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SREBP-1相关通路为靶点的NAFLD发生机制及治疗进展

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摘　要

非酒精性脂肪肝疾病(NAFLD)是引起肝损伤最常见的原因之一，其特征是肝脏外源性游离脂肪酸增多或内源性从头生成增加，导致肝细胞中甘油三酯的过度积累。甾醇调节元件结合蛋白(SREBPs)是一个转录因子家族，通过调控内源性胆固醇、脂肪酸(FA)、三酰基甘油和磷脂合成所需的一系列酶来调节脂质稳态。SREBP-1是增加肝脏脂肪酸和甘油三酯合成的主要转录因子，本文回顾了近年来以SREBP-1相关通路为靶点NAFLD的研究进展。

关键词

甾醇调节元件结合蛋白-1，非酒精性脂肪性肝病，信号通路，脂质生成

The Pathogenesis and Treatment Progress of NAFLD Targeted by SREBP-1 Related Pathway

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Abstract

Nonalcoholic fatty liver disease (NAFLD), one of the most common causes of liver injury, is characterized by an increase in exogenous free fatty acids or endogenous de novogenesis in the liver, resulting in excessive accumulation of triglycerides in liver cells. Sterol regulatory element bind-

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ing proteins (SREBPs) are a family of transcription factors that regulate lipid homeostasis by regulating a series of enzymes required for the synthesis of endogenous cholesterol, fatty acids (FA), triacylglycerol and phospholipids. SREBP-1 is the major transcription factor that increases hepatic fatty acid and triglyceride synthesis. This paper reviews the research advances in NAFLD targeting SREBP-1 related pathways.

Keywords

Sterol Regulatory Element Binding Protein 1 (SREBP-1), Nonalcoholic Fatty Liver Disease (NAFLD), Signal Transduction, Lipogenesis

1. 引言

非酒精性脂肪性肝病(NAFLD)全世界患病率为 16%~23%，并有逐年递增的趋势。它是由肝脏中脂质的积累引起的，这始于单纯的肝脏脂肪变性，可发展为非酒精性脂肪性肝炎(NASH)，如果不加以控制治疗甚至可能进展为肝硬化。NAFLD 与代谢紊乱有关的疾病(如糖尿病、肥胖症和高血压)密切相关，随着我国经济水平提高，糖尿病、肥胖症和高血压患病率逐年上升，因此为了控制和预防 NAFLD，研究其发生、发展是非常有必要的[1] [2] [3]。NAFLD 发生发展的病理过程中，肝细胞内过多的脂质沉积造成的脂毒性是第一步，而对脂毒性的研究中，最受关注的就是游离脂肪酸对于肝脏的影响。甾醇调节元件结合蛋白(SREBPs)是可以调控所有器官中胆固醇和脂肪酸生物合成过程的转录因子家族，被认为是肝脏中胆固醇生成和脂肪生成的主要调节因子，其中 SREBP-1 是影响脂肪酸合成的主要调控因子[4]。本文将综述近年来在非酒精性脂肪性肝病中，以 SREBP-1 相关通路为靶点的发生机制及治疗进展。

2. SREBP-1 的结构与激活

甾醇调节元件结合蛋白(SREBPs)是膜结合的碱性螺旋-环-螺旋亮氨酸拉链(bHLH-LZ)转录因子的一个亚类[5]。是脂质代谢的主要调节因子，能够调控一些负责脂肪生成、甾醇产生和脂质摄取的基因的表达[6]。哺乳动物细胞中 SREBPs 蛋白有三个亚型：SREBP-1a、-1c 和-2。SREBP-1 编码 SREBP-1a 和-1c 蛋白，-1a 蛋白比-1c 长 24 个氨基酸，具有较强的转录活性[7]。SREBP-1a 调节脂肪酸和胆固醇合成以及胆固醇摄取，而 SREBP-1c 主要控制脂肪酸合成[8]。SREBF2 编码 SREBP-2 蛋白，并在调节胆固醇合成和摄取中发挥重要作用[9]。

