DOI: 10.13376/j.cbls/2021048
文章编号：1004-0374(2021)04-0438-11

ChREBP在糖脂代谢和肿瘤中的作用及其机制的研究进展

崔中锐#，王敬泽#，向　禹#，童雪梅，吴丽芳*
(上海交通大学基础医学院生物化学与分子细胞生物学系，上海 200025)

摘　要：高发的糖尿病、肥胖症、脂肪肝等代谢性疾病和肿瘤对生活品质和生命健康带来极大威胁，寻找更加有效的药物靶标至关重要。碳水化合物反应元件结合蛋白(carbohydrate responsive element binding protein, ChREBP)是调控糖脂代谢的转录因子，显著影响肝脏糖酵解、脂质生成和胰岛素敏感性，在胰岛中促进β细胞适应性增殖，提示ChREBP对糖尿病等代谢性疾病的发展起重要作用。近年发现，ChREBP在肝癌、结直肠癌等肿瘤的发生发展中举足轻重。现就ChREBP的结构及特点、在正常组织和肿瘤中的作用及机制进行综述。ChREBP作为细胞代谢和肿瘤发生发展的纽带，为代谢性疾病和肿瘤研究提供了新的思路，其潜在靶标具有临床应用前景。

关键词：碳水化合物反应元件结合蛋白；代谢；细胞增殖；正常组织；肿瘤
中图分类号：Q519　　**文献标志码：**A

The advance in the role and mechanism of ChREBP in glycolipid metabolism and tumor

CUI Zhong-Rui#, WANG Jing-Ze#, XIANG Yu#, TONG Xue-Mei, WU Li-Fang*
(Department of Biochemistry and Molecular Cell Biology, Shanghai Jiao Tong University College of Basic Medical Sciences, Shanghai 200025, China)

Abstract: High incidence of metabolic diseases like diabetes, obesity, fatty liver and tumor poses a great threat to the quality of life and health. It is urgent to find more effective drug targets. ChREBP (carbohydrate responsive element binding protein) is a transcription factor that regulates glucose and lipid metabolism. ChREBP can significantly affect liver glycolysis, lipogenesis and insulin sensitivity, and promote the adaptive proliferation of β cells in islets, suggesting that ChREBP plays a vital role in the development of metabolic diseases like diabetes. In recent years, more and more studies have confirmed that ChREBP is of great importance in the initiation and development of tumor such as liver cancer, colorectal cancer and so on. This paper reviews the structure and characteristics of ChREBP, its function and mechanism in normal tissues and various tumors. As a link between cell metabolism and development of tumor, ChREBP provides new ideas for the study of metabolic diseases and tumors, and its potential targets have a promising clinical application.

Key words: ChREBP; metabolism; cell proliferation; normal tissues; tumor

碳水化合物反应元件结合蛋白(carbohydrate responsive element binding protein, ChREBP)由Yamashita等[1]于2001年首次发现，因其与肝脏L型丙酮酸激酶(L-type pyruvate kinase, LPK)基因启动子

收稿日期：2020-12-01；修回日期：2021-01-29
基金项目：国家自然科学基金面上项目(81972210)；上海交通大学医学院“大学生创新训练计划”2020年(第十三期)医学院级项目(1319027)；国家级项目(202010248339)
#共同第一作者
*通信作者：E-mail: wulifang@shsmu.edu.cn

区的碳水化合物反应元件(carbohydrate response element, ChoRE)特异性结合而得名。ChREBP是调节糖脂代谢的转录因子，虽然发现时间不长，但因其在肝脏糖酵解和脂肪合成调节中的关键作用而广受关注。2009年，Tong等[2]发现，ChREBP可影响细胞增殖和肿瘤进展。此后，研究人员对ChREBP在不同肿瘤发生发展中的作用及机制进行了探索。ChREBP参与多种代谢性疾病，如糖尿病、肥胖症、脂肪肝以及肿瘤的发展，其作用特点为理解细胞代谢和肿瘤之间的联系提供了新的视角。本文综述了近10年ChREBP在正常组织和肿瘤中的功能及作用机制的研究进展，期望为代谢性疾病和肿瘤的研究和治疗提供新的思路和治疗靶点。

1　ChREBP的结构及特点

ChREBP属于碱性螺旋-环-螺旋亮氨酸锌指(basic helix-loop-helix/leucine zipper, bHLH/Zip)转录因子，相对分子质量约95 kDa。它在物种间高度保守，在人、大鼠和小鼠中82%的氨基酸序列相同[1,3]。ChREBP在肝脏和脂肪组织中高表达，在小肠、胰岛、肾和脑等组织中亦有表达[4]。

已发现ChREBP有两种亚型：ChREBP-α和ChREBP-β[5]。ChREBP-α的C端含有一个bHLH/Zip结构域，介导ChREBP与*ChoRE*内的E-box结合；还有1个亮氨酸锌指样结构(leucine-zipper-like domain, Zip-like)和1个富脯氨酸区(proline-rich region)，介导蛋白质-蛋白质相互作用。ChREBP-α的N端有1个核定位信号(nuclear localization signal, NLS)和2个核输出信号(nuclear export signal, NES)，与其进出细胞核有关[1]；N端保守区含有葡萄糖感受模块(glucose sensing module, GSM)，包括一个低葡萄糖水平下抑制ChREBP转录活性的区域即低糖抑制域(low-glucose inhibitory domain, LID)和葡萄糖反应保守组件(glucose-response activation conserved element, GRACE)。GRACE介导ChREBP-α的活化，而低糖时LID抑制GRACE活化，降低ChREBP-α活性(图1)。与ChREBP-α相比，ChREBP-β缺少NES、NLS和LID区域。ChREBP-β只有GRACE，没有LID，任何葡萄糖条件下均具有活性[5](图1)。

ChREBP受葡萄糖调控，高糖条件下，磷酸戊糖途径和糖酵解促进5-磷酸木酮糖(xylulose-5-phosphate, Xu-5-P)、葡萄糖-6-磷酸(glucose-6-phosphate, G-6-P)和果糖-2,6-二磷酸(fructose-2,6-bisphosphate, F-2,6-2P)水平上升，从而降低cAMP水平并激活蛋白磷酸酶2A (protein phosphatase 2A, PP2A)，使ChREBP去磷酸化，增加DNA结合活性[6-8]。ChREBP被激活后，其NLS位点与核输入蛋白α (importin α)结合并入核[9]，在核内与Max样蛋白X (Max-like protein X, Mlx)形成异源二聚体，两个异源二聚体形成的四聚体结合到靶基因启动子上的*ChoRE*，激活转录[3,10]。饥饿条件下，肝脏内的cAMP和AMP水平增加，分别激活蛋白激酶A (protein kinase A, PKA)和AMP依赖性蛋白激酶(AMP-dependent protein kinase, AMPK)，使ChREBP磷酸化[11]；14-3-3蛋白与磷酸化的ChREBP结合，阻断importin α与NLS位点的结合，使ChREBP定位于细胞质，不能激活靶基因转录[9,12]。此外，ChREBP-α能特异诱导ChREBP-β表达[5]，ChREBP-α/Mlx复合体和HNF-4α (hepatocyte nuclear factor-4α)协同促进ChREBP-β的转录[13]。

