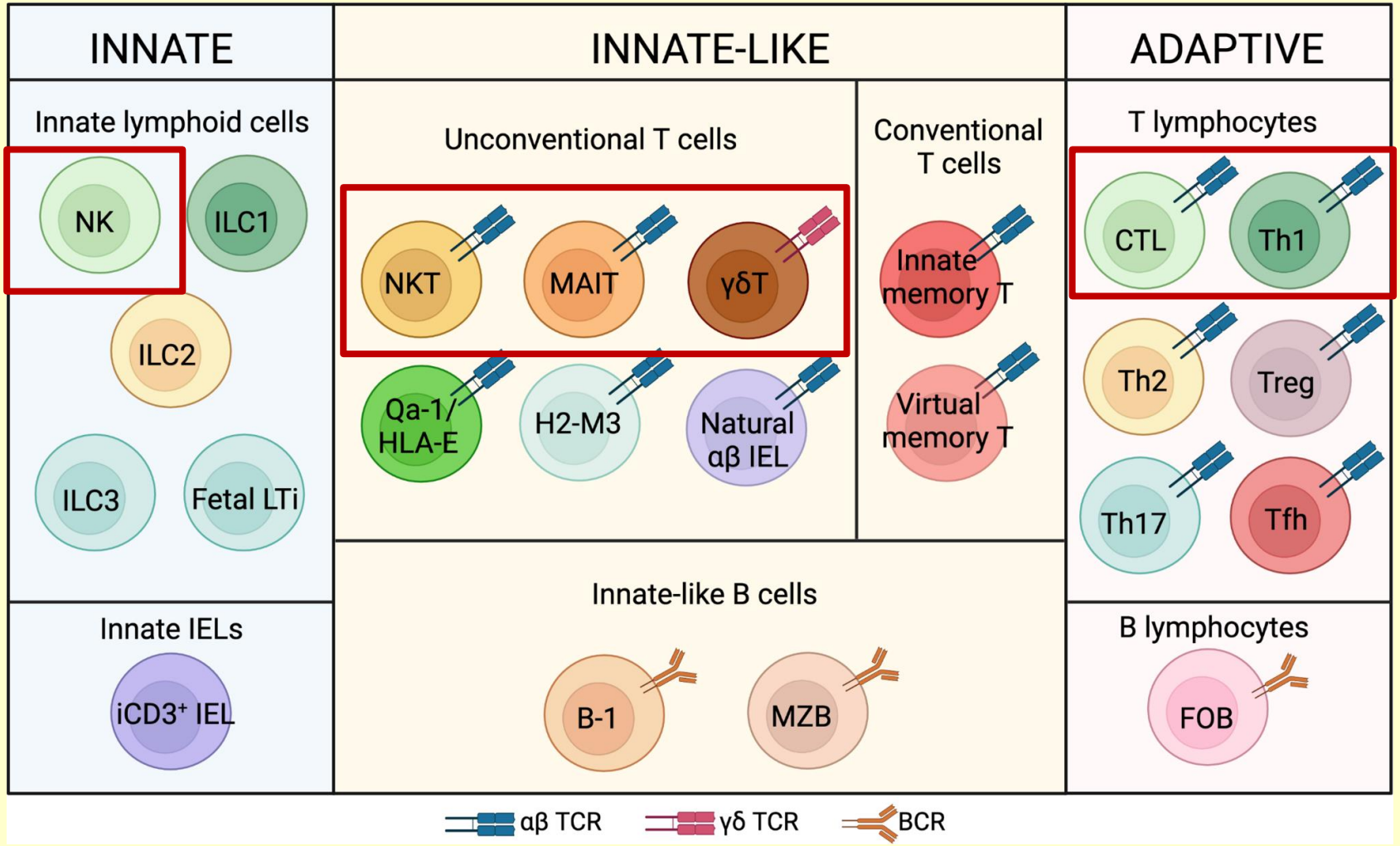
Basic Immunology

Lecture 17

Effector mechanisms of cell-mediated immune responses (CMI):

Innate, natural and adaptive effector lymphocytes

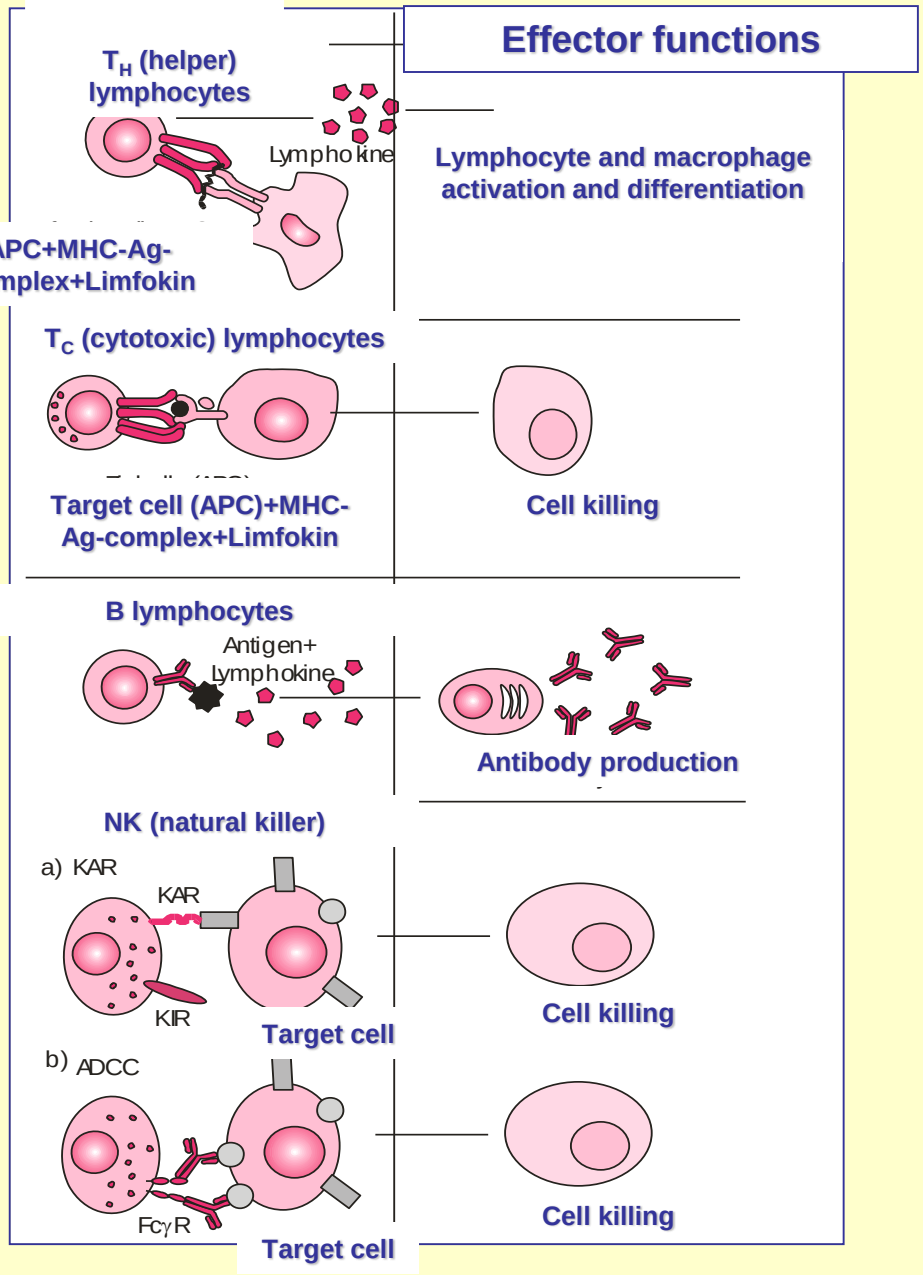
From: **Innate and Innate-like Effector Lymphocytes in Health and Disease**



https://journals.aai.org/jimmunol/article/209/2/199/234119/Innate-and-Innate-like-Effector-Lymphocytes-in

J Immunol. 2022;209(2):199-207. doi:10.4049/jimmunol.2200074

Effector functions of lymphocyte populations



Types of T Cell–Mediated Immune Reactions

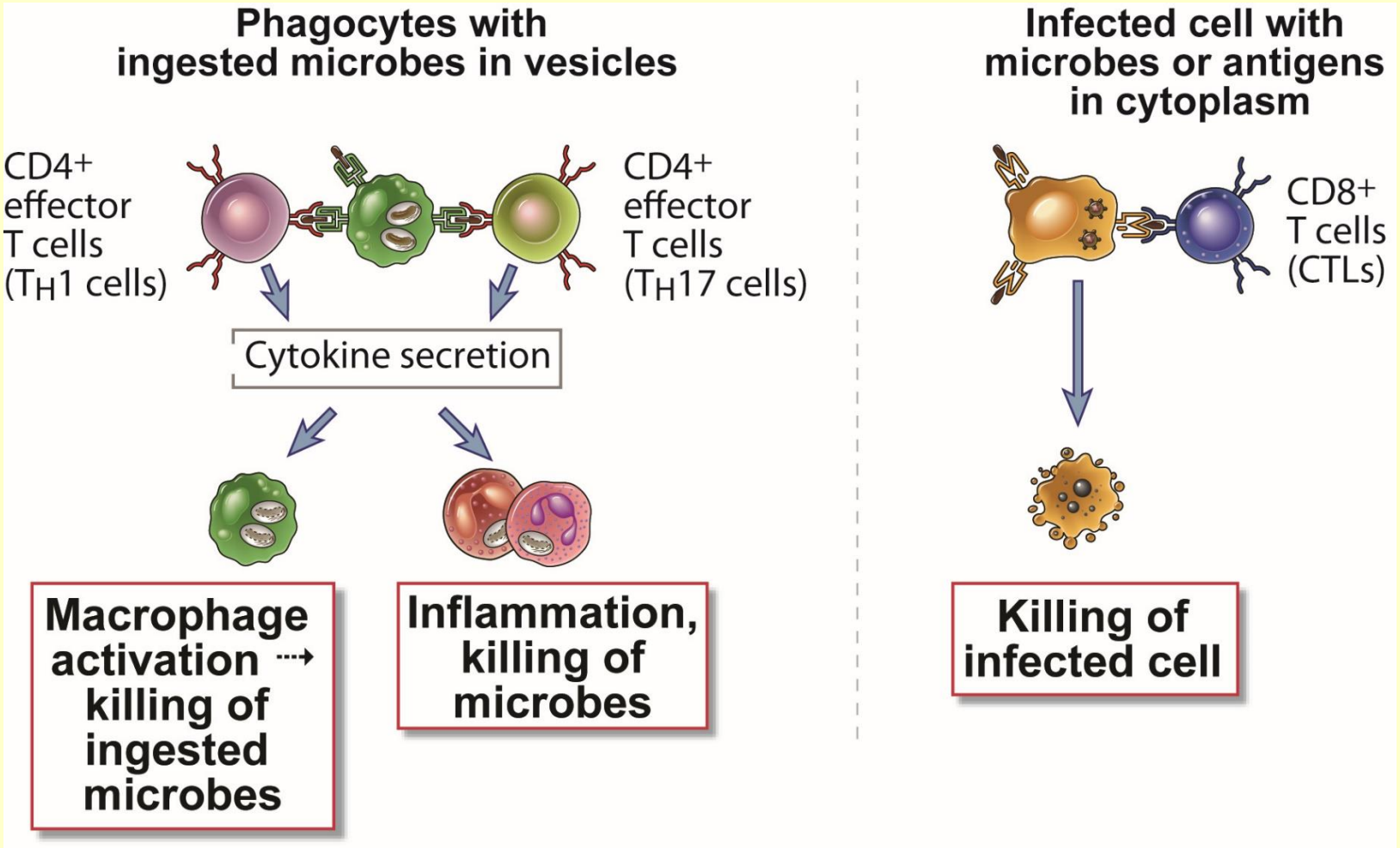
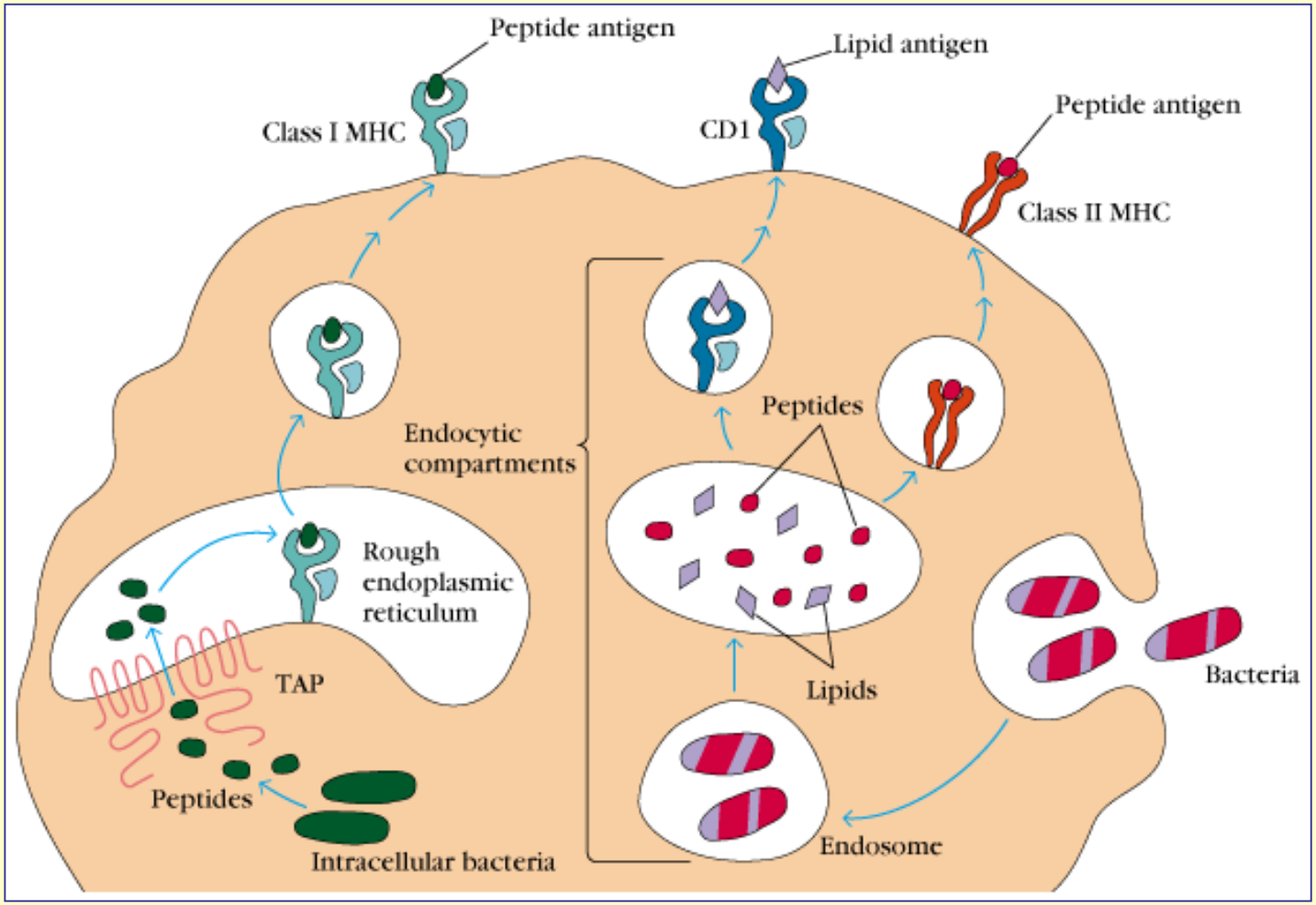


Fig. 10-1

Cell-mediated immune response (CMI)

