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Review 综述

# 肽聚糖水解产物：一类重要的信号分子

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**摘　要：**肽聚糖是细菌细胞壁的关键组分，对维持细菌形态、保持渗透压稳定至关重要。在细菌正常生长过程中，肽聚糖持续进行合成与水解，并维持动态平衡。肽聚糖水解酶是调控肽聚糖稳态的关键酶类，其水解产物可通过肽聚糖循环途径重新参与生物合成。近年来的研究表明，肽聚糖水解产物还可作为一类重要的信号分子调控抗生素耐药性、促进芽孢萌发、介导种间相互作用等关键生理过程，这极大地深化了人们对细菌生理调控机制的理解。因此，本文综述了细菌中肽聚糖水解酶的主要类型，并重点总结了肽聚糖水解产物作为信号分子调控生理过程的最新研究进展，为深入探究细菌肽聚糖的多重生理功能提供理论依据。

**关键词：**细菌细胞壁；肽聚糖；肽聚糖水解产物；信号分子；基因表达调控

# Peptidoglycan fragments as key signaling molecules

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**Abstract:** Peptidoglycan as a key component of the bacterial cell wall is essential for maintaining bacterial morphology and osmotic stability. During normal bacterial growth, peptidoglycan is continuously remodeled through synthesis and hydrolysis, achieving a dynamic equilibrium. Peptidoglycan hydrolases play a central role in regulating peptidoglycan homeostasis, and the hydrolysis products (peptidoglycan fragments) are recycled for biosynthesis *via* the peptidoglycan recycling pathway. Growing evidence indicates that peptidoglycan fragments function as important

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signaling molecules to regulate critical physiological processes such as antibiotic resistance, endospore germination, and interspecies interactions, greatly expanding our understanding of bacterial physiological regulation. This review summarizes the major classes of bacterial peptidoglycan hydrolases and highlights recent advances in the role of peptidoglycan fragments as signaling molecules in regulating cellular processes, providing a theoretical foundation for further exploration of the multifaceted physiological functions of bacterial peptidoglycan.

**Keywords:** bacterial cell wall; peptidoglycan; peptidoglycan fragments; signal molecules; gene expression regulation

肽聚糖(peptidoglycan)是细菌细胞壁的核心成分，对维持细胞形态和渗透压稳定起着至关重要的作用。其结构由聚糖链和短肽 2 部分构成：聚糖链由 N-乙酰葡糖胺(N-acetylglucosamine, GlcNAc)与 N-乙酰胞壁酸(N-acetylmuramic acid, MurNAc)通过 β-1,4 糖苷键交替连接而成；短肽则连接于 MurNAc 上，相邻短肽之间通过交联形成网状结构[1-2]。在短肽组成方面，革兰氏阴性菌[如大肠埃希氏菌(*Escherichia coli*)]以及部分革兰氏阳性菌[如枯草芽孢杆菌(*Bacillus subtilis*)]的肽聚糖通常为 L-Ala-D-Glu-*m*-$A_2$pm-D-Ala-D-Ala，其中第 3 位氨基酸为内消旋二氨基庚二酸(*meso*-diaminopimelic acid, *m*-$A_2$pm)；而大多数革兰氏阳性菌[如金黄色葡萄球菌(*Staphylococcus aureus*)]该位置则为 L-赖氨酸(L-lysine, L-Lys)[1-2]。

在细菌正常生长过程中，肽聚糖持续经历合成、水解与更新(turnover)。每一世代中约 50% 的肽聚糖会被更新[3-5]。革兰氏阳性菌因缺乏外膜，其肽聚糖水解产物(即肽聚糖片段)直接释放至培养基等外部环境；而革兰氏阴性菌中，大部分肽聚糖水解产物进入细胞质，通过肽聚糖循环(peptidoglycan recycling)途径重新参与肽聚糖的生物合成，仅有约 6%−8% 的组分被释放至胞外[3-5]。

