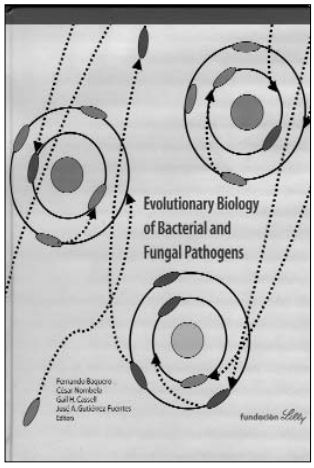

Evolutionary biology of bacterial and fungal pathogens

FERNANDO BAQUERO, CÉSAR NOMBELA, GAIL H. CASSELL, JOSÉ A.GUTIÉRREZ-FUENTES (EDS.)

2007, ASM Press, Washington, DC
622 pp, 22 × 29 cm
Price: US$ 119.95
ISBN: 978-1-55581-414-4

Interactions between microorganisms and humans range from a benign, even symbiotic collaboration to a form of competition that may become fatal for the host. Symbiotic indigenous microbiota colonize those regions of the human body that are in contact with the external environment, such as the skin, eyes, oral cavity, and gastrointestinal tract, in addition to some parts of the respiratory, urinary, and reproductive tracts. Despite the fact that humans are fully exposed to a wide variety of microorganisms, only certain populations are able to permanently inhabit the available body sites. In order for a microorganism to become established and thus to colonize a particular site, the environment of that site must satisfy the microorganism's nutritional and physicochemical requirements. In addition, the microorganism must be able to withstand host defenses, including various mechanical removing systems and the innate and acquired immune systems, as well as competition from the resident microbial community. At present, little is known about the mechanisms that enable the survival and long-term host tolerance of indigenous microbial communities or why these microorganisms do not elicit a damaging chronic inflammatory response. The evolutionary dynamics of host–pathogen interactions result in an ongoing process of natural selection in which there is adaptation and counter-adaptation by the two competing species. As pathogens develop new ways to avoid host recognition or elimination, host defenses must evolve in parallel to keep pace with them.

During the course of pathogen–host coevolution, there have been several infectious diseases that have notably shaped human history, especially those marked by the novel entrance into a population of a previously unknown infectious agent. Nonetheless, these opportunities seem to be limited since, among the millions of species of microorganisms (30 million species have been estimated for prokaryotes), only 1922 species of infectious agents have been recorded, of which 632 are bacteria (no archaea is known to be pathogenic), 499 helminths, 329 fungi, 145 protists, and 317 viruses and prions.

Evolutionary biology of bacterial and fungal pathogens is a multi-authored book based on a meeting organized by Fundación Lilly [www.fundacionlilly.com] in El Escorial, Madrid, in November 2004. The editors, Fernando Baquero, César Nombela, Gail H. Cassell, and José A. Gutiérrez-Fuentes (director of Fundación Lilly), have collaborated to produce an excellent textbook, introducing evolutionary biology to clinical microbiologists, infectious disease specialists, and public health professionals. The contributions of the invited authors have resulted in an impressive book of six sections comprising 49 chapters that cover topics fundamental to understanding the evolution of microbial pathogens. The book is preceded by a short Foreword by Julian Davies, who once more corroborates the dictum of the Spanish classical writer Baltasar Gracián: "Good, if it's short, twice as good".

Section I, "Evolutionary biology of microbial-host interactions" (chaps. 1–11). Bacteria gain no advantage by making their hosts ill and illness certainly confers few, if any host benefits. Virulence is a consequence of bacteria being in the wrong host, or at the wrong site in the right host. The strategies employed by bacterial pathogens, the number and nature of the virulence factors required to activate them, and the regulatory systems that control virulence gene expression are the result of coevolution between bacteria and their hosts. The emergence of a new "professional" pathogen (an organism adapted for circulation within the host population as a pathogen) from a non-pathogen is a relatively rare event, because it requires the selection of multiple adaptive changes. Each pathogen has a reservoir habitat and a virulence habitat. The reservoir habitat is defined as an environmental site, host organism or population, or specific body compartment where the pathogen can sustain itself and from where it can be transmitted to other habitats or hosts. The virulence habitat is a disease-susceptible host, or a specific compartment within that host, in which growth of the pathogen causes clinical infection, thereby inducing host damage either directly, by the production of toxic compounds, or indirectly, by provoking self-damaging host responses. Host genetic factors determine differences in host susceptibility to infection and contribute to the pattern of clinical disease. The host's immune response represents an important selective force because it creates indirect compe-

tition between pathogens by limiting the number of non-immune or susceptible hosts. Social changes, such as those arising through "globalization," and climate change are important determinants of the susceptibility to infections by different human populations.

Section II, "Evolutionary genetics of microbial pathogens" (chaps. 12–20). Evolution occurs through genetic variation and selection and is the fundamental strategy of life, allowing organisms to adapt to new environments and to adverse conditions. Variation in microbial pathogenesis is based on three mechanisms of genetic variability: point mutation, genetic rearrangements, and lateral gene transfer. Genomics and genome sequencing studies have corroborated that the position of genes in the chromosome (or genophore) is not random but is a result of selection. The relative positions of genes may influence their expression, mutational bias, and rearrangement, as well as paralogous gene evolution and the reductive evolutionary process. Besides its "original" set of genes, the genome of a bacterium may contain other elements from other bacteria: genomic islands, plasmids, and bacteriophages.

