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专论与综述

三种致病性耶尔森氏菌噬菌体的分离鉴定研究进展

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摘　要：3 种致病性耶尔森氏菌包括鼠疫耶尔森氏菌、假结核耶尔森氏菌和小肠结肠炎耶尔森氏菌，其噬菌体可用于耶尔森氏菌的诊断、防治和生态进化学研究。本文重点分析 3 种致病性耶尔森氏菌噬菌体的分离鉴定史。将 3 种耶尔森氏菌噬菌体基因组进行比较分析，并对各菌的噬菌体受体进行总结，为研究及利用 3 种耶尔森氏菌噬菌体提供思路。

关键词：耶尔森氏菌；噬菌体；基因多样性；噬菌体受体

Isolation and identification of three pathogenic *Yersinia* phages: a review

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Abstract: The three pathogenic *Yersinia* species *Yersinia pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica*, and the phages can be used for the diagnosis, control, and evolutionary research of *Yersinia*. This review focuses on the isolation and identification of phages of the three species, compares the genomes of the phages, and summarizes the receptors of them, which is expected to lay a basis for studying and utilizing the phages of the three *Yersinia* species.

Keywords: *Yersinia*; phages; gene diversity; phage receptor

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鼠疫耶尔森氏菌、假结核耶尔森氏菌和小肠结肠炎耶尔森氏菌是可感染人类的耶尔森氏菌；其中，鼠疫耶尔森氏菌毒性最强，是鼠疫的病原体，假结核耶尔森氏菌和小肠结肠炎耶尔森氏菌相对于鼠疫耶尔森氏菌毒性较低，这2种菌可引起食源性人畜共患疾病，称为耶尔森氏菌病[1]。这3种致病性耶尔森氏菌具备一定的亲缘关系，假结核耶尔森氏菌在4 100万年至1.86亿年前从小肠结肠炎耶尔森氏菌演化而来，而鼠疫耶尔森氏菌在约5 700–6 000年前的新石器时代的欧亚大陆上从假结核耶尔森氏菌进化而来，成为一个独立的分支，后2个物种在遗传上有更密切的联系[2-3]。

假结核耶尔森氏菌是一种肠道病原体，可导致自限性食源性肠道疾病，很少导致死亡；而鼠疫耶尔森氏菌是一种感染啮齿类动物的病原体，可通过跳蚤叮咬传播给包括人类在内的其他哺乳动物，导致鼠疫，死亡率极高；因此，两者在临床引起的传播机制和毒力因子库完全不同[2,4]。假结核耶尔森氏菌和小肠结肠炎耶尔森氏菌是通过粪口途径传播的动物源性食源性病原体，具有广泛的宿主，包括猪、狗、啮齿动物、鸟类和野生动物[5]。小肠结肠炎耶尔森氏菌感染人类后可引起多种胃肠疾病，最常见的可导致急性腹泻、末端回肠炎和肠系膜淋巴结炎[6]。

噬菌体是感染细菌的病毒，通过特异性识别宿主表面的受体吸附到宿主细胞上，并将核酸递送至宿主菌中，随后噬菌体基因被表达，劫持其细胞成分，繁殖后裂解宿主菌[7]。噬菌体在自然界分布极为广泛，且能高效裂解细菌，因此，噬菌体治疗已经成为治疗耐药菌感染的重要替代方式之一[8-9]。本文将对3种致病性耶尔森氏菌噬菌体做全面总结，介绍3种致病性耶尔森氏菌噬菌体分离鉴定史、分析比较3种噬菌体基因组，并对它们各种受体做全面总结。

