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The 'Microbial Genome Plasticity' section of the Institute of Hygiene addresses fundamental and applied research questions related to the geno- and phenotypic variability of bacterial pathogens which can cause disease in humans and animals. Using the enterobacterial species Escherichia coli as a model, we want to understand (i) what distinguishes commensals from pathogens, (ii) which bacterial traits are required to cause symptomatic or asymptomatic infection, and (iii) how do bacterial pathogens change during the course of an infection?

E. coli is a perfect model organism to study these questions because this species comprises harmless commensals as well as so-called 'intestinal pathogenic E. coli (IPEC)' variants, which cause diarrhoea as well as extra-intestinal pathogenic E. coli (ExPEC) causing mainly urinary tract infection (the most frequently occurring bacterial infection in industrial countries) as well as newborn meningitis. Additionally, ExPEC are important nosocomial pathogens and causative agents of septicemia. E. coli is not only a diarrheagenic or extra-intestinal human pathogen, but also responsible for intestinal as well as extra-intestinal infections of many animals. Using multidisciplinary approaches in combination with comparative and functional genomic analyses, we characterise virulence and fitness-associated genes of ExPEC and selected IPEC pathotypes.

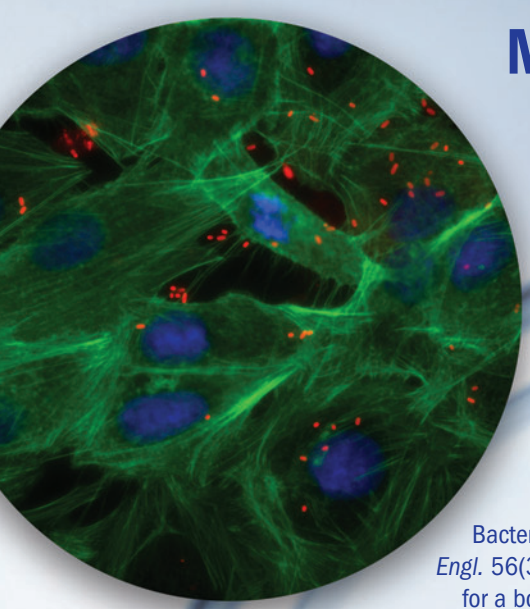
Bacterial chromosomes are flexible molecules; they evolve during the course of infection in humans. During infection, a variety of strong selective pressures are exerted on the pathogen. The resulting genetic changes that occur in pathogens might influence the clinical outcome and have an impact on diagnosis and epidemiology. Commensal and pathogenic bacteria interact in different ways with host barriers. Bacterium-host interaction may also differ depending on the niche or site of infection. It is thus our aim to identify bacterial properties and the molecular mechanisms involved in different forms of host-bacterium interaction, thus leading to different types of infection or colonisation. Successful infection or colonisation of a niche requires bacterial adaptation (i) to the growth conditions encountered and (ii) in response to the cross-talk at epithelial barriers. This cross-talk between pathogenic or commensal E. coli and host cells is often not well understood.

From a clinical perspective, the understanding of disease progression – e.g. during ascending urinary tract infection from bladder to kidney, or in the case of sepsis the bacterial translocation from the kidneys or from the intestine to the bloodstream – is a well-defined process. What is less well understood, despite decades of fundamental research, is this process from the microbial perspective. At a microbial pathogenesis level almost all our understanding of extra-intestinal disease progression is based on classical bacterial genetics studies on E. coli isolates from different niches using model infection systems. Characterising the E. coli genome plasticity and genes under selection are important key components to understand the mechanisms of E. coli pathogenesis.

To correlate genetic flexibility and bacterial fitness or virulence potential in response to in vivo growth, we investigate the (i) bacterium-host interaction at cellular barriers, (ii) genome-scale evolution and adaptation of E. coli in individual human hosts at different niches, and (iii) E. coli factors involved in metabolic adaptation to different host niches.

