SREBP2表达及活性调控的研究进展

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摘要 胆固醇稳态对细胞功能和机体健康至关重要, 胆固醇调节元件结合蛋白2(sterol-regulatory element binding protein 2, SREBP2)是维持胆固醇稳态的关键调控因子, 是一种位于细胞内质网的胆固醇敏感调节器。SREBP2的表达和功能主要受三个水平的调控: (1) *SREBF2*基因的转录调控, (2) SREBP2蛋白的转运与剪切调控, (3) nSREBP2的修饰及功能调控。该文系统地对上述三个阶段调控的研究进展及其在代谢性疾病中的作用进行了综述, 这将为靶向SREBP2研究胆固醇代谢及其代谢异常相关疾病的治疗提供理论参考。

关键词 胆固醇; 胆固醇调节元件结合蛋白2; 胆固醇稳态

Research Progress on Expression and Activity Regulation of SREBP2

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Abstract Cholesterol homeostasis is very important to cells and organisms. REBP2 (sterol-regulatory element binding protein 2) is a key regulator of cholesterol homeostasis located in the endoplasmic reticulum to sense cholesterol changes. The expression and functions of SREBP2 are mainly regulated at three levels: (1) transcriptional regulation of *SREBF2* gene, (2) transport and splicing regulation of SREBP2 protein, and (3) modification and functional regulation of nSREBP2. This study summerizes the research progress of the above three stages of regulation and their role in metabolic diseases, which will provide a theoretical reference for targeting SREBP2 to study cholesterol metabolism and the treatment of diseases related to abnormal metabolism.

Keywords cholesterol; SREBP2; cholesterol homeostasis

胆固醇(cholesterol)是帮助细胞发挥功能和维持机体健康的重要物质, 是维持细胞膜完整性和流动性的重要成分[1], 胆固醇还可作为前体合成各种氧化甾醇[2]和固醇类激素[3], 比如25-羟基胆固醇、27-羟基胆固醇和皮质醇、睾丸酮、雌二醇等, 胆固醇还参与了信号转导的过程, 在维持机体稳态过程中发挥了重要作用。此外, 胆固醇可直接修饰蛋白质并对其功能进行调节, 例如胆固醇能共价修饰Hedgehog和Smoothed蛋白[4]并促进Hedgehog通路的激活。因此, 胆固醇稳态对于维持细胞的正常功能至关重要[5]。

胆固醇在机体中的稳态受到严密的调控, 细胞胆固醇水平反映了外源摄取、生物合成、输出和酯化之间的动态平衡, 而胆固醇主要来源是食物获取和细胞生物合成, 其中食物获取量占1/5, 细胞生物合成占4/5。机体从食物中摄取胆固醇, 主要通过分布于

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小肠的上皮细胞NPC1L1(niemann-pick-C1-like 1)实现, 其作为胆固醇导入体介导肠道吸收胆固醇[6]。细胞内生物合成胆固醇, 是以乙酰辅酶A作为底物, 经甲羟戊酸途径合成, 该合成反应受限速酶HMG-CoA还原酶(hydroxy methylglutaryl coenzyme A, HMGCR)的调控[7], 其表达量和活性的升高可促进胆固醇合成。同时, 细胞可以利用表面受体低密度脂蛋白受体(low density lipoprotein receptor, LDLR)从血液中摄取低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C), 并进一步通过溶酶体作用降解蛋白质后获得游离胆固醇[8]。虽然所有哺乳动物细胞都能产生胆固醇, 但大多数细胞却不能分解该分子, 因此需要将多余的胆固醇从细胞内分泌出去或以胆固醇酯的形式储存在脂滴中, 而巨噬细胞可以利用ATP结合盒(ATP-binding cassette, ABC)转运蛋白家族蛋白ABCA1与ABCG1介导胆固醇的外流[9], ABCG5和ABCG8介导肝细胞和肠细胞胆固醇外流[10]。酰基辅酶A-胆固醇酰基转移酶(acyl coenzyme A-cholesterol acyltransferase, ACAT)可以催化胆固醇和脂肪酰基辅酶A形成胆固醇酯, 胆固醇酯作为细胞质脂滴储存在细胞内[11]。上述胆固醇代谢途径中的关键蛋白NPC1L1、HMGCR、LDLR的表达都受到胆固醇调节元件结合蛋白2(sterol-regulatory element binding protein 2, SREBP2)的转录调控, 因此SREBP2调控是胆固醇代谢调控的中心环节, 深入了解SREBP2的表达及活性调控将为研究胆固醇代谢奠定坚实的理论基础。