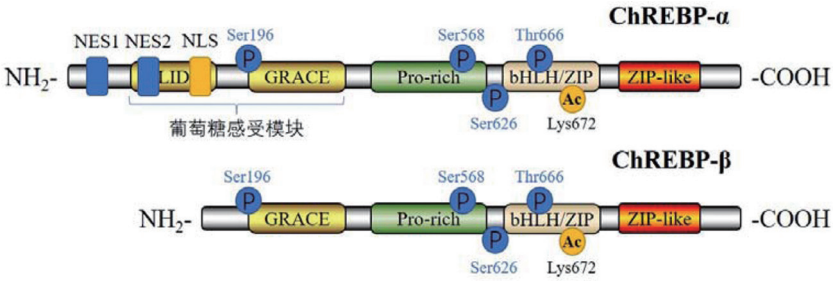
ChREBP的活性受磷酸化、乙酰化、糖基化等多种转录后修饰的调控(图2)。如前所述，磷酸化ChREBP定位于细胞质，活性受抑制。除了磷酸化修饰，ChREBP的糖基化、乙酰化等翻译后修饰亦可调节其活性。高糖激活氧连接的N-乙酰氨基葡萄糖转移酶(*O*-linked *N*-acetylglucosamine transferase, OGT)，诱导ChREBP糖基化，增强其转录活性[14-15]，此过程由HCF-1(host cell factor-1)介导[16]。ChREBP的氧连接的N-乙酰葡糖胺修饰(*O*-linked *N*-acetyl-glucosamine, *O*-GlcNAc)还能降低泛素介导的ChREBP降解[17]。这种糖基化的活化作用可被Ser140和Ser196位点的磷酸化阻断，表明磷酸化的活性抑制作用更为强烈[18]。高糖还激活组蛋白乙酰转移酶P300，使ChREBP的Lys672位点乙酰化，增强ChREBP转录活性[19]。2020年的研究发现，新的翻译后修饰，如脯氨酸羟基化，对高糖诱导下ChREBP的激活是必需的[20]。某些代谢产物也参与ChREBP的抑制或激活，如在饥饿时β-羟基丁酸、乙酰乙酸通过促进ChREBP与14-3-3蛋白相互作用，抑制ChREBP入核[21]。

2　ChREBP在正常组织中的作用及机制

2.1　ChREBP在肝脏代谢中的作用及机制

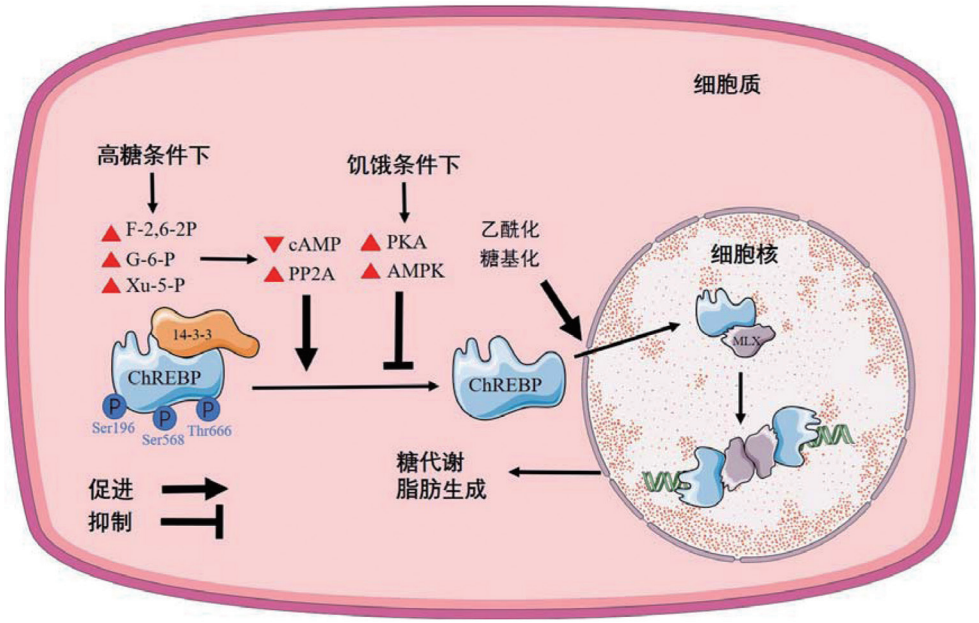
肝脏是糖代谢和脂肪代谢的主要场所。ChREBP是调节脂肪从头合成(*de novo* lipogenesis, DNL)的关键转录因子，在肝脏脂肪生成、维持全身葡萄糖稳态和胰岛素抵抗的发展过程中具有重要作用。肝脏ChREBP敲除使小鼠肝糖原含量升高、脂肪含量减

少，肝脏中的脂肪生成酶mRNA水平降低[4,22]，并改善了瘦素缺失(ob/ob)小鼠的肝脂肪变性[23]。ChREBP还可能通过诱导肝微粒体甘油三酯转运蛋白(microsomal triglyceride transfer protein, MTTP)表达促进极低密度脂蛋白分泌，形成高脂血症[24]。以上提示ChREBP在脂肪肝和血脂异常的发病中起重要作用(图3)。ChREBP在胰岛素抵抗中的作用仍有争议，多数研究表明，ChREBP对胰岛素敏感性具有不利影响。高果糖饮食(high fructose diet, HFrD)小鼠的肝内ChREBP激活可促进胰岛素抵抗，以及肝脏敲除ChREBP的瘦素缺失小鼠的胰岛素敏感性和葡萄糖耐量得到改善均支持这一观点[23,25]。然而，也有研究组得到不同的结果。Jois等[26]报道ChREBP对于维持肝脏胰岛素敏感性和全身葡萄糖稳态是必需的；Benhamed等[27]发现，ChREBP在高脂饮食小鼠肝脏中表达增加并减轻肝脏胰岛素抵抗，这与有益脂质如单不饱和脂肪酸(monoun-saturated fatty acids, MUFAs)的积累有关，且ChREBP的靶基因硬脂酰辅酶A去饱和酶1 (stearyl-CoA desaturase-1, SCD-1)参与其中的脂质改变并起有益作用(图3)。因此，ChREBP对胰岛素敏感性的矛盾可能是由于饮食影响，即在高脂饮食中ChREBP改变脂质组成



ChREBP-α的N端有LID域和GRACE域，介导葡萄糖对ChREBP活性的调控；NES和NLS与ChREBP的核出入有关；C端包含富脯氨酸区、bHLH/ZIP域和亮氨酸锌指样结构，同ChREBP与蛋白质和DNA的结合有关。与ChREBP-α相比，ChREBP-β缺失N端的LID域，因而在任何葡萄糖条件下都有较高活性。Ser568、Ser196、Ser626和Thr666为常见的磷酸化位点，Lys672为乙酰化位点。

图1 ChREBP的结构示意图



饥饿时，PKA使ChREBP的Ser196和Thr666位点磷酸化，使ChREBP与14-3-3蛋白结合并留在胞质中；AMPK使ChREBP的Ser568位点磷酸化，抑制ChREBP与其靶基因启动子的结合。高糖时，Xu-5-P、G-6-P和F-2,6-2P的水平上升，降低cAMP水平并激活蛋白磷酸酶2A，ChREBP去磷酸化，进入细胞核与Mlx结合为异二聚体调节靶基因转录。ChREBP的糖基化、乙酰化等翻译后修饰可增强其转录活性。

