MEDICAL COLLEGE OF WISCONSIN
CENTER FOR IMMUNOLOGY

Autoimmunity and how to treat it

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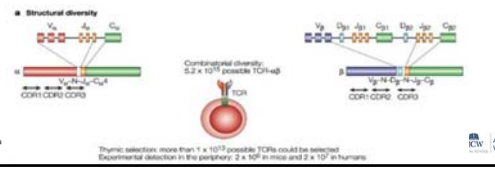
Disclosure

- None
- I will mention drug names and some brand names but I have no financial interest or any other ties to any of the companies that make these drugs

Why do we get autoimmunity?

- All people have cells in their body that see "self"
- Natural byproduct of creating diversity so we can see any organisms that exist and any that may evolved to be able to invade us

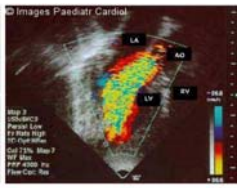


Why do we get autoimmunity?

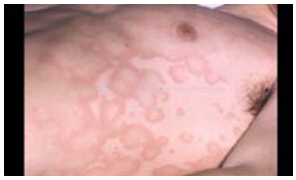
- Genetic factors (there are many of them)
  - Some genes tell us what organs *could* be attacked (MHC, HLA-B27)
  - Other genes set a minimum threshold for activation of the immune system (if too low, autoimmunity *could* occur)
  - Numerous genes come together to predispose someone to autoimmunity
- Environmental factors (e.g. infections)
- Because of all of these factors, autoimmune diseases tend to run in families…but they skip around (i.e. "skips a generation")
  - Think of it as Boggle…shake up a bunch of genes and if you get the right ones and the right environmental trigger you could get a disease

Rheumatic fever

- 4 year old boy develops sore throat, fever.
- Three weeks later developed knee swelling, pain, and fever that lasted 3 days. Given aspirin and resolved. 2 days later the left ankle was swollen. Rash developed.
- Seen by PMD. Found to have heart murmur and rash.



Aortic regurgitation



- This only occurs when infected with the bacteria that causes strep throat
- If you prevent infection the immune system turns off (penicillin)
- Most autoimmune diseases however don't work this way (always are there)

Types of autoimmune diseases

- As we learn about autoimmune diseases, we have become much better at treating them
- Different autoimmune diseases use different mechanisms to cause damage to our organs or tissues
  - Some are mediated by antibodies (B cells)
    - Break down into antibody mediated and immune complex mediated
  - Some are mediated by T cells
  - But there is considerable overlap
    - T cells help B cells
    - T cells and B cells use other immune cells and proteins to cause damage (e.g. neutrophils, complement proteins, etc)
    - They are all interconnected, but we simplify it to guide therapy

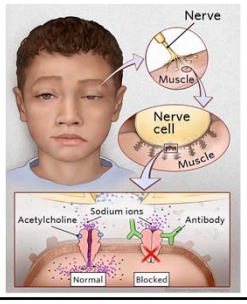
Diseases caused by antibodies

- Antibodies bind to self tissues or molecules
- This can lead to destruction of a cell (hemolytic anemia)
- Or they can block the function of a cell or even activate it

Antibody-mediated disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (αIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor–mediated inflammation	Nephritis, lung hemorrhages
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	Thyroid-stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

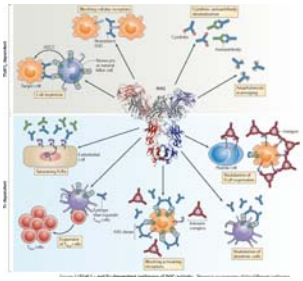
Antibody-Mediated Autoimmunity

- Myasthenia gravis- neuromuscular autoimmune disease
  - Autoantibodies form against the acetylcholine receptor block neuromuscular junction transmissions
  - Symptoms include drooping eyelids, mouth weakness and arm or leg weakness



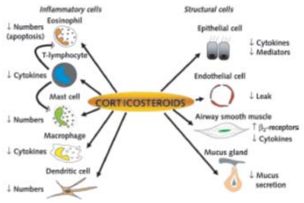
Treatment of antibody mediated diseases

- You can flood the system with healthy antibodies to block the bad ones (IntraVenous Immune Globulin)
  - IVIG is the antibodies from blood donors that is pooled and given to people
  - Usually repeated monthly
  - Very high doses are used (4x the normal dose of IVIG)
  - Generally very safe!!! Does not suppress the immune system like other medications
  - Unclear exactly how it works??



