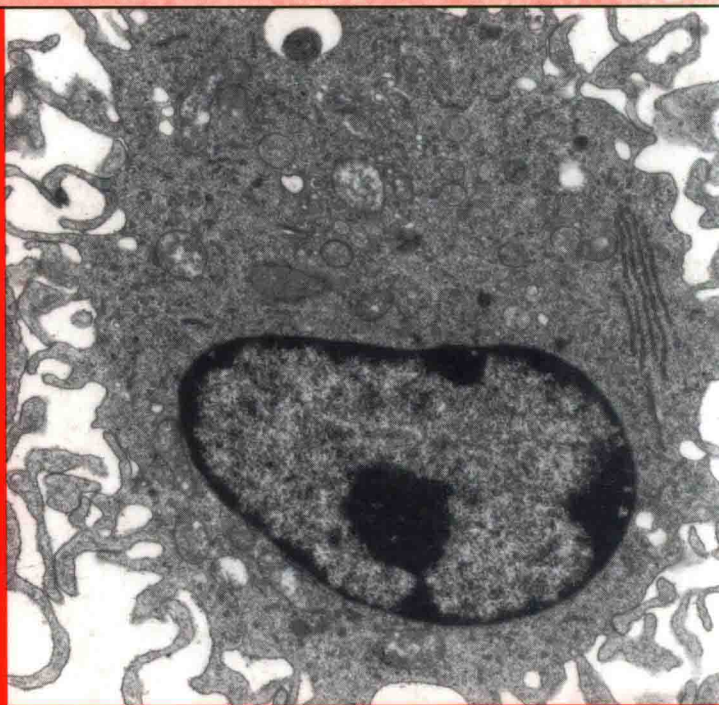


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ADVANCES IN MOLECULAR AND

# Dendritic Cell Interactions with Bacteria



Edited by  
**Maria Rescigno**

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# Dendritic Cell Interactions with Bacteria

EDITED BY

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## Dendritic Cell Interactions with Bacteria

Emerging evidence suggests that dendritic cells play a major role in the orchestration of the immune response to bacteria. This book introduces the reader to the complex world of dendritic cells and describes how the intimate interplay between dendritic cells, bacteria and the environment dictates either the induction of immunity or tolerance to the encountered micro-organisms. It discusses how this can allow organisms to tolerate beneficial bacteria and to react against pathogens, as well as the strategies pathogenic bacteria have evolved to escape dendritic cell patrolling. Expert contributors discuss everything from bacterial capture and recognition to their killing, processing and the induction of adaptive immunity. Particular focus is on the tissue context in which bacteria are handled by dendritic cells and on possible defects therein, which may potentially lead to chronic infection or inflammation. Graduate students and researchers will find this an invaluable overview of current dendritic cell biology research.

MARIA RESCIGNO is the Director of the Immunobiology of Dendritic Cells and Immunotherapy Research Unit at the European Institute of Oncology, Milan, Italy.

## Published titles

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Over the past decade, the rapid development of an array of techniques in the fields of cellular and molecular biology has 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, have been revolutionized. Perhaps the most exciting recent advance in microbiology, a fusion of classical microbiology, microbial molecular biology and eukaryotic cellular microbiology. 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, as well as 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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## Preface

Dendritic cells (DCs) comprise a family of professional antigen presenting cells that are unique in their ability to activate T lymphocytes. Dendritic cells patrol all the tissues at the interface with the external world, including skin and mucosal surfaces, for the presence of invaders. The DC system is characterized by a remarkable plasticity that allows the induction both of immunity and tolerance toward the encountered antigens. This is achieved through the combination of a number of different factors, including the subsets of DCs, their activation state and environmental cells that can regulate DC function. DCs are present in the periphery in an immature form that is particularly apt at capturing antigens and at deciphering the messages associated therein. After an activation stimulus that is delivered by some antigens (including bacteria) or by inflammatory cytokines released during inflammation, activated DCs acquire a migratory phenotype and reach the draining lymph node. Here, DCs present the antigens captured in the periphery and initiate T cell adaptive immune responses.

This book describes how the intimate interplay between dendritic cells, bacteria and the environment dictates the induction of immunity or tolerance to bacteria and how pathogenic bacteria have evolved strategies to escape DC patrolling. The first section introduces the complexity of the DC system describing the different subpopulations of DCs and their role in the induction of immune responses. This is followed by the description of a class of pathogen recognition receptors and their signaling pathways that are fundamental in the activation of DCs after recognition of bacterial structural components. These receptors, belonging to the Toll-like receptor family, are differentially expressed on DC subpopulations and contribute to generate functional diversity. To conclude this general part on DC function, there is

a description on how bacterial antigens are handled, processed and presented by DCs.

