From Basic to Clinical Immunology

Vladimir V. Klimov

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Tu se' omai al purgatorio giunto:

vedi là il balzo che 'l chiude dintorno:

vedi l'entrata là 've par disgiunto.

You have finally arrived in Purgatory:

There you can see the cliffs which wraps around it;

There is the entrance, where there is a split.

Dante Alighieri. La Divina Commedia.

Purgatorio. Canto IX, 49-51

Preface

Why is immunology so important? The immune system has involvement in almost all fields related to health and disease. Infections continue to confront human health and well-being on a global scale. Inflammation contributes to the lung, heart and joint diseases, and diabetes mellitus; cancers have to evade immune surveillance, and immune dysregulation leads to allergies that are increasingly prevalent across the world. Only improved understanding of the mechanisms by which microbes, allergens, and tumor cells cause disease will result in the development of diagnostic, therapeutic, and preventative strategies to combat this threat.

However, we are only beginning the voyage of immunology, and there is much we still need to research and understand. The study of basic immunology may provide students with an opportunity to relate the findings of fundamental scientific investigations to clinical problems. Since immunology is a very complex science, this manual has been arranged in a simplistic yet logical manner so that students could perceive basic principles of the subject and, at the same time, understand important particularities.

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About the Author

Vladimir Klimov, MD, PhD, DSc
is the head of Siberian State Medical University's Immunology and Allergy Department. He is the author of the multimedia course "Basic Immunology Overview," which was published online in the late 1990s and became popular among students and physicians throughout the world. For many years, Prof. Klimov contributed to immunology education internationally with great enthusiasm. This manual was written at the interface of fundamental and clinical immunology. "What is clinical immunology? It is a medical science about the commensal germs reactivation, breakdown of natural tolerance, and disorders in cancer containment," says Prof. Klimov.
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List of Abbreviations

AAMPs	Allergen-associated molecular patterns
AChR	Acetylcholine receptor
ACTH	Adrenocorticotropic hormone
ADA	Adenosine deaminase
ADDC	Antibody-dependent cellular cytotoxicity
ADH	Antidiuretic hormone, vasopressin
AFP	α fetoprotein
AHR	A signaling molecule
AIDS	Acquired immunodeficiency syndrome
AIM-2	"Absent in melanoma 2," a part of ALR
AIRE	Autoimmune regulator gene
AK2	Mitochondrial adenylate kinase 2
ALPS	Autoimmune lymphoproliferative syndrome
ALR	AIM-2-like receptor
APC	Antigen-presenting cell
APECED	Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy
AR	Activating receptor
ASC	An adapter protein
ASIT	Allergen-specific immunotherapy
ATM	Ataxia-telangiectasia mutated gene
ATP	Adenosine triphosphate
B2M	β_2 microglobulin
B7-1, B7-2	Costimulatory molecules, counterreceptors for CD28 and CTLA-4
BAFF	B-cell activation factor
BALT	Bronchus-associated lymphoid tissue
BAU	Bioequivalent allergen unit
BCR	B-cell receptor
BLC	B-lymphocyte chemoattractant, CXCL13
BRAK	Breast and kidney-expressed chemokine, CXCL14
BTK	Tyrosine kinase (Bruton's) gene
C1NH	C1 inhibitor gene
C2a, etc.	Complement fragments
C3bBb	Alternative pathway C3 convertase
C3bBb3b	Alternative pathway C5 convertase
C4b2b	Classical pathway C3 convertase
C4b2b3b	Classical pathway C5 convertase
CAMs	Cell adhesion molecules
cAMP	Cyclic adenosine monophosphate
CARD	Caspase activation and recruitment domain
CCL	A chemokine subfamily
CCP	Cyclic citrullinated peptide
CCR	A receptor to CCL and other chemokines
CD	Cluster of differentiation, a differentiation marker
cDC	Classical (conventional) dendritic cell, mDC
CEA	Carcinoembryonic antigen
CFS	Chronic fatigue syndrome
CFSE	Carboxyfluorescein succinimidyl ester, a fluorochrome
CgA	Chromogranin A
CGD	Chronic granulomatous disease
cGMP	Cyclic guanosine monophosphate
CH	Constant heavy domain
CL	Constant light domain
CLA	Cutaneous lymphocyte-associated antigen

CLIP	A component of Ii chain
CLR	C-type lectin receptor
CLS	Capillary leak syndrome
CMV	*Cytomegalovirus*
CNS	Central nervous system
ConA	Concanavalin A (mitogen)
COP	CARD-only protein
COPD	Chronic obstructive pulmonary disease
CpG	Motif in a PAMP molecule
CR	Complement receptor
CRD	Carbohydrate recognition domain
CREST	Syndrome composed of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
CRISPR/Cas9 technique	A novel gene editing technology (e.g., for vaccine development)
CSF	Colony-stimulating factor
CTACK	Cutaneous T-cell-attracting chemokine, CCL27
CTLA-4	Cytotoxic T lymphocyte-associated protein-4, CD152
CVID	Common variable immunodeficiency
CX3CL	A chemokine subfamily
CX3CR	A receptor to CX3CL and other chemokines
CXCL	A chemokine subfamily
CXCR	A receptor to CXCL and other chemokines
CYBB	Gene encoding phagocyte NADPH oxidase (phox) complex
DAF	Decay-accelerating factor, CD55
DAMPs	Damage-associated molecular patterns
DC	Dendritic cell
DGP	Deamidated gliadin peptide
DHEA	Dehydroepiandrosterone
DN	Double-negative (thymocytes)
DOCK8	A signaling molecule
DP	Double-positive (thymocytes)
DPI	Dry powder inhaler
dsDNA	Double-stranded DNA
dsRNA	Double-stranded RNA
DTaP-HepB-IPV	Vaccine against diphtheria, tetanus, pertussis, hepatitis B, polio
DTaP-IPV/Hib	Vaccine against diphtheria, tetanus, pertussis, polio, *H. influenzae* type b infection
EBV	*Epstein-Barr Virus*
ECA	Endothelial cell antigen
ECM	Extracellular matrix
ELC	EBI1 ligand chemokine, exodus-3, CCL19
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	A modification of ELISA
ENA-78	Epithelial-derived neutrophil-activating peptide 78, CXCL5
Fab	Fragment antigen binding
Fas	An apoptosis receptor, CD95
FasL	Ligand for Fas, CD178
Fc	Fragment crystallizable
FCFM	Flow cytofluorometry
FCGR3A	CD16 gene
FcR	Fc receptor
fDC	Follicular dendritic cell

