Lec9 PART 1 Summary, T-cell mediated immune response

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Cross Presentation

- **Class I MHC Pathway for CD8+ T Cells**
  - Requires protein antigens in the cytosol of infected presenting cells.
- **Virus Infection and Antigen-Presenting Cells (APCs)**
  - Viruses infect specific cell types and may be taken into APCs by **phagocytosis**.
  - APCs are not infected and do not **synthesize viral antigens** endogenously.
- **Solution: Cross-Presentation**
  - Dendritic cells **ingest infected cells, tumor cells, or proteins** expressed by these cells.
  - Antigens are initially on **MHC class II molecules** but are transferred to the cytosol.
  - Antigens enter the **class I MHC pathway** for recognition by **CD8+ T cells** and **Th1 cells**.

The Immunologic Synapse

- **TCR Complex Recognition**
  - When **TCR complex** recognizes **MHC-associated peptides** on an APC, multiple T cell proteins and signaling molecules gather at the T cell–APC contact site.
- **Formation of Immunologic Synapse (SMAC)**
  - The contact region between the T cell and APC is called the **immunologic synapse** or **supramolecular activation cluster (SMAC)**.
- **Key T Cell Molecules in the Synapse**
  - **TCR complex** (includes TCR, CD3, and ζ chains).
  - **CD4 or CD8 coreceptors**.
  - **Receptors for costimulators** (e.g., **CD28**).
  - **Enzymes and adaptor proteins** associated with transmembrane receptor cytoplasmic tails.

Privileged Sites

- Locations with **Limited Immune Response**
  - Examples include the **anterior chamber** of the **eye** and **testes**.
- Mechanism of Immune Privilege
  - High levels of **inhibitory proteins** such as:
    - **IL-10**
    - **TGF-β**
    - **Migration inhibition factor**
  - Expression of **FasL** on cells in these sites helps **prevent immune activation**.

Antigen-Presenting Cells (APCs)

- **Distribution and Types**
  - Found in **tissues, blood, and lymph nodes**.
  - Include **dendritic cells, macrophages, and B cells**.
- **Dendritic Cells**
  - **Primary activators of naive T cells**.
  - Present a wide range of antigens, including **viral, bacterial, and allergenic antigens**.
- **B Cells**
  - Bind **soluble, intact antigens** and present them to **T helper (Th) cells** through **MHC class II molecules**.

Dendritic Cell Activation

- **Immature Dendritic Cells**
  - Located in **tissues and infection sites**.
  - Express **low levels of MHC class I and II molecules** and **adhesion molecules**.
  - Express **high levels of phagocytic receptor PRRs**
- **Antigen Internalization**
  - Occurs through:
    - **Binding of antigens with PRRs**.
    - **Macropinocytosis**.
- **Maturation Process**
  - After engulfing a pathogen, they become **mature dendritic cells** and:
    - **Migrate to peripheral lymph nodes (LNs)**.
    - **Lose phagocytic activity**.
    - Increase **adhesion molecules, MHC, and co-stimulatory molecules**.
    - Secrete **chemotactic factors** to attract naive T cells to lymph nodes.

B Cells as APCs

- **Surface Immunoglobulins (IgM or IgD)**
  - Enable **highly efficient binding and internalization** of specific soluble antigens.
- **Antigen Processing**
  - Internalized antigens are processed in **intracellular vesicles**, binding to **MHC class II molecules**.
  - The MHC class II complex is then transported to the **cell surface** for recognition by **Th2 cells**.
- **Efficiency**
  - This process is highly **effective at low antigen concentrations** due to its specificity.

Memory T Cells

- **Types of Memory T Cells**
  - **CD4+ and CD8+ memory T cells (CD45RO+)** are divided into:
    - **Central Memory T Cells**: Express **CCR7** and **L-selectin**; home primarily to **lymph nodes**.
    - **Effector Memory T Cells**: Lack **CCR7** and **L-selectin**; home to **peripheral sites**, especially **mucosal tissues**.
- **Function in Secondary Infection**
  - Memory T cells in **peripheral tissues** can be directly activated by **pro-inflammatory cytokines** to initiate effector functions outside the **draining lymphoid tissue**.

