Ashdin Publishing
Journal of Evolutionary Medicine
Vol. 2 (2014), Article ID 235873, 3 pages
doi:10.4303/jem/235873

Perspective

THEORY

Resistance Is Mobile: The Accelerating Evolution of Mobile Genetic Elements Encoding Resistance

Gunther Jansen[1,2] and C. Athena Aktipis[2,3,4]

[1] *Department of Evolutionary Ecology and Genetics, University of Kiel, 24118 Kiel, Germany*
[2] *Wissenschaftskolleg zu Berlin, Institute for Advanced Study, 14193 Berlin, Germany*
[3] *Center for Evolution and Cancer, University of California, San Francisco, CA 94143, USA*
[4] *Department of Psychology, Arizona State University, Tempe, AZ 85287, USA*
Address correspondence to Gunther Jansen, gjansen@zoologie.uni-kiel.de

Received 16 May 2014; Revised 1 December 2014; Accepted 15 December 2014

Abstract The alarming spread of antibiotic resistance threatens to turn even the most routine treatments of bacterial infection into a Sisyphean task. This is not only a result of proliferation of antibiotic resistant microbes, but also a consequence of horizontal transmission of resistance genes by mobile genetic elements able to transfer resistance genes across bacterial species and environments. Here we discuss two important corollaries of the mobility of drug resistance genes. First, resident commensal microbes in the human gut may act as a reservoir for drug resistance genes which can be horizontally transferred to invading pathogens. Second, mobile genetic elements are under strong selective pressure to acquire drug resistance genes, which facilitates their ability to successfully survive and replicate. These factors lead to the evolution of a more mobile and complex resistome, which in turn increases the incidence of difficult-to-treat infectious diseases. We therefore urge that mobility of resident resistance genes be considered in empirical studies, theoretical models of the spread of resistance, and therapeutic decision making.

Keywords antibiotic resistance; microbiome; horizontal gene transfer; mobile genetic elements

1. Selection for antibiotic resistance

Antibiotic resistance genes accumulate across diverse environments such as farms and hospitals but also water and soil [3]. This is largely due to practices that sustain high selective pressures on bacteria to obtain and maintain resistance genes, including therapeutic and prophylactic drug applications in animal breeding, agriculture, and medicine, as well as household and industrial disinfection practices [2, 10, 13, 23]. Drug resistance genes are also present in the human gut because of strong selective pressures resulting from environmental and therapeutic exposure to antibiotics and pervasive interactions with drug resistant (though not necessarily pathogenic) environmental bacteria [12, 20]. Even in the absence of drug exposure, resistance genes persist in the human gut microbiome [9].

The presence and persistence of drug resistance genes in the human gut may pose a serious threat to the effectiveness of drugs in the case of infection with pathogenic bacteria. Microbes have the ability to transfer genetic material among the same or different species through a process called horizontal gene transfer [21], which can take several forms including uptake of naked DNA from external sources (transformation), bacteriophage-mediated transfer (transduction), pili-mediated plasmid transfer (conjugation), or transfer via small, phage-like particles known as gene transfer agents (GTAs) [11, 15]. Recently, also less known mechanisms have been shown to enable exchange of material between bacterial cells. Dubey and Ben-Yehuda [4] demonstrated that some bacteria, including *Bacillus subtilis*, *Staphylococcus aureus*, and *E. coli*, can directly exchange cytoplasmic molecules using small, 1 μm long and 30–130 nm wide tubular extrusions called nanotubes. Multiple nanotubes are typically formed simultaneously amongst bacterial cells in close contact, including between cells of unrelated species. These unspecific connections allow exchange of cytoplasmic molecules such as chloramphenicol acetyltransferase (Cat) or other enzymes that render receiving cells temporarily resistant to antibiotics. Moreover, nanotubes facilitate transfer of genetic information carried on, for example, nonconjugative plasmids, which may lead to hereditary antibiotic resistance. HGT is known to be a major mechanism in bacterial evolution [8], especially in populations exposed to stressful conditions.