Besides our interest in fundamental research projects, we are also interested in translating our findings regarding genomic and phenotypic differences between individual E. coli pathotypes or E. coli pathogens during the course of infection into the development of improved diagnostic, therapeutic or preventive approaches against E. coli infection. Furthermore, we study differential regulation of gene expression and metabolic traits, which may distinguish commensals from pathogens or different E. coli pathotypes.

The increasing number and the spread of (multi-)resistant E. coli variants represent a major problem regarding the treatment of E. coli infections. It is obvious that antibiotic resistance will develop to any drug used in human and veterinary medicine. To reduce antibiotic resistance, it is not only important to reduce the exposure of bacteria to antibiotics, but also to fast and reliable diagnostics and responsible antibiotic stewardship, but also to develop novel strategies of antimicrobial treatment. Accordingly, another research focus is on the characterisation of microbial genome plasticity and its impact on the evolution and spread of antibiotic resistances as well as on novel strategies, e.g. bacterial interference or photosensitisers, to combat bacterial infection.



Microbial Genome Plasticity

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PERSISTENCE OF FACULTATIVE PATHOGENS

The Institute of Hygiene's Professor Dr Ulrich Dobrindt discusses facultative pathogens, bacterial adaptation and risk assessment

Facultative pathogens can colonise their hosts without causing infection. Comparative and functional analyses of asymptomatic colonisers will help us to understand why these bacteria can establish symptomatic infections, but also asymptomatically colonise or persist in the human body. Asymptomatic colonisation and persistence can interfere with proper risk assessment and outbreak surveillance of many pathogens. Whole genome-based analyses of colonising and infecting isolates supports the risk assessment and novel therapeutic approaches against bacterial infections, as Professor Ulrich Dobrindt discusses.

On the zoonotic potential of avian pathogenic *E. coli*

Escherichia coli bacteria usually colonise as harmless commensals in the gut of healthy humans and many animals. In addition, intestinal pathogenic *E. coli* can cause diarrhoea. Extraintestinal pathogenic *E. coli* (ExPEC) are the most common cause of community and hospital-acquired extraintestinal infections including urinary tract infection and bacteremia. ExPEC infections in ruminants and poultry include mastitis and colibacillosis. Human ExPEC and avian pathogenic *E. coli* (APEC) derive from the same phylogenetic lineages or share common evolutionary roots. Accordingly, APEC are considered a reservoir of virulence and resistance-associated genes for human pathogens, and may pose a zoonotic risk. The detection of certain human ExPEC lineages in poultry-derived products, but less frequently in meat products from other food animals, corroborates the above-mentioned hypothesis. Even if this zoonotic risk cannot be generalised, but holds only true for a certain amount of human infections caused by APEC, it will be highly relevant for public health, food animal production and food safety to monitor the introduction of often antibiotic-resistant APEC lineages via contaminated food into the healthy human population.

In contrast to diarrhoeagenic *E. coli,* which are obligate pathogens, and thus usually directly associated with disease, human ExPEC and APEC are facultative pathogens. They persist as members of the normal intestinal microbiota without causing extraintestinal disease. To proof transmission of such APEC strains from poultry (products) or other environmental sources to humans, it is difficult to trace back clinical isolates to certain products due to the time period that lies between their acquisition and the establishment of an extraintestinal infection. Whole-genome sequencing (WGS) can support infection control surveillance and outbreak investigations also in such cases

