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mTOR核心通路在线粒体自噬过程中的调控作用

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摘 要:线粒体自噬(mitochondrial autophagy,mitophagy)是细胞内高度保守的质量控制机制,通过选择性清除受损或功能障碍的线粒体,维持线粒体功能完整性及细胞内稳态。哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)复合体(mTORC1/2)是细胞生长和代谢的核心调控枢纽,不仅参与细胞增殖调控,更通过整合多种信号通路和多种关键小分子蛋白,在介导线粒体自噬中发挥关键作用。研究表明,mTORC1/2通过双向调控mTOR-AMPK和PI3K-AKT-mTOR信号通路,促进作用域UNC-51样激酶1(ULK1) 复合体、转录因子EB(TFEB)等关键效应分子的激活,从而精细调控线粒体自噬的启动、包裹、溶酶体融合及降解等关键环节。值得注意的是,相较于mTORC1的深入研究,mTORC2在线粒体自噬中的调控机制仍存在显著认知空白。本综述系统阐释mTORC2影响线粒体自噬的最新进展,同时探讨其与mTORC1的功能协同性及在代谢应激条件下的双向调控特性,为深入解析mTOR信号网络在线粒体质量控制中的多维调控机制提供新视角。

关键词:线粒体自噬;mTOR;信号通路;调控机制;细胞功能
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The regulatory role of mTOR core pathways in mitochondrial autophagy

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Abstract: As a selective autophagy process, mitophagy is crucial for clearing dysfunctional mitochondria and maintaining cellular energy homeostasis and survival. Its core mechanisms are primarily categorized into ubiquitin-dependent pathways, such as the classic PINK1/Parkin pathway, and ubiquitin-independent pathways involving receptors like BNIP3. mTOR, a central kinase that senses nutrients, energy, and growth factors within the cell, forms two functionally distinct complexes, mTORC1 and mTORC2. These complexes work in concert to bidirectionally regulate each stage of mitophagy—from initiation and phagophore formation to final fusion with lysosomes for degradation. The article is primarily divided into two main sections, respectively discussing the topic from the perspectives of core mTOR-related signaling pathways and small molecular proteins. Among these, two representative mTOR-associated pathways are highlighted: the mTOR-AMPK-ULK1 pathway and the PI3K-AKT-mTOR pathway. The former is involved in autophagy initiation and serves as a key mechanism through which cells sense energy status and regulate the onset of autophagy. Under energy-sufficient conditions, it inhibits the formation of the initiation complex, thereby suppressing autophagy. The latter primarily responds to growth factor signals and generally functions to inhibit autophagy, playing an indispensable role in maintaining basal mitochondrial quality. Beyond these classic pathways, mTOR also precisely regulates specific stages of mitophagy by influencing a series of particular proteins. Proteins involved in regulating autophagosome formation and maturation include p300, WIPI2, UVRAG, and Pacer. Primarily under nutrient-rich conditions, these proteins enhance mTORC1 activity, thereby activating the expression of downstream cytokines to inhibit autophagosome formation. Additionally, TFEB, the master regulator of autophagy-lysosome gene expression, is a core protein governing lysosome biogenesis, and its activity is tightly controlled by

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mTORC1. Studies have shown that activating TFEB can promote mitophagy and exhibits therapeutic potential in disease models such as cancer. Based on the current research on mTOR, the following recommendations can be proposed: First, as an integrative hub within the mitochondrial quality control network, mTOR serves as a dynamic, multi-tiered regulatory nexus capable of achieving spatiotemporally precise regulation of mitophagy initiation, progression, and lysosomal degradation capacity. Future studies should place greater emphasis on the synergistic and antagonistic interplay between mTORC1 and mTORC2 in specific physiological and pathological contexts, as well as their crosstalk with stress signals from other organelles. Second, targeting the mTOR regulatory network represents a potential strategy for treating diseases associated with mitochondrial dysfunction. Given that the mTOR pathway is dysregulated and impacts mitophagy in a variety of disorders—including neurodegenerative diseases, metabolic disorders, and cancers—drug development aimed at precisely modulating this network holds considerable promise. Lastly, efforts should be strengthened to bridge the gap between fundamental mTOR-related mechanisms and clinical research, thereby offering more novel insights for clinical diseases. For example, delving deeper into atypical mitophagy pathways mediated by factors such as OPTN and ZDHHC13, and elucidating how these novel mechanisms interact with mTOR signaling, will deepen our understanding of the plasticity of mitochondrial quality control. This review systematically elucidates recent advances regarding the impact of mTORC2 on mitophagy, while exploring its functional synergy with mTORC1 and its bidirectional regulatory properties under metabolic stress conditions. It aims to provide novel perspectives for an in-depth analysis of the multifaceted regulatory mechanisms of the mTOR signaling network in mitochondrial quality control. Furthermore, it seeks to offer critical theoretical foundations and identify new drug targets for developing precision medicine strategies aimed at restoring mitochondrial quality.

