

细胞自噬中关键蛋白乙酰化修饰与 相关疾病诊治的研究进展

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摘要 自噬是一种在进化上保守的溶酶体依赖的降解途径。近十多年来, 自噬过程的分子机制研究得到了长足的发展。自噬过程中关键蛋白复合物的乙酰化修饰发挥了十分重要的作用。为此, 该文阐述了细胞自噬过程中主要蛋白复合物的乙酰化修饰作用进展, 并对蛋白质乙酰化修饰与肿瘤、神经退行性疾病等的关系作一总结。总之, 自噬过程中蛋白乙酰化修饰已经成为自噬研究的热点之一, 随着相关研究的不断深入, 其必将为相关疾病的治疗提供重要的理论基础。

关键词 翻译后修饰; 蛋白质乙酰化修饰; 自噬; 乙酰基转移酶; 去乙酰化酶

Research Progresses of Acetylation of Key Protein in Cell Autophagy and the Treatment of Related Diseases

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Abstract Autophagy is a conserved pathway that delivers cytoplasmic contents to the lysosome for degradation. In the past decade, the molecular mechanisms underlying autophagy have been extensively studied. Importantly, the key role of acetylated autophagy complexes has been identified and elucidated. This review systematically summarizes the current knowledge of acetylation of the key autophagy complexes, the function of these modifications, and their therapeutic functional implications in cancer and neurodegenerative diseases. In conclusion, acetylation has become the hot talk of autophagy researches. Understanding the acetylation of the autophagy machinery offers a unique window for the control of autophagy-related diseases.

Keywords post-translational modification; protein acetylation; autophagy; acetylase; deacetylase

蛋白质乙酰化是一种可逆的酶促反应过程。乙酰基转移酶可以将乙酰基团(CH₃C=O)从乙酰辅酶A转移至蛋白质。同理, 去乙酰化酶则可以逆转这

种反应^[1]。蛋白质赖氨酸(Lys, K)乙酰化是细胞内一种重要的蛋白质翻译后修饰过程。它不仅发生于细胞核内组蛋白、转录因子等上, 在细胞质和线粒体

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中也存在诸多蛋白的乙酰化修饰^[1-3]。

细胞自噬是一种在进化上保守的溶酶体依赖的降解途径。它是通过吞噬自身需要降解的蛋白或细胞器, 将其包裹进入囊泡并与溶酶体融合形成自噬溶酶体, 最后由溶酶体中的水解酶将内含物进行降解。细胞通过自噬可以实现细胞内蛋白或细胞器等成分的再循环。近年来一系列研究结果显示, 自噬相关蛋白可以受到乙酰基转移酶或去乙酰化酶的调控^[3-5]。在本文中, 我们将着重阐述自噬过程中关键蛋白的乙酰化修饰, 并对自噬相关蛋白乙酰化修饰与肿瘤、神经退行性疾病等的关系作一总结。梳理蛋白质乙酰化修饰在自噬中的作用必将为阐明自噬的分子机理及治疗其与自噬介导的相关疾病提供理论依据^[6]。

1 自噬过程中蛋白乙酰化修饰作用进展

自噬过程包括自噬的起始、成核、延伸、融合和降解等步骤, 在此过程中有一系列蛋白会发生乙酰化修饰, 提示蛋白乙酰化修饰在自噬过程中起着十分重要的作用^[5]。为此, 我们以自噬过程为主线深入阐述蛋白质乙酰化修饰在自噬中的作用(图1)。

