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自噬双向调节因子磷脂酶D:潜在的治疗靶点

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摘 要:磷脂酶D (phospholipase D,PLD)水解磷脂酰胆碱生成的磷脂酸(phosphatidic acid,PA)作为重要的脂质第二信使,参与调控细胞膜脂质修饰、信号转导及囊泡运输等过程。自噬作为维持细胞内稳态的核心机制,通过清除异常组分和维持能量循环,在细胞生长、发育及代谢平衡中发挥重要作用。PLD对自噬具有双向调控能力,其调控方向受亚细胞定位、微环境信号(如营养状态)及疾病背景的显著影响。本文综述了PLD活性与自噬的相互作用网络,重点解析了两者在肿瘤、神经退行性疾病等疾病发生发展中的协同机制,以期为开发PLD小分子抑制剂精准治疗自噬相关疾病提供新的见解。

关键词:磷脂酶D;磷脂酸;双向调节因子;自噬
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Bidirectional regulation of autophagy by PLD: a target for disease treatment

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Abstract: Phospholipase D (PLD) is an essential enzyme in lipid metabolism that facilitates the hydrolysis of phosphatidylcholine, resulting in the production of phosphatidic acid (PA) and choline. PA serves as an important lipid second messenger, participating in the regulation of critical cellular processes such as membrane lipid modification, signal transduction, and vesicle trafficking. Autophagy is a fundamental and conserved intracellular degradation system, acting as a core mechanism for maintaining cellular homeostasis. It performs essential functions by clearing damaged components and recycling biomolecules, thereby playing a vital role in cell growth, development, and metabolic balance. The interaction between PLD-mediated lipid signaling and the autophagic pathway represents a significant cellular regulation with profound implications for both normal physiology and disease states. This review explores the complex, bidirectional role of phospholipase D (PLD) in regulating autophagy. The way PLD influences autophagic flux, whether it promotes or inhibits it, is not fixed but rather depends on specific contextual factors. These factors include the distinct subcellular localization of PLD′s major isoforms (PLD1 and PLD2), microenvironmental signals such as nutrient availability, and the particular pathological context. We summarize the intricate molecular network through which the PLD-PA axis exerts this dual control, detailing its interactions with central autophagy regulators, including the mTORC1 complex, the AMPK-ULK1 axis, and the VPS34-Beclin 1 core machinery. This positions PLD as a dynamic modulator capable of fine-tuning autophagy in response to varying cellular conditions. The dysregulation of PLD-mediated autophagy is strongly associated with the pathogenesis of multiple human diseases. PLD′s role exhibits clear disease-specific patterns: it can promote autophagic flux in glioblastoma and breast cancer, yet suppress it in others like cervical and colorectal cancer. In neurodegenerative disorders, including Alzheimer′s and Parkinson′s diseases, deficient PLD activity often contributes to impaired autophagy and the accumulation of toxic proteins. Moreover, altered PLD-autophagy signaling is associated with the progression of liver diseases and polycystic

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kidney disease. Therefore, the PLD-PA axis appears to be a promising target for therapy. The future development of isoform-specific PLD modulators, strategically designed to correct the specific autophagic imbalance present in a given disease, offers a compelling avenue for the development of novel and precise therapeutic interventions.

Key words: phospholipase D; phosphatidic acid; bidirectional regulator; autophagy

磷脂酶D (phospholipase D，PLD)能够特异性水解磷脂酰胆碱中的磷酸二酯键生成磷脂酸(phosphatidic acid，PA)和胆碱[1-5]，其通常由 200~1 300个氨基酸组成[2,6]。在真核生物中，PLD的典型结构包含两个关键结构域：一个是位于C端的催化结构域，具有两个保守的HKD基序(HxKxxxxD)，负责催化活性；另一个是位于N端的调控结构域，在哺乳动物中通常表现为PX-PH结构域(phox-pleckstrin homology)，能够通过结合磷脂(如PIP_2等)激活自身酶活，从而参与脂质修饰、PA依赖性信号转导及囊泡运输等过程[2,5-9]。

作为调控细胞内磷脂代谢的关键酶，PLD能够通过产生PA调控细胞增殖、炎症、凋亡、自噬以及损伤修复等生理过程[7,10-14]。自噬作为细胞内清除异常组分并维持稳态的核心机制，其完整流程包括自噬诱导、隔离膜形成、自噬体成熟及其与溶酶体融合等阶段[15-20]。研究表明，PLD能够调控自噬体的形成和维持自噬通量，是自噬过程中不可或缺的调节分子[20-22]。值得注意的是，PLD对自噬的调控呈现显著的双重性：其作用方向取决于亚细胞定位、细胞状态或实验条件差异，既可作为正调控因子促进自噬，也可作为负调控因子发挥抑制作用[12]。

本文详细介绍PLD调控自噬的具体途径及其上下游相关分子，并对PLD过表达、抑制或消除如何影响自噬并最终引发相关疾病进行综述。PLD小分子抑制剂研究任重道远，本综述提出的一些独特见解可为PLD小分子抑制剂的研究、开发和临床应用提供指导。

1　PLD调节细胞自噬

迄今为止，已经鉴定出6种PLD异构体，其中仅PLD1和PLD2异构体具有水解酶活性，二者是存在于哺乳动物组织中的主要亚型[8]：前者分布于核周、高尔基体、核内体和细胞内囊泡中，后者在静息状态下位于质膜上[8,10,23-25]。作为关键脂质代谢酶，PLD能够通过水解膜脂成分从而调控膜流动性，并参与自噬小体的形成、成熟及其与溶酶体的融合[12,17,20,26]。PA作为PLD的核心催化产物，是在细胞和组织中承担其生理功能的主要载体[27]，既能够通过稳定自噬中的关键哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)复合物分子的结构和活性以维持对自噬的负调控，也能够招募膜融合相关蛋白促进自噬小体和溶酶体的融合从而正向调控自噬。这种双向调控特性使PLD-PA轴能够在不同状态和应激条件下双向调控自噬[12,28-30]。

