



蜱类病原体和共生菌多样性及其作用^{*}

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摘 要 蜱是一类专性吸血的体外寄生动物, 宿主包括哺乳类、鸟类、爬行类和两栖类。蜱是多种病原体贮存和传播的媒介, 由此带来的蜱传疾病危害人类和动物健康, 给畜牧业生产造成损失。因此, 蜱类研究具有重要的医学和经济学意义。根据已有的研究基础, 本文对蜱类病原体的多样性和危害, 蜱类-病原体-宿主互作机制, 蜱传疾病的防治, 蜱类共生菌多样性, 蜱类共生菌功能及作用机制等方面的研究进展进行综述。可以看出, 随着研究手段和技术的丰富, 蜱类研究也越来越深入。这些研究结果不仅能够揭示蜱类生物学规律, 也有助于有效地指导蜱传疾病防治。

关键词 蜱; 病原体; 共生菌; 蜱传疾病; 作用与机制

Diversity, and roles, of pathogens and symbionts in ticks

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Abstract Ticks are obligate blood-sucking arthropods, which can feed on mammals, birds, reptiles and amphibians. Ticks are reservoirs for various pathogens which they transmit to both humans and animals. The tick-borne diseases induced by these pathogens are not only harmful to human and animal health, but also cause significant economic losses to livestock farmers. Research on ticks is, therefore, both medically and economically important. This paper reviews previous research on the diversity of tick-borne pathogens, tick-pathogen-host interaction mechanisms, tick-borne disease prevention and control, tick symbiont diversity, function and the mechanisms underlying tick-symbiont interactions. An increase in the amount of research on ticks and technological advances has resulted in an obvious improvement in the quality of research and information available on these pests. These results can not only reveal more of the biology of ticks, but also help the prevention and control of tick-borne diseases.

Key words ticks; pathogens; symbionts; tick-borne diseases; function and mechanism

蜱是一类专性吸血的体外寄生动物, 在世界范围内分布, 宿主包括哺乳类、鸟类、爬行类和两栖类。全世界已发现 907 种 (Barker and Murrell, 2008), 中国已描述定名 125 种 (温廷桓和陈泽, 2016; 赵国平, 2018)。近年来, 也有一些蜱新种或新纪录种报道 (Nava *et al.*,

2013; Guo *et al.*, 2016, 2017)。除直接叮咬吸血和继发性感染外, 蜱传播多种病原体, 危害人类健康和畜牧业生产 (Jongejan and Uilenberg, 2004)。蜱传疾病的新发和再次发生均对公共健康产生较大的影响 (Hai *et al.*, 2014; Fang *et al.*, 2015)。研究表明莱姆病已扩展至美国全境, 引

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起关注。近期发生的非洲猪瘟疫情对我国的生猪产业产生一定冲击。户外活动的增多使得我们接触蜱类的机会不断增加,由于气候或人类活动的影响,蜱类种群也呈现出扩张态势(Estrada-Peña *et al.*, 2014),蜱传疾病发生区域随之扩大。随着研究的深入,一些新的蜱类病原体 and 蜱传疾病不断被发现(Zhou *et al.*, 2014; Kernif *et al.*, 2016)。到目前为止,有关蜱类病原体和蜱传疾病研究取得了一定的进展,如病原体的检测及致病机制、蜱传疾病发生趋势预测、蜱类-病原体-宿主互作机制等(Hovius *et al.*, 2007; Ogden, 2013; de la Fuente *et al.*, 2017)。但由于蜱传疾病种类繁多,危害较大,对它们的诊断和治疗仍显不足。另外,对于这些病原体危害风险的预测受到环境、媒介或宿主等诸多因素的影响,使得难以准确对其预测预报。因此,为了更好地控制蜱传疾病,还需要更为广泛和深入的研究。

蜱类同时携带和传播多种非致病性微生物,包括肠道微生物和母系遗传共生细菌等。其中,母系遗传共生细菌在蜱类宿主的适合度、营养适应、发育、生殖、抵御环境压力、免疫以及蜱媒病原体传播等方面均有影响,已成为研究热点(Narasimhan and Fikrig, 2015; Bonnet *et al.*, 2017)。由于共生菌的检测和研究手段不断发展,越来越多蜱类物种的共生菌感染情况得到研究,共生菌的功能及其机制得以揭示。如已在多种蜱类中发现专性共生菌类考克氏体 *Coxiella*-like symbiont (*Coxiella*-LE) 和类弗朗西斯氏体 *Francisella*-like symbiont (*Francisella*-LE) 为宿主的发育过程中提供必需营养(Guizzo *et al.*, 2017; Duron *et al.*, 2018)。在此情况下,这些共生菌可作为蜱类防治的潜在靶标。研究者借助比较基因组学和系统发育分析等阐释了一些共生菌与病原体的进化关系(Duron *et al.*, 2015; Gerhart *et al.*, 2016)。

蜱类病原体和共生菌研究是蜱类基础研究的重要内容,结合蜱类生态和生理生化等研究,可以更好地揭示蜱类生物学规律并指导蜱传疾病防治。综合分析已有研究结果,本文对蜱类病原体和共生菌研究进展报道如下。

1 蜱类病原体多样性及危害

蜱类病原体的检测和分析至关重要。目前,主要采用培养法、特异引物 PCR、16S rRNA 基因文库法、变性梯度凝胶电泳、高通量测序等手段检测病原体(庄璐, 2017)。可依据病原体的类型或研究目的等,选取相应的检测手段。

自研究以来,已有多篇综述文章对蜱类病原体及蜱传疾病进行了总结(Jongejan and Uilenberg, 2004; de la Fuente *et al.*, 2008; Dantas-Torres *et al.*, 2012; Manzano-Román *et al.*, 2012; Wu *et al.*, 2013; Shi *et al.*, 2018; Talagrand-Reboul *et al.*, 2018; 杨露等, 2018)。由此可知,几乎所有的蜱属中均有病原体感染,包括硬蜱属 *Ixodes*、血蜱属 *Haemaphysalis*、花蜱属 *Amblyomma*、革蜱属 *Dermacentor*、扇头蜱属 *Rhipicephalus*、锐缘蜱属 *Argas* 和钝缘蜱属 *Ornithodoros*。其中,不少蜱类具有重要的医学和经济学意义,如篦子硬蜱 *Ixodes ricinus*、血红扇头蜱 *Rhipicephalus sanguineus*、全沟硬蜱 *I. persulcatus* 和长角血蜱 *Haemaphysalis longicornis* 等。其他蜱属的一些物种由于种类较少或分布范围小,对它们病原体的研究相对较少。蜱类病原体种类较多,包括立克次氏体 *Rickettsia*、疏螺旋体 *Borrelia*、巴贝斯虫 *Babesia*、泰勒虫 *Theileria*、无形体 *Anaplasmataceae*、土拉弗朗西斯菌 *Francisella tularensis*、贝氏考克氏体 *Coxiella burnetii*、巴尔通体 *Bartonella*、肝簇虫 *Hepatozoon*、线虫 *Acanthocheilonema*、埃及小体 *Aegyptianella*、病毒及 *Candidatus* *Neoehrlichia mikurensis* 等。病原体的多重感染在蜱类中普遍存在,如篦子硬蜱可同时感染 *Anaplasmataceae*、*Bartonella*、*Borrelia*、*Rickettsia*、*Theileria* 和 *Candidatus* *Neoehrlichia mikurensis* 等(Vayssier-Taussat *et al.*, 2013)。不同地区分布的蜱类病原体感染类型存在差异,如采集自意大利和荷兰的篦子硬蜱的病原体感染类型明显不同(Nijhof *et al.*, 2007; Otranto *et al.*, 2014)。蜱类病原体具有较高的遗传多样性,借助分子生物学等手段,发现 *Rickettsia*、*Borrelia*、*Babesia*、*Theileria* 和

