

Cellular & Molecular Immunology



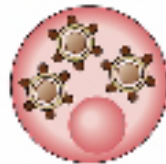




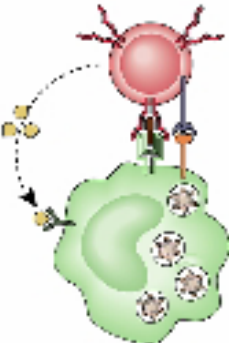

Cell-mediated Immunity

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Department of Pathology & Laboratory Medicine

April 6, 2009

Today's Presentation:

- **Overview**
- **Cellular Interactions In Humoral Immune Responses – Already done in a previous lecture (Raveche)**
- **Cellular Interactions In Cell-mediated Immune Responses**

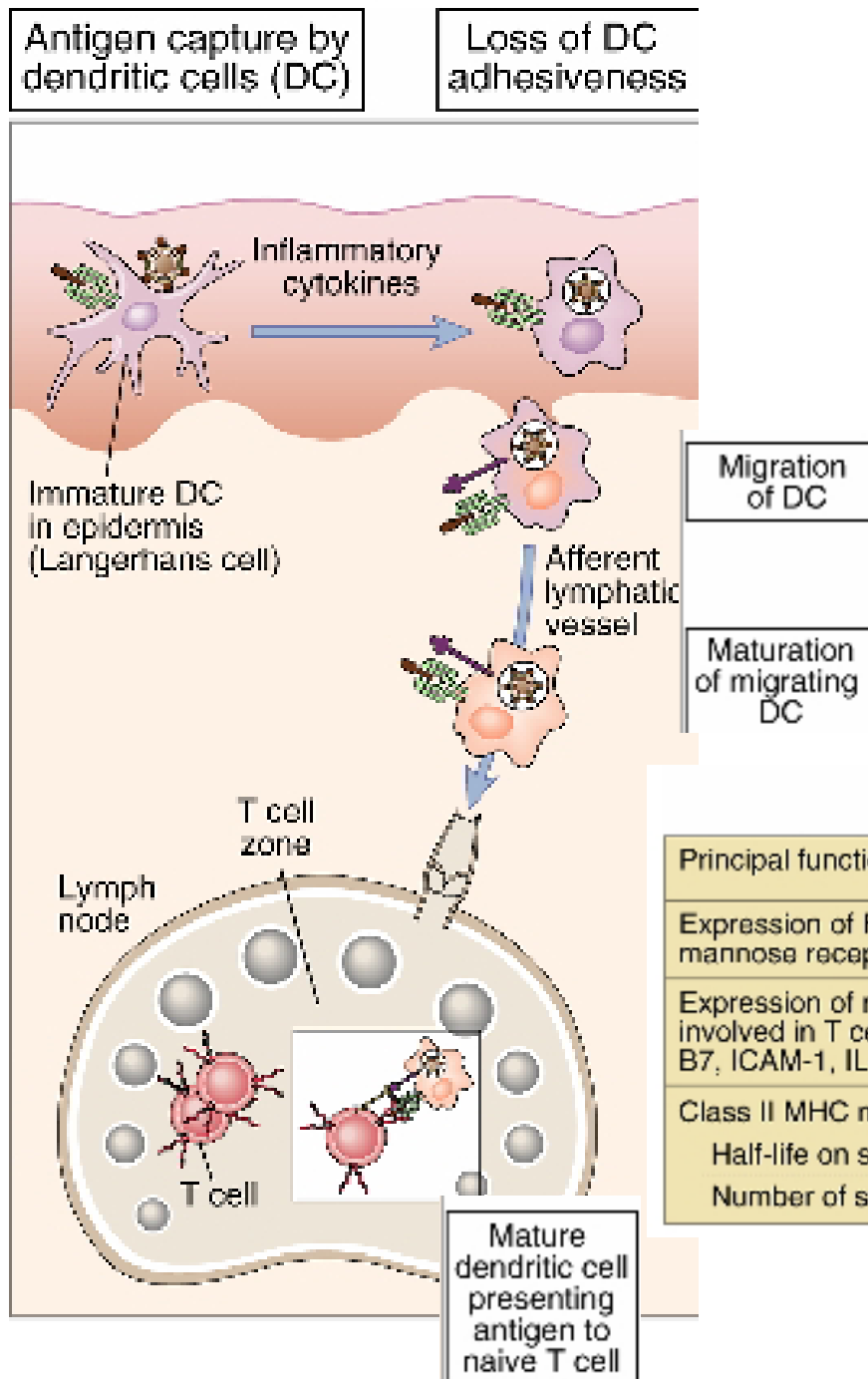
	Humoral immunity	Cell-mediated immunity	
Microbe	 <p>Extracellular microbes</p>	 <p>Phagocytosed microbes in macrophage</p>	 <p>Intracellular microbes (e.g., viruses) replicating within infected cell</p>
Responding lymphocytes	 <p>B lymphocyte</p>	 <p>Helper T lymphocyte</p>	 <p>Cytolytic T lymphocyte</p>
Effector mechanism	 <p>Secreted antibody</p>		
Transferred by	Serum (antibodies)	Cells (T lymphocytes)	Cells (T lymphocytes)
Functions	Block infections and eliminate extracellular microbes	Activate macrophages to kill phagocytosed microbes	Kill infected cells and eliminate reservoirs of infection

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Figure 1-2

Cellular interactions in immune responses are triggered by exposure to antigen

The fate of antigen in the body depends on:

- the nature of the antigen**
- the route of antigen entry**
- immunocompetence of the individual**



Role of dendritic cells in antigen capture and presentation

	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	—
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	— or low	++
Class II MHC molecules		
Half-life on surface	~10 hr	>100 hr
Number of surface molecules	~10 ⁵	~7 x 10 ⁶

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Fig. 5-6

Antigen capture by the immune system

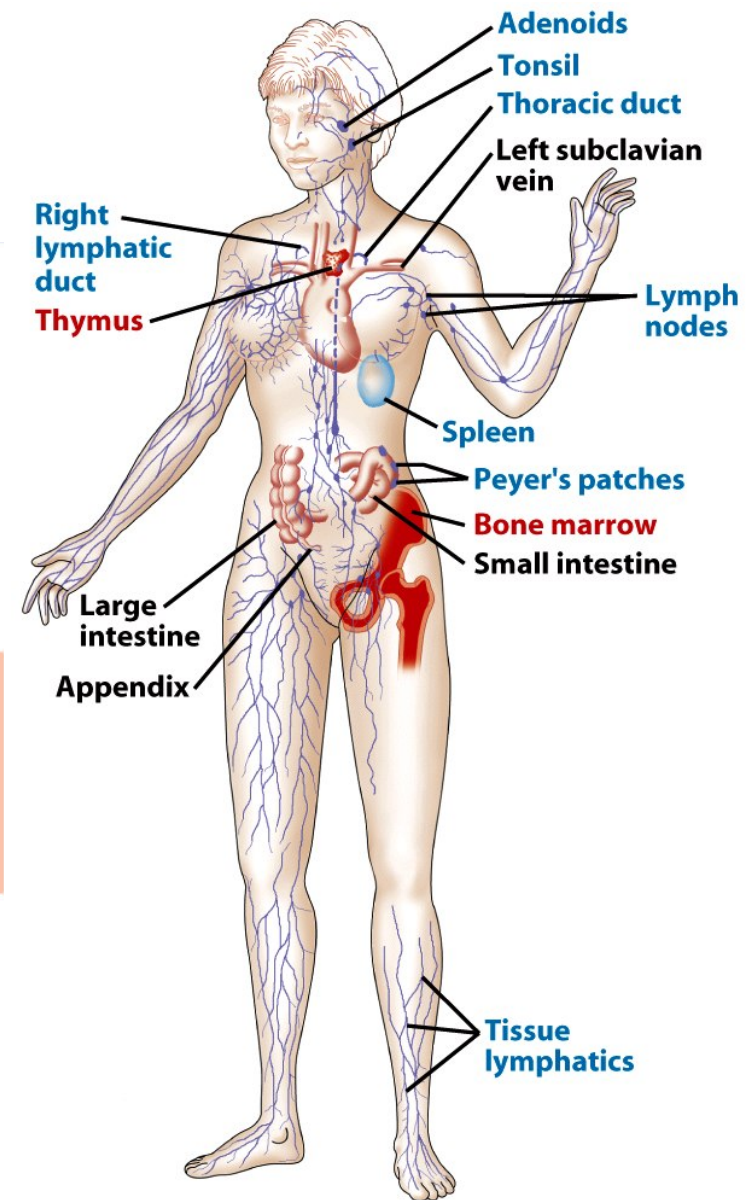
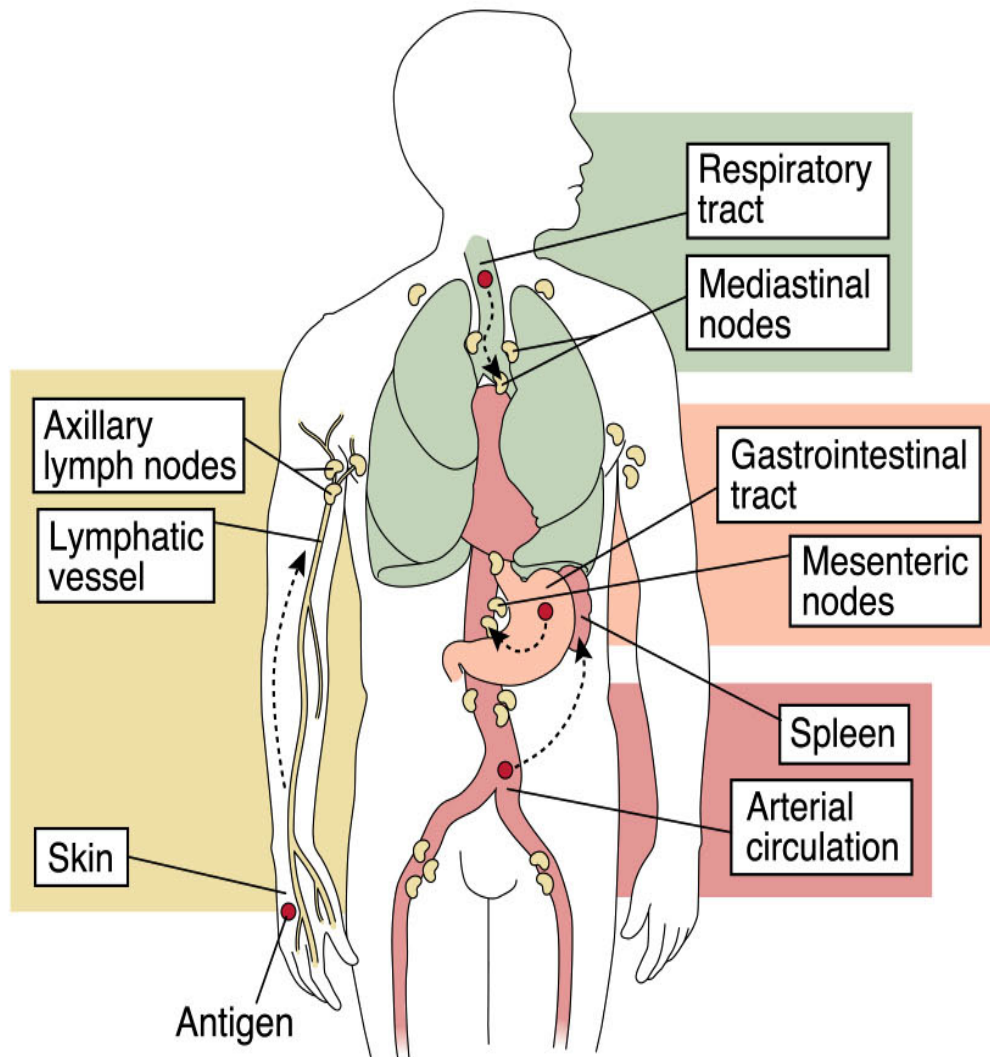
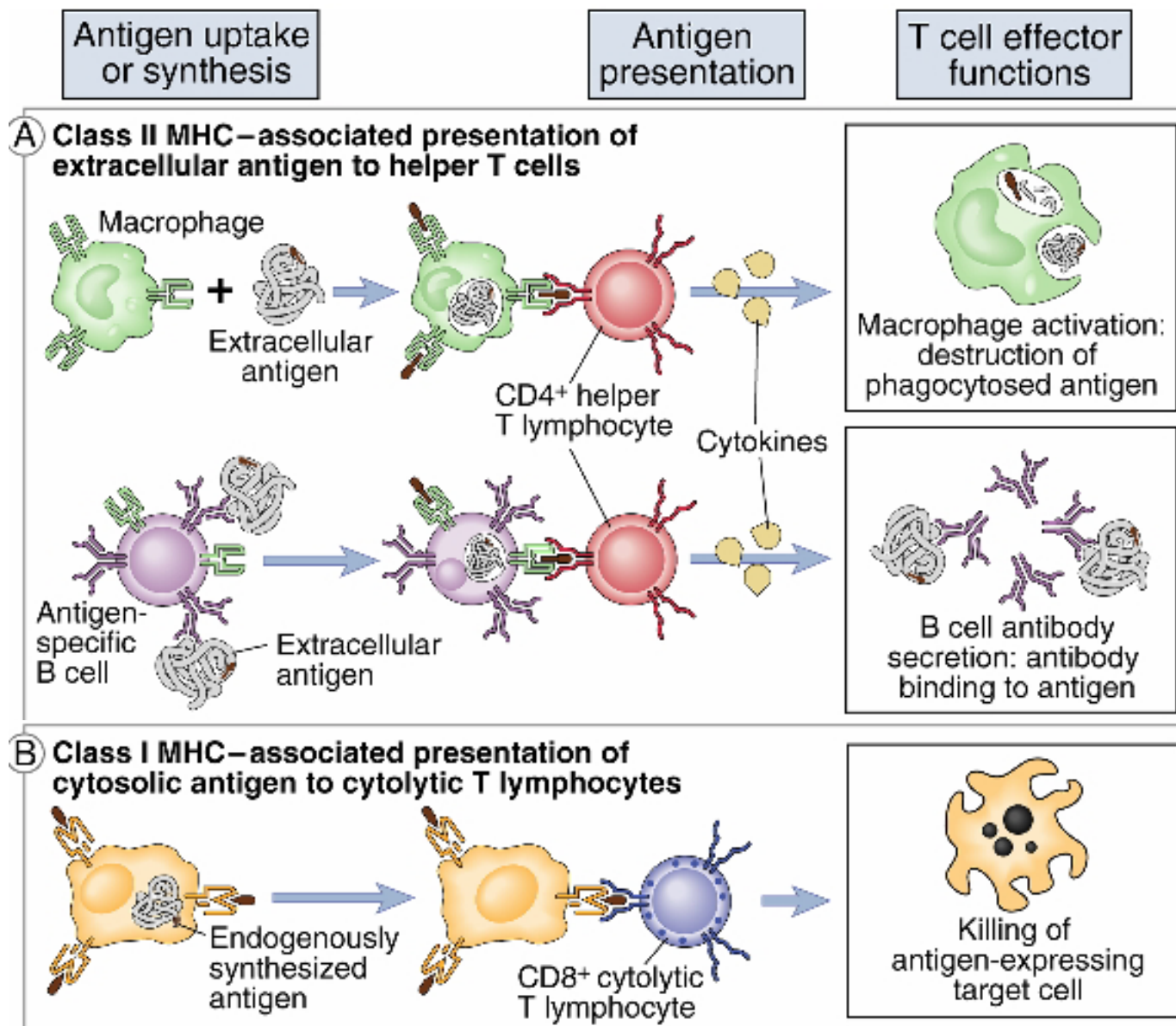


