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Edited by Brian Henderson, Petra C. F. Oyston
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Bacterial Evasion of Host Immune Responses

Our survival as multicellular organisms requires the constant surveillance of our internal and external (mucosal) environments by the multifarious elements of the innate and acquired systems of immunity. The objective of this surveillance, expensive as it is to the organisms, is to recognise and kill invading microorganisms. Over the past fifty years the cells and mediators involved in our immune defences have been painstakingly identified. However, it is only relatively recently that the ability of microorganisms to evade immunity has been recognised and investigated. *Bacterial Evasion of Host Immune Responses* introduces the reader to the mechanisms used by bacteria to evade both humoral and cellular immune responses, using systems ranging in complexity from the simple quorum sensing molecules – acyl homoserine lactones – to the supramolecular syringe-like devices of type III secretion systems. This book will be of interest to researchers and graduate students in microbiology, immunology, pharmacology, and molecular medicine.

BRIAN HENDERSON is professor of cell biology and runs the Cellular Microbiology Research Group at University College London. His research focuses on the role of molecular chaperones as microbial virulence factors and the mechanisms by which bacteria control host cytokine networks. He is the coauthor of the textbook *Bacterial Disease Mechanisms* (2002).

PETRA OYSTON is a principal scientist in the microbiology section of the Chemical and Biological Defence Sector, Porton Down, UK. She leads the Bacteriology Group there, where her work focuses on the regulation of genetic systems, vaccine development, genome sequencing, and pathogenicity of bacteria such as *Yersinia pestis*, Burkholderia spp. and *Francisella tularensis*.

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Over the past decade, the rapid development of an array of techniques in the fields of cellular and molecular biology have transformed whole areas of research across the biological sciences. Microbiology has perhaps been influenced most of all. Our understanding of microbial diversity and evolutionary biology, and of how pathogenic bacteria and viruses interact with their animal and plant hosts at the molecular level, for example, has been revolutionized. Perhaps the most exciting recent advance in microbiology has been the development of the interface discipline of cellular microbiology, a fusion of classic microbiology, microbial molecular biology, and eukaryotic cellular and molecular biology. Cellular microbiology is revealing how pathogenic bacteria interact with host cells in what is turning out to be a complex evolutionary battle of competing gene products. Molecular and cellular biology are no longer discrete subject areas but vital tools and an integrated part of current microbiological research. As part of this revolution in molecular biology, the genomes of a growing number of pathogenic and model bacteria have been fully sequenced, with immense implications for our future understanding of microorganisms at the molecular level.

Advances in Molecular and Cellular Microbiology is a series edited by researchers active in these exciting and rapidly expanding fields. Each volume will focus on a particular aspect of cellular or molecular microbiology and will provide an overview of the area and examine current research. This series will enable graduate students and researchers to keep up with the rapidly diversifying literature in current microbiological research.

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Advances in Molecular and Cellular Microbiology 2

Bacterial Evasion of Host Immune Responses

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Preface

From birth we are protected from bacterial infections by the complex system of cells and cell products, which have functional and signalling properties, known collectively as immunity. The immune system has three major functions: (1) the ability to recognise infectious agents such as bacteria; (2) the capacity to kill these infecting organisms; and (3) the integration of (1) and (2) through specific cell–cell signalling. It is now recognised that the nature of our immune systems has been shaped in the crucible of evolution by interactions with infectious agents. It is also emerging that the various organisms that can infect us have evolved multiple mechanisms to evade both arms of our immune system – innate and adaptive immunity.

This book describes some of the emerging mechanisms employed by bacteria to evade both humoral and cellular immunity. The first section deals with novel aspects of the recognition of, and the response to, bacteria by a key cell population – dendritic cells (e.g., through Toll-like receptors), and by lymphocytes via the nonpolymorphic CD1 MHC molecules that recognise nonpeptidic antigens. The final chapter in this section describes natural resistance-associated macrophage protein (NRAMP), a metal ion transporter important in susceptibility to infection by mycobacteria. Mycobacteria also encode NRAMP-like proteins revealing another twist in the ongoing battle between bacteria and their hosts for essential metal ions such as iron and zinc.

In the second section attention switches to the ability bacteria have to evade humoral immunity. It has been known for many years that the bacterial capsule can protect against complement. However, over the past decade or so it has emerged that bacterial pathogens have evolved a plethora of selective mechanisms for evading the major mechanisms of complement-mediated killing. Another powerful mechanism for evading antibodies

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and antibody-mediated complement activation is the production of selective immunoglobulin-degrading proteases and immunoglobulin-binding proteins. A third way to avoid the deleterious actions of antibodies is to keep altering the cellular antigens by the processes of phase and antigenic variation.

The final section in this book deals with bacterial evasion of cellular immunity. The role of type III secretion systems in the inhibition of phagocytosis and in the inhibition of the key transcription factor, NF-κB, are detailed in two separate chapters. A small number of bacteria produce proteins, termed superantigens, which are able to stimulate a large proportion of the T cell repertoire but in the process remove or inactivate these cells. Superantigens thus have the potential to decrease overall T cell responsiveness. A fascinating finding is that the signals involved in bacterial quorum sensing – such as the acyl homoserine lactones – are also able to inhibit immune responses, including the induction of cytokine synthesis. The consequences of the immunoinhibitory actions of these molecules is discussed. The remaining chapters describe how bacteria interact with immune cells to control the synthesis of cytokines, proteins that act to integrate the functions of immune cells. The ability of bacteria to produce a vast range of molecules with cytokine-inducing (or in some cases, inhibiting) actions and the consequence of this for the physiological control of functional cytokine networks is reviewed. The role of enterotoxins as cytokine-modulating agents capable of acting as local adjuvants or local cytokine inhibitors is described and the consequences of this for the host are reviewed.

This volume brings together experts in bacteria-host interactions to explain how bacteria are recognised by the immune system and how this recognition and its consequences can be negated to enable the bacteria to survive.

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