固醇调节元件结合蛋白-1信号通路研究进展

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摘要 固醇调节元件结合蛋白-1(sterol regulatory element-binding protein-1, SREBP-1)是脂质代谢重要的核转录因子之一, 主要调控脂肪酸、甘油三酯和胆固醇的生物合成。*SREBP-1*及其靶基因的异常表达能够引起胰岛素抵抗、糖尿病和脂肪肝等一系列代谢性疾病。因此, 认识SREBP-1信号通路上下游各因素的表达调控作用就显得非常重要。该文总结了受SREBP-1调控表达的靶基因的特点, 着重介绍了胰岛素等上游因子在SREBP-1调控过程中的作用, 为指导治疗各类代谢性疾病提供新的思路。

关键词 SREBP-1; 胰岛素; 靶基因; 脂质代谢

Progress in the Study of Sterol Regulatory Element Binding Protein-1 Signal Pathway

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Abstract Sterol regulatory element-binding protein-1 (SREBP-1) is one of the important nuclear transcription factors in lipid metabolism. SREBP-1 can regulate the biosynthesis of fatty acid, triglyceride and cholesterol. Abnormal expression of *SREBP-1* and its target genes can cause a series of metabolic diseases such as insulin resistance, diabetes and fatty liver disease. Therefore, it is very important to know the role of various factors in SREBP-1 pathway. In this review, we summarize the feature of target genes regulated by SREBP-1, emphatically introduce the role of insulin and other upstream factors in regulating SREBP-1, which will contribute to a better idea for the guidance and treatment of various metabolism diseases.

Keywords sterol regulatory element binding protein-1; insulin; target genes; lipid metabolism

固醇调节元件结合蛋白(sterol regulatory element-binding proteins, SREBPs)属于螺旋–环–螺旋–亮氨酸拉链(basic-helix-loop-helix leucine zipper, bHLH-LZ)转录因子家族, 包含三个亚型: SREBP-1a、SREBP-1c和SREBP-2[1-2]。SREBP-1a和SREBP-1c是SREBP1的两个亚型, SREBP-1优先调控表达那些与脂肪酸合成有关的基因, 而SREBP-2则优先调控与胆固醇合成、摄取有关的基因表达[3-4]。研究发现, SREBP-1的过量表达将引起脂质代谢的紊乱, 导致脂肪在非脂肪组织中过度积累, 从而引发肥胖、胰岛素抵抗和脂肪肝等代谢疾病[5]。虽然, SREBP-1调控脂代谢的下游靶基因已明确, 但调控SREBP-1途径的上游调控因子和通路仍相对模糊和复杂。因此, 该文将从SREBP-1的上下游信号通路来回顾和阐述其在脂质代谢调控中的作用。

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1 SREBP-1的结构和功能

SREBP-1a和SREBP-1c由位于17号染色体上的

*SREBP-1*基因编码, 人类SREBP-1蛋白质由1 147个氨基酸组成, 包括三个结构域: 由480个氨基酸组成的N-端转录活性结构域、80个氨基酸组成的疏水区和由590个氨基酸组成的C-端调节结构域[1]。合成后的SREBP-1蛋白通过中端疏水区绑定在内质网膜和细胞核膜上, 而N-端和C-端均朝向细胞质一面。SREBP-1a和SREBP-1c是从不同的转录起始位点生成的, 第一个外显子不同(分别是外显子1a和外显子1c), 其余外显子是一样的。SREBP-1a优先促进脂肪酸的大量合成, 其次才是胆固醇合成, 而SREBP-1c则在甘油三酯和磷脂形成中起关键作用[6]。

