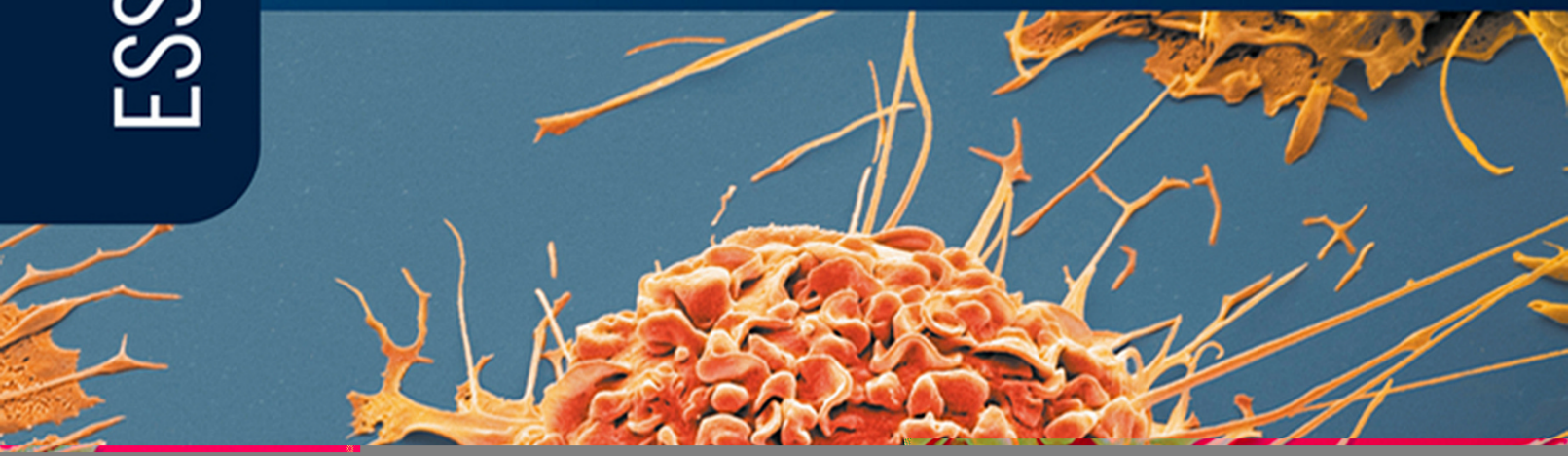
ESSENTIALS

ROITT'S ESSENTIAL IMMUNOLOGY

PETER J. DELVES | SEAMUS J. MARTIN
DENNIS R. BURTON | IVAN M. ROITT

THIRTEENTH EDITION



Roitt's Essential Immunology

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Thirteenth edition

Roitt's Essential Immunology

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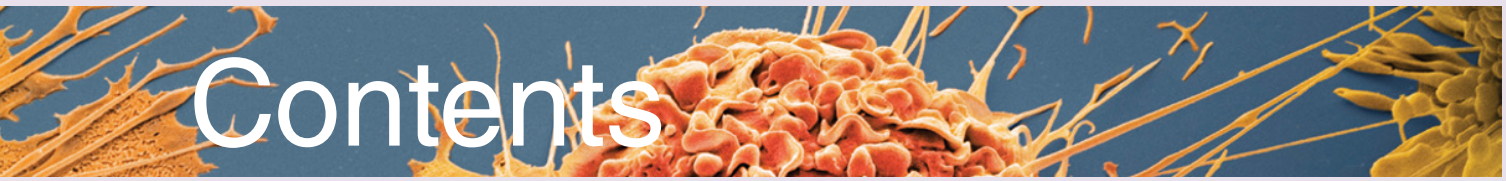

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About the authors

Peter J. Delves

Professor Delves obtained his PhD from the University of London in 1986 and is a Professor of Immunology at UCL (University College London). His research has focused on molecular aspects of antigen recognition. He has authored and edited a number of immunology books, and teaches the subject worldwide at a broad range of levels.

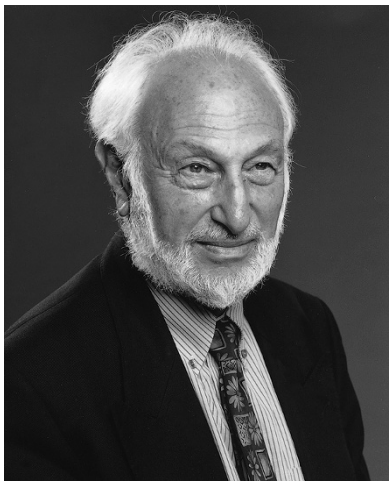
Seamus J. Martin

Professor Martin received his PhD from The National University of Ireland in 1990 and trained as a post-doctoral fellow at University College London (with Ivan Roitt) and The La Jolla Institute for Allergy and Immunology, California, USA (with Doug Green). Since 1999, he is the holder of the Smurfit Chair of Medical Genetics at Trinity College Dublin and is also a Science Foundation Ireland Principal Investigator. His research is focused on various aspects of programmed cell death (apoptosis) in the immune system and in cancer and he has received several awards for his work in this area. He has previously edited two books on apoptosis and was elected as a Member of The Royal Irish Academy in 2006 and as a member of The European Molecular Biology Organisation (EMBO) in 2009.

Dennis R. Burton

Professor Burton obtained his BA in Chemistry from the University of Oxford in 1974 and his PhD in Physical Biochemistry from the University of Lund in Sweden in 1978. After a period at the University of Sheffield, he moved to the Scripps Research Institute in La Jolla, California in 1989 where he is Professor of Immunology and Microbial Science. His research interests include antibodies, antibody responses to pathogens and rational vaccine design, particularly in relation to HIV.

Ivan M. Roitt



Professor Roitt was born in 1927 and educated at King Edward's School, Birmingham and Balliol College, Oxford. In 1956, together with Deborah Doniach and Peter Campbell, he made the classic discovery of thyroglobulin autoantibodies in Hashimoto's thyroiditis which helped to open the whole concept of a relationship between autoimmunity and human disease. The work was extended to an intensive study of autoimmune phenomena in pernicious anaemia and primary biliary cirrhosis. In 1983 he was elected a Fellow of The Royal Society, and has been elected to Honorary Membership of the Royal College of Physicians and appointed Honorary Fellow of The Royal Society of Medicine. His current research is focused on cancer.

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Peter Delves would like to acknowledge the enormous help provided by Biljana Nikolic in the delivery of education by the UCL Division of Infection & Immunity, and the huge support of his wife Jane and children Joe, Tom, and Jess.

Dennis Burton acknowledges funding for his research from the NIH, the Bill and Melinda Gates Foundation, the International AIDS Vaccine Initiative and the Ragon Institute of MGH, MIT and Harvard. I also thank my wife Carole and children Damian, Scott, and Julia for their support.

Ivan Roitt is eternally grateful to his wife Margaret and PA Christine and the uncontrolled events in his body which have sustained his mojo!

Preface

Greetings, dear reader! In the exciting world of scientific progress, immunology plays a prominent role and we have aimed to bring this edition to the cutting edge of the latest discoveries. Highlights of the new updates include:

- Tailoring of the adaptive immune response to pathogens, particularly in the skin by pattern recognition receptors
- New insights into the interaction between antibodies and Fc receptors, and immunoglobulin genetics
- Epigenetic control of T-cell activation
- T-cell recognition of lipid antigens and beautiful high-resolution images of interactions with other cells of the immune system
- Expanded discussion of novel events in cytokine biology
- Revised section on antibody interaction with viral proteins
- Recent developments in vaccinology including RNA vaccines
- Induction of cells suppressing a protective immune response by tumors, and recent breakthroughs in tumor immunotherapy
- Induction and maintenance of immunosuppression to curb graft rejection
- The role of inflammasomes in autoinflammatory disease

… and much more!