1.1　PLD对细胞自噬具有负调控作用

PLD的丰度和活性动态调控自噬小体的发生和成熟过程[12,22]。在HEK293和HeLa细胞中，特异性沉默PLD可显著提升细胞内LC3-II蛋白水平，在促进自噬小体形成的同时增强细胞内长寿蛋白的自噬降解和循环，表明PLD能够在自噬启动阶段发挥抑制作用[29]。而PA作为PLD的核心效应分子，参与活化mTOR复合物，并激活下游相关分子，从而在自噬过程中发挥负调控作用[19,20,31]。此外，PA可与多种效应蛋白相互作用从而调节其活性和功能[1,20]，从而影响自噬通路[12,22]。而PLD亚型的特异性调控进一步支持了其负向调控作用：抑制PLD2能够显著促进自噬体和溶酶体的融合，使自噬通量明显增加[31]。

1.1.1　PLD通过竞争性激活mTOR复合物抑制自噬

mTOR复合物分为mTORC1和mTORC2两种，在细胞生长代谢、存活、增殖和骨骼重排中发挥重要作用，通常被认为是自噬的核心负调节因子[32]。mTORC1是由mTOR、RPTOR (mTOR复合物1的调控相关蛋白)、MLST8 (mTOR相关蛋白，为LST8同源物)以及两个抑制亚基PRAS40 (AKT1底物1，即AKT1S1)和DEPTOR (包含mTOR相互作用蛋白DEP结构域)组成的多蛋白组装体。除了mTOR、MLST8和DEPTOR外，mTORC2还包含 RICTOR (雷帕霉素不敏感的mTOR伴侣)、MSIN1 (MAPK相关蛋白1，MAPKAP1)和PROTOR1/2 (mTOR的调控亚基)等分子[33]。其中，mTOR亚基中的FRB (FKBP12-rapamycin-binding)结构域是临床治疗使用的雷帕霉素的作用靶点，也是mTORC1抑制亚基PRAS40的主要结合位点[34,35]。

PLD催化生成的PA对于维持mTOR稳定性和活性至关重要[19,20,31]。它能够与雷帕霉素及PRAS40

竞争性地结合mTOR的FRB结构域，进而破坏和缩短FRB螺旋α4的C端构象变化，改变FRB结构域对底物的亲和力[34,36]。甚至在缺乏氨基酸、小G蛋白Rag GTPases（Rag guanosine triphosphatases）等条件下，PA仍然可以激活mTORC1[35,37]，磷酸化ULK1第757位丝氨酸[18]，从而抑制自噬发生。在人永生化囊性肾脏细胞（OX161）和常染色体显性多囊性肾病（autosomal dominant polycystic kidney disease，ADPKD）细胞中，抑制PLD的表达导致自噬负调控关键分子mTOR复合物及其上下游分子活性均出现明显下调，并伴随自噬通量增加，初步表明PLD与自噬负向调控密切相关。此外，研究人员发现，若将伯醇（1-BtOH）作为PLD的底物，其酶解产物是磷脂酰醇而不是PA。利用这种特性，以1-BtOH作为PLD的底物进行“酒精陷阱”实验，发现细胞中的mTOR复合物活性明显下调并激活自噬，进一步证实PLD-PA轴与自噬之间存在负调控关系[34]。

在某些疾病的发生发展过程中，PLD上调甚至能够导致雷帕霉素耐药，这在很大程度上是由于PA与雷帕霉素竞争性结合mTOR，最终增强了mTOR复合物活性从而促进细胞增殖并抑制细胞自噬[34]。上述研究表明，PLD能够经其产物PA与雷帕霉素竞争激活mTOR复合物，在维持自噬稳态和病理代偿中发挥负向调控作用。

1.1.2 PLD通过AMPK-ULK1轴抑制自噬

AMP活化蛋白激酶（adenosine 5′-monophosphate-activated protein kinase，AMPK）是由α-催化亚基、β-调节亚基和γ-调节亚基组成的异源三聚体，能够在ATP耗竭时通过感知AMP/ATP比例升高而被激活[38,39]。与mTOR复合物不同，AMPK是自噬的正向调控因子，也是线粒体动力学中的关键分子[40]。在自噬调控中，AMPK既能通过差异性调节ULK1磷酸化进而诱导细胞自噬[20]，也能通过ULK1诱导线粒体自噬，通过清除受损线粒体维持线粒体稳态平衡[18,40]。研究发现，在饥饿条件下，抑制PLD活性会导致AMPK磷酸化，进而通过双重机制差异性调节ULK1：抑制mTOR复合物活性并解除其与ULK1的结合，协同增强AMPK与ULK1的结合，通过差异性调控ULK1丝氨酸位点磷酸化（ULK1 Ser555磷酸化上调，ULK1 Ser757磷酸化下调）促进自噬[18]。以上结果表明，PLD可通过AMPK-ULK1轴调控自噬。

1.1.3 PLD通过VPS34-Beclin 1复合物解离抑制自噬

III型磷脂酰肌醇3-激酶（phosphatidylinositol 3-kinase catalytic subunit type 3，PI3KC3）复合物是自噬体膜成核的核心分子，包含PI3KC3、Beclin 1、UVRAG 和Rubicon等分子[18,33,41]。其中，VPS34（哺乳动物同源物为PI3KC3）通过催化生成磷脂酰肌醇3-磷酸（phosphatidylinositol-3-phosphate，PI3P）招募下游效应蛋白至前自噬膜，而Beclin 1作为支架蛋白直接调控复合物活性[42,43]。研究证实，VPS34可与Beclin 1相互作用诱导自噬[44-46]。PLD的产物PA能够降低Beclin 1对VPS34的亲和力，并与磷酸甘油酸激酶（phosphoglycerate kinase，PGK）和Beclin 1结合形成PA-PGK-Beclin 1复合物，竞争性地抑制VPS34-Beclin 1复合物的形成，进而抑制自噬[28,29]。此外，PA还能够增强Bcl 2与Beclin 1的相互作用，使Beclin 1从VPS34-Beclin 1复合物中被释放，从而抑制自噬。PLD过表达能够显著放大这种抑制作用，使自噬体形成严重受阻[18]。在饥饿条件下，PLD1抑制剂通过激活MAPK8/JNK通路，诱导Beclin 1从Bcl 2复合物中释放并重新组装形成VPS34-Beclin 1复合物，将自噬相关蛋白招募到合适的位置从而绕过mTOR独立激活自噬[18]。这表明，PLD可通过改变蛋白质之间的亲和力从而实现对自噬的精准抑制。

