NR4A1对糖脂代谢的调控作用

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收稿日期: 2018-08-14; 接受日期: 2018-10-09; 网络版发表日期: 2018-11-09

国家自然科学基金(批准号: 81670704, 81370881, 81170814)资助

摘要 孤核受体NR4A1又被广泛地称为Nur77, TR3或NGFI-B等, 是核受体NR4A家族中的重要成员, 它作为转录因子, 对体内多种生理过程都起到直接或间接的调控作用. 本综述根据该领域的研究进展, 以及本实验室的相关研究, 对NR4A1在糖脂代谢中的调控作用进行了简短的综述. 在胰岛 β 细胞中, 持续高糖高脂的压力会引起细胞的内质网应激和氧化应激, 而NR4A1能够抵抗由其引起的细胞凋亡, 从而缓冲或阻止糖尿病的发生和发展. 在脂肪组织中, NR4A1能够抑制脂肪细胞分化和脂质的生成, 从而影响肥胖的发生和发展.

关键词 NR4A1, 胰岛 β 细胞, 脂肪, 糖脂代谢

NR4A1(Nur77, TR3, NGFI-B)是核受体NR4A家族中的重要成员^[1,2], 该家族还有成员NR4A2和NR4A3. 目前仍未发现它的天然配体, 属于一种立早基因, 能够被多种生理信号和物理刺激所诱导表达. NR4A1分布在多种细胞中, 具有功能多样性, 对多种生理过程都发挥着重要作用^[3]. NR4A1对糖脂代谢也具有调控作用, 从而控制糖尿病、肥胖等疾病.

1 NR4A1结构特点与生物学功能

NR4A作为转录因子, 可以与特定的反应元件结合, 发挥转录激活的功能, 调节相关基因的转录表达. NR4A家族可以作为单体、同源二聚体或异源二聚体的形式与DNA结合. 单体形式的NR4A成员与NGFI-B反应元件(NBRE; AAAGGTCA)结合, NBRE序列由糖皮质激素受体反应元件的半位点(AGGTCA)加5'端另

外2个腺苷酸组成^[4,5]. 二聚体的NR4A成员与Nur反应元件进行结合, 这段序列是由多次重复的AAAT(G/A)(C/T)CA序列组成^[6,7]. 它们的结构与功能相近, 都有N端的转录活化区(activation function, AF)、DNA结合区(DNA-binding domain, DBD)、铰链区及配体结合区(ligand binding domain, LBD). 晶体X光衍射分析的结果表明, LBD区内包含招募激活剂的疏水口袋(pocket)^[8], 但是口袋太小, 无法与经典的配体结合, 因此迄今尚未发现其天然的配体, 对NR4A分子进行突变分析的结果表明NR4A是不依赖于配体的持续活化的转录因子^[9,10](图1).

NR4A1广泛表达于各种组织中, 以多种形式参与细胞功能的调控, 具有重要的生理功能, 包括细胞增殖、凋亡、分化、发育、免疫和代谢等生命活动^[11~13]. NR4A1调节细胞的增殖, 小鼠(*Mus*)去除NR4A3和Nur77(NR4A1)的表达可引发急性白血病的

引用格式: 秦丹丹, 王向东. NR4A1对糖脂代谢的调控作用. 中国科学: 生命科学, 2018, 48: 1229–1237

Qin D D, Wang X D. The regulation of NR4A1 on glucolipid metabolism (in Chinese). *Sci Sin Vitae*, 2018, 48: 1229–1237, doi: [10.1360/N052018-00153](https://doi.org/10.1360/N052018-00153)

图1 NR4A家族基因结构模式图(网络版彩图)

