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## Microbial pathogenesis

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The last two decades of the nineteenth century marked a period of true revolution, in which the foundations were laid for the development of microbiology as a scientific and medical discipline. It was during these years that most of the major bacterial agents of infection known today were discovered. Deadly bacteria such as pneumococci and meningococci, and the agents of typhoid fever, cholera, tuberculosis, tetanus, gas gangrene, bacillary dysentery and plague, were all isolated between 1880 and 1898. If we consider that only a few years before Louis Pasteur had proved that the theory of spontaneous generation was incorrect (1860), and that Robert Koch, in his studies of anthrax in cattle and sheep, had experimentally confirmed the germ theory of contagious disease (1876), we can realise that in a relatively short period of time there was a major qualitative leap in human knowledge and medical science. A century later, there can be no doubt that we are facing an analogous revolutionary situation which will have consequences on a similar scale for the future of microbiology, medicine and biological science in general.

The formal start of the new revolution dates back to the 1970s, with the development of molecular genetics and genetic engineering, but it did not really get going until the 1980s, when recombinant DNA technology began to be applied systematically to the study of the biology of microorganisms. This revolution has been boosted by the very recent development of genomic research, which is leading to another qualitative leap of enormous significance in the evolution of microbiological knowledge. Indeed, having available the complete sequence of the genome of a microorganism makes it possible to pass from a reductionist approximation, involving the isolated analysis of a particular gene locus and its function, to a holistic approach, in which the entire microbial physiology and the evolutionary process underlying it can be deciphered based on the information encoded in the DNA. The complete genome sequences of 20 microbes have already been determined, another 80 microbial genomes are currently being sequenced, and the trend is towards continual, exponential increase in the number of genomes available for study. We are currently

unable to predict any function for some 30% of the putative genes present in the sequenced genomes, which shows that we are still far from understanding, in functional terms, many aspects of the biology of microorganisms. Clearly, the years to come will define a post-genomic era in which emphasis will be placed on the development of instruments and technologies for the systematic functional analysis of the overwhelming mass of genetic information that will be available for study and exploitation.

The introduction of DNA techniques into the study of pathogenic microorganisms opened the way to the molecular analysis of virulence. The concomitant development of cell biology and the progressive application of its experimental approaches to the study of the interactions between microorganisms and host cells have made it possible, in this last decade of the millennium, to start elucidating the molecular and cellular mechanisms involved in the development of infectious disease. The rapid and significant accumulation of knowledge in this domain has led to the establishment of molecular microbial pathogenesis as a new scientific discipline that is now studied as an independent subject in many universities. A clear indicator of the relevance of this emerging scientific field is that 64% of the 113 microbial genome sequencing projects currently recognised by the TIGR database concern infectious agents. Therefore, once again, the investigation of pathogenic microorganisms is driving the progress in life sciences.

The development of molecular microbial pathogenesis and the advent of the new microbiological revolution based on genomic research coincide, at the end of this century, with a radical change in the panorama of transmissible diseases and the perception of their importance. We are now much less confident of being able to cope with the infectious agents with which we are faced because we are increasingly being deprived of a major weapon against them: antibiotics. The selective pressure resulting from the extensive use of these therapeutic agents over the last 50 years is disseminating resistance genes among pathogenic microorganisms in such a way that we are now at serious risk of suffering intractable, life-threatening infections. This is no fiction, it is the

simple truth. For example, multi-drug resistant clones of *Mycobacterium* have caused outbreaks of tuberculosis with no possibility of effective treatment, resulting in the death of the infected individuals. Also extremely alarming is the progressive emergence of resistance to vancomycin, the last resort for treating nosocomial infections with enterococci and staphylococci resistant to the usual antibiotics. This situation, together with the constant emergence of new infectious agents, and the re-emergence of others that were thought to have been banished forever, constitutes a clear threat that infectious diseases will once again become the principal cause of death and morbidity. The only way in which we can successfully deal with this situation is to move from empiricism to rationalism in the design and development of new weapons in the war against infection. The understanding of the most intimate molecular mechanisms of the pathogen–host interaction might enable us to identify microbial functions required for pathogenesis or disease transmission that can be specifically targeted by new medicines and vaccines. This is only possible if enough basic knowledge is generated by research in the field of microbial pathogenesis.

