

Damage-Associated Molecular Patterns in Human Diseases

Walter Gottlieb Land

Damage-Associated Molecular Patterns in Human Diseases

Volume 1: Injury-Induced Innate
Immune Responses

 Springer

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ISBN 978-3-319-78654-4 ISBN 978-3-319-78655-1 (eBook)
<https://doi.org/10.1007/978-3-319-78655-1>

Library of Congress Control Number: 2018945903

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

In 1994, roughly 10 years after I first met Walter Land, at his institution, the Division of Transplant Surgery at the University of Munich, a prospective study in renal transplantation was performed, using a single shot of a perioperatively given antioxidant. At that time, nobody would have thought that 8 years later follow-up data from this study would revolutionize the perception of immunology in transplant medicine. When in 2002 his damage hypothesis was formulated, I was in the lucky position as deputy director of his institution, to prove—for the first time—the existence of the heat shock protein 72 in renal and pancreatic transplants [1], a year later interpreted and published by Walter Land as an example of damage-associated molecular patterns (DAMPs). It also fills me with pride, having been witness to the creation of the term „DAMPs“, at a meeting in Pegnitz in 2003, by Polly Matzinger and Walter Land, two pioneers in the field of innate immunity, who also coined the danger/injury hypothesis in 1994.

Since then, Walter has been continuously committed to increasing the knowledge in innate immunity, into multiple, far-reaching fields of—not only human—immunological and evolutionary phenomena with an unprecedented visionary approach. Always his endeavor has been to introduce the danger/injury model into clinical medicine. Thus, who else but him could more suitably author this book on *Damage-Associated Molecular Patterns in Human Diseases?*

The ambitious goal of his work—including the foundation of a “DAMPs-Society”—is already being mirrored in the first Volume: *Injury-Induced Innate Immune Responses*. Here, an interested clinician who has not been in contact with innate immunity, so far, can detect all basic information needed for a deeper understanding of this novel immunological approach. In eight chapters, the book reaches into a wide spectrum of DAMP-induced innate mechanisms, its dialogue with the adaptive immune responses that is needed to understand the many implications of innate mechanisms in a large number of human diseases.

For me, as his successor in leading his groundbreaking educational institution “Walter Brendel Kolleg” for transplant medicine, it is obligatory to take the role of

DAMPs into consideration when assessing the pathogenesis of human diseases, not only in transplant medicine.

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Reference

1. Arbogast H, Arbogast S, Fertmann J, Hoffmann J, Sajzewa E, Land W. Expression of heat shock proteins in cadaveric human renal (and pancreatic) allografts – a role in activation of innate immunity? *Transplantation* 2002;74:266.

Preface

This book has been written by a retired transplant surgeon who is still keen to understand progress in immunology, in particular, in the field of innate immunity. In fact, recent developments in the field of modern immunology incorporate a novel paradigm, the danger/injury model, holding that any cell stress and/or tissue injury initiate immunity—and not primarily the presence and recognition of “nonself.” As an original contributor to this paradigm shift in immunology, I meanwhile noticed an increasing role of this concept in both human health and diseases. The linchpin of the model operating in both circumstances can be seen in the “DAMPs,” the abbreviation for “**d**amage-**a**ssociated **m**olecular **p**atterns.” These molecules are actively or passively emitted by stressed or injured, living or dying cells and, thus, alert the immune system to respond. However, their function is ambiguous: when adequately emitted, these molecules trigger controlled immune pathways resulting in homeostasis; when excessively or permanently produced, they trigger uncontrolled/exaggerated immune pathways leading to pathologies and diseases. In fact, we currently observe a growing impact of events of the anciently evolved, stress/injury-promoted innate immune system on etiopathogenesis, diagnosis, prognosis, prophylaxis, and treatment of human diseases whereby the DAMPs play a central role—a fact that has led to the title of the monograph. Doubtlessly, sooner or later, every physician will come across the DAMPs and include them in her/his diagnostic, prognostic, and therapeutic considerations.

Accordingly, this monograph is written for professionals from all medical and paramedical disciplines who are interested in the emerging role of injury/DAMP-induced inflammation and immunity in health and human diseases. Hence, it goes without saying that the book has not been written for experts in the field of innate immunity.

The book is divided into two parts: Volume 1 presents an overview of some basic aspects of innate immune responses as understood and interpreted by a retired transplant surgeon, by highlighting the function of DAMPs in promoting efferent innate immune responses and shaping adaptive immune responses; Volume 2, which will be published subsequently, covers the practical and clinical aspects of DAMP-promoted human diseases including traumatic, cardiovascular, metabolic, neurodegenerative, autoinflammatory, autoimmune, hematological, infectious, and malignant diseases. Emphasis will be put on the role of DAMPs in the pathogenesis of human diseases,

their use as biomarkers in diagnosis and prognosis as well as their exploitation as targets for future therapeutic strategies.

Volume 1, which you now hold in your hands, covers eight parts covering 37 chapters altogether. This organizational format was chosen to provide (within the various parts) an initial impression of the wide range of subjects and topics covered by the book title, on the one hand, and to deal with the details of a given cohesive topic in a separate chapter, on the other hand. Of note, all figures presented in this book are consciously oversimplified to spare the reader the burden of spending too much time with deciphering all the molecules and pathways involved. Also, the reader should not care for repetitions of terms and/or topics from previous parts. They are just made in order to save bothersome trouble for the reader in turning back to these points. Also, when referring to the forthcoming Volume 2 of the book, the term “Volume 2” only is almost always used.

