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群体感应信号分子 AIP 功能与作用机制研究进展

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摘 要: 群体感应(quorum sensing, QS)是微生物种群之间、微生物群落与植物之间相互作用的重要途径。调控群体感应过程的信号分子称为自诱导物(autoinducer, AI), 它们在生物发光、毒力因子分泌、孢子形成、次级代谢物合成以及生物膜的形成过程中均发挥着重要的调控作用。自诱导寡肽(autoinducing peptide, AIP)是细菌群落之间特异性交流的群体感应信号分子之一。本文综述了 AIP 的来源、结构、功能与作用机制方面的研究进展, 讨论了 AIP 在植物促生和生防中的应用潜力, 以期更好地理解微生物群落生态功能及其与植物互作的分子机制, 为群体感应信号分子在生态农业中的应用提供理论基础。

关键词: 群体感应信号分子; 自诱导寡肽(AIP); 作用机制

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Research Progress on Function and Mechanisms of AIPs: A Kind of Quorum Sensing Signal Molecules

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Abstract: Quorum sensing (QS) is an important way of interaction between microbial populations and between microbial communities and plants. The signaling molecules that regulate the quorum sensing process are called autoinducers (AIs), which play important regulatory roles in bioluminescence, virulence factor secretion, spore formation, secondary metabolite synthesis, and biofilm formation. Autoinducing peptides (AIPs) are one kind of the quorum sensing signaling molecules that specifically communicate between bacterial communities. This article reviewed the research progress in the source, structure, function and mechanisms of AIPs, and discussed their application potentials in plant growth promotion and biocontrol. It would be beneficial for better understanding the ecological function of microbial community and the molecular mechanism of interaction with plants, and may provide some help for the application of quorum sensing signaling molecules in ecological agriculture.

Key words: quorum sensing signal molecule; autoinducing peptide (AIP); mechanism

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微生物群落可分泌或感应微环境中的信号分子, 调控菌群数量与密度, 改变菌群生理、生化特性, 表现出单个细胞所不具备的特征, 即群体感应(quorum sensing, QS)[1-2]。20 世纪 70 年代, Nealson 等[3]对费氏弧菌(*Vibrio fischeri*)的发光机制进行了研究, 发现生物发光与细菌群体密度呈正相关, 细菌群体密度较低时不产生荧光, 细菌密度达到一定阈值时产生荧光。1994 年, Fuqua 等[4]首次把细菌群落之间的这种通信过程称为“群体感应”。群体感应是细胞之间通过信号传递系统实现信息交流, 从而改变细胞密度和群落结构的群体行为[5]。这种行为被认为是细胞感应特定环境信号

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分子并群体响应特定基因表达的结果[6]。调控这一过程的信号分子称为自诱导物(autoinducer, AI), 细菌进入群体感应模式时, AI 激活自诱导合酶基因表达, 从而增加胞外 AI 浓度, 调控群体细胞基因表达, 赋予微生物群落特定的生态功能[7-8]。

目前, 参与微生物群体感应的 AI 信号分子有 4 种: *N*-酰基高丝胺酸内酯类(*N*-acyl homoserine lactone, AHL)、寡肽类(autoinducing peptide, AIP)[9]、呋喃酰硼酸二酯类(furanosyl borate diester, FBD; 即 AI-2)和 AI-3 以及可扩散性信号因子(diffusible signaling factor, DSF)[10-11]。研究证实, AI 分子在生物发光、毒力因子分泌、孢子形成、次级代谢物产生以及生物膜的形成过程中均发挥着重要的调控作用[8]。其中, AIP 作为一类特殊的细菌群落代谢产物, 是细菌群落之间特异性交流的重要信号分子, 通过反馈作用调控种群数量, 对环境微生物多样性、群落结构、生态功能产生重要影响[12]。另外, AIP 分子还可能对植物生长发育、抗逆性产生影响[13]。AIP 的研究有助于理解微生物种群互作途径及分子机制, 有助于探讨微生物群落与植物促生、生防之间的有效作用方式, 可为群体感应信号分子在生态农业中的应用提供理论基础。

