An Introduction to Transplant Immunology

Michael D. Gautreaux, Ph.D., F(ACHI)
Objectives

• Compare and contrast innate and adaptive immunity at a basic level.

• Understand basic concepts of transplantation.

• Appreciate the research that led to the discovery of transplant immunology.

• Appreciate the role of laboratory in upholding the principles of the Declaration of Istanbul.
The First Transplant?

Sts. Cosmas and Damian c. 4th Century (modern-day Turkey/Syria)
Immunology

• Relatively “new” science
  – 1796

• Origin attributed to Edward Jenner
  – Invented vaccination (vacca)
  – Infected child with cowpox
    » then with smallpox
    » IRB won’t approve
Evolution of the Immune System

• Human species has gone through numerous phases in history characterized by different pathogen exposures

• Introduction of agriculture some 10,000 years ago made the spreading of new pathogens more likely

• The host-pathogen interaction is a very important relationship that serves to shape the immune system development early on in life.
Hygiene Hypothesis

• Our immune system has been strongly focused on fighting off infections, even early in infancy.

• The hygiene hypothesis states that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (such as the gut microbiome or probiotics), and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system.

• The lack of exposure is thought to lead to defects in the establishment of immune tolerance (Lost Friends)
Overview of Transplant Immunology

• Innate and Adaptive Immunity
• Transplantation
• Brief History of Field
• Immune Response
• Declaration of Istanbul
• Wrap Up
**Host Defense Systems**

**Innate**
- external barriers (skin, mucus membranes)
- secretory components (enzymes, histamine, oxygen radicals, etc.)
- certain leukocytes (phagocytes, NK cells, platelets)
- no increase in strength after exposure

**Adaptive** (Acquired)
- evoked during an immune response
- T & B cells
- Leukocytes (monocytes, neutrophils, mast cells)
- Soluble factors (antibodies, cytokines)
The central component of the innate immune system is exclusion.
The central component of the adaptive immune response is the binding of peptide to HLA (MHC) and the recognition of the complex by T-cells.
# Innate and Adaptive Immunity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>For molecules shared by groups of related microbes and molecules produced by damaged host cells</td>
<td>For microbial and nonmicrobial antigens</td>
</tr>
<tr>
<td>Diversity</td>
<td>Limited; germline encoded</td>
<td>Very large; receptors are produced by somatic recombination of gene segments</td>
</tr>
<tr>
<td>Memory</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Nonreactivity to self</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

## Components

<table>
<thead>
<tr>
<th></th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular and chemical barriers</td>
<td>Skin, mucosal epithelia; antimicrobial molecules</td>
<td>Lymphocytes in epithelia; antibodies secreted at epithelial surfaces</td>
</tr>
<tr>
<td>Blood proteins</td>
<td>Complement, others</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Cells</td>
<td>Phagocytes (macrophages, neutrophils), natural killer cells, innate lymphoid cells</td>
<td>Lymphocytes</td>
</tr>
</tbody>
</table>

Timing of Responses

[Diagram showing the timing of innate and adaptive immunity responses, with timelines for hours and days after infection.]

Shared and Unique Areas

Innate immunity

Adaptive immunity

Tissues
Myeloid cells
Lymphocytes

# Innate and Adaptive Immunity

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specificity</strong></td>
<td>For structural detail of microbial molecules (antigens); may recognize non-microbial antigens</td>
</tr>
<tr>
<td>For structures shared by classes of microbes (pathogen-associated molecular patterns)</td>
<td></td>
</tr>
<tr>
<td><strong># of molecules recognized</strong></td>
<td>&gt;$10^7$ antigens</td>
</tr>
<tr>
<td>~1000 molecular patterns</td>
<td></td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>Encoded by genes produced by somatic recombination of gene segments (greater diversity)</td>
</tr>
<tr>
<td>Encoded in germline; limited diversity (pattern recognition receptors)</td>
<td></td>
</tr>
<tr>
<td><strong># receptors</strong></td>
<td>Only 2 types of receptors (Ig and TCR), with millions of variations of each</td>
</tr>
<tr>
<td>&lt;100 different types of invariant receptors</td>
<td></td>
</tr>
<tr>
<td><strong>Distribution of receptors</strong></td>
<td>Clonal: clones of lymphocytes with distinct specificities express different receptors</td>
</tr>
<tr>
<td>Nonclonal: Identical receptors on all cells of the same lineage</td>
<td></td>
</tr>
<tr>
<td><strong>Genes encoding receptors</strong></td>
<td>Formed by somatic recombination of gene segments only in B and T cells</td>
</tr>
<tr>
<td>Germline encoded, in all cells</td>
<td></td>
</tr>
<tr>
<td><strong>Discrimination of self vs. non-self</strong></td>
<td>Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)</td>
</tr>
<tr>
<td>Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions</td>
<td></td>
</tr>
</tbody>
</table>

