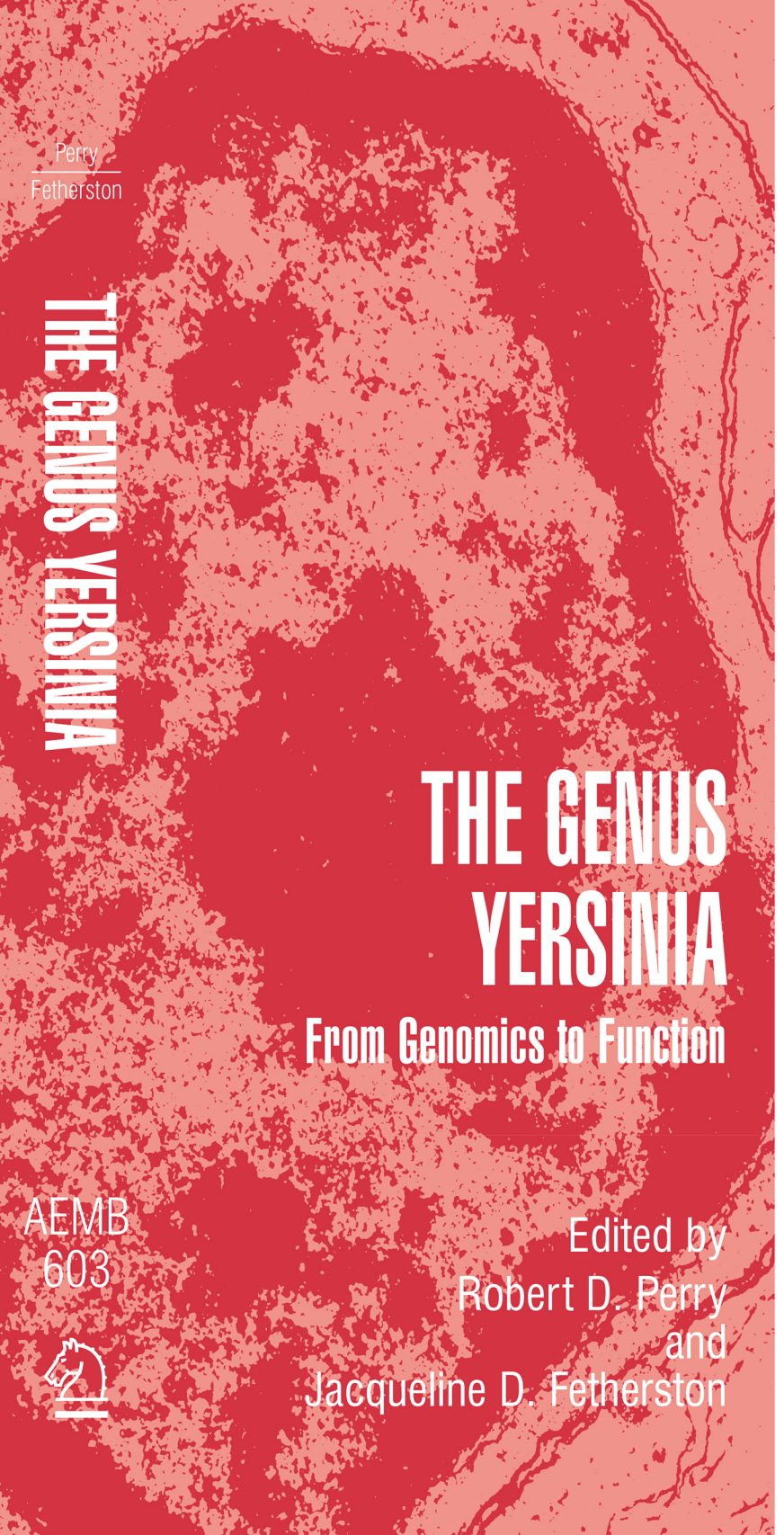

THE GENUS YERSINIA

From Genomics to Function

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Edited by
Robert D. Perry
and
Jacqueline D. Fetherston

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 603

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Preface

Picture 1. Logo for the 9th International Symposium on *Yersinia.* Logo design by Cesar Ibanez, Web Designer, American Society for Microbiology.

