CD4+ T Cells and Types 1 , 2, 3 Immunity

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Lecture outline

- Overview of T cell responses and T cell mediated immunity
- Discovery and definition of Th subsets
- Functions of subsets and roles in human disease
- Additional considerations: hybrid subsets, plasticity, non-Th sources of types 1, 2, 3 cytokines
- Therapeutic targeting of subset cytokines

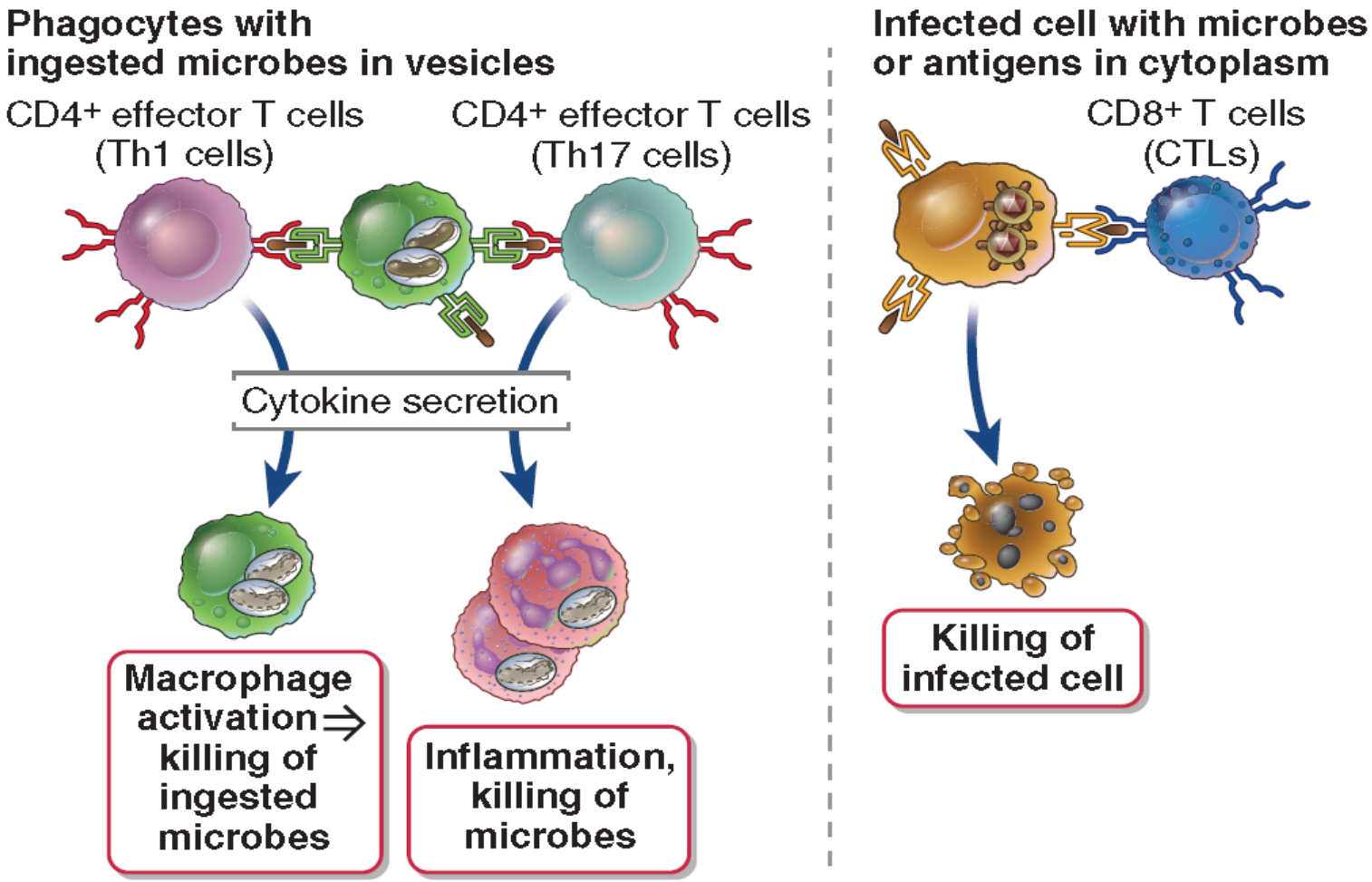
Types of T Cell–Mediated Immune Reactions

CD4+ helper T cells (Th)

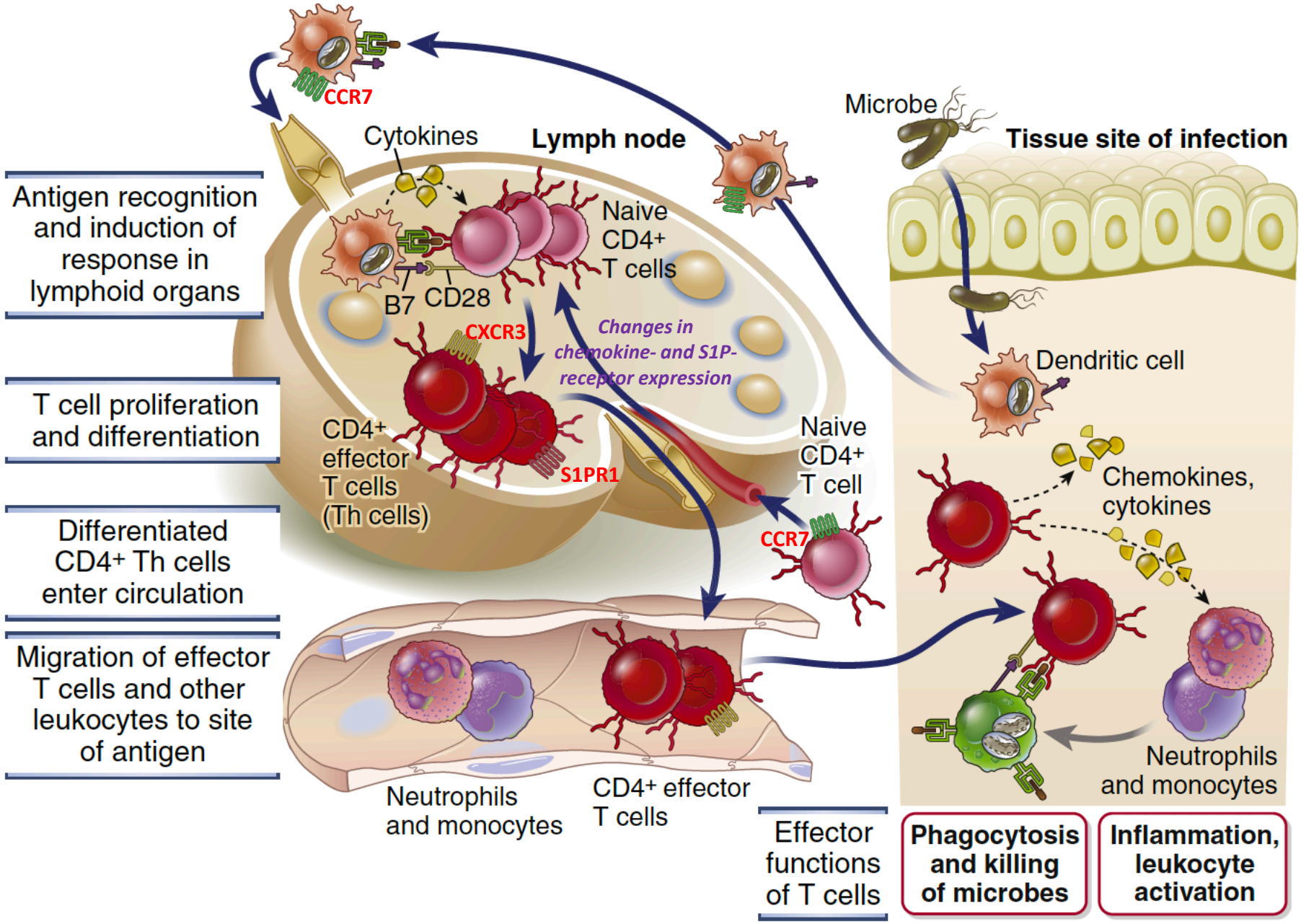
Microbes that live inside phagocytes
Microbes that are readily killed by phagocytes

CD8+ Cytotoxic T lymphocytes (CTL)

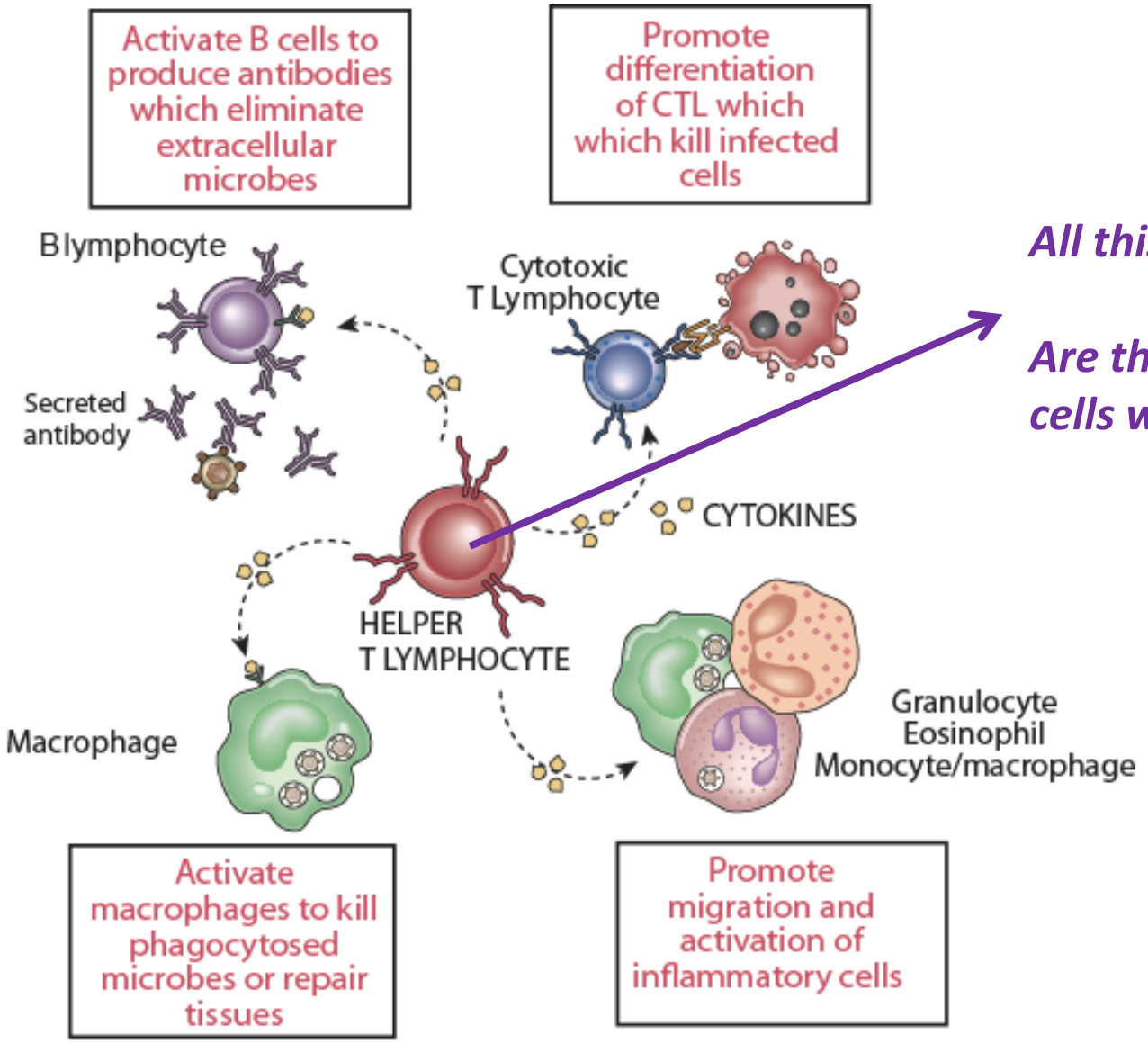
Microbes that live inside tissue cells



Steps in a CD4+ Helper T Cell Response



Cytokine-Mediated Functions of CD4+ Helper T Cells



All this done by one cell type?