*Cellular and Molecular Immunology, Ninth Edition*
Overview of Transplant Immunology

- Innate and Adaptive Immunity
- **Transplantation**
- Brief History of Field
- Immune Response
- Declaration of Istanbul
- Wrap Up
A Brief History of Transplantation

- 1823: First skin autograft-transplantation of skin tissue from one location on an individual's body to another location (Germany)
- 1905: First successful cornea transplant by Eduard Zirm (Czech Republic)
- 1908: First skin allograft-transplantation of skin from a donor to a recipient (Switzerland)
- 1933: First successful cadaveric AB-0 incompatible kidney transplant (donor was B(III) and the recipient has 0(I)) by Yuriu Yu. Voronoy (USSR)
- 1950: First successful kidney transplant by Dr. Richard H. Lawler (Chicago, U.S.A.)
- 1954: First living related kidney transplant (identical twins) (U.S.A.)
- 1955: First heart valve allograft into descending aorta (Canada)
- 1962: First kidney transplant from a deceased donor (U.S.A.)
- 1965: Australia's first successful (living) kidney transplant (Queen Elizabeth Hospital, SA, Australia)
- 1967: First successful liver transplant by Thomas Starzl (Denver, U.S.A.)
- 1968: First successful heart transplant by Christian Barnard (Cape Town, South Africa)
- 1981: First successful live-donor partial pancreas transplant by David Sutherland (Minnesota, U.S.A.)
- 1983: First successful lung lobe transplant by Joel Cooper at the Toronto General Hospital (Toronto, Canada)
- 1984: First successful double organ transplant by Thomas Starzl and Henry T. Bahnson (Pittsburgh, U.S.A.)
- 1986: First successful double-lung transplant (Ann Harrison) by Joel Cooper at the Toronto General Hospital (Toronto, Canada)
- 1999: First successful tissue engineered bladder transplanted by Gunther O. Hofmann
- 2000: First robotic donor nephrectomy for a living-donor kidney transplant in the world University of Illinois Medical Center
- 2004: First liver and small bowel transplants from same living donor into same recipient in the world University of Illinois Medical Center
- 2005: First successful ovarian transplant by Dr. P. N. Mhatre (Wadia Hospital, Mumbai, India)
- 2005: First successful partial face transplant (France)
- 2008: First baby born from transplanted ovary. The transplant was carried out by Dr. Sherman Silber at the Infertility Centre of St Louis in Missouri. The donor is her twin sister. [99]
- 2009: First transplant of a human windpipe using a patient's own stem cells, by Paolo Macchiarini (Barcelona, Spain)
- 2008: First successful transplantation of near total area (80%) of face, (including palate, nose, cheeks, and eyelid) by Maria Siemionow (Cleveland Clinic, U.S.A.)

Transplant Definitions

• Transfer of an organ or tissue from one organism (donor) to another (recipient).
  - Skin, kidney, heart, lung, etc.

