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Review 综 述

放线菌来源的羊毛硫肽研究进展

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Yang Zan, Liang Yixuan, Zhang Jun, He Zengguo. Research progress of lanthipeptides from *Actinomycetota*. *Acta Microbiologica Sinica*, 2022, 62(9): 3289–3305.

摘　要：羊毛硫肽(lanthipeptide)是一类由核糖体合成并经翻译后修饰的含羊毛硫氨酸或β-甲基羊毛硫氨酸的多肽。近年来，放线菌来源的羊毛硫肽因其突出的抗菌活性和罕见的生物活性而备受关注。本文重点对放线菌来源的不同类型的羊毛硫肽的结构特征及其特性进行了综述，讨论了生物或化学方法修饰天然羊毛硫肽和基因组挖掘发现结构新颖的羊毛硫肽在开发符合实际应用需求的放线菌来源的羊毛硫肽中的应用，并对放线菌来源的羊毛硫肽的应用潜力进行了总结和展望。

关键词：放线菌；羊毛硫肽；结构修饰；基因组挖掘

Research progress of lanthipeptides from *Actinomycetota*

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Abstract: Lanthipeptide are a group of ribosomally synthesized and post-translationally modified peptides (RiPPs), containing rare structure like thioether cross-links termed lanthionines (Lans) or

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methyllanthionines (MeLans). Recently, lanthipeptides that originated from the phylum *Actinomycetota* have been the research hotspot due to their outstanding antimicrobial activities and unusual bioactivities. This review focused on lanthipeptides produced by *Actinomycetota*, with special attention paid to their unique structure and property. Further discussion involved developing lanthipeptide of *Actinomycetota* origin to meet practical requirement through biological and chemical modifications of known lanthipeptides, as well as genome mining strategies for the discovery of novel lanthipeptides. Lastly, future application potential of lanthipeptide derived from *Actinomycetota* were summarized and prospected.

Keywords: *Actinomycetota*; lanthipeptide; structure modification; genome mining

羊毛硫肽(lanthipeptide)是自然界中广泛存在的一大类结构中含有羊毛硫氨酸(Lan)或β-甲基羊毛硫氨酸(MeLan)或 labionin (Lab) (图 1)的肽类化合物[1–2]，主要由厚壁菌门和放线菌门细菌的核糖体合成，并经过一系列翻译后修饰产生。在羊毛硫肽生物合成的过程中，首先由结构基因转录和翻译形成羊毛硫肽前体肽。接着，羊毛硫肽合成酶识别前体肽 N 端的前导肽(leader peptide)或 C 端的尾随肽(follower peptide)，对核心肽进行脱水和环化形成 Lan 或 MeLan。最后，在转运蛋白的作用下，前体肽被转运出细胞外被蛋白酶或转运蛋白的蛋白酶结构域切除前导肽或尾随肽，释放出成熟的羊毛硫肽[1–2] (图 2)。在一些羊毛硫肽生物合成基因簇中，除了脱水酶和环化酶外，还存在其他的修饰酶，在羊毛硫肽中引入了卤素[3–4]、二硫键[5]、C 端氧化脱羧[3–4,6]、赖氨酸丙氨酸桥[7–10]、D 型氨基酸[11]、糖基[12]、乙酰基[13]和亚砜基[14–16]等修饰。这些修饰与羊毛硫肽的生物活性及对蛋白酶、温度、pH 和 O_2 等的稳定性相关[17]，极大地增加了羊毛硫肽的结构多样性。

根据组装 Lan 或 MeLan 的羊毛硫肽生物合成酶的结构及功能差异，羊毛硫肽可分为 5 个亚型[11,18]。Ⅰ型羊毛硫肽合成酶含有独立的脱水酶 LanB 和环化酶 LanC[19–20]。不同于Ⅰ型羊毛硫肽合成酶，Ⅱ型、Ⅲ型和Ⅳ型羊毛硫肽的

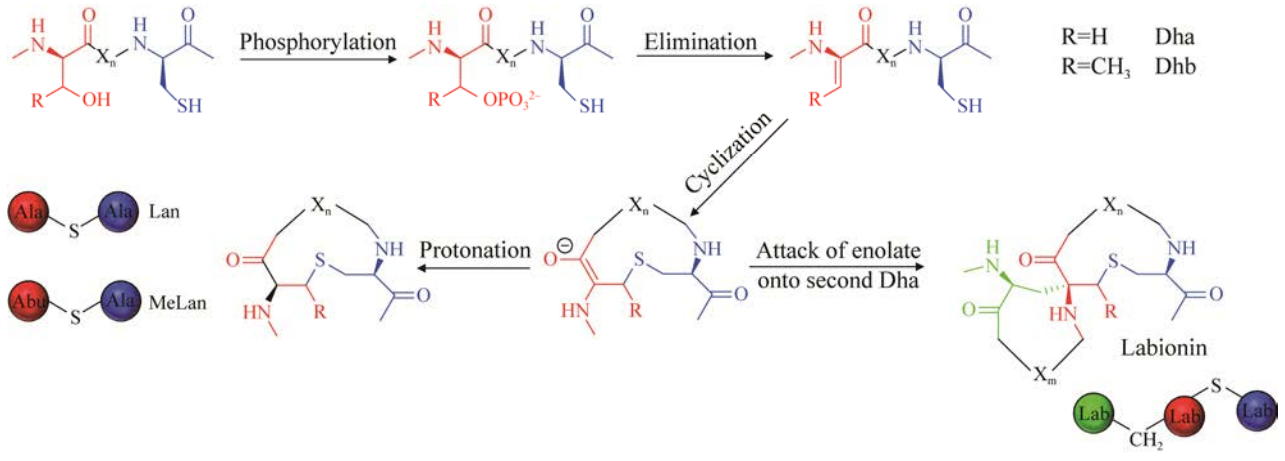

图 1　(Me)Lan 和 Lab 的生物合成[1]
Figure 1　Biosynthesis of (Me)Lan and Lab[1].

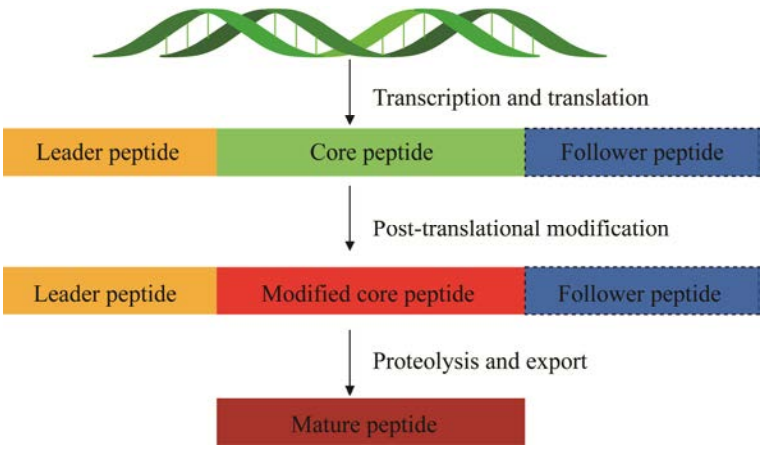

图 2　羊毛硫肽的生物合成[1−2]

Figure 2　Biosynthesis of lanthipeptide[1−2].

