The Adaptive Immune System: Function, Vaccination, and Disease

Zane H. Boyer
MacMillan Research Group
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Our Bodies’ Constant Fight Against Disease

Destruction of pathogens and mutated cells

- Bacteria
- Viruses
- Parasites
- Cancerous cells
Our Bodies’ Constant Fight Against Disease

Destruction of pathogens and mutated cells

Bacteria

Viruses

Parasites

Cancerous cells

The immune system works to maintain homeostasis and destroy pathogens
Our Bodies’ Constant Fight Against Disease

Destruction of pathogens and mutated cells

Cells of the Immune System

- T cell
- B cell
- NK cell
- Macrophage
- Dendritic cell
- Eosinophil
- Neutrophil
- Basophil
Our Bodies’ Constant Fight Against Disease

Adaptive and innate immune cells

**Adaptive Immune Cells**
- T cell
- B cell

**Innate Immune Cells**
- NK cell
- Macrophage
- Dendritic cell
- Eosinophil
- Neutrophil
- Basophil
Our Bodies’ Constant Fight Against Disease
Adaptive and innate immune cells

Adaptive Immune Cells
Specific immunity
Recognizes unique peptide or antigen motifs unique to a pathogen

T cell
B cell

Innate Immune Cells
Non-specific immunity
Not specific to any pathogen
Responds to variety of pathogen motifs, can be activated by peptides, nucleotides
First line of defense against infections and mutations

NK cell
Macrophage
Dendritic cell
Eosinophil
Neutrophil
Basophil
Our Bodies’ Constant Fight Against Disease

Adaptive and innate immune cells

Immune cells work in tandem to generate tailored immune response
Adaptive Immune System

Enabling aspects and failures of adaptive immunity

--- Ultra-specific targeting ---

Selective T cell receptors and antibodies enable adaptive immune specificity

--- Vaccines ---

Vaccines use adaptive immunity to grant long term protection from pathogens

--- Adaptive immune diseases ---

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
Adaptive Immune System

Outline

- Biological development of T and B cells and their receptors
- A timeline of vaccine discoveries and developments
- How vaccination primes our immune system
- Contrasts between vaccine types targeting poliovirus
- Autoimmunity and pathogens of adaptive immune cells
Biological Development of T and B Cells

- Red bone marrow
- Hematopoietic stem cell
- Lymphoid stem cell

Myeloid stem cell:
- Megakaryocyte
- Monocyte
- Neutrophil
- Erythrocyte

Lymphoid stem cell:
- Natural Killer
- B cell
- T cell

Dendritic cell
- Macrophage

Plasma cell
Biological Development of T and B Cells

HPSC differentiation

Cytokines

Glucose levels

Oxygen levels

Hematopoietic stem cell
Biological Development of T and B Cells

HPSC differentiation

Cytokines

Oxygen levels

Glucose levels

Hematopoietic stem cell

Myeloid stem cell

Lymphoid stem cell

Various chemical signals induce initial differentiation of HPSCs
Biological Development of T and B Cells

Lymphoid stem cell

Natural Killer
Differentiate in Bone Marrow

B cell

T cell
Differentiate in Thymus

Differentiation is determined by organ location of lymphoid precursors

Biological Development of T and B Cells

Differentiation is determined by organ location of lymphoid precursors

T Cell Development in the Thymus

The thymus is a small gland that resides upon the heart

Most thymus activity occurs in early years of life

T Cell Development in the Thymus

Lymphoid stem cells from bone marrow

Thymus Lobule

Cortex

Medulla

CD44

CD25

CD4

CD8

DN1

DN2

DN3

DN4

DP

How Do T Cells Become so Specific?

V(D)J recombination and positive selection

By Double Positive stage, T cells have complete TCRs

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V(D)J recombination and positive selection

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How Do T Cells Become so Specific?

V(D)J recombination and positive selection

By Double Positive stage, T cells have complete TCRs

Variable components of both chains enable TCR specificity, diversity

How Do T Cells Become so Specific?

