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Advances in the Regulation of Autophagy

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Abstract

In this review, we will describe the dynamic progress how cells form isolation membranes with the participation of various autophagy-related proteins under the stimulation of upstream signals such as MTOR and AMPK, and further extend to form autophagic characteristic structures "autophagosome", and how mature autophagosomes combine with lysosome to complete the degradation and reuse of cytoplasmic substances. In addition, the research progress of post-translational modification (including phosphorylation, glycosylation, ubiquitination, acetylation and mercaptan modification) in regulating autophagy was briefly reviewed. It was pointed out that post-translational modification of autophagic proteins played an important role in the process of autophagy. Understanding which amino acid residues in autophagic proteins are modified and confirming the expression of these modified amino acids in related diseases will provide important targets for disease diagnosis and treatment.

Keywords

Autophagy, MTOR, Post-Translational Modification

细胞自噬调控的研究进展

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摘　要

本文介绍了细胞在接受MTOR、AMPK等上游信号刺激下，在多种自噬相关蛋白参与下如何形成隔离膜、并进一步延伸形成自噬特征性结构“自噬体”以及成熟的自噬体如何与溶酶体结合完成胞浆物质的降解

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和再利用的动态过程，并简述了翻译后修饰(包括磷酸化作用、糖基化修饰、泛素化修饰、乙酰化修饰及硫醇修饰)如何调控自噬的研究进展，指出自噬蛋白的翻译后修饰在细胞自噬过程中发挥重要作用。理解自噬蛋白中哪个氨基酸残基被修饰，以及证实这些修饰氨基酸在相关疾病的表达状态，将会为疾病的诊断和治疗提供重要的靶点。

关键词

自噬，MTOR，翻译后修饰

1. 引言

细胞自噬(Autophagy)是一个进化保守的代谢过程，基于溶酶体自我消化损伤的细胞器、蛋白聚集体和胞浆组分(这种表述来源于希腊语，“auto”-self 和“phagia”-eating)，从而形成自身营养池。当细胞处于饥饿或应激状态时，通过自噬实现能量和营养再循环以做出对不同应激的适应性反应。自噬受很多高度保守的自噬相关分子 ATGs (Autophagy-related gene)调节，目前已被证实的有 36 个 ATG 分子参与自噬的发生。除了基本的“管家”功能外，还有一些刺激因素会诱导自噬发生，如细胞因子、应激、病原体、错误折叠或聚集的蛋白、损伤的细胞器甚至是蛋白合成的抑制[1] [2] [3]。

2. 细胞自噬的过程

自噬的发生，从起始到自噬体形成经历一系列膜的动态变化。首先，各种胞浆组分包括受损细胞器被“隔离膜”结构包裹，随后，新月形的隔离膜不断融合、延伸，直到形成完整的双层膜细胞器——自噬体(Autophagosome) (图 1)。

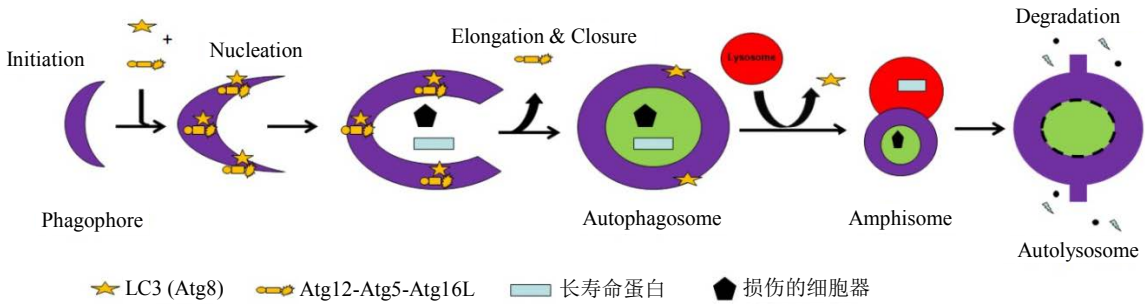

Figure 1. The process of autophagy
图 1. 细胞自噬过程

酵母中的自噬体形成时 Atg 蛋白聚集到液泡膜附近的一个点，自噬体在这个特异位点形成，因此称它为自噬前体结构“PAS”(pre-autophagosomal structure) [4]。在哺乳动物细胞中是否存在 PAS 结构仍不确定。

隔离膜形成、组装中一个重要复合物是 Class III PI3K 复合物(由 PIK3C3、p150、Atg14 和 BECN1 组成)，其主要功能是产生 PI3P (phosphatidylinositol-3-phosphate)，PIK3C3 复合体招募一些 PI3P 结合蛋白

后进一步招募两个泛素样蛋白连接复合物，Atg12-Atg5-Atg16L1 和 LC3/Atg8-PE (phosphatidylethanolamine)到隔离膜参与膜的进一步延伸[5]。

在正常条件下，大部LC3/Atg8主要在细胞质中，而当自噬被诱导发生时，LC3/Atg8则以LC3/Atg8-PE连接体形式定位于隔离膜两侧。LC3/Atg8可控制细胞自噬体的大小，因其始终存在于自噬体膜上，所以Atg8及其哺乳动物细胞同源物LC3的脂化水平被广泛用于衡量细胞自噬发生的指标。

