Chapter 9

T Cell-Mediated Immunity (CMI)
T細胞免疫

陳炳宏副教授
KMU生物科技學系
第一教學大樓N1020/1023 (分機: 2676)
bhchen@kmu.edu.tw
http://allergy.kmu.edu.tw

Learning objectives

- Understand how armed effector T cells are produced.
- Understand the general properties of armed effector T cells.
- Understand how T cell-mediated cytotoxicity is initiated and regulated.
- Understand how macrophages are activated by armed CD4 Th1 cells.

Part IV: The Adaptive Immune Response

T Cell-mediated Immunity (CMI)

T cells leave the thymus and circulate through the blood and lymphoid organs

Naïve T cells have not reacted with their specific antigen

- When a naïve T cell appropriately interacts with antigen it gets activated (proliferation and differentiation). → 2 (3) signals

  -Requires APCs + Ag, co-stimulatory signals, (cytokines)

- The result is that lots of antigen-specific cells acquire their effector function.

- That is, they become **armed effector T cells** that can act on target cells (usually infected self-cells).

Priming: The activation/clonal expansion of a naïve T cells when first encountering Ag

Tissue (immature) dendritic cells ingest foreign materials (antigens) (using innate mechanisms)

- inflammatory molecules (e.g., cytokine and bacterial products) cause their maturation.

- The most important APC type.

-e.g. Langerhan's cells

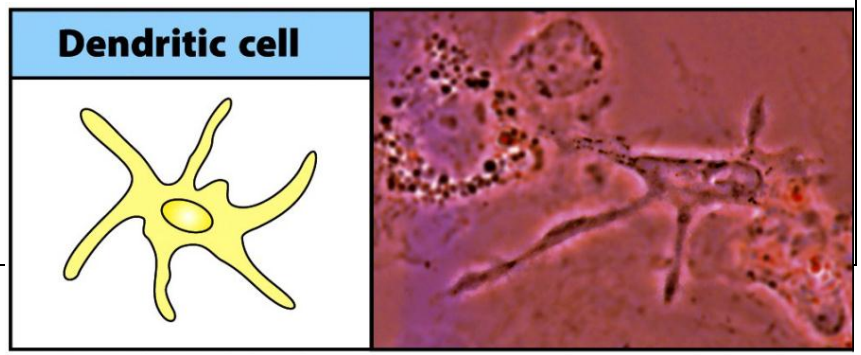


Figure 1-4 part 2 of 6 Immunobiology, 7ed. (© Garland Science 2008)

Mature dendritic cells migrate to regional lymphoid organs (e.g., lymph nodes).

They present **antigens** and **co-stimulatory molecules** (e.g. signal #2) to T cells.

Macrophages and **B cells** also take up foreign materials but these cells are usually the targets of armed effector T cells

Two major classes of T cell
- Helper (TH; CD4+)
- Cytotoxic (CTL; CD8+)

This chapter deals with **c**ell-**m**ediated **i**mmunity (CMI), that is, CTLs and TH1 (TH2 is left for the humoral immunity chapter)

What are their effector functions?

Principally against intracellular pathogens!!

	Cell-mediated immunity		Humoral immunity
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii* *Trichinella spiralis*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Effector T cell	Cytotoxic CD8 T cell CTL	T_H1 cell	T_H1 and T_H2 cells
Antigen recognition	Peptide:MHC class I complex on infected cell	Peptide:MHC class II complex on infected macrophage	Peptide:MHC class II complex on antigen-specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

Figure 8-1 Immunobiology, 6/e. (© Garland Science 2005)

	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells
Types of effector T cell			
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites
	CMI	**CMI/Humoral**	**Humoral**

CD4 T_H17 cells	CD4 regulatory T cells (various types)
	
Enhance neutrophil response	Suppress T-cell responses
Extracellular bacteria (e.g. *Salmonella enterica*)	

Cell-mediated immunity:

CD8,

CD4 (Th1)

CD4 (T-regulatory)

Humoral immunity:

CD4 (Th1 & Th2)

CD4 (Th17)

CD4 (T-regulatory)

Activation of Naïve T cells

- Occurs in peripheral lymphoid organs (e.g. lymph node)

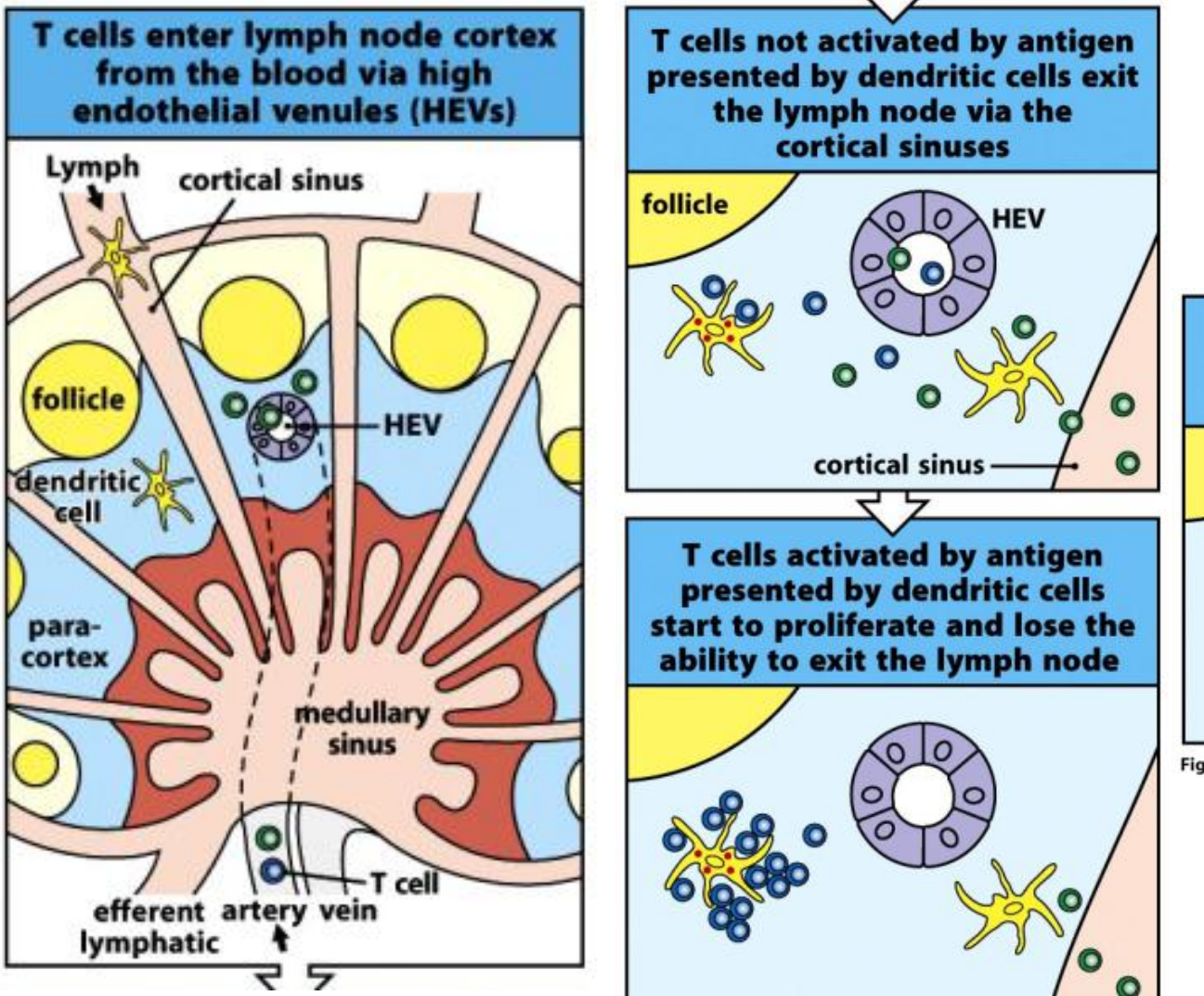
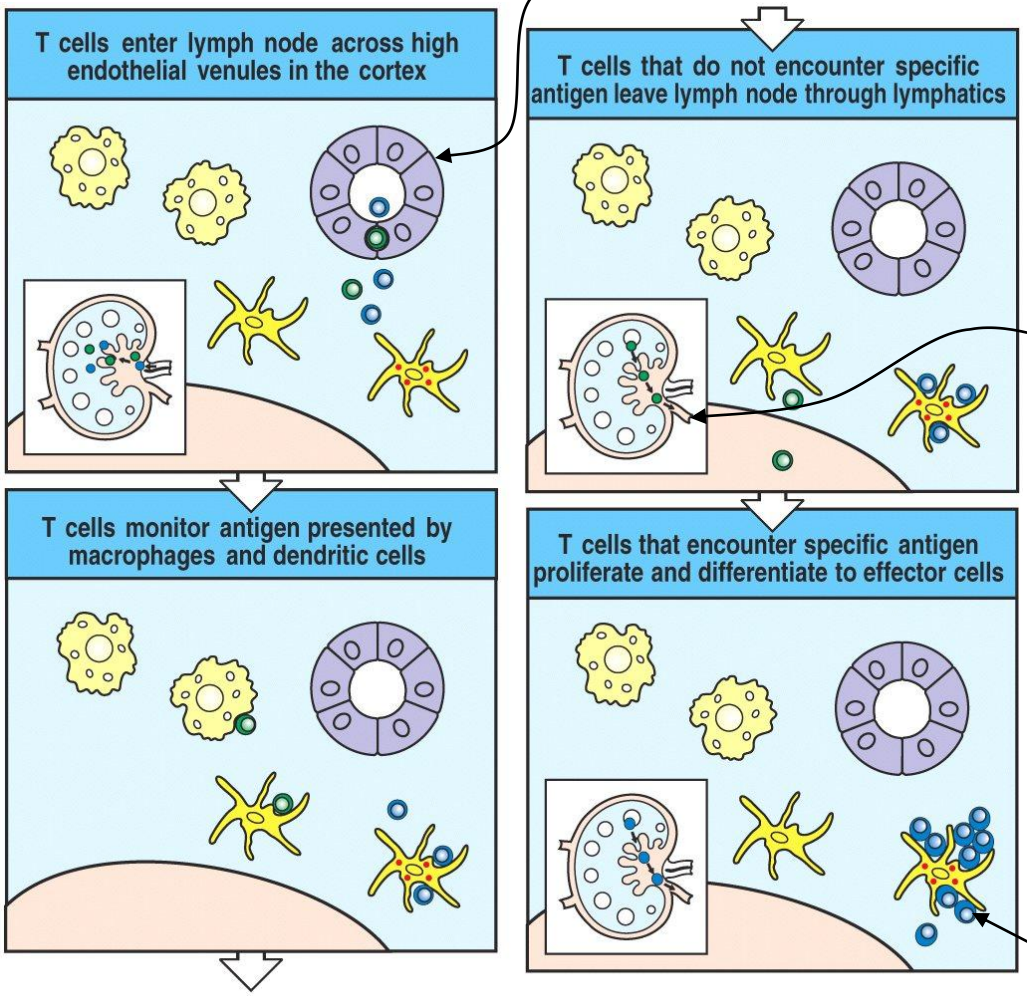


Fig. 9-2

Figure 8-2 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Encounter of antigens by T cells (TH;yes, CTL;?)

High endothelial venules (HEV)



- Naïve T cells migrate through the lymphoid organs and encounter thousands of dendritic cells per day.

  (termed "**T cell sampling**")

- If they do not bind antigen, they leave via the efferent lymph.

- Interactions with self-peptides plus MHC are necessary for **T cell survival** (a continued (+) selection by **weak binding**).

- If they bind antigen ***strongly***, they get ***activated*** (see next slide)

Fig 8.4 Naïve T cells encounter Ags while recirculating through peripheral lymphoid organs

Only 1 in 10,000 to 1,000,000 T cells can respond to a given Ag.

Therefore, cell activation & division is central to the immune response

Activation

Division

Exiting

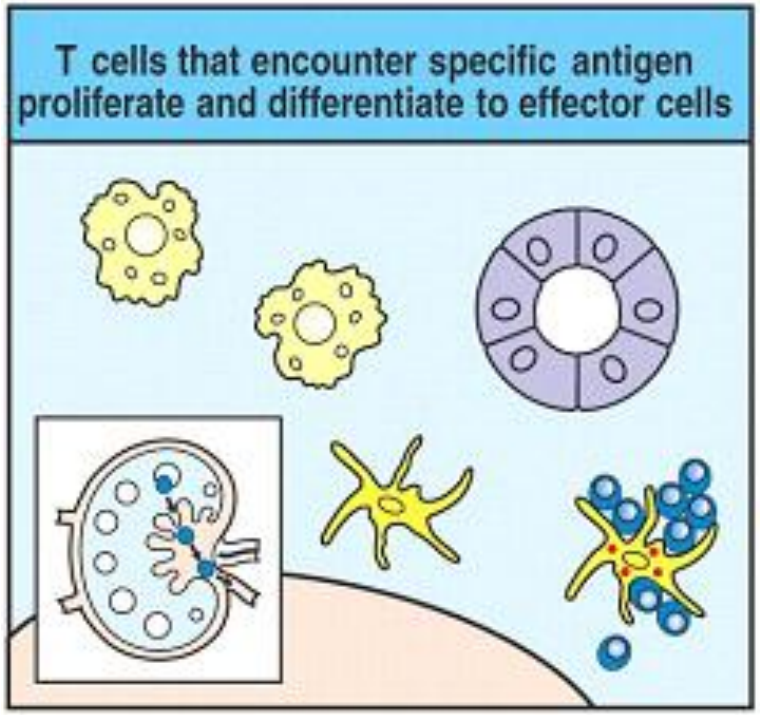


Fig 8.4 last frame

1. T cells get activated on dendritic cells, and
2. divide, acquire their effector function, and then
3. leave via the efferent lymph to go to
   - the site of the infection TH1,CTL(?), or
   - areas where B cells need help (TH2)

"**Homing**" → the return of naïve T cells to lymphoid tissues

Trapping of Ag-specific T cells for activation in lymph node

Fig. 9-3

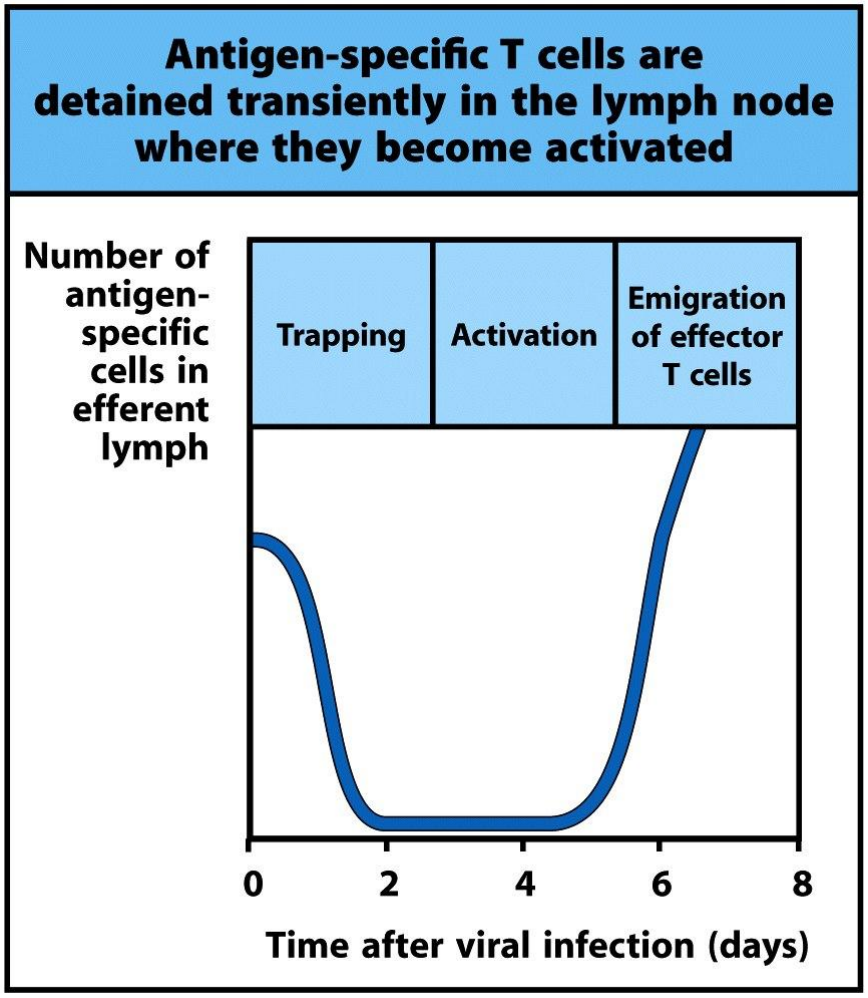


Figure 8-3 Immunobiology, 7ed. (© Garland Science 2008)

- High efficiency of trapping and activation of T cells often occurs within 2 days of Ag stimulation

- Why?

