

HOST DEFENSE

SMALL GROUP PROBLEM SOLVING SESSION

AUTOIMMUNE DISEASES

Small Group Classrooms

LEARNING GOALS

You will understand how the immune system maintains tolerance to self and what the clinical implications are when tolerance is lost.

To achieve these goals, you will be able to:

- Understand how genes can predispose a patient to autoimmune disease
- Identify antibodies can cause autoimmune disease
- Identify a new subset of T cells that are associated with autoimmune disease
- Explain how normal or "well-intended" host reactions can predispose one to an autoimmune disease.
- Understand how T regulator cells are critical to prevention of autoimmune disease
- Understand how environment can interact with specific genetic loci and trigger autoimmune disease
- Develop a conceptual approach to identifying sites in the immune response that may be clinically manipulated to limit the clinical expression of autoimmune diseases

BACKGROUND READING

1. Janeway 8th edition: 622-636-do not worry about the "epitope spreading concept". **Do NOT memorize any table in the text.** If I want you to know some concept of a specific disease it will be mentioned either in the lecture, lecture notes or small groups.
2. The posted articles on the HD website

DEVELOPED BY

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HOW TO SUCCEED IN SMALL GROUPS

Before coming to class:

1. Read assigned chapters/ pages and develop answers for **ALL** the questions in the 4 clinical vignettes

During the Small Group Session:

2. Each small group (**should be 4-5 peers- please do not sort yourselves into large groups-you will learn much less**) should discuss the four case studies and decide the best solutions to the specific integrating questions associated with each case.
3. After approximately an hour of discussion by the subgroups, the facilitator will recapitulate the answers to the integrating questions by selecting a subgroup to present a synthesis of their relevant discussions to the entire group. Facilitators will select, at their discretion, a small group for the discussion of the individual cases.
4. History has shown that students who don't contribute to the Small Groups do not do well in the Course (remember that about 25-30% of the final comes from small groups!) and also have been assaulted by their fellow group members
5. At the end of the session, a master answer sheet will be posted on the Host Defense website.

1. **AUTOIMMUNE ENDOCRINE DISEASES**

SCENARIO 1A (a true story)

A group of residents and attending physicians were relaxing late one night at a local bistro. One attending, an internist almost certainly, noted that their waitress had rather prominent eyes and a tremor. One thing led to another and he found her pulse to be 150 and regular and very large mass in her anterior neck. He referred her to an endocrinologist at Loyola. Two days later, she was evaluated. The patient reported increasing irritability, tremors and weight loss. The only other significant history was that her sister had a “bad thyroid” and her mother had rheumatoid arthritis. Physical examination revealed a blood pressure of 160/55 and a pulse of 140. She had a fine tremor of her fingers, velvety smooth skin and a firm, very large thyroid. Auscultation over the gland revealed a loud bruit. Blood analysis revealed a thyroid hormone level of 24ug/dl (normal 4-12) and her thyroid stimulating hormone (TSH) was almost undetectable.

QUESTIONS

1.
 - Does the patient’s gender and family history tell us anything about the etiology of the disease?
 - What genes would be likely suspects?
 - How could they mediate the development of an autoimmune disease?

2.
 - A specific antibody is usually the mediator of this disease; what is its antigenic specificity and isotype and how does it produce the disease?
 - T cells are also mandatory participants in the disease process. What, if any, antigenic specificities might they have and how do they drive the process?

3.

- How might a tissue microarray of her **thymus** tissue differ from that of a normal female thymus?
- Speculate how a tissue array of her **thyroid** differs from a normal thyroid.

SCENARIO 1B

An eight year old male from Coxsackie, NY developed fever, diarrhea and then profound diabetic ketoacidosis. There was almost no detectable insulin in his peripheral blood at a time when his blood glucose was 900 mg% (normal less than 126%). Autoantibodies to a virus and insulin were detected in his blood.

QUESTIONS

1. Walk through the possible immunologic reactions by which this patient developed diabetes. What is (are) the targets, what attacked it(them) and what systems failed, if any?

2.

- If this patient had X-linked agammaglobulinemia (remember that disease from a prior small group?), would it still be possible that he could develop diabetes?
- What does this astute observation in the New England Journal article tell you about the significance of detecting autoantibodies in a patient's blood.

2. **AUTOIMMUNE NEUROMUSCULAR DISEASE**

A 24 year male noted that he was unable to keep up with his teammates at their Saturday pickup basketball game. On the subsequent Monday, he was unable to rise from bed because of weakness. 24 hours later he was admitted from the Emergency Room to a Medical Intensive Care unit. Shortly thereafter he had to be placed on a mechanical ventilator because he was unable to move his muscles of respiration adequately. After a muscle biopsy (which did not reveal any infiltrating inflammatory cells), he then underwent plasmapheresis (removal of plasma proteins) and within 24 to 48 hours could be weaned from ventilatory support. He was discharged asymptomatic 7 days later. An immunologist in the Medical School was given the bag of plasma removed during the plasma pheresis. 5ml of this plasma was infused into mice and these animals, within 4-6 hours, were unable to crawl about their cage.