目前的研究进展表明，多种细胞器和质膜为自噬体膜的形成提供了脂类或重要蛋白。Ktistaki课题组通过研究ZFYVE1证实了内质网是自噬体膜的来源之一[6]。Lippincott-Schwartz和他的同事通过对LC3及ATG5的观察发现饥饿诱导的自噬体可以出现在线粒体位点上，认为线粒体也是自噬体膜潜在的来源之一[7]。最近的研究发现将细胞从4℃迅速转移到37℃，诱导其发生内吞的过程中，许多质膜标志物与自噬体早期结构出现共定位现象，且质膜标志物与隔离膜、自噬前体和自噬体都密切相关，表明质膜在由隔离膜发展为自噬体的过程中发挥了重要作用[8]。通过对酵母的研究发现许多低聚的高尔基复合物可通过参与高尔基-内体间的运输从而影响自噬体合成，因此高尔基体可能在酵母系统的自噬中发挥重要作用[9] [10]，但至今尚不清楚高尔基体是否在哺乳动物的自噬过程中发挥作用。有学者提出Atg9的穿梭可能为自噬体提供膜来源[11]，因此明确Atg9在穿梭中的具体作用可能为研究自噬体膜来源提供更多有用信息。近期的研究取得了很大进展，Hamasaki的研究证实内质网-线粒体接触位点(ER-mitochondria contact site)是自噬体形成的起始位点，当内质网-线粒体的接触位点被破坏后，自噬体形成受到严重抑制[12]。Ge的课题组认为ERGIC (ER-Golgi intermediate compartment)可能是自噬体形成的另一起点，非细胞实验证实内质网-高尔基体间隔是LC3B脂化过程的膜底物，细胞实验也证实了ERGIC对于自噬体的形成是必须的[13]。Graef等的研究认为内质网的排出位点(ER exit sites, ERES)是自噬体合成的起始以及膜来源的位点，ERES产生COPII被膜小泡，并能相互融合，形成“内质网–高尔基体中间体”，介导蛋白从内质网到顺面高尔基体的运输，为phagophore成核、延伸提供特定膜来源或结构平台[14]，但具体有哪些关键分子参与这一过程尚不清楚，需进一步研究来确认。

完整的双层膜自噬体形成后，将内容物运送到溶酶体以完成最终的降解过程。来自酵母的研究结果显示，Atg8从自噬体外膜释放可作为它解聚自噬发生的起始因子进而准备融合的信号[15] [16]。免疫电镜结果也表明多数Atg8只存在于成熟自噬体内膜上[17]。目前哺乳动物细胞的LC3B从外膜的释放是否可以作为自噬体与内吞体或溶酶体融合的信号尚不清楚。但与隔离膜相关蛋白如ATG16L1和ULK1不存在于成熟的自噬体上，表明它们在与溶酶体融合前已经从自噬体上分离。其中的机制及其是否成为自噬体与溶酶体融合的先决条件有待进一步研究证实，因此，自噬体成熟是一个既复杂又受精细调控的过程。

溶酶体是细胞内降解蛋白质、脂质、糖类和核酸等的重要细胞器。各种来源的物质(胞外、细胞表面或胞内的底物)通过胞内一些相互关联的运输途径运送到溶酶体进行降解，其终末产物被循环利用。溶酶体功能受损将阻断各种底物的降解，导致废物大量堆积，引起溶酶体病变。

自噬体和溶酶体均是膜包裹的能够行使独立功能的细胞器，自噬体分布相对随机，而溶酶体常位于细胞核附近的中心位置。因此，自噬体要与它们融合，先要运动到它们所在的位点，这个过程受到细胞内骨架蛋白及相关马达动力蛋白的调控[18]。当自噬体运动到目的地时，它就开始完成与溶酶体的融合过程。目前人们对于这个过程的理解基本都建立在对一般的胞内囊泡运输信号通路的基础上。此过程主要受Rab GTPases [19]、膜融合相关的栓系复合物[20]和SNAREs蛋白[21] [22]的调节和控制。先是Rab蛋白定位于特异的膜结构上，然后招募一些栓系分子，这些栓系分子可以作为一个桥梁将两种即将要融合的膜细胞器近距离联系起来。最终，SNARE蛋白组装到两细胞器膜接触的部位，促进两者的脂质双分子层融合。

3. 细胞自噬的调控

3.1. 营养信号通路与氧化应激调控自噬

大量的研究证明，在饥饿条件下，自噬体形成显著增多。这一过程主要由 MTOR 信号通路的调控。

MTOR 复合体 1 (MTORC1)由 MTOR、RAPTOR (regulatory-associated protein of MTORC1)，MLST8/GbL (mammalian lethal with Sec13 protein 8/G protein subunitblike)，DEPTOR (DEP-domain-containing and MTOR-interactive protein)和 PRAS40 (proline-rich AKT substrate of 40 kDa)组成，参与自噬的负调控。MTORC1 可被 RAPA (Rapamycin)显著抑制。正常情况下，RAPA 抑制 MTORC1 能有效诱导自噬，表明 MTOR 负调控自噬。胞外氨基酸通过 SLC1A5 和 SLC7A5 氨基酸运输载体转运入胞内，MTORC1 能直接感受氨基酸进入，且被磷酸化修饰[23]。Rag 的 Ras 相关小 GTP 水解酶能感应氨基酸变化，使 MTORC1 定位于 RHEB (含有 MTORC1 激活子)，从而激活 MTORC1 复合体[24]。氨基酸也可通过 Class III PI3K 激活 MTOR，从而抑制自噬[25]。MTORC1 除了调节 Atg1/ULK1 复合体，在酵母中还能磷酸化 Tap42，激活的 Tap42 负调控 PP2A，从而抑制自噬[26]。