1 三种致病性耶尔森氏菌噬菌体分离鉴定方法

耶尔森氏菌噬菌体分离鉴定方法与其他噬菌体相似。从环境样本中分离噬菌体大致遵循以下步骤：(1) 溶解；(2) 离心；(3) 过滤去除细菌，浓缩噬菌体；(4) CsCl梯度超速离心纯化噬菌体[10]。由于样品之间的物理差异，水、土壤、沉积物和粪便样品中噬菌体颗粒浓度不同，分离鉴定方法不同；从水样中有效回收和浓缩噬菌体需使用截留率至少为100 kDa或更小的超滤膜；从土壤或水生沉积物中获取噬菌体颗粒需要将其从多孔介质中提取到缓冲溶液中，缓冲溶液通过破坏噬菌体和多孔介质之间的静电和疏水相互作用来竞争和置换沉淀颗粒中的噬菌体[11-12]。从粪便样品中提取噬菌体有2种方法：基于切向流动过滤(tangential flow filtration，TFF)和聚乙二醇沉淀[10]。对于前噬菌体的分离，报道了2种常见方法：丝裂霉素C诱导和紫外光照射[13]。

提取噬菌体后，可通过双层琼脂平板斑块测定法、直接平板斑块测定法、小液滴斑块测定法或标准台式流式细胞仪来计数噬菌体[14]。鉴定一种新的噬菌体，可利用双层琼脂平板法形成单噬斑，挑取单噬斑进行纯化，利用电子显微镜观察噬菌体形态从而判断其分类[15]。噬菌体的宿主范围有窄有广，确定噬菌体宿主范围的第一步是测试大量细菌，第二步是在一组选定的潜在宿主上对每个噬菌体进行检测，第三步是确定噬菌体在易感菌株上的成斑率(efficiency of plating，EOP)[16]。

2 三种致病性耶尔森氏菌噬菌体分离

3 种耶尔森氏菌噬菌体均有分离鉴定的研究。近一百年来，鼠疫耶尔森氏菌噬菌体的研究最多，1919 年，D’Herelle 认为裂解性噬菌体可以用于治疗鼠疫[17-18]。随后，在 1925 年，D’Herelle 于 1920 年在印度支那从大鼠粪便中分离出高裂解性鼠疫噬菌体，并用该噬菌体治疗了 4 例腺鼠疫[19]。此后，研究人员对鼠疫噬菌体进行了分类，根据其抗原性质、形态、毒力、基因组结构和对鼠疫菌的特异性，将其分为 4 个血清型[20] (表 1)。

血清型 1 是最常见的，包括所有已知的裂解性鼠疫诊断噬菌体 phiA1122、Yepphi、Berlin 等，以及 Smith 和 Burrows 分离的其他 21 种噬菌体，这些噬菌体表现出 T7 样噬菌体；其中噬菌体 phiA1122 用于区分鼠疫耶尔森氏菌和假结核耶尔森氏菌[17,19-23,33]。血清型 2 噬菌体呈 P2 样，它们大多数为温和性噬菌体，包括噬菌体 L-94 和 L-413C 等，这些噬菌体与常见的噬菌体 P1、P2、P4 类似[17,20,30]。血清型 3 仅由一个噬菌体组成，即温和性噬菌体 II，血清型 4 以温和性噬菌体 Tal 和 513 为代表[32]。最近，Zhao 等公布了从芬兰图尔库污水中分离得到的 phiD1 和 phiEV-1 这 2 种鼠疫菌特异性噬菌体[34]。在中国云南分离出了 4 株鼠疫噬菌体：裂解性鼠疫特异性噬菌体 JC221、从齐氏姬鼠盲肠中分离出温和性噬菌体 L128m、噬菌体 LJ-7，以及噬菌体 PY060[35-38]。截至目前，最近分离出的噬菌体 phiD1、phiEV-1、JC221、L128m、LJ-7 和 PY060 还未进行血清型分类。

小肠结肠炎耶尔森氏菌根据不同的血清型进行分类，不同血清型的细菌感染的噬菌体也不同。因此，噬菌体已用于小肠结肠炎耶尔森氏菌的分型[39]。国内小肠结肠炎耶尔森氏菌噬菌体研究较少，从 1983 年到 2019 年，总共报道了 20 株小肠结肠炎耶尔森菌噬菌体。其中，17 株噬菌体与噬菌体 PY44 存在差异，这 17 株噬菌体在 37 °C 可裂解血清型 O:3 和 O:5，在 15 °C 下仅裂解血清型 O:3，这 17 株噬菌体并未命名，另外 4 株噬菌体命名为 JA、HB、Yep-YZU01 和 vB-YenM-X1，其中噬菌体 Yep-YZU01 形态属肌尾噬菌体科，并且能够裂解福氏志贺氏菌[40-42]。