2　SREBP-1的剪切活化

SREBP最初是连接在内质网膜上, 若要进入细胞核行使其转录调控功能, 其前体形式必须经过蛋白水解变成有活性的成熟核型SREBP(nSREBP)。这一过程受SREBP裂解激活蛋白(SREBP cleavage-activated protein, SCAP)和胰岛素诱导基因蛋白(insulin induced gene, Insig)调控。当细胞缺乏固醇时, SCAP与Insig蛋白分离, SCAP与外被蛋II(coat protein II, COPII)结合, 后者介导SCAP/SREBP复合体进入COPII蛋白包被的囊泡中并将其运送到高尔基体上, 经过位点1蛋白酶(site 1 protease, S1P)和位点2蛋白酶(site 2 protease, S2P)两次剪切后, SREBP前体释放出具有活性的N-端部分, 后者进入细胞核内, 结合到固醇调节元件(sterol regulatory element, SRE)序列上, 启动下游基因的表达。而当细胞内固醇含量增多时, Insig蛋白与SCAP作用, SCAP/SREBP复合体被滞留在内质网膜上, 无法进入细胞核发挥转录活性作用[1-2]。

3　SREBP-1调控的下游靶基因

细胞中转录因子激活或抑制靶基因的转录需要结合特定的顺式作用元件, 即转录因子结合位点(transcription factor binding site, TFBS)。TFBS是与转录因子结合的DNA片段, 长度从几个到十几个碱基对不等。转录因子常常同时调控若干个基因, 其在不同基因上的结合序列不完全相同, 但具有一定的相似性。每个转录因子的结合位点通常都有特定的立体结构, 称为模体[7]。传统研究认为, 转录因子nSREBP-1的结合位点应包含SREs(5′-TCACNCCAC-3′)和(或)E盒(5′-CANNTG-3′)两种模体[8-9]。

根据已知SREBP-1的两种TFBS模体信息, 目前研究较明确的SREBP-1靶基因包括: 乙酰辅酶A羧化酶(acetyl CoA carboxylase, *ACC*)[10-11]、脂肪酸合成酶(fatty acid synthetase, *FASN*)[12]、低密度脂蛋白受体(low density lipoprotein receptor, *LDLR*)[8]、甲状腺激素应答SPOT14(thyroid hormone responsive spot 14, *S14*)[13]、葡萄糖激酶(glucokinase, *GCK*)[14]和磷酸烯醇式丙酮酸激酶1(phosphoenolpyruvate carboxykinase 1, *PCK1*)[15]等与脂肪合成和葡萄糖代谢有关的基因。另据文献统计, 截止2008年, 已发现79个SREBP-1在肝组织中调控的靶基因[16]。而随着表达芯片的普及应用和对nSREBP-1结合位点的深入研究, nSREBP-1参与调控的靶基因谱也得到了极大的扩增。基于最新的ChIP-chip(chromatin immunoprecipitation-chip)和ChIP-seq(chromatin immunoprecipitation-sequence)的研究, 在全基因组内已发现上百个受nSREBP-1调控的候选基因[16-18]。

通过整合ChIP-seq和差异表达数据, 可将SREBP-1调控的基因分为三类模型: (1)SREBP-1直接调控的靶基因, 即存在临近TFBS的差异转录基因, 如*FASN*、线粒体甘油-3-磷酸酰基转移酶(glycerol-3-phosphate acyltransferase mitochondrial, *GPAM*)、乙酰乙酰CoA合成酶(acetoacetyl CoA synthetase, *AACS*)、甾醇14α-去甲基化酶(sterol 14α-demethylase, *CYP51*)、法尼基二磷酸合酶(farnesyl diphosphate synthase, *FDPS*)、角鲨烯环氧化酶(squalene epoxidase, *SQLE*)等[19-24]。(2)SREBP-1间接调控或远程调控的基因, 即不存在临近TFBS的差异转录基因。推测这些基因可能是SREBP-1或高糖条件下间接调控的基因, 如3-羟基-3-甲基戊二酰辅酶A合酶(3-hydroxy-3-methylglutaryl coenzyme A synthase, *HMGCS*)、乙酰辅酶A羧化酶α(acetyl CoA carboxylase α, *ACACA*)、法尼基二磷酸法尼基转移酶1(farnesyl-diphosphate farnesyltransferase 1, *FDFT1*)、苹果酸酶(malic enzyme, *MEL*)等, 它们表达差异虽然很大, 但基因临近区域没有发现相应的TFBS。这种间接调控的机制可能是SREBP-1通过其他转录因子(或共激活因子)相互作用而实现的对靶基因的调控[25]。(3)SREBP-1可能调控的靶基因, 即存在临近可疑的TFBS(测序数据分析提示可能是假阳性的TFBS)的差异转录基因, 如*Insig-1*、*PCK1*、

