



细菌溶血磷脂的生物合成及生物学功能

曹雪峰^{1,2}, 彭练慈^{1,2}, 方仁东^{1,2*}

1 西南大学动物医学院 动物健康与动物性食品安全国际联合实验室, 重庆 400715

2 草食动物科学重庆市重点实验室, 重庆 400715

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摘要: 溶血磷脂(lysophospholipids, LPLs)是细胞膜中的一类脂质代谢中间产物, 主要由磷脂分子被水解后生成。LPL的生物学功能与其前体磷脂有明显的区别。在真核细胞中, LPL是一种参与多种胞内生物信号调控的重要活性分子, 但在细菌中, LPL的生物学功能还未被充分揭示。LPL通常是细菌细胞膜中的次要组分, 在环境压力条件下其含量可显著升高。除了参与细胞膜磷脂代谢, LPL被认为在细菌环境适应性及致病性中发挥重要作用。其在细胞膜中的累积可以显著提高细菌在环境压力下的存活及增殖效率, 同时还是细菌感染过程中重要的信号分子。近期有研究表明, LPL可能是细菌新发现的潜在毒力因子。本文因此将结合最新研究数据, 对不同种类LPL的头合成通路以及LPL在细菌抵御环境压力和细菌-宿主互作等方面所发挥的生物学功能进行综述, 为对细菌致病机制和防治细菌感染的相关研究提供新的思路和参考借鉴。

关键词: 溶血磷脂; 细菌; 致病机制; 防治

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*Corresponding author. Tel: +86-23-46751547, E-mail: rdfang@swu.edu.cn

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De novo biosynthetic pathway and biological functions of bacterial lysophospholipids

CAO Xuefeng^{1,2}, PENG Lianci^{1,2}, FANG Rendong^{1,2*}

1 Joint International Research Laboratory of Animal Health and Animal Food Safety, College of Veterinary Medicine, Southwest University, Chongqing 400715, China

2 Chongqing Key Laboratory of Herbivore Science, Chongqing 400715, China

Abstract: Lysophospholipids (LPLs), lipid metabolism intermediates in the cell membrane, are mainly generated by the hydrolysis of phospholipid molecules. LPLs differ significantly from their precursor phospholipids in the biological functions. In eukaryotic cells, LPLs are bioactive molecules involved in the regulation of multiple biological signals. However, the roles of LPLs in bacteria have not been fully revealed. LPLs are a secondary component in bacterial cell membrane and can be significantly increased under environmental stress conditions. In addition to participating in the phospholipid metabolism in the cell membrane, LPLs are considered to play a role in the environmental adaptability and pathogenicity of bacteria. LPLs accumulated in the cell membrane can improve the survival and proliferation efficiency of bacteria under environmental stress or act as signaling molecules in the pathogenic processes of bacteria. Recent studies suggest LPLs as a potential novel virulence factor of bacteria. We review the current knowledge about the biosynthetic pathways of LPLs and the roles of LPLs in bacterial adaptation and host-bacterium interaction, providing references for the further research on bacterial pathogenesis and prevention of bacterial infections.

Keywords: lysophospholipids; bacteria; pathogenesis; prevention

磷脂是一种在细胞膜表面常见的复合脂类物质,其最显著的特点是与细胞膜上的蛋白质、糖脂、胆固醇等物质共同形成脂质双分子层。溶血磷脂(lysophospholipid, LPL)是磷脂双分子层中的次要组分^[1]。和二酰化的磷脂分子不同, LPL 只有一条酰基化脂肪酸链与中心甘油(glycerol)分子相连^[1]。在真核生物中, LPL 是一类具有生物活性的脂类信号分子,能介导多种细胞生理反应^[2-4]。常见的 LPL 包括溶血磷脂酸(lysophosphatidic acid, LysoPA)、溶血磷脂酰胆碱(lysophosphatidylcholine, LysoPC)、溶血磷脂酰乙醇胺(lysophosphatidylethanolamine, LysoPE)、

溶血磷脂酰甘油(lysophosphatidylglycerol, LysoPG)、溶血磷脂酰丝氨酸(lysophosphatidylserine, LysoPS)和溶血磷脂酰肌醇(lysophosphatidylinositol, LysoPI)^[5-7]。LPL 通常作为细胞膜磷脂生物合成的中间产物或在磷脂水解过程中被生成^[6]。其生物合成途径包括(图 1): (1) 特异性磷脂酶剪切磷脂的一条酰基链后, LPL 作为水解产物被生成^[8]; (2) 在七酰化脂多糖或三酰化磷脂的形成过程中,位于革兰氏阴性菌外膜上的脂质 A (lipid A)棕榈酰转移酶 PagP 将棕榈酸链从磷脂分子上转移到六酰化脂质 A 或另一种磷脂上后, LPL 作为副产物被生成^[9-11]; (3) 在革兰氏