Anaplasmataceae 等类群均有多种病原体, 且这些病原体可造成不同的疾病。如 *Babesia* 可在不同哺乳动物中造成巴贝斯虫病; 不同的泰勒虫引起的疾病类型差异较大; 蜱媒斑点热病原体为 *Rickettsia*, 目前已鉴定并确定分类地位的立克次体种类众多 (de la Fuente *et al.*, 2008)。在我国近 30 年来至少有 33 种新发蜱媒传染病病原体被发现 (Fang *et al.*, 2015)。随着蜱类样本采集范围的扩大和研究的深入, 将会发现和鉴定出更多的病原体。

由这些病原体造成的一些蜱传疾病, 如蜱媒斑点热 Tick-borne spotted fever、莱姆病 Lyme diseases、人粒细胞无形体病 Human granulocytic anaplasmosis (HGA)、人埃立克体病 Human ehrlichiosis、蜱媒森林脑炎 Tick-borne encephalitis (TBEV)、蜱媒回归热 Tick-borne relapsing fever、克里米亚-刚果出血热 Crimean-Congo hemorrhagic fever、Q 热 Q fever、发热伴血小板减少综合征 Severe fever with thrombocytopenia syndrome、土拉菌病 Tularemia、梨形虫病 Piroplasmosis 等, 在世界范围内具有重要影响 (de la Fuente *et al.*, 2008, 2017; 于志军和刘敬泽, 2015)。从全球来看, 由蜱类病原体导致的人类疾病超过 10 万例之多 (de la Fuente *et al.*, 2008)。在美国, 莱姆病的病例报道逐渐增多, 发生范围已扩展至美国全境, 主要是由于媒介蜱虫肩突硬蜱 *I. scapularis* 和病原体伯氏疏螺旋体 *Borrelia burgdorferi* 分布范围的扩大 (Eisen *et al.*, 2016)。同时, 蜱传疾病在世界范围内直接或间接危害畜牧业生产, 也带来防治成本的不断增加 (Jongejan and Uilenberg, 2004)。

2 蜱类-病原体-宿主互作机制

在蜱类病原体检测和分析不断完善的基础上, 研究者开始对蜱类-病原体-宿主互作机制展开研究, 以更好地进行蜱及蜱传疾病防治。蜱类-病原体-宿主相互作用较为复杂, 多种因素影响病原体的获取、保存和传播。如蜱类的宿主的范围, 篦子硬蜱可寄生的宿主种类远多于微小扇头蜱 *R. microplus*, 其携带的病原体多样性也较高

(Estrada-Peña *et al.*, 2015)。当然, 蜱类的宿主范围也决定了病原体在脊椎动物中的分布。

在蜱类与病原体的相互作用机制研究方面。2016 年, 第一个蜱类基因组即肩突硬蜱基因组首次报道 (Gulia-Nuss *et al.*, 2016), 不仅揭示了蜱类物种的系统进化问题, 为其他蜱种的研究提供了参考信息, 更有助于深入了解蜱类特有的生理生化过程, 如宿主搜寻、角质层合成、血餐摄取及消化、卵黄发生和生殖、非宿主阶段的生存、蜱类-病原体-宿主的相互作用机制等 (Sojka *et al.*, 2013; Chmelař *et al.*, 2016; de la Fuente *et al.*, 2016; Rio *et al.*, 2016)。Guerrero 等 (2010) 和 Cramaro 等 (2015) 也对和人类及动物健康相关的蜱类物种的部分基因组信息进行了分析。进一步研究发现, 采集于莱姆病较为流行的美国北部和中西部的肩突硬蜱和南部地区的蜱种有遗传分化, 有助于阐释莱姆病病原体的生活史和传播 (Gulia-Nuss *et al.*, 2016)。在该研究中, Gulia-Nuss 等 (2016) 同时鉴定出一些和人粒细胞无形体病及蜱传脑炎相关的蛋白。借助转录组、蛋白质组和代谢组等手段, 研究者发现了蜱类对无形体 *Anaplasma phagocytophilum* 的组织特异性响应 (Ayllón *et al.*, 2015; Villar *et al.*, 2015; Alberdi *et al.*, 2016)。由病原体引起的蜱类转录响应还涉及到埃立克体 *Ehrlichia chaffeensis* (Miura and Rikihisa, 2009)、*B. burgdorferi* (Bouquet *et al.*, 2016) 和蜱传脑炎病毒 (Weisheit *et al.*, 2015)。病原体对蜱类的转录调控也包括影响宿主的蛋白质含量 (Ayllón *et al.*, 2015)。在组学研究的基础上, Chmelař 等 (2016) 围绕蜱类与宿主的互作机制进行了综述。为了更好地探究基因功能, 该领域也引入了其他一些研究手段如蜱类细胞系和 RNA 干扰技术等 (Bell-sakyi *et al.*, 2007; de la Fuente *et al.*, 2007)。

综合已有的研究结果, de la Fuente 等 (2016) 提出在蜱类-宿主-病原体的互作关系中存在冲突与协作, 即病原体为了更好地传播和扩散, 会采取相似的策略调控蜱类或脊椎动物的生理过程, 如蜱类细胞骨架重排、细胞凋亡、内在免疫响应和胚胎发育等 (Kaufman, 2010; Hajdušek

et al., 2013; Cheeseman and Weitzmande, 2015; de la Fuente *et al.*, 2017) (图 1)。在此过程中, 蜱类或宿主也会做出反应以抑制其扩增和传播 (Sojka *et al.*, 2013)。从进化的角度看, 在相互适应的过程中, 三者之间存在一定的协作关系。如病原体感染能够提高蜱类的适合度, 以达到“双赢”的结果。无形体 *A. phagocytophilum* 感染可诱导肩突硬蜱抗冻蛋白的表达以帮助其应对寒冷环境 (Neelakanta *et al.*, 2010)。此类病原体还可以通过提高热激蛋白的表达水平影响蜱类的宿主搜寻行为、应对血餐压力和高温干燥环境等 (Busby *et al.*, 2012; Villar *et al.*, 2015)。其他病原体 (*Borrelia* spp. 和 TBEV) 的研究也发现提高蜱类适合度的现象, 感染的肩突硬蜱和全

沟硬蜱的宿主搜寻高度高于不感染个体以增加生存率 (Herrmann and Gern, 2015)。由病原体协助蜱类适应环境的情况还发生在 *B. burgdorferi* 和蓖子硬蜱中 (Herrmann and Gern, 2012)。这些病原体帮助蜱类进行生态适应的同时, 也保证了自身的传播 (Cabezas-Cruz *et al.*, 2017)。尚不明确脊椎动物能否从中直接获利。有假说认为宿主可能受益于蜱类对其的免疫调控能力 (Wikel, 2013)。例如, 在人类中, 蜱类叮咬可能导致对碳水化合物 α -半乳糖抗体水平的提高。虽然这一反应可能导致我们对红肉、蜱类叮咬和西妥昔单抗治疗出现过敏反应, 但也能够增加对病原体感染的保护 (Cabezas-Cruz *et al.*, 2015)。