My sources in writing this book mainly stem from the daily exploration of the MEDLINE database, especially PubMed (until autumn 2017). If not available online as a full-text article, I used the reprints requested by e-mail and sent by the corresponding authors in a thankful way. I would like to use this opportunity to thank all these colleagues for their generosity.

Certainly, this book reflects just the beginning of a new era in medical/clinical practice which is rapidly growing. In particular, the phenomenon of regulated cell death has taken center stage as a crucial source of DAMPs emission. In fact, the intersection between cell death and the immune system is currently regarded as one of the hottest topics in modern biomedical research; it is this scenario that is central to homeostatic healing responses, critical human pathologies, and the development of novel therapeutics. Accordingly, many topics here covered have to be re-written, modified, and amended in the near future. A veritable flood of new publications from this emerging research field awaits us.

Finally, having researched and written the book entirely on my own, I cannot blame others for its imperfections. Any errors or omissions have been made in good faith, and I plead for the reader’s indulgence.

Strasbourg, France

Walter Gottlieb Land

Acknowledgments

First and foremost, my dedication and heartfelt thanks go to my loving and supportive wife, Veronika, who provided me with unending inspiration throughout the process of writing this book.

This publishing endeavor would certainly not have been possible without the moral and financial support of the German Academy for Transplantation Medicine, represented by the Council Members Professor Björn Nashan, Professor Nikolaus Knoepffler, and Priv.-Doz. Dr. Helmut Arbogast. Furthermore, I am especially indebted to the distinguished members of the University of Strasbourg, Professors Seiamak Bahram, Jean Sibilia, and Philippe Wolf, who supported my project and managed holding my position as a Professeur Conventionné at the University of Strasbourg, France.

The completion of this project could not have been accomplished without the continuous support from some of my friends, to whom I am grateful for various reasons related to the project: Wolfgang Linss, Gerhard Storck, Hildebrecht Braun, Dr. Peter Schmidt, and Susanne Arbogast. Finally, I would also like to extend my thanks and appreciation to the whole Springer Nature staff, who edited my original prose and produced a high-quality product.

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Abbreviations

AA	Arachidonic acid
ABC	ATP-binding cassette
ABCs	Age-associated B cells
A β	Amyloid beta
ACD	Accidental cell death
Act	Activin
Act1	Activin1
ADAR1	Adenosine deaminases acting on RNA1
AGS	Aicardi–Goutières syndrome
AhR	Aryl hydrocarbon receptor
AIDS	Acquired immune deficiency syndrome
AIF	Apoptosis-inducing factor
AIM2	Absent in melanoma 2
AIRE	Autoimmune regulator gene
AITC	Allyl isothiocyanate
AKI	Acute kidney injury
Akt	Protein kinase B/PKB
ALI	Acute lung injury
ALOX	Arachidonate lipooxygenase
ALRs	Absent in melanoma 2 (AIM2)-like receptors
Alum	Aluminum sulfate
AMH	Anti-Müllerian hormone
AMPs	Antimicrobial peptides
AMPK-SKP2-CARM1	AMP-activated protein kinase; S-phase kinase-associated protein 2 (p45); coactivator-associated arginine methyltransferase 1
AnxA1	Annexin A1
AP	Alternative complement pathway
APP	Amyloid precursor protein
AP-1	Activator protein-1
APAF-1	Apoptotic protease activating factor 1
APCs	Antigen-presenting cells
ARDS	Acute respiratory distress syndrome
ARE	Antioxidant response element

ARG1	Arginase
ASCs	Antibody-secreting cells
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
ATFs	Activating transcription factors
ATG	Autophagy-regulated
ATM	Ataxia telangiectasia mutated
ATN	Acute tubular necrosis
ATP	Adenosine-5-triphosphate
ATR	Ataxia telangiectasia and Rad3 related
ATRIP	ATR-interacting protein
AZU1	Azurocidin 1
α -GalCer	Alpha-galactosylceramide
α -SMA	Alpha-smooth muscle actin
BAI 1	Brain-specific angiogenesis inhibitor 1
BAT	Brown adipose tissue
BAT3	HLA-B-associated transcript 3
Bb	Subunit activating factor B
BCAP	B-cell adapter for PI3K
BCG	Bacille Calmette–Guérin
BCL-2/10	B-cell lymphoma-2/10
BCR	B cell receptor
Bc16	B cell lymphoma 6
BH	BCL-2 homology
BiP	Binding immunoglobulin protein
BIR	Baculovirus inhibitor repeat-like domain (also abbreviated as NLRB)
BK virus	Polyomavirus 1
BLIMP1	B lymphocyte-induced maturation protein 1
BLM	Bleomycin
BMDCs	Bone marrow-derived DCs
BMPs	Bone morphogenic proteins
Bregs	Regulatory B cells
BTK	Bruton's tyrosine kinase
BTLA	B and T lymphocyte attenuator
bZIP	Basic region-leucine zipper
C	Complement
C-terminus	Carboxy-terminus
CAD	Cold agglutinin disease
CALR	Calreticulin
CAM	Calmodulin
cAMP	Cyclic adenosine monophosphate
CAPS	Cryopyrin-associated periodic syndrome
CARD	Caspase-activating and recruiting domain (also abbreviated as NLRC)