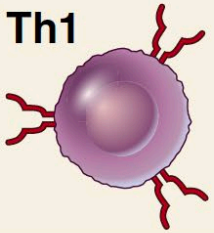
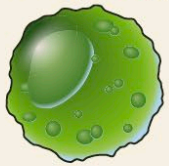
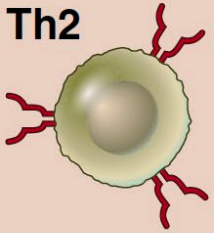
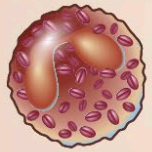
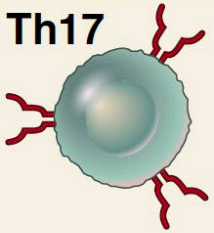
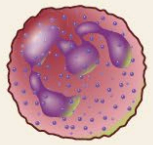
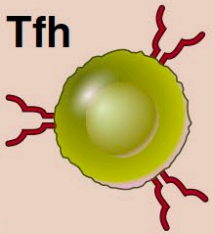
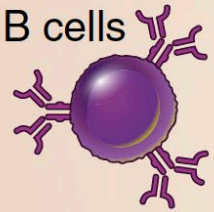
or

Are there subsets of helper T cells with different functions?

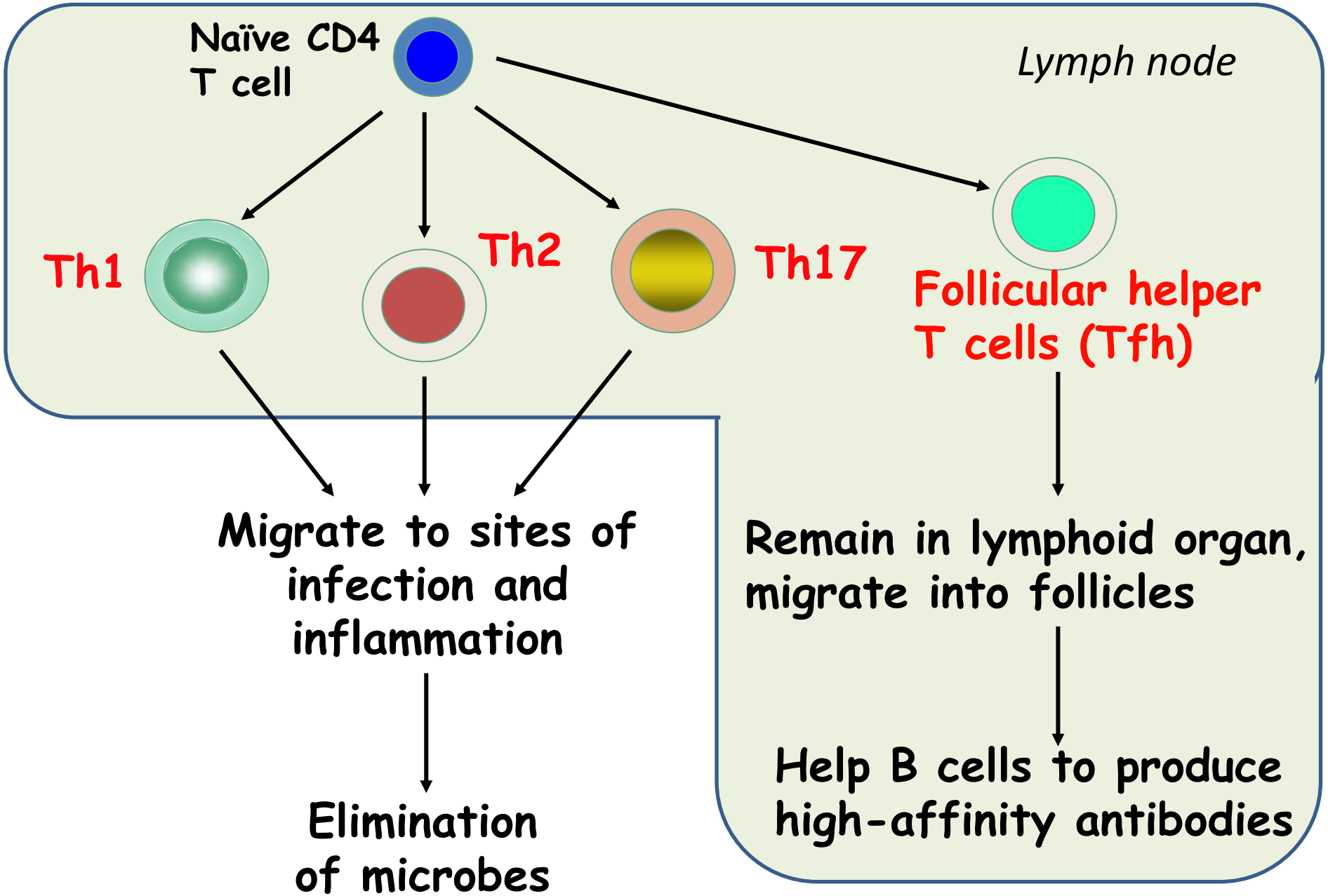
CD4+ Helper T cell subsets: Definitions and Properties

- Populations of CD4+ T cells that make restricted and non-overlapping sets of cytokines
- Distinct functions, migration properties, roles in disease
- Can be identified by gene or protein expression of:
  - Cytokines
  - Trafficking receptors
  - “Master” transcriptional regulators

Subsets of CD4+ Th Cells

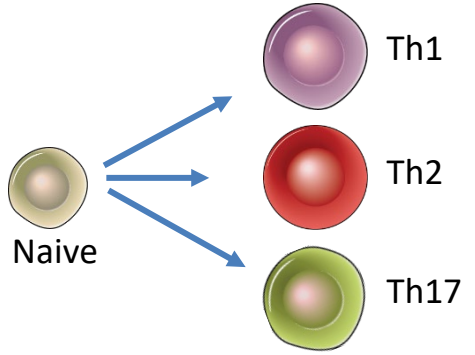
Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1 	IFN-γ	Macrophages 	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2 	IL-4 IL-5 IL-13	Eosinophils 	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17 	IL-17 IL-22	Neutrophils 	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh 	IL-21 (and IFN-γ or IL-4)	B cells 	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

CD4 Effector T Cell Subsets

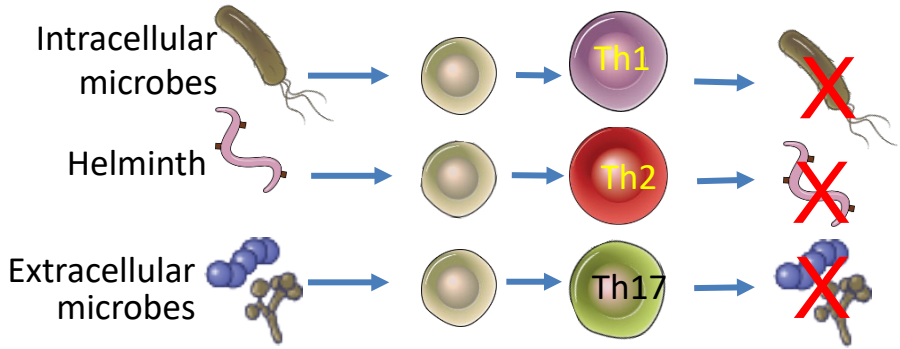


Differentiation of Th Subsets

Different subsets develop from uncommitted naïve CD4+ T cells

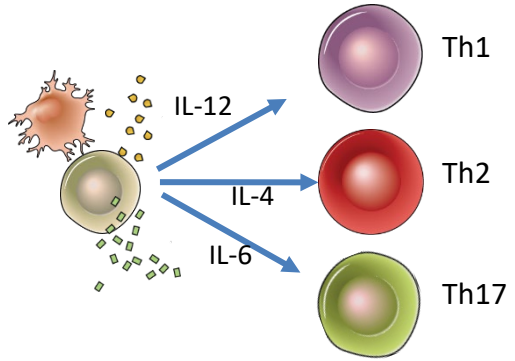


Each subset is induced by the types of microbes that subset is best able to combat



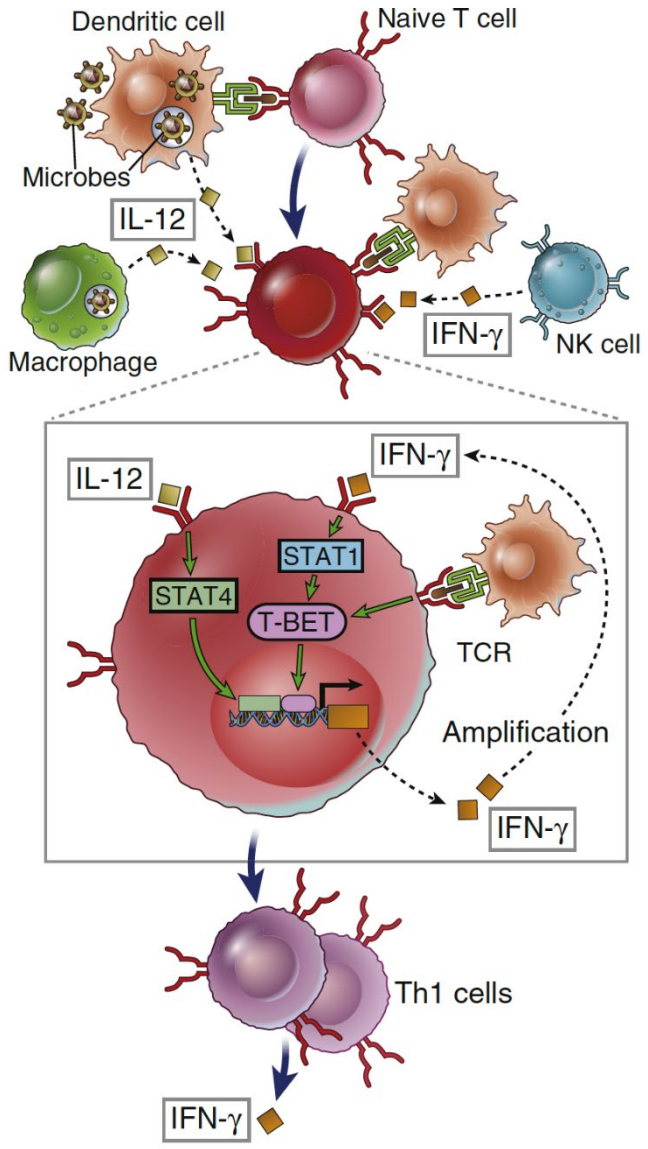
Cytokines produced at the site of antigen recognition drive differentiation into one or the other subset

Sources of cytokines that drive differentiation: APCs, responding T cells themselves, other host cells