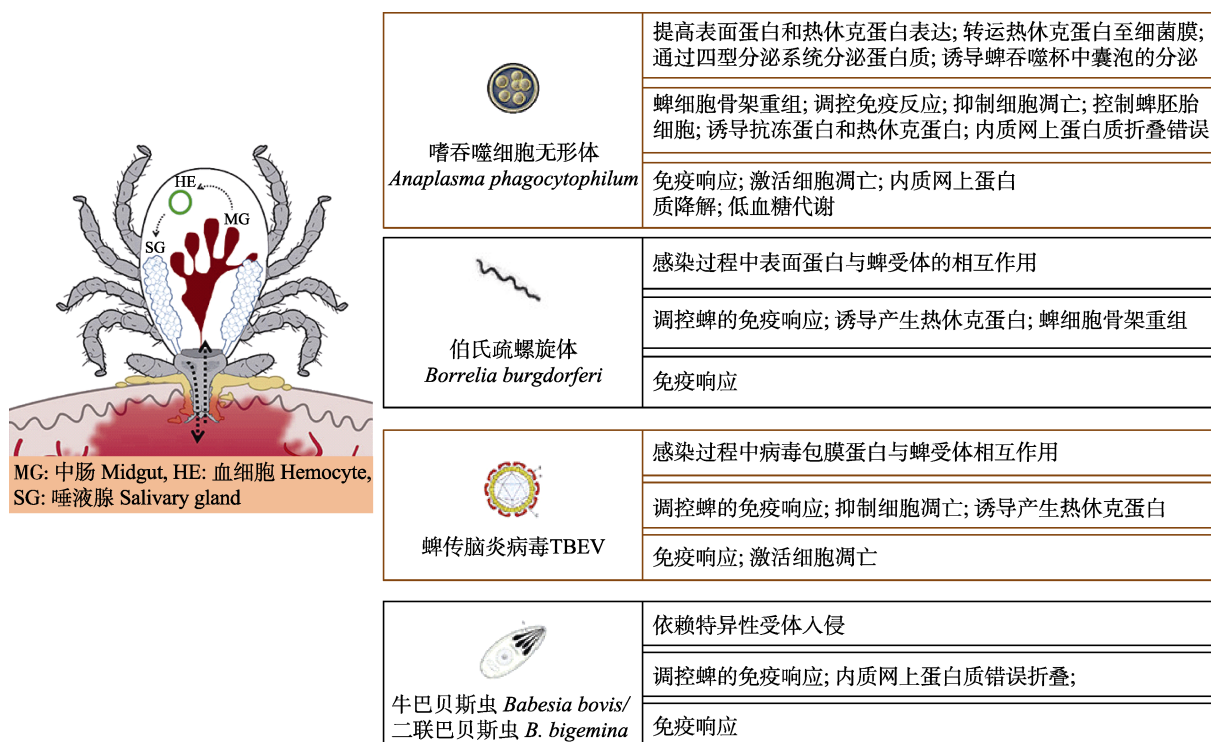


图 1 蜱类-病原体互作分子机制 (根据 de la Fuente 等, 2017 改绘)

Fig. 1 Tick-pathogen molecular interactions (redraw based on de la Fuente *et al.*, 2017)

3 蜱传疾病防控

由于蜱传疾病的经济学和流行病学意义, 对其防控一直受到重视。在蜱传疾病防控之前, 有必要开展蜱类种群及其病原体感染情况的分布研究, 并结合宿主、环境、气候等因素以预测蜱

类的适生区域, 评估蜱传疾病的发生风险和影响范围, 以更好地制定防控措施 (赵国平, 2018)。目前, 对蜱传疾病的防控主要集中于媒介蜱类的控制。化学杀虫剂是最为传统的防治方法, 依然广泛使用。在有效杀灭蜱类的同时, 也带来一系列的问题, 如蜱类产生抗药性, 对环境和肉类品

质的污染等, 进一步增加新药研究和畜牧业成本 (Graf *et al.*, 2004)。针对这些问题, 已经产生一些替代的蜱类防治方法, 如使用植物源杀虫剂 (Benelli *et al.*, 2016), 筛选生物防治用病原真菌 (Fernandes *et al.*, 2011), 开展合理使用杀虫剂的培训等。此外, 集合化学杀虫剂使用、生境管理、蜱类疫苗开发以及对蜱类和宿主遗传改造等措施的蜱类综合治理的对策在实践中取得了较好的效果 (de la Fuente and Contreras, 2015; Stafford III *et al.*, 2017)。蜱类-病原体-宿主互作研究发现的一些对蜱类生存、扩散和病原体传播较为重要的机制均可成为未来蜱类防治的新靶标, 为防治提供新的思路 (de la Fuente *et al.*, 2017; de la Fuente, 2018)。

4 蜱类共生菌概况

蜱类同时感染非致病性的微生物, 包括肠道

微生物和母系遗传共生菌等, 在蜱类的生理过程或病原体传播等方面具有重要作用 (Bonnet *et al.*, 2017)。除肠道微生物外, 越来越多的研究关注蜱类共生菌, 包括感染率、组织分布、多样性、对宿主的影响及机制等。蜱类共生菌较为多样, 到目前为止, 已在蜱类中发现至少 10 类共生菌, 分别为 *Coxiella*-LE、*Francisella*-LE、立克次氏体 *Rickettsia*、杀雄菌 *Arsenophonus*、螺原体 *Spiroplasma*、沃尔巴克氏体 *Wolbachia*、立克次式小体 *Rickettsiella*、线粒体纤原体 *Midichloria mitochondrii*、*Cardinium* 和 *Lariskella* (Duron *et al.*, 2017) (图 2)。其中, *Coxiella*-LE、*Francisella*-LE 和 *Midichloria mitochondrii* 为蜱类所特有 (Niebylski *et al.*, 1997; Lo *et al.*, 2006; Jasinskas *et al.*, 2007)。其余共生菌也分布于其他节肢动物中 (Noda *et al.*, 1997; Grindle *et al.*, 2003; Zchori-Fein and Perlman, 2004; Henning *et al.*,

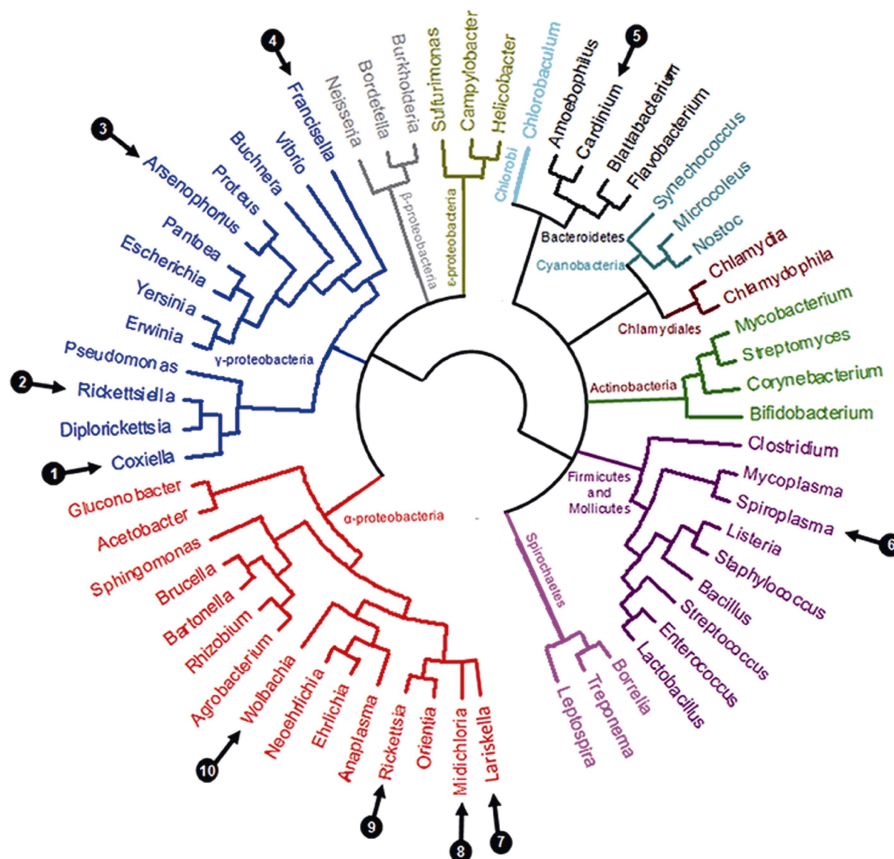


图 2 蜱类中 10 类母系遗传共生菌 (标号 1-10) 的进化关系 (Bonnet *et al.*, 2017)