合成酶是一个多功能酶，脱水和环化由同一个酶完成[21−23]。Ⅱ型羊毛硫肽合成酶 LanM 的 C 端环化结构域与Ⅰ型羊毛硫肽合成酶 LanC 和Ⅳ型羊毛硫肽合成酶 LanL 的 C 端环化结构域具有同源性，都含有保守的 Zn^{2+}结合位点，但其 N 端脱水结构域与其他羊毛硫肽合成酶不具有同源性。Ⅲ型和Ⅳ型羊毛硫肽合成酶都包含裂解酶、激酶和环化酶 3 个功能结构域，且二者具有同源性[21,24]，但Ⅲ型羊毛硫肽合成酶 LanKC 的 C 端的环化结构域中缺乏 Zn^{2+}结合位点[25−27](图 3)。此外，Ⅰ型羊毛硫肽合成酶的脱水作用是基于谷氨酰胺化的 tRNA 对丝氨酸/苏氨酸的羟基活化，而Ⅱ、Ⅲ和Ⅳ型羊毛硫肽合成酶则是基于丝氨酸/苏氨酸的羟基磷酸化[1]。Ⅴ型羊毛硫肽的合成酶(LxmKXY)是由 3 个相互独立的单功能蛋白质组成，与上述 4 种类型的羊毛硫肽合成酶之间无序列相似性[11]。

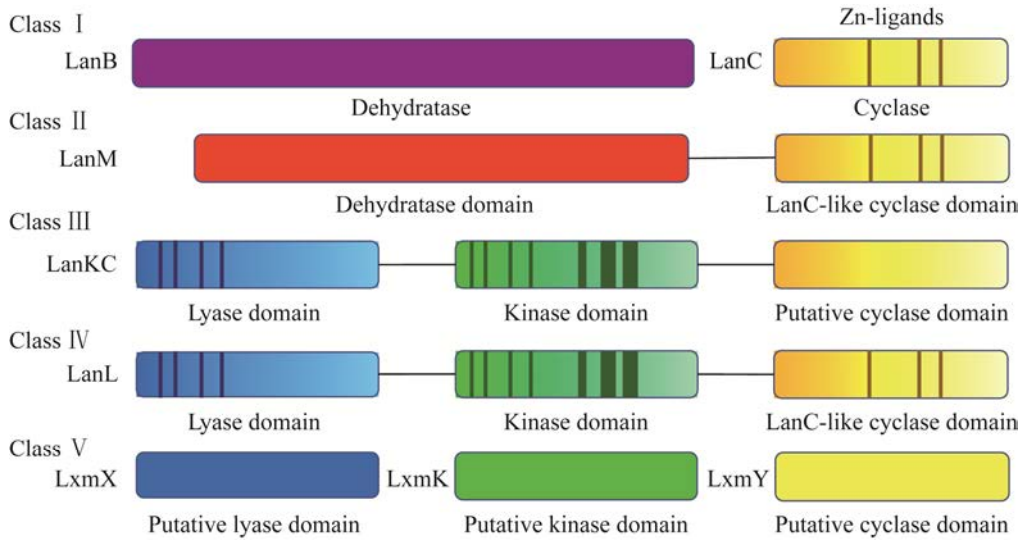

图 3　5 类羊毛硫肽合成酶[1,11]

Figure 3　Five types of lanthipeptide biosynthetic enzymes[1,11].

自 1928 年首个分离自 *Lactococcus lactis* 的羊毛硫肽 nisin 被发现以来，羊毛硫肽即因其突出的抗菌活性、良好的 pH 及温度稳定性和不易产生耐药性等诸多优点备受关注[28–29]。除了抗菌活性外，一些放线菌来源的羊毛硫肽还常常显示出抗肿瘤[30]、抗病毒[31–33]、调节血压[34–35]和镇痛[5,12]等生物活性。有些放线菌来源的羊毛硫肽甚至在进行临床前或临床试验，如 microbisporicin 治疗革兰氏阳性多重耐药菌(multi drug resistant，MDR)进入后临床前期试验阶段；duramycin 治疗囊性纤维化正在进行临床Ⅱ期试验；半合成的用于治疗艰难梭菌引起的感染的 actagardine 衍生物 NVB333 和 NVB302 分别进入了临床前和临床Ⅰ期试验阶段[36]。

1 放线菌来源的羊毛硫肽及其特性

尽管放线菌来源的羊毛硫肽(表 1)在某些方面的研究进展明显落后于细菌来源的羊毛硫肽，但放线菌羊毛硫肽合成过程中经历的翻译后修饰却最具有多样性及新颖性，如 microbisporicin 中色氨酸的卤化及脯氨酸的(二)羟基化[4,37–38]、cinnamycin 中赖氨酸丙氨酸桥[38–39]、NAI-112 中色氨酸的 N-糖基化[12]和 lexapeptide 中苯丙氨酸的 N,N-二甲基化[11]等翻译后修饰方式目前在其他微生物来源的羊毛硫肽中尚未发现。此外，目前只有放线菌能产生以上全部 5 种类型的羊毛硫肽[11,18]。

1.1 Ⅰ型羊毛硫肽

在放线菌产生的Ⅰ型羊毛硫肽中，planosporicin (羊毛硫肽 97518)和 microbisporicin (NAI-107)是其中最具代表性的 2 种，二者分别由 *Planomonospora alba*[40]和 *Microbispora corallina* 产生[4,38]。Planosporicin 和 microbisporicin 都由 24 个氨基酸残基构成，都含有 4 个 Lan 和 1 个 MeLan，且位置相同[41–42] (图 4)。然而，在 C 端 Lan 的形成过程中，microbisporicin 的 C 端

表 1 放线菌来源的羊毛硫肽及其特性

Table 1 Lanthipeptides produced by *Actinomycetota* and their property

Name	Producers	Number of amino acid residues	Posttranslational modification (apart from Dha, Dhb, Lan, MeLan and Lab)	Types	Bioactivity
Microbisporicin (NAI-107)[4,37–38,40]	*Microspora coralline*	24	(2-aminovinyl)-3-methyl-cysteine, tryptophan chlorination, proline hydroxylation	Ⅰ	Antimicrobial
NAI-108[3]	*Microspora coralline*	24	(2-aminovinyl)-3-methyl-cysteine, tryptophan bromination, proline hydroxylation	Ⅰ	Antimicrobial
Planosporicin[41–42]	*Planomonospora alba*	24	None	Ⅰ	Antimicrobial
NAI-857[43]	*Streptomyces* sp. 105857	24	None	Ⅰ	Antimicrobial
NAI-130[43]	*Streptomyces* sp. 106130	24	None	Ⅰ	Antimicrobial
NAI-114[43]	*Streptomyces* sp. 114623	24	None	Ⅰ	Antimicrobial
NAI-438[43]	*Streptomyces* sp. 99438	24	None	Ⅰ	Antimicrobial
Actagardine[44]	*Actinoplanes garbadinensis* *Actinoplanes liguriae*	19	C-terminal MeLan oxidized to sulfoxide	Ⅱ	Antimicrobial