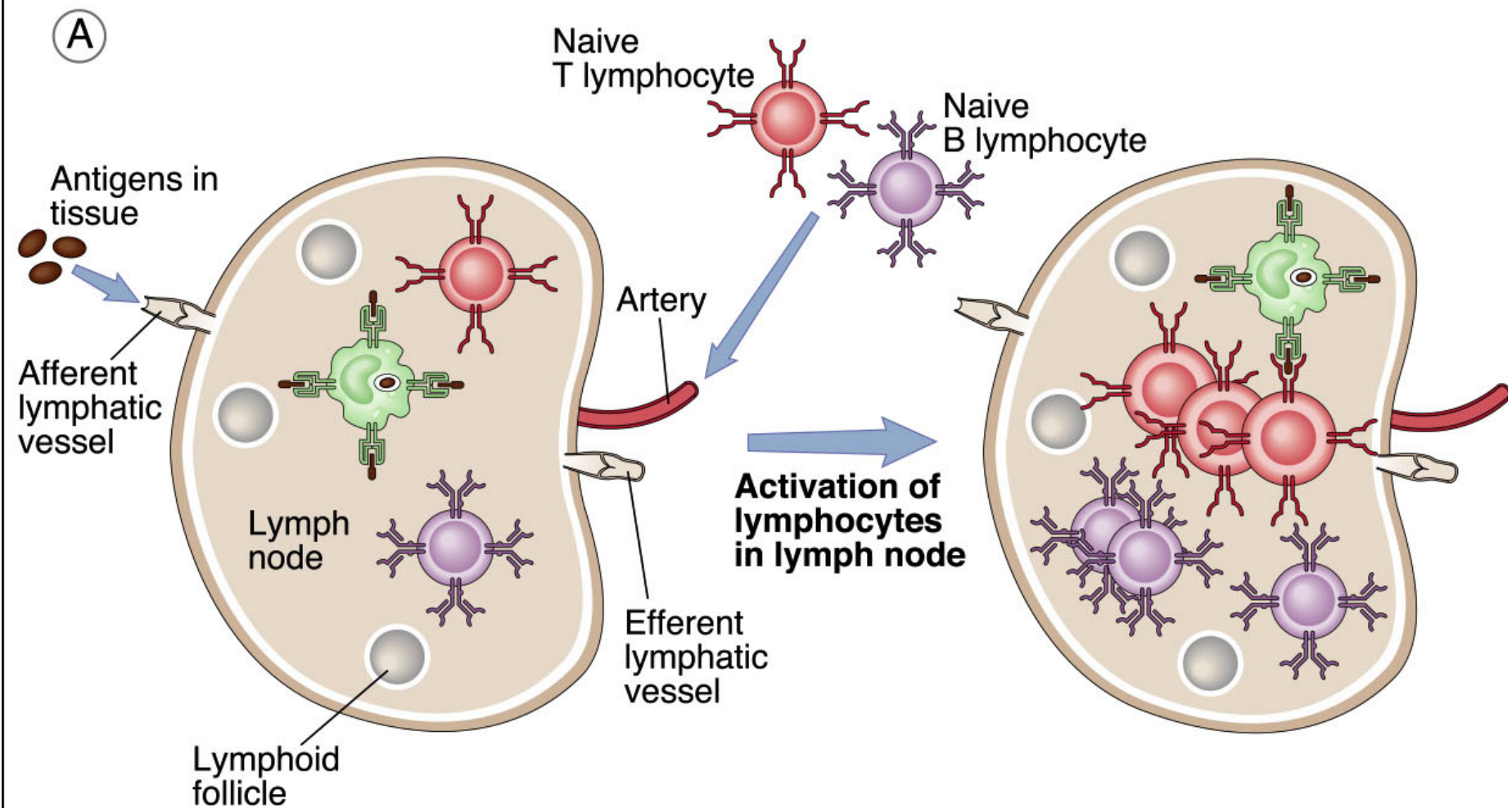
Figure 2-11
Kuby IMMUNOLOGY, Sixth Edition
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Presentation of antigen to T cells

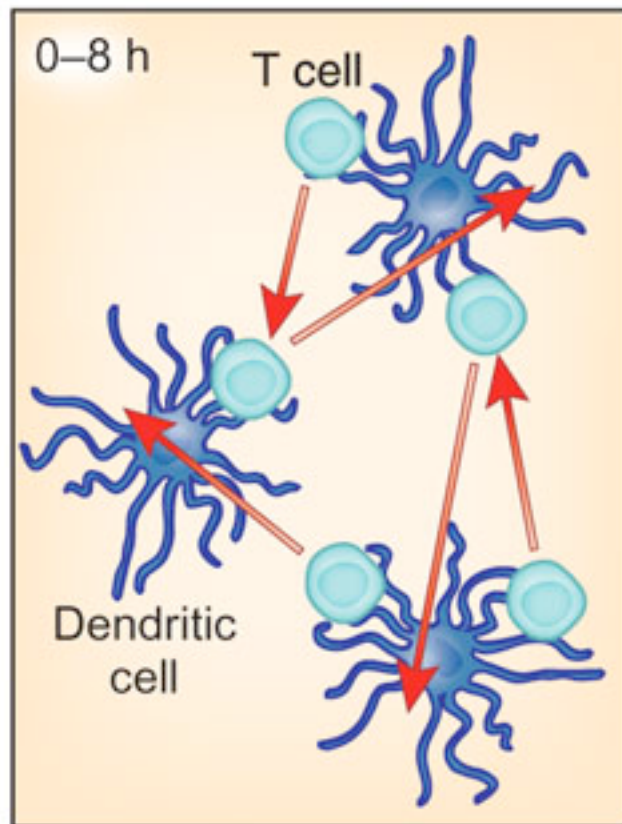


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Fig. 5-17

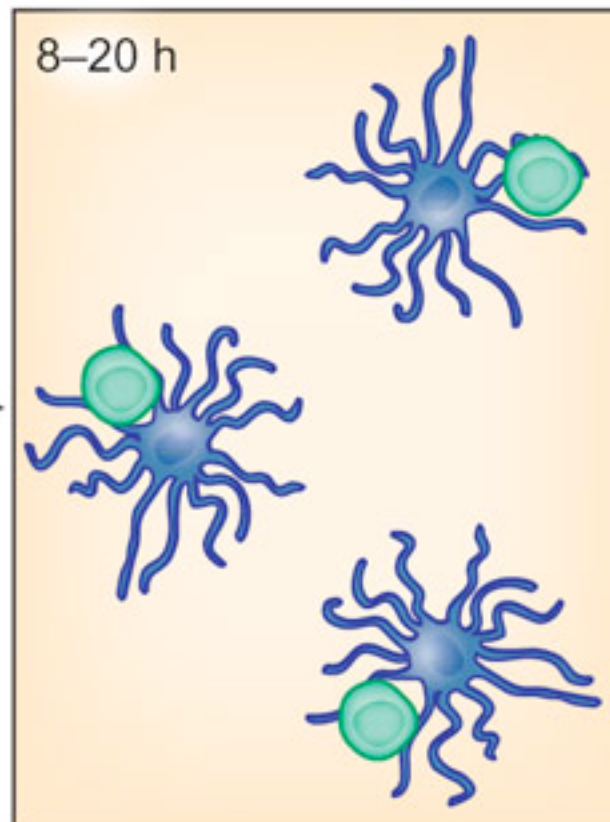
Sequence of events in an immune response



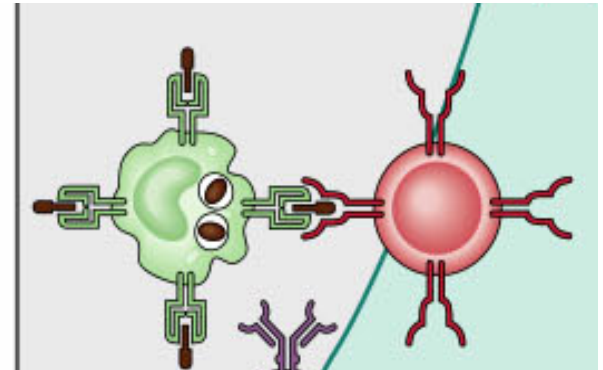
Phase I



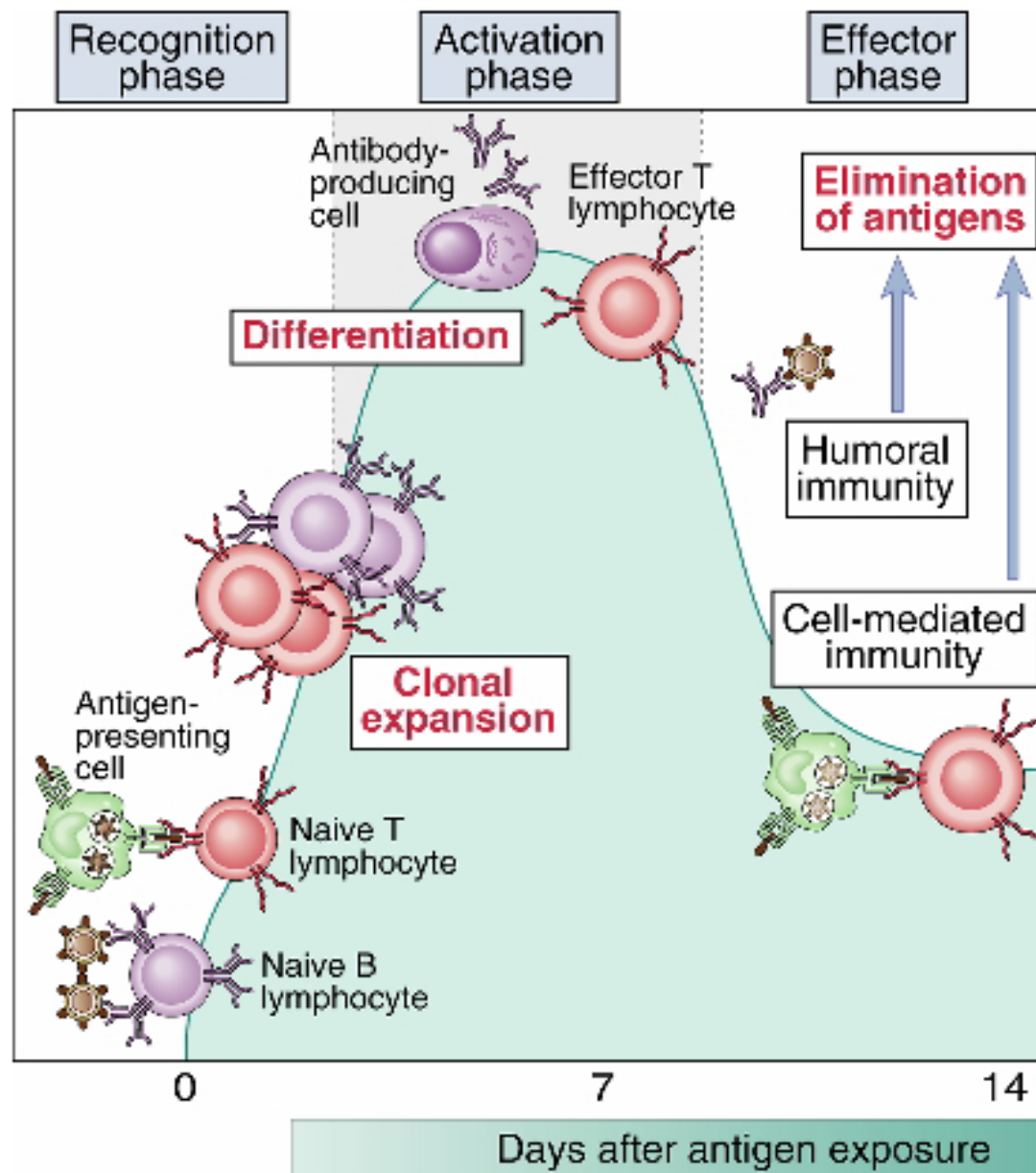
Phase II



Recognition

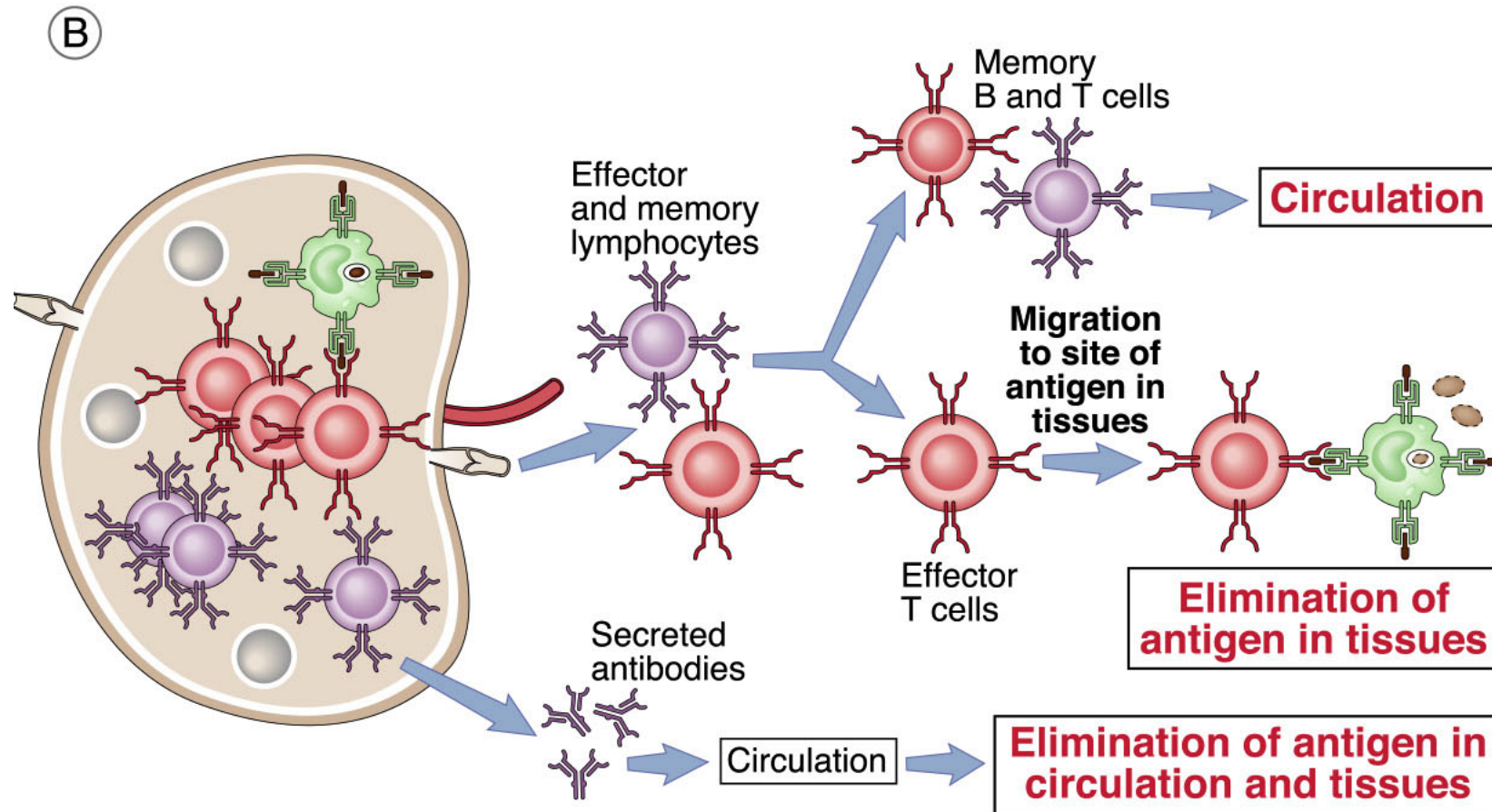


Phases of the adaptive immune response



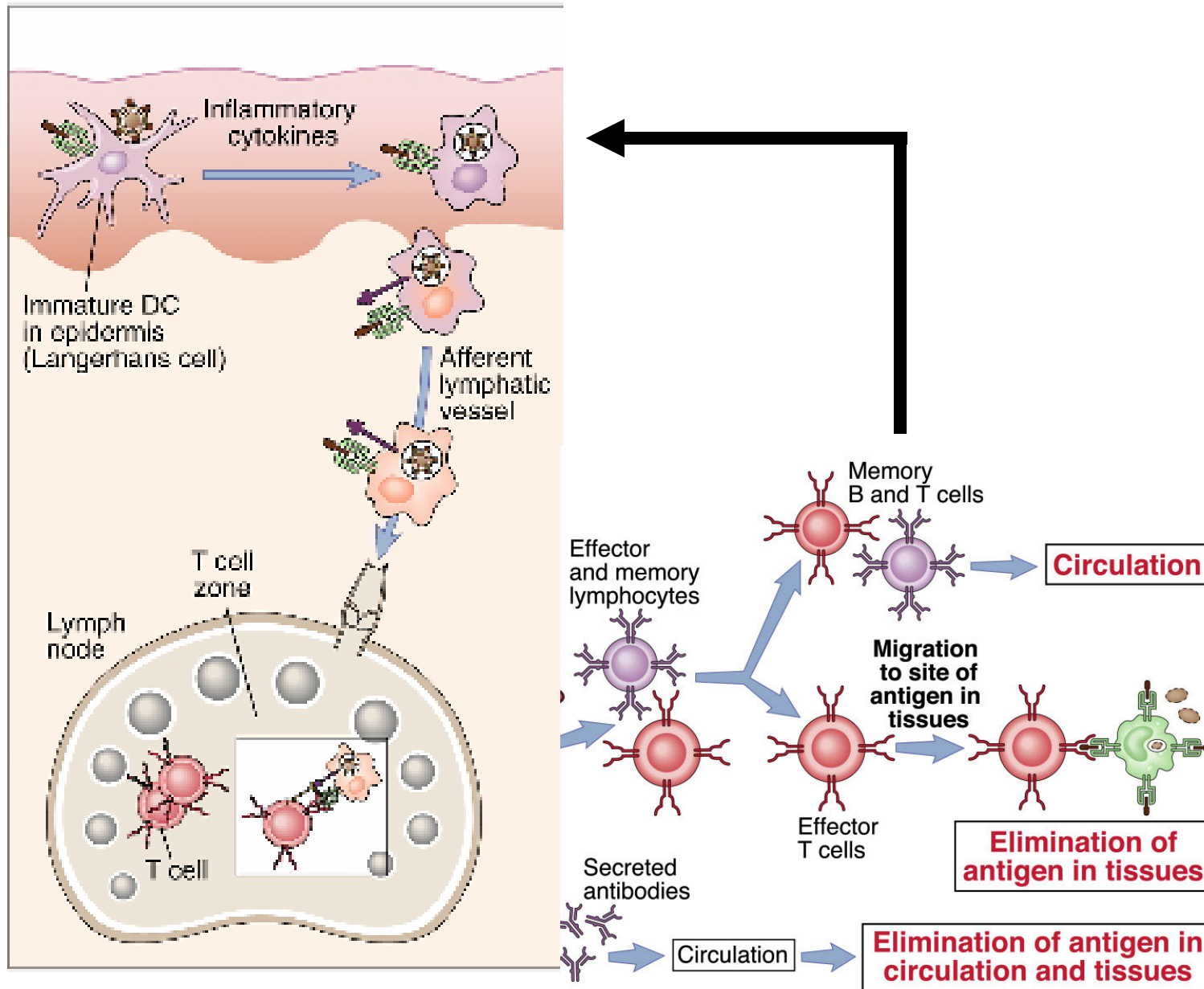
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Fig. 1-6

