

CD4 T cell subsets and cytokines

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Lecture outline

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

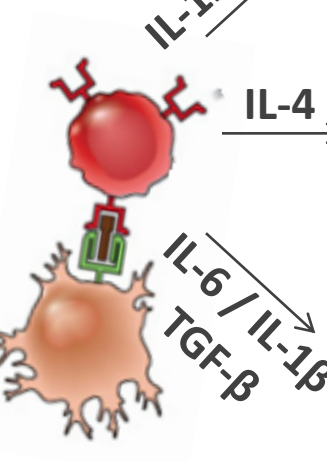




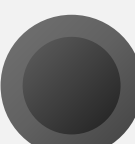
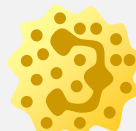
Discovery of Th1 and Th2 subsets

- 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

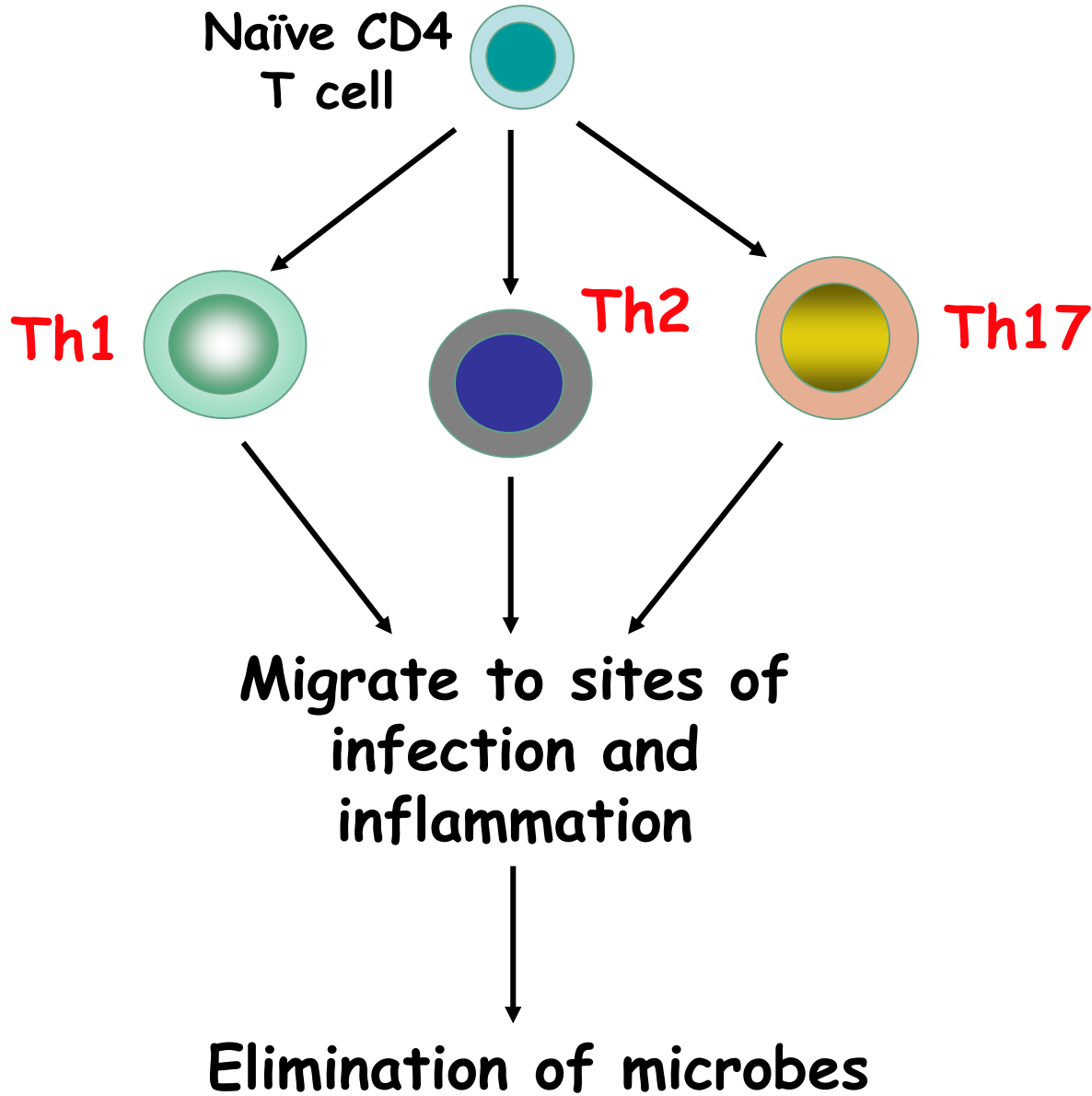
The discovery of the Th17 subset

- 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!)