We try to maintain the chatty style characteristic of all earlier editions, imagining that you and the authors are on either side of a fireplace discussing the issues informally, which we hope makes the process of assimilation less painful and quite probably enjoyable.

Peter J. Delves
Seamus J. Martin
Dennis R. Burton
Ivan M. Roitt

Abbreviations

AAV	adeno-associated virus
Ab	antibody
AChR	acetylcholine receptor
ACT	adoptive cell transfer
ACTH	adrenocorticotropic hormone
ADA	adenosine deaminase
ADCC	antibody-dependent cellular cytotoxicity
AEP	asparagine endopeptidase
Ag	antigen
AID	activation-induced cytidine deaminase
AIDS	acquired immunodeficiency syndrome
AIRE	autoimmune regulator
ALBA	addressable laser bead assay
ANCA	antineutrophil cytoplasmic antibodies
APC	antigen-presenting cell
ARRE-1	antigen receptor response element-1
ARRE-2	antigen receptor response element-2
ART	antiretroviral therapy
ASFV	African swine fever virus
AZT	zidovudine (3′-azido-3′-deoxythymidine)
BAFF	B-cell-activating factor of the tumor necrosis factor family
B-cell	lymphocyte which matures in bone marrow
BCG	bacille Calmette–Guérin attenuated form of tuberculosis
BCR	B-cell receptor
BM	bone marrow
BSA	bovine serum albumin
BSE	bovine spongiform encephalopathy
Btk	Bruton's tyrosine kinase
BUDR	bromodeoxyuridine
C	complement
Cα(β/γ/δ)	constant part of TCR α(β/γ/δ) chain
CALLA	common acute lymphoblastic leukemia antigen
cAMP	cyclic adenosine monophosphate
CCP	complement control protein repeat
CD	cluster of differentiation
CDR	complementarity determining regions of Ig or TCR variable portion
CEA	carcinoembryonic antigen
CFA	complete Freund's adjuvant
cGMP	cyclic guanosine monophosphate
ChIP	chromatin immunoprecipitation
CHIP	chemotaxis inhibitory protein
$C_{H(L)}$	constant part of Ig heavy (light) chain
CLA	cutaneous lymphocyte antigen
CLIP	class II-associated invariant chain peptide
CMI	cell-mediated immunity
CML	cell-mediated lympholysis
CMV	cytomegalovirus
Cn	complement component "n"
$C\overline{n}$	activated complement component "n"
iCn	inactivated complement component "n"
Cna	small peptide derived by proteolytic activation of Cn

CpG	cytosine phosphate-guanosine dinucleotide motif
CR(n)	complement receptor "n"
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	class switch recombination
CTLR	C-type lectin receptor
DAF	decay accelerating factor
DAG	diacylglycerol
DAMP	danger-associated molecular pattern
DC	dendritic cells
D gene	diversity minigene joining *V* and *J* segments to form variable region
DMARD	disease-modifying antirheumatic drug
DNP	dinitrophenyl
DTH	delayed-type hypersensitivity
DTP	diphtheria, tetanus, pertussis triple vaccine
EAE	experimental autoimmune (allergic) encephalomyelitis
EBV	Epstein–Barr virus
ELISA	enzyme-linked immunosorbent assay
EM	electron microscope
Eø	eosinophil
EPO	erythropoietin
ER	endoplasmic reticulum
ES	embryonic stem (cell)
ET	exfoliative toxins
F(B)	factor (B, etc.)
Fab	monovalent Ig antigen-binding fragment after papain digestion
$F(ab')_2$	divalent antigen-binding fragment after pepsin digestion
FACS	fluorescence-activated cell sorter
FasL	Fas-ligand
Fc	Ig crystallizable-fragment originally; now non-Fab part of Ig
FcγR	receptor for IgG Fc fragment
FDC	follicular dendritic cell
flt-3	flk-2 ligand
(sc)Fv	(single chain) V_H–V_L antigen binding fragment
GADS	GRB2-related adaptor protein
g.b.m.	glomerular basement membrane
G-CSF	granulocyte colony-stimulating factor
GEFs	guanine-nucleotide exchange factors
GM-CSF	granulocyte–macrophage colony-stimulating factor
gp*n*	*n* kDa glycoprotein
GRB2	growth factor receptor-binding protein 2
GSK3	glycogen synthase kinase 3
GVH	graft versus host
H-2	the mouse major histocompatibility complex
H-2D/K/L(A/E)	main loci for classical class I (class II) murine MHC molecules
HAMA	human antimouse antibodies
HATA	human antitoxin antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCMV	human cytomegalovirus
HEL	hen egg lysozyme
HEV	high-walled endothelium of postcapillary venule
HIV	human immunodeficiency virus
HLA	human major histocompatibility complex
HLA-A/B/C(DP/DQ/DR)	main loci for classical class I (class II) human MHC molecules

HMG	high mobility group
HR	hypersensitive response
HRF	homologous restriction factor
HSA	heat-stable antigen
HSC	hematopoietic stem cell
hsp	heat-shock protein
5HT	5-hydroxytryptamine
HTLV	human T-cell leukemia virus
H-Y	male transplantation antigen
IBD	inflammatory bowel disease
ICAM-1	intercellular adhesion molecule-1
Id (αId)	idiotype (anti-idiotype)
IDC	interdigitating dendritic cells
IDDM	insulin-dependent diabetes mellitus
IDO	indoleamine 2,3-dioxygenase
IEL	intraepithelial lymphocyte
IFNα	α-interferon (also IFNβ, IFNγ)
IFR	interferon-regulated factor
Ig	immunoglobulin
IgG	immunoglobulin G (also IgM, IgA, IgD, IgE)
sIg	surface immunoglobulin
Ig-α/Ig-β	membrane peptide chains associated with sIg B-cell receptor
IgSF	immunoglobulin superfamily
IL-1	interleukin-1 (also IL-2, IL-3, etc.)
iNOS	inducible nitric oxide synthase
IP_3	inositol trisphosphate
ISCOM	immunostimulating complex
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITP	idiopathic thrombocytopenic purpura
IVIg	intravenous immunoglobulin
JAK	Janus kinases
J chain	polypeptide chain in IgA dimer and IgM pentamer
J gene	joining gene linking *V* or *D* segment to constant region
*K*a(d)	association (dissociation) affinity constant (usually Ag–Ab reactions)
kDa	units of molecular mass in kilodaltons
KIR	killer immunoglobulin-like receptors
KLH	keyhole limpet hemocyanin
LAK	lymphokine-activated killer cell
LAMP	lysosomal-associated membrane proteins
LAT	linker for activation of T-cells
LATS	long-acting thyroid stimulator
LBP	LPS-binding protein
LCM	lymphocytic choriomeningitis virus
$Le^{a/b/x}$	$Lewis^{a/b/x}$ blood group antigens
LFA-1	lymphocyte function-associated antigen-1
LGL	large granular lymphocyte
LHRH	luteinizing hormone releasing hormone
LIF	leukemia inhibiting factor
LPS	lipopolysaccharide (endotoxin)
LRR	leucine-rich repeat
LT(B)	leukotriene (B etc.)
mAb	monoclonal antibody
MAC	membrane attack complex
MAdCAM	mucosal addressin cell adhesion molecule