BRIGGS等[12]于1993年首次发现SREBP2并将其成功分离, SREBP2是选择性地调控胆固醇代谢和摄取相关蛋白的转录因子。生理情况下, SREBP2的表达主要受内质网胆固醇含量的调控, 胆固醇含量升高时, SREBP2锚定在内质网上; 当内质网中胆固醇含量降低时, SREBP2从内质网上释放并被剪切为成熟体nSREBP2, nSREBP2与*LDLR*基因启动子的甾醇调节元件(sterol-regulatory element, SRE)结合, 激活*LDLR* mRNA转录[13], 促进LDL-C由血浆向胞内转运, 同时, 他汀类药物还通过激活nSREBP2来增加*HMGCR*和*PCSK9* mRNA的转录表达。因此, SREBP2的表达及其发挥生物学功能的过程受到严格的网络调控, 该调控网络中的任何异常均可导致疾病的发生或促进疾病的发展进程。本文将对SREBP2的表达和功能的调控机制进行综述, 为进一步研究其在病理生理条件下调控胆固醇代谢的机制提供线索, 同时为靶向SREBP2治疗相关疾病提供思路。

1 *SREBF2*基因的转录调控

SREBP是碱性螺旋–环–螺旋亮氨酸拉链(bHLH-Zip)转录因子家族的成员[14], 在哺乳动物的SREBP三种亚型中, SREBP1a和SREBP1c蛋白都是由SREBF1通过两个不同的启动子区域和选择性剪接产生的, *SREBP2*是由*SREBF2*基因转录的, 同时*SREBF2*的转录受多因素的调控。

在SRE和转录起始点之间有一个保守的胰岛素反应元件IRE(insulin response element), 转录因子FOXO3(forkhead box O3)可以与其结合[15]。其机制为SIRT6被FOXO3募集到*SREBP2*基因启动子上, 然后SIRT6使组蛋白H3的赖氨酸9和56去乙酰化, 从而抑制SREBP2及其靶基因表达[16], FOXO3是转录因子forkhead家族的一员, 主要通过特异性地识别基因启动子区上IRE序列调节下游目的基因的表达。TAO等[16]的研究表明, 在禁食或低浓度胰岛素/IGF-1的条件下, FOXO3可将SIRT6募集到*SREBP2*基因启动子上, 从而形成抑制SREBP2及其靶基因表达的表观遗传状态。FOXO3转录因子的沉默导致SIRT6的下调[17], 而胰岛素和其他生长因子可诱导FOXO3磷酸化, 抑制其转录活性。在饥饿条件下, 当FOXO3和SIRT6都活跃时, 胆固醇生物合成减少, 加上低密度脂蛋白受体介导的胆固醇从血液中摄取增加, 确保了体内胆固醇池的最大利用, 因此FOXO3和SIRT6可以协同调节SREBP2的转录调控。

除此之外, SREBP2也可进行自我调控, 成熟体nSREBP2入核后可以与*SREBF2*基因启动子中位于转录起始点上游的SRE结合, 诱导自身转录[18]。在*SREBF2*的启动子区域内, SRE和转录起始点之间还含有转录因子NF-Y[19]和SP1[20]的结合位点, 两者都可与nSREBP2协同作用, 有助于*SREBF2*基因启动子中的SRE被识别[18]。SUZUKI等[21]研究表明, 胰岛素可以调节大脑中*SREBF2*基因的表达和胆固醇的生物合成, 在胰岛素缺乏型糖尿病小鼠中, 胆固醇代谢的主要转录调节因子SREBP2及其下游基因在下丘脑和其他大脑区域的表达减少, 从而导致大脑胆固醇的合成和突触体胆固醇的含量减少。

