FEMS Microbiology Letters 2018 vol.365 N18

Antimicrobial resistance in mollicutes: Known and newly emerging mechanisms

Chernov V., Chernova O., Mouzykantov A., Medvedeva E., Baranova N., Malygina T., Aminov R., Trushin M.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

 This review is devoted to the mechanisms of antibiotic resistance in mollicutes (class Bacilli, subclass Mollicutes), the smallest self-replicating bacteria, that can cause diseases in plants, animals and humans, and also contaminate cell cultures and vaccine preparations. Research in this area has been mainly based on the ubiquitous mollicute and the main contaminant of cell cultures, Acholeplasma laidlawii. The omics technologies applied to this and other bacteria have yielded a complex picture of responses to antimicrobials, including their removal from the cell, the acquisition of antibiotic resistance genes and mutations that potentially allow global reprogramming of many cellular processes. This review provides a brief summary of well-known resistance mechanisms that have been demonstrated in several mollicutes species and, in more detail, novel mechanisms revealed in A. laidlawii, including the least explored vesicle-mediated transfer of short RNAs with a regulatory potency. We hope that this review highlights new avenues for further studies on antimicrobial resistance in these bacteria for both a basic science and an application perspective of infection control and management in clinical and research/production settings.

http://dx.doi.org/10.1093/femsle/fny185

Keywords

Antimicrobial resistance, Extracellular vesicles, Mollicutes, Omics technologies, Resistome, Vesicle-mediated transfer of nucleic acids

References

[1] Aminov I. History of antimicrobial drug discovery: Major classes and health impact. Biochemical Pharmacology. 2017;133:4–19.

[2] Aminov RI. The role of antibiotics and antibiotic resistance in nature. Environ Microbiol 2009;11:2970–88.

[3] Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. Front Microbio 2010;1:134.

[4] Ammar AM, Abd El-Aziz NK, Gharib AA et al. Mutations of domain V in 23S ribosomal RNA of macrolide-resistant Mycoplasma gallisepticum isolates in Egypt. J Infect Dev Ctries 2016;10:807–13.

[5] Amram E, Mikula I, Schnee C et al. 16S rRNA Gene Mutations Associated with Decreased Susceptibility to Tetracycline in Mycoplasma bovis. Antimicrob Agents Chemother. 2015;59:796–802.

[6] Anitha P, Anbarasu A, Ramaiah S. Computational gene network study on antibiotic resistance genes of Acinetobacter baumannii. Computers in Biology and Medicine 2014;48:17–27.

[7] Antunes NT, Assunção P, Poveda JB et al. Mechanisms involved in quinolone resistance in Mycoplasma mycoides subsp. capri. The Veterinary Journal 2015;204:327–32.

[8] Babu M, Bundalovic-Torma C, Calmettes C et al. Global landscape of cell envelope protein complexes in Escherichia coli. Nat Biotechnol. 2018;36:103–12.

[9] Balish MF, Distelhorst SL. Potential molecular targets for narrow-spectrum agents to combat Mycoplasma pneumoniae infection and disease. Front Microbiol 2016;7:205.

[10] Baranova NB, Malygina TY, Medvedeva ES et al. Genome Sequences of Acholeplasma laidlawii Strains with Increased Resistance to Tetracycline and Melittin. Genome Announc. 2018, doi: 10.1128/genomeA.01446-17.

[11] Barbosa C, Trebosc V, Kemmer C et al. Alternative evolutionary paths to bacterial antibiotic resistance cause distinct collateral effects. Mol Biol Evol. 2017;34:2229–44.

[12] Barroso G, Labarère J. Chromosomal gene transfer in Spiroplasma citri. Science. 1988;241:959–61.

[13] Bébéar CM, Bébéar C. Antimycoplasmal agents. In: Razin S, Herrmann R. (eds.). Molecular biology and pathogenicity of mycoplasmas. London, United Kingdom: Kluwer Academic/Plenum Publishers, 2002, 545–66.

[14] Bebear CM, Kempf I. Antimicrobial therapy and antimicrobial resistance. In: Blanchard A, Browning G (eds.). Mycoplasmas: Molecular biology, pathogenicity and strategies for control. UK: Horizon Bioscience, 2005, 535–69.

