综　述

DOI：10.3969/j.issn.2095-1264.2024.04.08
文章编号：2095-1264(2024)04-0436-06

自噬泛素样系统在肿瘤中的研究进展★

文志鹏[1,2]，卢　慧[1,2#]，李　琴[3]，聂佳丽[1,2]，樊兴华[1,2]，李　琳[1,2]，杨继红[1,2]，李　明[1,2*]，郑志昌[1,2]
([1]贵州医科大学附属医院 药学部，贵州 贵阳，550004；[2]贵州医科大学药学院，贵州 贵阳，550004；
[3]贵州医科大学附属医院 药物临床试验机构，贵州 贵阳，550004)

摘要：自噬是细胞中一种重要的代谢过程，主要负责蛋白质与受损细胞器的降解，并将分解产物用于细胞能量供应和蛋白质合成。细胞自噬水平在一定范围内维持动态平衡以适应外周环境，自噬过度激活或抑制会造成自噬水平失衡，进而导致包括肿瘤在内的多种疾病的发生。近年来研究表明，自噬对肿瘤的发生发展和放化疗敏感性具有复杂的调控作用，而自噬过程中的关键步骤受到自噬泛素样结合系统的严密调控。本综述将总结近年来有关自噬泛素样结合系统在肿瘤发生、发展与放化疗敏感性中的研究进展，以期为以自噬为靶点的肿瘤研究提供新的视野与策略。

关键词：自噬；肿瘤；化疗敏感性；肿瘤发生
中图分类号：R730　**文献标识码：A**

Research progress of autophagy ubiquitin-like conjugation system in cancer★

WEN Zhipeng[1,2], LU Hui[1,2#], LI Qin[3], NIE Jiali[1,2], FAN Xinghua[1,2], LI Lin[1,2], YANG Jihong[1,2], LI Ming[1,2], ZHENG Zhichang[1,2]*
([1]Department of Pharmacy, the Affiliated Hospital of Guizhou Medical University, Guiyang, 550004, Guizhou, China; [2] College of Pharmacy, Guizhou Medical University, Guiyang, 550004, Guizhou, China; [3]Drug Clinical Trial Institution, the Affiliated Hospital of Guizhou Medical University, Guiyang, 550004, Guizhou, China)

Abstract: Autophagy is an important cellular metabolic process, which is mainly responsible for the degradation of proteins and damaged organelles, as well as the degradation products for energy supply and protein synthesis. Autophagy is finely regulated to adapt the environment. Excessive activation or inhibition of autophagy can lead to the imbalance of autophagy level, and then lead to the development of a variety of diseases including tumors. Recent studies have shown that autophagy has a complex regulatory role in the occurrence and development of tumors and the sensitivity to radiotherapy and chemotherapy, while the key steps in the process of autophagy are strictly regulated by the autophagy ubiquitin-like conjugation system. Our review is aimed to summarize the effect of autophagy ubiquitin-like conjunction system on the occurrence and development of tumors and the sensitivity to radiotherapy and chemotherapy, so as to provide new perspectives and strategies for future tumor research based on autophagy.

Keywords: Autophagy; Cancer; Chemotherapy; Tumorigenesis

★基金项目：国家自然科学基金地区基金(82060667)；贵州省科技厅科技计划项目(黔科合基础-ZK[2021]一般563)。
作者简介：文志鹏，博士，副主任药师，研究方向：胶质瘤。
#共同第一作者：卢慧，硕士研究生，研究方向：胶质瘤。
*通信作者：李明，硕士，主任药师，研究方向：临床药学。

0 前言

细胞自稳态平衡是有机体进行各种生命活动的前提，细胞合成与代谢过程是维持自稳态平衡的关键。细胞可以感知外界环境变化，进而调控自身合成代谢或分解代谢反应速率，帮助细胞适应环境变化[1]。细胞内主要有两个降解系统，分别为泛素-蛋白酶体降解系统与自噬系统，两者相互区别又互有联系。泛素-蛋白酶体系统主要负责细胞内短寿蛋白的降解，该系统降解蛋白前需要一类被称为泛素的小分子蛋白与目标蛋白结合，被标记蛋白随后进入蛋白酶体完成降解。泛素与目标蛋白的结合对于后续目标蛋白的降解至关重要。泛素首先在泛素活化酶（ubiquitin-activating enzyme，E1）的作用下被激活，随后转移至泛素结合酶（ubiquitin-conjugating enzyme，E2），经泛素连接酶（ubiquitin ligase，E3）催化，与目标蛋白连接后进入蛋白酶体完成降解[2-4]。自噬主要负责胞质内长寿蛋白与受损细胞器的降解，其场所为溶酶体。自噬降解产物可用于细胞能量循环供应与蛋白合成，这对于细胞在应激环境中维持自稳态平衡具有重要意义[5-6]。