In average, only 1 per 10^4-10^6 T cells is activated and expanded

"Homing" of T cells

Fig. 9-4

- The return of T cells to peripheral lymphoid organs (from circulation).
- Assisted by several factors
  - Selectins: e.g. CD62L (T cell); weak adhesion → binds to 'addressins'
  - Chemokines: CCL21 (HEV & stroma cell), CXL12 (HEV)
  - Integrins: e.g. LFA-1 (T cell, induced by CCL21); strong adhesion

Addressins ('address tags')

- **Lymph node HEV**
  - **CD34, GlyCAM-1**
- **Mucosa**
  - **MAdCAM-1**

Binding of CCL21 (HEV) and CCR7 (naïve T)

→ Activation of LFA-1 on T cells (stops rolling)

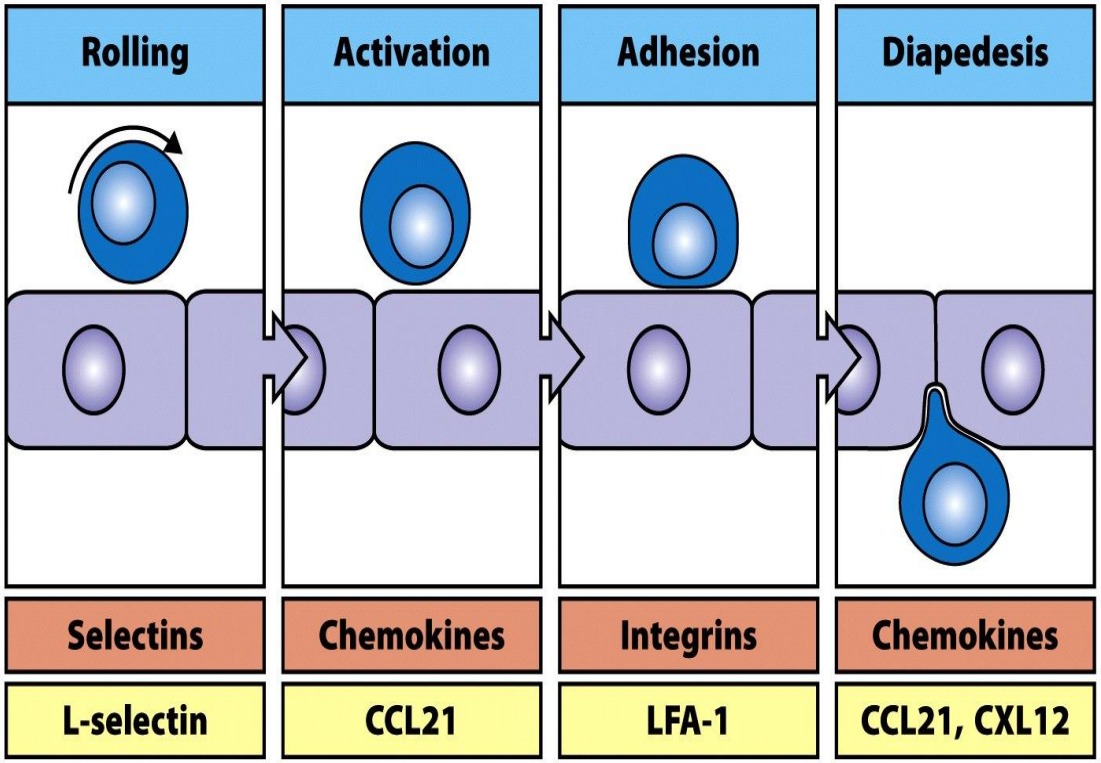


Figure 8-4 Immunobiology, 7ed. (© Garland Science 2008)

Binding of L-selectin and vascular addressin

- (Early phase) Selectin binds to the sulfated sialyl-Lewis^x sugar moieties on vascular addressins.

Fig. 9-5

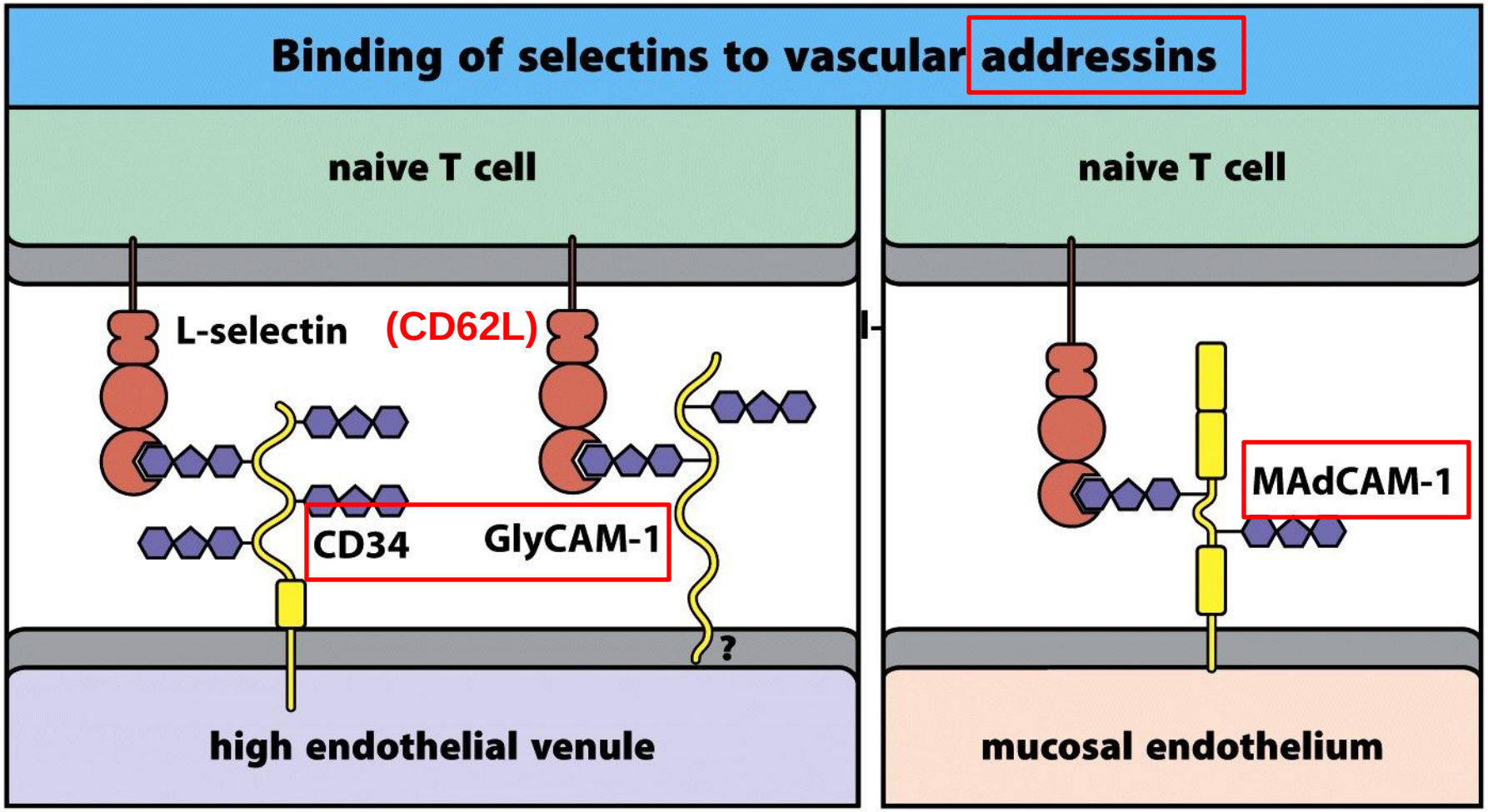


Figure 8-5 Immunobiology, 7ed. (© Garland Science 2008)

Binding of integrin and adhesion molecules

- (Mid. – late phase) Binding of leukocyte integrin to various adhesion molecules
- LFA-1: on all T cells (both naïve & effector), M, Neutrophils

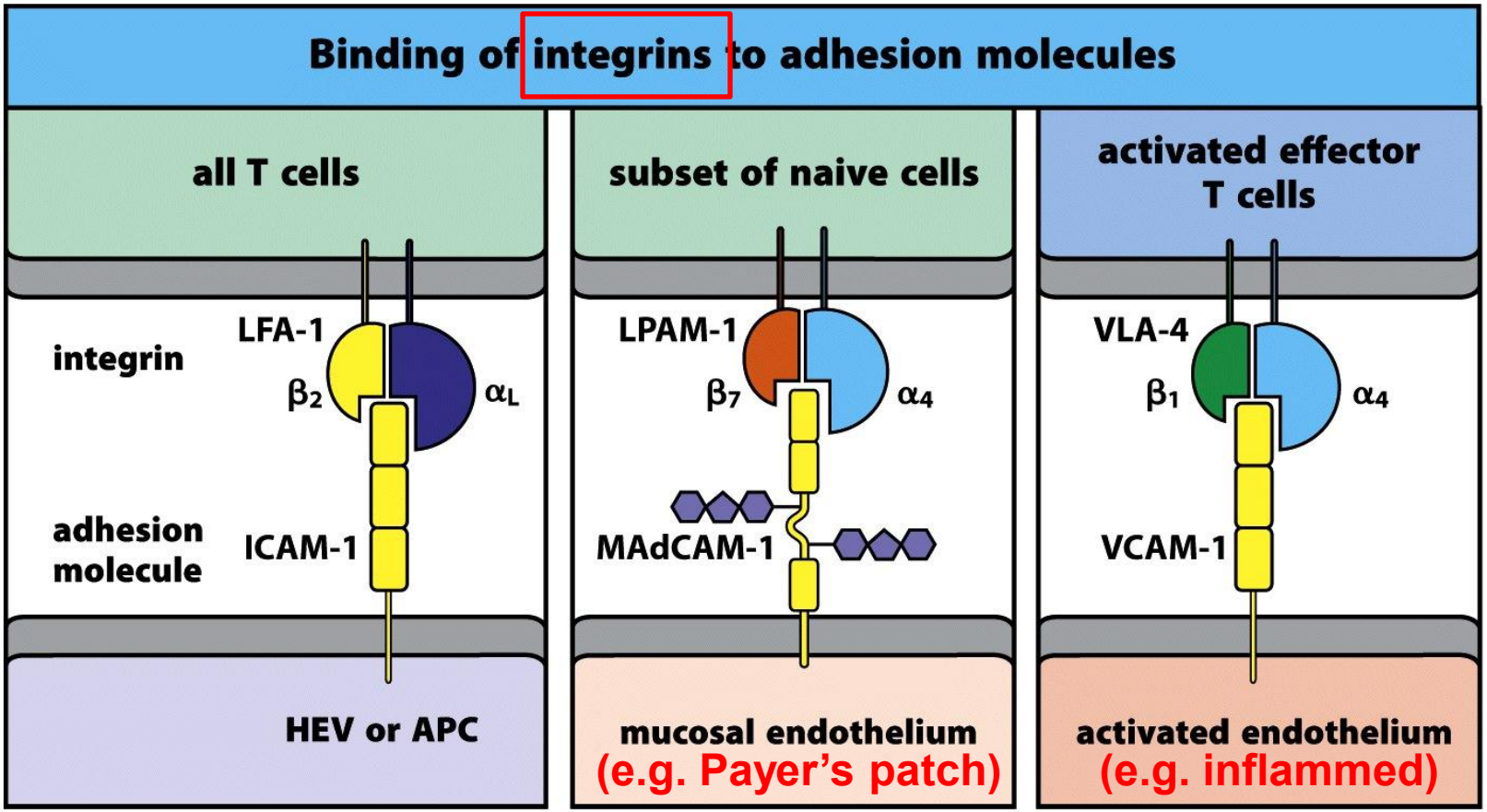
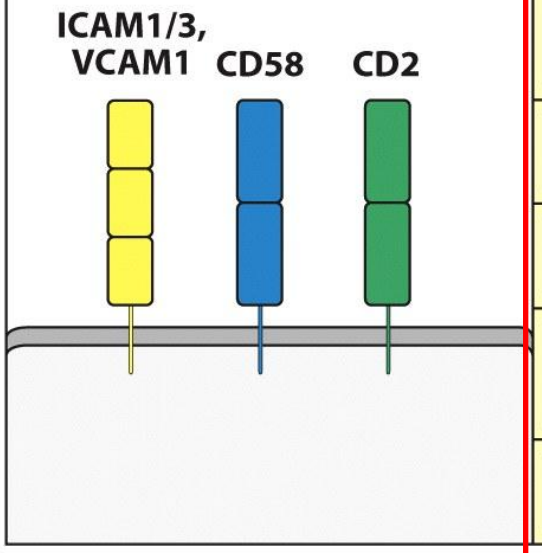


Figure 8-6 Immunobiology, 7ed. (© Garland Science 2008)

Other important adhesion molecules in leukocyte interactions

Fig. 9-7



Immunoglobulin superfamily	Name	Tissue distribution	Ligand	
	CD2 (LFA-2)	T cells	CD58 (LFA-3)	APC
	ICAM-1 (CD54)	Activated vessels, lymphocytes, dendritic cells	LFA-1, Mac-1	All T cells
	ICAM-2 (CD102)	Resting vessels	LFA-1	All T cells
	ICAM-3 (CD50)	Naive T cells	LFA-1	DCs
	LFA-3 (CD58)	Lymphocytes, antigen-presenting cells	CD2	All T cells
	VCAM-1 (CD106)	Activated endothelium	VLA-4	Act. T

Figure 9.7 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

All 3 ICAMs bind to the T-cell integrin LFA-1 !!!

How do lymphocytes enter into the lymphoid organs?