Sequence of events in an immune response



Antigen capture by dendritic cells (DC)

Loss of DC adhesiveness

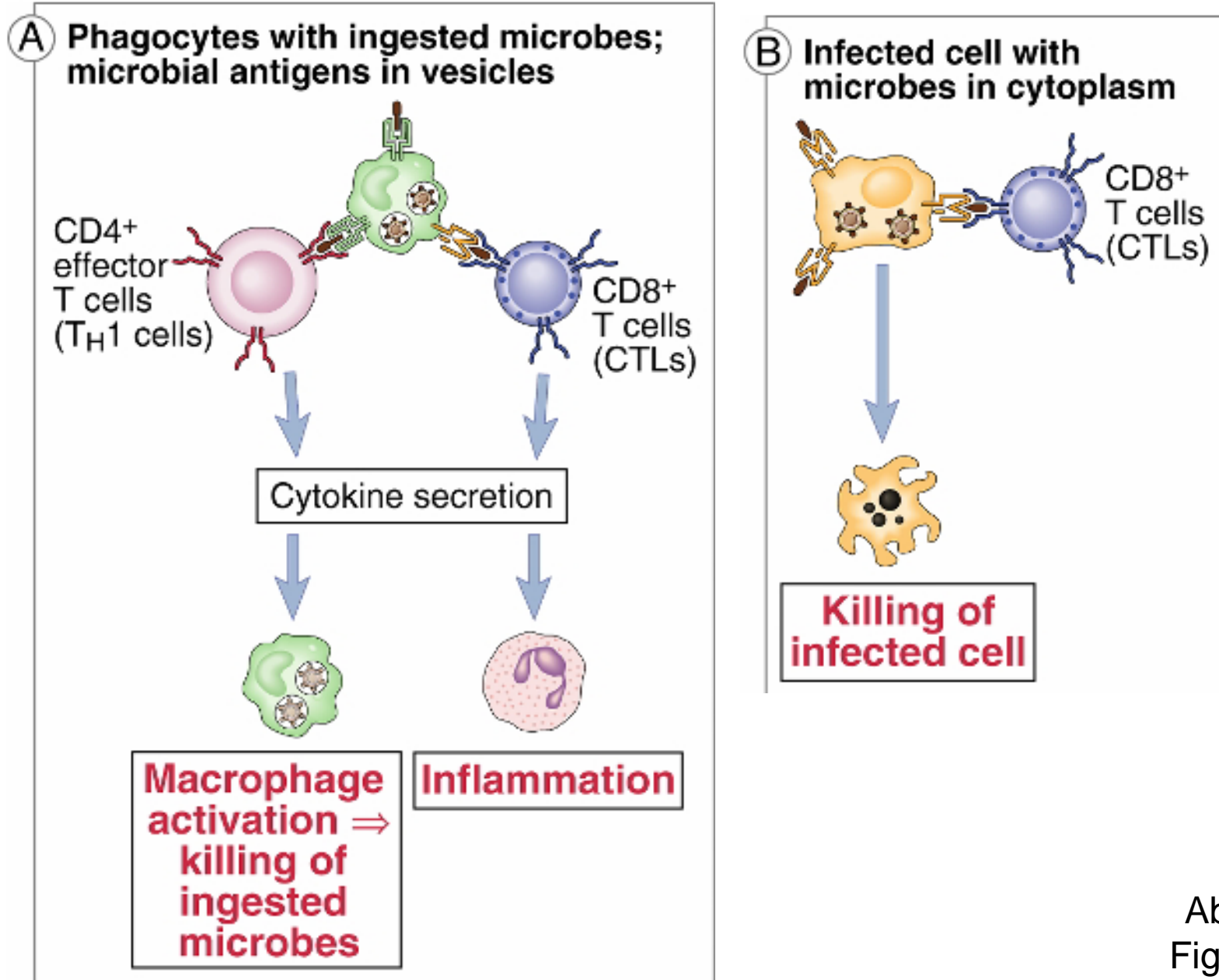


Cellular Interactions In Cell-mediated Immune Responses

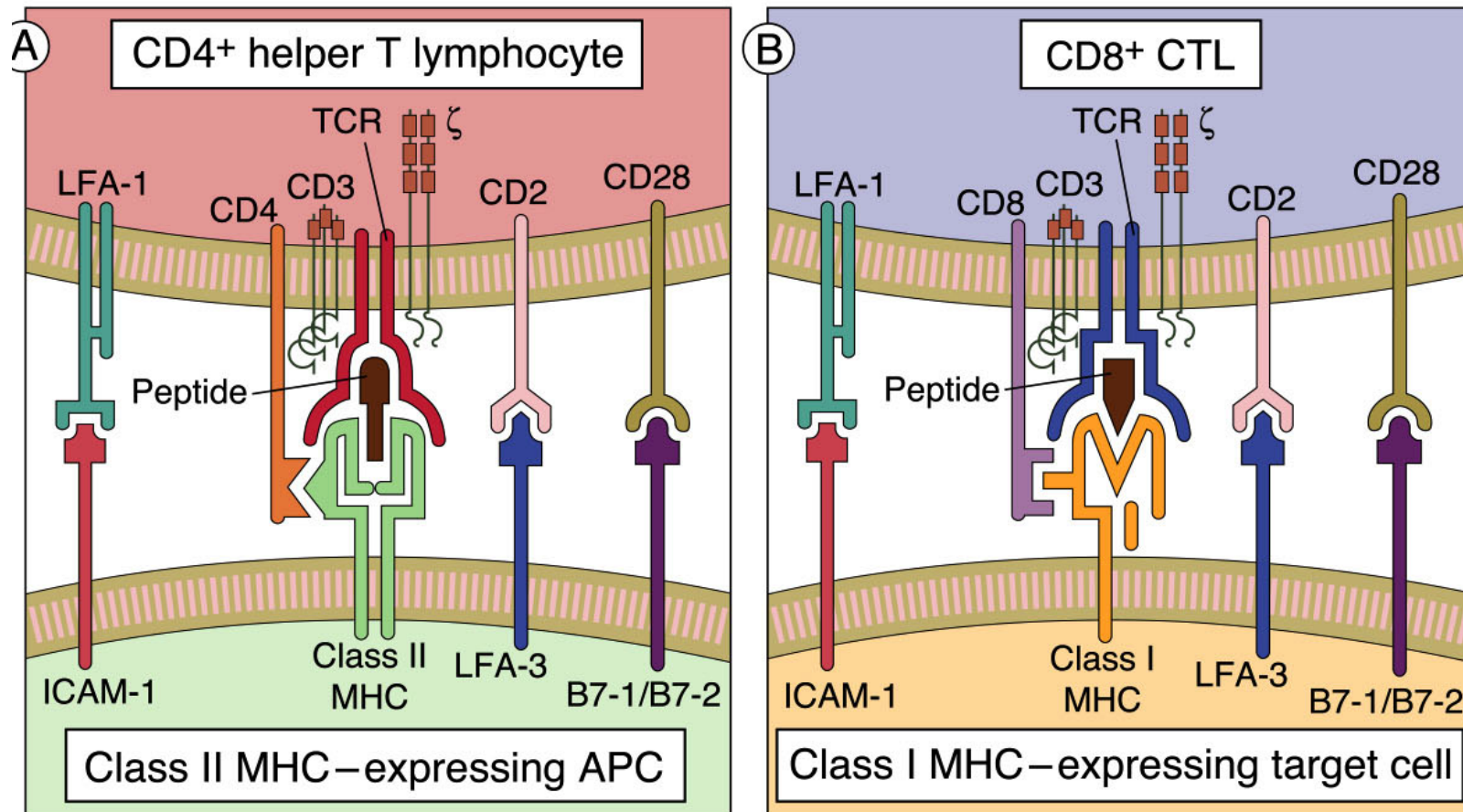
T cell independent CMI responses:

- Phagocytosis**
- NK cell cytotoxicity**
- Cytokines (e.g., TNF; IL-12)**
- Complement**

Cell mediated immunity with T cells



Responses at the molecular level: T cell accessory molecules and their ligands



Immunity to *Listeria monocytogenes*

Listeria monocytogenes = Intracellular pathogen

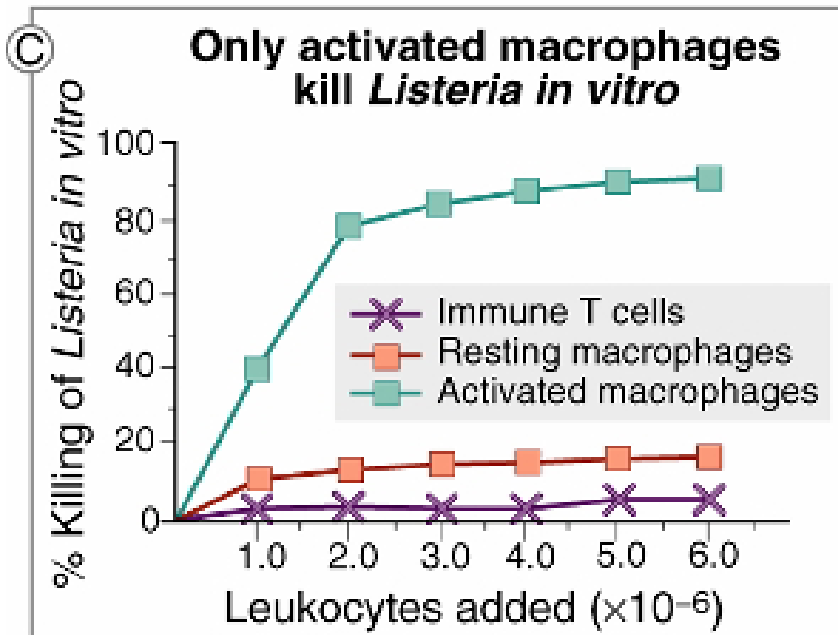
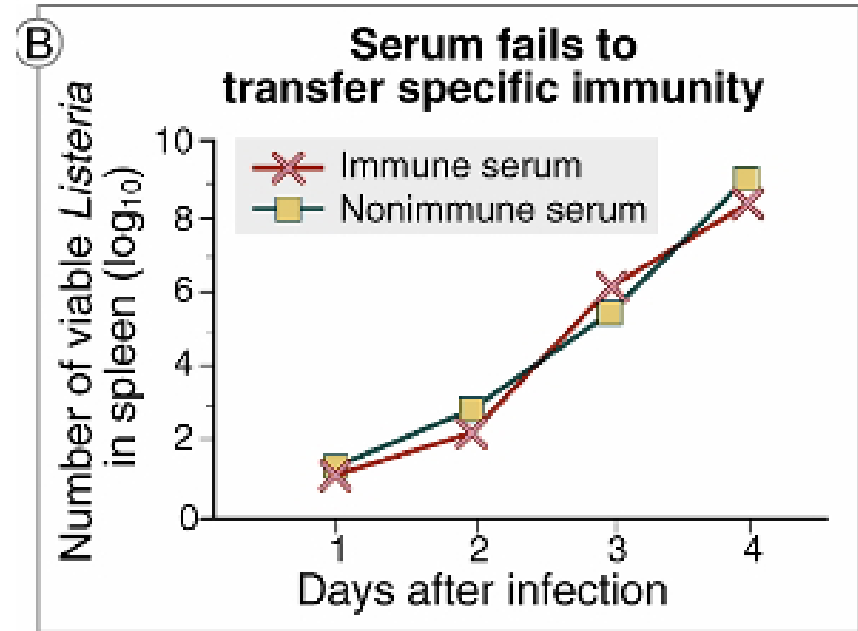
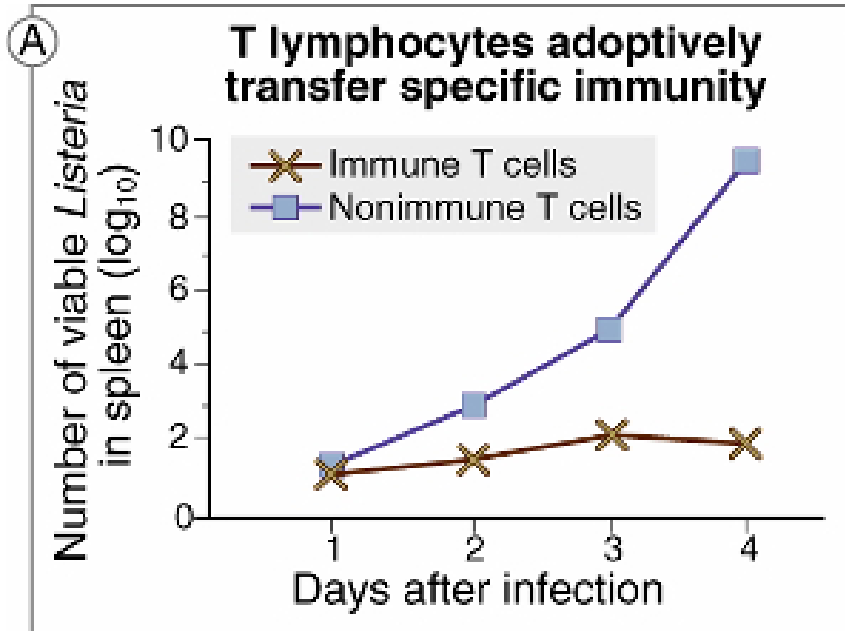
Experiment:

Inject mouse with killed *Listeria* bacteria to stimulate immunity that enables mouse to resist challenge injection with live organisms

Determine the mechanism of protection by transferring serum or cells from the immune mouse to a naïve recipient.

