Effector T Cell Subsets,
Cytokines

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Lecture outline

• Cytokines

• Subsets of CD4+ T cells: definitions, functions, development

• New therapeutic strategies targeting cytokines
The life history of T lymphocytes

Precursors mature in the thymus

Naïve CD4+ and CD8+ T cells enter the circulation

Naïve T cells circulate through lymph nodes and find antigens

T cells are activated and develop into effector and memory cells

Effector T cells migrate to sites of infection

Eradication of infection
T cell responses

Naïve CD4 and CD8 T cells:
Can recognize antigen but incapable of any functions

CD4+ helper T cells

CD8+ CTLs

Effector T cells

Proliferation

Differentiation

Cytokine secretion

Cell killing
CD4+ T cell responses

CD4+ T cells are activated in lymph node

Some effector T cells help B cells in LN; other effector T cells leave via lymphatics

Effector T cells migrate to sites of infection in tissues

Effector T cells activate phagocytes to destroy ingested microbes
Cytokine-Mediated Functions of CD4+ Helper T Cells

All this done by one cell type? or are there subsets of helper T cells with different functions?
Cytokines

• Secreted proteins that mediate and regulate immunity and inflammation
  - About 180 “cytokines” in the genome, about 40 well defined so far (excluding chemokines)

• Produced by many cell types (mostly cells of the immune system), act on diverse targets (often white blood cells)
  - The “interleukin” nomenclature

• Most act near site of production; blood cytokine assays are usually not informative (except in severe infections?)
Discovery of Th1 and Th2 subsets

• Immune responses to different microbes are quite distinct are very different
  • Mycobacteria: macrophage activation
  • Helminths: IgE + eosinophils
• Yet CD4+ helper T cells are required for all these responses
  • How can the “same” CD4+ T cells trigger such distinct reactions?
• Hypothesis: CD4+ T cells consist of subpopulations that mediate different responses
  • Identification of mouse CD4+ Th1, Th2 cells that produce distinct cytokines
The discovery of the Th17 subset

- Many inflammatory diseases (mouse models first) thought to be caused by Th1 cells were not prevented by eliminating Th1 cells or their cytokines
  - There must be another CD4+ T cell subset

- Led to the discovery of the Th17 subset (annoying nomenclature!)
# CD4⁺ helper T cell subsets

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<th>Defining cytokines</th>
<th>Target cells</th>
<th>Host defense</th>
<th>Role in disease</th>
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**Role in disease**:
- **Autoimmunity; chronic inflammation**
- **Allergy**
- **Autoimmunity**
CD4 effector T cell subsets

Naïve CD4 T cell

Th1 → Th2 → Th17

Migrate to sites of infection and inflammation

Elimination of microbes
**CD4 effector T cell subsets**

- **Naïve CD4 T cell**
  - **Th1**: Migrate to sites of infection and inflammation, Elimination of microbes
  - **Th2**: Remain in lymphoid organ, migrate into follicles, Help B cells to produce high-affinity antibodies
  - **Th17**: Follicular helper T cells (Tfh), Remain in lymphoid organ, migrate into follicles, Help B cells to produce high-affinity antibodies
# CD4+ T<sub>H</sub> Subsets

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CD4+ T cell subsets: definitions and general properties

- Populations of CD4+ T cells that make restricted and non-overlapping sets of cytokines
  - Early after activation, T cells can produce multiple cytokines
  - Progressive activation leads to “polarization”: production of selected cytokines

- Distinct functions, migration properties, roles in disease
Effector functions of $T_{H1}$ Cells

May be Tfh cells that produce IFN$\gamma$

Role of IFN$\gamma$ in B cell activation is established in mice but not in humans
Effector functions of $T_{H1}$ Cells: Phagocyte-Mediated Host Defense

1. Naive $T$ cell interacts with APC and bacteria.
2. $T_{H1}$ cells activated by IFN-$\gamma$.
3. Activated macrophage.
4. Classical macrophage activation (enhanced microbial killing).
Effector functions of TH2 Cells

Helminths or protein antigens → Naive CD4+ T cell → Proliferation and differentiation → IL-4, IL-13 → Alternative macrophage activation (enhanced fibrosis/tissue repair)

B cell → Th2 cells → IL-4, IL-13 → Eosinophil activation

IL-4, IgE → IgG4 (human), IgG1 (mouse) → Antibody production → Mast cell degranulation

Th2 cells → IL-5 → Intestinal mucus secretion and peristalsis
Classical and alternative macrophage activation

Classically activated macrophage (M1)
- Microbial TLR-ligands, IFN-γ
- ROS, NO, lysosomal enzymes
- IL-1, IL-12, IL-23, chemokines