自噬由三个连续的过程组成，分别是：自噬小体膜生成、自噬小体发育及溶酶体融合，其中自噬小体发育与成熟是关键调控步骤[7]。自噬过程受多种信号通路的严密调控，一类由自噬相关基因（autophagy-related gene，ATG）编码的蛋白在其中扮演了重要角色。根据编码蛋白的功能不同，ATGs可分为以下几类：（1）ULK1 蛋白复合体；（2）Beclin-1/PI3K 复合体；（3）ATG8 泛素样结合系统；（4）ATG12-ATG5 泛素样结合系统；（5）ATG9 循环系统。其中 ATG8 泛素样结合系统与 ATG12-ATG5 泛素样结合系统在调控自噬小体形成与成熟中发挥着重要作用[8-9]。

自噬水平失衡与自身免疫性疾病、神经退行性疾病、心血管疾病和肿瘤等多种疾病的发生发展有关[6, 10]。其中，自噬在肿瘤的发生、发展与治疗抵抗中同样发挥了重要而复杂的作用[5, 11-12]。本综述旨在概括自噬泛素样结合系统在肿瘤发生、发展与放化疗敏感性中的研究进展。

1 自噬泛素样结合系统

1.1 ATG12-ATG5 泛素样结合系统

ATG12 与泛素蛋白编码基因序列无明显同源性，但具有与泛素类似的蛋白质三维结构。ATG12 需要一系列类似 E1、E2 与 E3 的酶的催化才能发挥其生物学功能，调控自噬的发生发展[13-14]。ATG12 泛素样结合系统由 ATG7、ATG10 和 ATG5 构成。ATG7 的功能与 E1 相似，可将 ATG12 的羧基端羟基催化形成硫代酸酯，进而将其激活。ATG10 的功能与 E2 类似，可与激活的 ATG12 结合，随后与半胱氨酸结合进行催化反应。最后，ATG12 被传递到 ATG5，并与其赖氨酸残基以异构肽的形式结合[15]。目前研究表明，ATG12-ATG5 泛素样结合系统中可能缺少与 E3 功能类似的蛋白，ATG10 可能直接负责催化 ATG12 与 ATG5 的结合。ATG12-ATG5 结合后会立刻与 ATG16 结合形成蛋白复合体，ATG16 中的卷曲螺旋结构域会进一步促进自身同源体聚合[16]。新形成的 ATG12-ATG5-ATG16 复合体经过低聚化处理后生成包含四亚基蛋白的复合物，后者将与新生的自噬小体膜结合，促进自噬小体的延伸[17]。而破坏 ATG12-ATG5 泛素样结合系统可以抑制多种细胞的自噬水平[9, 18-20]。

1.2 ATG8 泛素样结合系统

ATG8-磷脂酰乙醇胺（phosphatidylethanolamine，PE）泛素样结合系统由 ATG8、ATG4、ATG7 和 ATG3 构成。ATG8 是一种分布于胞质的可溶性蛋白，经过类似泛素系统的反应后与自噬小体内膜上的 PE 以共轭形式结合，促进自噬小体的发育与成熟。ATG4 家族成员属于半胱氨酸水解酶，新合成的 ATG8 蛋白需要在 ATG4 家族成员的催化下水解羧基端多余的氨基酸残基，暴露羧基端上的甘氨酸残基，才能完成后续反应。ATG7、ATG3 分别作为 E1、E2 样酶，先后与 ATG8 以硫酯键的形式结合。ATG8 在上述蛋白的参与下传递至自噬小体内膜，与 PE 氨基酸残基以酰胺键的形式发生共轭结合。ATG8-PE 在细胞中分布广泛，几乎存在于所有的自噬相关结构。ATG8-PE 在自噬调控中具体的分子机制并不十分清楚。相关研究提示，ATG8-PE 可能在自噬小体膜的闭合与发育中发挥调控作用[21-25]。此外，有研究表明，ATG8 突变会导致自噬小体体积减少和膜闭合障碍，抑制自噬小体形成[26]。同样，另一项研究显示，干扰 ATG8 表达可导致自噬小体体积减少[27]。

1.3 ATG12-ATG5 与 ATG8 的相互调控

ATG12-ATG5 与 ATG8-PE 泛素样结合系统间存在相互调控作用。既往研究表明，敲除 ATG12、

ATG5或ATG10的表达，可导致ATG8泛素样结合系统功能缺陷[28-29]。同时，细胞外研究表明，利用PE-脂质体、ATP及纯化的ATG8、ATG7、ATG3蛋白可以促使ATG8-PE结合[30]。此外，有研究对大肠杆菌进行ATG12、ATG5、ATG7和ATG10过表达后提取到ATG12-ATG5复合体，将ATG12-ATG5复合体加入细胞外ATG8体系中可以促使ATG8-PE结合[31]。