(待续)

(续表 1)

Ala(0)-actagardine[14,45]		*Actinoplanes liguriae*	20	C-terminal MeLan oxidized to sulfoxide	II	Antimicrobial
Deoxyactagardine[45]		*Actinoplanes liguriae*	19	None	II	Antimicrobial
NAI-802[46]		*Actinoplanes* sp. 104802	21	None	II	Antimicrobial
Ala(0)-NAI-802[46]		*Actinoplanes* sp. 104802	22	None	II	Antimicrobial
Michiganin A[47]		*Clavibacter michiganensis* subsp. *michiganensis*	21	None	II	Antimicrobial
Duramycin[8–9]		*Streptomyces cinnamoneus*, *Streptomyces griseoluteus*	19	Lysinoalanine bridge , aspartic acid hydroxylation	II	Antimicrobial, antiviral, antitumor, treatment of cystic fibrosis
Cinnamycin[7,10]		*Streptomyces cinnamoneus*, *Streptomyces griseoluteus*	19	Lysinoalanine bridge, aspartic acid hydroxylation	II	Antimicrobial, antiviral, blood pressure regulation
Ancovenin[34]		*Streptomyces* sp. No. A647P-2	19	None	II	Blood pressure regulation
Mathermycin[39]		*Actinomycete Marinactinospora*	19	Lysinoalanine bridge, aspartic acid hydroxylation	II	Antimicrobial
Variacin[48]		*Kocuria varians*	25	None	II	Antimicrobial
Roseocin[49]	RosA2α	*Streptomyces roseosporus*	35	Disulfide bond	II	Antimicrobial
	RosA1β		33	None		
Labyrinthopeptins[5]		*Actinomadura namibiensis*	18–21	Disulfide bond	III	Antiviral, antinociceptive
NAI-112[12]		*Actinoplanes* sp. DSM 24059	22	MeLab, tryptophan N-glycosylation	III	Antimicrobial, antinociceptive
Stackepeptins[50]		*Stackebrandtia nassauensis* DSM-44728^T	31	None	III	Unknown
Erythreapeptin[51]		*Saccharopolyspora erythraea* NRRL 2338	27	None	III	Unknown
Avermipeptin[51–52]		*Streptomyces avermitilis* DSM 46492	22–24	None	III	Antimicrobial
Griseopeptin[51]		*Streptomyces griseus* DSM 40236	22	None	III	Unknown
Catenulipeptin[53]		*Catenulispora acidiphila*	27	None	III	Unknown
Curvopeptin[54]		*Thermomonospora curvata*	26	None	III	Unknown
Informatipeptin[55]		*Streptomyces viridochromogenes*	24	None	III	Unknown
SapB[26]		*Streptomyces coelicolor*	21	None	III	Surfactant
SapT[56]		*Streptomyces tendae*	21	None	III	Surfactant
AmfS[57]		*Streptomyces griseus*	43	None	III	Morphogen
Venezuelin[21]		*Streptomyces venezuelae*	22	None	IV	Unknown
Streptocollin[58]		*Streptomyces collinus* Tü 365	23	None	IV	Unknown
SflA[59]		*Streptomyces* sp. NRRL S-1022	19	None	IV	Unknown
Lexapeptide[11]		*Streptomyces rochei Sal35*	38	(N,N)-dimethyl phenylalanine, (2-aminovinyl)-3-methyl-cysteine, D-Ala	V	Antimicrobial

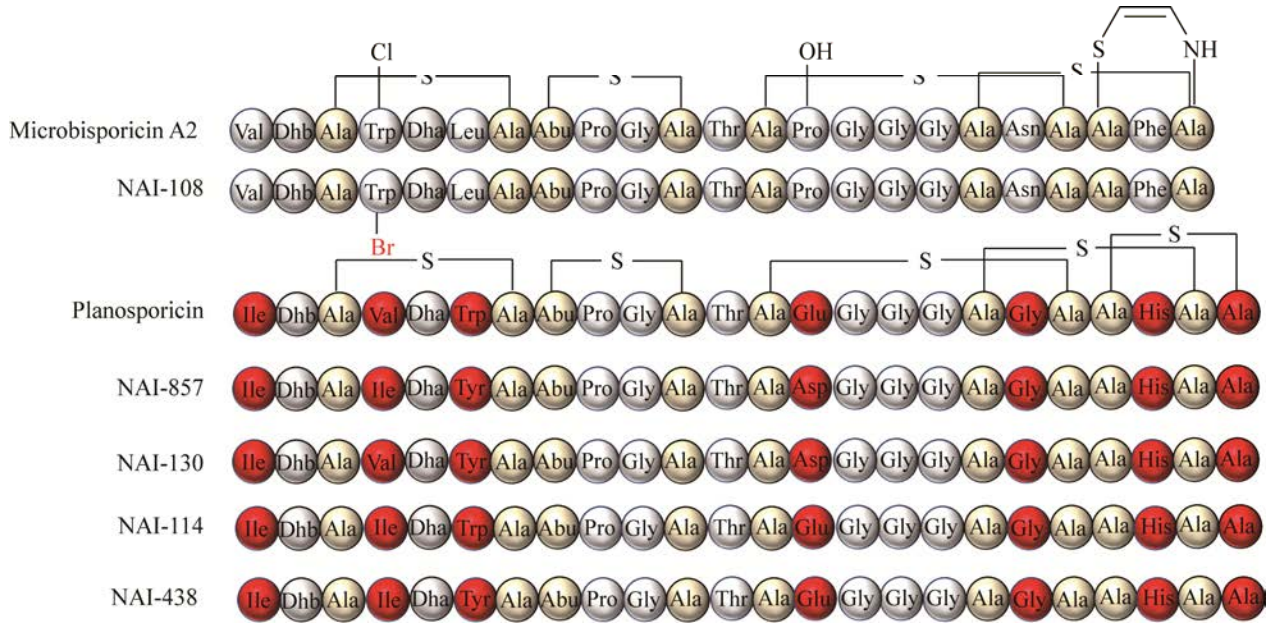

图 4　Ⅰ型羊毛硫肽 microbisporicin、NAI-108、planosporicin、NAI-857、NAI-130、NAI-114 和 NAI-438 的氨基酸序列

Figure 4　Peptide sequences of type Ⅰ lanthipeptides microbisporicin, NAI-108, planosporicin, NAI-857, NAI-130, NAI-114 and NAI-438. The thioether bonds that are shared by microbisporicin and NAI-108 are shown on the microbisporicin sequence. The thioether bonds that are shared by planosporicin, NAI-857, NAI-130, NAI-114 and NAI-438 are shown on the planosporicin sequence. Amino acids that differ from microbisporicin sequence are marked in red.

