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简 报

肝脏脂质代谢与自噬*

黄 莹, 张 芳, 丁文军†

(中国科学院大学生命科学学院环境与健康实验室, 北京 100049)

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摘 要 肥胖患者肝脏中过量的脂质堆积可引起肝细胞内质网应激、线粒体功能紊乱和脂毒性,该作用与胰岛素抵抗(IR)和非酒精性脂肪肝病(NALFLD)等代谢紊乱疾病的发生密切相关.自噬是细胞对内外持续性刺激的非损伤性应答反应,具有维持细胞结构和代谢平衡的功能.研究发现,自噬参与降解肝细胞内过多的脂质堆积,维持肝脏脂质代谢稳态.本文介绍了自噬调节肝脏脂质代谢的分子作用机制.

关键词 肥胖; 肝脏; 自噬; 脂质代谢

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Effect of autophagy on hepatic lipid metabolism in liver

HUANG Ying, ZHANG Fang, DING Wenjun

(*Laboratory of Environment and Health, College of Life Sciences, University of Chinese Academy of Sciences, Beijing* 100049, *China*)

Abstract It has been well demonstrated that lipid accumulation in liver of the obesity is involved in endoplasmic reticulum stress, mitochondria dysfunction, and lipotoxicity, which is associated with insulin resistance (IR) and nonalcoholic fatty liver disease (NAFLD). Autophagy has been considered to be an adaptive response to stress, contributing to cellular homeostasis. It has been found that autophagy is activated during hepatic lipid accumulation. Autophagy plays an essential role in maintaining hepatic lipid metabolism. This review summarizes recent studies to identify the molecular mechanism of autophagy maintaining hepatic lipid metabolism in the obesity.

Key words obesity; liver; autophagy; lipid metabolism

肝脏在脂质的消化、吸收、分解、合成及运输等代谢过程中发挥着重要作用,是体内生物转化作用的主要器官[1].研究表明,肥胖、过量饮酒和糖尿病等引起肝脏的脂质代谢紊乱[2].肝中过量

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† 通信作者,E-mail: dingwj@ucas.ac.cn

的脂质堆积诱导细胞内大量活性氧的生成,引起肝细胞内质网应激、线粒体功能紊乱及脂毒性,其与胰岛素抵抗(IR)和非酒精性脂肪肝病(NALFLD)的发生密切相关[3-5]. 近期的研究发现,自噬除降解肝脏中功能受损的线粒体和错误折叠蛋白以及调节细胞死亡外,还具有维持肝脏脂质代谢稳态的重要作用[6].

1　肥胖与肝脏脂质代谢紊乱

肥胖是体内脂肪,尤其是甘油三酯(TG)积累过多导致的一种状态. 按其病因不同,肥胖分为原发性肥胖和继发性肥胖[7]. 肥胖患者的血液中TG、游离脂肪酸(FFA)、总胆固醇(TC)、低密度脂蛋白胆固醇(LDL-c)、载脂蛋白 B100(ApoB-100)和极低密度脂蛋白胆固醇(VLDL-c)水平升高,以及高密度脂蛋白胆固醇(HDL-c)含量降低等代谢异常[8-9]. 尤其是肝脏脂质的代谢紊乱引起 IR,影响肝细胞脂类的氧化、储存和运输,并抑制自噬的发生[10]. 并且,IR 可加重脂肪组织和肌肉组织的脂质分解异常,引起肝细胞内的脂质过度积累和活性氧物质过量生成,导致线粒体功能紊乱和脂毒性等副作用[3-5].