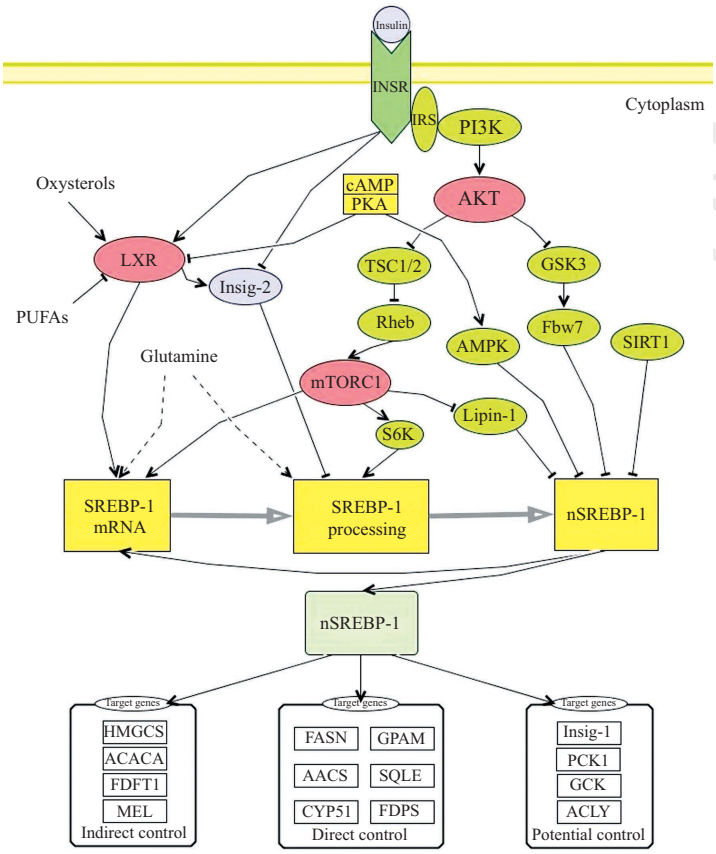

图1 SREBP-1的上下游信号通路

Fig.1 The upstream and downstream signal pathway of sterol regulatory element-binding protein-1

GCK、*ATP*柠檬酸裂解酶(ATP citrate lyase, *ACLY*)等[26-29](图1)。

4 上游因子对SREBP-1转录活性的调控

在体内SREBP-1表达和剪切加工是非常复杂的, SREBP-1的调控不仅受细胞内胆固醇水平的影响, 而且还受整个机体营养条件和激素水平的影响[30]。它们彼此相互联系又相互作用, 组成了复杂而又精细的调控网络, 在转录和转录后水平两方面调控着SREBP-1的活性, 从而起到维持体内脂质代谢平衡的作用。

4.1 胰岛素对SREBP-1的调控

胰岛素信号通路始于胰岛素受体底物-1(insulin receptor substrate-1, IRS-1)和/或IRS-2的酪氨酸磷酸化[31]。IRS磷酸化后接着激活下游磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)的活化, PI3K则催化细胞膜上的磷脂酰肌醇-4,5-二磷酸(phosphatidylinositol-4,5-bisphosphate, PIP2)变成磷脂酰肌醇-3,4,5-三磷酸(phosphatidylinositol-3,4,5-triphosphate, PIP3)[32]。PIP3能与丝氨酸/苏氨酸蛋白激酶(serine/threonine protein kinase, AKT)相互作用, 将AKT招募到细胞膜上并使之活化[33]。AKT是属于丝氨酸/苏氨酸激酶, 在细胞存活、凋亡、细胞大小、血管新生、细胞代谢和迁移中起重要作用[32-33]。雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是雷帕霉素的靶分子, 是一种丝氨酸/苏氨酸激酶, 是PI3K/AKT信号通路下游的一个效应蛋白, mTOR被磷酸化激活后, 通过激活p70S6K调控特定亚组mRNA的翻译[34]。p70S6K是核糖体40S小亚基S6蛋白激酶, 它通过磷酸化S6蛋白, 调控许多翻译元件等的合成[35-36]。糖原合成酶激酶3(glycogen synthase kinase 3, GSK3)属于丝/苏氨酸蛋白激酶, 在糖代谢、蛋白质合成、细胞分化和增殖等方面发挥重要作用。胰岛素、生长因子等信号分子可通过PI3K/PKB途径抑制GSK3, 激活的AKT又可引起GSK3的Ser9/21位点磷酸化, 阻止其与底物的结合[37](图1)。

