Editorial

Banin, Ehud; Hughes, Diarmaid; Kuipers, Oscar P.

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Editorial: Bacterial pathogens, antibiotics and antibiotic resistance

Antibiotics are arguably the most successful form of chemotherapy developed in the 20th century and perhaps over the entire history of medicine. Since their discovery and their introduction into commercial use over 70 years ago, antibiotics have saved innumerable human lives every day. Modern medicine depends on the effectiveness of antibiotics to treat and prevent various infections such as urinary tract, skin and soft tissue infections, pneumonia and also life-threatening infections such as endocarditis, meningitis and sepsis. Antibiotics are also required to maintain routine and advanced medical procedures such as cesarean sections and organ transplants. The ability of bacteria to develop resistance to antibiotics has been well documented. Initially, the arsenal of new antibiotics was sufficient to overcome the observed resistance and antibiotics were often taken for granted. However, as the pipeline of new antibiotics has decreased, bacterial resistance frequencies have continued to rise worldwide. In the last two decades, driven by the overconsumption and injudicious use of clinically used antibiotics, and the ongoing evolution and spread of mobile genetic resistance elements, increasing numbers of multidrug resistant (MDR) and even extremely drug-resistant (XDR) bacterial pathogens have emerged. These MDR bacteria increase patient morbidity, mortality and healthcare costs. In the last few years, several reports have highlighted the urgent and critical situation of antimicrobial resistance. For example, the US Centers for Disease Control and Prevention has defined antibiotic resistance as one of the world's most pressing public health problems, and it has estimated that tens of thousands of Americans already die each year from infections due to antibiotic-resistant bacteria (http://www.cdc.gov/getsmart/antibiotic-use/fast-facts.html). In the recent O'Neill report sponsored by the UK Government, it was estimated that by 2050 ~10 million people per year would be dying from antibiotic-resistant infections.

The current thematic issue of *FEMS Microbiology Reviews* brings together 11 reviews from expert groups that address the problems and issues associated with antibiotics and antibiotic resistance from several different angles. This includes reviews dealing with specific pathogens that show MDR and XDR and are a major cause of nosocomial infections; reviews addressing general mechanisms of antibiotic resistance such as biofilms, persistence, toxin–antitoxin systems, and the complexity of environmental and genetic modulation of resistance; and reviews dealing with new approaches to discover or develop the much needed next generation of antimicrobial agents.

IMPORTANT BACTERIAL PATHOGENS

In February 2017, The World Health Organization (WHO) has issued a global priority pathogens list (global PPL) of antibiotic-resistant bacteria to help in prioritizing the research and development of new and effective antibiotic treatments. The list contains 12 bacteria and bacterial families and is divided into three categories: critical, high and medium. *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing bacteria are listed in the critical section together with two additional pathogens. Navon-Venezia, Kondratyeva and Carattoli (2017) describe one member of this family, *Klebsiella pneumoniae*. *Klebsiella pneumoniae* is highly efficient in acquiring mutations, plasmids and genetic elements that confer antibiotic resistance. The authors provide a comprehensive overview of the evolution and diverse 'resistome' of this re-emerging pathogen which supports the development of MDR and XDR sequence types resulting in worldwide dissemination and outbreaks. Another pathogen listed in the WHO global priority list under the high category is *Staphylococcus aureus*, a common cause of nosocomial infections. Foster (2017) describes in detail the antibiotic targets and compounds commonly used to treat *S. aureus* infections, and the mechanisms of resistance that have been acquired. Prospects for combination therapy as well as new targets and drugs that may help in controlling infections associated with this notorious pathogen are also discussed.

Prior to the era of antibiotics, *Mycobacterium tuberculosis* was one of the most deadly and feared of all bacterial infections. Now the spectre of untreatable drug-resistant tuberculosis is again threatening to cause a global epidemic. Gygli *et al.* (2017) have written a very informative and insightful review of the current understanding of intrinsic drug resistance mechanisms in *M. tuberculosis*, and the remarkable capability of this pathogen to evolve resistance by mutation. They argue that the measures, urgently needed to tackle this global health problem, include improving the quality of public health systems in resource-limited settings, the introduction of cost-effective point-of-care diagnostic tools, novel antimycobacterial drugs and the development of an effective vaccine. Finally, they emphasize that research needs to focus more on *M. tuberculosis* strains which represent the variation within the species in order to properly assess the impact of novel drugs and planned interventions.