• Transfer of an organ or tissue from one site to another location in the same body.
  - CABG, rotationplasty (joint), bone, skin
  - Decellularized organ from donor re-seeded with autologous cells (tissue engineering)
Types of Transplants

- **Autologous**
  - Autograft; transplant of cells or tissue to the same person

- **Syngeneic**
  - Isograft; transplant of organ or tissue from a donor to a genetically identical recipient

- **Allogeneic**
  - Allograft; transplant of organ or tissue to genetically non-identical donor of the same species

- **Xenogeneic**
  - Xenografts; transplantation of cells, tissues or organs from one species to another
Destinations

• **Orthotopic**
  – Transplantation of tissue from a donor into its normal position in the body of the recipient
  – Split organs may end up in 2 recipients

• **Heterotopic**
  – Transplantation of tissue typical of one area to a different recipient site
  – Kidney transplants most common

• **Extracorporeal**
  – Located or occurring outside the body
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Historical Steps Elucidating Immune Response to Foreign Tissue

- Laboratory mouse used as a model system
- Early 1900s, researchers transplanting tumors in mice began to develop the “laws” of transplantation
- 1930s-1940s — Immunology meets genetics
  - Gorer identifies blood group locus encoding antigen II in mice
  - Snell independently maps gene controlling graft rejection to H (histocompatibility) locus
  - Both antigen II and H are the same yielding name “H-2” antigens
- Snell goes on to develop mouse strains to allow distinction of multiple histocompatibility genes, identify extensive polymorphism and complex genetics of system
Historical Steps Elucidating Immune Response to Foreign Tissue

• 1940s-1950s, Medawar, Burnet, Billingham begin to characterize immune response to foreign tissue and define immunologic tolerance using animal models
  – A History of Transplant Immunology, L. Brent, Academic Press 1997

• Studies of humans in 1950s and 1960s identify leukoagglutinins
  – Dausset observes alloreactive leukoagglutinins
  – Payne shows that pregnancy and transfusions induce leukoagglutinins

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Innate Response

- Initial tissue damage and stress leads to activation of the innate immune response

- Can cause damage through a variety of mechanisms

- Triggers adaptive immune response

- May bias the form that the adaptive immune response takes
Discrimination of Self from Non-self

- Self is “tolerated”
- Non-self (foreign tissue) is rejected
- Prior exposure to non-self causes stronger and more rapid rejection response (individual is “sensitized” to foreign tissue)
Immune Response Is Specific

- Recipient is not sensitized to tissue from the second donor
- Rejection to 2nd occurs based on timing of first exposure
Human Response Is Through HLA

Father’s blood

Mother’s serum

Agglutination of white blood cells (leukocytes)

Sensitization through transplant, transfusion, pregnancy
**Vector of Immune Response**

- **Patient (Recipient)**
  - Possibly immune compromised or sensitized

- **GvHD**

- **Rejection**

- **Graft (Donor)**
  - Solid organ graft: Graft cells & possibly passenger leukocytes
  - Hematopoietic stem cell graft: Stem cells & immune cells
  - Platelet transfusion: Source of sensitization
Adaptive Immune Response to Alloantigens

Role of T Lymphocytes
- Second skin graft from same donor to same recipient
- T cells transfer accelerated rejection from a sensitized donor to a naive recipient
- Graft shows accelerated (second-set) rejection

Role of B Lymphocytes
- Immune response to foreign tissue involves both T and B lymphocytes
- Response directed to major histocompatibility antigens

Agglutination: antibodies directed to cell surface antigens clump cells
Defining Human Leukocyte Antigen (HLA) Types

- Dausset, Payne, Bodmer, Van Rood begin to define HLA types (MAC or LA (HLA-A2)), 4a and 4b (Bw4/Bw6)
- HLA types vary among individuals
- HLA types are inherited in families

Mother’s serum agglutinates cells from father and some of their offspring

<table>
<thead>
<tr>
<th>Leukocytes</th>
<th>Husband</th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 1</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Serum 2</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>++</td>
</tr>
<tr>
<td>Serum 3</td>
<td>++</td>
<td>--</td>
<td>++</td>
<td>--</td>
</tr>
</tbody>
</table>

Mother’s serum agglutinates cells from father and some unrelated individuals
Sensitization to HLA Differences Can Result in Graft Rejection

• Individuals sensitized to foreign tissue make antibodies to the specific HLA types expressed by the tissue

• These antibodies, pre-existing in a patient receiving a kidney allograft, can cause hyperacute renal graft rejection
  – Studies in late 1960s, Kissmeyer-Nielson, Terasaki