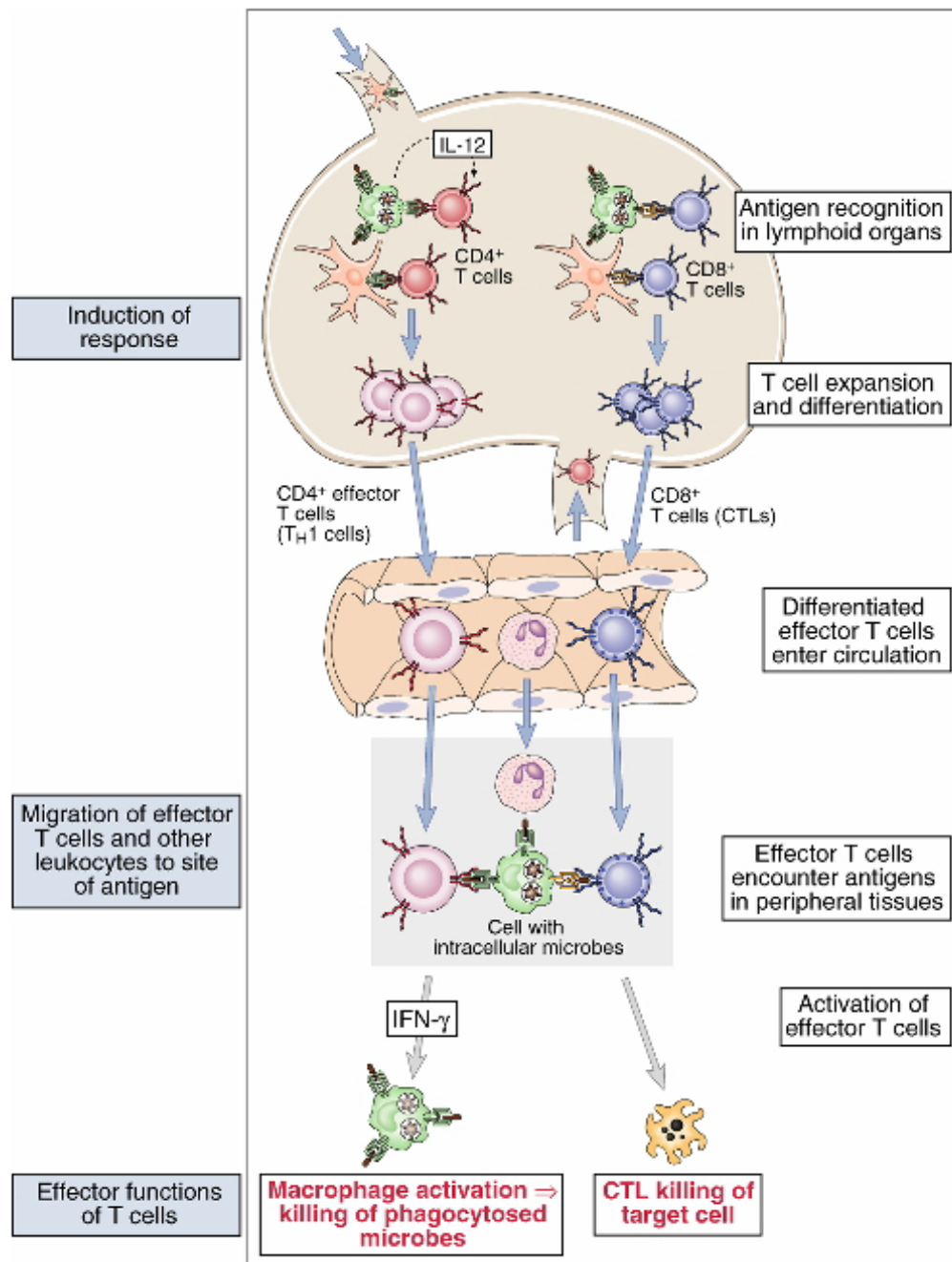
Then, challenge the recipient mouse and count the number of *Listeria* organisms in the spleen

Immunity to *Listeria monocytogenes*



Conclusions:

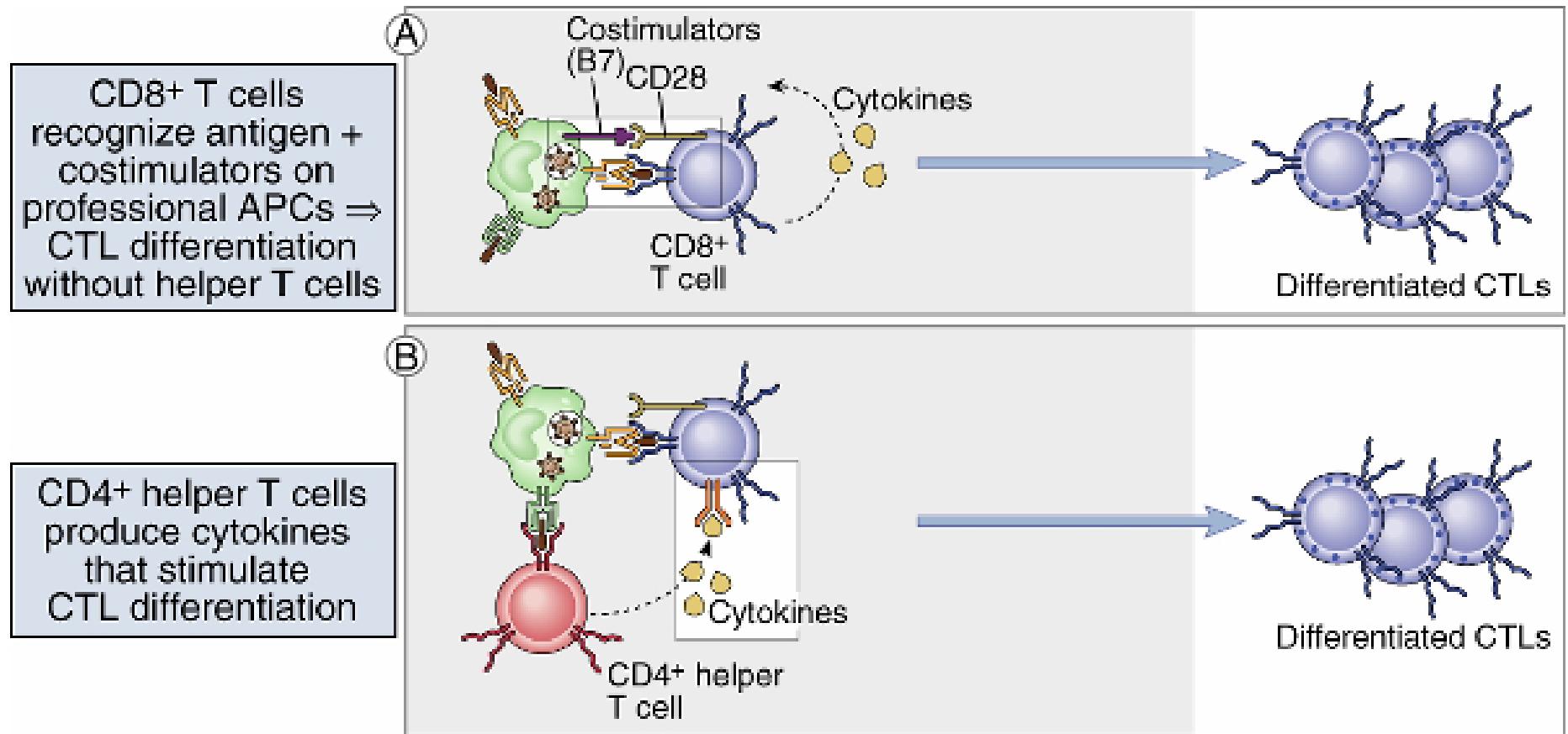
- Immune T cells are necessary, but not sufficient by themselves for immune protection.
- Immune T cells must activate macrophages to kill *L. monocytogenes*



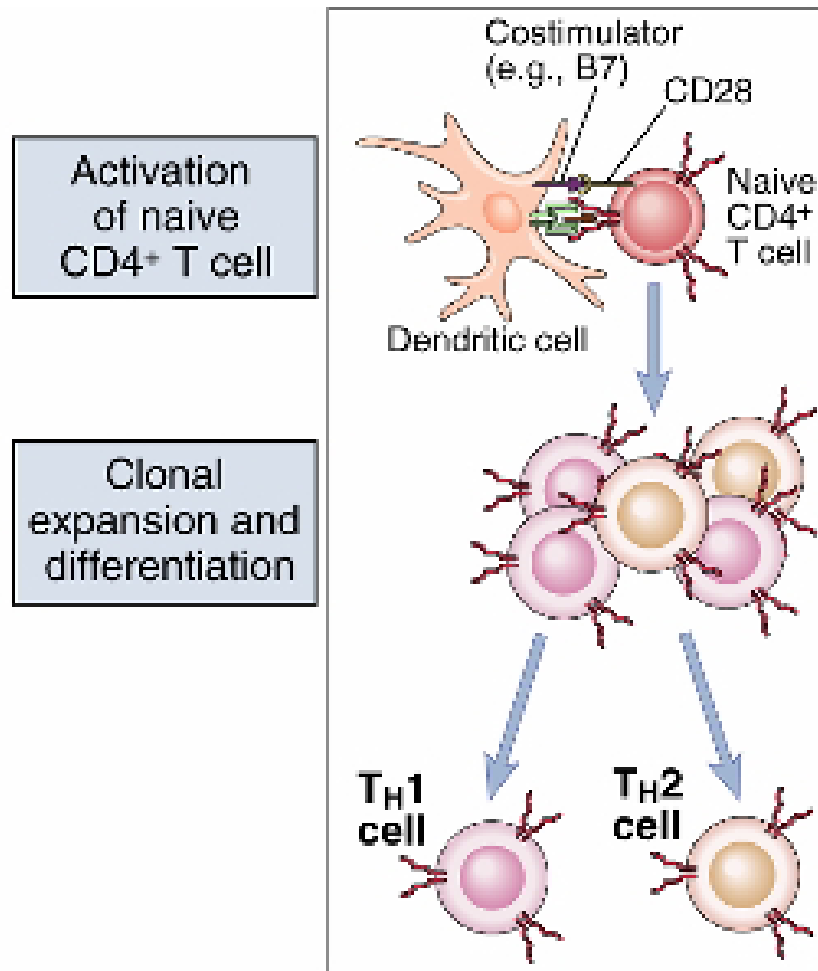
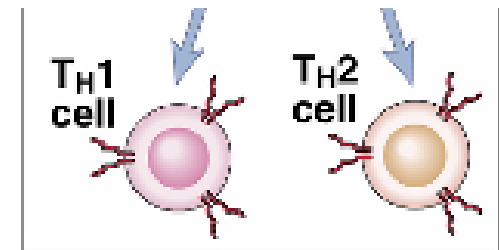
The induction and effector phases of cell-mediated immunity

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Fig 13-3

Role of co-stimulation and TH cells in stimulation/differentiation of CTLs



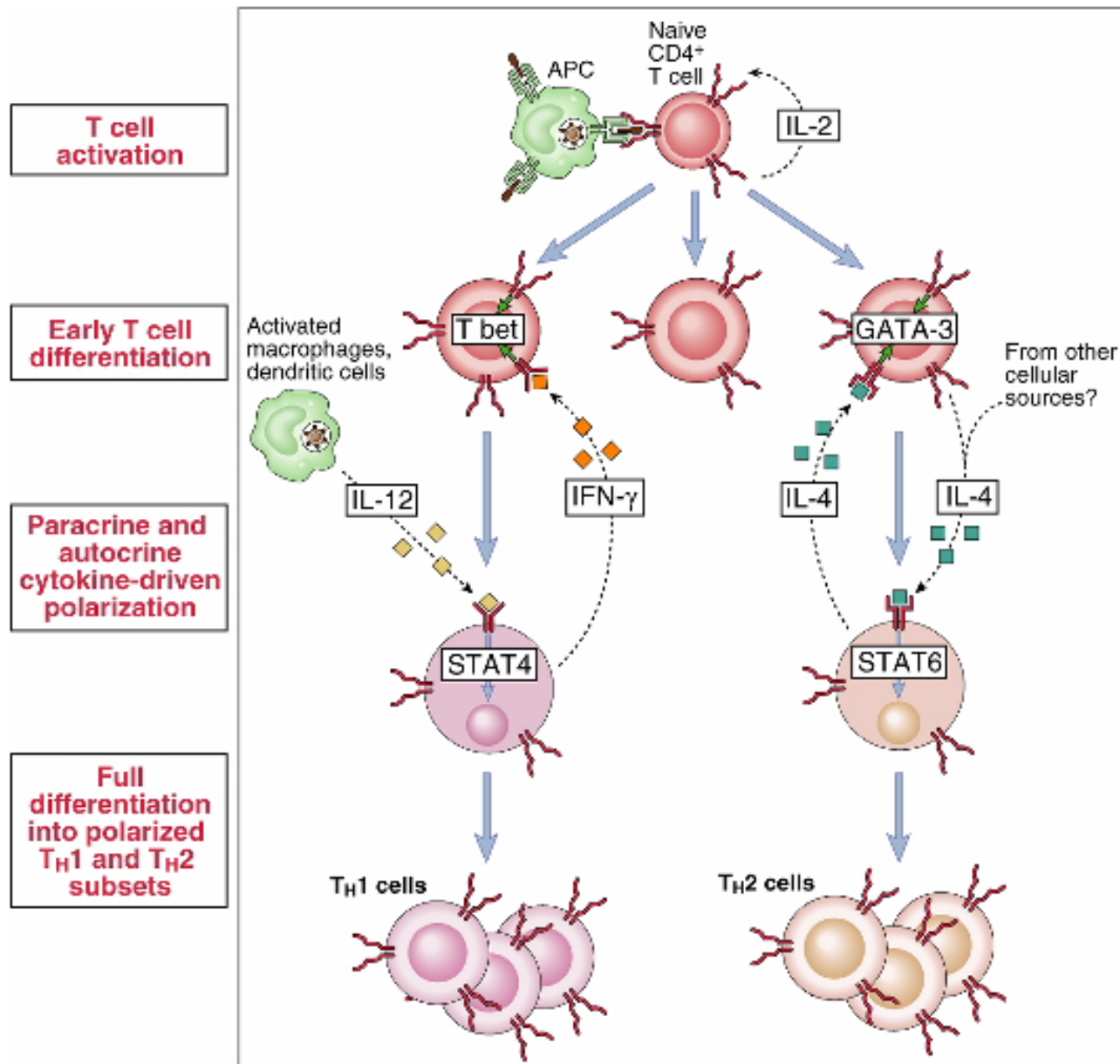
Properties of TH1 and TH2 subsets of CD4+ cells



Property	TH1 subset	TH2 subset
Cytokines produced		
IFN- γ	+++	-
IL-4, IL-5, IL-13	-	+++
IL-10	+/-	++
IL-3, GM-CSF	++	++
Cytokine receptor expression		
IL-12R β chain	++	-
IL-18R	++	-
Chemokine receptor expression		
CCR4	+/-	++
CXCR3, CCR5	++	+/-
Ligands for E- and P-selectin	++	+/-
Antibody isotypes stimulated	IgG2a (mouse)	IgE, IgG1 (mouse)/IgG4 (humans)
Macrophage activation	+++	-

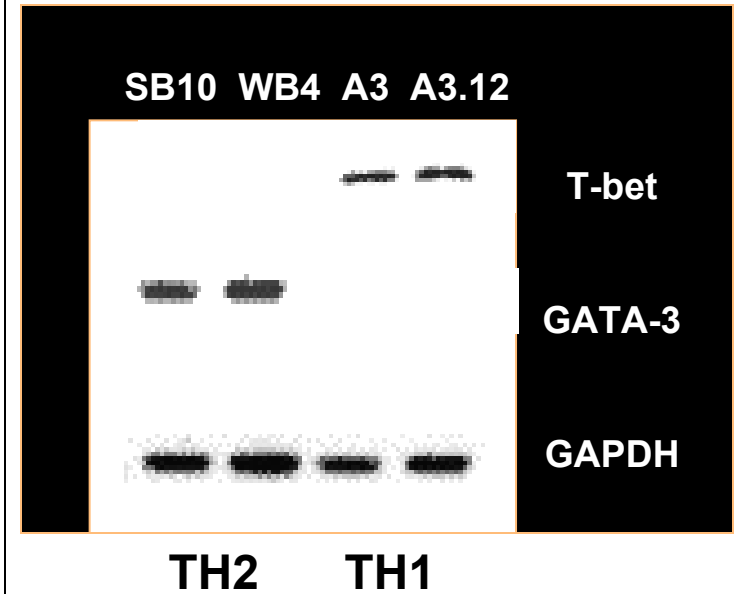
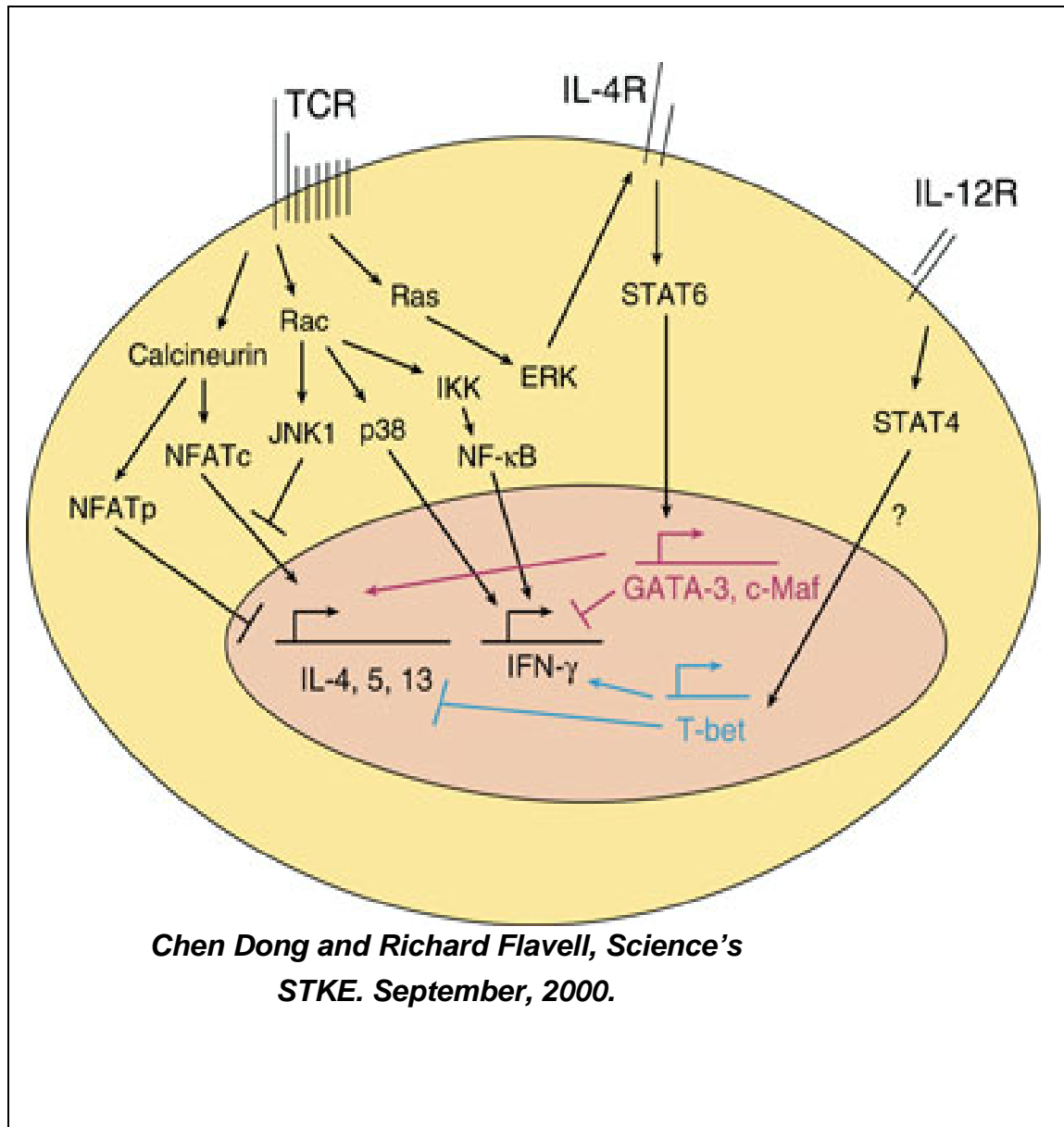
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Fig 13-6