[15] Beceiro A, Tomás M, Bou G. Antimicrobial Resistance and Virulence: a Successful or Deleterious Association in the Bacterial World? Clinical Microbiology Reviews 2013;26:185–230.

[16] Béven L, Castano S, Dufourcq J et al. The antibiotic activity of cationic linear amphipathic peptides: lessons from the action of leucine/lysine copolymers on bacteria of the class Mollicutes/lysine copolymers on bacteria of the class Mollicutes. Eur J Biochem 2003;270:2207–17.

[17] Béven L, Wróblewski H. Effect of natural amphipathic peptides on viability, membrane potential, cell shape and motility of mollicutes. Research in Microbiology 1997;148:163–75.

[18] Biller SJ, Schubotz F, Roggensack SE et al. Bacterial vesicles in marine ecosystems. Science. 2014;343:183–6.

[19] Bitto NJ, Chapman R, Pidot S et al. Bacterial membrane vesicles transport their DNA cargo into host cells. Sci Rep. 2017; 7:7072.

[20] Blanchard A, Bébéar CM. “Mycoplasmas of humans” in Molecular biology and pathogenicity of mycoplasmas, ed. Razin Sh., Herrmann R., New York: Kluwer), 2002, 45–71.

[21] Blenkiron C, Simonov D, Muthukaruppan A et al. Uropathogenic Escherichia coli releases extracellular vesicles that are associated with RNA. PLoS ONE. 2016, doi: 10.1371/jour-nal.pone.0160440.

[22] Bloch S, Nejman-Falenczyk ´ B, Dydecka A et al. Different Expression Patterns of Genes from the Exo-Xis Region of Bacteriophage λ and Shiga Toxin-Converting Bacteriophage 24B following Infection or Prophage Induction in Escherichia coli. PLoS ONE. 2014;9:e108233.

[23] Bonnington KE, Kuehn MJ. Protein selection and export via outer membrane vesicles. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2014;1843:1612–9.

[24] Borth WB, Jones VP, Ullman DE et al. Effects of Synthetic Ce-cropin Analogs on in Vitro Growth of Acholeplasma laidlawii. Antimicrobial Agents and Chemotherapy. 2001;45:1894–5.

[25] Breidenstein EBM, Khaira BK, Wiegand I et al. Complex ciprofloxacin resistome revealed by screening a Pseudomonas aeruginosa mutant library for altered susceptibility. Antimicrobial Agents and Chemotherapy 2008;52:4486–91.

[26] Calcutt MJ, Foecking MF. An Excision-Competent and Exogenous Mosaic Transposon Harbors the tetM Gene in Multiple Mycoplasma hominis Lineages. Antimicrob Agents Chemother 2015;59:6665–6.

[27] Cao J, Kapke PA, Minion FC. Transformation of Mycoplasma gallisepticum with Tn916, Tn4001, and integrative plasmid vectors. J Bacteriol 1994;176:4459–62.

[28] Chan H, Ho J, Liu X et al. Potential and use of bacterial small RNAs to combat drug resistance: a systematic review. IDR. 2017;10:521–32.

[29] Chattopadhyay MK, Jagannadham MV. Vesicles-mediated resistance to antibiotics in bacteria. Front Microbiol 2015;6:758.

[30] Chernov VM, Chernova OA, Mouzykantov AA et al. Extracellular Membrane Vesicles and Phytopathogenicity of Acholeplasma laidlawii PG8. The Scientific World Journal. 2012, doi: 10.1100/2012/315474.

[31] Chernov VM, Chernova OA, Mouzykantov AA et al. Extracellular Vesicles Derived from Acholeplasma laidlawii PG8. The Scientific World JOURNAL. 2011;11:1120–30.

[32] Chernov VM, Chernova OA, Sanchez-Vega JT et al. Mycoplasma contamination of cell cultures: vesicular traffic in bacteria and control over infectious agents. Acta Naturae. 2014a;6:41–51.

[33] Chernov VM, Mouzykantov AA, Baranova NB et al. Extracellular membrane vesicles secreted by mycoplasma Acholeplasma laidlawii PG8 are enriched in virulence proteins. Journal of Proteomics 2014;110:117–28.

[34] Choi JW, Kwon TY, Hong SH et al. Isolation and characterization of a microRNA-size secretable small RNA in Streptococcus san-guinis. Cell Biochem Biophys. 2018;76:293–301.

[35] Choi DS, Lee JM, Park GW et al. Proteomic analysis of microvesi-cles derived from human colorectal cancer cells. J Proteome Res 2007;6:4646–55.

[36] Clements MO, Eriksson S, Thompson A et al. Polynucleotide phosphorylase is a global regulator of virulence and persis-tency in Salmonella enterica. Proceedings of the National Academy of Sciences. 2002;99:8784–9.

[37] Cohen NR, Ross CA, Jain S et al. A role for the bacterial GATC methylome in antibiotic stress survival. Nat Genet 2016;48:581–6.

[38] Corral-Vázquez C, Aguilar-Quesada R, Catalina P et al. Cell lines authentication and mycoplasma detection as minimun quality control of cell lines in biobanking. Cell Tissue Bank. 2017;18:271–80.

[39] Da Silva GJ, Domingues S. Insights on the horizontal gene transfer of carbapenemase determinants in the opportunistic pathogen Acinetobacter baumannii. Microorganisms. 2016;4:29.

[40] Dauros Singorenko P, Chang V, Whitcombe A et al. Isolation of membrane vesicles from prokaryotes: a technical and biological comparison reveals heterogeneity. Journal of Extracellular Vesicles. 2017;6:1324731.

[41] Dauros-Singorenko P, Blenkiron C, Phillips A et al. The functional RNA cargo of bacterial membrane vesicles. FEMS Microbiol Lett. 2018;365. doi: 10.1093/femsle/fny023.

[42] Deatherage BL, Cookson BT. Membrane Vesicle Release in Bacteria, Eukaryotes, and Archaea: a Conserved yet Underappreci-ated Aspect of Microbial Life. Infect Immun 2012;80:1948–57.

[43] Dégrange S, Renaudin H, Charron A et al. Reduced susceptibility to tetracyclines is associated in vitro with the presence of 16S rRNA mutations in Mycoplasma hominis and Mycoplasma pneumoniae. J. Antimicrob. Chemother. 2008;61:1390–2.

[44] Dersch P, Khan MA, Mühlen S et al. Roles of regulatory RNAs for antibiotic resistance in bacteria and their potential value as novel drug targets. Front Microbiol. 2017;8:803.

[45] Devos S, Stremersch S, Raemdonck K et al. Intra- and Interspecies Effects of Outer Membrane Vesicles from Stenotrophomonas maltophilia on β-Lactam Resistance. Antimicrob Agents Chemother 2016;60:2516–8.

[46] Devos S, Van Putte W, Vitse J et al. Membrane vesicle secretion and prophage induction in multidrug-resistant Stenotrophomonas maltophilia in response to ciprofloxacin stress. Environmental Microbiology. 2017;10:3930–7.

[47] Dordet-Frisoni E, Sagné E, Baranowski E et al. Chromosomal transfers in mycoplasmas: when minimal genomes go mobile. mBio. 2014, doi: 10.1128/mBio.01958-14.

[48] Domingues S, Nielsen KM. Membrane vesicles and horizontal gene transfer in prokaryotes. Curr OpMicrobiol 2017;38:16–21.

[49] Dorward DW, Garon CF. DNA is packaged within membrane-derived vesicles of gram-negative but not gram-positive bacteria. Appl Environ Microbiol 1990;56:1960–2.

[50] Drexler HG, Uphoff CC. Mycoplasma contamination of cell cultures: Incidence, sources, effects, detection, elimination, prevention. Cytotechnology. 2002;39:75–90.

[51] Dubern JF, Diggle SP. Quorum sensing by 2-alkyl-4-quinolones in Pseudomonas aeruginosa and other bacterial species. Mol BioSyst. 2008;4:882–8.

[52] Dybvig K, Cassell G. Transposition of gram-positive transposon Tn916 in Acholeplasma laidlawii and Mycoplasma pulmonis. Science. 1987;235:1392–4.

[53] Ellen AF, Albers SV, Huibers W et al. Proteomic analysis of secreted membrane vesicles of archaeal Sulfolobus species reveals the presence of endosome sorting complex components. Extremophiles. 2009;13:67–79.

[54] Eterpi M, McDonnell G, Thomas V. Decontamination efficacy against Mycoplasma. Lett Appl Microbiol 2011;52:150–5.

[55] Fehri LF, Sirand-Pugnet P, Gourgues G et al. Resistance to antimicrobial peptides and stress response in Mycoplasma pulmonis. Antimicrobial Agents and Chemotherapy. 2005;49:4154–65.

[56] Fonseca-Aten M, Salvatore CM, Mejías A et al. Evaluation of LBM415 (NVP PDF-713), a novel peptide deformylase inhibitor, for treatment of experimental Mycoplasma pneumoniae pneumonia. Antimicrobial Agents and Chemotherapy 2005;49:4128–36.

[57] Frey J. Mycoplasmas of animals. In: Razin S, Herrmann R. (eds.). Molecular biology and pathogenicity of mycoplasmas. London, United Kingdom: Kluwer Academic/Plenum Publishers, 2002, 73–90.

[58] García-Castillo M, Morosini M-I, Gálvez M et al. Differences in biofilm development and antibiotic susceptibility among clinical Ureaplasma urealyticum and Ureaplasma parvum isolates. Journal of Antimicrobial Chemotherapy 2008;62:1027–30.

[59] Gaurivaud P, Laigret F, Bove JM. Insusceptibility of members of the class Mollicutes to rifampin: studies of the Spiroplasma citri RNA polymerase beta-subunit gene. Antimicrob Agents Chemother 1996;40:858–62.

[60] Ghosal A, Upadhyaya BB, Fritz JV et al. The extracellular RNA complement of Escherichia coli. MicrobiologyOpen. 2015;4:252–66.

[61] Gillings MR. Evolutionary consequences of antibiotic use for the resistome, mobilome and microbial pangenome. Front Microbio 2013;4:4.

[62] Gonorazky G, Laxalt AM, Dekker HL et al. Phosphatidylinositol 4-phosphate is associated to extracellular lipoproteic fractions and is detected in tomato apoplastic fluids. Plant Biol, Stuttg. 2012;14:41–49.

[63] Haddad N, Tresse O, Rivoal K et al. Polynucleotide phosphorylase has an impact on cell biology of Campylobacter jejuni. Front. Cell Infect. Microbiol. 2012;2:30.

[64] Händel N, Schuurmans JM, Brul S et al. Compensation of the metabolic costs of antibiotic resistance by physiological adaptation in Escherichia coli. Antimicrob Agents Chemother. 2013;57:3752–62.

[65] He X, Yuan F, Lu F et al. Vancomycin-induced biofilm formation by methicillin-resistant Staphylococcus aureus is associated with the secretion of membrane vesicles. Microbial Pathogenesis. 2017;110:225–31.

[66] Heeb S, Fletcher MP, Chhabra SR et al. Quinolones: from antibiotics to autoinducers. FEMS Microbiol Rev. 2011;35:247–74.

[67] Henderson B, Martin A. Bacterial virulence in the moonlight: multitasking bacterial moonlighting proteins are virulence determinants in infectious disease. Infect Immun 2011;79:3476–91.

[68] Hogenhout SA, Oshima K, Ammar el-D et al. Phytoplasmas: bacteria that manipulate plants and insects. Mol Plant Pathol 2008;9:403–23.

[69] Hu Y, Zhu Y, Ma Y et al. Genomic Insights into Intrinsic and Acquired Drug Resistance Mechanisms in Achromobacter xy-losoxidans. Antimicrob Agents Chemother. 2015;59:1152–61.

[70] Hwang S, Kim CY, Ji SG et al. 2016. Network-assisted investigation of virulence and antibiotic-resistance systems in Pseudomonas aeruginosa. Sci Rep. 19, 26223.

[71] Ito S, Shimada Y, Yamaguchi Y et al. Selection of Mycoplasma genitalium strains harbouring macrolide resistance-associated 23S rRNA mutations by treatment with a single 1 g dose of azithromycin. Sexually Transmitted Infections 2011;87:412–4.

[72] Jiang Y, Kong Q, Roland KL et al. Membrane vesicles of Clostridium perfringens type A strains induce innate and adaptive immunity. International Journal of Medical Microbiology 2014;304:431–43.

[73] Kadurugamuwa JL, Beveridge TJ. Bacteriolytic effect of membrane vesicles from Pseudomonas aeruginosa on other bacteria including pathogens: conceptually new antibiotics. J Bacteriol 1996;178:2767–74.

[74] Kim JH, Lee J, Park J et al. Gram-negative and gram-positive bacterial extracellular vesicles. Seminars in Cell & Developmental Biology 2015;40:97–104.

[75] Kim KM, Abdelmohsen K, Mustapic M et al. RNA in extracellular vesicles. WIREs RNA. 2017, doi: 10.1002/wrna.1413.

[76] Kim SW, Park SB, Im SP et al. Outer membrane vesicles from β-lactam-resistant Escherichia coli enable the survival of β-lactam-susceptible E. coli in the presence of β-lactam antibiotics. Sci Rep. 2018;8:5402.

[77] Kobayashi H, Uematsu K, Hirayama H et al. Novel toluene elimination system in a toluene-tolerant microorganism. Journal of Bacteriology 2000;182:6451–5.

[78] Koeppen K, Hampton TH, Jarek M et al. A novel mechanism of host-pathogen interaction through sRNA in bacterial outer membrane vesicles. PLoS Pathog. 2016, doi: 10.1371/jour-nal.ppat.1005672.

[79] Kojima A, Takahashi T, Kijima M et al. Detection ofMycoplas-main Avian Live Virus Vaccines by Polymerase Chain Reaction. Biologicals. 1997;25:365–71.

[80] Kulkarni HM, Nagaraj R, Jagannadham MV. Protective role of E. coli outer membrane vesicles against antibiotics. Microbiological Research 2015;181:1–7.

[81] Lazarev VN. The genes of antimicrobial peptides for the therapy of intracellular infections. Acta Naturae. 2009;1:121–3.

[82] Lazarev VN, Stipkovits L, Biro J et al. Induced expression of the antimicrobial peptide melittin inhibits experimental infection by Mycoplasma gallisepticum in chickens. Microbes and Infection. 2004;6:536–41.

[83] Le Roy C, Hénin N, Bébéar C et al. Evaluation of a Commercial Multiplex Quantitative PCR (qPCR) Assay for Simultaneous Detection of Mycoplasma genitalium and Macrolide Resistance-Associated Mutations in Clinical Specimens. J Clin Microbiol 2017;55:978–9.

[84] Lee EY, Choi DS, Kim KP et al. Proteomics in gram-negative bacterial outer membrane vesicles. Mass Spectrom Rev 2008;27:535–55.

[85] Lee EY, Choi DY, Kim DK et al. Gram-positive bacteria produce membrane vesicles: proteomics-based characterization of Staphylococcus aureus-derived membrane vesicles. Proteomics. 2009;9:5425–36.

[86] Lee J, Lee EY, Kim SH et al. Staphylococcus aureus Extracellular Vesicles Carry Biologically Active β-Lactamase. Antimicrob Agents Chemother 2013;57:2589–95.

[87] Lerner U, Amrama E, Ayling RD et al. Acquired resistance to the 16-membered macrolides tylosin and tilmicosin by Mycoplasma bovis. Vet. Microbiol. 2014;168:365–71.

[88] Lu C, Ye Tl, Zhu Gx et al. Phenotypic and genetic characteristics of macrolide and lincosamide resistant Ureaplasma urealyticum isolated in Guangzhou, China. Curr Microbiol 2010;61:44–49.

[89] Malge A, Ghai V, Reddy PJ et al. mRNA transcript distribution bias between Borrelia burgdorferi bacteria and their outer membrane vesicles. FEMS Microbiol Lett. 2018;365.

[90] Maniloff J. Phylogeny and evolution. In: Razin S, Herrmann R. (eds.). Molecular biology and pathogenicity of mycoplasmas. London, United Kingdom: Kluwer Academic/Plenum Publishers, 2002, 31–45.

[91] Martinez JL, Sánchez MB, Martínez-Solano L et al. Functional role of bacterial multidrug efflux pumps in microbial natural ecosystems. FEMS Microbiol Rev 2009;33:430–49.

[92] Mathieu A, Fleurier S, Frénoy A et al. Discovery and Function of a General Core Hormetic Stress Response in E. coli Induced by Sublethal Concentrations of Antibiotics. Cell Reports. 2016;17:46–57.

[93] McCormack WM. Susceptibility of mycoplasmas to antimicrobial agents: clinical implications. Clin Infect Dis 1993;17:S200–1.

[94] Medvedeva ES, Baranova NB, Mouzykantov AA et al. Adaptation of Mycoplasmas to Antimicrobial Agents: Acholeplasma laidlawii Extracellular Vesicles Mediate the Export of Ciprofloxacin and a Mutant Gene Related to the Antibiotic Target. The Scientific World Journal. 2014, doi: 10.1155/2014/150615.

[95] Medvedeva ES, Davydova MN, Mouzykantov AA et al. Genomic and proteomic profiles of Acholeplasma laidlawii strains differing in sensitivity to ciprofloxacin. Dokl Biochem Biophys 2016;466:23–27.

[96] Medvedeva ES, Malygina TY, Baranova NB et al. Adaptation of mycoplasmas to fluoroquinolones: Modulation of proteome and genotoxicity of extracellular vesicles of Acholeplasma laidlawii. Uchenye zapiski kazanskogo universiteta. Seriya es-testvennye nauki, 2017a;159:248–61.

[97] Medvedeva ES, Siniagina MN, Malanin SY et al. Genome Sequences of Acholeplasma laidlawii Strains Differing in Sensitivity to Ciprofloxacin. Genome Announc. 2017, doi: 10.1128/genomeA.01189-17.

[98] Montecalvo A, Larregina AT, Shufesky WJ et al. Mechanism of transfer of functional microRNAs between mouse dendritic cells via exosomes. Blood. 2012;119:756–66.

[99] Morozumi M, Hasegawa K, Kobayashi R et al. Emergence of macrolide-resistant Mycoplasma pneumoniae with a 23S rRNA gene mutation. Antimicrobial Agents and Chemotherapy 2005;49:2302–6.

[100] Mouzykantov AA, Baranova NB, Medvedeva ES et al. Exported mycoplasmal proteins: proteome of extracellular membrane vesicles of Acholeplasma laidlawii PG8. Dokl Biochem Biophys 2014;455:43–48.

[101] Mouzykantov AA, Medvedeva ES, Malygina TY et al. Plasticity of mycoplasmas: changes in the genomic profile, as well as in the cellular and vesicular proteomes of the Acholeplasma laidlawii in adapting the bacterium to different environmental conditions. BioNanoSci. 2016, doi: 10.1007/s12668-016-0362-2

[102] Mühlen S, Dersch P. Anti-virulence strategies to target bacterial infections. Curr Top Microbiol Immunol 2016;398:147–83.

[103] Olaitan AO, Diene SM, Assous MV et al. Genomic plasticity of multidrug-resistant NDM-1 positive clinical isolate of Providencia rettgeri. Genome Biol. Evol. 2016;8:723–8.

[104] Olsen I, Amano A. Outer membrane vesicles – offensive weapons or good Samaritans? Journal of Oral Microbiology. 2015;7:27468.

[105] Park HJ, Kang KM, Dybvig K et al. Interaction of cationic antimicrobial peptides with Mycoplasma pulmonis. FEBS Lett. 2013;587:3321–6.

[106] Paulsen IT, Nguyen L, Sliwinski MK et al. Microbial genome analyses: comparative transport capabilities in eighteen prokaryotes 1 1Edited by G. von Heijne. Journal of Molecular Biology 2000;301:75–100.

[107] Pereyre S, Gonzalez P, De Barbeyrac B et al. Mutations in 23S rRNA Account for Intrinsic Resistance to Macrolides in Mycoplasma hominis and Mycoplasma fermentans and for Acquired Resistance to Macrolides in M. hominis. Antimicrobial Agents and Chemotherapy. 2002;46:3142–50.

[108] Pereyre S, Goret J, Bébéar C. Mycoplasma pneumoniae: current knowledge on macrolide resistance and treatment. Front Microbiol 2016;7:974.

[109] Pereyre S, Guyot C, Renaudin H et al. In Vitro Selection and Characterization of Resistance to Macrolides and Related Antibiotics in Mycoplasma pneumoniae. Antimicrobial Agents and Chemotherapy. 2004;48:460–5.

[110] Pérez-Cruz C, Carrión O, Delgado L et al. New Type of Outer Membrane Vesicle Produced by the Gram-Negative Bacterium Shewanella vesiculosa M7 T: Implications for DNA Content. Appl Environ Microbiol 2013;79:1874–81.

[111] Piddock LJ. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clinical Microbiology Reviews 2006;19:382–402.

[112] Pietsch F, Bergman JM, Brandis G et al. Ciprofloxacin selects for RNA polymerase mutations with pleiotropic antibiotic resistance effects. J Antimicrob Chemother 2017;72:75–84.

[113] Prunier AL, Malbruny B, Laurans M et al. High Rate of Macrolide Resistance in Staphylococcus aureus Strains from Patients with Cystic Fibrosis Reveals High Proportions of Hyper-mutable Strains. J INFECT DIS 2003;187:1709–16.

[114] Putim C, Phaonakrop N, Jaresitthikunchai J et al. Secretome profile analysis of multidrug-resistant, monodrug-resistant and drug-susceptible Mycobacterium tuberculosis. Arch Microbiol. 2018;200:299–309.

[115] Quesenberry PJ, Aliotta J, Deregibus MC et al. Role of extracellular RNA-carrying vesicles in cell differentiation and reprogramming. Stem Cell Res Ther. 2015;6:153.

[116] Raherison S, Gonzalez P, Renaudin H et al. Evidence of Active Ef-flux in Resistance to Ciprofloxacin and to Ethidium Bromide by Mycoplasma hominis. Antimicrobial Agents and Chemotherapy. 2002;46:672–9.

[117] Raherison S, Gonzalez P, Renaudin H et al. Increased Expression of Two Multidrug Transporter-Like Genes Is Associated with Ethidium Bromide and Ciprofloxacin Resistance in Mycoplasma hominis. Antimicrobial Agents and Chemotherapy. 2005;49:421–4.

[118] Razin S, Hayflick L. Highlights of mycoplasma research—An historical perspective. Biologicals. 2010;38:183–90.

[119] Rosengarten R, Citti C, Glew M et al. Host-pathogen interactions in mycoplasma pathogenesis: virulence and survival strategies of minimalist prokaryotes. International Journal of Medical Microbiology 2000;290:15–25.

[120] Rumbo C, Fernández-Moreira E, Merino M et al. Horizontal Transfer of the OXA-24 Carbapenemase Gene via Outer Membrane Vesicles: a New Mechanism of Dissemination of Carbapenem Resistance Genes in Acinetobacter baumannii. Antimicrob Agents Chemother. 2011;55:3084–90.

[121] Schaar V, Nordström T, Mörgelin M et al. Moraxella catarrhalis Outer Membrane Vesicles Carry β-Lactamase and Promote Survival of Streptococcus pneumoniae and Haemophilus influenzae by Inactivating Amoxicillin. Antimicrob Agents Chemother 2011;55:3845–53.

[122] Schaar V, Uddbäck I, Nordström T et al. Group A streptococci are protected from amoxicillin-mediated killing by vesicles containing -lactamase derived from Haemophilus influenzae. Journal of Antimicrobial Chemotherapy. 2014;69:117–20.

[123] Schrempf H, Koebsch I, Walter S et al. Extracellular Streptomyces vesicles: amphorae for survival and defence. Microb Biotechnol 2011;4:286–99.

[124] Seemüller E, Garnier M, Schneider B. Mycoplasmas of plants and insects. In: Razin S, Herrmann R. (eds.). Molecular biology and pathogenicity of mycoplasmas. London, United Kingdom: Kluwer Academic/Plenum Publishers, 2002, 91–115.

[125] Sidjabat HE, Gien J, Kvaskoff D et al. The use of SWATH to analyse the dynamic changes of bacterial proteome of carbapanemase-producing Escherichia coli under antibiotic pressure. Sci Rep. 2018;8:3871.

[126] Simmons WL, Dybvig K. Biofilms protect Mycoplasma pulmonis cells from lytic effects of complement and gramicidin. Infection and Immunity 2007;75:3696–9.

[127] Song Z, Li Y, Liu Y et al. α-Enolase, an adhesion-related factor of Mycoplasma bovis. PLoS One. 2012, doi: 10.1371/jour-nal.pone.0038836.

[128] Su H-C, Khatun J, Kanavy DM et al. Comparative Genome Analysis of Ciprofloxacin-Resistant Pseudomonas aeruginosa Reveals Genes Within Newly Identified High Variability Regions Associated With Drug Resistance Development. Microbial Drug Resistance 2013;19:428–36.

[129] Su HC, Ramkissoon K, Doolittle J et al. The development of ciprofloxacin resistance in Pseudomonas aeruginosa involves multiple response stages and multiple proteins. Antimicrobial Agents and Chemotherapy. 2010;54:4626–35.

[130] Sulyok KM, Kreizinger Z, Wehmann E et al. Mutations associated with decreased susceptibility to seven antimicrobial families in field and laboratory-derived Mycoplasma bovis strains. Antimicrob Agents Chemother 2017, doi: 10.1128/AAC.01983-16.

[131] Taraskina AE, Savicheva AM, Akopian TA et al. Drift of tetM determinant in urogenital microbiocenosis containing mycoplasmas during treatment with a tetracycline antibiotic. Bull Exp Biol Med 2002;134:60–63.

[132] Teachman AM, French CT, Yu H et al. Gene Transfer in Mycoplasma pulmonis. Journal of Bacteriology. 2002;184:947–51.

[133] Tully JG. Special features of the acholeplasmas. In: Barile MF, Razin S. (eds.). The mycoplasmas, vol. 1. New York: Academic Press; 1979, 431–49.

[134] Uphoff CC, Drexler HG. Eradication of mycoplasma contamina-tions from cell cultures. Curr Protoc Mol Biol 2014;106:1–12.

[135] van Opijnen T, Dedrick S, Bento J. Strain dependent genetic networks for antibiotic-sensitivity in a bacterial pathogen with a large pan-genome. PLoS Pathog. 2016, doi: 10.1371/jour-nal.ppat.1005869.

[136] Waites KB, Lysnyansky I, Bebear CM. Emerging antimicrobial resistance in mycoplasmas of humans and animals. In: Browning GF, Citti C. (eds.). Mollicutes: molecular biology and pathogenesis. UK: Caister Academic Press, 2014, 289–322.

[137] Waites KB, Reddy NB, Crabb DM et al. Comparative in vitro activities of investigational peptide deformylase inhibitor NVP LBM-415 and other agents against human mycoplasmas and ureaplasmas. Antimicrobial Agents and Chemotherapy 2005;49:2541–2.

[138] Willems RJ, Top J, Smith DJ et al. Mutations in the DNA mismatch repair proteins MutS and MutL of oxazolidinone-resistant or -susceptible Enterococcus faecium. Antimicrobial Agents and Chemotherapy. 2003;47:3061–6.

[139] Wright GD. The antibiotic resistome: the nexus of chemical and genetic diversity. Nat Rev Micro. 2007;5:175–86.

[140] Xiao L, Crabb DM, Duffy LB et al. Mutations in ribosomal proteins and ribosomal RNA confer macrolide resistance in human Ureaplasma spp. International Journal of Antimicrobial Agents 2011;37:377–9.

[141] Xiao L, Crabb DM, Duffy LB et al. Chromosomal mutations responsible for fluoroquinolone resistance in Ureaplasma species in the United States. Antimicrob Agents Chemother 2012;56:2780–3.

[142] Yamaguchi Y, Takei M, Kishii R et al. Contribution of Topoiso-merase IV Mutation to Quinolone Resistance in Mycoplasma genitalium. Antimicrob Agents Chemother. 2013;57:1772–6.

[143] Yaron S, Kolling GL, Simon L et al. Vesicle-mediated transfer of virulence genes from Escherichia coli O157:H7 to other enteric bacteria. Applied and Environmental Microbiology 2000;66:4414–20.

[144] Yen P, Papin JA. History of antibiotic adaptation influences microbial evolutionary dynamics during subsequent treatment. PLoS Biol. 2017, doi: 10.1371/journal.pbio.2001586.