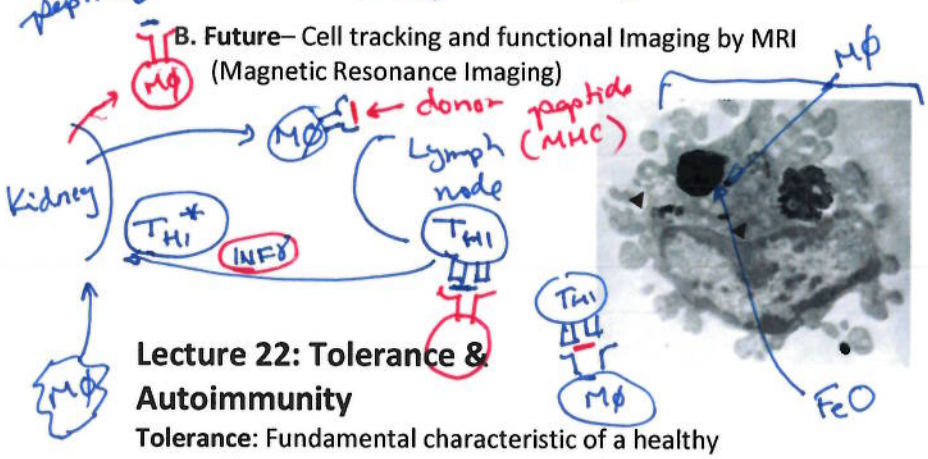
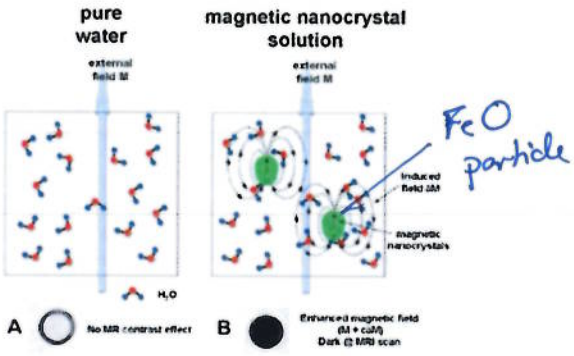
Detection of Transplantation Rejection:

A. Old/Present– Biopsy – looking for T_{H1} & Mϕ, problem is poor sampling

B. Future– Cell tracking and functional Imaging by MRI (Magnetic Resonance Imaging)





Lecture 22: Tolerance & Autoimmunity

Tolerance: Fundamental characteristic of a healthy immune system - system is usually unresponsive to antigen, unless there is a threat ("Danger hypothesis")

A) Central Tolerance:

Usual self-tolerance checkpoints in B and T-cell development (expression of all antigens in thymus by mTEC – AIRE factor).

Normal checkpoints in B & T-cell development.

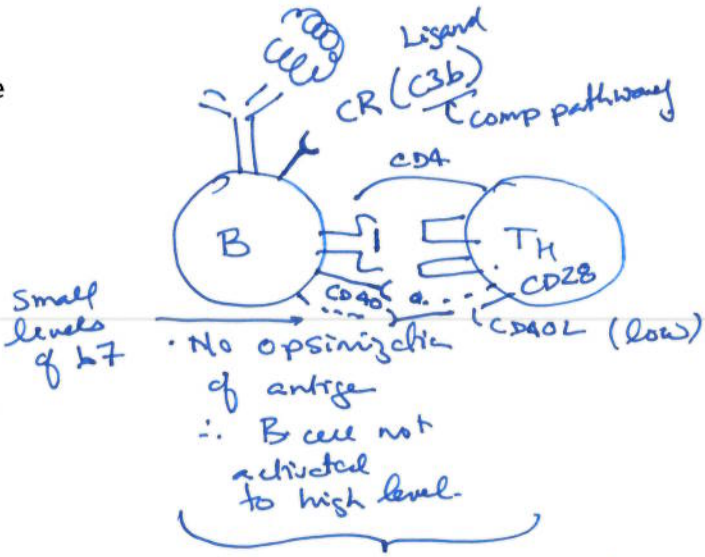
B) Peripheral Tolerance:

Anergy: B-cells

- Recognition of self-antigen will result in the presentation of self-peptides on MHC II, poor stimulation of T_H cells.
- Without strong 2nd signal from CD40-CD40L, B-cell becomes anergic.

