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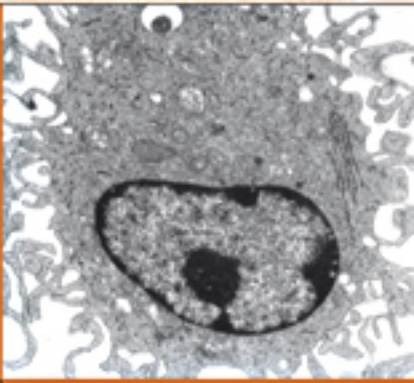
Dendritic Cell Interactions with Bacteria



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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.

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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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Dendritic Cell Interactions with Bacteria

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Contents

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 phagocytozing 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	γ-δ-glutyl-meso diaminopimelic acid
IFN	interferon
Ii	invariant chain
IKK	IκB 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-κB 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 α and HEAT-Armadillo motif
siRNA	small interfering RNA
SLE	systemic lupus erythematosus
SPI	*Salmonella* pathogenicity island
ssRNA	single-stranded RNA
STAT	signal transducer and activator of transcription
TAB	tubulin antisense-binding protein
TAK	TGFβ-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 IFNβ
TSLP	thymic stromal lymphopoietin
VSV	Vesicular stomatis virus

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PART I Dendritic cells and their role in immunity

CHAPTER 1

Subpopulations and differentiation of mouse dendritic cells

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1.1 DENDRITIC CELL SUBPOPULATIONS

Dendritic cells (DCs) have an essential function in the immune system by participating in primitive defense responses that constitute the innate immunity, as well as in the induction and regulation of antigen-specific immune responses. This allows DCs to control infections caused by parasitic and microbial pathogens, to block tumour growth and to exert a precise regulation of T cell, B cell and NK cell immune responses. In addition, DCs also fulfill a pivotal role in the induction and maintenance of T cell tolerance. The functional diversity characterizing the DC system relies essentially on the remarkable plasticity of the DC differentiation process, which dictates the acquisition of DC functional specialization through the generation of a large collection of DC subpopulations (reviewed by Shortman and Liu, 2002). Dendritic cells are located both in the lymphoid organs (such as the spleen or the lymph nodes), and in non-lymphoid tissues (such as the skin or the liver), and can be classified in two major categories: conventional DCs (cDCs), and plasmacytoid DCs (pDCs). Whereas in turn cDCs comprise multiple DC subpopulations endowed with specific functions, little is known about the functional heterogeneity of pDCs. A summary of the most relevant phenotypic and functional characteristics of the main DC subpopulations present in mice is shown in Table 1.1.

A first group of cDCs includes those that are common, and largely restricted, to the majority of organized lymphoid organs of the immune system, and perform their specific functions, as immature or mature DCs, within these organs. This group of lymphoid organ-restricted cDCs comprises three main DC subpopulations, namely $CD8^+$ $CD11b^-$ DCs (herein called $CD8^+$ DCs), $CD8^-$ $CD11b^+$ DCs (herein called $CD8^-$ DCs), and $CD8^-$ $CD11b^-$ DCs (herein called $CD11b^-$ DCs). $CD8^-$ DCs

Table 1.1. *Location and phenotypic characteristics of the principal mouse DC subpopulations*

	pDCs	*$CD8^+$ DCs*	*$CD8^-$ $CD4^+$ DCs*	*$CD8^-$ $CD4^-$ DCs*	*$CD11b^-$ DCs*	*Langerhans cells*	*Dermal DCs*
Location							
Thymus	Yes	Yes	No	Yes[a]	Few	No	No
Spleen	Yes	Yes	Yes	Yes	No	No	No
Skin	[b]	No	No	No	No	Yes	Yes
Peripheral LNs	Yes	Yes	Few	Yes	Few	Yes	Yes
Intestinal Peyer's patches	Yes	Yes	Few	Yes	Yes	No	No
Mesenteric LNs	Yes	Yes	Few	Yes	Yes	No	[c]
Other locations	Bone marrow, blood, lung	Liver		Liver	Liver	Epidermis, intestinal S-E, lung S-E, vagina S-E	Intestinal L-P,[d] bronchial L-P,[d] lung interstitium,[d] liver parenchyma,[d] kidney parenchyma,[d] CNS parenchyma[d]