Fig. 9-8

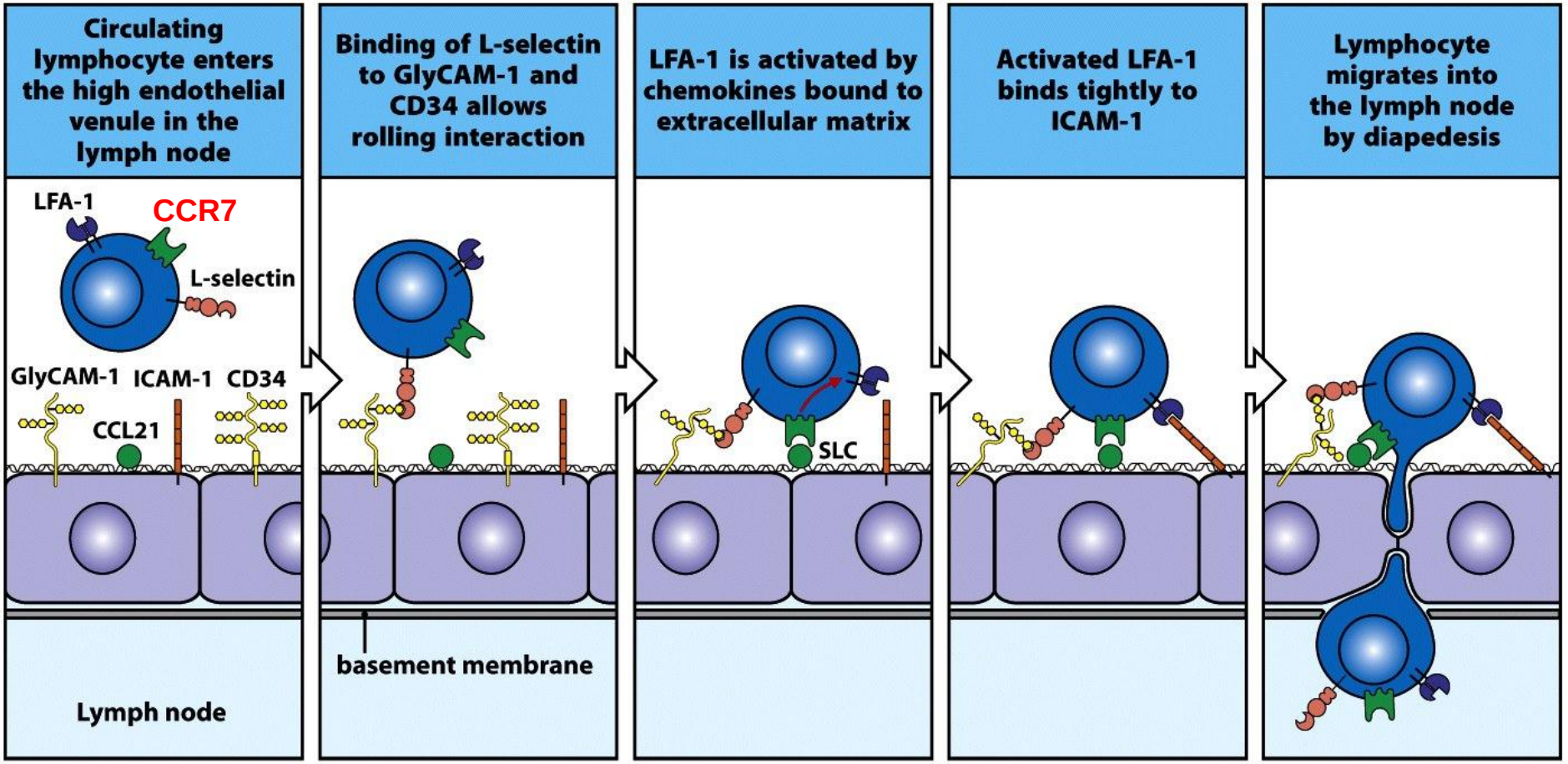


Figure 8-8 Immunobiology, 7ed. (© Garland Science 2008)

Rolling (weak)

Selectin & GlyCAM-1

CCL21 – CCR7 interaction

(rolling stops)

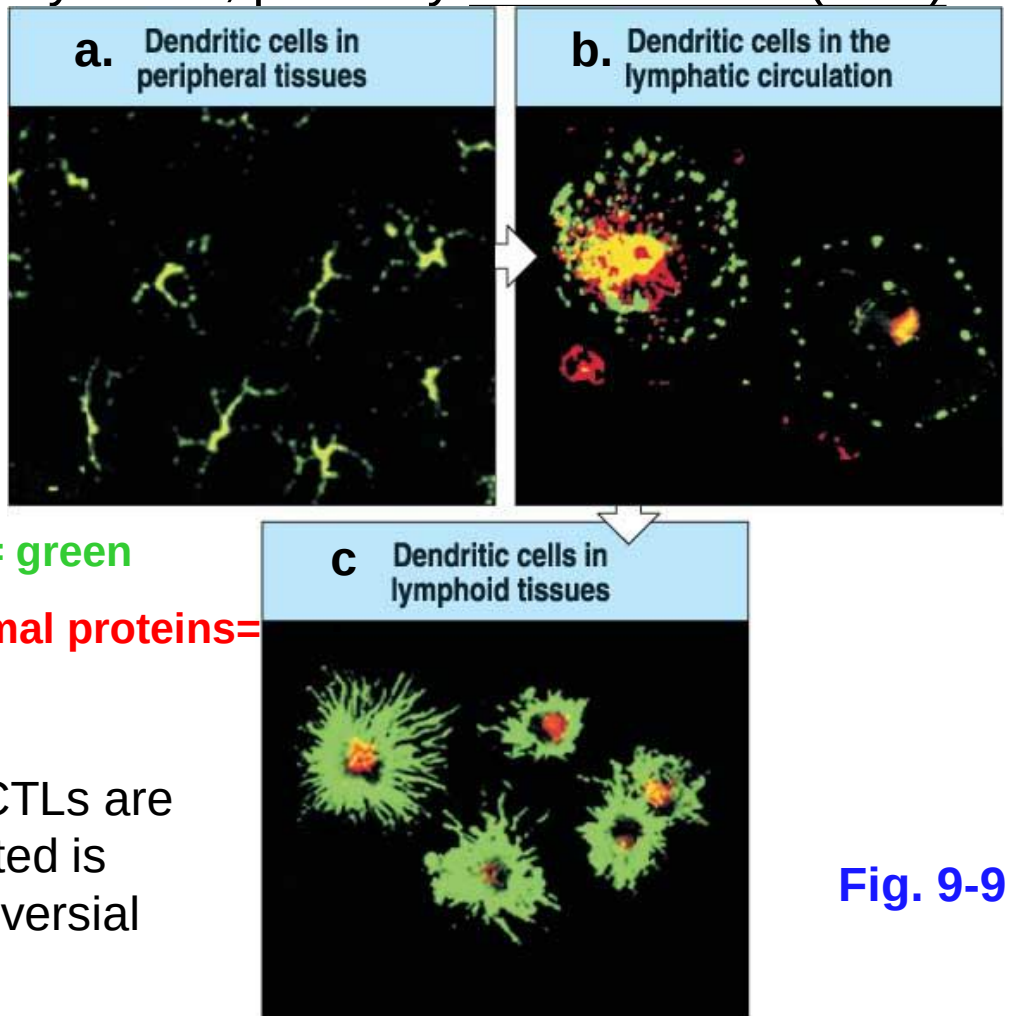
LFA-1 activated & binds to ICAM-1 (strong binding)

Diapedesis

T-cell responses are initiated by activated DCs in peripherals

→ requires **Ag + MHC** and **co-stimulation**.

→ done by APCs, primarily dendritic cells (DCs)



MHC II = green

Lysosomal proteins= red

How CTLs are activated is controversial

Dendritic cells

(a) - take up Ag in the periphery, and

- get activated by bacterial products or cytokines; then

(b) migrate to the regional lymphoid organ, and

(c) present Ag and co-stimulatory molecules to T cells

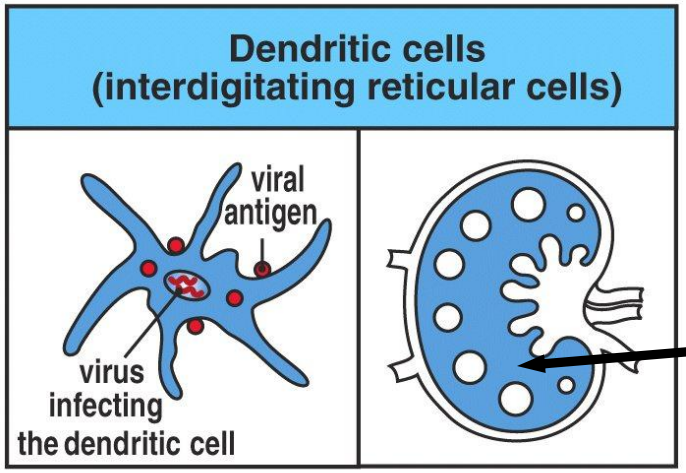
Fig. 9-9

Fig. 8-9 Immature DCs ingest Ag in the tissues

APCs in lymphoid organs

Interdigitating dendritic cells are primarily in the T cell areas and their primariy function is to activate helper T cells (TH)

Fig. 9-10



T cell area

DCs are the most potent activator of naïve T cells!!

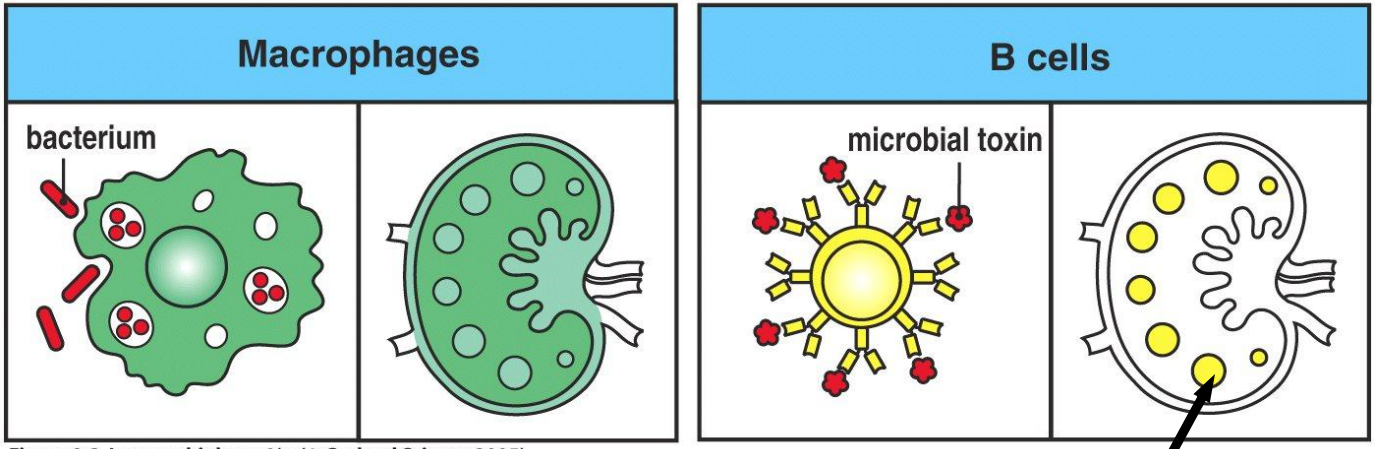


Figure 8-3 Immunobiology, 6/e. (© Garland Science 2005)

B cells circulate through the lymphoid organs. They will activate naïve T cells.

Macrophages mostly for filtering the lymph fluid. They are weak activators of T cells

B cell area

(Summary)

In general:

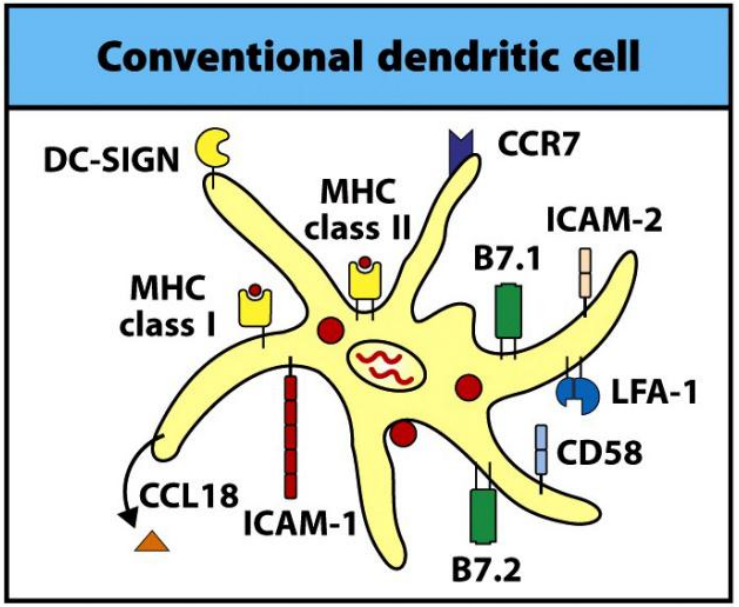
1. Mature dendritic cells (DCs) express high levels of both MHC-I and –II molecules
2. DCs mainly activate TH cells (and CTLs as well)
3. B cells and Macrophages are *targets* of activated TH cells

   -- although T cells can be activated by macrophages and even B cells, too.

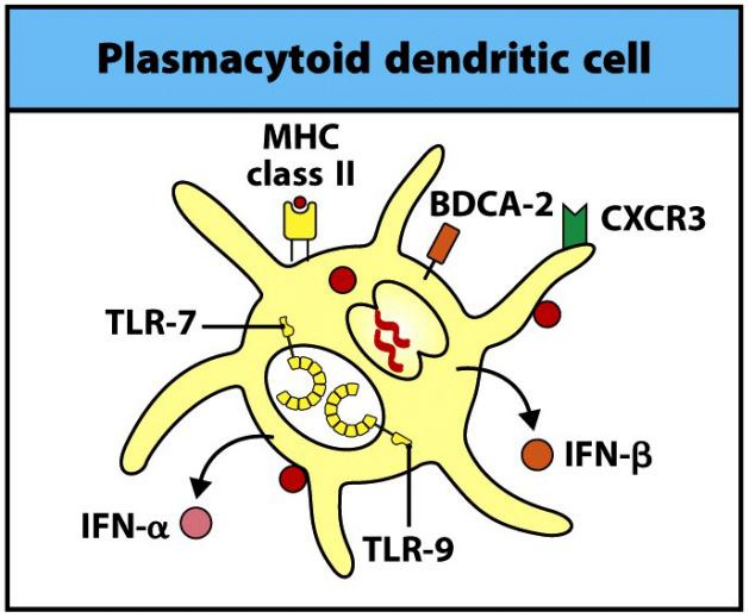
Two types of DCs

Fig. 9-11

- **Conventional DCs (cDCs)**
  - Participate in Ag presentation
  - Priming of naïve T cells, high levels of
    - MHC-I & -II expressions
    - B7.1 & B7.2 expression
    - ICAM-1 & LFA-1



- **Plasmacytoid DCs (pDCs)**
  - Sentinels for viral infections
  - Secretors of class-I IFN (α & β)



Routes of Ag processing by DCs (MHC-II)