1 AIP 来源及结构

AIP 是一类短肽分子(5~17 个残基), 呈线型或环状[14], C 端第 3~5 位是保守的半胱氨酸, 与 C 末端的氨基酸残基以硫酯键相连, 形成类脂[15], 有较好稳定性。部分 AIP 信号分子的结构如图 1 所示。AIP 主要由革兰氏阳性细菌分泌产生, 如金黄色葡萄球菌(*Staphylococcus aureus*)、枯草芽孢杆菌(*Bacillus subtilis*)、肺炎链球菌(*Streptococcus pneumoniae*)、产气荚膜梭菌(*Clostridium perfringens*)、粪肠球菌(*Enterococcus faecalis*)和李斯特菌(*Listeria monocytogenes*)等均能分泌 AIP[16]。不同细菌 AIP 的相对分子质量不同、结构不同, 表现出物种特异性。另外, AIP 分子在不同细菌细胞中的合成途径、含量及功能等也有所不同, 具体如表 1 所示。

2 AIP 生物学功能

2.1 调控生物膜形成

生物膜有助于增加细菌的定殖和其对抗生素的耐药性[17-18], 使病原菌能成功逃避免疫清除, 导

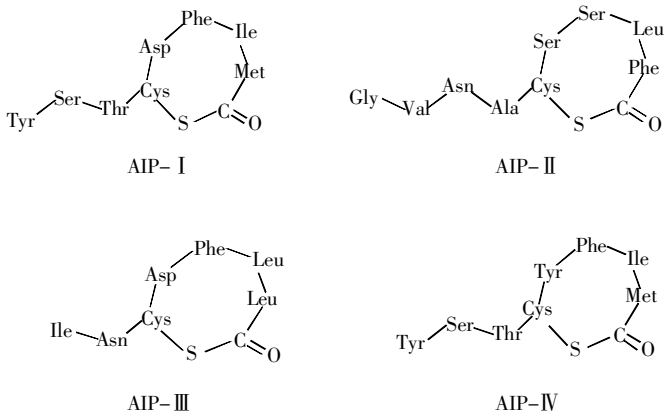

图 1 AIP 类信号分子的结构
Fig.1 Structure of AIP-like signaling molecules

表 1 革兰氏阳性细菌的 AIP
Table 1 The AIPs of Gram-positive bacteria

Gram-positive bacterium	AIP synthetic pathway	Amount of regulation	Whether it is related to bacterial growth state	Function	Reference
B. subtilis	ComX-ComQ-ComP-ComA	Less-more-less	Yes	Sporulation	[61-62]
S. aureus	AgrD-AgrB-AgrC-AgrA	Less-more-less	Yes	Biofilms, virulence factors	[73-75]
S. pneumoniae	ComC-ComAB-ComD-ComE BlpAB-BlpC-BlpH-BlpR	Less-more-less	Yes	Biofilms, virulence factors	[78]
C. perfringens	AgrD-AgrB	Less-more-less	Yes	Virulence factors	[46-47]
E. faecalis	FsrD-FsrB-FsrC-FsrA CylLL-CylM-CylB-CylA	Less-more-less	Yes	Biofilms, virulence factors	[81]
L. monocytogenes	AgrD-AgrB-AgrC-AgrA	Less-more-less	Yes	Biofilms, virulence factors	[14]

致持续性或反复性感染。此外, 其还可通过影响免疫细胞功能、活力等, 实现对先天免疫功能的影响[19]。研究发现, 细菌生物膜中存在群体感应系统, 其不仅可降低抗生素等药物对细菌的查杀效率, 也可使细菌拥有典型、高效的抗杀菌剂能力, 而且还可促进细菌胞外具有抵抗杀菌剂能力的生物膜的形成[20-21]。

