

CD4 T cell subsets Cytokines

Abul K. Abbas
UCSF

FOCiS

UCSF

University of California
San Francisco

advancing health worldwide™



Lecture outline

- Subsets of CD4+ T cells: definitions, functions, development
- Role of T cell subsets in disease
- Therapeutic strategies targeting subset-specific cytokines

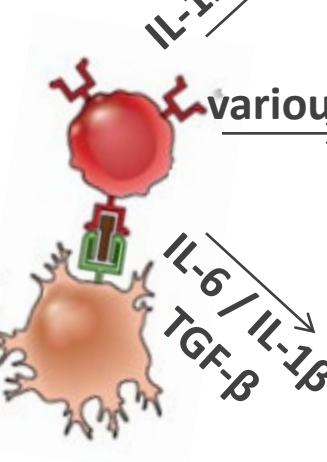





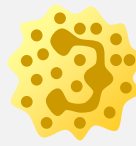
Discovery of helper T cell subsets

- Hypothesis: CD4⁺ T cells consist of subpopulations that mediate different types of immune responses
 - Identification of mouse CD4⁺ Th1, Th2 cells that produce distinct cytokines

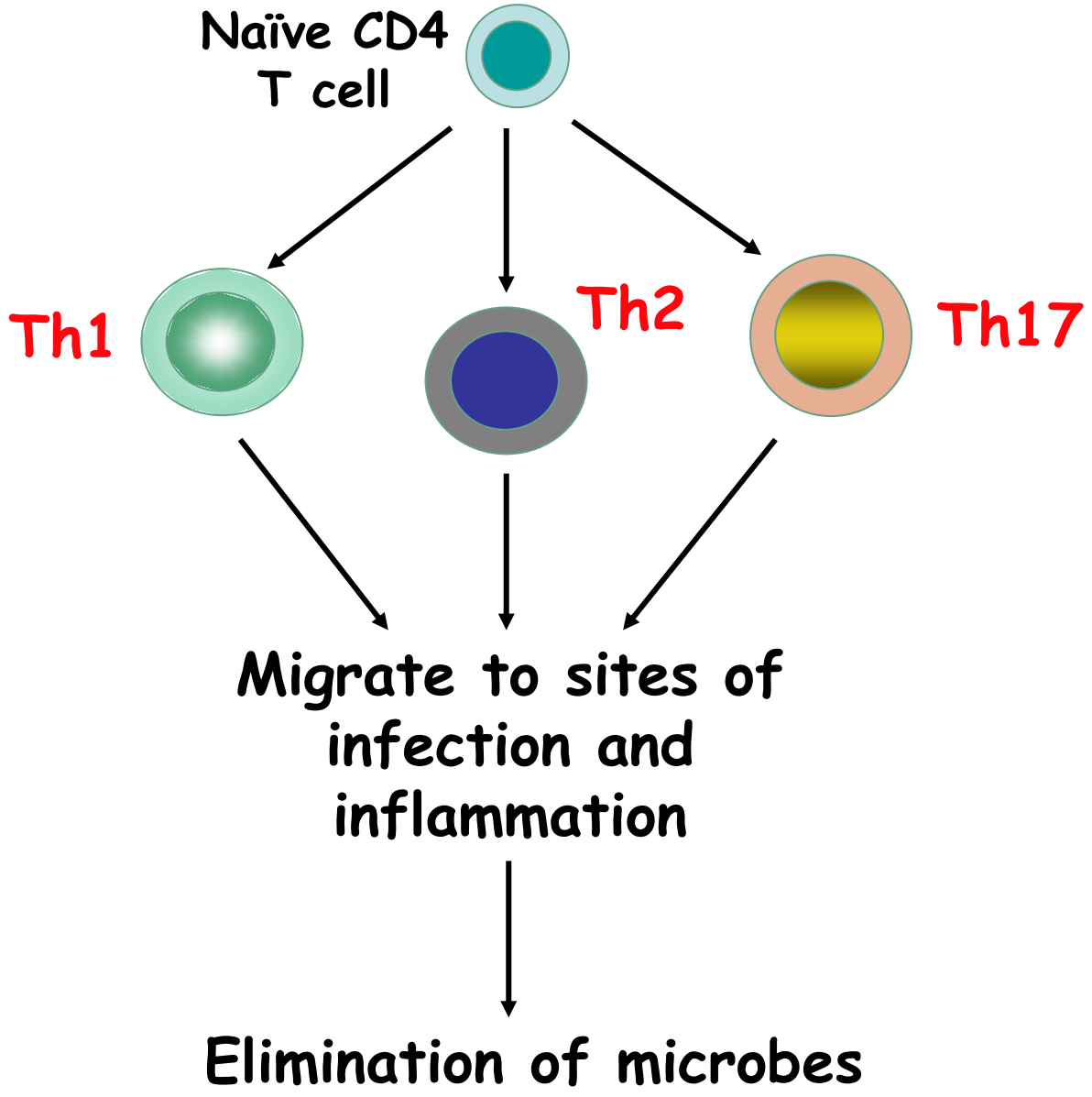
Discovery of helper T cell subsets

- Hypothesis: CD4⁺ T cells consist of subpopulations that mediate different types of immune responses
 - Identification of mouse CD4⁺ Th1, Th2 cells that produce distinct cytokines
- Inflammatory diseases (mouse models) thought to be caused by Th1 cells were not prevented by eliminating Th1 cells or their cytokines
 - Discovery of Th17 subset