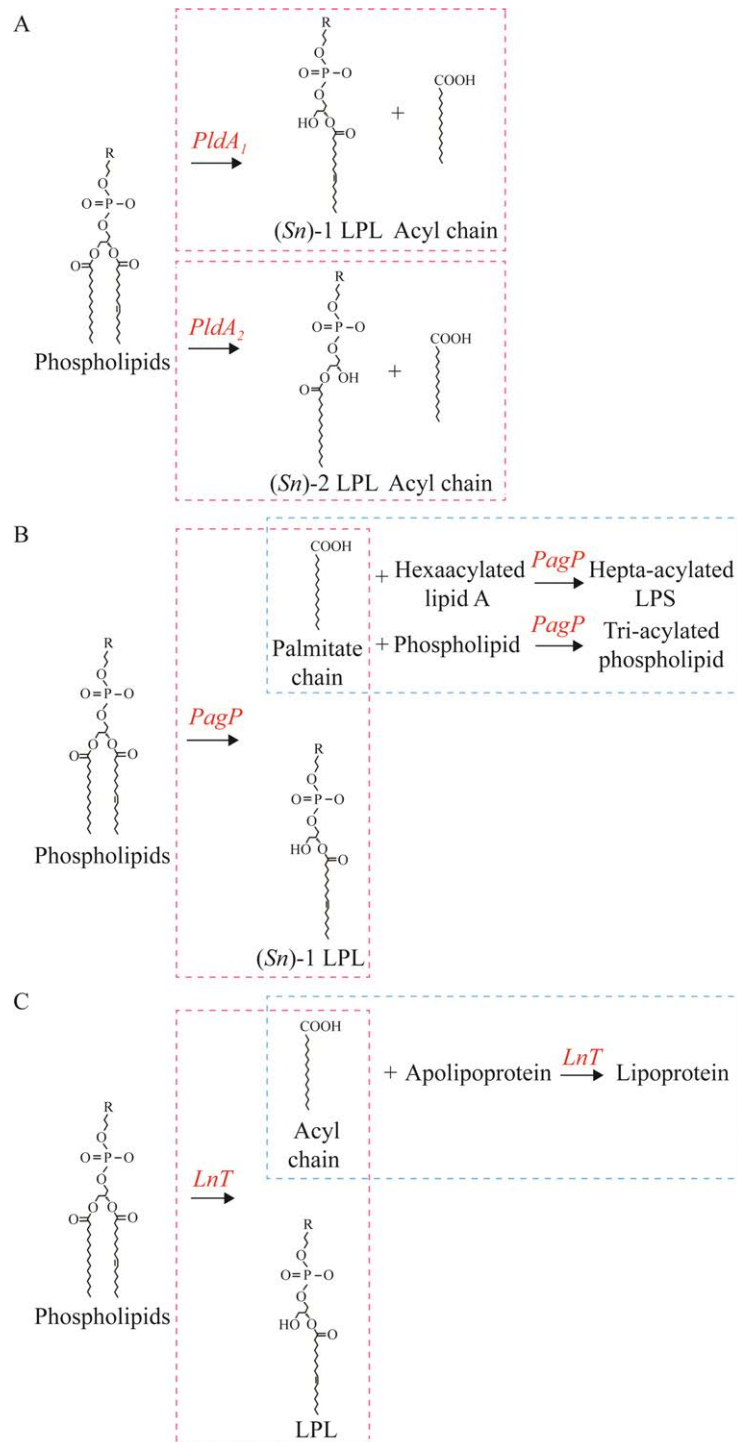


图 1 细菌 LPL 生物合成途径

Figure 1 The bacterial LPL biosynthesis pathways. A: LPL generated by phospholipase. B: LPL produced by PagP as by-product in the formation of hepta-acylated LPS and tri-acylated PG. C: LPL produced by Lnt as by-product in the lipoprotein *de novo* biosynthetic pathway. The pink dotted line represents the first step reaction, the blue dotted line represents the second step reaction. The involved enzymes and their cleavage sites are indicated in red.

阴性菌脂蛋白的成熟过程中, 载脂蛋白 *N*-酰基转移酶(apolipoprotein *N*-acyltransferase, Lnt)将磷脂分子中的一条脂肪酸链转移到脂蛋白前体上后, LPL 作为副产物被生成^[12-13]。在合成途径(1)中, 根据磷脂酶在磷脂分子上作用靶点的不同, 磷脂酶可被分为 A、B、C、D 这 4 种亚型。其中 A 型磷脂酶(phospholipase A, PldA)可在(*Sn*)-1 或(*Sn*)-2 位点剪切磷脂分子的一条酰基链, 因此又可以被进一步分为可在(*Sn*)-1 位点水解脂肪酰基酯键并生成(*Sn*)-1 LPL 的 PldA₁, 和在(*Sn*)-2 位点剪切酯键形成(*Sn*)-2 LPL 的 PldA₂^[14-15]。

在真核细胞中, LPL 的生物学功能已被广泛研究。除了作为细胞内脂质生物合成的中间前体外, LPL 还是 G 蛋白偶联信号通路中重要的信使分子。通过募集、激活 T 细胞、B 细胞和巨噬细胞, G 蛋白偶联信号通路可调控动物体内特定的免疫反应。此外, LPL 还可以作为多功能细胞生长因子被人 and 动物利用^[16-18]。LPL 在通常在组织间液和血浆中大量存在, 但在细胞中浓度很低。在人体中, 体液中 LPL 的确切含量尚不清晰, 但 lysoPC 被测定出是人体血浆中含量最丰富的 LPL, 其浓度约为 200–300 μmol/L^[19-21]。其他 LPL 在人体血浆中的浓度大约为: lysoPE (10–50 μmol/L)、lysoPI (1–15 μmol/L)、lysoPA (0.6–1.0 μmol/L)、lysoPG (0.4 μmol/L)、lysoPS (0.1 μmol/L)^[20,22-27]。

在细菌中, LPL 的生物学功能少有被研究。细菌中的 LPL 通常会通过二酰化磷脂的酰化反应或磷脂酶 B [也称为溶血磷脂酶, 它可以在(*Sn*)-1 和(*Sn*)-2 任意位点切割两种 LPL 的脂肪酸链]被分解^[28-30], 因此含量普遍极低。这可能是由于 LPL 的结构特点不利于细菌细胞膜磷脂双分子层的形成和稳定。LPL 是一种具有特殊非圆柱形几何结构的分子, 只能在液体中形

成胶束(微胶粒)结构, 无法形成稳定的双层结构, 因此 LPL 在细胞膜中的掺入会在磷脂双分子层中产生不稳定性, 从而破坏细胞膜的屏障作用^[31]。

之前的研究表明, 细胞膜中的类 LPL 锥形分子结构将增加脂质双分子层的曲度, 并改变整个细胞膜的横向压力分布, 导致细胞膜中形成渗漏边界, 和瞬时(或永久)的分子间隙, 使细胞膜出现非均质性的结构缺陷^[32]。同时, 膜胶束化和膜分子间隙的产生会破坏细胞膜的生理结构并使细胞膜的通透性增加^[5]。因此 LPL 的存在将会对细胞膜稳态带来巨大风险。基于以上原理, 宿主体内可将细菌膜磷脂降解为 LPL 的外源性 PldA₂被认为是一种高效的抗菌剂^[33]。虽然目前对细菌 LPL 的生物学功能还知之甚少, 但已有研究指出, 宿主分泌的 LPL 能有效的降低细菌在感染过程中的感染效率^[4]。同时, 在细菌感染过程中, LPL 在宿主免疫细胞中的含量也被发现显著升高, 但其作用机制还尚不清晰^[34-35]。此外, 在沙门氏菌(*Salmonella*)感染过程中, 宿主源 LPL 还被发现能够刺激细菌释放促炎单体鞭毛蛋白, 从而增强宿主对该细菌的先天免疫反应和炎症反应^[36]。