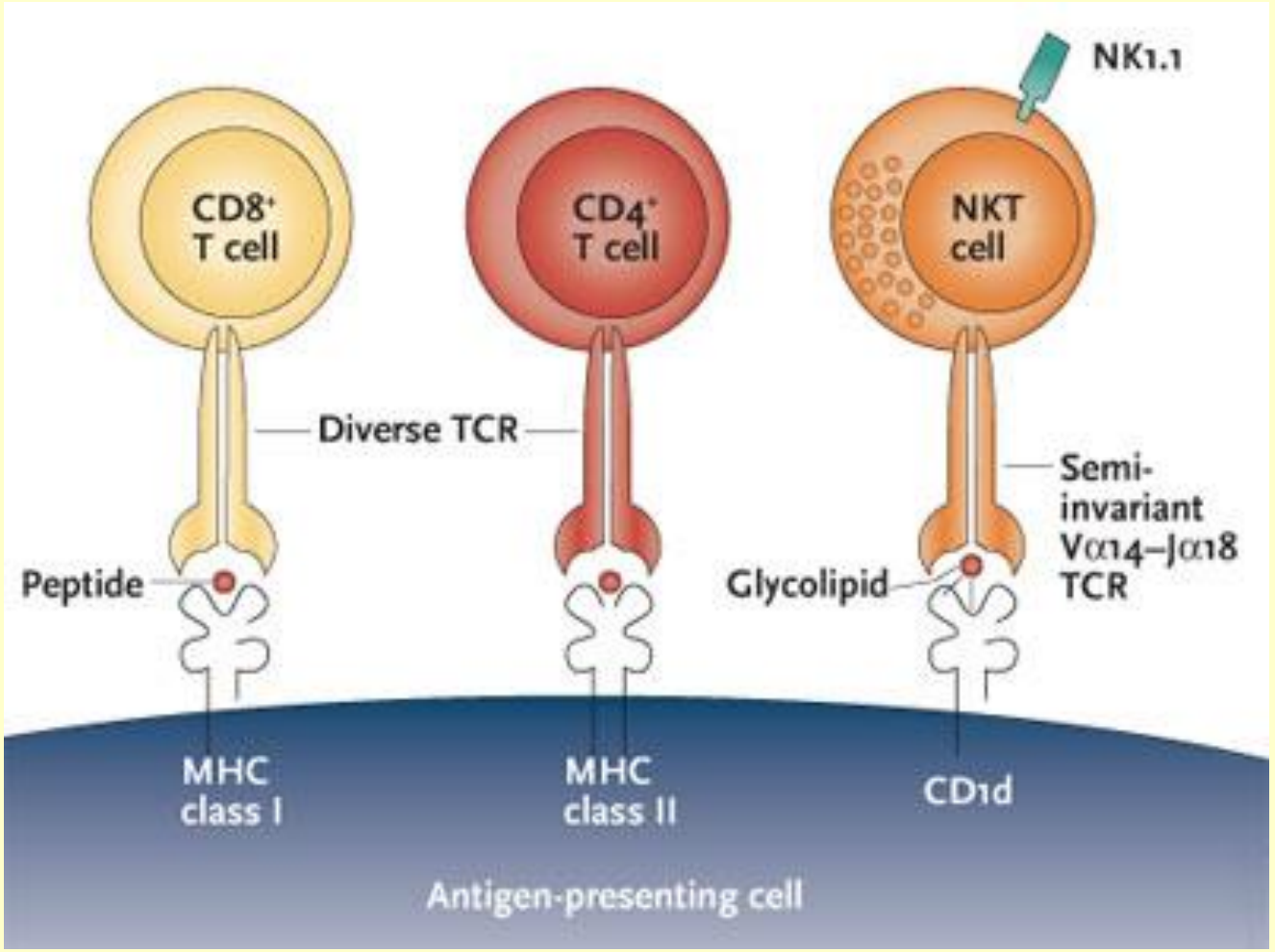
Cytotoxicity	***Th1 mediated macrophage activation***
Effector cells direct cytotoxic activity: - CD8+Tc → CTL - γδ T cells - NK cells, - Macrphages	**Effector cells** cytokine production: - T_{DTH} cells = Th1 cells - Macrophages
Target cell (cytosolic antigen): - allogen cells (transplantation minor histocompatibility antigen) - malignant cells - virally infected cells - chemically modified cells	**Antigen in phagolysosome:** - intracellular bacterium, fungi, parasite, virus - contact antigens (small molecules (haptén) skin protein complexes)

Presentation of intracellular and extracellular antigens



Cytosolic way **Phagolysosomes**

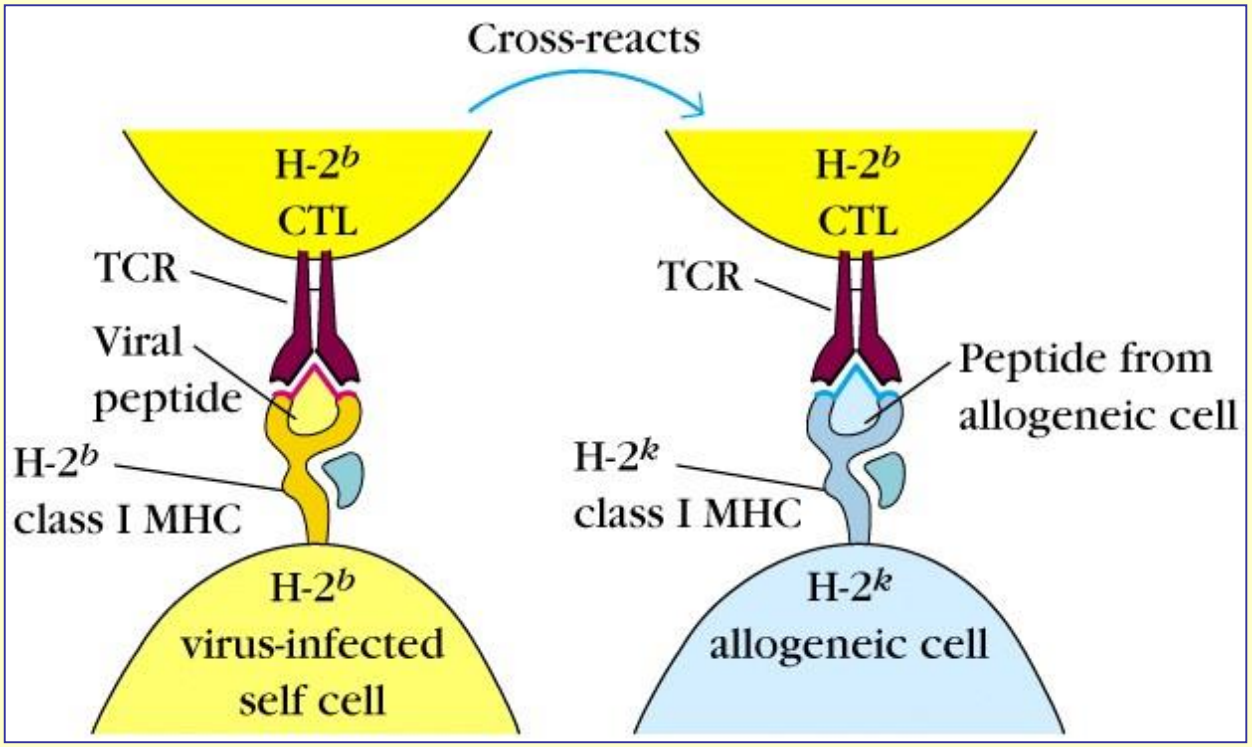
Antigen recognition of T and NKT cells



Cytotoxicity

1. CD8+ T cytotoxic cells
2. γδT cells
3. NKT and MAIT cells
4. NK cells

Antigen recognition of cytotoxic T cells



Activated Tc cells = effector CTL
TcRαβ, CD8+ cells
Antigen specific recognition with MHC- I restriction