Anergy: T – cells

- B7- CD28 required for complete T-cell activation – only provided by **activated** DCs, macrophages, B-cells. APCs only express high levels of B7 during activation, typically associated with the presence of a pathogen:
  - complement receptor on B-cell).
  - LPS + TLR 4 on macrophages,
- Without 2nd signal, T-cell becomes anergic



T_{REG} cells

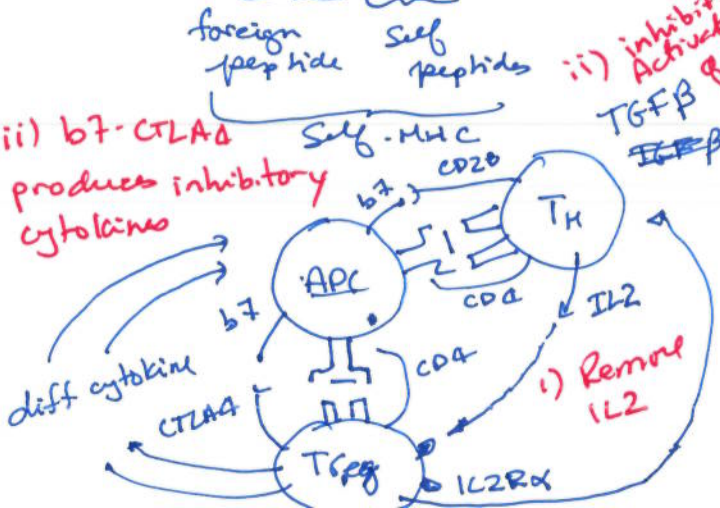
- Produced in T-cell development, recognize self-peptides.
- Express CD25 as a cells surface marker and Foxp3 transcription factor.

Immunosuppressive functions:

- Possess the α chain of IL2R, enhanced binding of IL-2 and preventing it from activating other T-cells.
- Secrete TGFβ (transforming growth factor) which inhibits T-cell activation.
- T_{REG} cells bind to self-antigen/MHC II complex, interaction of B7-CTLA-4 causes production of cytokines that suppress antigen presentation by APCs.

preT → T_{H0}, T_C, T_{reg}

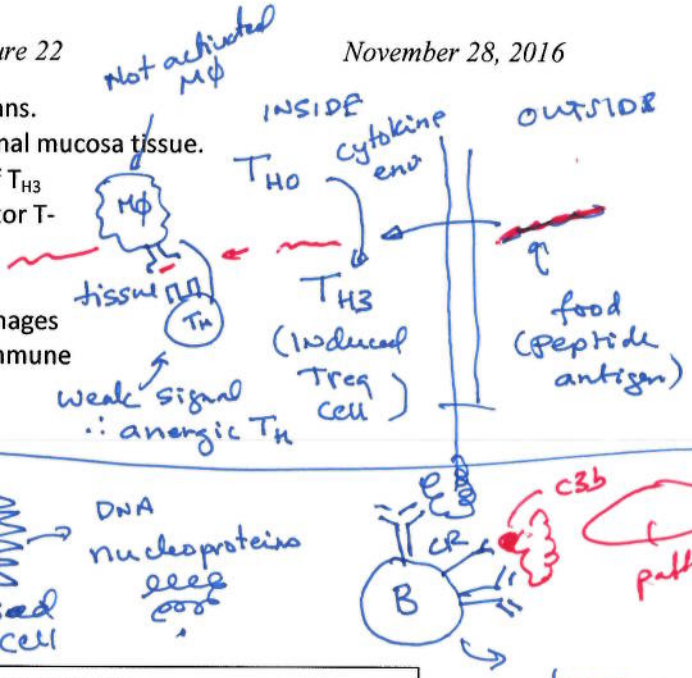
foreign peptide, Self peptides



Immuno-privileged sites: Eye/brain, reproductive organs.

Oral tolerance – Unique environment of gastrointestinal mucosa tissue.