由于 LPL 对细胞膜的潜在毒性作用, 因此细菌细胞膜中通过内外源性 PldA、PagP 或 Lnt 依赖的酶促反应所产生的 LPL 需要迅速清除^[37-38]。LplT (lysophospholipid transporter)是存在于部分革兰氏阴性菌中的一种 LPL 转移系统。细菌能利用 LplT 将细胞外膜内外叶及细胞内膜外叶的 lysoPE、lysoPG 和 lysoCL 转移至细胞内膜内叶^[37], 随后通过酰基-酰基转移蛋白合成酶(又称为 LPL 酰基转移酶, LPL Aas) acyl-ACP synthetase 被二次酰化后清除。因此 LplT-Aas 系统在保护革兰氏阴性菌免受外源 PldA₂ 攻击

过程中具有不可替代的作用^[28,39]。另一方面, LPL 对大多数革兰氏阳性菌有极强的细胞毒性, 因此 LPL 在革兰氏阳性菌中几乎不存在^[6,40-41]。

通常情况下, LPL 只占细菌磷脂总含量的不到 1%, 但环境压力会致使细菌细胞膜中 LPL 的含量显著升高^[37,42-44]。一些病原菌在遇到胆盐、高温和酸性等环境刺激时, 其 LPL 的分泌和释放都会急剧增加^[43,45-48]。之前的研究表明, 在低氧压力下空肠弯曲杆菌 (*Campylobacter jejuni*) 需要增加其细胞膜 LPL 的含量来维持细菌的运动活力^[42]。此外, 另一份研究^[49]和其他学者^[50]的相关研究还表明, 细菌微摩尔浓度级的 LPL 就足以对真核细胞造成细胞毒性。但关于细菌在压力环境中为何以及如何积聚高含量的 LPL 还没有被清晰的阐释。目前已有的研究表明, 当不同类型的磷脂, 比如适于双分子层形成的磷脂酰甘油 (phosphatidylglycerol, PG) 与会给细胞膜双分子层带来结构压力的锥形不饱和和磷脂酰乙醇胺 (phosphatidylethanolamine, PE) 混合时, 细胞膜内会出现不稳定, 此时以特定比例适当掺入 LPL 可以通过释放脂质双分子层的弹性弯曲压力来恢复细胞膜的稳定性^[51]。因此 LPL 的累积可能可以帮助细胞维持其膜结构稳态。此外, LPL 对细胞膜的曲度修饰可以改变某些膜蛋白的结构和功能^[52-53], 因此细胞膜 LPL 的累积也可能是细菌调控其环境应激反应的结构基础。另一方面, 在环境压力条件下 LPL 在细菌中的增加还有可能是源于 PldA 活性的升高。当细菌受到环境压力时, 细胞膜的完整性和不对称性会被破坏, 导致细菌 PldA 的活性通过钙离子依赖的二聚化机制被增强^[54-55], 从而诱发磷脂分子生成 LPL 的效率提高^[6,37]。虽然目前对细菌 LPL 生物学功能的了解还存在大量的空白, 但 LPL 被认为是细菌致病机制和炎症反应中被低估的重要因子。本文以下部分将

重点分类描述细菌中主要 LPL 的生物合成通路及生物学功能。

1 不同种类 LPL 的生物学特性

1.1 溶血磷脂酸 lysoPA

1.1.1 LysoPA 的特点

水溶性 lysoPA 是溶血甘油磷脂家族中结构最简单的分子。在真核细胞中, lysoPA 是细胞免疫反应中重要的生物标志物, 它能诱导包括细胞凋亡抑制、细胞趋化性、细胞因子和趋化因子分泌、血小板聚集和伤口愈合效率增强在内的多种免疫反应^[1,17,56-58]。在细菌中, 对 lysoPA 的了解仅限于它是磷脂酸 (phosphatidic acid, PA) 生物合成过程中的中间产物且在细胞中的含量极低^[59]。

细菌 lysoPA 被认为是所有甘油磷脂生物合成的前体, 可通过酰基-酰基转移蛋白合成酶依赖的 3-磷酸甘油酰基转移酶被催化合成 (图 2)^[6,60-61]。LysoPA 的生物合成是在细胞溶质中发生的, 由于缺乏相应的结合位点, lysoPA 无法被 LplT 转移系统识别和转运到细菌细胞膜中^[62]。但 lysoPA 能通过 PldA 介导的磷脂水解途径或在部分细菌和真核细胞中被具有溶血磷脂酶 D 活性的自体毒素 (autotoxin, ATX) 在细胞膜中催化生成 (图 2)^[1,37,63-65]。LysoPA 是除了 lysoPC 外另一个能在真核细胞中由 lysoPE、lysoPS 或者 lysoPI 通过 ATX 介导的催化反应生成的 LPL^[66]。

1.1.2 LysoPA 的功能

细菌 lysoPA 的生物生理学功能目前还未被清晰阐释。现有的研究表明, 幽门螺旋杆菌 (*Helicobacter pylori*) 鞭毛的合成效率与 lysoPA 在菌体中的积累呈正相关^[67]。

虽然目前对 lysoPA 功能的研究还相当匮乏, 但细菌源 lysoPA 被认为与动物健康紧密相关。最新研究一方面表明, 小鼠患结直肠肿瘤后, 其肠道菌群将发生显著改变, 同时粪便中