国外对小肠结肠炎耶尔森氏菌噬菌体报道较多，从 1991 年至今总共分离出 105 株小肠结肠炎耶尔森氏菌噬菌体，并对 105 株噬菌体做了全基因组测序，这 105 株噬菌体为：

表 1 鼠疫耶尔森氏菌噬菌体血清型分类

Table 1 Classification of *Yersinia pestis* phage serovars

血清型 Serovars	噬菌体 Phage	应用 Application	噬菌体类型 Phage type	噬菌体分类 Phage classification	参考文献 References
1	phiA1122, Yepphi, Pokrovskaya	诊断 Diagnose	裂解性 Lytic phage	短尾噬菌体科	[17,20-29]
	Berlin, Yepe2, YpP-R, YpP-G, H	–		Podoviridae	
	Y, YpsP-G	–			
2	N, Novoseltsev, H	–	温和性 Prophage	肌尾噬菌体科	[17,20,30]
	L-94	–	裂解性 Lytic phage	Myoviridae	
	L-413C	诊断 Diagnose	裂解性 Lytic phage		
3	II	–	温和性 Prophage	–	[31]
4	Tal, 513	–	温和性 Prophage	–	[32]

注：–：噬菌体未应用或未进行病毒分类

Not: –: Phage has not been applied or phage classified.

vB-YenP-φ80-18、φYeO3-12、PY54、vB-YecM-φR1-37、φR2-01、φR8-01、φYe-10、vB-YenP-AP5、vB-YenM-TG1 (TG1)、vB-YenM-φR1-RT (φR1-RT)、vB-YenP-AP10、KFS-YE、YeP1、YeP2、YeP3、YeP4、YeP5、X1、PY20、PY30、PY31、PY44、PY68、PY95 以及从荷兰分离出的 81 株噬菌体 fPS-xx[43-55] (表 2)。从荷兰猪粪便分离出 81 株小肠结肠炎耶尔森噬菌体，均可裂解血清型 O:3，23 株可裂解血清型 O:5 和 27，2 株可裂解血清型 O:9[43]。综上所述，分离报道的噬菌体以

表 2　小肠结肠炎耶尔森氏菌噬菌体

Table 2　*Yersinia enterocolitica* phage

血清型 Serotype	噬菌体 Phage	噬菌体分类 Phage classification	噬菌体类型 Phage type	参考文献 References
O:3	JA, HB, φYeO3-12	–	裂解性 Lytic phage	[40-43,46-52,54,56-58]
	PY20, YeP1, YeP2, YeP3	肌尾噬菌体科 Myoviridae	温和性 Prophage	
	vB-YecM-φR1-37, TG1, φR1-RT	肌尾噬菌体科 Myoviridae	裂解性 Lytic phage	
	φR8-01, vB-YenP-AP5, φYe-F10	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	
	YeP4, YeP5, YeP6	短尾噬菌体科 Podoviridae	温和性 Prophage	
	fPS-7-21, fPS-23-64, fPS-66-89	–	裂解性 Lytic phage	
O:4	vB-YenP-φ80-18	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	[44-45,48,59]
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae		
O:5	PY30, PY54	长尾噬菌体科 Siphoviridae	温和性 Prophage	[47-48,52,56-63]
	PY31	短尾噬菌体科 Podoviridae	温和性 Prophage	
	PY95, TG1, φR1-RT, vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae	裂解性 Lytic phage	
O:8	vB-YenP-φ80-18	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	[1,44-45,48]
	φR2-01	长尾噬菌体科 Siphoviridae		
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae		
O:9	JA, HB	–	裂解性 Lytic phage	[40-41,48,52,54]
	TG1, φR1-RT, vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae	裂解性 Lytic phage	
	YeP1, YeP2, YeP3	肌尾噬菌体科 Myoviridae	温和性 Prophage	
	YeP4, YeP5, YeP6	短尾噬菌体科 Podoviridae	温和性 Prophage	
O:20	vB-YenP-φ80-18	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	[44-45,48]
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae		
O:21	vB-YenP-φ80-18	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	[44-45,48]
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae		
27	PY30, PY54	长尾噬菌体科 Siphoviridae	温和性 Prophage	[47-48,52,56-57,59-63]
	PY31	短尾噬菌体科 Podoviridae	温和性 Prophage	
	PY95, TG1, φR1-RT, vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae	裂解性 Lytic phage	
32	vB-YenP-φ80-18	短尾噬菌体科 Podoviridae	裂解性 Lytic phage	[44-45,48]
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae		
1A	PY30, PY54	长尾噬菌体科 Siphoviridae	温和性 Prophage	[47-48,56-57,59-63]
	PY44, PY68	肌尾噬菌体科 Myoviridae	温和性 Prophage	
	vB-YecM-φR1-37	肌尾噬菌体科 Myoviridae	裂解性 Lytic phage	

