Immunodermatology

Immunology
DERMIES

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Outline

• Adaptive Immunity: T and B cell development, activation, function, and related diseases

• Innate Immunity: Complement, Toll-like receptors
Intro to Immunodermatology: T and B cell development, activation, function, and related diseases

Unless specified, all figures are from Janeway’s Immunobiology, 8th Edition and Cellular and Molecular Immunology, Abbas, 6th Edition
Review of Lymphoid Structures

Gut (peyer’s patches)
## Innate vs. Adaptive Immunity

<table>
<thead>
<tr>
<th>Phases</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Innate immunity</strong> (immediate: 0–4 hours)</td>
<td>Recognition by preformed, non-specific and broadly specific effectors, Removal of infectious agent (Ex: Complement, Defensins)</td>
</tr>
<tr>
<td><strong>Early induced innate response</strong> (early: 4–96 hours)</td>
<td>Recognition of microbial-associated molecular patterns, Inflammation recruitment and activation of effector cells, Removal of infectious agent (Ex: TLRs)</td>
</tr>
<tr>
<td><strong>Adaptive immune response</strong> (late: &gt;96 hours)</td>
<td>Transport of antigen to lymphoid organs, Recognition by naive B and T cells, Clonal expansion and differentiation to effector cells, Removal of infectious agent</td>
</tr>
</tbody>
</table>

- The first two phases rely on the recognition of pathogens by germ-line encoded receptors of the innate immune system.
- Only if an organism can breach these early lines of defense will an adaptive (specific) immune response occur.
- Adaptive Immunity occurs late because rare Ag-specific B or T cells have to encounter the Ag and undergo clonal expansion.
Innate vs. Adaptive Immunity

Cells of the Adaptive Immune System undergo V(D)J recombination and have Ag Specificity.
## Innate vs. Adaptive Immunity

<table>
<thead>
<tr>
<th>Receptor characteristic</th>
<th>Innate immunity</th>
<th>Adaptive immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity inherited in the genome</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expressed by all cells of a particular type (e.g. macrophages)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Triggers immediate response</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Recognizes broad classes of pathogens</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interacts with a range of molecular structures of a given type</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Encoded in multiple gene segments</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Requires gene rearrangement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonal distribution</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Able to discriminate between even closely related molecular structures</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Adaptive Immune System: Lymphocyte Development

- B cells are generated in the Bone Marrow and are released into the circulation.
- Immature T cell progenitors migrate to the thymus as DN (CD4-CD8-) TCR- progenitors.
- T cells enter the thymus at the corticomedullary junction.
Positive and Negative Selection

Positive Selection occurs in the cortex (with DP cells)

- Positive Selection ensures that T cells CAN recognize Ag in the context of MHC.
- If the CD4 molecule recognizes MHC class II, CD8 is down-regulated and the cell becomes a single-positive CD4+ T cell.
- If the CD8 molecule recognizes MHC class I, CD4 is down-regulated and the cell becomes a single-positive CD8+ cell.
- If no recognition takes place, the cell dies by neglect.

Negative Selection occurs in the medulla

- AIRE+ (AutoImmune REgulator) mTECs express self-Ag (thymic “self shadow”).
- T cells that recognize Ag with high affinity are deleted (death by apoptosis)
APECED

Autoimmune polyendocrinopathy candidaiasiis ectodermal dystrophy

- Autosomal recessive
- No central tolerance, so widespread autoimmunity (compare to IPEX, defect in peripheral tolerance – FoxP3+ Tregs)
- Other clinical associations – down syndrome – trisomy 21. Increased autoimmunity risk from impaired central tolerance from defective AIRE expression (gene on chromosome 21)

Gimenez-Barcons et al. Autoimmune predisposition in Down syndrome may result from a partial central tolerance failure due to insufficient intrathymic expression of AIRE and peripheral antigens. J Immuo 2014 Bologna, 3rd ed
Once positive and negative selection occurs, Naïve T cells exit into the periphery to be activated:
CD4 T cell Activation Requires 2 Signals

- CD4 and the TCR interact with MHC / Ag complexes on the APC.
- The APC (in the presence of an infection / inflammation) up-regulates costimulatory molecules (CD80/86) that interact with CD28 on the CD4 T cell.
- In the absence of costimulation, the T cell will become anergic.
T cell Activation Requires 2 Signals

What two molecules bind to form the “signal 2” or “danger signal” necessary for T cell activation?