出现^[14]。上调NR4A1及NR4A3可调节胰岛β细胞的增殖^[15]。中国科学技术大学的一个课题组发现: NR4A1过表达可抑制BAX的表达, 而且NR4A1可抑制P53的转录活性^[16]。还有人报道: 抑制NR4A1的活性便可抑制胰腺癌细胞及胰腺肿瘤的增长^[17]。NR4A1调节细胞的凋亡, NR4A1调节胰腺癌细胞的氧化应激及内质网应激, 敲除NR4A1在胰腺癌细胞中的表达致使细胞对氧化应激和内质网应激诱导所致凋亡途径的活化^[18]。研究表明, 内质网应激诱导剂可诱导胰岛β细胞中的NR4A1的表达, 而过表达NR4A1可上调Survivin的表达, 下调CHOP的表达, 从而可抑制内质网应激所致的细胞凋亡^[19]。也有报道表明: NR4A1具有促细胞凋亡的作用。有人发现过表达NR4A1及Nor-1可引起T-cell的凋亡, 而这种凋亡不同于脂肪酸合成酶(fatty acid synthase, FAS)配体所致的细胞凋亡^[20]。有几个研究团队的工作说明, 用一些特殊试剂可致使NR4A1分子从细胞核转运到细胞质中, NR4A1在细胞质中与Bcl-2分子结合从而改变了Bcl-2的构象, 构象改变的Bcl-2变成了促进细胞凋亡的分子^[17,21~23]。NR4A可以调节多种细胞信号通路, 包括蛋白激酶A, NF-κB, Wnt等。并且与多种恶性肿瘤有关, 包括乳腺癌、肺癌、结肠癌、膀胱癌和前列腺癌、多形性胶质细胞瘤、肉瘤、急性性和/或慢性骨髓性白血病等^[11]。

NR4A1的功能因细胞类型和刺激信号的不同而表现各异, 目前研究结果表明, NR4A1不仅参与了肝脏和骨骼肌的糖脂代谢, 还对胰岛β细胞的功能, 以及脂肪细胞中脂质生成具有一定的调节作用, 调控脂质、碳水化合物、能量稳态等多种信号通路和生理过程^[24~33]。

2 NR4A1在胰岛β细胞中对糖代谢的调控作用

糖代谢是经血液运输到各组织细胞, 例如肝脏、骨骼肌和胰腺等, 来进行合成代谢和分解代谢, 从而维持血糖浓度的相对恒定。研究表明, NR4A1通过

cAMP激活, 从而诱导肝脏中的糖异生^[27]。也有研究表明, NR4A1通过与LKB1结合, 抑制AMPK的磷酸化, 从而确保糖异生过程^[34]。另外, 敲除骨骼肌细胞中的NR4A1更容易发生胰岛素抵抗, 从而影响糖代谢^[25]。Kanzleiter等人^[35]证明, 运动后的肌肉细胞通过肾上腺素和AMP-PKA通路诱导NR4A1的表达。过表达NR4A1对大鼠(*Rattus norvegicus*)肌肉细胞的脂质氧化没有影响, 但促进了葡萄糖的氧化和糖原的合成^[36]。

胰岛β细胞功能受损, 胰岛素分泌绝对或相对不足, 或者胰岛β细胞的损失, 都会导致葡萄糖稳态异常以及糖尿病^[37~40]。而造成胰岛β细胞功能受损的主要病理机制是糖脂毒性。长期的高血糖可通过多种机制损害胰岛β细胞, 包括降低胰岛β细胞对血糖的感知和反应能力、影响胰岛素的合成与分泌、通过降低相关酶活性干扰葡萄糖代谢等。脂毒性主要是指进入胰岛β细胞的游离脂肪酸加重了细胞承受的负担, 给细胞制造了压力, 使细胞处于应激的状态, 甚至凋亡。而高糖造成的细胞应激主要包括内质网应激(endoplasmic reticulum stress)和氧化应激(oxidative stress)。多数研究表明, NR4A1参与调节内质网应激和氧化应激的过程, 也有研究表明NR4A1能够调控β细胞的增殖^[15]和胰岛素分泌^[41]。

2.1 NR4A1抵抗内质网应激引起的细胞凋亡

内质网应激是指持续的高血糖会使内质网中未折叠蛋白或者错误折叠蛋白积累过多, 超过了β细胞内质网的处理能力^[42~44]。这时候需要细胞内特定的信号通路来帮助其正确折叠, 激活未折叠蛋白反应(unfolded protein response, UPR)的信号通路, 用来缓解内质网应激的状态, 但是, 当细胞不能再适应内质网应激状态的时候, UPR反应也会诱导细胞产生凋亡^[45]。