2 ATG12-ATG5泛素样结合系统与肿瘤

2.1 ATG12-ATG5泛素样结合系统与肿瘤的发生发展

自噬在肿瘤的发生发展与治疗抵抗中发挥着复杂的调控作用。一方面，抑制自噬可能会导致正常细胞发生恶性转化；另一方面，放疗、化疗及靶向药物治疗会刺激肿瘤细胞自噬水平升高。抑制肿瘤细胞自噬活性可以提高肿瘤细胞的放化疗敏感性。笔者从ATG8泛素样结合系统和ATG12-ATG5泛素样结合系统出发，着重概括自噬泛素样系统中ATG蛋白在肿瘤发生发展与放化疗敏感性中的功能与机制。

自噬可以通过多方面抑制肿瘤的发展。相关研究表明，干扰ATG12可促进肝癌细胞凋亡，并抑制黑色素瘤与胶质母细胞瘤的侵袭[32-33]。自噬还可通过影响宿主代谢水平抑制肿瘤的生长与发展。Poillet-Perez等[34]研究表明，敲除小鼠的ATG7基因，可使小鼠血浆精氨酸酶降低，进而导致精氨酸水平降低；而精氨酸是肿瘤生长与发展的必要氨基酸，其水平降低可直接抑制小鼠体内多种肿瘤的生长。如前所述，ATG12经过ATG7的传递后与ATG5结合形成复合物，而干扰ATG5表达会破坏蛋白复合体的形成，显著抑制细胞自噬水平。因此，干扰ATG5表达可抑制多种肿瘤的发生发展，并提高放化疗敏感性[34-40]。KIT基因突变是AML患者常见的基因突变，相比于非突变患者，KIT突变患者预后较差。Larrue等[41]研究表明，KIT^{D816V}突变可以通过STAT3激活自噬，进而促进白血病细胞增殖；而干扰ATG7表达可抑制KIT^{D816V}驱使的自噬活性增加，并逆转肿瘤细胞的生长与增殖。

2.2 ATG12-ATG5泛素样结合系统与肿瘤治疗敏感性

化疗与放疗是临床治疗肿瘤的重要手段，放化疗敏感性对肿瘤患者的预后具有重要影响。自噬是影响放化疗敏感性的重要因素之一，抑制细胞自噬可以提高肿瘤的放化疗敏感性。既往研究表明，干扰ATG5表达可以增强顺铂、吉非替尼和埃罗替尼对肿瘤的杀伤效果[42-44]。同时，干扰ATG5也可以提高肺癌细胞对放疗的敏感性[45]。此外，ATG5对血液系统恶性肿瘤的化疗敏感性也有调控作用。相关研究表明，干扰ATG5表达可抑制白血病的发展，并提高其化疗敏感性[40, 46-47]。Sumitomo等[48]研究发现，在急性髓系白血病（acute myeloid leukemia, AML）小鼠模型中敲除ATG7或ATG5基因可以抑制肿瘤细胞的自噬水平，敲除ATG7表达还可以提高AML小鼠对阿糖胞苷的化疗敏感性，并显著改善小鼠的预后。Piya等[49]研究同样表明，ATG7表达与AML细胞的化疗敏感性显著相关，干扰ATG7表达可以提高白血病细胞对化疗药物的敏感性。进一步动物实验结果显示，干扰ATG7表达可以增强阿糖胞苷的抗肿瘤活性。值得注意的是，虽然大部分研究显示抑制细胞自噬水平可以遏制肿瘤的发生发展，但也有研究提示自噬在肿瘤的发生发展和治疗敏感性中可能扮演了不同角色。例如，有研究发现干扰ATG12-ATG5泛素样结合系统中的基因表达可以促进肿瘤的发生[50-53]；破坏ATG5-ATG12泛素结合系统可促进肿瘤细胞的迁移和侵袭[54-59]。上述研究共同提示，自噬在肿瘤中的作用重要且复杂，在不同条件下对不同肿瘤的作用可能完全不同，未来还需要进一步的研究探索自噬在肿瘤中的具体作用与分子机制。

3 ATG8泛素样结合系统与肿瘤

3.1 ATG8泛素样结合系统与肿瘤的发生发展

ATG8泛素样结合系统成员包括ATG8、ATG4、ATG7和ATG3。其中ATG4家族共包含四个成员，分别是ATG4A、ATG4B、ATG4C和ATG4D，分别在自噬中发挥相似又不同的调控功能[22]。ATG8在哺乳动物细胞中的同源体基因是MAP1LC3（LC3）。MAP1LC3共有3个亚型，分别为MAP1LC3A（LC3A）、MAP1LC3B（LC3B）和MAP1LC3C（LC3C），其中LC3B被认为是最重要的亚型。在自噬小体形成过程中，LC3B与自噬小体膜上的PE结合，参与自噬小体膜的发育与成熟。此外，自噬研究中常把LC3B作为自噬标志物[16]。