MALT	mucosa-associated lymphoid tissue
MAM	*Mycoplasma arthritidis* mitogen
MAP kinase	mitogen-activated protein kinase
MAPKKK	mitogen-associated protein kinase kinase kinase
MBL	mannose binding lectin
MBP	major basic protein of eosinophils (also myelin basic protein)
MCP	membrane cofactor protein (complement regulation)
MCP-1	monocyte chemotactic protein-1
M-CSF	macrophage colony-stimulating factor
MDP	muramyl dipeptide
MHC	major histocompatibility complex
MICA	MHC class I chain-related A chain
MIDAS	metal ion-dependent adhesion site
MIF	macrophage migration inhibitory factor
MIIC	MHC class II-enriched compartments
MLA	monophosphoryl lipid A
MLR	mixed lymphocyte reaction
MMTV	mouse mammary tumor virus
Mφ	macrophage
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	multiple sclerosis
MSC	mesenchymal stem cell
MSH	melanocyte stimulating hormone
MTP	microsomal triglyceride-transfer protein
MuLV	murine leukemia virus
NADP	nicotinamide adenine dinucleotide phosphate
NAP	neutrophil activating peptide
NBT	nitroblue tetrazolium
NCF	neutrophil chemotactic factor
NFAT	nuclear factor of activated T-cells
NFkB	nuclear transcription factor
NK	natural killer cell
NLR	NOD-like receptor
NO	nitric oxide
NOD	nonobese diabetic mouse
NZB	New Zealand Black mouse
NZB × W	New Zealand Black mouse × NZ White F1 hybrid
$\cdot O_2^-$	superoxide anion
OD	optical density
ORF	open reading frame
OS	obese strain chicken
Ova	ovalbumin
PAF(-R)	platelet activating factor (-receptor)
PAGE	polyacrylamide gel electrophoresis
PAMP	pathogen-associated molecular pattern
PBSCs	peripheral blood stem cells
PCA	passive cutaneous anaphylaxis
PCR	polymerase chain reaction
PERV	porcine endogenous retroviruses
PG(E)	prostaglandin (E etc.)
PHA	phytohemagglutinin
phox	phagocyte oxidase
PI3K	phosphatidylinositol 3-kinase
PIAS	protein inhibitor of activated STAT
pIgR	poly-Ig receptor

PIP_2	phosphatidylinositol diphosphate
PKC	protein kinase C
PKR	RNA-dependent protein kinase
PLC	phospholipase C
PLCγ2	phospholipase Cγ2
PMN	polymorphonuclear neutrophil
PMT	photomultiplier tube
PNH	paroxysmal nocturnal hemoglobinuria
PPAR	peroxisome proliferator-activated receptor
PPD	purified protein derivative from *Mycobacterium tuberculosis*
PRR	pattern recognition receptor
PTFE	polytetrafluoroethylene
PTK	protein tyrosine kinase
PWM	pokeweed mitogen
RA	rheumatoid arthritis
RANTES	regulated upon activation normal T-cell expressed and secreted chemokine
RAST	radioallergosorbent test
RF	rheumatoid factor
Rh(D)	rhesus blood group (D)
RIP	rat insulin promoter
RLR	RIG-like helicase receptor
RNAi	RNA interference
ROI	reactive oxygen intermediates
RSS	recombination signal sequence
SAP	serum amyloid P
SAP	sphingolipid activator protein
SAR	systemic acquired resistance
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus
SC	Ig secretory component
SCF	stem cell factor
scFv	single-chain variable region antibody fragment (V_H + V_L joined by a flexible linker)
SCG	sodium cromoglycate
SCID	severe combined immunodeficiency
SDF	stromal-derived factor
SDS	sodium dodecyl sulfate
SDS-PAGE	sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SEA (B etc.)	*Staphylococcus aureus* enterotoxin A (B etc.)
SEREX	serological analysis of recombinant cDNA expression libraries
siRNA	short-interfering RNA
SIV	Simian immunodeficiency virus
SLE	systemic lupus erythematosus
SLIT	sublingual allergen immunotherapy
SLP-76	SH2-domain containing leukocyte protein of 76 kDa
SOCs	suppressor of cytokine signaling
SPE	streptococcal pyogenic exotoxins
SRID	single radial immunodiffusion
SSA	streptococcal superantigen
STAT	signal transducer and activator of transcription
TACI	transmembrane activator and calcium modulator and cyclophilin ligand [CAML] interactor
T-ALL	T-acute lymphoblastic leukemia
TAP	transporter associated with antigen processing
TB	tubercle bacillus
Tc	cytotoxic T-cell

T-cell	thymus-derived lymphocyte
TCF	T-cell factor
TCR1(2)	T-cell receptor with γ/δ chains (with α/β chains)
TdT	terminal deoxynucleotidyl transferase
TG-A-L	polylysine with polyalanyl side-chains randomly tipped with tyrosine and glutamic acid
TGFβ	transforming growth factor β
Th(1/2/3/9/17)	T-helper cell (subset 1, 2, 3, 9, or 17)
THF	thymic humoral factor
Thp	T-helper precursor
TLI	total lymphoid irradiation
TLR	Toll-like receptor
TM	transmembrane
TNF	tumor necrosis factor
TNP	trinitrophenol
TPO	thrombopoietin
Treg	regulatory T-cell
Ts	suppressor T-cell
TSAb	thyroid stimulating antibodies
TSE	transmissible spongiform encephalopathy
TSH(R)	thyroid stimulating hormone (receptor)
TSLP	thymic stromal lymphopoietin
TSST	toxic shock syndrome toxin
TUNEL	TdT-mediated dUTP (deoxyuridine trisphosphate) nick end labeling
Vα(β/γ/δ)	variable part of TCR α(β/γ/δ) chain
VCAM	vascular cell adhesion molecule
vCJD	variant Creutzfeldt–Jakob disease
VCP	valosin-containing protein
VEGF	vascular endothelial cell growth factor
V	variable region gene for immunoglobulin or T-cell receptor
V_H	variable part of Ig heavy chain
VIMP	VCP-interacting membrane protein
VIP	vasoactive intestinal peptide
$V_{k/\lambda}$	variable part of k(λ) light chain
V_L	variable part of light chain
VLA	very late antigen
VLP	virus-like particle
VNTR	variable number of tandem repeats
VP1	virus-specific peptide 1
XL	X-linked
ZAP-70	zeta chain-associated protein of 70 kDa

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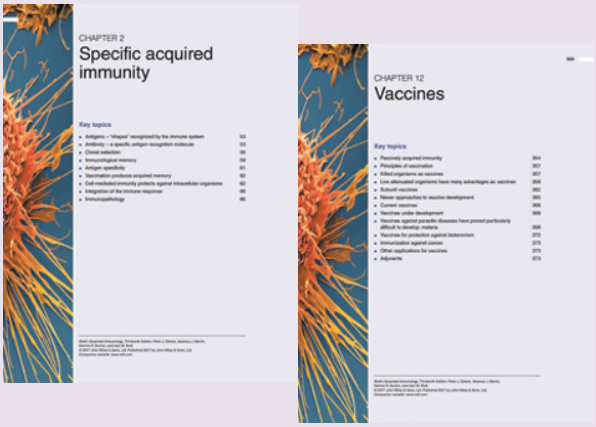