在细胞凋亡方面, NR4A1的促进和抑制作用还是有争议的。在成熟的β细胞淋巴瘤中, NR4A1的过量表达可以预防神经酰胺诱导的细胞死亡^[46]。NR4A1沉默或敲除可显著增加细胞凋亡, 并已在许多细胞系或转基因小鼠中得到证实^[47]。通过敲除或拮抗剂使NR4A1失活, 从而导致内质网应激/氧化应激和细胞凋亡的激活^[18]。Lee等人^[48]的研究表明, RNA干扰或NR4A1拮抗剂或相关化合物抑制NR4A1会诱导细胞凋亡、降低Survivin和其他调控基因的表达。Yu等人^[49]报道NR4A1高表达后能够通过上调Survivin的表达和下调

CHOP的表达来抵抗由内质网应激介导的细胞凋亡(图2)。然而,也有报道称NR4A1具有促进凋亡的作用。如前所述, NR4A1具有抗凋亡的作用跟人们发现它能导致凋亡的结论并不矛盾, 因为NR4A1是否作为促凋亡因子或抗凋亡因子取决于其细胞中的定位。NR4A1高表达后并定位于细胞核, 起转录因子的作用, 就会调控一些分子的表达来抑制细胞的凋亡; 相反, 如果某种因素使其从细胞核转位于细胞浆, 那么它就起促凋亡作用。

棕榈酸(palmitic acid, PA)会引发胰岛β细胞的内质网应激, 从而导致细胞凋亡。过表达NR4A1后, NR4A1能够通过直接结合Survivin, 使其转录激活, 另一方面还会间接下调CHOP来抑制细胞的凋亡。

2.2 NR4A1抵抗氧化应激引起的细胞凋亡

另一方面, 在胰岛β细胞线粒体消耗氧产生ATP过程中, 氧分子在呼吸链传递过程中会产生活性氧(reactive oxygen species, ROS), ROS可以直接损伤胰岛β细胞, 引起胰岛β细胞的凋亡^[50-52]。研究表明, 与其他组织相比, 胰岛β细胞内抗氧化物水平较低, 对ROS更敏感。在高糖高脂的环境下会使细胞产生过量的ROS, 胰岛β细胞抗氧化酶的表达水平不能承担过量的ROS, 从而导致氧化应激, 造成胰岛β细胞的直接损伤与凋亡, 胰岛素合成与分泌减少, 并使外周组织对胰岛素敏感性下降, 造成糖脂代谢紊乱, 最终促成糖尿病的发生

发展^[53-57]。

Mazuy等人^[58]通过siRNA敲低NR4A1的表达或阻断NR4A1的活性可以减少增殖、诱导细胞凋亡, 降低Bcl-2和Survivin等抗凋亡基因的表达, 同时抑制肿瘤生长。Lee等人^[18]还报道, 在胰腺癌细胞系Panc-1细胞中, NR4A1拮抗剂抑制NR4A1的表达后可诱导细胞凋亡以及多种氧化应激标志物的表达, 包括GRP78, CHOP, ATF4等。在胰岛β细胞中, Briand等人^[32]报道NR4A1可以间接下调胰岛素基因的表达。NR4A1在生理上与FOXO1相关, 后者抑制mafA的转录, 而mafA是胰岛素基因转录的重要因子。同时也有报道称, NR4A1基因敲除小鼠的空腹胰岛素含量显著增加^[25]。我们的研究表明, NR4A1可通过直接上调WT1, Survivin的蛋白表达来抵抗氧化应激引起的胰岛β细胞凋亡^[59]。Yang等人^[60]研究表明, NR4A1还具有通过增强GPX-1的表达来抵抗氧化应激所引起的胰岛β细胞凋亡的潜在功能(图3)。

持续的高糖环境使线粒体产生过多的活性氧(ROS), 诱发氧化应激, NR4A1能够通过多种途径抵抗由氧化应激引发的细胞凋亡, 包括p-JNK, WT1, Survivin和GPX-1的信号通路。

3 NR4A1对脂肪组织中脂代谢的调控作用

动物脂肪组织是由大量的脂肪细胞聚集而成, 脂

图2 NR4A1抵抗内质网应激引起的细胞凋亡的调控机制(网络版彩图)