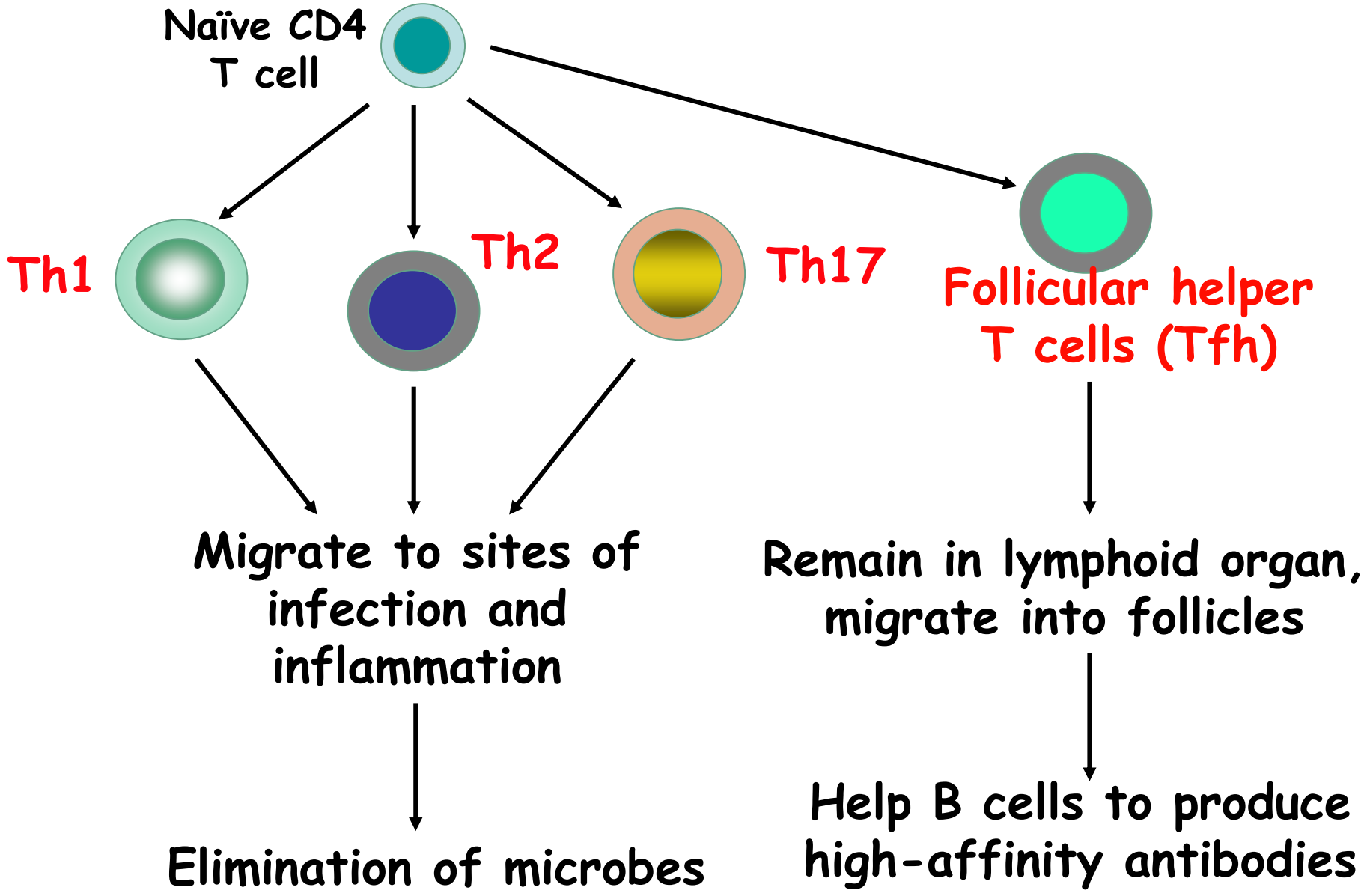
CD4⁺ helper T cell subsets

	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 	Parasites	Allergy
	Th17  IL-17 IL-22	Neutrophils 	Extracellular pathogens	Autoimmunity