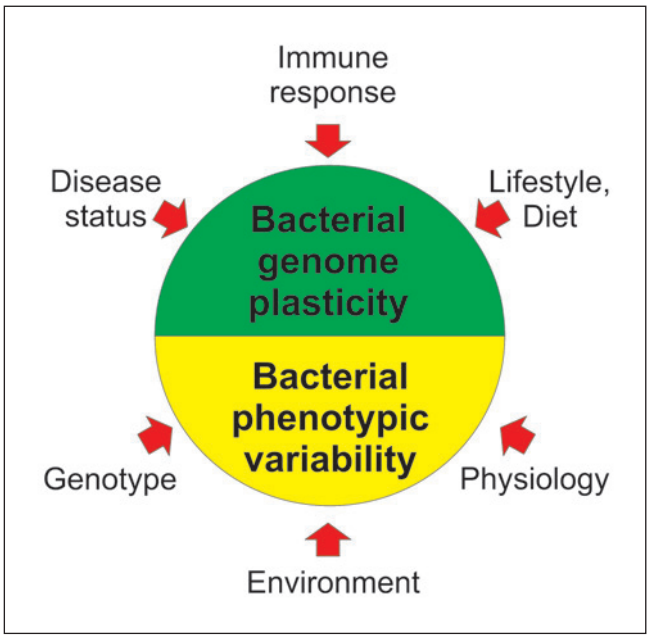

Fig. 1 Different host factors can affect genome plasticity and phenotypic variability of long term colonising or persisting bacteria. Host parameters (including the host innate and adaptive immune response, diet, lifestyle, disease status, physiology and genotype) drive bacterial adaptation and differential bacterial gene expression in response to the individual host situation or niche

outside of an outbreak scenario. WGS allows the identification of strains based on single nucleotide polymorphisms (SNPs). By comparing bacterial genome sequences, the genetic relatedness of isolates from food products and patients can be analysed. One challenging and critical point in such traceback or case-control studies is to agree on the level of genetic relationship that convincingly proves a particular product as the source of a given human clinical isolate, e.g. the number of SNPs.

Close relationships between hosts and bacteria: impact on personalised microbiomes and asymptomatic carriage

The close relationship between humans and their colonising microbes also becomes manifest in distinct human-associated microbiomes. Although in large parts unexplained, factors such as the environment, diet, host genetics and microbial exposure contribute to the shaping of the microbiota.[1] Similarly, long term colonising facultative pathogens living in close interaction with humans and animals have to adapt themselves to constantly changing growth conditions. They can often establish a lifestyle

that is at the intersection of commensalism and pathogenesis. These microbes are phenotypically variable and can manipulate host responses. This enables them to establish symptomatic infections, but also to asymptomatically colonise the human body. By switching between virulence and commensalism, they can cause recurrent or chronic health problems. Which factors direct whether or not bacteria enter the virulent or commensal lifestyle is often poorly understood. In addition, asymptomatic bacterial carriage can lead to mutations and altered gene expression in the host, which could contribute to the development of cancer or inflammatory diseases. The molecular basis of asymptomatic carriage of bacterial pathogens has not yet been fully investigated. We have to investigate in more detail bacterial traits which promote asymptomatic carriage as well as the impact of host and environmental stimuli (e.g. nutrient availability, hormones, host susceptibility factors) on bacterial colonisation without overt induction of host responses. The expected results are relevant for many bacterial pathogens including food pathogens and will thus improve risk assessment and food safety.

Analysis of bacterial adaptation during close bacterium-host interaction

Urinary tract infection (UTI) is a good model to study microbial adaptation to the human host, because the different lifestyles of uropathogens and asymptomatic colonisers are clearly displayed. Uropathogens destroy the mucosal barrier in the kidneys and cause severe disease. On the other hand, asymptomatic bacteriuria (ABU) is the most common form of UTI and resembles commensalism. Patients can be asymptomatically colonised with the same *E. coli* strain for extended periods of time and do not develop symptoms. ABU is protective against recurrent, symptomatic infection.[2,3] The inability of ABU isolates to induce a marked host response has generally been explained by a lack of virulence.[4,5] However, ABU *E. coli* strains can also actively modulate host gene expression. This prevents the induction of the host immune response, thus enhancing their persistence.[6] By modulating host gene expression, these bacteria may prevent a marked immune activation, thereby maintaining their commensal lifestyle. A deeper understanding of the mechanisms by which these bacteria modulate the host's immune response will support the development of improved strategies to treat and prevent disease-associated host responses.