2.1. SREBPs 的结构

SREBPs 表达水平和活性由内源性甾醇通过负反馈调节严格的控制，这与 SREBPs 的结构相关[10]。SREBPs 在膜结合核糖体上合成前体蛋白，其-NH2 端的 bHLH-Zip 结构域和-COOH 端一起延伸，面向胞质插入内质网膜中，两个跨膜螺旋被一个由 50 个氨基酸组成的短环隔开[11]。甾醇调节元件结合蛋白裂解激活蛋白(SCAP)是一种具有 8 个跨膜螺旋的内质网蛋白，其中包含一个可直接结合胆固醇的甾感应域，常与 SREBPs 以复合物的形式存在于细胞中。

2.2. SREBP-1 的激活

当甾醇充足时，SCAP-SREBP 复合物通过 SCAP 与一个名为胰岛素调节基因(INSIGs)的内质网蛋白结合而锚定在内质网中[12]。当缺乏甾醇时，SCAP 构象发生变化，与 INSIG 的亲和力降低，同时暴露了一种特殊的基序，促进辅原子复合物 II(COPII)产生特殊的转运囊泡，由 SCAP 介导将 SCAP-SREBP 复合物通过囊泡从内质网运输到高尔基体中依次进行两次连续的蛋白裂解[13] [14]。第一次裂解发生在 50 个氨基酸的腔内环内，通过位点 1 蛋白酶(S1P)将 SREBP 分成两半，-NH2 端的一半通过其单一的跨膜螺旋附着在膜上；第二次裂解发生在这个螺旋内，通过位点 2 蛋白酶(S2P)暴露出 bHLH-Zip 结构域[15] [16]，靶向定位于细胞核内，识别固醇调节元件 DNA 序列，促进 SREBPs 靶基因的转录，激活脂质合成和摄取[17] (见图 1)。其中 SREBP-1 的靶基因包括 ATP-柠檬酸裂解酶(ACL)、乙酰辅酶 a 羧化酶(ACC)、硬脂酰辅酶 a 去饱和酶(SCD)和脂肪酸合酶(FAS)，均是脂肪酸从头生成的关键酶。

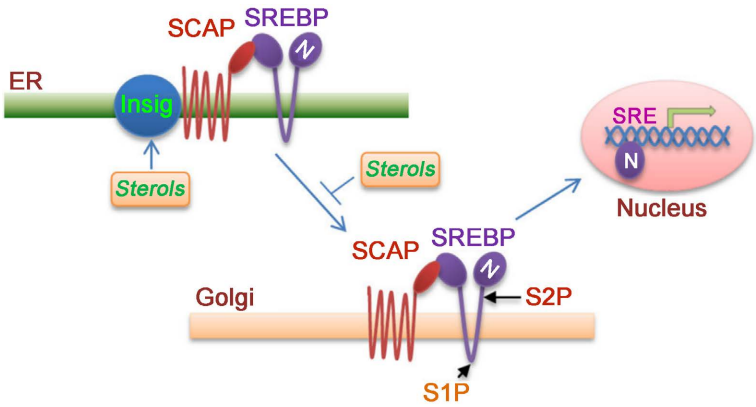

Figure 1. Sterol-regulated maturation model of SREBPs [80]
图 1. 甾醇调节的 SREBPs 成熟模型[80]

3. SREBP-1 相关通路

3.1. AMPK

AMP 活化蛋白激酶(AMPK)是一种丝氨酸/苏氨酸蛋白激酶，由一个具有催化功能的 α 亚基和具有调节作用的 β 和 γ 亚基组成，通过 AMP(腺苷一磷酸)与 γ 亚基的变构结合和通过 AMPK 激酶对 α 亚基上 Thr172 的磷酸化均可导致 AMPK 的激活，作为肝细胞的能量传感器，从而调节参与糖脂代谢的多种途径[18] [19]。AMPK 介导的 SREBP-1 前体在 Ser372 上的磷酸化抑制了其裂解、核易位和转录活性，导致 SREBP-1 靶基因，如 FAS、ACC 和 SCD 等的表达下调。AMPK 的激活通过抑制 SREBP 的活性来减少肝脏中的脂肪生成。相反，抑制 AMPK 会激活合成代谢途径，抑制分解代谢途径[20]。大量证据表明，AMPK 介导的 SREBP 信号通路是 NAFLD 发病的原因之一，因此增强 AMPK 活性被认为是一种可行的预防 NAFLD 发生和发展的治疗策略。