2. Mobile genetic elements

Horizontal gene transfer typically occurs via mobile genetic elements (MGEs), which are sequences of DNA that can move both within and between genomes. MGEs are selfish

genetic elements selected for their own multiplication, which is often costly for the host bacterium. They can take the form of conjugative and nonconjugative plasmids, insertion sequences, transposons, and viruses (prophages) or combinations thereof and disproportionally carry genes that only provide benefits in specific environments that host bacteria rarely encounter. Examples include genes encoding resistance to antibiotics, detergents or heavy metals, catabolic enzymes for rare substrates such as citrate, and plant or animal virulence factors. The local adaptation hypothesis [5] suggests that in antibiotic-rich environments MGE-associated resistance genes are fitter relative to chromosomally encoded genes because they (i) replicate faster, both via HGT and vertical transmission, and (ii) they come in contact with diverse chromosomal backgrounds, which ensures selective coenrichment with the most competitive clones in the environment. The selective advantage of MGE-associated resistance genes is further increased through coselection or hitchhiking with additional genes carried on the MGE, especially if these genes are also adaptive in that environment. This positive feedback loop explains why plasmids and integrons increasingly have gene cassettes encoding resistance to multiple antibiotics, heavy metals, disinfectants, virulence factors, and other genes useful in stressful (host) environments [7, 18, 21, 22].

MGEs as a whole receive additional fitness benefits from evolving the increased capability to capture resistance genes. This is enabled by incorporation of transposons, (pro)phages, integrative conjugative elements, and plasmids that enhance mobility [1, 14, 16]. MGEs have indeed already become highly modular: they are richly sprinkled with insertion sequences and transposons that enable genes to be quickly lost or gained through recombination and transposition [6]. Thus, it appears that bacteria have met the antibiotic assault of the last decades with the development of a highly versatile and sophisticated machinery selected for rapid adaptation to antibiotics: modular mobile genetic elements specialized to capture drug resistance genes.

3. Clinical implications

In the narrow niche formed by the human gut, HGT is up to 25 times more common than between bacteria from unrelated non-human environments, mostly because HGT occurs most frequently between ecologically similar bacteria (rather than between phylogenetically related strains) [19]. Animal models have shown that resistance genes can be transferred from resident microbes to bacteria passing through the digestive system via HGT [17]. The human gut microbiome may therefore act as a reservoir for resistance genes, transferring these genes to pathogens and commensals alike.

The mobility of drug resistance genes in the gut has several clinical implications. First, the effectiveness of broad spectrum drugs as a first line of defense may be compromised by the availability of resident resistance genes via HGT. Second, even successful eradication of an infection with a given drug may result in the inadvertent enrichment of resistance genes in the resident commensal community which may compromise future treatment with the same drug. And third, the accelerating evolution of MGEs may become an increasing problem in infectious disease at the public health level.

4. Scope of application

Applying these issues to clinical treatment and prevention, however, will require additional research and modeling. Many parameters that would allow for effective models are simply unknown, including MGE host range and actual rates of HGT among the same and different species. Bacteria sharing the same pathogenicity undergo significantly more HGT than would be expected at random [19]. This may be good news, as HGT between resident microbes and pathogenic microbes is likely to be rarer than within either group. However, this process has been insufficiently studied in order to understand the effects on treatment success and selection for resistance genes. Answering such questions may be facilitated by resistome sequencing, which may, in time, become a valuable part of infectious disease diagnostics. The development of drugs targeting MGEs or mechanisms of HGT could be a promising avenue for future work.

In conclusion, drug resistance evolution is not limited to simple competition between sensitive and resistant microbes. The process of HGT allows transmission of resistance from one species of microbe to another, making it possible for drug resistance to spread quickly. This may be accelerated because selfish MGEs are under selective pressure to capture drug resistance genes. Mobility of drug resistance via horizontal transfer and the increasing evolvability of MGEs should thus be considered in experimental approaches, models of the spread of resistance, and the development of clinical practices.

Acknowledgments This material is based upon work supported by the German Volkswagen Foundation grant I/84 163 and by National Institute of Health Grant Nos. F32 CA144331 and R01 CA170595-01. We thank the Institute for Advanced Study in Berlin, the Wissenschaftskolleg, for supporting both authors as Fellows during 2013-2014 when this paper was conceived and written.

References

[1] F. Baquero, A. P. Tedim, and T. M. Coque, *Antibiotic resistance shaping multi-level population biology of bacteria*, Front Microbiol, 4 (2013), 15.

[2] T. M. Barbosa and S. B. Levy, *The impact of antibiotic use on resistance development and persistence*, Drug Resist Updat, 3 (2000), 303–311.

[3] S. P. Djordjevic, H. W. Stokes, and P. Roy Chowdhury, *Mobile elements, zoonotic pathogens and commensal bacteria: conduits for the delivery of resistance genes into humans, production animals and soil microbiota*, Front Microbiol, 4 (2013), 86.

[4] G. P. Dubey and S. Ben-Yehuda, *Intercellular nanotubes mediate bacterial communication*, Cell, 144 (2011), 590–600.
[5] W. G. Eberhard, *Evolution in bacterial plasmids and levels of selection*, Q Rev Biol, 65 (1990), 3–22.
[6] M. R. Gillings and H. W. Stokes, *Are humans increasing bacterial evolvability?*, Trends Ecol Evol, 27 (2012), 346–352.
[7] M. S. Gilmore, F. Lebreton, and W. van Schaik, *Genomic transition of enterococci from gut commensals to leading causes of multidrug-resistant hospital infection in the antibiotic era*, Curr Opin Microbiol, 16 (2013), 10–16.
[8] R. Jain, M. C. Rivera, J. E. Moore, and J. A. Lake, *Horizontal gene transfer in microbial genome evolution*, Theor Popul Biol, 61 (2002), 489–495.
[9] C. Jernberg, S. Löfmark, C. Edlund, and J. K. Jansson, *Long-term impacts of antibiotic exposure on the human intestinal microbiota*, Microbiology, 156 (2010), 3216–3223.
[10] C. W. Knapp, J. Dolfing, P. A. Ehlert, and D. W. Graham, *Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940*, Environ Sci Technol, 44 (2010), 580–587.
[11] A. S. Lang, O. Zhaxybayeva, and J. T. Beatty, *Gene transfer agents: phage-like elements of genetic exchange*, Nat Rev Microbiol, 10 (2012), 472–482.
[12] T. Looft, T. A. Johnson, H. K. Allen, D. O. Bayles, D. P. Alt, R. D. Stedtfeld, et al., *In-feed antibiotic effects on the swine intestinal microbiome*, Proc Natl Acad Sci U S A, 109 (2012), 1691–1696.
[13] J. L. Martínez, *Antibiotics and antibiotic resistance genes in natural environments*, Science, 321 (2008), 365–367.
[14] D. Mazel, *Integrons: agents of bacterial evolution*, Nat Rev Microbiol, 4 (2006), 608–620.
[15] L. D. McDaniel, E. Young, J. Delaney, F. Ruhnau, K. B. Ritchie, and J. H. Paul, *High frequency of horizontal gene transfer in the oceans*, Science, 330 (2010), 50.
[16] D. A. Rowe-Magnus and D. Mazel, *The role of integrons in antibiotic resistance gene capture*, Int J Med Microbiol, 292 (2002), 115–125.
[17] A. A. Salyers, A. Gupta, and Y. Wang, *Human intestinal bacteria as reservoirs for antibiotic resistance genes*, Trends Microbiol, 12 (2004), 412–416.
[18] M. S. Sidhu, E. Heir, T. Leegaard, K. Wiger, and A. Holck, *Frequency of disinfectant resistance genes and genetic linkage with β-lactamase transposon Tn552 among clinical staphylococci*, Antimicrob Agents Chemother, 46 (2002), 2797–2803.
[19] C. S. Smillie, M. B. Smith, J. Friedman, O. X. Cordero, L. A. David, and E. J. Alm, *Ecology drives a global network of gene exchange connecting the human microbiome*, Nature, 480 (2011), 241–244.
[20] M. O. Sommer, G. Dantas, and G. M. Church, *Functional characterization of the antibiotic resistance reservoir in the human microflora*, Science, 325 (2009), 1128–1131.
[21] H. W. Stokes and M. R. Gillings, *Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram-negative pathogens*, FEMS Microbiol Rev, 35 (2011), 790–819.
[22] E. M. Wellington, A. B. Boxall, P. Cross, E. J. Feil, W. H. Gaze, P. M. Hawkey, et al., *The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria*, Lancet Infect Dis, 13 (2013), 155–165.
[23] Y. G. Zhu, T. A. Johnson, J. Q. Su, M. Qiao, G. X. Guo, R. D. Stedtfeld, et al., *Diverse and abundant antibiotic resistance genes in Chinese swine farms*, Proc Natl Acad Sci U S A, 110 (2013), 3435–3440.