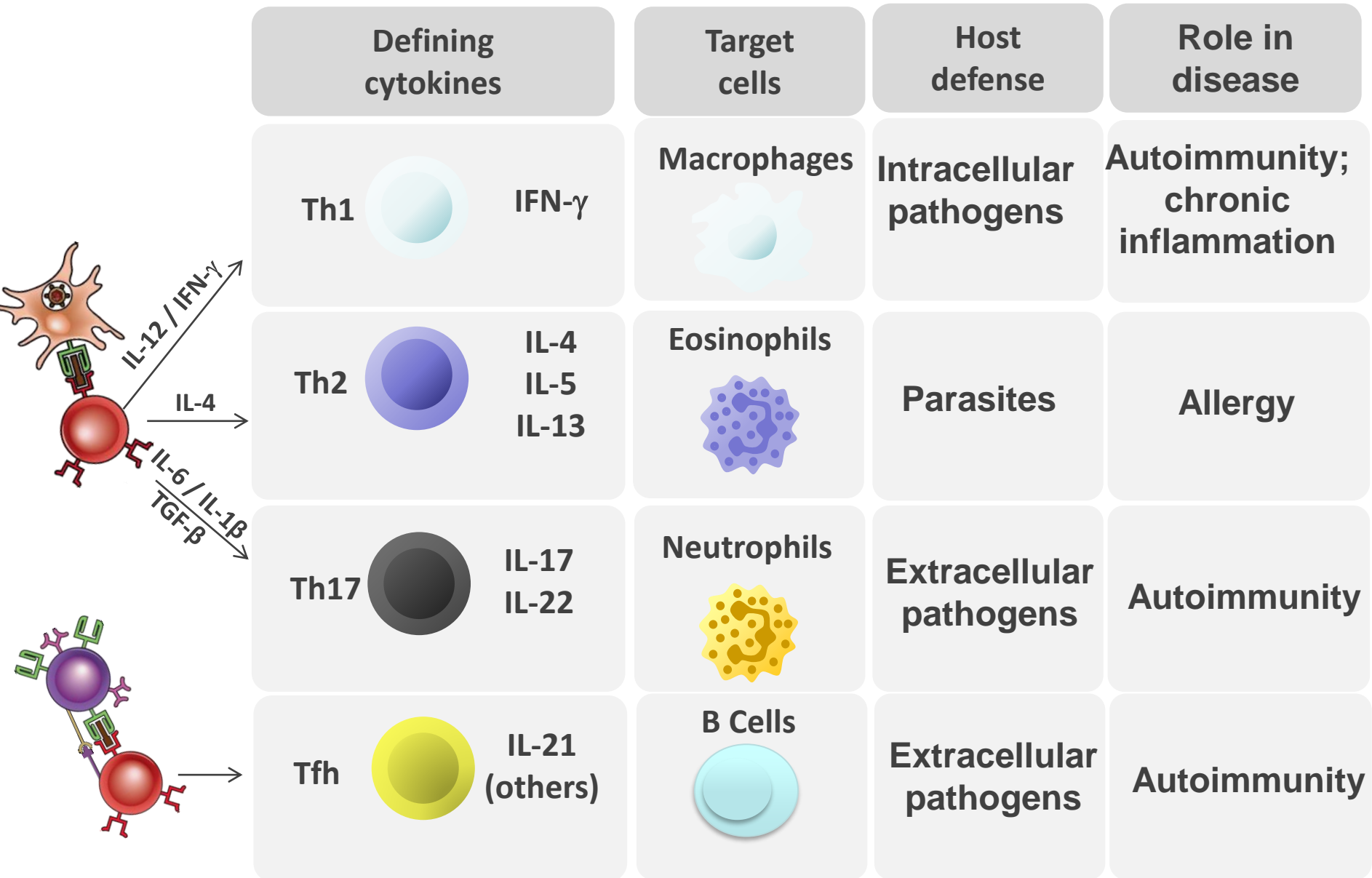
CD4 effector T cell subsets



CD4 effector T cell subsets



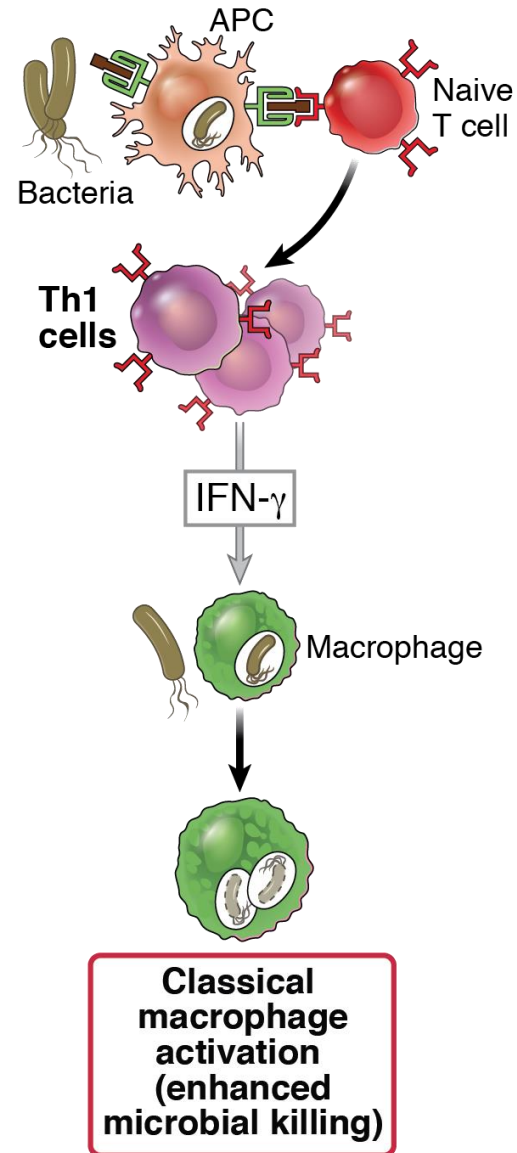