Phases of T Cell Responses

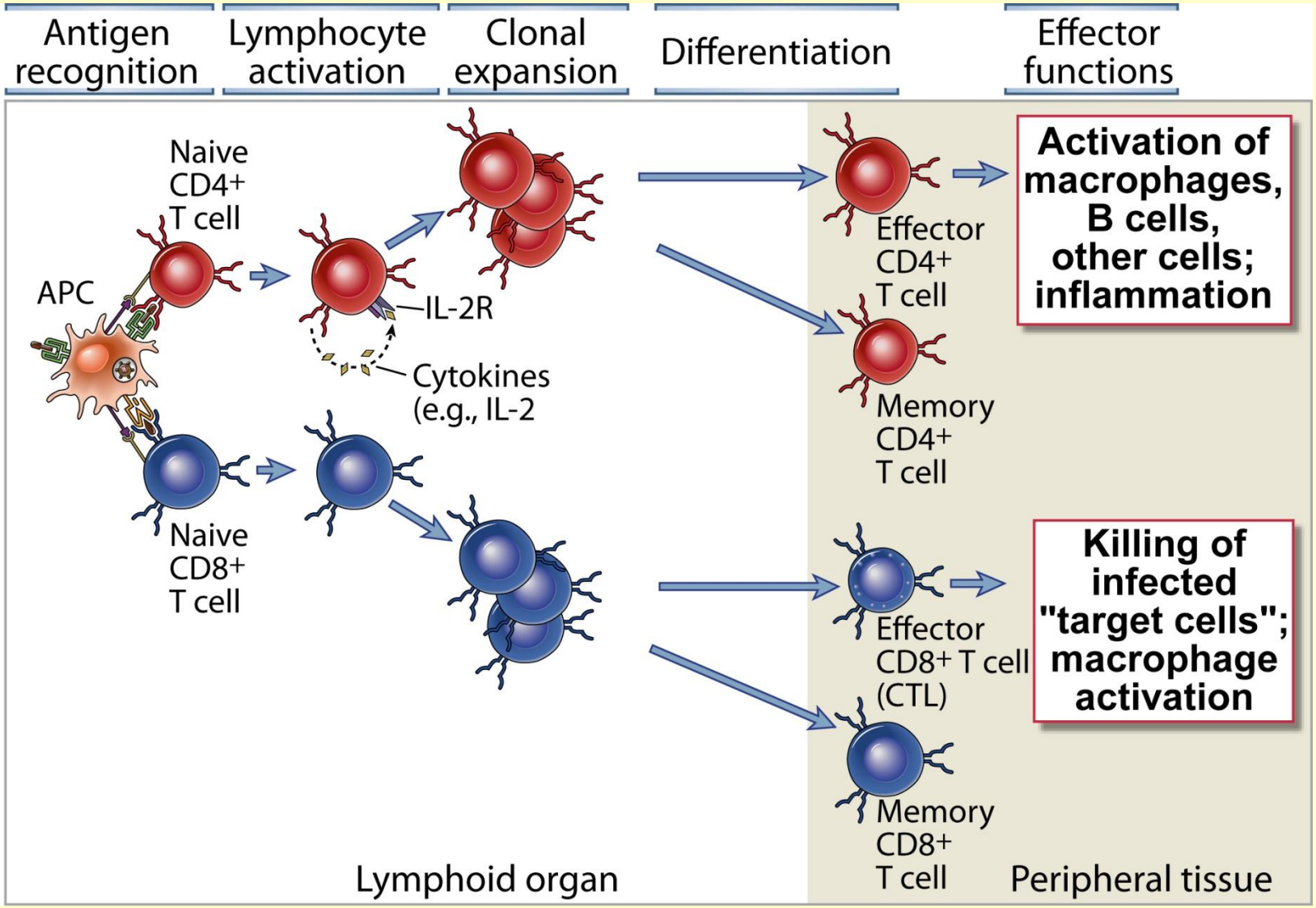


Fig. 9-2

Clonal Expansion of T cells

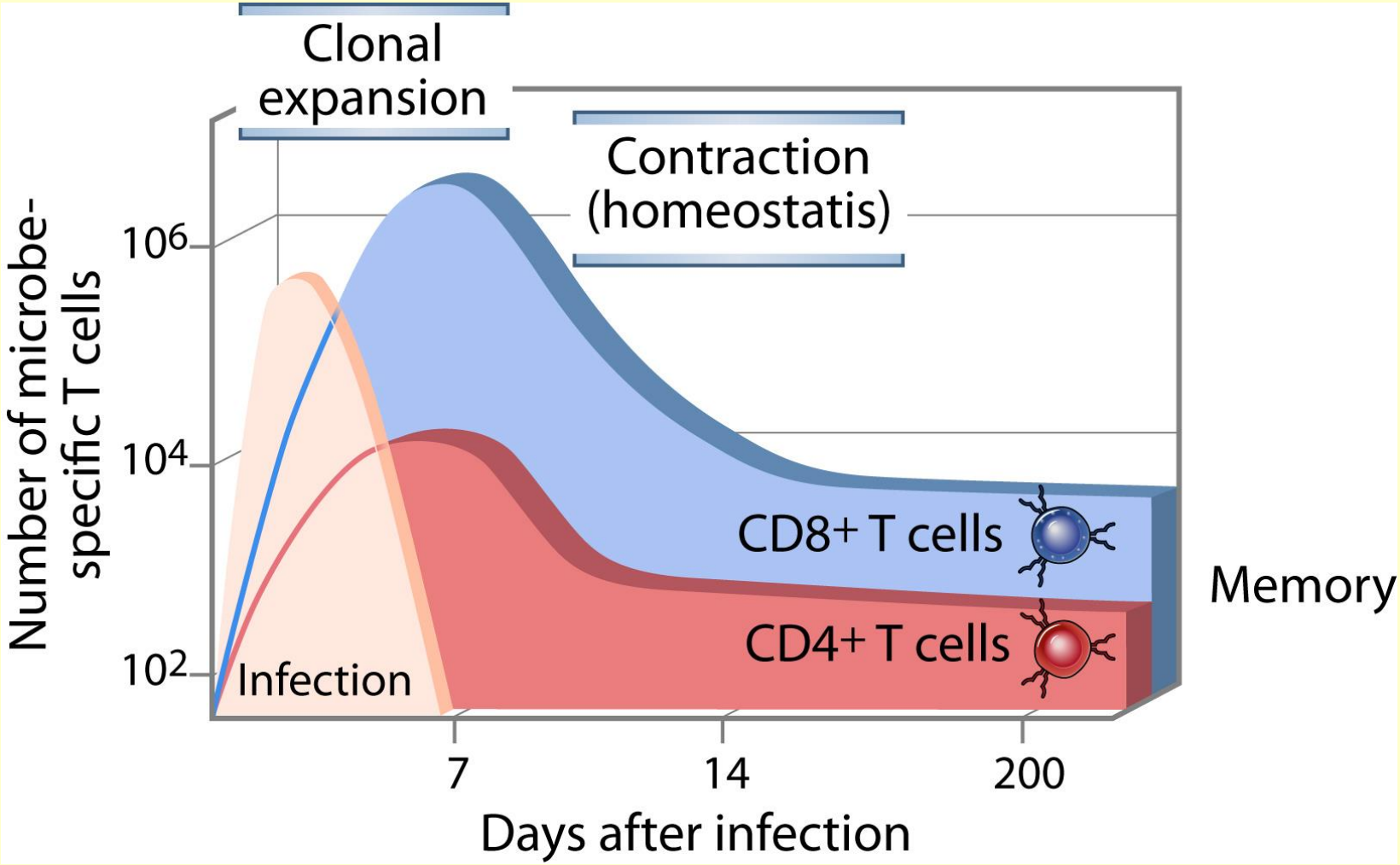


Fig. 9-12

How CD4+ T Cells Help CD8+ T Cells

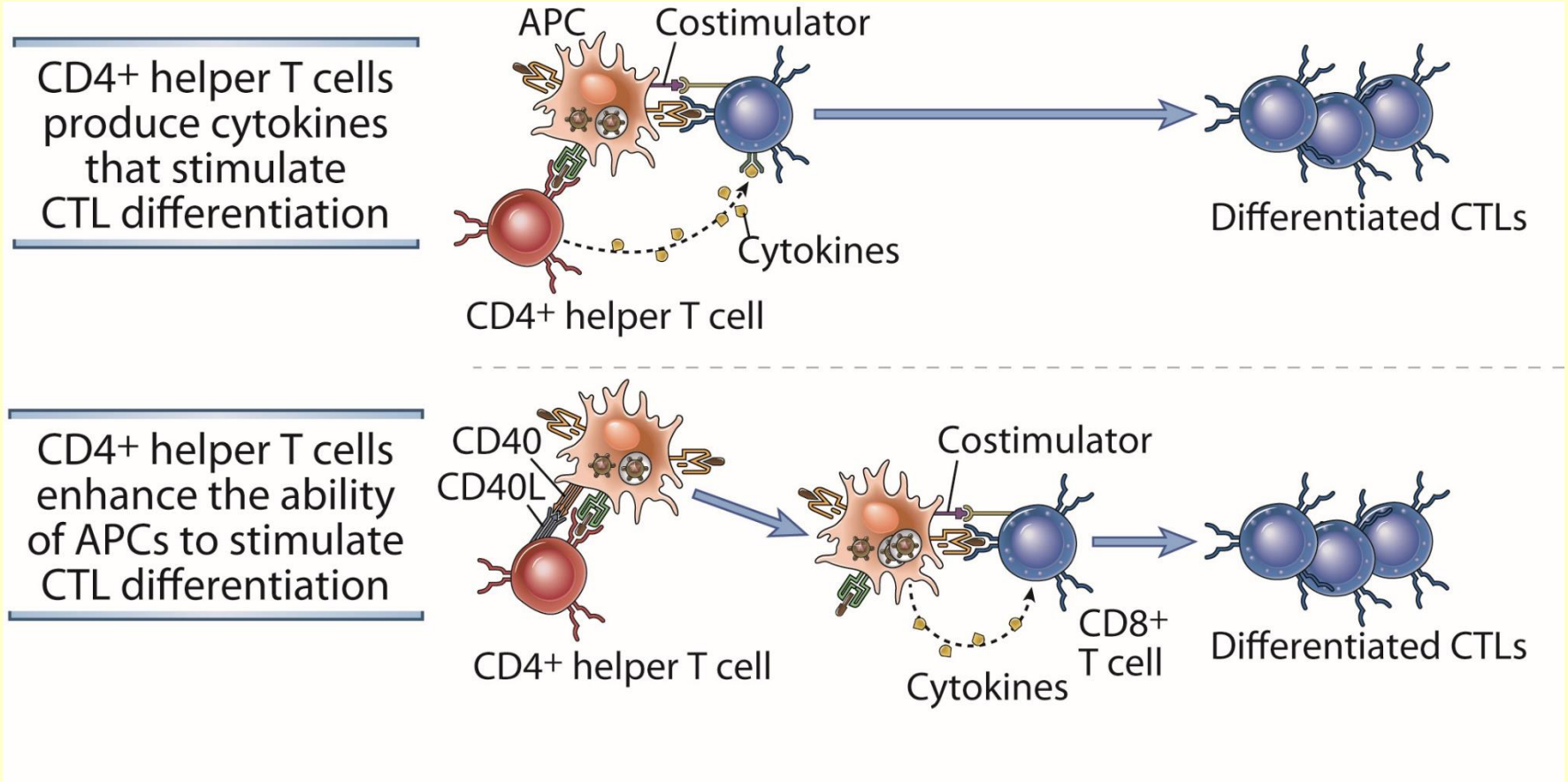
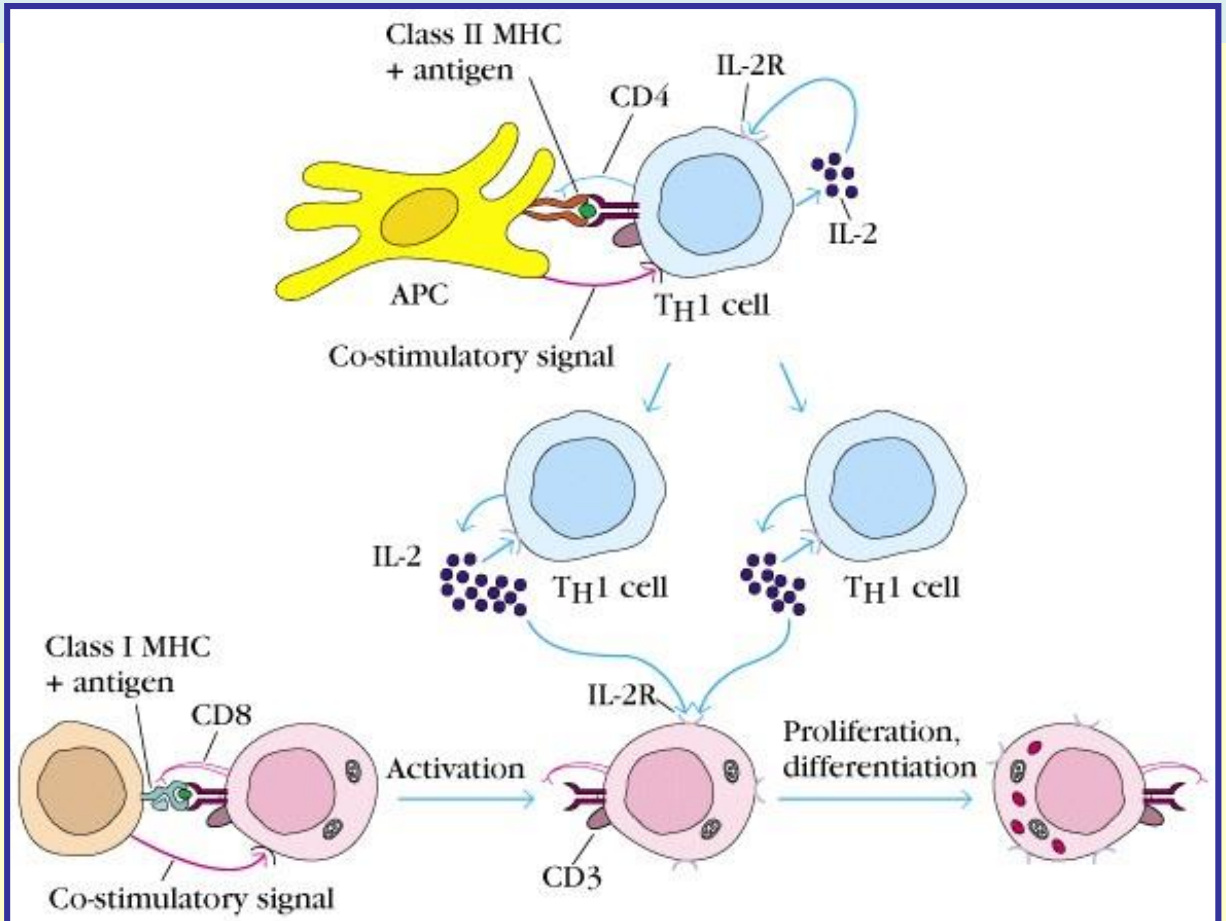


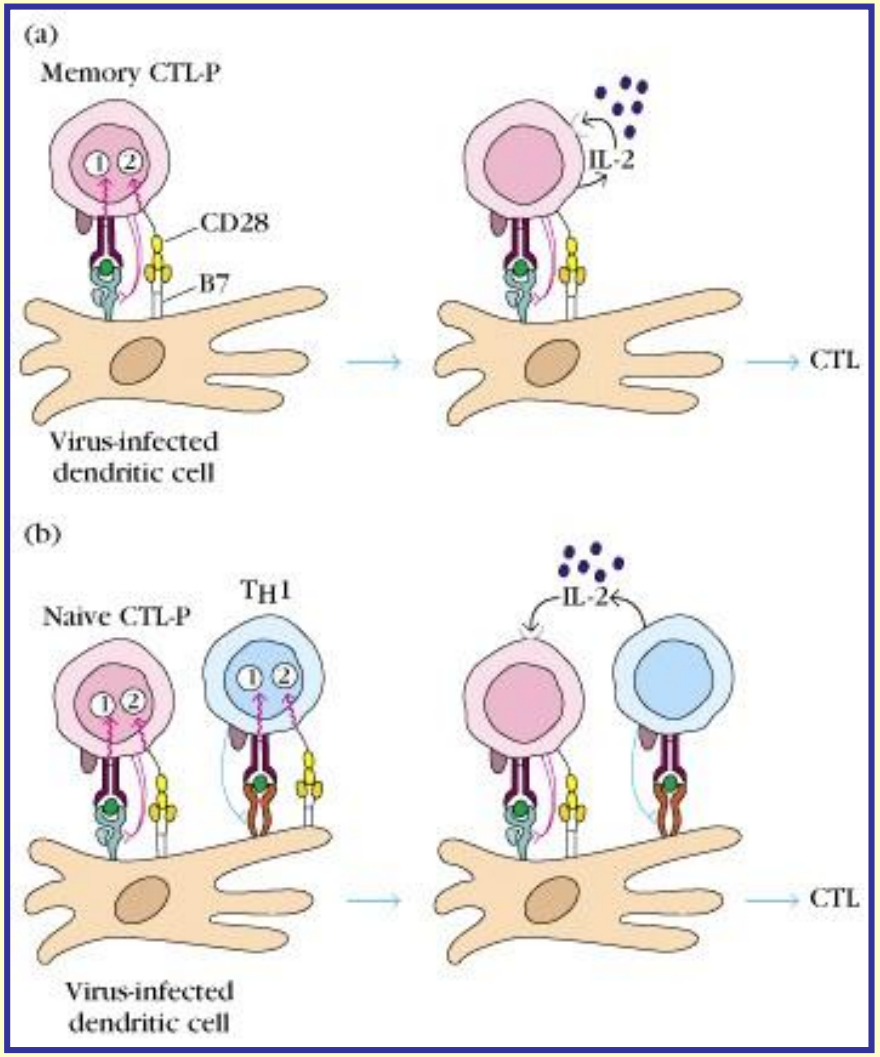
Fig. 9-18

Naive Tc cell activation



IL-2R expression	–	+	+
IL-2 expression	–	±	±
Proliferation	–	–	+
Effector cytotoxic function	–	–	+

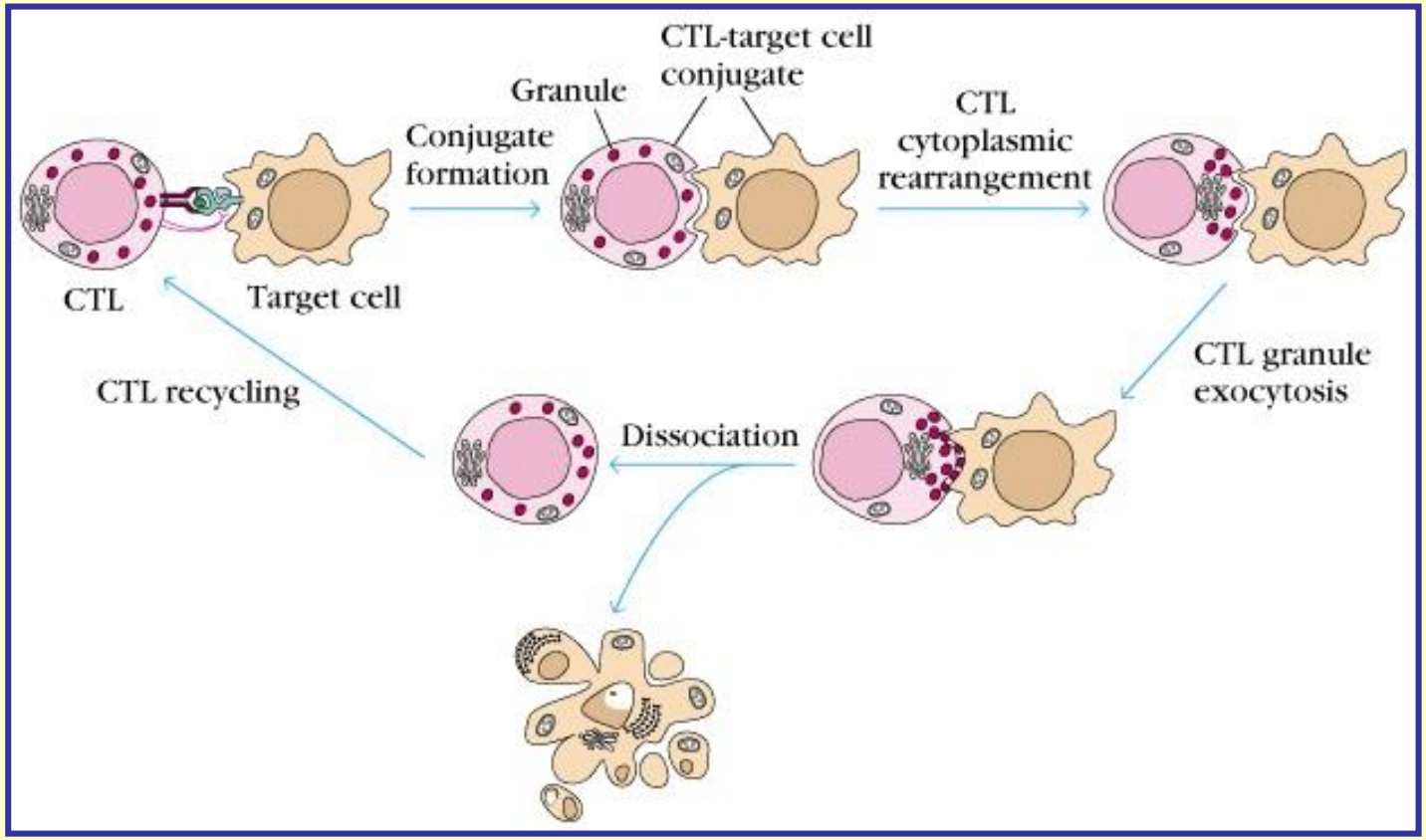
Activation of memory CTL doesn't require Th1 help



