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Review 综 述

伦茨菌属放线菌的研究进展

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摘要：伦茨菌属(*Lentzea*)由 Yassin 等于 1995 年建立，是一个经典的丝状稀有放线菌类群，目前共包含 23 个有效描述种。伦茨菌的细胞壁含有 *meso*-二氨基庚二酸，优势甲基萘醌成分为 MK-9(H_4)，磷酸类脂主要包括磷脂酰乙醇胺、双磷脂酸甘油、磷脂酰甘油和磷脂酰肌醇，基因组 DNA 的(G+C)含量为 68.6 mol%–79.6 mol%。伦茨菌代谢产物具有显著的生物活性多样性，包括 I 型人体免疫缺损病毒整合酶的抑制活性、抗肿瘤活性、抗结核活性等，在生物医药研究领域逐步显示出潜在的应用价值。本课题组在研究贵州石灰岩风化壳放线菌多样性时分离获得若干株伦茨菌，采用多相分类方法研究 *Lentzea xinjiangensis* DHS C013^T 和 *Lentzea pudingi* DHS C021^T 两株菌的分类学地位，证实均为伦茨菌属的新物种。在此研究基础上，引用有关文献和最新研究成果，对伦茨菌属的建立、分类学特征、生态位和物种分布、功能基因组、天然活性产物应用开发等方面的研究进展进行了综述。

关键词：伦茨菌属，多相分类，稀有放线菌，天然活性产物

微生物是天然活性产物的主要来源，其化合物种类繁多，得到广泛应用的主要有抗生素、抗肿瘤药物、免疫抑制剂、杀虫剂等。这些天然化合物或其先导化合物有 50%以上是由放线菌类群产生的，长期以来放线菌在生物制药领域一直占据着重要地位[1]。近年来，从非链霉菌属的稀有放线菌(rare actinomycetes)获得新化合物的数量呈明显上升态势，表现出化学结构新颖、生物活性多样、细胞毒性低的特点。化合物分子结构类型涉及大环内酯、聚酮、蒽醌、联吡啶类、多烯等类型化合物[2]，其中产生的一些抗菌药物如庆大霉素、红霉素、万古霉素和利福平等已成功应用于临床[3]，这些新型化合物的发现为应对日益增长的耐药性病原菌种类和新致病菌的出现而再次得到了国内外学者的高度关注。

伦茨菌属(*Lentzea*)是一类经典的丝状稀有放线菌，隶属于放线菌门(*Actinobacteria*)-放线菌纲(*Actinobacteria*)-假诺卡氏菌目(*Pseudonocardiales*)-

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假诺卡氏菌科(*Pseudonocardiaceae*)。随着分类学技术的发展，伦茨菌属的分类在建立之初发生过多次变动，重新修正伦茨菌属的分类地位，为后续新成员的分类研究提供科学依据。近年来，从伦茨菌分离获得越来越多的天然活性产物，愈发显示出该稀有放线菌类群在新药研发中的重要地位。此外，伦茨菌属产生的次级代谢产物具有多种生物活性，如环孢素 A 衍生物生物转化活性[4]，抑菌抗癌活性的天然产物十字孢碱[5]，蛋白质激酶的抑制剂活性等[6]。最引人关注的是伦茨菌 *Lentzea chajnantorensis* H45^{T} 产生的代谢产物对 I 型人体免疫缺损病毒(Human immunodeficiency virus type 1，HIV-1)整合酶具有显著的抑制活性[7]，这一发现有力推动了新型抗 HIV 治疗药物的研发进程。

1 伦茨菌属的建立及研究现状

1.1 伦茨菌属的建立

1995 年，Yassin 等在研究病原放线菌时，从一位女性的患腹膜癌、结肠癌组织培养物中获得一株放线菌命名为 IMMIB D-958。培养鉴定后发现该菌株与放线菌目的其他所有属的化学分类特征都不同，由此命名为白丝伦茨菌(*Lentzea albidocapillata*)[8]，并建立了伦茨菌属。

2000 年，Lee 等发现紫色糖丝菌(*Saccharothrix violacea*)与白丝伦茨菌(*L. albidocapillata*)在进化树上形成一个分枝且化学特征相似，提议撤销伦茨菌属并将白丝伦茨菌转移到糖丝菌属(*Saccharothrix*)[9]。2001 年 Labeda 等基于系统发育和化学分类学研究结果分析恢复伦茨菌属，并将新发表的 2 个菌种(*Lentzea albida* 和 *Lentzea californiensis*)以及糖丝菌属的 2 个菌种重新归类到伦茨菌属(*L. albidocapillata* 和 *Lentzea waywayandensis*)[10]。目前伦茨菌属共有 23 个有效描述种。另外两株 *Lentzea indica*[11]和 *Lentzea isolaginshaensis*[12]没有经过“List of Prokaryotic names with Standing in Nomenclature”的进一步确认，为非有效描述种。

大部分伦茨菌分离自土壤，也有的来自不同的极端环境如沙漠、酸性土壤及岩石风化土等。李文均团队报道从贵州喀斯特洞穴采集的样品中分离获得到伦茨菌[13]。Liu 等[14]首次从地衣中分离得到伦茨菌。纯培养获得的伦茨菌新物种相对较少，而陆续报道的宏基因组学研究结果显示伦茨菌属放线菌类群在地球生态系统中分布十分广泛。Germida 团队采用 16S rRNA 扩增测序技术研究油砂复垦区生长的一年生大麦和甜三叶草的根际菌群多样性，结果显示伦茨菌为优势属之一[15]。黄英团队综合免培养和纯培养分离方法系统分析了青藏高原土壤放线菌多样性特征，结果表明伦茨菌属丰度相对较高，并分离获得两株疑似新物种的伦茨菌[16]。Yang 等研究短期施用氮肥对土壤分解几丁质的细菌群落(chitinolytic community，chiA)的影响，发现在丰度最高的前 50 个 chiA 操作分类单元(operational taxonomic units，OTU)多数归类为放线菌门中的链霉菌、伦茨菌和游动放线菌[17]。Hasyimi 研究太平洋白虾 *Litopenaeus vannamei* 肠道微生物多样性组成，结果显示在属水平上伦茨菌属也具有较高的丰度[18]。

1.2 伦茨菌属与其近缘属的比较

伦茨菌属与邻近的束丝放线菌属(*Actinosynnema*)、动孢放线菌属(*Actinokineospora*)和糖丝菌属(*Saccharothrix*)同属于假诺卡氏菌科，