2　肝脏脂质代谢

2.1　肝脏脂质生成和氧化

肝脏脂质代谢包括脂肪酸的摄入、生成和氧化(图 1). 肝脏脂肪酸主要来源于血液中的 FFA 和肝细胞自身合成的内源性脂肪酸. 血液 FFA 经脂肪酸转运蛋白 2(FATP2)、脂肪酸转运蛋白 5(FATP5)和脂肪酸移位酶(FAT/CD36)的主动运输进入肝脏[11-13]. 此外,乙酰辅酶 A 羧化酶(ACC)和脂肪酸合酶(FAS)参与内源性脂肪酸的生成[14]. 肝脏内的短或中长链的脂肪酸可以直接经线粒体内膜进入线粒体,而超长链脂肪酸则由肉毒碱棕榈酰基转移酶 1(CPT1)转运至线粒体内进行 β 氧化,最终生成 ATP[15].

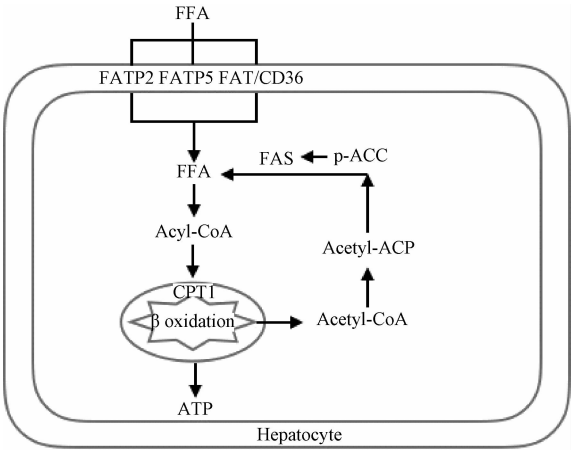

图 1　肝细胞脂质代谢

Fig. 1　Lipid metabolism in hepatocyte

2.2　肝脏脂质代谢的调节

激素、核受体和细胞内相关蛋白质协同调节肝脏的脂代谢(图 2). 脂肪组织分泌的脂联素既能上调 CPT1 的表达,增加肝脏脂质氧化;并抑制 FAS 和 ACC 的表达和肝脏脂质生成[16]. 瘦素则特异性抑制与肝脏脂肪合成相关的硬脂酰脱氢酶-1(SCD-1)mRNA 表达水平,降低肝脏中 TG 和 VLDL-c 含量[17]. 胰岛素影响溶酶体 DNA 酶(DNL)活性,抑制固醇调节元件结合蛋白-1c(SREBP-1c)和激活 Akt 信号通路,降低 VLDLs 的水平[18],抑制线粒体 β-羟-β-甲戊二酸单酰辅酶 A(HMG CoA)转录水平,促进脂肪酸的氧化[19]. 高血糖素样肽 1(GLP-1)增加 cAMP 抑制肝脏中脂质合成和促进脂质氧化[20]. 过氧化物酶体增殖物激活受体 α(PPARα)上调肝脏 FAT/CD36 的表达,促进脂质转入肝细胞内[21]. 此外,肝脏内源性脂肪酸的合成受到 PPARα 和过氧化物酶体增殖物激活受体 γ(PPARγ)调节[22-24]. 肝脏的核受体,如肝脏 X 受体(LXR)、FXR 和孕烷受体(PXR),维持肝脏内脂质稳态[25]. 当肝脏内 SREBP-1c 和碳水化合物应答元件结合蛋白(ChREBP)表达量升高时,肝脏的脂质合成增加[26-27],并参与 FAS 和 ACC 表达[28]. 另有研究表明,磷酸化 AMP 依赖蛋白激酶(p-AMPK)通过调节 ACC 磷酸化水

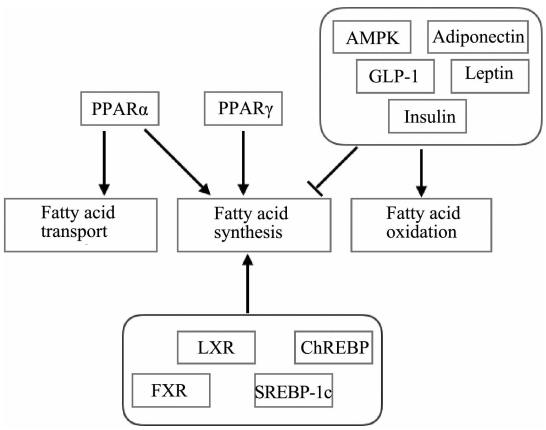

图 2　肝脏脂质代谢的机制

Fig. 2　Mechanism of lipid metabolism in liver

平,促进肝细胞内脂质氧化,降低脂质含量[29].

