A general overview of Immune system and Immunology

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Definition

- **Immune system**
  - a collection of biological processes within an organism that protects against disease by identifying and killing pathogens and tumor cells

- **Immunology**
  - a science that examines the structure and function of the immune system
The plague of Athens in 430 BC. *Thucydides* noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time.


1891, *Robert Koch* got his proofs, that *microorganisms* were confirmed as the cause of *infectious disease* (*Nobel Prize* in 1905).

1901, *Walter Reed* discovered *viruses* were confirmed as human pathogens, with the discovery of the *yellow fever*.

Late 19th century, great advance in the study of *humoral immunity* and *cellular immunity*. *Paul Ehrlich* proposed the *side-chain theory* to explain the specificity of the antigen-antibody reaction. *Elie Metchnikoff*, founded cellular immunology. (jointly awarded Nobel Prize 1908)
Vaccine developed with Immunology

- Big events of Vaccines

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1796</td>
<td>Smallpox vaccine</td>
</tr>
<tr>
<td>1885</td>
<td>Rabies vaccine</td>
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<tr>
<td>1955</td>
<td>Injectable polio vaccine</td>
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<tr>
<td>1962</td>
<td>Oral polio vaccine</td>
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<tr>
<td>1967</td>
<td>Smallpox eradication program started</td>
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<tr>
<td>1979</td>
<td>Smallpox eradicated from the world</td>
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<tr>
<td>1986</td>
<td>First recombinant human vaccine</td>
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<tr>
<td>1994</td>
<td>Last case of polio in the Americas</td>
</tr>
<tr>
<td>1998</td>
<td>Infant immunisation rate ~80%</td>
</tr>
<tr>
<td>1999</td>
<td>Eradication of polio and measles in sight</td>
</tr>
</tbody>
</table>

- Forward to late 20th century, hepatitis A, hepatitis B, polio, mumps, measles, rubella, diphtheria, pertussis, tetanus, HiB, chickenpox, rotavirus, influenza, meningococcal disease and pneumonia, etc.
### General characters of immune system components

<table>
<thead>
<tr>
<th>Innate immune system</th>
<th>Adaptive immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response is non-specific</td>
<td>Pathogen and antigen specific response</td>
</tr>
<tr>
<td>Exposure leads to immediate maximal response</td>
<td>Lag time between exposure and maximal response</td>
</tr>
<tr>
<td>No immunological memory</td>
<td>Exposure leads to immunological memory</td>
</tr>
<tr>
<td>Found in nearly all forms of life</td>
<td>Found only in vertebrates</td>
</tr>
</tbody>
</table>
Components and Mechanisms

**Infection**

**Innate system** (reacts in hours)

**Mechanical barriers**
- Coughing
- Sneezing
- etc.

**Humoral and chemical barriers**
- **Antimicrobial peptides** secreted by Skin and Respiratory tract
- Cellular barriers, mast cell **macrophages**, etc.
- Inflammation...

Pathogens are destroyed by non-specific attack
Layered defense Mechanisms

Infection

Innate system
(reacts in hours)

Mechanical barriers
• Coughing
• Sneezing
• etc.

Humoral and chemical barriers
• Antimicrobial peptides secreted by Skin and Respiratory tract
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• Inflammation ...

Pathogens are destroyed by non-specific attack

Adaptive system
(reacts in days)

Antigen presentation

Lymphocytes

T cell

B cell

Specific cytotoxic-T killer cell production

Specific antibody production
Lymphocytes, special types of leukocytes, are major derived from hematopoietic stem cells in the bone marrow.

<table>
<thead>
<tr>
<th>T cell</th>
<th>B cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognize a “non-self” target, such as pathogen</td>
<td>B cell antigen-specific receptor is an antibody molecule on the B cell surface</td>
</tr>
<tr>
<td>Activated only after antigens (epitops, small fragments of the pathogen) have been processed and presented in combination with a “self” receptor called a major histocompatibility complex (MHC) molecule</td>
<td>Recognizes whole pathogens without any need for antigen processing</td>
</tr>
<tr>
<td>Killer(Cytotoxic) T cells recognize antigens coupled to Class I MHC molecules (co-receptor called CD8 or CD8+), Helper T cells only recognize antigens coupled to Class II MHC molecules (co-receptor called CD4 or CD4+)</td>
<td>Each lineage of B cell expresses a different antibody, the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture</td>
</tr>
<tr>
<td>γδ T cells, Memory T cells, Regulatory T cells, Natural killer T cells</td>
<td></td>
</tr>
</tbody>
</table>
Adaptive immune system

- Killer T cell (Cytotoxic T cell)
Adaptive immune system

- Helper T cell
Adaptive immune system

- Helper T cell
Adaptive immune system

- Killer T cell
- MHC I
- MHC II
- B Cell
- CD8 cytotoxic T cell
- CD4 helper T cell
- Antigen-specific T cell receptor
- Cytokines
- Antigen-presenting cell (APC)
- Foreign (or self) antigen
- Antibodies
- Cell death
- Infected cells [displays foreign T cell epitope on its surface] or self (i.e., loss of self tolerance)
Immunological memory

- **Passive memory**
  - Newborn infants are protected by mothers antibody by 6 months

- **Active memory and immunization**
  - infection by activation of B and T cells
  - through vaccination
Disorders of human immunity