ANTIBIOTIC RESISTANCE

One of the modes by which bacteria exert antimicrobial resistance is through their ability to form biofilms. Biofilms

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are surface-attached bacteria encased in a self-produced extracellular polymeric matrix. The hallmark of the biofilm life style is increased resistance to a wide range of stressors including the immune system, disinfectants and antibiotics. The mechanisms underlying this resistance are complex. Hall and Mah (2017) provide insights into these mechanisms, which include the interaction of antibiotics with matrix components, reduced growth rates and a range of genetic determinants that specifically mediate resistance in the biofilm mode of growth. Notably, it is usually not one single mechanism that provides the resistance, but rather a combination of several of these mechanisms that manifests the extremely high resistance observed within biofilm cells.

Interestingly, an important mechanism that is shared between biofilm bacteria and free-living planktonic bacteria is persistence. Persistence is a transient tolerance state in which the antibiotic tolerance is non-genetic and persists within a susceptible population. Van den Bergh, Fauvart and Michiels (2017) provide a comprehensive overview of this fascinating mode of bacterial survival in the presence of antibiotics. The physiology, mechanism of formation, ecology and clinical importance are discussed, and future challenges and research directions are highlighted. Since persistence has been documented in most bacterial species, further understanding of this phenomenon can improve our therapeutic approaches and may even lead to the development of specific antimicrobial agents that target persister cells.

Toxin–antitoxin (TA) systems are ubiquitous among bacteria and play an important role in the dissemination and evolution of antibiotic resistance, for example, by maintaining MDR plasmids, by inducing persistence formation and by playing a role in biofilm formation. Yang and Walsh (2017) in their review discuss the variety of different TA systems that are currently known, and their role as drivers in the maintenance of antimicrobial resistance in pathogen populations. They also discuss how TA systems are often associated with antimicrobial genes present on the same plasmid as the TA itself, and how that coincidence can act to maintain the antimicrobial resistance genes even in the absence of the drug. In addition, they highlight how the mutagenic SOS system, which is induced by many commonly used antimicrobial drugs, including long-lived drugs such as fluoroquinolones, activates some TA systems, placing a continuing selective pressure on certain TA systems to be mobilized throughout bacterial populations.

A common misconception is to think of antibiotic resistance as being exclusively a function of particular resistance mutations or acquired foreign resistance genes. What is less appreciated is that both the environment and the overall genotype of the target bacteria can significantly modulate the phenotypic expression of antibiotic resistance. Hughes and Andersson (2017) in their review discuss examples of phenotypic modulation, and the important implication that knowing the identity of resistance mutations and genes is often insufficient information to accurately predict the resistance phenotype in the clinic. In an age of increasing reliance on DNA sequence data, this dissociation of genotype and phenotype has important consequences for the ability of clinical bacteriology to guide optimal therapy. They also estimate the degree to which there is a genetic 'dark matter' of currently unknown (or underappreciated) genes and mutations contributing to resistance in clinical isolates. Finally, they discuss whether and how we can identify the genetic features that contribute to making a successful pathogen, and whether we can understand, and predict, why some resistant clones succeed in spreading globally. One of the challenges in new antibiotic development is being able to predict resistance by horizontal gene transfer (HGT) early in the development process, while another is to understand genotypes at a depth that might allow the exploitation of weaknesses in resistance phenotypes. The authors argue that future work needs to more systemically generate genotype–phenotype maps that take into account the variable *in vivo* conditions in which bacterial pathogens reside, the genetic variability of natural strains, the potential for HGT from the pan-genome and the evolvability of foreign 'resistance' genes after transfer into a novel genetic environment. A central objective of studying the genetics of resistance is to understand how a phenotype is generated from the interplay between a genotype and a set of environmental conditions, and ideally to predict phenotypes from DNA sequences alone.