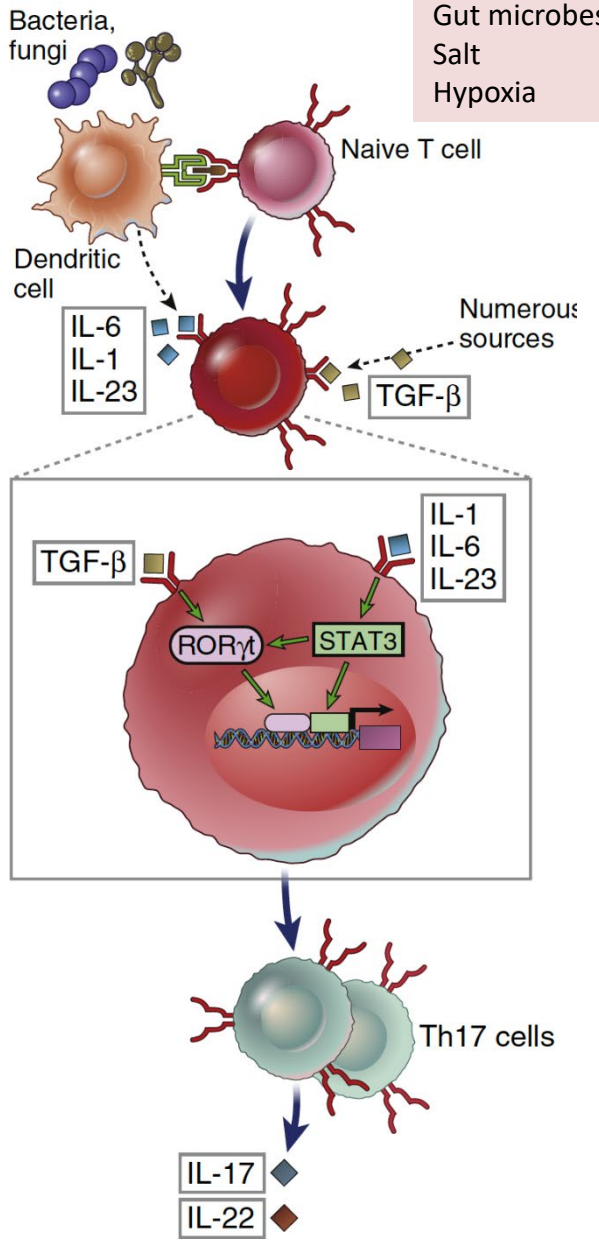
Differentiation of Th Subsets

Th1



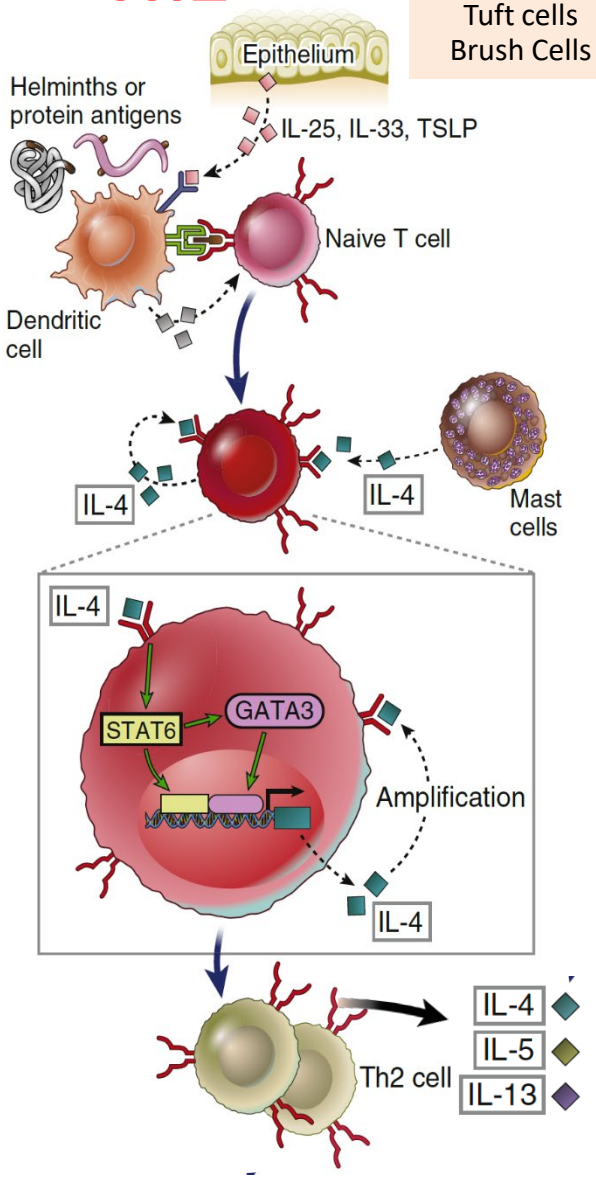
Th17

Fever
Gut microbes
Salt
Hypoxia



Th2

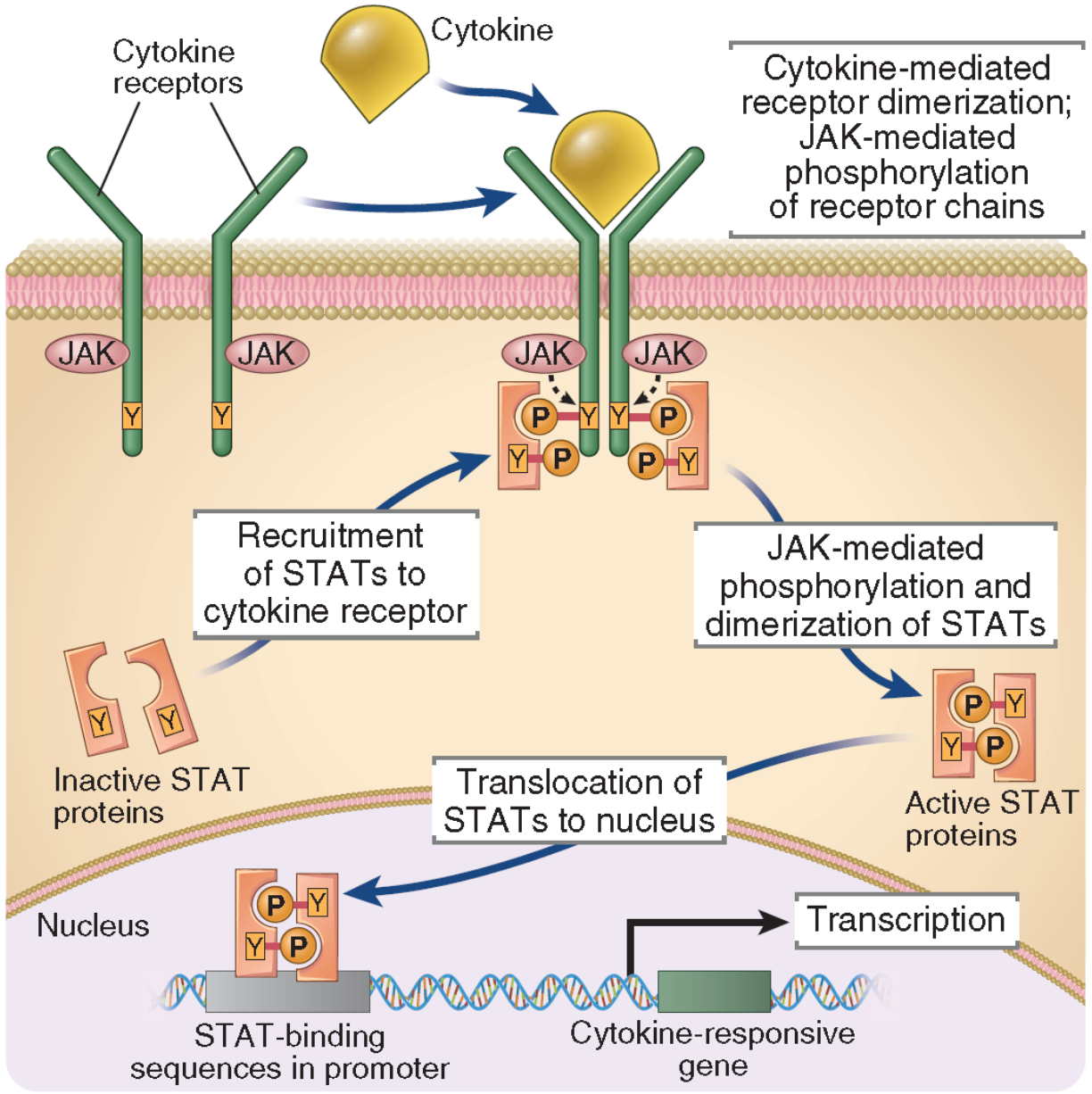
Injury
Tuft cells
Brush Cells



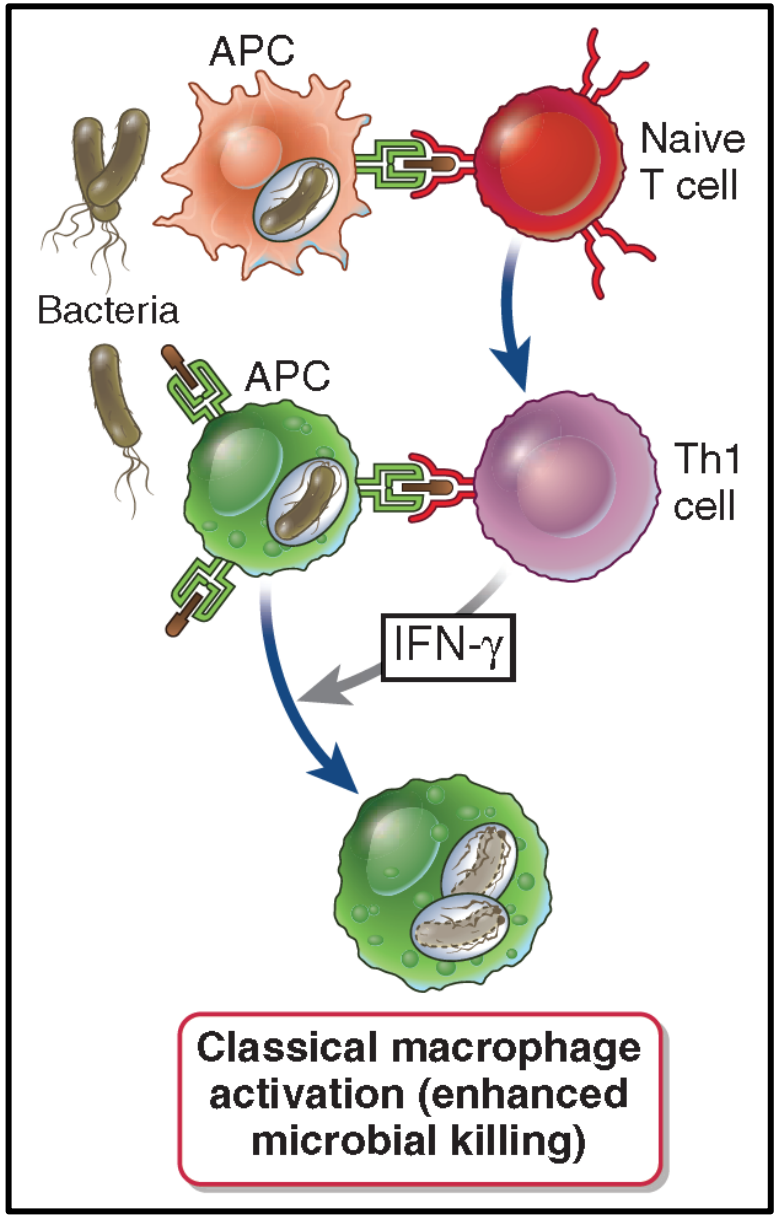
JAK-STAT Cytokine Signaling

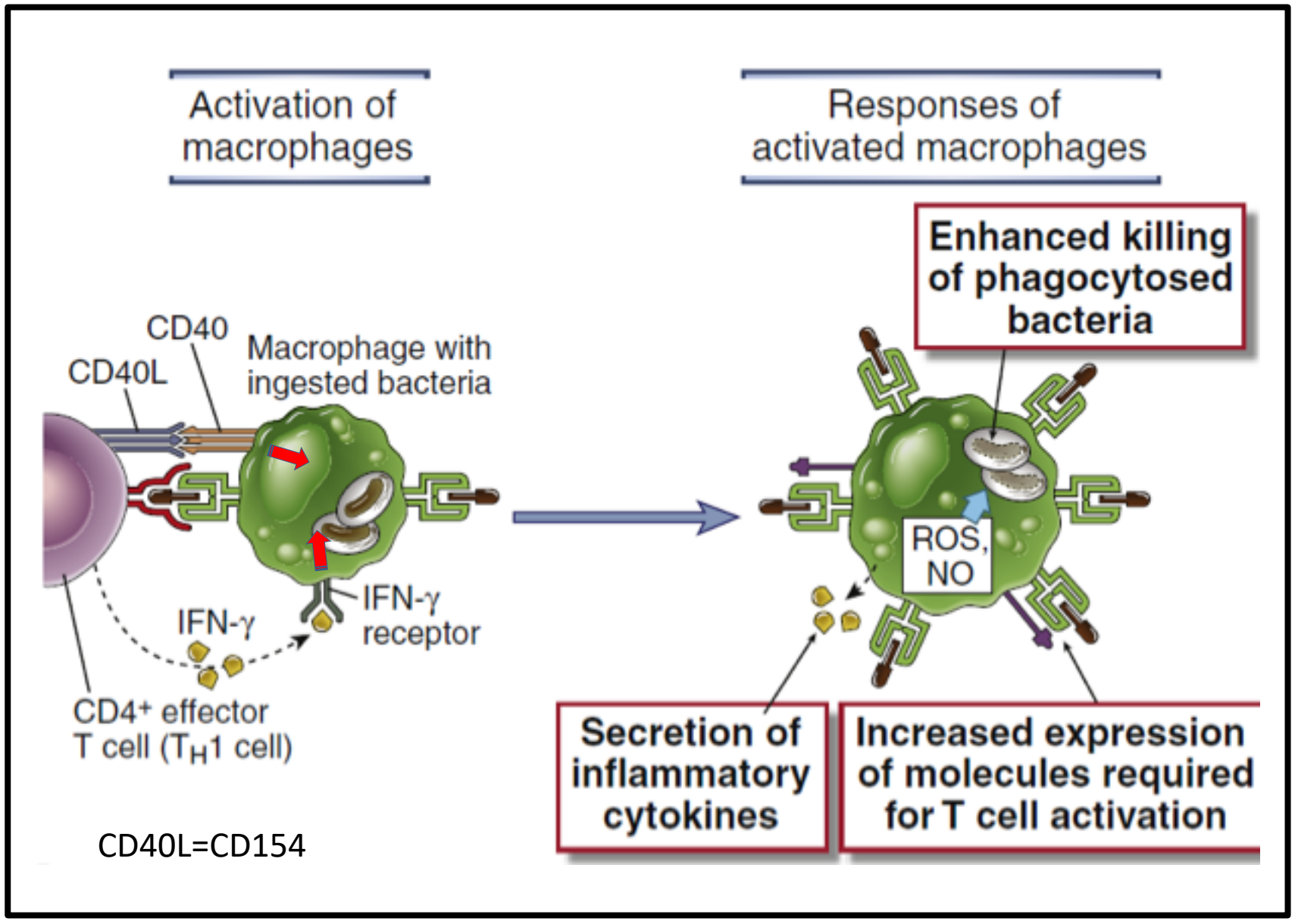
JAKS
Jak1
Jak2
Jak3
Tyk2

STATS
STAT1
STAT2
STAT3
STAT4
STAT5 (A and B)
STAT6



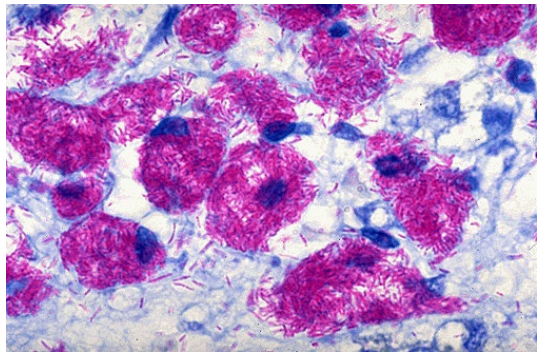
The Functions of Th1 Cells: Macrophage Activation



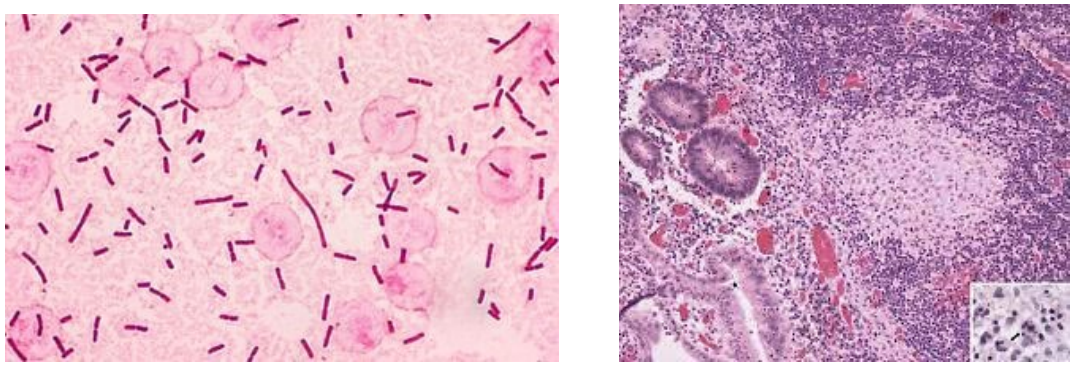


Human T_H1 cells: defense against intracellular microbes