Fig. 2 Evolutionary relationships between the ten genera maternally inherited tick symbionts (marked number 1-10) (Bonnet *et al.*, 2017)

2006; Werren *et al.*, 2008)。相较于其他吸血性节肢动物, 蜱类携带的共生菌最为多样 (Jiménez-Cortés *et al.*, 2018)。

在世界范围内, 已在 130 余种蜱类中发现上述共生菌的感染, 蜱类宿主包括硬蜱科和软蜱科的 8 个属。在一些分布广泛且危害较大的蜱类中, 共生菌的研究也较为深入, 如篦子硬蜱和美洲花蜱 *Amblyomma americanum* (Lo *et al.*, 2006; Zhong *et al.*, 2007; Clay *et al.*, 2008; Epis *et al.*, 2013)。在不考虑采样和检测偏倚性的前提下, *Coxiella*-LE 是蜱类中的主要共生菌。Duron 等 (2017) 研究发现, *Coxiella*-LE 在约 2/3 的蜱类中分布, 其他研究也显示该共生菌在蜱类中具有较高感染率 (Jasinskas *et al.*, 2007; Duron *et al.*, 2014)。*Rickettsia* 和 *Francisella*-LE 在蜱类中的感染也较为普遍, 蜱类宿主有几十种之多。*Midichloria mitochondrii* 特异性分布于蜱类的线粒体中, 宿主包括硬蜱、花蜱、血蜱、璃眼蜱、扇头蜱和钝缘蜱等 (Epis *et al.*, 2008)。其余共生菌在蜱类中较少, 对于蜱类的影响也有待研究。

共生菌的多重感染在蜱类中较为常见, 且存在比较复杂的感染类型。在 Duron 等 (2017) 的研究中, 发现 44 种蜱携带至少两种以上的共生菌, 篦子硬蜱和无色扇头蜱 *R. decoloratus* 种群感染的共生菌种类多达 6 种。通过高通量测序分析等, 也发现蜱类种群或个体可以同时感染多种共生菌 (Moutailler *et al.*, 2016)。至于蜱类多重感染的共生菌间是否存在相互作用, 这类研究甚少。在一些蜱类中, *Coxiella*-LE 感染率为 100%, 达到稳定感染 (Jasinskas *et al.*, 2007; Duron *et al.*, 2017), 而蜱类中其他共生菌则多为中等感染率 (Clay *et al.*, 2008; Lalzar *et al.*, 2012; Duron *et al.*, 2017)。共生菌的感染率与蜱类物种、蜱类宿主性别和地理种群等诸多因素相关。如 *Midichloria mitochondrii* 和 *Rickettsia* 在钝缘蜱 *Ornithodoros sonrai* 种群中具有较高的感染率, 而在其他种群中不感染 (Duron *et al.*, 2017)。Lo 等 (2006) 发现 *Midichloria mitochondrii* 在篦子硬蜱雌蜱中的感染较多。

利用组织解剖、PCR、荧光原位杂交和扫描电镜等技术对蜱类共生菌的组织分布研究发现, 一些共生菌存在组织特异性 (Klyachko *et al.*, 2007; Epis *et al.*, 2013; Lalzar *et al.*, 2014; Liu *et al.*, 2016)。在已经研究的蜱类中发现, *Coxiella*-LE 分布于宿主的卵巢和马氏管中, *Francisella*-LE 在卵巢、马氏管和唾液腺中感染, *Midichloria mitochondrii* 和 *Wolbachia* 则分布于卵巢和唾液腺中 (Narasimhan and Fikrig, 2015)。没有发现 *Rickettsia* 的组织特异性分布, 但 Lalzar 等 (2014) 研究揭示, 该菌在血红扇头蜱和图兰扇头蜱 *R. turanicus* 的肠道中密度相对较高。特异组织分布模式不仅保证共生菌的传播, 更为揭示共生菌的功能及机制提供基础。目前, 共生菌的组织分布研究只局限于少数蜱种, 共生菌的分布和功能的关系如何等也有待于进一步证实。因此, 未来还需要在这些方面加强研究。

5 蜱类共生菌功能及作用机制

近年来, 越来越多的研究发现共生菌通过多种方式影响蜱类宿主的生物学及病原体的传播。*Coxiella*-LE 是多种蜱类的专性共生菌, 为宿主生长发育所必需。Zhong 等 (2007) 将美洲花蜱体内的 *Coxiella*-LE 采用抗生素处理去除后, 宿主发育出现异常, 包括产卵期延长、卵孵化率下降、幼蜱生存率降低等。与之类似, *Coxiella*-LE 密度降低后, 长角血蜱的饱血体重、吸血时间、产卵量、产卵和孵化时间均受到较大影响 (Zhang *et al.*, 2017)。在微小扇头蜱中, *Coxiella*-LE 还与成蜱的发育密切相关 (Guizzo *et al.*, 2017)。Duron 等 (2017) 发现, 不感染 *Coxiella*-LE 的蜱类往往携带其他共生菌, 如 *Francisella*-LE、*Rickettsia* 和 *Rickettsiella* 等。亦有研究探讨这些共生菌的功能。近期研究证实 *Francisella* (F-Om) 能为宿主非洲钝缘蜱 *O. moubata* 提供 B 族维生素, 以保证正常生长发育 (Duron *et al.*, 2018)。去除太平洋硬蜱 *I. pacificus* 中的 *Rickettsia* 后, 宿主的产卵和生存没有明显变化 (Kurlovs *et al.*, 2014)。共生菌还影响蜱类的其他方面。

Kagemann 和 Clay (2013) 发现 *Arsenophonus* 通过降低美洲花蜱、肩突硬蜱和变异革蜱 *D. variabilis* 的活动力进而影响它们对宿主的搜寻成功率, *Rickettsia* 则能提高这些蜱类的活动力。在一些蜱类的卵子发生过程中, *Midichloria* 能够提供额外的 ATP (Sassera *et al.*, 2011)。在一些蜱类中, 共生菌感染会抑制病原体的增值和扩散, 研究表明安氏革蜱 *D. andersoni*、变异革蜱和肩突硬蜱中的 *Rickettsia* 就具有这种作用 (Macaluso *et al.*, 2002; Steiner *et al.*, 2008; Gall *et al.*, 2016)。

高通量测序和基因组测序的发展使得可以探究共生菌对蜱类的作用机制。如前所述, *Coxiella*-LE 为不少蜱类所必需。基因组测序表明, 该菌具有完善的 B 族维生素合成通路 (Gottlieb *et al.*, 2015; Smith *et al.*, 2015), 而蜱类的血餐中缺少这些营养成分。因此, *Coxiella*-LE 可为蜱类提供必需营养, 进而演化为专性共生菌。能为蜱类提供必需营养的共生菌还包括 *Francisella*-LE 和 *Rickettsia*。*Francisella*-LE 在蜱类中的营养作用已通过实验证实 (Duron *et al.*, 2018)。*Rickettsia* 的基因组中也存在合成叶酸的完整通路 (Hunter *et al.*, 2015)。综合来看, 这些共生菌在蜱类中的稳定感染和传播很大程度依赖于其对宿主的营养供给。