The 9th International Symposium on *Yersinia* was held in Lexington, Kentucky, USA on October 10-14, 2006. Over 250 *Yersinia* researchers from 18 countries gathered to present and discuss their research. In addition to 37 oral presentations, there were 150 poster presentations. This Symposium volume is based on selected presentations from the meeting and contains both reviews and research articles. It is divided into six topic areas: 1) genomics; 2) structure and metabolism; 3) regulatory mechanisms; 4) pathogenesis and host interactions; 5) molecular epidemiology and detection; and 6) vaccine and antimicrobial therapy development. Consequently, this volume covers a wide range of current research areas in the *Yersinia* field.

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A number of companies and institutions generously supported the symposium: Battelle, Fisher Scientific, Pfizer, the Great Lakes Research Center for Excellence in Biodefense (GLRCEB), the Southeastern Research Center for Excellence in Biodefense (SERCEB), and the University of Kentucky. The Symposium could not have been held without their support.

Practical organization of the meeting was professionally performed by the American Society for Microbiology, Department of Meetings and Industry Relations – a special thanks go to Traci Williams and Evangelos Koutalas for their efforts and organizational skills.

Andrey Anisimov kindly provided many of the photographs from the meeting that are in this volume.

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Picture 2. Luther Lindler introduces the Genomics Session. Photo by A. Anisimov.

Picture 3. Andrey Anisimov, Yuriy Knirel, Valentine Fedorova, Rima Shaikhutdinova, and Svetlana, Dentovskaya at the posters. Photo from A. Anisimov.

1
Comparative Genome Analyses of the Pathogenic Yersiniae Based on the Genome Sequence of *Yersinia enterocolitica* Strain 8081

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Abstract. This chapter represents a summary of the findings from the *Yersinia enterocolitica* strain 8081 whole genome sequence and the associated microarray analysis. Section 1 & 2 provide an introduction to the species and an overview of the general features of the genome. Section 3 identifies important regions within the genome which highlight important differences in gene function that separate the three pathogenic *Yersinia*s. Section 4 describes genomic loci conferring important, species-specific, metabolic and virulence traits. Section 5 details extensive microarray data to provide an overview of species-specific core *Y. enterocolitica* gene functions and important insights into the intra-species differences between the high, low and non-pathogenic *Y. enterocolitica* biotypes.

1.1 Introduction

Yersinia enterocolitica represents a key link in our understanding of how the pathogenic members of the *Yersinia* genus have evolved to produce diverse clinical manifestations. The disease potential of the human pathogenic *Yersinia* ranges from gastroenteritis for *Y. enterocolitica* and *Yersinia pseudotuberculosis*, which are primarily enteropathogens, to bubonic plague caused by *Yersinia pestis* (Perry and Fetherston 1997). It is estimated that *Y. enterocolitica* and *Y. pseudotuberculosis* diverged within the last 200 million years and that *Y. pestis* is a clone of *Y. pseudotuberculosis* that has emerged within the last 1,500–20,000 years (Achtman et al. 2004; Achtman et al. 1999; Wren 2003).

Since splitting from *Y. pseudotuberculosis, Y. enterocolitica* has evolved into a genetically and biochemically heterogeneous collection of organisms that has been divided into six biotypes differentiated by biochemical tests (1A, 1B, 2, 3, 4 and 5) (Wauters et al. 1987). These *in vitro* biotypes can be placed into three distinct lineages based on pathogenic potential: a mostly non-pathogenic group (biogroup 1A); a weakly pathogenic group that is unable to kill mice (biogroups 2 to 5); and a highly pathogenic, mouse-lethal group (biogroup 1B) (Mcnally et al. 2004; Prentice et al.