图3 NR4A1抵抗氧化应激引起的细胞凋亡的调控机制(网络版彩图)

脂肪细胞胞质中储存大量脂类,多数为甘油三酯,其余为磷脂及胆固醇等。脂肪组织是一个动态的组织,脂肪细胞大多数来自于脂肪组织内前脂细胞的分化^[61,62]。脂肪细胞内脂质的存储及其利用对维持细胞能量动态平衡起着重要的作用。而体内脂肪过量的积累就会造成肥胖,严重威胁人们的身体健康,也易诱发糖尿病等代谢相关疾病。

脂肪细胞分化是一个精细调节的过程,与机体能量的动态平衡、体脂沉积和代谢健康密切相关。脂肪细胞的分化状态是脂肪(甘油三酯)的合成与分解代谢动态平衡的结果。在营养过剩及缺乏运动的情况下,体内过剩的能量就会以甘油三酯的形式储存于脂肪细胞中,导致脂肪细胞不断分化,体积不断增大,从而造成肥胖。

3.1 脂肪分解

脂肪分解主要是将脂肪水解为甘油三酯,需要3个连续的步骤,至少涉及3种不同的酶:ATGL催化脂解的初始步骤,将甘油三酯转化为甘油二酯;HSL(hormone-sensitive lipase)主要负责把甘油二酯水解为单酰基甘油(monoglyceride, MG);而MG脂肪酶(MG-lipase, MGL)作为最后水解的一步。在这个过程中也存在很多的转录因子参与调控脂肪的分解。

3.2 脂肪生成

体外脂肪细胞的分化过程大致分为4个阶段:前脂细胞增殖、接触抑制、脂质合成、形成成熟脂肪细胞。脂肪细胞分化早期包括前体脂肪细胞因子(preadipocyte factor1, Pref-1)、脂蛋白酯酶(lipoprotein lipase, LPL)和脂肪细胞分化相关蛋白等标志分子,分化中晚期主要是乙酰辅酶A羧化酶(Acetyl-CoA carboxylase, ACC)、甘油三磷酸脱氢酶、ATP-柠檬酸水解酶、脂肪酸合成酶(fatty acid synthase, FAS)等标志分子。脂肪细胞分化是在多种转录因子的调控下,经过一系列成脂相关基因的顺序表达,而实现的其脂肪积累和形态学上的改变。近年来的研究表明,过氧化物酶体增殖物激活受体家族(peroxisome proliferators-activated receptors, PPARs)、CCAAT增强子结合蛋白家族(CCAAT/enhancer-binding protein family, C/EBPs)和固醇调节元件结合蛋白家族(sterol regulatory element binding proteins, SREBPs)中的某些转录因子在脂肪细胞分化过程中都发挥着重要的调节作用^[63,64]。

3.3 NR4A1对脂代谢的调控作用

研究报道, NR4A1对肝脏^[26,27]和肌肉^[30,31]中的葡萄糖和脂质代谢有影响。体内研究表明,与野生型小鼠相比,高脂肪饮食喂养的NR4A1敲除小鼠更容易患上肥胖症^[25]。Pols等人^[26]阐明NR4A1参与调节血浆脂蛋白以及肝脂代谢, NR4A1通过抑制SREBP1来下调脂形成相关酶类(如Scd1, Fas, Gpam)的表达,从而降低肝脏中甘油三酯的含量。在脂肪组织中, NR4A家族也与葡萄糖代谢和脂肪生成相关。首先,胰岛素能够诱导3T3-L1脂肪细胞中的NR4A1和NR4A3表达,从而调节胰岛素和葡萄糖的稳态^[28]。在3T3-L1细胞中,过表达NR4A3可增加胰岛素刺激葡萄糖摄取,其机制在于增强胰岛素受体底物蛋白(insulin receptor substrate, IRS)、蛋白激酶B(AKT)等蛋白的磷酸化,并且诱导Glut4蛋白转位到细胞质膜^[28]。另外, NR4A家族在脂肪生成过程中被诱导表达^[65]。一些研究表明NR4A家族可以作为脂肪生成的调节因子^[66,67],但也有研究提出NR4A家族并没有参与调控^[68]。Fumoto等人^[66]在3T3-L1中过表达或敲低Nur77都会抑制脂肪生成,而瞬时过表达会促进脂肪的生成。Chao等人^[67]证明了在3T3-L1或3T3-F442A前脂肪细胞中过表达NR4A可以

