Pathogenomics

Genome Analysis of Pathogenic Microbes

Edited by
Jörg Hacker and Ulrich Dobrindt

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Foreword

The determination of the genome sequences of many prokaryotic and eukaryotic organisms, together with the high-throughput techniques (transcriptomics, proteomics, metabolomics, interactomics, etc.) and the powerful tools of bioinformatics, have opened up to us all new perspectives for the deeper understanding of the basic mechanisms of life.

Because of the small size of bacterial genomes and the collinearity of their genetic information, prokaryotes are particularly suited to genome-based in-depth analysis of the essential processes which allow these microorganisms to survive and replicate in many different environments. Some of them can even multiply in those parts of the human body which are normally well protected by highly developed antimicrobial defense mechanisms. This latter property is the most outstanding evolutionary achievement of microbial pathogens that are capable of causing infectious diseases in humans.

The present monograph summarizes the state of genome-based research on some of the most important bacterial (and to a lesser extent viral and fungal) human pathogens today. The term pathogenomics has been coined for this new branch of microbiology. Not surprisingly, the major focus of pathogenomics was first on those human bacterial pathogens that (a) can cause major epidemics, especially in developing countries (e.g., *Shigella* spp. or *Vibrio cholerae*); (b) represent major health problems in almost all human societies in the form of food contaminants and/or agents of nosocomial infections (e.g., pathogenic *Enterobacteriaceae*, staphylococci, and streptococci); and (c), due to their frequent occurrence in humans (e.g., *Helicobacter pylori* and *Mycobacterium tuberculosis*) represent life-threatening problems not only for many people in developing countries, but also for immune-compromised and elderly persons in all the industrialized countries. These microorganisms therefore also represent the major objects described in this book.

A primary goal of pathogenomics is to use the new experimental tools in combination to unravel those genes – and gene arrangements – of pathogens that are essential for causing disease, and thereby to shed new light on the evolution, interbacterial gene transfer, and distribution of these virulence genes among bacterial populations. This area of pathogenomics, which is already highly advanced, makes up the largest part of this monograph.

The other, certainly not less important goal is to study the functional significance of the pathogen-specific genes in the infection process. In the years to come, the enormous amount of genetic information that has piled up in the last 10 years from the sequencing of the genomes of most of the important bacterial pathogens (and their closely related nonpathogenic environmental counterparts) will need to be functionally analyzed. It is anticipated that this functional pathogenomics will finally unravel the mechanisms of differential and coordinated regulation of the virulence genes, the structural, molecular, and physiological functions of their gene products, which will lead to a more comprehensive view on the pathogenic microorganisms. Some aspects of this most interesting future line of microbial research that can be expected to become the mainstream in future pathogenomics are already addressed in some of the chapters of this book.

Infections are the outcome of the encounter between the microbial pathogen and its host. Describing microbial infections in molecular terms therefore requires among other things a profound understanding of the host cell responses. The availability today of the genome sequences of man and some of the major model hosts in which microbial infections can be experimentally studied (the mouse in particular, but also alternative hosts such as amebae, the nematode *Caenorhabditis elegans, Drosophila melanogaster,* or the slime mold *Dictyostelium*) together with the new genetic and bioinformatics tools open up new avenues towards uncovering at least some of the basic host cell responses.

Whilst cellular microbiology has already delivered an enormous set of valuable host-response information at the cellular level, the new *in vivo* imaging techniques, siRNA technology, and the routine genetic manipulations of some of the abovementioned model hosts may now allow such molecular infection studies to be performed in real hosts. This monograph devotes several chapters to this important aspect of pathogenomics.

Science and, especially, the public and political worlds expect pathogenomics to provide novel ideas and strategies to combat infectious diseases through the rational design of better diagnostic tools and novel anti-infectives and vaccines. Indeed, some promising new developments deriving from pathogenomics are already visible and are in part outlined in some chapters of this monograph. These new approaches will most undoubtedly help in fighting the most dangerous infectious agents which still claim the highest death toll in mankind. However, scientists should be modest in their promises relating to the possibilities that arise from this exciting new field of science, since one major lesson which the attentive and critical reader of this monograph will quickly learn is the enormous genetic flexibility and adaptation potential of pathogenic microorganisms – and that means they will keep us busy for decades to come despite all the obvious successes of pathogenomics.