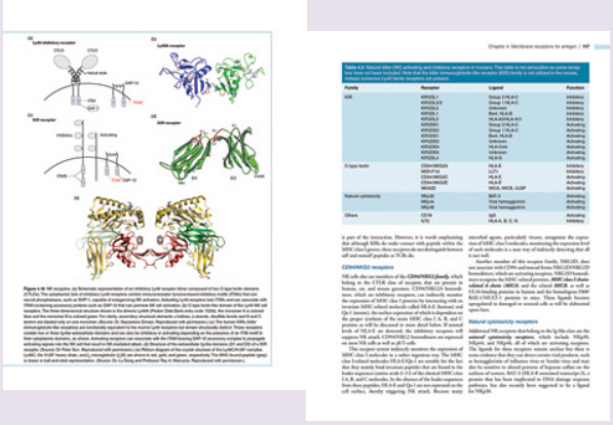

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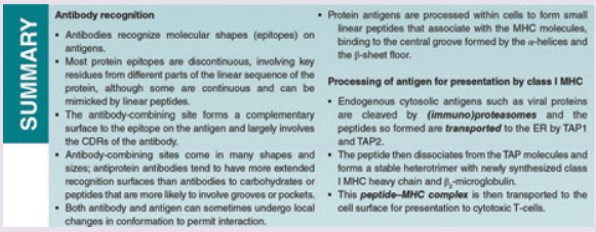

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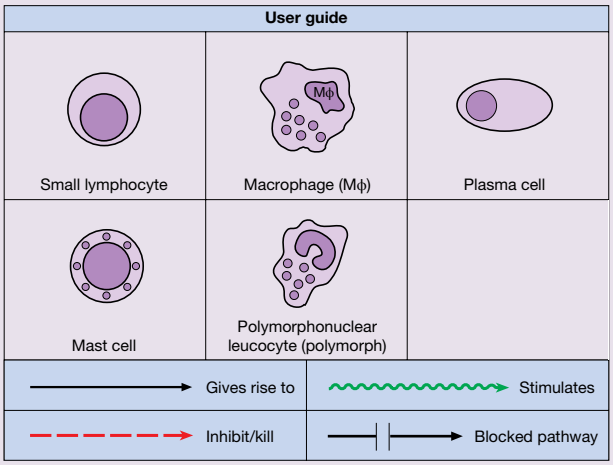
Cell guide

Throughout the illustrations, standard forms have been used for commonly occurring cells and pathways. A key to these is given in the figure below.



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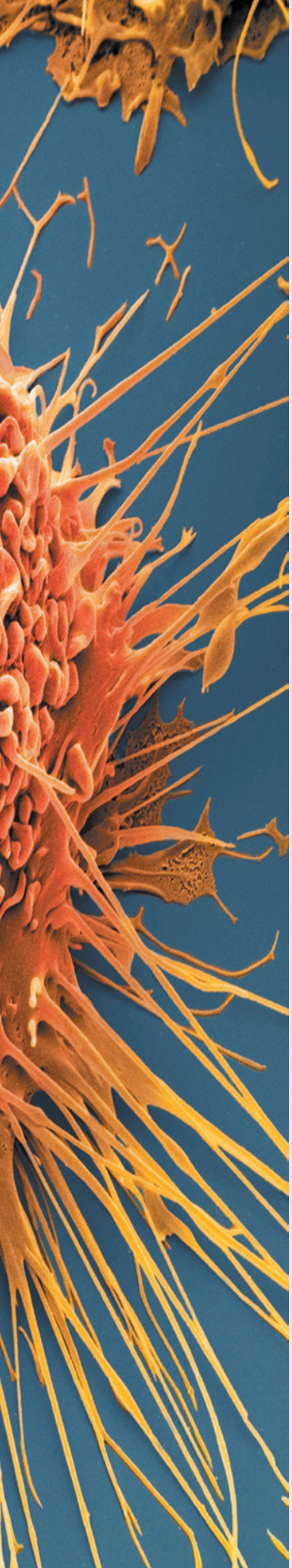
Part 1 Fundamentals of immunology



CHAPTER 1

Innate immunity

Key topics

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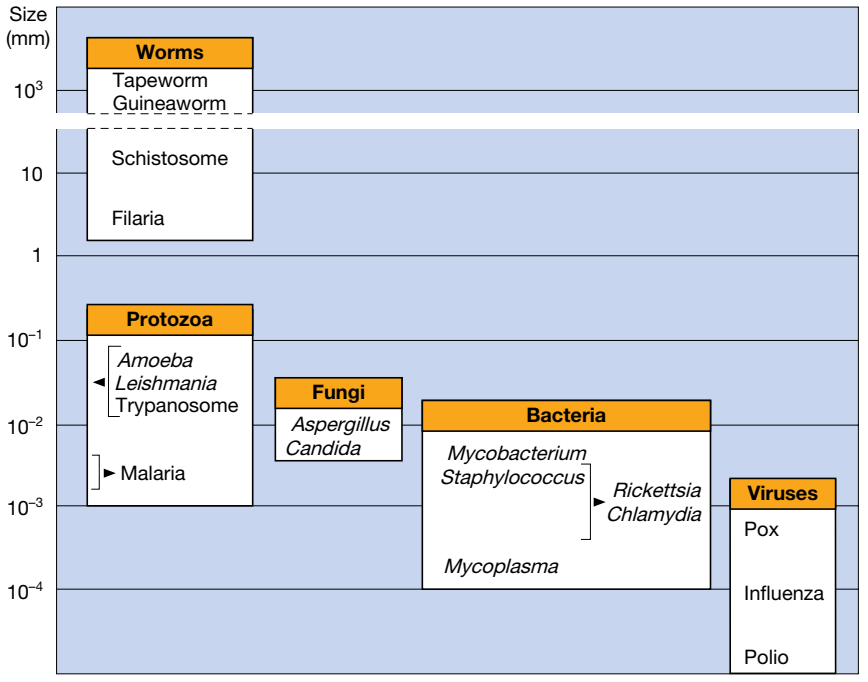

Figure 1.1 The formidable range of infectious agents that confront the immune system. Although not normally classified as such because of their lack of a cell wall, the mycoplasmas are included under bacteria for convenience. Fungi adopt many forms and approximate values for some of the smallest forms are given. Square brackets with right arrowheads indicate where a range of sizes is observed for the organism(s); square brackets with left arrowheads indicate list of organisms with a definite size.

Introduction

We live in a potentially hostile world filled with a bewildering array of infectious agents (Figure 1.1) of diverse shape, size, composition, and subversive character that would very happily use us as rich sanctuaries for propagating their "selfish genes" had we not also developed a series of defense mechanisms at least their equal in effectiveness and ingenuity (except in the case of many parasitic infections in which the situation is best described as an uneasy and often unsatisfactory truce). It is these defense mechanisms that can establish a state of immunity against infection (Latin *immunitas*, freedom from) and whose operation provides the basis for the delightful subject called "immunology."

Aside from ill-understood constitutional factors that make one species innately susceptible and another resistant to certain infections, a number of relatively nonspecific but nonetheless highly effective antimicrobial systems (e.g., phagocytosis, production of antimicrobial peptides and reactive oxygen species) have been recognized that are ***innate*** in the sense that they are not affected by prior contact with the infectious agent and take immediate effect upon encounter with anything that our immune systems deem to be an unwelcome guest. We shall discuss these systems and examine how, in the state of ***adaptive immunity***, their effectiveness can be greatly increased though custom tailoring of the response towards microbial intruders.