各属的化学特征整体相似但是仍有明显差异(表1)。伦茨菌能够形成良好的分枝状营养菌丝体，不产生孢囊结构，无游动孢子，而束丝放线菌成熟的气生菌丝形成孢子链，动孢放线菌的气生菌丝可产生游动孢子[19]。伦茨菌的菌落排列紧密，在ISP 2、ISP 3和ISP 4培养基上呈现黄色或褐色。在极性脂组成上，伦茨菌属放线菌没有羟基磷脂酰乙醇胺(hydroxy-phosphatidylethanolamine，OH-PE)，而其3个近缘属均有检出。伦茨菌脂肪酸类型主要以iso-/anteiso-分支饱和脂肪酸为主。伦茨菌全细胞糖中不含阿拉伯糖，糖丝菌全细胞糖中有甘露糖和鼠李糖。相比于假诺卡氏菌科中的其他放线菌属，伦茨菌属有更高的基因组DNA (G+C) mol/%含量。

1.3 伦茨菌属的多相分类特征

1.3.1 形态和生理生化特征：伦茨菌为革兰氏阳性菌，需氧，不耐酸，细胞直径为0.5–0.7 μm，长度为2–3 μm。培养菌落紧密，基质菌丝发育良好，气生菌丝分枝不规则，成熟后断裂成杆状。在不同琼脂培养基上形成不同颜色的基质菌丝和气生菌丝，有淡黄色或黄褐色的基质菌丝以及白色或黄白色的气生菌丝，*L. xinjiangensis*能在改良的Bennett琼脂上形成白色到黄色的气生菌丝[25]。大多数菌种不产生可溶性色素，除了*Lentzea kentuckyensis*在蛋白胨-铁琼脂培养基上产生一种浅棕色可溶性色素[26]，*Lentzea aerocolonigenes*在一些培养基上产生褐色的可溶性色素[27]。

该属大部分菌株生长温度范围一般为10–37 °C，*Lentzea terrae*、*L. xinjiangensis*、*Lentzea nigeriaca*和*Lentzea fradiae*在45 °C时依然能够存活[25,28–30]。适宜生长的pH为5–11。除了*Lentzea*

表1. 伦茨菌属及相关菌属的分类学特征

Table 1. Taxonomy characteristics of the genus *Lentzea* and related genera

Characteristics	*Lentzea*[8,19]	*Actinosynnema*[20]	*Actinokineospora*[21–22]	*Saccharothrix*[23–24]
T/°C	10–37	28–30	10–45	10–45
pH	5–11	6.0–8.5	5–10	6–9
NaCl tolerance/%	0–4	0–2	0–5	0–3
Colour of colony	Yellow	Pale greenish	Brown	Brown
Sporangia produced	None	Synnemata	None	None
Motile spores	No	Yes	Yes	No
Whole-cell sugars	Gal, Man, Rib	Gal, Man, Rha	Ara, Man, Rha	Gal, Man, Rha
Polar lipids	PE, DPG, PG, PI	PE, OH-PE, PI, PIM, DPG	PE, OH-PE	PE, OH-PE, PI, PIM, DPG, PG
Menaquinones	MK-9(H_2) MK-9(H_4)	MK-9(H_4) MK-9(H_6)	MK-9(H_4)	MK-9(H_4) MK-10(H_4)
Cellular fatty acid	iso-$C_{14:0}$ iso-$C_{15:0}$ iso-$C_{16:0}$ anteiso-$C_{15:0}$	$C_{17:0}$ anteiso-$C_{17:0}$ iso-$C_{16:0}$	iso-$C_{16:0}$ iso-$C_{15:0}$ iso-$C_{16:0}$2-OH	iso-$C_{16:0}$ $C_{17:1}\omega8c$ iso-$C_{15:0}$
DNA G+C content/mol%	68.6–79.6	71–73	69.1–73.0	67–76

Gal: galactose; Man: mannose; Rib: ribose; Ara: arabinose; Fru: fructose; Xyl: xylose; Rha: rhamnose; PE: phosphatidylethanolamine; PG: phosphatidylglycerol; PI: phosphatidylinositol; DPG: diphosphatidylglycerol; PIM: phosphatidylinositolmannoside; OH-PE: hydroxy-phosphatidylethanolamine.

flaviverrucosa、*Lentzea flava* 和 *L. terrae* 不能水解酪蛋白[27,29,31]，多数菌种能够水解酪蛋白和淀粉，目前发现的菌株中，只有 *Lentzea cavernae* 不能水解淀粉[32]；对于明胶的水解反应，*L. albidocapillata*、*L. jiangxiensis*、*L. pudingi*、*Lentzea soli*、*Lentzea waywayandensis* 和 *Lentzea rhizosphaerae* 呈阴性[8,33–37]。此外，只有 *L. flaviverrucosa*、*L. californiensis*、*L. waywayandensis* 和 *L. jiangxiensis* 的硝酸还原反应呈阳性[10,31,35,37]；能产生 H_2S 气体的只有 *L. cavernae* 和 *Lentzea roselyniae*。

1.3.2 化学分类特征：伦茨菌属成员细胞壁类型为Ⅲ型(*meso*-DAP)，全细胞糖由半乳糖、甘露糖、葡萄糖和核糖组成。*L. cavernae* 的全细胞糖含有阿拉伯糖、果糖、甘露糖和木糖[32]，而 *L. waywayandensis* 和 *L. aerocolonigenes* 只含有半乳糖以及鼠李糖。多数伦茨菌的主要甲基萘醌是 MK-9(H_4)和 MK-9(H_2)。除此之外，菌株 *L. soli* 的甲基萘醌还含有 MK-9(H_0)，*L. rhizosphaerae* 含有少量的 MK-9(H_6)。

脂肪酸结构包括直链饱和脂肪酸、不饱和脂肪酸和 iso-/anteiso-类型的支链饱和脂肪酸。多数伦茨菌种的脂肪酸都含有 iso-$C_{16:0}$、iso-$C_{15:0}$、$C_{16:0}$、10Me-$C_{16:0}$ 和 anteiso-$C_{15:0}$，*L. cavernae* 中含有 $C_{14:0}$[32]，*L. terrae* 的脂肪酸中含有不饱和脂肪酸 $C_{16:1}\omega7c$，*L. albidocapillata* 的脂肪酸是 3d 型(10-甲基支链脂肪酸)；该菌属部分成员的磷酸类脂组分有双磷脂酸甘油(diphosphatidylglycerol，DPG)、磷脂酰乙醇胺(phosphatidylethanolamine，PE)、磷脂酰肌醇甘露糖苷(phosphatidylinositolmannoside，PIM)、磷脂酰肌醇(phosphatidylinositol，PI)以及未鉴定的磷脂(unidentified lipid，UL)[26,29,33–35]，菌株 *L. flava* 含有溶血磷脂酰乙醇胺(lysophosphatidylethanolamine，Lyso-PE)[38]。