Being aware of the importance of this scientific domain and the necessity of promoting it in Spain, a monograph entitled “Molecular Pathogenesis of Bacterial Infections” was published in *Microbiología SEM* (vol. 12[2], June 1996), the former journal of the Spanish Society for Microbiology (SEM). Most of the articles in this monograph were based on the talks presented at an international summer school on bacterial virulence and pathogenic mechanisms that was organized by one of us (J.A. V.-B.) in collaboration with Jesús Navas at Laredo (Cantabria, Spain). The positive way in which it was received has led us to repeat the experience three years later, this time in *INTERNATIONAL MICROBIOLOGY*, the revamped journal of SEM. Some of the papers included in this new monograph are contributions to an international conference entitled “Molecular Mechanisms of Microbial Pathogenicity”, held in June 1998 at Complutense University of Madrid.

During this three-year interval a series of discoveries have significantly improved our understanding of the mechanisms of microbial virulence. One is the concept of pathogenicity islands, used to define those regions of the bacterial genome, usually large in size, that are present exclusively in pathogenic strains and that cluster together a variable number of virulence genes required for infection and illness. These are often unstable and contain genes or remnants of genes encoding integrases and transposases, or parts of the genome of bacteriophages incorporated into the bacterial chromosome, indicating that they were acquired as “virulence cassettes” by horizontal transfer from other bacteria. Thus, we are beginning to develop precise ideas about the way in which bacteria became pathogenic and how virulence evolves in bacterial populations to give rise to new pathogenic variants. One of the articles in this issue (E. Carniel) deals with the “high-pathogenicity island” of *Yersinia*, which is also present in other enterobacteria and comprises a group of genes involved in the biosynthesis, transport and regulation of a siderophore required for iron capture in the tissues of the host. Two other articles also turn round the pathogenicity island concept. One such article

(E. García et al.) deals with the highly variable gene clusters involved in the biosynthesis of the various types of the polysaccharide capsule, a major virulence factor in pneumococci. The other (R. Rotger and J. Casadesús) deals with the virulence plasmids involved in extraintestinal dissemination of some serotypes of *Salmonella*.

Of equal significance is the discovery that toxins and other bacterial products specifically modify small G-proteins, such as Rho, which regulate important cell processes. This aspect is illustrated by an article on bacterial protein toxins that alter cytoskeletal functions (J-F. Richard et al.). This and other findings (such as the capacity of *Listeria* to spread in host tissues using a propulsion system based on the induction of actin polymerisation; see the review by J. Wehland and U.D. Carl published in *INTERNATL. MICROBIOL.* 1:1–18, 1998), have demonstrated the sophisticated co-evolution of pathogenic bacteria and eukaryotic cells, and have contributed to the creation of a new scientific discipline called cellular microbiology, that has recently emerged from microbial pathogenesis.

This issue also includes three interesting reviews on the molecular mechanisms of virulence of the major human pathogens *Neisseria meningitidis* (X. Nassif), *Bordetella pertussis* (C. Loch) and *Legionella pneumophila* (Y. Belyi). Finally, we have also included a paper about the invasion mechanisms of the *Plasmodium* sporozoite (A. Sultan, from V. Nussenzweig’s laboratory in New York). Since protozoan parasites interact with essentially the same structures, compartments and immune effectors of the host as bacterial pathogens, these different microparasite organisms may have strategies in common for causing infection. Comparative studies of these strategies may therefore help us to extract general principles, improving our understanding of the mechanisms of microbial pathogenesis.

The articles in this issue provide a snapshot of the state of the art, an appraisal of current knowledge about the molecular mechanisms of microbial pathogenicity. One hundred years after the microbial nature of transmissible disease became clear, we just start to understand properly the details of how pathogenic microorganisms colonise and survive in host tissues. With the explosion of the genomic revolution, the perfecting of tools for the functional analysis of microbial genomes and the development of new experimental models for studying the process of infection in vivo, it is highly likely that in the first few years of the 21st century there will be a rapid series of major and exciting discoveries and advances in the field of microbial pathogenesis and its biotechnological and therapeutic applications.

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