综上所述, SREBF2主要通过FOXO3、SIRT、

NF-Y、SP1和nSREBP2对其启动子的不同区域进行调控, 从而确保体内胆固醇的稳态。

2 SREBP2蛋白的转运与剪切调控

SREBF2翻译成蛋白SREBP2后, 作为前体通过与SREBP裂解激活蛋白(SREBP cleavage activating protein, SCAP)紧密结合定位在内质网膜上。当胆固醇含量降至5%以下时转运活化过程被激活, SCAP/SREBP复合体从内质网(endoplasmic reticulum, ER)被转运到高尔基体, SREBP在此被激活, 高尔基体定位的膜蛋白孕激素和ADIPOQ受体3(adipoQ receptor 3, PAQR3)与SCAP/SREBP复合体相互作用, 并将它们锚定在高尔基体上, 增强SREBP的剪切从而促进脂质合成[22]。SREBP在高尔基体上需经过位点1蛋白酶(site 1 protease, S1P)和位点2蛋白酶(site 2 protease, S2P)的两步剪切[23]。具体过程为SCAP作为载体与SREBP2形成复合物, 并被CopII蛋白包裹[24], 从内质网转运到高尔基体。在高尔基体中, S1P将SREBP2的内质网膜腔内部分剪切成两个等大的单体, 接着, S2P裂解其跨膜区域, 剪去羧基端尾巴成为成熟体nSREBP2。SREBP2在高尔基体中被裂解后, 其羧基末端结构域CTD仍与SCAP结合, 并与SCAP一起回到内质网, 通过蛋白酶体将其降解消除[25], 而nSREBP2以同源二聚体的形式转位至核内发挥其启动子功能。当胆固醇水平升高时, 胆固醇与SCAP结合, 并触发SCAP与Insig的结合, Insig将SCAP锚定在内质网中[26], 使得SREBP向高尔基体的运输和随后的生脂基因的转录激活被抑制。

当胆固醇含量高的时候, 在TRC8和RNF145的调控下, CopII与SCAP分离, 复合物被滞留在内质网中。TRC8[27]能够直接与SREBP2和SCAP结合, 将SCAP-SREBP2-INSIG复合物滞留在内质网, RNF145[28]可以在CopII结合所必需的细胞质环内泛素化SCAP。内质网中的Insig蛋白从SCAP中解离后, 被gp78[29]和TRC8[30]泛素化, 并被蛋白酶体降解。SIRT6可以抑制SREBP2/SCAP复合体的裂解以及降低S1P和S2P的表达水平, 导致活性形式SREBP2的水平降低[31]。

综上所述, *SREBF2* mRNA被翻译并组装成SREBP2蛋白后, 通过囊泡运输被转运到内质网定置, 内质网的胆固醇含量为开启其功能的开关, SREBP2前体蛋白通过两步剪切成为活性预备状态的nSREBP2, 来响应细胞对脂质的需求[32]。此过程受到SCAP、S1P、S2P、TRC8、RNF145、gp78、MARCH6 E3连接酶和SIRT6对其定置、转位、剪切等步骤的调控。

3 nSREBP2蛋白入核转运过程的调控

SREBP2从内质网转运到高尔基体, 经过两次剪切之后, 成为成熟体nSREBP2, nSREBP2最终需要转位到核内, 经修饰成为活性形式, 作为下游靶基因转录因子, 与它们的启动子区域中的SRE结合发挥其启动转录的作用。