革兰氏阳性细菌主要通过二元信号转导系统, 即附属基因调节子(accessory gene regulator, Agr)系统, 来调控生物膜发育。AIP 与同源受体 AgrC 结构域结合后可激活 Agr 系统。研究证实, *agr* 基因的产物决定着生物膜的解离与生成, 向已形成的生物膜中加入 AIP 可以促进生物膜解离; 当 *agr* 基因缺失时, 金黄色葡萄球菌形成更为厚实的生物膜[22-23]。肺炎链球菌、粪肠球菌和李斯特菌产生的 AIP 分子正是通过该系统调控生物膜的形成。此外, Agr 系统调控的外毒素和蛋白酶(如半胱氨酸蛋白酶、丝氨酸蛋白酶等)在生物膜形成过程中也发挥着重要作用[24-27]。另有研究报道, AIP 可通过调节生物膜周期影响其提前成熟和分散, 从而抑制细菌耐药性[28-30]。因此, AIP 分子主要通过 *agr* 基因的表达调控细菌群落与其分泌物(如蛋白质、碳水化合物和裂解细胞中释放的胞外 DNA)的相互聚集或分散, 从而以负调控的方式影响生物膜发育, 是菌群定殖、繁殖、提高抗性及生态功能的物质基础, 同时在生物膜的发生发展、功能发挥及与宿主相互作用过程中发挥着关键作用。

2.2　调控毒力因子分泌

AIP 调控的 Agr 系统同时也控制着 100 多种毒力因子的表达[31]。高浓度 AIP 会降低表面附着蛋白的表达并增加外毒素和蛋白酶的表达[32]。金黄色葡萄球菌外毒素的表达主要由 RNAⅢ抑制毒素阻遏因子(Rot)正向调控, 其调控过程属于表1中的 AgrD-AgrB-AgrC-AgrA 途径。金黄色葡萄球菌的外毒素包括 α-毒素(Hla)、丝氨酸蛋白酶(SplA-F、SspA)、半胱氨酸蛋白酶(ScpA、SspB)、γ-溶血素(Hlg)、杀白细胞素(LukAB、LukGH)和脂肪酶(Geh)[33-36]等。其中, α-毒素、丝氨酸蛋白酶与许多感染的起始和进展相关, 是细菌致病性的重要决定因子[37-39]; ScpA 通过自溶裂解激活, 在细胞内通过杀死宿主上皮细胞发挥作用[40]; LukAB 可诱导细胞裂解, 与皮肤、软组织感染和肺炎相关[41-42]; γ-溶血素可以破坏宿主免疫系统, 改变金黄色葡萄球菌对抗原的免疫反应[43-45]。另外, 产气荚膜梭菌的群体感应系统也调节了一些毒力因子的表达, 如 α-毒素(*Clostridium perfringens* alpha toxin, CPA)、穿孔素 O (perfringolysin O, PFO)、β-毒素(*Clostridium perfringens* beta toxin, CPB)、ε 毒素(epsilon toxin, ETX)、β2-毒素(beta2 toxin, CPB2)、产气荚膜梭菌肠毒素(*Clostridium perfringens* enterotoxin, CPE)和 ι 毒素(iota toxin, ITX)[46-49]。这些毒素可诱导细胞裂解, 与膜完整性以及通透性的改变有关[50-53]。研究报道, AIP 通过调节宿主细胞黏附和毒力因子改变自身的感染能力, 以降低细菌耐药性[54-55]。

3　AIP 作用机制

细菌群体感应可分为 3 个时期: 1) 前期, 群体感应信号分子分泌; 2) 感应期, 信号分子积累并达到浓度阈值, 调控特定基因表达; 3) 后期, 即恢复期, 群体感应结束并恢复至群体感应前期状态[56-57]。目前普遍认为, 群体感应信号转换系统是细菌最常见的群体感应退出机制之一, AIP 正是通过该系统发挥其群体细胞通信功能, 该过程主要依赖群体感应系统与受体蛋白的相互作用[58]。首先, AIP 前体肽段经加工修饰后形成有活性且稳定的 AIP 信号分子[2, 59]; 然后, AIP 信号分子经组氨酸激酶受体和同源细胞质反应调节器组成的双组分系统或者 ATP 结合盒(ATP-binding cassette, ABC)转运系统运输至胞外[60]。胞外 AIP 浓度达到阈值后, AIP 会被双组分系统的感应识别元件识别并结合, 之后激活双组分磷酸激酶系统并使双组分磷酸激酶磷酸化, 进而促进响应调节蛋白磷酸化, 并与 DNA 特异性位点结合, 调控目的基因表达[61-62]。或者, 细胞质转录因子识别环境中达到阈值的 AIP, 再将 AIP 转运回胞内[15]。