图2 ChREBP的活化

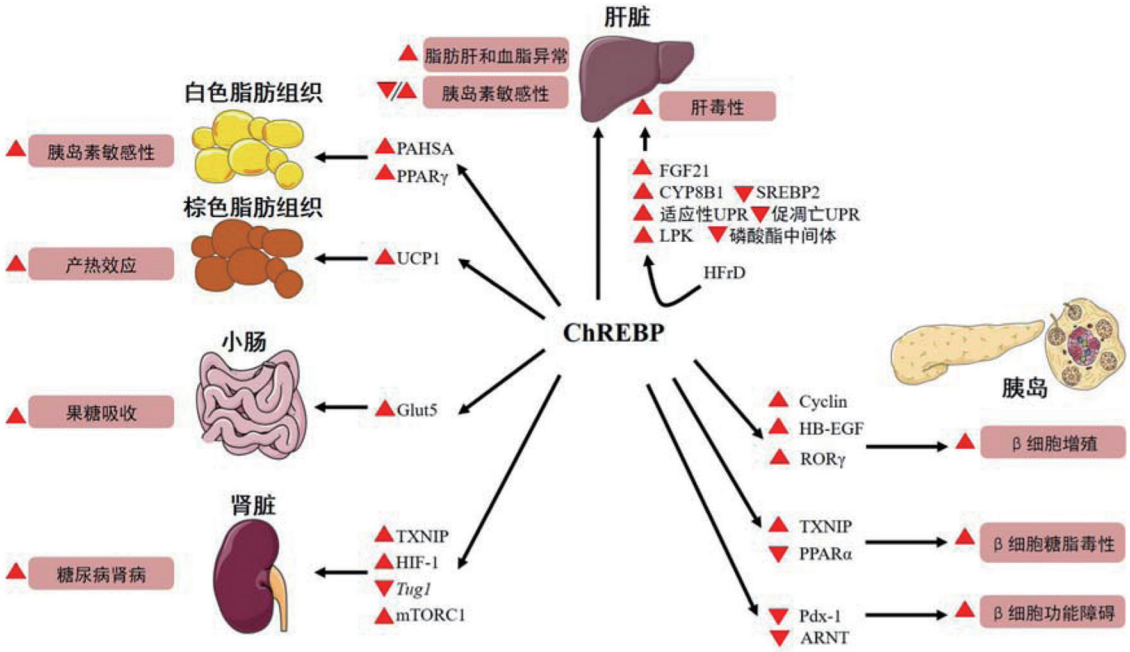


图3 ChREBP在正常组织中的作用及机制

的作用突出，表现出的有益作用更明显。

肥胖和相关综合征发生的重要原因之一是果糖的大量摄入，肝脏是果糖代谢的关键部位。HFrD野生型小鼠肝ChREBP表达增加，仅发生单纯性肝脂肪变性。而ChREBP全身敲除小鼠不耐受HFrD，脂肪酸合酶(fatty acid synthase, FASN)等脂肪合成酶表达降低，糖原含量增高，并出现肝损伤特征，如肝细胞肿胀、细胞核丢失等[28]。ChREBP对肝脏的保护机制可能是，HFrD诱导ChREBP表达，促进肝细胞内和血浆中成纤维细胞生长因子(fibroblast growth factor 21, FGF21)的升高，减少肝脏炎症发生[29](图3)；ChREBP还可以通过降低固醇调节组件结合蛋白-2 (sterol regulatory element binding protein-2, SREBP2)的表达以抑制胆固醇过度合成，或诱导胆固醇-12α-羟化酶(sterol-12α-hydroxylase, CYP8B1)表达以促进胆固醇排泄，减轻HFrD诱导的胆固醇过度合成造成的肝损伤[28,30](图3)；也可能是因为非折叠蛋白反应(unfolded protein reaction, UPR)通路被重新编程，抑制适应性UPR并激活促凋亡UPR[28](图3)；此外，过量的果糖摄入会导致ATP不受控制的消耗和中间代谢物的累积，高糖时ChREBP可能通过激活靶基因LPK，或抑制磷酸酯中间体的升高维持ATP稳态，减轻ATP失衡所致的肝损伤[31-32](图3)。这些结果证实了肝ChREBP在HFrD处理时激活肝内脂质生成、维持糖原稳态和对抗肝毒性的重要作用。然而，Kim等[33]通过小鼠器官特异性ChREBP敲除实验证明，在对抗HFrD诱导的肝毒性中，是肠内而非肝脏ChREBP起主导作用。这可能是由于小肠ChREBP敲除后，其吸收的大量果糖在小肠中代谢减少而加重了肝脏负荷。

总之，肝脏ChREBP是调节代谢稳态的关键因子，一方面参与了肝脂肪变性、胰岛素抵抗的进展，另一方面具有对抗HFrD诱导的肝毒性的重要作用，是果糖耐受所必需的转录因子。然而，肝脏脂肪变性与胰岛素抵抗发生缺乏相关性[27]，表明了胰岛素抵抗和肝脏脂质累积之间关系的复杂性。

2.2 ChREBP在脂肪组织中的作用及机制

人体脂肪组织主要包括白色脂肪组织(white adipose tissue, WAT)与棕色脂肪组织(brown adipose tissue, BAT)。ChREBP在两种脂肪组织中的作用不同。

在WAT中，ChREBP的表达与胰岛素敏感性之间的关系密切。在糖耐量下降或2型糖尿病(type 2 diabetes mellitus, T2DM)青少年的脂肪组织中ChREBP表达降低，提示ChREBP的表达与胰岛素敏感性呈正相关[34]。其机制可能是，脂肪组织ChREBP可提高脂肪从头合成效率，同时提高过氧化物酶体增殖物激活受体γ (peroxisome proliferator-activated receptor γ, PPARγ)的活性[35]；ChREBP还通过调节棕榈酸羟基硬脂酸(palmitic acid hydroxyl stearic acids, PAHSAs)通路，进而刺激葡萄糖摄取、减轻炎症反应和诱导胰岛素分泌等，以增强胰岛素敏感性[36](图3)。Herman等[5]进一步指出，高脂肪饮

食的小鼠脂肪组织中ChREBP-β表达下降并导致胰岛素抵抗，而ChREBP-α表达保持不变，是ChREBP-β而非ChREBP-α的表达与胰岛素敏感性相关。因此，脂肪组织ChREBP，尤其是ChREBP-β可能作为预测胰岛素抵抗和糖尿病进展的标志物。

在BAT中，ChREBP并非是调节全身胰岛素敏感性的关键因子，但仍具有独特的作用。Katz等[37]发现，ChREBP介导甲状腺激素和葡萄糖对解偶联蛋白1 (uncoupling protein 1, UCP1)的协同上调，增加线粒体活性，增加产热和减轻体重(图3)。该过程可能为ChREBP-α介导，因为BAT中只发现了ChREBP-α，而ChREBP-β的表达可能非常少以至检测不到[37]。然而，2020年的研究显示，BAT中ChREBP-β的过表达下调了与线粒体生成、自噬和呼吸有关的基因表达并抑制Dio2、UCP1等产热基因表达，减少BAT的产热[38]；低温环境下BAT中检测到ChREBP-β而不是ChREBP-α的表达量显著增加，产热减少[39]，提示ChREBP-β可能是一种产热抑制因子。上述结果表明，BAT中ChREBP不同亚型对下游调节的显著差异，且如果通过激活BAT产热来达到减轻体重和降低血糖的目的，ChREBP-α似乎是更适合的靶点。此外，在热中性条件下，ChREBP通过改变内源性脂肪酸的合成介导BAT的退化，产热减少，这与代谢不良有关[40]。总之，在不同条件下，ChREBP可能引起完全相反的效应，其两种亚型所起的作用还有待进一步研究。