Regulation of T Lymphocyte Responses

- **Purpose of Regulation**
  - To **prevent tissue damage** from overstimulation.
  - To **prevent autoimmunity**.
- **Regulation Methods**
  - **CTLA-4 Expression**: After antigen clearance, **CTLA-4** replaces **CD28** on T cells; binds **B7 on APCs** to inhibit T cell activity.
  - **Activation-Induced Cell Death (AICD)**: Persistent T cell activation leads to cell death through **Fas-FasL interactions** on NK cells and target T cells.
  - **Passive Cell Death**: Occurs when the antigen is eliminated.
  - **CD4 Regulatory T Cells (T regs)**: Induced in the presence of **IL-10 and TGF-beta**.
  - **PD-1 Engagement**:
    - **PD-1** on T cells binds **PD-L1** (on APCs and other tissue cells) or **PD-L2** (mainly on APCs).
    - Binding leads to **T cell inactivation** or, rarely, conversion to **T reg cells**.

New T Cell Phenotypes: Regulatory T Cells (T regs)

- **Subset**
  - Derived from **CD4 T cells**.
  - Express **FoxP3, CD25, and CD4** markers
- **Types of Regulatory T Cells**
  - **Naturally Occurring T regs**
  - **Induced T regs**: Formed in the presence of **IL-10** **and** **TGF-β**.

Generation of T reg Cells

- **Main Generation Sites**
  - Generated by **self-antigen recognition** in the **thymus** (central tolerance).
  - Also formed by recognition of **self and foreign antigens** in **peripheral lymphoid organs** (peripheral tolerance).
- **Differentiation**
  - T regs differentiate from **CD4+ T cells**.
  - Some T reg cells require **TGF-β** **and** **IL-2** for their generation.

Functions of T reg Cells

- **Immunosuppressive Cytokine Production**
  - Produce **IL-10** and **TGF-β** to suppress immune responses.
- **IL-2 Consumption**
  - Due to high **IL-2 receptor expression**, T regs absorb **IL-2**, reducing proliferation and differentiation in other IL-2–dependent cells.
- **Reduced APC Stimulation of T Cells**
  - Binding of **CTLA-4 on T regs** to **B7 molecules on APCs** diminishes APC ability to stimulate T cells.
- **Granzyme B Secretion**
  - Secrete **granzyme B**, acting on activated T cells.

T reg Cytokines

- **TGF-β**
  - Inhibits **T cells** and **macrophages**.
- **Interleukin-10 (IL-10)**
  - Inhibits **activated macrophages, dendritic cells, Th1 cells, and CD8 cells**.
  - Blocks **IL-12 production** by dendritic cells and macrophages, indirectly inhibiting **Th1 and CD8 cell activation**.
  - Suppresses **costimulatory molecule and class II MHC expression**.

Inappropriate T Cell Activation

- **T Cell Stimulation by Super Antigens**
  - **Super antigens** cause **non-specific activation of T cells**, leading to **massive cytokine release** from macrophages.
- **Causes of Super Antigen Activation**
  - Super antigens include **exoproteins** such as:
    - **Toxic shock syndrome toxin-1 (TSST-1)**
    - **Staphylococcal enterotoxins**
    - **Exfoliative toxins (ETA and ETB)**
    - **Leukocidin**
    - **Exotoxins A** from **Streptococcus pyogenes**, causing **toxic shock-like syndrome**.
  - Other pathogens include **EBV** and **HIV**.
- **Pathology of Super Antigens**
  - Super antigens bind inappropriately to the **Vß domain** of the **TCR** and **MHC class II**, activating a large number of T cells and causing high cytokine production.
  - T cells with **antigen-specific Vß domains** are more common (10%) than those with both **antigen-specific Vα and Vß TCRs** (0.01%).
- **Immunological Effects**
  - Elevated levels of **IL-1**, **TNF-alpha**, **and IL-2** result from increased macrophage activation by T cells.
  - Leads to symptoms like **fever**, **massive vascular leakage**, and **toxic shock syndrome (TSS)**.

Immunoglobulin Superfamily

- **Members of the Immunoglobulin Superfamily**
  - **Antigen receptors** of **T and B cells**
  - **CD3**
  - **Co-receptors CD4 and CD8**
  - **Most Fc receptors**
  - **CD28 and B7 adhesion molecules**
  - **Cytokine receptors**
  - **MHC molecules**