图 4 NR4A1在糖脂代谢中的调控模式图(网络版彩图)

抑制其脂肪的生成。我们的最新研究证明, NR4A1并不参与脂肪分解的过程, 但是可以通过直接激活GATA2表达来抑制PPAR γ 的转录表达, 并且通过间接上调P53来降低SREBP1c以及下游基因FAS的表达, 从而抑制脂肪细胞成熟和脂肪生成^[69]。多数研究表明, NR4A1对脂肪的生成具有抑制作用^[66,67], 但其中具体而完整的调控机制还有待于进一步的研究证实。此外, NR4A也可能与脂肪信号和转录过程具有协同作用, 其中有报道称NR4A1和NR4A3与Wnt信号通路或糖皮质激素受体具有相互作用, 而这些途径在脂肪形成过程中起着重要作用^[70-72]。

2型糖尿病也是一种慢性低度炎症, NR4A1表达水平升高与2型糖尿病患者慢性低度炎症状态及脂质代谢紊乱相关^[73]。有研究表明, 妊娠糖尿病患者的胎盘中Nur77表达升高, 诱导TNF- α 的表达以及IL-6和IL-8的表达和分泌^[74]。Chao等人^[67]证实, 抑制脂肪分化的炎症因子, 如TNF- α 和脂多糖, 能够诱导NR4A1的表达。Xie等人^[75]认为组蛋白乙酰化有助于调控高胆固醇血症中的NR4A1表达, 从而降低高胆固醇血症引起的炎症。NR4A1是一个重要的炎症调控因子, 而炎症反应又与体内的糖脂代谢密切相关, 因此, NR4A1通过炎症反应调节糖尿病和肥胖等疾病也具有重要的研

究价值。

4 总结与展望

NR4A1在体内的分布比较广, 能被多种刺激所活化。作为转录因子, NR4A1接受刺激后, 通过对靶基因调控区的特异性识别和结合发挥转录调控作用, 参与细胞增殖、凋亡, 肿瘤发生以及能量代谢等多种生理过程。其中能量代谢主要是通过肝脏、肌肉、脂肪组织中葡萄糖和甘油三酯的合成与分解来维持稳定。越来越多的研究表明, NR4A1协同另外两个家族成员(NR4A2和NR4A3)一起参与到体内的糖脂代谢中。在胰岛 β 细胞中, NR4A1能够抵抗由内质网应激和氧化应激引起的细胞凋亡, 从而改善糖尿病。而在脂肪组织中, NR4A1能够抑制脂肪的生成, 从而控制肥胖(图4)。因此, NR4A1在能量代谢方面, 尤其是糖脂代谢, 发挥着重要的作用, 是治疗糖尿病和肥胖等代谢疾病的潜在靶点。

在胰岛 β 细胞中, 持续的高糖环境引发内质网应激和氧化应激, NR4A1抵抗由其引起的细胞凋亡, 从而改善糖尿病。在脂肪组织中, NR4A1能够抑制脂肪细胞分化和脂质的生成, 从而控制肥胖。

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The regulation of NR4A1 on glucolipid metabolism

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The orphan nuclear receptor NR4A1 is widely known as Nur77, TR3 or NGFI-B. It is an important member of nuclear receptor NR4A family. As a transcription factor, it plays a direct or indirect regulatory role in various physiological processes. In this review, the regulatory effect of NR4A1 on glucose and lipid metabolism was summarized according to the research progress in this field and the relevant studies in our laboratory. In pancreatic β cells, the sustained or chronic high-glucose can cause endoplasmic reticulum stress and oxidative stress in the cell, while NR4A1 is able to resist cell apoptosis caused by these stresses; therefore, it prevents the occurrence and development of diabetes. In adipose tissue, NR4A1 can inhibit adipocyte differentiation and adipogenesis; therefore, it has the negative impact on obesity formation.

NR4A1, pancreatic β cells, adipose, glucose and lipid metabolism

doi: [10.1360/N052018-00153](https://engine.scichina.com/doi/10.1360/N052018-00153)