Memory CTL: autokrin IL-2 production

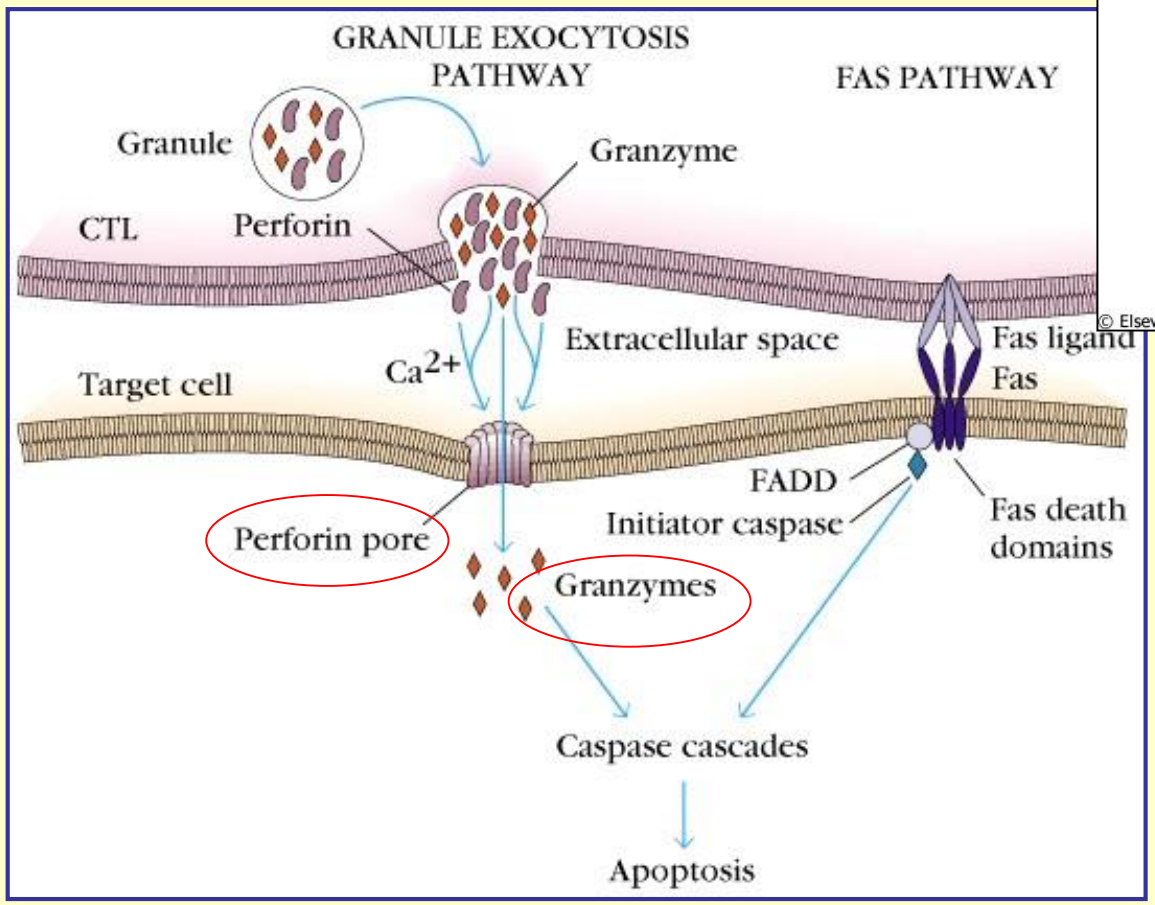
Naiv CTL: Th1 produces IL-2

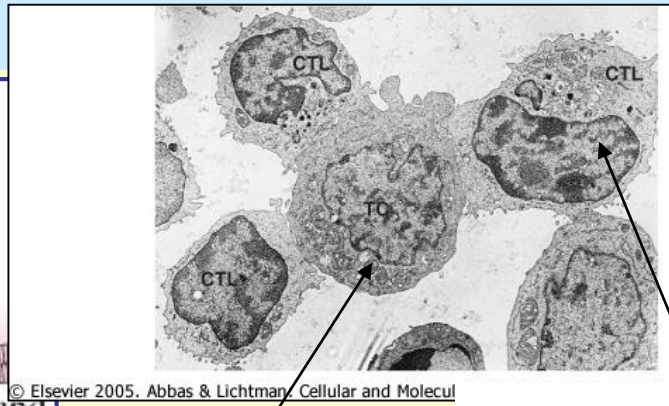
Steps of CTL-mediated target cell killing



1. Antigen recognition 2. Conjugation 3. CTL cytoplasmic rearrangement
4. CTL degranulation 5. Target cell apoptosis 6. Dissociation

Mechanisms of CTL induced apoptosis:





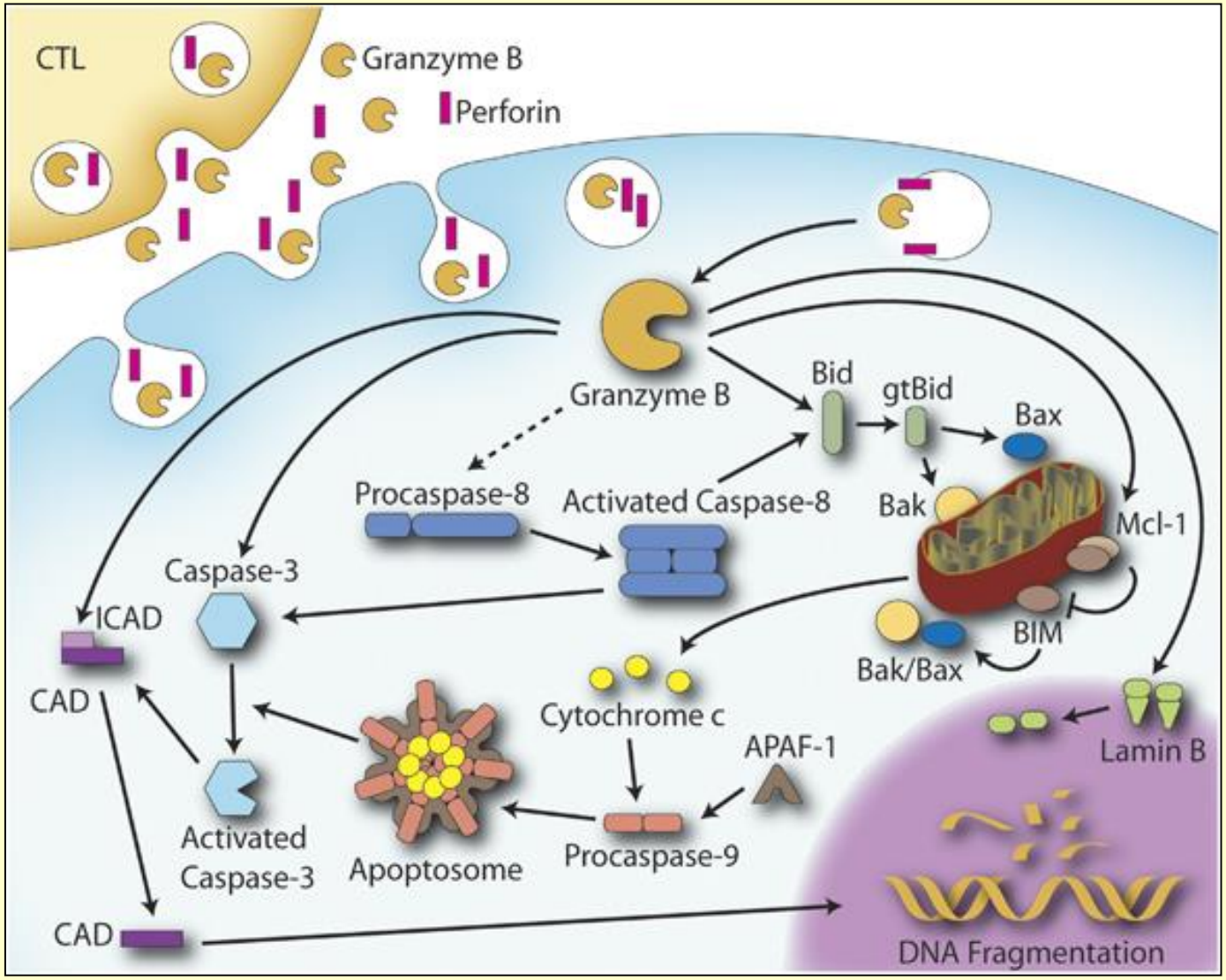
Target cell

Cytotoxic T-cell

Soluble effector molecules: perforins and granzymes

Membrane-bound effector molecules: Fas/Fas ligand (FAS-L)

The secretory mechanism of apoptosis



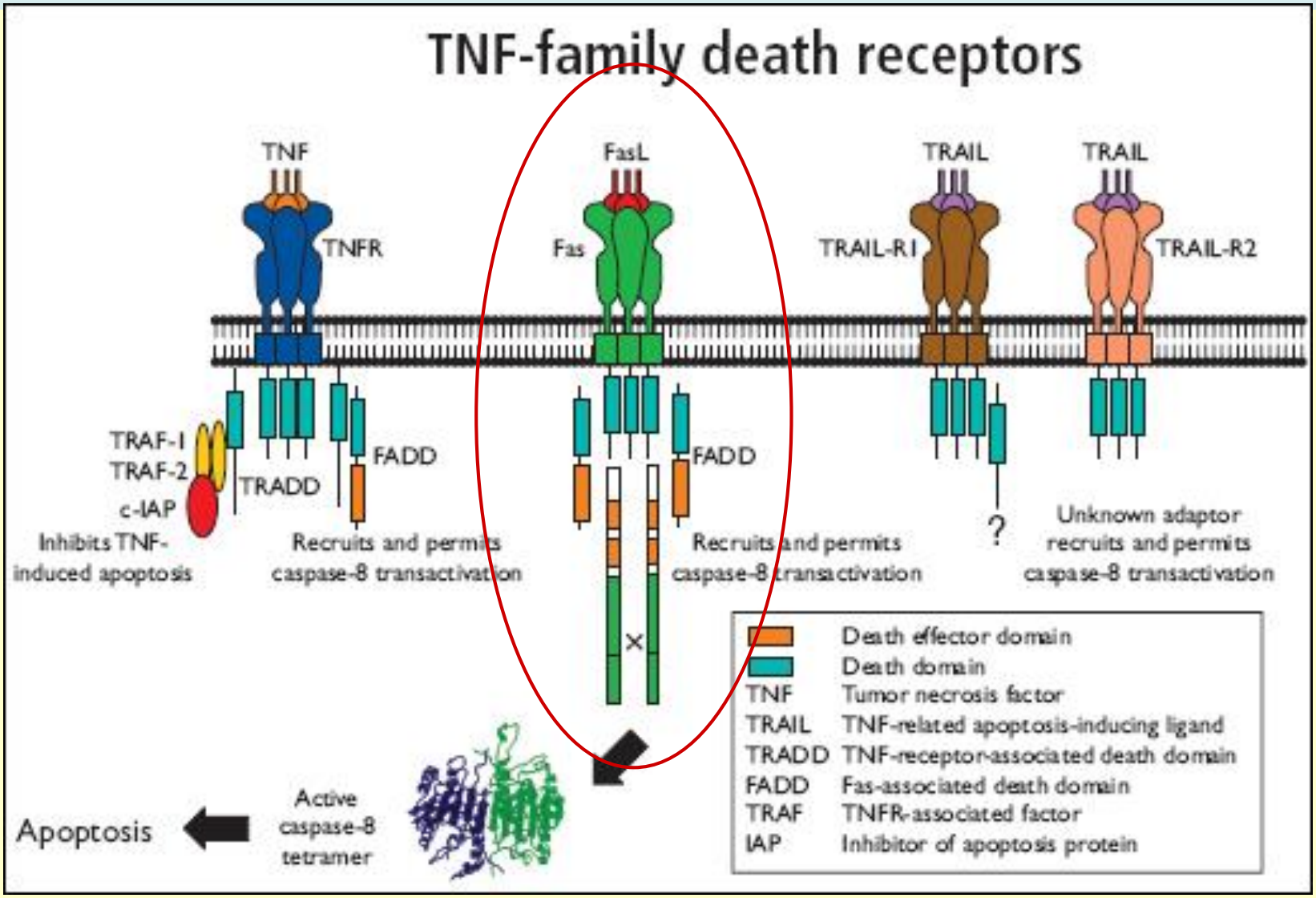
Granzyme B:

Induction of Apoptosis

Granzyme A:

