Lecture 1

- T cell receptors do not have any effector functions, while B cell receptors have effector functions done by the Fc portion of the antibody. Effector functions include complement fixation (activation) and phagocyte binding.
- B cell receptors can interact with chemicals/carbs/lipids/nucleic acids/proteins.
- The light chain consists of 1 variable domain and 1 constant domain.
- The heavy chain consists of 1 variable domain and 3 (when secreted) or 4 (when membrane-bound) constant domains.
- Immature B lymphocytes express IgM only.
- Mature NAÏVE B lymphocytes express IgM and IgD.
- TCRs do not exhibit class switching or affinity maturation.
- Allylic exclusion occurs in both T+B cell receptors.
- There are 2 D segments in beta chains and about 23 D segments in the heavy chain of antibodies.
- CD2/3=> T CELLS
- CD19, CD20, CD40, CD21=> B cells
- In B cells, TDT continues till the end of heavy chain synthesis. In T cells, till the end of light chain's.

Lecture 2

- Somatic recombination takes place in both light and heavy chain.
- Eventually, the heavy chain has one V, one D, and one J segment and four constant regions (Cu).
- VDJ recombination takes place on the germline DNA, then it's transcribed and translated.
- Light chain, 1 j segment, 1 v segment and 1 c segment.
- You need to remember that the heavy chain locus is on chromosome 14 and kappa chain locus is on chromosome 2 and lambda chain locus is on chromosome 22.
- 1. RAG1/2 (VDJ recombinase)
  2. Ku (repair): forming hairpin loop
  3. DNA kinase (artemis): reopening the loop
  4. TdT
  5. DNA ligase and XRCC4

Lecture 3

- **Live-attenuated:**
  - Vaccines are generally produced from **viruses** rather than bacteria.
  - Often **long**-term immunity.
  - Often contraindicated in **immunocompromised** individuals.
  - MMR, varicella (chickenpox), BCG, OPV
- **Non-live:**
  - **Less duration** of protection
    - **Whole pathogen** (inactivated by heat, radiation, or chemicals)
      - IPV, pertussis, rabies, HAV
    - **Subunit**:
      - Tetanus toxoid, influenza, acellular pertussis, pneumococcal polysaccharide, HBV

- Can be **purified** (acellular pertussis) or produced by **recombinant genetic engineering.**
- **Recombinant**: HBV (HBsAg), and first **malaria** vaccine. In this vaccine, the gene of a surface protein of the infectious form of **Plasmodium falciparum** is fused to the **HBsAg** gene.

▪ **Toxoid (inactivated toxins):**

- Used against bacteria that produce toxins.
- Protecting only against disease pathogenesis in vaccinated individuals but do not prevent infection or transmission.
- **No herd protection**

▪ **Polysaccharide and conjugate:**

- *Strep. Pneumonia, H. influenza B, N. meningitis* (polysaccharide capsule)
- Short-term protection
- Enhanced by coupling to a protein.
- T-independent → T-dependent by conjugation to a protein.

- **Adjuvants** are substances that can enhance and modulate the immunogenicity of the antigen by activating the innate immunity. Usually not needed for live attenuated (alum).

Lecture 4

- T cells have **CD28** that binds to **B7-1/2** on APCs.
- **CTLA-4 and PD-1** are T cells inhibitory receptors.
- **IL-2** stimulates the survival, proliferation, and differentiation of antigen-activated T cells.
- Migration and retention of effector and memory T cells at sites of infection (not naïve).
- TH1 produces IFN- γ.
- **IFN-γ** acts on B cells to promote **switching to certain IgG** subclasses and activates APCs.
- Cytokines produced by **TH2** cells are involved in **blocking entry and promoting expulsion of microbes**.
- TH2 produces:
  - IL-4: IgE production, TH2 differentiation, M2 (alternative pathway)
  - IL-5: activating eosinophils
  - IL-13: M2, mucus production
- TH17 recruits PMNs for extracellular microbes.
- The full activation of naive **CD8+** T cells and their differentiation into functional CTLs and memory cells **may require the participation of CD4+ helper cells.**

Lecture 5

- Antigens can be **immunogenic** (elicit response), **tolerogenic**, **immunological ignorance**.
- **Central** tolerance, **immature** lymphocytes with self-antigen, if the reaction is strong:
  - T/B cell **apoptosis**
  - B cell **receptor replacement**
  - CD4+ development of **Treg**
- **Peripheral** tolerance, **mature** lymphocytes with self-antigen, if reaction is strong:

- Apoptosis
- Anergy
- Treg

- **AIRE** (autoimmune regulator) handles the **thymic expression of peripheral tissue antigens.**
- **Anergy:**
  1. **T cells recognize the antigen <u>without</u> co-stimulation**. So, there will be no signal transmission or ubiquitin ligase gets activated.
  2. **B7** binds to **CTLA-4** or **PD-1** rather than CD28
     - ✓ **Note**: when there is inflammation, B7 increases and binds to CD28 thus activates T cells.
     - ✓ **PD-1** has ITIM that delivers inhibitory signals to T cell, with NO apoptosis.
- Treg cells are mostly CD4+, with CD25 (IL-2R) and FOXP3, mechanisms are:
  1. Produce **cytokines** (IL-10, TGF-B) that inhibit the activation of immune cells.
  2. Express **CTLA-4**
  3. Express **IL-2R** that consumes IL-2 and inhibits other T cells from it.
- Now let's talk specifically about B cells:
- **Central**, if there is strong interaction between a B cell and a self-antigen:
  - Receptor editing (exchange Ig light chains not heavy)
  - If failed, deletion
  - Anergy
- **NOTE:** B-cell tolerance is more far from perfect as most autoimmune diseases are related to antibodies.
- Peripheral:
  - Anergy
  - Apoptosis (B cells have high levels of FAS so they're killed by the extrinsic pathway)
  - Treg
- **Note**: in many cases, diseases associated with uncontrolled immune responses (sometimes, infections lead to exaggerated responses that cause collateral damage) are called autoimmune without formal evidence that the responses are directed against self-antigens.
- **Pemphigus vulgaris**: **skin** disease in which the patients develop **antibodies against desmosomes.**
- Examples on gene defects and their diseases:
  - **AIRE: APS-1**
  - **CTLA-4**
  - **FOXP3: IPES**
  - **FAS: ALPS**

B Single-gene defects that cause autoimmunity (mendelian diseases)

Gene(s)	Disease association	Mechanism
AIRE	Autoimmune polyendocrine syndrome (APS-1)	Reduced expression of peripheral tissue antigens in the thymus, leading to defective elimination of self-reactive T cells
CTLA4	Autosomal dominant immune dysregulation syndrome	Impaired inhibitory checkpoint and regulatory T cell function leading to loss of B and T cell homeostasis
FOXP3	Immune dysregulation, X-linked polyendocrinopathy and enteropathy (IPEX)	Deficiency of regulatory T cells
FAS	Autoimmune lymphoproliferative syndrome (ALPS)	Defective apoptosis of self-reactive T and B cells in the periphery

Lecture 6

- **SLE: chronic autoimmune disease**. The clinical presentation is heterogeneous, largely because of the **multiple genetic (of importance, C1q, C2 and C4) and environmental factors.**
  - Development of SLE can be induced by **B lymphocytes** (secreting autoantibodies), **T lymphocytes** (cytokines and co-stimulation) and **innate immunity** (IFN-gamma, reduced phagocytosis, and increased NET).
- **T1D: chronic inflammation of Langerhans cells (pancreas).**
  - Leads to hyperglycemia.
  - The strongest genetic association is with **HLA.**

- Development of T1D can be induced by:
  1. **Decreased efficiency of negative selection.**
  2. **FOXP3 Treg cells are suboptimal (decreased).**
  3. **Teff cells differentiation leading to inflammation against β cells and insulin (neoautoantigen)** in the liver (the cells that secrete insulin).
- **Grave's disease:**
  - Directed against **TSH receptor (neoautoantigen).**
  - Forming **autoantibodies that mimic TSH** (the ligand).
  - Leading to **hyperthyroidism** and **goiter**.

Lecture 7

- T cell receptors recognize both the peptide and MHC molecule.
- Each person can express **six** different types of **MHC-I**.
- Types of transplantation:
  - **Autograft** (within the same individual)
  - **Allograft** (from a donor to a non-genetically identical individual of the **same species**)
  - **Isograft** (genetically identical)
  - **Xenograft** (two different species)
- The molecules responsible for almost all strong (rapid) **rejection** are **MHC**.
- Allogeneic MHC molecules of a graft may be presented for recognition by the T cells of the recipient in two fundamentally different ways, called direct and indirect:
  - Direct: APC from the **graft** reacts with recipient T cell.
  - Indirect: APC from the **recipient** reacts with recipient T cell.
- Types of rejection:
  - **Hyperacute**: recipient already have preexisting antibodies that react with the graft leading to complement activation (inflammation) and blood clots.
  - **Acute**: usually takes days-weeks, **occur in all transplantations except for identical twins**.
    - By CTL and CD4+.
    - Alloantibodies bind to alloantigen (HLA) causing thrombosis.
  - **Chronic rejection**: repeated acute rejections.
  - **Rejection can be minimized** by **ABO test, tissue typing, cross matching and panel reactive antibody test (PRA).**
- Siblings are usually the best donors.
- **HLA-A, HLA-B, and HLA-DR** are most important for predicting survival of kidney allografts.
- Graft vs host disease (GVHD):
  - Allogeneic hematopoietic stem cell transplantation (HSCT)
  - GVHD can occur in HLA identical individuals, due to differences in minor histocompatibility antigens (miHA). Many miHA are encoded on the Y chromosome.
  - Here, the **donor** T cells attack the recipient.

Lecture 8

- How do tumor cells evade immune cells?
  - Tumors are often heterogeneous, for instance tumor cells may **no longer express the molecules** that are sensed by killer immune cells.

- Some tumor cells actively suppress T cells by expressing inhibitory molecule such as **PDL1**.
- Tumor cells can attract immune cells that suppress the activity of other immune cells (**Treg and myeloid cells**).

- **Coley's toxin:** injected bacteria into tumors to provoke immune response.
- Immunotherapy four general strategies:
  1. **Non-specific immune stimulation strategy**
     - Injecting **molecules** that bind to receptors and **activate** them (APCs)
     - **IFN-α and IL-2**
     - **BCG** can **help** patients with **bladder cancer**, the bacteria cause inflammation which increases the number of immune cells around the cancer.
  2. **Removing Immune-checkpoint blockade strategy**
     - **CTLA-4** by **Ab Ipilimumab**.
     - **PD1** by Ab.
  3. **Adoptive cell transfer strategy** is based **on extracting the immune cells** outside the patient, and **activating** them outside the body.
     - Extracting immune cells from the **tumor** (the cells have already learned to recognize the tumor)
     - Extracting immune cells from the **blood** (much easier, CAR T cells)
  4. **Vaccination** (direct the immune cells specifically to the cancer tissue)
     - **Tumor cells** can be extracted and edited (made them secrete growth factors that the immune system can detect) then imported into the human.
     - **APCs** are taken from the patient, mature outside the body and loaded with tumor antigen. When the cells are reintroduced into the patient, the Ag stimulates the immune cells and helps them recognize the tumor.
- Combining immunotherapy with chemotherapy or radiotherapy can lead to a better response in some patients.

Lecture 9

- Chronic granulomatous disease (**CGD**): defective production of superoxide anion, leading to failure to kill phagocytosed microbes (especially those producing catalase).
  - Because the infections are not controlled by phagocytes, **they stimulate chronic cell-mediated immune responses, resulting in T cell–mediated macrophage activation** and the formation of **granulomas** composed of activated macrophages.
  - Therapy: aggressive antibiotics and IFN-gamma.
- Leukocyte adhesion deficiencies (**LAD**): **failure** of leukocyte, particularly **neutrophil**, **recruitment** to sites of infection, resulting in severe **periodontitis.**
- Complement deficiency:
  - **C2 deficiency** is the most common.
  - The **only** clinical problem in **terminal complement components (MAC)** is ***Neisseria*** infections.
- **Chédiak-Higashi syndrome**: **mutations** in the gene encoding the lysosomal trafficking regulator protein **LYST, resulting in defective lysosome-phagosome fusion.**
- **Combined Immunodeficiencies:** affect both **humoral** and **cell-mediated** immunity.
- **SCID** results from **impaired T lymphocyte development** with or without defects in B cell maturation.

    - **DiGeorge** syndrome: defective development of the thymus (CATCH-22).
- **Defects in B cells: IgA deficiency is the most common.**
- **X-linked agammaglobulinemia: absence of gamma globulin. Fixed by injections of gamma globulin.**
- **Hyper-IgM** syndrome: **mutation in CD40 ligand**.
- Defects in **T Lymphocyte** Activation and Function: **Wiskott-Aldrich syndrome**, **thrombocytopenia** (reduced blood platelets).

Lecture 14

- Sepsis: organ dysfunction + infection
- Septic shock: sepsis + **hypotension**
- Sepsis includes:
    - **Innate** immune system (PRR)
    - Proinflammatory **cytokines** (IL-1/12/18, TNF)
    - **Complement** activation
        - ✓ **C5 decreases, sC59 increases**
    - **Coagulation** (DIC, thrombosis and hemorrhage)
    - **Barrier incompetency** (leukocytes adhere and migrate easily)
    - **Leakage** of intravascular proteins and plasma into the extravascular space
    - Increased **NETs**
    - Excessive **platelet** activation
    - **Innate response activator B cells** produce IL-3
    - **Immune suppression** (lymphocytes exhaustion, reduced HLA-DR)
- Treatment (immune modulation)
    - Immune **suppression** (blockade of C5a signaling)
    - Blood **purification**
    - Immune **stimulation**

Lecture 15

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