FERMT3	Gene encoding an intracellular protein, which interacts with β integrins
FEV1	Forced expiratory volume in 1 second
FGF	Fibroblast growth factor
FITC	Fluorescein isothiocyanate, a fluorochrome
FoxP3	A transcription factor
FVC	Full (forced) vital capacity of lungs
G6PD	Glucose-6-phosphate dehydrogenase
GABA	γ aminobutyric acid
GAD	Glutamate decarboxylase
GALT	Gut-associated lymphoid tissue
GATA-3	A signaling molecule
GBM	Glomerular basement membrane
GCP-2	Granulocyte chemotactic protein-2, CXCL6
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal tract
GLYCAM-1	Glycosylation-dependent cell adhesion molecule-1, a mucin-type CAM
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRB2	An adaptor protein
GROα	Growth-regulated protein-α, CXCL1
GROβ	Growth-regulated protein-β, MIP-2α, CXCL2
GROγ	Growth-regulated protein-γ, MIP-2β, CXCL3
GVHD	Graft-versus-host disease
H	Heavy (chain)
H1-H4	Histamine receptors
HCC-1	Hemofiltrate CC chemokine-1, CCL14
HE4	Human epididymis protein 4
HEP	Histamine equivalent prick test (unit of allergen activity)
HepA	Vaccine against hepatitis A
HepB	Vaccine against hepatitis B
HEV	High endothelial venules
HHV-8	*Human Herpes Virus 8*
Hib	Vaccine against *H. influenzae type b* infection
HIN200	Domain, which consists of hematopoietic expression, IFN-inducible and nuclear localization of 200 amino acids
HIV	*Human Immunodeficiency Virus*
HLA	Human leukocyte antigens, human histocompatibility complex
HPA	Hypothalamus–pituitary–adrenal (axis)
HPV	*Human Papilloma Virus*
HPV2, HPV4, HPV9	Vaccines against *Human Papilloma Virus* infection
HSV	*Herpes Simplex Virus*
5-HT	5-hydroxytryptamine, serotonin
hTM5	Human tropomyosin isoform 5
HZV	*Herpes Zoster Virus*
ICAM-1,-2,-3	Intercellular adhesion molecules
ICOS	A costimulatory molecule
IEL	Intraepithelial lymphocytes, γδT cells
IFNα,-β,-γ	Interferons
IFNGR1	IFNγRI gene
IGAD-1	IgA deficiency locus-1
IGF-1	Insulin-like growth factor 1
IGH	Locus of immunoglobulin H chain genes
IGK	Locus of immunoglobulin κ chain genes
IGL	Locus of immunoglobulin λ chain genes

IIV	Vaccine against seasonal influenza (flu)
IL	Interleukin
IL1ra	IL1 receptor antagonist
ILC	Innate lymphoid cell
IgM, IgG, IgA, IgE, IgD	Immunoglobulins or antibodies
IP-10	IFNγ-induced protein-10, CXCL10
IPEX	X-linked immunodysregulation, polyendocrinopathy, enteropathy syndrome
IR	Inhibitory receptor
I-TAC	IFN-inducible T-cell α chemoattractant, CXCL11
ITAM	Immunoreceptor tyrosine-based activation motif
ITGB2	CD18 gene
ITIM	Immunoreceptor tyrosine-based inhibitory motif
iTreg	Induced T-regulatory cell
IVIG	Intravenous immunoglobulin (administration)
JAK	Janus (tyrosine) kinase
Ki-67	A nuclear protein, a marker of the cell proliferation assay
KIR	Killer immunoglobulin-like receptor
KLRG1	Killer lectin-like receptor G1
L	Light (chain)
LAD	Leukocyte adhesion deficiency
LAT	An adaptor protein
LC-1	Liver cytosol antigen 1
Lck	A tyrosine kinase
LFA-1	Lymphocyte function-associated antigen-1, an integrin
LILR	Leukocyte immunoglobulin-like receptor
LKM	Liver/kidney microsomes
LMP-2, LMP-7	Components of the proteasome
LPS	Lipopolysaccharide
LRR	Leucine-rich domain
LTB4	Leukotriene B4
LTC4	Leukotriene C4
LTH	Lactotropic hormone, prolactin
LTi	Lymphoid tissue inducer cell
LTT	Lymphoblast transformation test
Lyn	A tyrosine kinase
M1	Type 1 macrophage
M2	Type 2 macrophage
MAC	Membrane attack complex, C5b6789...9
MadCAM-1	Mucosal vascular addressin cell adhesion molecule-1
MALT	Mucosa-associated lymphoid tissue
MBL	Mannose-binding lectin
MBP	Myelin basic protein
MCP-1	Macrophage chemoattractant protein-1, CCL2
MCP-2	Macrophage chemoattractant protein-2, CCL8
MCP-3	Macrophage chemoattractant protein-3, CCL7
M-CSF	Macrophage colony-stimulating factor
mDC	Myeloid (classical, conventional) dendritic cell, cDC
MDI	Meter-dose inhaler
MDSC	Myeloid-derived suppressor cell
MECL	A component of the proteasome
MEC	Mucosa-associated Epithelial Chemokine, CCL28

MEFV gene	Gene for pyrin
MenACWY, MenB, MPSV4	Meningococcal vaccines
MenCY-Hib	Vaccine against meningococcal and *H. influenzae* type b infections
MIG	Monokine induced by IFNγ, CXCL9
MIP-1α	Macrophage inflammatory protein-1α, CCL3
MIP-1β	Macrophage inflammatory protein-1β, CCL4
MIP-2α	Macrophage inflammatory protein-2α, GROβ, CXCL2
MIP-2β	Macrophage inflammatory protein-2β, GROγ, CXCL3
MMR	Vaccine against measles, mumps, rubella
MMRV	Vaccine against measles, mumps, rubella, varicella
mRNA	Messenger RNA
MSH	Melanocyte-stimulatory hormone
MTS, MTT	Dyes for the colorimetric proliferation assays
MuSK	Muscle-specific receptor tyrosine kinase
MyD88	An adapter protein for TLR signaling
MZ	Marginal zone (in the spleen)
NACHT	A central domain in NLRs
NALT	Nasal-associated lymphoid tissue
NAP-2	Neutrophil-activating peptide-2, CXCL7
NBN	Nibrin gene important for cell cycle
nBreg	Natural B-regulatory cell
NBT	Nitroblue tetrazolium
NCA	Neutrophilic cytoplasmic antigens
NCK	An adaptor protein
NCR	Natural cytotoxicity receptor
NET	Neutrophil extracellular trap during NETosis
NFAT	A transcription factor
NF-κB	A transcription factor
NK	Nature killer cell
NKG2/CD94	Natural killer (lectin-like) receptor G2/CD94
NKT	Nature killer T cell
NLR	NOD-like receptor
NLRP3	An inflammasome
NLRP3 gene	Gene for cryopyrin
NOD	Nucleotide-binding oligomerization domain
NSAIDs	Nonsteroid anti-inflammatory drugs
NSE	Neuron-specific enolase
nTreg	Natural T-regulatory cell
NU-ELISA	A modification of ELISA
OAS	2',5'-oligoadenylate-synthetase
p56^{lck}	A tyrosine kinase
PAF	Platelet-activating factor
PALS	Periarteriolar lymphoid sheaths (in the spleen)
PAMPs	Pathogen-associated molecular patterns
PCV13, PPSV23	Pneumococcal vaccines
pDC	Plasmacytoid dendritic cell
PDGF	Platelet-derived growth factor
PE	Phycoerythrin, a fluorochrome
PECAM-1	Platelet-endothelial cell adhesion molecule-1, CD31
PGD2	Prostaglandin D2
PHA	Phytohaemagglutinin (mitogen)
pIgR	Polymeric Ig receptor
PKR	Protein kinase R
PLCγ1, -2	Phospholipase Cγ
PMN	Polymorphonuclear leukocytes
PNU	Protein nitrogen unit (of allergen)