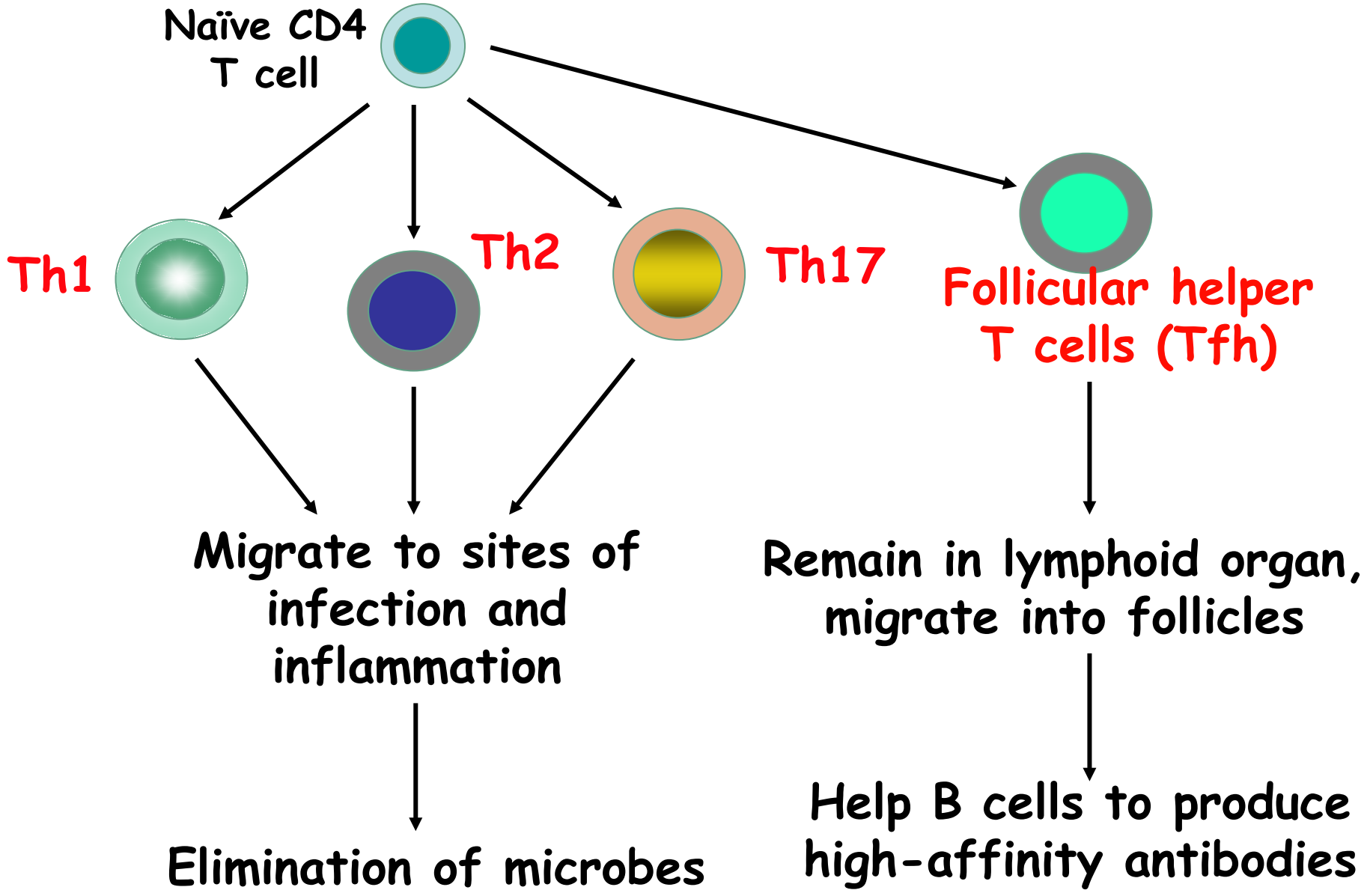
CD4⁺ helper T cell subsets

	Defining cytokines	Target cells	Host defense	Role in disease
 <p>IL-12 / IFN-γ</p> <p>various</p> <p>IL-6 / IL-1β TGF-β</p>	<p>Th1</p>  <p>IFN-γ</p>	<p>Macrophages</p> 	<p>Intracellular pathogens</p>	<p>Autoimmunity; chronic inflammation</p>
	<p>Th2</p>  <p>IL-4 IL-5 IL-13</p>	<p>Eosinophils</p> 	<p>Helminths</p>	<p>Allergy</p>
	<p>Th17</p>  <p>IL-17 IL-22</p>	<p>Neutrophils</p> 	<p>Extracellular pathogens</p>	<p>Autoimmunity</p>

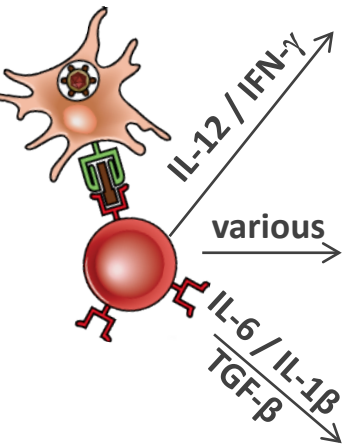


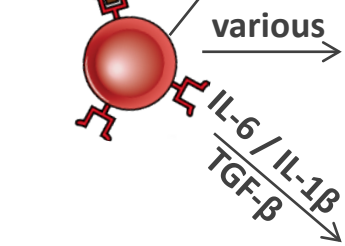


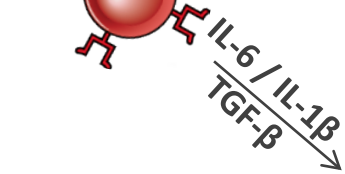

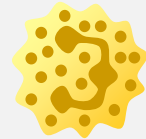
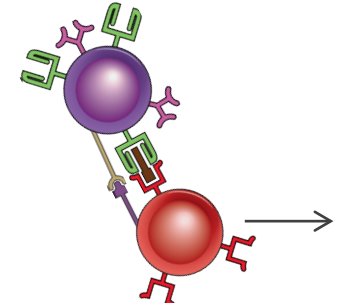


CD4 effector T cell subsets



CD4 effector T cell subsets



CD4⁺ T_H subsets

	Defining cytokines	Target cells	Host defense	Role in disease
	Th1  IFN-γ	Macrophages 	Intracellular pathogens	Autoimmunity; chronic inflammation
	Th2  IL-4 IL-5 IL-13	Eosinophils 	Helminths	Allergy
	Th17  IL-17 IL-22	Neutrophils 	Extracellular pathogens	Autoimmunity
	Tfh  IL-21 (others)	B Cells 	Extracellular pathogens	Autoimmunity

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

Functions of CD4 subsets

- **Th1: IFN γ -mediated macrophage activation**
 - Defense against intracellular microbes (cell-mediated immunity)

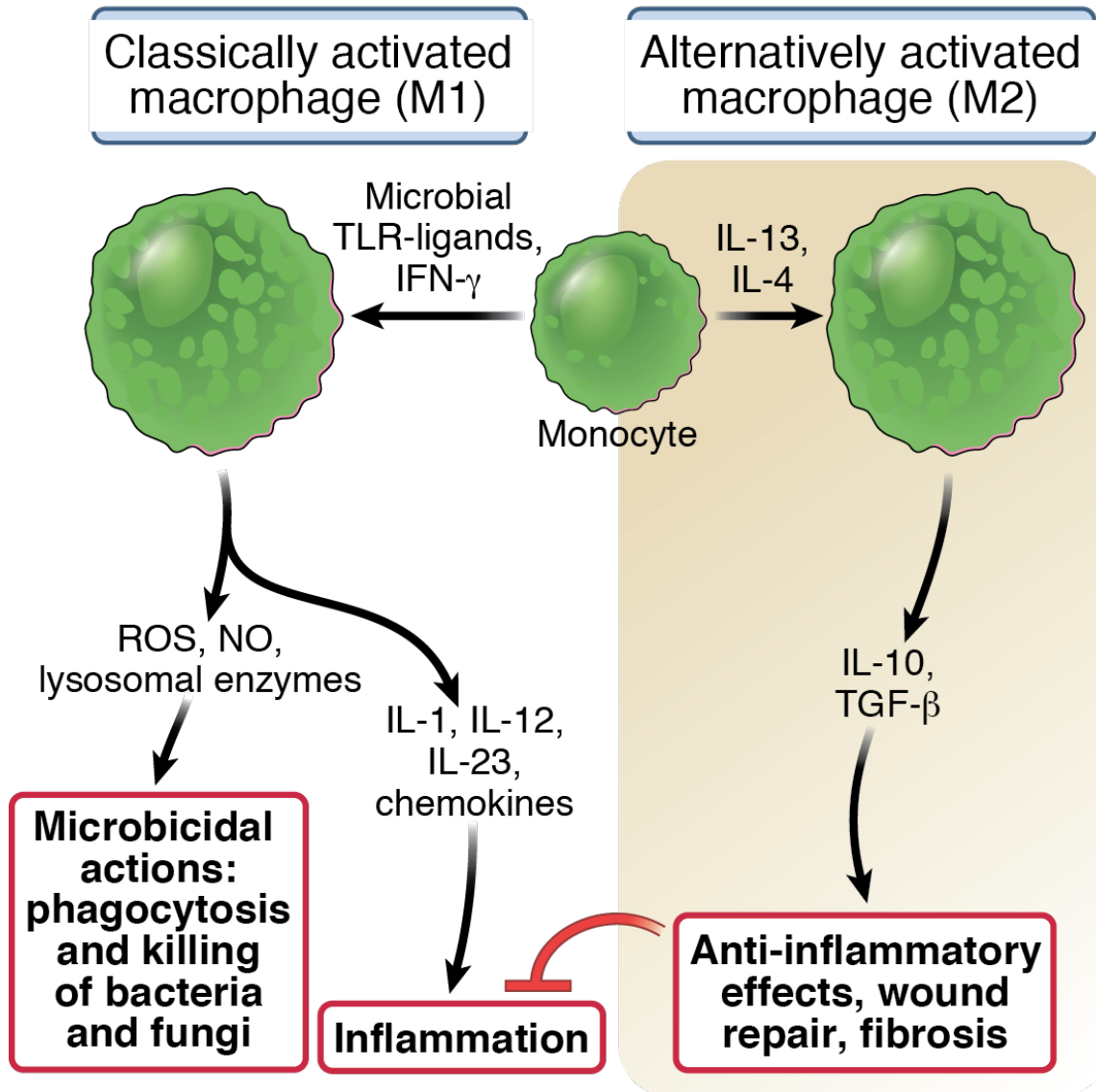
Functions of CD4 subsets

- Th1: IFN γ -mediated macrophage activation
 - Defense against intracellular microbes (cell-mediated immunity)
- Th2: IL5-mediated eosinophil activation
 - Defense against helminths
- Th2: IL4/13-mediated "alternative" macrophage activation
 - Tissue repair

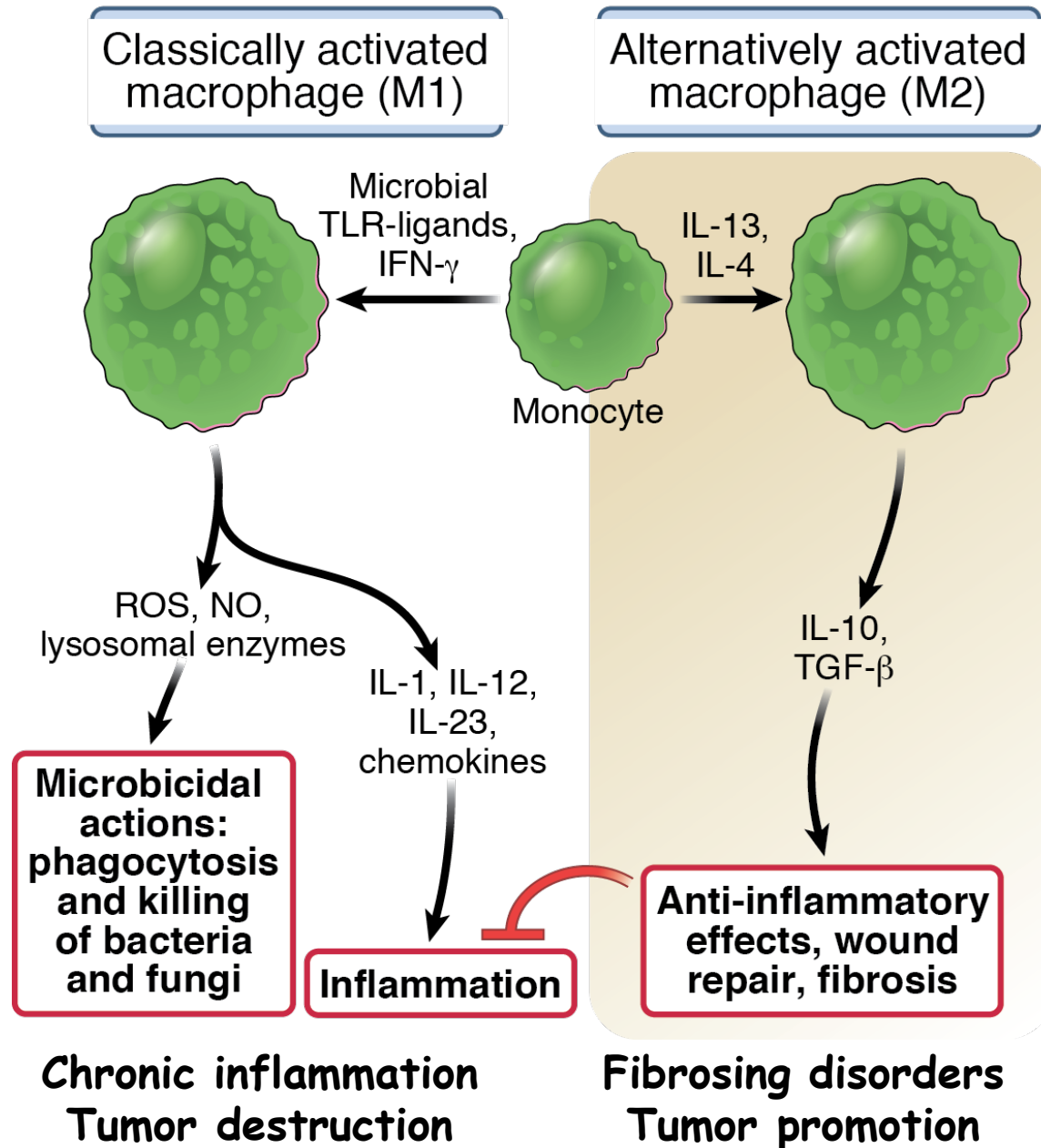
Functions of CD4 subsets

- Th1: IFN γ -mediated macrophage activation
 - Defense against intracellular microbes (cell-mediated immunity)
- Th2: IL5-mediated eosinophil activation
 - Defense against helminths
- Th2: IL4/13-mediated "alternative" macrophage activation
 - Tissue repair
- **Th17: recruitment of neutrophils, monocytes**
 - Defense against bacteria, fungi

Classical and alternative macrophage activation



Classical and alternative macrophage activation



"Types" of immunity

- Coordinated responses of ILCs (early) and Th subsets (later) in which the same sets of cytokines are produced, giving rise to the same functional outcomes
- Type 1 immunity: ILC1 + Th1
- Type 2 immunity: ILC2 + Th2
- Type 3 immunity: ILC3 + Th17

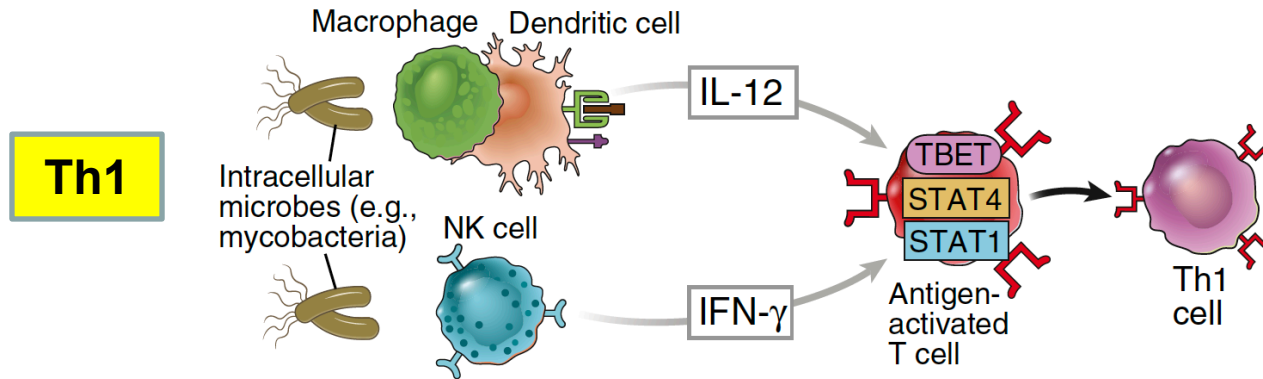
Genetic proof for the importance of different T cell subsets in humans

- Mutations affecting IL-12/IFN- γ cytokines or receptors \rightarrow defective Th1 responses \rightarrow atypical mycobacterial infections (mendelian susceptibility to mycobacterial disease)
- Mutations affecting Th17 development or IL-17 \rightarrow mucocutaneous candidiasis and bacterial abscesses (Job's syndrome, or hyperIgE syndrome [HIES])

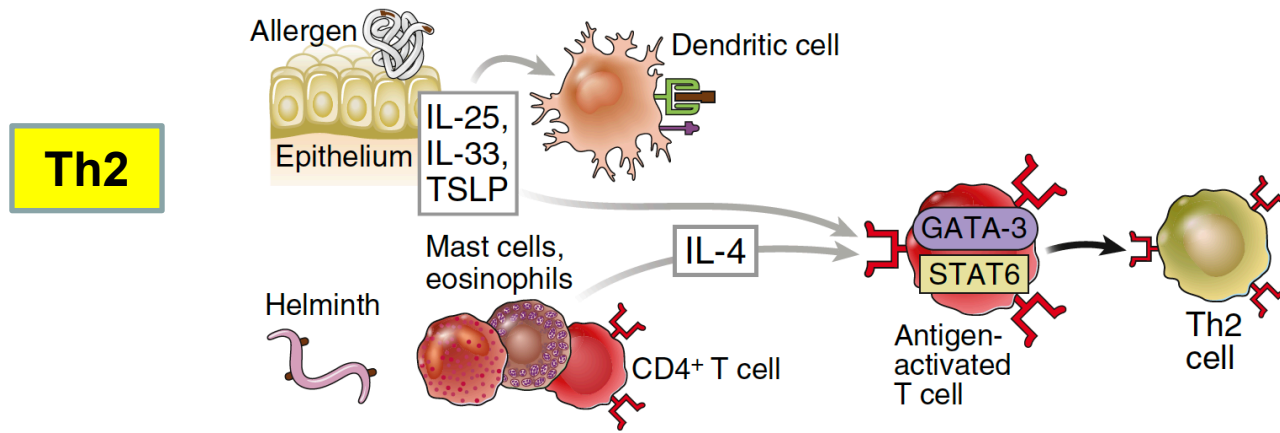
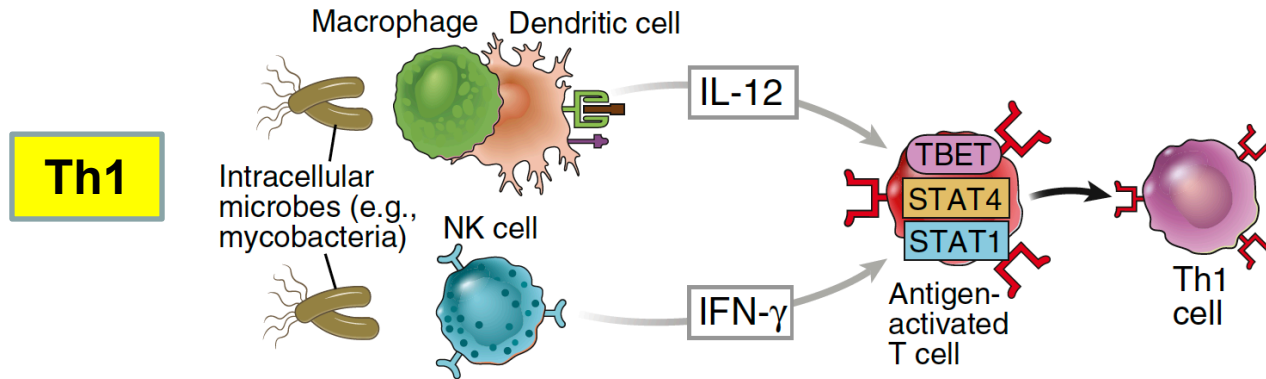
Roles of T cell subsets in disease

- **Autoimmune inflammatory diseases (psoriasis, MS, RA?, IBD?): Th1 and Th17**
 - Cytokines induce inflammation and activate neutrophils and macrophages
- **Autoantibody-mediated diseases**
 - Role of Tfh cells?
- **Allergies (e.g. asthma, atopic dermatitis): Th2**
 - IgE production, eosinophil activation

Differentiation of Th subsets: Th1

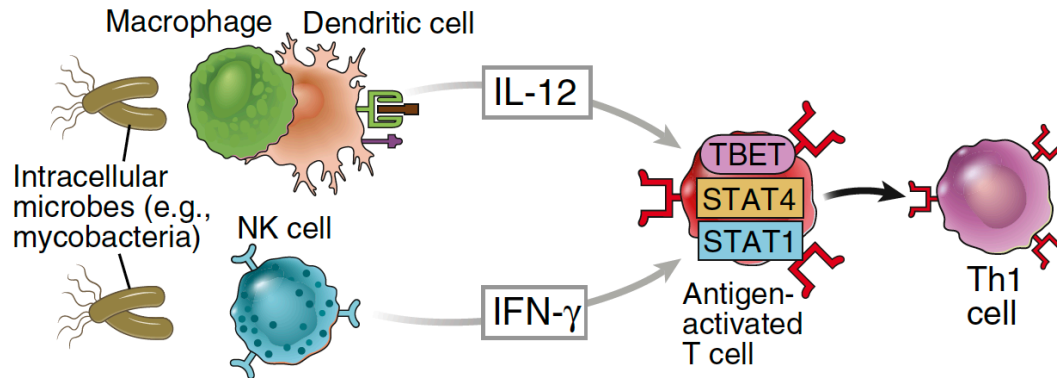


Differentiation of Th subsets: Th2

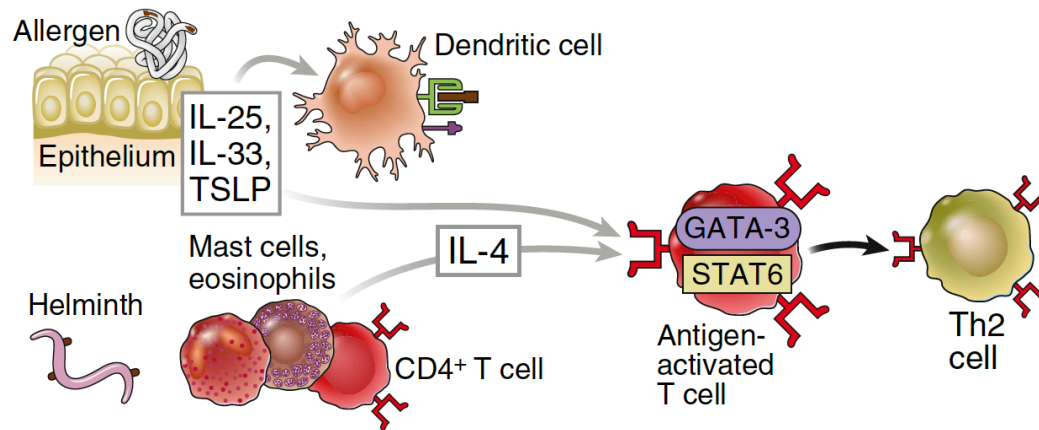


Differentiation of Th subsets: Th17

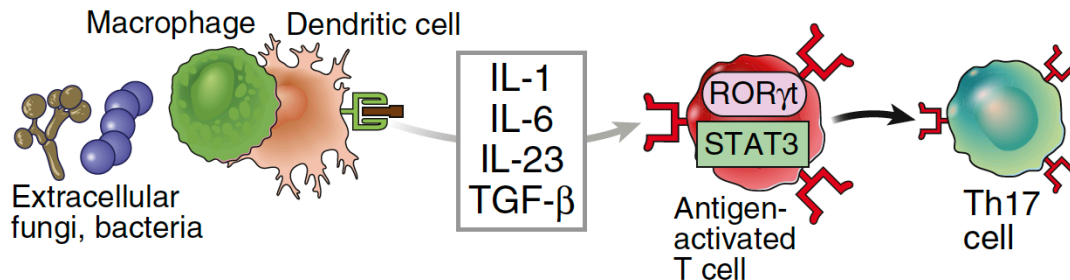
Th1



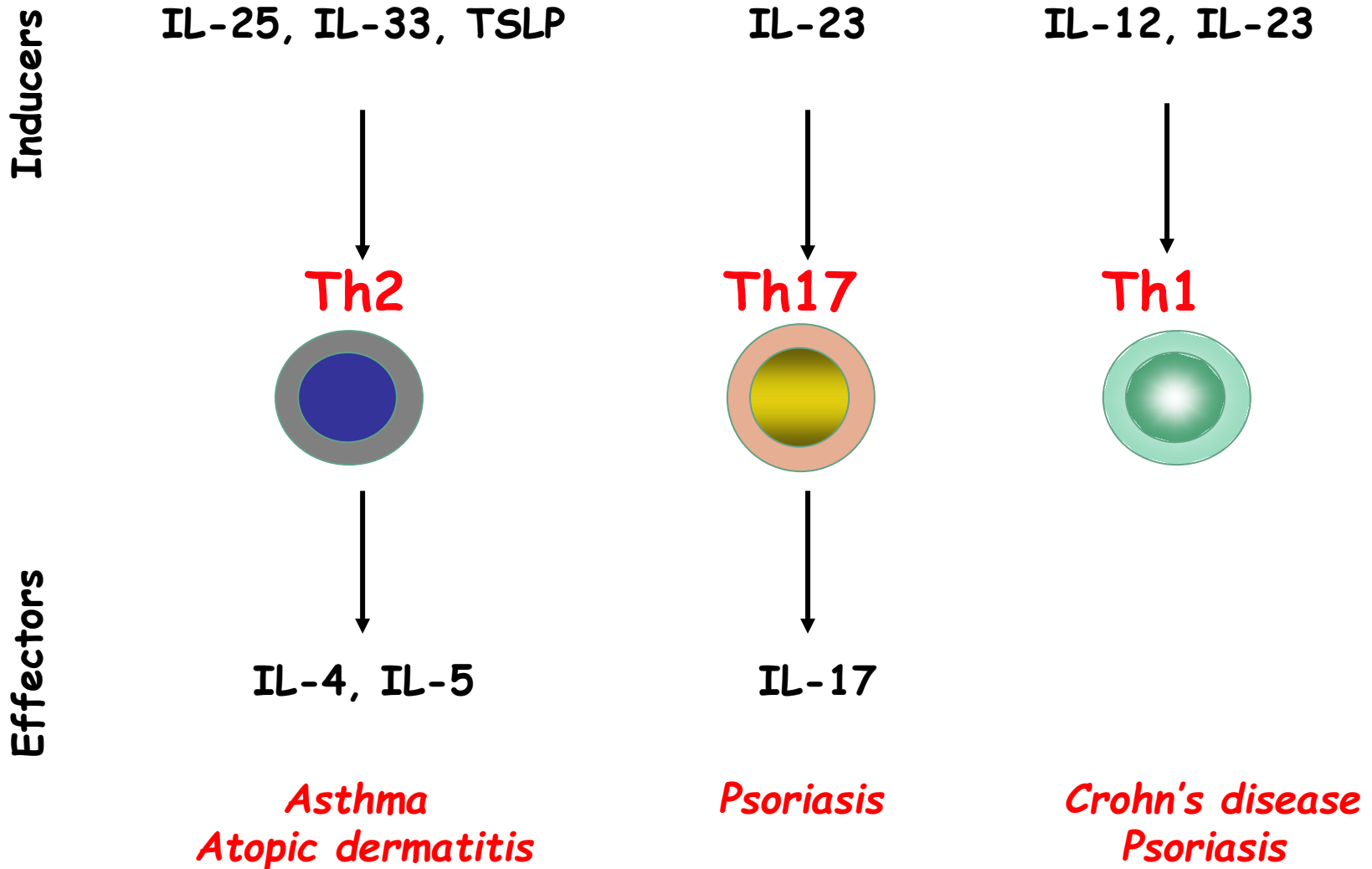
Th2



Th17

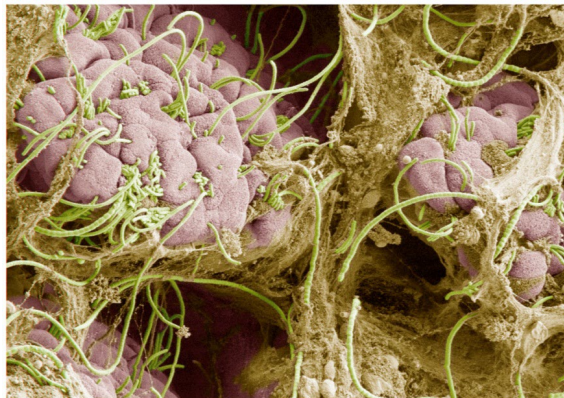


Therapeutic blocking of inducer and effector cytokines



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).



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 γ ?
 - Th9, Th22, etc?
- How stable or plastic are these subsets?
- Cross-regulation of subsets: how do different populations affect one another?

Memory T cells

- **Subsets**
 - Central memory: pool for rapid proliferation in lymphoid organs
 - Effector memory: eradicating microbes in tissues
 - Tissue-resident memory: significance and functions?
- **Generation and maintenance**
 - How activated T cells choose to become effector or memory cells is not established
 - Maintained by cytokines (IL-7, IL-15); other signals?