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·综述·

自噬在非酒精性脂肪性肝病发生发展中的作用

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【摘要】 非酒精性脂肪性肝病(NAFLD)是以弥漫性肝细胞脂肪变性为主要特征的临床病理综合征，包括单纯性脂肪性肝病以及由其演变的脂肪性肝炎、脂肪性肝纤维化和肝硬化。原有的“两次打击”学说不能完全解释其发病机制，涉及多种因素的多重打击学说提供了更全面的描述，包括脂质毒性、炎症反应、纤维化和基因表达改变。自噬是溶酶体对胞浆成分降解的一种代谢途径。自噬参与该病多种发病机制，导致细胞脂质堆积、炎症反应和纤维化。本篇综述总结了Unc-51样自噬激活激酶1、腺苷酸激活蛋白酶、哺乳动物雷帕霉素复合物1与自噬的关系，并详细描述了自噬如何参与非酒精性脂肪性肝病的发生发展。

【关键词】 非酒精性脂肪性肝病；自噬；Unc-51样自噬激活激酶1；腺苷酸激活蛋白酶；哺乳动物雷帕霉素复合物1

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Role of autophagy in the occurrence and development of Non-alcoholic fatty liver disease. *YANG Shi-wei, LI Ming-yi. Department of Hepatobiliary Surgery, the Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, Guangdong, CHINA*

【**Abstract**】 Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by diffuse hepatocyte steatosis, including simple fatty liver disease and its evolution of steatohepatitis, fatty liver fibrosis and cirrhosis. The original "two-blow" theory cannot fully explain its pathogenesis, and the multiple-blow theory involving a variety of factors provides a more comprehensive description, including lipid toxicity, inflammation, fibrosis and changes in gene expression. Autophagy is a metabolic pathway for lysosome to degrade cytoplasmic components, which is involved in a variety of pathogenesis of the disease, leading to cellular lipid accumulation, inflammation and fibrosis. This review summarizes the relationship between Unc-51 like autophagy activating kinase 1 (ULK1), AMP-activated protein kinase (AMPK), mammalian target of rapamycin complex 1 (mTORC1) and autophagy, and describes in detail how autophagy participates in the occurrence and development of non-alcoholic fatty liver disease.

【**Key words**】 Non-alcoholic fatty liver disease (NAFLD); Autophagy; Unc-51 like autophagy activating kinase 1 (ULK1); AMP-activated protein kinase (AMPK); Mammalian target of rapamycin complex 1 (mTORC1)

非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)是指男性每天摄入酒精少于30 g、女性每天摄入酒精少于20 g和没有其他明确的损肝因素所致的肝细胞内脂质过度沉积为主要特征的临床病理综合征，包括单纯性脂肪肝、脂肪性肝炎、脂肪性肝纤维化及脂肪性肝硬化[1-3]。随着人类生活方式的改变，NAFLD成为最常见的肝脏疾病之一，影响全球约25%的成年人，其与胰岛素抵抗、肥胖、2型糖尿病、代谢综合征等疾病相关，给人类健康带来了巨大的负担[3-9]。

在过去的几十年，NAFLD的评估取得了巨大的成就，但难以满足NAFLD患者筛查和诊断的迫切需要。非侵入性方法包括成像工具和血清生物标记物等，已经有了很大的发展。然而，活检仍然是诊断NAFLD最准确的方法，并且是评估疾病严重程度的金标准[3,10-15]。

NAFLD是一种复杂的疾病，胰岛素抵抗、肥胖、2型糖尿病、代谢综合征等为其易感因素。其致病因素和临床表现在不同个体中是高度异质的。1998年，可以

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解释部分NAFLD发病机制的“两次打击”学说被提出：第一次打击主要是肥胖、2型糖尿病、高脂血症等伴随的胰岛素抵抗，引起肝细胞内脂质过量沉积；第二次打击是脂质过量沉积的肝细胞发生氧化应激和脂质过氧化，导致线粒体功能障碍、炎症介质的产生，肝星状细胞的激活，从而产生肝细胞的炎症坏死和纤维化。研究表明，简单过时的“两次打击”学说不能完全解释其发病机制，包括脂质毒性、炎症反应、纤维化和基因表达改变的多重打击学说提供了更全面的阐述[3,7,16-18]。

自噬(源自希腊语，“自食其物”、“自食自噬”)是指细胞质货物传递至溶酶体发生降解的过程。自噬有三种形式包括分子伴侣介导的自噬、微自噬和巨自噬，其生理功能和作用方式不同[19]。大量研究表明，自噬参与多种人类疾病的发生发展，例如神经退行性疾病[20]、炎性疾病[21]、癌症[22]、脂质代谢障碍性疾病[23-24]。