半胱氨酸残基先被氧化脱羧，再与脱氢丙氨酸(Dha) (图 1)连接形成 S-aminovinyl-D-半胱氨酸[60]；而 planosporicin 的 C 端半胱氨酸残基则直接与 Dha 连接形成 Lan[42]。此外，microbisporicin 还存在 4 位色氨酸的氯化和 14 位脯氨酸的羟基化(microbisporicin A2)或二羟基化(microbisporicin A1)修饰，二者分别由 *mibH* 编码的黄素依赖型色氨酸卤化酶和 *mibO* 编码的细胞色素 P450 催化[4,37–38]。Planosporicin 和 microbisporicin 均是通过与合成细胞壁的前体 lipid II 结合，进而导致细胞壁合成受阻而发挥抗菌作用，但后者对革兰氏阳性菌，如葡萄球菌(*Staphylococcus*)、链球菌(*Streptococcus*)和肠球菌(*Enterococcus*)等的抗菌活性更强[37]。二者的抗菌活性差异可能与 12 位苏氨基酸残基和 18 位丙氨基酸残基之间区域的细微结构差异有关[42]。此外，尽管 microbisporicin 对革兰氏阴性菌 *Moraxella catarrhalis*、*Neisseria* spp.和 *Haemophilus influenzae* 有一定的抑菌作用，但对大肠杆菌(*Escherichia coli*)等肠杆菌科细菌、白色念珠菌(*Candida albicans*)和 L 型金黄色葡萄球菌(*Staphylococcus aureus*)不显示抑菌作用[37]。值得一提的是，microbisporicin 对耐药菌菌株如耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*，MRSA)、耐万古霉素肠球菌(vancomycin-resistant *Enterococci*，VRE)和耐青霉素的肺炎链球菌都有抑制作用，其效果甚至可与万古霉素和替考拉宁相媲美[37]。

除了 planosporicin 和 microbisporicin 外，研究人员还从其他种属的放线菌中发现了二者

的结构类似物。Maffioli 等在 4 株不同来源的放线菌发酵液中发现了 4 种仅在 4、6 或 14 位上氨基酸残基与 planosporicin 不同的结构类似物 NAI-857、NAI-130、NAI-114、NAI-438[43] (图 4)，它们均带 1 个负电荷。进一步研究发现，增加 planosporicin 带正电荷氨基酸残基的数量，可以提高其与 lipid Ⅱ结合的有效性，进而提高抗菌活性，且带 3 个正电荷时活性最强，此时其抗菌活性接近 microbisporicin。从 *Microbispora* sp. 107891 或 *Microbispora corallina* NRRL 30420 发酵液中，Maffioli 等还发现了 4 位色氨酸未被氯化、N 端第 1 个 Lan 被氧化成亚砜、N 端多出甘氨酸-脯氨酸-丙氨酸 3 个氨基酸残基和 14 位脯氨酸未被羟基化的 microbisporicin 结构类似物，对其活性进行研究发现，脯氨酸的羟基化和色氨酸的卤化会增强羊毛硫肽的抗菌活性，而 N 端第 1 个 Lan 的氧化和 N 端多出甘氨酸-脯氨酸-丙氨酸 3 个氨基酸残基则会降低其抗菌活性[61]。此外，Cruz 等发现 4 位色氨基酸残基被溴化的 NAI-108 对测试菌株的最小抑菌浓度(minimum inhibition concentration，MIC)比 microbisporicin 相同或更低[3]，这似乎暗示 4 位色氨酸残基被溴化的 NAI-108 的抗菌活性更强。

1.2 Ⅱ型羊毛硫肽

在放线菌产生的Ⅱ型羊毛硫肽中，研究较多的是 actagardine (gardimycin) (图 5)、cinnamycin、duramycin (Moli1901 或 lancovutide)和 ancovenin (图 6)[7–10,34,44]，它们均包含 19 个氨基酸残基。它们的区别表现在：(1) Lan 或 MeLan 数目不同：actagardine 包含 2 个 Lan 和 2 个 MeLan，而其余三者则只有 1 个 Lan 和 2 个 MeLan；(2) 修饰位点不同：actagardine 唯一的修饰位点是 C 端的 MeLan 被 *garO* 编码的荧光素酶单加氧酶氧化成亚砜键；而 cinnamycin 和 duramycin 修饰位点包括 6 位赖氨酸残基和 19 位丙氨酸残基之间形成的赖氨酸丙氨酸桥及 15 位天冬氨酸残基的羟基化修饰，ancovenin 则无任何修饰。上述 4 种羊毛硫肽中，actagardine、cinnamycin

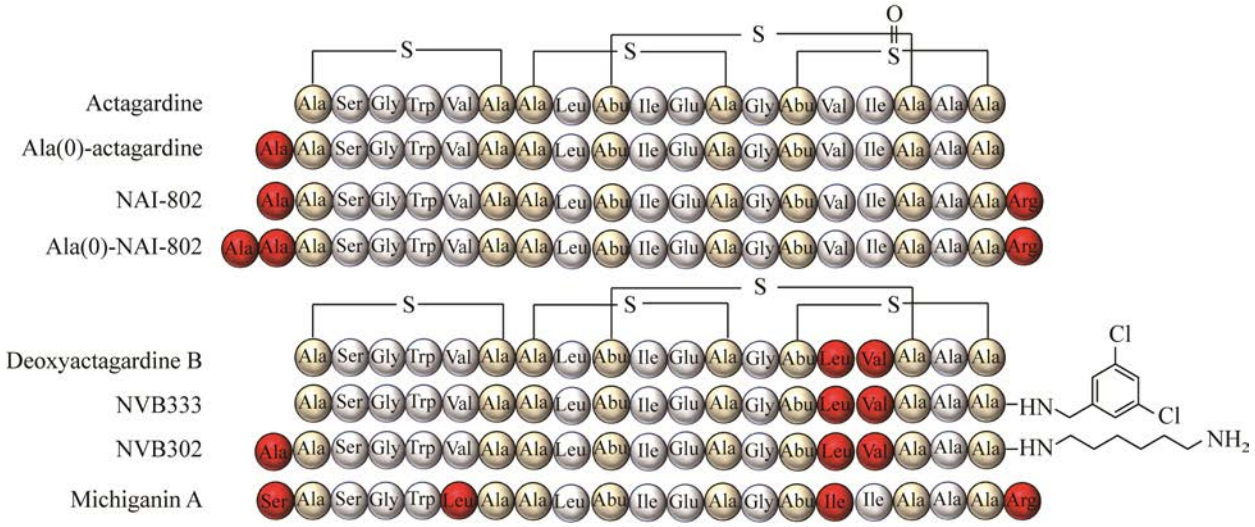

图 5 Ⅱ型羊毛硫肽 actagardine 及其结构类似物的氨基酸序列

Figure 5 Peptide sequences of type Ⅱ lanthipeptide actagardine and its analogue. The thioether bonds that are shared by actagardine, Ala(0)-actagardine, NAI-802 and Ala(0)-NAI-802 are shown on the actagardine sequence. The thioether bonds that are shared by deoxyactagardine B, NVB333, NVB302 and michiganin A are shown on the deoxyactagardine B sequence. Amino acids that differ from actagardine sequence are marked in red.