A: MHC and TCR
B: TCR and CD80/86
C: CD28 and MHC
D: CD80/86 and CD28
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T cell Activation Requires 2 Signals

T cell anergy occurs when:
A: TCR binds MHC in the absence of antigen
B: MHC and TCR signals occur without signal 2
C: Both signal 1 and signal 2 are engaged
D: In the presence of IL-2
T cell Activation Requires 2 Signals

T cell anergy occurs when:
A: TCR binds MHC in the absence of antigen
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Ag Processing and Presentation

- All nucleated cells express MHC class I
- APC express MHC class II
MHC Haplotypes (Chromosome 6)
T cell Activation Requires 2 Signals

Under normal conditions, keratinocytes express what class of MHC?
A: MHC class I
B: MHC class II
T cell Activation Requires 2 Signals

Under normal conditions, keratinocytes express what class of MHC?

A: MHC class I
B: MHC class II
MHC class I

- Class I presents ENDOGENOUS Ag.
- Viruses make proteins in the host cell.
- Class I peptide-binding grooves are pretty small (8-10aa). Proteases cleave pathogen proteins.
- TAP forms a “molecular tunnel” to allow these small peptides to enter the ER, where they can interact with MHC class I molecules.
- Loaded MHC I molecules bud through the ER-Golgi to the cell surface (paired with β2 Microglobulin)
T cell Activation Requires 2 Signals

MHC class I molecules bind to:
A: Peptide fragments of cytosolic proteins
B: Peptide fragments of proteins brought in by endocytosis and degraded
C: Fc Receptors
T cell Activation Requires 2 Signals

MHC class I molecules bind to:
A: Peptide fragments of cytosolic proteins
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C: Fc Receptors
**MHC class II**

- Class II (αβ) presents **EXOGENOUS** Ag.
- Phagocytes or B cells bring Ag in (endocytosis / opsonization) and process it.
- Phagocytosis “chews up” proteins into peptides, which can then be loaded on MHC class II molecules.
- MHC class II (like class I) is in the ER. The peptide binding site is bound by the **invariant chain** (prevents endogenous Ag binding).
- **Class II molecules bud from the ER-golgi and fuse with the phagolysosome.** The decreased pH degrades the invariant chain, leaving the peptide binding groove open.
- Exogenous peptides can then bind freshly-synthesized MHC II molecules and be displayed on the APC surface.
T cell Activation Requires 2 Signals

MHC class I molecules bind to:
A: Peptide fragments of cytosolic proteins
B: Peptide fragments of proteins brought in by endocytosis and degraded
C: Fc Receptors
T cell Activation Requires 2 Signals

MHC class I molecules bind to:

A: Peptide fragments of cytosolic proteins

B: Peptide fragments of proteins brought in by endocytosis and degraded

C: Fc Receptors
Drug Reactions Associated with MHC Haplotypes

Carbamazapine in Asian populations?

Carbamazapine in Caucasian / European populations?

Allopurinol?

Abacavir?
Drug Reactions Associated with MHC Haplotypes

Carbamazapine in Asian populations? HLA B*1502

Carbamazapine in Caucasian / European populations? HLA A*3101

Allopurinol? HLA B*5801

Abacavir? HLA B*5701
T cell Activation

T-cell activation requires both antigen and co-stimulatory signals.

- **No antigen**
  - APC
  - T-cell receptor
  - CD80
  - CD28
  - CD4
  - Naive T cell
  - No antigenic peptide
  - No response

- **No co-stimulation**
  - APC
  - MHC class II
  - T-cell receptor
  - CD4
  - CD28
  - Naive T cell
  - No activation
  - T cell becomes unresponsive

- **Both antigen and co-stimulation**
  - APC
  - foreign antibody
  - CD80 or CD86
  - pathogen
  - Naive T cell
  - T-cell activation
T cell Activation

The context in which a CD4 T cell is activated determines what type of CD4 T cell it will become.