Key words: mitophagy; mTOR; signal pathway; regulation mechanism; cell function

mTOR是丝氨酸/苏氨酸蛋白激酶家族的成员，在细胞内发挥促进合成代谢、维持能量状态的作用，通过其参与的两个复合体，即mTOR复合体1（mTORC1）和mTOR复合体2（mTORC2），mTOR在调控线粒体自噬的启动、受损线粒体清除与降解中发挥关键作用[1]。其中，mTORC1抑制自噬起始，而mTORC2通过代谢应激响应双向调节线粒体质量控制，两者协同维持细胞稳态，其精确互作机制仍是研究焦点。与mTOR相关的多条信号通路，如mTOR-AMPK-ULK1、PI3K-AKT-mTOR等，都与细胞生长、受体表达和疾病发生相关。线粒体自噬是一种细胞自噬系统对线粒体的靶向吞噬和破坏的过程，常在活性氧（reactive oxygen species，ROS）、营养缺乏、细胞衰老等应激作用下发生[2]，对维持细胞稳态有重要意义。线粒体自噬包括去极化、自噬体包裹、与溶酶体融合、被溶酶体降解四个阶段[3]。

目前较为明确的线粒体自噬机制主要分为泛素依赖性途径和非泛素依赖性途径[4]（图1）。前者依赖于线粒体表面蛋白的泛素化，由磷酸酯酶与张力蛋白同源物（PTEN）诱导蛋白1（PINK1）和乳头状蛋白

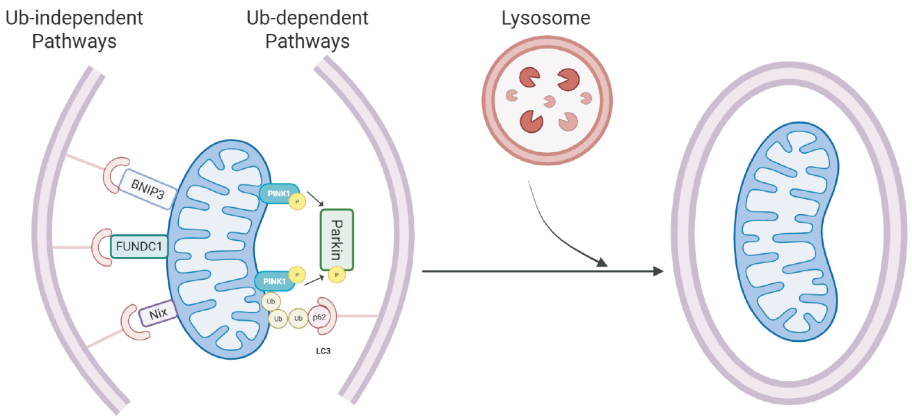

图1 传统的线粒体自噬机制：泛素依赖性途径和非泛素依赖性途径
（创建于BioRender. https://BioRender.com/kvy6kh2）

Figure 1 Traditional mitophagy mechanisms: the ubiquitin-dependent pathway and the non-ubiquitin-dependent pathway (Created in BioRender. https://BioRender.com/kvy6kh2)

(Parkin)相关的PINK/Parkin通路介导[5]：当膜电位受损时，PINK1在线粒体外膜上稳定聚集、Parkin蛋白被激活，空间构象发生改变，Parkin可介导线粒体外膜蛋白的泛素化修饰，PINK和 Parkin二者相互作用共同调节自噬过程[6]。而非泛素依赖性途径则直接募集自噬受体蛋白，如Nip3样蛋白X(NIX)、BCL2相互作用蛋白3样(BNIP3L)受体、BCL2相互作用蛋白3(BNIP3)受体、含有FUN14结构域1(FUNDC1)受体等[4,7]，使得自噬小体完成吞噬过程。

在此背景下，Chen等[8]研究了如何从药理学的角度影响星形胶质细胞中的线粒体自噬，发现使用烟酰胺核苷(nicotinamide nucleoside，NR)和二甲双胍(metformin)能够通过调节PINK/Parkin通路和mTOR-AMPK通路的活性，从而激活线粒体自噬过程，以此来挽救polg突变的星形胶质细胞。基于PINK/Parkin通路和mTOR/AMPK通路的关联，mTOR和线粒体自噬之间的关系值得更深一步研究。