已有大量研究表明，细菌通过多种信号分子调控自身基因表达以及控制自身行为，这些信号分子包括 N-酰基高丝氨酸内酯、寡肽、自诱导肽和吲哚等群体感应信号分子，环磷酸腺苷(cyclic adenosine monophosphate, cAMP)和环二鸟苷单磷酸(cyclic diguanosine monophosphate, c-di-GMP)等第二信使分子，以及“报警”信号分子鸟苷四磷酸(guanosine tetraphosphate, ppGpp)等[6]。近年来，越来越多的研究表明肽聚糖水解产物不仅能通过循环过程重新参与肽聚糖的生物合成，还能作为重要的信号分子调控多种关键生理过程[7-9]，极大地拓宽了对细菌生理调控机制的理解。基于此，本文系统总结肽聚糖水解产物作为信号分子调控的生理过程。

## 1 肽聚糖水解酶与肽聚糖组分

肽聚糖水解酶(peptidoglycan hydrolases)是指能够切开细菌肽聚糖中共价键的酶的总称。肽聚糖水解酶种类繁多，根据其酶切位点不同主要分为 4 类：溶菌糖基转移酶(lytic transglycosylases, LTs)可切割肽聚糖链中 MurNAc 和 GlcNAc 之间的 β-1,4 糖苷键，形成脱水的 MurNAc (1, 6-anhydroMurNAc, anhMurNAc)；肽聚糖酰胺酶(N-acetylmuramyl-L-Ala amidases)可水解 MurNAc 和短肽 N-末端 L-丙氨酸(L-alanine, L-Ala)之间的酰胺键，将短肽从糖链中切离；DD-内肽酶(DD-endopeptidases, DD-EPases)和 DD-羧肽酶(DD-carboxypeptidases, DD-CPases)均能水解 2 个氨基酸之间的酰胺键，其中前者水解相邻短肽间形成的交联，后者水解短肽中的 C-末端氨基酸(图 1)[4-5,10]。

细菌中存在大量肽聚糖水解酶，但不同细菌中肽聚糖水解酶的数量存在差异。例如，*E. coli* 中已发现 8 个 LTs (Slt70、MltA−G)、4 个

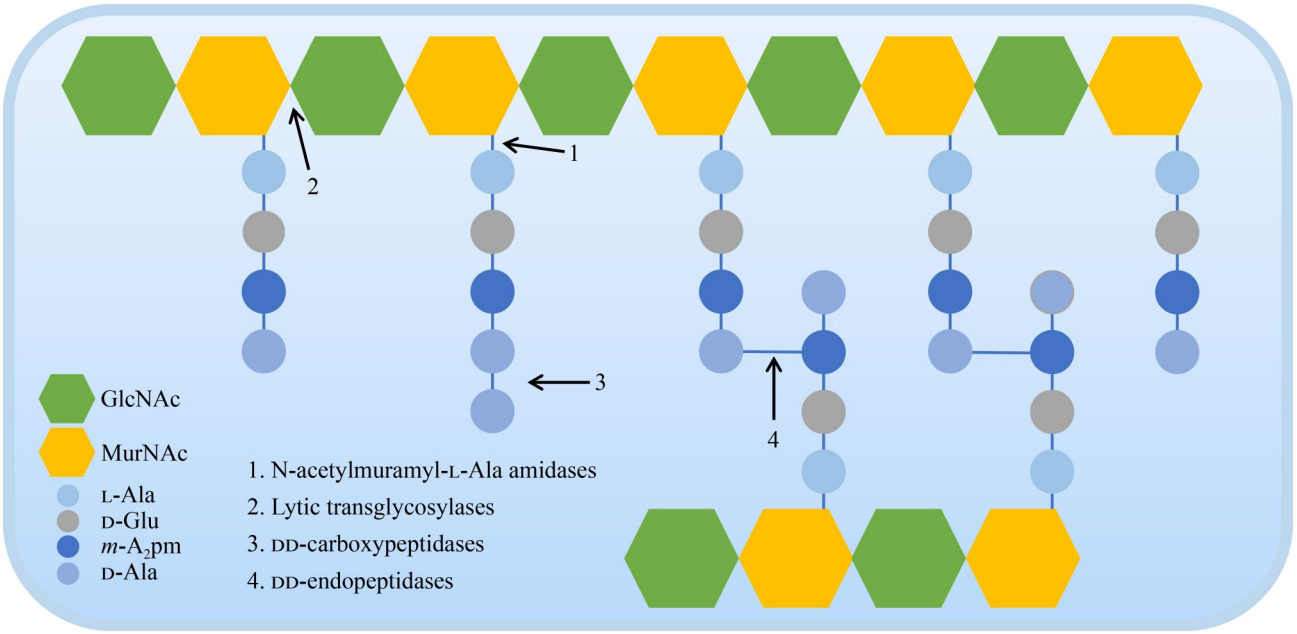


**图1　肽聚糖水解酶作用位点示意图**

Figure 1　Schematic of cleavage sites of peptidoglycan hydrolases.

