1

Effector T Cell Subsets, Cytokines

Abul K. Abbas
UCSF

FOCiS

UCSF
University of California
San Francisco
advancing health worldwide

2

Lecture outline

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

3

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

↓

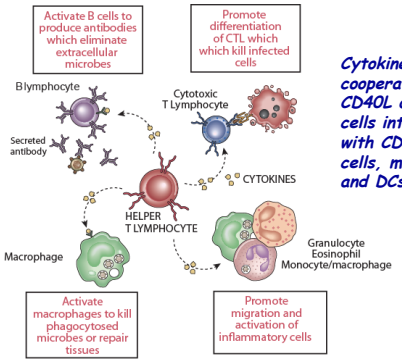
Effector T cells migrate to sites of infection

↓

Eradication of infection

4

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.

5

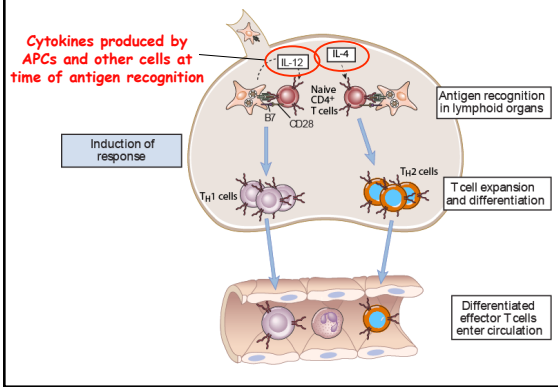
Cytokines

- 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

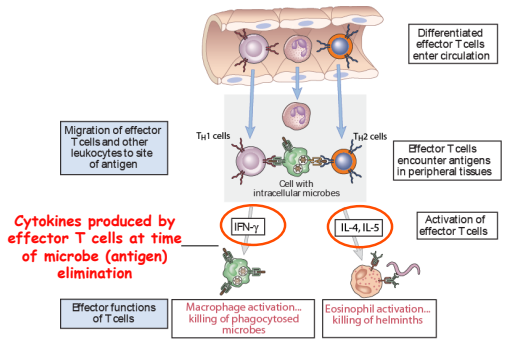
6

Cytokines act during induction of immune responses



7

Cytokines also act during effector phase of T cell responses



8

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+ Th1, Th2 clones that produce distinct cytokines

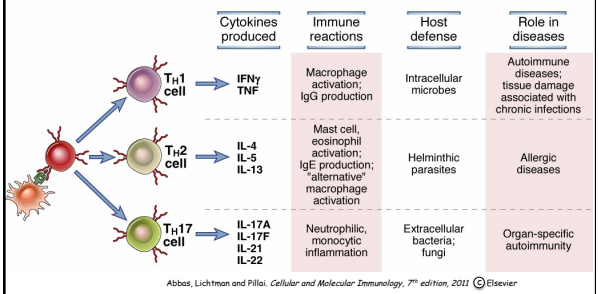
9

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!)

10

CD4+ T_H subsets



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

Take home messages

11

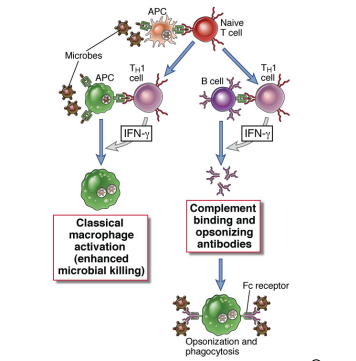
CD4+ T cell subsets: definitions and general properties