不少蜱类共生菌和病原体亲缘关系较近, 如 *Coxiella*-LE 和 *C. burnetii*、*Francisella*-LE 和 *F. tularensis*、*Rickettsia* 和一些病原体 *Rickettsia* (Bonnet *et al.*, 2017)。在不少的研究中, 很难对它们进行准确的区分, 尤其是 *Rickettsia*。借助系统发育分析和基因组学研究, 研究者对蜱类共生菌和病原体的进化关系进行了探讨。Gerhart 等 (2016) 发现斑点花蜱 *A. maculatum* 中的 *Francisella*-LE 可能由哺乳动物感染的病原体 *Francisella* 演化而来, 和病原体基因组相比, 其基因组中约 1/3 的编码基因发生失活。Duron 等 (2015) 研究 *Coxiella* 的演化关系, 提出 *Coxiella*-LE 演化为病原体 *C. burnetii* 的假说。作为共生菌和病原体的 *Rickettsia* 间的演化关

系, 在当前的研究数据来看, 较难明确 (Bonnet *et al.*, 2017)。

6 结论与展望

蜱类的发生和危害已成为世界性问题, 影响人类和动物健康, 危害畜牧业生产。对于蜱类及蜱传疾病的防治, 要重视蜱类基础生物学研究, 明确蜱类的分布、发生动态、繁殖机理、吸血机制等。对于蜱传疾病的发生, 要加强病原体的监测, 尤其是新发疾病的预测预防, 在此基础上进一步揭示病原体的致病机制等。共生菌在蜱类生物学中有较大影响, 要对此开展针对性的研究工作。在研究技术和手段不断丰富的今天, 蜱类的相关研究也要注重借鉴和引入新的技术和手段。这些围绕蜱类的基础研究, 不仅可以较好地揭示蜱类生物学规律, 也可以有效地指导蜱类和蜱传疾病的防治。我们还要意识到蜱类和蜱传疾病的防治是一个系统工程, 在实践过程中要建立综合治理的理念, 因时因地采取一些防治措施。

参考文献 (References)

- Alberdi P, Mansfield KL, Manzano-Román R, Cook C, Ayllón N, Villar M, Johnson N, Fooks AR, de la Fuente J, 2016. Tissue-specific signatures in the transcriptional response to *Anaplasma phagocytophilum* infection of *Ixodes scapularis* and *Ixodes ricinus* tick cell lines. *Frontiers in Cellular and Infection Microbiology*, 6: 20.
- Ayllón N, Villar M, Galindo RC, Kocan KM, Šima R, López JA, Jesús Vázquez J, Alberdi P, Cabezas-Cruz A, Kopáček P, de la Fuente J, 2015. Systems biology of tissue-specific response to *Anaplasma phagocytophilum* reveals differentiated apoptosis in the tick vector *Ixodes scapularis*. *PLoS Genetics*, 11(3): e1005120.
- Barker SC, Murrell A, 2008. Systematics and evolution of ticks with a list of valid genus and species names// Bowman AS, Nuttall PA(ed.). *Ticks: Biology, Disease, and Control*. New York, USA: Cambridge University Press. 1–31.
- Bell-Sakyi L, Zweygarth E, Blouin EF, Gould EA, Jongejan F, 2007. Tick cell lines: tools for tick and tick-borne disease research. *Trends in Parasitology*, 23(9): 450–457.
- Benelli G, Pavela R, Canale A, Mehlhorn H, 2016. Tick repellents and acaricides of botanical origin: a green roadmap to control tick-borne diseases? *Parasitology Research*, 115(7): 2545–2560.
- Bonnet SI, Binetruy F, Hernández-Jarguín AM, Duron O, 2017. The

- tick microbiome: why non-pathogenic microorganisms matter in tick biology and pathogen transmission. *Frontiers in Cellular and Infection Microbiology*, 7: 236.
- Bouquet J, Soloski MJ, Swei A, Cheadle C, Federman S, Billaud JN, Rebman AW, Kabre B, Halpert R, Boorgula M, Ancott JN, Chiu CY, Aucott JN, 2016. Longitudinal transcriptome analysis reveals a sustained differential gene expression signature in patients treated for acute Lyme disease. *MBio*, 7(1): e00100-e00116.
- Busby AT, Ayllón N, Kocan KM, Blouin EF, de la Fuente G, Galindo RC, Villar M, de la Fuente J, 2012. Expression of heat shock proteins and subolesin affects stress responses, *Anaplasma phagocytophilum* infection and questing behaviour in the tick, *Ixodes scapularis*. *Medical and Veterinary Entomology*, 26(1): 92–102.
- Cabezas-Cruz A, Estrada-Peña A, Rego RO, de la Fuente J, 2017. Tick-pathogen ensembles: do molecular interactions lead ecological innovation? *Frontiers in Cellular and Infection Microbiology*, 7: 74.
- Cabezas-Cruz A, Mateos-Hernández L, Pérez-Cruz M, Valdés JJ, de Mera IGF, Villar M, de la Fuente J, 2015. Regulation of the immune response to α -Gal and vector-borne diseases. *Trends in Parasitology*, 31(10): 470–476.
- Cheeseman K, Weitzman JB, 2015. Host-parasite interactions: an intimate epigenetic relationship. *Cellular Microbiology*, 17(8): 1121–1132.
- Chmelař J, Kotál J, Karim S, Kopacek P, Francischetti IM, Pedra JH, Kotsyfakis M, 2016. Sialomes and mialomes: a systems-biology view of tick tissues and tick-host interactions. *Trends in Parasitology*, 32(3): 242–254.
- Clay K, Klyachko O, Grindle N, Civitello D, Oleske D, Fuqua C, 2008. Microbial communities and interactions in the lone star tick, *Amblyomma americanum*. *Molecular Ecology*, 17(19): 4371–4381.
- Cramaro WJ, Revets D, Hunewald OE, Sinner R, Reye AL, Muller CP, 2015. Integration of *Ixodes ricinus* genome sequencing with transcriptome and proteome annotation of the naïve midgut. *BMC Genomics*, 16: 871.
- Dantas-Torres F, Chomel BB, Otranto D, 2012. Ticks and tick-borne diseases: a One Health perspective. *Trends in Parasitology*, 28(10): 437–446.
- de la Fuente J, 2018. Controlling ticks and tick-borne diseases looking forward. *Ticks and Tick-borne Diseases*, 9(5): 1354–1357.
- de la Fuente J, Antunes S, Bonnet S, Cabezas-Cruz A, Domingos AG, Estrada-Peña A, Johnson N, Kocan KM, Nijhof AM, Papa A, Rudenkon N, Villar M, Alberdi P, Torina A, Ayllón N, Vancova M, Golovchenko M, Grubhoffer L, Caracappa S, Fooks AR, Gortazar C, Rego ROM, 2017. Tick-pathogen interactions and vector competence: identification of molecular drivers for tick-borne diseases. *Frontiers in Cellular and Infection Microbiology*, 7: 114.
- de la Fuente J, Contreras M, 2015. Tick vaccines: current status and future directions. *Expert Review of Vaccines*, 14(10): 1367–1376.
- de la Fuente J, Estrada-Peña A, Venzal JM, Kocan KM, Sonenshine DE, 2008. Overview: ticks as vectors of pathogens that cause disease in humans and animals. *Frontiers in Bioscience*, 13(13): 6938–6946.
- de la Fuente J, Kocan KM, Almazán C, Blouin EF, 2007. RNA interference for the study and genetic manipulation of ticks. *Trends in Parasitology*, 23(9): 427–433.
- de la Fuente J, Villar M, Cabezas-Cruz A, Estrada-Peña A, Ayllón N, Alberdi P, 2016. Tick-host-pathogen interactions: conflict and cooperation. *PLoS Pathogens*, 12(4): e1005488.
- de la Fuente J, Waterhouse RM, Sonenshine DE, Roe RM, Ribeiro JM, Sattelle DB, Hill CA, 2017. Tick genome assembled: new opportunities for research on tick-host-pathogen interactions. *Frontiers in Cellular and Infection Microbiology*, 6: 103.
- Duron O, Binetruy F, Noël V, Cremaschi J, McCoy KD, Arnathau C, Plantard O, Goolsby J, Pérez de León AD, Heylen DA, Oosten RV, Gottlieb Y, Baneth G, Guglielmone AA, Estrada-Peña A, Opara MN, Zenner L, Vavre F, Chevillon C, 2017. Evolutionary changes in symbiont community structure in ticks. *Molecular Ecology*, 26(11): 2905–2921.
- Duron O, Jourdain E, McCoy KD, 2014. Diversity and global distribution of the *Coxiella* intracellular bacterium in seabird ticks. *Ticks and Tick-borne Diseases*, 5(5): 557–563.
- Duron O, Morel O, Noël V, Buysse M, Binetruy F, Lancelot R, Loire E, Menard C, Bouchez O, Vavre F, Vial L, 2018. Tick-bacteria mutualism depends on B vitamin synthesis pathways. *Current Biology*, 28(12): 1896–1902.
- Duron O, Noël V, McCoy KD, Bonazzi M, Sidi-Boumedine K, Morel O, Vavre F, Zenner L, Jourdain E, Durand P, Arnathau C, Renaud F, Trape J, Biguezoton AS, Cremaschi J, Dietrich M, Léger E, Appelgren A, Dupraz M, Gómez-Díaz GD, Dayo GK, Adakal H, Zoungrana S, Vial L, Chevillon C, 2015. The recent evolution of a maternally-inherited endosymbiont of ticks led to the emergence of the Q fever pathogen, *Coxiella burnetii*. *PLoS Pathogens*, 11(5): e1004892.
- Eisen RJ, Eisen L, Beard CB, 2016. County-scale distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the Continental United States. *Journal of Medical Entomology*, 53(2): 349–386.
- Epis S, Mandrioli M, Genchi M, Montagna M, Sacchi L, Pistone D, Sasser D, 2013. Localization of the bacterial symbiont *Candidatus* Midichloria mitochondrii within the hard tick *Ixodes ricinus* by whole-mount FISH staining. *Ticks and Tick-borne*