• Complement-dependent cytotoxicity (CDC) crossmatch becomes standard of practice in donor selection

• The appearance of donor-specific HLA-directed antibodies after transplant can lead to reduced graft survival

Terasaki, Transplantation, 2012, 93:751
Impact of Early Research on Studies of Immune System/Transplantation as Model

• MHC molecules present antigenic peptides to T lymphocytes, stimulating the adaptive immune response
  - Susceptibility/resistance to infectious disease, autoimmunity; drug sensitivity
  - Vaccine design
  - Immune escape of malignant cells

• Extensive genetic variation observed in MHC
  - Population biology; evolution including natural selection

• Ability to propagate transplanted cells/tissues in hosts in controlled environment
  - Transplantation as therapy, cellular therapies, pregnancy
  - Research models

Tasmanian devil; facial tumor disease, a contagious cancer, is decimating this species
Forming the Histocompatibility Community

• 1st organized in 1964 by Amos at Duke University
• Opportunity to share reagents and unpublished data, develop new methods and standardize them, standardize nomenclature, disseminate knowledge world-wide
• 16 workshops with some highlights listed below
  – 1964 microcytotoxicity assay
  – 1965 cell panel, computer for analysis
  – 1970 eleven HL-A specificities
  – 1972 world-wide populations
  – 1975 class II defined as HLA-D
  – 1987 DNA typing
• 2017 17th Workshop
• 2022 18th Workshop (www.ihiw18.org)

http://www.ihwg.org/about/history.html
The Southeast Organ Procurement Foundation (SEOPF) is formed as a membership and scientific organization for transplant professionals.

SEOPF implements the first computer-based organ matching system, dubbed the “United Network for Organ Sharing.”

SEOPF establishes the Kidney Center, the predecessor of the UNOS Organ Center, for round-the-clock assistance in placing donated organs.

First successful single-lung transplant performed.

Cyclosporine, the first of a number of drugs that effectively treat organ rejection by suppressing the human immune system, introduced.

National Organ Transplant Act (NOTA) passed.

United Network for Organ Sharing (UNOS) separates from SEOPF and is incorporated as a non-profit member organization.

SEOPF becomes American Foundation for Donation and Transplantation (AFDT)
Summary of History

• Beginning in early 1900s, the laws of transplantation were described
• Immunogenetic studies elucidating murine H-2 system began in 1930s
• For many years, the mouse was major model for MHC because of ability to address genetic diversity using inbred and congenic strains
• In 1950s, sensitization of humans to foreign tissue was observed; alloantibodies provide a tool to identify HLA types
• Research and collaboration through international workshops provided tools and standardization
• Led to understanding of immune response in health and disease, served as “the” model for genetic diversity and impact of natural selection, provided tools and models
Mechanisms of Allorecognition

- High frequency of alloreactive T cells arises because pathogen-specific memory T cells, as well as naïve T cells, can respond to allo-MHC
- Plasticity in TCR – MHC – peptide interaction produces cross-reactivity and activation
- Three pathways of activation (direct, indirect, semi-direct) predominate at different stages of rejection
- Minor antigens are recognized as MHC-bound peptides
- Naïve B cell activation requires recognition of foreign MHC by cell-surface antibody and T cell help
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Declaration of Istanbul

• Initiated in 2008 by the WHO
  - as a response to unethical behaviors associated with organ transplantation and specifically organ trafficking
  - to address the urgent and growing problems of organ sales, transplant tourism and trafficking in organ donors in the context of the global shortage of organs

• Doesn’t compel compliance
  - hoped that the principles and the proposals it outlines will guide and inspire better practices in transplantation.

• Endorsement of the Declaration
  - has been sought amongst the many professional societies associated with transplantation medicine.
The Istanbul Summit

158 representatives of scientific and medical bodies, government officials, social scientists, and ethicists from around the world

Istanbul (Turkey), April 30 - May 2, 2008
Organ Trafficking

• Act
  – the recruitment, transport, transfer, harboring or receipt of living or deceased persons or their organs

• By means of
  – the threat or use of force or other forms of coercion, abduction, fraud, deception, abuse of power or of a position of vulnerability, or payments to a third party to achieve control of the donor

• For purpose of
  – exploitation by the removal of organs for transplantation
DoI Definitions

- **Transplant commercialism**
  - a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used for material gain.