AMPK 信号通路感应细胞内能量。胞内 ATP/AMP 下降时，LKB1 激酶被激活进而激活 AMPK。活化的 AMPK 使 TSC1/2 复合体磷酸化激活，活化的 TSC1/2 通过 RHEB 来抑制 MTOR 从而激活自噬[27]，通过营养循环可再产生 ATP 从而缓解细胞的能量缺乏(图 2)。

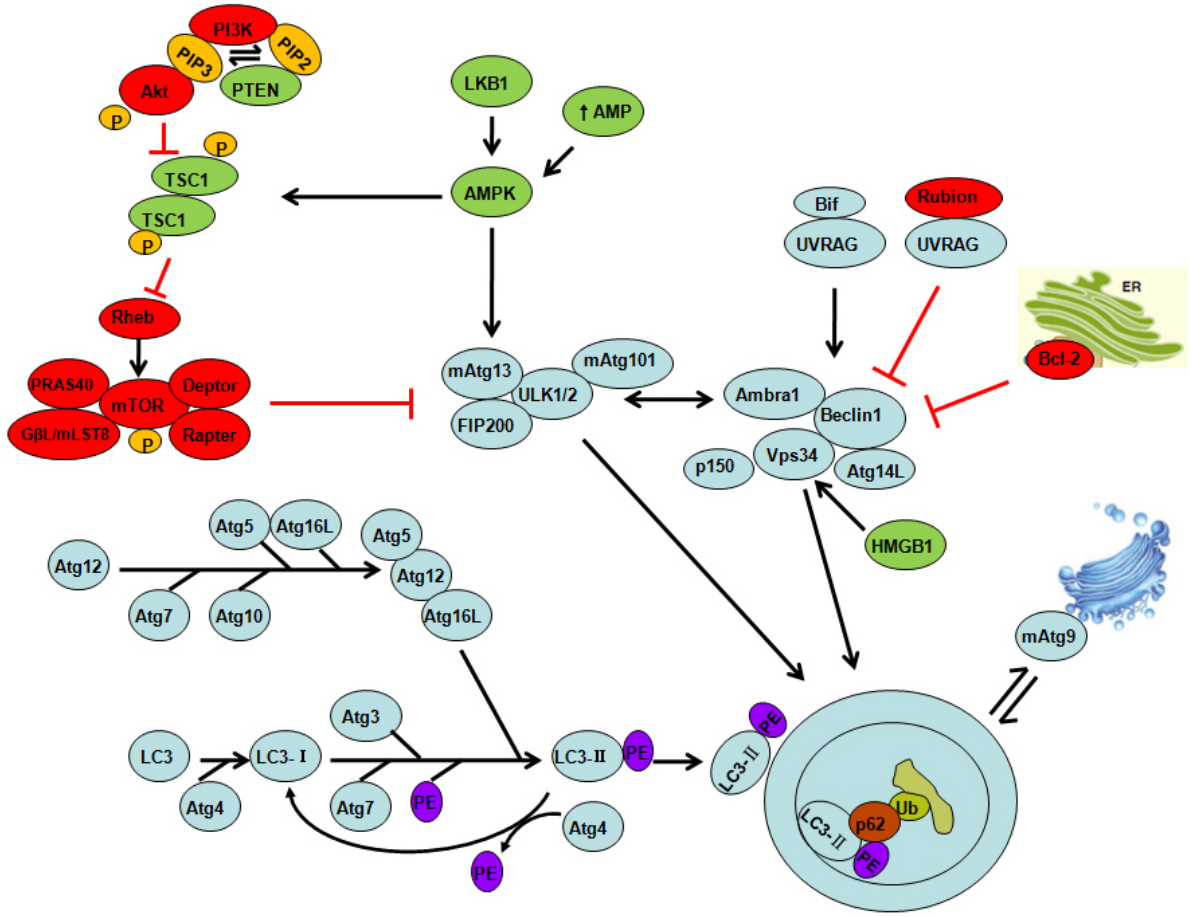

Figure 2. Signal regulation of autophagy
图 2. 细胞自噬的信号调控

氧化应激：ROS 能够诱导细胞自噬。产生 ROS 的主要场所是线粒体，而高水平的 ROS 也会损伤线粒体或其它细胞器，进一步增加自噬的产生。一些化合物可抑制线粒体电子传递链，诱导 ROS 产生和自噬性细胞死亡[28]。Atg4 (胱氨酸蛋白酶)可能是联系 ROS 和自噬诱导的因子，它可在自噬体和溶酶体融合前切割细胞自噬体外膜上的 Atg8/LC3。ROS 能氧化 Atg4 第 81 位半胱氨酸，抑制 Atg4 蛋白酶活性从而促进 Atg8/LC3 的脂化[29]，但 Atg4 并不是氧化调节自噬的唯一分子。过氧化氢可激活 PARP-1，进而激活 LKB1-AMPK 信号通路，诱导自噬的发生[30]。

3.2. 翻译后修饰对自噬的调节

自噬蛋白需要翻译后修饰的调节。磷酸化作用是迄今为止研究最为广泛的翻译后修饰，然后是泛素化和乙酰化作用。最近的研究发现自噬蛋白还有糖基化修饰和硫醇残基氧化还原反应调节。蛋白的翻译后修饰在蛋白结构、定位、活性和功能上起重要作用，如磷酸化作用可以调节催化活性及蛋白与蛋白的相互作用；糖基化作用能保证蛋白的正确折叠，泛素化作用参与信号降解，脂化则能使蛋白嵌入脂质膜[31] [32] [33] [34]。