E. coli adaptation to long term asymptomatic colonisation of the urinary tract involves reductive genome evolution: symptomatic uropathogens can evolve towards commensalism in human hosts by a reduction of their overall genome content, virulence gene inactivation and modification of transcriptional regulators. Extended sequencing and characterisation of ABU isolates confirmed that long term growth in the urinary tract selects for reductive evolution, including the loss or specific inactivation of virulence genes.[7] Interestingly, our genome-wide analysis of a single bacterial strain's evolution in different deliberately colonised patients led to the surprising insight that hosts personalise their colonising bacteria. Whole genome comparison of the ancestral ABU *E. coli* isolate and of its descendants after therapeutic bladder colonisation of different patients indicated a small number of mutations affecting bacterial metabolism and virulence. Transcriptome and proteome analyses of these isolates revealed unique gene expression and adaptation patterns in each patient. These results suggest that adaptive bacterial evolution is driven by individual host environments, in addition to stochastic events. Nevertheless, we need to understand how hosts personalise their microbiota and to what extent host factors affect bacterial adaptation.

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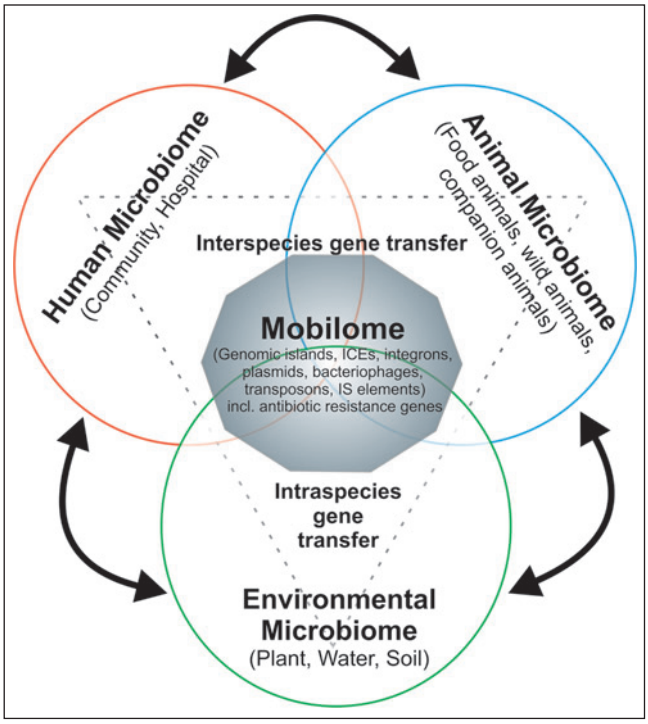
Armed for AMR

Professor Dr Ulrich Dobrindt of the Institute of Hygiene at the University of Münster discusses the evolution and spread of antibiotic resistance and calls for more holistic analyses

Antibiotic-resistant bacteria already existed in the environment before antibiotics were used in human medicine.[1] Besides promoting the development of new resistance traits, the way and extent we use antibiotics today in food production selects for existing resistant clones within microbial populations and promotes their expansion. The spread of antibiotic resistance genes and the development of multidrug resistance represent major threats to public health.[2,3]

As antibiotics are not only used in human and veterinary medicine, but also in animal food production and agriculture,[4,5] the environment plays an important role in the spread of antibiotic resistances, because it provides a multitude of relevant niches (soil, water, plants, animals) for the spread of resistance. The evolution of antibiotic resistance and the interplay of clinical and environmental bacteria is not yet well understood. In 2001, the European Council recommendation on the prudent use of antimicrobial agents in human medicine supported the idea that the occurrence of antibiotic resistance in human pathogens correlates with their occurrence in animals and the environment.[6] Against this background, the European Food Safety Authority (EFSA) has re-evaluated antibacterial products used as feed additives and their impact on resistance development to antibiotics of human and veterinary importance.[7] In 2010, 63,200 tonnes of antibiotics were used in livestock and this number is expected to increase to 105,600 tonnes in the year 2030.[8] It is easy to understand this excessive use of antibiotics promotes the emergence of antibiotic resistant pathogenic as well as commensal bacteria.