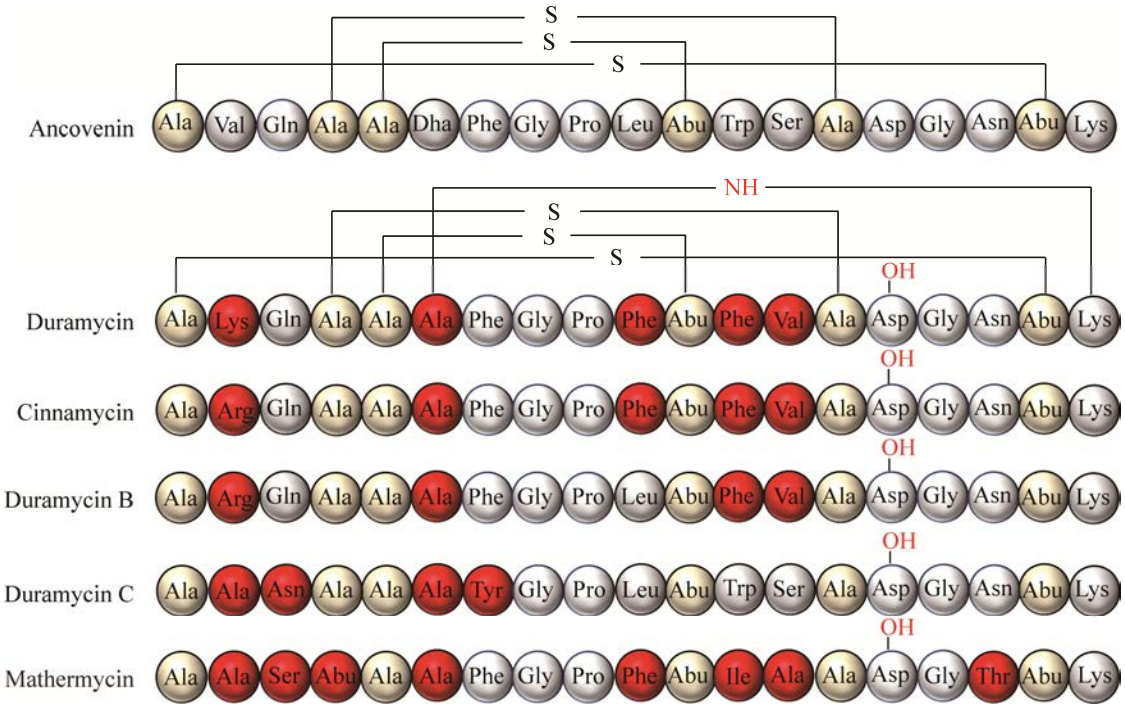

图 6　Ⅱ型羊毛硫肽 ancovenin、duramycin、cinnamycin、duramycin B、duramycin C 和 mathermycin 的氨基酸序列

Figure 6　Peptide sequences of type Ⅱ lanthipeptide ancovenin, duramycin, cinnamycin, duramycin B, duramycin C and mathermycin. The thioether bonds that are shared by duramycin, cinnamycin, duramycin B, duramycin C and mathermycin are shown on the duramycin sequence. Amino acids that differ from ancovenin sequence are marked in red.

和 duramycin 均显示出一定的抗菌活性，其中 actagardine 的抗菌活性最强，对革兰氏阳性致病菌如链球菌属和梭菌属的细菌表现出很强的拮抗作用，其抗菌效果与氨苄青霉素和头孢噻啶相当[44]。尽管 actagardine 的抗菌机理也是与合成细胞壁的前体 lipid Ⅱ结合，进而阻断细胞壁的合成，但是其活性远低于Ⅰ型羊毛硫肽 microbisporicin。与 actagardine 不同，cinnamycin 和 duramycin 是由于其 15 位天冬氨酸的羧基同磷脂酰乙醇胺的氨基之间的离子相互作用导致细胞壁的合成中断，进而造成细胞死亡[31]。而其 15 位天冬氨酸的羟基则进一步增强了二者与磷脂酰乙醇胺的结合强度，这也似乎可以解释结构类似的 15 位天冬氨酸未被羟基化修饰的 ancovenin 不显示抗菌活性。Cinnamycin 和 duramycin 除了对枯草芽孢杆菌(*Bacillus subtilis*)和厌氧菌表现出较好的抗菌活性外，对酵母菌等真菌也有一定程度的抑制作用[32–33]。除了抗菌活性外，cinnamycin、duramycin 和 ancovenin 还表现出罕见的多样性生物活性，如 cinnamycin 的抑制Ⅰ型单纯疱疹病毒增殖的活性[33]、ancovenin 和 cinnamycin 的血压调节作用[34–35]、duramycin 的治疗囊性纤维化活性[31,62]、cinnamycin 和 duramycin 的抗炎或抗过敏活性[63]及 duramycin 的抗病毒和抗肿瘤活性[30–31]等。

一些 actagardine 的结构类似物如 Ala(0)-actagardine[14]、NAI-802[46]和 Ala(0)-NAI-802[46]在几种不同的 *Actinoplanes* sp.中被发现。上述

3 种羊毛硫肽在结构上比 actagardine 多 1–3 个氨基酸残基，其中 Ala(0)-actagardine 的抗菌活性略高于 actagardine[14]，而 NAI-802 的抗菌活性则比 actagardine 高 2–4 倍[46]，这可能与 NAI-802 比 actagardine 多带 1 个正电荷有关。此外，研究人员还分别在 *Actinoplanes liguriae* NCIMB41362 和稀有放线菌 *Clavibacter michiganensis* 中发现了 actagardine 的 C 端 MeLan 未被氧化成亚枫的结构类似物 deoxyactagardine B[45]和 michiganin A[47] (图 5)。Deoxyactagardine B 在结构上仅 15 和 16 位氨基酸残基与 actagardine 不同，而将 deoxyactagardine B 前体肽合成基因，导入敲除了 actagardine 前体肽基因的 *Actinoplanes garbadinensis* 中，后者产生了 C 端 MeLan 被氧化成亚枫的 deoxyactagardine B 的氧化物 actagardine B[45]。Michiganin A 除了 C 端和 N 端各比 actagardine 多出 1 个氨基酸残基外，在 5 位和 15 位的氨基酸也不同于 actagardine。Michiganin A 的抗菌谱极窄，仅对产生菌的近缘致病菌菌株 *C. michiganensis* subsp. *sepedonicus* 2136 有较好的抗菌活性，且 MIC 在纳摩尔浓度[47]。