1.3.3 分子分类特征：伦茨菌属隶属于假诺卡氏菌科，在基于伦茨菌属及相关属代表菌株 16S rRNA 基因序列的系统发育进化树中(图 1)，伦茨菌属各成员在假诺卡氏菌科内聚在一起形成一个稳定的分支。伦茨菌属与束丝放线菌属的关系最为接近，二者趋近聚合形成一个系统进化分支。本实验室从中国贵州省石灰岩风化壳样品中分离到的伦茨菌株 *L. guizhouensis* DHS C013^T 与 *L. jiangxiensis* FXJ1.034^T 位于一个亚分支内，16S rRNA 基因序列相似性为 98.7%[39]。另一株 *L. pudingi* DHS C021^T 与 *L. albida* CGMCC 4.1727^T 的 16S rRNA 基因序列相似性为 98.8%[33]。伦茨菌属的特征性核苷酸位点是 TCAA (617–620)、GCC (843–845)[40]；伦茨菌属成员的基因组 DNA (G+C)mol%含量范围是 68.6%–79.6%。

1.4 基因组研究概况

截止 2020 年 12 月，NCBI 和 Ezbiocloud 的 Genome 数据库共收录了 19 株伦茨菌的基因组序列。借助 Type Strain Genome Server (https://tygs.dsmz.de/)对该 19 个菌种进行全基因组系统发育分析(图 2)，并使用 antiSMASH (5.2.0 版本)注释预测。数据显示，伦茨菌基因组相对较大，约为 8–10 Mb，拥有高达近万个蛋白编码基因(coding sequences，CDSs)，聚酮化合物合成酶(polyketide synthase，PKS)和非核糖体肽合成酶(non-ribosomal peptide synthetase，NRPS)基因簇也相当丰富(表 2)。*L. terrae* NEAU-LZS 42^T 基因组含有 9915 个 CDSs，*L. waywayandensis* DSM 44232^T 基因组含有 39 个次级代谢生物合成基因簇(biosynthetic gene clusters，BGCs)，*L. jiangxiensis* CGMCC 4.6609^T

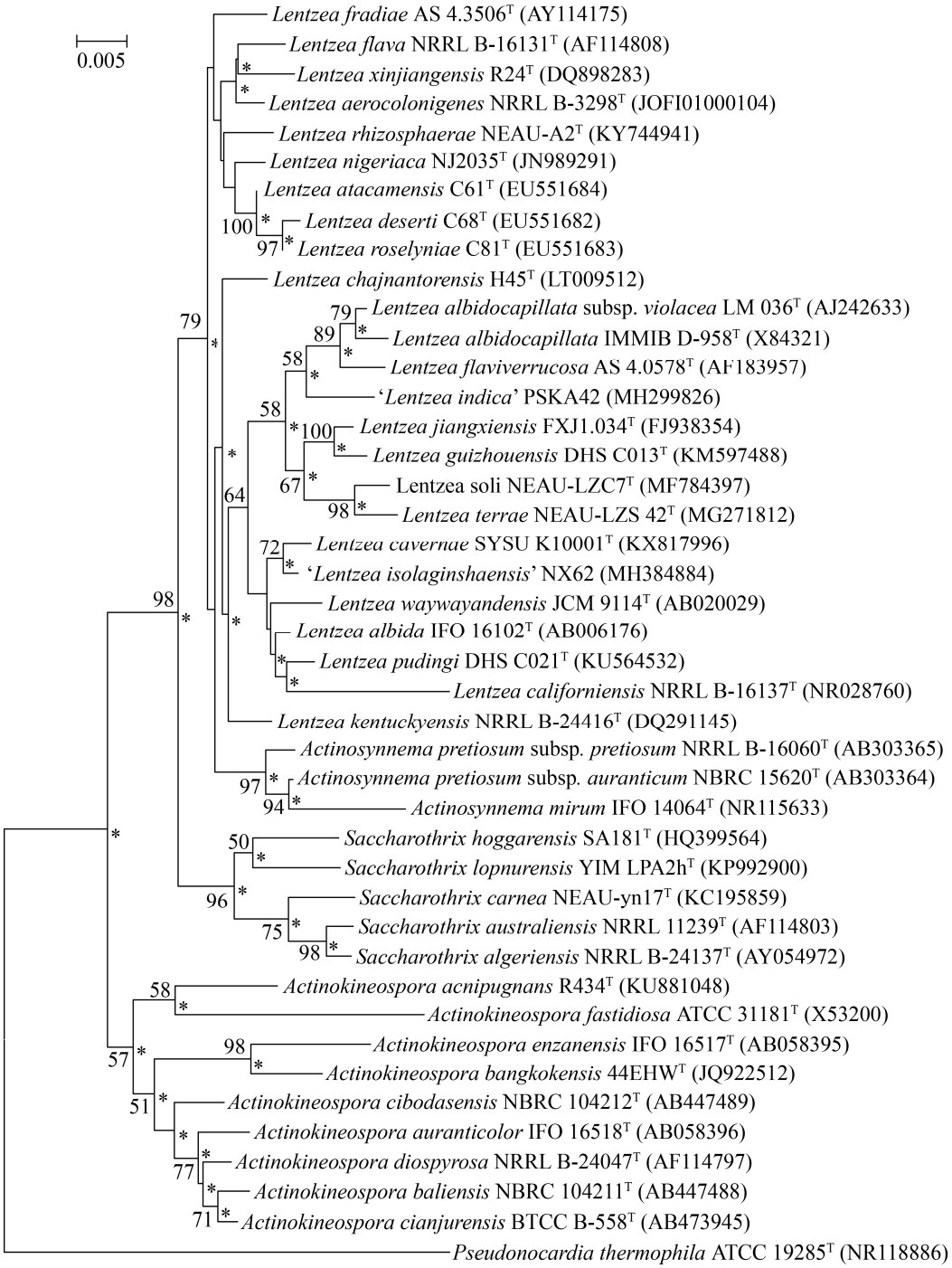

图 1. 邻近法构建的基于伦茨菌属及相关属代表菌株 **16S rRNA** 基因序列的系统发育进化树

Figure 1. Neighbour-joining phylogenetic tree based on 16S rRNA gene sequences of the representative members of the genera of *Lentzea*, *Actinosynnema*, *Saccharothrix* and *Actinokineospora*. Numbers at nodes indicate levels of bootstrap support based on a neighbour-joining analysis of 1000 resampled datasets, only values >50% were given. Asterisks indicate branches that were also recovered using the maximum-parsimony and maximum-likelihood methods (Data were not presented in this paper). The sequences in bracket indicate the accession number in NCBI. Bar: 5 nucleotide substitution per 1000 nucleotides.