众所周知, 胰岛素可以有效地诱导脂质的从头合成和调节生脂酶的活力[38]。越来越多的证据表明, 胰岛素通过多种途径来调节SREBP-1的活性, 包括

SREBP-1 mRNA的转录、SREBP-1的蛋白酶解加工过程和对成熟nSREBP-1的稳定性丰度的调控。

4.1.1　胰岛素对SREBP-1的mRNA水平的调控　作为自身的靶基因, *SREBP-1* mRNA水平可以被nSREBP-1诱导。此外, 当接触胰岛素时, 小鼠和大鼠肝脏中*SREBP-1c* mRNA水平急剧下降[39]。而当禁食条件下胰岛素水平受抑制时, 小鼠肝脏中*SREBP-1c*的转录就减少[40]。在体外培养的大鼠原代肝细胞中, 胰岛素能在6小时内能诱导*SREBP-1c* mRNA增高40倍[35,41]。同时, 当大鼠灌胃链脲霉素抑制胰岛素分泌时, *SREBP-1c* mRNA水平得到下降[42]。这些结果表明, 胰岛素能有效地诱导*SREBP-1c*的转录。

胰岛素对SREBP-1的转录调控主要通过PI3K/AKT/mTORC1(mammalian target of rapamycin complex 1)途径。研究表明, 胰岛素激活mTOR是通过AKT调节的磷酸化作用抑制结节性脑硬化复合物1/2(tuberous sclerosis complex1/2, TSC1/2)的功能[39], 而TSC1/2又能抑制脑中富含Ras的同源蛋白(Ras homolog enriched in brain, Rheb)的表达水平, Rheb则可磷酸化和激活mTOR[44-45](图1)。

当存在渥曼青霉素, 一种PI3K抑制剂时, 胰岛素诱导*SREBP-1c* mRNA增加的途径就会被阻断[39]。更重要的是, *SREBP-1*的转录也能被低浓度的雷帕霉素所阻断, 表明mTORC1在*SREBP-1*的转录中是必需的[39]。这些研究表明, 胰岛素增强*SREBP-1c* mRNA的转录主要是通过mTORC1调控的。

4.1.2　胰岛素对SREBP-1蛋白酶解加工过程的调控　除了调控*SREBP1c* mRNA水平, 胰岛素也能通过两种不同的方式来影响SREBP-1的蛋白酶解加工过程: (1)减少Insig-2的表达; (2)促进mTORC1诱导p70S6K的激活[39]。

机体内Insigs的表达水平与胰岛素相关。当禁食(低胰岛素)时, 小鼠体内*Insig-2*的转录和翻译有所增加, Insig-2通过与SCAP结合使SREBP滞留在内质网膜上, 进而SREBP-1的运输被阻断, 肝脏中不能产生成熟的nSREBP-1c[46]。作为SREBP-1的靶基因, Insig-1 mRNA和蛋白水平在禁食后也减少, 而当小鼠重新喂食(高胰岛素)后, *Insig-2*的转录就受到抑制, 由gp78介导*Insig-2*迅速泛素化[47], 释放SCAP/SREBP复合体运输到高尔基体。与此同时, 加工成熟的nSREBP-1c激活下游*Insig-1*基因, *Insig-1* mRNA和蛋白水平得到恢复[46]。这些结果揭示了胰岛素能通过调节Insig-2的表达来增强SREBP-1的蛋白酶解加工过程。