肝激酶 B1(LKB1)和钙调素依赖性蛋白激酶激酶(CaMKK)是 AMPK 主要的上游激酶，使 LKB1 的 Ser428 位点磷酸化可激活 AMPK，通过增加细胞内钙离子激活 CaMKK 从而激活 AMPK [21] [22] [23] (见图 2)。可通过促进 LKB1、CaMKK 与 AMPK 之间的相互作用调节 SREBP 转录活性以改善肝脂肪变。有研究发现，松柏醛呈浓度依赖性的降低细胞内的甘油三酯及胆固醇水平，改善细胞脂肪变性。它可以刺激 LKB1 磷酸化使 AMPK 激活，进而下调了 SREBP-1 的 mRNA 水平及蛋白水平，其靶基因 FAS、SCD-1 的表达相继减少，最终抑制细胞脂肪变。当使用 AMPK 抑制剂或者敲低 LKB1 后，上述变化大多都可被

逆转[24]。另一项研究显示，使用黄芩苷处理 NAFLD 小鼠模型以及 HepG2 细胞模型后，黄芩苷通过促进 CaMKK 磷酸化激活 AMPK，抑制 SREBP-1 表达，FAS、ACC、SCD 表达从而降低，最终使小鼠血清和肝脏中的甘油三酯、总胆固醇和游离脂肪酸水平降低，肝脂质积累受抑制[25]。此外，丁香烯、桦木酸亦被证实可以通过调控 CAMKK-AMPK-SREBP1 信号通路改善肝脂肪变性[26] [27]。