而 Fredenhagen 等分别在放线菌 *Streptoverticillium* strain R2075 和 *Streptomyces griseoluteus* R2107 中分离纯化出 duramycin B 和 duramycin C[9]。根据 Fredenhagen 等的建议，duramycin 类化合物的一级结构仅在 2、3、6、7、10、12 和 13 位氨基酸残基可能存在差异[9]。然而，首例报道的来源于海洋放线菌 *Marinactinospora thermotolerans* SCSIO 00652 的羊毛硫肽 mathermycin 的一级结构除了在 2、3、12 和 13 位氨基酸残基与 duramycin 不同外，在 4 和 17 位氨基酸残基也与 duramycin 不同，这似乎表明海洋来源的羊毛硫肽的结构更具有多样性。Mathermycin 对 *B. subtilis* 的抗菌活性强度和 cinnamycin 类似[39]。

除了上述羊毛硫肽外，在放线菌中还发现了双组分羊毛硫肽 roseocin (图 7)，这是首例来

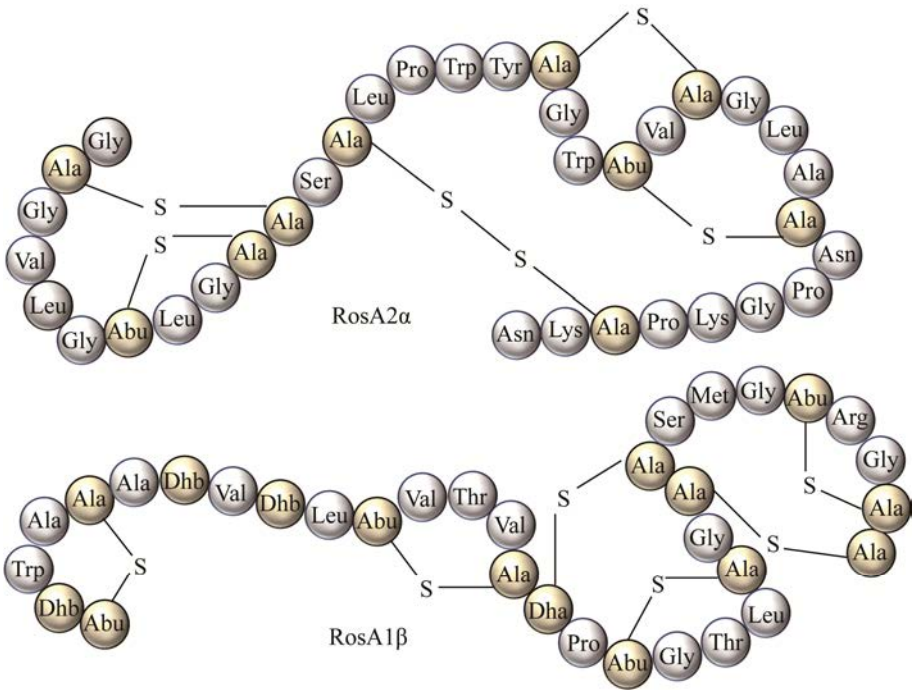

图 7 Roseocin 的氨基酸序列[49]

Figure 7 Peptide sequences of roseocin[49].

源于非厚壁菌门的双组份羊毛硫肽。Roseocin 包括 RosA2α 和 RosA1β，这 2 个组分单独添加时几乎没有抗菌活性，而一起添加时则表现明显的抗菌活性，甚至对 MRSA 和 VRE 也有一定的抑制效果[49]。而分离自 *Micrococcus varians* 的 variacin 在结构上与来源于 *L. lactis* 的 lacticin 481 在结构上有很高的相似性，除了 N 端比 lacticin 481 少 2 个氨基酸残基外，仅在 6、13 和 17 位氨基酸残基不同。Variacin 的热稳定性很好且在 pH 2–10 范围内非常稳定，对大部分革兰氏阳性测试菌株表现出较好的抑制效果[48]。

1.3 Ⅲ型羊毛硫肽

在放线菌产生的Ⅲ型羊毛硫肽中研究的最多的是 labyrinthopeptins (图 8)和 NAI-112 (图 9)，二者分别在 *Actinomadura namibiensis* DSM 6313 和 *Actinoplanes* sp. DSM 24059 发酵液中发现，均含有 2 个 Lab (图 1)，且都表现出较好的镇痛活性[5,12]。Labyrinthopeptins 包含 labyrinthopeptins A1、A2 和 A3，由 18–21 个氨基酸残基构成，除了 Lab，还包含 1 个二硫键[5]。NAI-112 包含 22 个氨基酸残基且不带电荷，是第 1 个报道存在 MeLab 和 N-糖基化的羊毛硫肽[12]。除了镇痛活性外，labyrinthopeptins 还表现出中等强度

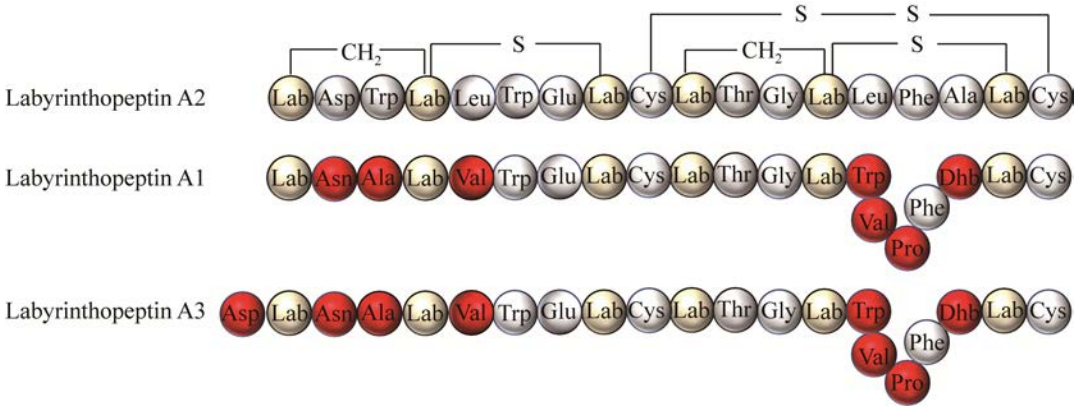

图 8 Labyrinthopeptin 的氨基酸序列

Figure 8 Peptide sequences of labyrinthopeptin. The thioether bonds that are shared by labyrinthopeptin A2, labyrinthopeptin A1 and labyrinthopeptin A3 are shown on the labyrinthopeptin A2 sequence. Amino acids that differ from labyrinthopeptin A2 sequence are marked in red.