2.3 ChREBP在小肠代谢中的作用及机制

ChREBP在小肠代谢中的作用表现在葡萄糖和果糖代谢方面。在小肠中，果糖借助果糖转运蛋白Glut5被吸收，其中超过90%在小肠中被代谢，少部分经门静脉进入肝脏代谢[41]。

如前所述，ChREBP全身敲除小鼠对HFrD不耐受，出现明显的体重减轻和肝毒性[4]，而ChREBP肝脏特异性敲除小鼠对HFrD较为耐受，说明前者果糖不耐受主要归因于肝外组织ChREBP的缺失[33]。进一步研究表明，小肠ChREBP对小鼠果糖耐受是必需的。全身或肠特异性敲除ChREBP (IChKO)小鼠在HFrD处理后，肠内Glut5、果糖水解酶、糖酵解酶和糖异生酶的表达显著减少，导致果糖吸收不良及代谢障碍，产生结肠液体积聚和扩张等果糖不耐受表现[33](图3)。总之，小肠ChREBP在全身果糖耐受中起了重要作用，但IChKO小鼠并未表现出ChREBP全身敲除小鼠那样的肝毒性，表明这种肝毒性可能还与其他组织中的ChREBP有关。

2.4 ChREBP在胰岛代谢中的作用及机制

关于β细胞增殖，尤其是葡萄糖促进β细胞增殖的具体机制的探索是糖尿病研究的中心焦点。大鼠实验表明，葡萄糖通过ChREBP促进β细胞增殖与分化[42-44]。在葡萄糖刺激下，ChREBP上调部分细胞周期调节因子，如cyclin D2、cyclin A2、cyclin E1等表达，促进β细胞增殖[44](图3)。由于ChREBP被激活后进入细胞核与DNA结合，因此，ChREBP可能直接激活细胞周期蛋白基因，这可能是联系葡萄糖代谢与细胞周期的重要机制。ChREBP也可通过激活多种靶基因，如肝素结合性EGF样生长因子(heparin-binding egf-like growth factor, HB-EGF)和RAR相关孤儿受体γ (RAR-related orphan receptor γ, RORγ)，促进β细胞增殖[43,45](图3)。除了直接调节周期因子和下游靶基因之外，ChREBP作为糖脂代谢的转录因子，很有可能也通过代谢途径促进β细胞增殖。实际上，小鼠高脂饮食亦诱导β细胞增殖，提示这种增殖效应可能是β细胞受营养物质影响作出的适应性改变[46]。ChREBP是否参与其中有待进一步研究。

然而，过量的葡萄糖会诱发β细胞脂质累积和功能受损，甚至细胞凋亡等糖脂毒性表现；而小鼠胰岛β细胞ChREBP过表达亦会引起糖脂毒性[47]，表明ChREBP与高糖引起的β细胞糖脂毒性存在相关性。一方面，ChREBP的靶基因硫氧还蛋白相互作用蛋白(thioredoxin-interacting protein, TXNIP)参与这一过程[48]。例如，哺乳动物雷帕霉素靶点蛋白(mammalian target of rapamycin, mTOR)可抑制ChREBP与Mlx结合及ChREBP-Mlx入核，使TXNIP蛋白表达减少进而减轻β细胞糖脂毒性[49](图3)；另一方面，高糖时β细胞ChREBP抑制PPARα表达，可能阻碍PPARα对β细胞的保护作用[50](图3)。ChREBP还对β细胞的多种葡萄糖反应性基因，如胰腺十二指肠同源盒1 (pancreatic and duodenal homeobox-1, Pdx-1)以及芳基烃受体核转运蛋白(aryl hydrocarbon receptor nuclear translocator, ARNT)有抑制作用，从而加重β细胞功能障碍[51-52](图3)。上述研究提示在糖尿病患者中，持续性高糖加剧的ChREBP激活可能会加重β细胞功能障碍和诱发糖脂毒性。因此，抑制ChREBP的表达或活性是治疗T2DM的潜在途径。

一般认为，ChREBP-α可以增强ChREBP-β的转录。低糖时ChREBP-α主要位于β细胞的胞质内，高糖时ChREBP-α进入细胞核，并结合到ChREBP外显子1b转录起始位点上游的*ChoRE*，驱动ChREBP-β表

达，促进β细胞增殖[53]。反过来，ChREBP-β抑制ChREBP-α入核。糖尿病患者胰岛ChREBP-β的表达水平升高，负反馈抑制ChREBP-α及其介导的由葡萄糖诱导的重要代谢基因的转录[54]。这为了解胰岛ChREBP-β的生理作用以及葡萄糖诱导的基因表达调控提供了新的视角。Sae-Lee等[55]进一步证明，β细胞ChREBP-β可以借助其上游的*ChoRE*调控自身的表达。这构建了ChREBP两种亚型之间的反馈调节机制，可以解释为什么饮食调节对ChREBP-β的影响更显著[5]。

2.5　ChREBP在肾脏代谢中的作用及机制

糖尿病肾病(diabetic nephropathy, DN)是糖尿病最具破坏性的慢性炎症性并发症，许多炎性细胞因子参与了DN的发病过程。研究发现，T2DM患者体内ChREBP水平升高，且与多种炎性细胞因子，包括TNFα、IL-1β和IL-6等的血清水平呈正相关，而在DN患者中升高更明显[56]，ChREBP可能参与DN的发病机制[57]。Zhang等[58]证实ChREBP缺陷对链脲霉素(streptozotocin, STZ)诱导的小鼠DN的发展具有保护作用，也印证了ChREBP与DN发病机制之间的联系。ChREBP可通过上调TXNIP水平、提高mTOR复合物1 (mTOR complex 1, mTORC1)活性、抑制足细胞*Tug1* (taurine upregulated gene 1)转录活性以及诱导低氧诱导因子(hypoxia-inducible factor-1, HIF-1)及其靶基因的表达促进DN发展[59-62](图3)。此外，慢性肾衰竭大鼠残余肾脏的中性脂质的大量累积促使肾小球硬化和肾小管间质损伤，伴随着ChREBP及其靶基因FASN和乙酰辅酶A羧化酶(acetyl-CoA carboxylase, ACC)的表达显著增加[63]；在葡萄糖-6-磷酸酶催化亚基(glucose-6 phosphatase catalytic subunit, G6pc)缺乏导致的小鼠早期肾病中也观察到ChREBP介导的脂质沉积，导致肾小球滤过屏障受损[64]。由此推测，ChREBP介导的脂质积累参与肾损伤的发生发展。

3　ChREBP在不同肿瘤组织中的作用及机制

大量证据显示，ChREBP与肿瘤有密切关系。在人肝细胞癌(hepatocellular carcinoma, HCC)、乳腺浸润性导管癌和结直肠癌(colorectal cancer, CRC)组织中，ChRBEP的表达水平明显高于正常组织，表明ChREBP参与多种肿瘤的发展和转移进程，且作为促癌因子与肿瘤的恶性程度呈正相关[65-67]。