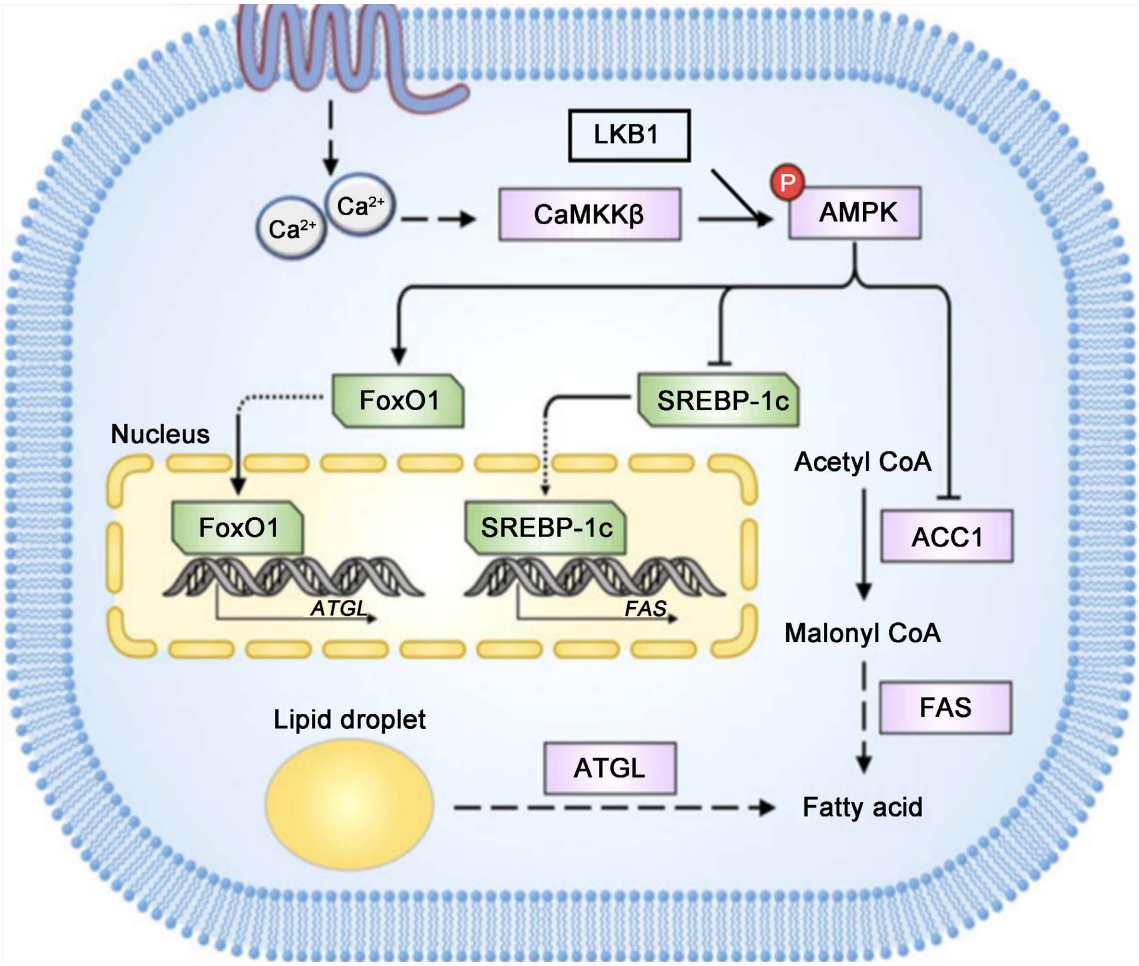

Figure 2. AMPK phosphorylation model induced by LKB1 and CaMKK [27]
图 2. LKB1 和 CaMKK 致 AMPK 磷酸化模型[27]

除了通过激活 AMPK 上游激酶激活 AMPK，最近的食品科学研究发现许多草药或食品的提取物也可以通过磷酸化激活 AMPK、抑制 SREBP-1 表达从而减轻肝脏脂肪变性，如藏红花素、牛樟芝提取物、S-蜂斗菜酯、绿茶多酚、*β*-丁香烷等[27] [28] [29] [30] [31]，虽然激活 AMPK 的具体作用机制尚不明确，但是为 NAFLD 的治疗及预防提供新的临床思路。

3.2. AKT

AKT，也称为蛋白激酶 B(PKB)是一种丝氨酸/苏氨酸激酶，有 AKT1、AKT2、AKT3 这三种亚型，分别由 PKB*α*、PKB*β* 和 PKB*γ* 编码。AKT1 在许多组织中广泛表达；AKT2 主要在对胰岛素高敏感的组织(如肝脏、胰腺、肌肉)中表达，在其他组织中表达水平较低；而 AKT3 仅在大脑和睾丸中表达[32]。它们具有 85%的同源性氨基酸序列以及相似的三维结构，由三个功能域组成：-NH2 端的 PH 结构域可调节

蛋白－蛋白和蛋白－脂质相互作用；中心激酶催化结构域与负责酶活性的蛋白激酶 A(PKA)和蛋白激酶 C(PKC)区域具有高度的同源性，磷酸化该结构域的 Tr308 是激活 AKT 的必要条件之一；-COOH 端的调控区域包含 Ser473，磷酸化该位点也是激活 AKT 的必要条件之一[33] [34]。