DNA-Fragmentation

Extrinsic Apoptosis pathway



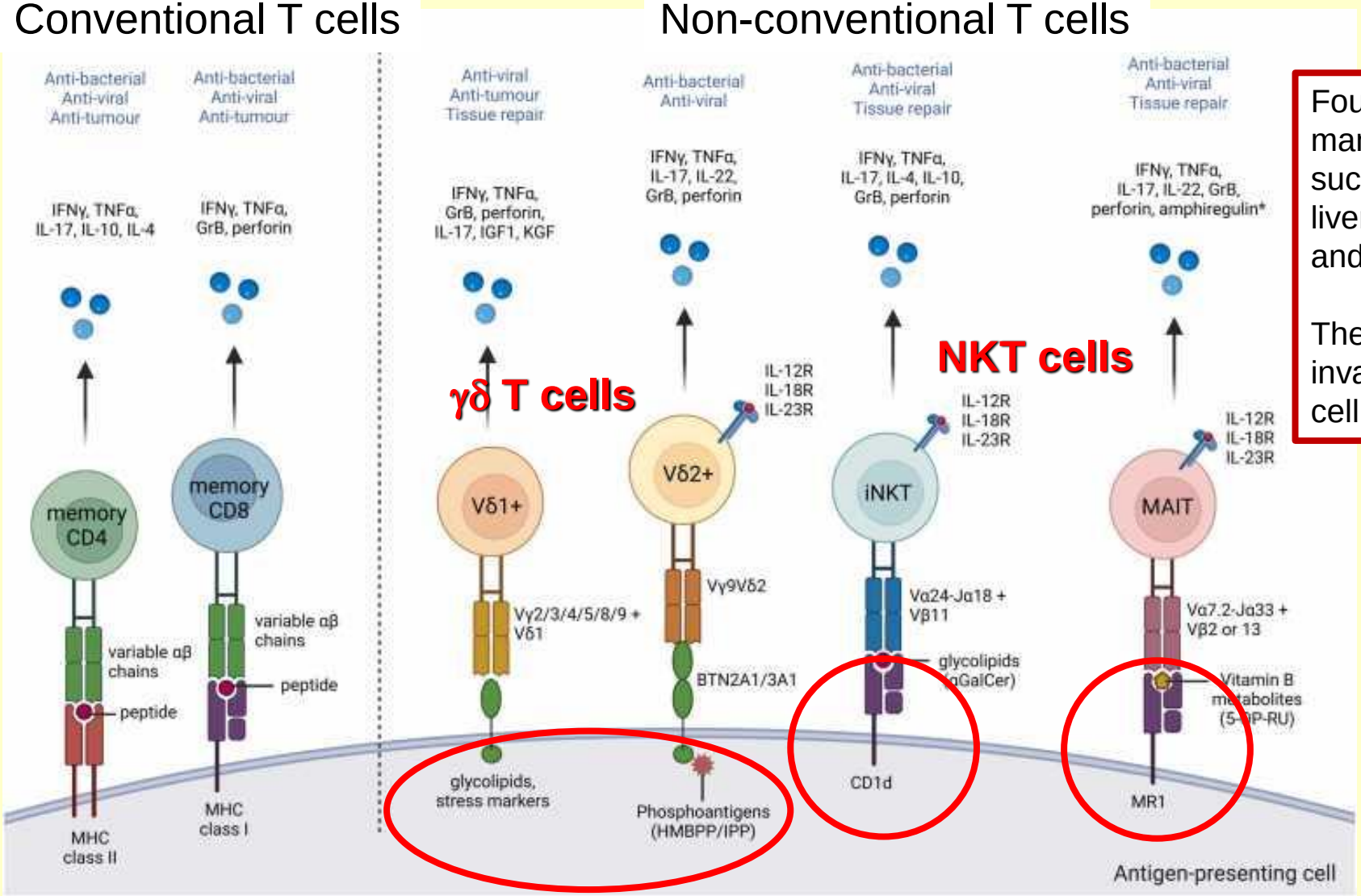
Cytotoxicity

1. CD8+ T cytotoxic cells
2. γδT cells
3. NKT and MAIT cells
4. NK cells

Antigen recognition of traditional and unconventional T cell subsets

Conventional T cells

Non-conventional T cells

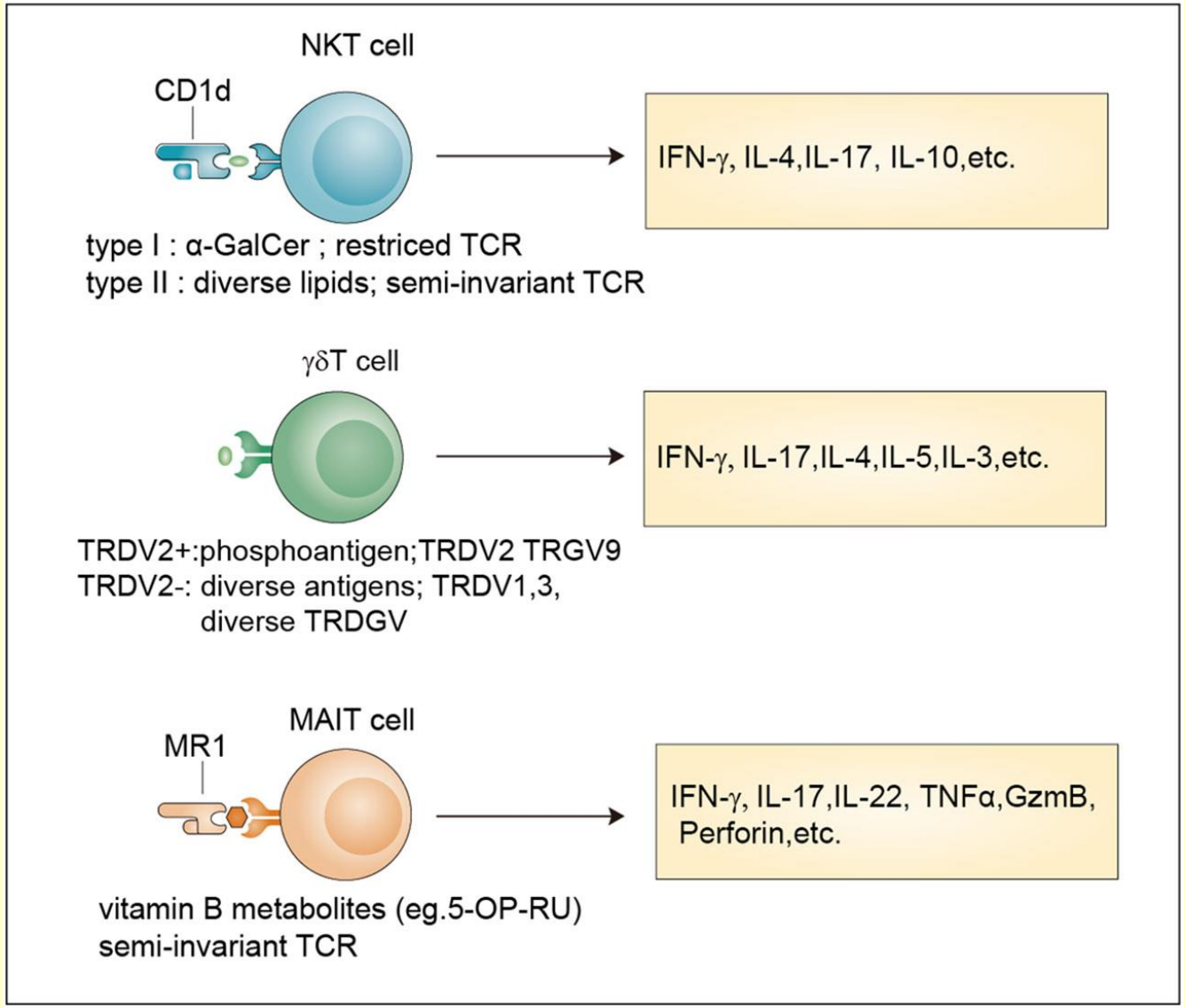


Found in many tissues such as the liver, lungs and intestine

They have an invariant T cell receptor

https://pmc.ncbi.nlm.nih.gov/articles/PMC10804939/

Non-conventional or natural T cell subsets



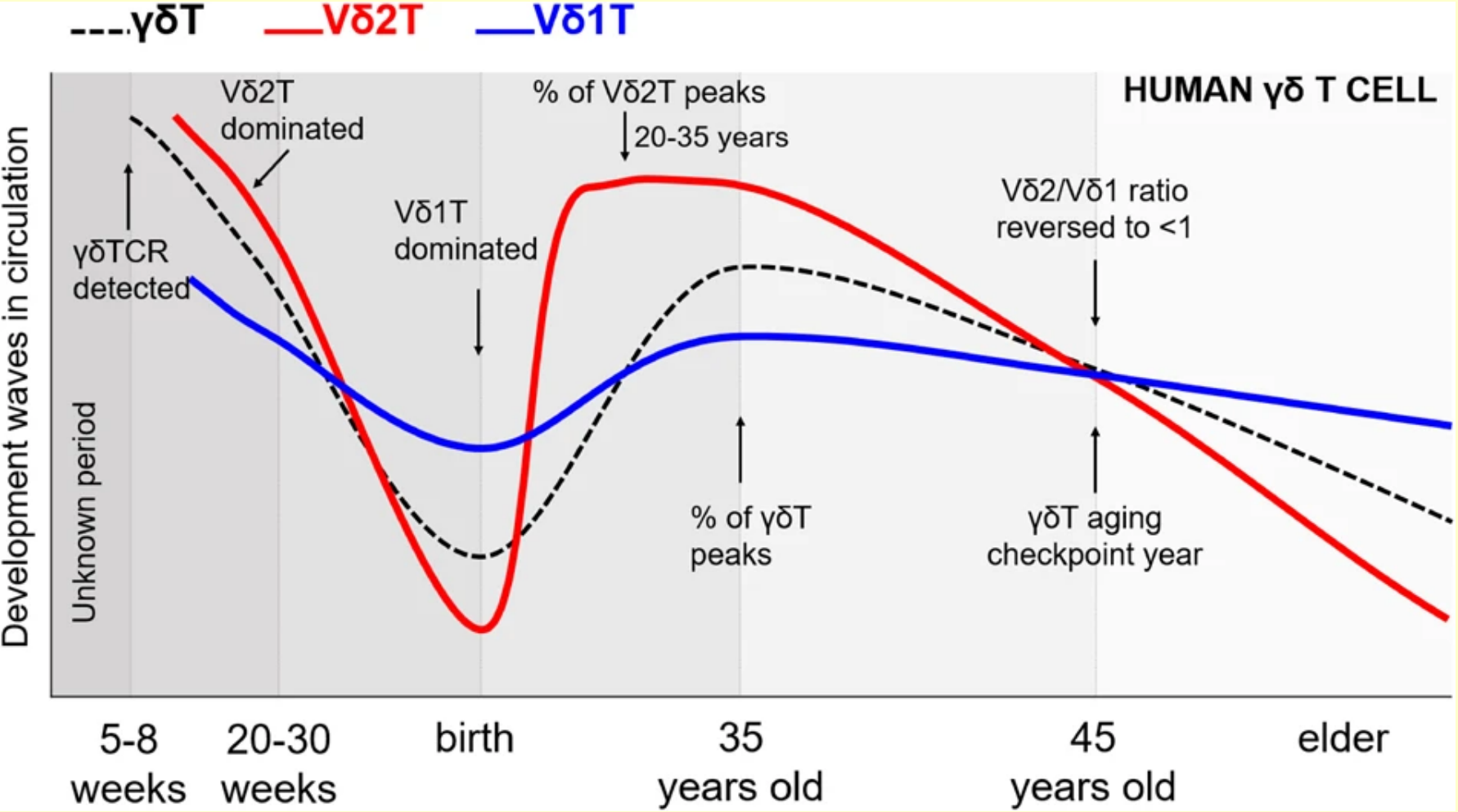
https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1273459/full

γδ T cells

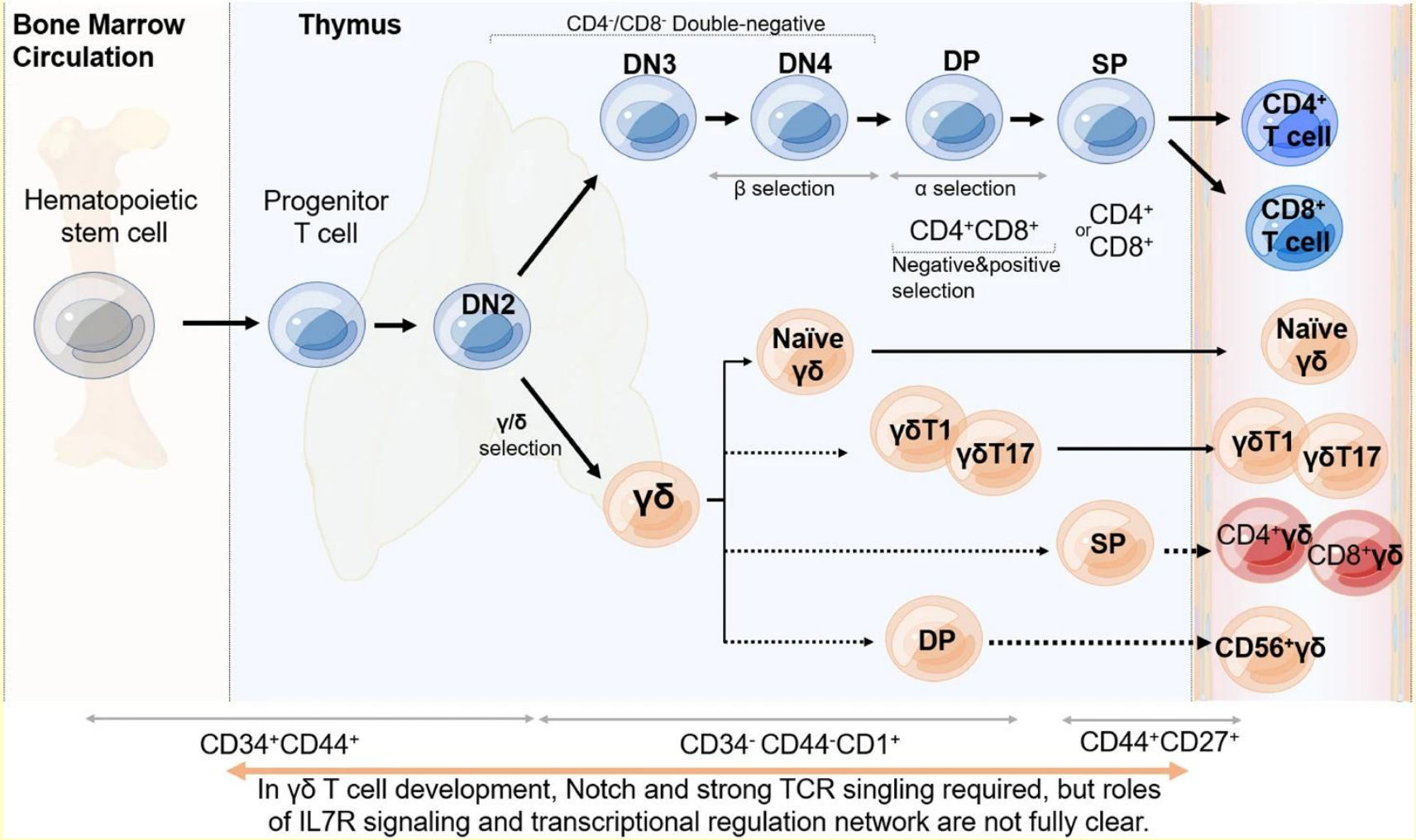
- 5 % of the T cells,
- Intraepidermal lymphocytes: CD4- and CD8-
- Intraepithelial lyphocytes: CD8+
- Produced in embryonic life, no recirculation,
- Limited, tissue specific TcR diversity → specialization to respond to certain antigens

- Ligand recognition: - non-MHC-retricted, but antigen specific
- Antigens: viral proteins, surface heat-shock proteins (produced in inflammatory responses) bacterial lipids, phosphatids through CD1 molecule
- Function: eliminate damaged cells and microbial invaders

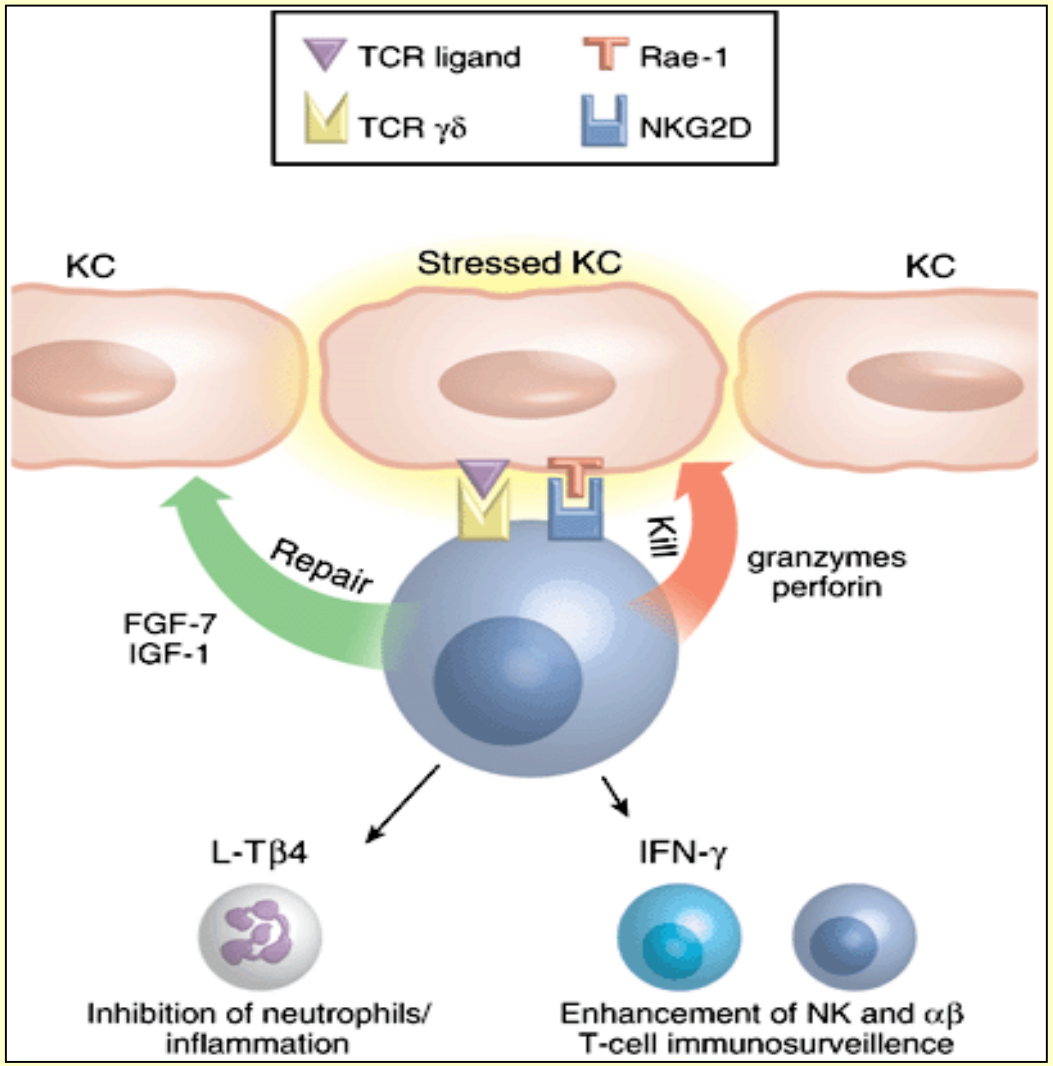
Appearance of the two main human γδ T cell subsets in the circulation



Human γδ T cell development and commitment in the thymus



γδ T cells



γδ T cells are most abundant in barrier tissues, including the skin, intestine and lungs

Tissue-specific CR subgroups expressing Vγ and Vδ combinations are found

Antigen specificity:

- butyrophilin (BTN) protein-bound bacterial phosphoantigens
- CD1, MR1 MHC-I-like proteins: bound antigens
- MIC-A and MIC-B (MHC class I chain linked protein) antigen – recognized by NKG2D KAR receptor

Natural Killer T cells = NKT

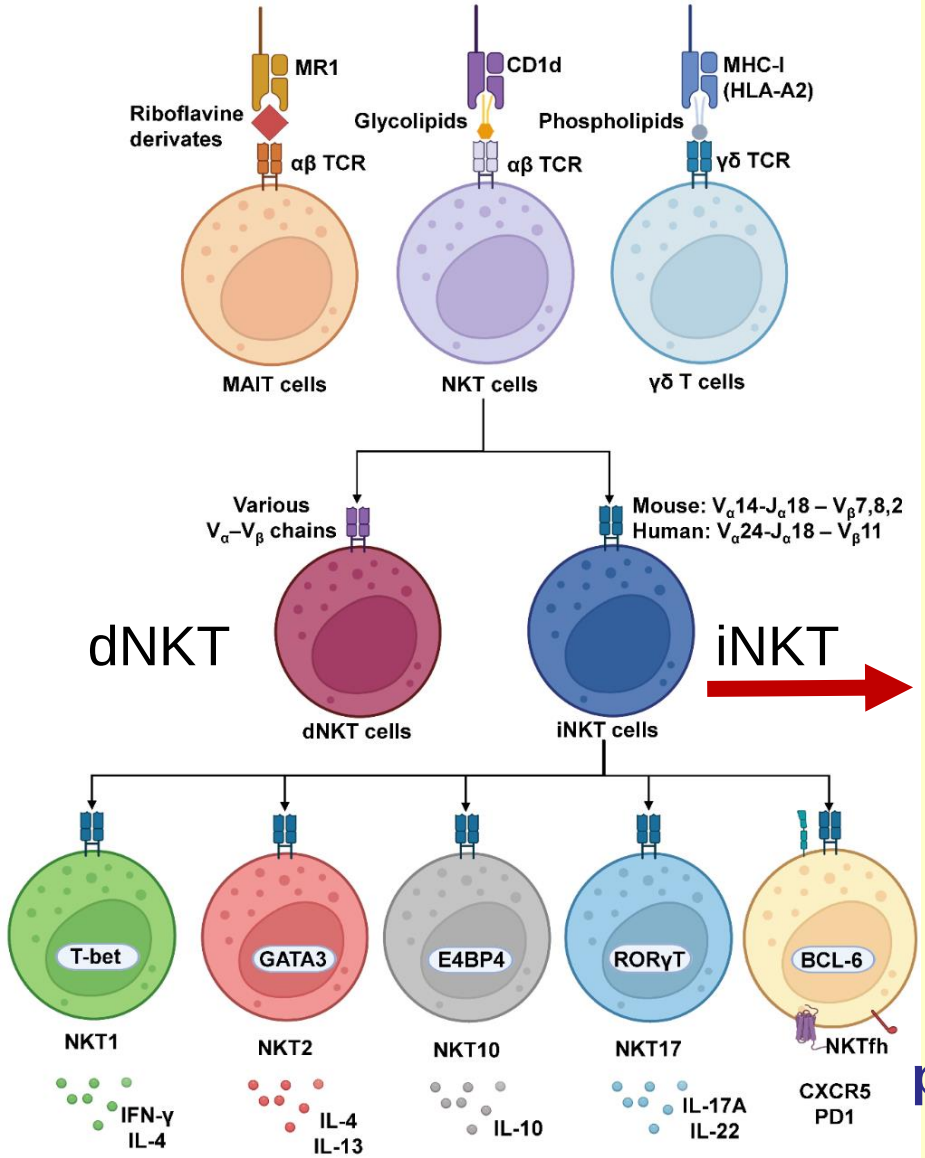
- 0,2% of the peripheral T cells
- Positive selection in the thymus on self phospholipid antigens
- **Antigen recognition**: microbial **phospholipids** and **glycolipids**, presented by the non-polymorphic **CD1d**
- **Markers:** invariant αβ TcR (iVα24-Jα18) with limited specificity, CD4 or DN or CD8αα + NK markers: NK1.1, CD56, CD16, CD161 (NKRP1)
- **Function**: fast cytokine production: IL-4, IFNγ, IL-10, IL-13, IL-17, IL- 21 TNFα

	Vα14 NKT	Conventional T
TCR	invariant Vα14	heterogenous TCR
Ligand	α-GalCer	peptides
MHC	monomorphic CD1d	polymorphic MHC
Major tissues	Liver, Spleen Bone marrow	Thymus, Spleen Lymph nodes
Development	GM-CSFR	no GM-CSFR

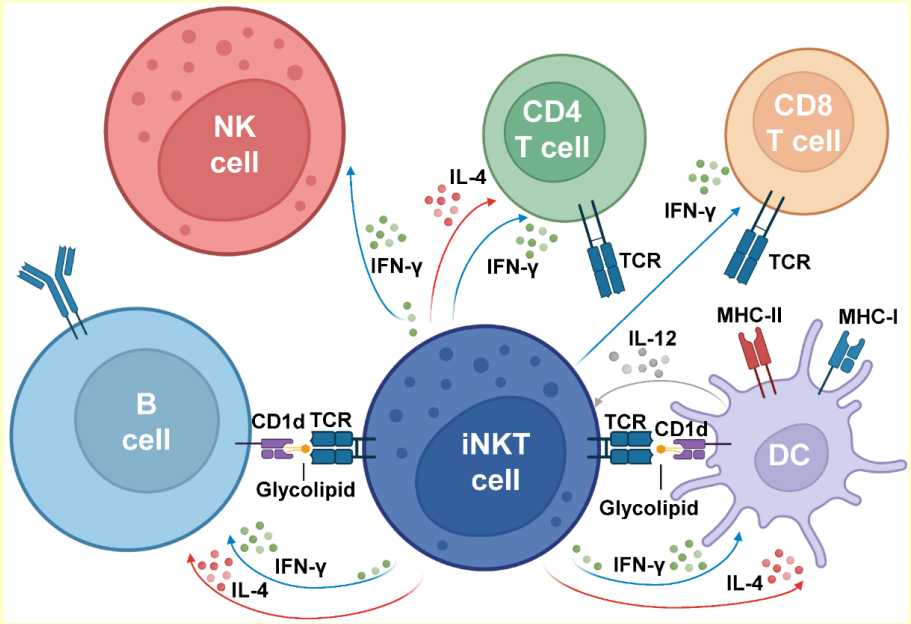
NKT cell types

	I	II	III	MAIT cells
Other names	Classic /**invariant NKT**	Non-classic	-	-
TCR repertoire	invariant Vα24-JαQ (Jα18), Vβ11	diverz	diverz	invariant Vα7.2-Jα33
Co-receptors	CD4, DN, CD8αα	CD4, DN	CD4, CD8αα	DN, CD8αα
NK cell receptor	CD56, CD161	CD56, CD161?	CD56, CD161?	CD161
Antigen presenting molecule	CD1d	CD1d	MHCI and II	MR1
Reactivity	αGalCer, iGb3?, GSL	sulphatide	?	Vitamin B subunits
Occurrence	Liver, thymus, spleen, bone marrow	Liver, spleen	Spleen, bone marrow, liver	Lamina propria, lungs, liver

iNKT cell subgroups – transactivation and polarisation



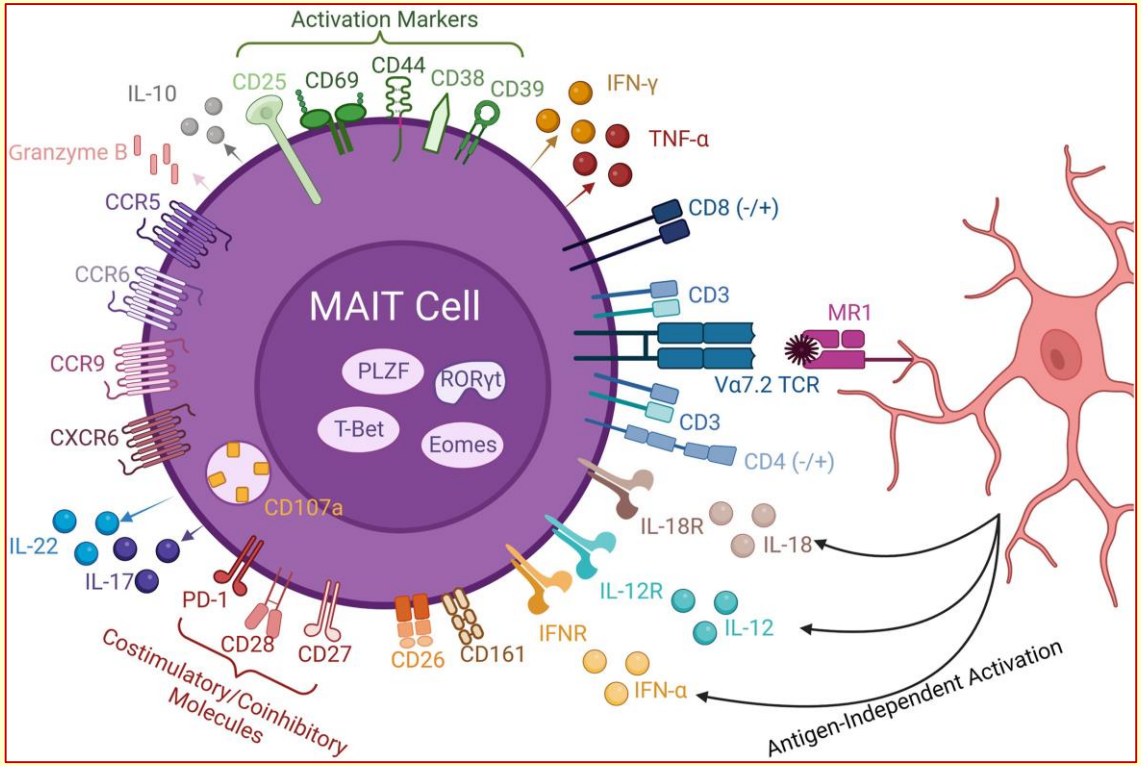
transactivation



polarisation

Cancers **2023**, *15*(24), 5737; https://doi.org/10.3390/cancers15245737

Role of MAIT cells



MAIT cells are predominantly found in the gastrointestinal tract, mesenteric lymph nodes and liver

Upon encounter with the commensal microbial flora, MAIT cells proliferate and develop a memory phenotype

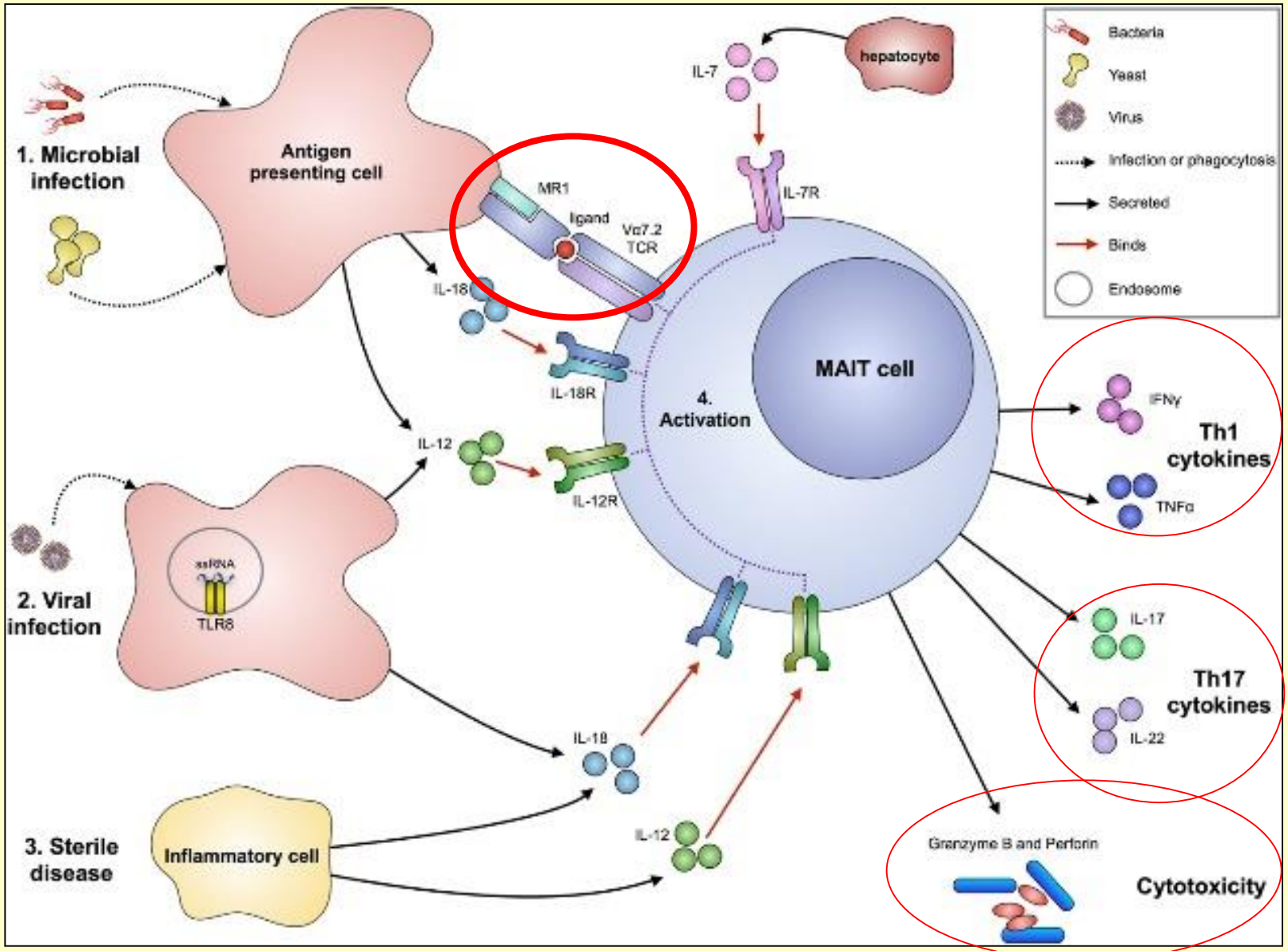
Important in antimicrobial antibacterial defence, produce cytokines

Recognition of microbially derived B vitamin (e.g. riboflavin) derivatives presented on MR1

Citokines can also activate

Markers: CD3, CD4, CD8, Valfa 7.2 TCR ? PD1, CD28, CD27, produce Granzym B

MAIT cell activation and polarisation



Cytotoxicity

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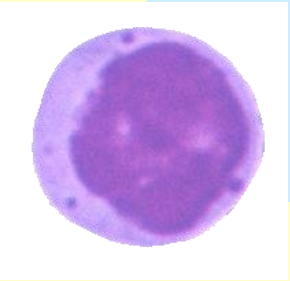
4. **NK cells**

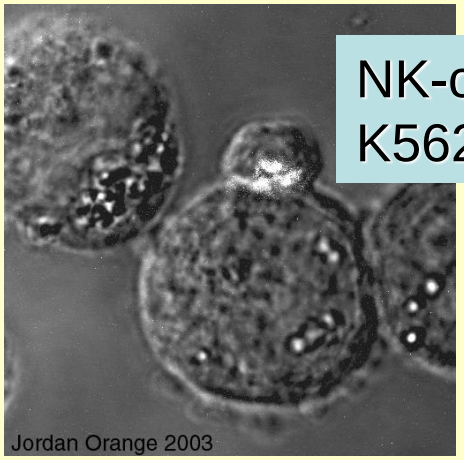


Natural killer cells (NK)

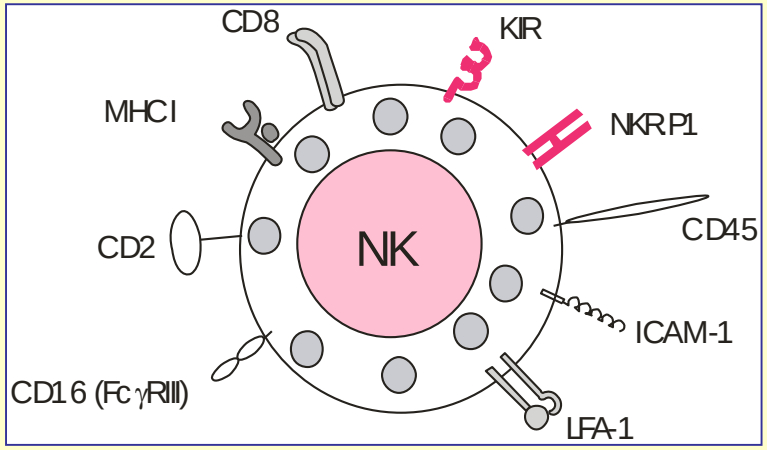
- 10-15% of lymphocytes = LGL cells

- **Phenotype:**
- TcR- CD3-, CD4-, CD8+/-, CD2+, CD16+ (FcγRIII) CD56+,
- They secrete cytokines: INFγ → immune regulation (Th1)

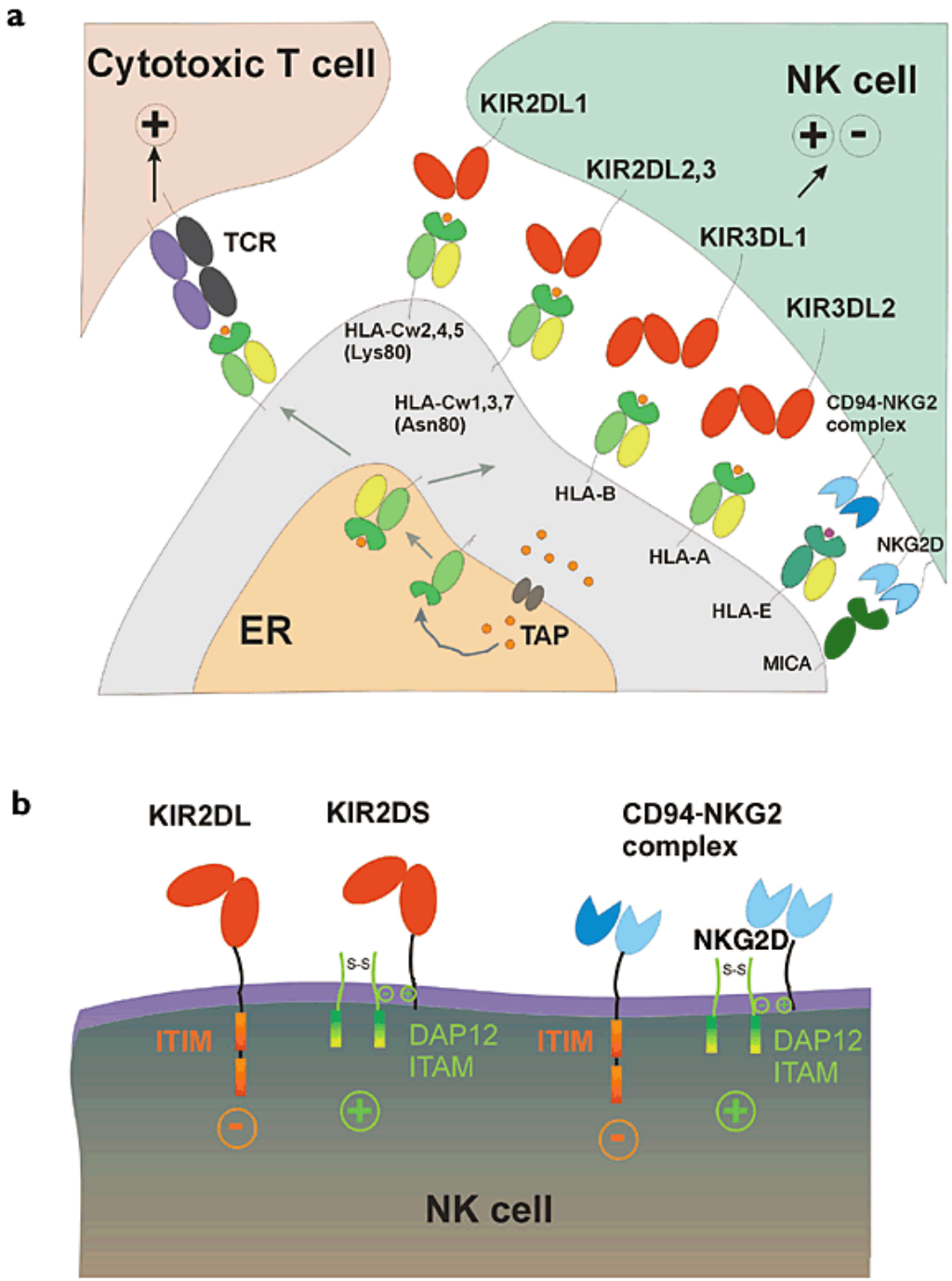
- **Function:** ***early*** response to infection with certain viruses, intracellular bacteria and tumor cells



NK-cells kill their target-cell K562 with perforin (white)



NK cell receptors

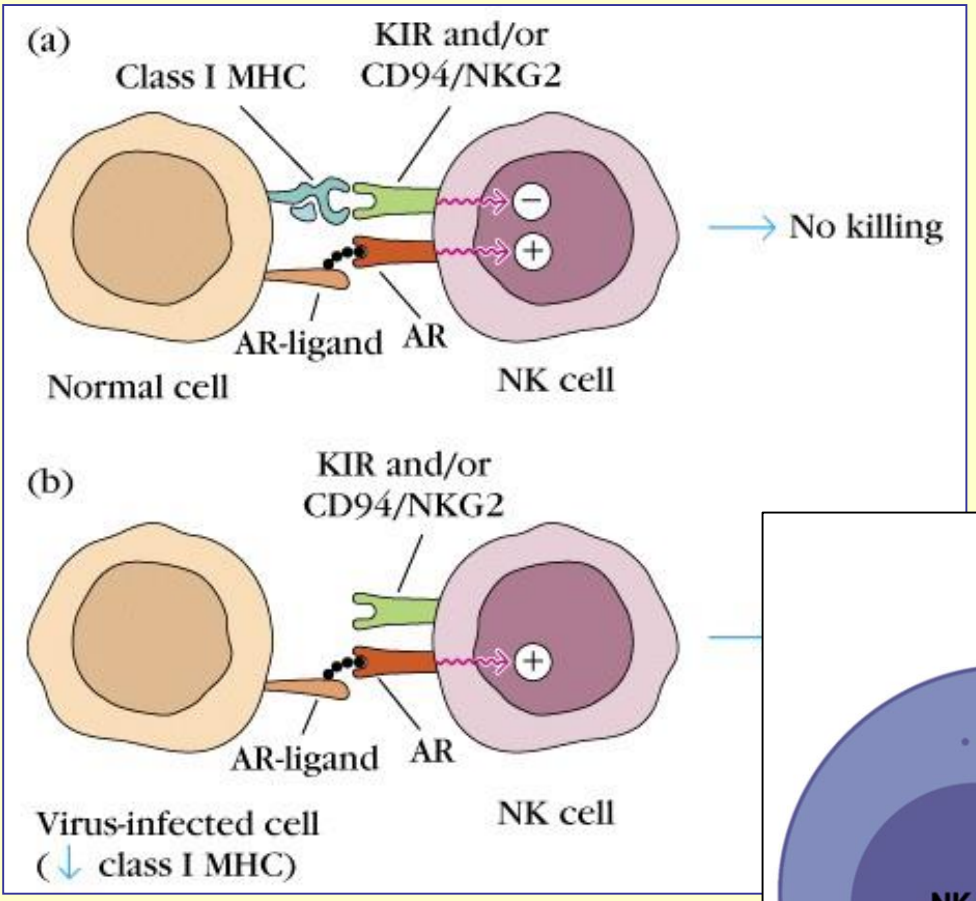


NK-cell receptors:

Killer inhibitory receptors (KIR): recognize normal self MHC-I molecules

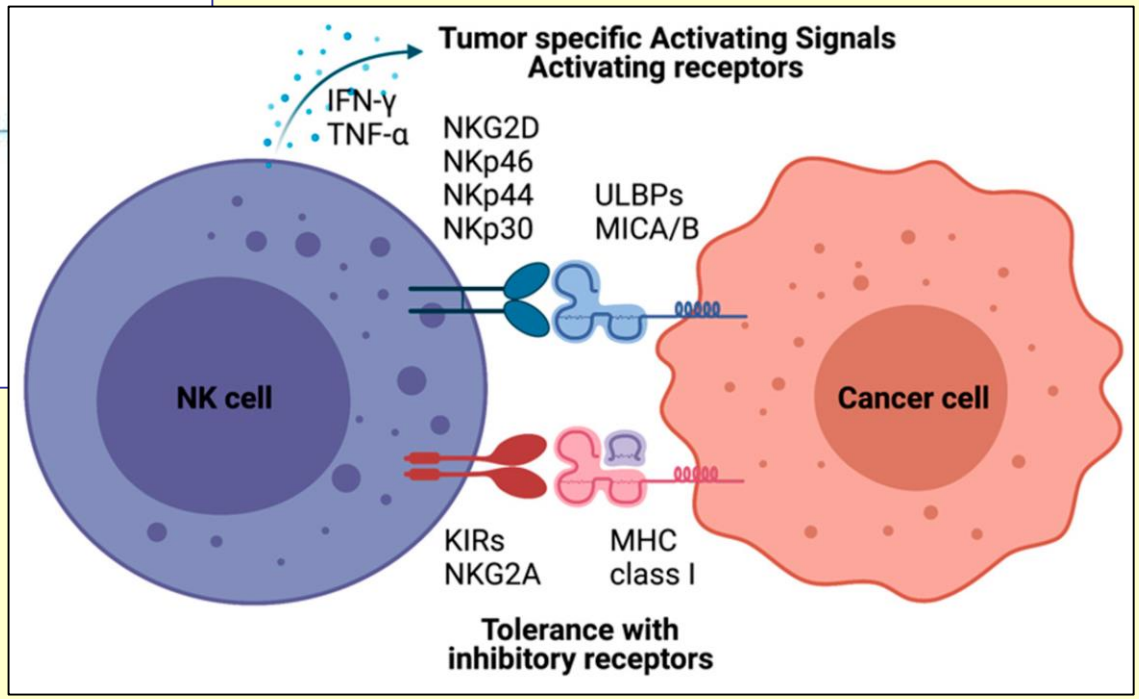
Killer activatory receptors (KAR): recognize aberrant glycosylation on tumor or virus infected cell surface

Opposite signal model of NK cell activation



Destruction of a virally infected cell

Tumour cell destruction



Antibody-dependent cellular cytotoxicity (ADCC)

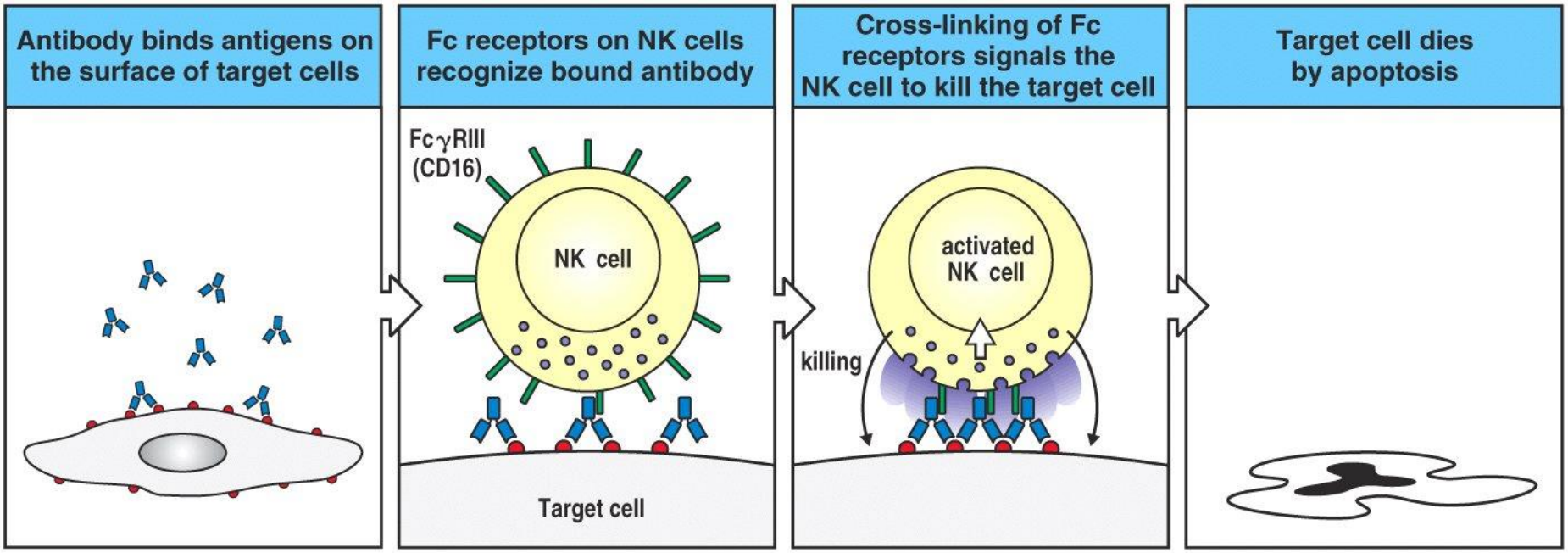


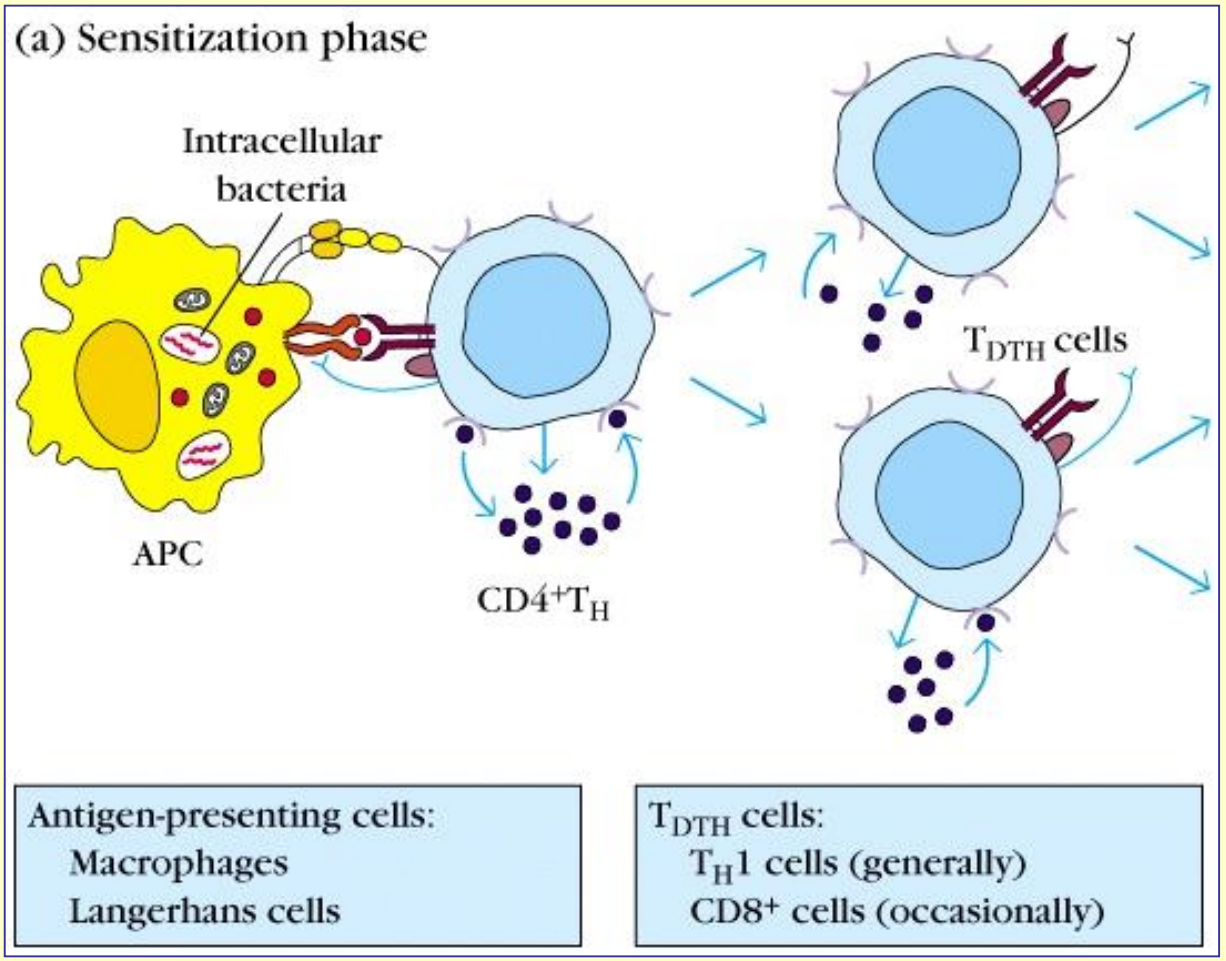
Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