Fig. 9-12

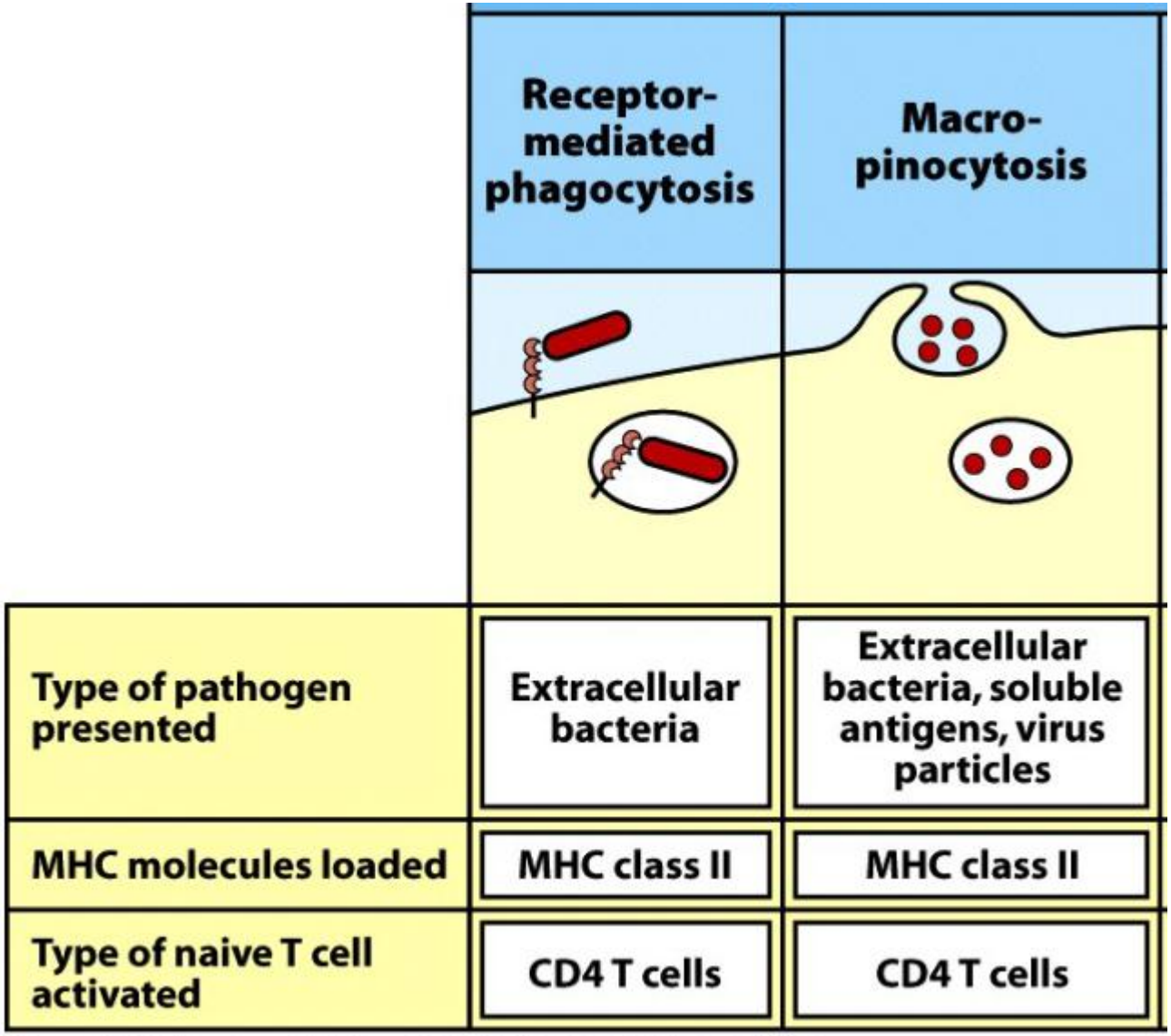
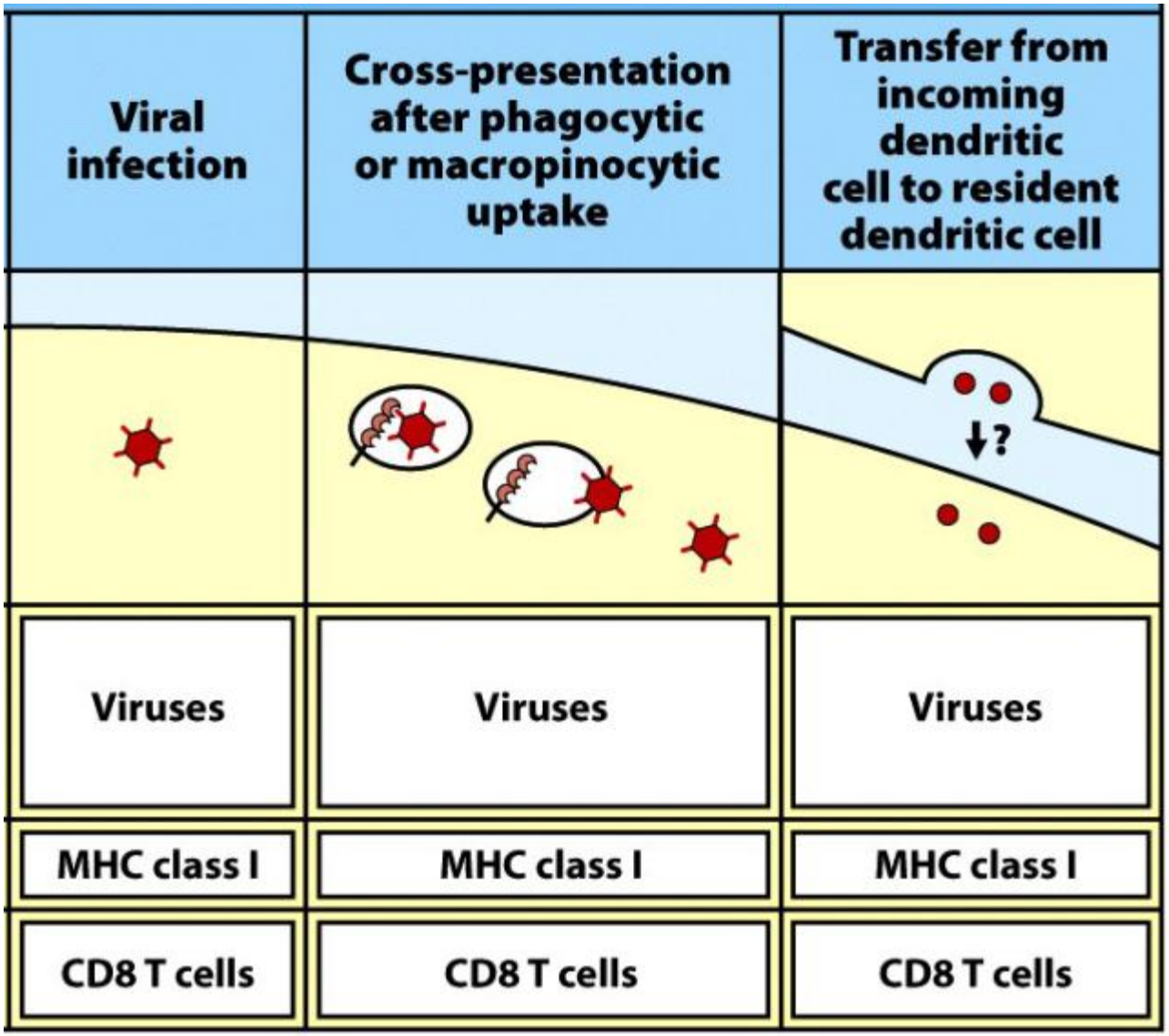
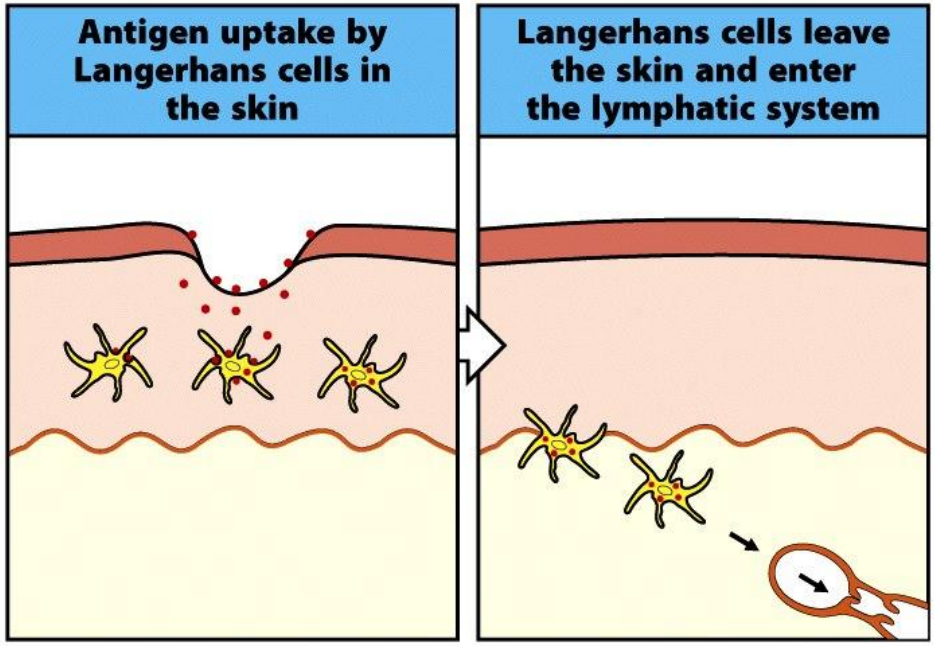


Figure 8-12 Immunobiology, 7ed. (© Garland Science 2008)

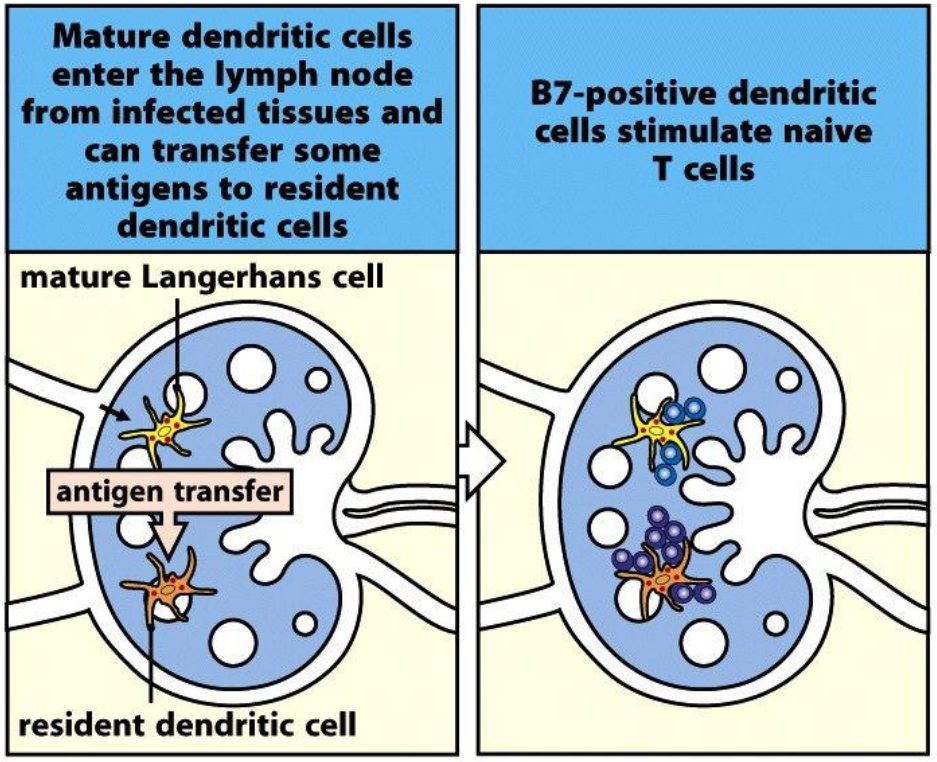
Routes of Ag processing by DCs (MHC-I)



Activation of Langerhans cells (a class of immature DCs) causes their maturation into mature DCs and their migration to the regional lymphoid organ



Immature



Mature

Fig. 9-13

Activation of skin Langerhans cells

Figure 8-13 Immunobiology, 7ed. (© Garland Science 2008)

Maturation of conventional DCs (2 stages)

Fig. 9-14

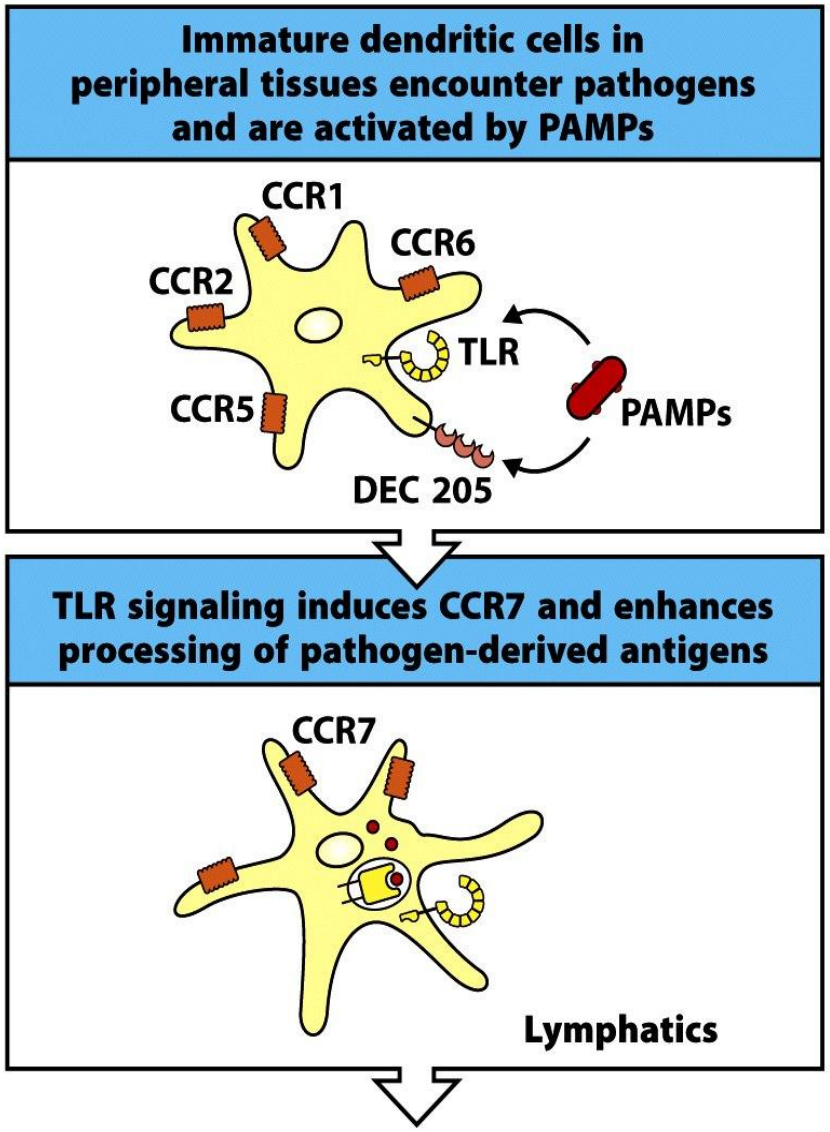


Figure 8-14 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)

- **Peripherals → lymphatics**
  - High expressions of
    - CCR1, 2, 5, 6; but not CCR7
    - Toll-like receptors (TLRs)
    - DEC205 (phagocytosis receptor)
  - PAMPs phagocytosed (via DEC205), and recognized by TLR
  - TLR signaling
    - → induction of CCR7 expression (DCs become '**licensed**')
    - → Ag processing

No B7-1 nor B7-2 expression yet!!

Maturation of conventional DCs (2 stages)

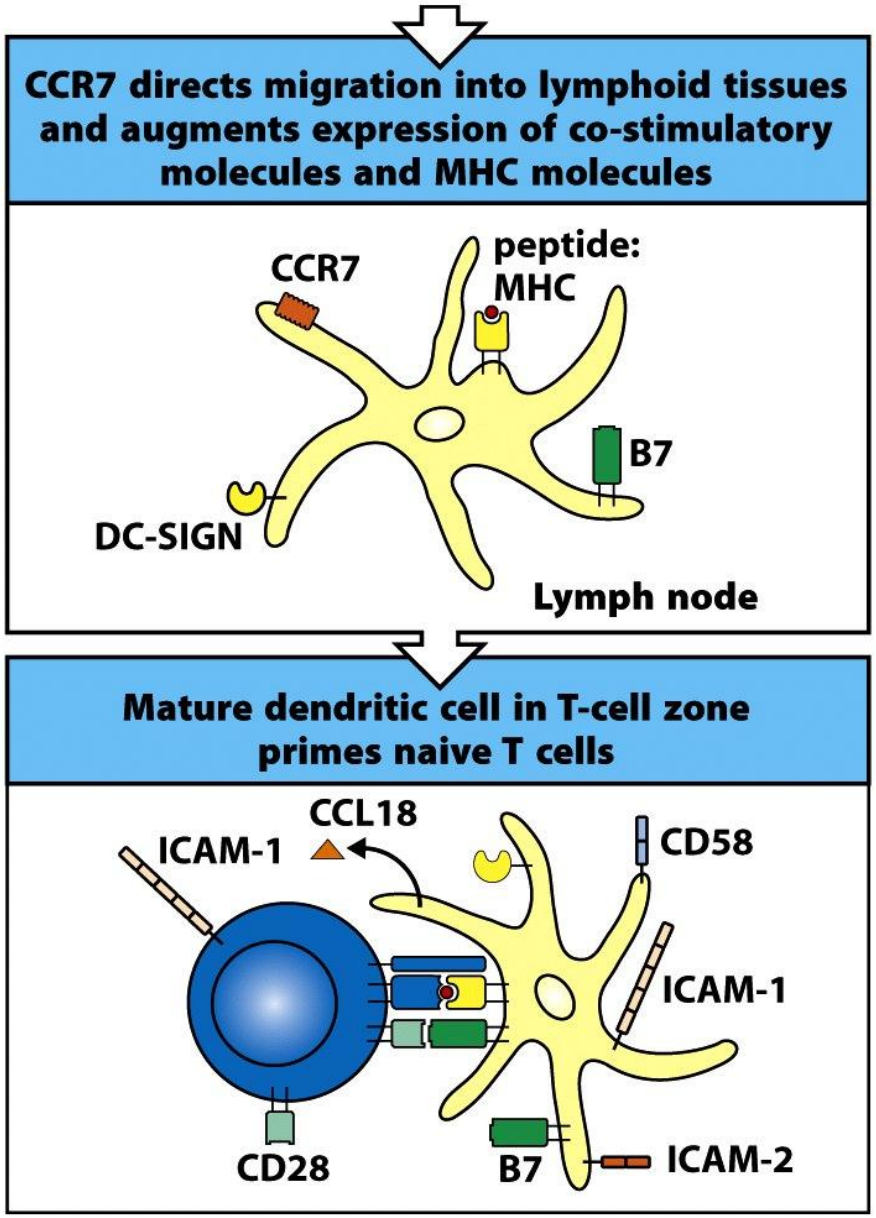
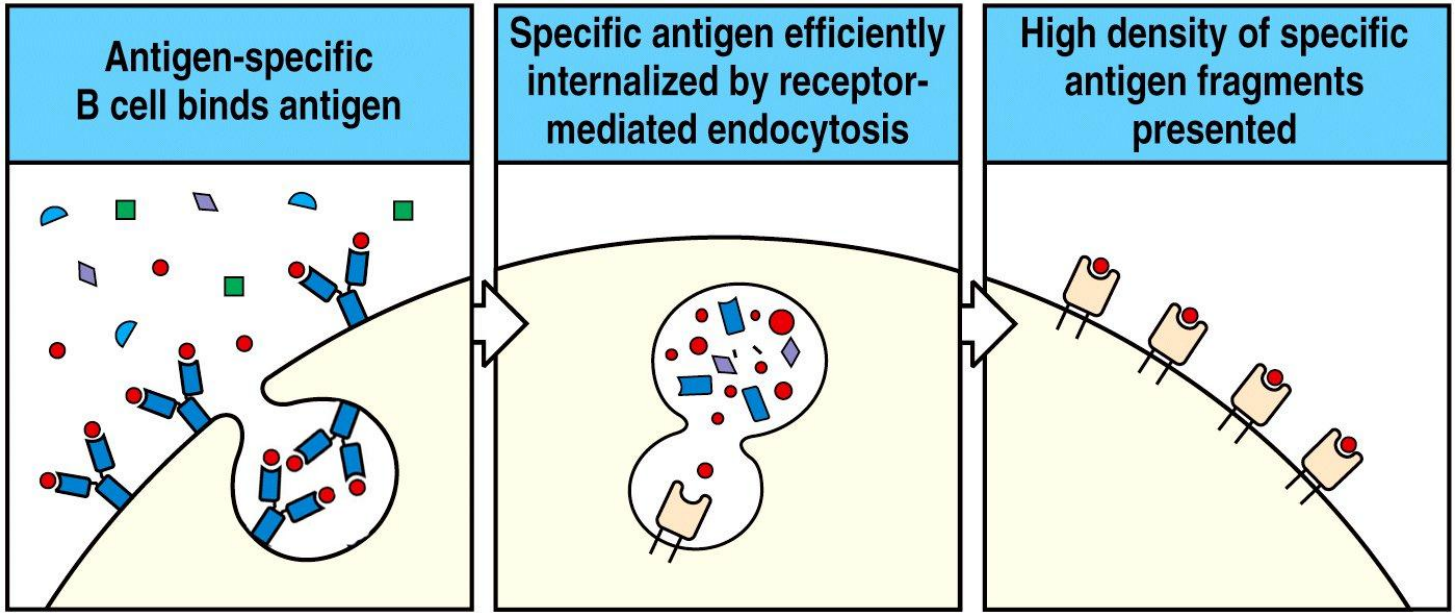