Development of TH1 and TH2 subsets



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Fig 13-7

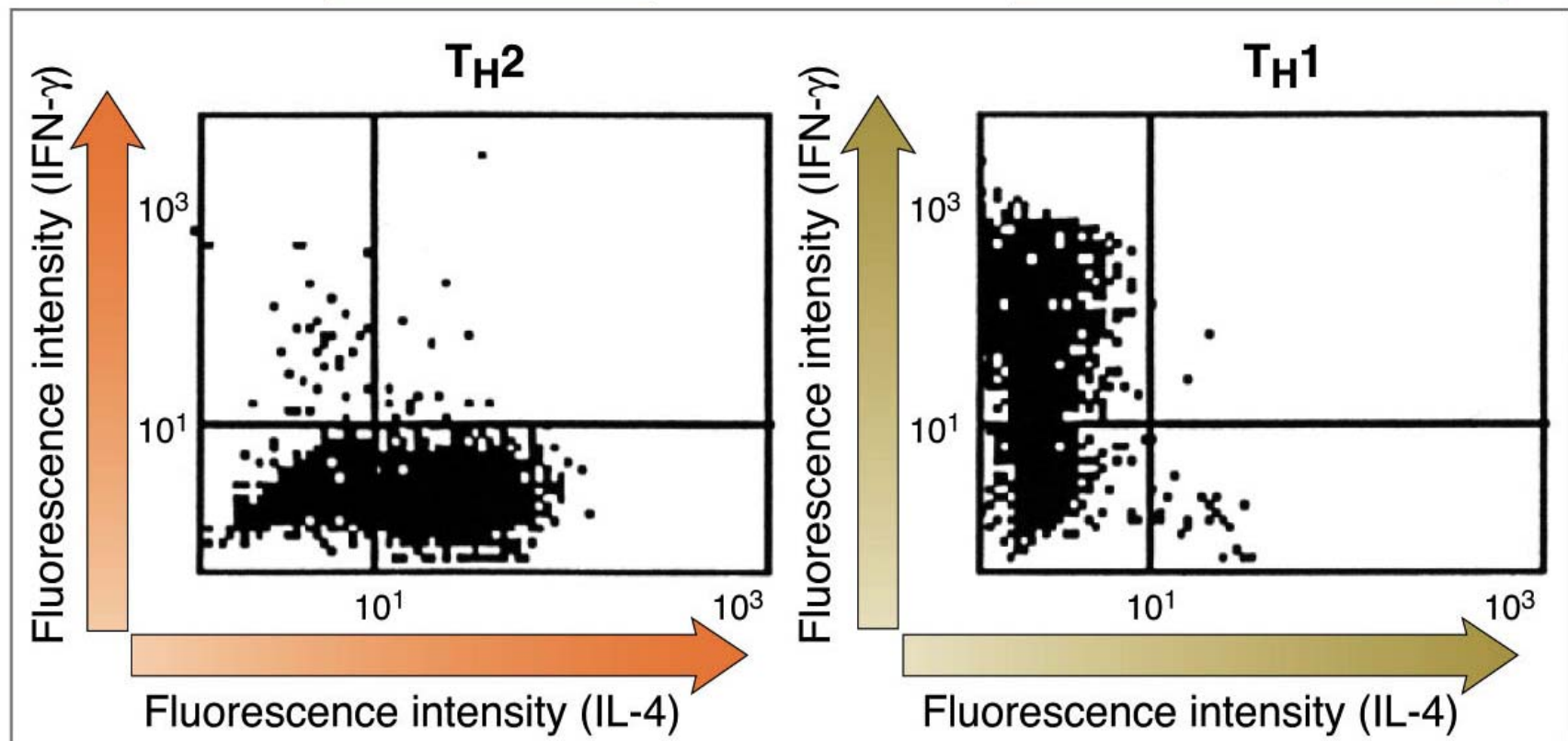
TH1 and TH2 use different cytokine transcription factors



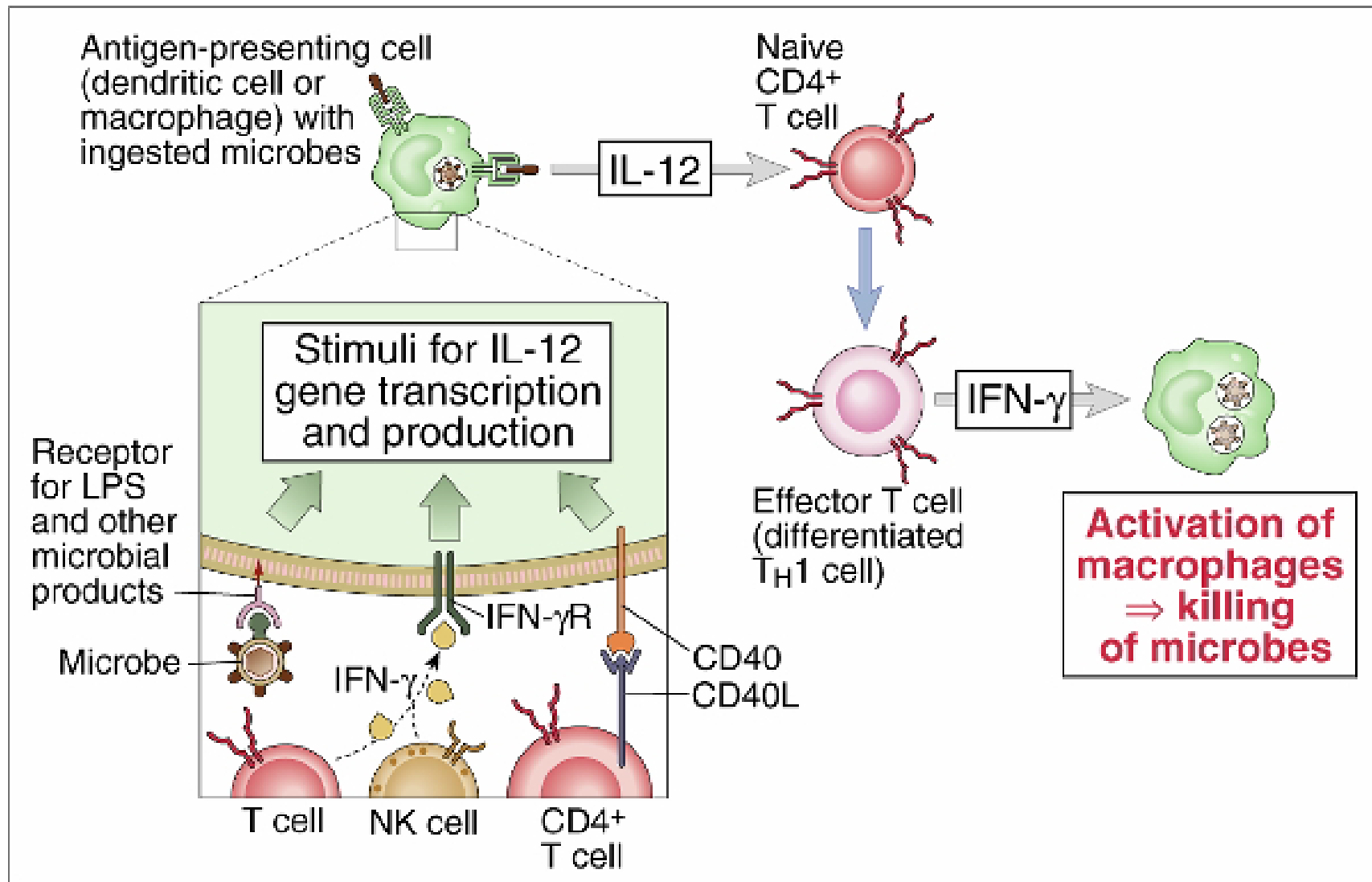
Cytokine production by differentiated TH1 and TH2 cells

T cells cultured with antigen + APCs + IL-4

T cells cultured with antigen + APCs + IL-12 (+ anti-IL-4 antibody)