Knowing when to make an immune response

The ability to recognize and respond to foreign entities is central to the operation of the immune system

The vertebrate immune system is a conglomeration of cells and molecules that cooperate to protect us from infectious agents and also provides us with a surveillance system to monitor the integrity of host tissues. Although the immune system is quite elaborate, as we shall see, its function can be boiled down to two basic roles: ***recognition*** of foreign substances and organisms that have penetrated our outer defences (i.e., the skin epithelium and the mucosal surfaces of the gut and reproductive and respiratory tracts) and ***elimination*** of such agents by a diverse repertoire of cells and molecules that act in concert to neutralize the potential threat. Thus, a critical role of the immune system is to determine what is foreign (what immunologists often call "nonself") from what is normally present in the body (i.e., self). As a consequence, the cells and molecules that comprise the innate immune system are preoccupied with detecting the presence of particular ***molecular patterns*** that are typically associated with infectious agents (Figure 1.2). Charlie Janeway dubbed such molecules ***pathogen-associated molecular patterns (PAMPs)*** and it is these structures that trigger activation of the innate immune system.

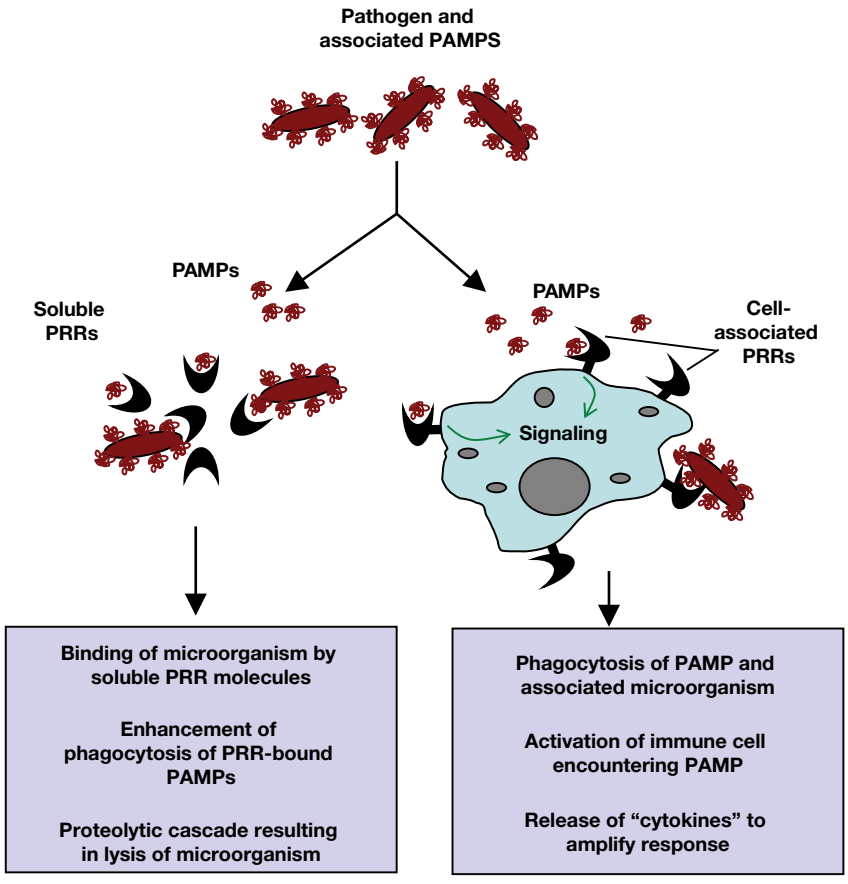

Figure 1.2 Pattern recognition receptors (PRRs) detect pathogen-associated molecular patterns (PAMPs) and initiate immune responses. PRRs can be either soluble or cell-associated and can instigate a range of responses upon encountering their appropriate ligands.

In addition to the fundamental roles of recognition and elimination of infectious agents, it is also very useful to be able to learn from encounters with pathogens and to maintain a reserve of cells that are able to respond swiftly to a new infection with a previously encountered microbe. Forewarned is forearmed, and in this situation it may be possible to deliver a decisive blow that ends a nascent infection before it has begun. Fortunately, our immune systems have also acquired this ability, which is what our ***adaptive immune system*** excels in, and this property is termed ***immunological memory***.

Immune responses need to be proportional to the infectious threat

Having established that recognition, elimination and memory of infectious agents are fundamental to the operation of an effective immune system, there is another important factor, ***proportionality***, which is key to ensuring that everything runs smoothly and that our immune systems do not lose sight of their purpose. This is because, as we shall see, the immune system can deploy a variety of weapons, each with their own risk of collateral damage, which can sometimes cause as much trouble as the infection itself. In extreme cases, the immune response can be much more destructive than the agent that triggered it (which is what underpins allergy) and in some situations this can lead to a sustained state of ***chronic immune activation*** where the immune system becomes confused between what is self and nonself and mounts sustained responses against its own tissues (called autoimmunity). Thus, there is a cost–benefit analysis that must be conducted during the initial stages of an infection to ascertain the nature of the infection, the level of infection, and whether the infectious agent is perturbing tissue function (by triggering cell death for example).

For these reasons, a number of ***immune regulatory*** mechanisms exist to ensure that immune responses are proportional to the level of threat that a particular infectious agent poses, as well as to ensure that immune responses are not directed against self and that responses directed against nonself are terminated when the infectious agent has been successfully eliminated from the body. Immune regulatory mechanisms (or ***immune checkpoints***) set thresholds for the deployment of immune responses and are vital to the proper operation of the immune system. As we shall see in later chapters, many diseases are caused by the failure of immune

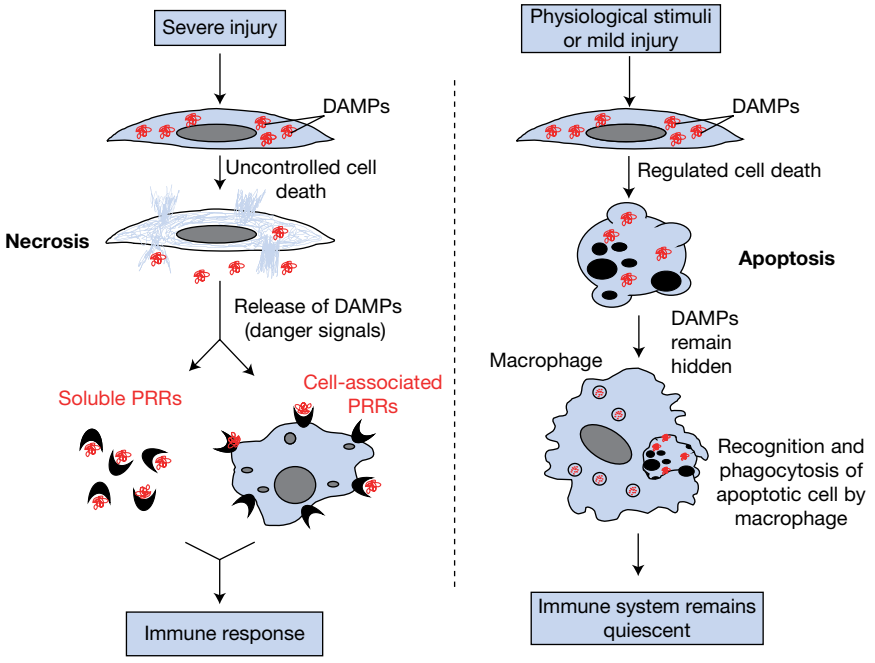

Figure 1.3 Necrotic cells release danger-associated molecular patterns (DAMPs), whereas apoptotic cells typically do not. Stimuli that induce necrosis frequently cause severe cellular damage, which leads to rapid cell rupture with consequent release of intracellular DAMPs. DAMPs can then engage cells of the immune system and can promote inflammation. On the other hand, because stimuli that initiate apoptosis are typically physiological and relatively mild, apoptotic cells do not rupture and their removal is coordinated by macrophages and other cells of the innate immune system, before release of DAMPs can occur. For this reason, apoptosis is not typically associated with activation of the immune system.

checkpoints, leading to conditions such as rheumatoid arthritis, Crohn's disease, and even cancer.

