

Antigen Presenting Cells

From Mechanisms to Drug Development

Edited by

Harald Kropshofer and Anne B. Vogt



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Preface

The history of Antigen Presenting Cells (APC) started in the second half of the 19th century when novel staining techniques entered the field of histopathology: the German pathologist Paul Langerhans was the first to describe irregularly shaped cells in the epidermis of the skin. These cells displayed long dendritic processes, thereby forming an almost continuous meshwork – an ideal feature to capture pathogens invading the body via the skin. The cells were termed “Langerhans cells”; however, at the time of their discovery nobody could be aware that Langerhans had stained the archetype of an APC that, subsequently, turned out to be key in triggering an immune response. Almost a century later, in the late 1960s, when it became immunology textbook knowledge that Langerhans cells contain racket-like Birbeck granules and can move from the epidermis to regional lymph nodes as so-called “veiled cells”, APC became a frequently reoccurring term in immunological journals. In the 1970s and 1980s, pioneering work with macrophages taught us what almost all APC have in common: they share the capacity to engulf exogenous antigens, decompose them into proteolytic fragments and present these peptide fragments on their cell surfaces bound to molecules of the major histocompatibility complex (MHC). The last 15 years of research on APC has been governed, on the one hand, by the elucidation of the molecular mechanisms of antigen processing, e.g., which molecules decide which antigenic peptides become immunodominant in triggering T lymphocytes, and, on the other hand, by exploring which role APC play in tolerance induction against self versus autoimmunity.

In *Antigen Presenting Cells*, the principal investigators in the field present the development of central principles in the regulation of immunity versus tolerance, as accomplished through the activity of APC. E. Unanue, one of the pioneers in antigen processing, describes how APC may contribute to the diversity of T cell responses against a given T cell epitope (Chapter 1). P. Knolle focuses on liver sinusoidal epithelial cells and their capacity to induce tolerance against antigens entering the body via the oral route (Chapter 2). Contributions by F. Momburg (Chapter 3) and A. Vogt (Chapter 4) give updates on MHC class I and class II processing pathways, respectively; in particular, they discuss accessory molecules explored during the last decade. S. Porcelli and D. B. Moody provide us with state-of-the-art knowledge on presentation of lipid antigens by non-MHC molecules of

the CD1 family (Chapter 5). H. Kropshofer and S. Spindeldreher give an overview of progress in the identification of naturally processed self-peptide antigens that are essential for the maintenance of a self-tolerant T cell repertoire (Chapter 6). In Chapter 7, M. Dustin and colleagues collected evidence on how the spatial organisation of key surface receptors on APC contribute to cytotoxic T cell activation. Chapter 8 by M. Bachmann and A. Oxenius highlight the more recent seminal discovery of Toll-like receptors that link innate and adaptive immune system functions, in particular through the expression on dendritic cells and macrophages. Two chapters by N. Stoy discuss the multiple roles that macrophages play in the maintenance of health or the induction of diseases (Chapters 9 and 10). Three other types of APC frequently implicated in diseases mediated by the immune system are polymorphonuclear neutrophils, microglial cells and B cells. Their significance in functioning as professional APC and their contribution to disease pathogenesis are outlined in Chapters 11–13 by B. Saha and A. R. Ashtekar, M. Carson and T. Dörner and P. E. Lipsky, respectively. M. Moser and colleagues and K. Shortman and L. Wu summarize recent progress in our understanding of how peripheral or thymic dendritic cells are principal inducers of self-tolerance (Chapters 14 and 15). Finally, L. Karlsson and colleagues discuss, from a pharmaceutical viewpoint, current options to exploit APC as drug targets in attempts to treat autoimmunity or cancer (Chapter 16).