注：–：噬菌体未进行病毒分类

Not: –: Phage has not been phage classified.

感染小肠结肠炎耶尔森氏菌血清型 O:3 为主，这些噬菌体对防治食源性疾病具有一定意义[64]。

假结核耶尔森氏菌噬菌体研究较少，从德国分离出一株宿主谱较广的裂解性噬菌体 PY100，该噬菌体还可感染小肠结肠炎耶尔森氏菌和鼠疫耶尔森氏菌，其包装机制与沙门氏菌噬菌体 P22 相似[65]。3 株用于诊断假结核耶尔森氏菌噬菌体(YpP-R、YpsP-G 和 YpsP-PST)，对鼠疫菌也有裂解活性[66]。2014 年从荷兰猪粪中分离出的 90 个噬菌体中，有 8 个对假结核耶尔森氏菌 O:1a 菌株具有特异性[43]。综上所述，分离出最多的噬菌体是小肠结肠炎耶尔森氏菌噬菌体，其次是鼠疫耶尔森氏菌噬菌体，研究较多的是鼠疫耶尔森氏菌噬菌体。这些噬菌体的来源最多是粪便，其次是污水，最后是动物体表。

3 三种致病性耶尔森氏菌噬菌体基因组多样性分析

目前，大量裂解鼠疫菌噬菌体基因组序列已被测序，包括短尾噬菌体科 phiA1122、Yep-phi、Berlin、Yepe2、YpP-R、YpP-G、YpsP-G 和 Yps-Y，以及肌尾噬菌体科 L-413C、PY100、YpsP-PST、phiD1 和 JC221 等[17,20-21,24,27,36,65-66]。通过比较分析认为 8 种短尾噬菌体科之间的相关性非常高，如噬菌体 phiA1122、YpP-R、YpP-Y 和 YpsP-G 几乎完全相同;噬菌体 phiA1122 与 YpP-R 的核苷酸序列相似性为 98.5%，与 YpP-Y 的核苷酸序列相似性为 90.9%，与 YpsP-G 的核苷酸序列相似性为 97.9%[34,66-67]。根据基因相似性，8 个相关的短尾噬菌体科可分为 2 个亚组：phiA1122 亚组(phiA1122、YpP-R、YpP-Y 和 YpsP-G)和 Yep-phi 亚组(Yep-phi、Berlin、Yepe2 和 YpP-G)[21,24]。

噬菌体 phiA1122 基因组不仅与 T7 噬菌体相似，也与 T3 噬菌体相似[17]。对 T3 噬菌体序列分析发现，T3 噬菌体是由 2 条耶尔森氏菌噬菌体之间重组产生的宿主范围变异体：其中一条与小肠结肠炎耶尔森氏菌特异性噬菌体 phiYeO3-12 密切相关，而另一条可能是噬菌体 phiA1122 或极其接近的亲属[17,68]。噬菌体 L-413C 经历了基因丢失和替换，以及在编码尾纤维蛋白 H 的基因中经历了重组事件，这导致了新的宿主特异性[20]。由此可见噬菌体的进化与细菌进化息息相关。