POP	PYD-only protein
PRRs	Pattern recognition receptors
PSA	Prostate-specific antigen
PSGL-1	P-selectin glycoprotein ligand-1, a mucin-type CAM
PWM	Pokeweed mitogen
PYD	Pyrin domain
qPCR	Quantitative polymerase chain reaction
RAAS	Renin-angiotensin-aldosterone system
RAG-1, RAG-2	Recombination-activating genes
RANTES	Regulation on activation, normal T-cell expressed and secreted, CCL5
RIA	Radioimmunoassay
RIG-1	Retinoid acid-inducible gene-1 for a part of RLP
RLP	RIG-1-like receptor
ROR-α, ROR-γt	Signaling molecules
ROS	Reactive oxygen species, oxygen radicals
RT-PCR	Reverse transcription polymerase chain reaction
RV1, RV5	Vaccine against rotavirus infection
SAA	Serum amyloid A
SALT	Skin-associated lymphoid tissue
SC	Secretory component of secretory IgA
SCDF-1	Stromal cell-derived factor-1, CXCL12
SCID	Severe combined immunodeficiency
SDS	Sodium dodecyl sulfate
SIRS	Systemic inflammatory response syndrome
SLA	Soluble liver antigen
SLC	Secondary lymphoid tissue chemokine, Exodus-2, CCL21
SLC35C1	Gene encoding a GDP-fucose transmembrane transporter
SLE	Systemic lupus erythematosus
SLP76	An adaptor protein
SLP/BLNK	An adaptor protein
SP	Single-positive (thymocytes)
SP-A, SP-D	Surfactant proteins
ssRNA	Single-stranded RNA
STAT3	A transcription factor
Syk	A tyrosine kinase
T3	Triiodothyronine
T4	Thyroxine
TALT	Tube-associated lymphoid tissue
TAM	Tumor-associated macrophage
TAN	Tumor-associated neutrophil
TAMPs	Tumor-associated molecular patterns
TAP-1, TAP-2	Transporters associated with antigen processing
T-bet	A signaling molecule
T_{CM}	Central memory T cell
TCR	T-cell receptor
TECK	Thymus-expressed chemokine, CCL25
T_{EM}	Effector memory T cell
Tfh	Follicular helper T cell
Tfr	Follicular regulatory T cell
TGFβ	Transforming growth factor-β
Th	Helper T cell
TIR	Toll/IL1 receptor, a part of TLR
TLR	Toll-like receptor
TNFα, TNFβ	Tumor necrosis factors
TRAD	Locus of TCR α and δ chain genes

TRB Locus of TCR β chain genes
TRG Locus of TCR γ chain genes
Tr1 Type 1 regulatory T cell
TRIF An adaptor protein for TLR signaling
TSH Thyroid-stimulating hormone, thyrotropin
tTG Tissue transglutaminase
uNK Uterine NK cell
VAR Vaccine against varicella
Vav A signaling molecule
VCAM-1 Vascular cell adhesion molecule-1, CD106
VDJC Immunoglobulin and TCR gene clusters
VH Variable heavy domain
VL Variable light domain
VLA-4 Very late activation antigen-4, an integrin
VLP Viruslike particle, a principle of the vaccine formation
WASP Wiskott-Aldrich syndrome protein
WBC White blood cells
WHO World Health Organization
XCL A chemokine subfamily
XCR A receptor to XCL and other chemokines
Y A CLR's domain
Zap70 A tyrosine kinase

List of Videos

Functional Organization of the Immune System

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-03323-1_1) contains supplementary material, which is available to authorized users.

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Learning Objectives

Knowledge. Upon successful completion of the chapter, students should be able to:

1. Draw the functional organization of immune system.
2. Distinguish between antigens and "molecular patterns."
3. Name and describe two main mechanisms of the immune system.
4. List the molecules of immune system and their functions.
5. Know the structure and functions of antibodies, B-cell receptors (BCRs), T-cell receptors (TCRs), and human leukocyte antigens (HLA).
6. Briefly summarize the basic facts about pattern recognition receptors (PRRs).
7. Be familiar with the cell adhesion molecules (CAMs).
8. Compare and contrast the functions of different cytokines and chemokines.
9. Outline the primary, secondary, and tertiary organs of the immune system.
10. Describe the cells of the immune system including T cells and B cells.
11. Explain the postulates of clonal selection theory.

Acquired Skills. Upon successful completion of the chapter, students should demonstrate following skills, including:

1. Interpret the knowledge related to the functional organization of the immune system.
2. Critically evaluate the scientific literature about structure and functions of the immune system.
3. Discuss the scientific articles from the current research literature to criticize experimental data and formulation of new hypotheses in basic immunology.
4. Attain a clear perception of the presented immunology definitions expressed orally and in written form.
5. Formulate the presented immunology terms.
6. Correctly answer quiz questions.

Attitude and Professional Behaviors. Students should be able to:

1. Have the readiness to be hardworking.
2. Behave professionally at all times.
3. Recognize the importance of studying and demonstrate a commitment.