- Diseases*, 4(1/2): 39–45.
- Epis S, Sasser D, Beninati T, Lo N, Beati L, Piesman J, Rinaldi L, McCoy KD, Torina A, Sacchi L, Clementi E, Genchi M, Magnino S, Bandi C, 2008. *Midichloria mitochondrii* is widespread in hard ticks (Ixodidae) and resides in the mitochondria of phylogenetically diverse species. *Parasitology*, 135(4): 485–494.
- Estrada-Peña A, de la Fuente J, Ostfeld RS, Cabezas-Cruz A, 2015. Interactions between tick and transmitted pathogens evolved to minimize competition through nested and coherent networks. *Scientific Reports*, 5: 10361.
- Estrada-Peña A, Ostfeld RS, Peterson AT, Poulin R, de la Fuente J, 2014. Effects of environmental change on zoonotic disease risk: an ecological primer. *Trends in Parasitology*, 30(4): 205–214.
- Fang LQ, Liu K, Li XL, Liang S, Yang Y, Yao HW, Sun RX, Sun Y, Chen WJ, Zuo SQ, Ma MJ, Li H, Jiang JF, Liu W, Yang XF, Gray GC, Krause PJ, Cao WC, 2015. Emerging tick-borne infections in mainland China: an increasing public health threat. *The Lancet Infectious Diseases*, 15(12): 1467–1479.
- Fernandes ÉK, Angelo IC, Rangel DE, Bahiense TC, Moraes ÁM, Roberts DW, Bittencourt VR, 2011. An intensive search for promising fungal biological control agents of ticks, particularly *Rhipicephalus microplus*. *Veterinary Parasitology*, 182(2/4): 307–318.
- Gall CA, Reif KE, Scoles GA, Mason KL, Mousel M, Noh SM, Baryton KA, 2016. The bacterial microbiome of *Dermacentor andersoni* ticks influences pathogen susceptibility. *The ISME Journal*, 10: 1846–1855.
- Gerhart JG, Moses AS, Raghavan R, 2016. A *Francisella*-like endosymbiont in the Gulf Coast tick evolved from a mammalian pathogen. *Scientific Reports*, 6: 33670.
- Gottlieb Y, Lázár I, Klasson L, 2015. Distinctive genome reduction rates revealed by genomic analyses of two *Coxiella*-like endosymbionts in ticks. *Genome Biology and Evolution*, 7(6): 1779–1796.
- Graf JF, Gogolewski R, Leach-Bing N, Sabatini GA, Molento MB, Bordin EL, Arantes GJ, 2004. Tick control: an industry point of view. *Parasitology*, 129(S1): S427–S442.
- Grindle N, Tyner JJ, Clay K, Fuqua C, 2003. Identification of *Arsenophonus*-type bacteria from the dog tick *Dermacentor variabilis*. *Journal of Invertebrate Pathology*, 83(3): 264–266.
- Guerrero FD, Moolhuijzen P, Peterson DG, Bidwell S, Caler E, Bellgard M, Nene VM, Djikeng A, 2010. Reassociation kinetics-based approach for partial genome sequencing of the cattle tick, *Rhipicephalus (Boophilus) microplus*. *BMC Genomics*, 11: 374.
- Guizzo MG, Parizi LF, Nunes RD, Schama R, Albano RM, Tirloni L, Oldiges DP, Vieira RP, Oliveira WHC, Leite MS, Gonzales SA, Farber M, Martins O, Jr ISV, Oliveira PL, 2017. A *Coxiella* mutualist symbiont is essential to the development of *Rhipicephalus microplus*. *Scientific Reports*, 7(1): 17554.
- Gulia-Nuss M, Nuss AB, Meyer JM, Sonenshine DE, Roe RM, Waterhouse RM, Sattelle DB, de la Fuente J, Ribeiro JM, Megy K, Thimmapuram J, Miller JR, Walenz BP, Koren S, Hostetler JB, Thiagarajan M, Joardar VS, Hannick LI, Bidwell S, Hammond MP, Young S, Zeng Q, Abrudan JL, Almeida FC, Ayllón N, Bhidé K, Bissinger BW, Bonzon-Kulichenko E, Buckingham SD, Caffrey DR, Caimano MJ, Croset V, Driscoll T, Gilbert D, Gillespie JJ, Giraldo-Calderon GI, Grabowski JM, Jiang D, Khalil SMS, Kim D, Kocan KM, Koci J, Kuhn RJ, Kurtti TJ, Lees K, Lang EG, Kennedy RC, Kwon H, Perera R, Qi Y, Radolf JD, Sakamoto JM, Sánchez-Gracia A, Severo MS, Silverman N, Simo L, Tojo M, Tornador C, Van Zee JP, Vázquez J, Vieira FG, Villar M, Wespiser AR, Yang Y, Zhu J, Arensburger P, Pietrantonio PV, Barker SC, Shao R, Zdobnov EM, Hanuser F, Grimmelikhuijzen CJP, Park Y, Rozas J, Benton R, Pedra JHF, Nelson DR, Unger MF, Tubio JMC, Yu Z, Robertson HM, Shumway M, Sutton G, Wortman JR, Lawson D, Wikel SK, Nene VM, Fraser CM, Collins FH, Birren B, Nelson KE, Caler E, Hill CA, 2016. Genomic insights into the *Ixodes scapularis* tick vector of Lyme disease. *Nature Communications*, 7: 10507.
- Guo T, Sun Y, Xu G, Durden LA, 2017. *Ixodes kangdingensis* (Acari: Ixodidae), a new species from the Siberian weasel, *Mustela sibirica* (Carnivora: Mustelidae) in China. *Parasitology Open*, (3): e7.
- Guo Y, Sun Y, Xu R, 2016. The genus *Ixodes* (Acari: Ixodidae) in China with three new record species. *Acta Parasitologica*, 61(4): 729–742.
- Hai VV, Almeras L, Socolovschi C, Raoult D, Parola P, Pages F, 2014. Monitoring human tick-borne disease risk and tick bite exposure in Europe: available tools and promising future methods. *Ticks and Tick-Borne Diseases*, 5(6): 607–619.
- Hajdušek O, Sima R, Ayllón N, Jalovecká M, Perner J, de la Fuente J, Kopáček P, 2013. Interaction of the tick immune system with transmitted pathogens. *Frontiers in Cellular and Infection Microbiology*, 3: 26.
- Henning K, Greiner-Fischer S, Hotzel H, Ebsen M, Theegarten D, 2006. Isolation of *Spiroplasma* sp. from an *Ixodes* tick. *International Journal of Medical Microbiology*, 296(S1): 157–161.
- Herrmann C, Gern L, 2012. Do the level of energy reserves, hydration status and *Borrelia* infection influence walking by *Ixodes ricinus* (Acari: Ixodidae) ticks? *Parasitology*, 139(3): 330–337.
- Herrmann C, Gern L, 2015. Search for blood or water is influenced by *Borrelia burgdorferi* in *Ixodes ricinus*. *Parasites & Vectors*, 8(1): 6.
- Hovius JW, van Dam AP, Fikrig E, 2007. Tick-host-pathogen