Figure 8-14 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

- **Lymphatics → lymph node**
  - High expressions of
    - CCR7, DC-SIGN
    - B7.1, B7.2
    - MHC-I & -II
    - ICAM-1 & -2
  - Attracted to L.N. by CCL21/CCL19 chemokines (via CCR7)
  - No longer phagocytic!!

B cells use BCRs to efficiently present Ags



1. B cells bind soluble antigens via their surface Ab (BCR)
2. Ags are endocytosed and presented as peptide:MHC-II complex

   → MHC-II from low to high after ingestion of Ag
3. Bacterial products (Ags) cause B cells to express high levels of B7
   → capable of stimulating naïve T cells.
4. Without the co-stimulatory signal, B cells presenting self-Ag to naïve T cells will cause the inactivation of these T cells (**anergic** or **unresponsive**)

Properties of various APCs

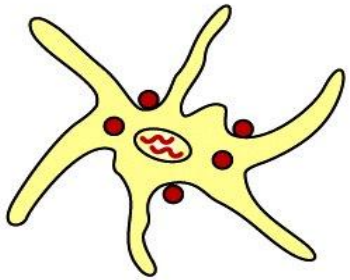
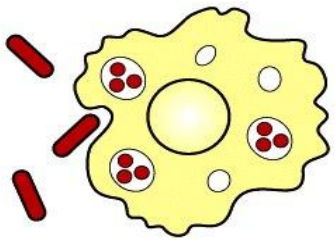
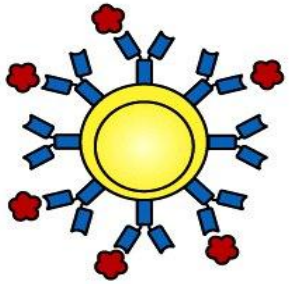
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Figure 8-16 Immunobiology, 7ed. (© Garland Science 2008)

Priming of naïve T cell by pathogen-activated DCs

Cell-surface adhesion molecules crucial in the interaction between T cell and APC

Unique in T cell-DC interaction

Fig. 9-17

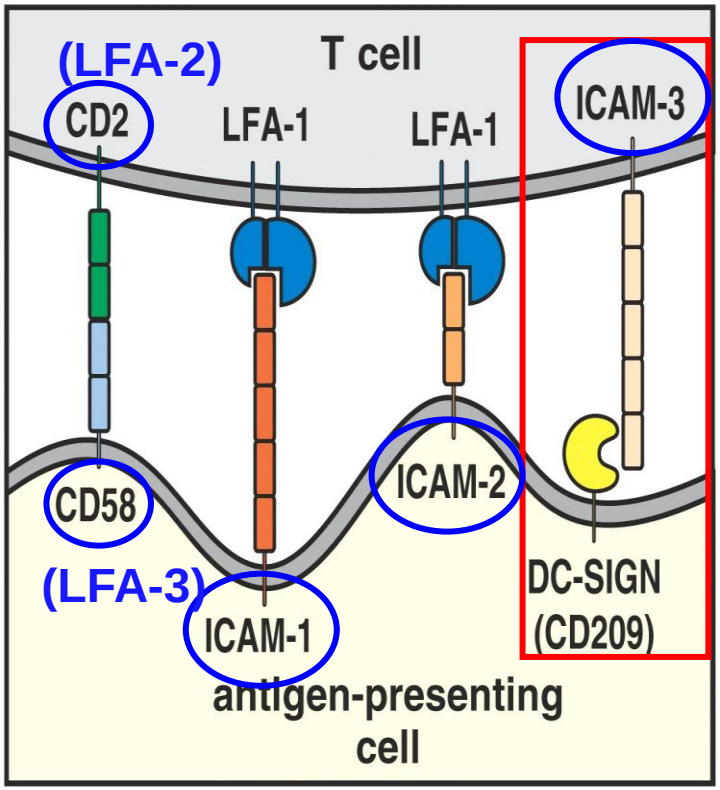


Figure 8-8 Immunobiology, 6/e. (© Garland Science 2005)

Ig superfamily members:
CD2, CD58, ICAM-1, -2, -3

Integrins:

[class]	[distribution]	[ligand]
LFA-1 (β2)	T cells	ICAM-1/-2
LFA-2	T cells	LFA-3
LFA-3	APCs, lym.	LFA-2

Fig. 9-25

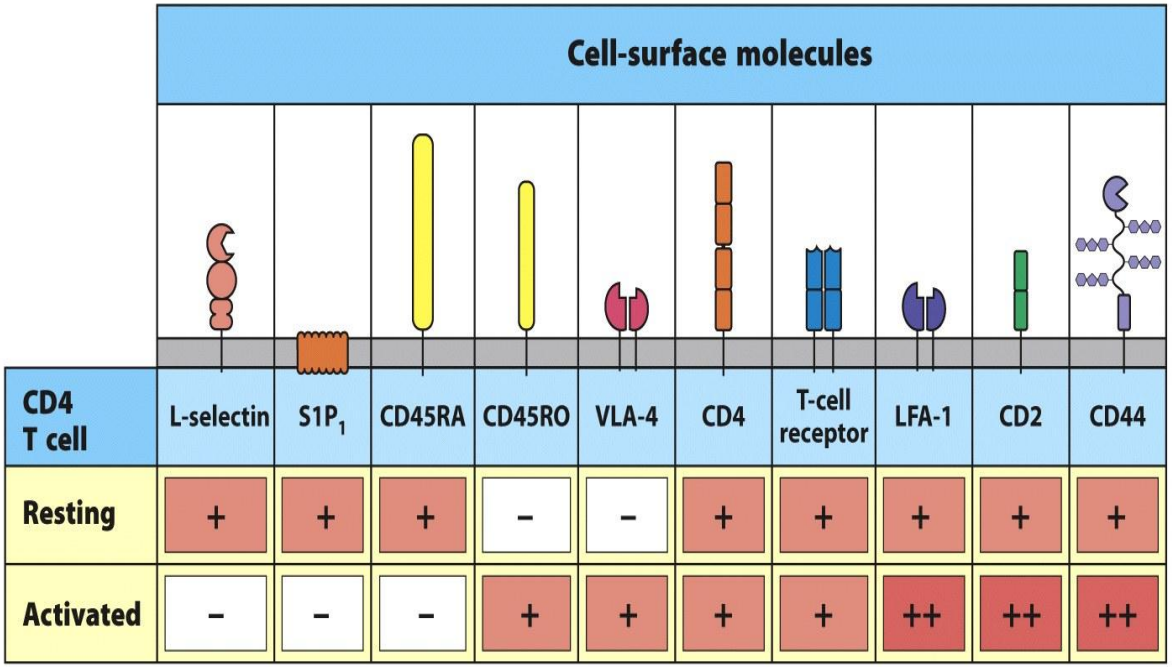


Figure 9.25 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Specific antigen recognition enhances interaction between T cells and APCs

Signal #1 = A + B + C (in order)

Fig. 9-18

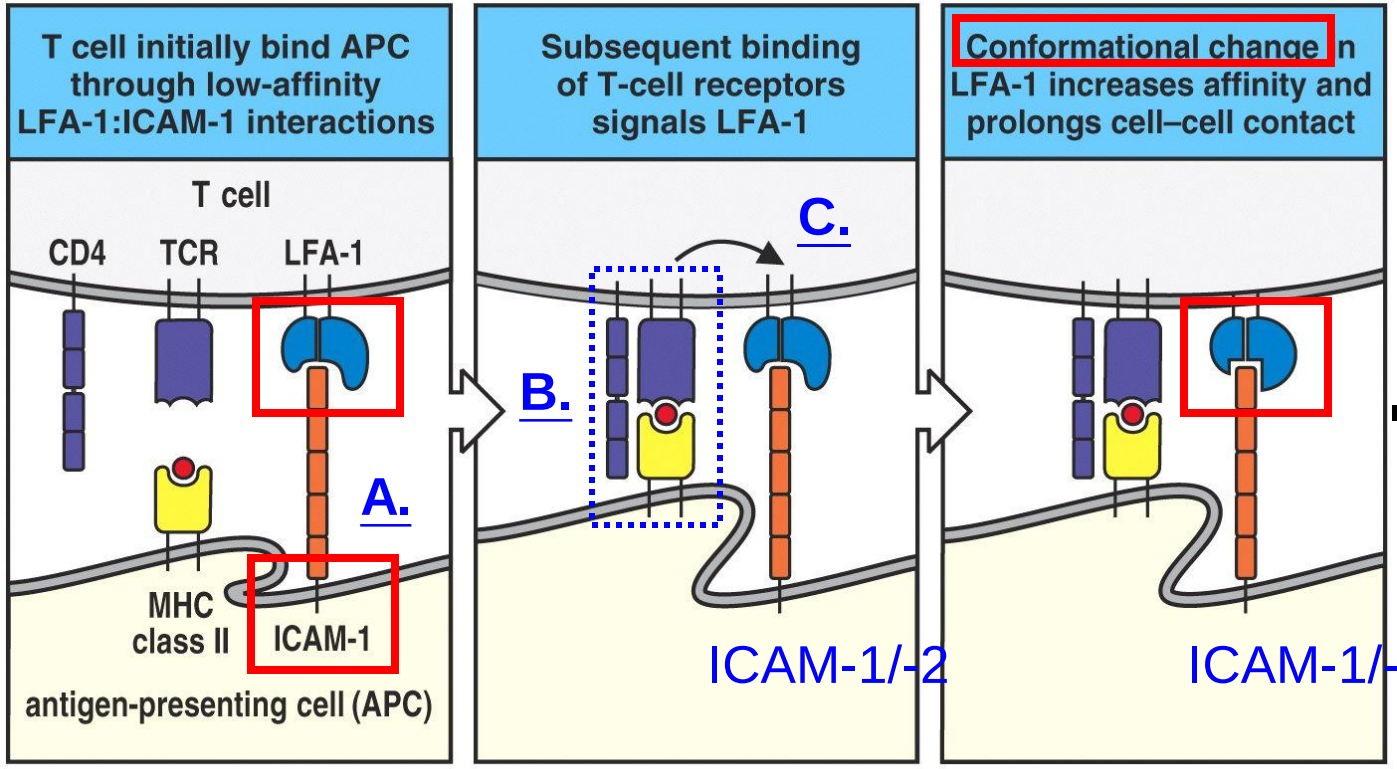


Figure 8-9 Immunobiology, 6/e. (© Garland Science 2005)

T cells proliferate and divide into effector cells (via CD28: B7.1/B7.2 interaction) **Signals #2 & #3**

Low-affinity transient binding
(between LFA-1 & ICAM-1)
→ T cell sampling can occur

High-affinity binding
(can last for several days)

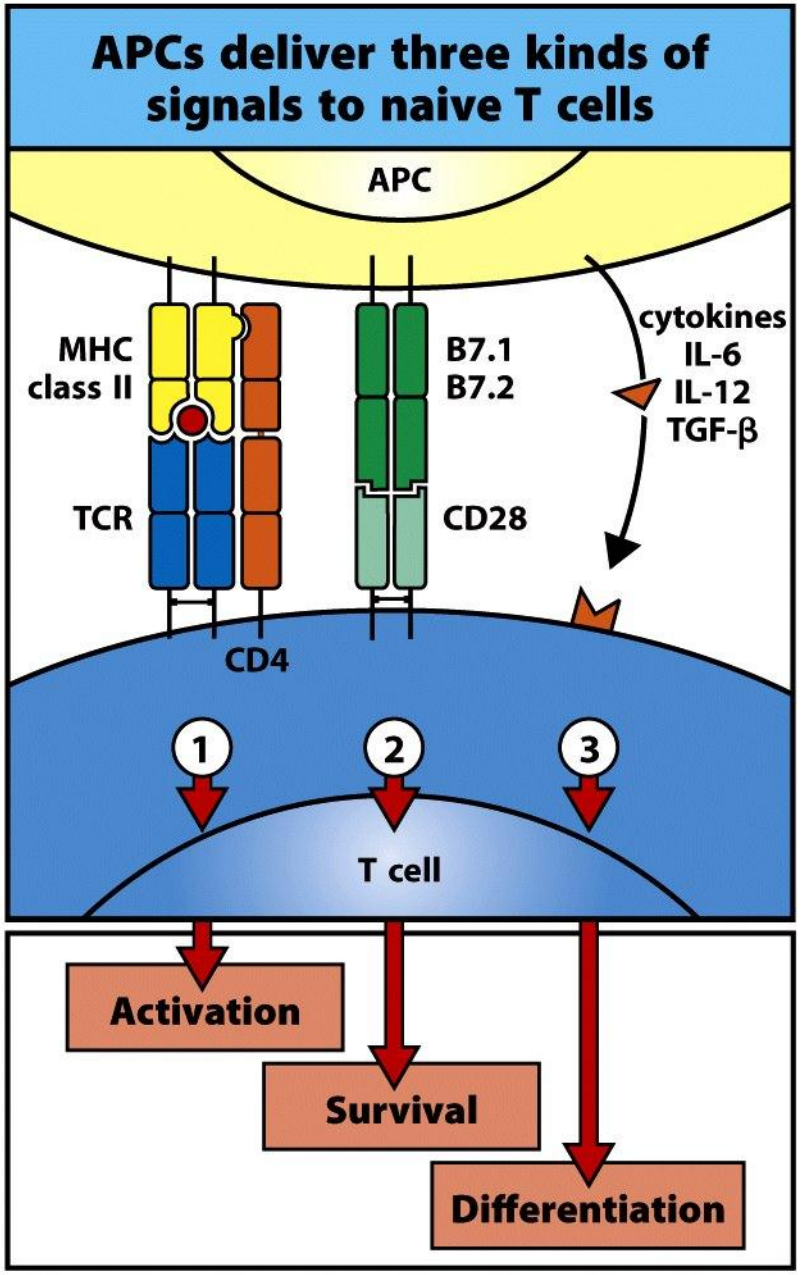


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)