3.2.1. 磷酸化作用调节自噬

磷酸化作用是将一个磷酸基团插到丝氨酸、苏氨酸和酪氨酸残基上，改变蛋白构造、活性和蛋白与蛋白相互作用[34]。

MTORC1 磷酸化抑制自噬：最有特征性的自噬调节子之一是 MTOR (mammalian target of rapamycin)。在营养丰富情况下，MTORC1 处于磷酸化状态，进而介导 ULK1 在 758 位丝氨酸磷酸化，抑制其活性。ULK1/ATG1 复合体也包括 FIP200/ATG17 (focal adhesion kinase (FAK) family interacting protein of 200 kDa)和 ATG101。细胞应激(如缺氧或营养剥夺)时，细胞内 MTORC1 蛋白激酶复合物被抑制，从而失去了对 ULK1 蛋白的抑制作用，导致 ULK1 蛋白激酶的自身磷酸化激活，活化的 ULK1 激酶磷酸化它的伙伴 ATG13 和 FIP200，参与自噬体的形成[35] [36]。

AMPK 和 AKT 调节 MTORC1：作为自噬起始的主要调节子，MTORC1 活性受多种上游信号通路调节。主要信号通路之一是 AKT/AMPK (AMP-activated protein kinase)级联酶反应。AMPK (AMP activated protein kinase)是细胞能量传感器，能量缺失能够使 LKBl (1iver kinase B1)磷酸化 AMPK，然后 AMPK 磷酸化 TSC2 (Tuberous sclerosis complex 2)。TSC2 是一个含有 GTP 酶活化蛋白(GAP) domain 的蛋白，能使 Rheb GTPase 失活，抑制 MTORC1 的活性。最近，AMPK 被证实直接磷酸化 RAPTOR，RAPTOR 是另一个 MTORC1 复合体蛋白，在能量应激时使 MTORC1 完全失活[37]。除了调节 MTORC1 的活性，AMPK 还能直接磷酸化 ULK1 来调节线粒体自噬和线粒体内平衡，由此产生 ULK1 激活的一条平行通路[38]。在葡萄糖饥饿下，活化的 AMPK 抑制 MTORC1 活性，解除其对 ULK1 的 Ser757 磷酸化，随后，AMPK 磷酸化 ULK1 的 Ser317 和 Ser777 位点，激活 ULK1 激酶并诱导细胞自噬[39]。

另一方面，PI3K class I (PI3KI)通过合成 phosphatidylinositol-3,4-diphosphate (PI-3,4-P2)和 phosphatidyl-inositol-3,4,5-trisphosphate (PI-3,4,5-P3)，招募含有 Pleckstrin Homology (PH) domain 的蛋白如 3-phosphoinositide-dependent protein kinase-1 (PDK1)或它的下游靶标 AKT，反过来激活 MTORC1，抑制细胞自噬，发挥负向调节自噬过程的作用[40]。AKT 也能直接磷酸化 PRAS40 激活 MTORC1 [41] [42]。

磷酸化作用调节 BECN1/PIK3C3 复合物：在哺乳动物细胞中，PIK3C3/VPS34 与 P150 (PI3-kinase P150 subunit)/VPS15 和 BECN1 (coiled-coil myosin-like BCL2-interacting protein 1)/ATG6 相互作用[43]，促进 phosphatidylinositol 3 phosphate (PI3P)的合成，参与 phagophore 的形成并能招募其它合作蛋白，如 ZFYVE1 (double FYVE domain-containing protein) [44]、WIPI family proteins (WD-repeated protein interacting with phosphoinositides) [44]和含有 FYVE domain 的 ALFY 蛋白[45]。还有一些蛋白能与 PIK3C3 复

合体相互作用，正向或负向调节此复合体的活性，这些蛋白包括：BECN1-associated autophagy-related key regulator (BARKOR)/ATG14、ultraviolet irradiation resistance-associated gene (UVRAG)/VPS38、BAX-interacting factor 1 (BIF1)以及 BECN1-regulated autophagy 1 (AMBRA1)和 RUBICON 中的活化分子。β cell lymphoma 2 (BCL2)和 BECN1 的相互作用受磷酸化的调节[46]。在营养过剩的条件下，BCL2 结合 BECN1 抑制自噬，当缺乏营养时，BCL2 被 c-Jun N-terminal protein kinase 1 (JNK1)在三个位点磷酸化，引起 BCL2 从 PIK3C3 复合体释放，自噬激活[47]。BECN1 也能被 death-associated protein kinase (DAPK)磷酸化，引起 BCL2-BECN1 复合体的解离[47]。激活的 ULK1 蛋白激酶可以直接磷酸化 BECN1 蛋白的第 14 位点的丝氨酸，而 ATG14 蛋白则可以特异性的促进 ULK1 蛋白对于 BECN1 蛋白的磷酸化。第 14 位点丝氨酸磷酸化的 BECN1 蛋白可以促进 PIK3C3 的激酶活性，进而促进细胞自噬的起始[48]。