1.1 自噬的起始阶段: ULK1复合体

ULK1(unc51-like autophagy activating kinase 1)复合体包括ULK1、FIP200(focal adhesion kinase family interacting protein of 200 kDa)、ATG13(auto-phagy-related protein 13)和ATG101, 在自噬起始阶段起着至关重要的作用^[7]。在细胞应激条件下, ULK1可以被哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)或AMPK等激酶激活从而启动自噬^[8]。研究表明, ULK1也可以受到乙酰基转移酶的调控。在缺乏外源性生长因子的条件下, 糖原合成酶3(glycogen synthase kinase 3, GSK3)激活并磷酸化下游的乙酰基转移酶KAT5, 进而乙酰化ULK1的K162和K606位点。这两个位点的乙酰化可以增加ULK1活性, 启动细胞自噬^[9]。进一步的研究发现, ULK1在K55、K62、K132、K625等位点也存在乙酰化修饰, 但这些位点对自噬的影响尚未提及^[9]。FIP200是一种脚手架蛋白, 是自噬起始复合体形成的另外一种调控蛋白^[6]。研究显示, 在去乙酰化酶SIRT3(sirtuins 3)敲除的U2OS细胞株或人源性肝细胞中, FIP200蛋白分别在K276、K883、K891、K1041和K1263等位点存在乙酰化水平的变化^[10-11]。

1.2 自噬的成核阶段: PI3K复合体

自噬起始以后, 自噬泡在III型PI3K复合体(phosphatidylinositol 3-kinase complex III, PI3KC3)的作用下参与成核。PI3KC3含有两种类型: PI3KC3-C1和PI3KC3-C2^[12]。PI3KC3-C1参与自噬的成核阶段^[13-14], 而PI3KC3-C2参与自噬体的成熟和胞吞^[15]。两种类型的PI3KC3复合物含有共同的亚基: Beclin-1、VPS34(vacuolar protein sorting 34)和PIK3R4(phosphoinositide 3-kinase regulatory subunit 4), 而ATG9、ATG14和Ambra是PI3KC3-C1复合物特有的亚基^[12]。

VPS34是III型磷脂酰肌醇激酶, 它可以催化底物磷脂酰肌醇(phosphatidylinositol, PI)磷酸化生成3-磷酸磷脂酰肌醇(phosphatidylinositol trisphosphate, PI3P)。VPS34乙酰化修饰决定着自噬成核的成败^[16]。它在K29位点的乙酰化会阻止VPS34与Beclin-1核心复合物的形成, K771位点的乙酰化会降低VPS34与其底物PI的亲合力, K781的乙酰化会降低VPS34激酶的活性^[16]。在HeLa细胞中检测到PIK3R4的K951位点存在乙酰化^[17]。

Beclin-1是III型PI3K复合体的关键蛋白。它可以通过结合VPS34和一些辅助因子(如UVRAG)形成复合物来调控自噬体成熟。Beclin-1存在乙酰化修饰^[18]。乙酰化后, Beclin-1可以招募Rubicon形成复合物, 抑制自噬体成熟, 促进细胞增殖和肿瘤生长^[19]。其中, Beclin-1的K430、K437两个位点可以分别受到乙酰基转移酶P300或去乙酰化酶SIRT1的调控^[19]。值得注意的是, Beclin-1的乙酰化与P300的相互作用会受到Beclin-1在丝氨酸409位点磷酸化的影响^[19]。这一结果提示, 蛋白的磷酸化或乙酰化存在互作。另外, 在人源性肝细胞中Beclin-1在K206位点也存在乙酰化修饰^[10]。

此外, 胞质蛋白HMGB1(high-mobility group box 1)可以激活PI3KC3复合物并促进自噬泡的成核。HMGB1乙酰化修饰可以调节这一过程。蛋白质乙酰化数据库里显示, 该蛋白分别在K2、K11、K12、K30、K43、K59、K76、K82、K154和K157位点存在多位点乙酰化修饰^[10,17,20-23]。p53蛋白作为HMGB1的上游调控蛋白, 它可以与HMGB1形成复合物并转移至胞质, 进而影响PI3KC3复合物, 从而调节自噬^[24]。p53同样含有多个位点的乙酰化, 包括K120、K164、K292、K305、K320、K370、K372、K373、K381、K382和K386^[10,25-27]。据报道, 在饥饿