The book thus offers a representative view of the present state of the art in the new research area of pathogenomics. It is a valuable and reasonably comprehensive source of information for scientists and advanced students who wish to become acquainted with this most exciting field of modern microbiology.

Würzburg, October 2005 *Werner Goebel*

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Preface

In the year 1995, the first full genome sequence of a free-living-organism, the bacterium *Haemophilus influenzae* strain Rd, was published. This publication, which appeared in the journal *Science*, represented the starting point for a new field in molecular biology called genomics. Today, 10 years later, complete genome sequences of almost all the major pathogenic microbes have been determined. As a consequence, a new discipline has arisen, which has been named "pathogenomics." As the name implies, pathogenomics is the analysis at the genomic level of the processes involved in bacterial pathogenesis caused by the interaction of pathogenic microbes and their hosts.

The present volume is the first handbook to be entirely devoted to the newly established discipline of pathogenomics. We are very grateful to our colleagues for their input, especially those associated with the German Pathogenomics competence network, established by the German Federal Ministry of Science and Education to analyze pathogenic microbes at the genomic level. Werner Goebel in particular – the network's speaker, who contributed the Foreword to this book's preface – has influenced the entire discipline with his spirit and his vision.

Our thanks are due to the staff at Wiley-VCH, most notably Andrea Pillmann, who encouraged us to put this book together. We are also very grateful to all our authors for their contributions to this important project.

Würzburg, September 2005 *Ulrich Dobrindt, Jörg Hacker*

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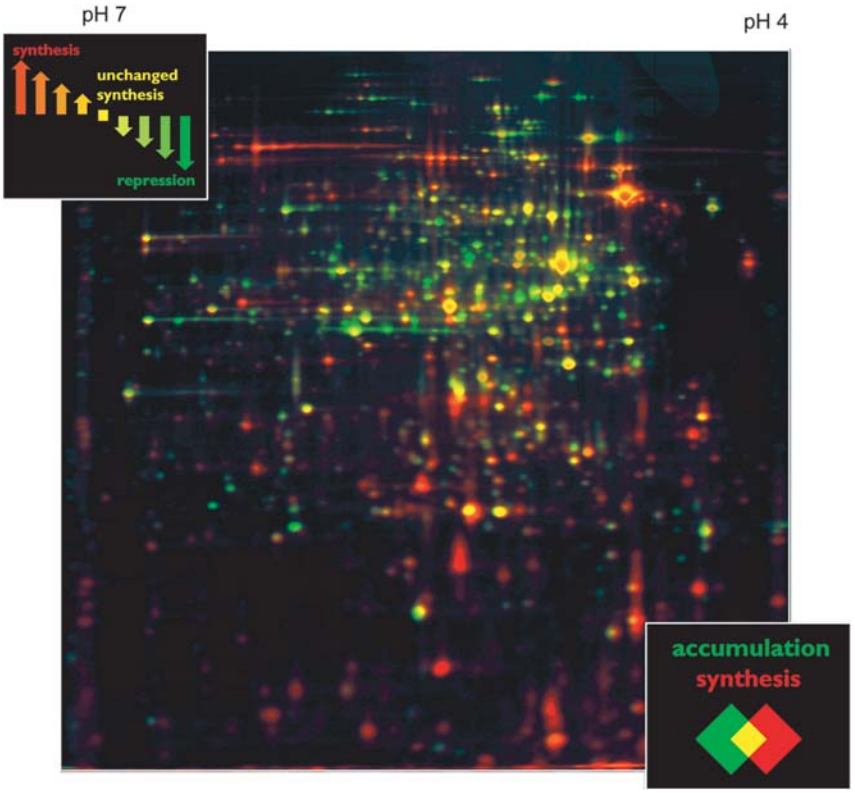