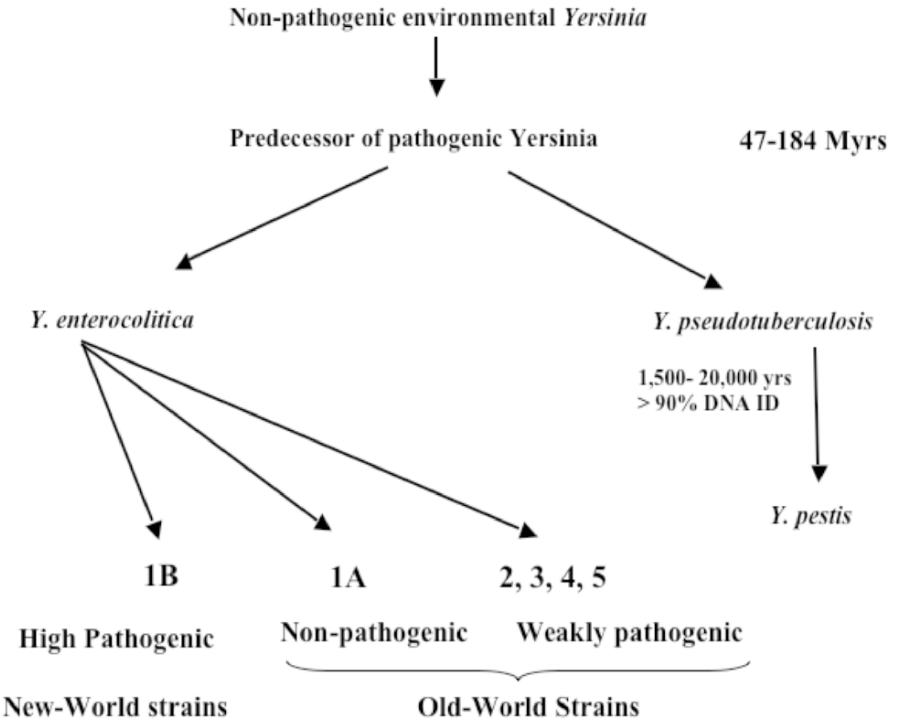

Fig. 1. A basic model describing the evolution of the pathogenic *Yersinia* (adapted from (Wren 2003)).

1991; Van Noyen et al. 1981; Wauters et al. 1987). These biogroups also form geographically distinct groups with biotype1B being most frequently isolated in North America (termed the 'New-World' strains), whereas biogroups 2-5 predominate in Europe and Japan (termed the 'Old-World' strains) (Schubert et al. 2004) (Fig. 1).

Representatives of the two other human pathogenic *Yersinia* species, *Y. pseudotuberculosis* strain IP32953 (referred to as *Y. pseudotuberculosis*), and *Y. pestis* (strains CO92 [biovar Orientalis], KIM10+ [biovar Mediaevalis], and 91001 [biovar Microtis]), have been sequenced (Chain et al. 2004; Deng et al. 2002; Parkhill et al. 2001; Song et al. 2004). Consequently, the three pathogenic *Yersinia* represent an ideal genus to study bacterial pathogenesis and the evolution of virulence (Wren 2003).

In this chapter we have condensed the whole genome sequence analysis of *Y. enterocolitica* strain 8081 biotype 1B (serotype 0:8). We provide examples of ancestral gene functions which appear to have been lost following the divergence of the pathogenic *Yersinia* from their last common ancestor. In addition, we have high-

lighted regions that appear to have been acquired by *Y. enterocolitica* strain 8081 and define it at the species through to the strain level. For a more complete analysis of the 8081 genome sequence and its comparative analysis to other *Y. entrocolitica* strains refer to (Thomson et al. 2006) and (Howard et al. 2006).

1.2 *Y. enterocolitica* 8081 Chromosome

The characteristics of the *Y. enterocolitica* chromosome are very similar to those of *Y. pestis* and *Y. pseudotuberculosis* (Table 1). The most notable differences lie in the numbers of insertion-sequence (IS) elements. Although *Y. enterocolitica* possesses fewer in total than the other yersiniae, their diversity is greater with 15 IS families in *Y. enterocolitica* compared to 4 and 5 in *Y. pseudotuberculosis* and *Y. pestis* (CO92), respectively.

Y. enterocolitica also possesses far fewer pseudogenes than *Y. pestis,* which is thought to have >140 (Parkhill et al. 2001). The recent expansion of a few types of IS element in *Y. pestis* and the accumulation of so many pseudogenes is thought to reflect a marked change in lifestyle (associated with specific plasmid-acquisition events) (Chain et al. 2004; Parkhill et al. 2001). Conversely, this also implies that *Y. enterocolitica* and *Y. pseudotuberculosis* have been stably maintained in a consistent niche.