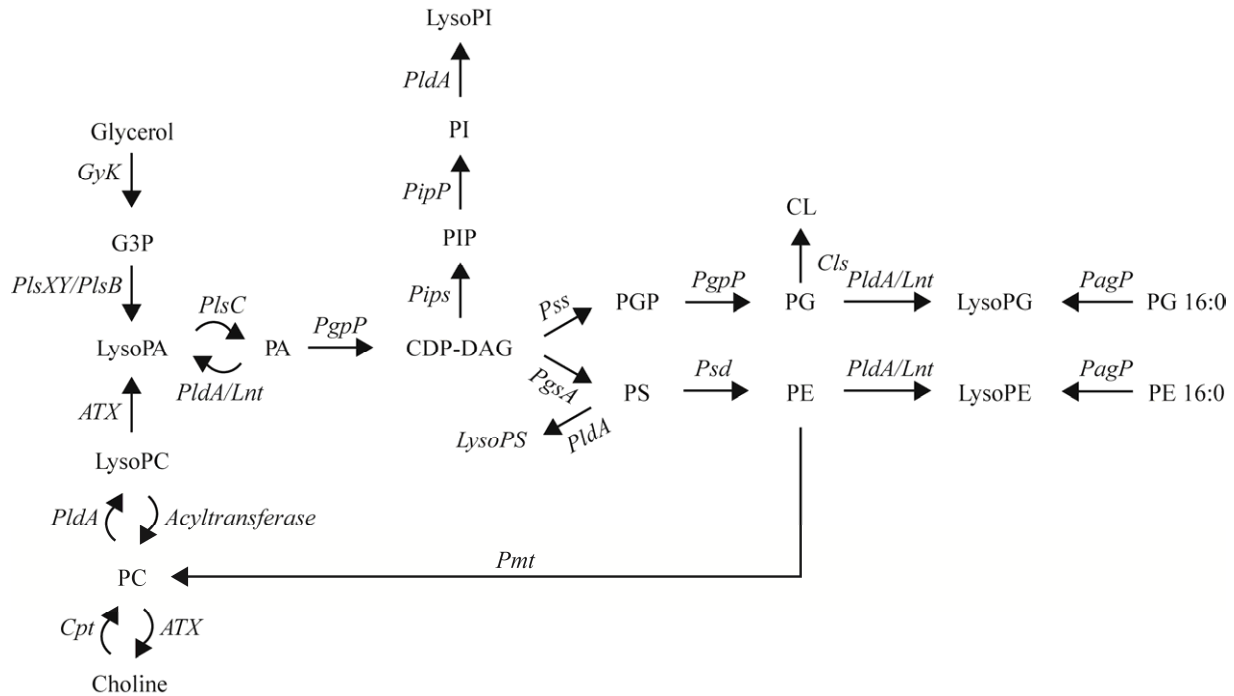


图 2 细菌细胞膜磷脂从头合成通路

Figure 2 The de novo biosynthetic pathway of bacterial membrane phospholipids. The enzymes involved in the different catalyzed reactions are indicated in the text. G3P: Glycerol-3-phosphate; CDP-DAG: Cytidine diphosphate-diacylglycerol; PGP: Phosphatidylglycerol-phosphate; PIP: Phosphatidylinositol phosphate; GyK: Glycerokinase; Pls: Acyltransferase; PldA: Phospholipase A; Lnt: Apolipoprotein *N*-acyltransferase; CdsA: Phosphatidate cytidylyltransferase; Pips: Phosphatidylinositolphosphate synthase; PipP: Phosphatidyl-inositolphosphate phosphatase; Pss: Phosphatidylserine synthase; Psd: Phosphatidylserine decarboxylase; PgsA: Phosphatidylglycerolphosphate synthase; PgpP: Phosphatidylglycerol phosphate phosphatase; Cls: Cardiolipin synthase; PagP: Lipid A palmitoyltransferase; Pmt: Phospholipid *N*-methyltransferase; ATX: Autotoxin.

lysoPA 和 lysoPC 含量也被发现显著升高^[68];另一方面, 在断奶仔猪日粮中添加植物乳酸杆菌 (*Lactobacillus plantarum*) 将增加泛菌属细菌的相对丰度, 同时能通过促进 1-棕榈酸 lysoPA 的产生显著提高仔猪对脂肪消化和吸收^[69]。因此, 来源于肠道菌群的 lysoPA 与动物肠道健康之间的相互平衡可能对维持肠道稳态十分重要。

1.1.3 宿主源 lysoPA 在细菌-宿主互动中的作用

除了细菌源 lysoPA, 宿主源 lysoPA 也能影响细菌的感染过程。通过促进肠道对盐类的吸收及抑制肠道对阴离子的分泌, 宿主自分泌的

lysoPA 能在缓解因为细菌感染而导致的急性腹泻中发挥重要作用^[70-71]。在此过程中, 宿主源 lysoPA 通过调控有丝分裂原活化蛋白激酶/细胞外信号通路调节激酶(MAPK/ERK)、G 蛋白 A (RhoA) 和 RhoA 激酶、富脯氨酸酪氨酸激酶^[72]、3 型 Na^+/H^+ 交换器^[64]、囊性纤维化跨膜传导调节蛋白^[73]、 Cl^-/OH^- 交换器^[74] 的分泌和功能来维持肠道离子稳态, 从而发挥缓解腹泻的作用。此外, 由于可以通过激活细胞外调节蛋白激酶 (ERK1/2)、丝氨酸/苏氨酸磷酸酶和 P13 激酶信号通路抑制细菌内毒素诱导的炎症反应, lysoPA 也

被认为是细菌性肠炎的有效抗炎剂^[71]。

1.1.4 LysoPA 对宿主的作用

LysoPA 在真核细胞中的生理生物学功能主要是通过激活细胞表面的 lysoPA 受体来完成。通过受体的激活, lysoPA 能介导上皮细胞凋亡、抑制细胞内抗肿瘤反应^[60,75]。将小鼠进行 lysoPA 受体缺失处理后, 小鼠的肠通透性被发现显著升高, 同时通过 H₂O₂ 诱导产生的结肠紧密连接蛋白和黏附连接蛋白的表达量被检测到明显减少^[39]。此外, 小鼠 lysoPA 受体缺失骨髓源树突状细胞在受到 LPS 刺激时, TNF- α 表达水平和 IL-10 分泌水平分别显著的升高和降低^[76]。细菌 lysoPA 对宿主 lysoPA 受体的激活还和细菌溶血性有关。相关研究表明, 由产气荚膜梭菌(*Clostridium perfringens*)引起的溶血是红细胞表面的 lysoPA 受体通过 Ca²⁺通道被产气荚膜梭菌激活, 从而造成红细胞裂解^[77-79]。因此 lysoPA 被认为是调控宿主细胞生理功能的重要因子。