APCs deliver 3 signals to activate T cells

Fig. 9-19

- Occurs in order
- #1 (TCR-MHC)
  - Initial activation
- #2 (CD28-B7)
  - Effective activation
  - Increased survival and proliferation
- #3 (cytokines & surface proteins)
  - Determine effector T responses

Variation in signal #3 causes CD4+ T cells to acquire different effector functions

Fig. 9-29

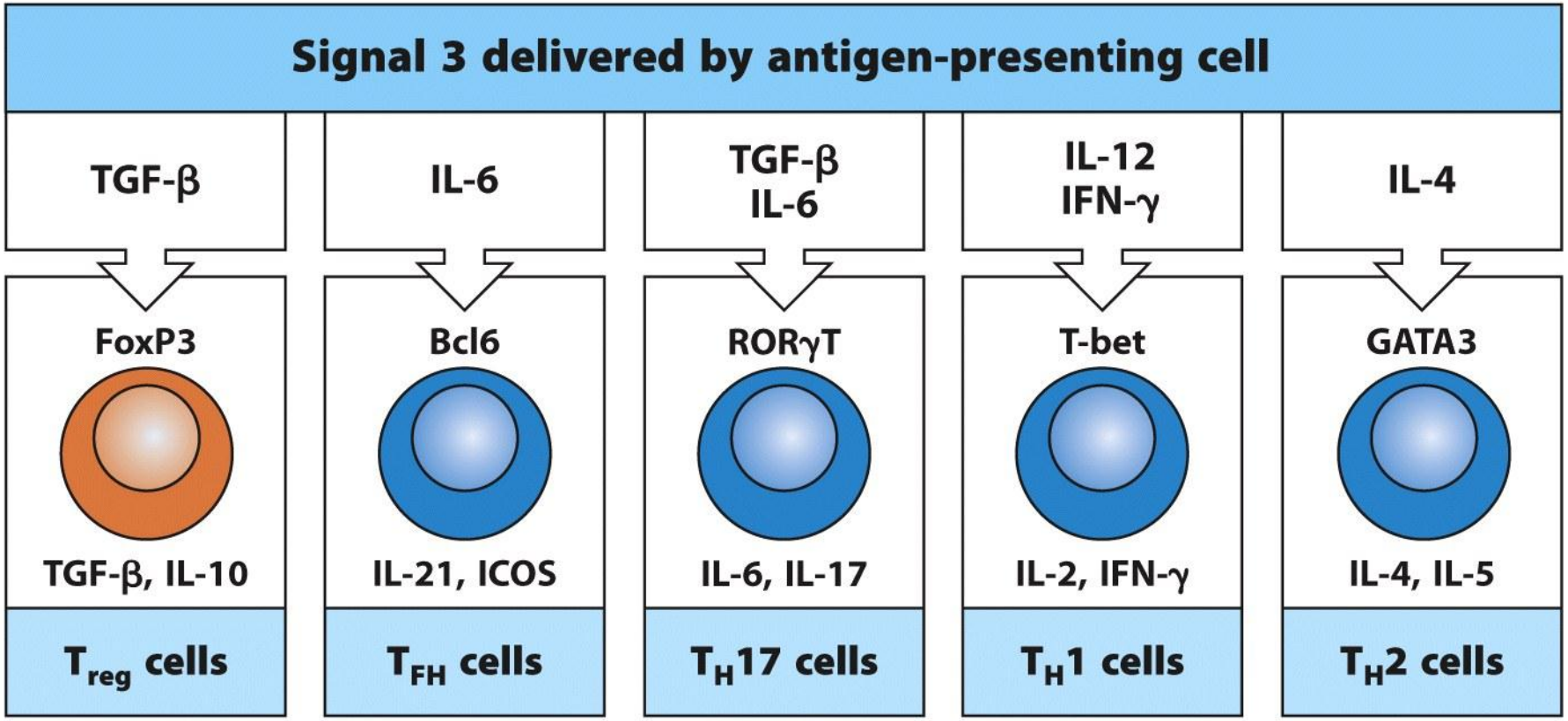


Figure 9.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

IL-2 drives resting T cells into activation

Fig. 9-20

Moderate affinity for IL-2

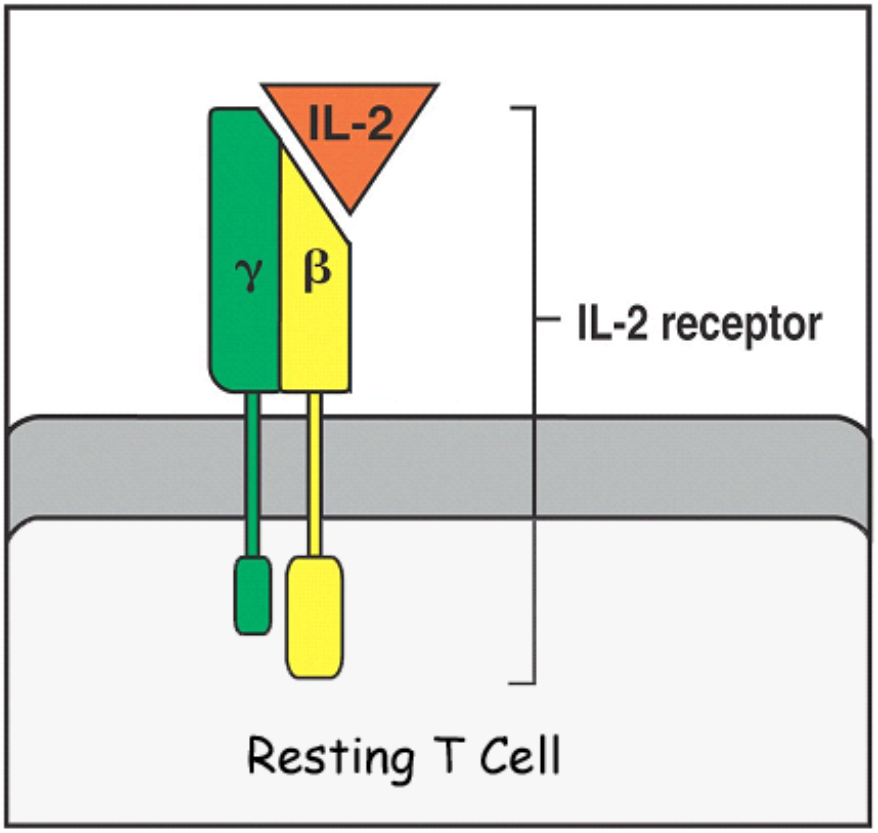


Figure 8-19 Immunobiology, 6/e. (© Garland Science 2005)

IL-2R β & γ chains

→ Constitutively expressed on resting T cells

High affinity for IL-2

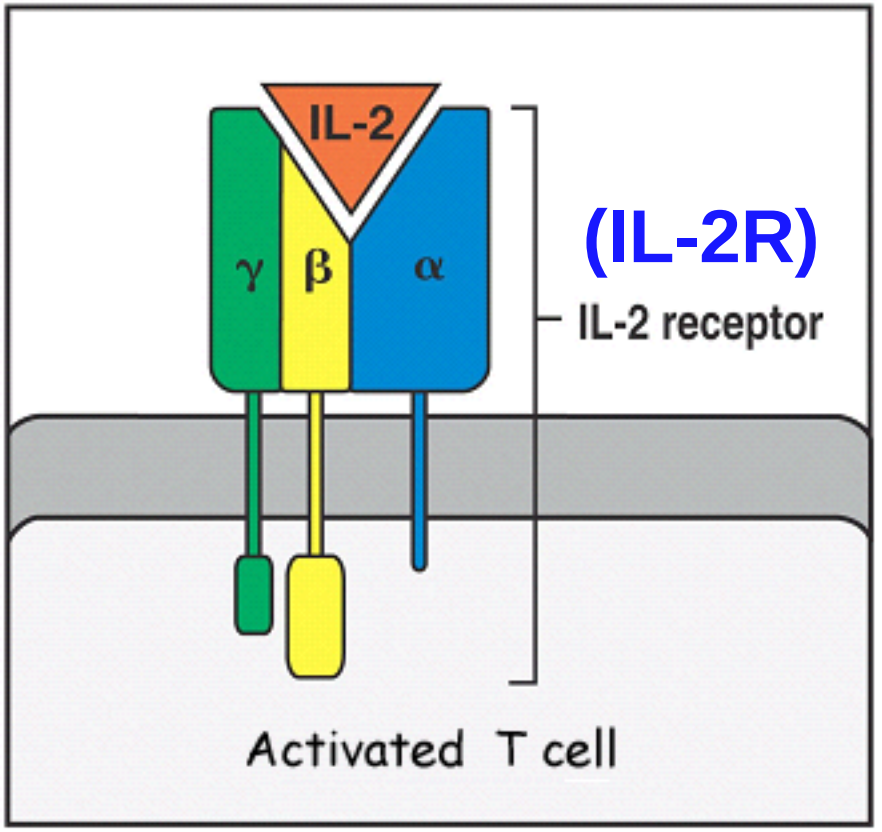


Figure 8-19 Immunobiology, 6/e. (© Garland Science 2005)

IL-2R α chain = CD25

Synthesis of CD25 is triggered by co-stimulation signal!!

IL-2 is key to Ag-induced T cell proliferation and differentiation

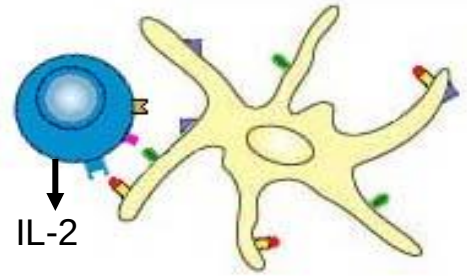


Fig. 9-21

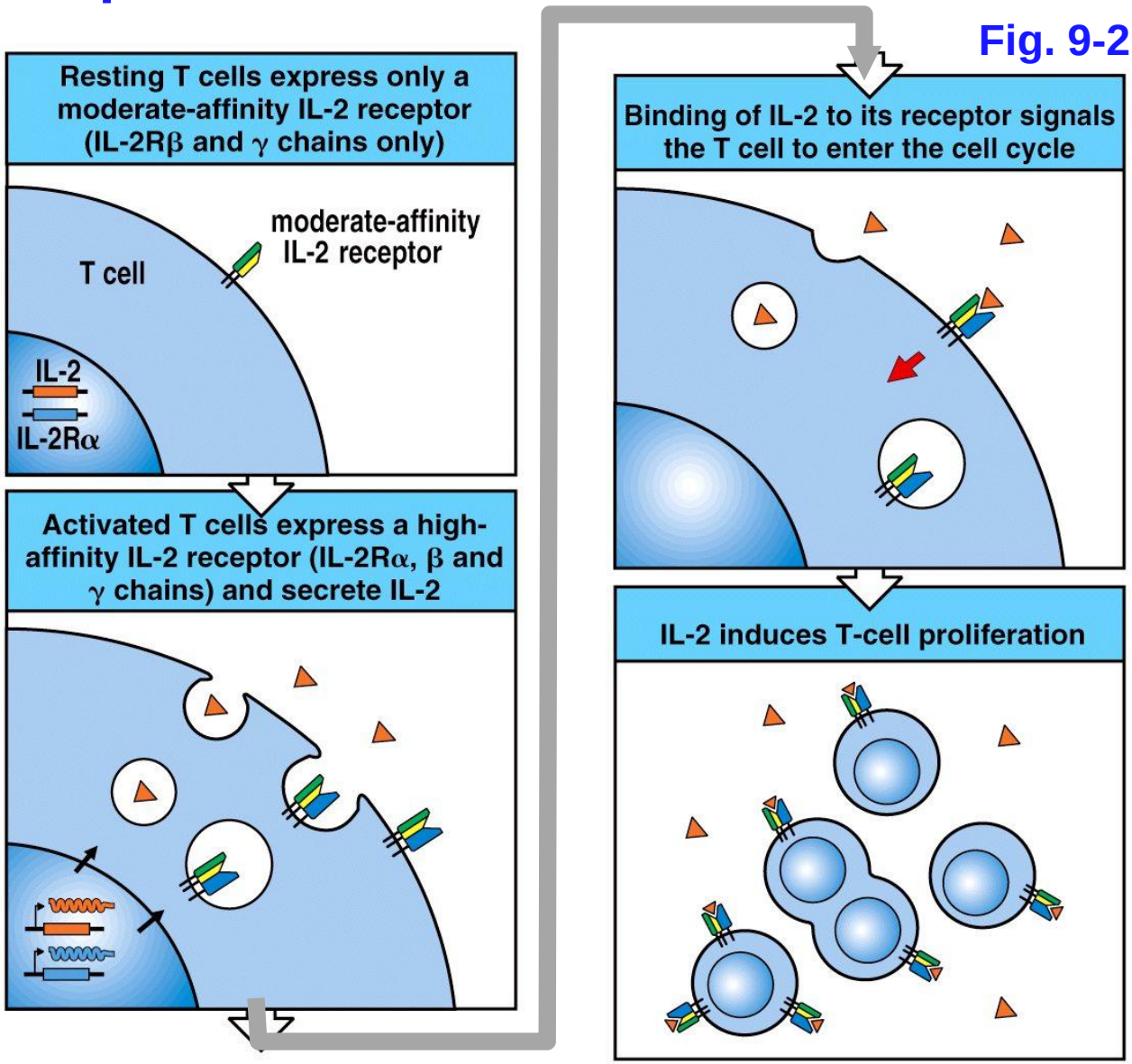


Figure 8-20 Immunobiology, 6/e. (© Garland Science 2005)

Autocrine stimulation (a cell makes a hormone that is secreted and stimulate the cell that made it)

Cells divide 2-3 times per day for 4 or 5 day ($2^{12} = 4096$)

IL-2 is also called "T-cell growth factor"

Signal #2: B7 on activated APC binds to CD28 on T cells

Outer ring (red) pSMAC	Inner circle (green) cSMAC
LFA-1:ICAM-1	TCR, CD4, CD28 MHC:peptide

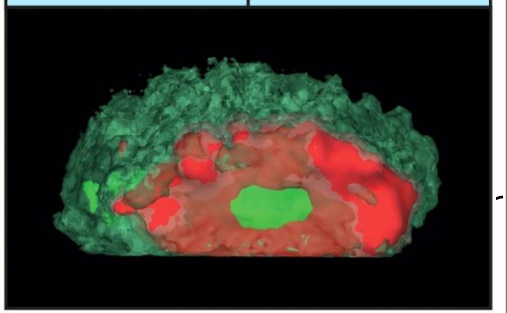


Figure 8-30 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 9-31

"**Synapse**" between the T cell and the APC (dendritic cell)