CD4⁺ T_H subsets



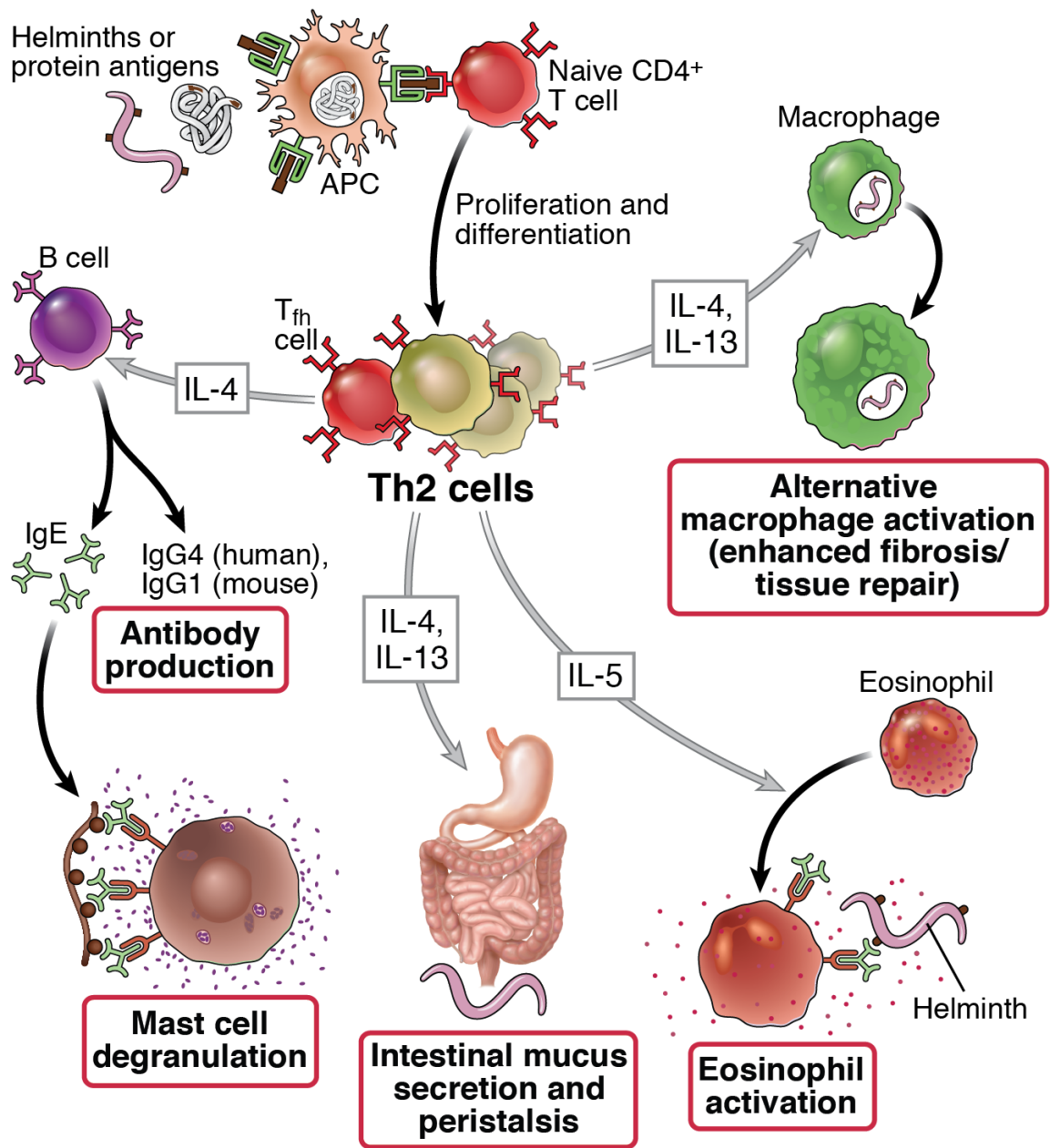
CD4+ T cell subsets: definitions and general properties