综上所述，根据目前的研究，PLD-PA轴可以通过竞争性激活mTOR复合物、AMPK-ULK1轴和促进VPS34-Beclin 1复合物解离抑制自噬。PLD抑制自噬的具体途径如图1所示。

1.2 PLD正调控自噬

在饥饿诱导的自噬发生中，PLD与自噬体标志蛋白LC3共定位于隔离膜，提示其直接参与自噬体形成过程[47]。功能研究表明，PLD1活性缺失可显著干扰LC3-II代谢动力学，并导致自噬体形态异常，证实其通过催化产物PA调控自噬体成熟[48]。这一报道与本文2.1中所述结论存在争议，这种矛盾可能源于PLD亚型的空间分布和功能差异：PLD1定位于内体系统，其生成的PA通过促进膜脂重塑直接驱动自噬前体膜延伸；而质膜定位的PLD2可能通过其他途径间接调控自噬进程，但由于相关研究较少，其具体机制仍有待进一步研究[12,21,28]。值得注意的是，PLD水解磷脂生成的PA在自噬调控中占主导地位，其作为膜转移分子可绕过mTOR信号直接招募ATG

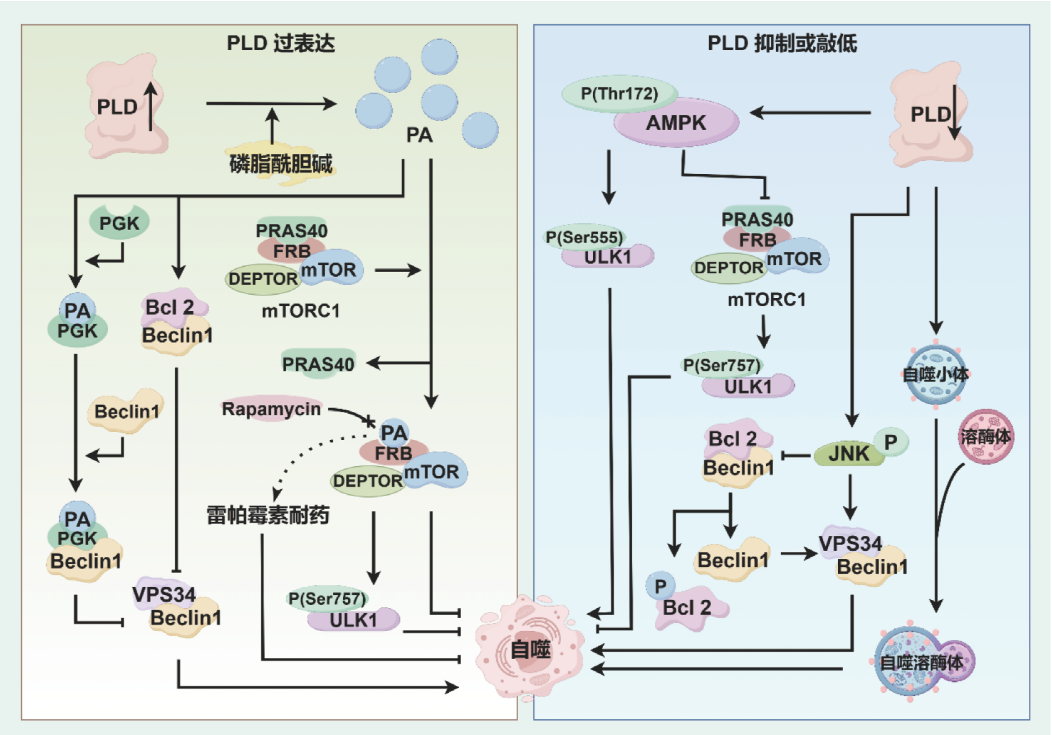

图 1　PLD负调控自噬的分子机制

PLD通过生成PA调控自噬进程。当PLD过表达时，其催化产生的PA可通过多重分子机制抑制自噬：(1) PA直接结合PGK，促进PA-PGK-Beclin 1复合物形成，竞争性阻断自噬，促进复合体VPS34-Beclin 1的组装；(2) PA通过增强Bcl 2与Beclin 1的结合，抑制VPS34-Beclin 1复合体功能；(3) PA竞争性结合mTORC1的FRB结构域，拮抗PRAS40的结合，从而激活mTORC1信号通路，通过磷酸化ULK1丝氨酸757位点抑制自噬；(4) PA与FRB结构域的结合还可诱导雷帕霉素耐药性，阻断雷帕霉素对自噬的激活作用。当使用PLD抑制剂或PLD-siRNA下调其表达时，自噬水平显著增强：(1)诱导AMPK苏氨酸172位点磷酸化，通过差异调控ULK1磷酸化级联反应激活自噬；(2)磷酸化AMPK可解除mTORC1对ULK1丝氨酸757位点的磷酸化抑制，协同促进自噬；(3)激活JNK磷酸化，进而诱导Bcl 2磷酸化，促使Beclin 1从Bcl 2-Beclin 1复合体中释放并与VPS34结合，形成功能性自噬复合体；(4)导致自噬小体及自噬溶酶体数量显著增加，该效应可被外源性PA所逆转。上述分子机制的系统解析为靶向PLD-PA信号轴调控自噬提供了重要理论依据。