Some virulence determinants are clustered in pathogenicity islands acquired by horizontal gene transfer from another, unknown bacterial species. Genomic islands are parts of the genomes of many bacteria, pathogenic as well as non-pathogenic, and pathogenicity islands were the first group of genomic islands to be described. In addition, many bacteria harbor extrachromosomal elements in the form of plasmids that carry genes conferring a selectable phenotypic character under specific niche conditions. Finally, bacteriophages (prophages), present in both pathogenic and non-pathogenic strains, shape bacterial evolution in that they are ideal carriers for horizontal DNA transfer. Based on our current understanding, ~12% of the *Escherichia coli* chromosome consists of phages, with 51 different functional prophages identified in 27 *E. coli* strains. Incorporation of external genomic elements gives rise within a population to clones with different pathogenicities. Such pathogenic clones are responsible for disease outbreaks and increases in bacterial infection frequencies. These observations have important implications for our understanding of infectious diseases and the public health measures required to reduce their detrimental and potentially devastating effects on society.

Section III, "Evolutionary biology of drug resistance" (chaps. 21–28). Antibiotic resistance is not only a clinical problem but also a unique opportunity to observe "evolution in real time." Antibiotic resistance may be regarded as the paradoxical consequence of successful antibiotic therapy. Antibiotics were initially developed for the treatment of bacterial infections in humans, but their miraculous effects quickly led to their use in other animals and in plants. Antibiotics are used both internally and externally, maintaining the health of people, animals, and agricultural crops, and have vastly changed the relationships between bacteria and humans. Today, we are witnessing another change—in the relationships among bacteria themselves. Almost as soon as it was known that certain substances could kill microorganisms, it was also recognized that some microorganisms could survive normally lethal doses of these same agents. The first clinical report of acquired resistance to an antimicrobial agent was published in 1937, when Crean, a naval genitourinary specialist, reported in *The Lancet* that six of 100 patients with gonorrhea were unresponsive to treatment with sulfonamides. Reports of resistance to penicillin appeared in 1941, and to streptomycin in 1946. The term ''antibiotic resistance'' soon acquired a notorious meaning. Traditionally, it was thought that exposure of bacteria to antibiotics caused the selection of pre-existing resistant variants, but it seems that, under certain conditions, an antibiotic may also increase the mutation rate of a bacterial population (hypermutable strains or mutators). Mutators increase the probability of favorable mutations and they can accelerate the evolutionary rates of resistant variants that become fixed in the population.

Sections IV–VI, "Evolutionary pathogenicity of gram-negative and gram-positive bacteria and of fungi (chaps. 29–49). Although a wide range of microorganism–host relationships can ultimately lead to disease, the two most general strategies used by pathogenic microorganisms are aggressive "frontal" assaults and "stealth" assaults. Typically, frontal assault strategies require that the infecting microorganism rapidly replicates, induces disease symptoms that overwhelm the innate defenses of the host, and then find a new host before engagement of the latter's "adaptive"' or "acquired" immune system, in which antigen-specific lymphocytes respond to antigen exposure. These microorganisms typically produce toxins or effector proteins that disrupt the normal function of the host cell. Stealth assaults, by contrast, typically involve a slower infection process, in which the microorganism subverts the host's innate and adaptive immune systems to set up a chronic or persistent infection. This section of the book includes a description of the pathogenic traits characteristic of several species of bacteria and fungi pathogens.

A major goal of *Evolutionary biology of bacterial and fungal pathogens* as a whole is to convey the idea that bac-

teria undertake similar forms of microbial variation in different habitats. The main distinction is that the habitat of a "natural" microorganism is the abiotic environment, while that of a pathogen is another living organism—the (human) host. Pathogens, but also non-pathogenic bacteria, harbor genetic elements that contribute to fitness adaptations in different environments. Microbial infections of humans are a relatively recent interaction, whereas the genetic and biochemical functions necessary for invasion and infection of the "modern host" probably evolved in an ancient environment from cell to cell interactions between microbes and protists or small invertebrates. As such, bacterial virulence factors have not evolved merely to cause disease in humans; rather, they are part of a general mechanism to coexist with, to cover, or to penetrate eukaryotic cells.

A significant and practical aspect of the book is its Glossary, which covers most of the evolutionary microbiology terms used in the book. Not only specialists but also advanced students will quickly find that the book is an essential part of any library of microbiology or related sciences. Moreover, microbiologists, and not only those active in the health sciences or field of infectious disease, will enjoy the opportunity to learn more about the natural history and evolution of "bad" microorganisms. As noted in the Foreword by Julian Davies, "All microbiology is environmental microbiology and has been for billions of years." Accordingly, pathogens can only be efficiently fought if we employ the knowledge developed by eco-evo approaches. Although the evolutionary origins of the relationships between prokaryotes and eukaryotes remain to be elucidated, we at least know the context in which they must be understood. As Francis Bacon wrote in *Advancement of Learning*: "If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties."

RICARDO GUERRERO
University of Barcelona
rguerrero@iec.cat