Defining future trends

This process is a major concern not only for animal, but also for human health, as some of these bacteria have zoonotic potential or serve at least as a reservoir for resistance genes, which can be transferred to other bacteria including human pathogens. Based on a recent decision of the European Commission regarding the monitoring of antimicrobial resistance in zoonotic and commensal agents in food-producing animals and meat, the detection of changes in antibiotic resistance patterns in animal populations should help define future trends in the occurrence of antimicrobial resistance.[9]

So far, attempts to prevent or counteract the occurrence and spread of antibiotic resistance in food animals were mainly based on a reduction of antibiotic use in food production. As a consequence, the use of antibiotics as growth promoters has been banned in the European Union.[10] However, this decision has several unexpected consequences, such as an overall negative impact on animal health, animal morbidity and increased levels of certain pathogens in livestock, which was considered to be associated with increased numbers of food-borne infections in the EU.[11] The biggest problem associated with the ban of antibiotics as growth promoters is the observed concomitant increase of therapeutic use of antimicrobial substances in animal production. Compared with the situation before the ban, the total amount of antibiotics used in conventional livestock breeding increased in some countries.[11] As the demand for animal products will constantly rise due to the growing human population, this calls for further improved knowledge regarding the emergence and spread of antibiotic resistance traits in order to develop strategies to counteract antibiotic resistance.

Microbial antibiotic resistance traits and individual mobile genetic elements (MGEs), on which resistance determinants are frequently located, have been intensively studied regarding the spread of antimicrobial drug resistance. However, the composition and dynamics of the global bacterial mobile gene pool in a given niche (humans, animals) or the environment, the so-called 'mobilome', has not been comprehensively studied so far. The mobilome consists of MGEs, including plasmids, bacteriophages, genomic islands (GEIs), integrative and conjugative elements (ICEs), integrons, and transposons. These MGEs can frequently carry antibiotic resistance genes and serve as vectors for the lateral dissemination of antibiotic resistance determinants between microbes. Among MGEs, plasmids, which can carry (multiple) resistance determinants, are among the most important vehicles for the spread of antibiotic resistance. In

order to better understand the constraints and driving forces of horizontal gene transfer (HGT), we have to determine the molecular basis of the bacterial host range of resistance plasmids, the contribution of environmental conditions to the transfer efficiency of such plasmids and the impact that resistance plasmid carriage has on the fitness and competitiveness of the recipient hosts.

Strengthening the holistic view

The uptake and exchange of bacteria between the environment, animals and humans increases the diversity and dynamics of the mobilome. In the wake of metagenomic analyses, the prevalence of antibiotic resistance genes in the commensal microbiota as well as compositional changes of the microbiota are more and more in the research focus. Recent analyses indicate that resistance genes are widely distributed in the intestinal gut microbiota of healthy individuals.[12-14] Accordingly, the detailed analysis of the intestinal mobilome, not only in humans, but also in companion and food animals is critical for our understanding of the spread of antibiotic resistance as well as for relevant preventive approaches.[14-17]

Although we are slowly beginning to elucidate (i) the impact of antibiotics on the composition of the microbiota and environmental microbial communities and (ii) the relevance of certain compositional changes of the microbiota regarding its impact on human health, our knowledge of the resistance mobilome in general, the interplay between different mobilome components and different members of the intestinal microbiota or environmental microbial communities is still limited.[15,16,18-20]

Accordingly, in order to improve tracking of antibiotic resistance, food safety and preventive as well as therapeutic health measures, we have to strengthen more holistic approaches including studies of the diversity, dynamics and evolution of antibiotic resistance genes and their vectors together with compositional analyses of their reservoirs in the environment, food animals and the human population.

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