CARS	Compensatory anti-inflammatory response syndrome
CBP	CREB-binding protein
CCRs	CC-chemokine receptors
CD (e.g., CD4)	Cluster of differentiation
CDAMPs	Cell death-associated molecular patterns
cDCs	Conventional dendritic cells
CDE	Clathrin-dependent endocytosis
CDNs	Cyclic dinucleotides
CD14	Glycosylphosphatidylinositol-anchored, membrane-associated protein
CD40L	CD40 ligand
CEP	Carboxyethyl pyrrole
CF	Cystic fibrosis
cFLIPs	Cellular FLICE-like inhibitory proteins
cGAMP	Cyclic GMP-AMP
cGAS	Cyclic GMP-AMP synthase
cGMP	Cyclic guanosine monophosphate
CHOP	Cytidine-cytidine-adenosine-adenosine-thymidine-enhancer-binding homologous protein
cIAP1	Cellular inhibitor of apoptosis protein 1
CICs	Cancer-initiating cells
CIE	Clathrin-independent endocytosis
CLs	Collectins
CLIP	MHC class II-associated invariant chain peptide (fragment)
CLPs	Common lymphoid progenitors
CLRs	C-type lectin-like receptors
CLR	Collagen-like region
CMA	Chaperone-mediated autophagy
CME	Clathrin-mediated endocytosis
CMKLR1	Chemokine-like receptor 1
CMV	Cytomegalovirus
CNC	Cap “n” collar structure
CNS	Central nervous system
CNX	Calnexin
CO	Carbon monoxide
CoChMo	Cobalt/chromium/molybdenum
COPD	Chronic obstructive pulmonary disease
COPII	Coat protein complex II
COXs	Cyclooxygenases
CP	Classical complement pathway
CpG ODN	Cytosine phospho-bound guanosine oligodeoxynucleotide
CpG	Cytosine phospho-bound guanosine
CR	Complement cell surface receptor

C3aR	Complement fragment C3a receptor
C5aR1	Complement fragment C5a receptor 1
C5aR2	Complement fragment C5a receptor 2
CRD	Carbohydrate-recognition domain
CREB	camp response element-binding protein
CRH	Corticotrophin-releasing hormone
CRIg	Complement receptor in the immunoglobulin G superfamily
CRL	Cullin-RING E3 ubiquitin ligase
CRP	C-reactive protein
CR1	Complement receptor type 1
CSCs	Colon-derived cancer stem cells
CsMBE	CNC-sMAF-binding elements
CT	C-terminal tail
cTECs	Cortex thymic epithelial cells
CTGF	Connective tissue growth factor
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CTLD	C-type lectin-like domain
CTLs	CD8 ⁺ cytotoxic T lymphocytes (= T cells)
CVD	Cardiovascular disease
CXCL	Chemokine (C-X-C motif) ligand
CXCR	C-X-C motif receptor
CYLD	Cylindromatosis (turban tumor syndrome)
C/EBP	CCAAT/enhancer binding protein
C3aR	C3a receptor
C5aR1 and C5aR2	C5a receptor 1 and C5a receptor 2
CIITA	MHC class II transcription activator (transactivator)
C1Inh	C1 inhibitor
C4BP	C4b-binding protein
DAF	Complement decay-accelerating factor
DAI	DNA-dependent activator of IFN regulatory factors
DAMPs	Damage/danger-associated molecular patterns
DAP	Diaminopimelic acid
DAPs	DNAX-activating proteins
DCs	Dendritic cells
DC-SIGN	Dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin
DD	Death domain
DDR	DNA damage response
DDX41	DEAD box polypeptide 41
Dectin-1	Dendritic cell-associated C-type lectin-1
DED	Death-effector domain
Der p 2	Dermatophagoides pteronyssinus group 2
DFNA5	Deafness-associated tumor suppressor
DISC	Death inducing signaling complex

DN	Double-negative (thymocytes)
DNA	Deoxyribonucleic acid
DNA-PK	DNA-dependent protein kinase
DNAM-1	DNAX accessory molecule-1
DNase II	Deoxyribonuclease II
DNMTs	DNA methylation is enhanced by DNA methyltransferases
DP	Double-positive (thymocytes)
DRAM1	DNA damage-regulated autophagy modulator 1
DSBs	Double-strand DNA breaks
dsRNA	Double-stranded ribonucleic acid
DTP	Diphtheria Tetanus and Pertussis
DUBs	Ubiquitin ligases/deubiquitinating enzymes
DUOX	Nicotinamide adenine dinucleotide phosphate-dependent dual oxidase
DZ	Dark zone
EAE	Experimental autoimmune (or allergic) encephalomyelitis
eATP	Extracellular ATP
EBV	Epstein–Barr virus
ECM	Extracellular matrix
ECs	Endothelial cells
EDA	Extra domain A
EETs	Epoxyeicosatrienoic acids
e.g.	For example
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
eIF2 α	Eukaryotic translation initiation factor 2 alpha
eIF4E	Eukaryotic translation initiation factor 4E
EMT	Epithelial-to-mesenchymal transition
EndMT	Endothelial-mesenchymal transition
Enhanceosome	Higher-order protein complex assembled at the enhancer and regulates expression of a target gene
EpCs	Epithelial cells
EpRE	Electrophile-responsive element
EP2/4	Prostaglandin E2/4 receptor
ER	Endoplasmic reticulum
ERAD	Endoplasmic reticulum-associated protein degradation
ERAP1/2	Aminopeptidases associated with antigen processing 1/2
ERGIC	Endoplasmic reticulum-Golgi intermediate compartment
ERK	Extracellular signal-regulated protein kinase
ESCRT	Endosomal sorting complexes required for transport
ETC	Electron transport chain
Ets	E26 transformation-specific