线粒体自噬作为典型高度保守的、对细胞稳态维持有重要意义的细胞进程，同样受多种复杂的mTOR通路调控。mTORC1和mTORC2在代谢应激下通过AMPK和AKT等途径双向调节自噬强度(图2)，维持线粒体质量动态平衡[1]。其中，mTORC1 是调控自噬的极具潜力的靶标，全程调控线粒体自噬。去极化过程是线粒体自噬的初始阶段，并且是触发线粒体自噬的关键步骤，会抑制呼吸作用。而呼吸作用抑制带来的能量供应不足会影响mTOR和腺苷酸活化蛋白激酶(adenosine 5-monophosphate (AMP)-activated protein kinase，AMPK)的响应[9]，通过整合营养与能量信号，调控ULK1复合物活性及转录因子EB(transcription factor EB，TFEB)介导的溶酶体生成，协调线粒体自噬的启动、吞噬体形成与降解过程。自噬小体的形成与p300和WD重复结构域，磷酸肌醇相互作用 2(WIPI2)相关，其成熟与Pacer、UVRAG高度关联，而这四种蛋白都受mTOR调节[10]。除小分子蛋

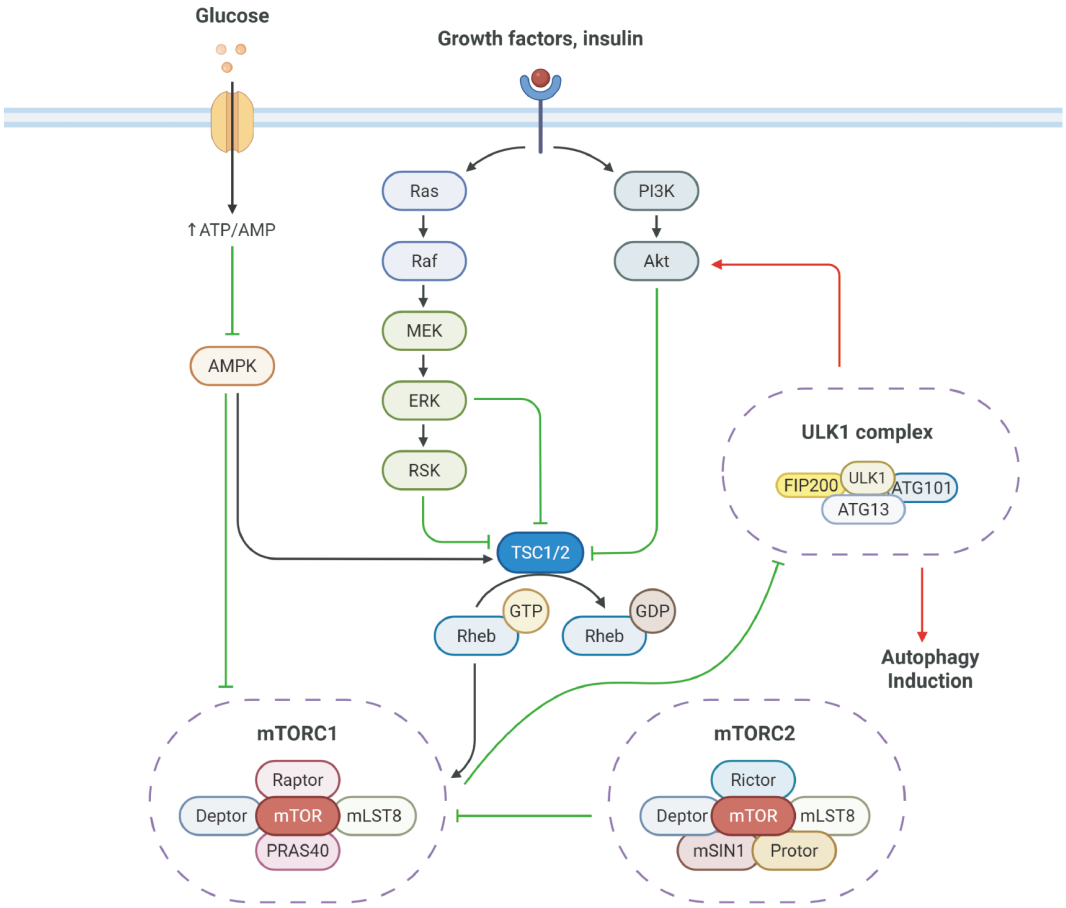

图2　mTOR对相关信号通路及小分子蛋白的调控作用(创建于BioRender. https://BioRender.com/xbeopqo)

Figure 2　Regulation of mTOR on related signaling pathways and small-molecule proteins (Created in BioRender. https://BioRender.com/xbeopqo)

