Attribution: University of Michigan Medical School, Department of Microbiology and Immunology

License: Unless otherwise noted, this material is made available under the terms of the Creative Commons Attribution–Noncommercial–Share Alike 3.0 License: http://creativecommons.org/licenses/by-nc-sa/3.0/

We have reviewed this material in accordance with U.S. Copyright Law and have tried to maximize your ability to use, share, and adapt it. The citation key on the following slide provides information about how you may share and adapt this material.

Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarification regarding the use of content.

For more information about how to cite these materials visit http://open.umich.edu/education/about/terms-of-use.

Any medical information in this material is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. Please speak to your physician if you have questions about your medical condition.

Viewer discretion is advised: Some medical content is graphic and may not be suitable for all viewers.
Citation Key
for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (USC 17 § 105)
Public Domain – Expired: Works that are no longer protected due to an expired copyright term.
Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.
Creative Commons – Zero Waiver
Creative Commons – Attribution License
Creative Commons – Attribution Share Alike License
Creative Commons – Attribution Noncommercial License
Creative Commons – Attribution Noncommercial Share Alike License
GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (USC 17 § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (USC 17 § 107) *laws in your jurisdiction may differ

Our determination DOES NOT mean that all uses of this 3rd-party content are Fair Uses and we DO NOT guarantee that your use of the content is Fair.

To use this content you should do your own independent analysis to determine whether or not your use will be Fair.
Return to Type I Diabetes and Overview of Immune Response

M1 – Immunology Sequence

Winter 2009
One of the first pathologies observed is infiltration of the pancreatic islets with leukocytes (inflammation—insulitis) and subsequent destruction of the beta cells in the islets. Since the beta cells produce insulin, loss of the beta cells results in loss of insulin production.

By the time a patient presents with the symptoms of diabetes, more than 90% of the beta cells have been destroyed.
Is the pattern of lymphocyte infiltration consistent with an ongoing infection?
Is the pattern of lymphocyte infiltration consistent with an ongoing infection?

No, no neutrophils. (But could be a viral infection.)

Neutrophils go to the site of an infection, because inflammatory mediators upregulate receptors on endothelial cells.
On Tuesday, Dr. Pietropaolo discussed that the beta cells of the pancreas are destroyed by an immunological mechanism in Type I diabetes. Dr. Fantone, discussed four types of immunopathology.

Which of the four types of immunopathology might be active in Type I diabetes?
What is the effector function (pathology) associated with pancreatic beta cell destruction?

Summary: Type I Reaction

- Antibody: IgE
- Effector Cells: Mast Cell & Eosinophil
- Complement: No
- Reaction: Minutes
Summary: Type II/III Reaction

- Antibody: IgM & IgG
- Effector Cells: Phagocytic
- Complement: Yes
- Reaction: 6-24 hours
Summary: Type IV Reaction

- Antibody: No
- Effector Cells: CD4+ T-lymphocytes, Monocyte/Macrophage; CD8+ T-lymphocytes
- Complement: No
- Reaction: 48-72 hours (skin test)
Are anti-self antibodies the primary cause of islet cell destruction (Type II/III immunopathology)?
Test for anti-self antibodies on islet cells

Anti-islet antibody

Tissue section of pancreatic islet

Anti-human IgG
Cytoplasmic islet-cell-antibody staining

Positive reaction

Negative reaction

If antibody mediated the destruction of the beta cells, would B lymphocytes necessarily infiltrate the pancreas? What type of leukocytes would more likely to be found?
If antibody mediated the destruction of the beta cells, would B lymphocytes necessarily infiltrate the pancreas? No, B cells act at a distance, by secreting antibodies.

What type of leukocytes would more likely to be found?

Neutrophils. A lack of neutrophils, antibody, or complement deposition in the pancreas argues that antibodies (including those binding to insulin) are not very important in the disease.
Are these anti-self antibodies the primary cause of islet cell destruction?

Probably not.

If antibodies were the cause, the histopathology would be characterized by the presence of immunoglobulin, complement, and neutrophils.

What are other candidates for the destruction?