- **Mendelian susceptibility to mycobacterial disease (MSMD):** inborn errors of IFN-γ mediated immunity
  - Mutations in genes encoding IL-12 receptor, IL-12, IFN-γ receptor, IFN-γ signaling molecules
- Most common infections are with microbes that can live inside phagocytes: *Mycobacteria, Salmonella*
- *IL-12 and IFN-γ required for Th1 differentiation; IFN-γ required for Th1 function (macrophage activation)*

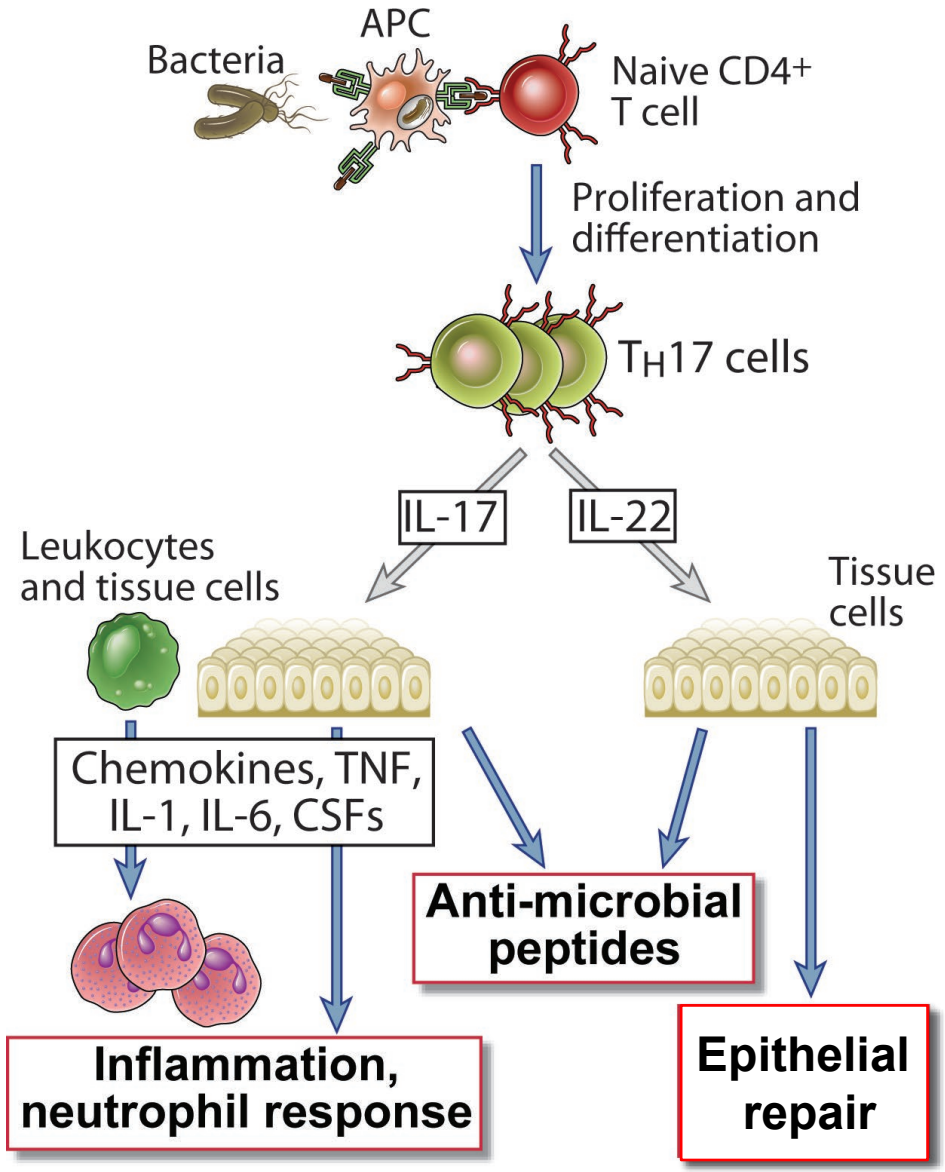


Mycobacteria

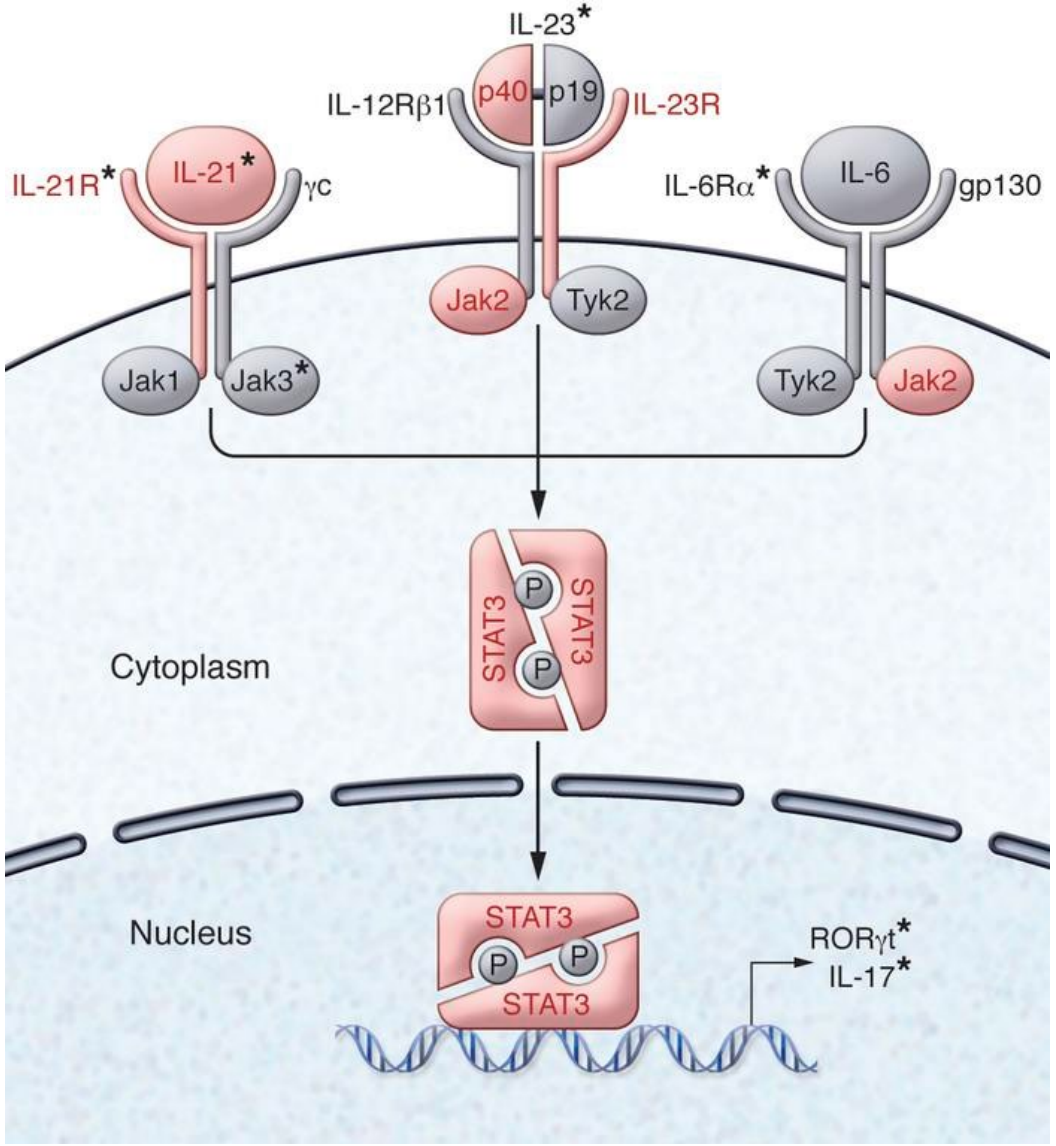


Salmonella

Functions of T_H17 cells



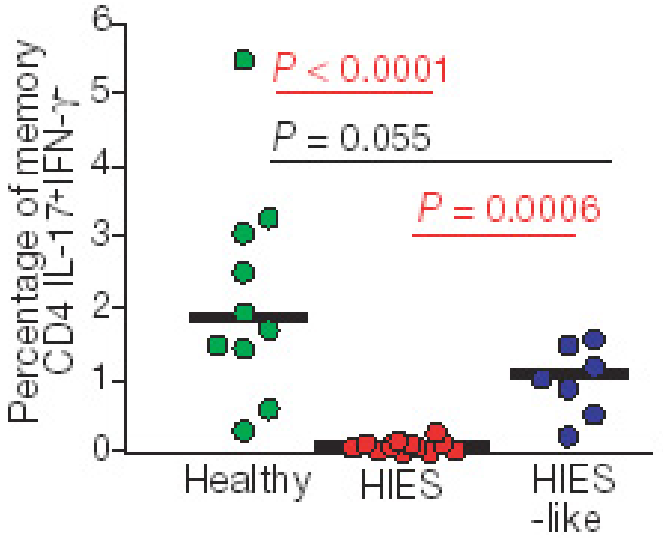
STAT3-dependent cytokines in Th17 differentiation