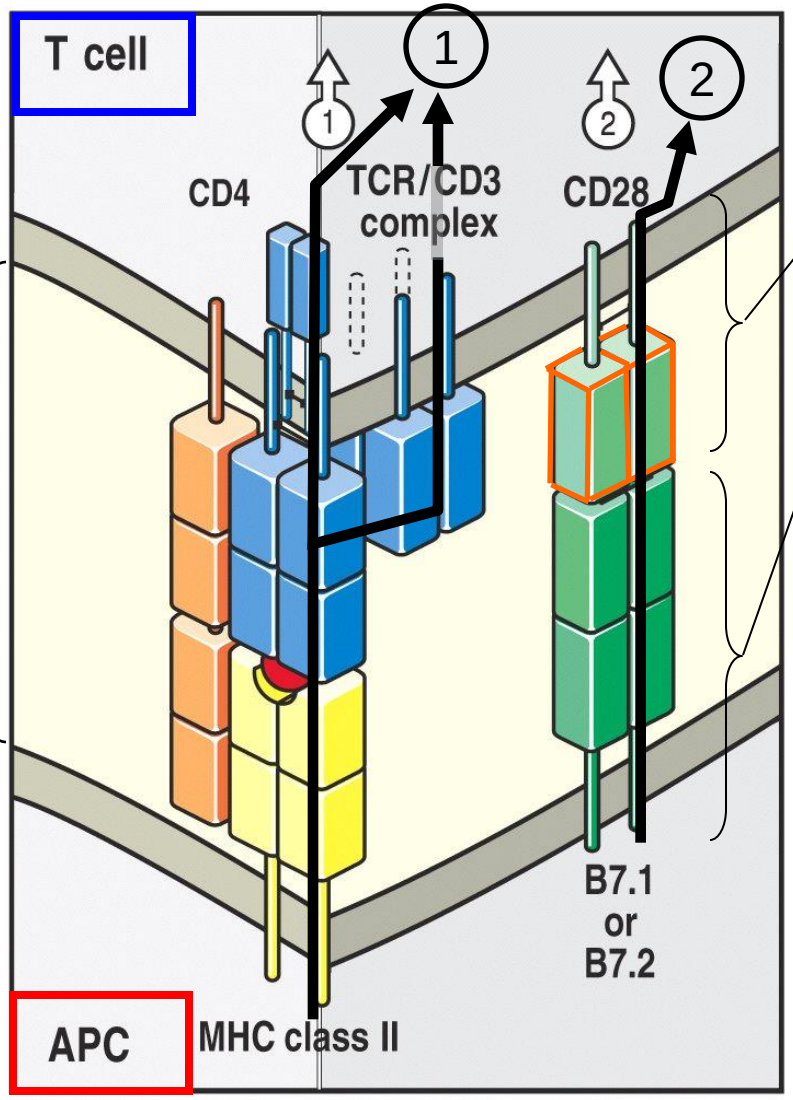


Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

CD28 is the receptor

B7 is the ligand

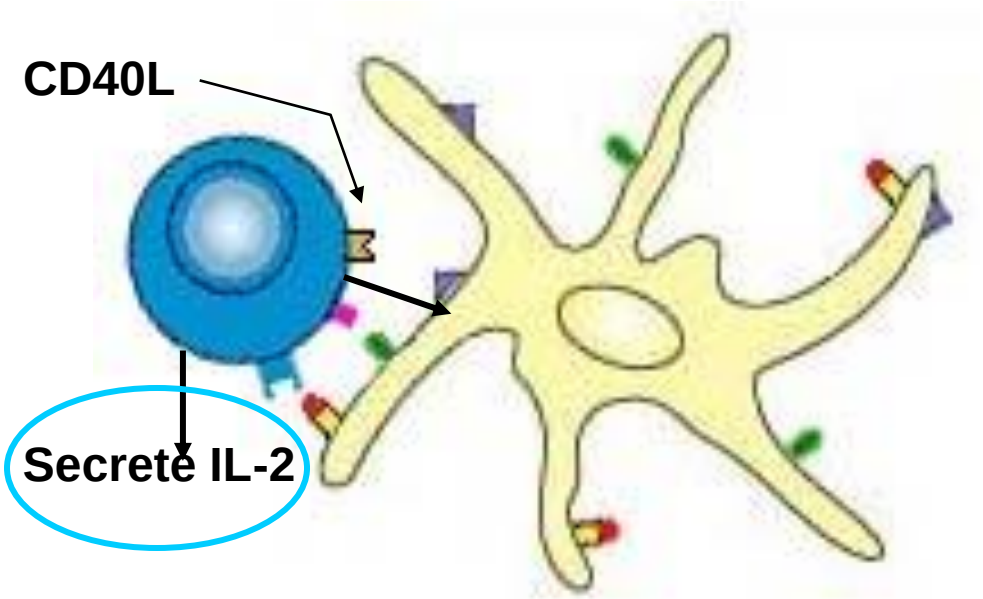
-There are 2 isoforms of B7
- B7.1 = CD80
- B7.2 = CD86

-Both are Ig superfamily members

IL-2 (T-cell growth factor) and IL-2 receptor are made by activated T cells

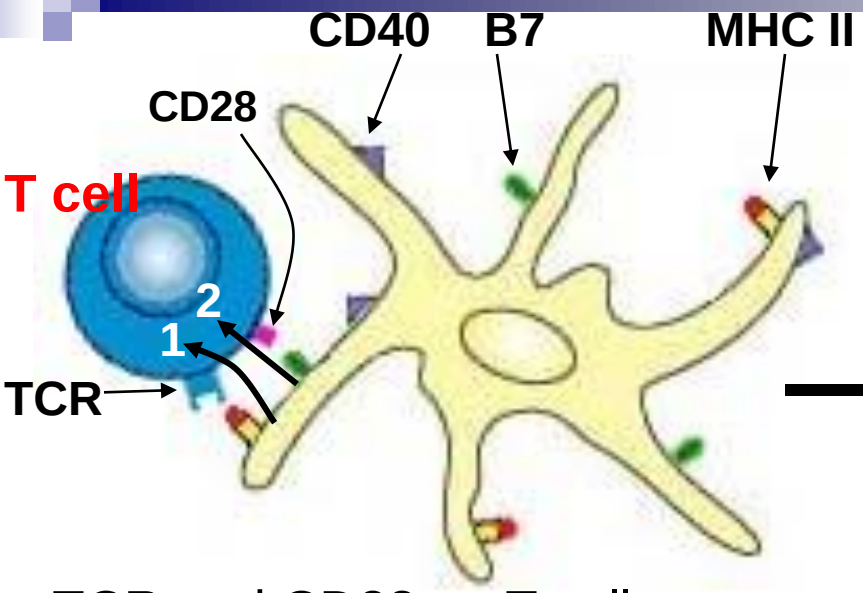
An autocrine loop

T cell get signals 1 and 2 resulting in T cell expression of **CD40L** and secretion of **IL-2**



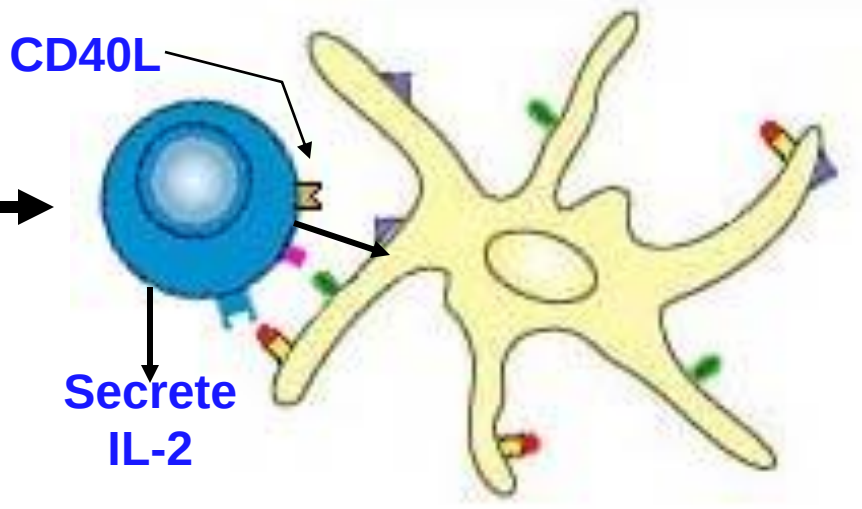
(Interleukin = IL)

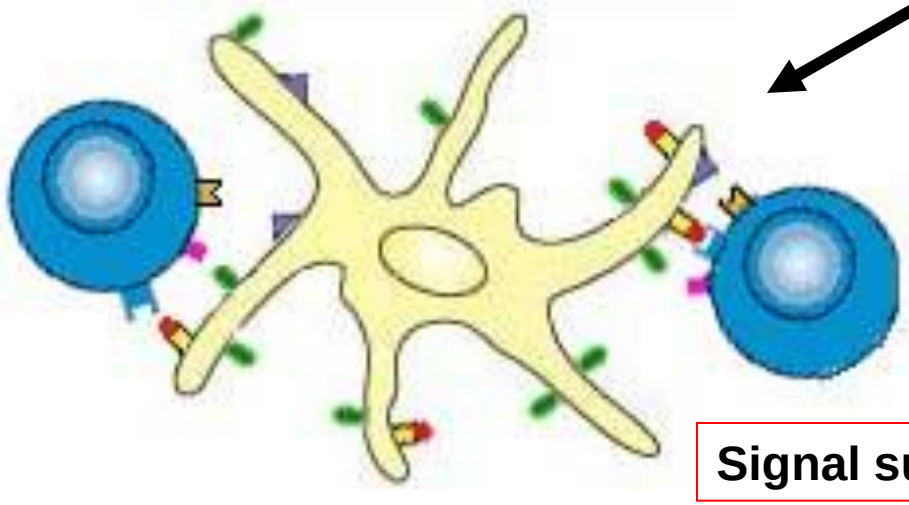
Mature DC



TCR and CD28 on T cell bind MHC II plus peptide and B7 on DC

T cell gets signals 1 and 2 resulting in T cell expression of CD40L and secretion of IL-2





CD40L binding to CD40 causes the DC to express high levels of B7 to better interact with T cells and activate them

Signal sustained by action of CD40

Signal #1 + #2 activate the T cell

Signal # 2 alone has **no effect** on the T cell

Signal #1 alone **inactivates** the T cell

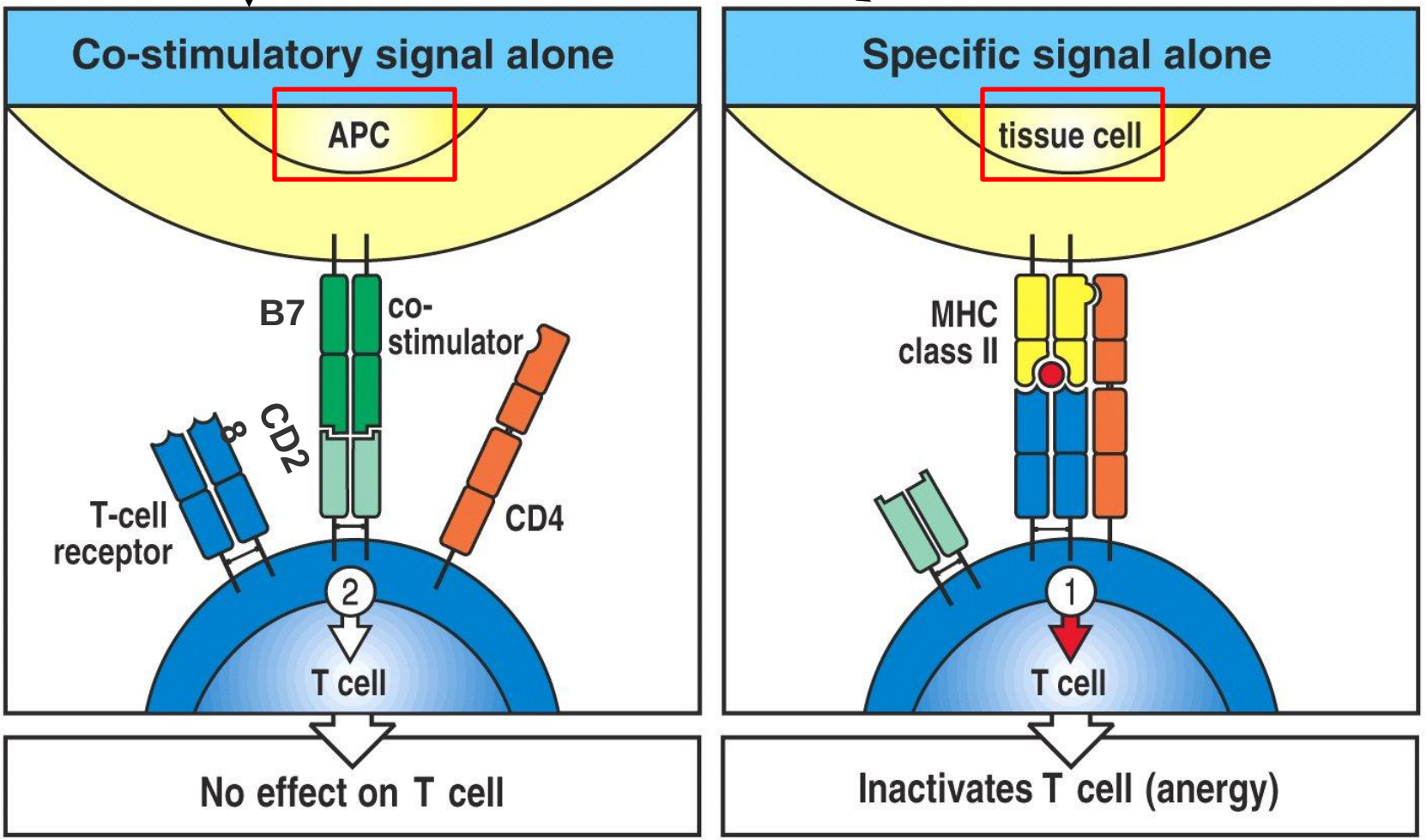


Figure 8-21 Immunobiology, 6/e. (© Garland Science 2005)

Signals #1 + #2 MUST come from the same cell (APC) !!

This can prevent tissue specific self-proteins from activating T cells.

Signal 1 without signal 2 leads to **anergy**

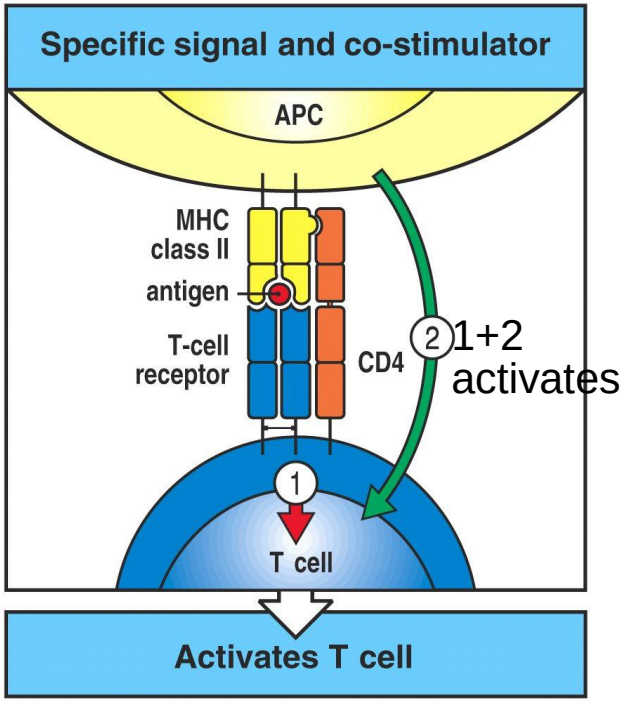


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

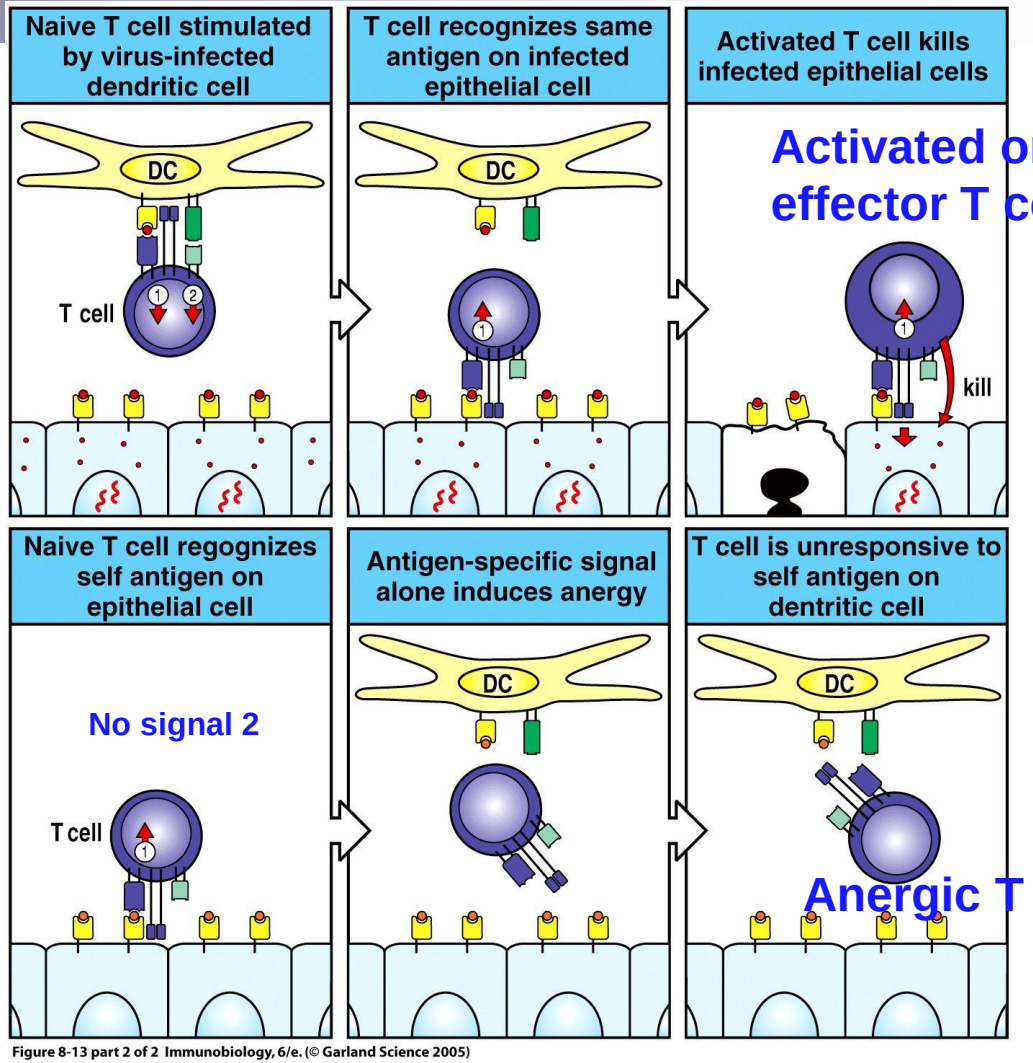


Figure 8-13 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Why?