1.1 Introduction

There is the explanation of such terms as "non-self," "self," and "former self" and what they matter in the immunology context. The reader can find a new idea related to the division of molecular patterns into PAMPs, AAMPs, DAMPs, and TAMPs. There is also the up-to-date description of structural features and functions of primary, secondary, and tertiary organs, cells, and molecules of the immune system. Clinical comments are accompanying almost evert unit.

1

1.2 Antigens and "Patterns"

Definitions

Antigen is a substance triggering the immune responses to constitute memory to this antigen. Antigens may be originated from "non-self," "former self," and even "self." Antigens are categorized as *complete* and *incomplete* (*haptens*), *T dependent* and *T independent*, and specified forms like *antigens of pathogens*, *allergens*, *tumor antigens*, *autoantigens*, etc.

Molecular patterns are low-molecular substances evoking the reactions of innate immunity with no memory. There are *pathogen-associated molecular patterns* (*PAMPs*), *allergen-associated molecular patterns* (*AAMPs*), *damage-associated molecular patterns* (*DAMPs*), and *tumor-associated molecular patterns* (*TAMPs*).

Any human body ("self") exists within a hostile environment including microbes ("non-self") and multicellular organisms ("non-self"). The external microbial environment and internal opportunistic germs, as well as even benign tumors, are not those places where any human body can know who to trust out here to survive. Fortunately, we have our immune system, which has evolutionarily known how to recognize "non-self," "self," and even "former self." To understand, it is necessary to define the "non-self" and "self" at the molecular level in detail.

An antigen is a substance containing such information about "non-self," "self," and/or "former self," which can trigger immune responses in the body to induce a very long and even lifelong memory to the event if it occurs. T-cell receptor (TCR) and B-cell receptor (BCR) can recognize antigens. Antigens of "self" are named autoantigens (or self-antigens), whereas tumor antigens present in fact "former self." In the enlarged sense, it is currently estimated that the "universe of antigens" make up about 10^{18} molecules in the environment. The antigens may be divided into complete and incomplete antigens (see ◘ Table 1.1).

Any antigen as an *immunogen* may trigger an immune response, i.e., the interaction of many cell types of the immune system, which leads to the formation of new cell types destroying the antigen-containing pathogen and commonly keeping a memory about this event for a long time. Naturally, vaccines contain only immunogens. An antigen as a *tolerogen* triggers *immune tolerance*, another type of interaction of cells of the immune system. Alternatively, it results in the "specific immunological silence" when none is killed and no tissues are damaged.

Antigenicity, specificity, and immunogenicity structurally and functionally characterize antigens.

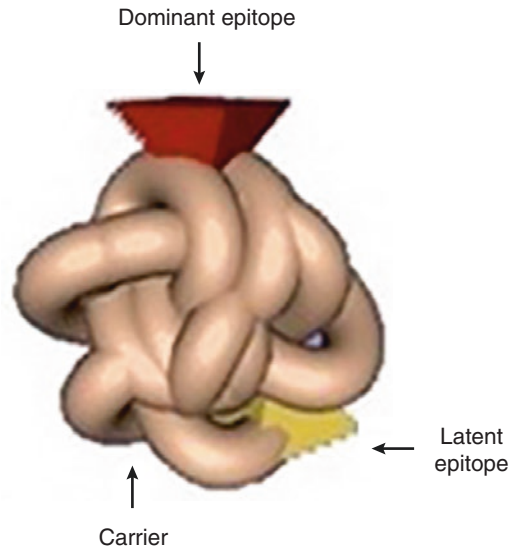
Antigenicity is the quality of an antigen to serve *ligand* for a *receptor*. The receptors for antigens are TCR and BCR.

Specificity is the antigen quality to be a unique molecule for only one receptor. An *epitope* or *antigenic determinant* is an informational unit of the antigen specificity. In the antigen molecule, an epitope may be dominant or latent (see ◘ Fig. 1.1). A carrier, the noninformation part of the antigen molecule, is required for any antigen to be complete.

Table 1.1 Antigens and haptens

Antigen type	Biochemical characterization of antigens	Immunogenicity (the power of immune response)	Formation of a precipitate with the specific antibody	Valence (a number of epitopes)
Complete antigens	Proteins, polysaccharides, lipopolysaccharides, and phospholipids	+	+	Polyvalent
Haptens (incomplete antigens):				
Complex haptens	Short peptides and saccharides, lipids, nucleic acids, and some medications	–	+	Divalent
Antigen type	Biochemical characterization of antigens	Immunogenicity (the power of immune response)	Formation of a precipitate with the specific antibody	Valence (a number of epitopes)
Simple haptens	Chemical radicals, amino acids, simple sugars, and other simple chemical substances	–	–	Monovalent

Fig. 1.1 Antigen structure



Immunogenicity is the quality to induce the adaptive immune responses of different power.

The majority of antigens are *T dependent* since they require the participation of helper T cells to constitute memory cells. *T-independent* antigens are capable of activating B cells on their own. In the past, there was a division of T-independent antigens into two types: type 1 (currently they all refer to PAMPs – see below) and type 2, which comprised highly repetitive surface epitopes, e.g., polysaccharides of encapsulated bacteria. Type 2 T-independent antigens can interact with many BCRs in a cross-linking manner and activate only mature B cells, whereas immature B cells remain anergized.

From a clinical point of view, children up to 4–6 years who have most immature B cells cannot produce antibodies at the high level required for defense against encapsulated bacteria, which may often be reactivated.

Small exogenous molecules which contain a conserved motif, *pathogen-associated molecular patterns* (*PAMPs*), are linked to a certain component of microbes. There are bacterial flagellin, peptidoglycan, lipopolysaccharide (endotoxin, LPS), viral dsRNA, and unmethylated CpG motifs of DNA. They may initiate different reactions of the *innate immunity* and do not induce immune memory. Other exogenous molecules, oligomeric components of allergen molecules, are *allergen-associated molecular patterns* (*AAMPs*), which may promote cross-reactivity of IgE allergy. Some endogenous molecules, *damage-associated molecular patterns* (*DAMPs*), are released outside the cell because of its injury. There are heat-shock proteins, extracellular matrix's (ECM's) proteins, S100, hyaluronan fragments, and nonprotein substances such as DNA, ATP, uric acid, and heparin. In physiological conditions, DAMPs serve structural and metabolic functions, being inaccessible to the immune system.

From a clinical point of view, in case of severe damage to own tissue, they may trigger peracute inflammation and toxification and promote toxic shock syndrome.

Tumor-associated molecular patterns (*TAMPs*) are low-molecular conserved components of tumor cells. On the one hand, they can upregulate innate defense against tumors, but, on the other hand, TAMP may, like a "double-edged sword," promote cancer growth and metastasis through weakening immune surveillance, the formation of chemoresistance, and the chronic inflammation favoring tumor progression.