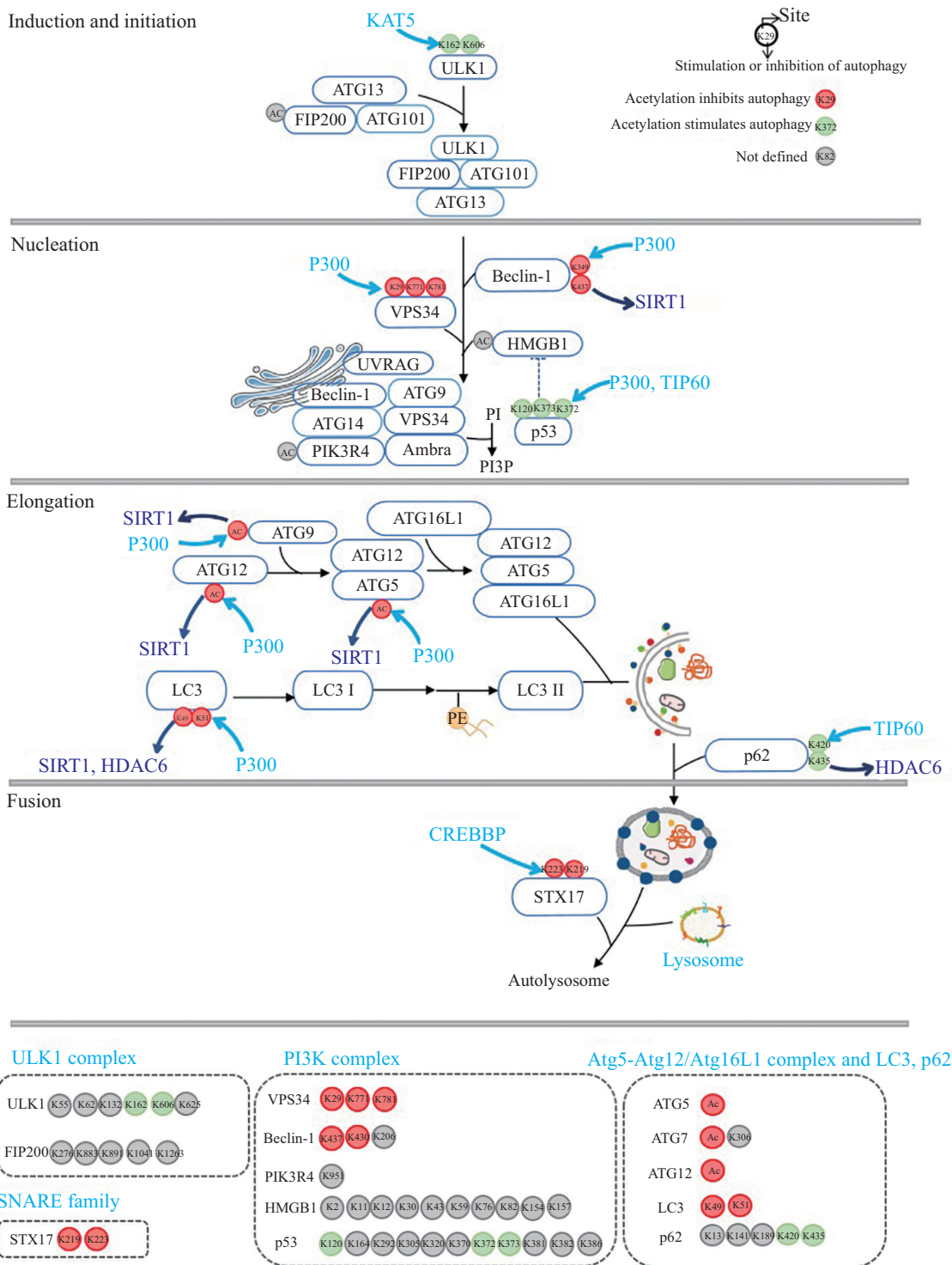


图1 自噬过程中主要复合体的乙酰化修饰特征

Fig.1 Characteristics of acetylation modification of the main complexes with autophagy

条件下, P300从核内穿出后乙酰化p53蛋白的K372和K373位点, 激活自噬途径^[28]。另据报道, 乙酰基转移酶TIP60(tat-interaction protein, 60 kDa)可以乙酰化p53蛋白K120位点, 促使p53在胞质中累积, 继而通过转录依赖性途径上调mTOR上游调控因子促