ET-1	Endothelin-1
FAD	Flavin adenine dinucleotide
FADD	Fas-associated protein with death domain
FAO	Fatty acid oxidation
FasL	Fas ligand
FB	The protease factor B, a component of the alternative complement pathway
FBG	Plasma-derived fibrinogen
Fc	Fragment crystallizable
FcRs	Fragment crystallizable receptors
FD	Serine protease factor D
FDCs	Follicular dendritic cells
FEEL	Fasciclin, EGF-like, laminin-type EGF-like and link
Fer-1	Ferrostatin-1
FH	Factor H, a soluble complement regulatory protein
fHA	Fragment of hyaluronan
FI	Factor I
FINs	Ferroptosis inducers
Flk	Fetal liver kinase
FN	Fibronectin
FNIII EDA/FNIII EDB	Alternatively spliced type III repeats extra domains A and B
Foxp3	Forkhead box protein 3
FP	Properdin
FPs	N-formylated (formyl) peptides
FPRs	Formyl peptide receptors
FPR2/ALX	Formyl peptide receptor 2
FTL	Ferritin L
GAF	γ -Activated factor
GAGs	Glycosaminoglycans
Gal-1-15	Galectin-1 to -15
GalNAc	N-acetylgalactosamine
GALT	Gut-associated lymphoid tissue
GAS	γ -Activated sequence
GATA-1/2/3	GATA-binding protein 1/2/3
G β L	G-like protein/GL
GCs	Germinal centers
G-CSF	Granulocyte colony-stimulating factor
GDFs	Growth and differentiation factors
GI tract	Gastrointestinal tract
GlcNAc	N-Acetylglucosamine
GlcA	Glucuronic acid
GlcN	Glucosamine acid
GM-CSF	Granulocyte-macrophage colony-stimulating factor
G-MDSCs	Granulocytic myeloid-derived suppressor cells

GPCRs	G protein-coupled receptors
GPI	Glycosylphosphatidylinositol
GR	Glutathione reductase
GPR91	G protein-coupled receptor 91
Grb2	Growth factor receptor-bound protein 2
GRP78	Glucose-regulated protein 78
GPX	Glutathione peroxidase
GPX4	Phospholipid-hydroxyperoxide-glutathione-peroxidase
GSDMD	Gasdermin D
GSH	(Reduced form of) glutathione
GSSG	(Oxidized form of) glutathione
GTP	Guanosine-5'-diphosphate
GTPase	Guanosine-5'-triphosphate hydrolase enzyme
GVHD	Graft-versus-host disease
$\gamma\delta$ T cells	Gammadelta T cells
HA	Hyaluronan fragment/polymer
HAMPs	Homeostasis-altering molecular processes
HATs	Histone acetylases
HBDs	Human β -defensins
HBV	Hepatitis B virus
hCAP18	Human cationic antimicrobial peptide 18
hCG	Human chorionic gonadotropin
HCMV	Human cytomegalus virus
HCV	Hepatitis C virus
HDACs	Histone deacetylases
HDMs	HMTs demethylases
HEK cells	Human embryonic kidney cells
HER2	Human epidermal growth factor receptor 2
HET-E	Incompatibility locus protein from the plant <i>Podospora anserina</i>
HFE	“High Fe” (for: HLA-H)
HIF-1 α	Hypoxia-inducible factor 1-alpha
HIN	Hematopoietic expression, interferon-inducible nature, and nuclear localization
HIN200	Hematopoietic interferon-inducible nuclear protein with 200-amino acid repeat
HIV	Immunodeficiency virus
HLA	Human leukocyte antigen
HMG	High mobility group
HMTs	Histone methyltransferases
HMGB1	High mobility group box 1 protein
HNPs	Human neutrophil peptides
HO	Hydroxyl radicals
HOCl	Hypochlorous acid
HPA	Hypothalamic-pituitary-adrenal

HpETE	Hydroxyperoxyeicosatetraenoic acid
HPV	Human papilloma virus
HS	Heparin sulfate
HSCs	Hematopoietic stem cells
HSCs	Hepatic stellate cells
HSFs	Heat shock transcription factors
HSPs	Heat shock proteins
HSR	Heat shock response
HSTs	Histatins
HSV	Herpes simplex virus
HUS	Hemolytic uremic syndrome
H ₂ O ₂	Hydrogen peroxide
H3K27	27th amino acid in histone H3
H3K4me1	Lysine 4 in histone H3
H3K4me3	Tri-methylation of lysine 4 on histone H3
4-HNE	4-Hydroxynonenal
IAP	Inhibitor of apoptosis
IAPP	Islet amyloid polypeptide
IAV	Influenza A virus
IBD	Inflammatory bowel disease
ICAM	Intercellular adhesion molecule
ICD	Immunogenic cell death
ICOS	Inducible costimulator
ICOSL	Inducible costimulator ligand
iDCs	Immature dendritic cells
IDO	Indoleamine 2,3-dioxygenase
IdoA	Iduronic acid
IE	Immediate early
iE-DAP	For: dipeptide, gamma-D-glutamyl-meso-diaminopimelic acid
IECs	Intestinal epithelial cells
IFI16	Interferon-inducible protein 16
IFNARs	IFN- α receptors
IFNs	Interferons
IFN- α , - β , - γ	Interferon-alpha, -beta, -gamma
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgE	Immunoglobulin E
Ig-like	Immunoglobulin-like
IGF	Insulin-like growth factor
IGFR	Insulin-like growth factor receptor
IgM	Immunoglobulin M
IgSF	Immunoglobulin superfamily
IgV	Immunoglobulin variable
IKK complex	IKb kinase complex