Tissue damage can also instigate an immune response

Aside from infection, there is a growing recognition that tissue damage, leading to nonphysiological cell death, can also provoke activation of the immune system (Figure 1.3). In this situation, the molecules that activate the immune system are derived from self but are not normally present within the extracellular space, or in a particular cellular compartment (for example when mitochondrial DNA is released into the cytoplasm). Such molecules, for which Polly Matzinger coined the term ***danger signals***, are normally safely sequestered within healthy cells and organelles and only escape when a cell dies via an uncontrolled mode of cell death, called ***necrosis*** (see Videoclip 1). Necrosis is typically caused by tissue trauma, burns, certain toxins, as well as other nonphysiological stimuli, and is characterized by rapid swelling and rupture of the plasma membranes of damaged cells. This permits the release of multiple cellular constituents that do not normally escape from healthy cells or organelles.

The precise identity of the molecules that act as danger signals – now more commonly called ***danger-associated molecular patterns (DAMPs)*** or alarmins – is an area of active investigation at present, but molecules such as HMGB1, a chromatin-binding protein, as well as the immunological messenger proteins interleukin-1α (IL-1α) and IL-33, represent good candidates. It might seem surprising that the immune system can also be activated by self-derived molecules, however, this makes good sense when one considers that events leading to necrotic cell death are often rapidly followed or accompanied by infection. Furthermore, if a pathogen manages to evade direct detection by the immune system, its presence will be betrayed if it provokes necrosis within the tissue it has invaded.

Before moving on, we should also note that there is another mode of cell death that frequently occurs in the body that is both natural and highly controlled and is not associated with plasma membrane rupture and release of intracellular contents. This mode of cell death, called ***apoptosis*** (see Videoclip 2), is under complex molecular control and is used to eliminate cells that have reached the end of their natural lifespans. Apoptotic cells do not activate the immune system because cells dying in this manner display molecules on their plasma membranes (e.g., phosphatidylserine) that mark these cells out for removal through phagocytosis before they can rupture and release their intracellular contents. In this way, DAMPs remain hidden during apoptosis and such cells do not activate the immune system (Figure 1.3).

Pattern recognition receptors detect nonself

Pattern recognition receptors (PRRs) raise the alarm

To identify potentially dangerous microbial agents, our immune systems need to be able to discriminate between "non-infectious self and infectious nonself" as Janeway elegantly put it. Recognition of nonself entities is achieved by means of an array of ***pattern recognition receptors and proteins*** (collectively called pattern recognition molecules) that have evolved to detect conserved (i.e., not prone to mutation) components of microbes that are not normally present in the body (i.e., PAMPs).

In practice, PAMPs can be anything from carbohydrates that are not normally exposed in vertebrates, proteins only found in bacteria, such as flagellin (a component of the bacterial flagellum that is used for swimming), double-stranded RNA that is typical of RNA viruses, as well as many other molecules that betray the presence of microbial agents. The cardinal rule is that a ***PAMP is not normally found in the body but is a common and invariant feature of many frequently encountered microbes***. Pattern recognition molecules also appear to be involved in the recognition of DAMPs released from necrotic cells.

Upon engagement of one or more of these pattern recognition molecules with an appropriate PAMP or DAMP, an immune response ensues (Figure 1.2). Fortunately, we have many ways in which an impending infection can be dealt with, and indeed it is a testament to the efficiency of our immune systems that the majority of us spend most of our lives relatively untroubled by infectious disease.

A variety of responses can occur downstream of pattern recognition

One way of dealing with unwelcome intruders involves the binding of soluble (humoral) pattern recognition molecules, such as ***complement*** (an enzyme cascade we will deal with later in this chapter), ***mannose-binding lectin***, ***C-reactive protein***, or ***lysozyme***, to the infectious agent. The binding of soluble pattern recognition molecules to a pathogen has a number of outcomes (Figure 1.2).

First, this can lead directly to ***killing of the pathogen*** through destruction of microbial cell wall constituents and breaching of the plasma membrane because of the actions of such proteins. Second, humoral factors are also adept at coating microorganisms (a process called ***opsonization***) and this greatly enhances their uptake through ***phagocytosis*** and subsequent destruction by phagocytic cells.

Other PRRs are cell associated and engagement of such receptors can also lead to ***phagocytosis*** of the microorganism followed by its destruction within phagocytic vesicles. Just as importantly, cellular PRR engagement also results in the activation of signal transduction pathways that greatly enhance the ***effector functions*** of cells bearing these receptors (such as increasing their propensity for phagocytosis or the production of antimicrobial proteins) and also culminate in the release of soluble messenger proteins (***cytokines***, ***chemokines***, and other molecules) that mobilize other components of the immune system. PRR engagement on effector cells can also result in ***differentiation*** of such cells to a more mature state that endows specialized functions on such cells. Later we will deal with a very important example of this when we discuss the issue of dendritic cell maturation, which is initiated as a consequence of engagement of PRR receptors on these cells by microbial PAMPs. Therefore, pattern recognition of a pathogen by soluble or cell-associated PRRs can lead to:

- direct lysis of the pathogen
- opsonization followed by phagocytosis
- direct phagocytosis via a cell-associated PRR
- enhancement of phagocytic cell functions
- production of antimicrobial proteins
- production of cytokines and chemokines
- differentiation of effector cells to a more active state.

There are several classes of pattern recognition receptor

As we shall see later in this chapter, there are a number of different classes of cell-associated PRRs (Toll-like receptors [TLRs], C-type lectin receptors [CTLRs], NOD-like receptors [NLRs], RIG-I-like receptors [RLRs], among others) and it is the engagement of one or more of these different categories of receptors that not only enables the ***detection of infection***, but also conveys information concerning the ***type*** of infection (whether yeast, bacterial, or viral in origin) and its ***location*** (whether extracellular, endosomal, or cytoplasmic). In practise, most pathogens are likely to engage several of these receptors simultaneously, which adds another level of complexity to the signaling outputs that can be generated through engagement of these receptors. This, in turn, enables the ***tailoring of the subsequent immune response*** towards the particular vulnerabilities of the pathogen that raised the alarm.