白外,自噬小体形成同样受一个被称为吞噬体组装位点(phagocytic assembly site,PAS)的多聚体结构所调控,它整合了包括ULK、ATG13、FIP200等在内的众多通路蛋白,mTOR通过直接作用于通路蛋白介导线粒体自噬[11]。溶酶体这一关键细胞器的生物合成与TFEB高度相关,而TFEB同样受到mTOR相关信号的调控[12],它的激活往往抑制自噬的进行[13];而mTORC2则主要通过作用于磷脂酰肌醇3-激酶(PI3K)下游的重要靶蛋白AKT(即蛋白激酶B protein kinase B,PKB)来影响线粒体自噬。不同的mTOR通路由于其靶向蛋白的不同,对线粒体自噬的影响阶段也有所不同。

本文将从中选取两条与mTOR有关的代表通路——mTOR-AMPK-ULK1和PI3K-AKT-Wnt-mTOR,以及与mTOR相关的小分子蛋白TFEB、Pacer、UVRAG、P300、WIPI2,针对其对线粒体自噬的调控机制和相关研究进展进行综述。

1 信号通路

1.1 mTOR-AMPK-ULK1通路与自噬启动

mTOR在通路中主要起着感知环境营养含量变化的作用,能量充足的时候被激活,促进细胞内新陈代谢,增强线粒体的呼吸作用,促进生长发育。AMPK是真核细胞内调控能量稳态的重要激酶,为细胞正常生理活动所需的能量提供了基本保障,促进产能反应的发生,抑制相应的耗能过程[14]。鱼藤酮和抗霉素A是线粒体呼吸链复合物抑制剂,其诱导的线粒体自噬需要AMPK参与[15]。mTOR与AMPK的作用相互拮抗,mTOR-AMPK信号通路是目前已知的与线粒体自噬过程较为密切的信号通路,它依赖于线粒体膜上的蛋白[16],主要与自噬的启动过程有关。

ULK1是mTOR-AMPK-ULK1介导的营养感知通路中重要的一环,通过形成ULK1复合物调节自噬启动。ULK1复合物通常由ULK1蛋白和ATG13、ATG101、FIP200相互作用形成[17]。利用ULK1敲除细胞系和非磷酸化突变体的重组细胞可证实,在营养匮乏的情况下,mTORC1的抑制作用消除[18],并被释放到受损的线粒体中,说明ULK1的磷酸化对线粒体自噬和细胞存活十分重要。而在营养充足时,活化的mTORC1直接结合并磷酸化ULK1,阻断其与自噬必需蛋白ATG13和FIP200形成复合物;AMPK也可以通过抑制ULK1上至少4个相关位点(Ser52、Ser317、Ser467、Ser777)的磷酸化,阻止自噬体膜起始,最终抑制自噬启动[19]。mTORC1在细胞内能量充足时抑制ULK1复合物的形成[20],抑制线粒体自噬的启动;如果细胞内能量不足,细胞需要通过线粒体自噬来清除多余线粒体减少能量消耗[21],此时mTOR-AMPK通路则会向着提高细胞内能量水平的方向调控[22]:被激活的AMPK抑制了磷酸化的mTOR1,导致其与PAS分离。同时,在AMPK作用下,ULK1的部分特异性磷酸化被解除[23],而其他特定位点发生磷酸化[24],特别是ULK1蛋白的Thr180位点自磷酸化[10]。此外,FIP200、ATG等其他通路蛋白也磷酸化,进而形成了活化的ULK1复合物,促进线粒体自噬的启动[25]。一旦ULK1复合物定位完成,即到达自噬的形成位点,自噬过程便得以启动。这一磷酸化依赖的调控机制实现了细胞在能量充足时限制自噬的精确控制。

目前包括代谢类疾病、神经系统疾病在内的很多疾病的创新疗法都是基于mTOR-AMPK-ULK1信号通路对自噬的影响而开发的。如有研究表明,五味子苷B、紫檀芪可以通过mTOR/AMPK信号通路诱导自噬,减轻肝脂肪变性并促进脂肪酸氧化,从而缓解非酒精性脂肪肝(non-alcoholic fatty liver disease,NAFLD)[26,27]。Zheng等[28]致力于探索胶质母细胞瘤的新型疗法,发现青藤碱酯衍生物可通过AMPK/mTOR/ULK1通路诱导线粒体凋亡和自噬。而Wang等[29]发现厚朴酚通过激活AMPK/mTOR/ULK1通路促进自噬,可改善阿尔兹海默症(Alzheimer's disease,AD)病理和认知能力下降。