IL-1→x	Interleukin-1→x
ILCs	Innate lymphoid cells
IL	Interleukin
ILs	Interleukins
IL-1R→ IL-xR	Interleukin-1 receptor → interleukin-x receptor
IL-1RAcPb	IL-1 receptor accessory protein
IL-18BP	IL-18 binding protein
Inhs	Inhibins
iNKT cell	Invariant natural killer T cell
iNOS	Inducible nitric oxide synthase
IPS-1	Interferon promoter-stimulating factor-1
IRAK	Interleukin-1-receptor-associated kinase
IRAP	Insulin-responsive aminopeptidase
IRE-1	Inositol-requiring enzyme-1
IRE1 α	Inositol-requiring enzyme 1 alpha
IRF	Interferon regulatory factor
IRI	Ischemia/reperfusion injury
iRHOM2	Inactive rhomboid protein 2
IRS	Insulin receptor substrate
ISGs	IFN-stimulated genes
ISGF(s)	Interferon-stimulated gene factor(s)
ISRE	IFN-stimulated response element
ITAM	Immunoreceptor tyrosine-based activation motif
ITGB8	Integrin β 8
ITIM	Immunoreceptor tyrosine-based inhibition motif
iTregs	Inducible T regulatory cells
IVR	Intervening region or BACK domain
I κ B	I κ B (inhibitor of NF κ B)
JAK	Janus kinase
JNK	c-Jun-N-terminal protein kinase
KEAP1	Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1
KIRs	Killer cell immunoglobulin-like receptors
KO	Knockout
KSHV	Kaposi sarcoma-associated herpesvirus
Ku	Ku70–Ku80
LAG-3	Lymphocyte-activation gene 3
LAMP-1/2	Lysosome-associated membrane protein-1/2
LAP	Latency-associated protein
LBRC	Lateral border recycling compartment
LCs	Langerhans' cells
LC3	Light-chain 3
LDL	Low-density lipoprotein
LDNs	Low-density neutrophils
LFA-1	Lymphocyte function-associated antigen-1

LGP2	Laboratory of genetics and physiology 2
LLC	Long latent complexes
LL-37	Leucine-leucine-37 (human cathelicidin)
LMP2/7	Low molecular mass polypeptides 2/7
LMW	Low molecular weight
lncRNAs	Long noncoding RNAs
LOX-1	Lectin-like oxidized low-density lipoprotein receptor 1
LP	Lectin complement pathway
LPDCs	Lamina propria dendritic cells
LPS	Lipopolysaccharide
LRP1	Low-density lipoprotein receptor-related protein 1 (also known as CD91)
LRRs	Leucine-rich repeats
LRRFIP1	Leucine-rich repeat and flightless I interacting protein 1
LT	Lethal toxin
LTi	Lymphoid-tissue inducer
LTs	Leukotrienes
LTA	Lipoteichoic acid
LTBP	Latent TGF- β binding protein
LUBAC	Linear ubiquitin chain assembly complex
LXA4	Lipoxin A4
lysoPS	Lysophosphatidylserine
LZ	Light zone
MAC	Membrane attack complex
MAG	Myelin-associated glycoprotein
MAIT cells	Mucosal-associated invariant T cells
Malt1	Mucosa-associated lymphoid tissue lymphoma translocation gene 1
MAMPs	Microbe-associated molecular patterns
MAPKs	Mitogen-activated protein kinases
MARCO	Macrophage receptor with collagenous structure
MARE	MAF responsive element
MASPs	Mannose-binding lectin-associated proteases
MAVS	Mitochondrial antiviral signaling proteins
MBL	Mannose-binding lectin
MCETs	Mast cell extracellular traps
MCMV	Mouse cytomegalus virus
M-CSF	Monocyte/macrophage colony-stimulating factor
M-CSFR	Macrophage colony-stimulating factor receptor
MDA	Malondialdehyde
MDA5	Melanoma differentiation-associated gene 5
mDCs	Myeloid dendritic cells
MDP	Muramyl dipeptide
MDSCs	Myeloid-derived suppressor cells
M-MDSCs	Monocytic myeloid-derived suppressor cells

MD-2	Myeloid differentiation factor 2
MECL-1	Multicatalytic endopeptidase complex subunit
MEK	MAPK/ERK kinase
Meso-DAP/iE-DAP	Meso-diaminopimelic acid/d-glutamylmeso-diaminopimelic acid
MetS	Metabolic syndrome
MGL	Macrophage galactose-type lectin
MHC	Major histocompatibility complex
MHC-I	Major histocompatibility complex class I
MHC-II	Major histocompatibility complex class II
MHV-68	Murine gammaherpesvirus-68
MICA	MHC class I chain-related A
MICB	MHC class I chain-related B
MICs	MHC class I chain-related proteins
MICL	Myeloid inhibitory C-type lectin-like receptor
Mincle	Macrophage-inducible C-type lectin
MIP-1/2	Macrophage inflammatory proteins-1/2
miRNA	MicroRNA
MIS	Müllerian inhibiting substance
MLKL	Mixed lineage kinase domain-like protein
mLST8	Mammalian lethal with sec-13
MMP	Mitochondrial membrane permeabilization
MMPs	Matrix metalloproteinases
MMR	Macrophage mannose receptor
MMTV	Mouse mammary tumor virus
MOF	Multiple organ failure
MPK	MAP kinase
MPI	Macrophage inflammatory protein
MPO	Myeloperoxidase
MPT	Mitochondrial membrane permeability transition
MR	MHC-related
mRNA	Messenger RNA
MRN	Mre11–RAD50–NBS1
MRP	Multidrug resistance-associated protein
MRPs	Myeloid-related proteins
MR1	MHC class I-related protein
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells
mSin1	Mammalian stress-activated map kinase-interacting protein 1
MSU	Monosodium urate
mtDNA	Mitochondrial DNA
mTECs	Medullary thymic epithelial cells
mTOR	Mammalian target of rapamycin
mTORC1/2	Mammalian target of rapamycin (mTOR) complex 1/2