Cells of the immune system release messenger proteins that shape and amplify immune responses

An important feature of the immune system is the ability of its constituent cells to communicate with each other upon encountering a pathogen to initiate the most appropriate response. As we shall see shortly, there are quite a number of different "ranks" among our immune forces, each with their own particular arsenal of weapons, and it is critical that a measured and appropriate response is deployed in response to a specific threat. This is because, as we have already alluded to, many of the weapons that are brought into play during an immune response are destructive and have the potential to cause collateral damage. Furthermore, initiation and escalation of an immune response carries a significant metabolic cost to

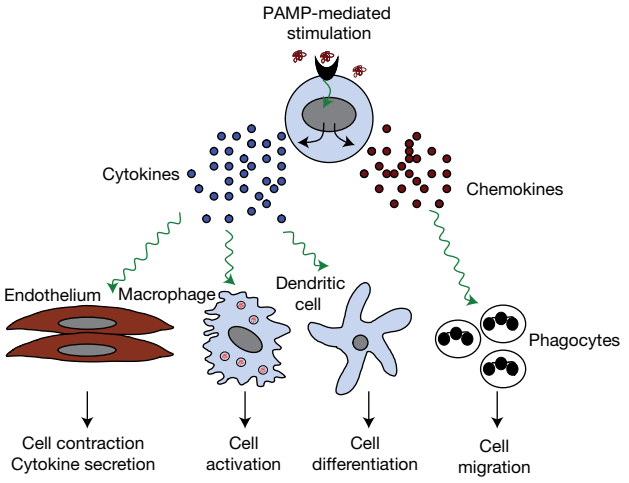

Figure 1.4 Cytokines and chemokines can have pleiotrophic effects. Stimulation of cells of the innate immune system frequently leads to the production of inflammatory cytokines and chemokines that trigger responses from other cell types, as depicted. Note that the effects of chemokines and cytokines shown are not exhaustive.

the organism (due to the necessity to make numerous new proteins and cells). Thus, communication among the different immune battalions is essential for the initiation of the correct and proportional response to the particular agent that triggered it. Although cells of the immune system are capable of releasing numerous biologically active molecules with diverse functions, two major categories of proteins – ***cytokines*** and ***chemokines*** – have particularly important roles in shaping and escalating immune responses.

Cytokines are a diverse group of proteins that have ***pleiotropic effects***, including the ability to activate other cells, ***induce differentiation*** to particular effector cell subsets and enhance microbicidal activity (Figure 1.4). Cytokines are commonly released by cells of the immune system in response to PAMPs and DAMPs, and this has the effect of altering the ***activation state*** and ***behavior*** of other cells to galvanize them into joining the fight. Chemokines are also released upon encountering PAMPs/DAMPs and typically serve as ***chemotactic factors***, helping to lay a trail that guides other cells of the immune system to the site of infection or tissue damage. Both types of messenger proteins act by diffusing away from the cells secreting them and binding to cells equipped with the appropriate plasma membrane receptors to receive such signals.

The interleukins are an important class of cytokines

A particularly important group of cytokines in the context of immune signaling is the interleukin (IL) family, which has over 40 members at present, numbered in the order of their discovery. Thus, we have IL-1, IL-2, IL-3, IL-4, etc. Interleukins, by definition, are cytokines that signal between members of the leukocyte (i.e., white blood cell) family. However, these molecules often have effects on other tissues that the immune system needs to engage in the course of initiating immune responses. So, although ***interleukins are heavily involved in communication between immune cells***, these cytokines also have profound effects on endothelial cells lining blood capillaries, hepatocytes in the liver, epithelial cells, bone marrow stem cells, fibroblasts, and even neurons within the central nervous system. It is also important to note that ***the same interleukin can trigger different functional outcomes*** depending on the cell type that it makes contact with; these are simply "switch" molecules that can turn different functions on or off in the cells they encounter. The function that is switched on, or off, will depend on the target cell and the other cytokine signals that this cell is receiving in tandem. Thus, just as we integrate lots of different sources of information (e.g., from colleagues, friends, family, newspapers, TV, radio, books, websites, social media, etc.) in our daily lives that can all influence the decisions we make, ***cells also integrate multiple sources of cytokine information to make decisions*** on whether to divide, initiate phagocytosis, express new gene products, differentiate, migrate, and even die. We will discuss cytokines, chemokines, and their respective receptors at length in Chapter 8.

Immune responses are tailored towards particular types of infection

Not all pathogens are equal

We will shortly get into the specifics of the immune system, but before doing so it is useful to consider the diversity of infectious agents that our immune systems may encounter (Figure 1.1), and to contemplate whether a "one size fits all" immune response is likely to suffice in all of these situations. One of the frustrations expressed by many students of immunology is that the immune system appears to be almost byzantine in its complexity. Although this is indeed partly true, the reasons for this are two-fold. First, because there are different types of infection, ***immune responses need to be tailored towards the particular class of infection*** (whether viral, extracellular bacterial, intracellular bacterial, worm, fungal, etc.) in order to mount the most effective immune response towards a particular infectious agent. Second, although there is indeed complexity in the immune system, there is also a great deal of order and repeated use of the same basic approach when recognizing pathogens and initiating an immune response. Therefore, although many of molecules used in the pursuit of pathogen recognition belong to different classes, many of these plug into the same effector mechanisms as soon as the pathogen is successfully identified. So, dear reader, please bear with us while we try to make sense of the apparent chaos. But meanwhile, let us get back to pathogens to consider why our immune systems need to be fairly elaborate and multi-layered.

Infectious agents are a broad church and have evolved different strategies to invade and colonize our bodies, as well as to evade immune detection. Some, such as yeasts and extracellular

bacteria, are happy to live in the extracellular space, stealing nutrients that would otherwise nourish our own tissues. Others, such as intracellular bacteria and viruses, invade the cytoplasm and even our genomes and may lurk for months or years within our bodies. Then there are the large worms (helminths) and unicellular eukaryotic protozoa that live parasitic lifestyles with their own particular adaptations.

Because of the diversity of infectious agents, all of which have their own strategies to evade and neutralize the best efforts of our immune systems, we have responded by evolving multiple ways of dealing with intruders, depending on the nature of the infectious agent and how this type of infection is best dealt with. Indeed, it is the constant threat of infection (rather than environmental change) that is the major driver of natural selection over the short term, as viruses and bacteria can mutate with frightening speed to acquire adaptations that can leave their hosts highly vulnerable to infection. For this reason, genes that are involved in the functioning and regulation of the immune system are among the most diverse among human and animal populations (i.e., undergoing the fastest rates of mutation) and are frequently duplicated into large gene families (which are typically variations on a very useful theme) that permits us to hedge our bets and stay ahead in the ongoing battle against those organisms that would have us for lunch.

Because of the diverse nature of the infectious agents that we are confronted with, ***immune responses come in a number of different flavors*** and are ***tailored towards the nature of the pathogen that provoked the response*** in the first place. As the book progresses, we will elaborate on this concept in much more detail, but do keep this in mind when trying to understand the underlying simplicity among the apparent complexity of the immune responses that we will encounter.

There are different types of immune response

So, what do we mean by different types of immune response? We are not going to be exhaustive at this stage, but let us consider the difference between how our immune system might deal with a virus versus an extracellular bacterium. For both pathogen classes, a system that enables us to recognize these agents and to remove them, either by destroying them (through membrane lysis) or by eating them up (through phagocytosis) followed by degradation within endosomes, would likely be very effective. And indeed, our immune systems have evolved a number of ways of doing both of these things; as we have mentioned earlier, there are multiple classes of proteins that ***recognize and lyse bacteria and viruses*** in the extracellular space (complement, acute phase proteins, antimicrobial peptides) and the same proteins are frequently involved in ***decorating infectious agents for recognition and phagocytosis*** by phagocytic cells (e.g., macrophages and neutrophils) that are specialized in doing just that. Molecules that are involved in the decoration of infectious agents to prepare them for removal are called ***opsonins*** (from the Greek, to prepare for eating) in immunological parlance. So far, so good.