All the "patterns" evoke similar reactions of the innate immunity. They are recognized by Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs), which are currently an actively growing area of research.

■ Quiz

Reading a question, please choose only one right answer.

Question 1

Antigens trigger:

1. NETosis.
2. Reactions of the innate immunity.
3. Adaptive immune responses.
4. Phagocytosis.

Question 2

Complete antigens are:

1. Short peptides, and saccharides, lipids, nucleic acids.
2. Immunoglobulins.
3. Proteins, polysaccharides, lipopolysaccharides, and phospholipids.
4. Chemical radicals, amino acids, simple sugars.

Question 3

Any epitope is:

1. An informational unit of the antigen specificity.
2. A pathogen-associated molecular pattern.
3. T-cell receptor.
4. B-cell receptor.

Question 4

Tolerogen triggers:

1. Immune responses.
2. Innate immunity.
3. Phagocytosis.
4. Immune tolerance.

Question 5

A complete antigen contains:

1. A carrier only.
2. Epitopes and a carrier.
3. Only antigenic determinants.
4. Damage-associated molecular patterns.

Question 6

Haptens are:

1. Complete antigens.
2. A carrier for epitopes.
3. Incomplete antigens.
4. Pathogen-associated molecular patterns.

Question 7

What TCR stands for?

1. T-cell receptor.
2. T cellular reaction.
3. T-cell-mediated response.
4. T-cell resistance.

Question 8

Estimated number of "universe of antigens" is about:

1. 10^{18}.
2. 10^{13}.
3. 10^{10}.
4. 10^{8}.

Question 9

Complex haptens are:

1. Polyvalent.
2. Ambivalent.
3. Monovalent.
4. Divalent.

Question 10

B-cell receptor (BCR) can:

1. Trigger T-cell-mediated responses.
2. Recognize antigens.
3. Activate phagocytosis.
4. Activate complement.

Question 11

Damage-associated molecular patterns (DAMPs) are:

1. Low-molecular conserved components of tumor cells.
2. Oligomeric components of allergens.
3. Bacterial flagellin, peptidoglycan, and lipopolysaccharide, viral dsRNA, etc.
4. Heat-shock proteins, ECM's proteins, S100, hyaluronan fragments, etc.

Question 12

Pathogen-associated molecular patterns (PAMPs) are:

1. Complex haptens.
2. Low-molecular conserved components of tumor cells.
3. Bacterial flagellin, peptidoglycan, and lipopolysaccharide, viral dsRNA, etc.
4. Oligomeric components of allergens.

Question 13

Allergen-associated molecular patterns (AAMPs) are:

1. Oligomeric components of allergens.
2. Heat-shock proteins.
3. Bacterial flagellin, peptidoglycan, and lipopolysaccharide.
4. Unmethylated CpG motifs of DNA.

Question 14

All the "patterns" trigger:

1. Immune tolerance.
2. T lymphopoiesis.
3. Thymus involution.
4. Reactions of the innate immunity.

Question 15

Toll-like receptors (TLRs) are related to:

1. Hormone receptors.
2. Pattern recognition receptors (PRRs).
3. Cytokine receptors.
4. Chemokine receptors.

Question 16

Antigens may be derived from:

1. "Former self" only.
2. "Non-self" only.
3. "Non-self," "former self," and "self."
4. "Self" only.

1.3 Immunological Mechanisms

Definitions

Immunity (*Latin* "*immunitas*") is a universal biological phenomenon that develops many programs based on the unique genotype of the body ("self") in foreign surroundings, from the birth of the body to its death. There are two major types of immunity, *innate immunity*, which is phylogenetic and polyspecific, and *adaptive immunity*, which is acquired during an ongoing individual life.

Immunology is a life science that studies the immune system, immunological mechanisms, and immunopathology in humans, animals, and other living beings.

In contrast to other systems, the *immune system* is responsible for support of the balance or homeostasis between "non-self," "self," and "former self." The end effects of two major types of immunological mechanisms, innate immunity and adaptive immunity, may be:

1. *Immune containment* of infection and tumors
2. *Immune clearance* of the infection and tumors.

1.3.1 Innate Immunity

The innate immune subsystem upon activation has a wide array of recruited molecules and cells, which may destroy invading pathogens very quickly but not very effectively.

1. *Physical and chemical barriers:*
   - Keratinization in the skin
   - Mucus formation on the mucosal epithelium and ciliary clearance in the respiratory tract
   - Production of various antimicrobial factors such as lysozyme, lactic and fatty acids, etc. in secretions
   - Deactivation of dangerous microbes by digestive enzymes and peristalsis in the GI tract
2. *Microbial antagonism* to pathogenic microbes due to the body's own mutualistic and commensal microorganisms
3. The *liver* due to oxidation of xenobiotics, detoxification, and synthesis of many defense factors
4. *Cytotoxicity by complement*
5. *Phagocytosis* and *NETosis*

6. *Acute phase reaction* (C-reactive protein, serum amyloid A, mannose-binding lectin, etc.)
7. *Natural antibodies* produced by CD5+B cells
8. *Antimicrobial peptides* such as α defensins, cathelicidins, lactoferrin, dermicidin, etc.
9. *Natural cytotoxicity* due to innate lymphoid cells (ILCs) including NK cells, NKT cells, and γδT cells plus *natural cytostasis* induced by interferons (IFNs)

1.3.2 Adaptive Immunity

The adaptive immune responses take some days and weeks to be finished. However, they are more effective in eliminating invading pathogens than the innate immunity. Furthermore, they develop the immune memory to the invading pathogens.

- **B-Cell-Mediated (Humoral) Responses**

1. *Simple B-cell response* – formation of only one class of immunoglobulins, IgM, but no long-term memory. This type of response may be triggered by "patterns" too.
2. *Advanced B-cell response* – switching antibodies after each other: IgM, IgG, IgA, and even IgE, and inducing the formation of long-lived memory plasma cells and lifelong memory B cells.

- **T-Cell-Mediated Responses**

3. *Inflammatory CD4+T-cell response* that leads to the production of effector CD4+T cells and the lifelong memory CD4+T cells.
4. *Cytotoxic CD8+T-cell response*, which results in the formation of cytotoxic CD8+T cells capable of apoptosis in target cells and lifelong memory CD8+T cells.