MTP-RN	Mitochondrial permeability transition-regulated necrosis
MVBs	Multivesicular bodies
MYA	Million years ago
MyD88	Myeloid differentiation primary response gene 88
MZ	Marginal zone
MZ B cells	Marginal zone B cells
M1/M1-like	Macrophages with predominantly pro-inflammatory activities
M2/M2-like	Macrophages with predominantly anti-inflammatory/regenerative activities
MIIC	MHC-II-rich (enriched) compartments
N-terminus	Amino-terminus
NACHT domain	Neuronal apoptosis inhibitor protein (NAIP), MHC-class II transactivator/transcription activator (CIITA), plant het product (HET-E), and telomerase-associated protein 1 (TP1) protein
NADPH	Nicotinamide adenine dinucleotide phosphate
NAIP	Neuronal apoptosis inhibitor protein
NAP-2	Neutrophil-activating peptide-2
NAs	Nucleic acids
NATs	Natural antisense transcripts
NBD	Nucleotide-binding domain
NCRs	Natural cytotoxicity receptors
nDNA	Nuclear DNA
NE	Neutrophil elastase
NEAT1	The nuclear enriched abundant transcript 1
Nec-1	Necrostatin-1
necl	Nectin-like
Nef	Negative regulatory factor (of HIV)
NEK7	NIMA related kinase 7
NEMO	NF- κ B essential modulator
NESs	Nuclear export sequences
NETs	Neutrophil extracellular traps
NETosis	Formation of NETs by neutrophils
NFAT	Nuclear factor of activated T cells
NF- κ B	Nuclear factor kappa B
NGS	Next-generation sequencing studies
NHEJ	Nonhomologous end joining
nIgM	Natural immunoglobulin M
NIK	NF- κ B-inducing kinase
NK cells	Natural killer cells
NKG2	Natural killer group 2
NKG2D	Natural killer group 2 D
NKR	Natural killer cell receptor

NKT cells	Natural killer T cells
NLRs	Nucleotide-binding oligomerization domain (NOD) leucine-rich repeat receptors
NLRA	NLR-acidic transactivation domain
NLRB	Baculoviral inhibitory repeat-like domain (also abbreviated as BIR)
NLRC	Caspase activation and recruitment domain (also abbreviated CARD)
NLRP	Pyrin domain
NLRP3	Nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3
NLS	Nuclear localization signal (sequence)
NMHC-II	Nonmuscle myosin heavy chain IIA
NO	Nitric oxide
NOD	Nucleotide-binding oligomerization domain
noldals	Nodal growth differentiation factors
NOS	Nitric oxide synthetase
NOX	Nicotinamide adenine dinucleotide phosphate-dependent oxidase
Nrf1/Nrf2	Nuclear factor-erythroid 2 p45-related factors 1/2
NRP1	Neuropilin 1
nTregs	Natural T regulatory cells
O ⁻	Superoxide anions
OAAMs	Oxidative arachidonic acid metabolites
OAS	2'-5' oligoadenylate synthase
ODNs	Oligodeoxynucleotides
OLAMs	Oxidative linoleic acid metabolites
ONOO ⁻	Peroxynitrite
OSEs	Oxidation-specific epitopes
OVA	Ovalbumin
OxCL	Oxidized cardiolipin
OxLDLs	Oxidized low-density lipoproteins
OXPHOS	Oxidative phosphorylation
OxPLs	Oxidized phospholipids
OxPS	Oxidized phosphatidylserines
OX40L	OX40 ligand
¹ O ₂	Singlet oxygen
PAAN	Parthanatos AIF-associated nuclease
PACER	P50-associated COX-2 extragenic RNA
pAgs	Phosphoantigens or phosphoagonists
PAMPs	Pathogen-associated molecular patterns
PANX1	Pannexin 1
PAR	Protease-activated receptor
PARP-1	Poly (ADP-ribose) synthetase-1
Parthanatos	Poly ADP-ribose polymer

PBMCs	Peripheral blood mononuclear cells
PC	Phosphatidylcholine
PCNA	Proliferating cell nuclear antigen
PC-OxPL	PC headgroup of OxPL
PD-1	Programmed cell death protein-1
PDGF	Platelet-derived growth factor
PD-L1/2	Programmed cell death protein ligand 1/2
PDPK1	3-Phosphoinositide-dependent protein kinase-1
pDCs	Plasmacytoid dendritic cells
PE	Phosphatidylethanolamine
PECAM-1	Platelet endothelial cell adhesion molecule-1
PERK	Protein kinase R (PKR)-like endoplasmic reticulum kinase
PG	Phosphatidylglycerol
PGE2	Prostaglandin E2
PGN	Peptidoglycan
PGRPs	Peptidoglycan recognition proteins
PGs	Proteoglycans
PIPs	Phosphatidylinositol phosphates
PIKKs	Phosphatidylinositol 3 kinase-related kinases
PI3K	Phosphatidylinositol 3 kinase
PI3K/Akt	Phosphatidylinositol 3 kinase/Akt
PIP2	Phosphatidylinositol biphosphate
PIP3	Phosphatidylinositol triphosphate
PKA	Protein kinase A
PKC	Protein kinase C
PKR	Protein kinase regulated by dsRNA (dsRNA-dependent protein kinase R)
PLC	Peptide loading complex
PLC	Phospholipase C
pMHC	Peptide/major histocompatibility complex
pMHC-I	Peptide/MHC class I complexes
pMHC-II	Peptide/MHC class II complexes
pMLKL	Pseudokinase MLKL
PMNs	Polymorphonuclear neutrophils
P-MDSCs	Polymorphic (PMN) myeloid-derived suppressor cells
Pn	Aggregated form of properdin
PNG	Peptidoglycan
PNH	Paroxysmal nocturnal hemoglobinuria
poly (I:C)	Polyinosinic:polycytidylic acid
Pol III	RNA polymerase III
PPAR- γ	Peroxisome proliferator activating receptor-gamma
P-PRE-DCs	Plasmacytoid precursor-DCs
PRAS40	Proline-rich Akt substrate 40kDa
PRMs	Pattern recognition molecules