<table>
<thead>
<tr>
<th>Types of effector T cell</th>
<th>CD8 cytotoxic T cells</th>
<th>CD4 T_{H1} cells</th>
<th>CD4 T_{H2} cells</th>
<th>CD4 T_{H17} cells</th>
<th>CD4 regulatory T cells (various types)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main functions in adaptive immune response</td>
<td>Kill virus-infected cells</td>
<td>Activate infected macrophages</td>
<td>Provide help to B cells for antibody production</td>
<td>Enhance neutrophil response</td>
<td>Suppress T-cell responses</td>
</tr>
<tr>
<td>Pathogens targeted</td>
<td>Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria</td>
<td>Microbes that persist in macrophage vesicles (e.g. mycobacteria, Listeria, Leishmania donovani, Pneumocystis carinii) Extracellular bacteria</td>
<td>Helminth parasites</td>
<td>Extracellular bacteria (e.g. Salmonella enterica)</td>
<td>Candida / Staph</td>
</tr>
</tbody>
</table>
T cell Activation

The **context** in which a CD4 T cell is activated determines what type of CD4 T cell it will become.

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Effector Functions of T cells: CD4 Th1

Th1 cells make **IFNγ**, which activates MΦ. Activated MΦ can clear infections such as TB / leprosy that would otherwise survive inside them. MΦ activation induced MΦ-production of **TNFα**, which further stimulates MΦ in an autocrine manner.
Effector Functions of T cells: CD4 Th1

Granulomas require Th1 cells (IFNγ) and MΦ (TNFα)
Effector Functions of T cells: CD4 Th1

Bolgobia, 3rd Ed.
Effector Functions of T cells: CD4 Th1

What is the main macrophage-activating cytokine?
A: IL-4
B: IL-5
C: IFN$\gamma$
D: TNF$\alpha$
Effector Functions of T cells: CD4 Th1

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A: IL-4
B: IL-5
C: IFN\(_\gamma\)
D: TNF\(\alpha\)
Effector Functions of T cells: CD4 Th1

Which of the following represents a Th1 response?
A: Lepromatous Leprosy
B: Tuberculoid Leprosy
Which of the following represents a Th1 response?

A: Lepromatous Leprosy

B: Tuberculoid Leprosy
Effector Functions of T cells: CD4 Treg

Effector Functions of T cells: CD4 Th1

A 4y/o boy is diagnosed with IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked). What gene is mutated?

A: FoxP3
B: GATA3
C: Tbet
D: RORγt
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A: FoxP3
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C: Tbet
D: RORγt
Effector Functions of T cells: CD4 Treg

Eczematous dermatitis in an infant with IPEX syndrome. Photographs courtesy of Jennifer Urban, MD
Effector Functions of T cells: CD4 Th2

- Th2 cells are also important helper T cells
- Th2 cells are necessary for B cell class switching (Humoral Immunity)
B cell Activation

- B cells always secrete IgM in response to encounter with Ag.
- Activated B cells can then interact with Ag-specific T cells to generate B cell memory (IgG)
- The next exposure to the same response will induce a more rapid and more robust response.

The Germinal Center reaction occurs during the initial response to Ag.
B cell Activation

- IgM and IgD are produced first because the genes are first.
- Class switching (in Germinal Centers) leads to alternative splicing that allows for the use of different constant regions.
- IgM is a pentamer (10 Ag binding sites)
- IgA can exist as a dimer (mucosal immunity)
- IL-4 promotes class-switching to IgG and IgE (IL-4 + IL-13 -> IgE)
- IL-5 promotes class-switching to IgA

Class switching refers to the isotype (heavy chain constant region).