肽聚糖酰胺酶(AmiA、AmiB、AmiC 和 AmiD)以及 6 个 DD-CPases 和/或 DD-EPases (PBP4、PBP4b、PBP5、PBP6、PBP6b 和 PBP7)[3,11]；霍乱弧菌(*Vibrio cholerae*)具有 8 个 LTs、2 个 DD-CPases、5 个 DD-EPases，但仅有 1 个肽聚糖酰胺酶(AmiB)[12]。

细菌在世代生长过程中肽聚糖层持续进行合成、水解与更新，但始终处于动态平衡状态[1,10]。在上述肽聚糖水解酶的共同作用下，肽聚糖被水解成结构多样的肽聚糖水解产物(如 GlcNAc、GlcNAc-MurNAc-tripeptide、1, 6-anhMurNAc-peptides 以及 D-Glu-*m*-$A_2$pm 等)，这些组分在糖链长度、短肽的氨基酸个数以及短肽间是否交联等方面呈现出高度的多样性[13-14]。在实验室条件下，绝大多数肽聚糖水解产物通过肽聚糖循环途径重新参与生物合成；然而，当细菌面临噬菌体、竞争者等生物胁迫以及肽聚糖靶向抗生素等非生物胁迫时，肽聚糖水解产物的组成和丰度均会发生显著变化，导致其在细胞内积累或大量分泌至胞外，进而作为信号分子发挥作用[7-9,15-16]。

## 2　肽聚糖水解产物作为信号分子调控多种生理过程

越来越多的研究表明，肽聚糖水解产物不仅能通过循环过程重新参与肽聚糖的生物合成，还能作为信号分子实时监控细菌的生长状态，进而调控多种生理过程，如诱导抗生素耐药性、促进芽孢萌发以及介导物种间的相互作用等(图 2)[7-9]。

### 2.1　诱导抗生素耐药性

#### 2.1.1　革兰氏阴性菌中抗生素耐药性的诱导

关于肽聚糖水解产物对基因表达的调控，目前研究最为清楚的是阴沟肠杆菌(*Enterobacter cloacae*)和弗氏柠檬酸杆菌(*Citrobacter freundii*)等肠杆菌科细菌以及铜绿假单胞菌(*Pseudomonas aeruginosa*)等细菌中 β-内酰胺酶基因 *ampC* 的诱导表达调控，β-内酰胺酶 AmpC 能够水解 β-内酰胺类抗生素，进而使细菌产生耐药性[17-22]。这些细菌中 *ampC* 基因的表达受该