3 自噬与肝脏脂代谢

自噬是真核生物细胞内普遍存在的一种自稳机制[30].在营养缺乏或者应激状态下,自噬通过消除/降解和再利用细胞内衰老或者失能细胞元件、细胞器和蛋白质,维持细胞内的能量平衡[31].研究发现,在饥饿时,自噬通过降解肝细胞内脂滴,将脂肪酸释放到细胞内线粒体进行氧化,调节肝细胞内的脂质储藏和能量平衡[32-33].若肝细胞的自噬受到抑制,易发生脂毒性和内质网应激[34].

3.1 自噬的形成

自噬主要为大自噬、小自噬和分子伴侣介导的自噬[35-36].小自噬和分子伴侣介导的自噬分别指不同的特殊细胞自噬过程,而大自噬则指传统的细胞自噬.自噬体是由双层膜包裹的细胞质组成,自噬体与溶酶体融合后,溶酶体中酶降解自噬小体中的细胞组分[30].在生理条件下,自噬受到外界营养物质、以及脂质代谢相关蛋白和胰岛素等因素的调节[6].

细胞内自噬小体的形成机制较为复杂,由 30 多个自噬相关基因共同协调完成[37].如图 3 所示,调节细胞内大自噬生成的主要途径有:1)哺乳动物雷帕霉受体蛋白(mTOR)阻止 Atg1 与 Atg13-Atg17 结合抑制自噬,当 mTOR 抑制时,自噬水平升高[38];2)活化的 Atg1-Atg13-Atg17 复合体促进脂质细胞膜上 beclin-1-Vps34 复合体的形成[39-40];3)Atg7 介导 Atg12 与 Atg5 的结合,与 Atg16 发生作用,在自噬体膜上形成 Atg12-Atg5-Atg16 复合体后与自噬小体分离[41-42].在自噬信号的作用下,Atg7 诱导 LC3-I 与自噬小体膜上的磷脂酰乙醇胺形成 LC3-II,引起自噬小体膜的延伸和闭合[43].

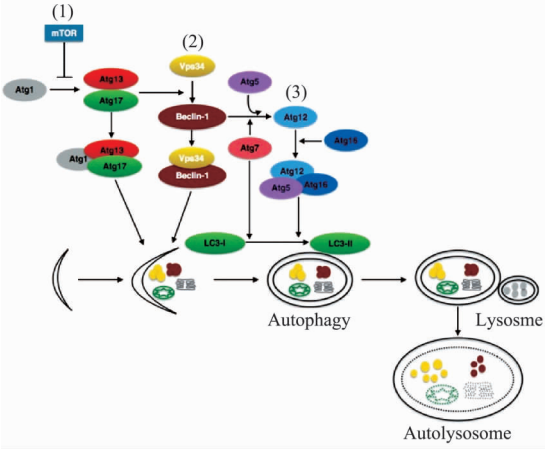

图 3 自噬形成的分子机制

Fig.3 Mechanism of autophagy

3.2 自噬调节肝脏脂代谢

当肝脏中的脂质积累升高时,引起自噬水平降低,自噬小体的膜结构发生改变,抑制自噬小体与溶酶体结合,影响自噬降解脂质的作用[44].研究表明,用自噬的抑制剂 3-MA 处理肝细胞后,细胞 TG 和胆固醇的水平明显升高;Atg5 或者 Atg7 敲除小鼠的肝脏发生 TG 积累[45].另有的研究表明,当肝脏内过度脂质积累引起自噬水平降低时,发生单纯炎症向 NAFLD 及其并发症演变.如果降低肝脏的脂质积累,则可以恢复肝脏自噬水平,预防肝损伤或者 NAFLD 及其并发症的发生[46].