Microbicidal actions: phagocytosis and killing of bacteria and fungi

Inflammation

Tumor destruction

Alternatively activated macrophage (M2)
- IL-13, IL-4
- IL-10, TGF-β

Anti-inflammatory effects, wound repair, fibrosis

Tumor promotion
The essential functions of $T_H2$ cells

**Tissue homeostasis and repair**

**Barrier immunity:** elimination of microbes at epithelial barriers
Some common misconceptions about Th1 and Th2 subsets

- **MISCONCEPTION:** Th1 = cell-mediated immunity, Th2 = humoral immunity
  - **FACT:** the production of the most useful IgG antibodies is dependent on IFN\(\gamma\) (best defined in mice); Th2 cells stimulate the production of very few Ig isotypes (IgE, IgG4 [IgG1 in mice])

- **MISCONCEPTION:** Th1 and Th2 subsets exist only in mice and are not found in humans
  - **FACT:** prolonged immune stimulation induces Th1 and Th2 cells even in humans (autoimmune diseases, allergies)
Effector functions of TH17 Cells

- Bacteria
- APC
- Naive CD4+ T cell
- Proliferation and differentiation

Th17 cells

- IL-17
- IL-22

Leukocytes and tissue cells

- Chemokines, TNF, IL-1, IL-6, CSFs

Epithelial cells

- Anti-microbial peptides

Increased barrier integrity

Inflammation, neutrophil response
Genetic proof for the importance of different T cell subsets in humans

- Mutations affecting IL-12/IFN-γ cytokines or receptors → defective Th1 responses → atypical mycobacterial infections

- Mutations affecting Th17 development or IL-17 → mucocutaneous candidiasis and bacterial abscesses (“Job’s syndrome”)
Roles of T cell subsets in disease

- Autoimmune inflammatory diseases (psoriasis, MS, RA?, IBD?): Th1 and Th17
  - Cytokines induce inflammation and activate neutrophils and macrophages

- Allergies (e.g. asthma): Th2
  - Stimulation of IgE responses, activation of eosinophils
  - Old suggestions that some autoimmune/inflammatory diseases (SLE, ulcerative colitis) are Th2-mediated are likely incorrect
Therapeutic targeting of subset-specific cytokines

- Antibodies that block IL-17 and IL-17R are very effective in psoriasis
  - May make Crohn’s disease worse

- Antibody (anti-p40) that inhibits development of Th1 and Th17 cells is effective in IBD, psoriasis

- Anti-IL-13 is effective in asthma patients who have a strong Th2 signature
Differentiation of Th subsets from naïve CD4+ T cells: general principles

- Different subsets develop from the same naïve CD4+ T cells
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• Cytokines produced at the site of antigen recognition drive differentiation into one or the other subset

• Major sources of cytokines: APCs responding to microbes (TLR and other signals), responding T cells themselves, other host cells
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- Each subset is induced by the types of microbes that subset is best able to combat
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• Transcriptional activation of cytokine genes is followed by epigenetic modifications of the cytokine locus
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Microbes Drive Differentiation of the $T^H_1$ Subsets Needed for their Defense
Microbes Drive Differentiation of the $T_H$ Subsets Needed for their Defense
Microbes Drive Differentiation of the $T_H$ Subsets Needed for their Defense
Influence of the microbiome on T cell subset development

- Components of the gut flora differentially affect the proportion of functionally distinct subsets of T cells in both the intestine and other tissues.
- Individual species of bacteria influence differentiation of T cell subsets, particularly Th17 cells and Treg cells.
- The presence of a single species of bacteria in gut (e.g. SFB) can affect susceptibility to autoimmune disease manifest in other tissues (e.g. joints).
Identification of T cell subsets

- Cytokine products
  - Often “mixed” phenotypes

- “Lineage-specific” transcription factors

- Epigenetic changes, e.g. demethylated cytokine gene loci

- Other markers (receptors for chemokines and other cytokines, surface proteins): probably not definitive
Helper T cell subsets: unresolved questions

• What is the significance of cells that produce various mixtures of cytokines or limited sets of cytokines?
  • Th17 cells that make IFN$_\gamma$?
  • Th9, Th22, etc?

• How stable or plastic are these subsets?

• Cross-regulation of subsets: how do different populations affect one another?
Therapeutic targeting of cytokines and their receptors

- TNF (RA, IBD, psoriasis)
- IL-6R (RA)
- IL-1 (RA)
- IL-2R (graft rejection)
- IL-12/IL-23 p40 (IBD, psoriasis)
- IL-17 (psoriasis, MS)
- IL-13, IL-4R (asthma)
- Type I IFN receptors (SLE)

- JAK inhibitors; other small molecules?