1.2 PI3K-AKT-mTOR通路与自噬抑制

PI3K-AKT-mTOR通路是真核细胞中影响mTOR活性的又一关键通路。在这条通路中,PI3K调节能量代谢,参与细胞内各种生物学过程[30];AKT参与调控细胞周期、自噬和凋亡[31];mTOR则是调节自噬的重要信号分子,可被AKT 激活。PI3K激酶作为信号通路中的上游分子,可被酪氨酸激酶受体、G蛋白偶联受体或RAS样蛋白激活,从而成为自噬信号级联的触发器。PI3K被激活后,将细胞膜上的二磷酸磷脂酰肌醇(phosphatidylinositol diphosphate,PIP2)转化为三磷酸磷脂酰肌醇(phosphatidylinositol trisphosphate,PIP3)。PIP3是磷脂酰肌醇依赖性激酶1(phosphatidylinositol dependent kinase 1,PDK1)的重要锚点,促进AKT的招

募,并在特定位点磷酸化下游AKT,引发AKT的激活[32]。激活的AKT抑制一种富含RAS同源物的GTP酶激活蛋白TSC1或TSC2,导致它们与溶酶体分离,破坏溶酶体的功能结构,最终激活了Rheb,这是一种结合GTP的mTORC1激活剂,至此整个通路完成了通过AKT依赖性磷酸化抑制TSC1/2导致mTORC1激活的目标[19],进而抑制自噬启动和破坏溶酶体完整结构,使其无法发挥清理和维持内环境的作用。

mTORC2在线粒体自噬中的作用也通过PI3K-AKT-mTOR信号通路实现,主要通过调控其下游信号通路,尤其在应激条件下具有双向调节功能:营养充足时抑制自噬以维持线粒体结构和功能,而在应激或损伤条件下,mTORC2活性降低可促进受损线粒体的清除。这种动态调控使mTORC2成为线粒体调控的关键节点,其作用机制涉及代谢感知、转录调控及线粒体动力学网络的整合。首先,mTORC2通过磷酸化AKT的Ser473位点完全激活AKT,后者进一步磷酸化FoxO转录因子(如FoxO1/3),抑制其核转位,从而减少促线粒体自噬基因(如BNIP3、NIX)的表达。在营养充足时,这一机制维持线粒体稳态并抑制不必要的自噬。其次,mTORC2通过调控SGK-1(与AKT同源的AGC激酶)影响FoxO3活性,SGK-1的激活可直接抑制ULK1表达并抑制线粒体自噬的启动和执行。此外,mTORC2与AMPK存在交互作用,在能量应激时,AMPK通过抑制mTORC2活性解除对FoxO的抑制,从而激活线粒体自噬。研究还表明,rictor是mTORC2的核心骨架,是mTORC2完整性和功能的关键,在基础状态下能够稳定住线粒体使其不发生自噬,而当rictor被敲除后会导致线粒体功能紊乱并激活PINK1-Parkin通路,提示mTORC2通过维持线粒体完整性间接调控自噬。

近年来,众多研究揭示PI3K-AKT-mTOR信号通路在调节肾脏细胞的自噬功能方面扮演至关重要的角色。研究者们常常聚焦于这一通路,以保护细胞线粒体的稳定性,并借此治疗临床上的某些特定疾病[33]。脂质代谢异常导致的异位积聚是糖尿病肾病(diabetic nephropathy,DN)的主要特征之一,过多的脂质会导致活性氧产生增加,引发线粒体功能障碍[34]。Zhao等[35]发现益肾化湿颗粒能够显著降低PI3K/AKT/mTOR信号通路的活性,参与肠-肝轴调节DN的脂质代谢,这一发现为干预糖尿病并发症提供新的思路;无独有偶,慢性肾小球肾炎(chronic glomerulonephritis,CGN)是终末期肾脏疾病的主要病因之一,在传统中药的应用层面,Liu等[36]采用《伤寒论》中以白树内酯等为主要活性成分的真武汤,证明其能通过抑制PI3K-AKT-mTOR通路和上调AMPK通路来诱导细胞的线粒体自噬。同时使用真武汤联合PI3K激动剂胰岛素样生长因子-1(insulin-like growth factor-1,IGF-1)仍然可以明显下调PI3K-AKT-mTOR通路,进一步表明了真武汤能抑制该通路,从而改善肾脏线粒体功能。