V(D)J recombination and positive selection

α Chain
How Do T Cells Become so Specific?

V(D)J recombination and positive selection

α Chain

DNA

Germline DNA

Recombination

Rearranged DNA

Transcription

RNA

Primary transcript RNA

Splicing

mRNA

How Do T Cells Become so Specific?

V(D)J recombination and positive selection

α Chain

DNA

Germline DNA

Recombination

Rearranged DNA

Transcription

RNA

Primary transcript RNA

Splicing

mRNA

Translation

Protein

Polypeptide chain

How Do T Cells Become so Specific?

V(D)J recombination and positive selection

β Chain

**How Do T Cells Become so Specific?**

*V(D)J recombination and positive selection*

**β Chain**

Approximately $10^{15}$ αβ TCRs are possible from V(D)J recombination.
How Do T Cells Become so Specific?

V(D)J recombination and positive selection

Approximately $10^{15}$ αβ TCRs are possible from V(D)J recombination

T cells expressing various recombined TCRs are tested by thymus cells

T cells expressing TCRs that bind MHC proteins are stimulated and enabled to progress

T Cell Development in the Thymus

Lymphoid stem cells from bone marrow

CD44

CD4

CD25

CD8

CD4

CD8

DN1

DN2

DN3

DN4

DP

**T Cell Development in the Thymus**

- **Lymphoid stem cells from bone marrow**

- **Thymus Lobule**
  - **Cortex**
  - **Medulla**

- **CD4**
- **CD8**
- **CD44**
- **CD25**

- **DN1**
- **DN2**
- **DN3**
- **DN4**
- **DP**

- **Mature T cells**
  - **CD4+**
  - **CD8+**

Negative Selection of TCRs

**Negative Selection of TCRs**

No MHC binding

MHC w/ Self peptide

TCR

Excessive MHC binding

MHC w/ Self peptide

TCR


**Negative Selection of TCRs**

1. **No MHC binding**
   - MHC w/ Self peptide
   - TCR
   - **Death by Neglect**

2. **Moderate MHC binding**
   - MHC w/ Self peptide
   - TCR
   - **Permissive growth**

3. **Excessive MHC binding**
   - MHC w/ Self peptide
   - TCR
   - **Apoptosis**

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Positive Selection of TCRs

Moderate MHC binding

MHC w/ Self peptide

TCR

Potent binding of MHC-I

MHC-I

CD8

TCR

Potent binding of MHC-II

MHC-II

CD4

TCR

Double positive CD4+ CD8+ T cells

CD8+ Cytotoxic T cells

CD4+ T Helper cells

Mature T Cells Exit the Thymus

Mature, naive T cells enter circulatory and lymphatic systems

Mature T Cells Exit the Thymus

Mature, naive T cells enter circulatory and lymphatic systems

Biological Development of T and B Cells

- Lymphoid stem cell
  - Differentiate in Bone Marrow
    - Natural Killer
    - B cell
  - Differentiate in Thymus
    - T cell

Differentiation is determined by organ location of lymphoid precursors

Biological Development of T and B Cells

Differentiation is determined by organ location of lymphoid precursors

B cell Development

- Red bone marrow
- Immunoglobulin B cell receptor (BCR)

**B Cell Development**

- **Red bone marrow**
- **B cell**
- **Immunoglobulin B cell receptor (BCR)**
- Can be anchored to membrane (BCR) or soluble (Ab)

B Cell Development

Red bone marrow

B cell

Immunoglobulin B cell receptor (BCR)

Joining
Variable
Constant

Ig light chain is analogous to TCRα

**B Cell Development**

Red bone marrow

B cell

Immunoglobulin B cell receptor (BCR)

- Joining
- Variable
- Constant
- Hinge
- Diversity

Ig heavy chain is analogous to TCRβ


How Do B Cells and Antibodies Become so Specific?