- 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

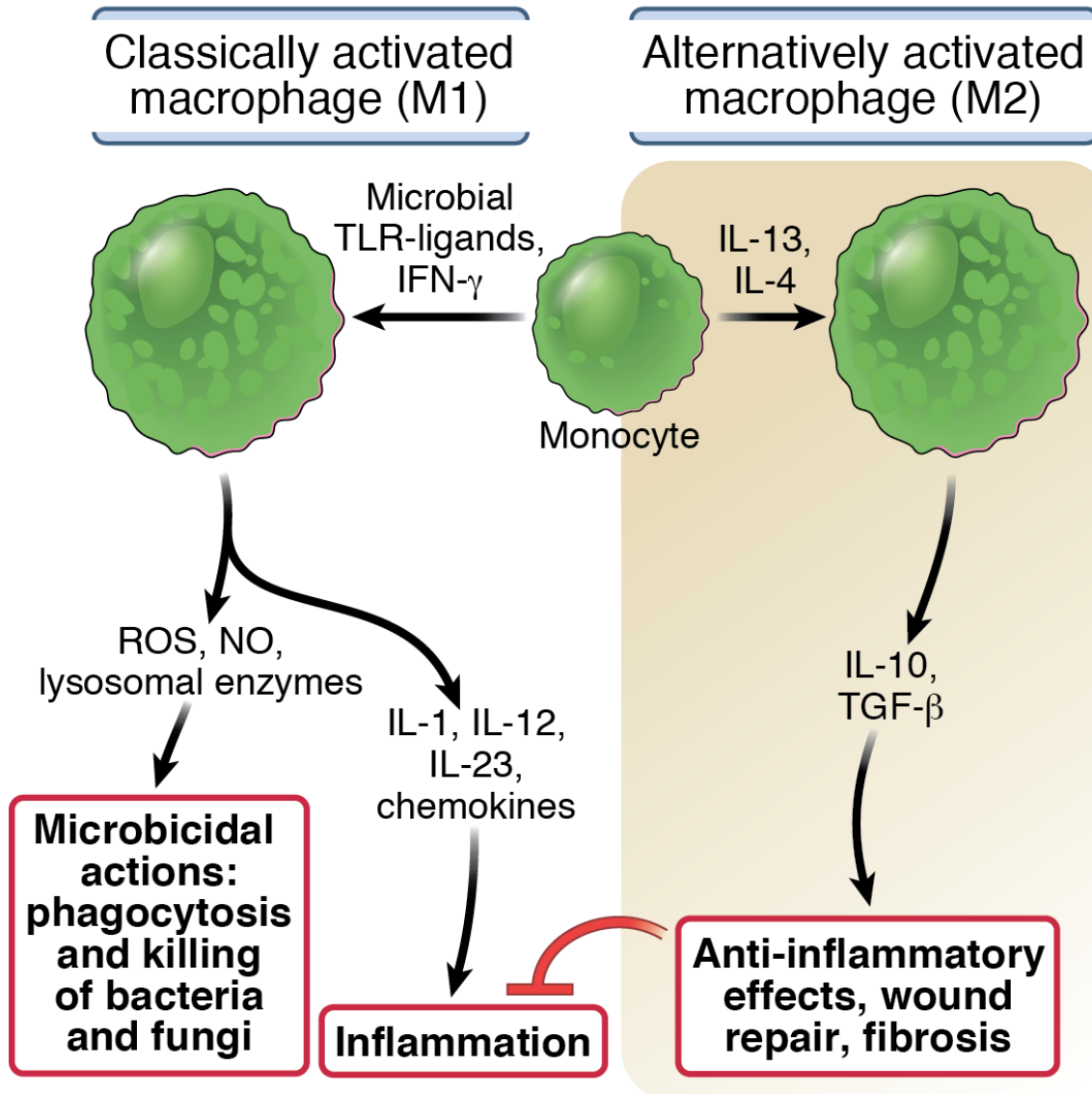
Effector functions of T_H1 cells: Phagocyte-mediated host defense