磷酸化作用调节 ATG9：与其它的 ATG 蛋白不同，ATG9 是位于 PAS 上的跨膜蛋白[49]。ATG9 与 WIPI-1/ATG18 相互作用，从反式高尔基体网和晚期内体运输磷脂到 PAS [50]。这种再定位过程依赖 ULK1/ATG 复合体和 PIK3C3 激酶活性[51]。自噬过程中 ATG9 穿过细胞的运输机制仍不清楚，但是近来酵母的一个研究显示 ULK1/ATG1 能直接磷酸化 ATG9，这个磷酸化事件对于晚期招募 ATG8/LC3 和 WIPI-1/ATG18 到 PAS，进一步激活自噬体的形成是必须的[51]。

磷酸化作用调节 ATG8/LC3：LC3 (microtubule associated protein-light chain 3)在哺乳动物细胞的类似物 GABARAP (gamma-aminobutyric acid receptor-associated protein)和 GABARAPL2/GATE-16，它们与 ULK1/ATG1 相互作用对囊泡运输和神经元的延伸有重要作用[52]。蛋白激酶 A (PKA)能够磷酸化 LC3 (磷酸化位点为 Ser12) [53]，抑制 LC3 的脂化，导致自噬的抑制。蛋白激酶 C (PKC)也能磷酸化 LC3 (磷酸化位点为 Thr6 和 Thr9)，但这两个位点的 Thr 的磷酸化对 PKC 介导的自噬抑制没有明显影响，换句话说，PKC 抑制自噬不依赖于 LC3 的磷酸化[54]。此外，LC3、GABARAP 和 GABARAPL1 也能被 mitogen-activated protein kinase 15 (MAPK15)/ERK8 磷酸化，诱导它们的脂化，导致接下来的自噬体形成和 SQSTM1 降解[55]。细胞营养缺乏或氨基酸饥饿时，促进 MAPK15 在自噬体定位，能够阻止 LC3 被 PKA 磷酸化抑制。近来的一项研究显示 ULK1、ATG13 和 FIP200 与 LC3 通过 LC3-interacting region (LIR) domain 相互作用，目前认为 LC3 蛋白是招募 ULK1 复合体到自噬体上的脚架蛋白[56]。

磷酸化作用调节 SQSTM1/p62、ATG29 和 ATG31：SQSTM1 (sequestosome 1)/p62 在 ubiquitin-associated (UBA) domain Ser403 位点被 casein kinase 2 (CK2)磷酸化[57]。这个修饰增加了 SQSTM1/p62 对泛素化底物的亲和力。近来的研究显示，在酵母中 ATG29 (三聚物复合体 ATG17-ATG31-ATG29 的一部分)被磷酸化，这个修饰对其与 ATG11 的结合发挥重要作用，并且对 ATG17-ATG31-ATG29 复合体招募到 PAS，以及 ATG1 的招募非常重要[58]。

参与线粒体自噬的蛋白磷酸化：线粒体自噬(mitophagy)对线粒体的质量控制是非常重要的，它受多个蛋白和通路调节[59]。线粒体膜的去极化使 PINK1 (PTEN induced putative kinase 1)稳定在线粒体外膜上，在线粒体外膜上招募并磷酸化 PARKIN/PARK2 (parkin RBR E3 ubiquitin protein ligase)，一个 E3 泛素蛋白连接酶[60]。外膜 GTP 酶线粒体融合蛋白 GTPase Mitofusin 2 (MFN2)对招募 PARKIN 到线粒体上发挥重要作用。然后，PINK1 磷酸化 MFN2，诱导其被 PARKIN 泛素化[61]。线粒体上的 PARKIN 泛素化多个线粒体底物包括 voltage-dependent anion channel 1 (VDAC1)和 MFN1/2 [62] [63]，这些修饰的蛋白被效应蛋白 SQSTM1/p62 识别，通过与 LC3/ATG8 蛋白相互作用把受损的线粒体带到自噬体。

除了 PINK1 和 PARKIN 的参与，去极化的线粒体也能独立地招募 ATG9A 和 ULK1 起始 phagophore 的形成，在招募 LC3 之前，招募 WIPI-1、ATG14、ZFYVE1 和 ATG16L1，促进隔离膜的延伸。然而，ULK1 激酶的底物在这个过程中未被证实[64]。低氧或线粒体解偶联也引起 ULK1 激酶的上调和转位到片段化的线粒体，继而磷酸化 FUN14 Domain Containing 1 (FUNDC1)。ULK1 转位到线粒体需要 ULK1 和

FUNDC1 之间的相互作用，FUNDC1 的磷酸化促进 FUNDC1 结合 LC3，诱导线粒体靶标进入自噬体以降解[65]。

溶酶体膜上 TFEB 的磷酸化：除了在自噬的起始过程中发挥重要作用，MTORC1 还会与 TFEB (transcription factor EB)相互作用，从而参与溶酶体循环。在正常条件下，MTORC1 与 TFEB 在溶酶体膜上共定位，并且 MTORC1 可以磷酸化 TFEB 而阻止它运输到核。在饥饿条件下，MTORC1 被抑制，因而释放 TFEB 转位到核以活化参与溶酶体生成和自噬的基因，包括 LC3B、WIPI、ATG9B 和 SQSTM1 [66] [67] [68]。