How Do B Cells and Antibodies Become so Specific?

How Do B Cells and Antibodies Become so Specific?

V(D)J Recombination grants access to $\sim10^{12}$ antibody variable fragments (Fv)

Positive and Negative Selection of BCRs

Positive and Negative Selection of BCRs

Positive and Negative Selection of BCRs

- **Non-functional BCR**: Lack of PI3K signaling leads to cell death.
- **Innocuous BCR**: Tonic PI3K signaling promotes survival, development.
- **Auto-reactive BCR**: Triggered somatic hypermutation or cell death.

Somatic Hypermutation: Further Diversification of Immunoglobulins

In blood or lymph

Binding of foreign antigens triggers hypermutation

In bone marrow

Binding of self antigens can trigger hypermutation

Somatic Hypermutation: Further Diversification of Immunoglobulins

Clonal Expansion

Somatic Hypermutation: Further Diversification of Immunoglobulins

Heavy Chain DNA Locus

Accumulated mutations in variable region

Replication with $10^6$ fold more frequent mutations

Somatic Hypermutation: Further Diversification of Immunoglobulins

Hypermutated B cells

Moderate binding

Low binding

No binding

High binding

Somatic Hypermutation: Further Diversification of Immunoglobulins

Hypermutated B cells

High binding

Plasma cells

Memory B cells

Affinity Maturation

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IgM as Dominant Isotype

IgM Pentamer  IgM Monomer
(humoral)      (membrane bound)

**Affinity Maturation**

**IgM as Dominant Isotype**
- IgM Pentamer (humoral)
- IgM Monomer (membrane bound)

*Naturally lower affinity, less potent at promoting innate immunity*

**IgG as Dominant Isotype**
- IgG Monomer (humoral and membrane bound)

*Naturally higher affinity, more potent at promoting innate immunity*

T_{fh} cell recognizes a peptide generated from antigen recognized by BCR

Tfh cell recognizes a peptide generated from antigen recognized by BCR

Naive B cell and Tfh cell interact, initiate B cell activation, affinity maturation

Endocytosis of antigen and receptor

B cell (endocytosing)

B cell (activated)

Downstream signaling

Cytokines

MHC II

CD4

TCR

CD40

CD40L

Affinity Maturation

IgM is the first antibody in the primary immune response.

- First exposure to antigen
- Days: 0, 7, 14, 21, 28, 35
- Amount of antibody:
  - IgM:
  - IgG:

- IgG appears earlier than in primary immune response.
- Final concentration of IgG is higher than in primary response.

Parija, S. C. Microbiology and Immunology 2nd Ed. 2012.
Adaptive Immune System

Enabling aspects and failures of adaptive immunity

--- Ultra-specific targeting ---

Selective T cell receptors and antibodies enable adaptive immune specificity

--- Vaccines ---

Vaccines use adaptive immunity to grant long term protection from pathogens

--- Adaptive immune diseases ---

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
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Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines
Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases
Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
A Timeline of Vaccine Development

12th Century
- Variolation was developed in Turkey, Africa, China, Europe

1774
- Benjamin Jesty infects sons and wife with cowpox pus during smallpox epidemic

1786
- Edward Jenner inoculates child with cowpox, demonstrates immunity to smallpox

1877-1885
- Louis Pasteur proposes germ theory, generates first attenuated vaccines

1882
- Robert Koch identifies M. tuberculosis as cause of tuberculosis

immunize.org
A Brief History of Vaccines. The World Health Organization.
Pead, P. J. Lancet. 2006, 368(9554), 2202.
A Timeline of Vaccine Development

1896
Cholera and typhoid vaccines invented

1915
First inactivated vaccine

1918
Influenza pandemic kills 50 million people, promotes flu vaccine research

1940s
Flu and DTaP vaccines created, penicillin became mass produced, smallpox was eradicated in the US

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A Timeline of Vaccine Development