1.4 Organization of the Immune System at a Glance

The immune system of the body consists of organs, cells, and molecules, and a complex interplay of them all governs immune processes at two major levels. They may be defined as the following:

1. *Systemic level*, which includes the bloodstream, thymus, bone marrow, and spleen and is responsible for defense against pathogens if they invade the internal space of the body
2. *Skin and mucosal level* that includes the surface and mucosal barriers, tonsils, adenoids, Peyer's patches, solitary or isolated follicles, appendix, lymph nodes, lymphatic vessels, etc. at which the immune system functions if the pathogens enter the body locally or the barrier's opportunistic microbes are being reactivated

The primary or central organs of the immune system are the *thymus* and *bone marrow*. All cells related to the immune system originate from the bone marrow, and even some lymphocytes, B cells, are differentiated there, whereas other lymphocytes, T cells, are matured in the thymus. Furthermore, the thymus governs the whole immune system.

The secondary or peripheral organs of the immune system include the *spleen*, *lymph nodes*, *numerous disseminated lymphoid elements*, *appendix*, *lymphatics*, *skin*, and even *liver*. An essential part of the secondary organs is organized in *mucosae-associated lymphoid tissue* (*MALT*), which may become a place where many immune processes of the innate and adaptive immunity proceed to protect the body against numerous pathogens.

If the participation in the immune processes to take into consideration cells of the immune system may be classified by their functional activity and divided into four groups:

1. Antigen-Presenting Cells (APCs):
   Dendritic cells (DCs), macrophages, and B cells
2. Immunoregulatory cells:
   Natural T regulatory cells (nTreg) and their induced subsets, natural B regulatory cells (nBreg)
   Adaptive helper T-cell subsets: type 1 helper T cells (Th1), type 2 helper T cells (Th2), follicular helper T cells (Tfh), follicular regulatory T cells (Tfr), type 9 helper T cells (Th9), type 17 helper T cells (Th17), and type 22 helper T cells (Th22)
3. Effector cells:
   Inflammatory CD4+T cells, cytotoxic CD8+T cells, plasma cells as antibody-producing cells, γ$\bar{o}$T cells, NKT cells, innate lymphoid cells (ILCs) including NK cells, monocytes, macrophages, neutrophils, eosinophils, mast cells, etc.
4. Memory cells:
   Memory CD4+T cells, memory CD8+T cells, memory B cells, long-lived plasma cells

Molecules of the immune system may be divided into some groups:

1. Antigen-recognizing and antigen-binding molecules:
   - Immunoglobulins or antibodies: IgM, IgG, IgA, IgE, and IgD
   - B-cell receptor (BCR)
   - T-cell receptor (TCR)
   - Transfer factors (soluble TCR's fragments)
   - Human histocompatibility antigens (HLA)

2. Pattern recognition receptors (PRRs):
   - Toll-like receptors (TLRs)
   - C-type lectin receptors (CLRs)
   - NOD-like receptors (NLRs)
   - RIG-1-like receptors (RLRs)
   - AIM-2-like receptors (ALRs)

3. Cell adhesion molecules (CAMs):
   - Immunoglobulin superfamily
   - Integrins
   - Selectins
   - Mucosal vascular addressins or mucin-type glycoproteins
   - Tumor necrosis factor (TNF) receptor superfamily
   - Cadherin superfamily
   - Extracellular matrix (ECM) proteins or Link family

4. Cytokines and chemokines:
   - Interleukins (ILs)
   - Colony-stimulating factors (CSFs)
   - Interferons (IFNs)
   - Tumor necrosis factors (TNFs)
   - Chemokines
   - Others

5. Various mediators of immune inflammation

Definitions

A *ligand* is a soluble molecule, which is bound to a complementary or specific *receptor* expressed on a cell. The receptor may also be bound to a *counter-receptor* on another cell.

Signaling is a series of reactions from the ligand/receptor complex toward the genome of the target cell, which results in a particular action or functional activity of the cell.

CD Nomenclature. *CD* means *cluster of differentiation*. Due to the hybridoma technology developed by the Nobel Laureates G.J.F. Köhler and C. Milstein (1984), it has become possible to define certain molecules, which are expressed at the different stages of cell differentiation. CD molecules may be signaling molecules, receptors, counter-receptors, cell adhesion molecules, etc. The use of the monoclonal antibodies enabled the identification of cell surface molecules providing targets for immunophenotyping of cells. Currently, it is a conventional rule to utilize them as cell markers in immunology (see ◘ Table 1.2). These markers are also applied to link cells of the immune system with certain immune functions. To date, the CD molecules for humans are numbered up to 371.

To summarize the general vision of the immune system at a glance, see ◘ Table 1.3.

Table 1.2 Some CD markers

Cluster designation	Cells
CD34+	Lymphoid and myeloid progenitors
CD3+	T cell
CD4+	Helper T cell
CD8+	Cytotoxic T cell
CD19+	B cell
$CD16^{hi}56^{lo}$	NK cell
CD68+	Macrophage
CDw199+	CC chemokine receptor type 9, encoded by CCR9 gene; a β chemokine receptor involved in mucosal immunity

^{hi} denotes *high* expression, ^{lo} means *low* expression, *w* means *workshop* (not well-characterized to use this molecule as a conventional marker)

Table 1.3 "Formula" of immunity

Feature	Innate immunity	Adaptive immunity
Trigger	"Patterns"	Antigens
Development	Rapid	Slow
The fate of a pathogen	Immune containment	Immune clearance
Memory	Phylogenetic polyspecific memory to pathogens; no formation of monoclonal memory after a primary infection	Formation of long-term monoclonal memory after a primary infection
Crucial cells	Phagocytes, NK cells, mast cells, etc.	T cells and B cells
Effector events	"Acute phase" reaction, complement activation, phagocytosis, NETosis, pyroptosis, simple inflammation, apoptosis	Antigen neutralization by antibodies, CD4+T-cell-initiated immune inflammation, CD8+T-cell-induced apoptosis in target cells
Paradigm	Pattern recognition theory	Clonal selection theory
Immunopathology	Immunodeficiency, autoinflammatory disorders	Immunodeficiency, autoimmune diseases, allergic disorders

1

■ Quiz

Reading a question, please choose only one right answer.

Question 1

Systemic level's organs are:

1. Mucosal barriers.
2. Thymus, bone marrow, and spleen.
3. Peyer's patches and isolated follicles.
4. Lymph nodes and lymphatic vessels.

Question 2

The primary organs of the immune system are:

1. The skin.
2. Mucosal barriers, tonsils, and adenoids.
3. Thymus and bone marrow.
4. Peyer's patches, isolated follicles, and appendix.