Processing and presentation of antigens are central to the initiation of adaptive immune responses. Future therapeutics to control immune responses will come from a deeper understanding of the molecular details involved in antigen processing. In autoimmunity, a major goal can be to interfere with the proteolytic machinery that generates autoepitopes in dendritic cells or B cells. Targeting the B cell surface marker CD20 with monoclonal antibodies in rheumatoid arthritis is another example underlining the potential importance of APC in the design of new therapeutic approaches to control autoimmune diseases. New vaccine strategies for the treatment of infectious diseases and tumors will also rely on our combined knowledge about the functioning of APC. Breakage of tolerance imposed by dendritic cells, identification of appropriate tumor peptides presented on APC or the activation of dendritic cells by novel adjuvants through Toll-like receptors, thereby enhancing the presentation of tumor-associated antigens, could lead to successful immunotherapy of tumors. Achieving these goals in clinical trials should become reality. The fundamental work of our colleagues presented in this book will help to pave the way towards novel therapeutics and individualized health care.

Basel, April 2005

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List of Abbreviations

AC	Adenylate cyclase
ADC	Arginine decarboxylase
AI	Arginase I
AL	Argininosuccinate lyase
AM	Alveolar macrophage
AMP	Anti-microbial peptide
AP-1	Activator protein-1
AS	Argininosuccinate synthase
BMP	Bone morphogenetic protein
Bsk	Basket (<i>Drosophila</i>)
C/EPB	CCAAT/enhancer binding protein
cAMP	Adenosine 3',5'-cyclic monophosphate
CAT	Cationic amino acid transporter
CBP	CREB-binding protein
CK2	Casein kinase 2
COX	Cyclooxygenase
CREB	cAMP response element binding protein
CRP	C-reactive protein
Dach1	Dachshund protein (currently known to suppressor Smads in some cells)
DAP12	Adaptor protein of 12kDA (adaptor for TREM2)
DC-LAMP	DC-lysosomal-associated membrane protein
DC-SIGN	DC-specific ICAM-3-grabbing nonintegrin
DEC-205	DC receptor comprising decalectin with 10 contiguous, C-type lectin domains; homologous to the macrophage mannose receptor (MR)
DIF	Dorsal-related immune factor
Dome	Domeless (<i>Drosophila</i>)
DREDD	A death domain-containing <i>Drosophila</i> homolog of caspase 8
EAE	Experimental autoimmune (allergic) encephalomyelitis
EIF2 α	Eukaryotic translation initiation factor 2 α
ELAM-1	Endothelial leukocyte adhesion molecule-1

EP	E-prostanoid (PGE ₂) receptor
EPAC1	Exchange protein activated by cAMP 1
ERK	Extracellular signal-regulated kinase
ET-1	Endothelin-1
FADD	Fas-associated protein with death domain
FAN	Factor associated with neutral sphingomyelinase activation
FIZZ	A chitinase marker of alternative macrophage activation
GAS	γ -activated sequences
GCN2K	General control non-derepressible-2 kinase
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HDAC	Histone deacetylase
HMGB1	High-mobility group box 1 protein
Hop	Hopscotch (<i>Drosophila</i>)
HSC	Hepatic stellate cell
HSP	Heat shock protein
ICE	IL-1 β -converting enzyme (caspase-1)
ICER	Inducible cAMP early repressor
IDO	Indoleamine 2,3-dioxygenase
IFRL	Innate functional response linkage
IKK γ	I κ B kinase γ
IL-18BP	IL-18-binding protein
IL-1Ra	IL-1 receptor antagonist
iNOS	Inducible nitric oxide synthase
IRF	Interferon regulatory factor
ISG	Interferon-stimulated gene
ISGF3	A complex comprising STAT1, STAT2 and IRF-9
ISRE	IFN- α/β -stimulated response element
Jak	Janus kinase
JNK	c-Jun N-terminal kinase
KC	Kupffer cell
LAM	Lipoarabinomannan
LBP	Lipopolysaccharide binding protein
LC	Langerhans cell
LLO	Listeriolysin O
LPS	Lpopolysaccharide
Mal/TIRAP	MyD88 adaptor-like/TIR domain-containing adaptor protein
MAM	Microbial-associated molecule
ManLAM	Mannosylated (mannose-capped) lipoarabinomannan
MAPK	Mitogen-activated protein kinase
MBL	Mannose-binding lectin
MCP	Monocyte chemoattractant protein
M-CSF	Macrophage colony-stimulating factor
MD-2	Myeloid differential protein-2
MDL-1	Myeloid DAP12-associating lectin-1