protor 1/2	Protein observed with rictor 1 and 2
PRP19	Pre-mRNA-processing factor 19
PRRs	Pattern recognition receptors
PS	Phosphatidylserine
PSGL-1	P-selectin glycoprotein ligand 1
pSTATs	Phosphorylated STATs
PtdSer	Phosphatidylserine
Ptgs2/Cox2	PG-endoperoxide synthase 2
PTMs	Post-translational modifications
PTPC	Permeability transition pore complex
pTregs	Peripherally derived T regulatory cells
PTX3	The long pentraxin 3
Pu.1	A transcription factor
PUFAs	Polyunsaturated fatty acids
PVN	Paraventricular nucleus
PVR	Poliovirus receptor
PYD	Pyrin domain (also abbreviated as NLRP)
PYHIN	Pyrin and HIN domain-containing protein
P2XRs	P2X purinoceptors
P2YRs	P2Y purinoceptors
QPD	Glutamine–proline–aspartate
RA	Rheumatoid arthritis
RAE	Retinoic acid early
RAET	Retinoic acid early transcript
RAET1	Retinoic acid early inducible protein 1
RAF	Rapidly accelerated fibrosarcoma
RAG	Recombination activating gene
RAGE	Receptor for advanced glycation end products
RANK	Receptor activator of NF- κ B
RANKL	Receptor activator of NF- κ B ligand
RANTES	Regulated on activation, normal T cell expressed and secreted
Raptor	Regulatory-associated protein of mammalian target of rapamycin
RAR	Retinoic acid receptor
Ras	Rat sarcoma; Ras proteins: a family of related proteins
RCD	Regulated cell death
RHAMM	Receptor of hyaluronan-mediated motility
RHIM	RIP homotypic interaction motif
rictor	Rapamycin-insensitive companion of mTOR
RIG-I	Retinoic acid-inducible gene (protein) I
RING	RING finger domain
RING	Really interesting new gene
RIP	Receptor-interacting protein
RIPK1-3	Receptor-interacting serine/threonine-protein kinase 1-3

RISP	Rieske iron-sulfur protein
RLH	RIG-I-like helicase
RLR	RIG-I-like receptor
RLRs	Helicase retinoic acid-inducible gene I (RIG-I)-like receptors
RN	Regulated necrosis
RNS	Reactive nitrogen species
RO [•]	Alkoxy radicals
RO ₂ [•]	Peroxy radicals
ROR α	Retinoic acid receptor (RAR)-related orphan receptor-alpha
ROR γ t	Retinoic acid receptor-related orphan receptor-gamma t
ROS	Reactive oxygen species
RPA	Replication protein A
rRNA	Ribosomal RNA
RSL3	Ras-selective lethal small molecule 3
rSOD	Recombinant superoxide dismutase
RSV	Respiratory syncytial virus
RTKs	Receptor tyrosine kinases
RT1	Major histocompatibility complex in the rat
SAMPs	Suppressing/inhibiting DAMPs
SAP	Or: serum amyloid P component
SAP	Or: SLAM-associated protein
SAP130	Histone deacetylase complex subunit SAP130
SCF	Stem cell factor
SCF/RTK	Stem cell factor/receptor tyrosine kinase
SCRs	Short consensus repeats
SEF	Strain energy function
SEFIR	SEF/IL17R
Setdb2	SET domain bifurcated 2
SFPQ	Splicing factor proline/glutamine-rich
SGK1	Serum/glucocorticoid-regulated kinase 1
SH2/3	Src homology region 2/3
SHP-2	Src homology region 2-containing protein tyrosine phosphatase 2
SIGIRR	Single immunoglobulin interleukin-1 receptor-related protein
SIGLECS	Sialic acid-binding immunoglobulin-like lectins
SiO ₂	Crystalline silica
siRNA	Small interfering RNA
Sirp α ⁺	Signal regulatory protein α positive
SIRS	Systemic inflammatory response syndrome
SLAM	Signaling lymphocytic activation molecule
SLC	Small latent complex
SLE	Systemic lupus erythematosus