进自噬^[29]。

1.3 自噬的延伸阶段: ATG5-ATG12/ATG16L1复合体和LC3脂化

自噬泡的延伸依赖于两种泛素样结合系统: ATG5-ATG12-ATG16L1共轭系统与ATG8脂化系

统^[30]。ATG5-ATG12-ATG16L1复合物参与自噬泡的延伸^[31], 并为ATG8的脂化提供场所^[32]。首先在E1泛素活化酶ATG7和E2泛素结合酶ATG10的作用下, ATG5和ATG12之间通过一个类泛素反应结合形成ATG12-ATG5, 然后该复合物通过非共价键与ATG16L1结合形成ATG5-ATG12-ATG16L1。这一复合物定位于胞质中^[31]。相关研究表明, P300或SIRT1可以分别升高或降低ATG5、ATG7和ATG12的乙酰化水平, 抑制P300进而促进自噬泡的延伸^[4,33-35]。目前在MV4-11细胞中已检测到ATG7蛋白K306位点存在乙酰化修饰^[22]。

ATG8与磷脂酰乙醇胺的共价链接过程, 即为ATG8脂化^[36]。ATG5-ATG12-ATG16L1复合物具有类E3连接酶活性, 也可以促进ATG8脂化并转位至自噬体膜, 参与自噬体膜的延伸与闭合^[37]。ATG8在哺乳动物细胞存在三种类型, 分别为LC3(microtubule-associated protein 1 light chain 3)、GABARAP(γ -aminobutyric acid receptor-associated protein)和GATE-16(Golgi-associated ATPase enhancer of 16 kDa)^[38]。LC3是目前研究最为深入的蛋白^[39], 它的脂化可以促进自噬泡的形成和驱动自噬降解底物的募集。值得关注的是, LC3蛋白也可发生乙酰化修饰。P300乙酰化的LC3阻断了其与自噬货物受体p62的相互作用, 防止了p62对无自噬活性的LC3的靶向自噬, 有效地保证了自噬货物的选择性降解^[40]。此外, LC3蛋白的乙酰化也可以抑制泛素-蛋白酶体介导的蛋白质降解途径, 延长LC3蛋白在细胞内的半衰期^[40]。与之对应的是, LC3蛋白的去乙酰化可以启动自噬。SIRT1可以在K49和K51位点去乙酰化LC3, 发生了去乙酰化的LC3进一步与核蛋白DOR相互作用, 通过DOR重新回到细胞质内, 之后与胞质蛋白ATG7等作用, 参与自噬泡膜的延伸^[41]。此外, 在血清饥饿诱导自噬的HeLa细胞中, 组蛋白去乙酰化酶HDAC6可以介导磷脂酰乙醇胺(phosphatidylethanolamine, PE)偶联的LC3II快速去乙酰化, 进而促进自噬体的延伸^[42]。由此可见, LC3的乙酰化在自噬的延伸阶段至关重要。

自噬衔接蛋白p62可以识别“货物”, 将货物运送至自噬泡内并与LC3结合起来^[43]。据报道, 饥饿处理的人胚胎肾293细胞中, TIP60可以乙酰化p62蛋白K420和K435位点, 增强其与泛素的亲和力, 促进p62与泛素的结合从而促进货物的降解^[44]。反之, HDAC6可以去乙酰化p62, 阻止这一过程^[44]。此外,

质谱数据库显示该蛋白在K13、K141、K189存在多位点的乙酰化修饰^[17,44], 这些位点的功能值得深入研究。

1.4 融合与降解: SNARE蛋白家族

自噬体与内体或溶酶体的融合, 为自噬体成熟, 也是自噬货物降解的必经之路^[45]。有研究显示, SNARE(soluble NSF attachment protein receptor)蛋白家族可以拉近自噬体膜和溶酶体膜并驱动膜的融合, 介导自噬体的成熟。SNARE蛋白家族成员STX17可以与VAMP8相互作用驱动自噬体膜与溶酶体膜的融合^[45]。SHEN等^[45]指出, 细胞在饥饿等胁迫条件下, 乙酰基转移酶(CREBBP, CBP)活性下调, 使得STX17蛋白在K219和K223位点去乙酰化, 从而增强了STX17与SNARE蛋白家族成员SNAP29之间的相互作用, 促进STX17-SNAP29-VAMP8 SNARE复合物的形成。此外, STX17的去乙酰化也增强了与其HOPS复合体(homotypic fusion and vacuole proteinsorting complex)之间的相互作用, 促进了自噬体与溶酶体的融合。