- 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

Take home messages

12

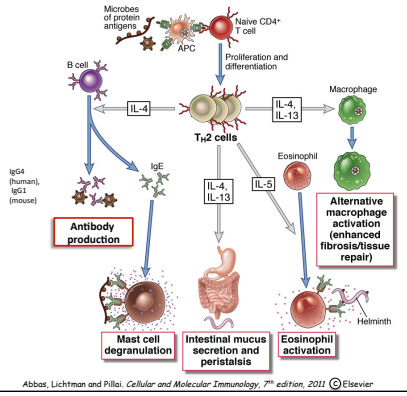
Effector functions of T_H1 Cells



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

13

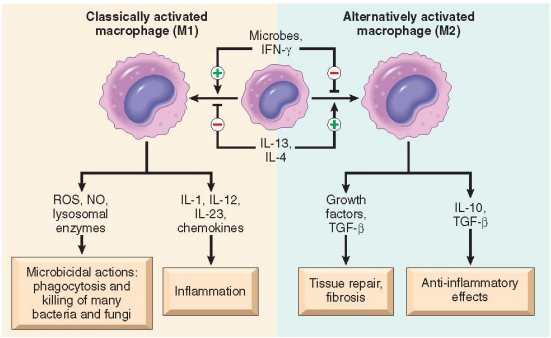
Effector functions of T_H2 Cells



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

14

Classical and alternative macrophage activation



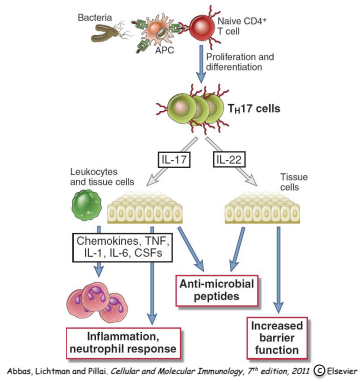
15

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)**

16

Effector functions of T_H17 Cells



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

17

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")

18

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

19

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
- Anti-IL-13 is effective in asthma patients who have a strong Th2 signature

20

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

- Different subsets develop from the same naïve CD4+ T cells

21

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

22

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**

23

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**
- **Transcriptional activation of cytokine genes is followed by epigenetic modifications of the cytokine locus**

24

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
- Transcriptional activation of cytokine genes is followed by epigenetic modifications of the cytokine locus
- **Cytokines produced by each subset amplify that subset and inhibit the others (basis of "polarization")**

25

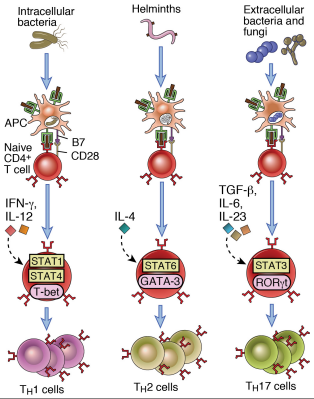
Differentiation of Th subsets from naïve CD4+ T cells: general principles

- 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
- Transcriptional activation of cytokine genes is followed by epigenetic modifications of the cytokine locus
- Cytokines produced by each subset amplify that subset and inhibit the others (basis of "polarization")

Take home messages

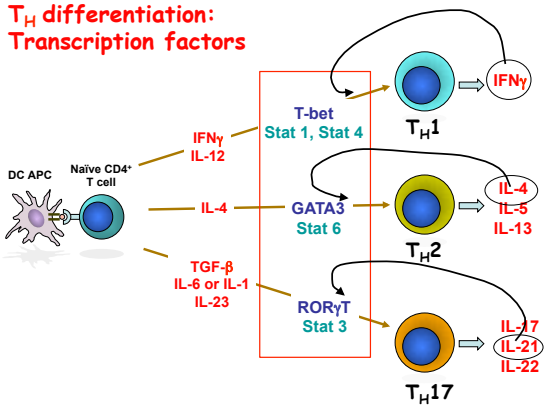
26

Development of Th subsets



27

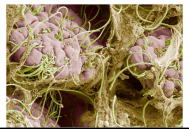
T_H differentiation: Transcription factors



28

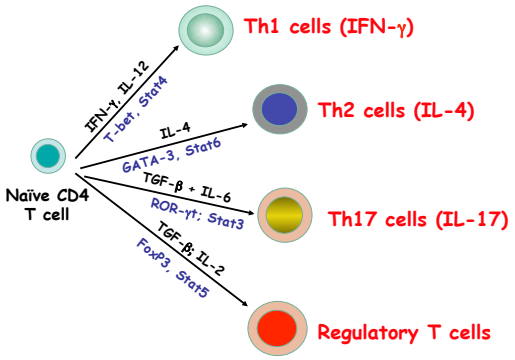
Influence of the microbiome on T cell subset development

- 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).



29

Regulatory T cells are another subset



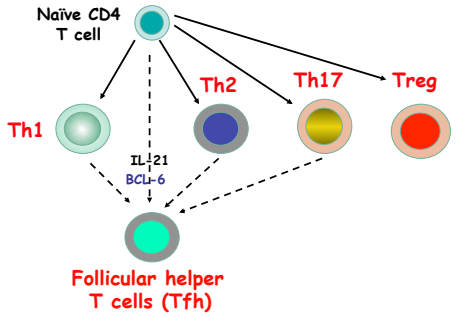
30

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?)

31

Another CD4 helper T cell subset?



32

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

33

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?

34

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 T_H1 and T_H17
- 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?