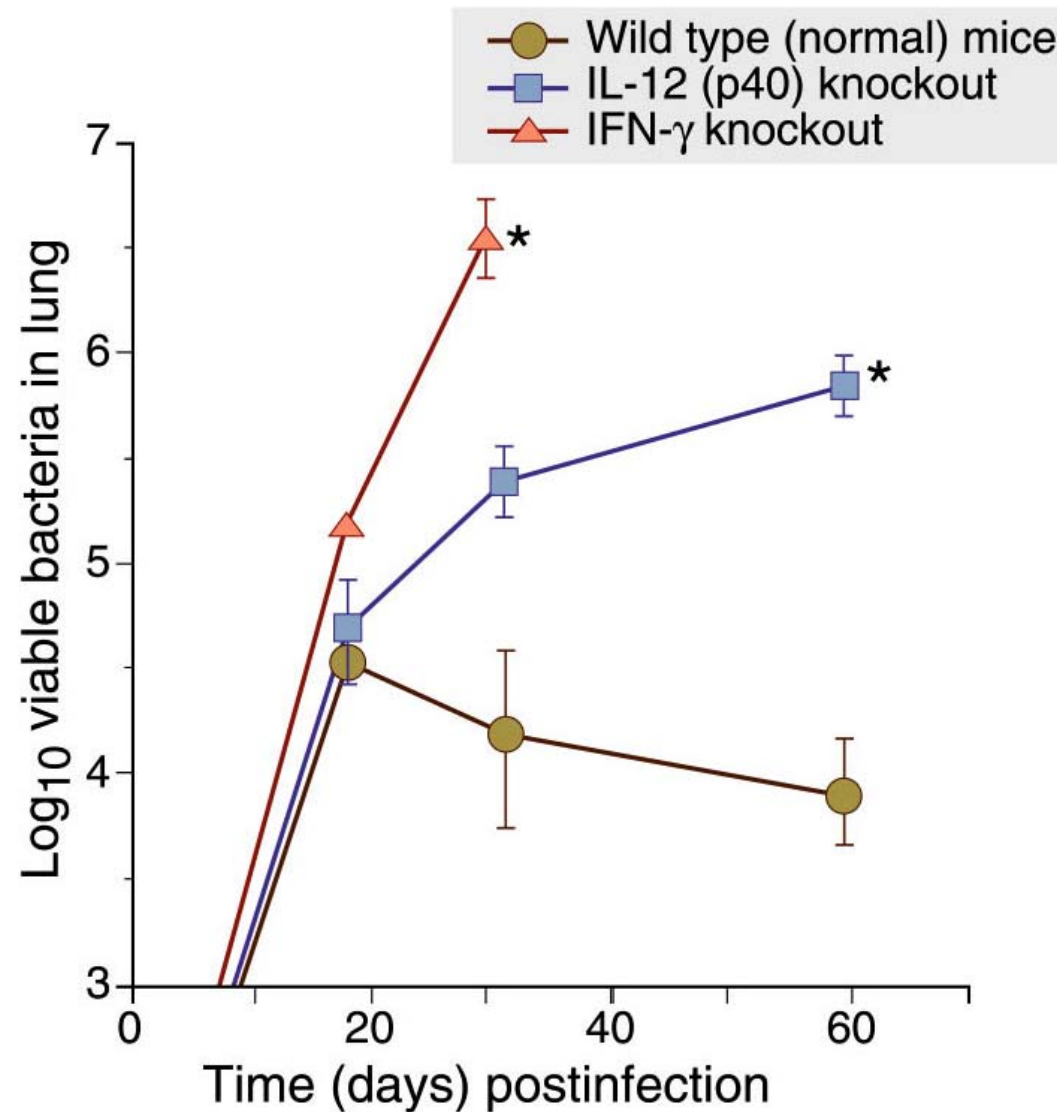


Role of IL-12 and IFN- γ in cell-mediated immunity



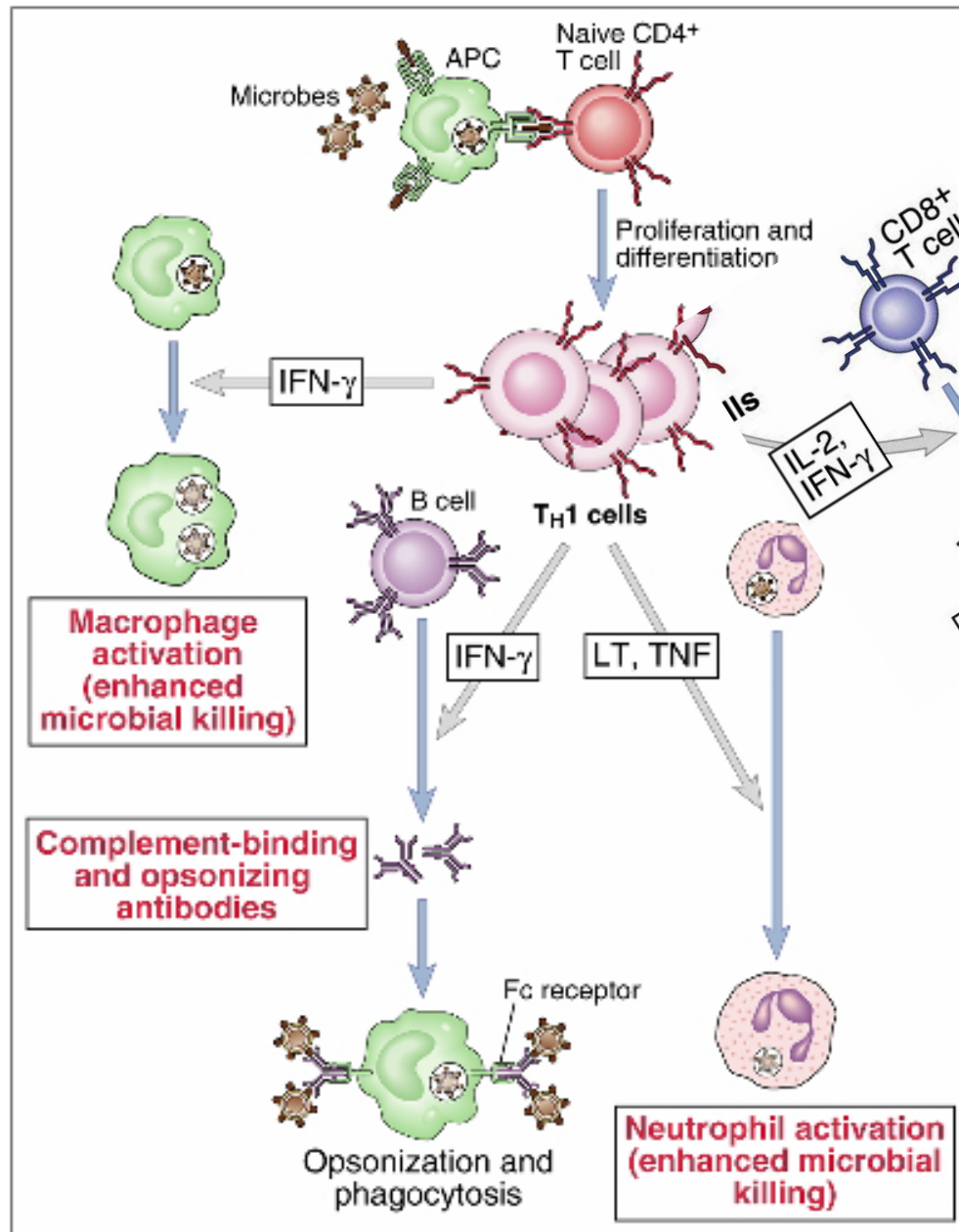
Abbas Fig 13-8

Role of IL-12 and IFN- γ in Cell Mediated Immunity



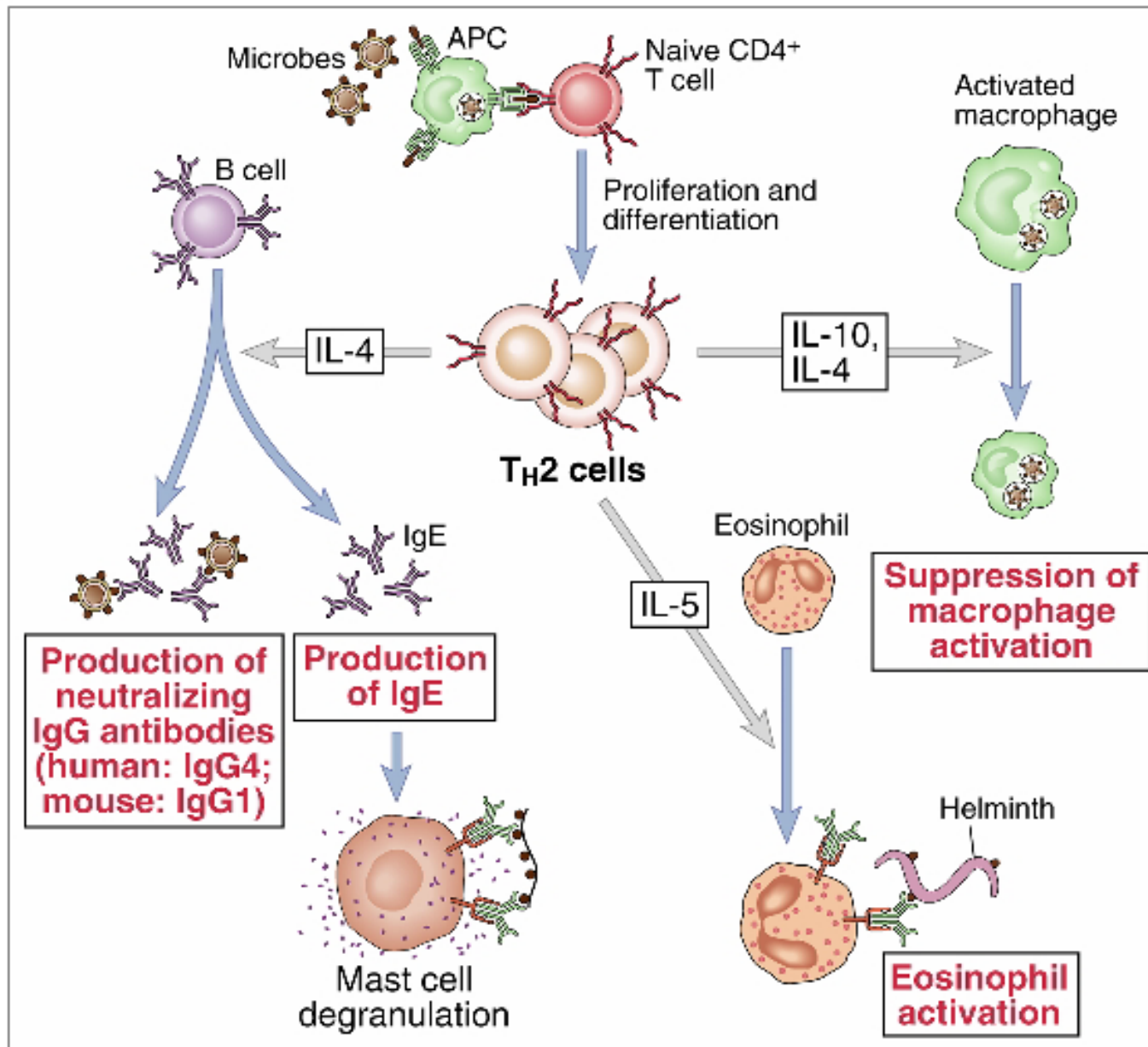
Effector functions of TH1 cells

**General Rule:
If Th 1 cells are
involved, think
CMI responses**



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Fig 13-9

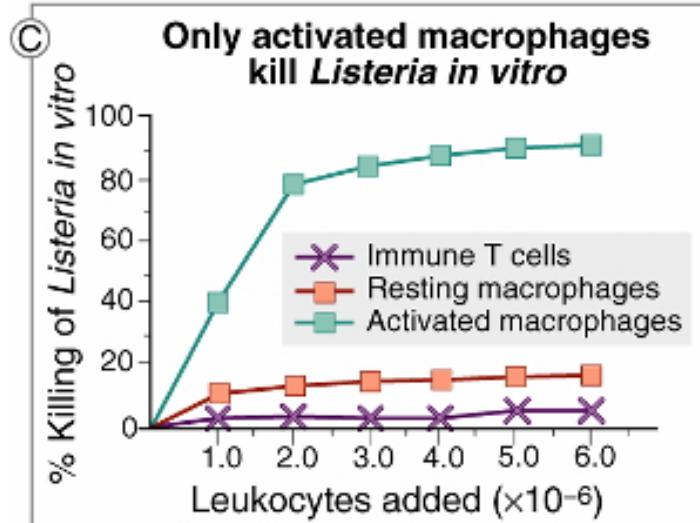
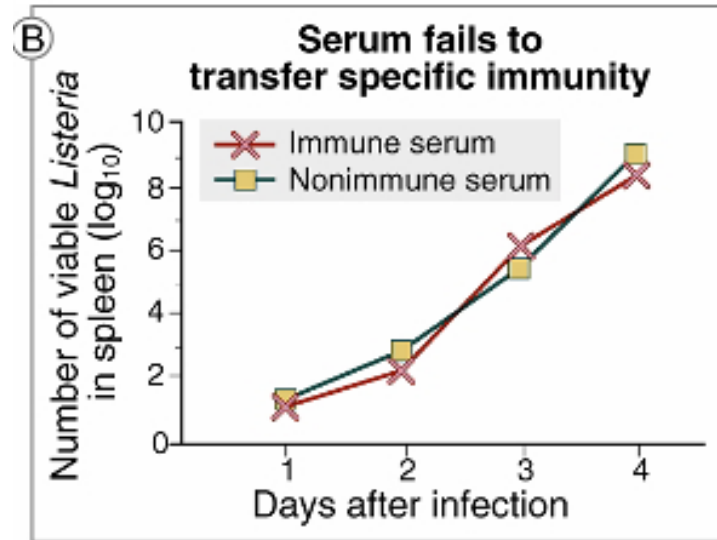
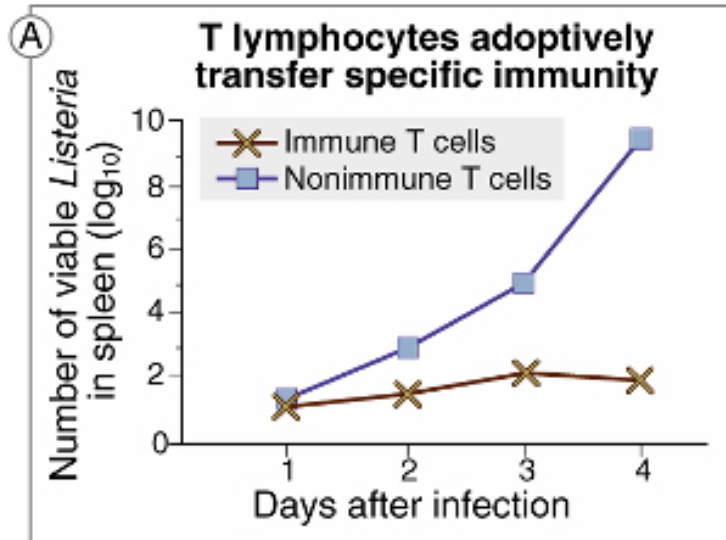
Effector functions of TH2 cells



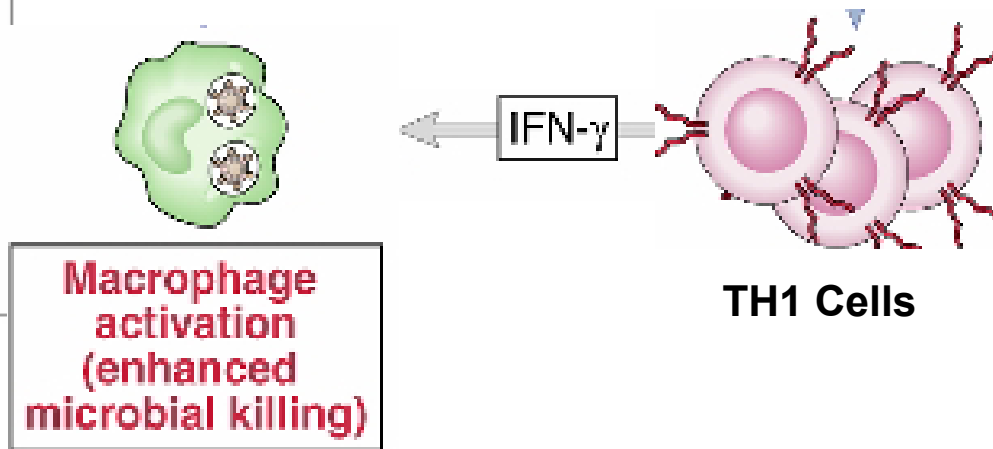
General Rule: If Th 2 cells are involved, think humoral immune responses

Abbas Fig 13-10

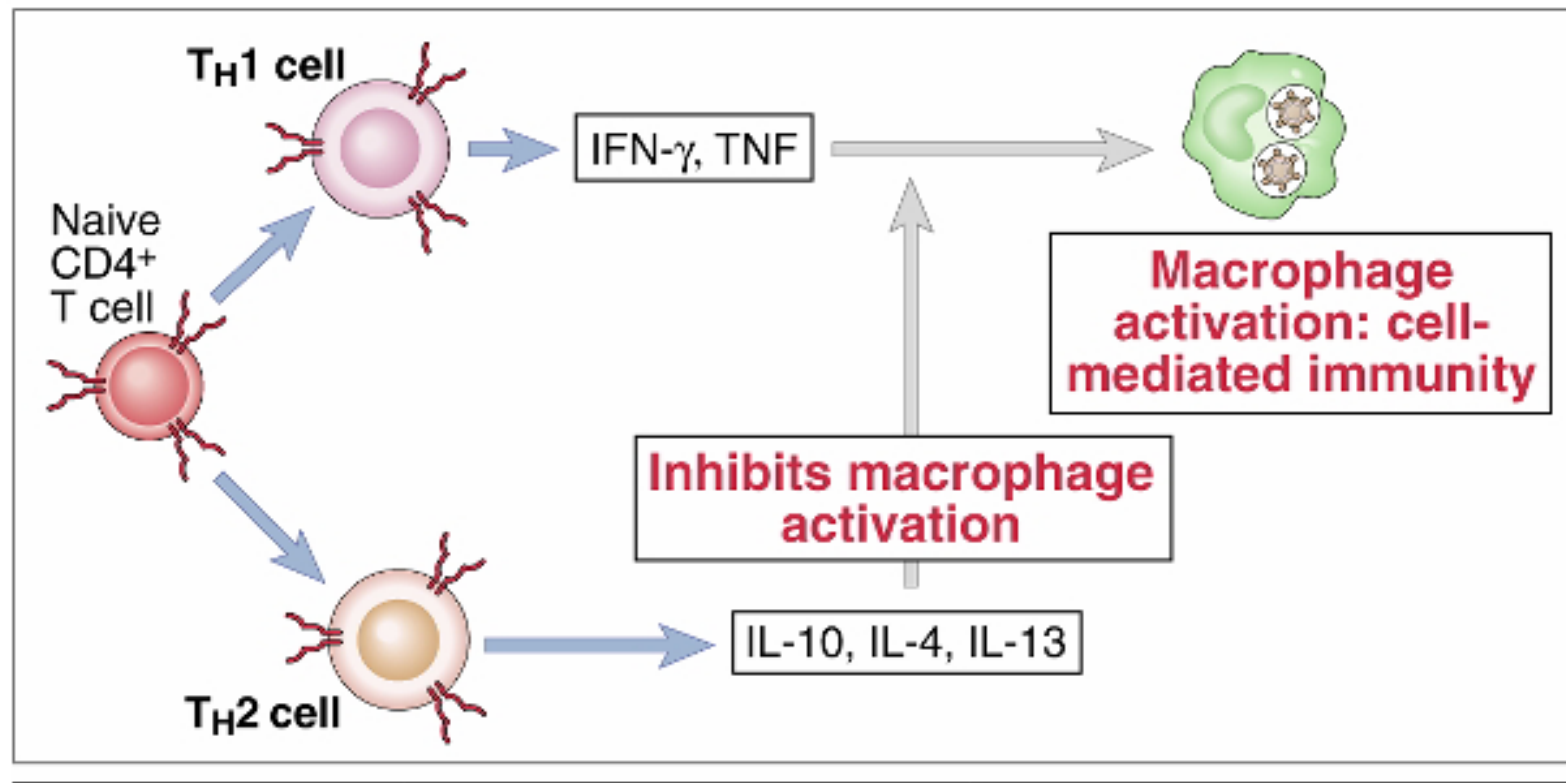
Cell-mediated immunity to *Listeria monocytogenes*



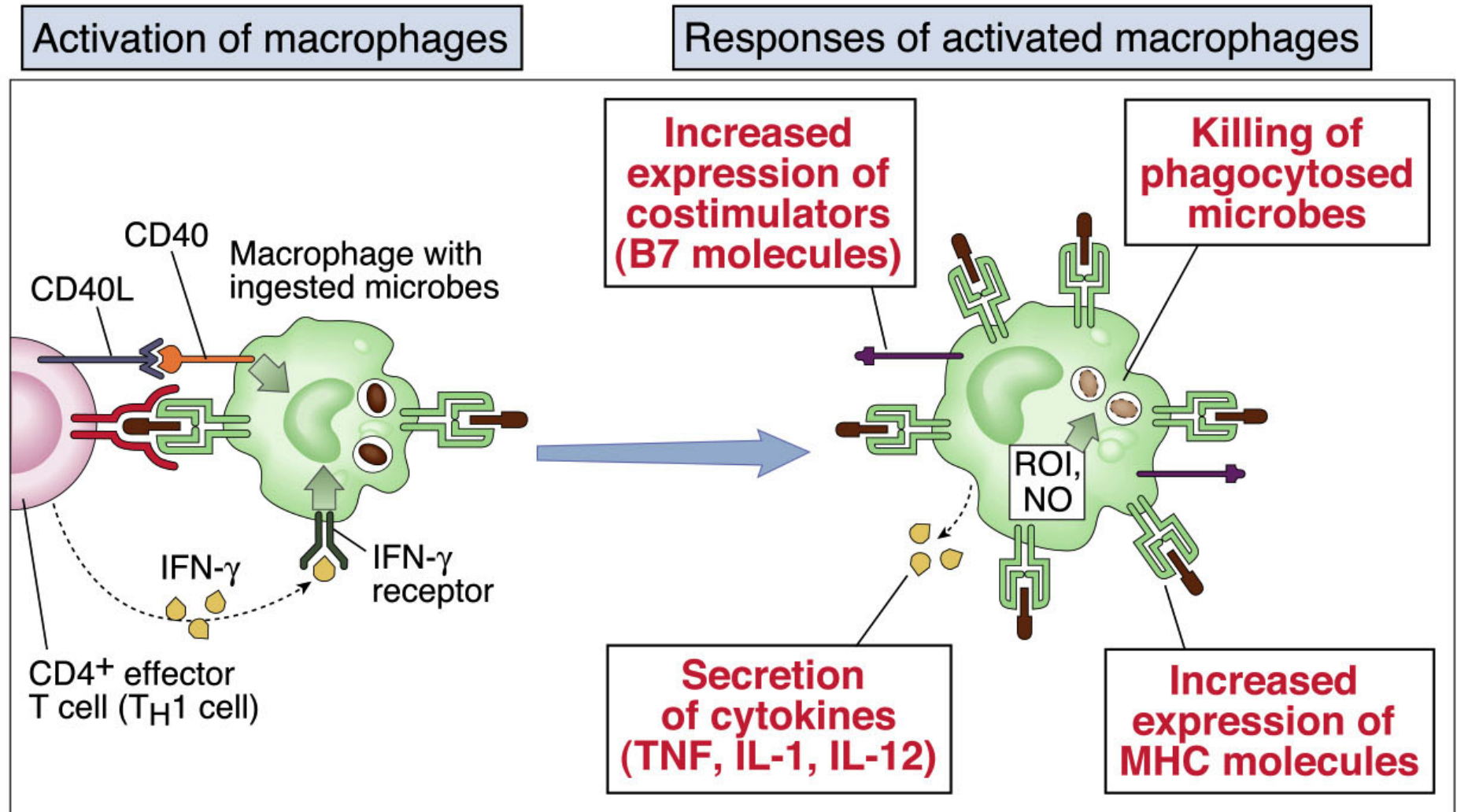
Which TH subset mediates the protective effect – TH1 or TH2?



