# Antigen Presenting Cells

From Mechanisms to Drug Development

*Edited by*
*Harald Kropshofer and Anne B. Vogt*


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## Contents

## 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 (*Drosophila*) |
| 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 (*Drosophila*) |
| DREDD | A death domain-containing Drosophila homolog of caspase 8 |
| EAE | Experimental autoimmune (allergic) encephalomyelitis |
| EIF2$\alpha$ | Eukaryotic translation initiation factor 2$\alpha$ |
| 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 | $\gamma$-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 (*Drosophila*) |
| HSC | Hepatic stellate cell |
| HSP | Heat shock protein |
| ICE | IL-1$\beta$-converting enzyme (caspase-1) |
| ICER | Inducible cAMP early repressor |
| IDO | Indoleamine 2,3-dioxygenase |
| IFRL | Innate functional response linkage |
| IKK$\gamma$ | I$\kappa$B kinase $\gamma$ |
| 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-$\alpha/\beta$-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-$\kappa$B essential modulator (IKK$\gamma$) |
| NF-$\kappa$B | Nuclear factor-$\kappa$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 (*Drosophila*) |
| RAGE | Receptor for advanced glycation end-products |
| RANK(L) | Receptor activator of NF-$\kappa$B |
| RANTES | Regulated on activation, normal T cell-expressed and secreted protein (CCL5) |
| RIP | Receptor-interacting protein |
| S2 | Steiner 2 cells (*Drosophila*) |
| 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-$\beta$-activated kinase |
| TAM | Tumor-associated macrophage |
| TGF-$\beta$ | Transforming growth factor-$\beta$ |
| 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 (*Drosophila*) |
| 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-$\beta$ (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

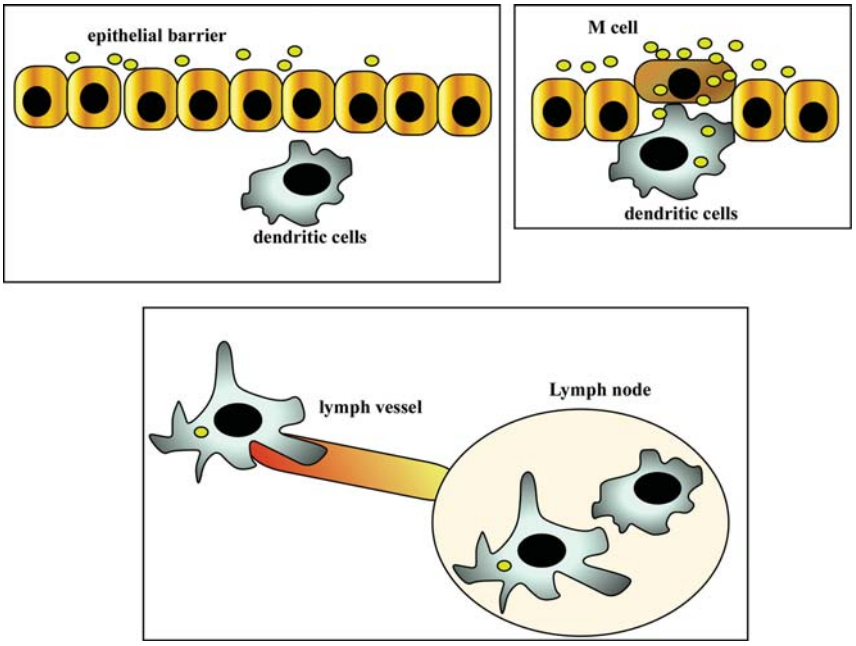


**Figure 2.1** Outline of the conventional view that antigens are in peripheral tissue by dendritic cells and are transported by migratory dendritic cells to the lymph node where interaction with naive T lymphocytes occurs. Initial contact of antigens or pathogens in these peripheral microenvironments is believed to determine the functional outcome of ensuing immune responses. (This figure also appears on page 28.)

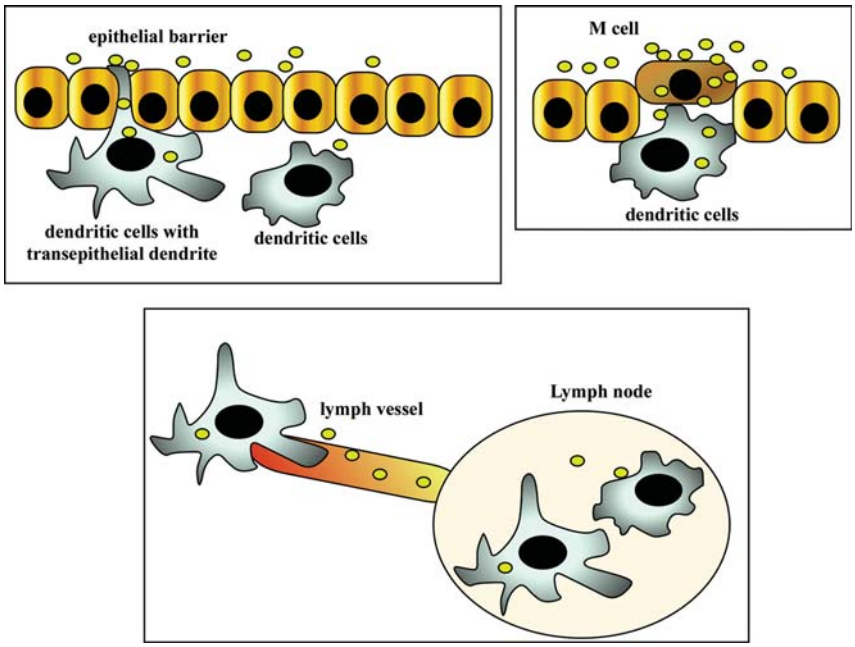


**Figure 2.2** Recent work has provided evidence that dendritic cells reach via dendritic extensions, e.g. transepithelial dendritis in the gut, the outside world and directly sample antigens as well as microorganisms. Moreover, antigens that have reached peripheral tissue may directly gain access to 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.)