1 自噬的调节和信号通路

1.1 ULK1 Unc-51样自噬激活激酶1 (unc-51 like autophagy activating kinase 1，ULK1)在自噬启动和发生过程中发挥着重要作用。在自噬启动中，ULK1与自噬相关基因13、自噬相关基因101、家族相互作用蛋白200紧密结合形成ULK1复合体，充当自噬起始复合物[22,25]。同时，ULK1是多种自噬调节因子的靶点。法尼酯受体 (farnesoid X receptor，FXR)是自噬的关键生理性抑制因子，其抑制环腺苷酸反应元件结合蛋白(cAMP response element binding protein，CREB)的活性，使ULK1活性下降。FXR-CREB轴是调节ULK1的关键生理开关，从而在摄食/禁食循环中对自噬进行持续的调节[26-27]。受体蛋白FUNDC1 (FUN14 domain containing 1)是哺乳动物细胞内的线粒体受体蛋白，其将ULK1募集到受损的线粒体以启动线粒体自噬。因此，通过FUNDC1-ULK1途径，自噬促进受损线粒体更新，维持线粒体质量控制，抑制脂质蓄积[25,28]。在自噬发生过程中，ULK1将突触融合蛋白17 (syntaxin17，STX17)招募到自噬小体中，并增加STX17对突触体相关蛋白29的亲和力，促进自噬小体与溶酶体的融合[29]。因为ULK1在自噬启动和发生过程中的重要作用，氧化应激等细胞刺激因素通过刺激ULK1而影响自噬。在自噬激活后，细胞通过Cul3-KLHL20连接酶复合物使ULK1泛素化，继而降解的方式关闭自噬启动信号[25]。这是细胞的自我保护机制。

1.2 AMPK、mTORC1 腺苷酸激活蛋白酶(AMP-activated protein kinase，AMPK)分别通过增加Ⅲ型磷脂酰肌醇3激酶信号通路活性途径和抑制哺乳动物雷帕霉素复合物1 (mammalian target of rapamycin complex 1，mTORC1)激活途径，促进ULK1Ser 317位点和Ser 777位点磷酸化，进而增强自噬活性[30]。然而，当mTORC1激活后复合物中的mTOR磷酸化并使ULK1 Ser 757位点磷酸化，阻断了AMPK与ULK1之间的相互作用，导致自噬活性被抑制[31-32]。AMPK可感知细胞能量状态，是自噬的强烈诱导剂。缺氧、活性氧簇、葡萄糖不足等因素通过AMPK磷酸化途径直接激活ULK1，刺激自噬启动[25,32-34]。mTORC1同样通过感知细胞能量状态发挥作用，是自噬的抑制剂，在自噬过程中起负反馈调节的作用。例如：活性氧簇分别通过激活钙/钙调素依赖的蛋白激酶激酶2介导的AMPK磷酸化途径和诱导溶酶体Ca^{2+}释放，触发PPP3/钙调神经磷酸酶依赖性的转录因子EB (transcription factor EB，TFEB)核转位途径，促进TFEB核异位导致自噬活性增加，并清除活性氧簇，减少的活性氧簇对mTORC1的抑制作用减弱。mTORC1活性增强并抑制自噬活性[34-35]。

2 NAFLD中的自噬

2.1 自噬与脂质毒性 脂质毒性是指由于非脂肪组织(包括肝脏，心脏，骨骼肌和胰腺)中脂肪酸和脂质的积累引起细胞功能障碍和/或细胞死亡[36]。细胞主要通过将脂肪酸进行β-氧化和以中性脂质分子形式储存入脂质小滴(lipid droplets，LDs)来抵抗脂质毒性[37]。在能量充足状态下，LDs由中性脂质分子在内质网脂质双层的酰链之间沉积形成[38]。在能量缺乏状态下，溶酶体将LDs中的脂质降解为脂肪酸，脂肪酸进一步发生氧化反应以提供能量[39-40]。在脂质培养的肝细胞中发现，自噬的抑制触发了肝细胞中LDs积累的增加，并且脂质积累优先发生在胞质LDs中。同时，在饥饿的高脂饮食小鼠肝脏中发现，含脂质的膜结构或自噬小体样囊泡明显减少，表明外源性脂质的增加降低了自噬系统与LDs之间相互作用的效率[41]。另外，在长期饥饿状态下，膜细胞器自噬分解而释放的脂肪酸会被包装到新的LDs中，LDs高度聚集并且紧邻线粒体以防止酰基肉碱积累，而酰基肉碱是直接破坏线粒体功能的脂毒性元凶[42]。但特异性家族相互作用蛋白200缺乏症小鼠实验证明了肝细胞中自噬抑制作用会减弱新生脂肪形成的程序并减少肝脂肪变性[43-44]。ULK1作为自噬启动结合蛋白，除通过调节自噬活性途径防止细胞脂质毒性损害外，也可通过自噬以外的途径发挥细胞保护作用[37]。