既往研究表明，干扰LC3表达可抑制乳腺癌细胞的增殖、迁移与侵袭[60]，并促进乳腺癌与肝癌的化疗敏感性[61-62]。ATG4B被认为是ATG4家族中酶

活性最强的成员，干扰ATG4B表达可抑制多种肿瘤的发生发展，并提高其化疗敏感性[34, 38, 63-65]。既往体外酶活性研究发现，相比于ATG4A与ATG4B，ATG4C与ATG4D的酶活性较低，可能在自噬调控中功能有限，但最新的研究认为ATG4C与ATG4D在自噬中亦发挥了各自的作用[22]。相关研究表明，干扰ATG4C可以抑制胶质母细胞瘤的发展与乳腺癌干细胞的易感性[66-67]；干扰ATG4D可以抑制白血病细胞的分化[68]。此外，干扰ATG3表达可以抑制肝癌的发生与侵袭[69-70]，还可抑制白血病细胞的分化并促进肿瘤细胞凋亡[68]。

3.2 ATG8泛素样结合系统与肿瘤治疗敏感性

ATG8泛素样结合系统在肿瘤治疗敏感性中同样发挥着重要的调控作用。Huang等[38]研究表明，干扰ATG4B表达可以促进替莫唑胺和放疗对胶质瘤的杀伤作用。干扰ATG3表达可以提高包括鼻咽癌、肺癌、鳞状细胞癌在内的多种肿瘤的放化疗敏感性[35, 71-72]。

4 总结

自噬在肿瘤的发生发展及放化疗敏感性中扮演着重要角色。作为自噬过程中的关键步骤，自噬小体形成与发育受到ATG8泛素样结合系统和ATG12-ATG5泛素样结合系统的严密调控，并在肿瘤的发生发展与治疗抵抗中扮演重要角色。破坏ATG8泛素样结合系统与ATG12-ATG5泛素样结合系统功能将抑制多种肿瘤的发展，并提高其放化疗敏感性。虽然过往研究提示自噬泛素样调控系统可能是肿瘤治疗的潜在重要靶点，但考虑到自噬对肿瘤调控的复杂性，有关自噬在肿瘤治疗与预防中的应用仍然需要未来大量的研究进一步探索与明确。

参考文献

[1] GOLDSTEIN D S. How does homeostasis happen? Integrative physiological, systems biological, and evolutionary perspectives [J]. Am J Physiol Regul Integr Comp Physiol, 2019, 316(4): R301-R317. DOI: 10.1152/ajpregu.00396.2018.

[2] MANASANCH E E, ORLOWSKI R Z. Proteasome inhibitors in cancer therapy [J]. Nat Rev Clin Oncol, 2017, 14(7): 417-433. DOI: 10.1038/nrclinonc.2016.206.

[3] OH E, AKOPIAN D, RAPE M. Principles of ubiquitin-dependent signaling [J]. Annu Rev Cell Dev Biol, 2018, 34: 137-162. DOI: 10.1146/annurev-cellbio-100617-062802.

[4] YAU R, RAPE M. The increasing complexity of the ubiquitin code [J]. Nat Cell Biol, 2016, 18(6): 579-586. DOI: 10.1038/ncb3358.

[5] LEVY J M M, TOWERS C G, THORBURN A. Targeting autophagy in cancer [J]. Nat Rev Cancer, 2017, 17(9): 528-542. DOI: 10.1038/nrc.2017.53.

[6] LEVINE B, KROEMER G. Biological functions of autophagy genes: a disease perspective [J]. Cell, 2019, 176(1/2): 11-42. DOI: 10.1016/j.cell.2018.09.048.

[7] ZENS B, SAWA-MAKARSKA J, MARTENS S. *In vitro* systems for Atg8 lipidation [J]. Methods, 2015, 75: 37-43. DOI: 10.1016/j.ymeth.2014.11.004.

[8] ZHANG L, LI J J, OUYANG L, et al. Unraveling the roles of Atg4 proteases from autophagy modulation to targeted cancer therapy [J]. Cancer Lett, 2016, 373(1): 19-26. DOI: 10.1016/j.canlet.2016.01.022.

[9] LYSTAD A H, CARLSSON S R, SIMONSEN A. Toward the function of mammalian ATG12-ATG5-ATG16L1 complex in autophagy and related processes [J]. Autophagy, 2019, 15(8): 1485-1486. DOI: 10.1080/15548627.2019.1618100.