Ag specificity stays the same!!
B cell Activation

- IgM and IgG fix complement (classical pathway)
- IgE promotes allergic responses
- IgG crosses the placenta
- IgA protects mucosal barriers

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgM</th>
<th>IgA1</th>
<th>IgA2</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy chain</td>
<td>γ₁</td>
<td>γ₂</td>
<td>γ₃</td>
<td>γ₄</td>
<td>μ</td>
<td>α₁</td>
<td>α₂</td>
<td>δ</td>
<td>ε</td>
</tr>
<tr>
<td>Molecular weight (kDa)</td>
<td>146</td>
<td>146</td>
<td>165</td>
<td>146</td>
<td>970</td>
<td>160</td>
<td>160</td>
<td>184</td>
<td>188</td>
</tr>
<tr>
<td>Serum level (mean adult mg ml⁻¹)</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0.5</td>
<td>1.5</td>
<td>3.0</td>
<td>0.5</td>
<td>0.03</td>
<td>5 x 10⁻⁵</td>
</tr>
<tr>
<td>Half-life in serum (days)</td>
<td>21</td>
<td>20</td>
<td>7</td>
<td>21</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Classical pathway of complement activation

- Alternative pathway of complement activation

- Placental transfer

- Binding to macrophage and phagocyte Fc receptors

- High-affinity binding to mast cells and basophils

- Reactivity with staphylococcal Protein A
Hyper IgM syndrome

- Most commonly XLR (affects males)
- Defects in CD40, CD40L, NFκB
- Inability to class-switch: Increased IgM, low IgG/A/E
- Bacterial, fungal, viral infections – pyogenic skin infections

Targeting Th Cell Subsets in Dermatology

- APC
- MHC/Ag
- TCR
- CD80/86
- CD28

- Th
  - Ustekinumab
  - IL-12
  - IL-23

- Th1
  - IFN\(\gamma\)
  - Dupilumab
  - IL-4
  - IL-17
  - IL-22

- Th2
  - Dupilumab
  - IL-4
  - IL-5
  - IL-13

- Th17
  - IL-17
  - IL-22

- Treg
  - IL-10

- Mφ
  - TNF\(\alpha\)
  - Etanercept
  - Infliximab
  - Adalimumab
  - Golimumab
  - Certolizumab
  - Secukinumab
  - Ixekizumab
  - Brodalumab
Innate vs. Adaptive Immunity

- The first two phases rely on the recognition of pathogens by germ-line encoded receptors of the innate immune system.
- Only if an organism can breach these early lines of defense will an adaptive (specific) immune response occur.
- Adaptive Immunity occurs late because rare Ag-specific B or T cells have to encounter the Ag and undergo clonal expansion.
**Complement**

- **CLASSICAL PATHWAY**
  - Antigen:antibody complexes

- **LECTIN PATHWAY**
  - Lectin binding to pathogen surfaces

- **ALTERNATIVE PATHWAY**
  - Pathogen surfaces

---

IgG (x2) or IgM

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**Complement activation**

- Recruitment of inflammatory and immunocompetent cells
- Opsonization of pathogens
- Killing of pathogens
**Complement**

**CLASSICAL PATHWAY**
- Antigen:antibody complexes (pathogen surfaces)
  - C1q, C1r, C1s
  - C4
  - C2

**LECTIN PATHWAY**
- Mannose-binding lectin or ficolin binds carbohydrate on pathogen surfaces
  - MBL/ficolin, MASP-2
  - C4
  - C2

**ALTERNATIVE PATHWAY**
- Pathogen surfaces
  - C3
  - B
  - D

**C3 Convertase!!**
- C4b,2a

**C3 Convertase!!**
- C3 Convertase!!

**C3b,Bb**
- (And Properiden)

**C3 !!**

**C1 !!**

- Peptide mediators of inflammation, phagocyte recruitment
- Binds to complement receptors on phagocytes
- Opsonization of pathogens
- Removal of immune complexes

**Membrane-attack complex, lysis of certain pathogens and cells**
- Terminal complement components
  - C5b
  - C6
  - C7
  - C8
  - C9
Complement

- C3a and C5a = Anaphylotoxins (C5a most potent)

- Opsonins – C3b / C5b (C3b most potent)

