿瘤的发生与凋亡

p53 是一个转录因子, 介导细胞周期的阻滞和细胞凋亡, 在基因毒性应激时被激活。通过 p53 蛋白的氨基末端、亮氨酸拉链和 C/EBP β 的 RD2 区的相互作用, C/EBP β 介导其靶基因的转录激活[99]。C/EBP β 可能促进囊内肿瘤细胞的血源性扩散, 而且其抗凋亡效应有助于肿瘤细胞的存活[100]。在高级别的神经胶质瘤中 C/EBP β mRNA 和蛋白质水平比低级别的神经胶质瘤高, 而且表达高水平 C/EBP β 的病人生存时间较短。在体外干扰抑制 C/EBP β 时抑制神经胶质瘤的增殖和入侵。因此, 增加 C/EBP β 的表达有助于肿瘤的入侵和扩散, C/EBP β 还可以作为神经胶质瘤的一个预见性标记[101]。C/EBP β 3 非翻译区是个具有肿瘤抑制活性的调控元件[102], 删除这一区域的 3 个短的序列可以减弱其肿瘤抑制活性, 表现为延迟细胞生长, 降低细胞在软琼脂和一般培养条件下集群形成能力, 在裸鼠中还可以降低肿瘤的发生, 原因在于 3 非翻译区的缺失改变肿瘤相关基因的表达谱[103]。此外, C/EBP β 参与了浆细胞的分化和存活重要转录因子的调节网络, 这有助于对多发性髓细胞瘤的治疗[104]; C/EBP β 还可以抑制人类结肠癌细胞在裸鼠体内的生长[105]。

3.6　C/EBP β 参与病毒转录

C/EBP β 控制 NF-kappa-B 相关的信号从而参与多个病毒的转录调控。C/EBP β 调控多留病毒 JC(JCV)的转录, 在 JCV 的非编码控制区(NCCR)有 NF-kappa-B 结合位点, 可以激活病毒转录[106, 107], 而 C/EBP β 同样可以结合到这一位点, 抑制基本的和 NF-kappa-B 刺激的 JCV 的转录活性。共沉淀实验证实了 NF-kappa-B/p65、C/EBP-LIP 和 JCV DNA 四聚体的存在; NCCR 区突变分析证实 p65 和 C/EBP β 结合到临近但包含完全不同碱基的基序上, 而且这两个位点都可以抑制基础的和 p65 诱导的转录。因此, C/EBP β 负调控 JCV, 再加上 NF-kappa-B 的活性, 可以控制 JCV 在潜伏期和活化期之间的平衡[108]。在 Hela 细胞中过表达 C/EBP β 可以封锁 TNF 介导的 l kappa-B-alpha 启动子的可诱导性, 增加共表达的 p65 在细胞核中的水平和 NF-kappa-B 活性。在 *C/EBP β* 敲除的细胞中, l kappa B-alpha 的组成性表达水平显著升高, 但是稳定性不足。用 TNF 刺激可以提高 l kappa B-alpha 的 mRNA 水平, 但其自调控的恢复能力完全被阻断[109]。C/EBP β 是 CCR5 的一个重要调控因子并且可能在 HIV 病理中也有相应的

作用[110]。CCR5 基因的启动子区和内含子 3 端各有一个 C/EBP β 应答区域。在骨髓细胞中(U937), 这两个区域都有活性, 但相互独立; 在淋巴样细胞(Jurkat)中, CCR5 基因内含子内的 C/EBP β 应答区域是必须的; 在 HIV 感染的病人中, C/EBP β 表达显著增加, 并且和 AIDS 病人的 $CCR5^+$淋巴样细胞高循环率和低 CD4 淋巴样细胞数目相关。在 SIV LTP 的最小区域内有两个 C/EBP β 结合位点: JC1(−100 bp)和 DS1 (+134 bp)。这两个位点都能够介导 IFN beta 诱导的 LTR 活性和病毒复制能力下调, JC1 对于基础水平的转录是很重要的; 在原巨噬细胞中 DS1 位点对病毒的复制时必须的[111] 。

4 展 望

CEBP β 在细胞分化与增殖、肝脏再生、肿瘤发生与凋亡等多个细胞进程中发挥重要作用, 还包括机体能量代谢及生殖系统的功能。在发挥重要作用的同时, C/EBP β 的表达调控也是严密的, 包括转录水平调控、转录后调控、翻译调控以及翻译后的调控如磷酸化、乙酰化和 SUMO 介导的转录后修饰。C/EBP β 涉及多种不同的通路, 处于有机体基因表达调控的节点上, 随着研究的深入, C/EBP β 或许会为治疗肿瘤、肥胖及相关症状等方面提供新的思路。

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