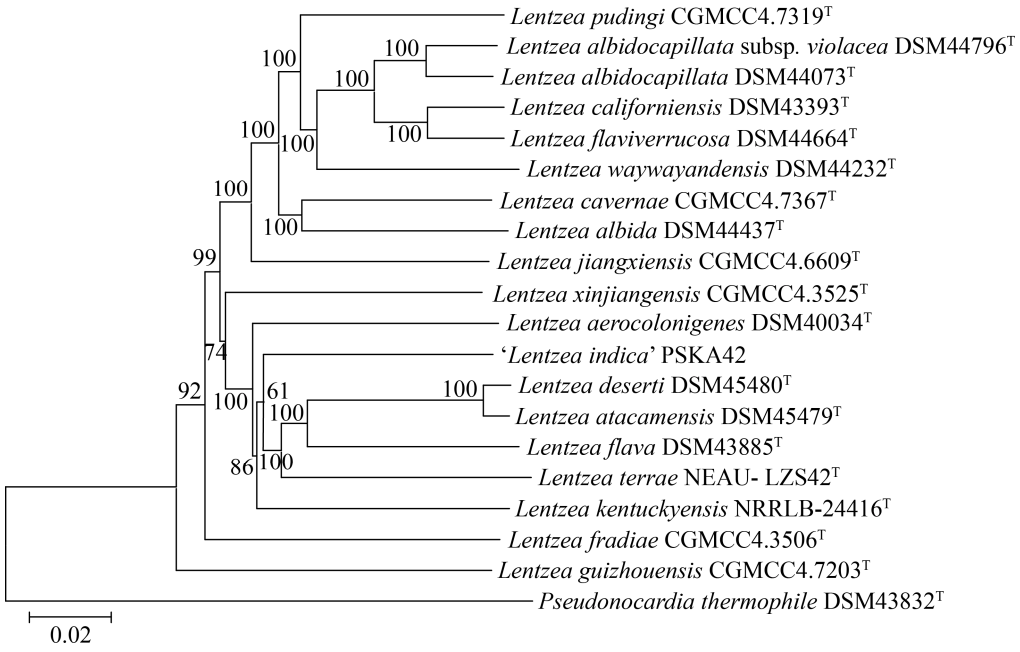

图 2. 基于 TYGS 服务器中伦茨菌属基因组序列的系统发育树

Figure 2. Phylogenomic tree based on genome sequences of the *Lentzea* genus in the TYGS server. Tree inferred with FastME 2.1.6.1 from GBDP distances calculated from genome sequences. The branch lengths are scaled in terms of GBDP distance formula d5. The numbers above branches are GBDP pseudo-bootstrap support values >60% from 100 replications, with an average branch support of 94.6%. The tree was rooted at the midpoint. Bar: 2 nucleotide substitution per 100 nucleotides.

表 2. 伦茨菌属基因组特征

Table 2. Features of *lentzea* genomes

Species	Genome size/bp	CDSs	rRNAs	tRNAs	BGCs	PKS	NRPS
L. albida DSM 44437^T	9441135	8818	15	65	35	7	10
L. terrae NEAU-LZS 42^T	10581732	9915	7	64	33	2	10
L. albidocapillata DSM 44073^T	8639486	8185	14	62	28	2	9
L. flaviverrucosa DSM 44664^T	9468454	8932	6	71	30	5	8
L. albidocapillata subsp. *violacea* DSM 44796^T	8671075	8301	17	66	30	4	10
L. waywayandensis DSM 44232^T	10153412	9339	15	67	39	4	13
L. kentuckyensis NRRL B-24416^T	10210611	9374	5	63	35	10	9
L. xinjiangensis CGMCC 4.3525^T	8684108	8199	14	62	37	7	14
L. atacamensis DSM 45479^T	9306230	9058	8	68	26	4	8
L. californiensis DSM 43393^T	8998498	8539	18	69	29	5	8
L. deserti DSM 45480^T	9529573	9224	8	68	32	6	9
L. flava DSM 43885^T	9746996	9203	16	68	28	3	8
L. fradiae CGMCC 4.3506^T	8508028	8020	15	60	36	5	15
L. guizhouensis DHS C013^T	9997872	9760	15	69	35	8	9
L. jiangxiensis CGMCC 4.6609^T	8591279	8027	12	67	37	7	15
L. aerocolonigenes NBRC 13195^T	10698154	9898	10	67	27	2	9
L. indica PSKA42	9967419	8731	18	61	37	9	14
L. pudingi CGMCC 4.7319^T	9209073	8539	5	69	26	4	7
L. cavernae CGMCC 4.7367^T	9738430	9120	5	64	33	4	10

基因组含有 22 个 PKS 和 NRPS 基因簇。基因组研究表明，*Lentzea* sp. ATCC 31319 基因组上存在聚酮类抗生素乳霉素(thiolactomycin，TLM)生物合成基因簇[41]。

2 伦茨菌属的应用研究

2.1 HIV-1 整合酶抑制活性

抗 HIV 治疗通常包括针对病毒复制周期不同阶段使用不同药物以及联合治疗，主要问题是病毒突变率高，导致耐药病毒的出现。为了克服这一问题，最初是让患者接受不同药物的联合治疗，以减少耐药突变株的选择，后来经过改进，开发出针对病毒复制周期内确定额外的药物靶点的新方法[42]。HIV-1 整合酶是病毒复制周期中的关键酶之一，它负责将逆转录的病毒互补 DNA (cDNA)整合到宿主细胞基因组中[43]，该靶点对开发新的抗 HIV 治疗具有很强的选择特异性。