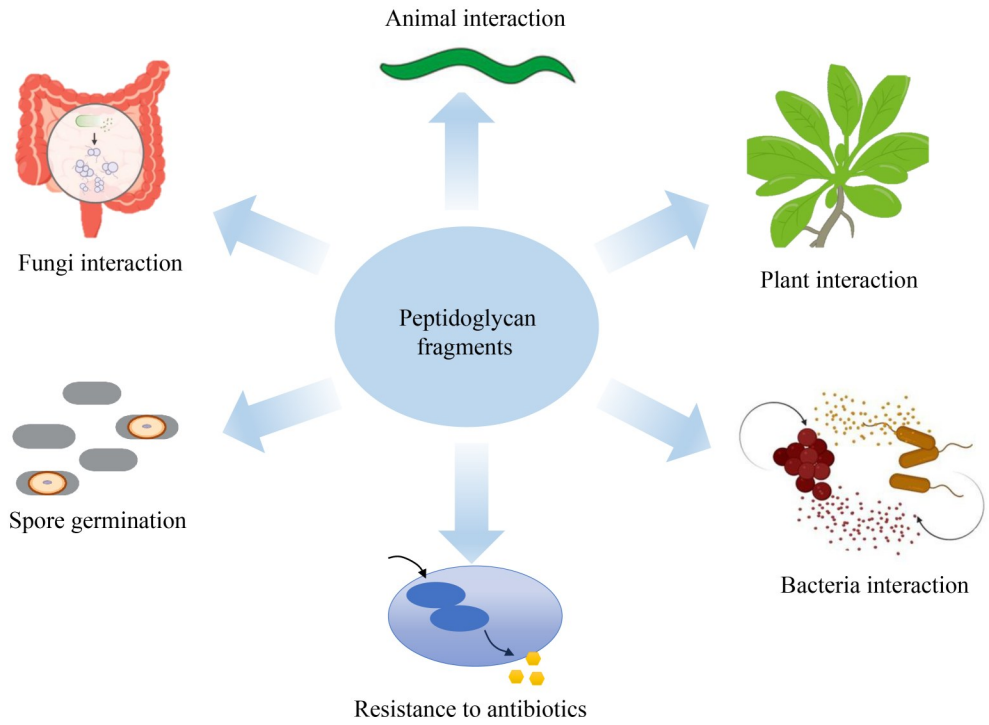


**图2 肽聚糖水解产物是一类重要的信号分子**

Figure 2 Peptidoglycan fragments as key signaling molecules.

类抗生素诱导，基因组中 *ampC* 与 *ampR* 相邻排列，但转录方向相反，*ampR* 基因编码的 LysR 家族转录因子 AmpR 能够与不同的肽聚糖片段结合，从而诱导或阻遏 *ampC* 基因的表达；当缺乏 β-内酰胺类抗生素时，肽聚糖更新过程中产生的肽聚糖水解产物经通透酶 AmpG 进入细胞质，在肽聚糖酰胺酶 AmpD 和 β-乙酰氨基葡糖苷酶 NagZ 的共同作用下，细胞质中的 anhMurNAc-peptides 浓度较低，而三肽 L-Ala-D-Glu-*m*-$A_2$pm 含量较高，可进一步形成肽聚糖生物合成的前体分子 UDP-MurNAc-pentapeptide，其作为阻遏信号分子与 AmpR 结合，从而抑制 *ampC* 的转录；当抗生素存在时，肽聚糖生物合成受阻导致肽聚糖水解产物大量增加并进入细胞质，由于 AmpD 饱和使得 anhMurNAc-peptides 大量积累，其中的 anhMurNAc-tripeptide 作为诱导信号分子与 AmpR 结合，引起 AmpR 构象改变并激活 *ampC* 的转录[17-22]。对 *P. aeruginosa* 的研究发现，AmpR 实际上是一种全局调控因子，还能够调控蛋白酶、毒力因子甚至群体感应等相关基因的表达[8,23-24]，这表明含有 AmpR 的细菌中肽聚糖水解产物能够作为信号分子通过 AmpR 调控众多生理过程。

除 AmpR 介导的调控通路外，肽聚糖水解产物也能通过激活双组分系统(two-component system)调控耐药基因的表达。经典的双组分系统包含组氨酸激酶(histidine kinase)和应答调控蛋白(response regulator)，前者位于细胞质膜，感知信号后自磷酸化并将信号传递至位于细胞质中的应答调控蛋白，进而调控基因的转录[25]。嗜水气单胞菌(*Aeromonas hydrophila*)中 β-内酰胺酶基因的诱导表达受双组分系统 BlrAB 调控[26-27]。当 β-内酰胺类抗生素存在时，二糖五肽单元(GlcNAc-MurNAc-pentapeptide)含量显著升高，并且万古霉素(与 D-Ala-D-Ala 特异性结合的抗生素)处理后 β-内酰胺酶基因的表达受到抑

制，这表明二糖五肽单元很有可能作为信号分子激活 BlrAB，诱导 β-内酰胺酶基因的表达[28]。

*V. cholerae* 无编码 β-内酰胺酶的基因，但其对 β-内酰胺类抗生素具有耐受性(tolerance)，即在高浓度杀菌性抗生素存在时细菌虽不能生长但仍保持存活能力[29-30]。研究发现这种抗生素耐受性受双组分系统 VxrAB (也称为 WigKR)调控；VxrAB 不仅被 β-内酰胺类激活，还能被 D-环丝氨酸和磷霉素等靶向细胞壁生物合成的抗生素激活，通过上调整个肽聚糖生物合成通路中关键基因的表达来提高细菌对 β-内酰胺类抗生素的耐受性[31-33]。由于 VxrAB 能被结构不同的细胞壁靶向抗生素激活，其组氨酸激酶 VxrA 可能并非与抗生素直接结合，最新的结构生物学研究证实了该推测[34]。VxrA 直接结合的信号分子很有可能是肽聚糖损伤后产生的某种肽聚糖水解产物，但目前尚未被成功鉴定。