Burkett PR, Meyer zu Horste G, Kuchroo VK. J Clin Invest. 2015;125:2211-9

What is the function of human T_H17 cells?
…required for defense against extracellular microbes

- Human Stat3 mutations result in HIES*, characterized by infections, as well as many other clinical manifestations
  - Recurrent staphylococcal abscesses or mucocutaneous candidiasis
- HIES patients have impaired T_H17 responses.
- Supports role for T_H17 cells in resistance to extracellular bacterial and fungal infections



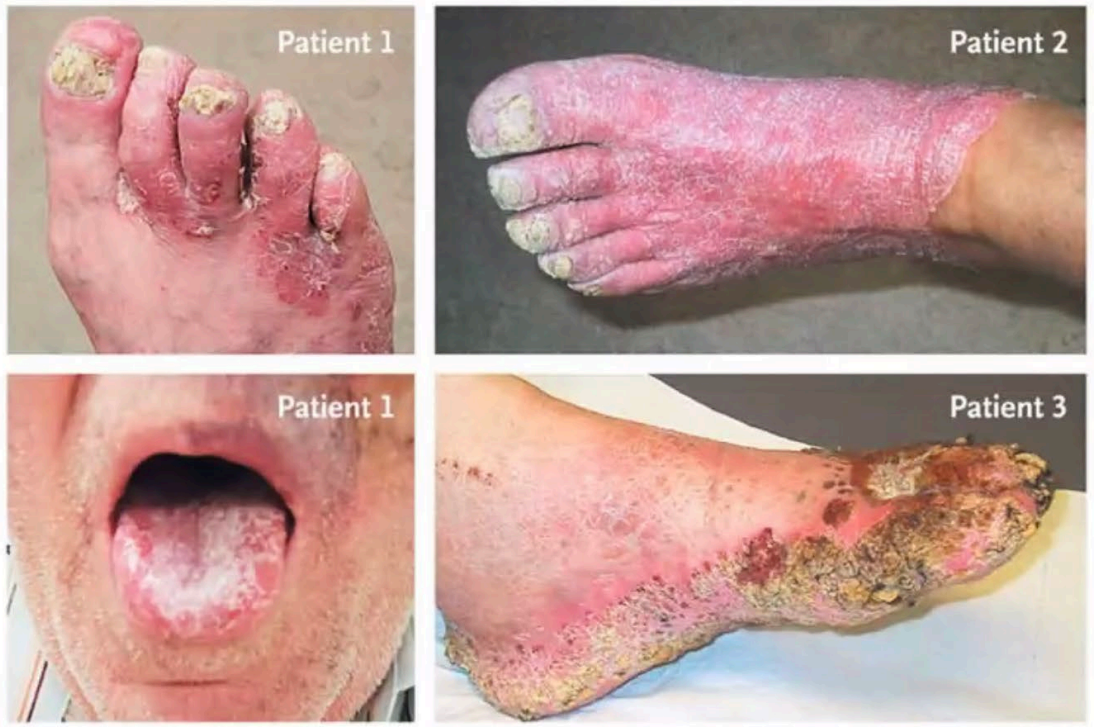
Milner JD et al
Nature 452, 773-776. 2008

*Hyper-IgE Syndrome, aka Job's syndrome

What is the function of human T_H17 cells?

…required for defense against extracellular microbes

CMC: Chronic mucocutaneous candidiasis (defective anti-fungal immunity)

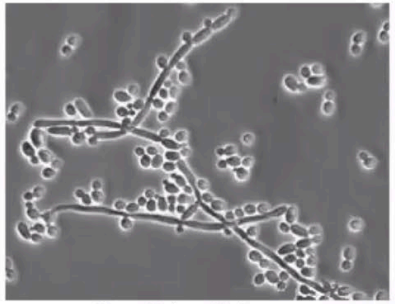


Van de Veerdonk FL, et a. NEJM. 2011. 365:54.

Genes:
Dectin-1, CARD9
Th17 biology (IL-17F, IL-17RA, IL-17RC, ACT1, STAT3, RORγt)

STAT1 hyperactivation

Cytokine autoantibodies



Candida albicans

What are the functions of human Th1 vs. Th17 cells?

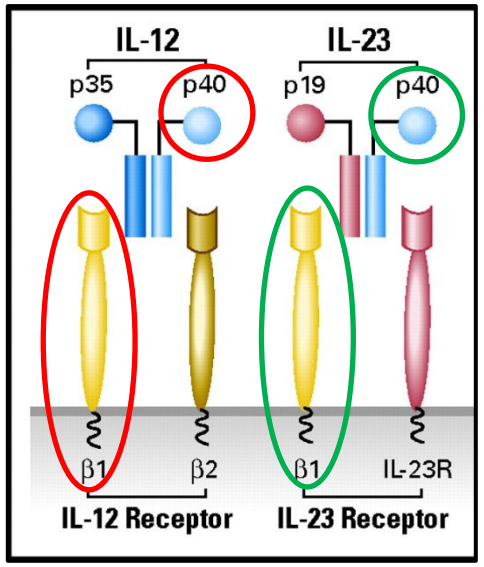
- Mendelian susceptibility to mycobacterial disease (MSMD): inborn errors of IFN-γ immunity.
- Some genes involved: IL-12Rβ1, IFN-γR1, IL-12p40, IFN-γR2, STAT-1, IRF8,
- Most common infections with deficiencies in IFN-γR and STAT1:
  BCG, environmental mycobacteria, M. tuberculosis, Salmonella
- Most common infections with deficiencies of IL-12p40, IL-12Rβ1:
  Mycobacteria, Salmonella, Candida

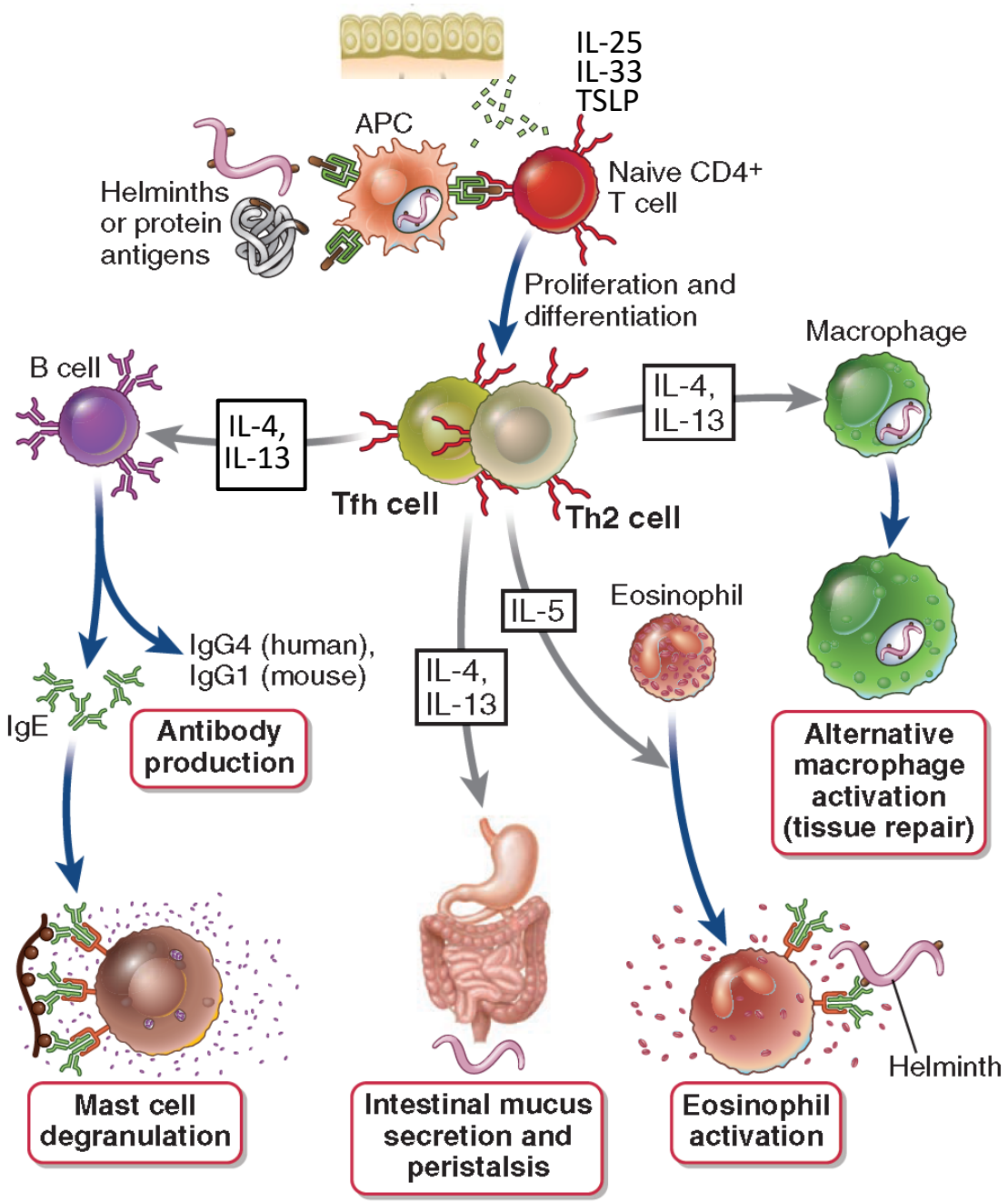
Why both intracellular and extracellular infections in IL-12p40 and IL-12Rβ1 deficiencies?