SLRPs	Small leucine-rich proteoglycans
SMAC	Second mitochondria-derived activator of caspase
Smad	Similar to mothers against decapentaplegic
sMAF	Small musculoaponeurotic fibrosarcoma proteins
SMCs	Smooth muscle cells
sMD-2	Soluble MD-2
SNAP	Synaptosomal-associated protein
SNARE	Soluble n-ethylmaleimide-sensitive factor attachment protein receptor protein
SNPs	Single nucleotide polymorphisms
SNS	Sympathetic nervous system
SNX17	Sorting nexin 17
SOCS	Suppressors of cytokine signaling
SOD	Superoxide dismutase
SP	Single-positive (thymocytes)
SPA→D	Surfactant proteins A→D
SPMs	Specialized pro-resolving mediators
SP1	Site-1 protease
SP2	Site-2 protease
SRs	Scavenger receptors
Src	Sarcoma kinase
SREC-1	Scavenger receptor expressed by ECs-1
SREs	Smad-responsive elements
SSBs	Single-strand DNA breaks
ssDNA	Single-stranded DNA
ssRNA	Single-stranded ribonucleic acid
STAT 1/2/3/4	Signal transducer and activator of transcription 1/2/3/4
STING	Stimulator of interferon genes
sTLR	Soluble TLR
STX	Syntaxin
ST2	Suppressor of tumorigenicity 2; originally: growth stimulation expressed gene 2
ST2/IL-1RAP	ST2/IL-1R accessory protein
SUCNR1	Succinate receptor 1
SWI/SNF	Switch/sucrose nonfermentable
Syk	Spleen tyrosine kinase
S1PR2	Sphingosine-1-phosphate receptor-2
S6K1	S6 kinase 1
TAA	Tumor-associated antigens
TAB 1/2/3	Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 1/2/3
TACE	TNFα-converting enzyme
TAK1	Transforming growth factor-β-activated kinase 1
TAMs	MerTK receptor tyrosine kinases

TANK	Tumor necrosis factor (TNF)-receptor-associated factor (TRAF) family member-associated NF- κ B activator
TAP	Transporter associated with antigen processing
TAXI	Transporters associated with the eXecution of inflammation
TBK1	TANK-binding kinase 1
TCA	Tricarboxylic acid
TCR	T cell receptor
TD antigens	T cell-dependent antigens
TFAM	Transcription factor A inside the mitochondrial inner membrane
TFEB	Transcription factor EB
Tfh cells	Follicular T helper cells
TGF- β	Transforming growth factor-beta
TGF- β RI-III	TGF- β type I-III receptor
TGN	Trans-Golgi network
Th	T helper cell
THRIL	TNF and HNRNPL-related immunoregulatory long noncoding RNA
Th1/Th2	T helper cell type 1/type 2
Th3	T helper type 3
Th0	T helper cell type 0
TI antigens	T cell-independent antigens
TIF1 γ	Transcriptional intermediary factor 1 gamma
TIGIT	T cell immunoglobulin and ITIM domain
TIM1/4	T cell immunoglobulin and mucin domain containing 1 and 4
TIR	Toll/interleukin (IL)-1 receptor
TIRAP	TIR-associated protein
TLRs	Toll-like receptors
TLSP	Thymic stromal lymphopoietin
TNC	Tenascin-C
TNF	Tumor necrosis factor
TNFSF	TNF superfamily
TNFR	Tumor necrosis factor receptor
TNFRSF	TNF receptor superfamily
tolDCs	Tolerogenic dendritic cells
TP	Terminal (complement) pathway
TRADD	TNFR1-associated death domain protein
TRAF	Tumor necrosis factor (TNF) receptor-associated factor
TRAIL	TNF-related apoptosis-inducing ligand
TRAILR	TNF-related apoptosis-inducing ligand receptor
TRAJ33	T cell receptor alpha joining 33
TRALI	Transfusion-related acute lung injury
TRAM	TRIF-related adaptor molecule

TRAV1-2	T cell receptor alpha variable 1-2
TRBV6/20	T cell receptor beta variable 6/20
Tregs	T regulatory cells
Trex1	Exonuclease 1
TRIF	Toll/IL-1(TIR)-domain containing adaptor inducing interferon- β
TRIM 25	Tripartite motif-containing protein 25
tRNA	Transfer RNA
TRP	Transient receptor potential
TRPA1	Transient receptor potential cation channel subfamily A member 1
TRPM8	Transient receptor potential cation channel subfamily M member 8
TRPV1-4	Transient receptor potential vanilloid subtype 1–4
TRX	Thioredoxin
Trx-1	Thioredoxin-1
Trx-2	Thioredoxin-2
Tr1	T regulatory type 1 cells (Foxp3 ⁻ IL-10 ⁺ T cells)
TSAs	Tissue-specific self-antigens
TSLP	Thymic stromal lymphopoietin
tTregs	Thymus T regulatory cells
TXNIP	Thioredoxin-interacting protein
TYK2	Tyrosine kinase 2
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
T1SS (T2SS, T3SS)	Type I (II, III) secretion system
UBA	Ubiquitin-binding-association
UCP1	Uncoupling protein 1
ULBPs	UL16-binding proteins
ULK1	UNC-51-like kinase 1
UPR	Unfolded protein response
UPS	Ubiquitin-proteasome system
UPS	Unconventional protein secretion
UQCRB	Ubiquinol-cytochrome c reductase binding protein
UQCRFS1	Ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1
UV	Ultraviolet
VACV	Vaccinia virus
VAMP	Vesicle-associated membrane protein
VCAM-1	Vascular cell adhesion molecule-1
VEGFs	Vascular endothelial growth factors
VEGFRs	Vascular endothelial growth factor receptors
VLA4	Very late antigen 4
VNUT	Vesicular nucleotide transporter
VPR	Viral protein R

VSMCs	Vascular smooth muscle cells
VSV	Vesicular stomatitis virus
VWF	Von Willebrand factor
WAT	White adipose tissue
WPBs	Weibel–Palade bodies
XPB1	X-box binding protein 1
XIAP	X-linked inhibitor of apoptosis protein
XOR	Xanthine oxidoreductase
ZBP1	Z-DNA binding protein 1
ZKSCAN3	Zinc finger with KRAB and SCAN domains 3