2.2 自噬与炎症反应 脂多糖通过干扰素基因刺激因子(stimulator of interferon，STING)使干扰素调节因子3 (interferon regulatory factor 3，IRF3)磷酸化，启动先天免疫基因的转录[45]。同时，脂多糖促进AMPK磷酸化，介导ULK1激活。ULK1通过抑制STING-IRF3途径，使免疫基因转录减少[46]。另一方面，脂多糖诱导P38丝裂原活化蛋白激酶和Ⅲ类磷脂酰肌醇3激酶活性增加，促进细胞自噬，以去除危害因素，防止炎症反应继续加重[47]。核因子κB (nuclear factor kappa-B，NF-κB)诱导多种炎性趋化因子、细胞因子和细胞因子前体等促炎因子导致炎症发生，也通过调节自噬活性防止炎症反应过度活化[48-50]。在巨噬细胞中，脂多

糖诱导NF-κB依赖的泛素结合蛋白62表达，激活自噬，抑制了炎性体的活化[50]。T细胞对宿主抵抗病原体入侵至关重要。T细胞受体通过衔接蛋白B细胞淋巴瘤因子-10 (B cell lymophoma-10，BCL-10)介导，将激活信号传至NF-κB，而泛素结合蛋白62介导的自噬可选择性降解BCL10，导致T细胞活化减弱，抑制了细胞免疫[51]。在细胞中，炎症因子激活炎症的同时，通过自噬相关途径反向抑制炎症的过度活化。当NAFLD患者存在肝细胞自噬缺陷时，炎症的负反馈机制被破坏，导致炎症持续加重，加快了疾病发展进程[52]。

2.3 自噬与纤维化 肝纤维化是一个动态的过程，其特征是任何病因的慢性肝损伤导致肝星状细胞活化并分泌高密度细胞外基质，导致细胞外基质的净积累，最后导致肝脏瘢痕形成。肝星状细胞激活将静止的、储存维生素A的细胞分化为增殖的、致纤维化的肌成纤维细胞，这一过程现已被公认为人类肝损伤中纤维化的主要驱动因素[3,53]。锌指蛋白36通过与3'端非翻译区富含AU元件结合，促进ATG16L1mRNA衰变和自噬失活，导致肝星状细胞活化[54]。亚精胺能通过激活微管相关蛋白1S介导的自噬增强mTOR活性，继而增强核因子E2相关因子2活性，抑制肝星状细胞活化以达到保护肝脏的作用[52,55-56]。活性氧簇、脂多糖等因素通过凋亡信号调节激酶1介导JNK、P38、MAPK等蛋白磷酸化，激活自噬活性，抑制视黄酸信号传导以抑制肝星状细胞活化[57-59]。

2.4 自噬与遗传学 随着全基因组联盟的发展，与NAFLD进展相关的遗传因素已被人们所熟知，其中研究最热门的基因是Patatin样磷脂酶3 (patatin-like phospholipase domain containing 3，PNPLA3) [60]。在小鼠实验中发现，自噬的抑制会增加肝LDs上PNPLA3和TG的水平。此外，与自噬失活相关的脂肪变性的发展取决于PNPLA3的表达[61]。

3 小结

自噬参与多种NAFLD发生发展的机制，包括脂质毒性、炎症反应、纤维化和基因表达改变。这些致病机制中，AMPK和mTORC1不仅可以通过调节ULK1的信号传导调节自噬，而且可以通过其他途径作用于自噬过程。另一方面，AMPK、mTORC1和ULK1也可通过自噬以外途径影响细胞内代谢稳态。自噬在维持胞内稳态时表现出两面性，但最终目标都是维持内环境稳态。然而，反复的胞外刺激和胞内代谢紊乱会不可避免地引起自噬激活/抑制导致肝细胞损伤。因此，在NAFLD的发生发展中，自噬可能不仅通过一种机制发挥作用，而是随着时间的推移与多种机制相互作用，导致肝脂质蓄积，炎症因子增加，细胞外基质增加，最终导致纤维化。目前，尚无批准用于NAFLD的特效药物，这可能是由于有多种机制参与NAFLD的发生发展所致。自噬在NAFLD发生发展中表现出的重要性，让其有机会成为治疗NAFLD的关键。

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