在细胞核中, 成熟的nSREBP2转录因子是不稳定的[33], 稳定的nSREBP2需要其特定位点被磷酸化修饰, 才可以发挥其转录活性, 而另一个位点的磷酸化则会降低其活性, 同时, 甲基化也会抑制其活性。nSREBP2的转录活性首先是通过其TAD与辅助因子CBP/p300(组蛋白乙酰转移酶)和MED15的结合来控制的, CBP/p300同时也会乙酰化SREBP-DBD中的赖氨酸残基, 从而增强细胞核内SREBP的稳定性。在细胞核中脂蛋白1(Lipin1)是一种磷脂酸性磷酸酶, 抑制nSREBP2的水平, 而mTOR复合物1(mTORC1)可以通过磷酸化Lipin1, 抑制Lipin1进入细胞核从而升高nSREBP2的水平[34]。nSREBP2还可以被ERKs和AMPK磷酸化, 分别导致转录活性的增强和降低, 也可以被甲基化修饰以降低转录活性[35]。饥饿时, SIRT1会去除细胞核内SREBP的乙酰化, 导致nSREBP降解[32]。被丝氨酸/苏氨酸蛋白激酶GSK3磷酸化的nSREBP2可以被Fbxw7-Cullin-1 E3连接酶泛素化, 并被蛋白酶体降解[36], 这种降解背后的代谢触发因素目前尚不清楚, 但在细胞内脂质稳态的调节环中, SREBP2本身驱动miR-182的表达, 从而降低Fbxw7连接酶的表达[37]。UBC9对SREBP2的SUMO(small ubiquitin-like modifier)化降低了它的反式激活能力[38], 生长因子诱导的SREBP2的磷酸化抑制了SUMO化，从而增加了SREBP的转录活性[39]。ZHANG等[40]的研究表明, 生脂转录因子碳水化合物反应元件结合蛋白(carbohydrate-responsive element-binding protein, ChREBP)促进nSREBP2的泛素化。NAVARRO-IMAZ等[41]认为, SND1(staphylococcal nuclease and tudor domain containing 1)的过度表达诱导SREBP2的过度激活, 而SREBP2的过度激活反过来又诱导SND1的表达。

4 多种信号通路对SREBP2的调控

随着对SREBP2的深入研究，人们发现p53、Akt、ROS、微环境pH及葡萄糖等信号通路均能对SREBP2的功能进行调控。目前MOON等[42]的研究显示，p53通过转录诱导胆固醇转运蛋白ABCA1(ATP-binding cassette transporter A1)来阻断SREBP-2的激活，相反突变型p53通过与SREBP2结合，上调甲戊酸通路酶的mRNA表达从而促进乳腺癌的转移[43]。在癌症中，Akt和SREBP2之间存在双向关系，Akt过度活跃(通常在癌症中发现)激活SREBP2，增加脂质积累，从而促进Akt信号转导，这最终促进了癌细胞的增殖[44]。有研究报道，细胞外酸性pH(pH6.8)通过刺激核易位和启动子与其靶标结合以及细胞内酸化，触发了SREBP2的激活[45]。FERRIS等[46]发现，在糖尿病的小鼠中SREBP2的转录降低导致脑胆固醇合成的减少。2型糖尿病(diabetes mellitus type 2, T2DM)小鼠的肝细胞中发现HMGCR和SREBP2的表达相对于对照组受到了抑制作用[47]，临床研究表明血糖控制良好的糖尿病患者的SREBP2表达水平较高[48]。有研究表明，H_2O_2处理可显著增加*SREBP2*、*HMGCR*和*HMGCS*等与胆固醇合成和摄取有关的基因的mRNA表达水平[49]，这表明了ROS在改变胆固醇代谢中起着重要作用。

现有的研究表明，SREBP2可以受多种信号分子的调控，虽然具体的调控机制目前还不清楚，但是这对未来更好地研究SREBP2提供了一定的理论基础。

5 SREBP2转录调控的基因及其在代谢性疾病中的作用

SREBP2作为转录因子可通过识别SRE调控*LDLR*和*HMGCR*等基因的转录，它们在胆固醇稳态调控过程中发挥关键作用。LDLR介导的内吞作用使细胞从血浆中获得胆固醇，或通过甲羟戊酸途径从头合成胆固醇[13]。SREBP2可以与*LDLR*[50]、*HMGCR*[51]等基因上的SRE-1发生特异性结合，直接参与细胞内胆固醇代谢的调控，以维持胆固醇稳态。像LDLR一样，PCSK9的表达水平也是主要在转录水平受SREBP2的调控[52]。因此，SREBP2对于正常的细胞和系统功能至关重要，而SREBP2介导的胆固醇平衡失调不仅是心血管疾病的诱因，也会导致越来越多的其他疾病和癌症的发生发展。SREBP2的调控出现异常时，机体将会发生胆固醇代谢异常，从而引起相关疾病的发生或者促进疾病的进展。