对已知的小肠结肠炎耶尔森氏菌噬菌体基因组分析比较发现，与 T7 样噬菌体基因组相似的噬菌体有：具有广泛宿主性耶尔森噬菌体 fHe-Yen3-01、φYeO3-12、vB-YenP-AP10、R8-01[1,47,69-71]。其中噬菌体 φYeO3-12 与 T3 样噬菌体基因组也具有相似性[72]。噬菌体 φR2-01 与 T5 样噬菌体基因组具有相似性[46]。具有广泛宿主谱噬菌体 fHe-Yen9-01 与噬菌体 fHe-Yen3-01 同一时期分离，其基因组与大肠杆菌噬菌体 T4 相似[70]。噬菌体 PY54 与大肠杆菌噬菌体 N15 和产酸克雷伯噬菌体 φKO2 基因组相似，这 3 种噬菌体属于 λ 噬菌体的一个特殊亚组，它们的前噬菌体复制为具有共价闭合的发夹末端(端粒)的线性质粒[62-63,71,73-75](表 3)。

通过在 NCBI 比较分析发现，噬菌体 vB-YenP-φ80-18 与果胶杆菌噬菌体 MA13 和克罗诺杆菌噬菌体 Dev-CD-23823 具有相似性。经分析发现，基因组相似的 2 株噬菌体其宿主不一定相同，由此可见噬菌体基因组的相似程度与宿主谱的广泛程度可能无关，噬菌体的宿主谱广泛与否可能与其尾部蛋白有关。

表 3 耶尔森氏菌噬菌体基因组分析

Table 3 Genome analysis of *Yersinia* phage

宿主 Host strain	噬菌体 Phage	相似噬菌体 Similar phage	序列相似程度 Sequence similarity (%)	参考文献 References
鼠疫耶尔森氏菌 *Yersinia pestis*	phiA1122	T7	89.0	[17,58,67]
		T3	25.0	
		YpP-R	98.5	
		YpP-Y	90.9	
		YpsP-G	97.9	
	Yep-phi	Berlin	98.1	[21,24]
		Yepe2	95.8	
		YpP-G	95.8	
		phiA1122	60.2	
	YpsP-PST	T4	−	[21,76]
	L-413C	Wφ	−	[20,34]
	JC221	PYPS2T	<80.0	[36]
		phiD1		
		YpsP-PST		
小肠结肠炎耶尔森菌 *Y. enterocolitica*	vB-YenP-φ80-18	fHe-Yen3-01	98.4	[44-45]
	φYeO3-12	T3	>70.0	[46,69,72]
	PY54	N15	−	[54,62-63,71, 73-75]
		φKO2	−	
		YeP1, YeP2	61.7	
	vB-YecM-φR1-37	φKZ	−	[48,77-78]
	vB-YenP-AP5	φSG-JL2	−	[51]
	φR2-01	T5		[1]
	φYe-10	φYeO3-12	97.0	[50]
		vB-YenP-AP5	89.0	
	TG1	φR1-RT	91.0	[52]
	vB-YenP-AP10	T7	−	[1]
	R8-01	T7	−	[1]
	YeP1	YeP2, YeP3	99.0	[54]
	YeP4	YeP5, YeP6	99.9	[54]
	X1	PY100	99.5	[54]

注：−：噬菌体序列相似度未知

Not: −: The similarity of phage sequences is unknown.