除此之外,与PI3K-AKT-mTOR通路有关的干细胞疗法也正被应用于治疗多种疾病[37]。目前广泛研究的骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMSCs)具有强大的增殖能力和多向分化潜能,免疫调节功能也是它的一大亮点[38],然而提取过程中不可避免的损失造成可用数量较少,限制了其临床应用。于是Li等[39]着力于探索数量更为丰富、更易获取且对供体危害小的毛囊间充质干细胞(hair follicle mesenchymal stem cells,HF-MSCs)在溃疡性结肠炎(ulcerative colitis,UC)方面的应用,发现缺氧诱导的衍生外泌体(hypoxic-induced tubular exosomes,Hy-Exos)通过旁分泌作用,被特定细胞摄取后促进其活力和增殖恢复,促进抗炎因子的表达。PI3K-AKT-mTOR通路在这个过程中调节氧化应激和炎症发展,并参与哺乳动物自噬的调控。该通路信号上调,而Hy-Exos恰好逆转了这一变化,减少炎症反应的发生,促进线粒体融合,维持线粒体动态稳定,最终增强线粒体自噬减轻UC。虽然干细胞外泌体治疗效果优势明显,但其在临床应用上的报道还相对尚少,在临床转化过程中的适用性和潜力也还需要重点探索,同时由于毛囊干细胞移植后存活率较低[40],通常在对mTOR通路产生调控作用之前就已经失活,因此对其大规模临床应用还需要与干细胞治疗相结合,以及开展更多方面的研究。

2　小分子蛋白

mTOR是线粒体自噬相关信号通路中的关键一环,这些通路通过影响mTOR的活性来实现对线粒体自噬过程的调控。除了这些传统的mTOR调控通路外,线粒体自噬还能够被一些特殊的小分子蛋白独立调节。然而,参与线粒体自噬启动的调控蛋白众多,相互作用复杂,目前所研究的AMPK、AKT等

也可能仅是冰山一角。在寻找参与自噬启动的蛋白过程中，Hamasaki团队[41]发现ZDHHC13酶可以对ULK1进行棕榈酰化修饰，通过抑制mTORC1的活化修饰作用，招募ATG13等蛋白促进上游ULK1复合物的形成和定位，最终启动自噬。同时，在内源性途径诱导细胞凋亡过程中，线粒体膨胀导致的线粒体内膜暴露、线粒体内膜蛋白泛素化也会介导线粒体自噬的启动，如Saunders等[43]发现由线粒体内膜蛋白OPTN独立介导的非常规线粒体自噬方式，区别于常规的泛素依赖的PINK/Parkin信号通路，它的作用途径既不以结合FIP200开始，也不需要ULK1/2激酶的参与，而是利用TBK1激酶来直接结合III类PIK3复合物来启动线粒体自噬，揭示了自噬途径的可塑性。线粒体自噬背后的调节网络还有更多未知与挑战有待探索，而其研究成果可以为相关疾病的预防和治疗提供新的思路。为了填补线粒体自噬非传统机制的空白，研究者们在探索过程中，多是以mTOR为核心，以线粒体自噬的一般过程为线索，选取了与之高度相关的四种蛋白，从而为线粒体自噬的信号转导过程研究提供新的思路。

2.1 调节自噬小体形成与成熟的相关蛋白

mTOR形成的两种复合物mTORC1和mTORC2中，mTORC2主要通过激活AKT、mTOR1间接影响线粒体自噬，而mTORC1则是影响线粒体自噬的主要复合物，主要起到抑制自噬的作用。通过对mTORC1上游和下游的研究，充分考虑研究的可行性和目的，我们最终选择了p300、WIPI2、UVRAG、Pacer四种小分子蛋白，其中前两者与自噬小体的形成有关，而后两者与自噬小体的成熟有关[10]。

乙酰转移酶p300是靶向mTOR1的上游重要调节因子，它在mTOR-AMPK信号通路同样发挥重要作用，通过定位而非活性的改变调控mTOR1的活性[44]。在营养充足条件下，p300从细胞核转位至细胞质，乙酰化mTORC1的重要组件raptor，促进mTORC1的激活，抑制自噬。在饥饿状态下，AMPK磷酸化p300，诱导p300进入细胞核，从而减少raptor的乙酰化，抑制mTORC1并激活自噬[45]。

有些蛋白质既能形成复合物通过非传统途径调控线粒体的自噬，也能够通过已明确的信号转导途径发挥作用，如WIPI2是自噬体合成的关键蛋白。WIPI2可与VCP-UFD1-NPLOC4复合物、ATG12-ATG5-ATG16复合物相互作用，形成的复合物被招募至受损的线粒体，介导泛素化的线粒体外膜蛋白降解、自噬体的合成和线粒体自噬的发生[46,47]。同时，WIPI2和PI3K1复合体的形成高度相关，其聚集受到PI3KC1的亚基Rubicon的介导[48]。PI3KC1在自噬体生物发生相关的膜结构上生成磷脂酰肌醇3-磷酸(PI3P)，而WIPI2能够结合PI3P，进而介导线粒体自噬[49]。在体外激酶反应和质谱分析中，研究人员发现mTORC1可通过降解WIPI2抑制线粒体自噬：WIPI2的Ser395位点是mTORC1的直接磷酸化底物，这种磷酸化作用增强了WIPI2与E3泛素连接酶Huwe1的相互作用，促进WIPI2的泛素化和降解[50]。

紫外线辐射抗性相关基因产物(UV radiation resistance-associated gene product，UVRAG)与线粒体自噬的发生也存在一定的相关性，能够介导自噬小体的成熟和自噬体与溶酶体的融合[51]。但不同于前文所提及的已有相关明确机制的小分子蛋白，UVRAG在不同细胞中对线粒体自噬的调控作用仍需进一步探索。在U2-骨肉瘤细胞(U2OS)中，通过免疫印迹法只检测到了UVRAG对内质网自噬的调控作用，未检测到其与线粒体自噬的关联[52]；但在白血病细胞K652中，其对线粒体自噬有明显的增强作用[53]：通过参与形成PI3KC3-II，催化PI3P产生，参与线粒体自噬。RUBICON(Rundomain Beclin-1-interacting and cysteine-rich domain-containing protein)是一种自噬负调节因子，是与UVRAG功能相互拮抗的关键蛋白，mTORC1结合并磷酸化UVRAG，从而正向调节UVRAG与RUBICON的结合，可拮抗UVRAG介导的自噬体成熟过程，这也将mTORC1的作用范围拓展到自噬的末期。

UVRAG相关自噬增强蛋白(protein associated with UVRAG as autophagy enhancer，Pacer)是与自噬体成熟相关的另一蛋白，其为脊椎动物特有的自噬调控分子，能被mTORC1共价可逆修饰。一方面，Pacer能直接与PI3KC3复合物中的UVRAG蛋白直接相互作用，从而解除其对Vps34激酶的抑制作用[54]；另一方面，Pacer也能将PI3KC3和HOPS复合物招募到自噬膜泡上，进而促进自噬体和溶酶体的融合。总的来说，mTORC1能够介导Pacer磷酸化、抑制Pacer乙酰化，通过干扰Pacer与Stx17和HOPS复合物的结合抑制自噬体成熟，达到抑制线粒体自噬的效果[55]。

2.2 调节溶酶体发生的相关蛋白与线粒体自噬过程

溶酶体是线粒体自噬过程中最为重要的细胞器

之一。线粒体被自噬小体包裹后形成的线粒体自噬体接下来将会与溶酶体融合[56]，使其内部受损或老化的线粒体充分暴露于溶酶体的酸性环境中，接着溶酶体内丰富的水解酶将降解线粒体，完成对线粒体的清除和回收，维持线粒体平衡和细胞稳态[57]。因此，与溶酶体发生有关的细胞因子或蛋白在整个自噬过程中就显得尤为重要，而mTOR则可以抑制这些基因的转录来间接抑制线粒体自噬。

TFEB属于碱性螺旋-环-螺旋亮氨酸拉链转录因子MiT/TFE家族，在自噬-溶酶体生物发生、细胞能量稳态维持和代谢过程中发挥重要作用，它也被认为是自噬-溶酶体生物发生的主调控因子，可以上调溶酶体发生、融合、降解等活动相关的一系列基因[58]，转录调节控制溶酶体的胞吐等作用。当线粒体应激时，可以mTOR独立的方式激活TFEB，同时Parkin介导的TFEB在线粒体自噬诱导下的核定位也受到自噬相关基因的下游调控[59]。除此之外，TFEB 的过表达会促进线粒体自噬相关因子的表达，如WIPI、VPS11、ATG9B 和LAMP1等(图3)。 Zheng等[61]发现尿素A(urea A，UA)能通过激活肿瘤巨噬细胞中TFEB介导的信号通路来促进线粒体自噬，从而抑制乳腺癌的发展。TFEB作为全方位调控溶酶体的重要因子，在维持健康和治疗疾病方面极具潜力，明确其作用范围并推动其走向临床转化，将成为促进医学技术发展的重要驱动力。

线粒体自噬包括去极化、自噬体包裹、与溶酶体融合、被溶酶体降解四个阶段[3]，mTOR可以通过调节溶酶体发生的相关蛋白在四个过程中发挥动态调控作用。首先，在营养充足时，mTORC1通过抑制TFEB 的核转位[57]，减少溶酶体生物合成相关基因表达，间接影响线粒体损伤标记(如PINK1/Parkin通路)的激活[23]，从而对线粒体自噬起到了系统性的抑制作用。其次，当自噬体膜开始扩展时，活化的mTORC1可以直接磷酸化 ULK1(Ser757)，阻断其与AMPK的结合，抑制ULK1-ATG13-FIP200等复合物的形成[19]，mTORC2则可以通过PKC通路调节细胞骨架重组，影响自噬体膜的扩展。接着，在与溶酶体融合阶段，TFEB的活性被mTORC1抑制，使自噬体与溶酶体的融合过程无法正常进行，延缓了自噬的进程。最后，在被溶酶体降解阶段，mTORC1发挥双向调节作用，一方面，该状态下的mTORC1能够解除其对溶酶体酶合成的抑制作用，增强溶酶体的降解功能；另一方面，也能够调控核糖体S6激酶(RSK)，促进降解产物的再循环利用。

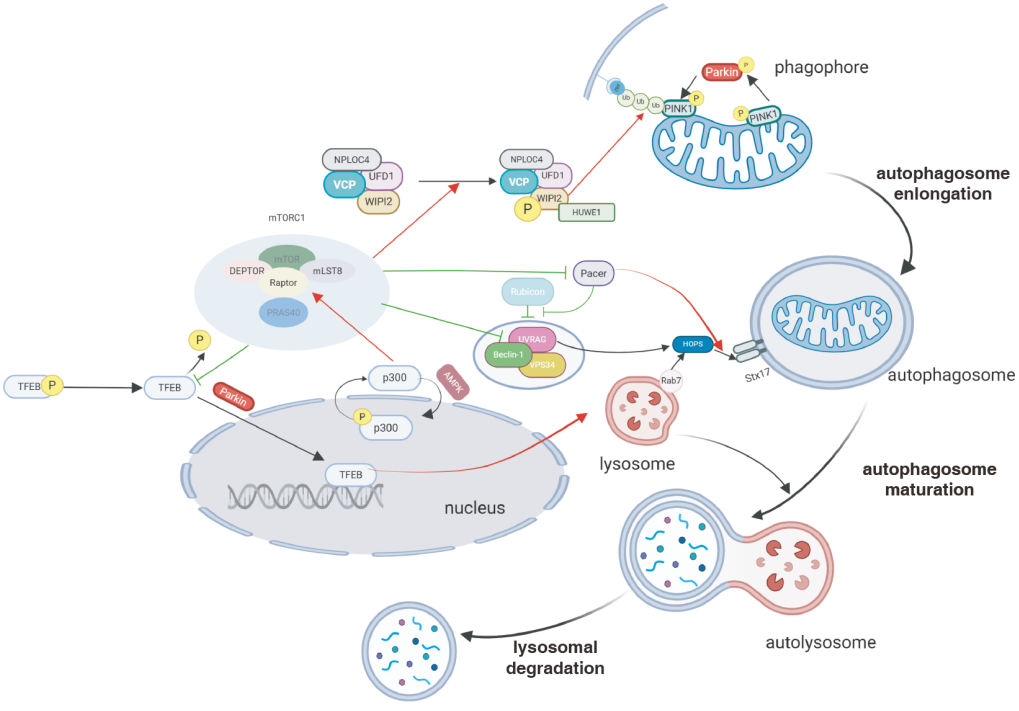

图3　溶酶体及其相关基因在线粒体自噬中的作用(创建于BioRender. https://BioRender.com/e27x918)

Figure 3　Role of lysosomes and related genes in mitophagy
(Created in　BioRender.　https://BioRender.com/e27x918)

3 总结与展望

线粒体自噬去除细胞中受损或衰老的线粒体，并促进功能齐全的线粒体更新循环，以此来维持线粒体稳态和细胞功能，而线粒体自噬过程受损会对机体造成不同程度的损害，从而引发代谢、损伤等相关的疾病。mTOR相关通路已被证实在细胞线粒体自噬过程中具有不同程度的调控作用，通过mTOR-AMPK通路和ULK1蛋白调控自噬小体的生物发生，影响自噬的启动过程；由PI3K-AKT-mTOR通路抑制炎症反应的产生，维持自噬进行；同时调节TFEB等溶酶体发生基因的转录，保证溶酶体的融合和降解。mTOR在自噬过程中主要发挥感受细胞能量水平的作用，能够根据细胞具体的能量状态来决定是否需要抑制自噬或清除多余线粒体。通过加强其核心调控机制的研究，对mTOR相关治疗策略从基础研究转化到临床实践有着重要意义。随着Co-IP、RNAi筛选及RNA-seq分析等技术为研究信号通路提供了便捷途径，mTOR的分子调控机制也逐渐明晰：促进合成代谢并抑制自噬诱导，维持线粒体和细胞内稳态。mTOR信号失调是许多人类疾病的病因之一，用 mTOR抑制剂调节自噬为多种疾病提供了新的治疗策略。随着医学技术日新月异的发展，将其与药物治疗、干细胞治疗等手段相结合，有望在未来攻克癌症、肾脏疾病、神经退行性疾病等重大难题。

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