近期，本实验室从自然环境分布广泛的希瓦氏菌(*Shewanella*)中挖掘出一套调控 β-内酰胺酶 BlaA 诱导表达的双组分系统 PghKR[35-36]。与 VxrAB 类似的是，PghKR 也能被多种结构不同的肽聚糖靶向抗生素(包括 β-内酰胺类、D-环丝氨酸、万古霉素和默诺霉素等)激活，但与其他组氨酸激酶不同的是，PghK 及其同源蛋白的周质空间结构域部分包含碳水化合物结合模块(carbohydrate-binding module, CBM)[36-37]。该模块广泛存在于碳水化合物水解酶中，已被证明可以特异性结合糖类底物，包括单糖、二糖、寡糖和多糖等[38-40]。因此，PghK 很有可能直接结合肽聚糖损伤后产生的肽聚糖糖类片段，进而将信号通过磷酸化传递到细胞内，启动 β-内酰胺酶的诱导表达[36]。与该推测一致的是，溶菌糖基转移酶的缺失提高了细菌中 β-内酰胺酶的表达[41]。此外，PghKR 系统激活后还能触发细菌严紧反应(stringent response)，通过延滞生长提高细菌在细胞壁靶向抗生素作用下的存活能力[36,42]。因此，这些双组分系统中与组氨酸激酶直接结合的肽聚糖水解产物有待进一步鉴定。

### 2.1.2 革兰氏阳性菌中抗生素耐药性的诱导

尽管革兰氏阳性菌中 β-内酰胺酶基因的诱导表达调控机制与革兰氏阴性菌不同，但研究表明该过程也由肽聚糖水解产物介导[43]。*S. aureus* 和地衣芽孢杆菌(*Bacillus licheniformis*)中 β-内酰胺酶基因(*blaZ*/*P*)的诱导表达受阻遏蛋白 BlaI 和与膜结合的青霉素受体蛋白 BlaR1 控制[44-49]。当无 β-内酰胺类抗生素存在时，BlaR1 未被激活，BlaI 形成的二聚体与 *blaZ*/*P* 和 *blaIR1* 操纵子之间的启动子区结合，从而阻止 *blaZ*/*P* 基因的转录；当抗生素存在时，肽聚糖合成酶 PBP1a 部分乙酰化失活致使肽聚糖更新加速以及肽聚糖水解产物增多，进入细胞质中的四肽 L-Ala-γ-D-Glu-*m*-$A_2$pm-D-Ala (*B. licheniformis*)或 L-Ala-γ-D-Glu-L-Lys-D-Ala (*S. aureus*)增加，在 L,D-羧肽酶 YkfA 的作用下形成三肽 L-Ala-γ-D-Glu-*m*-$A_2$pm 或 L-Ala-γ-D-Glu-L-Lys；另一方面，抗生素致使 BlaR1 受体乙酰化，进而激活其位于细胞质中的蛋白酶活性，将三肽水解成二肽 γ-D-Glu-*m*-$A_2$pm 或 γ-D-Glu-L-Lys。该二肽可以作为共激活因子(coactivator)将阻遏蛋白 BlaI 失活，进而激活 *blaZ*/*P* 基因的转录，表达的 β-内酰胺酶将 β-内酰胺类抗生素水解，进而使细菌产生耐药性[43,50-52]。

革兰氏阳性菌还能通过编码额外的低亲和力 PBP (如 *S. aureus* PBP2a)实现对 β-内酰胺类抗生素产生耐药性。PBP2a 编码基因 *mecA* 的诱导表达模式与 *blaZ/P* 类似，也受相应的阻遏蛋白 MecI 和青霉素受体蛋白 MecR1 控制，并且二肽 γ-D-Glu-L-Lys 同样作为共激活因子调控基因的表达[43,48,50,53]。