4 三种致病性耶尔森氏菌噬菌体受体分析

噬菌体感染细菌的第一步是吸附到细菌表面受体，涉及噬菌体上的受体结合蛋白与细胞外层结构的识别和结合[79-80]。脂多糖(lipopolysaccharide，LPS)是革兰阴性菌外膜的主要成分，也是常见的噬菌体受体；噬菌体通过结合 LPS，进而将其基因组注入细菌[81]。对噬菌体识别细菌受体的了解，可增加我们对感染过程的理解，有助于实施针对病原菌高效噬菌体疗法[82]。

鼠疫菌的 LPS 缺乏 O 抗原，仅由核心多糖和脂质 A 组成，大多数鼠疫噬菌体受体是核心多糖[83]。如噬菌体 phiA1122 受体是核心多糖 Kdo/Ko (3-脱氧-D-甘露-oct-2-吡喃磺酸/D-甘油-D-滑石粉-oct-2-吡喃磺酸)区；噬菌体 L-413C、P2vir1、phiJA1、phiA1122、Pokrovskaya、T7Yp、YpP-Y 和 YpsP-PST 受体为核心多糖中 6 种不同成分[67,84]。并非所有鼠疫杆菌噬菌体都使用 LPS 核心多糖作为其唯一的受体，如噬菌体 YpP-R 的受体为核心多糖之外[67]。除了以 LPS 作为受体外，部分鼠疫噬菌体还以 LPS 之外的细胞膜为受体，如噬菌体 YeP-phi 利用外膜蛋白 Ail 和 OmpF 作为受体[85]。丝状噬菌体 YpfΦ 受体尚未鉴定，由于该噬菌体宿主谱较广，因此可能使用几种细胞表面分子作为受体[86] (表 4)。

小肠结肠炎耶尔森菌根据表型特征分为 6 个生物群，主要根据脂多糖(LPS)中 O-特异性多糖的差异分类，目前按照 O-特异性多糖差异将其血清型分为 57 种[88]。噬菌体 vB-YenP-φ80-18、φYeO3-12 和 vB-YenP-AP5 受体为 O-特异性多糖[45,51]。噬菌体 φR8-01、vB-YenM-TG1/TG1 和 vB-YenM-φR1-RT/φR1-RT 受体为核心多糖[1,52]。有些噬菌体的受体不止一个，如噬菌体 vB-YenM-TG1/TG1 和 vB-YenM-φR1-RT/φR1-RT，受体除核心多糖外还有外膜蛋白 OmpF[52]。

噬菌体 φYeO3-12、vB-YenP-AP5、phiYe-F10 和 φR8-01 宿主谱窄与它们的受体有关，这些噬菌体的受体不以完整的 LPS 感染小肠结肠炎耶尔森氏菌[52]。这些噬菌体已经鉴定出宿主细胞识别、吸附和启动感染所必需的相关受体结合蛋白(RBP)；例如，在噬菌体 φYeO3-12，源自 645 个氨基酸(aa)残基的 17 基因的产物的尾纤维蛋白被认为是主要的宿主范围决定因素；将噬菌体 φYeO3-12 替换噬菌体 T3 中的同源基因，可将肠杆菌噬菌体 T3 变成感染小肠结肠炎耶尔森氏菌的噬菌体[72,89]。

5 三种致病性耶尔森噬菌体应用

鼠疫耶尔森氏菌具有高度传染性，起病快，如不及时治疗，死亡率较高[90]。噬菌体能够特异性识别并感染宿主，因此，鼠疫耶尔森氏菌噬菌体 L-413C 和 phiA1122 已用于鼠疫诊断[17,20,84]。已有研究利用噬菌体 L-413C 和 phiA1122 的受体结合蛋白和荧光蛋白作为报告载体，同时利用实时定量 PCR 的方式，可以快速检测培养物和人血清中的鼠疫杆菌，对鼠疫诊断和防控有一定的作用[91-95]。研究表明，噬菌体 L-413C 和 phiA1122 在动物研究中显示出高稳定性和安全性，单次注射噬菌体 phiA1122 可保护 20%–40%的小鼠免受致死剂量鼠疫杆菌的侵袭，表明该噬菌体具备对鼠疫的防治作用[94]。