雷帕霉素靶蛋白(mTOR)也是一种丝氨酸/苏氨酸蛋白激酶，包括 mTOR 复合物 1 (mTORC1)和 mTOR 复合物 2 (mTORC2)。前者对雷帕霉素敏感，由 mTOR、Raptor 和 mLST8 组成，主要调节细胞生长和能量代谢；后者对雷帕霉素不敏感，由 mTOR、Rictor、Sin1 和 mLST1 组成，主要参与细胞骨架的重建和细胞存活[35]。AKT 可以直接磷酸化 mTORC1 的 Ser2448 位点直接激活 mTORC1；也可以通过磷酸化结节性硬化症蛋白 2 (TSC2)，导致 TSC2 对 Rheb (一种 ras 相关的 GTPase)活性的抑制作用减弱，从而促进非活性的 Rheb-GDP 变成具有活性的 Rheb-GTP 间接激活 mTORC1。mTORC2 可以直接通过磷酸化 Ser473 来促进 AKT 的激活，这为与 AKT 一起募集至细胞膜的磷酸肌醇依赖蛋白激酶 1 (PDK1)磷酸化 Thr308 位点最终使 AKT 完全活化奠定了基础[36] (见图 3)。mTORC1 和 mTORC2 目前已被确定为 SREBP1 主要的上游效应因子[37] [38]。

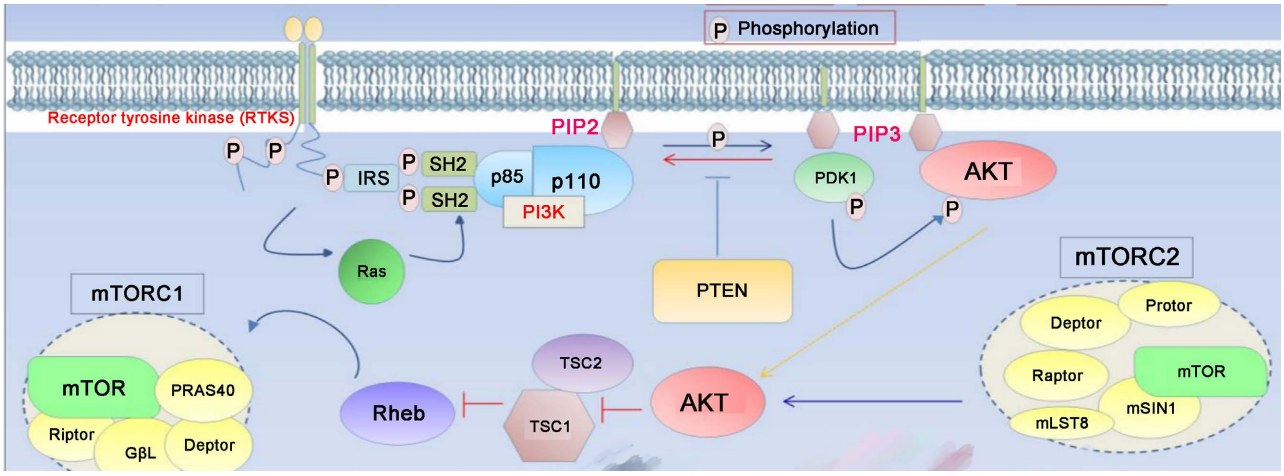

Figure 3. AKT/mTOR signaling pathway [79]
图 3. AKT/mTOR 信号通路[79]

有研究表明，鞣花酸(EA)可抑制 AKT (Thr308)磷酸化，减弱 AKT/mTORC1 通路下游的效应因子 SREBP-1 的表达，导致 FAS 的转录和翻译过程受限，从而减轻了肝脂肪变性模型中脂质的积累[39]。熊去氧胆酸(UDCA)通过其在肝脏中具有细胞保护作用和抗凋亡活性，被广泛应用于治疗胆汁淤积性肝病(如胆结石和原发性胆汁性肝硬化)的非手术治疗[40] [41]。另一项研究发现 UDCA 也可以通过调节 AKT/mTOR 信号转导来减轻肝脂肪变性。在由 OA 诱导的肝脂肪变性 LO2 细胞模型中，脂质积累非常明显；然而予以不同浓度(特别是 2 mmol/L)的 UDCA 可显著地抑制脂质积累、改善 ALT、AST、GGT 等生化指标，与此同时 AKT、mTOR 的激活以及 SREBP-1 的表达明显地受到了抑制[42]。由此可见，AKT/mTOR 通路可作为一个治疗 NAFLD 及其相关并发症的潜在靶点。