研究发现阿塔卡马沙漠中微生物类群也十分丰富[44–45]，从中分离出许多放线菌新物种[46–47]。从其中 *L. chajnantorensis* H45^T 菌株的天然代谢产物中分离出 6 种结构新颖的二烯和单烯糖苷化合物 Lentzeaosides A–F，活性检测结果显示对 HIV-1 整合酶表现出不同水平的抑制活性[7]。抗病毒治疗以整合酶为靶点是对逆转录酶和蛋白酶抑制剂的宝贵补充[48]，具有潜在的应用前景。化学全合成的雷特格韦(Raltegravir)是美国食品药物管理局(Food and Drug Administration，FDA)批准的第一个 HIV-1 整合酶抑制剂，多用于治疗对多种抗逆转录病毒药物耐药的患者[49]。

2.2 生物转化功能

环孢素 A (cyclosporine A，CsA)是一种抑制细胞亲环素的环肽，用作器官移植的关键免疫抑制剂。CsA 的抑制活性依赖于其与亲环素的结合，其复合物抑制钙调神经磷酸酶在 T 细胞中的作用[50]。Sasamura 研究团队发现 *Lentzea* sp. 7887 (与 *L. albidocapillata* subsp. *violacea* LM 036^T 的 16S rDNA 相似性为 99.2%)能够催化 CsA 衍生物 FR901459 多个位点发生羟基化反应，生物转化后表现出更好的免疫抑制活性[51]。同时发现底物分散剂大豆粉能有效提高该生物转化效率[52]。最新研究证实 *Lentzea* sp. 7887 的细胞色素 P450 可以催化抗真菌药物 Sordaricin 发生 6-羟基化反应[53]。

2.3 伦茨菌的其他应用

1976 年，学者首次从菌株 *Streptomyces staurosporeus* (现修正为 *L. albida*)中分离出吲哚咔唑化合物十字孢碱(staurosporine)[54]。已知该化合物能和迄今发现的约 90%人类激酶发生作用[55]，具有良好的抗真菌、降血压作用[56]和抑制血小板聚集的特性[57]，尤其是研究证实十字孢碱具有很好的抗癌活性。为减小其毒副作用，化学家已对其进行大量结构修饰，获得了多个高效低毒的十字孢碱衍生物[58]。另一伦茨菌 *L. aerocolonigenes* sp. 代谢产生的瑞贝霉素(rebeccamycin)也具有显著的抗肿瘤活性[59]。

从放线菌中分离得到的众多天然产物中许多都具有抗菌活性，很少有针对结核病原菌的研究。由结核分枝杆菌引起的结核病因耐药性问题，导致结核病难以短期治愈。最近研究首次发现 *L. albidocapillata* subsp. *violacea* AS08 对结核分枝杆菌 *Mycobacterium tuberculosis* H37Rv 表现出显著的拮抗作用，具有抗结核活性[60]。该伦茨菌是从印度喜马拉雅山脉西北部未开发地区的土壤中分离获得，早前研究证实 *L. albidocapillata*

subsp. *violacea* AS08 产生的代谢产物具有多种生物活性，包括抗氧化、降胆固醇、杀虫等活性[61]。

聚乳酸(poly lactic acid，PLA)是一种生物可降解、低过敏性、抗菌、环保、多功能的高分子化合物[62–63]，并且广泛应用于缝合线、支架、可吸收伤口闭合产品等生物医学领域[64]。Nimisha 等研究发现菌株 *L. waywayandensis* ATCC 51594 能够显著提高聚乳酸的生物降解率[65]；国内学者堵国成团队进一步研究发现 *L. waywayandensis* sp.代谢产生的胞外蛋白酶在降解 PLA 膜的过程中起到关键催化作用[66]。

3 展望

伦茨菌属发现和建立相对较晚，但是在过去的二十余年里从伦茨菌中陆续分离获得多种新颖的天然活性产物。这些天然产物通常具有显著的抗癌、生物降解、抗 HIV 等活性。尤其是 HIV-1 整合酶抑制活性的发现，在艾滋病治疗作为当今医学领域的热点和难点的大背景下，提供了 HIV 治疗药物研发新思路，突显出稀有放线菌伦茨菌属类群在生物医药领域的巨大价值。

截至目前有效发表的伦茨菌属物种还相对较少，可能仍然有许多新成员尚未被发现。在多样且复杂的地球极端环境中新物种资源挖掘依然存在很大空间，诸如海洋、极地、沙漠等特殊生境赋予了放线菌独特的基因型、特殊的生理机制以及丰富的代谢类型。据估计自然界中仍有 90%以上的放线菌未被发现，而绝大多数微生物很难被培养，这就需要研究人员不断探索、改进培养基成分、创新分离技术来提高稀有放线菌的分离效率。已有研究表明在选择培养基中加入镧系等稀土元素可以培养出之前在实验室无法生长的微生物[67]。另外，利用组学技术在微生物群落研究中的优势，分析复杂环境中的微生物群落组成多样性及其与周围环境或宿主之间的关系，特别是能获得难以培养的微生物信息，有针对性地优化选择分离方法，促进难培养稀有放线资源的积累。同时，基于稀有放线菌基因组信息的新型基因簇的深度挖掘，针对沉默基因簇采用各种激活手段加强基因表达，增加结构新颖天然产物的产出，让稀有放线菌伦茨菌属类群成为新药研发的宝贵资源。

参 考 文 献

[1] Zheng QW. Advances have been made in the synthetic biology of natural products of actinomycetes in Shanghai Institute of Biotechnology. *Pesticide Market News*, 2017(5): 47–48. (in Chinese)
郑庆伟. 上海生科院在放线菌天然产物的合成生物学方面取得进展. 农药市场信息. 2017(5): 47–48.

[2] Zhang JC, Yang XQ, Zhou H, Yang YB, Ding ZT. New natural products of rare actinomycetes from 2006 to 2018. *Chinese Journal of Organic Chemistry*, 2019, 39(4): 982–1012. (in Chinese)
张举成, 杨雪琼, 周皓, 杨亚滨, 丁中涛. 2006–2018 年稀有放线菌中的新天然产物. 有机化学, 2019, 39(4): 982–1012.

[3] Lazzarini A, Cavaletti L, Toppo G, Marinelli F. Rare genera of actinomycetes as potential producers of new antibiotics. *Antonie Van Leeuwenhoek*, 2000, 78(3/4): 399–405.