Figure 1　Molecular mechanisms of PLD negatively regulating autophagy

PLD regulates autophagy by generating PA. When PLD is overexpressed, PA can inhibit autophagy through multiple molecular mechanisms: (1) PA binds to PGK directly, promoting the formation of the PA-PGK-Beclin 1 complex and competitively blocking the assembly of the VPS34-Beclin 1 complex; (2) PA inhibits the VPS34-Beclin 1 complex by enhancing the binding of Bcl 2 to Beclin 1; (3) PA binds to the FRB domain of mTORC1 competitively and antagonizes the binding of PRAS40, thereby activating the mTORC1 signaling pathway and inhibiting autophagy by phosphorylating ULK1(Ser757); (4) The binding of PA to the FRB domain can also induce rapamycin resistance, blocking the activation of autophagy by rapamycin. When PLD inhibitors or PLD-siRNA are used to down-regulate PLD expression, the autophagy is significantly enhanced: (1) PLD absence induces phosphorylation of AMPK(Thr172) and activates autophagy by regulating the phosphorylation cascade of ULK1 differentially; (2) Phosphorylated AMPK can relieve the phosphorylation inhibition of ULK1(Ser757) by mTORC1 and synergistically promote autophagy; (3) PLD exhaustion activates JNK phosphorylation, which in turn induces Bcl 2 phosphorylation, promoting the release of Beclin 1 from the Bcl 2-Beclin 1 complex and its binding to VPS34 to form a functional autophagy complex; (4) PLD absence leads to a significant increase in the number of autophagosomes and autophagolysosomes, and this effect can be reversed by exogenous PA. The above systematic analysis provides an important theoretical basis for regulating autophagy by targeting the PLD-PA signaling axis.

蛋白至自噬膜组装位点；当PLD活性被抑制时，PA水平急剧下降导致自噬体-溶酶体融合受阻，引发自噬体堆积，而该效应可被外源性PA处理特异性逆转，进一步验证了PLD-PA轴在自噬调控中的核心作用[6,26,37,49]。

1.2.1 PLD通过调节膜流动性促进自噬

作为各种囊泡融合事件的关键调控分子，PLD在体内受到多种因素的调控，包括HCLS1结合蛋白3（HCLS1 binding protein 3，HS1BP3）和ADP核糖基化因子6（ADP-ribosylation factor 6，Arf6）[19,50-52]。

当PLD活性受损时，PA水平下降导致膜流动性改变，进而干扰自噬体形成[17,26]。有研究表明，抑制PLD1虽不显著影响含自噬小体的细胞的数量，但常引发自噬小体异常聚集[31]，提示抑制PLD1活性可能通过阻止自噬小体与溶酶体的融合，造成自噬通量受损，从而阻断聚集蛋白的降解[12,20]。

PLD1和HS1BP3能分别与ATG16L1阳性膜和TFRC阳性膜共定位，后者是一种循环的内体衍生膜，是隔离膜的来源[19]；这种分别共定位的现象暗示，两者可能竞争性参与细胞自噬进程。HS1BP3被证实是PLD1活性的负调控因子，其缺失能够提升PLD1活性，促进PLD1与ATG16L1共定位并促进PA生成，进而加速自噬小体的形成及其与溶酶体的融合。这一过程往往伴随LC3脂化、p62降低和自噬通量增加等，揭示了PLD1的促自噬效应[19,49]。在自噬后期，PLD1从晚期核内体膜转移到自噬体膜[47]，其过表达能够导致LC3-II明显减少，标志着自噬溶酶体融合增强。然而，当HS1BP3正常表达时，其与PLD1竞争性结合隔离膜，显著抑制PLD1介导的自噬体形成，这一效应也独立于mTOR信号[19,49]，进一步证实了PLD1是自噬小体形成和融合的核心分子。

与HS1BP3相反，Arf6作为PLD的正调控因子，能够通过GTPase酶活性激活PLD，进而促进磷脂酰胆碱水解生成PA[53,54]。后者通过增强细胞膜的流动性来调控质膜向隔离膜的转变，从而促进自噬体的形成[26,53]。这种调控机制在肿瘤中极为常见，与肿瘤细胞中的囊泡运输密切相关[55]。当突变体Arf6-N48R阻断PLD的激活时，其选择性结合PLD的催化结构域而不是PX-PH结构域，导致PLD的N端被截断，抑制LC3-I向LC3-II的转化，最终削弱自噬[6,26]。有趣的是，这一调控机制同样独立于mTOR信号通路，证实在HS1BP3的负向调控和Arf6的正向调控下，PLD能正向调控自噬。

1.2.2 PLD受VPS34调控而促进自噬

VPS34与PLD类似，能够通过改变亚细胞定位和细胞微环境实现对自噬的双向调控[56]。在饥饿诱导的自噬中，PLD1作为自噬体膜动力学的重要调控因子，依赖于与VPS34协同作用：VPS34通过结合PLD1的PX结构域调控其在自噬体中的亚细胞定位，PLD1在自噬后期富集并转移到自噬小体外膜，促进自噬体成熟；而PI3K抑制剂（如3-MA）或溶酶体酸化抑制剂（巴菲霉素A1）可以阻断PLD介导的PA生成，并抑制LC3阳性腔室扩张，从而有效抑制自噬体成熟[33,47]。此外，研究表明沉默VPS34可有效降低50%的PLD丰度，同时抑制自噬，证实二者之间存在正向调控关系[47]。以上研究揭示，在饥饿条件下，PLD能够作为VPS34的下游效应体，协同促进自噬晚期进程。

1.2.3 PLD通过AKT-Beclin 1通路促进自噬

AKT，即蛋白激酶B（protein kinase，PKB），在调控细胞存活、增殖及代谢重编程中发挥关键作用，能够特异性抑制细胞自噬通量，其异常激活与肿瘤进展密切相关[54]。在胶质母细胞瘤中，PLD2催化生成的PA能够将AKT募集到膜上，诱导Beclin 1 Ser295磷酸化，进而阻断自噬抑制复合物Rubicon与Beclin 1的相互作用[57,58]。有趣的是，通过比较不同细胞系发现，在没有血清的情况下，AKT只能在PA存在的情况下才能被激活和募集，且该调控是一种仅存在于胶质瘤细胞等部分细胞系中的、独立于mTOR途径的细胞特异性调控[59]。进一步研究表明，抑制PLD或AKT后，溶酶体和自噬体融合抑制剂（巴菲霉素A1）处理无法减少自噬小体的形成，表明PLD-AKT轴能够通过驱动自噬体-溶酶体融合正向调控自噬[59]。这表明PLD在胶质细胞瘤中以PA依赖性方式重塑AKT-Beclin 1信号通路，以促进自噬晚期融合进程。