- C5b starts MAC

- MAC = C5-C9
Complement and Angioedema

**Hereditary Angioedema** = Defect in C1 esterase inhibitor (Gene = Serping1, Chromosome 11)
- Binds to C1s/C1r (levels of C1q ARE NORMAL in HAE)
- C1 esterase inhibitor normally inhibits complement cascade
- In its absence, increased activity of classical pathway (hydrolyze all of your C2/C4) -> **LOW C2 and C4**
- In its absence, greatly increased **BRADYKININ** levels (physiology not well understood) -> capillary leak
- Androgens increase C1 esterase inhibitor synthesis from the liver.
- **Type 1**: Absent C1 esterase inhibitor
- **Type 2**: Defective C1 esterase inhibitor
Complement and Angioedema

**Acquired C1 esterase inhibitor deficiency** – due to destruction of C1 esterase inhibitor (Abs)
- Type 1: B cell dyscrasias
- Type 2: Autoimmune
- Either way, same story as hereditary angioedema, but LOW C1q (Immune complexes)

Can treat both types (HAE and AAE) with C1 esterase inhibitor concentrate (from plasma of donors).
Complement

Of the complement components, the most potent neutrophil chemoattractant is:
A: C5a
B: C3b
C: Properidin
D: C1q
Of the complement components, the most potent neutrophil chemoattractant is:

A: C5a
B: C3b
C: Properidin
D: C1q
Complement

Of the complement components, the most potent opsonin is:
A: C5a
B: C3b
C: Properidin
D: C1q
Complement

Of the complement components, the most potent opsonin is:

A: C5a
B: C3b
C: Properidin
D: C1q
### Innate Immunity: Pattern Recognition Receptors

#### Innate immune recognition by Toll-like receptors

<table>
<thead>
<tr>
<th>Toll-like receptor</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR-1:TLR-2 heterodimer</td>
<td>Peptidoglycan</td>
</tr>
<tr>
<td></td>
<td>Lipoproteins</td>
</tr>
<tr>
<td></td>
<td>Lipoarabinomannan (mycobacteria)</td>
</tr>
<tr>
<td></td>
<td>GPI (T. cruzi)</td>
</tr>
<tr>
<td></td>
<td>Zymosan (yeast)</td>
</tr>
<tr>
<td>TLR-2:TLR-6 heterodimer</td>
<td>dsRNA</td>
</tr>
<tr>
<td>TLR-3</td>
<td></td>
</tr>
<tr>
<td>TLR-4 dimer (plus MD-2 and CD14)</td>
<td>LPS (Gram-negative bacteria)</td>
</tr>
<tr>
<td></td>
<td>Lipoteichoic acids (Gram-positive bacteria)</td>
</tr>
<tr>
<td>TLR-5</td>
<td>Flagellin</td>
</tr>
<tr>
<td>TLR-7</td>
<td>ssRNA</td>
</tr>
<tr>
<td>TLR-8</td>
<td>G-rich oligonucleotides</td>
</tr>
<tr>
<td>TLR-9</td>
<td>Unmethylated CpG DNA</td>
</tr>
</tbody>
</table>

#### Bacterial proteoglycans can be recognized by TLRs at the cell’s surface or by NOD proteins in the cytosol. Both lead to the activation of the transcription factor NFkB and the expression of pro-inflammatory genes.
Innate Immunity: Pattern Recognition Receptors
Gram positive bacteria like p. acnes primarily signal through which extracellular TLR?

A: TLR2
B: TLR7
C: TLR4
D: TLR3
Complement

Gram positive bacteria like p. acnes primarily signal through which extracellular TLR?

A: TLR2
B: TLR7
C: TLR4 (peptidoglycan)
D: TLR3
Complement

Gram negative bacteria primarily signal through which extracellular TLR?

A: TLR2
B: TLR7
C: TLR4
D: TLR3
Complement

Gram negative bacteria primarily signal through which extracellular TLR?

A: TLR2 (LPS)
B: TLR7
C: TLR4
D: TLR3
Complement

Imiquimod partially induces immune responses by engaging which TLR pathway?

A: TLR2
B: TLR7
C: TLR4
D: TLR3
Imiquimod partially induces immune responses by engaging which TLR pathway?

A: TLR2

B: TLR7 (native ligand is ssRNA)

C: TLR4

D: TLR3
Summary

Understanding immunologic pathways is key for understanding many dermatologic diseases and treatments