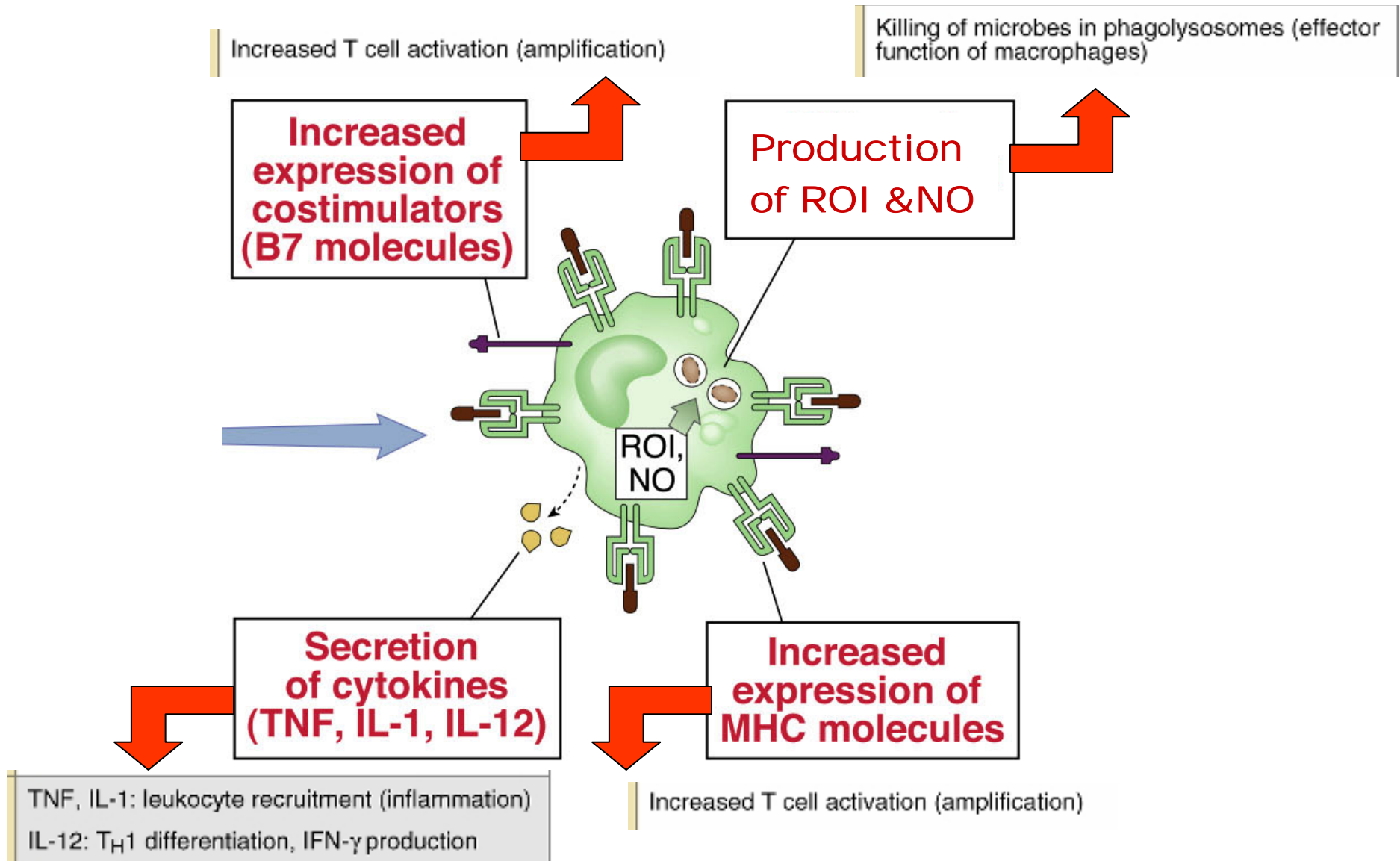
TH1 – TH2 Crosstalk



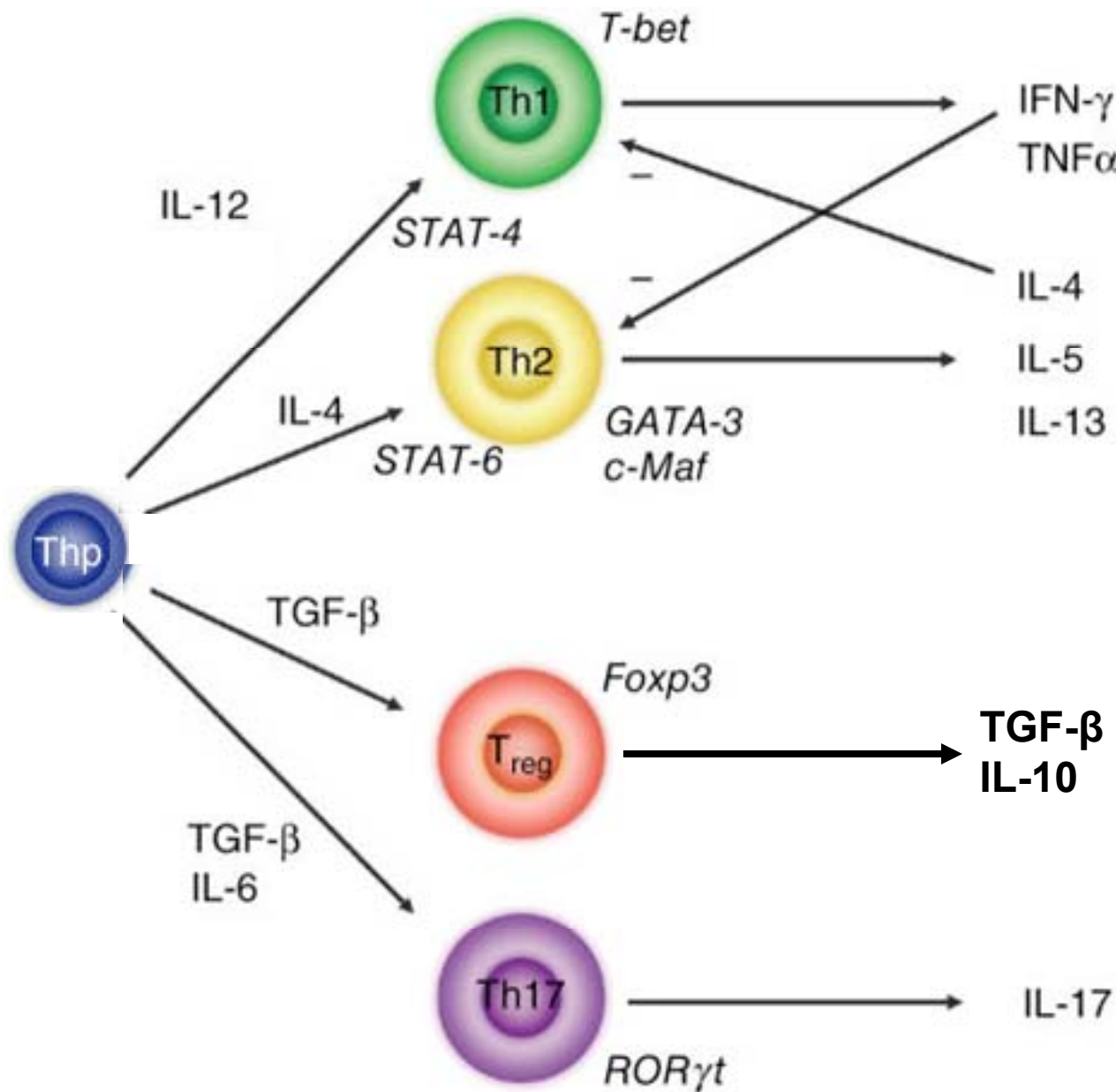
TH cell-mediated macrophage activation



Activation and functions of macrophages in cell-mediated immunity

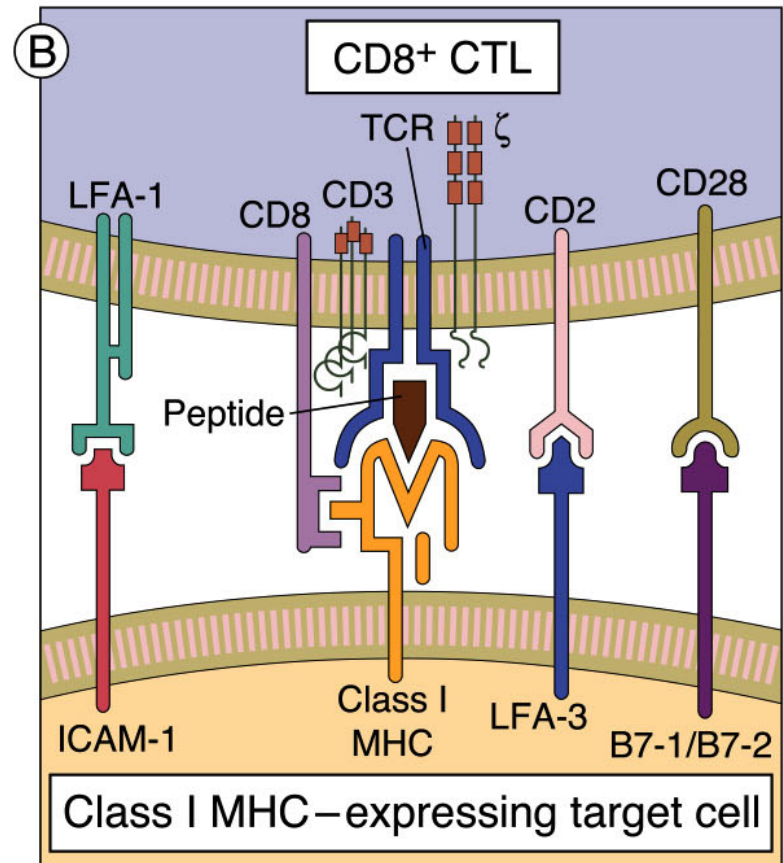
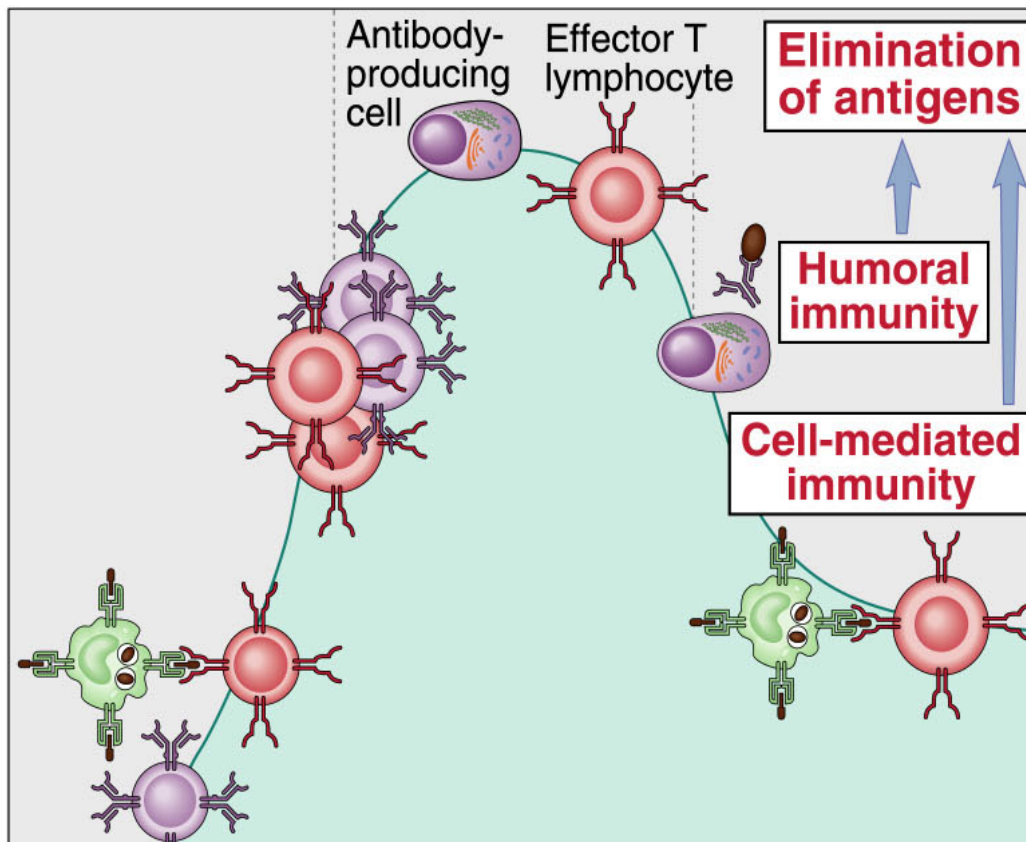
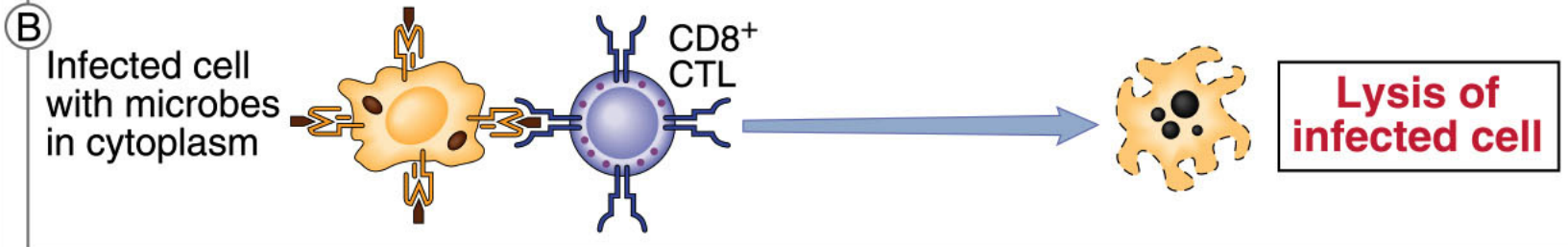


Development of T regulatory (Treg) and T Helper 17 (TH17) Cells

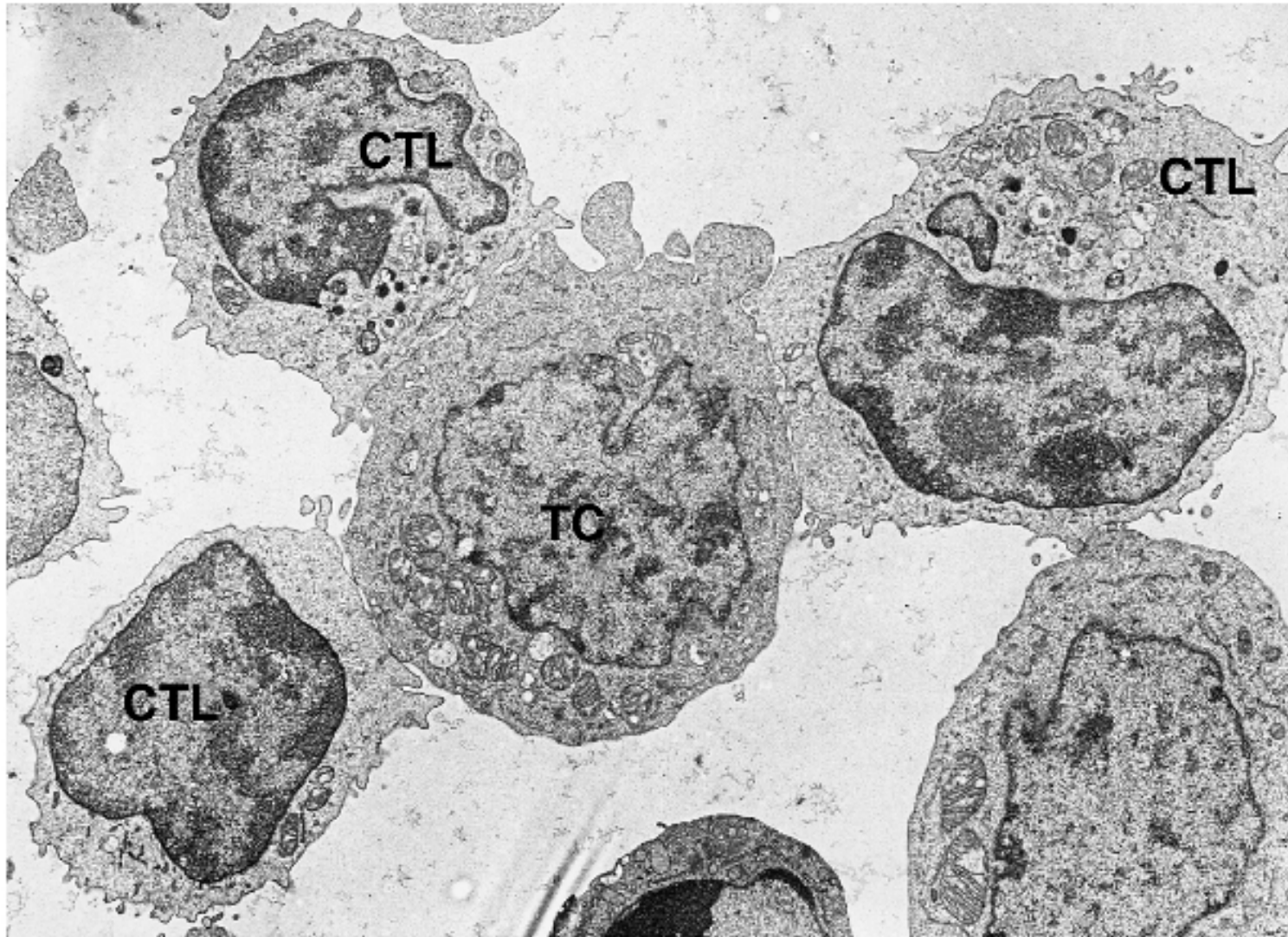


Afzali; Clin Exp
Imm; 148:32, 2007.