Although general characteristics of the *Y. enterocolitica* genome are similar to those of *Y. pseudotuberculosis* and *Y. pestis*, these figures disguise considerable

Table 1. Properties of all the published *Yersinia* genomes

Property	Y. enterocolitica 8081	Y. pestis CO92[a]	Y. pestis KIM10+[b]	Y. pestis 91001[c]	Y. pseudotuberculosis IP32953[d]
Size	**4,615,899**	**4,653,726**	**4,600,755**	**4,595,065**	**4,744,671**
G+C content	**47.27%**	**47.64%**	**47.64%**	**47.65%**	**47.61%**
Number of CDSs	**4,037**	**4,012**	**4,198**	**4037**	**3,974**
Coding density	**83.8%**	**83.8%**	**86%**	**81.6%**	**82.5%**
Ave. gene size	**968 bp**	**998 bp**	**940 bp**	**966 bp**	**998 bp**
rRNA operons	**7**	**6**	**7**	**7**	**7**
tRNA	**81**	**70**	**73**	**72**	**85**
Pseudogenes[e]	**67**	**149**	**54**	**141**	**62**
IS elements	**60**	**139**	**122**	**109**	**20**
Prophage regions	**4**	**4**	**3**	**ND**	**5**

[a](Parkhill et al. 2001), [b](Deng et al. 2002), [c](Song et al. 2004), [d](Chain et al. 2004), [e]Figures taken from original publication. ND - not determined. Taken from (Thomson et al. 2006).

variation in gene repertoire. A comparison of orthologous gene sets shared between *Y. enterocolitica, Y. pestis* (strain CO92), and *Y. pseudotuberculosis* (Fig. 2) showed a core set of 2,747 CDSs shared by all, as well as a significant number of CDSs being unique to *Y. enterocolitica* (~29%)*, Y. pseudotuberculosis* (~9%), or *Y. pestis* (~11%).

Perhaps the biggest surprise from the genome was the number of CDS's shared exclusively between *Y. enterocolitica* and either *Y. pseudotuberculosis* or *Y. pestis*.

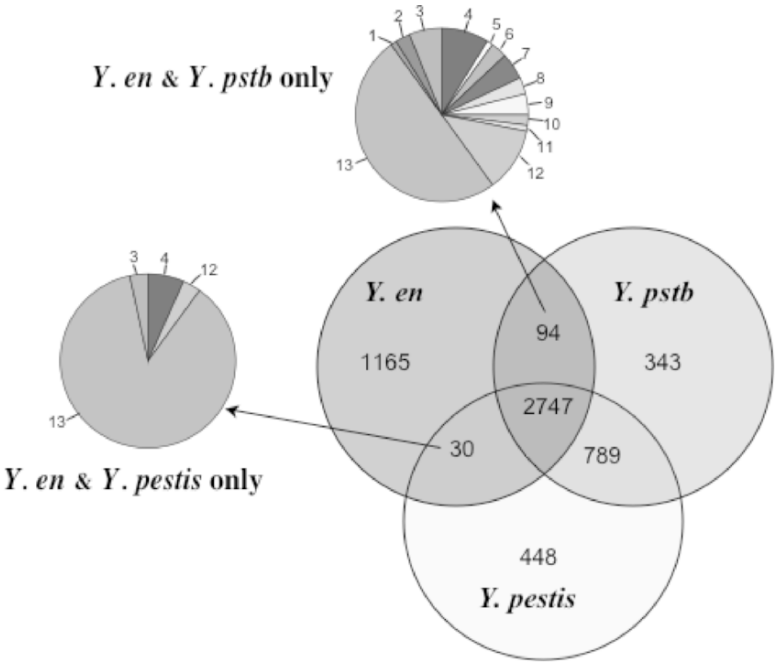

Fig. 2. Distribution of orthologous CDSs in *Y. enterocolitica* 8081, *Y. pestis* CO92, and *Y. pseudotuberculosis* IP32953. The Venn diagram shows the number of genes unique or shared between two other *Yersinia* species. The associated pie charts show the breakdown of the functional groups assigned for CDSs in relevant sections of the Venn diagram. Number code for the pie charts is as follows: pathogenicity and virulence [1]; general regulation [2]; and miscellaneous function [3]; conserved hypothetical proteins [4]; chemotaxis and motility [5]; protective responses [6]; transport and binding proteins [7]; adaptations to atypical conditions [8]; synthesis and modification of macromolecules [9]; central intermediary metabolism [10]; energy metabolism [11]; periplasmic/exported/lipoproteins [12]; laterally acquired (including prophage CDSs) [13]. *Y. en, Y. enterocolitica* strain 8081; *Y. pstb, Y. pseudotuberculosis* strain IP32953; *Y. pestis, Y. pestis* strain CO92.