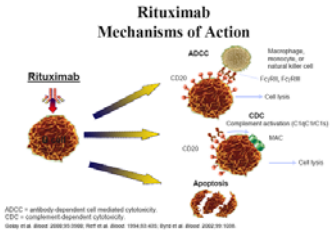
Treatment of antibody mediated diseases

- Steroids (actually corticosteroids, such as prednisone)
  - Very powerful anti-inflammatory medication
  - Usually doesn't cure the disease, just helps with symptoms
  - HORRIBLE SIDE EFFECTS if taken too long
    - Weight gain, acne (teenagers love them)
    - osteoporosis, diabetes, cataracts, poor wound healing, infections



Treatment of antibody mediated diseases

- Rituximab
  - An antibody made in the lab that is given to people to kill their B cells
  - Very specific with few side effects (other than not having B cells of course)
  - Developed for the treatment of B cell cancers



The age of "Biologics"

- We can now produce antibodies against any molecule or cell in the human body
- Fairly simple to do (immunize a mouse, find the clone that binds your protein of interest, clone that into a human form, sell for a ton of money)
- These are called biologics

HUMIRA® adalimumab

Stelara® (ustekinumab)

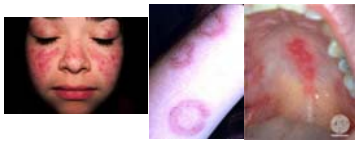
Immune complex mediated diseases

- In immune complex diseases, antibodies bind things (proteins, free DNA, etc) while circulating
- These complexes then deposit places (kidneys, skin, joint) and cause inflammation
- Similar things happen to healthy people in response to drugs or viruses
  - After penicillin some people get rashes
  - After viruses kids can get transient arthritis

Immune complex disease	Antibody specificity	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s)	Nephritis
Serum sickness (clinical and experimental)	Various protein antigens	Systemic vasculitis, nephritis, arthritis
Arthus reaction (experimental)	Various protein antigens	Cutaneous vasculitis

Example of immune complex disease

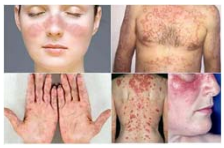
- 14 year old girl with fatigue, stiff hands, fevers, rash
- Exam shows butterfly rash on face, oral ulcers, arthritis of small joints of hand
- Labs show hemolytic anemia, renal failure
- Dx: systemic lupus erythematosus

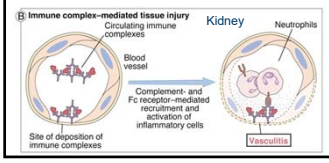


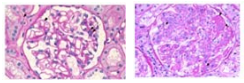
Mucocutaneous	Organs (-itises)	Lab
• Malar rash • Discoid rash • Photosensitivity • Oral/nasal ulcers	• Arthritis • Serositis • Cerebritis • nephritis	• ANA • Immune – dsDNA – Anti-Sm • Autoimmune cytopenias – ITP – AIHA

Systemic Antibody-Mediated Autoimmunity

- Systemic lupus erythematosus (SLE)
  - Anti-nuclear autoantibodies
  - Symptoms include rash, painful and swollen joints, fever, hair loss, fatigue
  - Self-reactive antibodies lead to tissue damage







Normal kidney Lupus kidney

Treatment of SLE

- Corticosteroids
- Plaquenil (a drug made to treat malaria with mild immunosuppressive effects)
- Antimetabolites
  - These drugs inhibit DNA synthesis and cell growth
  - Many were generated as chemotherapy for cancer
    - Methotrexate
    - Azathioprine (Imuran)
    - Mycophenolate (Cellcept)
- Biologics
  - rituximab, belimumab (binds B cell activating factor or BAFF)

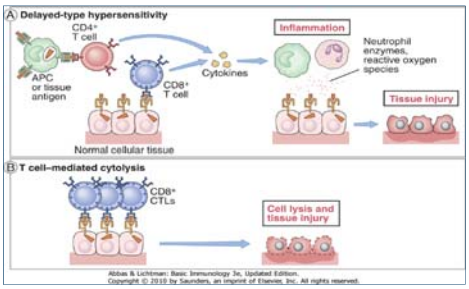
T cell mediated diseases

- A variety of autoimmune diseases are mediated mainly by T cells
- CD8 T cells directly kill cells
- CD4 cells release cytokines to cause inflammation and damage

Disease	Specificity of pathogenic T cells	Genetic associations	Clinicopathologic manifestations
Type 1 (insulin-dependent) diabetes mellitus	Pancreatic islet antigens	Insulin, PTPN22	Impaired glucose metabolism, vascular disease
Rheumatoid arthritis	Unknown antigens in joint	PTPN22	Inflammation of synovium and erosion of cartilage and bone in joints
Multiple sclerosis	Myelin proteins	CD25	Demyelination of neurons in the central nervous system, sensory and motor dysfunction
Inflammatory bowel disease	Unknown, ? role of intestinal microbes	NOD2	Inflammation of the bowel wall; adbominal pain, diarrhea, hemorrhage
Contact sensitivity (e.g. poison ivy reaction)	Modified skin proteins		DTH reaction in skin, rash
Chronic infections (e.g. tuberculosis)	Microbial proteins		Chronic (e.g. granulomatous) inflammation
Viral hepatitis (HBV, HCV)	Virally encoded proteins (e.g. EBNA)		CTL-mediated hepatocyte death, liver dysfunction; fibrosis
Superantigen mediated diseases (toxic shock syndrome)	Polyclonal (microbial superantigens activate many T cells of different specificities)		Fever, shock related to systemic inflammatory cytokine release

