Sensitization phase → Activation → Response
(2 weeks)

- (Sec → days)
- (I) (II)
- fast slow

Immune response → amplified
→ tissue damage
(death)

HSI (Antigen → Allergens → parasites)

S: T helper → IL-4 → IgE
Basophil

A: Antigen → Cross-link of IgE molecule

R: i) Degranulation → TNFα
(Mast cells) Histamine → in permeability
(flushed flow into airways)

- Smooth muscle contraction
(narrowing of airways)

- Long term mediators
Leukotriene. J × 100 more active
prostaglandins than histamine
-DMUCA

Later response: Eosinophil → ROS (reactive oxygen)
(activated by IgE)
(activated by IgE)

Treatment:
- Allergy shots. ↑ IgG (due to site of injection)
  IgG constant.
  IgG bind to antigen, prevent binding to IgE/Mast cell.
- Ab against IgE (constant region) blocks binding to Fc receptor.
**HS II**

- Cell surface antigen
- Protein required for MHC presentation
- Drug → modified protein
- Autoantigen + antigen
- Cells lysed/destroyed:
  1. ADCC - NK cells (Fc receptor)
  2. Complement activation (MAC)
  3. Macrophage Neutrophil via Fc receptor

**AIR:**

- Modified protein (autoantigen)

**HS III**

(Immunization) → Soluble antigen

S: IgG/IgM

**AIR:**

- Immune complex
  - No MAC because there is no membrane
  - Cell death
  - Complement activation (Fc receptor in close proximity)
  - Antibody + inflammation
  - Neutrophil
  - Cytolysis
  - Local reaction → Necrosis of cells

**Systemic reaction → Serum sickness**

(Whole body inflammation)

Common with antibody treatments (immune response to "drug"
- Avoided by using humanized antibodies

**HS III**

No Antibody involved!

- Modified protein (metal ions, human) (oil from poison oak)
- Prescribed in class II MHC (APC)
- Activation of Th1 cells → Th1

**Th1 / Macrophages**

- Human peptide
A/R: 2nd exposure

TH cells → Activated → INFγ → Macrophages activated

2-4 days.

Immune deficiencies

A) Acquired → HIV.
   i) Life cycle
   ii) Clinical outcome (untreated)
   iii) Treatment

ii) Mucosal tissue

M-Tropic virus

CD4 and CCRS5 receptors

Replication process: entry
- RNA → DNA (Reverse transcriptase)
- DNA → Integrated (Integrate)

Latent virus: DNA → Viral RNA → New virus

iii) TH cell death

Ab binds to surface TH
- ADCC
- Complement (MAC)
- Mφ
- Tc1 (via MHC I)

Death of Lymph nodes

Death due to common infections

Time → Antigenic drift (small change) makes Ab ineffective
iii) Treatment:

- drug targets → Reverse Transcription (ART)
  - Protease inhibitor
- monotherapy → antigenic drift
  → drug resistance (2 weeks)
- HAART → 3 drugs given at same time
  → resistance is very rare
  HIV level in blood ≈ 20

Primary Immunodeficiencies (genetic)

- INNATE System → Complement, complement components, TLR, cytokines.

- Acquired System:
  SCID → T- B- RAG1/RAG2, enzymes in nucleotides metabolism
  → T- B+ Signalling → IL-2-RY missing, J- D-T-
  - JAK missing
  - missing thymus

Ab deficiencies

- CVID IgM only
- hyper IgM: T & B activation. CD40 (CD40L)
- IgA: transport across mucosal membrane is blocked
  MHC II / TCR 07 / CD28
Autoimmunity - Summary

1. Definition of autoimmune disease
2. Examples of autoimmune diseases
3. Mechanisms of autoimmunity – role of T lymphocytes, antibodies

4. Auto-reactive T cells – Thymic selection
   Self-antigen presentation defects

5. Type 1 Diabetes – Pathological findings in pancreatic islets
   Genetic susceptibility: HLA - VNTR INS - CTLA4
   Epitope spreading
1. Definition of autoimmune disease

Tissue damaging responses mediated by auto-reactive T lymphocytes (both CD8 and CD4) and auto-antibodies

Damage to the tissues must be consistent with autoimmune-mediated processes (T lymphocytes, antibodies)

MHC HLA association

Benefits of Immunosuppression
2. Examples of autoimmune diseases

**Organ/tissue-specific:**

Type 1 diabetes (islet beta cells)

Hashimoto’s disease (thyroid)

Graves disease (thyroid)

Multiple sclerosis (myelin)

**Non-organ/tissue specific:**

Systemic Lupus Erythematosus (SLE) (anti-nuclear antibodies reacts with nuclei of all cell types: skin, kidney, joints, etc)

Rheumatoid arthritis (citrullinated proteins)
3. Mechanisms of autoimmunity – role of T lymphocytes, antibodies

Steps toward autoimmune disease

A) Existence of auto-reactive T lymphocytes

B) Triggering factors (viral infection)

C) Target tissue damage (cytotoxicity, antibody-mediated)

D) Inefficient regulatory mechanisms (to reduce autoimmunity)
4. Auto-reactive T cells – Thymic selection
Self-antigen presentation defects

Defective self-antigen presentation in the thymic epithelium during clonal selection:

HLA molecules (mainly Class II) do not properly present self-antigens to the T cell-receptor

T-cell receptor affinity is low and defective, in contrast, it should be high and specific.