CD4+ T cells + macrophages

CD8+ T cell cytotoxicity
What does the lymphocyte infiltration of the pancreatic islets indicate about the pathology of Type I diabetes?
Since the infiltration is mostly lymphocytes, the pathology is not Types I, II, or III (mast cells, eosinophils, neutrophils would be expected).

However, the lymphocyte infiltration is consistent with a Type IV reaction.
To understand the lymphocyte infiltration better, what more detailed histological test would you like to perform?
To understand the lymphocyte infiltration better, what more detailed histological test would you like to perform?

To distinguish between DTH and cytotoxicity by CD8+ cells, look for macrophages, and also do immunofluorescence with anti-CD4 and anti-CD8 antibodies conjugated with fluorescein.
Test for anti-self antibodies on islet cells

Tissue section of pancreatic islet

(Morphology would define the presence of macrophages or neutrophils.)
Normal pancreas

Insulin-dependent diabetic pancreas

Figure 11.9
<table>
<thead>
<tr>
<th>Population</th>
<th>Type I Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR3/DR4</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
One can imagine that Type I diabetes is initiated as follows:

1. Some physical trauma or infection causes damage to the islets.
2. Inflammatory cells (macrophages, neutrophils) enter the islets, cause further damage (on a micro scale).
3. Epitopes on self proteins like insulin or GAD that are not exposed in a healthy islet, are now exposed, and these epitopes are taken up by dendritic cells and macrophages. Those individuals who are DR3/DR4 heterozygotes are more likely to present the critical self peptide on their MHC class II molecules.
4. A CD4+ T cell clone specific for the self peptide:MHC class II complex is activated, begins to divide and differentiate.
5. This CD4+ T cell clones provides help to both B cell clones and CD8+ T cell clones that recognize other self epitopes expressed by islet cells. These self epitopes recognized by B cells cannot have been expressed in bone marrow, and the self epitopes expressed by CD8+ T cells cannot have been expressed in the thymus.

6. Cytotoxic CD8+ T cells or antibodies secreted by plasma cells begin to destroy islet cells, leading to Type I diabetes.

7. Alternatively, CD4+ T cells might activate macrophages, which in turn destroy the islet cells.
Differentiation of T helper cells

Antigen recognition

Proliferation

Characteristic Cytokines

Major functions

Cell-mediated Immunity
  - DTH
  - Macrophage activation

Humoral Immunity
  - B-cell help
  - Eosinophil stimulation
  - Mast cell stimulation
  - Macrophage deactivation

APC

Thp

Precursor CD4 T cells

Th0

IL-12
IFN-γ

Th1

IFN-γ

IL-4

Th2

Activated effector T cells

IL-4

University of Michigan Department of Microbiology and Immunology
CTL induces programmed cell death (apoptosis) in target cells.

Fig 6.24
Cytokines: AT&T of the immune response

• The major means for inflammatory cell activation
• Two-way communication between innate and acquired immune response
• Two-way communication between cells of the acquired immune response
Have immunologists defined the autoantigen that is recognized by the CD4+ T cell, leads to an immune response, and ultimately to Type I diabetes?
Have immunologists defined the autoantigen that is recognized by the CD4+ T cell, leads to an immune response, and ultimately to Type I diabetes?

No, it is not defined. However, it is almost surely an antigen expressed by a pancreatic beta cell.

There remains a small chance that the anti-insulin and anti-GAD antibodies are the cause of the Type I diabetes. Alternatively, pancreatic beta cells might be damaged via some other type of pathology, releasing insulin and GAD antigens so that APCs can take them up and present them to Th and B cells. In this scenario, anti-self antibodies would be a result of Type 1 diabetes. Current thinking favors the latter scenario.
An immune response to a pathogen is fundamentally the same as an immune response to a self antigen of the islet cell.

