New paradigm in immunology

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Overview of host response to stimuli

Antigen

Minutes Hours Days Weeks

Adaptive immunity

Lymphocytes, plasma cells

Cur Opin Immunol, 2001
Figure 8-27 part 2 of 2  Immunobiology, 6/e. (© Garland Science 2005)
### History of research in immunology

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
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<tbody>
<tr>
<td><strong>Discovery of phagocytosis by Metchnikoff (1845–1916)</strong> founder of innate immunity</td>
<td><strong>Serum Therapy by Kitasato and Behring (1890)</strong></td>
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<td><strong>Side-chain theory of antibody by Ehrlich (1900)</strong></td>
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<td><strong>Clonal selection by Burnet (1957)</strong></td>
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<td>After 1960’s</td>
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<tr>
<td>Primary structure of antibodies</td>
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<td>Discovery of IgE and mechanism of allergy</td>
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<td>Discovery of T and B cells</td>
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<td>Discovery of histocompatibility antigens</td>
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<td>Development of monoclonal antibodies</td>
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<td>Mechanism of antibody diversity</td>
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<td>After 1996</td>
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<tr>
<td>Role of Drosophila Toll in antifungal response</td>
<td>Cloning of T cell receptor</td>
</tr>
<tr>
<td>Discovery of mammalian Toll-like receptors (TLRs) and identification of their function</td>
<td>Cloning of cytokines involved in antibody production</td>
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<td>Th1 and Th2 responses</td>
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<td>Identification of molecules involved in antibody diversity</td>
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</tbody>
</table>
Overview of host response to stimuli

Antigen

Innate immunity
Phagocytes, APC

Adaptive immunity
Lymphocytes, plasma cells

Cur Opin Immunol, 2001
Innate immunity and adaptive immunity
PAMPs vs PRRs

![Diagram showing PAMPs and PRRs in the immune system](image)
PRR-mediated control of checkpoints of adaptive immunity
1. Broad coverage
2. Rapid response
3. Appropriate response, e.g. avoiding enhancing antibody, atopic Ab and autoimmunity
4. Good memory
Overview of host response to stimuli

Innate-like immunity
B1, MZB, NKT, γδT

Antigen

Phagocytes, epithelium

Innate immunity

Lymphocytes, plasma cells

Cur Opin Immunol, 2001
How innate immunity “turns-on” and “regulates” adaptive immune response in health and disease
**Self vs non-self**

a) 1959, original SNS model said that lymphocytes are activated by recognition of foreign things.

b) 1969, 1st modification: B cells die when they see antigen (signal one) unless rescued by help (signal two).

c) 1975, 2nd modification: T helper cells die when they see antigen unless rescued by co-stimulation (signal two) from APCs.

d) 1989, 3rd modification (INS): APCs do not co-stimulate unless activated via PRRs (receptors for evolutionarily distant infectious non-self).

e) 1994, 4th modification (Danger model: major change) APCs are activated by endogenous cellular alarm signals from distressed or injured cells.

**Fig. 1.** A history of immunological models.
**Stranger model of immune activation**

(Pathogen (PAMP) (Infectious non-self)

Pattern Recognition Receptor (PRR)
Types and location of microbial sensors
(Pattern-Recognition Receptors - - - PRRs)

Toll-like receptors (TLRs)
LIPOPEPTIDES
Di-acyl
Tri-acyl
Flagellin
LPS
dsRNA
ssRNA
CpG
DNA
Uropathogenic bacterial products
β-glucans
Mannans
Microbial diacylglycerides
CD36
Dectin
MR
DC-SIGN
HIV
NOD1
NOD2
Muramyl dipeptides
Casp1
NFκB
MAPK
NFκB
RIG-1
Viral RNA

Non-TLR
General components of innate immune receptor

- Recognition unit (leucine-rich repeat LRR)
- TIR domain
- Adapter
- IRAKs
- TRAF6
- NF-KB

Kinase cascade
General components of innate immune receptor

Microbe (PAMP)

Recognition unit (leucine-rich repeat LRR)

TIR domain

Adapter

IRAKs

TRAF6

NF-KB

Kinase cascade

Transcription factor

Antimicrobial peptides, enzyme

Inflammatory cytokines (IL-8, TNF-α)

Apoptosis

Adhesion molecules
TLR signaling

MyD88-dependent and MyD88-independent
APC response after stimulated by PAMP / DAMP

» Appearance of adhesion molecules
» Cytokine and chemokine production
» Antimicrobial peptide production
» Apoptosis
» Inflammation
» Alerting adaptive immune system
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**Danger signals:**

- **Infectious non-self (exogenous)**
- **Damage tissue (non-infectious self) (endogenous)**

- **Fig. 1: A hierarchy of danger signals**

  - **Exogenous vs endogenous**
Tissue damaging model of immune activation

DAMPs
TNF-α, IL-1
ATP
HSP
Proteases
Necrosis
Apoptosis
Uric acid

DAMP = danger associated molecular pattern

eg, HSP, uric acid crystal, ATP, IL-1, HMGB1, oxidized LDL,
Advanced glycated end products (diabetes)
Discrimination between viable cell, necrosis and apoptosis

Nat Rev Immunol 8:279, 2008
Cell death & inflammation
Stranger       Tissue damage