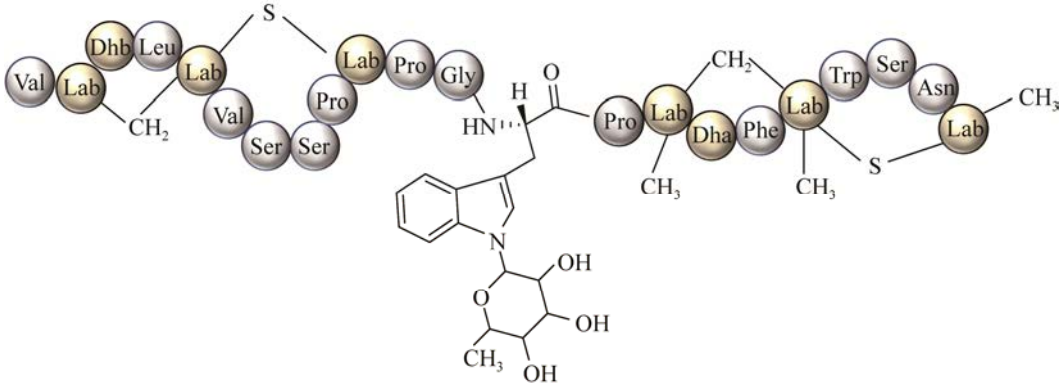

图 9 NAI-112 的氨基酸序列[12]

Figure 9 Peptide sequence of NAI-112[12].

的抗病毒活性[5,64]，而 NAI-112 还显示出中等强度抗菌活性[12]。

Ⅲ型羊毛硫肽前体肽中一般含有保守的丝氨酸/丝氨酸/半胱氨酸结构，这导致翻译后修饰的成熟肽中一般含有 Lab，而在某些翻译后修饰不完全的情况下还含有 Lan，有些甚至只含有 Lan，但 Lab 和 Lan 的总数一般为 2[50,54]。羊毛硫肽 SapB[26]、SapT[56]、AfmS[57]和 curvopeptin[54]中均不含 Lab，且只表现出表面活性剂或多效信号分子生物活性。而 catenulipeptin 虽然含 2 个 Lab，但也仅表现出一定的表面活性剂活性[53]。此外，erythreapeptin[51]、avermipeptin[51−52]、griseopeptin[51]和 informatipeptin[55]中含有 Lab 或(和) Lan，且 Lab 和 Lan 的总数均为 2，但除了 avermipeptin B 表现出较强的抗革兰氏阳性菌活性外[52]，剩余的生物活性目前尚不清楚。

值得一提的是，近期从 *Stackebrandtia nassauensis* 中分离出含有 3 个 Lab 的超大型羊毛硫肽 stackepeptin A、N 端比 stackepeptin A 少 1 个甘氨酸残基的 stackepeptin B 及只含有 N 端 1 个 Lab 的 stackepeptin D 和含有靠近 N 端 2 个 Lab 的 stackepeptin C[50]。不同于其他Ⅲ型羊毛硫肽，上述 4 种 stackepeptin 结构类似物中 Lab 和 Lan 的总数为 3，且前导肽的缺失似乎不影响羊毛硫肽的脱水过程。这也暗示天然的Ⅲ型羊毛硫肽可能远远超过目前所发现的数量和类型。

1.4 Ⅳ型羊毛硫肽

Venezuelin 是第一个被发现的Ⅳ型羊毛硫肽，分离自 *S. venezuelae*，含 22 个氨基酸残基，1 个 Lan 和 3 个 MeLans (图 10)[21]。Streptocollin 是从 *Streptomyces collinus* Tü 365 中分离的 venezuelin 结构类似物，Lan 和 MeLan 的数目和位置与 venezuelin 相同，但其 N 端比 venezuelin 多 1 个氨基酸且在 1、4 和 17 位氨基酸残基与 venezuelin 不同(图 10)[58]。而近期分离的 SflA 则与上述 2 种羊毛硫肽结构不同，不但氨基酸构成无任何相似性而且只含有 1 个 Lan 和 1 个 MeLan (图 10)[59]。与其他类型的羊毛硫肽不同，上述 3 种Ⅳ型羊毛硫肽除了脱水和环化修饰外，无其他任何翻译后修饰，且均未表现出明显的生物活性。

1.5 V型羊毛硫肽

Lexapeptide 是目前唯一报道的V型羊毛硫肽[11]。它分离自 *Streptomyces rochei* Sal35，由 38 个氨基酸残基构成，除了脱水氨基酸及 Lan 外，还存在 N,N-二甲基苯丙氨酸、S-aminovinyl-D-半胱氨酸和 D-丙氨酸结构(图 11)。Lexapeptide 的抗菌活性非常强，对革兰氏阳性菌尤其是 MRSA、

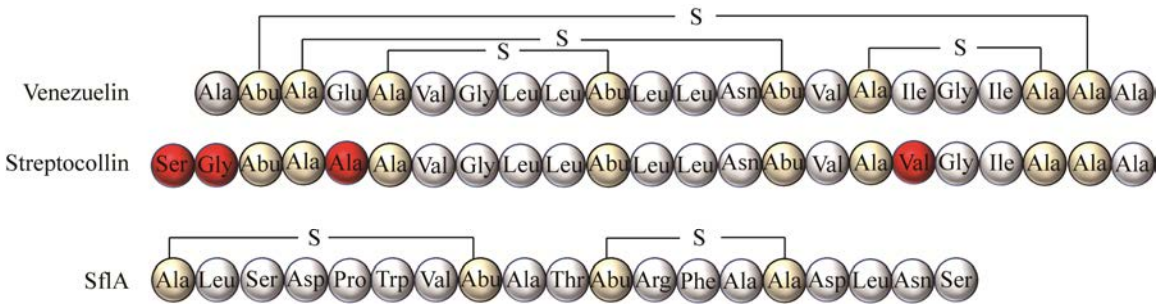

图 10 Ⅳ型羊毛硫肽 venezuelin、streptocollin 和 SflA 的氨基酸序列

Figure 10 Peptide sequence of type Ⅳ lanthipeptide venezuelin, streptocollin and SflA. The thioether bonds that are shared by venezuelin and streptocollin are shown on the venezuelin sequence. Amino acids of streptocollin that differ from venezuelin sequence are marked in red.