First polio vaccine licensed

1955

Global and US smallpox and measles eradication programs launched

1966-1967

Last case of wild polio in western hemisphere

1991

Trivalent live oral polio vaccine, numerous measles vaccines developed

1961-1963

Smallpox is eradicated

1980

First “cancer” vaccine approved by FDA

2006

immunize.org

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Vaccines: Frontline Protection from Viral and other Diseases

**Vaccine preventable pathogens**

### Viruses
- Varicella
- Influenza
- Hepatitis A/B
- HPV
- Measles
- Mumps
- Rubella
- Poliovirus
- Rotavirus
- RSV
- Rabies
- Smallpox
- Yellow Fever
- Dengue
- Shingles

### Bacteria
- Diphtheria
- HiB
- Meningococcal
- Clostridium tetani
- Bordetella pertussis
- Mycobacterium tuberculosis

>20 Vaccine preventable viruses and bacteria

*Diseases & the Vaccines that Prevent Them. CDC. 2024.*
# Vaccines: Frontline Protection from Viral and other Diseases

Vaccine preventable pathogens

## 2023 Recommended Immunizations for Children from Birth Through 6 Years Old

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 Month</th>
<th>2 Months</th>
<th>4 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>15 Months</th>
<th>18 Months</th>
<th>19-23 Months</th>
<th>2-3 Years</th>
<th>4-6 Years</th>
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<tbody>
<tr>
<td>Hepatitis B</td>
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<td>RV* (Rotavirus)</td>
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<td>DTaP (Diphtheria, Pertussis, &amp; Tetanus)</td>
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<td>Hib*</td>
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<td>COVID-19** (Coronavirus disease 2019)</td>
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<td>COVID-19**</td>
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<td>Flu* (Influenza)</td>
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<td></td>
<td>Flu (One or Two Doses Yearly)*</td>
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<td>MMR (Measles, Mumps, &amp; Rubella)</td>
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<td>MMR</td>
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<td>MMR</td>
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<tr>
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<tr>
<td>HepA* (Hepatitis A)</td>
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<td>HepA*</td>
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</table>

*Recommended Immunizations. CDC. 2023.*
Vaccines: Frontline Protection from Viral and other Diseases

Classes of vaccine

**Traditional Vaccines**

- **Inactivated (killed)**
  - e.g. HepA, Flu, Polio

- **Live attenuated**
  - e.g. MMR, Rotavirus, Smallpox, Chickenpox

- **Subunit/Toxoid**
  - HepB, HPV, Diphtheria, Tetanus, Meningococcal

**RNA Vaccines**

- mRNA vaccine against SARS-CoV-2

US Department of Health and Human Services.
Vaccines: Frontline Protection from Viral and other Diseases

Classes of vaccine

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RNA Vaccines

mRNA vaccine against SARS-CoV-2
Vaccines: Frontline Protection from Viral and other Diseases

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**Inactivated Vaccines**

- Inactivated with heat or chemicals (ethylenimine, formaldehyde)
- Incredibly safe, cannot cause infection
- Stable, easily mass produced
- Primarily function through initial BCR activation
- Weaker immune activation
- Requires numerous doses
Vaccines: Frontline Protection from Viral and other Diseases

--- Live Attenuated Vaccines ---

- In vitro viral passaging results in mutations depleting viral dangers
- Target macrophages and dendritic cells
- Potent, provide long lasting immunity
- Require refrigeration to remain stable
- Attenuated virus can regain pathogenicity, can rarely cause disease outbreaks
Subunit/Toxoid Vaccines

- Viral or bacterial proteins or inactivated toxins promote immunity
- Targets APCs and BCR
- Often long lasting immunity, very safe
- Require adjuvant to boost immune response
- Requires optimization of adjuvant and subunit to promote proper immunity
Vaccines: Frontline Protection from Viral and other Diseases

Distinctions between vaccine types

Primary Immune Response

IgM is the first antibody in the primary immune response

Amount of antibody

Vaccination

Days

Exposure to pathogen

Final concentration of IgG is higher than in primary response

IgG appears earlier than in primary immune response
Vaccines: Frontline Protection from Viral and other Diseases

Distinctions between vaccine types

Primary Immune Response

- IgM is the first antibody in the primary immune response.
- IgM is present at the earliest time point (0 days).
- IgG appears later and reaches a higher concentration.