QUESTIONS

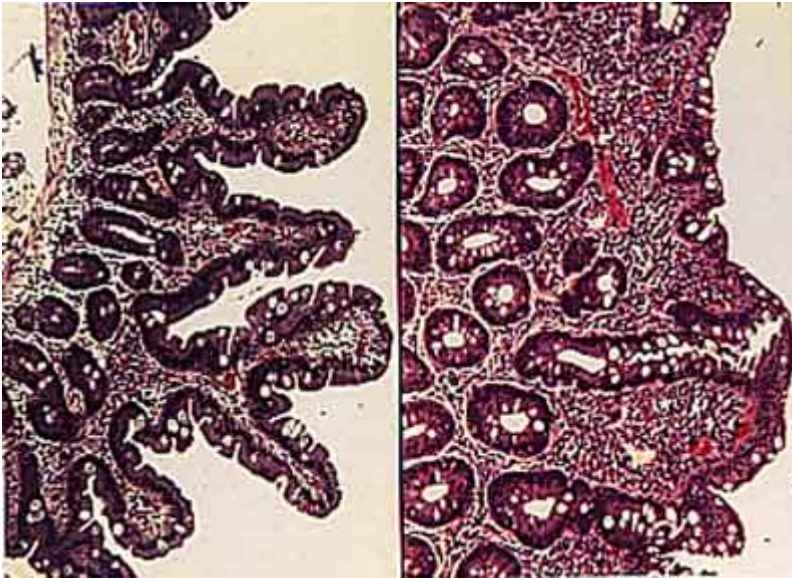
1. The plasma apparently contained a factor(s) that caused weakness. What proteins are the most likely suspects and is a plasma factor specific for something that will cause muscle weakness?
2. Are you surprised that the muscle biopsy showed no immune effector cells? What immunohistopathologic studies might be helpful in understanding this disease?
3. Patients with an auto-immune inflammatory muscle disease called polymyositis have symptoms of muscle weakness somewhat like the basketball player but their biopsies show muscle necrosis and lymphocytes. How is the pathogenesis of polymyositis different than the disease the basketball player had?
4. Understanding this disease is an example of how clinical application of basic research findings and technology can be combined to provide for improved patient care-Can you explain how an eel is involved?

3. Environmental Triggering of Auto-immune diseases

- A. Case History:** An eighteen year old female developed bloating and severe diarrhea during "rush week" at Partee University. She had no significant past medical history other than a vaguely remembered time in middle school when she also had diarrhea and severe weight loss. The latter was so severe that her parents

thought she had an eating disorder and had her evaluated by a psychiatrist. She became asymptomatic after her mother "changed her diet for a while". Her current physical examination in the university infirmary was not remarkable. She had no lymphadenopathy and no rash. Her stool was tested for infectious parasites and found to be negative for all pathogens.

The initial bloodwork revealed multiple autoantibodies. A procedure was performed in the GI lab and the biopsy is shown below. A biopsy from a normal is shown on the left.



1. What procedure was done and what is the diagnosis?

Is the history typical for your diagnosis and what autoantibodies were most likely detected?

2. This disease is the prototype for an autoimmune disease that develops as the result of complex interplay between identified genes, a known autoantigen(s) and T cells. Discuss the contribution of each to the disease

- 3.
- Are the autoantibodies in this disease pathogenic or diagnostic or both?
 - Would looking for cytokine expression possibly be helpful? And which ones might you look for? You can actually get ahead of the clinical immunology literature if you think this one through!

- 4.
- Now understanding the immunology of her diagnosis, can you **explain** her history, past and present?
 - Can you develop a strategy for treatment that will allow her to drink beer at rush week next year (maybe)?

B. Rheumatoid arthritis (RA) is a common autoimmune arthritis that is characterized by the presence of immune complexes in synovial joint fluid. Like most other autoimmune diseases, it is more common in females and is associated with certain MHC II loci. Recent epidemiologic evidence now strongly links smoking to RA (and several other autoimmune diseases). Most patients with RA, and some “normal” smokers who are destined to develop RA, have high titers of anti- citrulline antibodies in their serum. It is known that arginine is converted to citrulline by a post translational process and that highly citrullinated peptides are found in inflammatory exudates.

Assemble the following in a logical sequence that would explain how a smoker might develop RA:

- a. Joint fluid
- b. Pro-inflammatory cytokines
- c. B cell
- d. anti-citrullinated antibodies in joint space
- e. toxic smoke products
- f. Auto-immune MHC class II locus
- g. Synovial fluid macrophages
- h. enzyme that activates conversion of arginine to citrulline
- i. Th2 cell
- j. Synovial fluid neutrophils
- k. anti-citrullinated antibodies in bronchial fluid
- l. heavily citrullinated proteins

Then predict at least 3 places in the sequence where a clinician could interfere with the process and ameliorate or prevent RA

4. Genetic Mutations associated with autoimmunity

There are 3 well described genetic defects associated with severe autoimmune clinical phenotypes.

- a. Those with **FoxP3 mutations** have immunodysregulation, polyendocrinopathy, enteropathy and the transmission is X-linked (IPEX syndrome). Speculate on why they have hormonal deficiencies and what cell may be missing from their repertoire.

- b. Those with **AIRE defects** have polyendocrinopathy, candidiasis (a fungal infection), and ectodermal dysplasia (APECED syndrome). Speculate on why these patients have low calcium in their blood, are infertile, have deep voices and abnormal skin and bone formation.

c. Patients with a **defect in Fas mediated apoptosis** have markedly increased size of their lymph nodes and spleen and produce huge amounts of IgG antibodies. Speculate why they have more lymphoid tissue than normal and why they have an unusual number of CD3+, CD4- & CD8- cells circulating in their peripheral blood.