Question 3

The skin and mucosal level includes:

1. Mucosal barriers, tonsils, and adenoids.
2. The thymus, bone marrow, and spleen.
3. The central nervous system.
4. Endocrine glands.

Question 4

Adaptive immunity is:

1. Immune responses.
2. Reactions of innate immunity.
3. Phagocytosis.
4. Complement.

Question 5

Pathogen-associated molecular patterns (PAMPs) are:

1. Complex haptens.
2. Low-molecular conserved components of tumor cells.
3. Bacterial flagellin, peptidoglycan, and lipopolysaccharide, viral dsRNA, etc.
4. Oligomeric components of allergens.

Question 6

Antigen-presenting cells (APCs) are:

1. T cells.
2. Natural T regulatory cells (nTreg).
3. Dendritic cells (DCs), macrophages, and B cells.
4. NK cells.

Question 7

The clonal selection theory explains:

1. Adaptive immunity.
2. Formation of inflammasomes.
3. NETosis.
4. Innate immunity.

Question 8

What BCR stands for?

1. B-cell receptor.
2. B cellular reaction.
3. B-cell-mediated response.
4. B-cell resistance.

Question 9

Neutrophils are related to:

1. Antigen-presenting cells (APCs).
2. Memory cells.
3. Follicular regulatory T (Tfr) cells.
4. Effector cells.

Question 10

Selectins are:

1. Immunoglobulins.
2. Cell adhesion molecules (CAM).
3. Cytokines.
4. Antigen-recognizing and antigen-binding molecules.

Question 11

T-cell receptor (TCR) can:

1. Trigger B-cell-mediated responses.
2. Recognize antigens.
3. Activate phagocytosis.
4. Activate complement.

Question 12

Damage-associated molecular patterns (DAMPs) are:

1. Low-molecular conserved components of tumor cells.
2. Oligomeric components of allergens.
3. Heat-shock proteins, ECM's proteins, S100, hyaluronan fragments, etc.
4. Bacterial flagellin, peptidoglycan, and lipopolysaccharide, viral dsRNA, etc.

Question 13

Interleukins (ILs) are related to:

1. Cytokines.
2. Cell adhesion molecules (CAM).
3. Pattern recognition receptors (PRRs).
4. Human histocompatibility antigens (HLA).

Question 14

All the "patterns" trigger:

1. B cells.
2. T cells.
3. Thymus involution.
4. Reactions of the innate immunity.

Question 15

CD3 molecules are expressed by:

1. B cells.
2. T cells.
3. Macrophages.
4. Eosinophils.

Question 16

Antigens may be derived from:

1. "Former self" only.
2. "Non-self" only.
3. "Self" only.
4. "Non-self," "former self," and "self."

1.5 Molecules of the Immune System

Methodically, molecules of the immune system will be presented in detail before organs and cells of the system are considered.

1.5.1 Antigen-Recognizing and Antigen-Binding Molecules

Definitions

Immunoglobulin or *antibody* is an effector molecule of the B-cell-mediated responses, which is secreted by plasma cells and interacts to appropriate antigen specific to this antibody. In *Homo sapiens*, there are *IgM*, *IgG*, *IgA*, *IgE*, and *IgD* classes of the immunoglobulins.

Antigen-recognizing receptors themselves sense antigens. However, each antigen-recognizing complex of B cells and T cells consists of:

1. An *antigen-recognizing receptor* itself, which recognizes "non-self" and "former self"
2. An *accessory* antigen receptor's *molecule*, which is required for signaling and re-expressing antigen-recognizing receptors
3. A *coreceptor*, which recognizes HLA molecules ("self")

Human leukocyte antigen (*HLA*) *molecule* is a major histocompatibility complex in *Homo sapiens*. *Class I HLA* molecules are expressed on cell surfaces throughout the body, whereas *Class II HLA* molecules are displayed on cells of the immune system only.

■ **Quiz**

Reading a question, please choose only one right answer.

Question 1

The coreceptor, which senses HLA II molecules, is:

1. CD8.
2. CD16.
3. CD4.
4. CD22.

Question 2

What the immunoglobulin molecule is pentameric?

1. IgM.
2. IgG.
3. IgA.
4. IgE.

Question 3

These molecules inform cells of the immune system about the autologous state of cells on which they are expressed:

1. LFA-1.
2. CD3.
3. CD4.
4. HLA I.

Question 4

HLA genes are located on chromosome:

1. 6.
2. 14.
3. 7.
4. 22.

Question 5

A groove in the HLA molecule is required:

1. For HLA expression.
2. For antigen loading.
3. For HLA splitting.
4. For HLA polymorphism.

Question 6

This immunoglobulin is divided into subclasses:

1. IgM.
2. IgD.
3. IgG.
4. IgE.

Question 7

This immunoglobulin exerts a quality to placental transfer:

1. IgM.
2. IgE.
3. IgG.
4. IgA.

Question 8

Molecule, non coreceptor, associated to TCR is:

1. CD3.
2. CD4.
3. CD8.
4. CD79a/CD79b.

Question 9

Molecules are associated to BCR are:

1. CD3 chains.
2. CD79a/CD79b.
3. CD4 and CD8.
4. Cytokines.

Question 10

IgG is synthesized at low concentration:

1. In senescence.
2. In babies at the age of 3–6 months.
3. In teenagers.
4. In pregnant women.

Question 11

By which part does an immunoglobulin bound an antigen?

1. By Fc fragment.
2. By hinge area.
3. By Fab fragment.
4. By constant domains.

Question 12

Immunoglobulins are synthesized by:

1. Plasma cells.
2. T cells.
3. Mast cells.
4. Macrophages.

Question 13

The coreceptor, which recognizes HLA I molecules, is:

1. CD4.
2. CD21.
3. CD8.
4. CD19.

Question 14

Diversity of antibodies inside a species is:

1. Allotypy.
2. Isotypy.
3. Affinity.
4. Idiotypy.

Question 15

IgE is responsible for:

1. Type I hypersensitivity.
2. Type II hypersensitivity.
3. Type III hypersensitivity.
4. Type IV hypersensitivity.

Question 16

Antibody, which indicates either any recent pathogenic infection or a reactivation of opportunistic microbes:

1. IgA.
2. IgE.
3. IgG.
4. IgM.

1.5.1.1 Immunoglobulins

Immunoglobulins or *antibodies* are effector molecules of the B-cell-mediated responses, which are secreted by plasma cells. Any antibody is a glycoprotein composed of many amino acid residues, and that is its primary structure. The carbohydrate content of the immunoglobulin molecules varies between 2% and 12%. A monomeric IgG molecule consists of two identical *light* (*L*) and two identical *heavy* (*H*) *chains* (see ◘ Fig. 1.2). They are attached to each other by disulfide (S-S) and hydrogen (H+…O−) bonds forming the secondary structure of the immunoglobulin molecule. Both the chains contain a series of repeating, homologous units, which fold in separation into a domain in a globular manner, and that is the tertiary structure of the immunoglobulin molecule. In addition, there are *constant* (*CL*, *CH1*, *CH2*, and *CH3*) and *variable* (*VL* and *VH*) *domains*. The molecule can be divided into Fc fragment ("fragment crystallizable"), responsible for nonspecific effector activity, and two identical Fab fragments or antigen-binding sites, which bind antigens. Finally, the whole molecule is conformed as the functionally active compound. That is the quaternary structure of the immunoglobulin molecule.