[4] Yabutani T, Tsujimoto M, Ohira S, Shimizu S, Nakano H. Strain improvement of *LentZea* sp. 7887 for higher yield per unit volume on hydroxylation of cyclosporine derivative FR901459. *Bioscience, Biotechnology, and Biochemistry*, 2017, 81(7): 1456–1459.

[5] Nakano H, Ōmura S. Chemical biology of natural indolocarbazole products: 30 years since the discovery of staurosporine. *The Journal of Antibiotics*, 2009, 62(1): 17–26.

[6] Tamaoki T, Nomoto H, Takahashi I, Kato Y, Morimoto M, Tomita F. Staurosporine, a potent inhibitor of phospholipid

Ca^{+} dependent protein kinase. *Biochemical and Biophysical Research Communications*, 1986, 135(2): 397–402.

[7] Wichner D, Idris H, Houssen WE, McEwan AR, Bull AT, Asenjo JA, Goodfellow M, Jaspars M, Ebel R, Rateb ME. Isolation and anti-HIV-1 integrase activity of lentzeosides A-F from extremotolerant *LentZea* sp. H45, a strain isolated from a high-altitude Atacama Desert soil. *The Journal of Antibiotics*, 2017, 70(4): 448–453.

[8] Yassin AF, Rainey FA, Brzezinka H, Jahnke KD, Schaal KP. *Lentzea* gen. nov., a New Genus of the Order *Actinomycetales*. *International Journal of Systematic Bacteriology*, 1995, 45(2): 357–363.

[9] Lee SD, Kim ES, Roe JH, Kim J, Kang SO, Hah YC. *Saccharothrix violacea* sp. nov., isolated from a gold mine cave, and *Saccharothrix albidocapillata* comb. nov.. *International Journal of Systematic and Evolutionary Microbiology*, 2000, 50(Pt 3): 1315–1323.

[10] Labeda DP, Hatano K, Kroppenstedt RM, Tamura T. Revival of the genus *LentZea* and proposal for *Lechevalieria* gen. nov.. *International Journal of Systematic and Evolutionary Microbiology*, 2001, 51(3): 1045–1050.

[11] Maiti PK, Mandal S. *LentZea indica* sp. nov., a novel actinobacteria isolated from Indian Himalayan-soil. *Antonie Van Leeuwenhoek*, 2020, 113(10): 1411–1423.

[12] Wang LW, Li YM, Li YM. *LentZea isolaginshaensis* sp. nov., an actinomycete isolated from desert soil. *Antonie Van Leeuwenhoek*, 2019, 112(4): 633–639.

[13] Zhang WQ, Fang BZ, Han MX, Li S, Dong L, Jiang HC, Li WJ. Diversity and antibacterial activity of culturable actinobacteria in Karst cave soil in Xingyi, Guizhou. *Acta Microbiologica Sinica*, 2020, 60(6): 1063–1073. (in Chinese)
张万芹, 房保柱, 韩明贤, 李帅, 董雷, 蒋宏忱, 李文均. 贵州兴义喀斯特洞穴可培养放线菌多样性及抗菌活性初筛. 微生物学报, 2020, 60(6): 1063–1073.

[14] Liu CB, Jiang Y, Wang XY, Chen DB, Chen X, Wang LS, Han L, Huang XS, Jiang CL. Diversity, antimicrobial activity, and biosynthetic potential of cultivable actinomycetes associated with lichen symbiosis. *Microbial Ecology*, 2017, 74(3): 570–584.

[15] Mitter EK, de Freitas JR, Germida JJ. Bacterial root microbiome of plants growing in oil sands reclamation covers. *Frontiers in Microbiology*, 2017, 8: 849. DOI: 10.3389/fmicb.2017.00849.

[16] Huang J, Yan BF, Huang Y. Diversity of culturable actinobacteria from soils collected in Ali, Naqu and Haixi Districts on the Qinghai-Tibet Plateau.. *Acta Microbiologica Sinica*, 2017, 57(9): 1342–1351. (in Chinese)
黄娇, 闫兵法, 黄英. 青藏高原阿里、那曲和海西地区土壤可培养放线菌的多样性. 微生物学报, 2017, 57(9): 1342–1351.

[17] Ouyang Y, Norton JM. Short-term nitrogen fertilization affects microbial community composition and nitrogen mineralization functions in an agricultural soil. *Applied and Environmental Microbiology*, 2020, 86(5): e02278-19.

[18] Hasyimi W, Widanarni W, Yuhana M. Growth performance and intestinal microbiota diversity in Pacific white shrimp *Litopenaeus vannamei* fed with a probiotic bacterium, honey prebiotic, and synbiotic. *Current Microbiology*, 2020, 77(10): 2982–2990.

[19] Goodfellow M, Kämpfer P, Busse HJ, Trujillo ME, Suzuki KI, Ludwig W, Whitman WB. Bergey's manual® of systematic bacteriology. New York, NY: Springer New York, 2012.

[20] Labeda DP, Goodfellow M, Chun J, Zhi XY, Li WJ. Reassessment of the systematics of the suborder *Pseudonocardineae*: transfer of the genera within the family *Actinosynnemataceae* Labeda and Kroppenstedt 2000 emend. Zhi et al. 2009 into an emended family *Pseudonocardiaceae* Embley et al. 1989 emend. Zhi et al. 2009. *International Journal of Systematic and Evolutionary Microbiology*, 2011, 61(6): 1259–1264.

[21] Toru H. *Actinokineospora*: A new genus of the *Actinomycetales*. *Actinomycetologica*, 1988, 2(1): 31–45.

[22] Lei YJ, Xia ZF, Luo XX, Zhang LL. *Actinokineospora pegani* sp. nov., an endophytic actinomycete isolated from the surface-sterilized root of *Peganum harmala* L.. *International Journal of Systematic and Evolutionary Microbiology*, 2020, 70(7): 4358–4363.

[23] Liu JJ, Sun Y, Liu JR, Wu YJ, Cao CL, Li RP, Jiang JH. *Saccharothrix deserti* sp. nov., an actinomycete isolated from desert soil. *International Journal of Systematic and Evolutionary Microbiology*, 2020, 70(3): 1882–1887.

[24] Labeda DP, Testa RT, Lechevalier MP, Lechevalier HA. *Saccharothrix*: a New Genus of the *Actinomycetales* Related to *Nocardiopsis*. *International Journal of Systematic Bacteriology*, 1984, 34(4): 426–431.

