Effector T Cells and Cytokines

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Lecture outline

- Cytokines
- Subsets of CD4+ T cells: definitions, functions, development
- New therapeutic strategies targeting cytokines
Cytokines

- Secreted proteins that mediate and regulate immunity and inflammation
  - About 180 “cytokines” in the genome, about 30 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

Therapeutic Targeting of Cytokines

- TNF antagonists (RA, IBD, Psoriasis)
- IL-1RA (RA)
- IL-2R (Kidney transplant rejection)
- IL-6 antagonists (RA, Multiple Myeloma)
- Anti-IL-12p40 (IBD, RA)
  - will inhibit T_h1 and T_h17
- Anti-IL-17 (Psoriasis, RA)
- Anti-IL-4 (Asthma)
- Anti-IL-5 (Asthma)
- Anti-type I IFN (SLE)
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

- Activate B cells to produce antibodies which eliminate extracellular microbes
- Promote differentiation of CTL which kill infected cells
- Secrete antibody
- Macrophage
- Cytotoxic T lymphocyte
- Helper T lymphocyte
- Eosinophil
- Monocyte/macrophage
- Promote migration and activation of inflammatory cells
- Activate macrophages to kill phagocytosed microbes or repair tissues
Induction of T cell responses

Cytokines produced by APCs and other cells at time of antigen recognition

Effector phase of T cell responses

Cytokines produced by effector T cells at time of microbe (antigen) elimination
Discovery of Th1 and Th2 subsets

- 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+ T cell clones that produce distinct cytokines

Discovery of the Th17 subset

- Inflammatory diseases (e.g. mouse model of multiple sclerosis) previously attributed to Th1 reactions were worsened by eliminating IFNγ, the signature cytokine of Th1 cells

- Disease shown to be dependent on a cytokine IL-23 (related to IL-12)

- IL-23 stimulates the development of CD4+ T cells that produce IL-17
**CD4+ T<sub>H</sub> subsets**

<table>
<thead>
<tr>
<th>Cytokines produced</th>
<th>Immune reactions</th>
<th>Host defense</th>
<th>Role in diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNγ</td>
<td>Macrophage activation; IgG production</td>
<td>Intracellular microbes</td>
<td>Autoimmune diseases; tissue damage associated with chronic infections</td>
</tr>
<tr>
<td>IL-4, IL-5, IL-13</td>
<td>Mast cell, eosinophil activation; IgE production; alternative macrophage activation</td>
<td>Helminthic parasites</td>
<td>Atopic diseases</td>
</tr>
<tr>
<td>IL-17, IL-21, IL-22</td>
<td>Neutrophilic, monocytic inflammation</td>
<td>Extracellular bacteria; fungi</td>
<td>Organ-specific autoimmunity</td>
</tr>
</tbody>
</table>

**Take home messages**

**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\(_H\)1 Cells

- Classical macrophage activation (enhanced microbial killing)
- Complement binding and opsonizing antibodies
- Fe-receptor
- Opsonization and phagocytosis

Effector functions of T\(_H\)2 Cells

- Antibody production
- Mast cell degranulation
- Intestinal muscle secretion and peristalsis
- Eosinophil activation
- Alternative macrophage activation (enhanced fibrovascular tissue repair)
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; Th2 cells stimulate the production of very few Ig isotypes (IgE, IgG4)

- **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**

- Membrane
  - IL-17
  - Chemokines
  - TNF, IL-1, CSF

- Inflammation
  - Increased barrier function

- Antimicrobial peptides
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 T cells themselves, other host cells
- Each subset is induced by the types of microbes that subset is best able to combat

Take home messages

Differentiation of Th subsets from naïve T cells: general principles -- 2

Process of Th differentiation consist of 3 phases:
1. Induction: production of subset-specific transcription factors, synthesis of subset-specific cytokines
2. Commitment: epigenetic changes in cytokine gene loci lead to stable cytokine production
3. Amplification: cytokines produced by T cells promote development of more of the same subset and suppress development of other subsets

Take home messages
Development of Th subsets from naïve CD4+ T cells

TH differentiation: Cytokines determine lineage commitment
**T\(_{H}\) differentiation:**

**Transcription factors**

- IFN\(_{\gamma}\)
- IL-12
- IL-4
- TGF-\(\beta\)
- IL-6 or IL-1
- IL-23
- ROR\(\gamma\)T (Stat 3)

**Th subset differentiation**

- **Th1**
  - IFN\(_{\gamma}\)
  - IL-4
  - IL-12
  - GATA3 (Stat 6)
  - Th1 cells

- **Th2**
  - IFN\(_{\gamma}\)
  - IL-4
  - IL-13
  - IL-5
  - Th2 cells

- **Th17**
  - IL-17
  - IL-21
  - IL-22
  - Th17 cells
Regulatory T cells are another subset

- Th1 cells (IFN-γ)
- Th2 cells (IL-4)
- Th17 cells (IL-17)
- Naïve CD4 T cell
- Th1
- Th2
- Th17
- Regulatory T cells

Follicular helper T cells (Tfh)

- Characteristics of Tfh:
  - Express CXCR5, ICOS
  - Transcription factor: BCL-6
  - Cytokines secreted: IL-21 + IL-4 or IFNγ (or IL-17?)

- Functions of:
  - Migrate to lymphoid follicles, and help B cells (class switching, affinity maturation)
Helper T cell subsets: progress and questions

• Elucidation of CD4+ subsets has revealed fundamental aspects of control and functions of immune responses
• Cytokines that drive subset development (e.g. IL-12/IL-23 p40) or are produced by different subsets (e.g. IL-17A) are important therapeutic targets
• Unresolved questions:
  - Signals that induce different subsets in vivo
  - How stable or plastic are these subsets?
  - Cross-regulation of subsets: when are different populations induced and how do they affect one another?

Take home messages

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)
  - Recruitment of leukocytes
Development of rational therapy: a triumph of Immunology

CTLA-4.Ig (block costimulation)

Calcineurin, mTOR inhibitors (inhibit signaling)

Anti-IL-2R (block cytokine receptor)

Antigen-presenting cell (APC)

CD28

IL-2

Anti-IL-17A

TNF, IL-1 antagonists (block cytokines)

Anti-p40

Inflammation

Anti-integrin antibodies (block adhesion)

TNF, IL-12, IL-23 (p40)

IL-1, IL-17A