目前, AIP 作用机制的研究主要集中在枯草芽孢杆菌的感受态调控系统 ComQXPA (competence QXPA)和金黄色葡萄球菌的 Agr 系统[55, 63-65]。其中, ComQXPA 调控系统的主要信号途径为 ComX-ComQ-ComP-ComA, 主要涉及两种 AIP 信号分子: ComX 信息素和感受态及产孢因子(competence and sporulation factor, CSF)[66-67](图 2)。*comx* 编码的 55 个色氨酸残基经异戊二烯修饰后形成 ComX 信息素前体(pre-ComX)[67-68], 后者再经异戊二烯转化酶 ComQ 修饰形成 ComX[69], ComX 信息素多为 10 个氨基酸残基的多肽, 可经 ABC 转运系统转运至细胞外。研究显示, ComX 可以和细胞膜上的跨膜蛋白组氨酸蛋白激酶 ComP 相互作

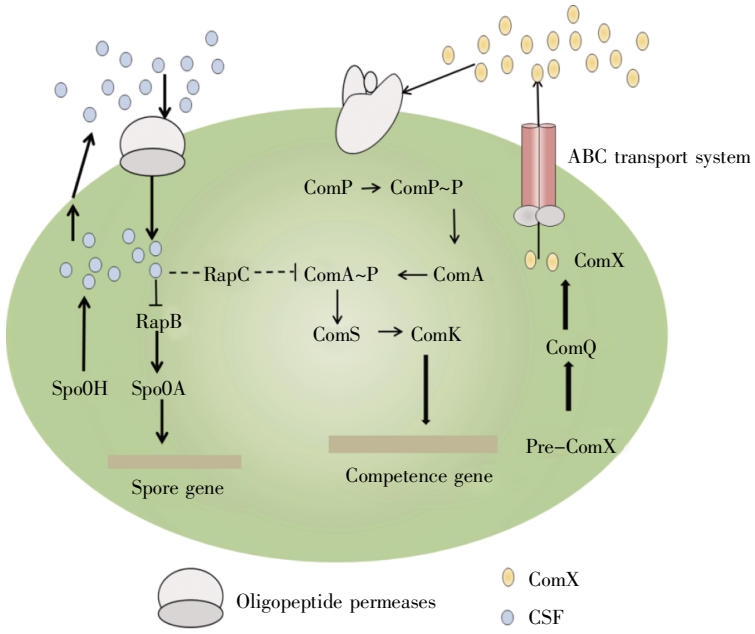

图 2 枯草芽孢杆菌 ComQXPA 群体感应系统(修改自文献[63])
Fig.2 ComQXPA quorum sensing system of *B. subtilis* (modified according to Reference [63])

用, 激活组氨酸蛋白激酶并使之磷酸化(ComP~P), 进而促进应答调节蛋白磷酸化(ComA~P), ComA~P 促进 *coms* 表达, 使得胞内 ComS 蛋白的浓度增加, 进而降低 ComK 被水解的速度, ComK 进一步诱导感受态基因的表达, 使得枯草芽孢杆菌进入感受态, 提高生产性能[70]。目前研究认为, ComX信息素和 CSF 的作用机制与枯草芽孢杆菌磷酸化信号转导系统 Rap 蛋白和组氨酸蛋白激酶的活性密切相关[71]。RapA、RapB 和 RapE 均是磷酸化信号转导系统的负调控因子, 调控芽孢形成相关基因表达。CSF 是 5 个氨基酸残基的寡肽, 由前体肽 PhrC 的 C 端裂解形成, Phr 肽的基因位于 Rap 磷酸酶基因下游, 且有部分重叠, 二者形成 Rap-Phr 信号盒, 参与调节孢子生成与感受态形成。逆境下, 胞外 CSF 积累达到阈值后可抑制 RapB 活性, 从而促进孢子生成, 协助 ComX 信息素促进枯草芽孢杆菌进入感受态; 同时, RapC 也可通过调节响应蛋白 ComA 的活性调控枯草芽孢杆菌感受态的形成, 以共同提高菌体的生产性能[72-75] (图2)。