ChREBP是某些原癌基因发挥作用所必需的。在HCC中，敲除ChREBP后*AKT/c-Met*基因诱导的小鼠肝细胞癌的发生率和恶性程度降低，此过程可能由ChREBP的靶基因FASN介导[68]；ChREBP还通过诱导MID1IP1 (midline1 interacting protein 1)表达，激活*c-Myc*并抑制*p21*发挥致癌作用[69](图4)。在CRC中，Smad-泛素化调节因子2 (Smad-ubiquitination regulatory factor 2, SMURF2)通过蛋白酶体途径促进ChREBP泛素化和降解，以及FLII (flightless I homolog)作为ChREBP的转录共抑制因子抑制ChREBP的活性均能抑制结直肠癌细胞的增殖[70-71]；ChREBP敲除则可诱导氧化应激，激活*p53*并诱导下游*p21*基因转录，二者构成细胞周期G_1检查点发挥抑癌作用[2]；此外，ChREBP通过促进靶基因SCD-1表达，一方面诱导上皮-间质转化(epithelial-to-mesenchymal transition, EMT)，另一方面改变脂肪酸组成以抑制抑癌基因*PTEN*的活性，促进肿瘤的进展[72](图4)。这提示ChREBP可通过介导脂质代谢异常直接或间接参与癌基因的激活过程，参与肿瘤发展。而在HCC和CRC中均发现晚期糖基化终末产物(advanced glycation end products, AGEs)诱导的活性氧(reactive oxygen species, ROS)使ChREBP表达升高，促进肿瘤细胞增殖[73-74](图4)，进一步揭示了高血糖与肿瘤之间的潜在联系。在雄激素抵抗的前列腺癌(castration-resistant prostate cancer, CRPC)中，雄激素剪切变异体AR-V7上调，其不需要与雄激素结合就能发挥雄激素受体的调控功能，包括促进细胞增殖，这可能是CRPC的产生机制之一[75]。Kaushik等[76]发现，在过表达AR-V7的细胞中己糖胺合成通路(hexosamine biosynthetic pathway, HBP)被抑制，进而通过SP1 (specific protein 1)促进ChREBP表达，调控细胞周期，增强CRPC样细胞的致瘤性(图4)。然而，许多肿瘤细胞中HBP途径却异常活跃，HBP末端产物UDP-GlcNAc能作为OGT的底物增加细胞中*O*-GlcNAc修饰的水平[77-78]，这种代谢转变可能有助于调节肿瘤信号通路和细胞增殖，ChREBP是否在其中起到其他作用尚未可知。

然而，ChREBP在不同肿瘤组织中作用不同。有些情况下，ChREBP发挥抑癌作用。在非小细胞肺癌(non-small cell lung cancer, NSCLC)中，转化生长因子β1 (transforming growth factor β 1, TGFβ1)通过抑制ChREBP，降低FASN表达，反而增强EMT，促进肿瘤转移，这可能是因为FASN的降低有利于代谢向氧化磷酸化转变，为肿瘤转移提供足够能量[79](图4)。在急性髓性白血病(acute myelogenous leukemia, AML)中，ChREBP通过促进TXNIP表达，

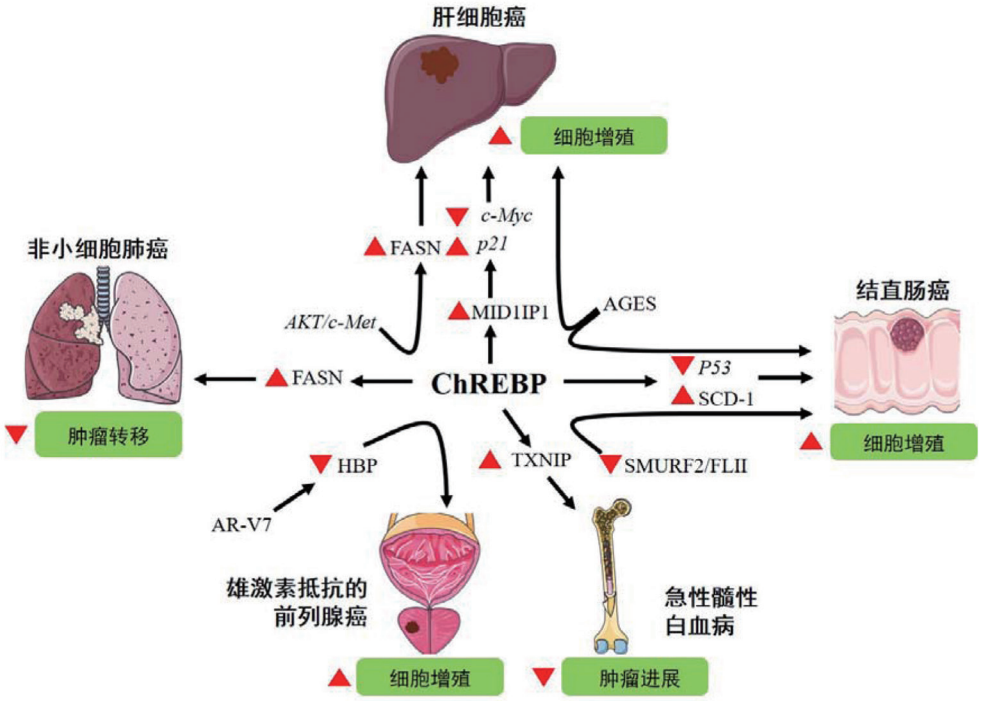


图4 ChREBP在肿瘤组织中的作用及机制

降低急性髓细胞白血病1蛋白(runt-related transcription factor 1, RUNX1)和ROS水平，促进白血病细胞分化[80]，抑制肿瘤发展(图4)。其中，TXNIP除了在白血病中的作用，还具有抑制乳腺癌高增殖活性和雌激素依赖性细胞生长的作用[81]。目前ChREBP仅被发现在少数肿瘤中发挥抑癌作用，与其激活的特殊下游靶点有关，其是否同时发挥促癌作用及二者间的平衡尚有待探索。

4 问题与展望

动物或细胞实验均证实，ChREBP在维持全身葡萄糖稳态和能量代谢中起着关键作用，其过度表达或激活与胰岛素抵抗有关。然而在肝脏和脂肪组织中，ChREBP对胰岛素抵抗发展的影响仍未得出统一结论，多数研究认为ChREBP下调肝胰岛素敏感性，而上调脂肪组织胰岛素敏感性。在生理条件下，ChREBP在葡萄糖刺激下转录并激活，众多研究指出这一过程与肝脂肪变性、胰岛素抵抗、氧化应激等病理过程紧密联系，这有助于解释非酒精性脂肪肝病、糖尿病、糖尿病肾病等疾病的变化及发生发展，ChREBP有可能成为新的检测指标，有望成为防治T2DM及其并发症的新靶点。