Review of immune responses to two types of pathogens—extracellular (usually bacteria) and intracellular (viruses and some bacteria). Return to the BIG PICTURE, without concerning ourselves with all of the details.
Simplified overview of an immune response

Often eliminated by innate immunity: neutrophils or macrophages

Th, B, Tc

IgM, IgG, IgA

Dendritic cell or macrophage

Killing

Help

Clostridium tetani

Image Sources Undetermined
Differences between innate and adaptive immunity

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response is instant maximal response</td>
<td>Response is antigen-dependent</td>
</tr>
<tr>
<td>Not antigen-specific</td>
<td>Antigen-specific</td>
</tr>
<tr>
<td>Exposure results in no immunological memory</td>
<td>Exposure results in immunological memory</td>
</tr>
<tr>
<td>Recognition by antibody and T cell receptors</td>
<td></td>
</tr>
</tbody>
</table>

Response is antigen-dependent
There is a lag time between Exposure and maximal response
Exposure results in immunological memory
Recognition by antibody and T cell receptors
Activated APC

Ig production

Killing microbes

Naive T cells

Activated Effector T cells

APC

TCR

Costimulatory molecule

MHC

Peptide

Help

T cell
Figure 3.8

Top

Class I

Intracellular

Class II

Extracellular
(and intracellular)
Human MHC genes are highly polymorphic.
Each individual express only two of these alleles by co-dominance.
Antigen processing and presentation to T lymphocytes

**MHC class I** pathway (cytosolic source)
Present antigen to **CD8** T cells
Virus and intracellular bacteria
Mutated tumor antigen

**MHC class II** pathway (endosomal source)
Present antigen to **CD4** T cells
Bacteria
Activation of naive T cells requires two independent signals.
Where do the anti-virus or anti-bacteria cell T cells and B cells come from in the first place?

They arise from random, antigen-independent differentiation.

T cells and B cells derive from the bone marrow.
orange arrow: CACAGTG
blue arrow: GGTGGTTTGT
The T cell receptor resembles a membrane-bound Fab fragment of antibody.

- Bivalent
- Secreted and membrane-bound forms

- Monovalent
- Membrane-bound form
A. Specificity of recognition by cells and molecules—each antigen is distinguished from (almost) all other antigens.

B. Diversity of recognition--The immune response can recognize ten million or more different antigens.
A simple view of the thymic selection

**CD4^+CD8^+ TCR^+**

- **Weak**
  - Too weak or No binding to self MHC → Death by neglect
  - Poor recognition of peptide-MHC or Partial signal to T cells → Survive

- **Strong**
  - Good binding to activating peptide:self-MHC complexes → Clonal deletion (apoptosis)
Tolerance--Depending on how an antigen is encountered, the immune system can become non-responsive to that antigen. Individuals are (usually) tolerant to self antigens.
Simplified overview of an immune response

Often eliminated by innate immunity: neutrophils or macrophages

Clostridium tetani

Dendritic cell or macrophage

IgM, IgG, IgA

Th

B

Tc

help

killing
For extracellular pathogens, once CD4+ T cells are activated, they will help B cells to become activated, differentiate, and produce antibodies. The antibodies eliminate the pathogen by neutralization, by opsinization for macrophages or neutrophils, by complement mediated lysis, and so on.
Simplified overview of an immune response

Often eliminated by innate immunity: neutrophils or macrophages

Dendritic cell or macrophage

Th, B, Tc

IgM, IgG, IgA

help

killing

Clostridium tetani
For intracellular pathogens, once CD4+ T cells are activated, they may help CD8+ T cells to divide, differentiate, and become cytotoxic. Alternatively, the CD4+ T cells may produce large amounts of interferon-γ, and activate macrophages. Both cytotoxic CD8+ T cells and activated macrophages eliminate the intracellular pathogen by killing the cell in which it resides. Many intracellular bacteria grow only in macrophages, and activated macrophages kill bacteria growing in them better than do macrophages not exposed to interferon-γ, etc.
Transplantation reactions are mediated by T cells recognizing allogeneic MHC molecules
Summary

1. The immune response is a FANTASTICALLY interesting inter-relating set of biological effects that result in protection against pathogens.

2. At times the immune response goes awry, leading to autoimmune disease and allergies.

3. Its difficult to learn immunology in eight days.
Additional Source Information
for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 14: Source Undetermined
Slide 15: Source Undetermined
Slide 28: University of Michigan Department of Microbiology and Immunology
Slide 34: Image Sources Undetermined
Slide 36: University of Michigan Department of Microbiology and Immunology
Slide 46: University of Michigan Department of Microbiology and Immunology
Slide 48: Image Sources Undetermined
Slide 50: Image Sources Undetermined