Autoimmune Disease Lecture (4/14)

REVIEW OF TOLERANCE

Central tolerance- occurs in the generative lymphoid organs
Peripheral tolerance- occurs in peripheral tissues

TCELLS

Central tolerance- Negative selection of Tcells

High affinity recognition of antigens in the thymus leads to elimination of those Tcells

Peripheral tolerance in Tcells

1. Anergy- results from the recognition of antigens w/o costimulators
   1a. Tcells receive signals from their TCR but no costimulatory signal (B7) is received to bind to the Tcell's CD28
   1b. Rather than activating CD28, the APC's B7 molecule activates an inhibitory receptor on the Tcell, CTLA-4. The hypothesis for this is that resting APCs express just enough B7 to activate CTLA-4, but not enough to activate CD28. Therefore, the Tcell becomes anergic rather than active.
2. Repeated stimulation by self antigens causes apoptosis of the Tcell
   Repeated activation by any antigen (more often occurs with self antigens however since they are always present while microbial antigens are not) leads to the expression of Fas (the death receptor) on the Tcell as well as Fas ligand. When Fas and Fas ligand associate, it results in T cell apoptosis.
3. Development of regulatory Tcells.
   These develop when the TCR recognizes an antigen in the absence of a costimulator (similar to the development of anergy)

BCELLS

Central tolerance- negative selection of Bcells

High affinity recognition of antigens in the bone marrow leads to elimination of those Bcells

Peripheral tolerance of Bcells

Anergy results when B cells recognize self antigens w/o Tcell help

AUTOIMMUNE DISEASE

Autoimmune disease is a failure of tolerance. The immune system attacks self antigens. These antigens can

A. Alter function
   Example: **Graves disease**
   Antibodies to surface R's can act as agonists or antagonists to the receptor. In the case of **Graves disease**, antibodies to the TSH receptor act as agonists, causing excessive release of thyroid hormones.
B. Destroy self- tissues (most autoimmune disesases)

Autoimmune diseases can also be divided into

A. Organ specific (**multiple sclerosis, diabetes**)
B. Systemic (**Lupus**)

Genetics of Autoimmue Diseases

1. HLA- certain haplotypes of HLA increase your risk of developing autoimmunity

2. Sex – more common in females
3. Mutations/polymorphisms in immune regulatory molecules
   a. AIRE (autoimmune regulator)- a transcription factor (TF) responsible for generating protein diversity in the thymus.
      -If mutated, central tolerance is affected. Causes **autoimmune polyglandular syndrome**, in which endocrine organs are attacked.
   b. Fox P3- TF responsible for generating regulatory Tcells
      If mutated, **immune-dysregulation, polyendocrinopathy, enteropathy, & X-linked (IPEX)** results

RHEUMATOID ARTHRITIS- inflammation and damage specifically to joints
TH1 cells specific for a joint antigen cause inflammation
-TH1 cells secrete cytokines, including TNFalpha, which causes swelling & the accumulation of macrophages and neutrophils in the joint
(TNFalpha is the dominant cytokine found in rheumatoid joints)
-This causes cartilage damage, which ultimately damages the joint
CD4 TH1 cells, macrophages, neutrophils, Bcells, and mast cells are all involved
IgM anti-IgG autoantibodies found in the joints of those with this disease
These autoantibodies called *rheumatoid factor* (also found in other autoimmune diseases)
Now it is thought that not a joint-specific antigen, but a widely expressed antigen, is responsible for the disease.
-Glucose-6-phosphate isomerase (GPI) has been implicated.
-For some reason, a GPI specific TCR is not eliminated by central tolerance
-TCR recognizes GPI and is activated. Bcells are also activated to make anti-GPI
-The anti-GPI causes macrophages and neutrophils to attack the joint
But GPI is everywhere, why is the damage only in the joints?
-GPI is usually intracellular, but extracellular secretion occurs in the joints.
-This secretion must occur for anti-GPI to bind GPI, causing arthritis