ChREBP的不同通路对同一代谢效应可能有差异，甚至有相反的影响，如在小鼠β细胞中ChREBP靶基因FGF21诱导胰岛素基因的表达并保护β细胞免受应激诱导的凋亡，从而改善胰岛素敏感性[82]，而这与其他靶基因，如TXNIP的作用相反。一方面可能有其他因素影响ChREBP对这些不同靶基因最终的诱导效应，如辅因子肝X受体α (liver X receptor α, LXRα)[83]；另一方面可能与ChREBP两种亚型的独特关系有关。在肝脏、β细胞和BAT中，两种ChREBP亚型的作用差异已经得到部分阐述。此外，高果糖显著诱导小鼠肝脏ChREBP-β表达而不是ChREBP-α的表达，同时ChREBP下游靶基因表达增加，说明ChREBP-β的表达能更好地反映总ChRBEP的转录活性[25]。脂肪组织激素敏感性脂肪酶(hormone-sensitive lipase, HSL)的敲除增强了胰岛素敏感性，这与ChREBP-β而不是ChREBP-α对靶基因超长链脂肪酸延伸酶6 (elongase of very long chain fatty acids 6, ELOVL6)的诱导显著相关，也说明了ChREBP-β对葡萄糖代谢和胰岛素信号的突出影响[84]。因此，可以进一步探索其他组织中是否也存在类似的关系。

目前ChREBP在糖脂代谢方面的作用了解较多，ChREBP还与氨基酸代谢、物质运输、胚胎发育和细胞运动相关的其他功能基因存在联系[85-86]。例如ChREBP能通过降低成骨基因*Runx2*的表达和碱性磷酸酶(alkaline phosphatase, ALP)活性，抑制骨形态发生蛋白-2 (bone morphogenetic protein-2, BMP2)诱导的成骨细胞分化[87]，但ChREBP是否是通过影响

糖脂代谢来改变这些功能基因仍需进一步阐明。ChREBP在肌肉中有少许表达，其可能介导葡萄糖对肌肉代谢活动的影响，但是否具有特异的作用仍需研究[88]。

很多代谢紊乱相关疾病，如糖尿病和肥胖会增加患各种癌症的风险[89]；同时，许多肿瘤表现出活跃的有氧糖酵解、脂肪酸从头合成和核苷酸生物合成，以维持肿瘤细胞生长和增殖，这三条代谢途径在很大程度上受到ChREBP的正性调节。因此，ChREBP很可能在细胞代谢紊乱与肿瘤之间起着中介的作用。在肝癌和结直肠癌细胞中，敲除ChREBP后细胞增殖和肿瘤生长被抑制，这里ChREBP表现出原癌基因的特点。而在白血病中，ChREBP呈现出抑制肿瘤的作用，在非小细胞肺癌中ChREBP则抑制其转移。ChREBP在不同肿瘤中所起作用不同甚至相反，这些差异的原因及ChREBP在更多肿瘤中的作用值得进一步探索。ChREBP-α和ChREBP-β这两种亚型，在一些代谢的功能上表现出显著差异[5,13]，可能是上游信号和调节因子不同所致，而二者在肿瘤细胞增殖方面的各自作用未见报道。目前ChREBP在细胞增殖方面的机制研究尚不透彻，了解其在代谢和生长中关键信号通路中的确切作用，能为探索肿瘤发生发展的机制，并针对这些途径进行药物开发和靶向治疗，提供新的思路和理论依据。

[参　考　文　献]

[1] Yamashita H, Takenoshita M, Sakurai M, et al. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proc Natl Acad Sci USA, 2001, 98: 9116-21

[2] Tong X, Zhao F, Mancuso A, et al. The glucose-responsive transcription factor ChREBP contributes to glucose-dependent anabolic synthesis and cell proliferation. Proc Natl Acad Sci USA, 2009, 106: 21660-5

[3] Cairo S, Merla G, Urbinati F, et al. WBSCR14, a gene mapping to the Williams--Beuren syndrome deleted region, is a new member of the Mlx transcription factor network. Hum Mol Genet, 2001, 10: 617-27

[4] Iizuka K, Bruick RK, Liang G, et al. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc Natl Acad Sci USA, 2004, 101: 7281-6

[5] Herman MA, Peroni OD, Villoria J, et al. A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. Nature, 2012, 484: 333-8

[6] Arden C, Tudhope SJ, Petrie JL, et al. Fructose 2,6-bisphosphate is essential for glucose-regulated gene transcription of glucose-6-phosphatase and other ChREBP target genes in hepatocytes. Biochem J, 2012, 443: 111-23

[7] Kabashima T, Kawaguchi T, Wadzinski BE, et al. Xylulose 5-phosphate mediates glucose-induced lipogenesis by xylulose 5-phosphate-activated protein phosphatase in rat liver. Proc Natl Acad Sci USA, 2003, 100: 5107-12

[8] Kawaguchi T, Takenoshita M, Kabashima T, et al. Glucose and cAMP regulate the L-type pyruvate kinase gene by phosphorylation/dephosphorylation of the carbohydrate response element binding protein. Proc Natl Acad Sci USA, 2001, 98: 13710-5

[9] Jung H, Takeshima T, Nakagawa T, et al. The structure of importin α and the nuclear localization peptide of ChREBP, and small compound inhibitors of ChREBP-importin α interactions. Biochem J, 2020, 477: 3253-69

[10] Stoeckman AK, Ma L, Towle HC. Mlx is the functional heteromeric partner of the carbohydrate response element-binding protein in glucose regulation of lipogenic enzyme genes. J Biol Chem, 2004, 279: 15662-9

[11] Kawaguchi T, Osatomi K, Yamashita H, et al. Mechanism for fatty acid "sparing" effect on glucose-induced transcription: regulation of carbohydrate-responsive element-binding protein by AMP-activated protein kinase. J Biol Chem, 2002, 277: 3829-35

[12] Ge Q, Huang N, Wynn RM, et al. Structural characterization of a unique interface between carbohydrate response element-binding protein (ChREBP) and 14-3-3β protein. J Biol Chem, 2012, 287: 41914-21

[13] Meng J, Feng M, Dong W, et al. Identification of HNF-4α as a key transcription factor to promote ChREBP expression in response to glucose. Sci Rep, 2016, 6: 23944-57

[14] Guinez C, Filhoulaud G, Rayah-Benhamed F, et al. *O*-GlcNAcylation increases ChREBP protein content and transcriptional activity in the liver. Diabetes, 2011, 60: 1399-413

[15] Park J, Lee Y, Jung EH, et al. Glucosamine regulates hepatic lipid accumulation by sensing glucose levels or feeding states of normal and excess. Biochim Biophys Acta Mol Cell Biol Lipids, 2020, 1865: 158764-74

[16] Lane EA, Choi DW, Garcia-Haro L, et al. HCF-1 regulates *de novo* lipogenesis through a nutrient-sensitive complex with ChREBP. Mol Cell, 2019, 75: 357-71.e7

[17] Yang AQ, Li D, Chi L, et al. Validation, identification, and biological consequences of the site-specific *O*-GlcNAcylation dynamics of carbohydrate-responsive element-binding protein (ChREBP). Mol Cell Proteomics, 2017, 16: 1233-43

[18] Sakiyama H, Fujiwara N, Noguchi T, et al. The role of O-linked GlcNAc modification on the glucose response of ChREBP. Biochem Biophys Res Commun, 2010, 402: 784-9

[19] Bricambert J, Miranda J, Benhamed F, et al. Salt-inducible kinase 2 links transcriptional coactivator p300 phosphorylation to the prevention of ChREBP-dependent hepatic steatosis in mice. J Clin Invest, 2010, 120: 4316-31

[20] Heidenreich S, Weber P, Stephanowitz H, et al. The

glucose-sensing transcription factor ChREBP is targeted by proline hydroxylation. J Biol Chem, 2020, 295: 17158-68