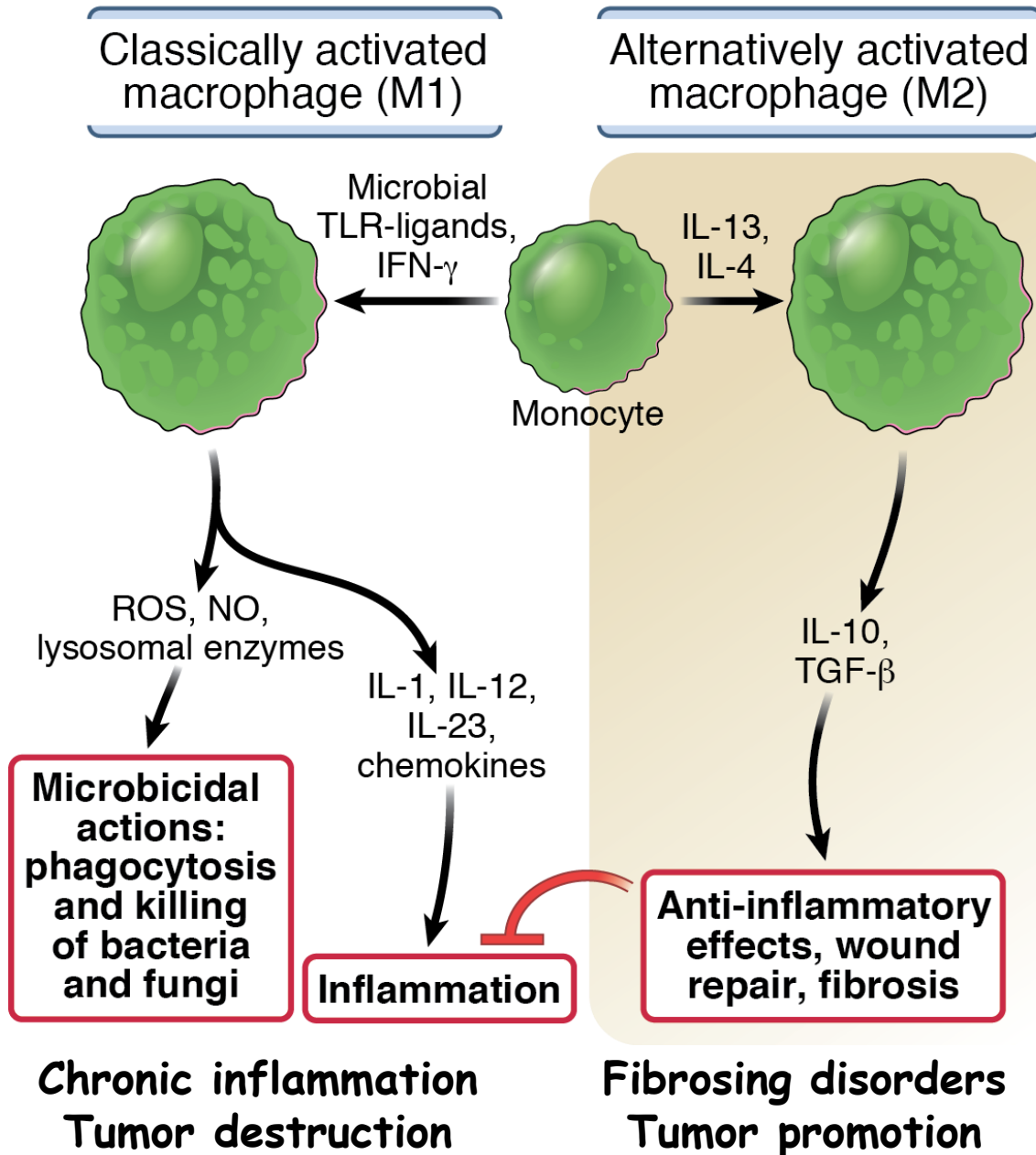
Effector functions of T_H2 cells



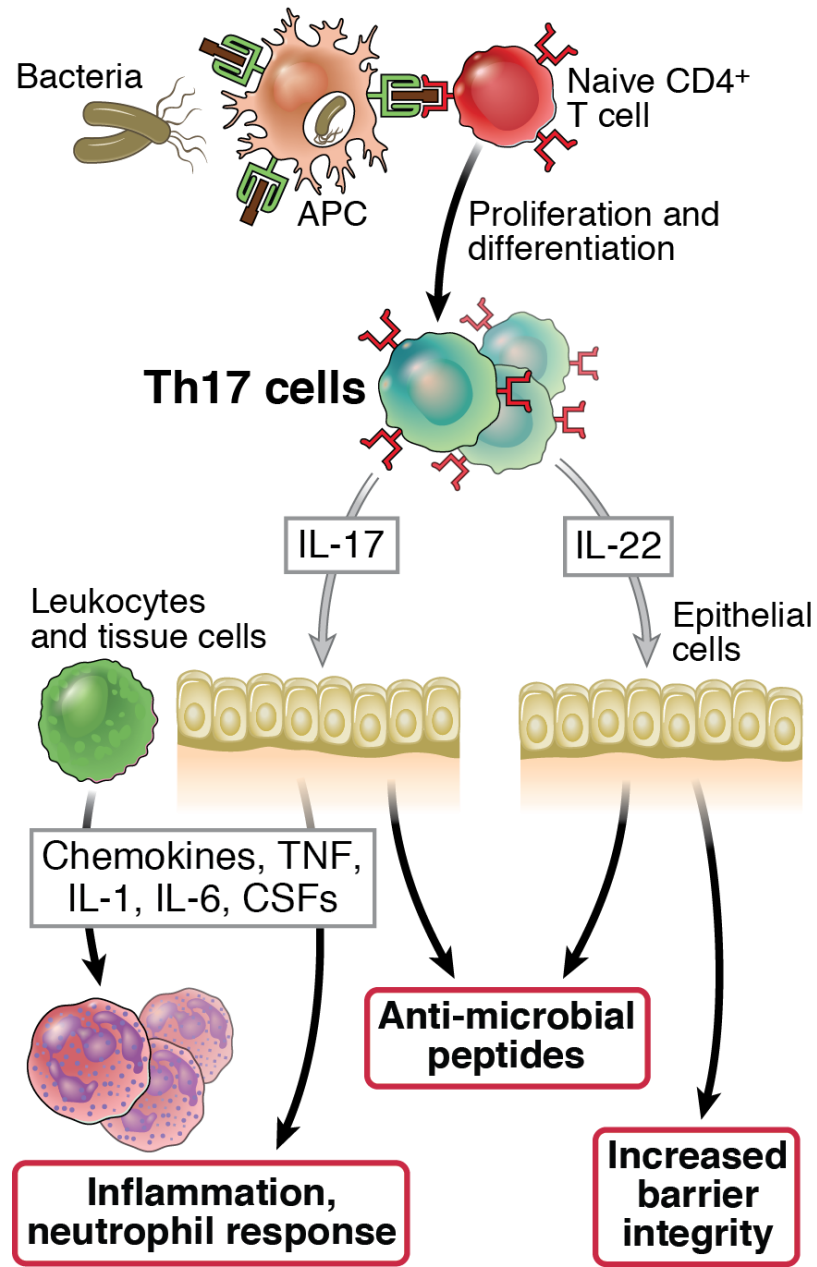
Classical and alternative macrophage activation



Classical and alternative macrophage activation



Effector functions of T_H17 cells



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”)