综上所述, 细胞自噬过程中关键蛋白质发生了乙酰化修饰, 影响了自噬进程。此外, 细胞核内组蛋白、转录因子, 胞质内微管蛋白、线粒体相关蛋白的乙酰化修饰也是调节自噬不可缺少的一部分, 同样值得关注^[46-47]。

2 蛋白质乙酰化修饰介导的细胞自噬与相关疾病靶向治疗的研究进展

蛋白质乙酰化介导的细胞自噬参与多种疾病的发生发展过程, 如肿瘤^[48]、神经退行性疾病^[48-49]等。因此, 调节乙酰基转移酶或去乙酰化酶的活性会改变细胞自噬的活性, 从而为临床上相关疾病的治疗提供新的策略。

2.1 肿瘤

自噬与肿瘤的发生发展有密切联系^[50]。胞质蛋白总体乙酰化水平的变化及其自噬固有蛋白的乙酰化修饰都可以调节自噬途径, 进而影响肿瘤细胞的存活^[51]。

组蛋白去乙酰化酶(histone deacetylases, HDACs)介导的自噬过程对肿瘤细胞的生长起到了决定性的作用。HDACs抑制剂的体外细胞培养系统和动物模型的相关研究结果显示, HDACs抑制剂可以显著抑制多种肿瘤细胞的增殖, 诱导肿瘤细胞

的凋亡^[52],这也使得调节HDACs活性进行靶向治疗肿瘤成为了可能。目前,根据化学结构,HDACs抑制剂可分为三类:I类为短链脂肪酸,如丁酸钠、丙戊酸;II类为异羟肟酸,如辛二酰苯胺异羟肟酸(N-hydroxy-N-phenyloctanediamide, SAHA)^[53];III类为环状四肽,如曲霉毒素。其中,I类药物丁酸钠可以通过抑制HDACs活性进而降低大肠癌细胞、白血病细胞等多种肿瘤细胞的增殖,具有较强的抗癌功效^[54-58]。丙戊酸则可以诱导非凋亡性的细胞自噬性死亡,用于治疗神经胶质瘤等疾病^[59-60]。II类药物SAHA或OSU-HDAC42可以通过下调AKT1-mTOR依赖的自噬固有通路,从而引起内质网应激介导的肝癌细胞自噬,提高了对肝癌的治疗效果^[5]。值得关注的是,2015年上市的帕比司他(farydak)是一种广谱HDACs抑制剂,通过增加自噬固有蛋白如ATG7的乙酰化水平来抑制自噬,显著降低血液中未成熟的白细胞、淋巴细胞的生存率^[51],适用于髓样白血病、多发性骨髓瘤的治疗^[61]。

此外,临床上还有一种热量限制模拟物的治疗方法,是通过降低细胞质蛋白的总体乙酰化水平从而诱导自噬以提高肿瘤细胞的免疫原性的^[51]。

2.2 神经退行性疾病

神经元内错误折叠和聚集的蛋白质可通过自噬溶酶体途径降解,也可通过分子伴侣或泛素-蛋白酶体系统降解。如果这些途径受到抑制,细胞则无法及时处理错误折叠的蛋白质,从而在神经元内累积引起神经元变性^[62]。在对阿尔茨海默病、帕金森病和亨廷顿病相关动物模型的研究中发现,P300、CBP和去乙酰化酶SIRT1、SIRT2及其调控的自噬相关蛋白的乙酰化修饰参与疾病的发生发展^[63-65]。