1.2 溶血磷脂酰胆碱 lysoPC

1.2.1 LysoPC 的特点

LysoPC, 又称为溶血卵磷脂, 是一种磷脂酰胆碱(phosphatidylcholine, PC)的衍生物, 在 PC 的一个脂肪酸链被磷脂酶切割后产生。LysoPC 能进一步被催化生成 lysoPA, 或者通过 PC 生成胆碱(图 2)^[6,37,80]。在大多数动物组织中, lysoPC 是含量最丰富的 LPL, 也是部分生理和病理过程的核心分子^[1,81]。但目前只有少数原核生物被认为能够分泌 lysoPC, 其中包括根癌农杆菌(*Agrobacterium tumefaciens*)、铜绿假单胞菌(*Pseudomonas aeruginosa*)、肺炎衣原体(*Chlamydia pneumoniae*)、约氏黄杆菌(*Flavobacterium johnsoniae*)和伯氏疏螺旋体(莱姆病病原)(*Borrelia burgdorferi*)等^[61,82]。

和 lysoPA 类似, lysoPC 也不是 LplT 转移

系统的可识别底物。因为其过大的胆碱头部基团会阻挡转运所必需的酶进入 LplT 的结合位点^[6,37]。虽然包括奈瑟氏淋球菌(*Neisseria gonorrhoeae*)、大肠杆菌(*Escherichia coli*)、霍乱弧菌(*Vibrio cholera*)、鼠伤寒沙门氏菌(*Salmonella Typhimurium*)、幽门螺旋杆菌(*Helicobacter pylori*)、空肠弯曲杆菌(*Campylobacter jejuni*)、多形拟杆菌(*Bacteroides thetaiotaomicron*)、枯草芽孢杆菌(*Bacillus subtilis*)、乳酸杆菌(*Lactobacillus sp.*)和产气荚膜梭菌(*Clostridium perfringens*)在内的多种细菌都无法分泌 lysoPC, 但这些细菌被认为可以利用宿主体内的 lysoPC 参与自身代谢^[61]。在动物肠道中, 食源性 PC 可被胰磷脂酶降解为 lysoPC^[6,37,83], 间接表明 lysoPC 对大多数肠道菌相对无毒。

1.2.2 LysoPC 对细菌的作用

在真核细胞中, lysoPC 的生物学功能已被充分研究。除了作为脂质代谢的前体, 宿主体内的 lysoPC 还被认为是炎症严重程度的生物标志因子^[6,37]。最近的研究指出, 宿主体内 lysoPC 水平的降低可能与宿主死亡风险的升高有所关联^[84]。

在细菌中, 对 lysoPC 生物生理学功能的了解目前还存在大量空白。在有限的研究中, 内源性 lysoPC 被发现能调控细菌膜蛋白的功能^[6]。假结核耶尔森菌(*Yersinia pseudotuberculosis*)分泌的内源 lysoPC 能通过调控外膜蛋白 F 的活性来选择性过滤胞内外的亲水性溶质^[85]。大肠杆菌的大电导机械力敏感通道(mechanosensitive channel with very large conductance, MscL)可被内源 lysoPC 触发至完全开放状态, 从而应对膜张力所带来的渗透压力^[86]。全打开的 MscL 是一个大间隙的充水空, 可被细菌用作紧急安全阀。霍乱弧菌能利用内源 lysoPC 作为营养物质来重塑细胞壁磷脂的结构和分布^[87]。

外源性 lysoPC 对细菌的影响主要体现在改变抗菌素活力上。例如, 外源 lysoPC 可以通过提高细菌细胞膜通透性迅速杀死革兰氏阳性耐甲氧西林金黄色葡萄球菌 MRSA (methicillin-resistant *Staphylococcus aureus*)^[88]; 还可以提高金黄色葡萄球菌 *S. aureus* 对部分抗生素(例如金霉素)的敏感性^[88]。外源 lysoPC 对革兰氏阴性菌更多的是非直接作用, 例如, lysoPC 能提高多粘菌素 B 对鼠伤寒沙门氏菌, 肺炎克雷伯菌 (*Klebsiella pneumoniae*) 和铜绿假单胞菌 (*Pseudomonas aeruginosa*) 的杀菌效果^[89-91]。这种非直接影响的机制可能是 lysoPC 通过提高细胞膜通透性使抗菌物质更容易进入菌体内^[87]。

1.2.3 LysoPC 在细菌致病中的作用

除了可以改变细菌细胞膜的结构, 外源 lysoPC 还在病原菌的细胞侵袭和炎症中发挥着重要作用^[92]。沙门氏菌感染宿主后能利用宿主细胞释放的 lysoPC 促进其侵袭蛋白 Sips 和 1 型毒力岛转录调控因子 HliA 的表达, 从而增强其对宿主细胞的侵袭效率^[93]。在这个过程中, 宿主源 lysoPC 还可以通过调控沙门氏菌的 cAMP (cyclic adenosine 3,5'-monophosphate) 依赖性信号通路, 诱导其鞭毛蛋白的合成和分泌, 从而通过结合 5 型 Toll 样受体反向激活宿主的炎症和先天性免疫反应^[36]。在结核分枝杆菌 (*Mycobacterium tuberculosis*) 感染过程中, 虽然尚不清楚 lysoPC 在其中发挥的作用, 但 lysoPC 在宿主巨噬细胞和吞噬体内的水平被发现显著升高^[34-35]。外源 lysoPC 还对耻垢分枝杆菌 (*Mycobacterium smegmatis*) 原生质球(spheroplasts) 有剧毒, 因为 lysoPC 可以破坏和裂解原生质球的细胞膜。但 lysoPC 对完整的耻垢分枝杆菌并没有毒性作用, 这可能是由于耻垢分枝杆菌细胞膜上的 YhhN 家族蛋白可以拮抗 lysoPC 对细胞的损伤^[94]。

此外, 细菌分泌的 lysoPC 还能影响宿主的部分生理学功能。来源于宿主肠道菌群的 lysoPC 能破坏肠道的屏障功能并与宿主炎症肠病的发生有密切关联^[95]。埃希氏菌(*Escherichia*)、嗜胆菌(*Bilophila*)、肠杆菌(*Enterorhabdus*)和戈尔多尼巴氏菌(*Gordonibacter*)这 4 种革兰氏阴性菌与宿主粪便中 lysoPC 含量的增加有密切联系。高浓度的 lysoPC 在体内和体外均被证实能诱导宿主的免疫应答和破坏宿主细胞之间的紧密连接^[95]。因此来源于肠道菌群的 lysoPC 被认为能损伤肠道上皮屏障, 并且是引起宿主结肠炎的重要致病因子。