金黄色葡萄球菌的群体感应过程是通过 AIP 调控 Agr 系统实现的, Agr 系统是一种二元信号转导系统, 由两个 RNA 转录本 RNA Ⅱ 和 RNA Ⅲ 组成, 启动子 P2、P3 分别启动相应的转录单位 RNA Ⅱ 和 RNA Ⅲ 的转录[76](图 3)。AIP 前体肽 AgrD (46 aa)经膜蛋白酶 AgrB 水解产生长度为 7~9 个氨基酸的成熟 AIP, AIP 与激酶 AgrC 结合后激活自身磷酸化功能, 活化调节因子 AgrA 并使其与启动子 P2、P3 结合以启动 RNA Ⅱ 和 RNA Ⅲ 的转录, 从而调控下游基因的表达[77-78]。RNA Ⅱ 编码 AgrA、AgrB、AgrC 和 AgrD; RNA Ⅲ 编码多个寡肽, 调节转录因子与毒力因子表达, 激活 Agr 系统[79-82]。与其他群体感应信号分子(AHL 和 AI-2)的作用机制相似, 磷酸化的 AIP 通过调控相关基因的转录及表达, 改变细菌生理状态[83], 使微生物群落表现出特定的生态学功能。

与 Agr 系统相似的群体感应系统还包括: 肺炎链球菌中的 ComABCDE 和 BlpABCSRH 系统、产气荚膜梭菌中的 Agr-like 系统、粪肠球菌中的 Fsr (faecalis system regulator)调节系统。ComABCDE 系统由感受刺激肽(competence-stimulating peptide, CSP; 17 aa)调控[84]。BlpABCSRH 途径与ComABCDE 途径类似, 它调节各种细菌素及其免疫蛋白的产生[85], 这两种调控系统都与生物膜的定殖有关[86]。在产气荚膜梭菌基因组中研究人员发现了 Agr 系统中的 *agrB* 和 *agrD* 同源物[46-47], 它们调节毒素的产生; 与金黄色葡萄球菌不同的是, Agr-like 系统不包含 *agrC-agrA* 双组分系统[46]。粪肠球菌中的 Fsr 调节系统是由自诱导肽 GBAP (gelatinase biosynthesis-activating pheromone; 含 11 个氨基酸残基的内酯环)调控的[87], 它可以促进毒素和生物膜的形成。另外, 研究人员在肺炎链球菌、产气荚膜梭菌和粪肠球菌中还发现了一种 LuxS 群

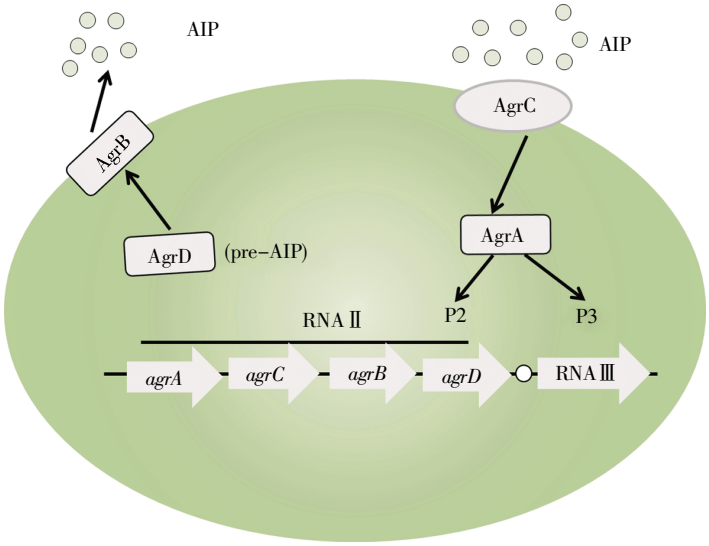

图 3　金黄色葡萄球菌的群体感应系统(修改自文献[53, 77])
Fig.3　Quorum sensing system of *S. aureus* (modified according to References [53, 77])