阿尔茨海默病是一种起病隐匿的进行性神经系统退行性疾病,其最主要的两大病理特征为错误折叠的 β -淀粉样蛋白在大脑中沉积形成淀粉样蛋白斑块和tau蛋白乙酰化导致的神经纤维缠结在神经元内累积^[66]。在阿尔茨海默病的细胞模型中,SIRT1的激活剂白藜芦醇可以通过降低Beclin-1的乙酰化水平,减少淀粉样蛋白斑块的沉积,促进神经元存活,减少海马区神经的退行性变,改善学习障碍^[67]。阿尔茨海默病与tau蛋白的乙酰化显著关联。在阿尔茨海默病疾病早期,P300可以使得神经元内tau蛋白高度乙酰化,抑制tau蛋白通过自噬-溶酶体途径的降解,进而导致以tau蛋白为主的神经纤维

缠结^[68-69]。P300抑制剂的介入可以使得神经元内tau蛋白得以清除,同样这一过程也会受到HDAC6、SIRT2等去乙酰化酶的调控^[63]。进一步的研究发现,药物双水杨酯(salsalate)抑制大脑组织中P300的活性,阻断tau的乙酰化,有效地阻止脑中以tau蛋白为主的神经纤维缠结,逆转tau引起的记忆缺陷和脑细胞死亡^[66]。ESTEVEZ等^[18]也强调了P300可以乙酰化自噬固有蛋白Beclin-1,阻止自噬泡与溶酶体融合,影响胞内聚集体的清除,导致阿尔茨海默病神经元变性。

帕金森病是一种常见的中老年人神经系统退行性疾病。来自帕金森病患者的成纤维细胞显示,乙酰化酶与去乙酰化酶活性的失衡会导致自噬相关蛋白、组蛋白等的乙酰化水平变化,自噬活性降低进而导致神经元变性^[70-71]。DE OLIVERIRA等^[72]在大鼠帕金森病模型中的研究中指出,抑制SIRT2后会诱导 α 突触核蛋白K6和K10位点乙酰化,进而促进其通过自噬-溶酶体途径降解,从而降低 α 突触核蛋白聚集引起的细胞毒性。这一研究提示,调节SIRT2活性在治疗帕金森病中的应用价值。

亨廷顿病是一种常染色体显性遗传的神经退行性疾病,它是由于亨廷顿基因发生突变而导致的。突变的亨廷顿蛋白会在胞内产生聚集引起细胞功能异常并导致神经退行性变^[73]。JEONG等^[74]发现,CBP可乙酰化亨廷顿蛋白的K444位点,进而促进突变型亨廷顿蛋白的自噬清除,从而逆转突变型亨廷顿蛋白在纹状体神经元中的毒性作用,达到保护神经元的作用。

3 结语

综上所述,蛋白质乙酰化修饰在细胞自噬过程中发挥了十分重要的作用。蛋白质乙酰化修饰贯穿了自噬从起始至终止的整个阶段。迄今为止,借助高分辨率质谱定量技术、基因拼接技术和多功能化学探针等技术,已检测到自噬过程中固有蛋白及其相关调节蛋白诸多位点的乙酰化修饰,并对这些位点进行了功能探究。值得注意的是,还存在相当比例的乙酰化修饰位点对自噬的影响尚未阐明。

蛋白质乙酰化修饰介导的细胞自噬参与多种疾病,包括肿瘤、神经退行性疾病等。以乙酰基转移酶或去乙酰化酶活性改变为基础的干预方法也为相关疾病的治疗提供了策略。然而,鉴于目前诸多

HDACs抑制剂对酶的非专一性及HDACs本身作用的底物较多,药物的靶向治疗受到了限制。开发更具专一性的HDACs抑制剂成为当务之急。

此外,在细胞自噬中,蛋白质的乙酰化与蛋白磷酸化、泛素化等修饰方式之间存在交互作用,这些交互作用对自噬的影响也是值得重视的研究领域。

总之,研究自噬过程中蛋白乙酰化修饰对于阐明细胞自噬的分子机制具有十分重要的意义,也为相关疾病的治疗提供了理论依据。

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