- p40 shared by IL-12 and IL-23
- IL-12Rβ1 shared by both IL-12R and IL-23R

- IL-12 needed for Th1 differentiation
- IL-23 needed for Th17 differentiation

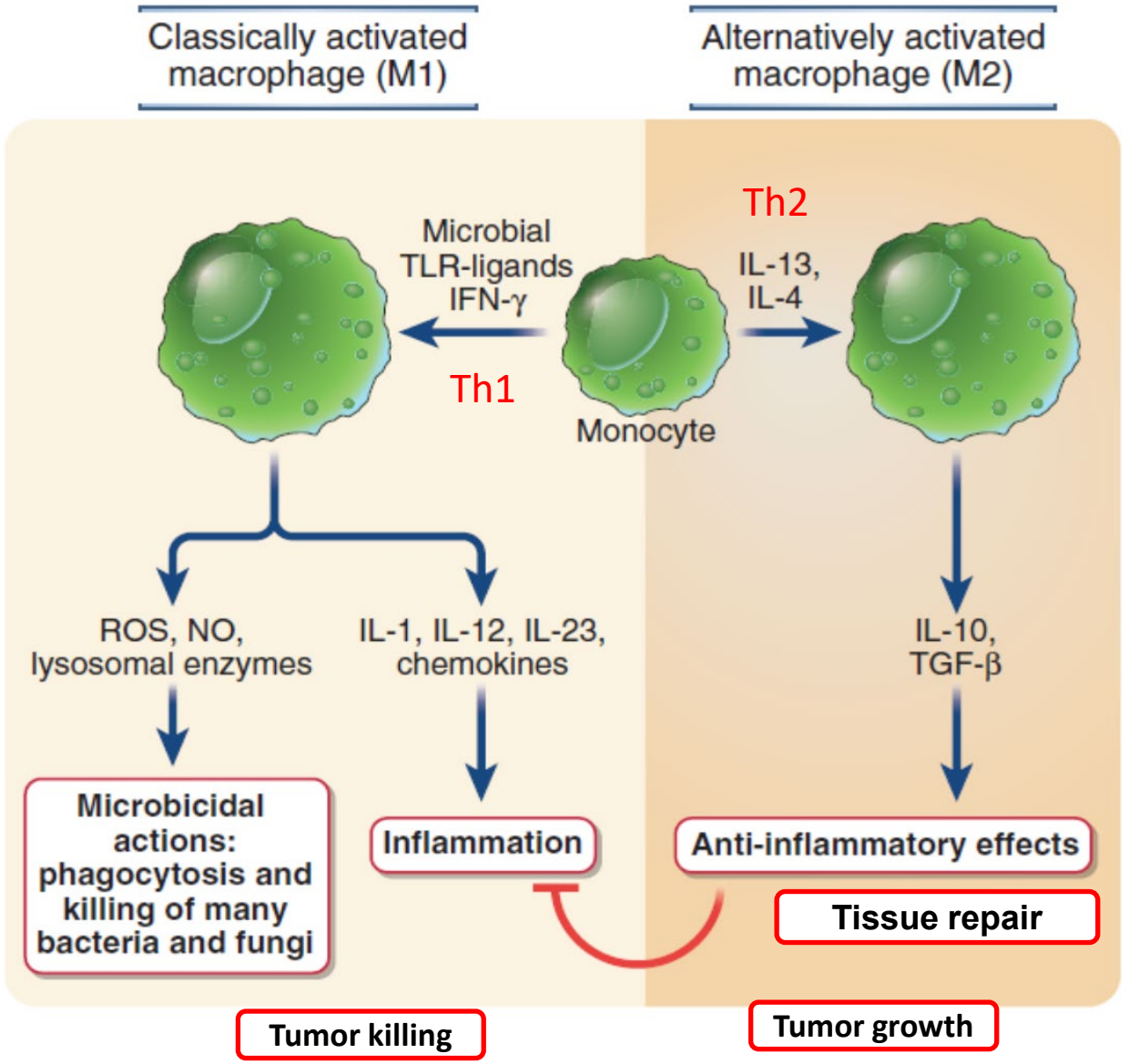
Implications for mAb drug therapies





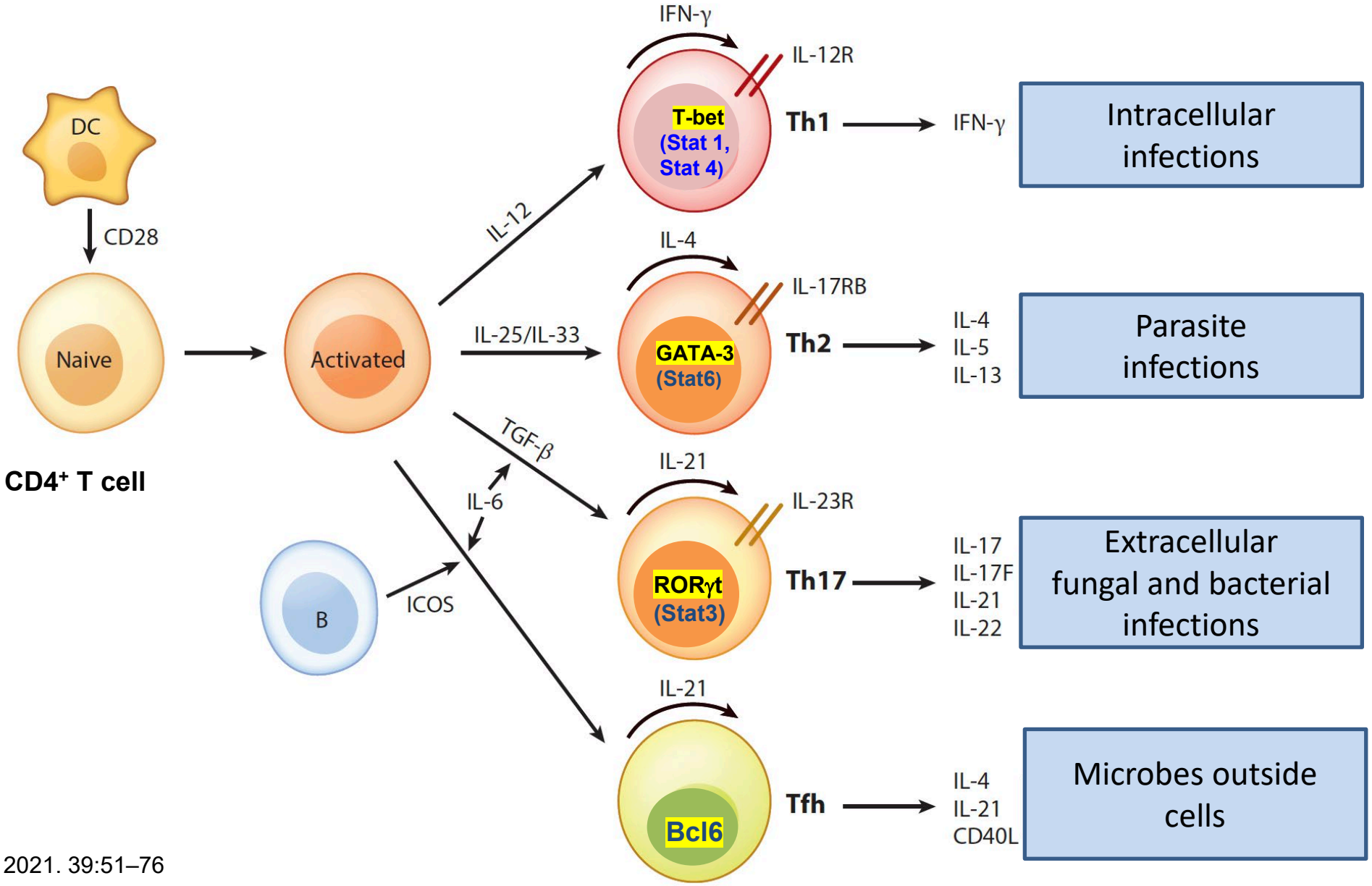
Functions of T_H2 Cells

Macrophage Activation: Classical & Alternative



Th differentiation:

Summary of Cytokines and Transcription Factors Involved



Chen Dong
Annu. Rev. Immunol. 2021. 39:51–76

The real story about Th subsets is more complicated!

- *Additional subsets related to classic subsets*
- *Other sources of the same helper cytokines besides CD4+ Th cells*
- *CD4+ Th cells that blur Th 1, 2, 17 distinctions*
- *Plasticity of Th subsets*

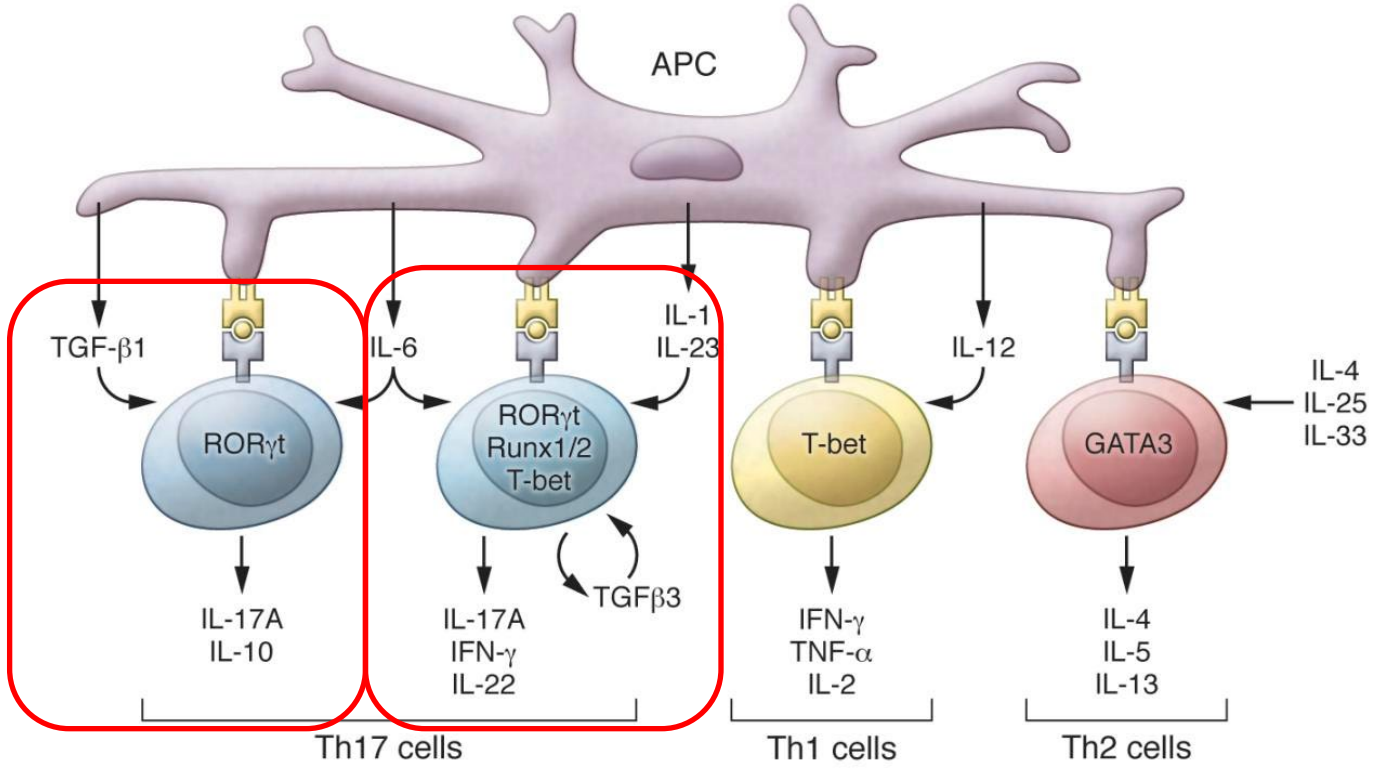
Th cells that make both IL-17 and IFN-γ are important in defense and disease

- Bi-allelic loss-of-function mutations in *RORC* (encodes RORγT) result in candidiasis and mycobacteriosis[#]
- Patients lack IL-17A/F-producing T cells (expected)…explains candidiasis
- Patients also have impaired IFN-γ response to mycobacterium (unexpected). IFN-γ production is impaired in:
  - γδ T cells
  - Th1* (a.k.a "nonclassic Th17) subset:
    αβ TCR, $CD4^+$ T bet^+ $ROR\gamma T^+$ IFN-γ^+, IL-17A$^+$ CCR6$^+$,CXCR3$^+$

[#]Okada S… Casanova JL. Science. 2015.349:606-13.

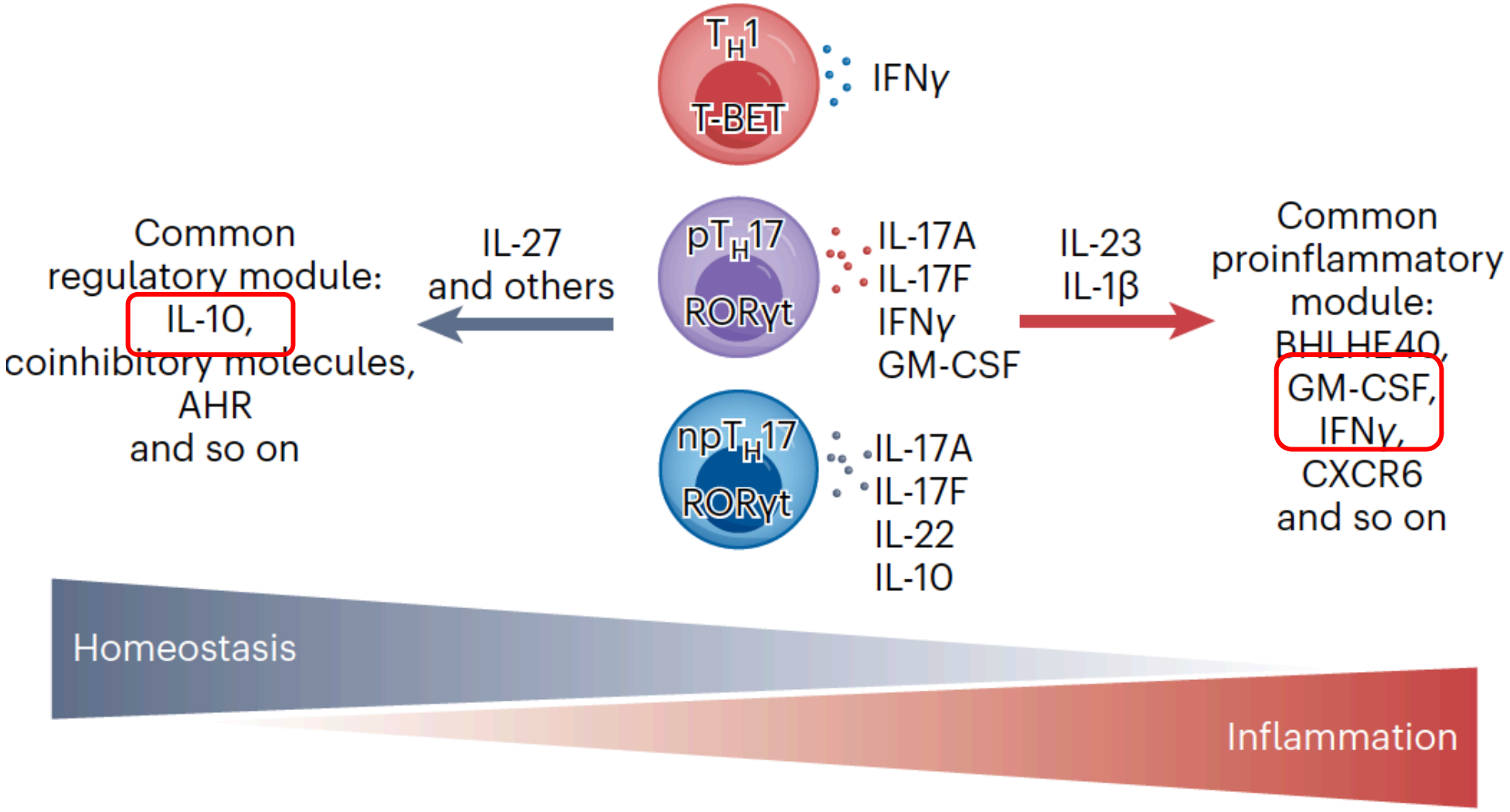
Dual IFNγ/IL-17 producing Th cells (Th1*) may be the major pathogenic effectors in many diseases[#]

- Can be derived from already differentiated classic Th17 cells in response to **IL-23**
- More abundant than Th1 or Th17 at sites of inflammation in mouse model diseases (EAE) and human diseases (Crohn's, atherosclerosis)



[#] see: Burkett PR, Meyer zu Horste G, Kuchroo VK. J Clin Invest. 2015;125:2211-9

Homeostatic and Pathogenic Cells Related to Th17 cells

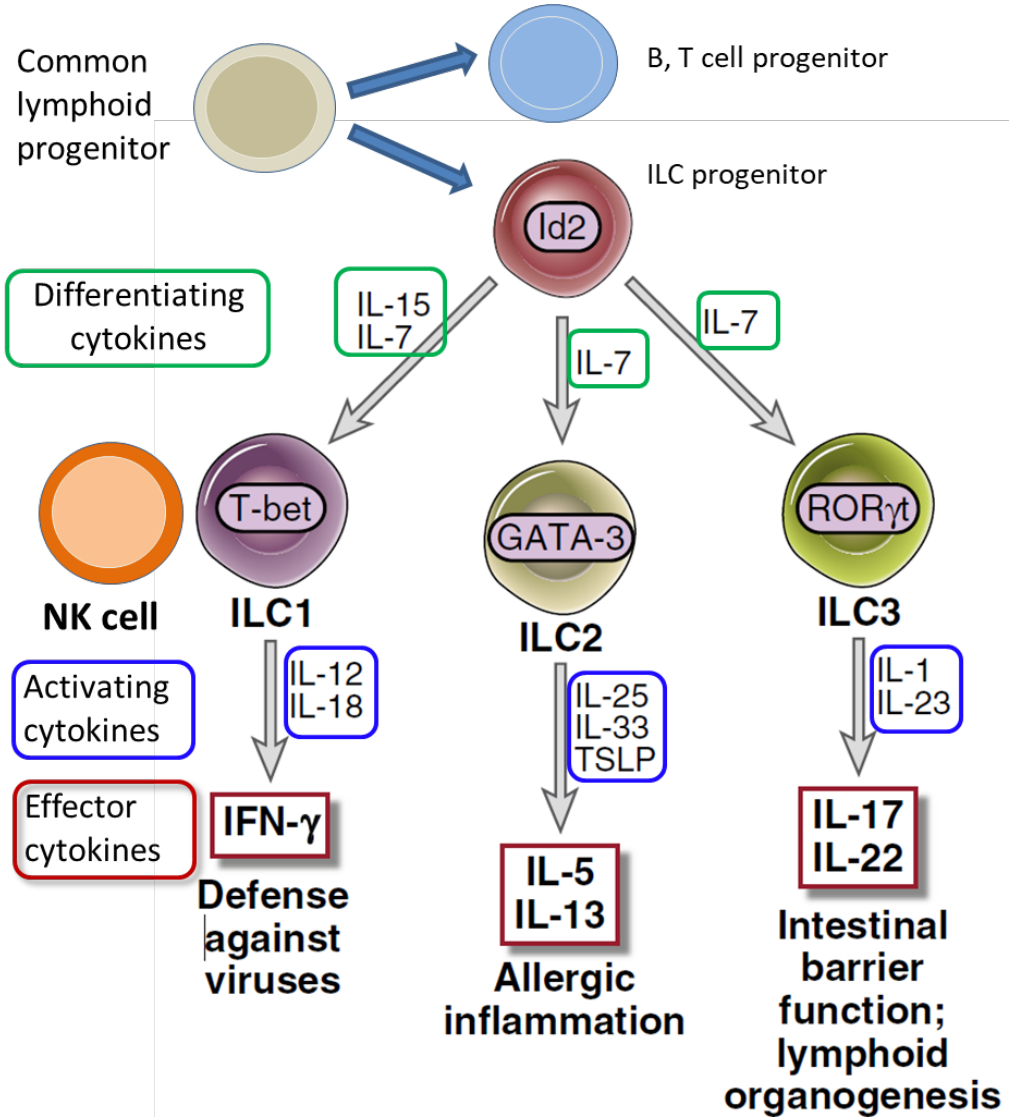


Alexandra Schnell 1,2, Dan R. Littman3,4 & Vijay K. Kuchroo 1,2 TH17 cell heterogeneity and its role in tissue. Inflammation. Nature Immunology Review 2023

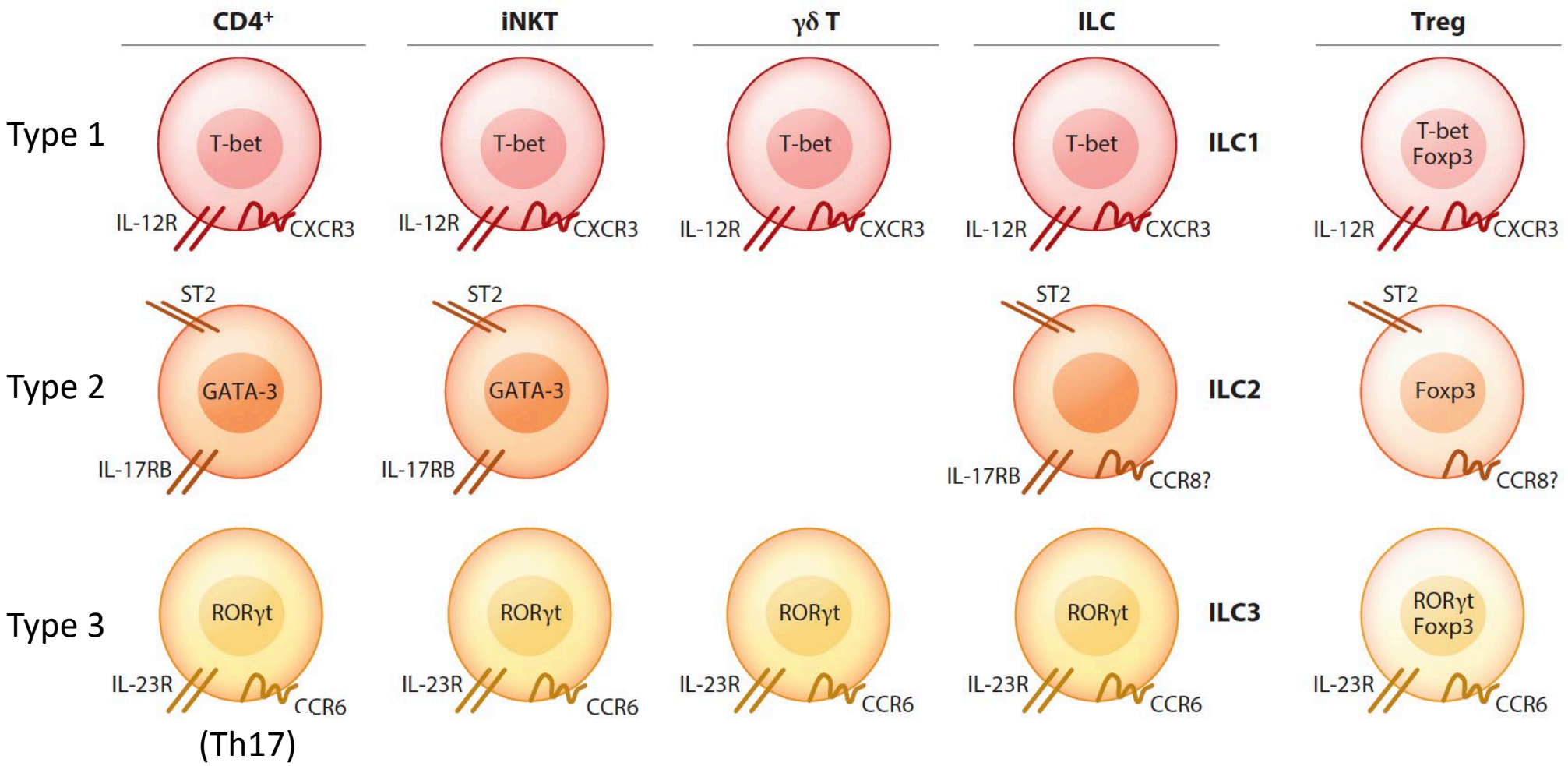
Other sources of the same helper cytokines besides CD4+ Th cells

Innate Lymphoid Cells

- *No T cell or B cell antigen receptors*
- *Activated by cytokines*
- *Effector functions mediated by cytokines*
- *Subsets analogous to helper T cell subsets*
- *Present in tissues before infection-- contribute to early cytokine responses in host defense and inflammatory diseases*



Types 1, 2, 3 cells beyond Th's



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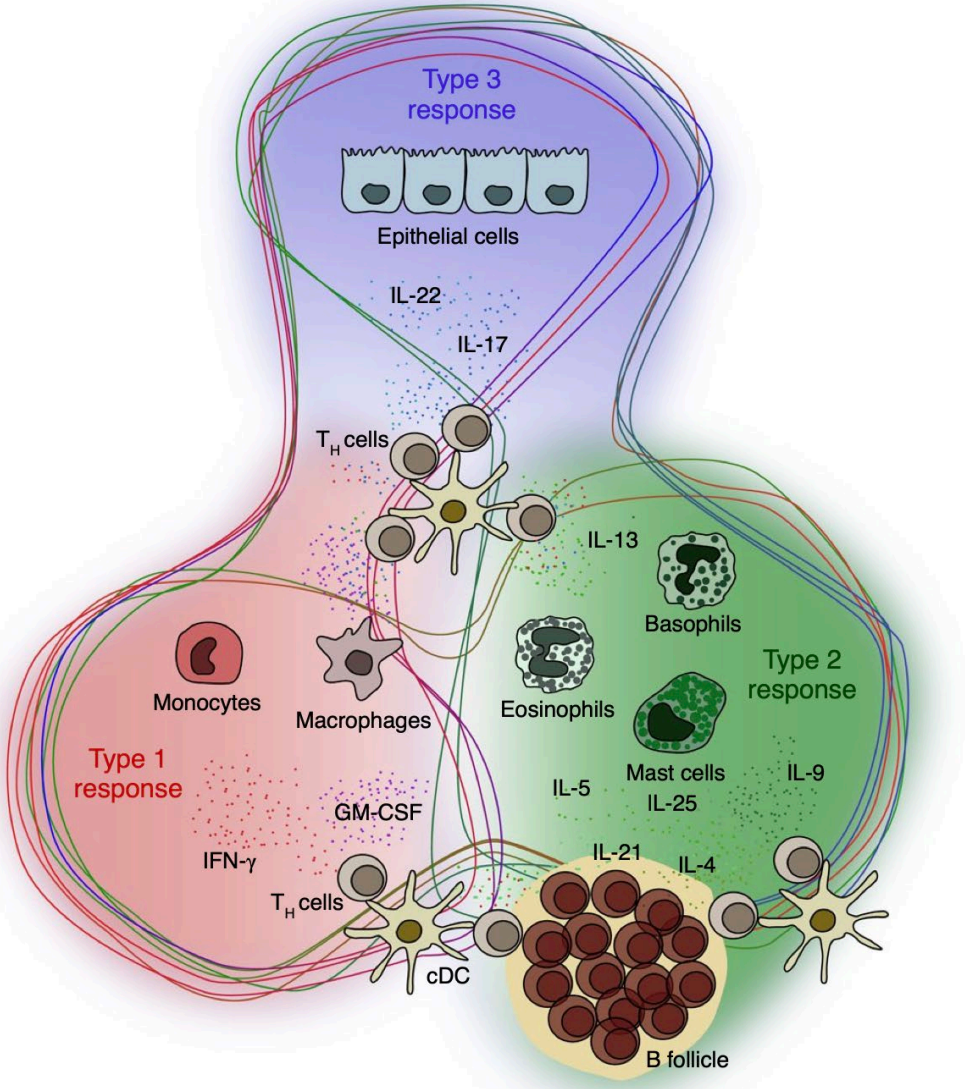
Other sources of the same helper cytokines besides CD4+ Th cells