MEK	Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
MEKK3	Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase 3
MGL	Macrophage galactose-type C-type lectin
MIG	Monokine induced by IFN-gamma
MIP	Macrophage Inflammatory Protein
MKP-1	Mitogen-activated protein kinase phosphatase-1
MMP	Matrix metalloproteinase
MMRR	Microbial molecular recognition receptor
MR	Mannose receptor
MSK1	Mitogen and stress-activated protein kinase 1
MTB	Mycobacterium tuberculosis
MyD88	Myeloid differentiation primary-response protein 88
NEMO	Nuclear factor- κ B essential modulator (IKK γ)
NF- κ B	Nuclear factor- κ B
NO	Nitric oxide
NOD mouse	Non-obese diabetic mouse
NOD1/2	NOD-LRRs 1/2: nucleotide-binding oligomerization domain-leucine-rich repeats 1 and 2
NOHA	N ^G -hydroxy-L-arginine
OAT	Ornithine acetyltransferase
ODC	Ornithine decarboxylase
OVA	Ovalbumin
P5C	Pyrroline-5-carboxylate
PACAP	Pituitary adenylate cyclase-activating polypeptide
PAMP	Pathogen-associated molecular pattern
PAMP	Pathogen-associated molecular pattern (see also MMAR)
PDE	Phosphodiesterase
PG	Peptidoglycan
PGRP	Peptidoglycan recognition protein
PI3K	Phosphoinositide 3-kinase
PKA	Protein kinase A
PRR	Pattern recognition receptor
Puc	Puckered (<i>Drosophila</i>)
RAGE	Receptor for advanced glycation end-products
RANK(L)	Receptor activator of NF- κ B
RANTES	Regulated on activation, normal T cell-expressed and secreted protein (CCL5)
RIP	Receptor-interacting protein
S2	Steiner 2 cells (<i>Drosophila</i>)
SCID	Severe combined immunodeficiency
SHP2	Src homology 2 domain-containing protein-tyrosine phosphatase-2 (PTPN11)
SOCS	Suppressors of cytokine signaling

STAT	Signal transducer and activator of transcription
TAK1	Transforming growth factor- β -activated kinase
TAM	Tumor-associated macrophage
TGF- β	Transforming growth factor- β
TICAM1	(also called TRIF)
TICAM2	TICAM1 bridging adaptor
TIMP	Tissue inhibitor of matrix metalloproteinase
TIMP	Tissue inhibitor of metalloproteinase
TIR	Toll-IL-1 receptor
Tollip	Toll-interacting protein
TORC1	Target of rapamycin complex 1
TotA	Turandot A (<i>Drosophila</i>)
TRADD	TNF-receptor-associated death domain
TRAF	TNF receptor-associated factor
TRAP	Tartrate-resistant acid phosphatase
TREM	Triggering receptor expressed on myeloid cells
TRIF	Toll-IL-1 receptor homology domain-containing adaptor inducing interferon- β (also called TICAM-1)
Upd	Unpaired
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
Ym1	A chitinase marker of alternative macrophage activation