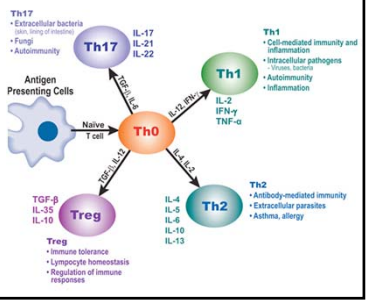
Abbreviations: DTH, delayed-type hypersensitivity; NOD2, nucleotide-binding oligomerization domain containing 2; PTPN22, protein tyrosine phosphatase N22

T cell mediated diseases



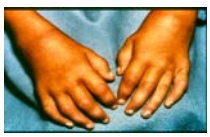
CD4 T Cell Fates

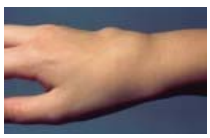
- Following activation T cells differentiate one of several subsets
- Each T cell subset has unique functions
  - TH17 in psoriasis
  - TH2 cells an allergy
  - TH1 cells in rheumatoid arthritis



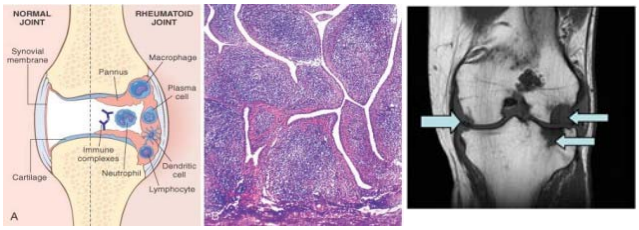
Treatment of T cell diseases

- 16 year old female with 8 weeks of morning stiffness in hands, joint swelling, low grade fevers
- Exam demonstrates swelling and pain of many joints in her fingers and her wrists
- Lab studies showed high inflammatory markers and rheumatoid factor positive
- Dx: Rheumatoid arthritis





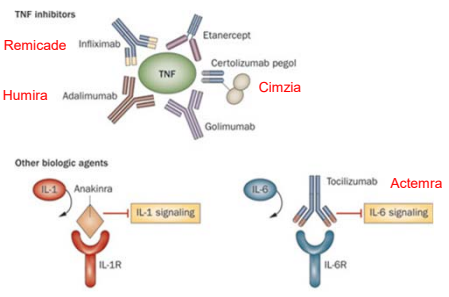
Arthritis: Pathology



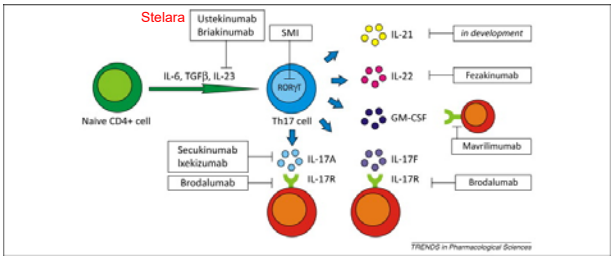
Treatment of rheumatoid arthritis

- Corticosteroids (largely directly into joints to limit systemic effects)
- Antimetabolites
  - These drugs inhibit DNA synthesis and cell growth
  - Many were generated as chemotherapy for cancer
    - Methotrexate
    - Azathioprine (Imuran)
    - Mycophenolate (Cellcept)
- Biologics
  - We use lots of biologics in RA treatment

Biologics for arthritis



IL17 Biologics
Used in arthritis, psoriasis, Crohn's, etc.



Treatment of T cell mediated diseases is disease specific

- Type 1 diabetes mellitus, Grave's disease, thyroiditis
  - Not treated with immunosuppressant medications
  - Basically by the time you realize you have this the organ is gone
  - Treated with insulin or thyroid hormone replacement
- Multiple sclerosis
  - Interferon alpha, other biologics,
  - Interestingly, TNF blockers were predicted to be very good…but ended up making things worse
- Sometimes it's trial and error as to which biologics works

Summary

- Autoimmune disorders are relatively common.
- Autoimmune diseases occur due to a mix of genetic and environmental factors….we don't really know why.
- We treat based on the mechanism of disease.
- Biologics are rapidly expanding and have shown some amazing results…..but are costly.