Secondary Immune Response

- Exposure to the pathogen triggers a secondary immune response.
- IgM is present at the earliest time point (0 days).
- IgG appears earlier and reaches a higher concentration than in the primary response.

Vaccination timeline:

<table>
<thead>
<tr>
<th>Days</th>
<th>Amount of Antibody</th>
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<tr>
<td>0</td>
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<td>7</td>
<td>IgM, IgG</td>
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<tr>
<td>14</td>
<td>IgG</td>
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<tr>
<td>21</td>
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<tr>
<td>28</td>
<td></td>
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<tr>
<td>35</td>
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</tbody>
</table>

Final concentration of IgG is higher than in the primary response.

IgG appears earlier than in the primary immune response.
Vaccines: Frontline Protection from Viral and other Diseases

Vaccination mechanism

Mature B cell binds antigen

Co-activation by T cell targeting antigen

Clonal expansion, somatic hypermutation, class switching

Vaccine particles

Lymph node

Naive or memory CD8+ T cell

APC

Naive or memory CD4+ T cell

APC

MHC-I TCR CD80/CD86 CD28 CD70 CD27

MHC-II TCR CD80/CD86 CD70 CD27

CD40 L

IL-12 Type I IFN
Vaccines: Frontline Protection from Viral and other Diseases

Vaccination mechanism

Mature B cell binds antigen

Co-activation by T cell targeting antigen

Clonal expansion, somatic hypermutation, class switching

Viral vaccines often target DCs first while bacterial vaccines target macrophages
Vaccines: Frontline Protection from Viral and other Diseases

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**RNA Vaccines**

- mRNA vaccine against SARS-CoV-2
New Pfizer Results: Coronavirus Vaccine Is Safe and 95% Effective

The company said it planned to apply for emergency approval from the Food and Drug Administration “within days.”
Vaccines: Frontline Protection from Viral and other Diseases

mRNA vaccine function
Vaccines: Frontline Protection from Viral and other Diseases

mRNA vaccine function
Why are certain types of vaccines used instead of others?
Case Study: Polio Inactivated and Live Vaccines

Before widespread immunization, Polio caused 500,000 deaths or paralyzes per year
Case Study: Polio Inactivated and Live Vaccines

Only two countries with endemic poliovirus as of 2020

History of Polio Vaccination. The World Health Organization.
Case Study: Polio Inactivated and Live Vaccines

--- Inactivated poliovirus vaccine (IPV) ---

Contains inactivated version of all 3 polio strains

Promotes immunity in bloodstream, prevents disease but less effective at infection prevention

Cannot cause paralysis

--- Oral Poliovirus Vaccines (OPVs) ---

Contains attenuated version of 1-3 polio strains

Promotes immunity in intestine, prevents paralysis and transmission

Attenuated virus mutates and causes paralysis, infectious disease in 1 out of 2.4 million cases.
**Case Study: Polio Inactivated and Live Vaccines**

**POLIO TODAY**
Wild polio has been eradicated in Africa, but more than 400 cases of vaccine-derived polio have been recorded over the past 12 months.

*Cases recorded 19 Aug 2019 - 18 Aug 2020*
- Vaccine-derived polio cases
- Wild polio cases
  (in addition to vaccine-derived polio cases)

**Oral Poliovirus Vaccines (OPVs)**
Contains attenuated version of 1-3 polio strains

- Promotes immunity in intestine, prevents paralysis and transmission
- Attenuated virus mutates and causes paralysis, infectious disease in 1 out of 2.4 million cases.