The cleavage of a monomeric antibody with papain enables the obtaining of two different fragments, two Fab and one Fc. Each Fab fragment can bind a single antigen molecule with no precipitation, whereas an Fc fragment can constitute crystals. The cleavage of a monomeric antibody with pepsin enables the obtaining of one fragment composed of two Fc fragments and capable of binding two antigen molecules with precipitation. Finally, the cleavage of a monomeric antibody with disulfide enables the obtaining of separated H chains and L chains.

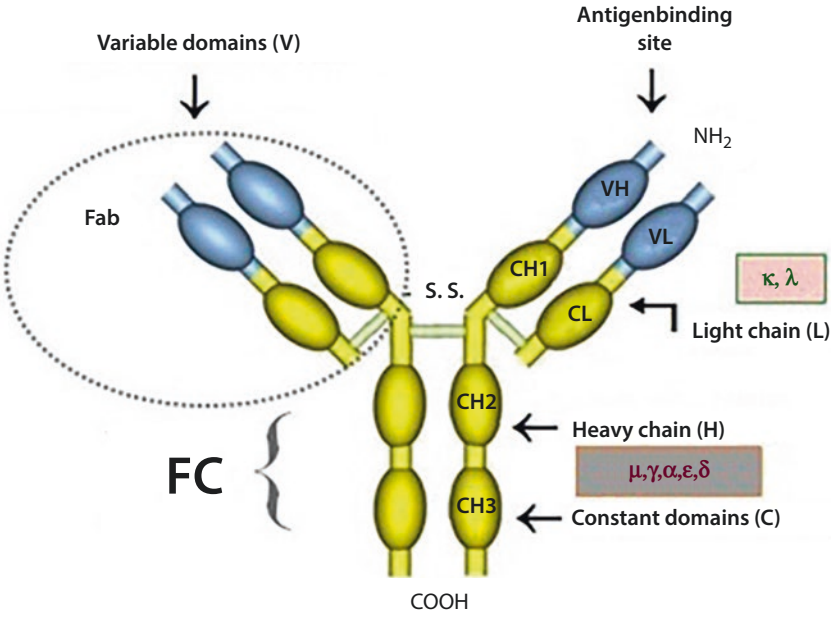


Fig. 1.2 Structure of the immunoglobulin molecule

Antibodies are characterized by some qualities as follows.

- *Affinity* is the quality of an immunoglobulin molecule to be bound to antigen, one to one, firmly on the base of close agreement of their specificities.
- *Avidity* is the same quality based on polyvalence of the antigen-binding sites.
- *Cross-reactivity* is the ability of one antibody to bind to different antigenic epitopes.
- *Isotypy* is a diversity of antibodies inside a species. In humans, there are IgM, IgD, IgG, IgA, and IgE isotypes or classes.
- *Allotypy* is an individual antibody diversity based on the inheritance of different alleles.
- *Idiotypy* is a clonal antibody diversity.

Antibody isotypes differ from each other in some qualities (see Table 1.4).

The Nobel Prize in 1972 was awarded jointly to G.M. Edelman and R.R. Porter for their research on the chemical structure of antibodies.

Genes for different chains are located on different chromosomes. Genes on chromosome 2 encode κ-type L chains, genes on chromosome 22 are related to λ-type L chains, and genes on chromosome 14 encode H chains.

IgM is the sizeable pentameric antibody secreted into the blood during a simple B-cell-mediated response and at the beginning of an advanced B-cell-mediated response. As a rule, IgM has low affinity and high avidity for the antigen.

From a clinical viewpoint, IgM may indicate either any recent pathogenic infection or a reactivation of opportunistic microbes. IgM can mobilize the 1st component of complement and opsonize bacteria and fungi during phagocytosis. In healthy adults, it makes up 0.6–2.0 g/L. As a monomer, IgM is a part of BCR on immature B cells.

Table 1.4 Physicochemical qualities of immunoglobulin isotypes

Feature	IgM	IgG	IgA	IgE	IgD
Form	Pentameric	Monomeric	Monomeric (serum IgA) or dimeric (secretory IgA)	Monomeric	Monomeric
Heavy chain	μ	γ	α	ε	δ
Accessory chain	J		Secretory component (SC) including pIgR		
Subisotypes (subclasses)		1 (65%) 2 (20%) 3 (10%) 4 (5%)	1 2		
Number of constant domains	40H, 10 L	6H, 2 L	6H, 2 L (12H, 4 L)	8H, 2 L	6H, 2 L
Molecular mass (kDa)	950	150	160 (385)	190	180
Half-life (days)	5	23	6	2.5	3
Serum concentration in healthy adults (g/L)	0.6–2.0	8–16	0.7–3.0	0.003	0.04
Placental transfer		+			
Fc receptors		$Fc_{\gamma}RI$ (CD64) $Fc_{\gamma}RII$ (CD32) $Fc_{\gamma}RIII$ (CD16)	$Fc_{\alpha}R$ (CD89)	$Fc_{\varepsilon}RI^{hi}$ $Fc_{\varepsilon}RII^{lo}$ (CD23)	

IgD is another part of the BCR, which appears on mature B cells. Soluble IgD is present in the bloodstream in a small concentration but may participate in some immune processes such as defense, tolerance, and allergic reactions. Also, IgD is expressed by anergic B cells.

IgG is the most common isotype of antibody found in the bloodstream. In healthy adult humans, IgG accounts for 6.0–16.0 g/L. IgG is characterized by high affinity for antigen having only two antigen-binding sites though. There are four IgG subisotypes (IgG1, IgG2, IgG3, and IgG4) in humans, named in order of their abundance in the bloodstream. The immunoglobulins of almost all subisotypes provide the most effective