Exam IV Review Material:

Previous material that you should review:

1. Overview of the inflammatory response, e.g. activation and timeline, cytokines.
2. Complement system.
3. Role of organ systems in the immune response.
4. Antibody structure, comparison to TCR structure.
5. Genetics of diversity between B and T-cell receptors – similarities and differences.
6. Activation of B and T-cells via MHC-TCR interactions – importance of diversity levels and specificity.
7. Important steps in B-cell development pre/post activation (checkpoints, affinity maturation, class switching)
8. Important steps in T-cell development (checkpoints), including role of major T-cell subsets (T_{H1}, T_{H2}, T_{H17}, T_{Reg})

Exam Coverage:

~30% - questions on broad key concepts in immunology
~5% - based on presentations
~65% - focused on last lectures (but can require knowledge from earlier material).

A. Infectious Diseases:
Response to parasitic infections.
- Sensitization-basophil → T_{H2} response IgE (primed by basophils, IL-4).
- Activation
- Effector
- General role of mediators released by mast cells & eosinophils

B. Hypersensitivities:


HS3: Ab-immune complex. Local and systemic. Activation of complement → C3a C5a lead to recruitment of neutrophils, causing tissue damage. Use of humanized antibodies to prevent serum sickness.

HS4: process, phases, mediators, cells and molecules involved in CD4+ (T_{H1} & macrophage).

C. Immunodeficiencies:

Primary (genetic) Immunodeficiencies:
1. Innate: Review major proteins that are involved in innate response, e.g. TLR4, IL-1, IL-8, TNFα, INFγ. How would the lack of one of these affect the innate response?
2. Complement: Review major steps and functions of the complement pathway. Deficiencies can occur at any step – you should be able to describe the effect of loss of a complement component on the immune response.
3. B-cell disorder:
   IgA deficiency – common (1/800). What is the immunological consequence of this disorder?
4. SCID – severe combined immunodeficiency

General comment: If you understand T- and B-cell development and signaling, you should be able to predict the result of a particular genetic deficiency.

Two types:

T’B: no T- or B-cells
   - Metabolic deficiencies in nucleotide metabolism
   - RAG1/RAG2

T’B’: IL2 simulation is required for T-cell maturation.
   - Loss of IL2 gamma chain
   - Loss of kinase (JAK) in IL2 signal pathway
6. T- and B-cells are present by defective in one or more of the following:
   - Missing MHC II
   - T-cell lacks Zap70 kinase, which is required for signaling that TCR-MHC interaction has occurred.
   - CD40 (B-cells) CD40L (T-cells) is missing – lead to problems in class switching & no affinity maturation.
   - B7/CD28

**Acquired Immunodeficiency (HIV):**

Overview of life cycle of virus and important clinical drug targets:
   i. Reverse transcriptase - both nucleotide and non-nucleotide inhibitors
   ii. HIV protease, competitive inhibitors.
   iii. HAART treatment – why is this necessary, what are the advantages?
   iv. High error rate of reverse transcriptase results in escape from drug sensitivity.

**Clinical Stages of Infection:**
   A) Pre-clinical (2-8 weeks)
      - Infection of macrophages via CD4 and CCR5 co-receptor.
      - Macrophages are not killed, but take virus to lymph nodes, etc.
      - Usually there is a viral shift from M-tropic to T-tropic, use of CD4 & different co-receptor to infect T-cells.
   B) Acute (~8 weeks) [Seropositive]
      - T₄ helper cells are killed by viral replication, TCTL activity, Ab mediated killing.
   C) Chronic (10 years)
      - Antibody response is initially able to contain virus, but continual loss of T₄ cells results in drop in Ab production & destruction of lymph nodes.
   D) Crisis phase (10-12 years) (T₄ count < 200/ ml)
      - Immune system is destroyed, infected individual dies from secondary infections.

Natural resistance mechanisms and how they were detected and characterized (ΔCCR5).

**D> Autoimmunity**

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. 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; immunokines/cytokines: mobilize innate immune cells and augment activity of adaptive immune cells against tumor, or a tumor-specific response; some antibodies can be conjugated to toxins, radioactive molecules to target specific cells and kill them selectively; tumor-infiltrating leukocytes (derived from the tumor, expanded in the lab, and administered back into patient).
     - Pros: cells are tumor-derived and already “experienced” the antigens; cells 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.
   - 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.
     - 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