Polio Vaccine. Children’s Hospital of Philadelphia. 2024.
Case Study: Polio Inactivated and Live Vaccines

Why is OPV used anywhere?
Case Study: Polio Inactivated and Live Vaccines

--- Inactivated poliovirus vaccine (IPV) ---

- Cost per dose: $2.74
- Administration cost per dose: $1.78
- Total cost per dose: $4.52
- Protects individual

--- Oral Poliovirus Vaccines (OPVs) ---

- Cost per dose: $0.13
- Administration cost per dose: $0.95
- Total cost per dose: $1.08
- Protects community

Socioeconomic factors play large role in vaccine usage, availability

Case Study: Polio Inactivated and Live Vaccines

**Novel Oral Poliovirus Vaccines (nOPVs)**

Novel gene editing and analysis enabled next generation vaccines

Approved in March 2021, over one billion doses administered

Used in controlling vaccine derived polio outbreaks

Adaptive Immune System
Enabling aspects and failures of adaptive immunity

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**Ultra-specific targeting**

Selective T cell receptors and antibodies enable adaptive immune specificity

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**Vaccines**

Vaccines use adaptive immunity to grant long term protection from pathogens

---

**Adaptive immune diseases**

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
Adaptive Immune System
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Adaptive immune diseases
Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

Autoimmune diseases

Celiac  Type 1 Diabetes

Immune cells recognize and target self antigens
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

--- Autoimmune diseases ---

Celiac  Type 1 Diabetes

--- Pathogens of immune cells ---

Measles  HIV

Immune cells recognize and target self antigens
Pathogens evolved to target immune cells and evade neutralization
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

Autoimmune diseases
- Celiac
- Type 1 Diabetes

Pathogens of immune cells
- Measles
- HIV

Immune cells recognize and target self antigens
Pathogens evolved to target immune cells and evade neutralization
Autoimmune Diseases
Dysfunction of the adaptive immune system

Wide variety of autoimmune diseases resulting from immune targeting of distinct tissues, organs, or non-specific self proteins

Autoimmune Diseases
Dysfunction of the adaptive immune system

No MHC binding
MHC w/ Self peptide
TCR
Death by Neglect

Moderate MHC binding
MHC w/ Self peptide
TCR
Permissive growth

Excessive MHC binding
MHC w/ Self peptide
TCR
Apoptosis

Autoimmune Diseases
Dysfunction of the adaptive immune system

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Excessive MHC binding
MHC w/ Self peptide
TCR

Death by Neglect
Permissive growth
Permissive growth

Celiac Disease
Dysfunction of the adaptive immune system

- Affe... world populations
- Results in malabsorption of nutrition, vitamins, as well as anemia, osteoporosis, infertility, cancer, etc.
Celiac Disease

Dysfunction of the adaptive immune system

Genetic Predisposition
- HLA-DQ2 or/and HLA-DQ8+ at MHC on antigen-presenting cells

Environmental Factors
- Intake of indigestible gluten, such as wheat, barley, rye, etc.

Celiac Disease
- Autoimmune disease in small intestine
- Affects 1% of world populations
- Results in malabsorption of nutrients and vitamins, as well as anemia, osteoporosis, infertility, cancer, etc.