1.3 溶血磷脂酰乙醇胺 lysoPE

1.3.1 LysoPE 的特点

LysoPE 是细菌中最主要也是被研究的最为广泛的两性 LPL。LysoPE 主要存在于革兰氏阴性菌的外膜中, 能够给细胞膜提供正向弯曲压力^[1,6,96-97]。细菌源 lysoPE 能在细菌死亡后被释放到外界环境中, 但目前还未发现活菌能够直接将 lysoPE 分泌到菌体外^[4]。在人和动物中, lysoPE 仅微量存在于组织之中, 在血浆中含量略高(血清中含量第二的 LPL; 浓度为 10–50 $\mu\text{mol/L}$, 或血清总磷脂量的 1%)^[1]。

细菌 lysoPE 可通过内源 PlidA 介导的 PE 水解反应或脂质 A 棕榈酰转移酶 PagP 介导的六酰化 LPS、三酰化 PG 合成反应被产生(图 2)^[6,10-11,37,98]。由于 lysoPE 能给细胞膜带来正向弯曲压力和其自身的类洗涤剂特点, lysoPE 被认为不适合掺入细胞膜脂质双分子结构中。因此通过细菌的脂质稳态调控, lysoPE 通常会被快速转化为 PE^[6,99-100]。但在一些细菌尤其是病原菌中, 在特定压力条件下, 其细胞膜中 lysoPE 的含量会显著增加^[6,37]。最近的研究表明, 在空肠弯曲杆菌中, 随着氧气浓度的上升, 其细胞膜中 lysoPE 的含量最高可达细菌总磷脂

含量的 34%^[42]。在其他研究中,环境中的可用葡萄糖、高温或者苯酚类杀虫剂可诱导假结核耶尔森菌(*Yersinia pseudotuberculosis*)中 lysoPE 的含量从约 1% 上升至 16.3%^[46,101-102]。在 8 °C 下生长的假结核分枝杆菌中,细菌生长稳定期细胞中 lysoPE 可达磷脂总含量的 45%^[103]。在霍乱弧菌中,胆盐可刺激其细胞膜 lysoPE 的含量从 2% 增加到 30%^[43]。在幽门螺旋杆菌中,酸性压力可以使其 lysoPE 的含量升高且同时诱导尿素酶细胞毒素 A 的释放^[48,104]。压力条件下细菌 lysoPE 含量的增加有可能是因为磷脂酶 PldA 活性的增强。噬菌体裂解^[105]、大肠菌素释放^[106]、乙二胺四乙酸(ethylenediamine tetraacetic acid, EDTA)处理^[107]或者热刺激^[47]均可提高大肠杆菌 PldA 的活性^[48,104]。

在大肠杆菌中, lysoPE 酰基链的长度介于 14–18 个碳原子之间,其中以 lysoPE 18:1 和 lysoPE 16:1 最为常见^[99,108]。在空肠弯曲杆菌中,其 lysoPE 酰基链的长度被发现介于 12–20 个碳原子之间,且在各长度的脂肪酸链上均有检测到饱和、不饱和以及含环丙烷结构,其中以 lysoPE 14:0 和 lysoPE 19:0c 的含量最高^[42,109]。在霍乱弧菌中,有 3 种不同长度脂肪酸链的 lysoPE (C16、C18 和 C20)被发现,其中 lysoPE 16:0 和 lysoPE 18:1 为最主要的亚类^[43,110]。在幽门螺旋杆菌中,目前仅检测出 lysoPE 18:1^[111]。

1.3.2 LysoPE 对细菌的作用

LysoPE 被证实是真核细胞必需的生长因子和细胞外调节因子^[112],也被发现具有分子伴侣的特点。例如,在尿素变性后, lysoPE 能促进柠檬酸合成酶和 α -葡萄糖苷酶的功能性折叠^[46-47]。在细菌中, lysoPE 被认为同时具有分子伴侣和化学伴侣的性质,可以直接影响细菌膜蛋白的结构和功能。LysoPE 在细菌细胞膜中含量的升高一方面可促进额外的铁离子内流进入菌体

内^[99],但同时会破坏细菌细胞膜稳态对膜结构造成严重损伤,造成细菌生长抑制以及细胞间质的渗漏,极端情况下导致细胞溶解^[113]。在大肠杆菌中,细胞膜中高含量的 lysoPE 会导致细胞外膜和内膜的界限消失,造成细胞质颗粒变性和空泡化^[113]。LysoPE 在细胞膜中的累积还会破坏膜脂质对称性,引起细胞外膜渗透屏障的破坏,从而使大肠菌素-铁复合体和万古霉素等物质更容易进入细胞周质,分别导致细菌复制增殖的促进和抑制^[99]。

LysoPE 还在细菌拮抗外界环境压力过程中发挥着重要作用。在幽门螺旋杆菌和假结核分枝杆菌中, lysoPE 的积累是细菌适应酸性环境或抵御抗生素压力的必要条件^[48,102]。细菌抗酸可能涉及到的分子机制包括:(1) 通过改变细胞膜和外膜蛋白的构象阻断质子内流以及细胞周质、细胞质分子伴侣与其配体的识别、结合,从而调控细胞内 pH^[114];(2) 通过激活细胞膜上的氯离子传导通道(chloride channel, ClC),使质子以不带电的 HCl 形式进入菌体,随后解离为 H⁺和 Cl⁻,降低菌体内 pH^[115-116];(3) 通过重塑细胞内膜磷脂的组成,降低质子渗透性,从而拮抗酸性外环境^[117]。细菌耐抗生素的机制可能是通过降低细菌膜孔蛋白通道的通透性,抑制抗生素的转运^[102,118]。目前已知 lysoPE 在细胞膜中的掺入可以导致膜局部曲度的改变,引起膜蛋白(包括孔蛋白)构象及功能的改变^[53]。但 lysoPE 介导细菌耐酸及耐药的具体机制还有待进一步研究。

此外,压力条件下 lysoPE 在细胞内膜上的重分配会改变细胞膜双分子层的变形能,导致膜蛋白构象中自由能的改变^[119],随后可反作用于蛋白,调控蛋白的分泌、扩散和嵌入^[120]。因此, lysoPE 在细菌膜上的精确分布为细菌必需膜蛋白的正确装配提供了结构基础^[121-122]。