In the second section, attention switches to the role of DCs in the initiation and orchestration of innate immune responses. The section begins describing how dendritic cells can directly participate in the uptake of bacteria across mucosal surfaces and its consequences in terms of DC activation. After microbial recognition, DCs act first as innate immune cells that release inflammatory mediators that can strengthen and amplify the innate immune response. In particular a novel monocyte-derived DC population called TipDCs that produces large amounts of tumor necrosis factor (TNF) and inducible nitric oxide synthase (iNOS) is reported. Then DCs can leave the infected site to reach the draining lymph node for T cell activation. Thus, DCs represent a link between innate and adaptive immunity because their activation can lead on one side to the recruitment and activation of innate immune cells like granulocytes, macrophages and natural killer (NK) cells and on the other side to the activation of adaptive immune cells. To achieve this, DCs can act on their own or in concert with other innate immune cells like NK cells, as discussed in the last chapter of this section.

The following section deals with the initiation of adaptive immune responses that is conducted by DCs that have deciphered and integrated signals deriving from the bacteria, the infected tissue and the recruited immune cells. Two major examples of DC handling of strictly or facultative intracellular bacteria have been considered, namely *Legionella* and *Salmonella*. It is described how differently from macrophages, DCs have evolved strategies to handle and control intracellular growth of *Legionella* and to activate effective adaptive immune responses to control bacterial infection. Interestingly, DCs can present bacterial antigens also when they are non-infected after phagocytosing infected cells. This process also known as cross-presentation is unique to DCs and favors the activation of T cell responses toward *Salmonella*, *Listeria* and *Mycobacterium*.

Finally, strategies developed by bacteria to evade DC recognition and activation are discussed in the fourth section. Here pathogen recognition receptors are thoroughly discussed as possible targets for pathogens to modulate immune function of antigen presenting cells. It is described that the cross-talk between different classes of pathogen recognition receptors can lead to suppression or activation of immune responses. In the following chapter the ability of bacteria or their products to suppress the immune response through the skewing of T cell responses toward regulatory T cells or to subtypes which are inappropriate for bacterial elimination is reported.

A major drawback of improper bacterial handling can result in chronic inflammatory responses particularly at sites continuously exposed to bacteria like the gut. Here, commensal bacteria are beneficial to the host as they help digesting ingested food through the degradation of complex sugars and metabolites. In order to tolerate “good” bacteria, the immune system has developed strategies to cohabitate with beneficial bacteria and discriminate harmful pathogens. When these strategies are disrupted, inflammatory responses can arise leading to inflammatory bowel disease as discussed in the last chapter of this section.

In conclusion, this book has brought together experts in several fields of dendritic cell–bacteria interaction from their capture and recognition to their killing, processing and induction of adaptive immunity. Much attention has been focused on the tissue context where bacteria are handled by DCs. When defects either in bacterial handling or in the interaction with the environment are encountered, chronic infection or inflammation can arise.

## Abbreviations

|        |                                                   |
|--------|---------------------------------------------------|
| APC    | antigen-presenting cell                           |
| ASK    | apoptosis signal-regulating kinase                |
| BCG    | bacillus Calmette-Guerin                          |
| BIR    | baculoviral inhibitors of apoptosis repeat        |
| CARD   | caspase recruitment domain                        |
| CD     | Crohn's disease                                   |
| cDC    | conventional DC                                   |
| CLP    | common lymphoid progenitor                        |
| CLR    | C-type lectin-related                             |
| CMP    | common myeloid progenitor                         |
| CRD    | carbohydrate-recognition domain                   |
| CT     | cholera toxin                                     |
| CTL    | cytotoxic T lymphocytes                           |
| DALIS  | dendritic cells aggresome-like induced structures |
| DC     | dendritic cell                                    |
| DRIP   | defective ribosomal product                       |
| dsRNA  | double-stranded RNA                               |
| DSS    | dextran sodium sulfate                            |
| EC     | epithelial cell                                   |
| ER     | endoplasmic reticulum                             |
| ERAD   | ER-associated degradation                         |
| ERAP   | endoplasmic reticulum aminopeptidase              |
| FADD   | Fas (TNFRSF6)-associated via death domain         |
| FAE    | follicle-associated epithelium                    |
| GALT   | gut associated lymphoid tissue                    |
| GFP    | green fluorescent protein                         |
| GM-CSF | granulocyte-macrophage colony-stimulating factor  |