3.2.2. 糖基化修饰调节自噬

除了被磷酸化修饰，丝苏氨酸残基也能被 O-linked attachment of b-N-acetyl-glucosamine (O-GlcNAc)修饰。与经典的 O-和 N-连接的糖基化不同，经典的糖基化受限在内质网和高尔基体上，而 O-GlcNAcylation 发生在细胞核、细胞浆和线粒体蛋白。目前约有 1000 多个蛋白以 O-GlcNAc 乙酰葡糖胺为靶点，在调节蛋白酶体活性[69] [70]、信号转导[71] [72] [73] [74]、细胞核运输[75]、翻译和转录[76]以及凋亡[77] [78]过程中发挥重要作用。

Uridine-diphosphate-N-acetylglucosamine (UDP-GlcNAc)是 O-GlcNAcylated 蛋白形成的重要糖供者。O-GlcNAc 转移酶(OGT)催化 O-GlcNAcylated 蛋白，O-GlcNAcylation 蛋白的总体水平受精确调节，其产生由 OGT 催化，其去除 β-N-acetylglucosaminidase (OGA)催化。既然丝苏氨酸残基既是糖基化也是磷酸化的靶点，对于它们来说完成一种修饰后再完成另一种修饰是完全有可能的，然而，越来越多的证据表明在两种修饰之间存在复杂的相互作用。例如，减少 OGA 的 280 位点磷酸化，升高 148 位点磷酸化，可使细胞中 O-GlcNAc 水平增多[79]。越来越多的以 O-GlcNAc 为靶点的激酶被证实，以及 OGT 和 OGA 与激酶和磷酸酶都形成短暂的复合体，这些都能支持糖基化和磷酸化之间存在广泛的相互作用。

而 O-GlcNAc 水平的改变最常见的是与慢性疾病相关，如糖尿病和癌症。现在比较明确的是 O-GlcNAc 对哺乳动物细胞的生存能力是非常重要的，依据 OGT 或 OGA 缺陷小鼠能引起胚胎致死[80] [81]。O-GlcNAc 蛋白水平升高能增强细胞对大范围的应激刺激的耐受[82]。另一方面，在秀丽隐杆线虫，OGA 失去功能，会使总体 O-GlcNAcylation 水平升高，进而升高 TAU、b-amyloid 和 andpolyglutamine 诱导的细胞毒性[82]；相比之下，OGT 失去功能，会降低 O-GlcNAcylation 水平，进而减弱相同聚集物诱导的毒性[82]。有趣的是，无论缺少 OGT 还是缺少 OGA 都会引起自噬体的积累，然而尚不清楚 O-GlcNAc 循环在调节自噬流中发挥作用的机制[82]。另一方面，在营养剥夺时，自噬主要的调节分子 BCL2 和 BECN1 都发生 O-GlcNAcylation [83]。此外，MTORC1 复合体的重要调节子 AKT 和 AMPK 也都是 O-GlcNAcylation 的靶标[84] [85]。总的说来，这些结果为应激状态下 O-GlcNAcylation 对自噬的调节作用提供了强有力的支持。

在神经退行性疾病的哺乳动物细胞和啮齿类动物模型中，OGA 在神经元和人类大脑中 mRNA 和蛋白水平上都呈现高表达[86] [87]。O-GlcNAc 循环失调随着年龄的增长而升高，这是一个已知的神经退行性疾病发展的风险因素[88] [89]。其中，TAU 是在大脑中研究最广泛的 O-GlcNAcylated 蛋白，因为它的磷酸化与阿尔茨海默病密切相关。在阿尔茨海默病的大脑中，TAU 的 O-GlcNAcylation 下调，细胞过表达 OGT cDNA 或 shRNA，分别下调或上调 TAU 的磷酸化[90] [91]。在体内和体外实验，阿尔茨海默病鼠模型用 OGA 抑制剂处理显示 TAU 的 O-GlcNAcylation 增多，磷酸化减少[92] [93] [94]。到目前为止，O-GlcNAcylation 在介导帕金森病的病理生理作用方面还不清楚，然而，a-突触核蛋白(a-synuclein)被 O-GlcNAc 修饰，减弱了它在体内的聚集[95]。近来研究显示过表达 OGA，可以抑制 O-GlcNAcylation 进而导致 SQSTM1/p62 下调，LC3B-II 上调，自噬流增强。谷氨酸盐果糖-6-磷酸酰胺转移酶是一个氨基己

糖生物合成途径中重要的酶，重氮丝氨酸可以抑制谷氨酸盐果糖-6-磷酸酰胺转移酶从而导致 Neuro2A 细胞(小鼠来源的神经母细胞)中 O-GlcNAcylation 减少，进而引起 LC3B-II 上调和 SQSTM1/p62 下调，通过促进自噬流减少了这些细胞中由突变的 HUNTINGIN 外显子 1 片段导致的细胞毒性[96]。