Low or defective affinity allows T-cell clones to gain circulation instead of being destroyed.

Insufficient self-antigen presentation (low antigen expression in the thymus) - even if affinity is high - allows auto-reactive T lymphocytes to escape negative selection.
5. **Type 1 Diabetes** – Pathological findings in pancreatic islets

Genetic susceptibility: HLA - VNTR INS - CTLA4

Epitope spreading

Epitope spreading is a process whereby epitopes distinct from and non-cross-reactive with an inducing epitope become major targets of an ongoing immune response.

Once beta cells breaks, they release antigens that trigger de novo immune responses

chronicity
Review Guide

Cancer/Tumor Immunology
I & II
\[ E = mc^2 \]

\[ M = OB/TSB \]

M = Malignancy

OB = Oncogene Behavior

TSB = Tumor Suppressor Behavior
1. Cellular transformation and malignancy:

Nature and causes:

- Uncontrolled division of cells into a mass (tumor) that dysregulates local and systemic physiologic homeostasis often resulting in metastasis and formation of secondary and tertiary tumors.

- Failure to control cell division process, maintain orderly cell death/senescence, regulate cell differentiation process, protect from DNA damage, failure of immune surveillance.

- Alterations in chromatin structure (aneuploidy/translocations/breaks, mutations) and behavior (epigenetic changes) leading to genomic instability alter gene products that regulate cell growth and homeostasis.

- Key gene products that control cell growth: ONCOGENES and TUMOR SUPPRESSORS.

- Multistep process is needed for a cell to become malignant; accumulation of different “hits” in the genome results in an imbalanced regulation of cell growth in favor of the activity of oncogenes.
2. Immune surveillance and malignancy:

- Innate immune cells (neutrophils, NK cells, macrophages, dendritic cells) look for anomalies in the environment in which they migrate through;
  - malignant cells express altered “self” proteins and these can be recognized as “danger”.

- Differences among tumor-specific antigens and tumor-associated antigens and “neo-antigens” can determine the level of tumor cell “stealthiness”.

- However, malignant have learned to be stealthy: induction of local immunosuppression.

- NK cells are important in immune surveillance: Class I MHC.
3. Inflammation in malignancy:

-Is inflammation a good thing?

-Pro: activation of innate immune cells leads to natural adaptive responses

-Con: anti-tumor effector cells can further fuel genomic instability making tumor more malignant and aggressive; ROS
4. Tumor immunotherapy:
   - Passive approach:

   **Monoclonal antibodies**: target tumor-specific Ags for specificity; some antibodies can be conjugated to toxins, radioactive molecules to target specific cells and kill them selectively;

   **Immunokines/cytokines**: mobilize innate immune cells and augment activity of adaptive immune cells against tumor, or a tumor-specific response;

   **Tumor-infiltrating leukocytes** (derived from the tumor, expanded in the lab, and administered back into patient).
4. Tumor immunotherapy:
   - Passive approach:

**Pros:**
- Cells are tumor-derived and already “experienced” the antigens;
- Cells (TILs) can be frozen for future use;
- Antibodies are very specific to antigens and cell types, easy to manufacture;
- Immunoconjugates can carry toxins that are activated very specifically and only by tumor cells

**Cons:**
- Potential for bystander damage when using toxin and radioactivity-conjugated antibodies;
- Adoptive cell therapy will often not result in memory to tumor-specific/associated antigens;
- For antibodies, the patient can mount antibodies against the therapeutic antibody;
- In cell therapy using tumor infiltrating leukocytes, during the expansion in the lab, some carryover immunosuppressive cells contaminating the preparation could be expanded;
- Tumors can also change the antigens they express nullifying targeted antigen treatments.
4. Tumor immunotherapy:  
   - **Adaptive approach:**

   **Cell therapy:**
   - tumor-antigen-pulsed dendritic cells-generation of adaptive anti-tumor antigen responses;

   - T-cells treated with tumor antigen in lab, expanded in lab, and administered into patient.
4. Tumor immunotherapy:
   - Adaptive approach:

**Pros:**
- can be targeted to tumor-specific/tumor-associated antigens;
- T-cells can acquire memory;
- therapeutic cells can be frozen for future use;
- cells can be genetically-engineered to increase action

**Cons:**
- cell therapy is expensive;
- short lifespan of cells;
- priming with cytokines associated with side effects and might activate latent viruses