Non-Th17 Sources of IL-17 in Inflammatory Diseases

- **γδ T cells: Psoriasis**
- **CD8+ T cells: Psoriasis**
- **Neutrophils: Arthritis, Dermatitis**
- **iNKT cells: Various**
- **ILCs: Inflammatory bowel disease**

Anti-IL-17 therapy would theoretically apply to of all of these

Types 1 ,2 and 3 Immunity Model based on Target cells



Orbital model based on Th cell targets

- Type 1 cells that primarily activate and attract mononuclear phagocytes such as monocytes, macrophages and DCs (Th1, ILC1, NK, CTL)
- Type 2 cells targeting B cells, mast cells, basophils, and eosinophils (Th2, TH9, ILC2,)
- Type 3 cells acting on non-hematopoietic cells at barrier tissue sites, including epithelial cells and stromal cells (Th17, ILC3, Th22, CD8 T cells)

Tuzlak, S. et al. Repositioning TH cell polarization from single cytokines to complex help. Nat. Immunol. (2021).

mAb Targeting Type Type 1 , 2, and 3 Diseases

Type 1

- IFN-γ: Primary HLH (Emapalumab)

Type 2

- IL-5: Eosinophilic asthma (Reslizumab, Mepolizumab)
- IL-13: Atopic dermatitis (Tralokinumab)
- IL-13/4 receptor: Atopic dermatitis (Dupilumab)

Type 3

- IL-17A: Psoriasis, RA, Ankylosing spondylitis (Secukinumab)
- IL-17RA: Psoriasis, Psoriatic arthritis (Brodalumab)
- IL-23p19 Psoriasis (Guselkumab)

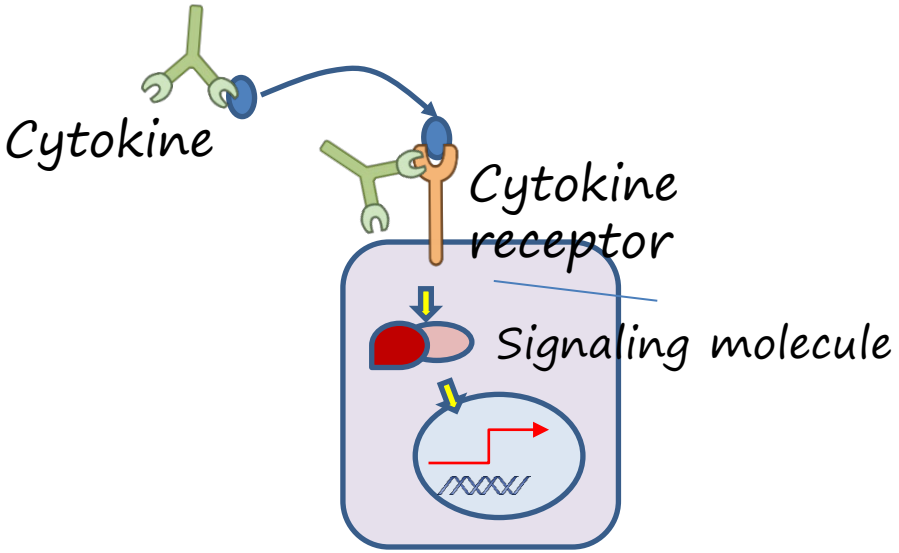
Type 1 and 3

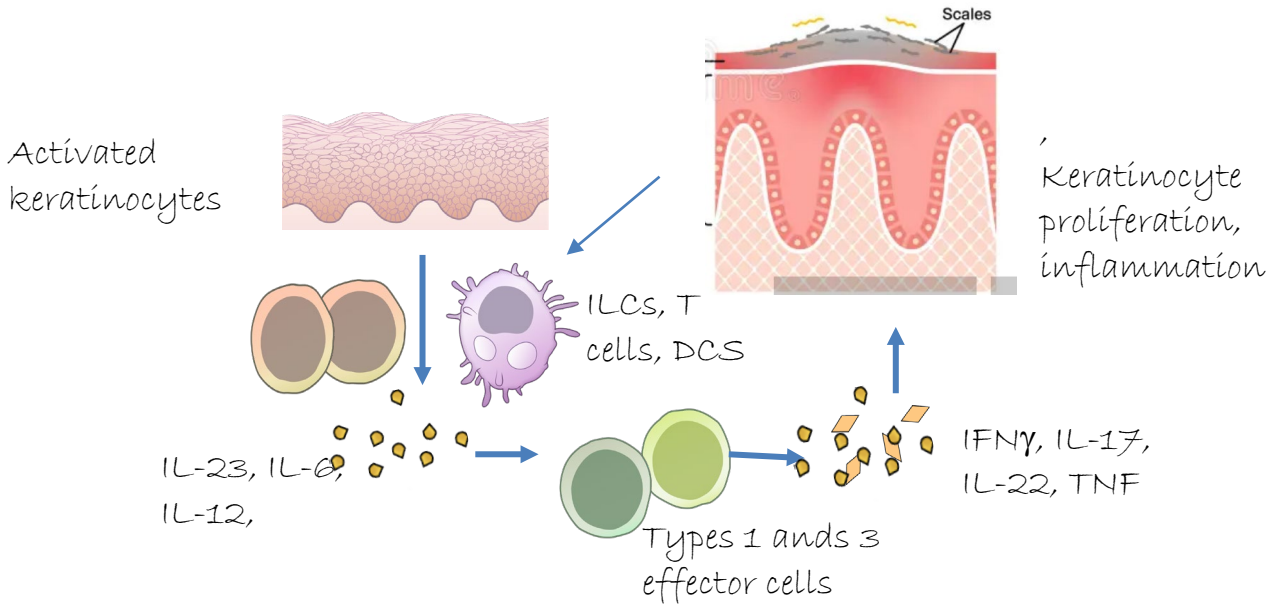
- IL-23 and IL12 p40: Psoriasis, Psoriatic arthritis (Ustekinumab)

Blocking the production or action of cytokines

Remarkable advances in treatment of many inflammatory diseases using mAbs that block cytokines or cytokine receptors

- Plaque psoriasis (PS)is a good example of one of those diseases.
- In PS Type 3 responses, dependent on IL-23 and characterized by IL-17, TNF and IL-22 mediated inflammation are dominant.
- Type 1 responses with interferon gamma production also contribute
- mAbs targeting IL-23, IL23R, and IL-17 are now in wide use to treat PS



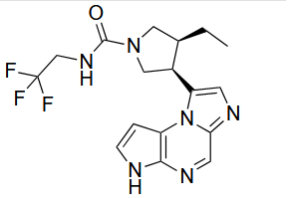


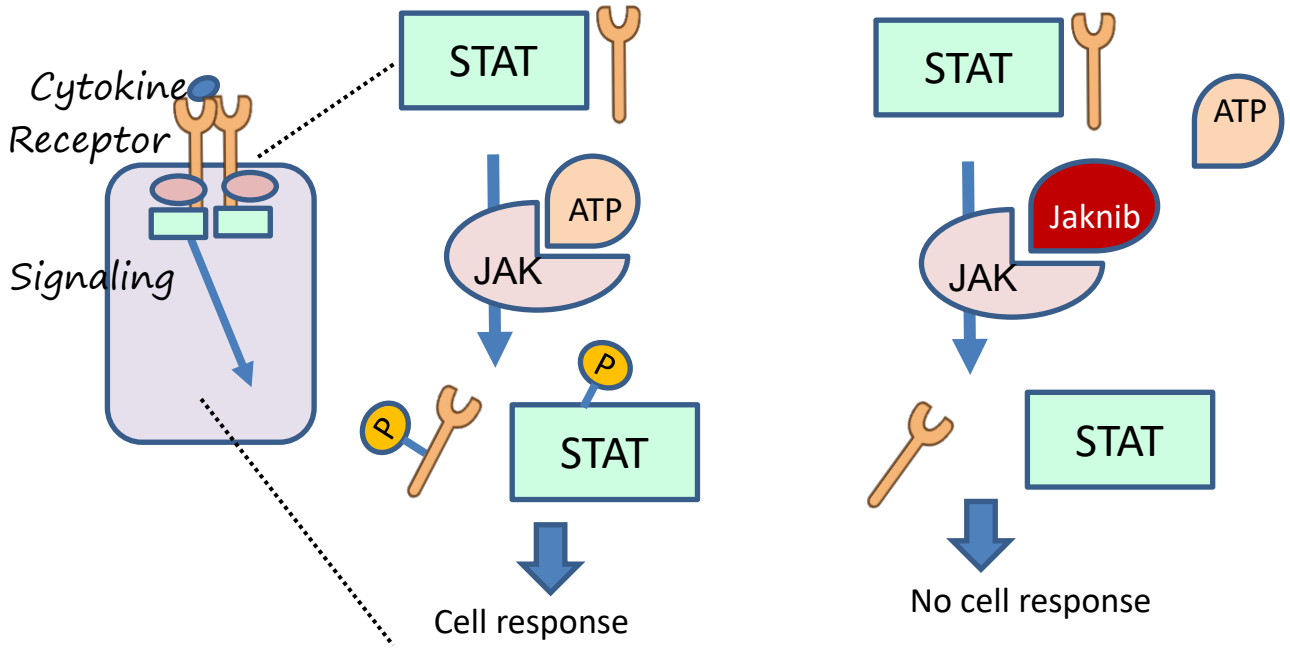
JAK inhibitors (JAKinibs)

Jakinibs are small molecule inhibitors of JAKs that block ATP binding to the enzymes' active sites

Each Jakinib developed has a different range of specificities for the different JAKs

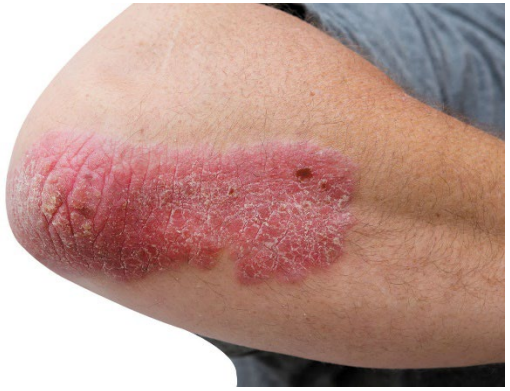
Specificities of Jakinibs in clinical use: pan JAK, JAK1/JAK2, JAK1



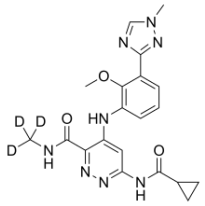


JAK inhibitors (JAKinibs)

Plaque PSA



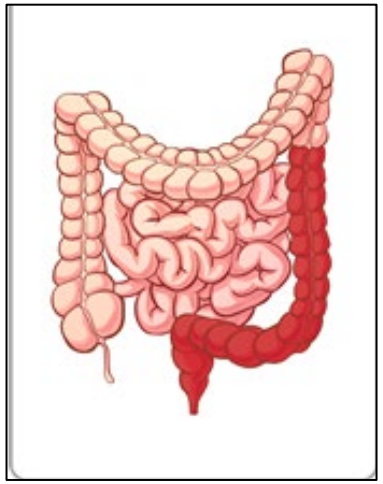
Deucravacitinib (Tyk2)



RA

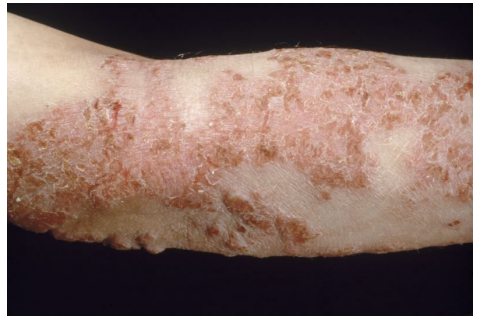
Ruxolitinib (JAK1/2)
Tofacitinib (JAK 1/2/3)
Baricitinib (JAK 1/2)
Upadacitinib (JAK1)

UC



Tofacitinib (JAK 1/2/3)

AD



Upadacitinib (JAK1)
Abrocitinib (JAK1)