3.2.3. 泛素化修饰调节自噬

自噬体膜的延伸涉及了自噬蛋白 ATG8/LC3 和 ATG12 的泛素样反应。E1 样蛋白 ATG7 激活 ATG8/LC3 和 ATG12，然后分别通过 E2 样蛋白 ATG3 和 ATG10，分别与 phosphatidylethanolamine (PE) 和 ATG5 结合。在一个类似 E3 样活性的过程中，ATG16 与 ATG12-ATG5 结合并刺激 ATG8/LC3-PE 结合。泛素化作用，通过结合 8-kDa 泛素到蛋白的赖氨酸残基，能调节自噬活性。MTORC1 调节子 DEPTOR、ULK1、BCL-2、BECN1 和 BNIP1 能被泛素化。在富含生长因子的条件下 SCF (Skp-cullin-F-box protein) 泛素化 DEPTOR，抑制 DEPTOR，释放 MTORC1，减少自噬[97] [98]。ATG4B 泛素化作用是通过 RING finger protein 5 (RNF5)，导致 ATG4B 的泛素化降解，反过来影响 LC3 的产生和自噬的抑制[99]。通过 TRAF6 (TNF receptor-associated factor 6)泛素化 ULK1 稳定激活的 ULK1 复合体，因此促进自噬[100]。通过 TRAF6 泛素化 BECN1，促进 TLR4 依赖的自噬[101]，而 PARKIN 泛素化 BCL2 促进了与 BECN1 相互作用导致自噬的抑制[102]。 通过 NEDD4 (neural precursor cell-expressed developmentally downregulated 4)泛素化 BECN1 促进 BECN1 降解，抑制自噬[103]。通过线粒体定位的 E3 连接酶 RNF185 泛素化 BNIP1 (BCL2/adenovirus E1B 19-kDa interacting protein 1)促进 SQSTM1/p62 和 LC3 的招募[104]。

UBR4 (Ubiquitin protein ligase E3 component N-recognin 4)是内胚层派生的，在卵黄囊的自噬激活细胞中高表达，在胚胎发育中有重要作用。证据显示 UBR4 促进细胞内细胞器和大分子被递送到自噬体，但 UBR4 的底物有哪些分子，以及它的泛素连接酶活性在这个过程中的发生机制目前还不明确[105]。

核糖体自噬(ribophagy)是在饥饿状态时，依赖 LTN1 (一个 60S 核糖体相关的 E3 连接酶)的迅速减低，随后引起核糖体蛋白 RPL25 泛素化减少的过程[106]。

线粒体自噬(mitophagy)也被 PARKIN 介导的泛素化调节[107] [108]。PARKIN 是一个 E3 泛素连接酶，可以在去极化的线粒体上泛素化 MFN1 和 MFN2，然后降解，进而促进线粒体自噬[73]。在 HeLa 和 SHSY5Y 细胞中，PARKIN 也泛素化 VDAC1，在 HeLa 细胞中 PARKIN/PINK1 介导的线粒体自噬需要 VDAC1 分子[62]。在鼠胚胎成纤维细胞 mouse embryonic fibroblasts (MEFs)中，VDAC1 单泛素化不负责线粒体去极化诱导的线粒体自噬[109]，然而，VDAC 1、2 和 3 都缺乏时，线粒体自噬在 MEFs 中受到损害[110]。

有证据表明，在应对线粒体膜的去极化时，包括 TOM20 和 FIS1 在内的线粒体蛋白池会被 PARKIN 和泛素化蛋白酶体介导的机制所降解，这两种机制在线粒体自噬中都有重要作用[111]。PARKIN 依赖的泛素化蛋白亲和纯化(ubiquitylome)近来已经被进一步的扩展到涉及蛋白酶体装配、新陈代谢和凋亡的蛋白[112]。目前线粒体蛋白广谱的泛素化在调节线粒体自噬中彼此间是协同的还是拮抗的仍然未知。近来发现经 PARKIN 泛素化是由线粒体去泛素化酶 USP30 的反向作用所调节[113]。除了 PARKIN 以外，可能还有其它的泛素化连接酶参与线粒体自噬的蛋白修饰。MARCH-V (Membraneassociated RING-CH-V) 被证实是与 MFN2 相互作用的线粒体泛素化连接酶，在 COS7 细胞中泛素化 DRP1，并且过表达 MARCH-V 能增多长管状线粒体。MARCH-V 也能以 MFN1 依赖的方式促进线粒体的延伸，在应对应激反应时，MFN1，而不是 MFN2 在 HeLa 细胞中诱导线粒体延伸[114]。目前还不清楚 MARCH-V 是如何参与了线粒体自噬调节。

泛素化结合蛋白借助其 LIR 在运送泛素化蛋白到自噬体的过程中发挥重要作用。这些泛素化结合蛋白包括 SQSTM1/p62、NBR1 (neighbor of BRCA1 gene 1)、组蛋白脱乙酰酶 6 HDAC6 (histone deacetylase

6)、NDP52 (the nuclear dot protein 52 kDa)和视神经蛋白 OPTN (optineurin) [115] [116] [117] [118]。SQSTM1/p62 也与 TRIM50、TRAF6、MURF2 和 KEAP1 相互作用，促进靶蛋白的泛素化和它们后续的降解[119] [120] [121] [122]。OPTN 和 NDP52 在异源自噬(xenophagy)中有重要作用[123]。BH3-only 家族蛋白 NIX [124] [125]、BNIP3 (BCL2/adenovirus E1B 19-kDa interacting protein 3) [126]和 FUNDC1 (FUN14 domain containing 1) [127]通过识别包含广泛的泛素化外部膜蛋白的线粒体，在线粒体自噬中发挥重要功能。