|         |                                                       |
|---------|-------------------------------------------------------|
| HCV     | Hepatitis C virus                                     |
| HLA     | human leukocyte antigen                               |
| IAP     | inhibitors of apoptosis                               |
| IBD     | inflammatory bowel disease                            |
| IDC     | immature DC                                           |
| IE-DAP  | $\gamma$ - $\delta$ -glutyl-meso diaminopimelic acid  |
| IFN     | interferon                                            |
| Ii      | invariant chain                                       |
| IKK     | I $\kappa$ B kinase                                   |
| IL      | interleukin                                           |
| iNOS    | inducible nitric oxide synthase                       |
| IRAK    | IL-1R-associated kinase                               |
| IRF     | interferon regulatory factor                          |
| ISGF    | IFN-stimulated gene factor                            |
| ISRE    | IFN-stimulated regulatory element                     |
| ITAM    | immunoreceptor tyrosine-based activation motif        |
| JNK     | c-Jun N-terminal kinase                               |
| KIR     | killer Ig-like receptors                              |
| LAM     | lipoarabinomannan                                     |
| LLO     | listeriolysin O                                       |
| LP      | lamina propria                                        |
| LPS     | lipopolysaccharide                                    |
| LRR     | leucine-rich repeat                                   |
| LTA     | lipoteichoic acid                                     |
| mAB     | monoclonal antibody                                   |
| MAL     | MyD88 adaptor-like                                    |
| MAPKK   | mitogen activated protein kinase kinase               |
| MAPKKK  | mitogen activated protein kinase kinase kinase        |
| MDP     | muramyl dipeptide                                     |
| MEF     | mouse embryonic fibroblast                            |
| MHC     | major histocompatibility complex                      |
| MLN     | mesenteric lymph nodes                                |
| NCR     | nitrogen catabolite repressor                         |
| NDV     | Newcastle disease virus                               |
| NEMO    | NF- $\kappa$ B essential modulator                    |
| NF      | nuclear factor                                        |
| NK      | natural killer                                        |
| NOD     | nucleotide-binding oligomerization domain             |
| Nod-LRR | nucleotide oligomerization domain-leucine-rich repeat |
| OVA     | chicken ovalbumin                                     |

|       |                                                                       |
|-------|-----------------------------------------------------------------------|
| PAMP  | pathogen associated molecular patterns                                |
| pDC   | plasmacytoid DC                                                       |
| PGN   | peptidoglycan                                                         |
| PI3P  | phosphoinositol-3-phosphate                                           |
| PKR   | protein kinase R                                                      |
| PP    | Peyer's patches                                                       |
| PPAR  | peroxisome-proliferator-activated receptor                            |
| PRR   | pathogen recognition receptor                                         |
| RICK  | Rip-like interacting caspase-like apoptosis-regulatory protein kinase |
| RIG   | retinoic acid-inducible protein                                       |
| RIP   | receptor interacting protein                                          |
| SARM  | sterile $\alpha$ and HEAT-Armadillo motif                             |
| siRNA | small interfering RNA                                                 |
| SLE   | systemic lupus erythematosus                                          |
| SPI   | <i>Salmonella</i> pathogenicity island                                |
| ssRNA | single-stranded RNA                                                   |
| STAT  | signal transducer and activator of transcription                      |
| TAB   | tubulin antisense-binding protein                                     |
| TAK   | TGF $\beta$ -activating kinase                                        |
| TAP   | transporter associated with antigen processing                        |
| TBK   | TANK-binding kinase                                                   |
| TGF   | transforming growth factor                                            |
| TipDC | tumor infiltrating pDC                                                |
| TIR   | Toll/IL1 receptor                                                     |
| TIRAP | TIR domain-containing adaptor protein                                 |
| TJ    | tight junction                                                        |
| TLR   | Toll-like receptor                                                    |
| TNF   | tumor necrosis factor                                                 |
| TRAM  | TRIF-related adaptor molecule                                         |
| TRIF  | TIR domain-containing adaptor inducing IFN $\beta$                    |
| TSLP  | thymic stromal lymphopoietin                                          |
| VSV   | Vesicular stomatis virus                                              |

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