MULTIPLE SCLEROSIS- axons and myelin in the CNS are attacked
Plaques of dissoluted myelin, lymphocytes, & macrophages are throughout the CNS
Many symptoms can occur, depending on what type of fiber is attacked
Sensory problems, motor problems, fatigue, cognitive difficulties, autonomic problems (bowel & bladder), etc.
<u>Symptoms come & go (*Relapse & remit*)</u>
-But, patient does not return to completely normal during remission
-Therefore, with each relapse, the disease becomes worse.
-*Secondary progressive*- relapsing & remitting is occurring
-*Primary progressive*- no remission period occurs
Symptoms are worse in the heat
FOR DIAGNOSIS- requires 2 or more attacks disseminated in time & location
<u>Etiology of MS</u>
Usually Caucasian, female, 20-40 years old, lives far from equator
4 fold greater risk if the individual has HLA-DR2
<u>Disease thought to be due to CD4 TH1 response</u>- excessive secretion of IFNgamma & TNFalpha
Problems with this hypothesis

1. Mice without IFNgamma develop more severe disease
2. Blocking TNFalpha made MS worse in humans.
3. Depleting CD4 cells in humans with MS failed to cure it.

Some believe that the immune response may be secondary to neurodegeneration.

ANIMAL EXPERIMENTATION WITH MS

EAE (Experimental autoimmune encephalomyelitis) is induced in mice

EAE is a MS induced experimentally

To induce the disease, a myelin-associated protein is injected with an adjuvant
(Remember the adjuvant is the second signal needed for a Tcell response)

Proteins used included, MBP (myelin basic protein), PLP (proteolipid protein, MOG (myelin oligodendroglial glycoprotein)

These all were able to indude EAE, but NOT WITHOUT THE ADJUVANT

Inject mouse A with MBP + adjuvant→ EAE occurs

Inject mouse B with MBP only→ healthy

Inject mouse C with Tcells from mouse B + MBP + adjuvant→ healthy!!!!

Therefore, tolerance was developed in mouse B

(Possibly due to regulatory T cells)

Feeding mice MBP also prevents future EAE

TCR's recognize MBP but are not activated, therefore producing regulatory Tcells

MS & EPSTEIN-BARR VIRUS

Molecular mimicry occurs- a viral peptide is similar to self antigen
EBV has an IL-10-like protein
IL-10 is an immunosuppressor of TH1.

If IL-10 is also recognized by the same TCRs that recognize the EBV antigen,

-IL-10 activity is blocked

-TH1 activity is increased

EBV(-) people have 1/10 the risk of getting MS

MS MAY ALSO BE ASSOCIATED WITH INJURY TO CNS

CNS antigens do not normally reach lymphoid tissues due to blood brain barrier

Therefore, no negative selection of TCRs for CNS antigens occurs

An injurous event can cause lymphocytes to be exposed to CNS antigens, such as MBP

TREATMENTS USED IN MS

1. Anti-inflammatory steroids
2. Copolymer-1 (Copaxone)

   This causes a TH2 shift in the immune response
3. IFNbeta

   Decreases MHC II expression

   Increases soluble VCAM

   VLA on Tcells normally binds to endothelial VCAM, allowing Tcell entry through blood vessel walls into the CNS

   Excess soluble VCAM binds up the VLA, resulting in less T cell entry
4. Anti-VLA antibody (Tysabin)

Also prevents Tcell entry into the CNS
Twice as effective as IFNbeta

Risk of taking both IFNbeta & Tysabin- could cause progressive multifocal leukoencephalopathy
-leads to demyelination & death w/in 1-4months
-RARE

OTHER AUTOIMMUNE DISEASES

Type I diabetes- beta cells of pancreas attacked
Systemic Lupus Erythmatosus- DNA attacked
Myasthenia Gravis- nicotinic Ach receptors attacked

I received all of my information from the lecture notes and our two immuno books- if anyone has questions about anything, feel free to email me @ KaciLyne@gmail.com
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