高胆固醇血症由成人生活中的不良的生活习惯诱发或由家族性高胆固醇血症等遗传倾向引起，导致出生时胆固醇水平升高和高胆固醇的早期表现[53]。肝LDLR和PCSK9调节血浆LDL-C的清除率：LDLR促进血浆清除，而PCSK9相反[54]。SREBP2在转录水平上调控PCSK9的表达，JIA等[55]的研究表明，丹参酮IIA可以通过调节SREBP2-PCSK9信号通路蛋白的表达，从而减轻高脂血症大鼠肝脏中的脂质沉积。二烯丙基二硫化物(diallyldisulfide, DADS)是一种从大蒜中提取的挥发性硫化物，有研究表明DADS可以抑制PCSK9表达并通过PI3K/Akt-SREBP2途径增加LDL摄取来改善脂质代谢[56]。

动脉粥样硬化是心血管疾病中最常见的慢性炎症疾病[57]，在所有诱导因素中，脂质起主要作用，氧化应激和炎症是驱动心血管疾病进展的主要原因。GOPOJU等[58]的研究表明，氧化应激通过刺激SREBP2介导LDLR摄取胆固醇，最终导致动脉粥样硬化，而二甲双胍治疗可以改善氧化应激诱导的动脉粥样硬化期间的脂质稳态。最近的研究报道3-羟基邻氨基苯甲酸(3-hydroxyanthranilic acid, 3-HAA)可以降低HepG2细胞培养物中的SREBP-2表达和核易位以及载脂蛋白B分泌，降低$LDLR^{-/-}$小鼠的动脉粥样硬化[59]。

冠状动脉疾病(coronary heart disease, CHD)是对人类健康的严重威胁，也是全球范围内人类死亡的主要原因[60]。LIU等[61]的研究结果发现，*Insig1*基因与CHD相关，所以作者认为SREBP2激活相关通路基因之间可能对CHD有潜在的交互作用。现有的研究报道NBEAL1控制SREBP2加工和胆固醇代谢，作者认为NBEAL1的低表达可能通过下调LDLR水平导致冠状动脉疾病的风险增加[62]。

非酒精性脂肪肝疾病(nonalcoholic fatty liver disease, NAFLD)是一种脂质代谢异常的疾病，其发病原因部分归因于胆固醇代谢紊乱和交感神经过度活跃[63]。肝脏中过多的胆固醇积累会触发SREBP2介导的反馈机制，从而降低LDLR的表达，LDLR途径的失调与NAFLD及相关代谢紊乱密切相关[64]，但具体作用以及其他影响LDLR通路的病理因素还需要进一步的研究。交感神经递质神经肽Y(neurotransmitter neuropeptide Y, NPY)的过量表达

与NAFLD和胆固醇蓄积呈正相关。有研究证明了NPY可以激活SREBP2-HMGCR途径, 从而促进肝脏胆固醇的合成[63]。同时OTENG等[65]的研究表明, 工业反式脂肪酸通过激活SCAP-SREBP2轴刺激肝细胞胆固醇合成途径促进NAFLD。

酒精性脂肪肝是由于长期大量饮酒导致的肝脏疾病, 酒精诱导的胆固醇合成增加与肝脏SREBP2及其靶基因*HMGCR*的激活密切相关, YANG等[66]的研究表明, 甜菜碱通过广泛调节肝脂代谢减轻慢性酒精性脂肪肝。