1.3.3 LysoPE 的抗菌活性

除了对细菌细胞膜结构的修饰作用之外, lysoPE 还具有抗菌活性。家蝇(*Musca domestica*)分泌的 lysoPE (16:1)被发现具有抗菌活力^[123]。从拟杆菌门噬几丁质菌属(*Chitinophaga* spp.)细菌中分离纯化的 lysoPE 在浓度为 4–16 $\mu\text{g}/\text{mL}$ 时具有抗革兰氏阴性卡他莫拉菌(*Moraxella catarrhalis*)的活性, 在浓度为 16–64 $\mu\text{g}/\text{mL}$ 时具有抗革兰氏阳性藤黄微球菌(*Micrococcus luteus*)的活性^[124]。LysoPE 的抗菌活性被认为和选择性抑制细菌钾离子转运系统有关^[123]。细菌需要钾离子来完成许多细胞生理反应, 包括维持细胞内酶的活性、pH 稳态和膜电位调节等^[125]。通过阻碍细菌对钾离子的摄取, lysoPE 可对细菌造成致死性损伤^[123]。但是该假设并不能完全解释为什么 lysoPE 不会影响大多数革兰氏阳性菌的生长, 因为革兰氏阳性菌只有一个单操作性的钾离子转运通道, 而革兰氏阴性菌具有多个此通道, 因此选择性系统抑制被认为会对革兰氏阳性菌带来致命的影响^[6,126-127]。LysoPE 的抗菌活性还有可能是因为外源 lysoPE 可以选择性掺入细菌细胞膜中, 透化细胞膜。有报道表明, lysoPE 水平在细胞膜中的升高会导致细菌细胞膜的瓦解并激活细菌的自溶机制, 造成细胞壁成分和胞内物质(例如酶)的大量外流^[104]。

1.3.4 LysoPE 在细菌-宿主互作中的作用

细菌分泌的 LysoPE 还能对宿主产生重要影响。尽管 lysoPE 在细菌中普遍存在, 但长期以来被认为在调节宿主与微生物的相互作用中并不重要^[128], 目前这种观点正在被逐渐改变。海洋无脊椎水螅虫(*Hydractinia echinata*)幼虫的变态反应就依赖于细菌 LPL。幼虫与 LPL 混合物(16:0/18:1 lysoPG、18:0 lysoPE 和 16:0 lysoPA)的物理接触被证实是幼虫向群体成虫阶段转化的必需条件^[129]。人和动物体内共生菌群分泌的

lysoPE 被报道可以通过修复肠上皮层的完整性保护宿主肠道^[4]。细菌释放的 lysoPE 还能通过修复 H_2O_2 引起的宿主紧密连接蛋白和黏附连接蛋白表达抑制来维持肠道的屏障功能^[4,130]。马岛噬冷菌(*Algoriphagus machipongonensis*)生成的 lysoPE 是促进原生动物领鞭毛虫(*Salpingoeca rosetta*)从单细胞结构发育成多细胞玫瑰花结结构的激活因子和协同增效因子。在此过程中 lysoPE 通过激活磺酰脂玫瑰花结诱导因子参与领鞭毛虫玫瑰花结发育的起始、稳定和成熟阶段的生物调控, 帮助了其玫瑰花结完整结构的形成, 并催化花结的成熟^[128]。但另一方面, 细菌分泌的 lysoPE 对宿主细胞有毒性作用。我们最新的研究表明, 来源于空肠弯曲杆菌的 lysoPE (尤其是短链 lysoPE)能够通过激活宿主细胞的氧化应激反应透化宿主细胞的细胞膜^[49]。而在嗜肺军团菌(*Legionella pneumophila*)感染过程中, 宿主细胞线粒体膜中 lysoPE 和 lysoPC 的累积可通过激活线粒体细胞色素 C 的释放引起细胞凋亡^[131]。因此 lysoPE 在细菌-宿主互作中具有双向调节作用。

但目前, lysoPE 在宿主细胞上的特异性受体还未被识别。有报道表明溶血磷脂酸受体 (lysophosphatidic acid receptor, LPAR)能被 lysoPE 直接识别或在真核细胞中通过自体毒素将 lysoPE 转化为 lysoPA 后被识别。在 LPAR 被 lysoPE 激活后会促进蛋白激酶 K (protein kinase C, PKC)的活化, 随后促进细胞紧密连接的形成和黏附连接蛋白的异位, 增强上皮层的完整性^[132-133]。

1.4 溶血磷脂酰甘油 lysoPG

LysoPG 是细菌细胞膜中另一个次要 LPL 组分, 能通过 PldA_2 介导的磷脂酰甘油 (phosphatidylglycerol, PG)水解反应或 PagP 催化的脂质 A 合成反应被生成^[6,37,134]。和 lysoPE 类似, lysoPG 能被革兰氏阴性菌的溶血磷脂转

运系统(lysophospholipid transporter, LplT)从细菌细胞膜中转出, 随后被内源酰基转移酶 Aas 酰化。在大肠杆菌中 lysoPG 的重塑效率是 lysoPE 的 3 倍^[135]。由于 LplT 转运过程中对 lysoPG 和 lysoPE 的底物结合亲和力、转运速率相似^[62], lysoPG 的高重塑率可能是由于酰基转移酶 Aas 对 lysoPG 的亲和力更高。LysoPG 在细菌细胞膜中仅极少量存在的原因也因此被认为是 lysoPG 极易被重酰化以补充膜磷脂所致^[40]。但我们最近的研究结果表明, 缺少 LplT 转运系统的空肠弯曲杆菌 *C. jejuni* 最高可储存约为总磷含量 27% 的 lysoPG 在其细胞膜中^[42,109]。

目前对 lysoPG 的生物生理学功能的了解还相当匮乏。在大肠杆菌中, lysoPG 可能在细胞外膜中扮演着荚膜多糖锚定物的角色^[136]。在人和动物中, lysoPG 的含量在出现急性冠脉综合征的组织中剧增, 且被认为和心血管疾病的发病有关^[20]。在恶性疟原虫(*Plasmodium falciparum*) 中, 其自身分泌的 lysoPG 有助于其在宿主红细胞内的生长发育^[137]。但以上研究均未对 lysoPG 作用的具体通路或机制进行进一步的研究。

1.5 溶血磷脂酰丝氨酸 lysoPS

1.5.1 LysoPS 的特点

LysoPS 和其他 LPL 最大的不同是其头部结构是一个磷酸-L-丝氨酸分子。这个头部基团能与 LPL 甘油主链 sn-3 位置上的氢氧化物结合形成磷酸酯键, 从而合成甘油磷酸-L-丝氨酸^[6,138]。分泌型 PldA 是 lysoPS 生物合成的关键酶(图 2)^[1,6]。在细胞内, lysoPS 可被从 C10 的短链脂肪酸到 C24 的长链脂肪酸的多种脂质酰化而生成^[139]。

1.5.2 LysoPS 的功能

在真核细胞中, lysoPS 是一种重要的生物活性脂质, 在包括巨噬细胞活化、肥大细胞脱颗粒、白细胞激活和调节性 T 细胞成熟等免疫

反应过程中发挥重要作用^[140]。在如曼氏血吸虫(*Schistosoma mansoni*)的寄生虫中, 其体表膜中富含 lysoPS 和 lysoPE, 这两种 LPL 在调控寄生虫与宿主的互作中发挥重要作用^[141]。和其他 LPL 类似, lysoPS 存在于细菌细胞膜中, 但仅微量存在于如脱硫弧菌属(*Desulfovibrio* sp.)的特定细菌中^[61]。因此 lysoPS 在细菌中的生物学功能目前还尚不清晰。有报道表明, 在悉生小鼠中定殖的大肠杆菌与在无菌小鼠中定殖的大肠杆菌相比具有更高浓度的 lysoPS^[142]。还有研究推测植物乳酸杆菌分泌的存在于胞外膜泡中的 lysoPS 可能是生物体内或体间信息传递的必需脂类介质^[63]。但以上报道均未对 lysoPS 的具体作用机制进行进一步研究。最近有学者指出, 肠道菌群分泌的 lysoPS 在克罗恩病(Crohn's disease)中可诱发宿主体内辅助性 T 细胞(Th1)的免疫病理反应, 包括在结肠中促进能产生 IFN- γ 的 CD4⁺ T 细胞的积累、增强 Th1 细胞的效应、调节 Th1 细胞的生物能量代谢和诱导 Th1 细胞表观遗传变异等^[143]。因此, 细菌 lysoPS 可能是细菌致病和肠道炎症发展过程中的一种重要生物活性脂类因子。

1.6 溶血磷脂酰肌醇 lysoPI

1.6.1 LysoPI 的特点

lysoPI 是内源溶血甘油磷脂的另一种亚类, 其头部结构为肌醇分子。LysoPI 是由 PldA 水解磷脂酰肌醇(phosphatidylinositol, PI)的一条脂肪酸链后被生成(图 2), 其酰基链绝大多数以 C16:0, C18:0 或 C24:0 的形式存在^[1,6,144]。通常来说, 合成 PI 和 lysoPI 是真核细胞特有的代谢途径, 但需氧放线菌(*Actinomycetes*)、粘球菌(*Myxococcus*)和部分 δ -变形菌(*Deltaproteobacteria*)含有丰富的 PI^[61,145]。

1.6.2 LysoPI 的生物学功能

在某些真核细胞系中, lysoPI 具有影响细

胞生长、分化和活力(精子获能)的能力^[146-147]。但因为 lysoPI 在细菌中少有被检测到, 因此对其生物学功能的了解仅停留在细菌-宿主互动上^[61]。在一项最新的研究中, 一种新型蜜蜂乳酸杆菌 (*Lactobacillus apis*) 被发现能够促进蓝蜂的 lysoPI 代谢, 并且能够增强蜜蜂的记忆力, 但其具体机制尚不清晰^[148]。幽门螺旋杆菌也被报道能诱导动物组织上皮细胞中 lysoPI 的合成^[149]。

在另一项研究中, lysoPI 18:0 被发现在肺结核病人的血浆中含量升高^[150], 虽然这部分 lysoPI 被认为是与结核分枝杆菌 (*Mycobacterium tuberculosis*) 相关联, 但目前的研究手段无法区分 lysoPI 是由细菌直接分泌还是由细菌刺激宿主分泌而产生。在人体内, 对 lysoPI 的研究较为充分, lysoPI 被发现是一种人内源性大麻素神经递质^[151], 能够诱导细胞增殖、迁移及肿瘤过程中内皮细胞的活化^[152-153]。此外, 人 G 蛋白偶联蛋白 55 (G protein-coupled protein receptor 55, GPR55) 被认为是 lysoPI 的受体^[154]。总之, lysoPI 在真核细胞中大量存在并在许多重要生物生理学过程中发挥重要作用, 宿主体内的菌群很有可能通过参与 lysoPI 的分泌来调控宿主体内的部分生化反应。

2 总结

细菌被膜(细胞壁、细胞膜)是保护细胞免受恶劣多变的外部环境影响的重要多层外部屏障结构。作为重要的生物活性信号分子, LPL 能通过间接影响细菌细胞膜脂质层的完整性, 改变细菌的细胞结构和功能。最近的相关研究指出 LPL 在细菌侵袭和环境压力适应过程中发挥着重要作用。但在这个快速发展的领域, 细菌 LPL 对细胞带来的生理学影响还存在大量的未知。本综述阐释了 LPL 在细菌生理学以及在细菌-宿主互动过程中所发挥的功能。目前的研究

表明, 环境的改变和宿主的免疫反应是细菌长期面临的生存压力, 细菌因此进化出了 LPL 调控机制来改变其被膜的物理结构以适应多种严苛的细胞外环境。分泌型 LPL 被认为不仅具有抗菌效力还具有细胞毒性。因此, 一方面, 细菌可以通过自身 LPL 的分泌在与其他细菌的竞争中取得生存优势和提高自身对宿主的感染效率; 另一方面, 细菌胞外的宿主源 LPL 能够作为碳源被细菌利用并储存, 帮助病原体在感染宿主过程中存活^[155-157]。综上所述, LPL 是细菌中一种重要的生物分子, 对 LPL 在细菌中发挥的多重生物学功能以及 LPL 如何影响细菌-宿主之间互动的更深入研究将有助于人类更进一步揭开细菌生存及感染的自然规律, 同时也为传染病防控及公共卫生治理提供新的方向和思路。

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