最近, Owen等[39]通过人源APOE启动子表达组件产生了一种附加表位的*SREBP-1c*的转基因大鼠。这种转基因大鼠排除了胰岛素对*SREBP-1*转录的影响。内源性的*SREBP-1c* mRNA在没有抑制剂的情况下, 转基因大鼠体内的SREBP-1c可增加14倍。而当添加雷帕霉素后, *SREBP-1c* mRNA水平下调了85%。有趣的是, 用LYS6K2抑制mTORC1下游的S6K后, 内源性*SREBP-1c* mRNA的表达并不受影响[39]。同样, 在6 h内胰岛素能把转基因编码的nSREBP-1c的蛋白水平提高12倍。而当添加LYS6K2后, nSREBP-1c能减少74%, 但雷帕霉素处理组却只降低了64%。考虑到胰岛素不影响*SREBP-1c*的mRNA水平, 说明LYS6K2抑制SREBP-1c的蛋白酶解加工过程并不发生在转录水平上[39]。总之, 胰岛素能通过PI3K/AKT/mTORC1途径激活S6K来增强SREBP-1的蛋白酶解过程, 但尚不清楚S6K通过何种途径增加了这个过程(图1)。

4.1.3　胰岛素对成熟核型nSREBP-1的调控　胰岛素除了能调节*SREBP-1*的mRNA水平和蛋白酶解加工过程外, 它还能调节核型nSREBP-1的稳定和丰度。已有研究证实, 胰岛素信号通路在AKT处有分支点, 其中一条就是上面提到的激活mTORC1来调节SREBP-1的活性, 而另一条则是通过GSK3/Fbw7途径来抑制nSREBP-1的降解。AKT能在其第9个丝氨酸残基上磷酸化GSK3, GSK3的磷酸化抑制了糖原合成酶的作用[36]。当nSREBP-1与靶基因上的DNA连接后, 招募的GSK3能磷酸化nSREBP-1上的第434位丝氨酸[48-49], 接着, nSREBP-1上第430位丝氨酸和第426位苏氨酸也被GSK3磷酸化[49], 最后, 泛素连接酶SCF-Fbw7也被招募, 导致nSREBP-1的泛素化降解[48-49]。也有研究证实, SCF-Fbw7能降解nSREBP-2, 内源性Fbw7的失活使核型nSREBP-1和nSREBP-2变得稳定[50]。因此, 胰岛素能通过AKT这条通路抑制GSK3的表达, 从而减少Fbw7对核型nSREBP-1的抑制来稳定体内nSREBP-1的含量[51]。

上述已提到mTORC1作为AKT下游的因子能够通过调节转录和加工过程来控制SREBP-1c的表达。但最近, Peterson等[52]证明, mTORC1能通过类脂-1(Lipin-1)来提高nSREBP-1的丰度。这种Lipin-1在细胞核中的聚集能抑制*SREBP-1*的转录。虽然,

mTORC1/Lipin-1调节nSREBP-1表达水平的机制还不清楚, 但研究显示, lamin A可能参与了这一过程的调控, 更深入的机制有待进一步的研究(图1)。

综上所述, 胰岛素经由AKT激活SREBP-1至少通过两种机制: (1)通过抑制GSK3来增强nSREBP-1的稳定性; (2)通过mTORC1的激活来增加SREBP-1的表达。而mTORC1对SREBP-1的作用又能划分为三个阶段: (1)mTORC1能在转录水平提高*SREBP-1c* mRNA的表达; (2)mTORC1能通过激活S6K加强SREBP-1的蛋白酶解加工过程; (3)mTORC1能抑制Lipin-1来增加成熟型nSREBP-1的含量。

4.2 肝X受体对SREBP-1的调控

肝X受体(liver X receptor, LXR)是另一个重要的固醇调控转录因子。它有两种亚型, LXRα和LXRβ。LXR和类视黄醇X受体(retinoid X receptor, RXR)形成异二聚体, 共同调节SREBP的转录水平和蛋白加工过程。