3.2.4. 乙酰化修饰调节自噬

自噬途径的调节组分也被赖氨酸乙酰化作用所调控。营养饥饿迅速地耗尽乙酰辅酶 A，导致下游胞浆蛋白乙酰化，与自噬的增强相关[128] [129]。在果蝇脑中敲除乙酰辅酶 A 合成酶也显示自噬和寿命延长。组蛋白和非组蛋白的乙酰化和去乙酰化已被报道在自噬调节中有重要作用。由饥饿或 MTORC1 的抑制引起的细胞保护性自噬，导致组蛋白乙酰化转移酶 hMOF/KAT8/MYST1 的下调和随之发生的 H4K16ac (histone H4 lysine 16)的去乙酰化。当 chromatin immunoprecipitation-sequencing (ChIP-seq)定量分析显示乙酰化的 H4K16 (H4K16ac)减少时，用 global run-on-sequencing assay 测序分析结果显示，编码 LC3 和 ULK1 在内的 55 个自噬相关基因表达水平发生改变[130]。

饥饿诱导的微管高度乙酰化也促进自噬和细胞存活。在这种情况下，微管高度乙酰化由 a-微管蛋白乙酰转移酶 a-tubulin acetyltransferase-1 (aTAT-1/MEC-17)介导，其活性由 p-300 抑制，由 AMPK 激活[131]。关于微管高度乙酰化如何促进自噬尚不清楚，但是微管乙酰化可能影响了它与微管相关蛋白的相互作用，包括 LC3 蛋白家族。

自噬蛋白的乙酰化在自噬流中也发挥重要作用。乙酰转移酶 p-300 可以乙酰化 ATG5、ATG7、LC3 和 ATG12 蛋白，从而抑制自噬[132]。在剥夺了生长因子的细胞中，糖原合酶(GSK-3)在乙酰转移酶 TIP60 86 位点丝氨酸磷酸化，导致其激活。TIP60 反过来通过乙酰化激活 ULK1，在自噬的诱导中有重要作用[133]。此外，LC3B-II 在 HeLa 细胞中血清饥饿诱导的自噬中显著去乙酰化。组氨酸脱乙酰激酶 HDAC6 被 HDAC6 抑制剂 tubacin 抑制，或被 *HDAC6* siRNA 敲减，会导致 LC3B-II 乙酰化增强，伴有 SQSTM1/p62 降解，提示 LC3B-II 乙酰化状态与自噬性清除相关[134]。

Liu W 科研团队报道[135]，脱乙酰酶 Sirt1 能够使 LC3 去乙酰化(去乙酰化位点为 K49 和 K51)，导致 LC3 与核蛋白 DOR 相互作用，与 DOR 一起返回到胞浆，进而与 ATG7 及其它自噬分子结合并与磷脂酰乙醇胺结合到自噬前体膜上，去乙酰化的 LC3 与自噬因子的结合改变了 LC3 从胞核到胞浆的分布，因此，乙酰化－去乙酰化循环使得 LC3 能够有效地以活化的形式从胞核到胞浆进行重新分布，在胞浆中对自噬发挥关键作用使得细胞更好地应对外部营养缺乏的情况。

SIRT1 (哺乳动物去乙酰酶)可以去乙酰化几种 ATG 蛋白，如 ATG5、ATG7 和 LC3。*SIRT1* 缺失能引起自噬损伤导致 SQSTM1/p62 水平升高和自噬体形成抑制[136]。

靶蛋白的翻译后修饰也能调节它们的自噬性清除。HDAC1 的抑制或 CBP 介导的乙酰化的激活显示突变的 HUNTINTIN(HTT)的乙酰化增多、清除增多以及神经毒性减少[137]。这些研究显示乙酰化在多个水平影响了自噬。

3.2.5. 硫醇修饰调节自噬

氧化还原反应敏感蛋白在半胱氨酸残基上(R-SH)有高度反应的硫醇组[138] [139]。在关键的半胱氨酸残基上硫醇修饰已被认为是自噬－溶酶体途径的调节机制[140] [141]。研究表明重组体 ATG4 的活性由接近活性位点(Cys81)的半胱氨酸残基的 H_2O_2 修饰所调节[29]。在 PARKIN 中有两个高度保守的半胱氨酸，其中任何一个半胱氨酸发生突变而功能缺失，均可导致 PARKIN 可折叠性和活性丧失以及线粒体自噬功

能丧失，这些功能的缺失都与帕金森病密切相关[62] [142]。

PARKIN 半胱氨酸(Cys59、Cys95 和 Cys182)也能被 H_2S 所修饰，导致疏水合作用 sulfhydration，能拮抗相同残基的致病性亚硝化作用，竞争性提高 PARKIN 活性和神经保护性效应[143]。相似地，另一个帕金森疾病相关蛋白 DJ-1 与线粒体自噬相关，DJ-1 的抗氧化性能以及其转位到线粒体都需要一个重要的半胱氨酸残基(Cys106) [144]。 这些研究显示半胱氨酸在适当的自噬功能维护中有重要作用，增多的反应产物能修饰重要的自噬蛋白以改变它们的功能。

4. 结论和未来的方向

自噬蛋白的翻译后修饰在细胞自噬过程中发挥重要作用。作为大部分包含可修饰的丝氨酸、苏氨酸、赖氨酸或半胱氨酸残基的蛋白，在应对营养缺乏、生长因子剥夺、高氧、低氧等应激状态下，常会发生辅助修饰，从而决定生物学活性。这方面的研究还有许多问题有待阐明，如在自噬蛋白中翻译后修饰是如何影响经典自噬或选择性自噬流的，翻译后修饰的细胞、组织特异性调节是如何获得的。理解自噬蛋白中哪个氨基酸残基被修饰，以及证实这些修饰氨基酸在相关疾病的表达状态，将会为疾病的诊断和治疗提供重要的靶点[145]，具有重要的理论和应用价值。

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