## 2.2 促进芽孢萌发

芽孢杆菌目(*Bacillales*)和梭菌目(*Clostridiales*)等革兰氏阳性菌在营养匮乏时会形成抗逆性强的休眠体——芽孢，从而渡过不利的环境；当生长条件适宜时，L-Ala 等营养物质可以作为萌发剂促进芽孢萌发[54-55]。研究发现肽聚糖水解

产物也可以作为信号分子促使芽孢的萌发[56-58]。值得注意的是，芽孢萌发时需要的 L-Ala 等萌发剂浓度远高于生理浓度，而需求的肽聚糖水解产物浓度极其微量(约 0.1 pg/mL)，这表明肽聚糖水解产物更有可能在生理条件下指示芽孢所处的生存环境[57]。进一步研究发现，*B. subtilis* 中起到促进芽孢萌发作用的肽聚糖片段是二糖三肽(GlcNAc-MurNAc-L-Ala-γ-D-Glu-*m*-$A_2$pm)和二糖四肽(GlcNAc-MurNAc-L-Ala-γ-D-Glu-*m*-$A_2$pm-D-Ala)，并且其短肽中第 3 位的氨基酸(*m*-$A_2$pm)至关重要；而 *S. aureus* 等大多数革兰氏阳性菌来源的二糖三肽中相应的位置为 L-Lys，这种二糖三肽无法促进 *B. subtilis* 芽孢的萌发[57]。

肽聚糖水解产物促进芽孢的萌发依赖于受体蛋白 PrkC，肽聚糖和二糖三肽无法促进 *prkC* 基因缺失的细菌芽孢萌发[57]。PrkC 蛋白属于 Ser/Thr 激酶(serine/threonine kinase)，由位于细胞质中的 N-末端激酶结构域和位于细胞膜外侧的 C-末端结构域组成，其显著的特征是 C-末端结构域包含 3 个 PASTA (penicillin-binding and Ser/Thr kinase-associated)重复，该重复结构负责与肽聚糖直接结合[57,59-60]。肽聚糖水解产物与芽孢萌发之间的特异性与 PrkC 有关，*B. subtilis* 中 PrkC 能够响应其自身的肽聚糖，但无法响应 *S. aureus* 的肽聚糖[57]。最新的研究显示，*B. subtilis* 肽聚糖经变溶菌素(mutanolysin)酶解后产生的肽聚糖水解产物并不能促进芽孢萌发，而在一定程度上抑制了由 L-丙氨酸等萌发剂引起的芽孢萌发；相反，纯化后的肽聚糖单体和二聚体则促进了由萌发剂引起的芽孢萌发[61]。总之，肽聚糖水解产物在芽孢萌发过程中的作用还有待进一步探究(表 1)。

## 2.3 介导种间相互作用

肽聚糖水解产物除作为胞内信号分子调控细菌自身的生理过程外，还能作为种间信号分子调控细菌之间以及细菌与真核生物(如真菌、植物和动物等)之间的相互作用。

### 2.3.1 细菌之间的相互作用

许多感染性疾病由多种微生物混合感染引起，微生物之间通常存在协同作用，导致疾病严重程度增加。*P. aeruginosa* 是微生物混合感染中最主要的病原菌之一，当其与革兰氏阳性菌共培养时，后者产生的肽聚糖及其水解产物 GlcNAc 能够提高 *P. aeruginosa* 中假单胞菌喹诺酮信号(*Pseudomonas* quinolone signal, PQS)群体感应信号分子、弹性蛋白酶和绿脓菌素等多种毒力因子的含量，进而增强其感染能力，同时也能增强其对革兰氏阳性菌的杀伤力[62-63,70]。*P. aeruginosa* 中的双组分系统 PA0600-PA0601 可能负责肽聚糖及其水解产物的感知与信号传递，当应答调控蛋白 PA0601 缺失后细菌不再响应革兰氏阳性菌来源的肽聚糖及其水解产物[63,71]。

*B. subtilis* 通过产生非核糖体肽类和聚酮类抗生素杀死周围的其他微生物(竞争者)[72-73]。研究发现其他细菌产生的肽聚糖能够诱导 *B. subtilis* 合成抗生素，且敏感竞争者来源的肽聚糖对抗生素合成的诱导程度显著高于抗性竞争者，抗生素的诱导表达伴随着细菌生长速度变慢，表明细菌的代谢负担增加[64]。肽聚糖的感知与调控细菌感受态的双组分系统 ComP/ComA 有关，ComA 缺失会使 *B. subtilis* 无法响应其他细菌产生的肽聚糖，抗生素的合成不再被诱导[64,74]。

