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

Functions of CD4+ T cells are mediated by cytokines

Cytokines work in cooperation with CD40L on helper T cells interacting with CD40 on B cells, macrophages and DCs.
**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?)

**Take home messages**

**Cytokines also act during effector phase of T cell responses**

- Immune responses to mycobacteria and helminths are very different but CD4+ T cells are required for both
  - 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 clones that produce distinct cytokines

**Discovery of Th1 and Th2 subsets**
The discovery of the Th17 subset

- The first two subsets were identified on the basis of distinct cytokine profiles and were called type 1 and type 2 helper T cells (Th1 and Th2).
- Many inflammatory diseases (mouse models first) thought to be caused by Th1 cells were not prevented by eliminating Th1 cells or their cytokines.
- Led to the discovery of the Th17 subset (annoying nomenclature!)

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
4. Effector T cells, cytokines

Effector functions of T_{H}2 Cells

Antibody production
- IgG4 (human), IgG1 (mouse)

Abbas, Lichtman and Pillai. Cellular and Molecular Immunology, 7th edition, 2011

Classical and alternative macrophage activation

Classically activated macrophage (M1)
- IFN-γ
- ROS, NO, proinflammatory enzymes
- IL-1, IL-12, IL-23, chemokines
- Microbial actions: phagocytosis and killing of many bacteria and fungi
- Inflammation

Alternatively activated macrophage (M2)
- IL-4, IL-13
- Growth factors, TGF-β
- Anti-inflammatory effects

Effector functions of T_{H}17 Cells

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 IFNγ (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)
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

- Th1: autoimmune and inflammatory diseases (IBD?, MS?, RA?); tissue damage in infections (e.g. Tb)
  - Activation of macrophages, CTL responses; production of injurious antibodies
- Th2: allergies (e.g. asthma)
  - Stimulation of IgE responses, activation of eosinophils
- Th17: inflammatory diseases (MS, IBD, RA, psoriasis)
  - Recruitment of leukocytes (inflammation)
  - ~2/3rd IL17-producing cells are not CD4 Th17

Differentiation of Th subsets from naïve CD4+ T cells: general principles

- Different subsets develop from the same naïve CD4+ T cells
- 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
Differentiation of Th subsets from naïve CD4+ T cells: general principles

- Different subsets develop from the same naïve CD4+ T cells
- Cytokines produced at the site of antigen recognition drive differentiation into one or the other subset
- Major sources of cytokines: APCs responding to microbes, T cells themselves, other host cells
- Each subset is induced by the types of microbes that subset is best able to combat
- Commitment to each subset is driven by transcription factors
- Cytokines produced by each subset amplify that subset and inhibit the others (basis of “polarization”)
4. Effector T cells, cytokines

Th1 differentiation

Th2 differentiation

Th17 differentiation

T\(_{H}\) differentiation: Transcription factors
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).

Follicular helper T cells (Tfh)

- Some effector T cells express the chemokine receptor CXCR5, migrate to lymphoid follicles, and help B cells (isotype switching, affinity maturation)
- Characteristics of Tfh:
  - Surface CXCR5, ICOS
  - Transcription factor: BCL-6
  - Cytokines secreted: IL-21 + IL-4 or IFNγ (or IL-17?)
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 signals induce different subsets in vivo?
  - How do different microbes induce production of different subset-inducing cytokines?

- How stable or plastic are these subsets?

- What is the significance of cells that produce various mixtures or sets of cytokines?
  - Th17 cells that make IFNγ may be highly pathogenic
  - What about Th9, Th22, etc etc?

- Cross-regulation of subsets: how do different populations affect one another?

Therapeutic Targeting of Cytokines

- TNF antagonists (RA, IBD, Psoriasis)
- IL-1RA (RA)
- IL-2R (graft rejection, MS?)
- Anti-IL-6 receptor (RA, JIA)
- Anti-IL-12/23 p40 (IBD, psoriasis)
  - will inhibit Th1 and Th17
- Anti-IL-17A, IL-17 receptor (Psoriasis)
- Anti-IL-13 (Asthma)
- Anti-type I IFN (SLE)

Potential of small molecule inhibitors of subset-specific transcription factors?