DAMP receptor

Tissue damaging receptors (endogenous --- DAMPs)
### Endogenous ligands of TLRs

<table>
<thead>
<tr>
<th>TLR</th>
<th>Ligands</th>
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<tbody>
<tr>
<td>TLR2</td>
<td>HSP60, HSP70, Gp96, Minimally modified LDL, HMGB1</td>
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<tr>
<td>TLR3</td>
<td>mRNA</td>
</tr>
<tr>
<td>TLR4</td>
<td>HSP60, HSP70, Gp96, Fibronectin, Heparan sulphate, Oligosaccharides of hyaluronic acid, Surfactant protein-A, HMGB1</td>
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<tr>
<td>TLR7</td>
<td>mRNA</td>
</tr>
<tr>
<td>TLR9</td>
<td>DNA, Chromatin-IgG complexes</td>
</tr>
</tbody>
</table>

HSP: heat shock protein; LDL: low density lipoprotein; HMGB1: high mobility group B1; Gp: 96 kDa glycoprotein of the endoplasmic reticulum
Recognition of endogenous signals
Factors that influence binding & signaling of self ligands to TLR
Tissue damaging receptors (endogenous ---DAMPs)
Proposed consequences of TLR recognition of exogenous vs endogenous ligands
Activation of inflammatory response by exogenous and endogenous danger signals through same TLR

**PAMP**
- Exogenous (pathogen)
  - Bacterial molecule
  - TLR
  - Siglec-G
  - CD24

**DAMP**
- Endogenous (tissue damage)
  - Host molecule (HMGB1)

**Inflammation**
- Pathogen elimination
- Collateral tissue damage
- Adaptive immunity

**Inflammation**
- Limitation of tissue damage
- ? tissue reconstruction
Selective repression pathway discriminating PAMP & DAMP

TLR/NLR

CD24

SHP-1

PAMP

DAMP

Inflammatory cytokines

Inflammatory cytokines

TRENDS in Immunology

Vol 30, 2009
Th17
IL-17
IL-23, IL-6, IL-1, TGF-β

Treg
TGF-β
IL-10

T H1
IFN-γ

T H2
IL-4
IL-5
IL-13
IL-10

Naive T cell

PAMP or Pathogen
Pathogen
Endocytic PRR

Dendritic cell

Toll
CD28
CD80/86
MHC-II
TCR

IL-12

IL-23, IL-6, IL-1, TGF-β

IL-23, TGF-β
CD4⁺ T cell subset differentiation

New T₉, T₂₂, TFH
Antigen presenting cells

Blood monocytes

- GM-CSF+ IL-4
- M-CSF

Dendritic cell

Macrophage

Activity: subpopulations, maturation state, recognition signal, microenvironment
Central role of TSLP in driving DC maturation for Th2-cell response
Cell-extrinsic recognition

Extracellular pathogen

infected cell
PAMP recognition by cell-surface TLRs

- LPS binds to MD2 and TLR4, activating the MyD88-dependent pathway
- Triacyl lipopeptide binds to TLR2-CHI (TLR1), activating the MyD88-dependent pathway
- Diacyl lipopeptide binds to TLR2-CHI (TLR6), activating the TRIF-dependent pathway
- Flagellin binds to TLR5

- Endosome activation of TLR4

- Early NF-κB activation
- Late NF-κB activation

- Inflammatory cytokines
- Type 1 IFN
- Inflammatory cytokines

MyD88-dependent pathway
TRIF-dependent pathway

Nat Immunol 11, 2010
PAMP recognition by intracellular TLRs
Location of PRRs

- Toll-like receptors (TLRs)
- LIPOPEPTIDES Di-acyl Tri-acyl
- dsRNA
- LPS Flagellin
- ssRNA
- MAPK
- CpG DNA
- ?
- Uropathogenic bacterial products
- NOD1
- NOD2
- NFκB
- Casp1
- Cardif
- RIG-1
- Viral RNA
- Microbial diacylglycerides
- CD36
- β-glucans
- Mannans
- DC-SIGN
- HIV
Cell-intrinsic recognition
Endosomal and cytosolic pathways for pathogen detection

**a** Endosomal pathways

- Apoptotic cell
- Virus
- Bacteria
- Intracellular parasite

**b** Cytosolic pathways

- NLR
- RLR

- Salmonella
- Lipopolysaccharide (LPS)
- ATP
- Anthrax LT
- Francisella
- Vaccinia virus
- Cytomegalovirus
- Picornaviridae
- Paramyxoviridae
- Orthomyxoviridae
- Rhabdoviridae
- Flaviviridae

Inflammasome formation

- IL-1β
- IL-18

Type I IFN

Proinflammatory cytokines

Type I IFN

CARD

Pyrin domain

Nacht domain

LRR

Helicase domain

HIIN domain

Nat Immunol 11, 2010
Detection of self & non-self nucleic acids by cytosolic receptors

Nat Immunol 11, 2010
Clinical trials of TLR drugs

<table>
<thead>
<tr>
<th>TLR</th>
<th>Drug</th>
<th>Action</th>
<th>Application</th>
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<tr>
<td>TLR3</td>
<td>poly I:C analogs</td>
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<td>HIV, HBV</td>
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<td>CpG-ODN</td>
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HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus

Proc Jpn Acad, Ser B 85:143 2009