[25] Wang W, Zhang Z, Tang Q, Mao J, Wei D, Huang Y, Liu Z, Shi Y, Goodfellow M. *Lechevalieria xinjiangensis* sp. nov., a novel actinomycete isolated from radiation-polluted soil in China. *International Journal of Systematic and Evolutionary Microbiology*, 2007, 57(12): 2819–2822.

[26] Labeda DP, Donahue JM, Sells SF, Kroppenstedt RM. *Lentzea kentuckyensis* sp. nov., of equine origin. *International Journal of Systematic and Evolutionary Microbiology*, 2007, 57(8): 1780–1783.

[27] Labeda DP. Transfer of "*Nocardia aerocolonigenes*" (Shinobu and Kawato 1960) Pridham 1970 into the genus *Saccharothrix* Labeda, testa, Lechevalier, and Lechevalier 1984 as *Saccharothrix aerocolonigenes* sp. nov.. *International Journal of Systematic Bacteriology*, 1986, 36(1): 109–110.

[28] Zhang JL, Xie Q, Liu ZH, Goodfellow M. *Lechevalieria fradiae* sp. nov., a novel actinomycete isolated from soil in China. *International Journal of Systematic and Evolutionary Microbiology*, 2007, 57(4): 832–836.

[29] Li D, Jiang H, Han L, Li Y, Zhao J, Jiang S, Wang X, Xiang W. *Lentzea terrae* sp. nov., isolated from soil and an emended description of *Lentzea soli*. *International Journal of Systematic and Evolutionary Microbiology*, 2018, 68(11): 3528–3533.

[30] Camas M, Veyisoglu A, Tatar D, Saygin H, Cetin D, Sazak A, Guven K, Sahin N. *Lechevalieria nigeriaca* sp. nov., isolated from arid soil. *International Journal of Systematic and Evolutionary Microbiology*, 2013, 63(10): 3750–3754.

[31] Xie Q, Wang YM, Huang Y, Wu YL, Ba FS, Liu ZH. Description of *Lentzea flaviverrucosa* sp. nov. and transfer of the type strain of *Saccharothrix aerocolonigenes* subsp. staurosporea to *Lentzea albida*. *International Journal of Systematic and Evolutionary Microbiology*, 2002, 52(5): 1815–1820.

[32] Fang BZ, Han MX, Liu L, Zhang ZT, Liu WL, Shen JT, Wang Y, Zhang WQ, Wei DQ, Li WJ. *LentZea cavernae* sp. nov., an actinobacterium isolated from a Karst cave sample, and emended description of the genus *LentZea*. *International Journal of Systematic and Evolutionary Microbiology*, 2017, 67(7): 2357–2362.

[33] Cao CL, Yuan B, Qin S, Jiang JH, Tao FX, Lian B. *LentZea pudingi* sp. nov., isolated from a weathered limestone sample in a Karst area. *International Journal of Systematic and Evolutionary Microbiology*, 2017, 67(11): 4873–4878.

[34] Li DM, Zheng WW, Zhao JW, Han LY, Zhao XL, Jiang H, Wang XJ, Xiang WS. *LentZea soli* sp. nov., an actinomycete isolated from soil. *International Journal of Systematic and Evolutionary Microbiology*, 2018, 68(5): 1496–1501.

[35] Li X, Zhang L, Ding Y, Gao Y, Ruan J, Huang Y. *Lentzea jiangxiensis* sp. nov., isolated from acidic soil. *International Journal of Systematic and Evolutionary Microbiology*, 2012, 62(10): 2342–2346.

[36] Zhao JW, Li WC, Shi LL, Wang H, Wang XJ. *Lechevalieria rhizosphaerae* sp. nov., a novel actinomycete isolated from rhizosphere soil of wheat (Triticum aestivum L.) and emended description of the genus *Lechevalieria*. *International Journal of Systematic and Evolutionary Microbiology*, 2017, 67(11): 4655–4659.

[37] Labeda DP, Lyons AJ. *Saccharothrix texasensis* sp. nov. and *Saccharothrix waywayandensis* sp. nov.. *International Journal of Systematic Bacteriology*, 1989, 39(3): 355–358.

[38] Grund E, Kroppenstedt RM. Transfer of Five *Nocardiopsis* Species to the Genus *Saccharothrix* Labeda et al. 1984. *Systematic and Applied Microbiology*, 1989, 12(3): 267–274.

[39] Cao CL, Zhou XQ, Qin S, Tao FX, Jiang JH, Lian B. *LentZea guizhouensis* sp. nov., a novel lithophilous actinobacterium isolated from limestone from the Karst area, Guizhou, China. *Antonie Van Leeuwenhoek*, 2015, 108(6): 1365–1372.

[40] 徐丽华, 李文均, 刘志恒. 放线菌系统学：原理、方法及实践. 北京: 科学出版社, 2007.

[41] Tao W, Yurkovich ME, Wen S, Lebe KE, Samborskyy M, Liu Y, Yang A, Liu Y, Ju Y, Deng Z, Tosin M, Sun Y, Leadlay PF. A genomics-led approach to deciphering the mechanism of thiotetronate antibiotic biosynthesis. *Chemical Science*, 2016, 7(1): 376–385.

[42] Maes M, Loyter A, Friedler A. Peptides that inhibit HIV-1 integrase by blocking its protein-protein interactions. *The FEBS Journal*, 2012, 279(16): 2795–2809.

[43] Sherman MP, Greene WC. Slipping through the door: HIV entry into the nucleus. *Microbes and Infection*, 2002, 4(1): 67–73.

[44] Crits-Christoph A, Robinson CK, Barnum T, Fricke WF, Davila AF, Jedynak B, McKay CP, Diruggiero J. Colonization patterns of soil microbial communities in the Atacama Desert. *Microbiome*, 2013, 1(1): 28.

[45] Bull AT, Asenjo JA, Goodfellow M, Gómez-Silva B. The Atacama desert: technical resources and the growing importance of novel microbial diversity. *Annual Review of Microbiology*, 2016, 70: 215–234.

[46] Okoro CK, Brown R, Jones AL, Andrews BA, Asenjo JA, Goodfellow M, Bull AT. Diversity of culturable actinomycetes in hyper-arid soils of the Atacama Desert, *Chile*. *Antonie Van Leeuwenhoek*, 2009, 95(2): 121–133.

[47] Bull AT, Asenjo JA. Microbiology of hyper-arid environments: recent insights from the Atacama Desert, *Chile*. *Antonie Van Leeuwenhoek*, 2013, 103(6): 1173–1179.