Celiac Disease

Dysfunction of the adaptive immune system

Celiac Disease

Dysfunction of the adaptive immune system

Gluten-containing food → Gliadin — PQ rich peptides

Small intestinal lumen

Small intestinal lamina propria

Normal conditions

Celiac Disease

Dysfunction of the adaptive immune system

Gluten-containing food

Gliadin — PQ rich peptides

Transglutaminase

Deamidated gliadin

Normal conditions

Celiac Disease

Dysfunction of the adaptive immune system

Gluten-containing food

Gliadin — PQ rich peptides

Transglutaminase

Deamidated gliadin

HLA-DQ2/DQ8+
Antigen-presenting cell

Disease conditions

Celiac Disease
Dysfunction of the adaptive immune system

Gluten-containing food

Transglutaminase
TG2

HLA-DQ2/DQ8+
Antigen-presenting cell

Small intestinal lumen

Small intestinal lamina propria

Immunological response

Disease conditions

Gliadin — PQ rich peptides

Deamidated gliadin

Dysfunction of the adaptive immune system

Celiac Disease

Celiac Disease

Dysfunction of the adaptive immune system

Gluten-containing food

Gluten-containing food → Gliadin — PQ rich peptides → HLA-DQ2/DQ8+ Antigen-presenting cell (APC) → T cell → Activated T cell

Transglutaminase (TG2)

Deamidated gliadin → APC

Immunological response

Small intestinal lumen

Small intestinal lamina propria

Disease conditions

Cytotoxic T cell → B cell

Malabsorption; anemia, osteoporosis, infertility, cancer, etc.

Gliadin — PQ rich peptides


Type 1 Diabetes
Dysfunction of the adaptive immune system

THE GLOBAL BURDEN OF TYPE 1 DIABETES

9 million children and adults have type 1 diabetes
1,476,000 children have type 1 diabetes
38% of all newly diagnosed type 1 diabetes patients are children under 20
175,000 Deaths per year due to T1D Rising +3% per year.

$81 BILLION is spent on type 1 diabetes globally per year (3.5x more than 2000)
The cost of care has skyrocketed +686%

By 2040 15 MILLION will have type 1 diabetes

Type 1 Diabetes
Dysfunction of the adaptive immune system

Islets of Langerhans in the pancreas

Cell types secrete distinct hormones and express tissue-specific proteins

α cell  β cell  δ cell

Glucagon  Insulin  Somatostatin
Type 1 Diabetes
Dysfunction of the adaptive immune system

Islets of Langerhans in the pancreas

1. Cell types secrete distinct hormones and express tissue-specific proteins

   Glucagon  Insulin  Somatostatin

2. In type 1 diabetes, a T effector cell recognizes peptides from β cell proteins and kills the β cell.

   Cytotoxic T cell

   Immune attack

α cell  β cell  δ cell  α cell  β cell  δ cell

Type 1 Diabetes
Dysfunction of the adaptive immune system

1. Cell types secrete distinct hormones and express tissue-specific proteins

2. In type 1 diabetes, a T eff cell recognizes peptides from β cell proteins and kills the β cell.

3. Glucagon and somatostatin are produced by α and δ cells, but no insulin is produced.

Islets of Langerhans in the pancreas

Glucagon  Insulin  Somatostatin

α cell  β cell  δ cell

Cytotoxic T cell

Immune attack

Glucagon  Somatostatin

α cell  β cell  δ cell

α cell  δ cell

Treatments for Autoimmune Diseases

Dysfunction of the adaptive immune system

A variety of treatments exist, but no cures, indicating need for further research into adaptive immunity
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

--- Autoimmune diseases ---

Arthritis
Type 1 Diabetes

Immune cells recognize and target self antigens

--- Pathogens of immune cells ---

Measles
HIV

Pathogens evolved to target immune cells and evade neutralization
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

Autoimmune diseases
- Arthritis
- Type 1 Diabetes

Pathogens of immune cells
- Measles
- HIV

Immune cells recognize and target self antigens
Pathogens evolved to target immune cells and evade neutralization
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

Measles

HIV

Targets CD150 surface marker

Dendritic cell
Macrophage
B cell
T cell

Targets CD4, CCR5 surface markers

Macrophage
CD4+ T cell
Adaptive Immune Diseases
Failures and pathogens of adaptive immune cells

Measles

- Extremely transmissible
  - 90% of exposed unvaccinated people develop disease
  - 3% of patients die or experience brain damage
  - Many severe effects occur after recovery from measles

97% Effective Vaccine
No treatment

Hagen, A. American Society for Microbiology. 2019.
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Measles infected memory B cell