1.2.4 PLD通过动态调控mTOR活性促进自噬

尽管PA通常通过结合mTORC1的FRB结构域发挥自噬抑制作用，但最新研究显示其调控方向可能具有结合位点依赖性：当PLD靶向mTORC1的抑制性亚基DETOR时，PA可以竞争性取代DETOR，进一步加强对mTORC1的抑制，从而激活自噬[28,31,60,61]。这种双向调控特性表明，PA与mTORC1结合后的功能取决于其结合位点的空间特异性——当结合至FRB结构域时维持自噬抑制状态，而靶向DEPTOR结合域则通过破坏复合物稳定性触发自噬激活。这表明，PLD-PA轴可通过动态重构mTORC1的分子构象，实现对自噬的多重调控。

综上所述，PLD-PA轴可以通过调节膜流动性、与VPS34协同作用、促进AKT-Beclin 1通路和竞争性结合mTOR DETOR等方式促进自噬。PLD促进自噬的具体途径如图2所示。

值得注意的是，VPS34表达下调或HS1BP3过表达会抑制PLD的活性。当PLD活性受抑制时，PA生

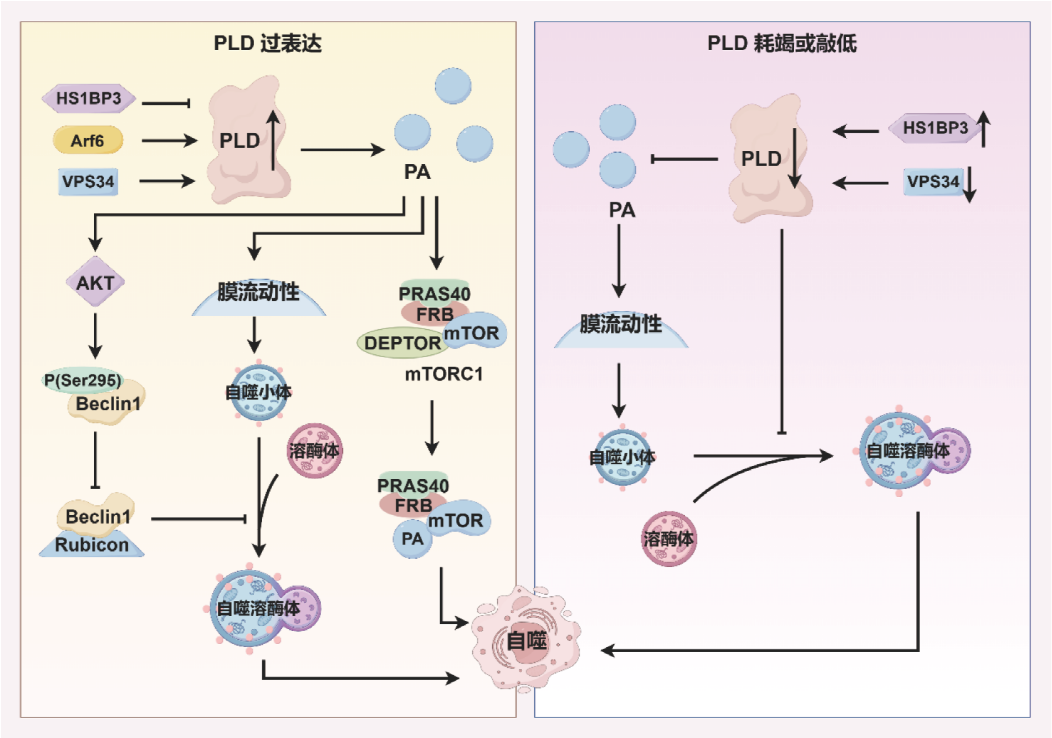

图 2　PLD正向调控自噬的分子机制

Arf6和VPS34可正向调控PLD表达，而HS1BP3通过竞争性结合自噬体前体膜抑制PLD活性。PLD产生的PA可通过双重作用促进自噬：一方面通过激活AKT激酶诱导Beclin 1第295位丝氨酸磷酸化，阻断Beclin 1-Rubicon复合体形成；另一方面通过增强膜流动性促进自噬体和自噬溶酶体的形成。此外，PA还可置换mTORC1复合体中的DEPTOR亚基，通过抑制mTOR信号通路激活自噬。

Figure 2　Molecular mechanisms of PLD positively regulating autophagy

Arf6 and VPS34 can positively regulate the expression of PLD, while HS1BP3 inhibits PLD activity by competitively binding to the autophagosome precursor membranes. PA can promote autophagy through dual effects. On one hand, it can induce the phosphorylation of Beclin 1 (Ser295) by activating AKT kinase, thereby blocking the formation of the Beclin 1-Rubicon complex. On the other hand, it promotes the formation of autophagosomes and autophagolysosomes by enhancing membrane fluidity. Additionally, PA can replace DEPTOR in the mTORC1 complex and activate autophagy by inhibiting mTOR signaling pathway.

成减少将导致膜流动性下降，进而阻碍自噬体形成；同时，PLD活性缺失还会直接抑制自噬体与溶酶体的融合过程，最终共同导致自噬通量下降。

2　PLD调控的自噬与疾病的关系

PLD凭借其独特的磷脂酰基转移酶活性，通过动态调控PA的水平与亚细胞定位，在肿瘤、神经退行性疾病及其他疾病的发生和发展中发挥着举足轻重的作用。例如，PLD活性异常增加可以诱导激活癌症中重要的致癌信号MAPK和mTOR[4]。自噬在维持细胞稳态以及降解有毒聚集体和受损细胞器方面发挥关键作用[62]。而PA作为重要的脂质第二信使，通过改变蛋白质之间的亲和力、加强膜流动性等方式调控自噬以维持细胞稳态。当自噬被阻断时，大量异常物质在细胞中积累而无法降解，导致细胞死亡[62]。而当自噬过度激活，进行性自噬可诱导病变细胞死亡，抑制疾病发生发展。这种利用PLD-PA轴在体内通过多种分子机制进行调控的自噬网络为研究精准医疗干预方案提供了理论依据。