体感应系统。*luxS* 基因编码 *S*-核糖-同型半胱氨酸酶, 该酶催化 *S*-核糖-同型半胱氨酸水解为同型半胱氨酸和 4,5-二羟基-2,3-戊二酮(4,5-dihydroxy-2,3-pentandione, DPD), DPD 分子可以与水反应生成 AI-2[88-90], 在调控生物膜形成过程中发挥重要作用[89, 91-92]。

综上可知, 细菌群落中可能同时有几种群体感应系统参与调控群落互作及功能性状, 相应地, 也有多种类型 AIP 分子调控着细菌群体感应过程。相应机制的解析在新型群体感应抑制剂的开发和应用方面有很大意义, 例如: 天然产物或人工合成的群体感应淬灭剂在抑制致病菌毒素分泌、生物膜形成及耐药性方面有很好的应用潜力[93-95], 为保障食品安全和缓解细菌耐药性问题提供了新的思路。

4　小结与展望

群体感应信号分子是微生物生态学领域的研究热点, 相关研究主要聚焦于细菌群体感应信号分子及其类似物、微生态功能及其与植物互作机制。目前研究认为, 低浓度信号分子不能发挥作用, 须达到浓度阈值才能与受体蛋白结合调控目的基因表达。AIP 可通过感受态调控系统 ComQXPA、辅助基因调节系统 Agr 以及 LuxS 系统等调控目的基因的转录和翻译, 进而调节细菌孢子生成、感受态形成、生物膜形成、毒力因子分泌等生物学过程。

枯草芽孢杆菌群体感应系统的主要调控途径为 ComX-ComQ-ComP-ComA, ComX 和 CSF 是枯草芽孢杆菌与植物相互作用过程中重要的 AIP 信号分子, 它们可调节菌群密度及群落结构, 从而提高枯草芽孢杆菌繁殖与产孢能力。众多研究证实, 枯草芽孢杆菌是一类非常重要的植物促生菌, 在植物根际有较强的定殖能力[96-98], 它可以产生特异性次生代谢产物(如抗生素、抗菌蛋白或酶、挥发性物质等), 形成不利于病原微生物生长的微环境, 抑制或杀死植物病原菌[99]。作为促生菌和生防菌, 枯草芽孢杆菌已在棉花[100-101]、水稻[102]、油菜[103]、大豆[104]等作物中得到广泛应用, 效果显著。有研究报道, ComX 和 CSF 信号分子还可能通过调控枯草芽孢杆菌的产生来促进植物生长[13]。因此, 未来 AIP 作为植物促生剂或生防剂在作物绿色防控及生态农业中具有巨大的应用潜力。另外, 群体感应信号分子对病原菌慢性感染的发展至关重要, 其作用机制的研究将有助于阻止细菌的定殖与感染, 在临床医学方面有一定的应用价值。

目前, 群体感应信号分子 AI-2 在细菌中的调控机制不是很清楚。AIP 作为一种有潜力的植物促生剂, 进一步研究其和 AI-2 与植物的互作机制很有必要。此外, 未来还需要更多地关注植物致病菌相关的微生物群体感应信号分子, 及其对致病菌定殖与感染的调控机制。更多植物益生菌群体感应信号分子作用机理的揭示, 有助于人们更好地理解微生物群落在植物表面的定殖、繁殖及作用机理, 可为进一步阐明 AIP 的微生态功能及其对植物生长发育的影响等问题提供重要的

基础资料。

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