Measles infected memory T cell

Hagen, A. American Society for Microbiology. 2019.
Measles and Immune Amnesia
Failures and pathogens of adaptive immune cells

Measles infected memory B cell

Measles infected memory T cell

Measles specific CD8+ T cell

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Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Recovery from measles provides lifelong immunity to measles, deteriorates immunity to all other pathogens

Hagen, A. American Society for Microbiology. 2019.
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Five years to recover healthy levels of immunity

Hagen, A. American Society for Microbiology. 2019.
Measles and Immune Amnesia
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Five years to recover healthy levels of immunity

Repeated immunization

2023 Recommended Immunizations for Children from Birth Through 6 Years Old

- HepB
  - Hepatitis B
- RV
  - Rotavirus
- DTaP
  - Diphtheria, Tetanus & Pertussis
- Hib
  - Haemophilus influenzae type b
- PCV13, PCV15
  - Pneumococcal disease
- IPV
  - Polio
- COVID-19
  - Coronavirus disease 2019
- Flu
  - Influenza
- MMR
  - Measles, Mumps, & Rubella
- Varicella
  - Chickenpox
- HepA
  - Hepatitis A

Highlights necessity of measles vaccination in all communities

Hagen, A. American Society for Microbiology. 2019.
Measles and Immune Amnesia

Future therapies

Measles polymerase inhibitor

Benefits

Can decrease immune amnesia, other measles symptoms

Helps prevent lethal bacteria superinfection

Best applied before or at peak viral titer

Human Immunodeficiency Virus

Pathogenesis of HIV

AIDS pandemic led to ~40 million deaths over past four decades

No vaccine available

Numerous antiretroviral therapies

Human Immunodeficiency Virus
Pathogenesis of HIV

Human Immunodeficiency Virus

Pathogenesis of HIV

CD4 binding enables HIV entry into T cells

Human Immunodeficiency Virus
Pathogenesis of HIV

Human Immunodeficiency Virus

Pathogenesis of HIV

Caspase triggered apoptosis

CD4+ T cell

Human Immunodeficiency Virus

Pathogenesis of HIV

Caspase triggered apoptosis

CD4+ T cell

CD8+ T cell

Human Immunodeficiency Virus
Pathogenesis of HIV

Caspase triggered apoptosis

CD8+ T cell

T cell directed apoptosis

Human Immunodeficiency Virus

HIV progression to AIDS

Human Immunodeficiency Virus

HIV progression to AIDS

Behavioral differences:
- Primary infection
- Acute HIV syndrome
  - Wide dissemination of virus
  - Seeding of lymphoid organs
- Clinical latency
- Constitutional symptoms

CD4+ Lymphocyte Count (cells/mm$^3$)

HIV RNA Copies per mL plasma

Human Immunodeficiency Virus

HIV progression to AIDS

Human Immunodeficiency Virus
HIV progression to AIDS

Combination Anti retroviral therapy

Reduced risk of transmission by 96%
Can prolong life from ~2 years to >40 years

HIV Reverse Transcription into genome

Severely hinders possible curative treatments
Leads to lifelong infection with HIV

Human Immunodeficiency Virus
HIV progression to AIDS

Currently no vaccine for HIV

Phase I trial has begun in the US and South Africa

CMV viral vector will deliver HIV material to prevent establishment of HIV infections

Further vaccine research may enable greater control of HIV in lower income nations

Adaptive Immune System

**Ultra-specific targeting**
Selective T cell receptors and antibodies enable adaptive immune specificity

**Vaccines**
Vaccines use adaptive immunity to grant long term protection from pathogens

**Adaptive immune diseases**
Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens
Adaptive Immune System

Questions?

--- Ultra-specific targeting ---
Selective T cell receptors and antibodies enable adaptive immune specificity

--- Vaccines ---
Vaccines use adaptive immunity to grant long term protection from pathogens

--- Adaptive immune diseases ---
Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens