Lec8 Summary. T-cells, TCR, & antigen presentation

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αß TCR

- Comprises **90-95%** of blood T cells.
- **Two polypeptide chains**: α and ß.
- **CD Coreceptor Binding MHC**:
  - **CD4+ (Th)** binds **MHC II**.
  - **CD8+ (Tc)** binds **MHC I**.
- **TCR Complex**:
  - Made of **αß receptor, ζ chain**, and **two CD3 signaling proteins**.
- **Chain Structure**:
  - **One variable region**
  - **One constant region**
  - **Hinge region**
  - **Transmembrane segment**
  - **Cytoplasmic tail**
- **Chain Linking**:
  - **Covalent linkage** by a **disulfide bridge** between extracellular **cysteine residues**.
- **TCR Function**:
  - Specifically **recognizes peptide-MHC complexes**.
- **Hypervariable Regions**:
  - Found on **both Vα and Vß**, similar to those of **antibodies**.
  - Located on the **Ag-binding site**, called **CDR**.
  - **3 CDR sites** per each.

Costimulatory Receptors on T Cells

- **Antigen Binding**:
  - **TCR - CD4/8 binding** to **antigen-MHC complex** on APCs provides the **first signal**.
- **Coreceptor Binding**:
  - **T cell coreceptors**: CD4 and CD8 proteins.
    - **CD8** binds **MHC class I**.
    - **CD4** binds **MHC class II**.
  - **CD3 and ζ chain** contribute to signal transmission within T cells.
  - These receptors provide the **second signal** for **lymphocyte activation**.

- **CD28**:
  - **Early accessory molecule** inducing **signaling**.
  - **Binds B7 on APCs**, initiating **T cell proliferation** via **IL-2 cytokine and receptor** expression.
  - **CTLA-4 binds B7** post-antigen clearance, regulating **T cell activity** and leading to **T cell death**.
- **CD2**:
  - **Glycoprotein** on over **90% of mature T cells and NK cells**.
  - Main ligand: **LFA-3 (CD58)**.
  - Functions as a **signal transducer**.
- **CD40L - CD40 Interaction**:
  - **Occurs on B cells**, essential for **B cell activation** and **isotype switching**.
- **Signal 3 - Cytokine Effect**:
  - **IL-2 growth factor** from **Th and Tc cells** stimulates **T cell and B cell proliferation**.
- **Outcomes Based on Signal Presence**:
  - **Absence of any signal** leads to **T cell anergy and tolerance**.
  - **Presence of all signals** results in **T cell proliferation and differentiation** into **effector** and **memory cells**.
- **Effector Cells**:
  - **CD4 cells** differentiate into **Th1, Th2, or Th17 lymphocytes**.
  - **CD8 cells** differentiate into **cytotoxic T lymphocytes (CTL)**.

T Cells Roles

- **Involved in**:
  - **Defense against pathogens**:
    - **Tc** cells target **intracellular pathogens**.
    - **Th** cells assist in **extracellular pathogen defense**.
  - **Tumor immune response**
  - **Graft rejection**
  - **Autoimmune diseases**

CD4+ Th Cells

- **Characteristics**:
  - **CD4 marker** (a glycoprotein) on T cells, representing **70% of peripheral T cells**.
  - Central in **modulating immunity** through **cytokine secretion**:
    - **Th2**: Activates B cells and immunoglobulin secretion.
    - **Th1**: Activates macrophages and dendritic cells.
    - **Th17**: Induces cellular chemotaxis and inflammation.

Differentiation of Th1, Th2, Th17 Cells

- **Activation**:
  - **Naïve CD4 T cells** activated by **APCs** (antigen-presenting cells) in the **secondary lymph node**.
  - Activated **CD4+ T cells** then **proliferate and differentiate** into effector cells.
- **Th2 Differentiation**:
  - Mediated by **CD4 binding with B cells** as APCs in response to **allergens, small extracellular microbes, or worms**.
  - **Presence of IL-4** from B cells induces Th2.
  - **Th2 cytokines (IL-4, IL-6)** activate B cells, **promoting antibody production**.
- **Th1 Differentiation**:
  - Triggered by **Th binding to DCs** that secrete **IL-12 and IFN-gamma**.
  - Targets **intracellular pathogens** in macrophage vesicles.
  - Provides **helper functions** to **APCs**, especially macrophages and dendritic cells.
- **Th17 Differentiation**:
  - Stimulated by **DCs secreting IL-6 and TGF-beta** in response to **extracellular bacteria and fungi**.
- **Treg Cells**:
  - **Suppress immune response** and **tumor activity**.

Antigen Effect in Priming TH1, TH2, or TH17 Cells

- **CD4 T Cell Differentiation**:
  - **Nature and amount of ligand** during **primary stimulation** influences the **functional phenotype** of CD4 T cells.
- **TH2 Differentiation**:
  - Occurs when **B cells present low levels** of a **small antigen, toxin, or worm** that binds weakly to the T-cell receptor.
  - TH2 cells **produce IL-4 and IL-5**.
  - **Active in**:
    - **Stimulating naive B cells** to make antibodies.
    - **Activating eosinophils**.
  - Targets typically **extracellular helminths or allergens**.
- **TH1 Differentiation**:
  - Occurs with a **high-density ligand** that binds **strongly to the T-cell receptor**.
  - TH1 cells **secrete IFN-gamma**.
  - **Most effective** in **activating macrophages** to target **intracellular pathogens** in macrophage **phagosomes**.

Regulation Between TH2 and TH1 Subsets

- **TH2 Cells**:
  - **Produce IL-4**, which **inhibits TH1 activation** in macrophages, reducing **autoimmunity**.
- **TH1 Cells**:
  - **Secrete IFN-γ**, inhibiting **IL-4** and **TH2 growth**, decreasing **allergy**.
- **Balance and Effects**:
  - **TH1 Dominance**: Increases **autoimmunity**, promotes **cancer and allergy**.
  - **TH2 Dominance**: Decreases **autoimmunity**.
  - **TH17**: Linked to **autoimmune diseases**.
- **Therapeutic Potential**:
  - **Cytokine manipulation** may help **control immune responses** by influencing the **TH1/TH2 balance**.

T-Helper	Cytokine	Function of Cytokine
TH2	IL-4	Leads to B cell activation and antibody secretion.
	IL-5	Activates eosinophils to react against worms.
	IL-10	Suppresses macrophages.
TH1	IFN-gamma	Activates CD8 T cells, macrophages, and NK cells for direct killing of infected cells.
	IL-2	Supports CD8 T cell activation and enhances immune response.
	IgG1, IgG3	Activates B cells to secrete opsonizing antibodies, enhancing phagocytosis.
		Helps in cell-mediated immunity and facilitates neutrophil activation.
TH17	IL-17	Recruits neutrophils and macrophages to the infection site.
		Induces inflammation, which may contribute to autoimmune diseases.

CD8 Cells

- **Characteristics**:
  - **CD8 T cells** express the **CD8 molecule** and represent **30%** of peripheral T cells.
- **Activation**:
  - **Naïve CD8 cells** are activated by **antigens on MHC class I** molecules from:
    - **Self or infected APCs** (e.g., **viruses, intracellular pathogens**, or **malformed tumor cells**).
    - Activation requires **IL-12** and **IFN-gamma**.
- **Function**:
  - **Kills infected cells** (e.g., **viruses**, **intracellular pathogens**) and **cancer cells**.
  - **Cytotoxic T lymphocytes (CTLs)** eliminate infection reservoirs by destroying infected cells.

- **Direct Activation**:
  - **Antigens** are presented to **CD8 cells** along with **type 1 interferon (IFN)** from infected cells.
- **Indirect Activation**:
  - **TH1 cells** secrete **IFN-gamma**, stimulating **CD8 cells**.

Direct Killing by CD8 Cells

- **Mechanisms**:
  - **Production of perforins** and **secretion of granzymes**.
  - **Induction of apoptosis** via the **FasL-Fas pathway**.

Fas-FasL Pathway

- **Function**:
  - **Fas-FasL binding** activates **caspases** in the target cell, triggering **apoptosis**.
  - Important for:
    - **NK and CD8 T cell killing** of target cells.
    - **T cell regulation**.
    - **Killing of T cells by NK cells** (known as **activation-induced cell death (AICD)**).
- **Mutation Consequences**:
  - **FAS/FasL mutation** leads to **Autoimmune Lymphoproliferative Syndrome (ALPS)**, characterized by:
    - **Lymphocyte accumulation**
    - **Defective apoptosis**
    - **Humoral autoimmunity**.