- interactions in Lyme borreliosis. *Trends in Parasitology*, 23(9): 434–438.
- Hunter DJ, Torkelson JL, Bodnar J, Mortazavi B, Laurent T, Deason J, Thephavongsa K, Zhong J, 2015. The *Rickettsia* endosymbiont of *Ixodes pacificus* contains all the genes of de novo folate biosynthesis. *PLoS ONE*, 10(12): e0144552.
- Jasinskas A, Zhong J, Barbour AG, 2007. Highly prevalent *Coxiella* sp. bacterium in the tick vector *Amblyomma americanum*. *Applied and Environmental Microbiology*, 73(1): 334–336.
- Jiménez-Cortés JG, García-Contreras R, Bucio-Torres MI, Cabrera-Bravo M, Córdoba-Aguilar A, Benelli G, Salazar-Schettino PM, 2018. Bacterial symbionts in human blood-feeding arthropods: patterns, general mechanisms and effects of global ecological changes. *Acta Tropica*, 186: 69–101.
- Jongejan F, Uilenber G, 2004. The global importance of ticks. *Parasitology*, 129(S1): S3–S14.
- Kagemann J, Clay K, 2013. Effects of infection by *Arsenophonus* and *Rickettsia* bacteria on the locomotive ability of the ticks *Amblyomma americanum*, *Dermacentor variabilis*, and *Ixodes scapularis*. *Journal of Medical Entomology*, 50(1): 155–162.
- Kaufman WR, 2010. Ticks: physiological aspects with implications for pathogen transmission. *Ticks and Tick-borne Diseases*, 1(1): 11–22.
- Kernif T, Leulmi H, Raoult D, Parola P, 2016. Emerging tick-borne bacterial pathogens. *Microbiology Spectrum*, 4(3): 295–310.
- Klyachko O, Stein BD, Grindle N, Clay K, Fuqua C, 2007. Localization and visualization of a *Coxiella*-type symbiont within the lone star tick, *Amblyomma americanum*. *Applied and Environmental Microbiology*, 73(20): 6584–6594.
- Kurlov AH, Li J, Cheng D, Zhong J, 2014. *Ixodes pacificus* ticks maintain embryogenesis and egg hatching after antibiotic treatment of *Rickettsia* endosymbiont. *PLoS ONE*, 9(8): e104815.
- Lalzar I, Friedmann Y, Gottlieb Y, 2014. Tissue tropism and vertical transmission of *Coxiella* in *Rhipicephalus sanguineus* and *Rhipicephalus turanicus* ticks. *Environmental Microbiology*, 16(12): 3657–3668.
- Lalzar I, Harrus S, Mumcuoglu KY, Gottlieb Y, 2012. Composition and seasonal variation of *Rhipicephalus turanicus* and *Rhipicephalus sanguineus* bacterial communities. *Applied and Environmental Microbiology*, 78(12): 4110–4116.
- Liu LM, Li LX, Liu JN, Yu ZJ, Yang XL, Liu JZ, 2016. Population dynamics of multiple symbionts in the hard tick, *Dermacentor silvarum* Olenov (Acari: Ixodidae). *Ticks and Tick-borne Diseases*, 7(1): 188–192.
- Lo N, Beninati T, Sasser D, Bouman EAP, Santagati S, Gern L, Sambri V, Masuzawa T, Gray JS, Jaenson TGT, Bouattour A, Kenny MJ, Guner ES, Kharitononkov IG, Bitam I, Bandi C, 2006. Widespread distribution and high prevalence of an alpha-proteobacterial symbiont in the tick *Ixodes ricinus*. *Environmental Microbiology*, 8(7): 1280–1287.
- Macaluso KR, Sonenshine DE, Ceraul SM, Azad AF, 2002. Rickettsial infection in *Dermacentor variabilis* (Acari: Ixodidae) inhibits transovarial transmission of a second *Rickettsia*. *Journal of Medical Entomology*, 39(6): 809–813.
- Manzano-Román R, Díaz-Martín V, de la Fuente J, Pérez-Sánchez R, 2012. Soft ticks as pathogen vectors: distribution, surveillance and control//Shah MM(ed.). *Parasitology*. Rijeka, Croatia: InTech. 125–162.
- Miura K, Rikihisa Y, 2009. Liver transcriptome profiles associated with strain-specific *Ehrlichia chaffeensis*-induced hepatitis in SCID mice. *Infection and Immunity*, 77(1): 245–254.
- Moutailler S, Moro CV, Vaumourin E, Michelet L, Tran FH, Devillers E, Cosson J, Gasqui P, Van VT, Mavingui P, Vourch G, Vayssier-Taussat M, 2016. Co-infection of ticks: the rule rather than the exception. *PLoS Neglected Tropical Diseases*, 10(3): e0004539.
- Narasimhan S, Fikrig E, 2015. Tick microbiome: the force within. *Trends in Parasitology*, 31(7): 315–323.
- Nava S, Venzal JM, Terassini FA, Mangold AJ, Camargo LMA, Casas G, Labruna MB, 2013. *Ornithodoros guaporensis* (Acari, Ixodida: Argasidae), a new tick species from the Guaporé River Basin in the Bolivian Amazon. *Zootaxa*, 3666(4): 579–590.
- Neelakanta G, Sultana H, Fish D, Anderson JF, Fikrig E, 2010. *Anaplasma phagocytophilum* induces *Ixodes scapularis* ticks to express an antifreeze glycoprotein gene that enhances their survival in the cold. *The Journal of Clinical Investigation*, 120(9): 3179–3190.
- Niebylski ML, Peacock MG, Fischer ER, Porcella SF, Schwan TG, 1997. Characterization of an endosymbiont infecting wood ticks, *Dermacentor andersoni*, as a member of the genus *Francisella*. *Applied and Environmental Microbiology*, 63(10): 3933–3940.
- Nijhof AM, Bodaan C, Postigo M, Nieuwenhuijs H, Opsteegh M, Franssen L, Jebbink F, Jongejan F, 2007. Ticks and associated pathogens collected from domestic animals in the Netherlands. *Vector-Borne and Zoonotic Diseases*, 7(4): 585–596.
- Noda H, Munderloh UG, Kurti TJ, 1997. Endosymbionts of ticks and their relationship to *Wolbachia* spp. and tick-borne pathogens of humans and animals. *Applied and Environmental Microbiology*, 63(10): 3926–3932.
- Ogden N, 2013. Changing geographic ranges of ticks and tick-borne pathogens: drivers, mechanisms and consequences for pathogen diversity. *Frontiers in Cellular and Infection Microbiology*, 3: 46.
- Otranto D, Dantas-Torres F, Giannelli A, Latrofa MS, Cascio A,