最新研究表明，外源细菌裂解后产生的肽聚糖可被 *V. cholerae* 识别为“危险信号”，显著诱导其形成生物被膜，从而保护细菌免受噬菌体感染或其他因素引起的细胞裂解；进一步研究发现，外源肽聚糖也能诱导其他多种细菌形成生物被膜，暗示该现象在细菌中广泛存在[75]。经内肽酶或溶菌糖基转移酶消化后的肽聚糖仍保留生物被膜诱导能力，推测二糖四肽(tetrapeptide anhydro-disaccharides)可能是真正起作用的信号分子，肽聚糖对生物被膜的诱导与第二信使 c-di-GMP 水平增加有关[75]。

综上所述，微生物群落中某些细菌能够感

**表1 肽聚糖水解产物及其调控的生理过程**

Table 1 Physiological function regulated by peptidoglycan fragments

| Peptidoglycan fragment | Species | Sensor/regulator | Physiological function | References |
|---|---|---|---|---|
| anhMurNAc-peptides/ UDP-MurNAc-pentapeptide | *E. cloacae*, *C. freundii* | AmpR | Induce/repress expression of β-lactamase AmpC | [17,21] |
| anhMurNAc-peptides/ UDP-MurNAc-pentapeptide | *P. aeruginosa* | AmpR | Induce/repress expression of β-lactamase AmpC and other virulence factors | [23-24] |
| GlcNAc-MurNAc-peptides | *A. hydrophila* | BlrAB | Induce expression of β-lactamase AmpC | [28] |
| Unknown | *Shewanella oneidensis* | PghKR | Induce expression of β-lactamase BlaA and trigger stringent response | [35-36] |
| Unknown | *V. cholerae* | VxrAB (WalKR) | Increase β-lactam tolerance | [31-33] |
| γ-D-Glu-*m*-$A_2$pm (or-L-Lys) | *S. aureus*, *B. licheniformis* | BlaI | Act as coactivator to inactivate BlaI | [43,46] |
| γ-D-Glu-L-Lys | *S. aureus* | MecI | Act as coactivator to inactivate MecI | [46] |
| GlcNAc-MurNAc-peptides | *B. subtilis* | PrkC | Promote spore germination | [57] |
| GlcNAc, peptidoglycan from Gram-positives | *P. aeruginosa* | PA0600-PA0601 | Enhance virulence | [62-63] |
| Peptidoglycan from sensitive competitors | *B. subtilis* | ComP/ComA | Induce antibiotic production | [64] |
| GlcNAc, MurNAc-dipeptides anhydro-MurNAc-dipeptides | *C. albicans* | Cyr1p | Promote hyphal growth | [65-67] |
| MurNAc-tripeptide, MurNAc-dipeptide | *Arabidopsis thaliana*, *Oryza sativa*, *Nicotiana tabacum* | NOD1/NOD2/ lysin-motif proteins | Activate innate immunity | [68-69] |

知环境中的肽聚糖，通过诱导毒力因子和抗菌物质的产生以及促进生物被膜的形成最终提高自身竞争优势。

### 2.3.2 细菌与真菌之间的相互作用

白色念珠菌(*Candida albicans*)是一种感染人类的机会致病真菌，其在酵母态与菌丝态之间的转变与致病性密切相关[76]。早在 50 年前的研究发现，血清中的 GlcNAc 能够诱导该菌从酵母态转变为菌丝态[76]。近些年的研究表明，anhMurNAc-L-Ala-D-Glu 和 MurNAc-L-Ala-D-Glu 对形态转变的调控最为有效，这些肽聚糖组分能够与腺苷酸环化酶 Cyr1p 的富含亮氨酸重复(leucine-rich-repeat, LRR)结构域结合，通过激活环磷酸腺苷依赖蛋白激酶(cAMP-dependent protein kinase A, cAMP-PKA)信号通路促进菌丝生长[65-66]。近期研究发现，β-内酰胺类抗生素处理肠道共生细菌后会致使细菌释放大量的肽聚糖水解产物(被称为“肽聚糖风暴”)，其中多个组分能够诱导 *C. albicans* 菌丝生长以及在肠道中的扩散[67]，表明临床中细胞壁靶向抗生素的使用可能会对 *C. albicans* 感染疾病的治疗带来显著风险。