- **Immunodeficiencies**
  - components of the immune system are inactive
  - alcoholism, and drug use are common causes of poor immune function
  - can be inherited or 'acquired'
    - Inherited: Chronic granulomatous disease, congenital immunodeficiency
    - Acquired: AIDS, some types of cancer

- **Autoimmunity**
  - fails to properly distinguish between self and non-self, and attacks part of the body

- **Hypersensitivity**: immune response damages the body's own tissues
  - Type Alternative names Often mentioned disorders
  1. Allergy (immediate) • Asthma
  2. Cytotoxic, antibody-dependent • Autoimmune hemolytic anemia
  3. Immune complex disease • System lupus
  4. Delayed-type hypersensitivity (DTH), cell-mediated immune memory response, antibody-independent • Multiple sclerosis
**Cancer immunology:** another important role of the immune system is to identify and eliminate tumors

- Tumors express antigens that are not found on normal cells
- Main is to destroy the abnormal cells using killer T cells
- Tumor cells often have a reduced number of MHC class I molecules on their surface, thus avoiding detection by killer T cells
- Some tumor cells also release products that inhibit the immune response
Other mechanisms

- **Antimicrobial peptides** called defensins, innate immune response found in all animals and plants
- The **complement system** and phagocytic cells, most forms of invertebrate life
- **Invertebrates** do not generate lymphocytes or an antibody-based humoral response
  - Bacteria unique using the restriction modification system to protect themselves from viral pathogens, called **bacteriophages**
  - Prokaryotes also possess acquired immunity, through a system that uses CRISPR sequences to retain fragments of the genomes of phage that they have come into contact with in the past, which allows them to block virus replication through a form of **RNA interference**
- **Plant**
  - Plant produces a localized **hypersensitive response**, whereby cells at the site of infection undergo rapid **apoptosis** to prevent the spread of the disease to other parts of the plant
  - **Systemic acquired resistance (SAR)** is a type of defensive response used by plants that renders the entire plant resistant to a particular infectious agent
  - **RNA silencing** mechanisms are particularly important in this systemic response as they can block virus replication
Manipulation in medicine

- **Immunosuppressive drugs**
  - control autoimmune disorders or inflammation when excessive tissue damage occurs
  - prevent transplant rejection after an organ transplant

- **Inflammatory drugs**
  - control the effects of inflammation

- **Vaccines**
  - Induce a antigen, that infect a host, while evading detection or destruction by the immune system
New area: Immunoinformatics

- Immunoinformatics: application of informatics techniques to molecules of the immune system
  - From 1989, till now > 1000 papers
  - To effective prediction of immunogenicity
    - T cell epitopes (antigens)
    - MHC I, MHC II binding complex
    - T cell receptors (TCRs), etc.

- Databases

<table>
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<tr>
<th>Database</th>
<th>Description</th>
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<tr>
<td>IGMT</td>
<td>the International ImmunoGeneTics Information System for Immunoinformatics</td>
</tr>
<tr>
<td>IPD</td>
<td>The Immuno Polymorphism Database</td>
</tr>
<tr>
<td>SYFPEITHI</td>
<td>Database for Searching and T-Cell Epitope Prediction</td>
</tr>
<tr>
<td>MHCPEP</td>
<td>T-cell epitope and MHC-binding data</td>
</tr>
<tr>
<td>FIMM</td>
<td>MHC–peptide interactions</td>
</tr>
<tr>
<td>JenPep</td>
<td>kinetic, thermodynamic, functional, and cellular data within immunobiology</td>
</tr>
</tbody>
</table>

**Immunoinformatics - Predicting Immunogenicity In Silico.** Edited by Darren R. Flower, 2007, Humana Press Inc.
**Vaccine development**

- **Pathogen:**
  - With antigens and toxicity
- **Vaccine**
  - With antigens and no toxicity

Once an T-cell epitope be identified, the corresponding vaccine can be easily developed.
T cell epitopes (antigen) prediction

- **dataset**
  - 203 10-mer cytotoxic cell (CTL) clone was derived from tumor-infiltrated lymph node cells of a melanoma patient
  - Antigen recognition was assessed using a chromium release assay (Valmori et al, *J. Immunol.* 161 (1998) 6956)

- **Informatics method**
  - Least-squared Support Vector machines (LS-SVMs)
    - A refined version of SVM
    - Result in a set of linear equations instead of a quadratic programming problem of SVMs
LS-SVM modeling

- Grid search for parameters
  - Sig$^2$ and gamma
- TP, TN, Roc curve

Results Analysis

- Area under the ROC curve
  - training set (LOO): 0.9875
  - test set: 0.9734

Comparisons of different methods use 10-fold crossvalidation

<table>
<thead>
<tr>
<th>Methods</th>
<th>TN(%)</th>
<th>TP(%)</th>
<th>Total(%)</th>
<th>ROC area</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVM(^1)</td>
<td>92.24</td>
<td>76.21</td>
<td>87.86</td>
<td>0.919</td>
</tr>
<tr>
<td>BioSVM(^2)</td>
<td>93.06</td>
<td>83.29</td>
<td>90.31</td>
<td>0.931</td>
</tr>
<tr>
<td>LS-SVM</td>
<td>98.2</td>
<td>94.44</td>
<td>97.54</td>
<td>0.963</td>
</tr>
</tbody>
</table>

Immune system is one of the most important components of life form.

Immunoinformatics has much potential as a newly discovered research area.

Challenge: Post-translational modification on Immune system molecules.

How to dig out the relationships between immune system and post-translational modification (PTM)?