2.1　PLD调控的自噬与肿瘤相关

作为一种脂质信号转导酶，PLD在乳腺癌、胃癌、肾癌等多种恶性肿瘤中呈现异常高表达，其催化活性增强可导致产物PA水平明显升高。研究表明PLD及PA的异常程度与疾病分期、不良预后等密切相关，是肿瘤发生和发展中的重要信号分子[63-65]。PLD和PA作为调节人体生理功能的重要分子，能够竞争性结合mTOR不同位点，也能够参与AMPK-ULK1等多种通路从而调控自噬的发生发展[59]。PA还能作为多种细胞表面受体的下游效应物，在肿瘤发生和转移过程中触发和调节细胞内信号转

导[1]。靶向抑制PLD活性已被证实能够抑制肿瘤细胞生长和转移[1,7,18]。PLD临床研究也表明,氯喹与PLD1和溶酶体抑制剂联合使用能够协同阻断癌细胞自噬通路,比单一使用氯喹更敏感[28]。结合各种相关研究,小分子PLD抑制剂有望成为癌症治疗新策略。但就肿瘤而言,自噬是一把双刃剑,既能够抑制肿瘤的发生和发展,也能够帮助肿瘤细胞承受化疗药物治疗后的代谢应激,防止细胞死亡[18,20,66,67],其状态与细胞所处环境、疾病进展情况息息相关。因此,聚焦于PLD亚型的具体调控作用及特异性小分子抑制剂开发,结合自噬状态进行个体化指导治疗是未来精准治疗的趋势。

2.1.1 乳腺癌

乳腺癌是女性中发病率最高的恶性肿瘤,目前临床上常使用雌激素受体阻滞剂进行治疗,通过阻止卵巢产生激素来预防乳腺癌的发生和发展[67,68],但其发病机制尚不明确。PLD活性增加是在乳腺癌中最先被报道的[55,69],研究表明,PLD1能够通过维持自噬通量增强肿瘤细胞的代谢应激能力[55]:在营养不良(如葡萄糖缺乏)环境中,乳腺癌细胞不经PI3K-AKT通路,而是通过PLD1催化生成PA以维持自噬通量,促进癌细胞生长[35]。PLD1抑制剂可阻断溶酶体与自噬体融合,抑制自噬小体中的异常物质降解,使得p62等过度积累,最终诱导癌细胞死亡[70]。值得注意的是,PLD2在低侵袭性乳腺癌中高表达[20],而PLD2抑制剂和组蛋白去乙酰化酶(histone deacetylase,HDAC)抑制剂联合使用可促进乳腺癌细胞死亡并减缓癌症进展[71]。这些研究提示,开发PLD亚型特异性抑制剂,精准干预自噬进而治疗肿瘤具有极大的潜力。

2.1.2 宫颈癌

作为女性第二大常见癌症,宫颈癌的发病机制与人乳头瘤病毒(human papillomavirus,HPV)感染密切相关,后者能够通过干扰PLD产生PA及PI3K-AKT-mTOR信号通路从而诱发宫颈癌[72,73]。宫颈癌细胞的LICN00511 IncRNA能够与转录因子视色素X受体α (retinoic X receptor α,RXRA)结合,显著增强PLD1启动子的活性,进而提高PLD1的转录水平并降低Beclin 1在细胞中的表达,下调LC3B-II/LC3B-I比值并抑制自噬。这种PLD1依赖性自噬缺陷能够加速癌细胞增殖和侵袭,而沉默LICN00511能够有效逆转该反应并增强细胞自噬和凋亡[73]。近年来随着研究的深入和筛查的提高,宫颈癌发病率呈下降趋势,但如何遏制宫颈癌的发生发展以及如何治疗仍值得探索。靶向LICN00511或抑制PLD活性,能够有效抑制宫颈癌细胞的增殖和恶性侵袭,为开发干扰RNA或者小分子抑制剂用于宫颈癌治疗指明了方向。

2.1.3 结直肠癌

结直肠癌是一种由炎症性肠病发展而来的遗传性癌症,其特征性分子事件包括PLD1和PLD2的异常高表达和高磷酸化[74,75]。研究表明,PLD是结直肠癌微环境的关键调节因子[76],通过激活mTOR并抑制AMPK活性,从而差异性调节ULK1复合物不同丝氨酸位点的磷酸化,进而抑制自噬小体的形成及其与溶酶体的融合,最终抑制自噬[20]。PLD被抑制会显著提升LC3-II蛋白水平,促进自噬小体形成进而促进自噬。动物实验也证实,与正常小鼠相比,PLD缺陷小鼠的肠道肿瘤发生率大大降低,生存率显著提高[53,54]。因此,PLD小分子抑制剂临床研究对靶向调控自噬进而预防结直肠肿瘤发生意义重大。

2.1.4多形性胶质母细胞瘤

多形性胶质母细胞瘤(GBM)是一种进展迅速、侵袭性强、致死性高的原发性脑肿瘤[34,77],其表现为PI3K-AKT通路明显失调进而驱动自噬异常激活,临床治疗非常具有挑战性[78]。研究表明,PLD2催化生成的PA能够通过与AKT的PH结构域结合,增加PI3P对AKT的亲和力,抑制自噬负向调控复合物Beclin 1-Rubicon的结合,进而促进自噬启动[42]。在应激和营养剥夺条件下,PLD抑制剂能够有效抑制PLD2的活性,通过减少PA的生成抑制AKT对自噬的促进作用,但在营养充足条件下并无影响。AKT参与机体多种生理功能,因此相较于靶向AKT予以治疗,在饥饿状态下靶向PLD2能够特异性解除自噬异常激活,从而有效缓解胶质母细胞瘤进展[11]。

2.2 PLD调控的自噬与神经退行性疾病相关

神经退行性疾病,如阿尔茨海默病、帕金森病和路易体痴呆等,通常以异常蛋白聚集体(如β-淀粉样蛋白)积聚于神经元内为典型病理特征[62]。研究表明,这些患者脑组织中的PLD活性降低,其功能缺陷进一步加剧了病情的发展。PLD可在人神经元中正常表达,促进神经内分泌细胞胞外分泌和突触生长,但当PLD1活性降低时,自噬体与溶酶体融合障碍可导致自噬通量受损,引发LC3、p62、泛素化蛋白聚集

体异常积累，自噬系统崩溃[79-82]。值得注意的是，针对神经退行性疾病患者脑组织自噬小体中α-突触核蛋白异常积累的问题，可以通过过表达PLD1缓解，证实了PLD1在神经退行性疾病中的重要作用[79]。因此，维持神经系统疾病患者PLD的活性可能在延缓和抑制疾病的发生和发展方面发挥至关重要的作用。

2.3 PLD调控的自噬与肝脏疾病相关

2.3.1 肝纤维化

肝纤维化是由多种慢性肝脏损伤引起的病理过程，其核心机制在于肝星状细胞(hepatic stellate cells，HSCs)的异常激活和细胞外基质(I型胶原)过度沉积[60]。研究表明，PLD1能够通过诱导自噬显著促进HSCs中I型胶原蛋白的降解，从而发挥抗纤维化作用[60,83]。这一调控过程独立于传统的mTOR信号之外[84]，提示PLD1可能直接通过产物PA招募自噬相关蛋白等方式调控自噬[60,83]。当PLD1活性被抑制时，自噬通量受损导致I型胶原蛋白异常积累从而加速纤维化进程，但靶向PLD1的小分子激动剂或PA类似物能够逆转该抑制现象[83]，为肝纤维化提供了潜在治疗方案。

2.3.2非酒精性脂肪肝

非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)是一种与胰岛素抵抗相关的慢性肝病，也是2型糖尿病的重要危险因素，其发病机制与肝脏中各种脂质代谢物沉积密切相关[85,86]。PLD在肝脏中高表达，能够通过生成PA促进自噬小体-溶酶体的融合以参与代谢调控网络[10,87]。抑制PLD1活性可导致PA生成减少，引发自噬通量受损，进而使肝细胞内脂质代谢受阻形成脂质蓄积，最终加速NAFLD病理进程[87]。因此，靶向PLD1以维持其正常水平从而调控自噬在抑制或延缓NAFLD进展中发挥重要作用。

2.4 PLD调控的自噬与多囊肾病相关

PLD生成的PA作为mTOR复合物稳定的关键分子，是激活自噬所必需的[16]。在多囊性肾病(PKD)细胞模型中，PLD和mTOR复合物的基础活性增加，导致mTOR上下游磷酸化增加从而抑制自噬。研究发现PLD抑制剂和厚朴酚(honokiol)能够阻断PA生成，并且通过“酒精陷阱”实验进一步证实了PA对mTOR的核心调控作用——外源PA补充甚至能够逆转PKD细胞的自噬抑制[34]。尽管雷帕霉素在临床上对PKD的疗效较差，但其联合PLD抑制剂能够在ADPKD和OX161细胞模型中实现协同性自噬调控，为克服传统mTOR靶向治疗的耐药性提供了新思路[34]。因此，开发PLD小分子抑制剂及其联合治疗用药方案是治疗PKD的一个重要研究方向。

2.5 PLD调控的自噬与视网膜疾病相关

视网膜色素上皮细胞(retinal pigment epithelium，RPE)在维持视网膜和光感受器的正常生理功能中起着关键作用[88]。炎症是视网膜疾病发病的主要因素之一，不同因素诱发的炎症可导致糖尿病视网膜病变、视网膜色素变性、葡萄膜炎甚至失明等[26,28]。视网膜疾病的病理进程与PLD介导的自噬调控紊乱密切相关。研究表明，RPE中高活性的PLD通过生成PA激活mTORC1复合物，形成“PLD-PA-mTORC1”信号级联，进而抑制自噬活性[16]。这种自噬失衡显著削弱RPE细胞对脂多糖等炎症因子的清除能力，导致慢性炎症微环境持续激活，最终驱动糖尿病视网膜病变。因此，靶向抑制RPE特异性PLD的活性以恢复自噬稳态，为防治视网膜退行性病变提供了新的思路。

综上所述，PLD调控的自噬与乳腺癌、宫颈癌等肿瘤以及神经退行性疾病、肝脏疾病、多囊肾病和视网膜疾病相关(图3)。值得注意的是，由于自噬在不同病理过程中的生物学效应具有异质性，虽然靶向调控PLD介导的自噬可为上述疾病提供潜在治疗策略，但在其他疾病类型中，无论PLD发挥促自噬或抑自噬作用，其过表达均会通过异常调控自噬稳态而加剧疾病进展。这一发现提示，PLD靶向治疗需根据特定疾病的自噬调控网络进行精准干预。

3 结论及未来发展方向

本综述详细讨论了PLD如何通过正向或负向调控自噬参与疾病发生发展。一方面，PLD可以通过竞争性结合mTOR复合物的FRB结构域、抑制AMPK，进而差异性调控ULK1磷酸化和降低VPS34-Beclin 1亲和力来抑制自噬小体形成；另一方面，作为脂质第二信使，PA可通过诱导细胞膜负曲率促进吞噬体囊泡形成，并通过调节PLD亚细胞定位，提高自噬体-溶酶体融合效率，正向驱动自噬进程[16]。自噬作为细胞稳态的核心调控机制，可以通过溶酶体降解受损蛋白和细胞器并维持细胞代谢循环，但其过度激活或抑制可触发程序性死亡或异

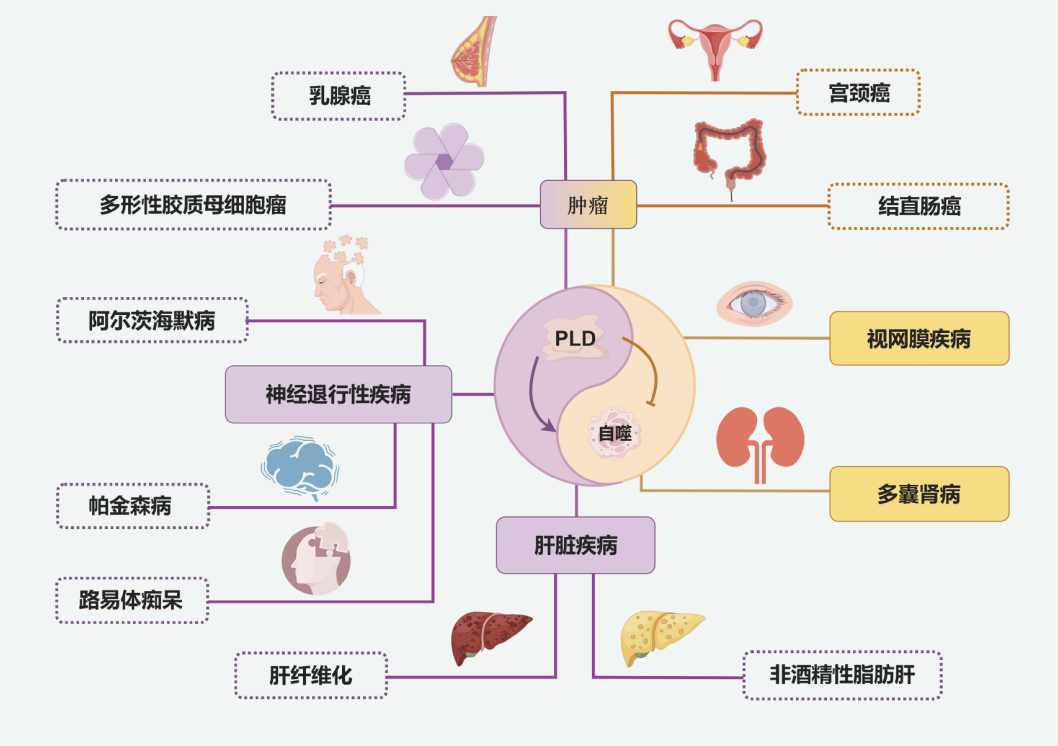

图 3 PLD调控的自噬相关疾病

PLD双向调控自噬通路,在不同疾病中呈现差异化。在乳腺癌和胶质母细胞瘤中,PLD表现为促进自噬;而在宫颈癌和结直肠癌中,则发挥自噬抑制作用。在神经退行性疾病(如阿尔茨海默病、帕金森病及路易体痴呆)及肝脏疾病(肝纤维化与非酒精性脂肪性肝病)中,PLD显著激活自噬通路。相反,在多囊肾病和视网膜病变模型中,PLD对自噬进程呈现负向调控作用。注:图中紫色标注代表PLD在该疾病中促进自噬,黄色标注表示抑制作用。

Figure 3 PLD-regulated autophagy associated diseases

PLD bidirectionally regulates the autophagy pathway, exhibiting differentiated regulatory characteristics in various diseases. In breast cancer and glioblastoma, PLD promotes autophagy, while it inhibits autophagy in cervical cancer and colorectal cancer. In neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Lewy body dementia, as well as liver diseases like liver fibrosis and non-alcoholic fatty liver disease, PLD significantly activates the autophagy pathway. Conversely, in models of polycystic kidney disease and retinopathy, PLD has a negative regulatory effect on the autophagy process. The purple marking in the figure indicates that PLD promotes autophagy in this disease, while the yellow marking indicates an inhibitory effect.

常物质累积,形成恶性循环[89]。研究表明,PLD介导的自噬失衡在肿瘤(如乳腺癌、胶质母细胞瘤)、神经退行性疾病(如阿尔茨海默病)及肝肾疾病(如肝纤维化、多囊肾病)中具有重要病理意义,如在肝纤维化中,PLD1激活自噬以降解I型胶原,若其功能缺失将加剧细胞外基质沉积,加重肝纤维化[60,83]。这些发现提示,靶向调控PLD亚型及其微环境依赖的调控网络,为开发自噬相关疾病的精准治疗策略提供了新方向。

PLD及其产物PA在自噬中展现双向调控特性,其作用方向高度依赖亚细胞定位及病理微环境。通过分析发现,在“饥饿或应激”状态下PLD往往能够促进自噬,而在“营养充足”条件下PLD通常抑制自噬,但现有的数据并不足以让我们下定论,因为大量处于“普通”条件下的实验很难归类其营养状态及微环境,仅能得出PLD能够“促进”或“抑制”自噬的结论。PLD与自噬之间的内在联系是否与营养条件密切相关,这种动态调控能否使PLD成为细胞适应环境变化的关键分子开关,是一个非常值得探索的方向。

尽管PLD是多种疾病治疗的潜在靶点,其抑制剂开发面临多重挑战。第一代抑制剂(如伯醇)因非特异性阻断PA生成导致严重副作用(如酒精中毒),临床应用受限[90]。亚型选择性抑制剂(如PLD2抑制剂halopemide)虽在精神病和视网膜疾病中初步有效,但其多巴胺受体交叉反应性引发机制争议[26,64,80]。一些研究也证实了细胞骨架蛋白α-肌动蛋白和β-肌动蛋白对PLD有抑制作用,但其抑制作用和机制有待进一步研究[7]。而目前针对于PLD

抑制剂的研究仍止步于动物实验，在小鼠模型中PLD抑制剂对血栓性疾病疗效显著，但在人类临床试验中效果有限，提示需优化模型系统[48,64,90]。未来研究需更聚焦于亚型特异性设计（如靶向PLD1的抗纤维化药物）及精准递送技术（如纳米载体靶向自噬体膜），以减少脱靶效应并增强疗效。

PLD的双向调控特性要求针对疾病微环境设计差异化策略：在自噬抑制相关疾病（如视网膜病变）中靶向激活PLD，而在自噬过度激活的肿瘤中则选择性抑制PLD活性。本文针对目前已有研究进行了总结与分析，未来通过整合单细胞组学、动态自噬监测及多靶点联合用药，有望实现对PLD调控网络的精准干预，为自噬相关疾病治疗开辟新路径。

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