细胞内 TG 和胆固醇酯(CE)主要以脂滴(LD)的形式存在,脂滴广泛地存在于多种组织细胞中,如脂肪细胞、肝细胞和肌肉细胞等.脂滴含有 TG 构成的脂质核心,脂核表面覆盖有单层磷脂,在单层磷脂内镶嵌着在结构上具有相关性的 PAT 家族蛋白,包括脂滴包被蛋白(perilipin)、脂肪生成相关蛋白(ADRP)等,脂滴在脂类代谢与存储、膜转运、蛋白降解中起着重要的作用[47].研究发现,自噬可以分解脂肪和降解脂滴[45,48].当包裹脂滴的自噬小体与溶酶体融合后,脂滴被降解成 FFA,FFA 在线粒体内氧化分解生成 ATP[45,49].在饥饿状态下,LC3 出现在脂滴表面,其中,LC3-II 与脂滴包被蛋白相互作用,通过自噬降解脂质,该过程是由自噬小体识别脂滴表面的脂滴包被蛋白介导的[50].最新研究发现,分子伴侣介导的自噬降解 perilipin 2 和 perilipin 3 参与肝细胞的脂质代谢[51].

4 自噬与调节脂质代谢相关蛋白

自噬小体的形成受到 Atg 家族相关蛋白和肝脏脂质代谢相关蛋白的调节.而且,肝脏脂质相关蛋白也影响肝细胞的自噬水平.

4.1 自噬对脂质代谢相关蛋白表达调节

研究发现,下丘脑 Atg7 缺失小鼠的摄食量增加,能量消耗降低,体重升高,表明下丘脑自噬受到抑制后,降低瘦素水平[52].在营养充足时,细胞自噬水平受到抑制,mTORC1 磷酸化抑制瘦素入核,上调 FAS 表达水平[53].细胞实验发现,3-MA

抑制肝细胞自噬,其胞内的 PXR 水平增加[54].

4.2　脂质代谢相关蛋白调节自噬形成

研究表明,AMPK 磷酸化升高肝细胞自噬水平,促进脂质氧化[55].脂联素、SREBP-2 和 PPARγ 上调 LC3-II 蛋白的表达水平,升高细胞内自噬水平[56-58],而 PPARα 和 FXR 抑制肝脏的自噬水平[59].此外,高胰岛素血症和胰岛素抵抗与自噬水平的变化有关[56].高胰岛素血症和高脂饮食小鼠的肝脏的 LC3-II 蛋白表达水平降低,自噬受到抑制;同时还发现,当肝脏中 p62 蛋白表达增加时,其 Atg5 和 Atg7 的表达下降[56].尽管胰岛素通过 mTOR 信号通路调节自噬形成,但不影响 Atg 相关基因的表达;胰岛素抑制 FOXO1 转录,降低细胞内自噬水平[56].动物实验也发现,核受体 PXR 缺失引起小鼠肝细胞的 LC3-II 和 Beclin-1 蛋白水平下降[60].

5　小结

近年来,肥胖导致的肝脏脂代谢紊乱对健康的影响倍受关注.上述研究表明,自噬在肝脏脂代谢中起到的关键作用,主要通过自噬溶酶体降解细胞内脂滴,降低肝脏脂质堆积,从而改善脂代谢紊乱.同时,参与脂质代谢相关的激素、核受体和蛋白也调节肝细胞内自噬水平.自噬在肝脏脂质代谢的分子机制为明确肥胖导致肝脏脂代谢紊乱的发病机制及其药物治疗提供了一定的理论依据.

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