肝细胞癌(hepatocellular carcinoma, HCC)是人类最致命和最普遍的癌症之一[67], 肥胖是HCC的关键危险因素[68]。有研究表明, 患有NASH肥胖患者中有3%~15%会发展为肝硬化, 而患有肝硬化的NASH中有4%~27%会转变为HCC[69]。有研究提示, 肝癌HepG2细胞中SREBP2的表达水平显著高于其在正常肝细胞LO2中的表达水平[70]。LI等[71]的研究表明, 通过抑制SREBP途径抑制从头合成脂质可预防肝癌。

糖尿病肾病(diabetic nephropathy, DN)是糖尿病患者并发的一种慢性肾病, 也是糖尿病最严重的慢性并发症之一[72]。DN是终末期肾脏病的主要原因, SUN等[73]的研究发现, SCAP-SREBP2-HMGCR/LDLR通路的激活导致高脂/蔗糖喂养和链脲佐菌素(streptozocin, STZ)诱导的大鼠肾脏胆固醇积聚, 从而导致糖尿病肾损伤, 而阿托伐他汀可以减少肾脏中胆固醇的合成。有研究表明, CML[Nε-(carboxymethyl) lysine]可上调HMGCR、LDLR、SREBP2和SCAP的mRNA和蛋白表达, 作者认为CML可能通过干扰细胞内胆固醇的反馈调节而导致DN, 抑制CML诱导的脂质堆积可能是DN进展过程中潜在的肾脏保护作用[72]。

胆固醇代谢与大肠癌(colorectal cancer, CRC)紧密相关[74]。ZHANG等[75]的研究表明, CRC肝转移途径涉及SREBP2依赖性胆固醇生物合成的激活, 抑制这种胆固醇的生物合成途径可以抑制CRC肝转移。WEN等[76]的研究表明, SREBP2的下调可以改变结肠癌中的细胞代谢, 从而抑制肿瘤的生长并降低了与癌症干细胞相关的基因的表达。胆固醇可以通过miR-33a-PIM3通路调节CRC的发展, 而*SREBP2* mRNA的表达则受到胆固醇的抑制[77]。

SCAP-SREBP2对NLRP3炎症体激活的促进作用则不依赖于nSREBP2调控甲羟戊酸途径中胆固醇生物合成基因的转录活性, 而是通过促进SCAP-SREBP2的表达而激活NLRP3炎症体和产生IL-1b[78]。NPC1在细胞内胆固醇转运过程中发挥了重要功能, 人*NPC1L1*基因含有两个SRE位点, 由SREBP2激活[79], 在小鼠启动子中也存在多个SRE位点, 已有的研究表明SREBP2是肝脏*NPC1L1*启动子的重要转录因子。最近的研究表明, 长链非编码RNA(lncRNA) SNHG16通过直接调节miR-195/SREBP2轴, 加速胰腺癌的发展, 促进脂肪生成[80]。

综上所述, SREBP2及其调控的下游基因的异常激活会通过调控胆固醇的代谢影响疾病的发生发展, SREBP2作为胆固醇代谢相关基因调控的中心环节, 有望成为治疗相关疾病的重要靶标。

6 小结

胆固醇是细胞膜中不可缺少的成分, 在生命过程中起着至关重要的作用。在正常生理状态下, SREBP2通过调控*LDLR*和*HMGCR*等基因的表达维持生物体内胆固醇稳态, 其本身的转录、翻译、定位、转位、稳定性、活性受到严格的网络调控。SREBP2及其对下游基因的异常调控将会导致心血管疾病、脂肪肝、糖尿病、肿瘤等疾病的发生发展。本研究从*SREBP2*基因的转录调控、SREBP2蛋白的转运与剪切调控、nSREBP2的修饰及功能调控以及SREBP2在代谢性疾病中的作用四个方面对SREBP2相关的研究进行了综述, 系统地总结了SREBP2相关的研究, 本综述使我们从分子遗传学的角度深化了对SREBP2调控胆固醇合成机制的认识, 可为针对胆固醇代谢治疗相关疾病提供坚实的理论参考。

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