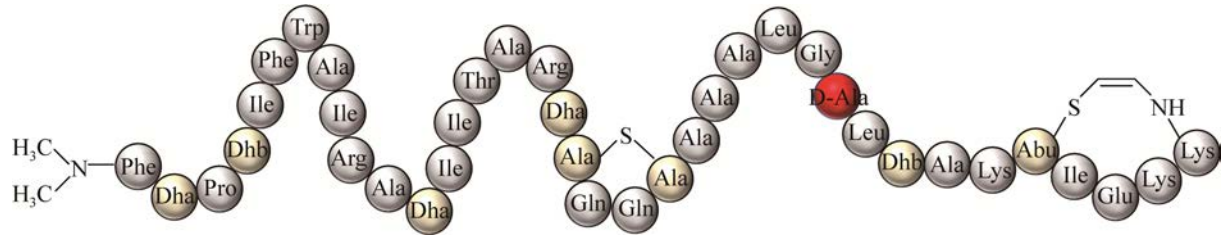

图 11　V型羊毛硫肽 lexapeptide 的氨基酸序列[11]

Figure 11　Peptide sequence of type V lanthipeptide lexapeptide[11].

MRSE、*Enterococcus faecalis* 和 *Mycobacterium smegmatis* 的 MIC 比 nisin 和万古霉素低。进一步研究还发现，D-丙氨酸的存在极大地提高了 lexapeptide 对 *M. smegmatis* 和 *S. aureus* 的抗菌活性。此外，lexapeptide 还表现出比 nisin 更好的 pH 和热稳定性。

2　羊毛硫肽的结构修饰

放线菌产生的羊毛硫肽一般都经历了多种翻译后修饰，这些翻译后修饰极大地增加了羊毛硫肽的结构多样性[15,18]。然而，微生物产生的天然羊毛硫肽，一般都有抗菌活性不高、抗菌谱较窄或理化性质缺陷等缺点。对天然的羊毛硫肽进行结构修饰不仅可以在一定程度上改善上述缺点，而且有助于阐明羊毛硫肽的构效关系，并在此基础上设计出更符合实际应用需求的羊毛硫肽或其衍生物。

目前，对天然的羊毛硫肽进行结构修饰的方法主要有生物和化学 2 种[15]。生物学方法修饰羊毛硫肽主要包括：改变培养基成分[3]；核心肽的定点突变[65]；引入其他来源的修饰酶[7]；模块化组装[66]；选择压力法[67]或终止密码子抑制法[68]引入非天然氨基酸等。尽管目前羊毛硫肽的生物学修饰研究得比较多的是来源于 *L. lactis* 的 nisin[28]，但修饰羊毛硫肽所遵循的原理如羊毛硫肽修饰酶的底物宽泛性等却在各种羊毛硫肽生物合成过程中普遍适用。

化学法修饰羊毛硫肽主要采用半合成方法对天然的羊毛硫肽的结构进行化学修饰。主要包括以下 3 种：(1) 对羊毛硫肽内部氨基酸残基进行基团修饰，如前述的通过酯化或酰胺化增加羊毛硫肽所带正电荷[43,46]；(2) 对末端氨基酸进行修饰，如对 deoxyactagardine B 的 C 端修饰而得到了 NVB302 和 NVB333[69–70]和 actagardine 的 N 端氨基酸修饰[14]；(3) 与其他活性化合物共价连接形成杂合物，如形成羊毛硫肽-羊毛硫肽杂合物[71]和羊毛硫肽与其他化合物杂合物[72]。这些修饰极大地增加了放线菌来源的羊毛硫肽的多样性，促进了对羊毛硫肽构效关系的认识，为发现活性更强或(和)理化性质更优的羊毛硫肽及其衍生物奠定了基础。

3　羊毛硫肽的基因组挖掘

微生物天然产物合成相关基因簇在实验室条件下一般处于低表达或沉默状态，找到并启动这些基因簇将为发掘结构新颖的天然产物提供新的机遇。随着对羊毛硫肽生物合成机制研究的不断深入和生物信息学的飞速发展，结构新颖的羊毛硫肽，尤其是放线菌来源的羊毛硫肽的发掘效率得到了极大地提升，同时也在一定程度上避免了已知羊毛硫肽的重复分离。

一般来说，羊毛硫肽的生物合成基因簇中某些序列非常保守，如Ⅰ型羊毛硫肽的 LanC[73]、Ⅱ型羊毛硫肽的 LanM[49]、Ⅲ型羊毛硫肽核心

肽中的丝氨酸-(Xxx)$_2$-丝氨酸-(Xxx)$_{2–5}$-半胱氨酸(Xxx=任意氨基酸)[51,53]、Ⅳ型羊毛硫肽的LanL[21]和V型羊毛硫肽的 LxmK 等[11]。通过同源比对搜索含目标序列的基因再结合异源表达和液质联用(high performance liquid chromatography-mass spectrum, HPLC-MS)等方法，从放线菌中发现了多个新的羊毛硫肽如erythreapeptin[51]、avermipeptin[51]、griseopeptin[51]、catenulipeptin[53]、stackepeptin[50]和双组份羊毛硫肽 roseocin[49]等。

此外，随着基因组测序数目的增多，数据挖掘和分析工具越来越被广泛地应用于天然产物的挖掘。羊毛硫肽类天然产物挖掘工具如antiSMASH、BAGEL 和 RiPPquest 等促进了新的羊毛硫肽如 avermipeptin B[52]、mathermycin[39]和 informatipeptin[55]等的发现。本课题组近期从距离海边 1 km 左右的松树根部土壤中分离得到 1 株耐盐的放线菌，对其基因组框架图用antiSMASH 分析表明其具有合成 2 个Ⅰ型羊毛硫肽及 1 个Ⅲ型羊毛硫肽的潜力，并通过初步纯化确定该羊毛硫肽的分子量在 2 000 Da 左右，且具有抗 MRSA 活性。

4 结语

目前已经发现的放线菌只是自然界全部放线菌的“冰山一角”。随着越来越多不同来源的放线菌尤其是海洋放线菌的发现与分离，放线菌来源的羊毛硫肽的数量将会迅速增加，人们对放线菌来源的羊毛硫肽的生物合成机制和构效关系等的认识将进一步深入。届时，对已经发现放线菌来源的羊毛硫肽采用生物和化学法进行结构修饰以设计出符合人类应用需求的羊毛硫肽的可能性将迅速提升，同时通过基因组挖掘结构新颖的放线菌来源的羊毛硫肽的效率也会有明显的提高。

抗生素耐药性已经成为 21 世纪最严重的威胁人类生命安全的难题之一，研究和发掘新型抗菌药物以抑制耐药菌株的传播和发展迫在眉睫。放线菌能产生目前已知全部类型的羊毛硫肽，其中一些结构新颖的羊毛硫肽或其衍生物已经表现出较好的抑菌效果，或许有希望成为应对这一难题的强有力武器。

此外，尽管一些放线菌来源的羊毛硫肽已经显示出调节血压、抗肿瘤、抗病毒和镇痛等稀缺的生物学活性，但放线菌来源的羊毛硫肽尤其是生物活性尚不清楚的Ⅲ型和Ⅳ型羊毛硫肽的应用价值还存在巨大的开发空间。可以预见，放线菌来源的羊毛硫肽在人类健康相关产业中必定会发挥举足轻重的作用。

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