表 4 耶尔森氏菌噬菌体受体分析

Table 4 Analysis of *Yersinia* phage receptor

宿主 Host strain	噬菌体 Phage	受体 Receptor	分类 Classification	序列检索号 Sequence accession No.	参考文献 References
鼠疫耶尔森氏菌 *Yersinia pestis*	phiA1122	Kdo/Ko of LPS	T7 样噬菌体 T7 phage	NC004777	[17,27-28,84]
	YpsP-G	–	T7 样噬菌体 T7 phage	NC047940	[21,66]
	Yep-phi	LPS, OmpF, Ail	T7 样噬菌体 T7 phage	NC023715	[21-24]
	Berlin	–	T7 样噬菌体 T7 phage	NC008694	[24]

(待续)

(续表 4)

	Yepe2	−	T7 样噬菌体 T7 phage	NC011038	[24]
	PhiJA1	Kdo/Ko of LPS	T4 样噬菌体 T7 phage	−	[29,63,67]
	L-94	−	P2 样噬菌体 P2 phage	−	[20,30]
	L-413C	GlcNAc of LPS	P2 样噬菌体 P2 phage	NC004745	[29,66-67]
	P2 vir1	GlcNAc of LPS	P2 样噬菌体 P2 phage	−	[67]
	T7 Yp	Hep(I)/Glc of LPS	T7 样噬菌体 T7 phage	−	[67]
	YpfΦ	−	丝状病毒 Filamentous phage	−	[86]
鼠疫耶尔森氏菌、假结核耶尔森氏菌 *Yersinia pestis*, *Y. pseudotuberculosis*	YpP-R	Beyond the LPS core	T7 样噬菌体 T7 phage	JQ965701, JX000007	[29,66-67]
	YpP-G	−	T7 样噬菌体 T7 phage	JQ965702	[21,24,66]
	YpP-Y	Hep(I)/Glc of LPS	T7 样噬菌体 T7 phage	NC047939	[29,66-67]
	YpsP-PST	Hep(II)/Hep(III) of LPS	T4 样噬菌体 T4 phage	KF208315	[29,66-67,76]
鼠疫耶尔森氏菌、假结核耶尔森氏菌、小肠结肠炎耶尔森氏菌 *Yersinia pestis*, *Y. pseudotuberculosis*, *Y. enterocolitica*	PY100	−	T1 样噬菌体 T1 phage	AM076770	[48,62,77,87]
小肠结肠炎耶尔森氏菌 *Y. enterocolitica*	vB-YenP-φ80-18	O-PS	T7 样噬菌体 T7 phage	HE956710.1	[45]
	PY54	−	λ 样噬菌体 λ phage	NC005069	[45,47,59-63]
	φYeO3-12	O-PS	T7 样噬菌体 T7 phage	NC001271.1	[72]
	vB-YecM-φR1-37	OC	−	NC016163.1	[48,77]
	φR8-01	IC	T7 样噬菌体 T7 phage	HE956707.1	[49]
	φR2-01	BtuB	T5 样噬菌体 T5 phage	HE956708.1, NC019919	[1]
	vB-YenP-AP5	O-PS	T7 样噬菌体 T7 phage	KM253764.1, NC025451	[51]
	φYe-F10	−	T7 样噬菌体 T7 phage	KT008108.1, NC047755	[51]
	TG1	OmpF and IC	T4 样噬菌体 T4 phage	KP202158.1, NC028820	[52]
	φR1-RT	OmpF and IC	T4 样噬菌体 T4 phage	HE956709.1, NC019909	[52]
可感染多种耶尔森氏菌 *Yersinia* spp.	fHe-Yen3-01	−	T7 样噬菌体 T7 phage	KY318515, NC047805	[70]
可感染多种耶尔森氏菌 *Yersinia* spp.	fHe-Yen9-01	−	T4 样噬菌体 T4 phage	KY593455	[70]

注：−：噬菌体受体未知或序列检索号未知；Glc：D-葡萄糖苷酶；GlcNAc：N-乙酰-D-氨基葡萄糖；Hep：L-甘油-D-甘露糖-丙酮吡喃糖；Kdo：3-脱氧-D-甘露糖-辛-2-吡喃葡萄糖酸；Ko：D-甘油-D-塔洛-辛-2-吡喃葡萄糖酸；LPS 是革兰氏阴性菌外膜上的成分，在小肠结肠炎耶尔森菌中由脂质 A (LA)、内核(IC)、外核(OC)和 O-特异性多糖(O-PS)组成