Phenotype							
CD11c	+ int	+ high	+ high	+ high	+ high	+ high	+ high
CD11b	−	+ low	+ high	+ high	−	+ high	+ high
CD8	+[e]	+	−	−	−	− (→ +)[f]	−
CD4	+[e]	−	+	−	−	−	−
B220	+	−	−	−	−	−	−
CD62L	+	−	−	−	Not analyzed	−	−
DEC-205	−	+ high	−	−	−	+ high	+ low

Abbreviations: CNS, central nervous system; LNs, lymph nodes; L-P, lamina propria; S-E, stratified epithelium.

Notes

[a] Thymic $CD8^-$ DCs have been reported to express low levels of CD4, although it has been suggested that in fact $CD8^-$ thymic DCs are $CD4^-$, since CD4 appears to be picked up by thymic DCs from surrounding $CD4^+$ T cells.

[b] pDCs are absent from the skin in steady state, but can be recruited to this location during inflammation.

[c] DCs with similar characteristics than those defining dermal DCs after migration to the peripheral LNs are found in the mesenteric LNs; these cells have been claimed to correspond to intestinal L-P DCs.

[d] Interstitial DCs that have been suggested to be functionally related to dermal DCs have been described in these locations.

[e] pDCs have been demonstrated to upregulate both CD8 and CD4 during activation.

[f] Langerhans cells have been demonstrated to upregulate CD8 during in vivo maturation and migration from the skin to the draining lymph nodes.

can be in turn subdivided in $CD8^-$ $CD4^+$ DCs and $CD8^-$ $CD4^-$ DCs. Whereas $CD8^+$ DCs and/or $CD8^-$ DCs are present in the thymus, spleen, lymph nodes and lymphoid tissue of the intestinal and respiratory tracts (reviewed by Shortman and Liu, 2002), the $CD11b^-$ DC subpopulation appears to be predominantly related to the intestinal lymphoid system (reviewed by Johansson and Kelsall, 2005), representing approximately one-third of the DCs found in the Peyer's patches and mesenteric lymph nodes. $CD8^+$ DCs and $CD8^-$ DCs do not appear to migrate or recirculate to other effector organs of the immune system to fulfill their functions. In this sense, $CD11b^-$ DCs have been tentatively included in this category since they appear to be present in the majority of lymphoid organs (reviewed by Johansson and Kelsall, 2005), but their immunobiology, and particularly their migratory behavior, remains largely unknown.

A second group of cDCs comprises those located, in an immature state, in antigen-uptake sites within non-lymphoid organs. Upon contact with an antigen, these DCs migrate through the lymph vessels to the lymph nodes, where they interact with antigen-specific T cells, and in some cases with other effector cells of the immune system, including DCs, NK cells and B cells. This group of migrating-cDCs comprises Langerhans cells (located in the epidermis, and other stratified and pseudo-stratified epithelia of the intestinal, respiratory and reproductive tracts), and interstitial DCs. These in turn include dermal DCs, and other interstitial DC subpopulations, as those found in the lamina propria of the intestinal and respiratory tracts, as well as those located in the lung interstitium, and in the parenchyma of the liver, kidney and CNS.

A number of experimental evidences suggest that in the steady state both lymphoid-organ restricted cDCs and migrating-cDCs are generated locally from blood-borne, immediate DC precursors, originating in the bone marrow (reviewed by Ardavín, 2003). Interestingly, during ongoing immune responses, a strong increase in the absolute number of both lymphoid organ-restricted cDCs and migrating-cDCs has been reported, raising the problem of the identity of the immediate DC precursors responsible for the generation of these de novo-formed DCs. It could be hypothesized that the same precursors are responsible for the generation of cDCs under steady state and infection. Alternatively, during infection, apart from, or instead of the precursors functioning in steady state, additional inflammatory precursors, with equivalent or complementary DC differentiation potential, could be recruited. Although this remains an open issue in DC biology, different research groups have reported that during inflammation and/or infection, monocytes, which represent so far the best known DC