[21] Nakagawa T, Ge Q, Pawlosky R, et al. Metabolite regulation of nucleo-cytosolic trafficking of carbohydrate response element-binding protein (ChREBP): role of ketone bodies. J Biol Chem, 2013, 288: 28358-67

[22] Ishii S, Iizuka K, Miller BC, et al. Carbohydrate response element binding protein directly promotes lipogenic enzyme gene transcription. Proc Natl Acad Sci USA, 2004, 101: 15597-602

[23] Dentin R, Benhamed F, Hainault I, et al. Liver-specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in ob/ob mice. Diabetes, 2006, 55: 2159-70

[24] Niwa H, Iizuka K, Kato T, et al. ChREBP rather than SHP regulates hepatic VLDL secretion. Nutrients, 2018, 10: 321-32

[25] Kim MS, Krawczyk SA, Doridot L, et al. ChREBP regulates fructose-induced glucose production independently of insulin signaling. J Clin Invest, 2016, 126: 4372-86

[26] Jois T, Chen W, Howard V, et al. Deletion of hepatic carbohydrate response element binding protein (ChREBP) impairs glucose homeostasis and hepatic insulin sensitivity in mice. Mol Metab, 2017, 6: 1381-94

[27] Benhamed F, Denechaud PD, Lemoine M, et al. The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. J Clin Invest, 2012, 122: 2176-94

[28] Zhang D, Tong X, Van Dommelen K, et al. Lipogenic transcription factor ChREBP mediates fructose-induced metabolic adaptations to prevent hepatotoxicity. J Clin Invest, 2017, 127: 2855-67

[29] Fisher FM, Kim M, Doridot L, et al. A critical role for ChREBP-mediated FGF21 secretion in hepatic fructose metabolism. Mol Metab, 2017, 6: 14-21

[30] Hoogerland JA, Lei Y, Wolters JC, et al. Glucose-6-phosphate regulates hepatic bile acid synthesis in mice. Hepatology, 2019, 70: 2171-84

[31] Shi JH, Lu JY, Chen HY, et al. Liver ChREBP protects against fructose-induced glycogenic hepatotoxicity by regulating L-type pyruvate kinase. Diabetes, 2020, 69: 591-602

[32] Agius L. Dietary carbohydrate and control of hepatic gene expression: mechanistic links from ATP and phosphate ester homeostasis to the carbohydrate-response element-binding protein. Proc Nutr Soc, 2016, 75: 10-18

[33] Kim M, Astapova II, Flier SN, et al. Intestinal, but not hepatic, ChREBP is required for fructose tolerance. JCI Insight, 2017, 2: e96703-16

[34] Kursawe R, Caprio S, Giannini C, et al. Decreased transcription of ChREBP-α/β isoforms in abdominal subcutaneous adipose tissue of obese adolescents with prediabetes or early type 2 diabetes: associations with insulin resistance and hyperglycemia. Diabetes, 2013, 62: 837-44

[35] Zhao T, Wu K, Hogstrand C, et al. Lipophagy mediated carbohydrate-induced changes of lipid metabolism via oxidative stress, endoplasmic reticulum (ER) stress and ChREBP/PPARγ pathways. Cell Mol Life Sci, 2020, 77: 1987-2003

[36] Yore MM, Syed I, Moraes-Vieira PM, et al. Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. Cell, 2014, 159: 318-32

[37] Katz LS, Xu S, Ge K, et al. T3 and glucose coordinately stimulate ChREBP-mediated Ucp1 expression in brown adipocytes from male mice. Endocrinology, 2018, 159: 557-69

[38] Wei C, Ma X, Su K, et al. ChREBP-β regulates thermogenesis in brown adipose tissue. J Endocrinol, 2020, 245: 343-56

[39] Sanchez-Gurmaches J, Tang Y, Jespersen NZ, et al. Brown fat AKT2 is a cold-induced kinase that stimulates ChREBP-mediated *de novo* lipogenesis to optimize fuel storage and thermogenesis. Cell Metab, 2018, 27: 195-209.e6

[40] Schlein C, Fischer AW, Sass F, et al. Endogenous fatty acid synthesis drives brown adipose tissue involution. Cell Rep, 2021, 34: 108624-42

[41] Jang C, Hui S, Lu W, et al. The small intestine converts dietary fructose into glucose and organic acids. Cell Metab, 2018, 27: 351-61.e3

[42] Soggia A, Flosseau K, Ravassard P, et al. Activation of the transcription factor carbohydrate-responsive element-binding protein by glucose leads to increased pancreatic β cell differentiation in rats. Diabetologia, 2012, 55: 2713-22

[43] Maachi H, Fergusson G, Ethier M, et al. HB-EGF signaling is required for glucose-induced pancreatic β-cell proliferation in rats. Diabetes, 2020, 69: 369-80

[44] Metukuri MR, Zhang P, Basantani MK, et al. ChREBP mediates glucose-stimulated pancreatic β-cell proliferation. Diabetes, 2012, 61: 2004-15

[45] Schmidt SF, Madsen JG, Frafjord K, et al. Integrative genomics outlines a biphasic glucose response and a ChREBP-RORγ axis regulating proliferation in β cells. Cell Rep, 2016, 16: 2359-72

[46] Stamateris RE, Sharma RB, Hollern DA, et al. Adaptive β-cell proliferation increases early in high-fat feeding in mice, concurrent with metabolic changes, with induction of islet cyclin D2 expression. Am J Physiol Endocrinol Metab, 2013, 305: E149-59

[47] Poungvarin N, Lee JK, Yechoor VK, et al. Carbohydrate response element-binding protein (ChREBP) plays a pivotal role in β cell glucotoxicity. Diabetologia, 2012, 55: 1783-96

[48] Minn AH, Hafele C, Shalev A. Thioredoxin-interacting protein is stimulated by glucose through a carbohydrate response element and induces β-cell apoptosis. Endocrinology, 2005, 146: 2397-405

[49] Chau GC, Im DU, Kang TM, et al. mTOR controls ChREBP transcriptional activity and pancreatic β cell survival under diabetic stress. J Cell Biol, 2017, 216: 2091-105

[50] Boergesen M, Poulsen L, Schmidt SF, et al. ChREBP mediates glucose repression of peroxisome proliferator-