Not: −: Phage receptor is unknown or sequence retrieval number is unknown; Glc: D-glucopyranose; GlcNAc: N-acetyl-D-glucosamine; Hep: L-glycero-D-manno-heptopyranose; Kdo: 3-deoxy-D-manno-oct-2-ulopyranosonic acid; Ko: D-glycero-D-talo-oct-2-ulopyranosonic acid; LPS, a component found on the outer membrane of Gram-negative bacteria, is in *Y. enterocolitica* composed of lipid A (LA), inner core (IC), outer core (OC), and O-specific polysaccharide (O-PS).

噬菌体编码的肽聚糖降解活性可起到水解细胞壁的作用，因此，已经产生了纯化的噬菌体裂解酶来特异性靶向革兰氏阳性病原体；革兰氏阴性菌的外膜保护肽聚糖不被降解，因此对噬菌体裂解酶具有抗性[19,95-97]。

鼠疫耶尔森氏菌产生一种细菌素，即鼠疫素，它需要依赖于 TonB 转运蛋白 FyuA 通过外膜转运到其目标，以杀死对鼠疫素敏感的鼠疫耶尔森氏菌[98]。根据鼠疫素的特性，设计了一种嵌合蛋白，由鼠疫素的氨基末端结构域与噬菌体 T4 溶菌酶融合而成；溶菌酶-鼠疫素穿过外膜并攻击肽聚糖层，随后杀死在其细胞表面表达 FyuA 的鼠疫杆菌菌株[19,95]。噬菌体还可用于鼠疫疫苗的制备，如荚膜蛋白和低钙反应 V 抗原已被用作抗腺鼠疫和肺鼠疫的疫苗[99]。

小肠结肠炎耶尔森氏菌和假结核耶尔森氏菌可在食品制造或加工过程中污染[100]。为防止疾病发生，有研究将噬菌体喷于厨房用具等人工污染模型中，实验证明可减少小肠结肠炎耶尔森氏菌和假结合耶尔森氏菌污染[1]。噬菌体除了可以用于食源性疾病的防治，还可用于小肠结肠炎耶尔森氏菌的诊断，通过噬菌体受体结合蛋白与免疫荧光方式检测小肠结肠炎耶尔森氏菌，如噬菌体 vB-YenP-AP5、vB-YenM- TG1 (TG1)和 vB-YenP-φ80-18[1,52]。

噬菌体裂解宿主菌的能力不同，它们可能使用不同的受体吸附，利用多种噬菌体混合物可能比单一噬菌体具有更宽的宿主范围，并且可以降低噬菌体耐受菌株的产生，从而提高噬菌体治疗的疗效[21]。Rashid 等证明了“噬菌体鸡尾酒” YPP-100，可以消除各种被鼠疫杆菌污染的物体表面，表明“噬菌体鸡尾酒”可以减少耐受噬菌体菌株的产生[21]。

6 展望

噬菌体繁殖与细菌进化生态学密切相关[101]。噬菌体的繁殖往往导致细菌的死亡。细菌为了抵抗噬菌体的感染，进化出多种抵抗噬菌体的机制，如 CRISPR-CAS 系统[102-104]。因此，耶尔森氏菌及其噬菌体的相互抵抗机制，及其长期共进化的生态学意义，均值得进一步研究，有望发现新的抵抗机制或共进化规律。

在食品行业，噬菌体已经用于预防奶酪生产和肉类加工时的李斯特菌和大肠杆菌污染[100]。小肠结肠炎耶尔森氏菌及假结合耶尔森氏菌也会导致食源性疾病，其噬菌体在预防食源性疾病中具有一定的应用价值。此外，鼠疫在我国疫原地仍有散发病例，其噬菌体能否用于阻断和预防鼠疫的传播，是一个值得研究的领域。

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