- **Travel for transplantation**
  - the movement of organs, donors, recipients or transplant professionals across jurisdictional borders for transplantation purposes.

- **Transplant tourism**
  - involves organ trafficking and/or transplant commercialism, or
  - organs, professionals and transplant centers devoted to providing transplants to patients from outside a country or region, undermine the country’s ability to provide transplant services for its own population.
Available on the website

• Full text of the Declaration of Istanbul
• Some proposals on how to promote the ethical practice of donation and transplantation
• Latest information on organ trafficking
• Patient Information/Brochure translated into many languages

Patient Information brochure

Materials to Help Combat Organ Trafficking and Transplant Tourist

www.declarationofistanbul.org
Dr Michael Gautreaux
President, American Society for Histocompatibility and Immunogenetics

Dear Dr Gautreaux,

As the Co-Chairs of the Executive Committee of the Board of Councillors of the Declaration of Istanbul Custodian Group (DICG), we are writing to thank the American Society for Histocompatibility and Immunogenetics (ASHI) for endorsing the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (DoI). On the following page, we would also like to share with you some information about the role that endorsing organizations can play in supporting the DoI and DICG activities.

In order to stay up-to-date with DICG activities and news relating to organ trafficking and transplant tourism around the world, ASHI can follow the DICG Facebook page or Twitter account. The DICG sends a quarterly newsletter via email to members and representatives of the endorsing organizations. This will be sent to the current President of ASHI, or a designated representative if you prefer. We ask that you add the address media@declarationofostanbul.org to your list of safe senders, to facilitate communications from our media account.

General information about the DICG’s mission and current Board can be found on our website: www.declarationofostanbul.org. We will be delighted to address any particular questions that you or the members of ASHI may have. Please don’t hesitate to get in touch at any time to discuss opportunities for collaboration. We look forward to working with you and the ASHI leadership and members in the coming years.

Warm regards,

Elmi Müller Dominique Martin
Co-chairs, DICG Executive Committee
Organizations which endorse the Declaration...

- require that speakers at scientific and educational meetings on clinical organ transplantation disclose whether the clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul.

- have an established mechanism for determining the appropriateness of accepting presentations on clinical organ transplantation based on the disclosure of a consistency with the Principles of the Declaration of Istanbul.

- establish mechanisms to promote, implement and uphold the Declaration (for example, through ethics committee activity, awards and membership criteria).
What can the lab personnel do?

- Raise with transplant administrators if a patient appears to have participated in transplant tourism or some other form of organ trafficking.

- Understand that obstacles and disincentives to organ donation (living and deceased donor).
  - Vote!

- Share information, expertise and technology with labs in countries seeking to improve organ donation efforts.
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Soapbox Time!

WE'RE GONNA NEED
A BIGGER SOAPBOX
Why Do We Cover So Much *Basic* Science?

- 2016 Specialists’ Course Evaluation
  - [The Basic Immunology Lectures are] “too simplified for director level.
CHS Examination

Chart 2

Percentage Correct Answers

<table>
<thead>
<tr>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>2017</td>
<td>2018</td>
</tr>
</tbody>
</table>

- General Laboratory Skills
- H&I Testing
- Test Results and Reporting
- H & I Testing Principles and Theory
- Quality Systems
- Supervisory Functions
Why Do We Cover So Much Basic Science?

• Knowledge of the science of immunogenetics is essential for proper performance and interpretation of the tests.

• We as a community need to understand the science so that we can explain why our testing is vitally important in the transplant field.
  - Younger people may want to be in this field
  - Patients & families are always looking for information
  - Policymakers are not sure what we do
    » “Don’t they just stick some blood in a computer and get the result?”
  - “Regular” people don’t know why what we do is important
    » Voters and taxpayers
  - Medical Professionals
Thanks!