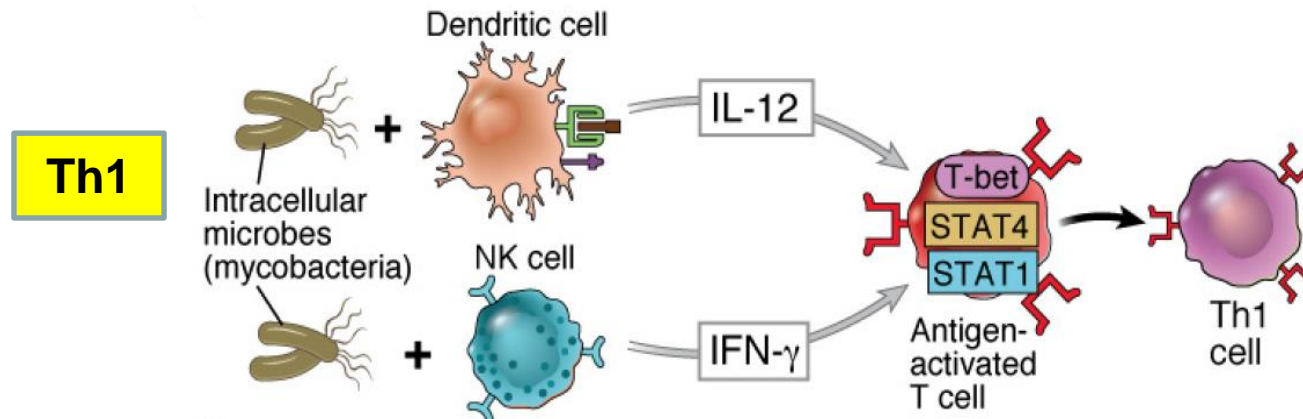
Roles of T cell subsets in disease

- **Autoimmune inflammatory diseases (psoriasis, MS, RA?, IBD?): Th1, Th17 and Tfh cells**
 - Cytokines induce inflammation and activate neutrophils and macrophages
 - Tfh cells stimulate antibody production
- **Allergies (e.g. asthma): Th2**
 - Stimulation of IgE responses, activation of eosinophils

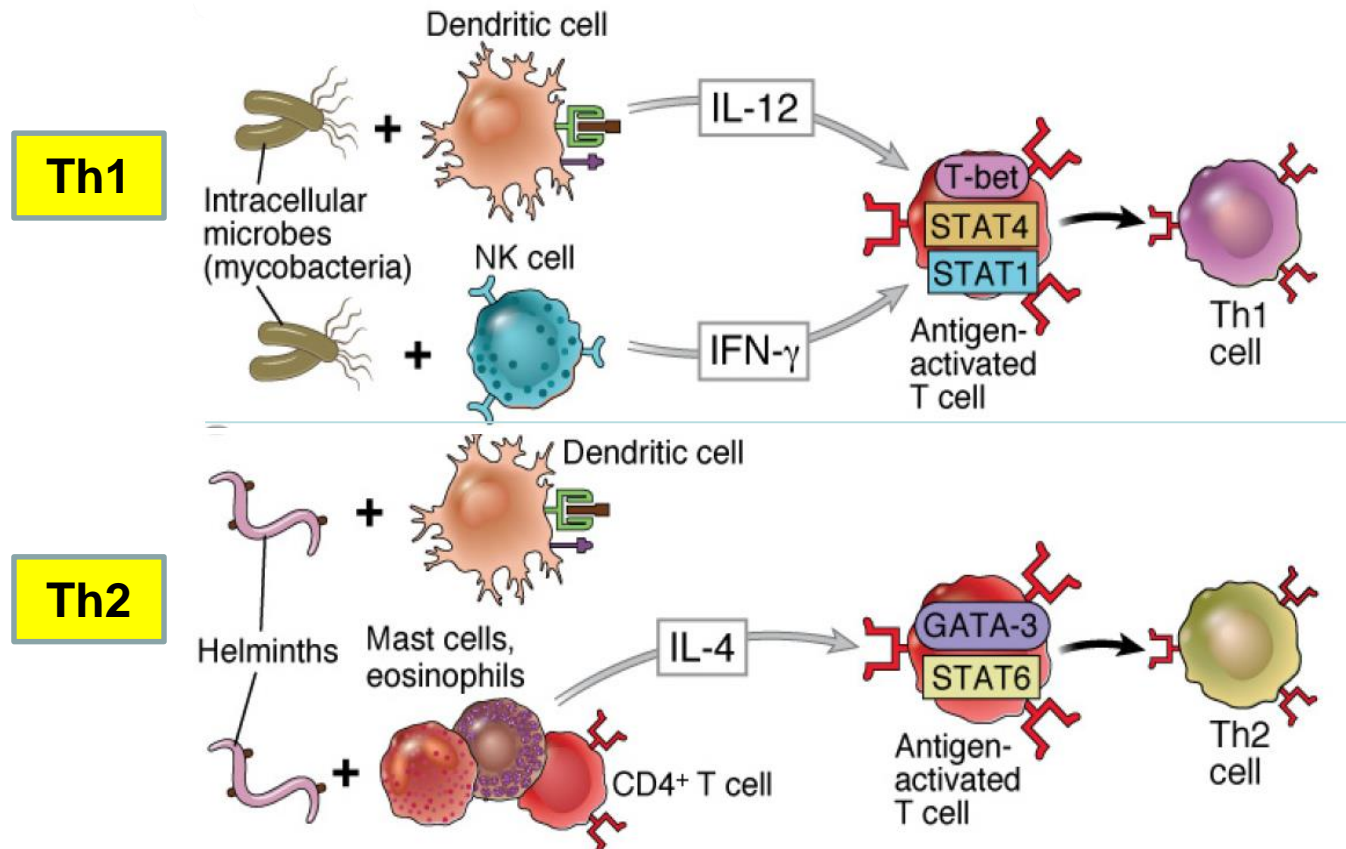
Therapeutic targeting of subset-specific cytokines