[10] BRAVO-SAN PEDRO J M, KROEMER G, GALLUZZI L. Autophagy and mitophagy in cardiovascular disease [J]. Circ Res, 2017, 120(11): 1812-1824. DOI: 10.1161/CIRCRESAHA.117.311082.

[11] LI X H, HE S K, MA B Y. Autophagy and autophagy-related proteins in cancer [J]. Mol Cancer, 2020, 19(1): 12. DOI: 10.1186/s12943-020-1138-4.

[12] WHITE E, MEHNERT J M, CHAN C S. Autophagy, metabolism, and cancer [J]. Clin Cancer Res, 2015, 21(22): 5037-5046. DOI: 10.1158/1078-0432.CCR-15-0490.

[13] CAPPADOCIA L, LIMA C D. Ubiquitin-like protein conjugation: structures, chemistry, and mechanism [J]. Chem Rev, 2018, 118(3): 889-918. DOI: 10.1021/acs.chemrev.6b00737.

[14] MIZUSHIMA N. The ATG conjugation systems in autophagy [J]. Curr Opin Cell Biol, 2020, 63: 1-10. DOI: 10.1016/j.ceb.2019.12.001.

[15] MIZUSHIMA N, NODA T, YOSHIMORI T, et al. A protein conjugation system essential for autophagy [J]. Nature, 1998, 395(6700): 395-398. DOI: 10.1038/26506.

[16] MARIÑO G, LÓPEZ-OTÍN C. Autophagy: molecular mechanisms, physiological functions and relevance in human pathology [J]. CMLS, Cell Mol Life Sci, 2004, 61(12): 1439-1454. DOI: 10.1007/s00018-004-4012-4.

[17] GEORGE M D, BABA M, SCOTT S V, et al. Apg5p functions in the sequestration step in the cytoplasm-to-vacuole targeting and macroautophagy pathways [J]. Mol Biol Cell, 2000, 11(3): 969-982. DOI: 10.1091/mbc.11.3.969.

[18] PENG X, WANG Y T, LI H Y, et al. ATG5-mediated autophagy suppresses NF-κB signaling to limit epithelial inflammatory response to kidney injury [J]. Cell Death Dis, 2019, 10(4): 253. DOI: 10.1038/s41419-019-1483-7.

[19] KIM N Y, HAN B I, LEE M. Cytoprotective role of autophagy against BH3 mimetic gossypol in ATG5 knockout cells generated by CRISPR-Cas9 endonuclease [J]. Cancer Lett, 2016, 370(1): 19-26. DOI: 10.1016/j.canlet.2015.10.008.

[20] MURROW L, DEBNATH J. ATG12-ATG3 connects basal autophagy and late endosome function [J]. Autophagy, 2015, 11(6): 961-962. DOI: 10.1080/15548627.2015.1040976.

[21] KAUFFMAN K J, YU S L, JIN J X, et al. Delipidation of mammalian ATG8-family proteins by each of the four ATG4 proteases [J]. Autophagy, 2018, 14(6): 992-1010. DOI: 10.1080/

15548627.2018.1437341.
[22] AGROTIS A, PENGO N, BURDEN J J, et al. Redundancy of human ATG4 protease isoforms in autophagy and LC3/GABARAP processing revealed in cells [J]. Autophagy, 2019, 15(6): 976-997. DOI: 10.1080/15548627.2019.1569925.
[23] WIRTH M, ZHANG W X, RAZI M, et al. Molecular determinants regulating selective binding of autophagy adapters and receptors to ATG8 proteins [J]. Nat Commun, 2019, 10(1): 2055. DOI: 10.1038/s41467-019-10059-6.
[24] JACQUET M, GUITTAUT M, FRAICHARD A, et al. The functions of Atg8-family proteins in autophagy and cancer: linked or unrelated? [J]. Autophagy, 2021, 17(3): 599-611. DOI: 10.1080/15548627.2020.1749367.
[25] NGUYEN T N, PADMAN B S, USHER J, et al. Atg8 family LC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation [J]. J Cell Biol, 2016, 215(6): 857-874. DOI: 10.1083/jcb.201607039.
[26] NAKATOGAWA H, ICHIMURA Y, OHSUMI Y. Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion [J]. Cell, 2007, 130(1): 165-178. DOI: 10.1016/j.cell.2007.05.021.
[27] XIE Z P, NAIR U, KLIONSKY D J. Atg8 controls phagophore expansion during autophagosome formation [J]. Mol Biol Cell, 2008, 19(8): 3290-3298. DOI: 10.1091/mbc.e07-12-1292.
[28] SUZUKI K, KIRISAKO T, KAMADA Y, et al. The pre-autophagosomal structure organized by concerted functions of APG genes is essential for autophagosome formation [J]. EMBO J, 2001, 20(21): 5971-5981. DOI: 10.1093/emboj/20.21.5971.
[29] MIZUSHIMA N, YAMAMOTO A, HATANO M, et al. Dissection of autophagosome formation using Apg5-deficient mouse embryonic stem cells [J]. J Cell Biol, 2001, 152(4): 657-668. DOI: 10.1083/jcb.152.4.657.
[30] ICHIMURA Y, IMAMURA Y, EMOTO K, et al. *In vivo* and *in vitro* reconstitution of Atg8 conjugation essential for autophagy [J]. J Biol Chem, 2004, 279(39): 40584-40592. DOI: 10.1074/jbc.M405860200.
[31] HANADA T, NODA N N, SATOMI Y, et al. The Atg12-Atg5 conjugate has a novel E3-like activity for protein lipidation in autophagy [J]. J Biol Chem, 2007, 282(52): 37298-37302. DOI: 10.1074/jbc.C700195200.
[32] GUO W N, WANG H N, YANG Y Q, et al. Down-regulated miR-23a contributes to the metastasis of cutaneous melanoma by promoting autophagy [J]. Theranostics, 2017, 7(8): 2231-2249. DOI: 10.7150/thno.18835.
[33] MACINTOSH R L, TIMPSON P, THORBURN J, et al. Inhibition of autophagy impairs tumor cell invasion in an organotypic model [J]. Cell Cycle, 2012, 11(10): 2022-2029. DOI: 10.4161/cc.20424.
[34] POILLET-PEREZ L, XIE X Q, ZHAN L, et al. Autophagy maintains tumour growth through circulating arginine [J]. Nature, 2018, 563(7732): 569-573. DOI: 10.1038/s41586-018-0697-7.
[35] MAKOWSKA A, EBLE M, PRESCHER K, et al. Chloroquine sensitizes nasopharyngeal carcinoma cells but not nasoepithelial cells to irradiation by blocking autophagy [J]. PLoS One, 2016, 11(11): e0166766. DOI: 10.1371/journal.pone.0166766.
[36] ZHENG K, LI Y, WANG S X, et al. Inhibition of autophagosome-lysosome fusion by ginsenoside Ro via the ESR2-NCF1-ROS pathway sensitizes esophageal cancer cells to 5-fluorouracil-induced cell death via the CHEK1-mediated DNA damage checkpoint [J]. Autophagy, 2016, 12(9): 1593-1613. DOI: 10.1080/15548627.2016.1192751.
[37] YU L, GU C P, ZHONG D S, et al. Induction of autophagy counteracts the anticancer effect of cisplatin in human esophageal cancer cells with acquired drug resistance [J]. Cancer Lett, 2014, 355(1): 34-45. DOI: 10.1016/j.canlet.2014.09.020.
[38] HUANG T Z, WAN X C, ALVAREZ A A, et al. MIR93 (microRNA-93) regulates tumorigenicity and therapy response of glioblastoma by targeting autophagy [J]. Autophagy, 2019, 15(6): 1100-1111. DOI: 10.1080/15548627.2019.1569947.
[39] WU H B, YANG S, WENG H Y, et al. Autophagy-induced KDR/VEGFR-2 activation promotes the formation of vasculogenic mimicry by glioma stem cells [J]. Autophagy, 2017, 13(9): 1528-1542. DOI: 10.1080/15548627.2017.1336277.
[40] LIU Q, CHEN L G, ATKINSON J M, et al. Atg5-dependent autophagy contributes to the development of acute myeloid leukemia in an MLL-AF9-driven mouse model [J]. Cell Death Dis, 2016, 7(9): e2361. DOI: 10.1038/cddis.2016.264.
[41] LARRUE C, HEYDT Q, SALAND E, et al. Oncogenic KIT mutations induce STAT3-dependent autophagy to support cell proliferation in acute myeloid leukemia [J]. Oncogenesis, 2019, 8(8): 39. DOI: 10.1038/s41389-019-0148-9.
[42] CHEN J H, ZHANG L M, ZHOU H, et al. Inhibition of autophagy promotes cisplatin-induced apoptotic cell death through Atg5 and Beclin 1 in A549 human lung cancer cells [J]. Mol Med Rep, 2018, 17(5): 6859-6865. DOI: 10.3892/mmr.2018.8686.
[43] CIRCU M, CARDELLI J, BARR M P, et al. Modulating lysosomal function through lysosome membrane permeabilization or autophagy suppression restores sensitivity to cisplatin in refractory non-small-cell lung cancer cells [J]. PLoS One, 2017, 12(9): e0184922. DOI: 10.1371/journal.pone.0184922.
[44] ZHENG Y, SU C, ZHAO L, et al. Chitosan nanoparticle-mediated co-delivery of shAtg-5 and gefitinib synergistically promoted the efficacy of chemotherapeutics through the modulation of autophagy [J]. J Nanobiotechnology, 2017, 15(1): 28. DOI: 10.1186/s12951-017-0261-x.
[45] JO G H, BÖGLER O, CHWAE Y J, et al. Radiation-induced autophagy contributes to cell death and induces apoptosis partly in malignant glioma cells [J]. Cancer Res Treat, 2015, 47(2): 221-241. DOI: 10.4143/crt.2013.159.
[46] FOLKERTS H, HILGENDORF S, WIERENGA A T J, et al. Inhibition of autophagy as a treatment strategy for p53 wild-type acute myeloid leukemia [J]. Cell Death Dis, 2017, 8(7): e2927. DOI: 10.1038/cddis.2017.317.
[47] WATSON A S, RIFFELMACHER T, STRANKS A, et al. Autophagy limits proliferation and glycolytic metabolism in acute myeloid leukemia [J]. Cell Death Discov, 2015, 1: 15008. DOI: 10.1038/cddiscovery.2015.8.
[48] SUMITOMO Y, KOYA J, NAKAZAKI K, et al. Cytoprotective autophagy maintains leukemia-initiating cells in murine myeloid leukemia [J]. Blood, 2016, 128(12): 1614-1624. DOI: 10.1182/blood-2015-12-684696.
[49] PIYA S, KORNBLAU S M, RUVOLO V R, et al. Atg7 sup-

pression enhances chemotherapeutic agent sensitivity and overcomes stroma-mediated chemoresistance in acute myeloid leukemia [J]. Blood, 2016, 128(9): 1260-1269. DOI: 10.1182/blood-2016-01-692244.

[50] YOO B H, KHAN I A, KOOMSON A, et al. Oncogenic RAS-induced downregulation of ATG12 is required for survival of malignant intestinal epithelial cells [J]. Autophagy, 2018, 14 (1): 134-151. DOI: 10.1080/15548627.2017.1370171.

[51] LIN H H, CHUNG Y, CHENG C T, et al. Autophagic reliance promotes metabolic reprogramming in oncogenic KRAS-driven tumorigenesis [J]. Autophagy, 2018, 14(9): 1481-1498. DOI: 10.1080/15548627.2018.1450708.

[52] SUN K, XU L Y, JING Y Y, et al. Autophagy-deficient Kupffer cells promote tumorigenesis by enhancing mtROS-NF-κB-IL1α/β-dependent inflammation and fibrosis during the preneoplastic stage of hepatocarcinogenesis [J]. Cancer Lett, 2017, 388: 198-207. DOI: 10.1016/j.canlet.2016.12.004.

[53] XUE F, HU L, GE R L, et al. Autophagy-deficiency in hepatic progenitor cells leads to the defects of stemness and enhances susceptibility to neoplastic transformation [J]. Cancer Lett, 2016, 371(1): 38-47. DOI: 10.1016/j.canlet.2015.11.022.

[54] TAN D M, ZHOU C, HAN S, et al. microRNA-378 enhances migration and invasion in cervical cancer by directly targeting autophagy-related protein 12 [J]. Mol Med Rep, 2018, 17(5): 6319-6326. DOI: 10.3892/mmr.2018.8645.

[55] CATALANO M, D'ALESSANDRO G, LEPORE F, et al. Autophagy induction impairs migration and invasion by reversing EMT in glioblastoma cells [J]. Mol Oncol, 2015, 9(8): 1612-1625. DOI: 10.1016/j.molonc.2015.04.016.

[56] JO Y K, ROH S A, LEE H, et al. Polypyrimidine tract-binding protein 1-mediated down-regulation of ATG10 facilitates metastasis of colorectal cancer cells [J]. Cancer Lett, 2017, 385: 21-27. DOI: 10.1016/j.canlet.2016.11.002.

[57] GÖRGÜLÜ K, DIAKOPOULOS K N, AI J Y, et al. Levels of the autophagy-related 5 protein affect progression and metastasis of pancreatic tumors in mice [J]. Gastroenterology, 2019, 156(1): 203-217.e20. DOI: 10.1053/j.gastro.2018.09.053.

[58] WANG Y H, XIONG H, LIU D, et al. Autophagy inhibition specifically promotes epithelial-mesenchymal transition and invasion in RAS-mutated cancer cells [J]. Autophagy, 2019, 15(5): 886-899. DOI: 10.1080/15548627.2019.1569912.

[59] GARCÍA-FERNÁNDEZ M, KARRAS P, CHECINSKA A, et al. Metastatic risk and resistance to BRAF inhibitors in melanoma defined by selective allelic loss of ATG5 [J]. Autophagy, 2016, 12(10): 1776-1790. DOI: 10.1080/15548627.2016.1199301.

[60] HAMURCU Z, DELIBAŞI N, GEÇENE S, et al. Targeting LC3 and Beclin-1 autophagy genes suppresses proliferation, survival, migration and invasion by inhibition of Cyclin-D1 and uPAR/Integrin β1/Src signaling in triple negative breast cancer cells [J]. J Cancer Res Clin Oncol, 2018, 144(3): 415-430. DOI: 10.1007/s00432-017-2557-5.

[61] LV S G, WANG X L, ZHANG N, et al. Autophagy facilitates the development of resistance to the tumor necrosis factor superfamily member TRAIL in breast cancer [J]. Int J Oncol, 2015, 46(3): 1286-1294. DOI: 10.3892/ijo.2014.2812.

[62] PENG W X, DU T, ZHANG Z H, et al. Knockdown of autophagy-related gene LC3 enhances the sensitivity of $HepG_2$ cells to epirubicin [J]. Exp Ther Med, 2015, 9(4): 1271-1276. DOI: 10.3892/etm.2015.2266.

[63] LIU P F, HSU C J, TSAI W L, et al. Ablation of ATG4B suppressed autophagy and activated AMPK for cell cycle arrest in cancer cells [J]. Cell Physiol Biochem, 2017, 44(2): 728-740. DOI: 10.1159/000485286.

[64] YANG A N, HERTER-SPRIE G, ZHANG H K, et al. Autophagy sustains pancreatic cancer growth through both cell-autonomous and nonautonomous mechanisms [J]. Cancer Discov, 2018, 8(3): 276-287. DOI: 10.1158/2159-8290.CD-17-0952.

[65] BLESSING A M, RAJAPAKSHE K, BOLLU L R, et al. Transcriptional regulation of core autophagy and lysosomal genes by the androgen receptor promotes prostate cancer progression [J]. Autophagy, 2017, 13(3): 506-521. DOI: 10.1080/15548627.2016.1268300.

[66] WEN Z P, ZENG W J, CHEN Y H, et al. Knockdown ATG4C inhibits gliomas progression and promotes temozolomide chemosensitivity by suppressing autophagic flux [J]. J Exp Clin Cancer Res, 2019, 38(1): 298. DOI: 10.1186/s13046-019-1287-8.

[67] ANTONELLI M, STRAPPAZZON F, ARISI I, et al. ATM kinase sustains breast cancer stem-like cells by promoting ATG4C expression and autophagy [J]. Oncotarget, 2017, 8(13): 21692-21709. DOI: 10.18632/oncotarget.15537.

[68] JIN J, BRITSCHGI A, SCHLÄFLI A M, et al. Low autophagy (ATG) gene expression is associated with an immature AML blast cell phenotype and can be restored during AML differentiation therapy [J]. Oxid Med Cell Longev, 2018, 2018: 1482795. DOI: 10.1155/2018/1482795.

[69] LI J, HU S B, WANG L Y, et al. Autophagy-dependent generation of Axin2+ cancer stem-like cells promotes hepatocarcinogenesis in liver cirrhosis [J]. Oncogene, 2017, 36(48): 6725-6737. DOI: 10.1038/onc.2017.272.

[70] LI J, YANG B, ZHOU Q, et al. Autophagy promotes hepatocellular carcinoma cell invasion through activation of epithelial-mesenchymal transition [J]. Carcinogenesis, 2013, 34(6): 1343-1351. DOI: 10.1093/carcin/bgt063.

[71] APEL A, HERR I, SCHWARZ H, et al. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy [J]. Cancer Res, 2008, 68(5): 1485-1494. DOI: 10.1158/0008-5472.CAN-07-0562.

[72] LEE J G, WU R E. Combination erlotinib-cisplatin and Atg3-mediated autophagy in erlotinib resistant lung cancer [J]. PLoS One, 2012, 7(10): e48532. DOI: 10.1371/journal.pone.0048532.

校稿: 于静　李征

本文引用格式： 文志鹏, 卢慧, 李琴, 等. 自噬泛素样系统在肿瘤中的研究进展[J]. 肿瘤药学, 2024, 14(4): 436-441. DOI: 10.3969/j.issn.2095-1264.2024.04.08.

Cite this article as: WEN Zhipeng, LU Hui, LI Qin, et al. Research progress of autophagy ubiquitin-like conjugation system in cancer[J]. Anti-tumor Pharmacy, 2024, 14(4): 436-441. DOI: 10.3969/j. issn. 2095-1264.2024.04.08.