However, once the virus enters a cell, the proteins and phagocytic cells mentioned above will no longer be of any use in dealing with this type of infection as proteins cannot freely diffuse across the plasma membrane to either lyse or tag the infectious agent for phagocytosis. So, it is here that the immune response to an extracellular bacterial infection versus an intracellular viral infection must diverge, as now we need a way of looking inside cells to see whether they are infected or not. Consequently, we have evolved a number of ***intracellular PRRs that can detect pathogens that have entered cells***, and this results in the production of signals (e.g., cytokines and chemokines) that alert the immune system to the presence of an infectious agent. Just as importantly, we have also evolved a fiendishly clever way of displaying the breakdown products of pathogens to cells of the adaptive immune system (***major histocompatibility complex*** [MHC] molecules are centrally involved in this process) irrespective of whether the infectious agent lives inside or outside the cell. We will deal with MHC molecules extensively in Chapters 4 and 5. The latter process enables a cell that has been infected by a virus to display fragments of viral proteins on its plasma membrane, within grooves present in MHC molecules that have evolved for this purpose, thereby alerting cells of the immune system to the nature of its predicament. Ingenious!

So, how does our immune system deal with a virus or other pathogen that has invaded a host cell? Although some specialized phagocytic cells (i.e., macrophages) can kill intracellular bacteria that have invaded them, most cells cannot do this very effectively and so another solution is required. For most other cell types, this is achieved through ***killing the infected cell*** (typically by apoptosis) and removing it through ***phagocytosis***, which is easy to write, but involves a series of steps that permit the recognition of infected host cells, the delivery of the "kiss of death" and the engulfment of the infected corpse in a manner that minimizes the escape of the pathogen lurking within. Our immune systems have solved the intracellular infection problem by evolving cells (called ***cytotoxic T-cells*** and ***natural killer cells***) that have the ability to detect infected cells and to kill them; we will deal with natural killer (NK) cells in detail later in this chapter.

Obviously, such powers of life or death carry with them the heavy responsibility of ensuring that uninfected cells are not accidently killed, as it is a basic tenet of multicellularity that one does not go around randomly killing good cellular citizens. Thus, a number of checks and balances have been incorporated into this killing system to ensure that only errant cells are dispatched in this way. We will deal with the detailed mechanisms of cytotoxic T-cell-mediated killing in Chapter 8.

However, some pathogens require a different approach, which involves sending in large numbers of highly phagocytic cells (such as neutrophils) into a tissue that can also deploy destructive proteases, carbohydrases (such as lysozyme), and other nasty molecules into the extracellular space in order to quickly overwhelm and destroy a rapidly dividing pathogen, or a worm parasite. This type of response comes with a certain

degree of collateral damage (due to the use of enzymes that do not discriminate between friend and foe) and is typically only mounted when this is warranted.

From the preceding discussion, we hope that it will be evident that ***different types and severities of immune responses are necessary to fight different types of infection*** and it is for this reason that the immune system has a variety of cells and weapons at its disposal. Thus, there are different types of immune response, broadly dictated by whether a pathogen lives ***intracellularly or extracellularly***.

The PRRs of the innate immune system generate a molecular fingerprint of pathogens

As we have already alluded to, the PRRs not only help to identify the ***presence*** of infectious agents through detection of their associated PAMPs, but they also convey information as to the ***nature*** of the infectious agent (whether of fungal, bacterial or viral origin) and the ***location*** of the infectious agent (whether extracellular, intracellular, endosomal, cytoplasmic, or nuclear). This is because, as we shall see later, the various classes of PRRs (e.g., Toll-like receptors, C-type lectin receptors, NOD-like receptors, cytoplasmic DNA sensors) are specific for different types of pathogen components (i.e., PAMPs), and reside in different cellular compartments. Thus, we have an ingenious system where the combination of PRRs that is engaged by an infectious agent conveys important information about the precise nature and location of infection and generates a ***molecular fingerprint of the pathogen***. In turn, ***this information is then used to shape the most effective immune response*** towards the particular pathogen class that provoked it.

Cytokines help to shape the type of immune response that is mounted in response to a particular pathogen

We have already mentioned that cytokines are involved in communication between cells of the immune system and help to alert the correct cell types that are appropriate for dealing with different classes (i.e., whether viral, bacterial, yeast, etc.) of infectious agents. Cytokines are also capable of triggering the ***maturation and differentiation*** of immune cell subsets into more specialized ***effector cell*** classes that possess unique capabilities to enable them to fight particular types of infection. In this way, detection of an infection (i.e., PAMPs) by a particular class of PRR is translated into the most appropriate immune response ***through the production of particular patterns of cytokines and chemokines***. These cytokine patterns then call into play the correct cell types and trigger maturation of these cells into even more specific effector cell subtypes. Later, in Chapter 8, we will see how this process is used to produce specialized subsets of T-cells that are central to the process of adaptive immunity. Let us now look at how the different layers of our immune defenses are organized.

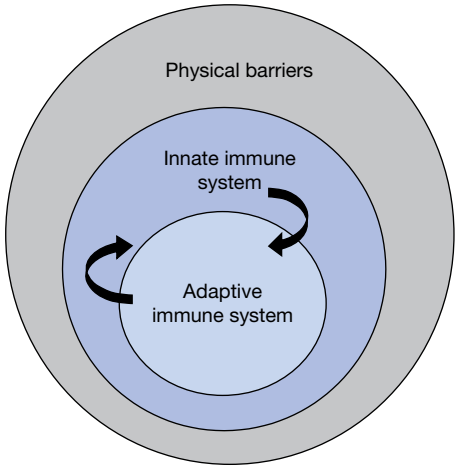

Figure 1.5 The vertebrate immune system comprises three levels of defense. The physical barriers of the skin and mucosal surfaces comprise the first level of defense. Infectious agents that successfully penetrate the physical barriers are then engaged by the cells and soluble factors of the innate immune system. The innate immune system is also responsible for triggering activation of the adaptive immune system, as we will discuss later in this chapter. The cells and products of the adaptive immune system reinforce the defense mounted by the innate immune system.

Innate versus adaptive immunity

Three levels of immune defense

Before we get into the details, we will first summarize how the immune system works in broad brushstrokes. The vertebrate immune system comprises three levels of defense (Figure 1.5). First, there is a ***physical barrier*** to infection that is provided by the skin on the outer surfaces of the body, along with the mucous secretions covering the epidermal layers of the inner surfaces of the respiratory, digestive, and reproductive tracts. Any infectious agent attempting to gain entry to the body must first breach these surfaces that are largely impermeable to microorganisms; this is why cuts and scrapes that breach these physical barriers are often followed by infection. The second level of defense is provided by the ***innate immune system***, a relatively broad-acting but highly effective defense layer that is largely preoccupied with trying to kill infectious agents from the moment they enter the body. The actions of the innate immune system are also responsible for alerting the cells that operate the third level of defense, the ***adaptive (or acquired) immune system***. The latter cells represent the elite troops of the immune system and can launch an attack that has been specifically adapted to the nature of the infectious agent using sophisticated weapons such as antibodies. As we shall see, the innate and adaptive immune systems each have their own particular advantages and disadvantages and therefore act cooperatively to achieve much more effective immune protection than either could achieve in isolation.