activated receptor α expression in pancreatic β-cells. J Biol Chem, 2011, 286: 13214-25
[51] Da Silva Xavier G, Sun G, Qian Q, et al. ChREBP regulates Pdx-1 and other glucose-sensitive genes in pancreatic β-cells. Biochem Biophys Res Commun, 2010, 402: 252-7
[52] Noordeen NA, Khera TK, Sun G, et al. Carbohydrate-responsive element-binding protein (ChREBP) is a negative regulator of ARNT/HIF-1β gene expression in pancreatic islet β-cells. Diabetes, 2010, 59: 153-60
[53] Zhang P, Kumar A, Katz LS, et al. Induction of the ChREBPβ isoform is essential for glucose-stimulated β-cell proliferation. Diabetes, 2015, 64: 4158-70
[54] Jing G, Chen J, Xu G, et al. Islet ChREBP-β is increased in diabetes and controls ChREBP-α and glucose-induced gene expression via a negative feedback loop. Mol Metab, 2016, 5: 1208-15
[55] Sae-Lee C, Moolsuwan K, Chan L, et al. ChREBP regulates itself and metabolic genes implicated in lipid accumulation in β-cell line. PLoS One, 2016, 11: e0147411-27
[56] 陈琰, 白倩, 蔡妍, 等. 2型糖尿病患者血清ChREBP水平与糖尿病肾病的相关性. 中国现代医学杂志, 2019, 29: 21-6
[57] Chen Y, Wang YJ, Zhao Y, et al. Carbohydrate response element binding protein (ChREBP) modulates the inflammatory response of mesangial cells in response to glucose. Biosci Rep, 2018, 38: BSR20180767
[58] Zhang W, Li X, Zhou SG. Ablation of carbohydrate-responsive element-binding protein improves kidney injury in streptozotocin-induced diabetic mice. Eur Rev Med Pharmacol Sci, 2017, 21: 42-47
[59] Long J, Galvan DL, Mise K, et al. Role for carbohydrate response element-binding protein (ChREBP) in high glucose-mediated repression of long noncoding RNA Tug1. J Biol Chem, 2020, 295: 15840-52
[60] Isoe T, Makino Y, Mizumoto K, et al. High glucose activates HIF-1-mediated signal transduction in glomerular mesangial cells through a carbohydrate response element binding protein. Kidney Int, 2010, 78: 48-59
[61] Suzuki S, Yokoyama A, Noro E, et al. Expression and pathophysiological significance of carbohydrate response element binding protein (ChREBP) in the renal tubules of diabetic kidney. Endocr J, 2020, 67: 335-45
[62] Chen N, Mu L, Yang Z, et al. Carbohydrate response element-binding protein regulates lipid metabolism via mTOR complex1 in diabetic nephropathy. J Cell Physiol, 2021, 236: 625-40
[63] Cho KH, Kim HJ, Kamanna VS, et al. Niacin improves renal lipid metabolism and slows progression in chronic kidney disease. Biochim Biophys Acta, 2010, 1800: 6-15
[64] Clar J, Gri B, Calderaro J, et al. Targeted deletion of kidney glucose-6 phosphatase leads to nephropathy. Kidney Int, 2014, 86: 747-56
[65] Ribback S, Che L, Pilo MG, et al. Oncogene-dependent addiction to carbohydrate-responsive element binding protein in hepatocellular carcinoma. Cell Cycle, 2018, 17: 1496-512
[66] Airley RE, McHugh P, Evans AR, et al. Role of carbohydrate response element-binding protein (ChREBP) in generating an aerobic metabolic phenotype and in breast cancer progression. Br J Cancer, 2014, 110: 715-23
[67] Lei Y, Zhou S, Hu Q, et al. Carbohydrate response element binding protein (ChREBP) correlates with colon cancer progression and contributes to cell proliferation. Sci Rep, 2020, 1: 4233-42
[68] Hu J, Che L, Li L, et al. Co-activation of AKT and c-Met triggers rapid hepatocellular carcinoma development via the mTORC1/FASN pathway in mice. Sci Rep, 2016, 6: 20484-95
[69] Jung JH, Lee HJ, Kim JH, et al. Colocalization of MID1IP1 and c-Myc is critically involved in liver cancer growth via regulation of ribosomal protein L5 and L11 and CNOT2. Cells, 2020, 9: 985-98
[70] Li Y, Yang D, Tian N, et al. The ubiquitination ligase SMURF2 reduces aerobic glycolysis and colorectal cancer cell proliferation by promoting ChREBP ubiquitination and degradation. J Biol Chem, 2019, 294: 14745-56
[71] Wu L, Chen H, Zhu Y, et al. Flightless I homolog negatively regulates ChREBP activity in cancer cells. Int J Biochem Cell Biol, 2013, 45: 2688-97
[72] Ran H, Zhu Y, Deng R, et al. Stearoyl-CoA desaturase-1 promotes colorectal cancer metastasis in response to glucose by suppressing PTEN. J Exp Clin Cancer Res, 2018, 37: 54-68
[73] Chen H, Li Y, Zhu Y, et al. Advanced glycation end products promote ChREBP expression and cell proliferation in liver cancer cells by increasing reactive oxygen species. Medicine (Baltimore), 2017, 96: e7456-62
[74] Chen H, Wu L, Li Y, et al. Advanced glycation end products increase carbohydrate responsive element binding protein expression and promote cancer cell proliferation. Mol Cell Endocrinol, 2014, 395: 69-78
[75] Dehm SM, Schmidt LJ, Heemers HV, et al. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. Cancer Res, 2008, 68: 5469-77
[76] Kaushik AK, Shojaie A, Panzitt K, et al. Inhibition of the hexosamine biosynthetic pathway promotes castration-resistant prostate cancer. Nat Commun, 2016, 7: 11612-23
[77] Jang TJ, Kim UJ. O-GlcNAcylation is associated with the development and progression of gastric carcinoma. Pathol Res Pract, 2016, 212: 622-30
[78] Zeng Q, Zhao RX, Chen J, et al. O-linked GlcNAcylation elevated by HPV E6 mediates viral oncogenesis. Proc Natl Acad Sci USA, 2016, 113: 9333-8
[79] Jiang L, Xiao L, Sugiura H, et al. Metabolic reprogramming during TGFβ1-induced epithelial-to-mesenchymal transition. Oncogene, 2015, 34: 3908-16
[80] Zeng H, Gu H, Chen C, et al. ChREBP promotes the differentiation of leukemia-initiating cells to inhibit leukemogenesis through the TXNIP/RUNX1 pathways. Oncotarget, 2016, 7: 38347-58
[81] Park JW, Lee SH, Woo GH, et al. Downregulation of

TXNIP leads to high proliferative activity and estrogen-dependent cell growth in breast cancer. Biochem Biophys Res Commun, 2018, 498: 566-72

[82] Wente W, Efanov AM, Brenner M, et al. Fibroblast growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. Diabetes, 2006, 55: 2470-8

[83] Fan Q, Norgaard RC, Grytten I, et al. LXRα regulates ChREBPα transactivity in a target gene-specific manner through an agonist-modulated LBD-LID interaction. Cells, 2020, 9: 1214-39

[84] Morigny P, Houssier M, Mairal A, et al. Interaction between hormone-sensitive lipase and ChREBP in fat cells controls insulin sensitivity. Nat Metab, 2019, 1: 133-46

[85] Jeong YS, Kim D, Lee YS, et al. Integrated expression profiling and genome-wide analysis of ChREBP targets reveals the dual role for ChREBP in glucose-regulated gene expression. PLoS One, 2011, 6: e22544-57

[86] Velazquez-Villegas L, Noriega LG, Lopez-Barradas AM, et al. ChREBP downregulates SNAT2 amino acid transporter expression through interactions with SMRT in response to a high-carbohydrate diet. Am J Physiol Endocrinol Metab, 2021, 320: E102-12

[87] Kim KM, Kim EJ, Jang WG. Carbohydrate responsive element binding protein (ChREBP) negatively regulates osteoblast differentiation via protein phosphatase 2A Cα dependent manner. Int J Biochem Cell Biol, 2020, 124: 105766-74

[88] Hanke N, Scheibe RJ, Manukjan G, et al. Gene regulation mediating fiber-type transformation in skeletal muscle cells is partly glucose- and ChREBP-dependent. Biochim Biophys Acta, 2011, 1813: 377-89

[89] Xu CX, Zhu HH, Zhu YM. Diabetes and cancer: associations, mechanisms, and implications for medical practice. World J Diabetes, 2014, 5: 372-80