Color Plates

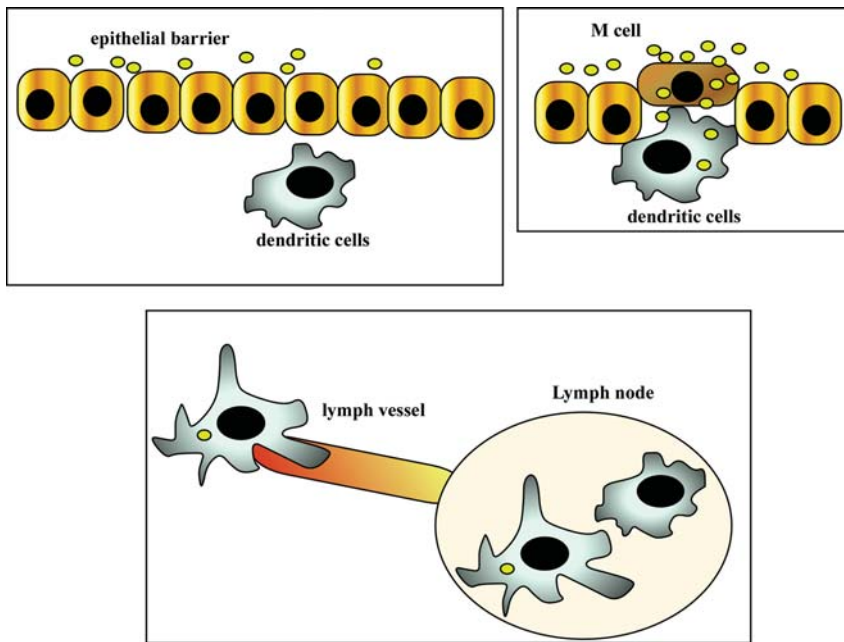


Figure 2.1 Outline of the conventional view that antigens are in peripheral tissue by dendritic cells and are transported by migratory dendritic cells to the lymph node where interaction with naive T lymphocytes occurs.

Initial contact of antigens or pathogens in these peripheral microenvironments is believed to determine the functional outcome of ensuing immune responses. (This figure also appears on page 28.)

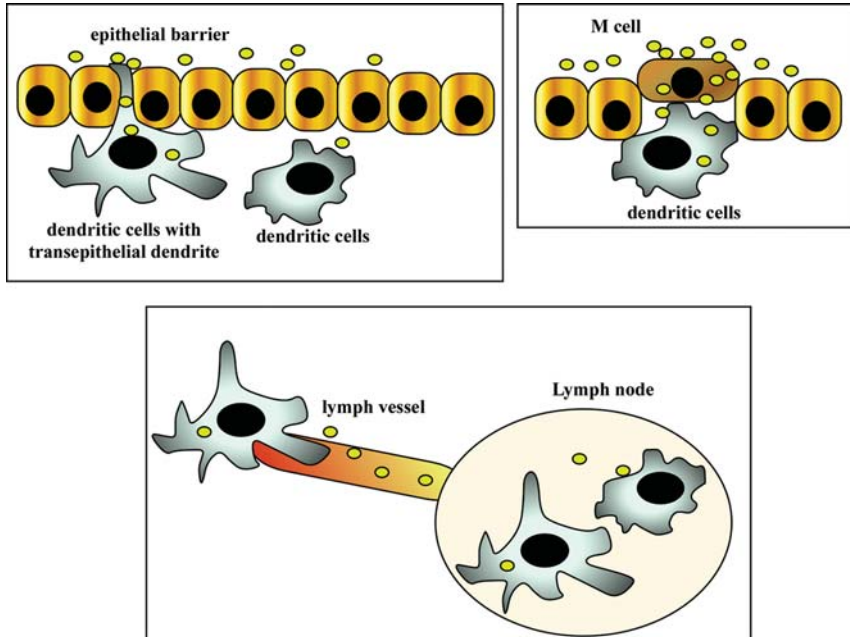


Figure 2.2 Recent work has provided evidence that dendritic cells reach via dendritic extensions, e.g. transepithelial dendrititis in the gut, the outside world and directly sample antigens as well as microorganisms. Moreover, antigens that have reached peripheral tissue may directly gain access to lymph nodes, via defined anatomic structures, and in the lymph node interact with a, presumably, resident dendritic cell

population. Bypassing peripheral antigen sampling migratory dendritic cells it remains an open question how specific information about the need for induction of immune responses is transferred to the lymph node, or whether this pathway is uniquely used for induction of immune tolerance towards tissue-autoantigens.

(This figure also appears on page 32.)