由于在*SREBP-1c*基因启动子区域有两个LXR应答元件(liver X receptor response elements, LXREs), 所以LXR能提高*SREBP-1*的转录水平[53]。然而, 在ATP结合盒亚家族A1(ATP-binding cassette subfamily A1, *ABC1*)、胆固醇酯转移蛋白(cholesterolester transfer protein, *CETP*)和细胞色素P450家族7亚科A(cytochrome P450 family 7 subfamily A, *CYP7A*)这些其他LXR靶基因的启动子区域, 发现只有一个LXRE[54-56], 表明LXR和RXR对SREBP-1c有强烈的激动作用。事实上, 即使在体内胆固醇过载的情况下, LXR或RXR也能够显著地增强*SREBP-1c*的转录并诱导相应脂肪酸合成的增加[46]。相反, 多不饱和脂肪酸通过抑制异二聚体LXRα/RXRα与*SREBP-1c*启动子区LXREs相连, 减少了*SREBP-1c* mRNA的水平和脂肪生成[57](图1)。

氧固醇(oxysterol)是LXR天然的激活剂, 包括24,25-环氧胆固醇和25-羟基胆固醇[58]。24-羟基胆固醇、25-羟基胆固醇和27-羟基胆固醇是众所周知的SREBP-1酶解加工过程的抑制剂, 但它们在临床上不被用来治疗高脂血症, 因为它们同时也能激活LXR[58]。最近, Zhang等[59]研究表明, 肝脏中LXRα表达缺失时, 一种人工合成的LXR激动剂能够诱发抵抗动脉粥样硬化, 主要原因可能是LXR的靶基因*SREBP-1*主要在肝脏中表达, 而体内特定敲除LXRα基因后能够显著减少SREBP-1在肝脏中的表达, 从而减少脂肪酸的合成(图1)。

有趣的是, 尽管LXR能有效地激活SREBP-1c和提高前体SREBP-1c的表达, 但LXR并不能增加体内nSREBP-1和其靶基因的含量[60-61]。这表明LXR增加*SREBP-1c* mRNA水平的作用在蛋白酶解加工过程中受到限制。相应研究也证实, LXR能调节Insig-2 mRNA和蛋白水平的表达, 使SREBP-1c滞留在内质网膜上(图1)。

另一方面, 有研究表明, 胰岛素能显著上调LXR的表达[62]。小鼠体内敲除*LXR*基因后明显抑制了胰岛素调节诱导的与脂肪酸和胆固醇代谢相关酶系的表达[63], 提示LXR和胰岛素的交互作用在调节胆固醇和脂肪酸代谢中起重要作用(图1)。

4.3 cAMP/PKA对SREBP-1的调控

胰高血糖素、肾上腺素和其他物质能上调体内环腺苷-3′,5′-单磷酸(cyclic adenosine-3′,5′-monophosphate, cAMP)的表达, cAMP能激活一系列胞外的信号通路从而调控各种细胞内的功能。cAMP依赖的激酶, 蛋白激酶A(protein kinase A, PKA)在体内与脂质代谢相关, 在生理条件下, 肝脏中的脂肪生成酶如FASN、硬脂酰辅酶A去饱和酶(stearoyl coenzyme A desaturase, SCD)和甘油-3-磷酸酰基转移酶(glycerol-3-phosphate transferase, GPAT)受胞内cAMP水平的负反馈调控[64]。

最近一项研究表明, PKA通过调节LXR的活力来抑制SREBP-1c的表达[65]。PKA能使LXR磷酸化, 这种磷酸化阻碍了LXR/RXR异二聚体的形成, 从而抑制LXR与靶基因*SREBP-1*上LXREs的连接, 减少了*SREBP-1*的转录。Lu等[66]发现, SREBP-1a氨基末端第338位丝氨酸也是PKA磷酸化的一个位点。SREBP-1c第314位的丝氨酸与SREBP-1a上的338位丝氨酸一样, 也能被PKA磷酸化。这些发现提示, cAMP/PKA信号通路能磷酸化SREBP-1来减少其反式激活, 从而导致SREBP-1的相关靶基因表达减少。