### 2.3.3 细菌与动植物之间的相互作用

由于肽聚糖是细菌细胞壁中特有的成分，为防御病原细菌的感染，植物和动物进化出广泛的肽聚糖感知系统，从而监控细菌的存在。在宿主中肽聚糖能够作为微生物相关的分子模式(microbe-associated molecular patterns, MAMPs)被特异性受体识别，进而激活宿主的天然免疫，提高宿主防御细菌感染的能力[9,77]。目前，在昆

虫、哺乳动物以及拟南芥(*Arabidopsis thaliana*)、水稻(*Oryza sativa*)和烟草(*Nicotiana tabacum*)等多种模式植物中均已发现肽聚糖作为 MAMPs 促进宿主防御能力[68,78]。动物宿主细胞中主要含有 2 种感知肽聚糖的受体：核苷酸结合寡聚化结构域蛋白 1 (nucleotide-binding oligomerization domain protein 1, NOD1)和 NOD2，其中 NOD1 优先感知含有 *m*-$A_2$pm 的 MurNAc-tripeptide，而 NOD2 检测含有 L-Lys 的肽聚糖以及 MurNAc-dipeptide[68]。与此不同的是，植物宿主细胞中感知肽聚糖的受体是含有溶解素基序(lysin-motif, LysM)的蛋白[78-80]，该基序在细菌的肽聚糖水解酶中广泛存在。

除激活宿主天然免疫外，研究表明肽聚糖水解产物对宿主的生理功能有重要的益处。通过模式动物实验研究发现，肠道中 *E. coli* 产生的肽聚糖组分(GlcNAc-MurNAc-peptides)对于秀丽隐杆线虫(*Caenorhabditis elegans*)的发育和觅食行为具有重要作用，这些肽聚糖组分在线粒体中积累，通过与 ATP 合酶直接结合而促进 ATP 产生，进而抑制氧化胁迫[81]。由此可见，肽聚糖不仅是宿主细胞感知病原细菌的信号分子，还是宿主正常生理功能所依赖的信号分子。

## 3 总结与展望

肽聚糖是细菌特有的细胞壁结构组分。目前，其水解产物通过肽聚糖循环途径重新参与生物合成过程已有深入研究，而其作为信号分子调控关键生理过程的研究正逐渐兴起。与群体感应信号分子类似，肽聚糖水解产物不仅能作为胞内信号调控细菌自身基因表达，还可作为种间信号分子介导细菌与其他物种间的相互作用。肽聚糖位于细菌外表面，是细菌感知外界环境的“第一道防线”，其水解产物能动态反映细菌所处生长环境的变化，既可作为促进休眠细胞恢复生长的信号，又能作为预警信号，提升细菌在不利环境中的生存适应能力。

然而，当前对肽聚糖水解产物信号功能的认识仍处于初步阶段，主要受限于 2 个方面：一是肽聚糖水解酶种类繁多、数量庞大且功能存在冗余；二是信号分子精确的产生机制及其作用靶点(受体/感应蛋白)大多尚未明确。基于此，未来亟需加强的研究方向包括：(1) 解析肽聚糖水解产物产生与感知的分子机制，具体涵盖建立特定生理/环境条件与特定肽聚糖水解产物的对应关系，鉴定识别不同肽聚糖水解产物信号的关键受体蛋白以及阐明信号传递的下游通路及其调控的基因网络；(2) 深入研究肽聚糖信号在细菌适应胁迫(如抗生素、营养匮乏)、生物被膜形成、休眠与复苏以及宿主-微生物/微生物-微生物互作中的具体作用机制；(3) 利用合成生物学手段精确操控特定肽聚糖水解产物的产生或感知，以期定向调控细菌的生理状态，如增强抗生素敏感性、抑制毒力、促进益生作用等；(4) 加强对非模式细菌及复杂微生物群落中肽聚糖信号功能的研究，揭示其在更广泛生态位中的多样性与重要性。

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