Fig. 3.2 Protein pattern of heat-shocked *B. subtilis* cells. During exposure to heat shock (37–to 48 °C), *B. subtilis* cells were pulse-labeled with ^{35}S-L-methionine. After the separation of crude protein extract by 2-D gels, the proteins were visualized by silver staining and the protein synthesis rate was determined by phosphoimaging. The two images were overlaid with the aid of the Delta-2D software package (dual-channel imaging technique [11]; Decodon, Greifswald, Germany). The red-labeled proteins form the heat stress stimulon. (This figure also appears on page 48.)

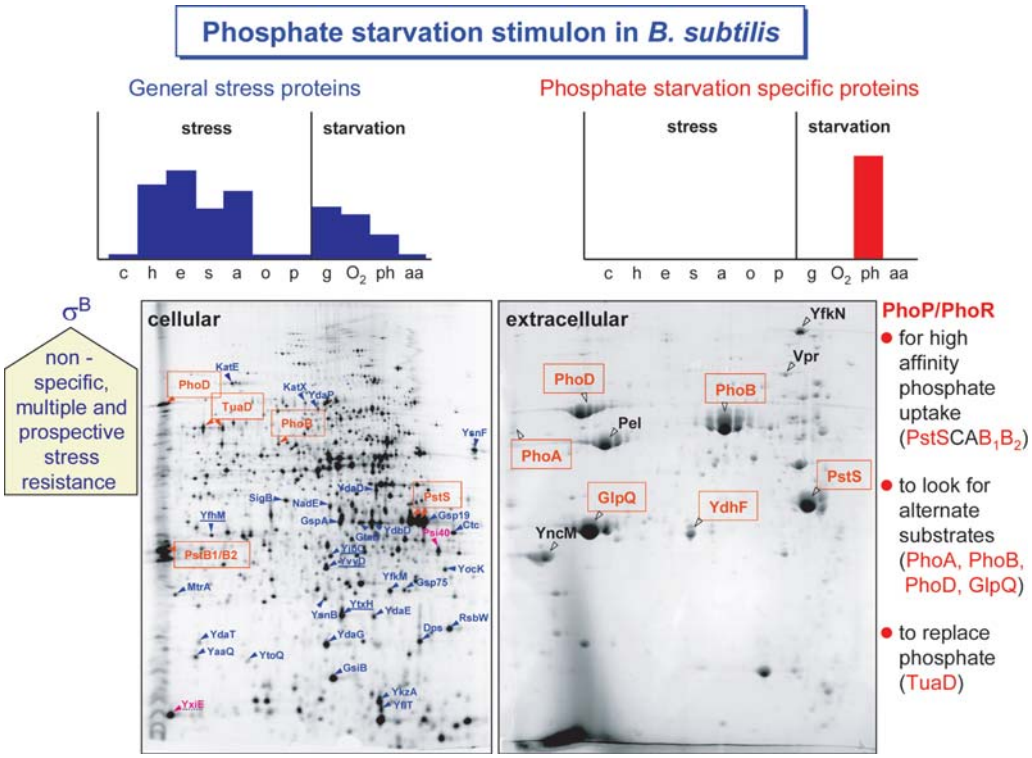

Fig. 3.4 The phosphate starvation stimulon of *B. subtilis* consists of both general stress proteins also induced by phosphate starvation (σ^B regulon, σ^B-dependent proteins marked in blue) and starvation-specific proteins (PhoR regulon, marked in red). The stress/starvation induction profile of both groups and the functions of the proteins are indicated. C, control; h, heat stress; e, ethanol stress; s, NaCl stress; a, pH 5.5; o, oxidative stress (H_2O_2); p, puromycin; g, glucose starvation; O_2, oxygen starvation; ph, phosphate starvation; aa, amino acids starvation. (This figure also appears on page 50.)