3.3. FXR

法尼酯 X 受体(FXR)是核受体超家族的一个成员。在哺乳动物中有两种成员：FXRα 和 FXRβ [43]。FXRα 基因编码四种蛋白亚型：FXRα1-α4，在肝脏和回肠中广泛表达，其亚型的相对表达可能具有物种特异性，在小鼠中，四种亚型在肝脏中均有大量表达[44]，而在人的肝脏中，α1、α2 的表达比 α3、α4 更占优势[45]。FXRb 在人类和灵长类动物中是一种假基因，没有明确的生理意义[46]。FXR 具有典型的核

受体结构：A)不依赖配体、可与共调节蛋白相互作用的转录激活域(AF1)；B)高度保守的能够识别特定DNA 序列的核心 DNA 结合域(DBD)；C)作为连接器的铰链区；D)可与配体结合、与共调节蛋白相互作用的-COOH 端配体结合域(LBD)；E)依赖配体、能促进不同调控蛋白的相互作用的激活功能域(AF2) [47] [48] [49] [50] (见图 4)。FXR 通过与配体结合激动，刺激多种基因的转录，调节脂质、葡萄糖和胆汁酸的动态平衡，参与炎症反应[51] [52]。SREBP-1 就是其下游目标基因之一，激活 FXR 可以下调 SREBP-1 及其下游靶基因的表达，降低甘油三酯水平，以达到改善 NAFLD 的目的[53]。

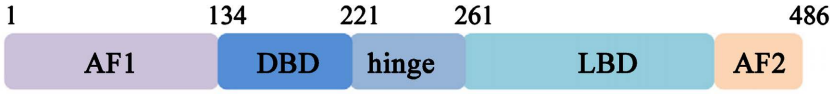

Figure 4. FXR structure [80]
图 4. FXR 结构[80]

棘皮酸(由刺五加中分离出的一种吡二烯二萜)，具有抗炎和肝保护作用，它可以促进 FXR 表达增加，进而抑制 SREBP-1 表达，减轻肝脏脂质积累及脂肪酸合成。而当使用 FXR 的拮抗剂——胃甾酮后，SREBP-1 表达增加，肝脏脂质过度堆积[54]。沙夫托苷是黄芪的一种生物活性化合物，传统上用于治疗肝炎和胆石症。进来，有研究小组用沙夫托苷干预体内、体外的 NAFLD 模型以及敲除 FXR 小鼠的原代肝细胞，结果显示：使用沙夫托苷干预后，NAFLD 模型中肝细胞的 FXR 表达下降受到抑制，SREBP-1 表达降低，小鼠血清和肝组织中的胆固醇和甘油三酯明显减少。表明沙夫托苷可通过控制 FXR-SREBP-1 信号通路减少脂质积累来改善 NAFLD [55]。因此，调控 FXR-SREBP-1 信号通路可以减轻肝脏脂肪变性，FXR 激动剂在 NAFLD 的临床应用中具有重要的治疗作用。

3.4. Micro-RNA

microRNAs (miRNAs)是动物中自然发生的、最丰富的一类小的非编码 RNA，由 19~25 个核苷酸组成。在基因组中无处不在，是与环境相关的影响基因表达的重要调控因子[56]。miRNAs 主要与其靶 mRNA 分子的 3'非翻译区(3' UTR)相互作用，调节蛋白质合成，影响多种信号通路：细胞内的大多 miRNAs 可以通过直接与靶 mRNA 的 3' UTR 结合来发挥其功能[57]；部分 miRNAs 可以转移到核中调控靶基因的表达[58]；一些 miRNAs 还可以被打包进囊泡分泌到细胞外循环中，细胞外囊泡通过受体依赖性或非受体依赖性的方式被其他细胞胞吞，释放 miRNAs，调节靶基因基因表达[59]。除了参与细胞程序性死亡及癌症的调节[60]，miRNAs 还被证实参与了几乎所有代谢稳态过程，包括脂肪发生，脂肪生成和葡萄糖刺激的胰岛素分泌[61] [62] [63] [64] [65]，进而影响了 NAFLD 发病机制的代谢途径[66]，例如：miR-21 可通过 PPARα 通路控制脂质的 β-氧化[67]，miR-206 可通过 LXRα 通路调控脂肪的从头生成[68]，miR-758 可通过作用于 ABCA1 通路影响胆固醇稳态等[69]。