[48] Craigie R. HIV integrase, a brief overview from chemistry to therapeutics. *The Journal of Biological Chemistry*, 2001, 276(26): 23213–23216.

[49] Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clinical Infectious Diseases*, 2009, 48(7): 931–939.

[50] Ho S, Clipstone N, Timmermann L, Northrop J, Graef I, Fiorentino D, Nourse J, Crabtree GR. The mechanism of action of cyclosporin A and FK506. *Clinical Immunology and Immunopathology*, 1996, 80(3): S40–S45.

[51] Sasamura S, Kobayashi M, Muramatsu H, Yoshimura S, Kinoshita T, Ohki H, Okada K, Deai Y, Yamagishi Y, Hashimoto M. Bioconversion of FR901459, a novel derivative of cyclosporin A, by *LentZea* sp. 7887. *The Journal of Antibiotics*, 2015, 68(8): 511–520.

[52] Yabutani T, Shimizu S, Nakano H. Pilot-scale whole-cell biocatalysis for the hydroxylation of cyclosporine derivative, FR901459, at higher concentrations by *LentZea* sp. 7887 using soybean flour as a novel substrate dispersant. *Journal of Bioscience and Bioengineering*, 2017, 123(1): 56–62.

[53] Ueno M, Kobayashi M, Fujie A, Shibata T. Cloning and heterologous expression of P450Lent4B11, a novel bacterial P450 gene, for hydroxylation of an antifungal agent sordaricin. *The Journal of Antibiotics*, 2020, 73(9): 615–621.

[54] Ōmura S, Asami Y, Crump A. Staurosporine: new lease of life for parent compound of today's novel and highly successful anti-cancer drugs. *The Journal of Antibiotics*, 2018, 71(8): 688–701.

[55] Crespo A, Zhang X, Fernández A. Redesigning kinase inhibitors to enhance specificity. *Journal of Medicinal Chemistry*, 2008, 51(16): 4890–4898.

[56] Hachisu M, Hiranuma T, Koyama M, Sezaki M. Antihypertensive compounds with potent protein kinases inhibitory activity. *Life Sciences*, 1989, 44(19): 1351–1362.

[57] Schächtele C, Seifert R, Osswald H. Stimulus-dependent inhibition of platelet aggregation by the protein kinase C inhibitors polymyxin B, H-7 and staurosporine. *Biochemical and Biophysical Research Communications*, 1988, 151(1): 542–547.

[58] Liu M, Jia H, Sha Y. Research progress in derivatization and structure-activity relationships of staurosporine. *Journal of Shenyang Pharmaceutical University*, 2014, 31(3): 224–240. (in Chinese)
刘敏, 贾号, 沙宇. 十字孢碱的衍生化及构效关系研究进展. 沈阳药科大学学报, 2014, 31(3): 224–240.

[59] Bush JA, Long BH, Catino JJ, Bradner WT, Tomita K. Production and biological activity of rebeccamycin, a novel antitumor agent. *The Journal of Antibiotics*, 1987, 40(5): 668–678.

[60] Hussain A, Rather M, Shah A, Bhat Z, Shah A, Ahmad Z, Parvaiz Hassan Q. Antituberculotic activity of actinobacteria isolated from the rare habitats. *Letters in Applied Microbiology*, 2017, 65(3): 256–264.

[61] Selvin J, Shanmughapriya S, Gandhimathi R, Seghal Kiran G, Rajeetha Ravji T, Natarajaseenivasan K, Hema TA. Optimization and production of novel antimicrobial agents from sponge associated marine actinomycetes *Nocardiopsis* dassonvillei MAD08. *Applied Microbiology and Biotechnology*, 2009, 83(3): 435–445.

[62] Sedlarik V, Saha N, Sedlarikova J, Saha P. Biodegradation of blown films based on poly(lactic acid) under natural conditions. *Macromolecular Symposia*, 2008, 272(1): 100–103.

[63] Lim LT, Auras R, Rubino M. Processing technologies for poly(lactic acid). *Progress in Polymer Science*, 2008, 33(8): 820–852.

[64] Zhao YM, Wang ZY, Wang J, Mai HZ, Yan B, Yang F. Direct synthesis of poly (D, L -lactic acid) by melt polycondensation and its application in drug delivery. *Journal of Applied Polymer Science*, 2004, 91(4): 2143–2150.

[65] Nair NR, Nampoothiri KM, Pandey A. Preparation of poly(l-lactide) blends and biodegradation by *LentZea waywayandensis*. *Biotechnology Letters*, 2012, 34(11): 2031–2035.

[66] Lin J, Zhou JW, Kang Z, Du GC, Chen J. Isolation, identification of poly lactic acid degrading microorganisms and optimization of the degradation process. *Microbiology China*, 2013, 40(9): 1560–1569. (in Chinese)
林娟, 周景文, 康振, 堵国成, 陈坚. 聚乳酸降解菌株筛选鉴定及降解过程优化. 微生物学通报, 2013, 40(9): 1560–1569.

[67] Skovran E, Martinez-Gomez NC. Just add lanthanides. *Science*, 2015, 348(6237): 862–863.

Recent advance on the genus *Lentzea*

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Abstract: The genus *Lentzea*, established by Yassin et al in 1995, is a typical group of filamentous rare actinomycetes. This genus currently contains 23 valid species, and its typical taxonomic characteristics includes: *meso*-diaminopimelic acid in the cell wall; MK-9(H_4) as the dominant menaquinone; the principal phosphate lipids include phosphatidylethanolamine, diphosphatidylglycerol, phosphotidylinositol and phosphatidylglycerol; the G+C content of genomic DNA is 68.6 mol%–79.6 mol%. Metabolites from strains of the genus *Lentzea* have significant diversity of biological activities, including human immunodeficiency virus type 1 integrase inhibitory activity, anti-tumor activity, anti-tuberculosis activity and so on, gradually showing the potential application value in biopharmaceutical research. Our research group isolated several strains of the genus *Lentzea* during the study on actinobacterial biodiversity of limestone crust in Guizhou province, and *Lentzea xinjiangensis* DHS C013^T as well as *Lentzea pudingi* DHS C021^T were proposed as novel species of the genus using the polyphasic taxonomy methods. On the basis of our study, the relevant literatures and the latest research findings, this paper reviews the establishment and taxonomic characteristics of the genus *Lentzea*, ecological diversity, functional genome and application of natural active metabolites.

Keywords: *Lentzea*, polyphasic taxonomy, rare actinomycetes, active metabolites

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