AMP激活蛋白激酶(AMP-activated protein kinase, AMPK)作为一类高度保守的丝氨酸/苏氨酸激酶, 在细胞和整个生理水平调控着体内的能量平衡[67-69]。PKA是AMPK上游的一个调节因子, 研究表明, 使用一种PKA的抑制剂H89能够反向提高细胞内cAMP的表达水平, 从而通过PKA的激活来增加AMPK的磷酸化作用[70], 而AMPK又能直接磷酸化SREBP-1c, 也因此能直接抑制SREBP-1c的酶解加

工, 阻止核型nSREBP-1c转运至细胞核中[71], 从而影响脂质代谢过程。这些结论表明, 体内营养水平通过cAMP/PKA途径调节LXR和AMPK的活力来控制SREBP-1的表达和脂肪生成(图1)。

4.4 PUFAs对SREBP-1的调控

多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)可以通过多种机制减少SREBP-1c的表达, 包括降低*SREBP-1c*的转录, 减少SREBP-1c的蛋白酶解加工和降低mRNA的稳定性[72-73]。PUFAs抑制肝脏中*SREBP-1a*和*SREBP-1c*的mRNA水平, 但并不减少*SREBP-2*的表达水平[72]。有研究表明, PUFAs下调*SREBP-1*的转录活性是通过LXR依赖的方式或一种独立的机制[72]。肝脏中PUFAs抑制SREBP-1的蛋白加工过程, 主要是通过它们影响神经鞘脂类的代谢[73]。CHO细胞中PUFAs抑制了SREBP-1的剪切加工后增加了鞘磷脂酶的活力[74-75], 而孵育鞘磷脂酶后细胞内nSREBP-2也得到抑制[76]。因此, PUFAs抑制SREBP加工可能引起质膜中胆固醇的重新分配(图1)。

4.5 调控SREBP-1的其他途径

最近研究发现, 谷氨酰胺(lutamine)也能调控SREBP-1的基因表达和蛋白酶解加工过程, 这一发现将氨基酸代谢和脂代谢联系了起来。谷氨酰胺似乎能够增加多个SREBP-1靶基因的mRNA水平。谷氨酰胺通过加强转录因子Sp1(specificity protein 1)与*SREBP-1a*启动子的连接来提高*SREBP-1*基因的表达。谷氨酰胺也能增加SREBP-1蛋白的酶解加工过程, 这一过程可能是刺激了SREBP-SCAP复合物从内质网到高尔基体的运输而实现的[77](图1)。

Ponugoti等[78]的实验表明, NAD^+依赖的脱乙酰酶1(NAD^+-dependent deacetylase 1, SIRT1)能直接作用SREBP-1c, 使之脱乙酰化从而减少其蛋白的表达和相应靶基因的表达[78]。此外, SIRT1在体内禁食状态下也能下调SREBP-1c的表达[79]。然而, 这些研究都聚焦在肝组织上, 最近的研究显示, 骨骼肌细胞中的SIRT1也能调控SREBP-1c的表达。有趣的是, 当*SREBP-1*启动子区的LXR应答元件被删除后, SIRT1对SREBP-1c的表达调控就完全消除了, 表明肌细胞中SIRT1对SREBP-1c的调控是通过LXR的脱乙酰作用来实现的[80](图1)。

5 结论

SREBP-1作为体内重要的核转录因子, 不但在胆固醇和脂肪酸代谢中发挥着重要的调控作用, 而且也是代谢综合征等相关疾病的关键连接点, 它在机体中的调控作用越来越受到人们的重视。通过基因芯片和测序技术的运用, 对SREBP-1调控的下游靶基因的了解已相对清晰, SREBP-1调控的靶基因可分为: 直接调控、间接调控和可能调控三类[7]。而另一方面, 对各因素调控SREBP-1的具体机制和作用并不十分了解, 目前已知胰岛素在调控SREBP-1的过程中起重要作用, 包括*SREBP-1* mRNA的转录、SREBP-1的蛋白酶解加工过程和对成熟nSREBP-1的稳定性丰度的调控。因此, 为了更深入全面理解SREBP-1的调控机制, 有必要集合和整理SREBP-1的最新研究进展, 通过运用生物信息学分析方法勾画出更细致全面的信号通路, 为SREBP-1相关代谢疾病的防治提供新的靶点, 以期在治疗方面开辟出一条新的途径。

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