miR-122 已被证明可以通过靶向 SREBP-1 来调节脂肪酸代谢：该项研究比较了 NASH 患者与正常人的 474 种 miRNAs 的表达，通过 microRNA 微阵列分析并用 RT-PCR 验证，发现 miR-122 的表达存在差异性，在 NASH 受试者中，miR-122 水平显着降低；然后在体外沉默和过度表达 miR-122 发现 SREBP-1 的 mRNA 水平及蛋白质水平分别相应的增加和降低[70]。miR-33 除了被认为是治疗动脉粥样硬化的潜在治疗靶点外[71]，也被发现对肥胖和肝脂肪变性具有调节作用。有研究小组通过利用敲除 miR-33 的小鼠发现缺乏 miR-33 导致高脂饮食诱导的肥胖和肝脏脂肪变性的显着加重与 SREBP-1 的表达上调有关，证明了 SREBP-1 是 miR-33 的靶点[72]。可见，miRNAs 在脂质代谢中发挥着重要作用，对 NAFLD 的治疗具有重要的潜力和应用价值。

3.5. 其他

除了上述因子，还有其他通过影响 SREBP1 转录活性的调控因子可作为 NAFLD 的治疗靶点。

肝脏 X 受体(LXR)也属于核受体超家族，参与肝脏脂质生成，LXR-SREBP1 通路异常激活是导致 NAFLD 原因之一[73]。有研究发现长非编码 RNA(lncRNA)Blnc1 是诱导 SREBP1 应答 LXR 激活的必要条件，它在肥胖和 NAFLD 小鼠的肝脏中表达明显升高，在肝脏中被特异性灭活可消除高脂肪饮食诱导的肝脂肪变性和胰岛素抵抗[74]。

以前的研究表明肾素-血管紧张素系统(RAS)在 NAFLD 中起着复杂的作用。有研究发现血管紧张素原(AGT)特异性过表达可以抑制 SREBP1 及其下游分子 ACC，FASN 的表达，减轻肝脏脂肪变性；当抑制 AGT 表达时，得到的结果与上述情况相反，证明了 AGT 可通过 SREBP-1 通路调控 NAFLD 的发生与发展[75]。

与有相同体重指数(BMI)的男性相比，绝经前的女性 NAFLD 发病率更低[76]。这种保护作用可能与雌激素限制肝脏脂肪积累的能力有关。激活芳基烃受体(AhR)通路导致雌激素代谢酶细胞色素 P450 1A1 (CYP1A1)的过表达，除了参与脂肪酸氧化的过氧化物酶体增殖激活受体(PPARα)的表达显著降低，SREBP-1 及其下游生脂基因的表达也明显增加，甘油三酯积累及肝损伤标志物显著升高，17β-雌二醇(E2)对肝脂肪变性的保护作用减弱[77]。

4. 小结

NAFLD 与肥胖、血脂异常及胰岛素抵抗密切相关，肝细胞中的游离脂肪酸及甘油三酯含量增加促进了 NAFLD 的发生与发展。SREBP-1 是介导脂肪生成激活的主要转录因子，阻断 SREBP-1 的激活可以下调肝细胞脂肪酸和甘油三酯合成所需关键酶的表达，从而抑制脂肪酸的从头合成。因此，抑制 SREBP-1 表达可以减轻甚至逆转肝脏脂肪变性。大量的系统研究表明，SREBP-1 对脂质代谢的分子机制受多因素的调控，而这些因素正在被深入探索和分析，这有可能为 NAFLD 的治疗策略提供新的思路。

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