CTL-mediated Cytotoxicity



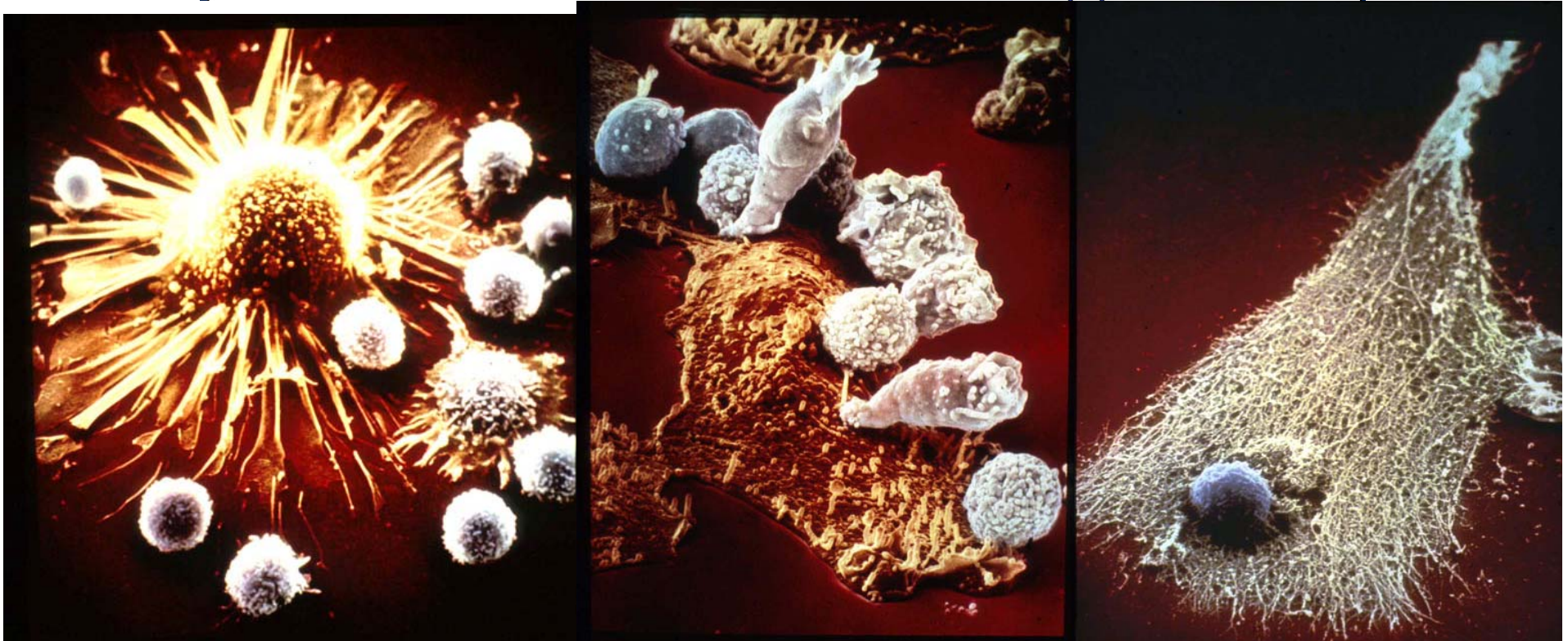
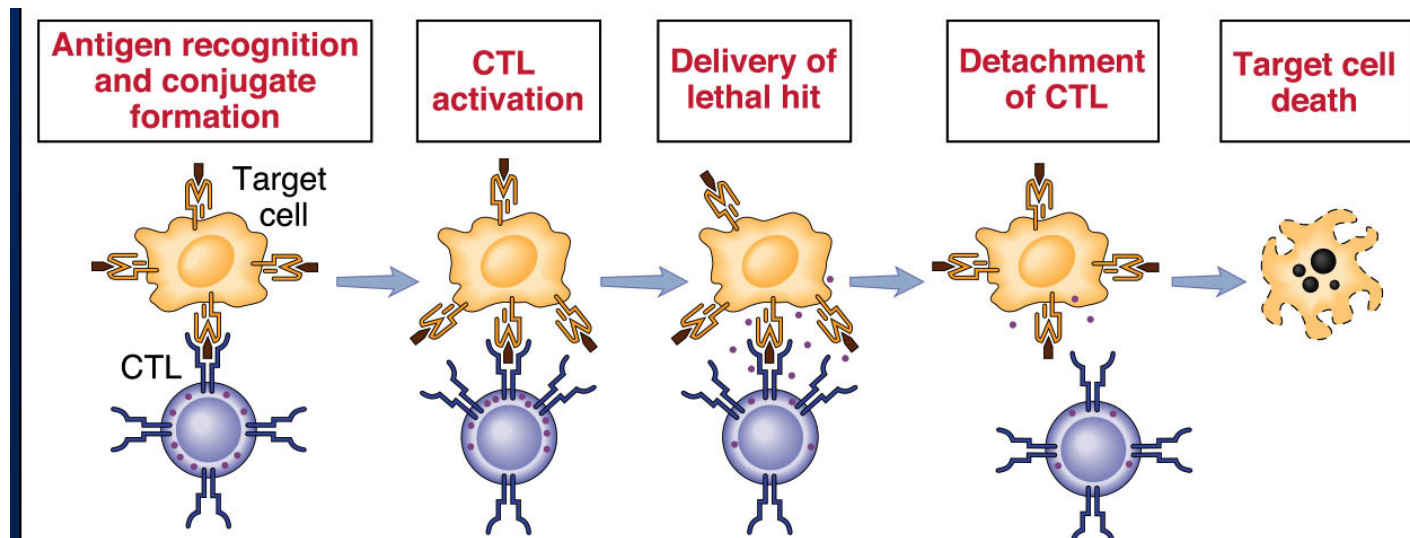
Conjugate formation between CTL and a target cell



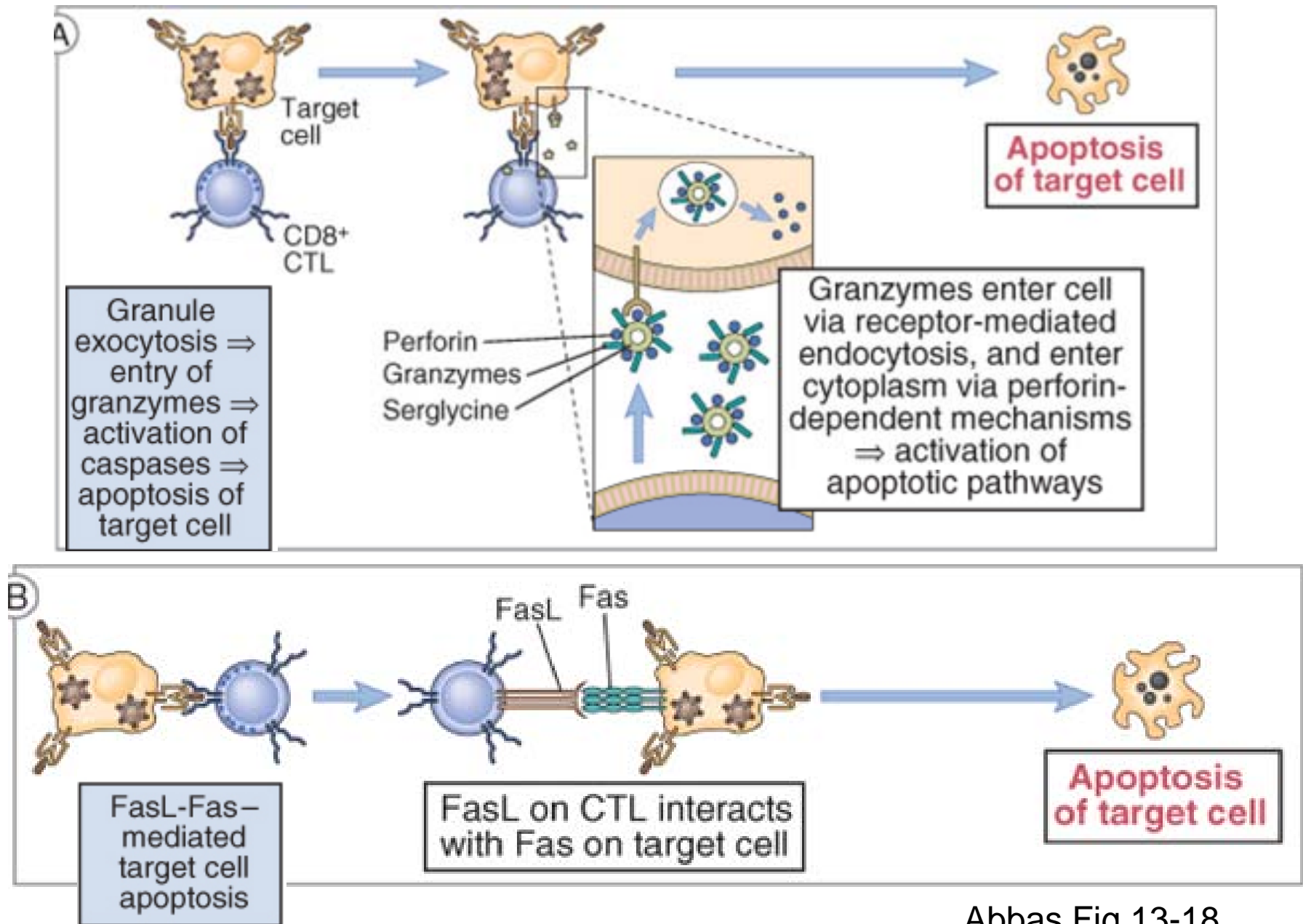
Abbas Fig 13-17

Steps in CTL-mediated lysis of target cells

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Fig 13-16

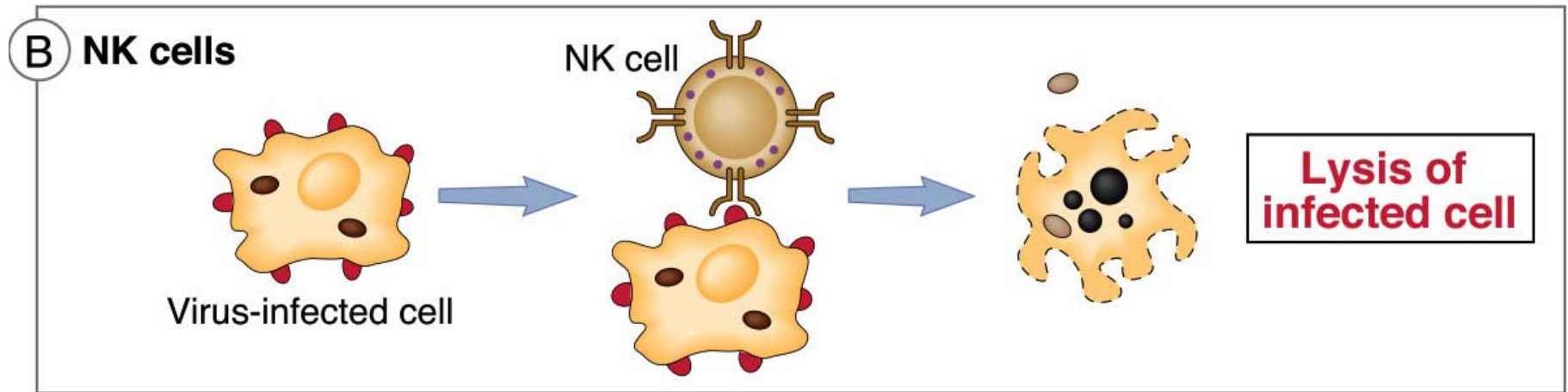


Mechanisms of CTL-mediated lysis

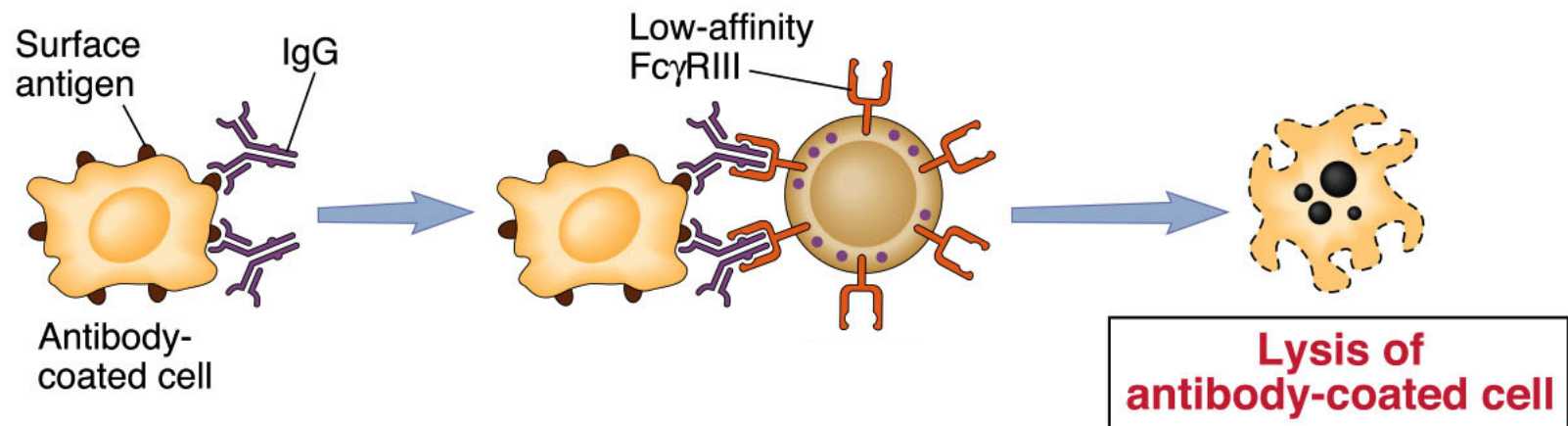


Abbas Fig 13-18

NK Cell mediated Cytotoxicity



Antibody Dependent Cell-mediated Cytotoxicity (ADCC)



**ADCC Effector Cells = NK cells,
macrophages, eosinophils**

Cell-mediated Immunity (CMI) - Summary

- A principal role of CMI is to detect and eliminate cells that harbor intracellular pathogens
- The same CMI mechanisms detect and eliminate other “non-self” cells in the body, including tumor cells and cells within transplanted organs
- Effector cells that mediate CMI include TH cell subsets (TH1, TH17), cytotoxic cells (CTL, NK cells), and cytokine-activated macrophages
- CMI effector T cells work in concert with cells of the innate immune system (dendritic cells, macrophages) and are dependent on them for antigen presentation and/or production of cytokines that drive TH cell differentiation
- CMI effector macrophages and NK cells work in concert with antibodies from B cells to recognize antibody-coated cells and eliminate them.