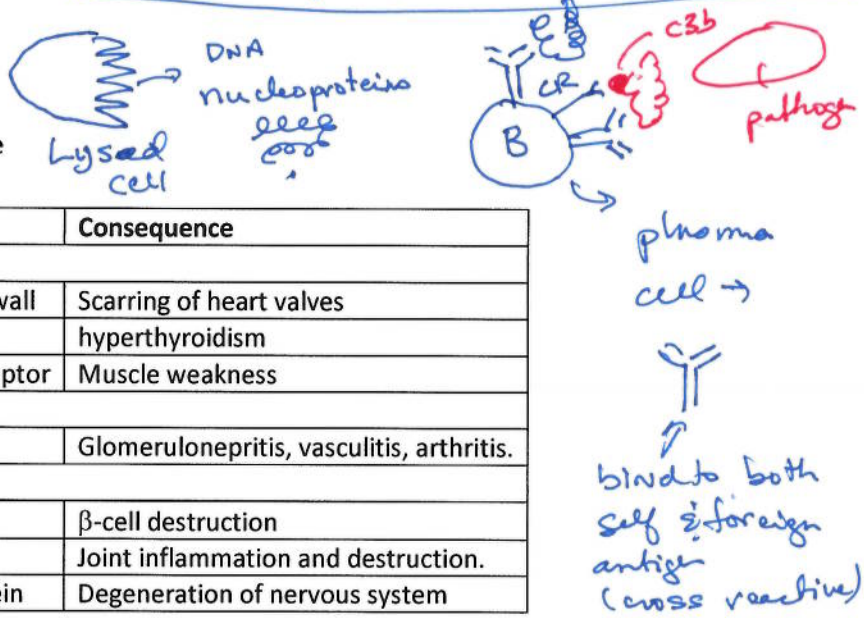
- Low levels of antigen induce the production of T_{H3} cells in the intestinal mucosal (known as adaptor T-regulatory cells or induced T-regs).
- High levels of antigen may become systemic, however presentation by unactivated macrophages leads to anergy of B/T cells, not an acquired immune response.



Autoimmunity:

Activating mechanism:

- Molecular mimicry (MM)
- Release of normally sequestered antigens
- Coincident activation of autoimmune cells by activation.



Disease	Autoantigen	Consequence
Cellular Antigens (Type II HS)		
Rheumatic fever	Steptococcal cell wall	Scarring of heart valves
Graves' disease	TSH receptor	hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Muscle weakness
Soluble Antigens (Type III HS)		
Lupus	DNA, histones	Glomerulonepritis, vasculitis, arthritis.
T_{H1} + Macrophages (Type IV HS)		
Diabetes – type I	β-cell antigen	β-cell destruction
Rheumatoid Arthritis	unknown	Joint inflammation and destruction.
Multiple sclerosis	Myelin basic protein	Degeneration of nervous system

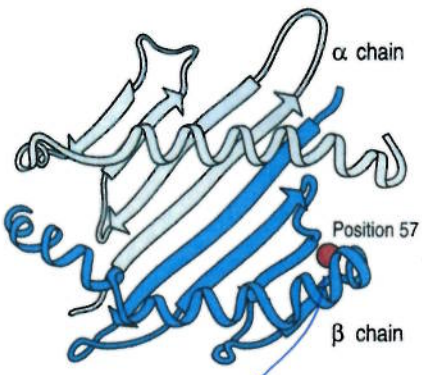
Rheumatic Fever:

Antibodies against cell-wall of *Streptococcus pyrogenes* cross react with epitopes on heart, joints, kidney.

- Activation of complement and ADCC by NK cells leads to tissue damage and inflammation.
- Response limited because auto antigens don't activate T_H cells, once the pathogen is gone antibody production drops.

Type I diabetes:

- **Insulin produced by β-cells** in the pancreas in response to high blood glucose levels.
- Genetic predisposition for certain alleles of **HLA-DQ**, one of the many class II human MHC.
- Residue 57β = Asp, protective, others increase risk.
- Although insulin is expressed by mTEC cells (thymocytes) its binding to non-Asp57 HLA-DQ is weak, therefore T-cells that recognize insulin are not killed by self-tolerance selection.
    - T_{H1} cells can become activated by presentation of insulin on proAPC. Secrete INFγ which activates macrophages, leading to destruction of insulin producing β-cell.
    - Antigens released by β-cells can lead to additional autoimmune (antigen spreading), leading to rapid death of β-cell due to recognition of other β-cell antigens.



Asp = high affinity peptide (insulin) binding → strong T_H interaction (killed in Thymus)

Not Asp → weak stimulation of T_H-cells when insulin is bound. (autoreactive T_H cells)

Why is 57β = Asp protective? What are the properties of that MHC?