IDENTIFICATION AND DEVELOPMENT OF NOVEL ANTIBIOTICS AND REACTIVATION OF EXISTING ANTIBIOTICS

In addition to controlling the use of available antibiotics, there is clearly an urgent need to find new targets and design new antibiotic compounds to fight MDR and XDR pathogens, and this clearly is a complex mission. Development can be based on (i) designing a new antibiotic derivative of a known antibiotic family with improved properties, (ii) discovering new chemical structures that act on known or a novel bacterial target or (iii) employing alternative therapeutics such as phages or antibodies. The scientific challenges of discovering novel-mechanism antibiotics are difficult. Moreover, the regulatory hurdles to new antibiotics have become increasingly complex and the fact that antibiotics are short-course treatments makes antibiotics less profitable for the pharmaceutical industry compared to long-term therapies for chronic conditions. Thus, it is not surprising that many major pharmaceutical companies have limited their investments in antibiotic innovation, and most of the new antibiotic compounds are new derivatives of known families. The current situation highlights the urgent need to find novel approaches to combat antibacterial resistance. One such approach is based on nanotechnology, which offers an opportunity for the discovery of novel compounds with antimicrobial activity as well as the use of 'nanofunctionalization' to restore antimicrobial activity of existing antibiotics. Natan and Banin (2017) provide a detailed overview of the most recent advancements in using nanotechnology to develop antimicrobial agents. They cover both nanoparticles that possess intrinsic antimicrobial activity such as silver and metal oxides and nanoparticles that serve as cargo for various antimicrobial agents. The mechanisms of action, toxicity and prospects for commercialization are also discussed.

Van der Meij *et al.* (2017) focus on antibiotic production by *Actinomycetes*, one of the richest sources of antibiotics to date, by studying the chemical ecology of this group. Most *Actinomycetes* thrive in symbiosis with other organisms such as plants, fungi or even sponges, which benefit from compounds produced by the *Actinomycetes*. In return, the *Actinomycetes* can obtain nutrients from the host they interact with. The authors discuss how these interactions direct the biosynthesis of natural products, such as antibiotics. Thus, current approaches focus on finding the right environmental cues and elicitors to stimulate the production of these potential new antibiotics. Since these compounds cannot be found by conventional screening of strains in laboratory media, there are excellent chances of finding novel drugs this way.

Tracanna *et al.* (2017) also argue there is an urgent need for novel compounds that can supplement the current collection of antibiotics and that nature is still providing a rich source of antimicrobial molecules, which can either be used as such or as scaffolds for novel drug development. To make optimal use of the plethora of genomes that have been sequenced, state-of-the-art mining tools have been developed that can quickly identify existing and novel antimicrobial molecules. Currently, tens of thousands of biosynthetic gene clusters have been identified that could encode the biosynthesis of thus far unknown molecules. Various approaches are described to identify and further characterize these molecules, including the use of metabolic, environmental and metagenomic data to chart biosynthetic diversity. They also make the point that ecological information can help to prioritize useful antimicrobial functions. The review also includes a discussion on how function-based mining for antimicrobials can be employed e.g. by use of protein domains for genome mining, based on predicted function, or by use of mode of action information. These efforts will eventually help to identify new promising antibiotic candidates that need to be further characterized and tested for real-life applicability.

Finally, Pachon-Ibanez *et al.* (2017) address the suitability of defensins as therapeutic antimicrobial agents. Defensins are broad-spectrum antimicrobial peptides which form an important part of the human innate immunity system, not only displaying antibacterial, but also antiviral and antifungal activities. The authors discuss their potential as antibiotic therapeutics as well as their potential ability to avoid the problems of resistance development. The review describes the advances made in the development of defensins and their derivatives as antimicrobial agents for clinical use, as well as the optimization of their antimicrobial activity and the improvement of their manufacturing.

In the last 70 years, mankind has enjoyed the power of antibiotics; however, at the current rate of antibiotic resistance development we are getting closer and closer to the postantibiotic era. This *FEMS Microbiology Reviews* thematic issue on antimicrobial resistance highlights both the challanges and the possible approaches that can be taken to overcome and outsmart these bacteria. Research over the past years has taught us that this is going to be an ongoing challange, yet with the current advancement in our understanding of resistance and mode of action, and in research tools at the molecular, structural and chemical level, we believe that we can still find ways to combat this threat. However, to have a realistic chance of success it is imperative that research efforts, and funding for basic and applied research in this field, are significantly increased. Time is not on our side.

This thematic collection of reviews can be found at https://academic.oup.com/femsre/pages/antimicrobial_therapy

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Ehud Banin
Faculty of Life Sciences, Bar-Ilan University,
82900 Ramat-Gan, Israel

Diarmaid Hughes
Medical Biochemistry and Microbiology, Uppsala University,
75123 Uppsala, Sweden

Oscar P. Kuipers
University of Groningen, Molecular Genetics,
9747AG Groningen, the Netherlands
E-mail: o.p.kuipers@rug.nl