T_H –cell mediated macrophage activation

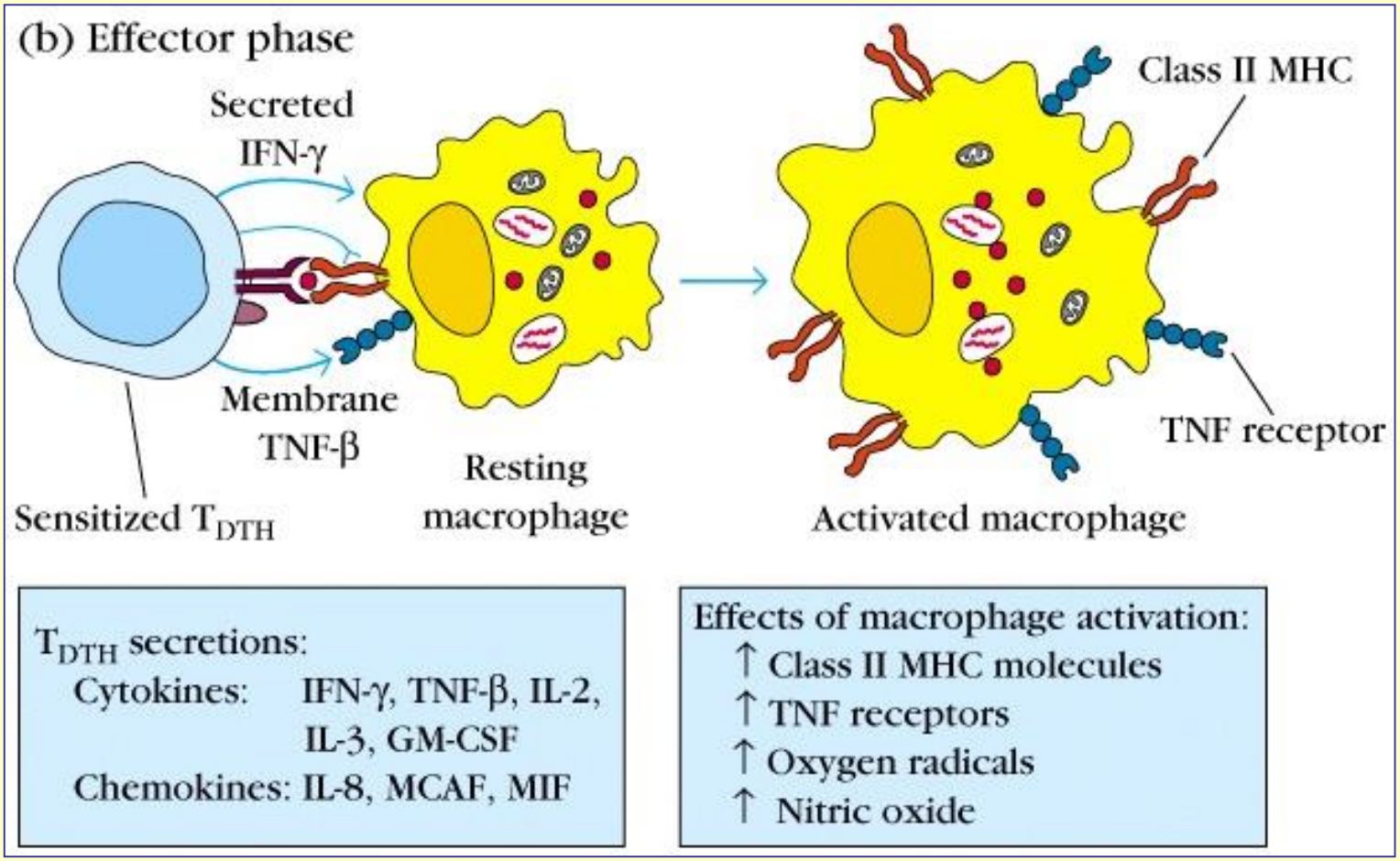
Delayed type hypersensitivity = DTH

Immuneresponses against intravesicular microorganisms

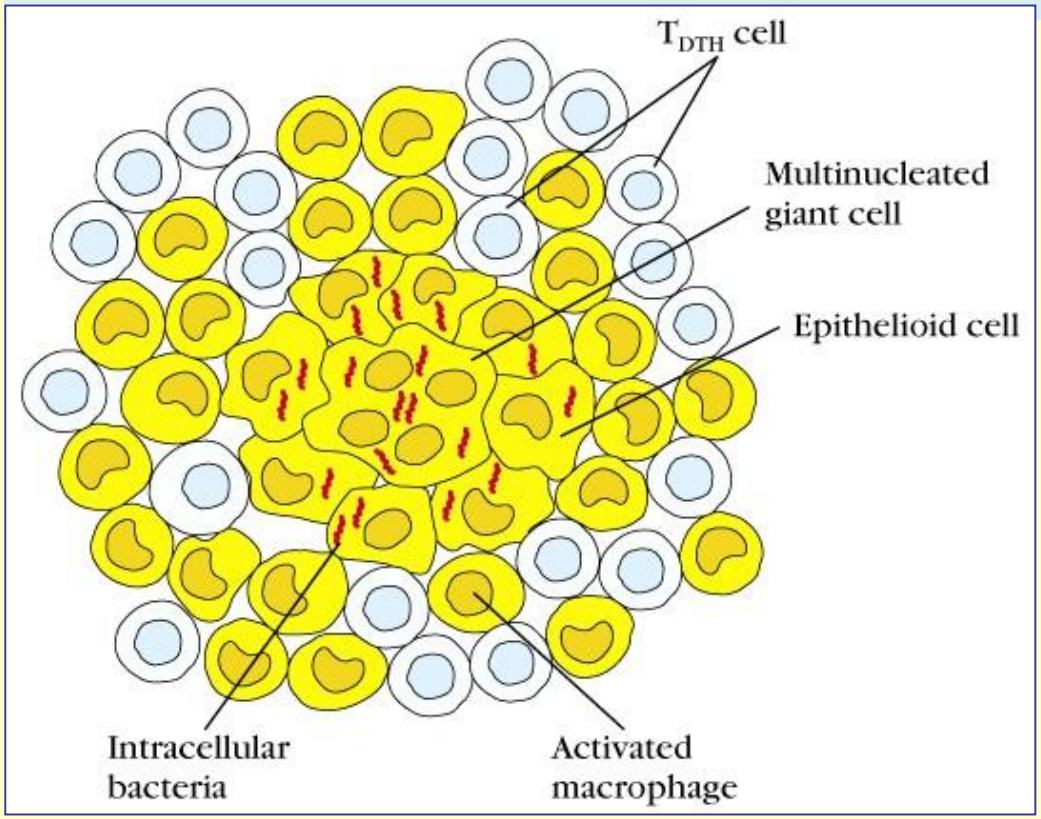
I. Sensitization:

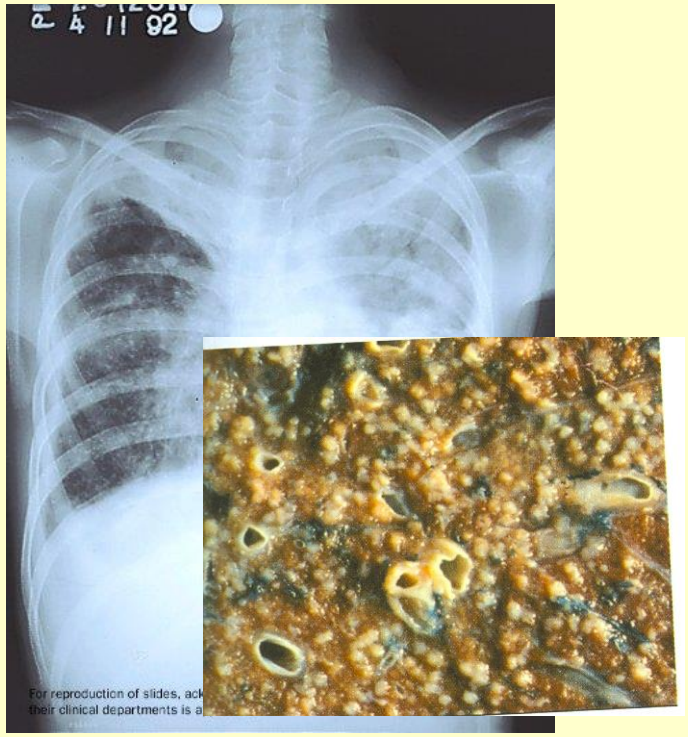


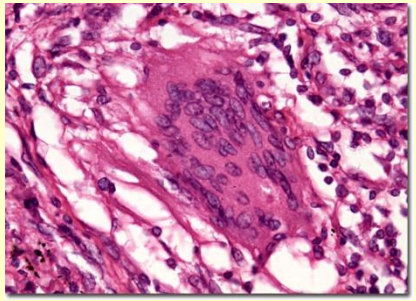
II. Effector phase



Prolonged DTH – granuloma formation

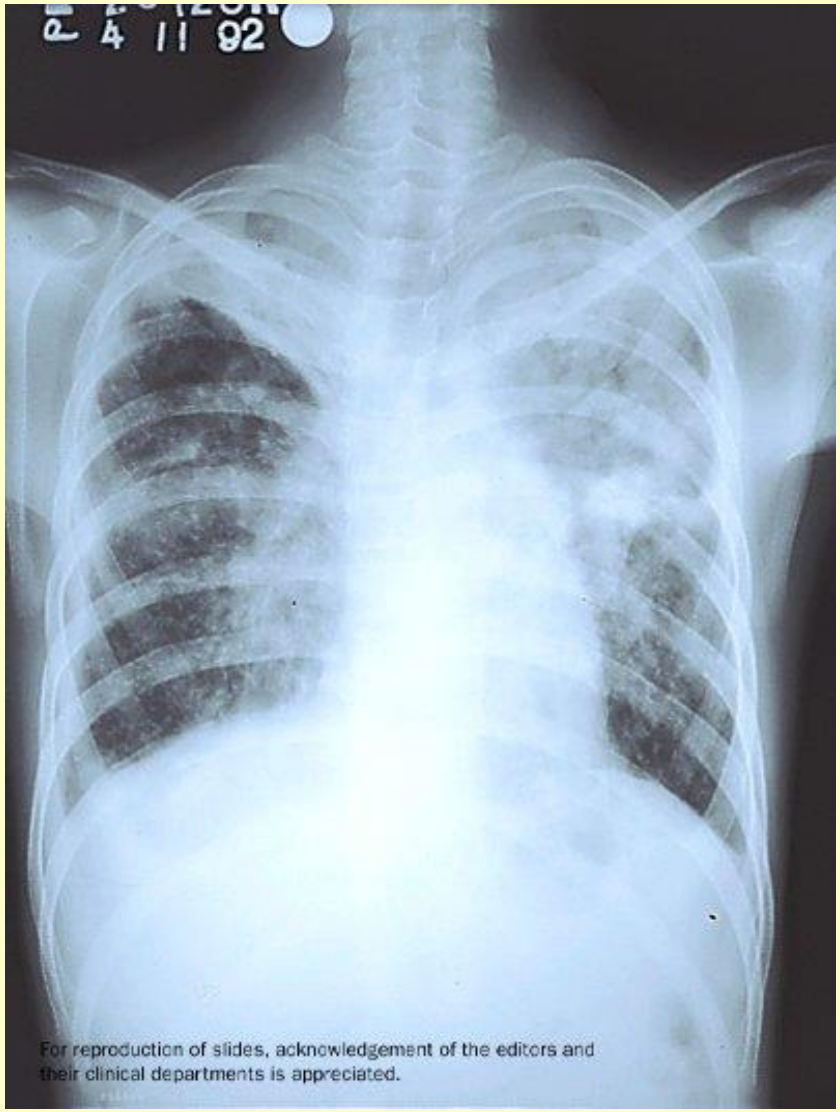






Miliaris tuberculosis

Prolonged DTH – granuloma formation



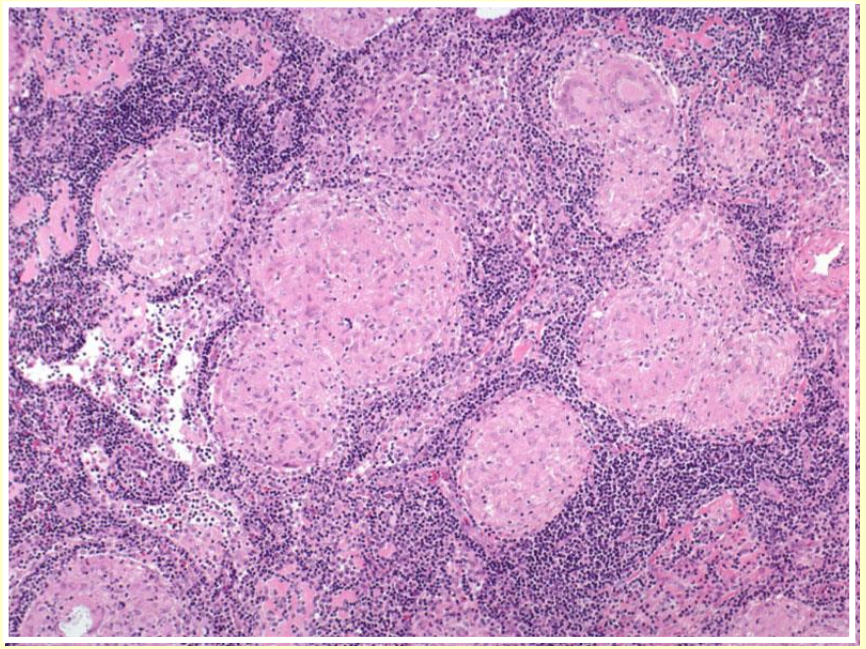


TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	Contact antigens
Intracellular fungi	Picrylchloride
Pneumocystis carinii	Hair dyes
Candida albicans	Nickel salts
Histoplasma capsulatum	Poison ivy
Cryptococcus neoformans	Poison oak
Intracellular parasites	
Leishmania sp.	

Effect of contact antigens