- 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

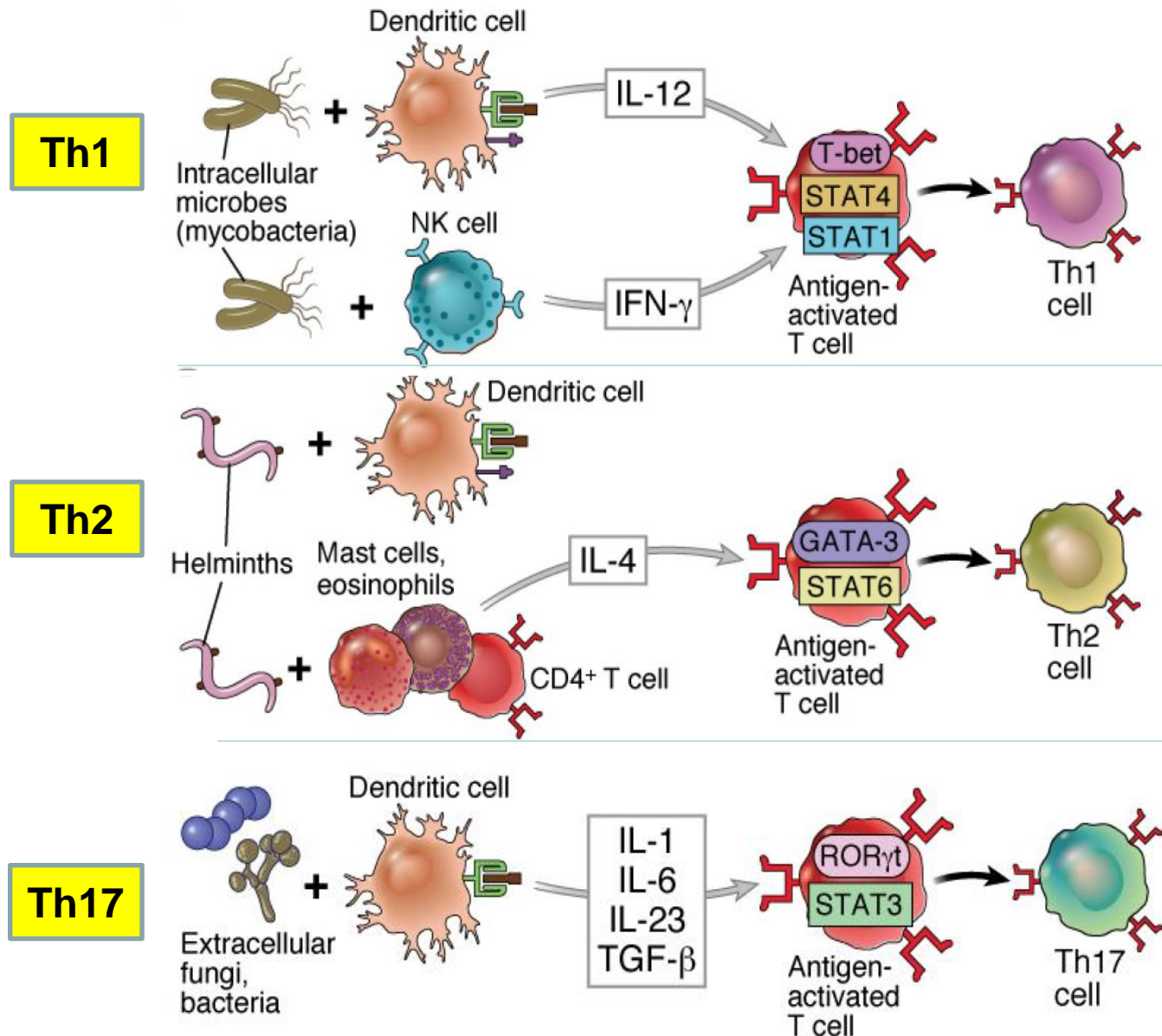
Th subset response is designed to combat different types of pathogens



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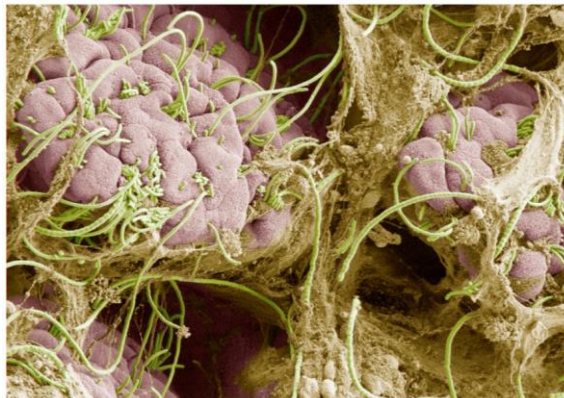


Th subset response is designed to combat different types of pathogens



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?