- Cazzin S, Ravagnan S, Montarsi F, Zanzani SA, Manfredi MT, Capelli G, 2014. Ticks infesting humans in Italy and associated pathogens. *Parasites & Vectors*, 7(1): 328.
- Rio RV, Attardo GM, Weiss BL, 2016. Grandeur alliances: symbiont metabolic integration and obligate arthropod hematophagy. *Trends in Parasitology*, 32(9): 739–749.
- Sassera D, Lo N, Epis S, D'Auria G, Montagna M, Comandatore F, Horner D, Peretó J, Lucinao AM, Franciosi F, Ferri E, Crotti E, Bazzocchi C, Daffonchio D, Sacchi L, Moya A, Latorre A, Bandi C, 2011. Phylogenomic evidence for the presence of a flagellum and cbb 3 oxidase in the free-living mitochondrial ancestor. *Molecular Biology and Evolution*, 28(12): 3285–3296.
- Shi J, Hu Z, Deng F, Shen S, 2018. Tick-borne viruses. *Virologica Sinica*, 33(1): 1–23.
- Smith TA, Driscoll T, Gillespie JJ, Raghavan R, 2015. A *Coxiella*-like endosymbiont is a potential vitamin source for the lone star tick. *Genome Biology and Evolution*, 7(3): 831–838.
- Sojka D, Franta Z, Horn M, Caffrey CR, Mareš M, Kopáček P, 2013. New insights into the machinery of blood digestion by ticks. *Trends in Parasitology*, 29(6): 276–285.
- Stafford III KC, Williams SC, Molaei G, 2017. Integrated pest management in controlling ticks and tick-associated diseases. *Journal of Integrated Pest Management*, 8(1): 28.
- Steiner FE, Pinger RR, Vann CN, Grindle N, Civitello D, Clay K, Fuqua C, 2008. Infection and co-infection rates of *Anaplasma phagocytophilum* variants, *Babesia* spp., *Borrelia burgdorferi*, and the rickettsial endosymbiont in *Ixodes scapularis* (Acari: Ixodidae) from sites in Indiana, Maine, Pennsylvania, and Wisconsin. *Journal of Medical Entomology*, 45: 289–297.
- Talagrand-Reboul E, Boyer PH, Bergström S, Vial L, Boulanger N, 2018. Relapsing fevers: neglected tick-borne diseases. *Frontiers in Cellular and Infection Microbiology*, 8: 98.
- Vayssier-Taussat M, Moutailler S, Michelet L, Devillers E, Bonnet S, Cheval J, Hébert C, Eloit M, 2013. Next generation sequencing uncovers unexpected bacterial pathogens in ticks in Western Europe. *PLoS ONE*, 8(11): e81439.
- Villar M, Ayllón N, Alberdi P, Moreno A, Moreno M, Tobes R, Mateos-Hernandez L, Weishelt S, Bell-Sakyi L, de la Fuente J, 2015. Integrated metabolomics, transcriptomics and proteomics identifies metabolic pathways affected by *Anaplasma phagocytophilum* infection in tick cells. *Molecular & Cellular Proteomics*, 14(12): 3154–3172.
- Weisheit S, Villar M, Tykalová H, Popara M, Loecherbach J, Watson M, Růžek D, Grubhoffer L, de la Fuente J, Fazakerley JK, Bell-Sakyi L, 2015. *Ixodes scapularis* and *Ixodes ricinus* tick cell lines respond to infection with tick-borne encephalitis virus: transcriptomic and proteomic analysis. *Parasites & Vectors*, 8(1): 599.
- Wen TH, Chen Z, 2016. The world list of ticks. 1. Argasidae and Nuttalliellidae (Acari: Ixodida). *Chinese Journal of Parasitology and Parasitic Diseases*, 34(1): 58–69. [温廷桓, 陈泽, 2016. 世界蜱类名录 1. 软蜱科与纳蜱科(螨亚纲: 蜱目). 中国寄生虫学与寄生虫病杂志, 34(1): 58–69.]
- Werren JH, Baldo L, Clark ME, 2008. *Wolbachia*: master manipulators of invertebrate biology. *Nature Reviews Microbiology*, 6(10): 741.
- Wikel S, 2013. Ticks and tick-borne pathogens at the cutaneous interface: host defenses, tick countermeasures, and a suitable environment for pathogen establishment. *Frontiers in Microbiology*, 4: 337.
- Wu XB, Na RH, Wei SS, Zhu JS, Peng HJ, 2013. Distribution of tick-borne diseases in China. *Parasites & Vectors*, 6(1): 119.
- Yang L, Zhu CQ, Ding CX, Hu D, Lv RC, Tan LW, 2018. Review on important tick-borne viruses. *Acta Parasitologica et Medica Entomologica Sinica*, 25(3): 181–192. [杨露, 朱长强, 丁晨曦, 胡丹, 吕瑞辰, 谭伟龙, 2018. 蜱携带重要人畜共患病病毒研究概况. 寄生虫与医学昆虫学报, 25(3): 181–192.]
- Yu ZJ, Liu JZ, 2015. Progress in research on tick-borne diseases and vector ticks. *Chinese Journal of Applied Entomology*, 52(2): 1072–1081. [于志军, 刘敬泽, 2015. 蜱传疾病及其媒介蜱类研究进展. 应用昆虫学报, 52(2): 1072–1081.]
- Zehori-Fein E, Perlman SJ, 2004. Distribution of the bacterial symbiont *Cardinium* in arthropods. *Molecular Ecology*, 13(7): 2009–2016.
- Zhang CM, Li NX, Zhang TT, Qiu ZX, Li Y, Li LW, Liu JZ, 2017. Endosymbiont CLS-HI plays a role in reproduction and development of *Haemaphysalis longicornis*. *Experimental and Applied Acarology*, 73(3/4): 429–438.
- Zhao GP, 2018. Spatial distribution of ticks and their hazard prediction in China. Doctoral dissertation. Beijing: Academy of Military Medical Sciences. [赵国平, 2018. 中国蜱类空间分布及其危害预测. 博士学位论文. 北京: 中国人民解放军军事医学科学院.]
- Zhong J, Jasinskas A, Barbour AG, 2007. Antibiotic treatment of the tick vector *Amblyomma americanum* reduced reproductive fitness. *PLoS ONE*, 2(5): e405.
- Zhou X, Xia S, Huang JL, Tambo E, Zhuge HX, Zhou XN, 2014. Human babesiosis, an emerging tick-borne disease in the People's Republic of China. *Parasites & Vectors*, 7(1): 509.
- Zhuang L, 2017. Progress on tick-borne diseases and detection methods. *Chinese Frontier Health Quarantine*, 40(6): 441–445. [庄璐, 2017. 蜱传疾病及病原体检测方法研究进展. 中国环境卫生检疫杂志, 40(6): 441–445.]