- So only antigens associated with inflammation activate T cells (right-top), and

- Self Ags inactivate anti-self T cells (maintenance of tolerance; not in bone marrow but **peripheral tolerance**). (right-bottom)

- Thus, auto immune diseases are avoided.

CTLA-4 modulates activation of T cells by attenuating signal #2 (termination signal)

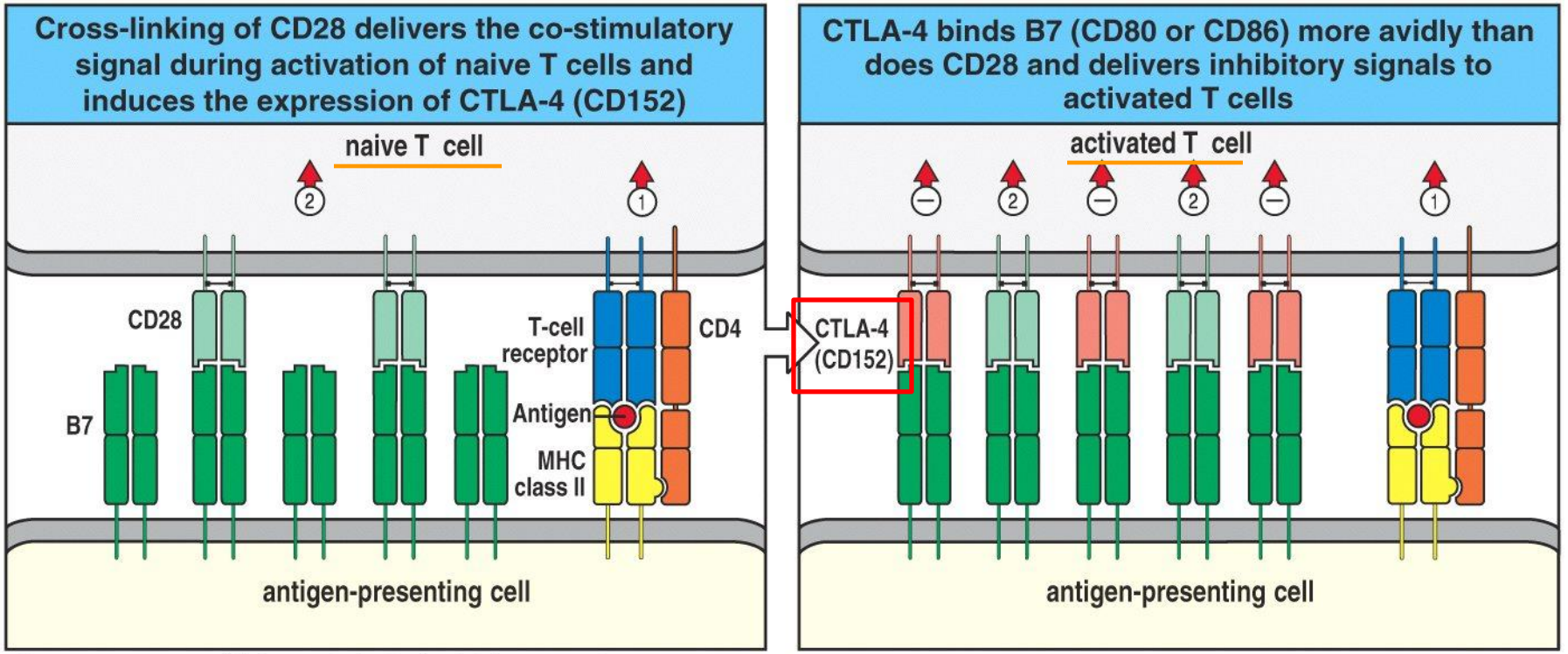


Figure 8-12 Immunobiology, 6/e. (© Garland Science 2005)

(1). Activated T cells express **CTLA-4** on their surface, thus limiting signal# 2.

Similar to Fig. 9-22

(2). CTLA-4 exhibits higher affinity to B7 than CD28 to B7 (>20 times higher)

Macrophage presentation of proteins (self or foreign) in the ***absence*** of co-stimulation will cause the *inactivation* of naïve T cells

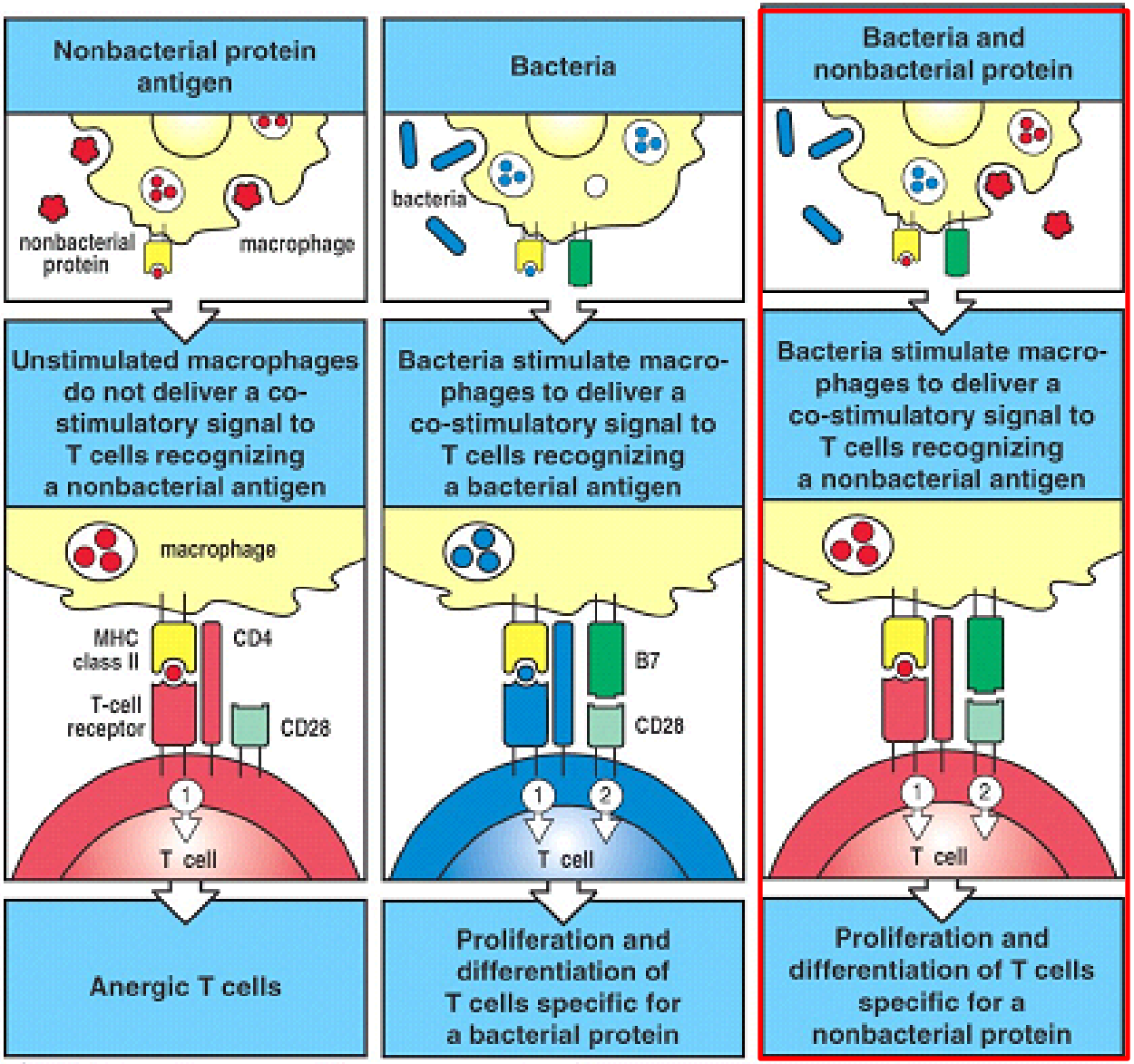


Figure 8-16

Macrophages

1. Resting

MHC-II (- to low); B7 (-)

2. Activated

MHC-II (high); B7 (+)

So, how do you make antibodies (vaccines) to non-bacterial antigens or purified proteins?

↓

The addition of **adjuvants**

Activated T cells **DO NOT** need co-stimulation signals to carry out their function!!

Effector T cells = Activated T cells

Co-stimulation **ONLY** required for activation

Proliferate and acquire effector function (differentiate)

No co-stimulation is required to carry out the effector function

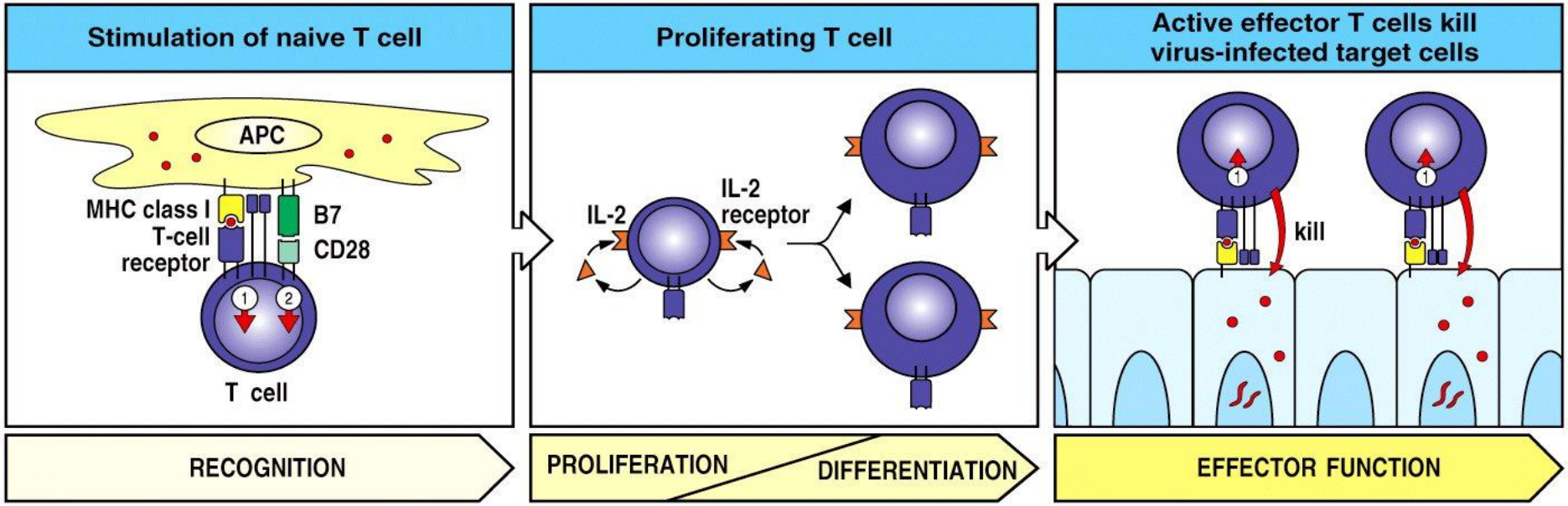


Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 9-24

Naïve immature CD4+ cells leave the thymus having the potential to become either TH1 or TH2 (uncommitted). Referred to as **TH0**.

After antigenic stimulation, they begin to acquire effector functions but are still **uncommitted TH0 cells**

Cytokines and unknown factors drive the cells to become TH1 or TH2.

Generally, one expects the response to be dominated by TH1 (CMI) or TH2 (humoral immunity), not a balanced response

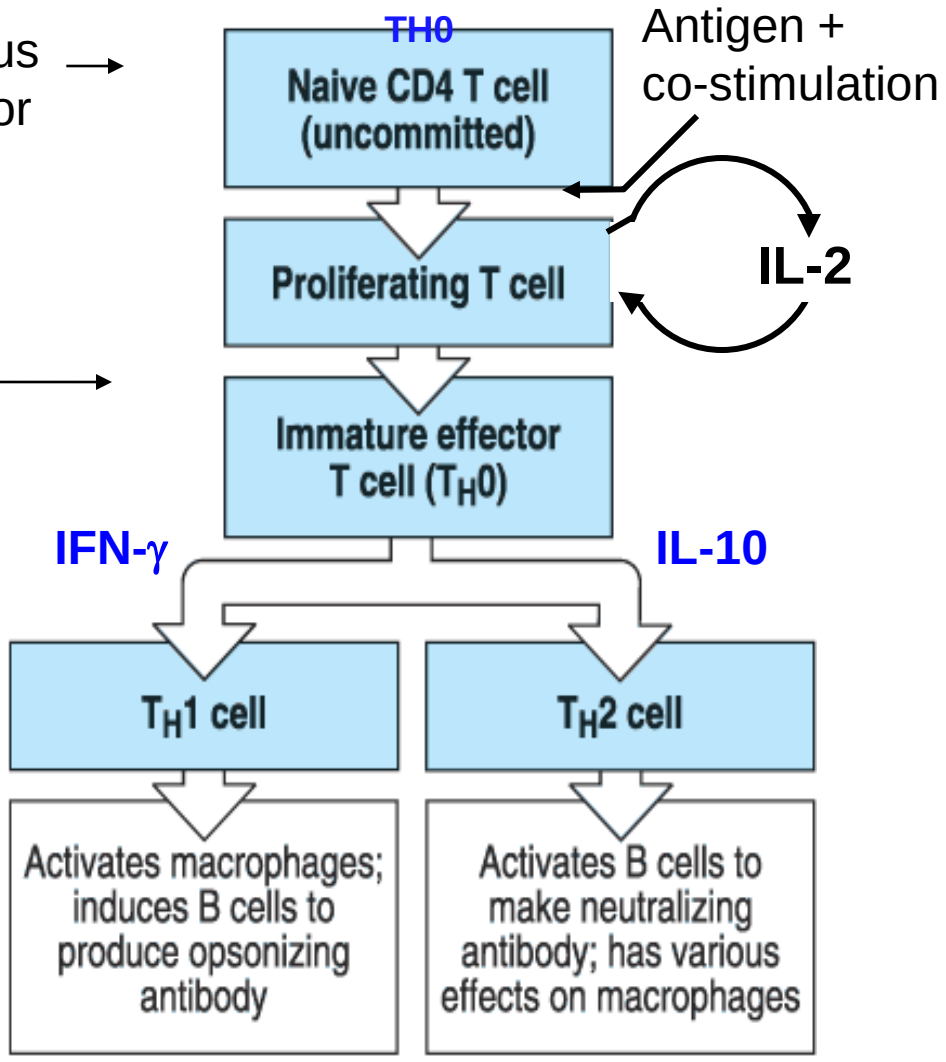


Fig 8.24 © 2001 Garland Science

Leprosy (see Fig. 11.6)

(I) Naïve CD8+ T cells can be activated on virus-infected DCs → anti-tumor CD8 T cells

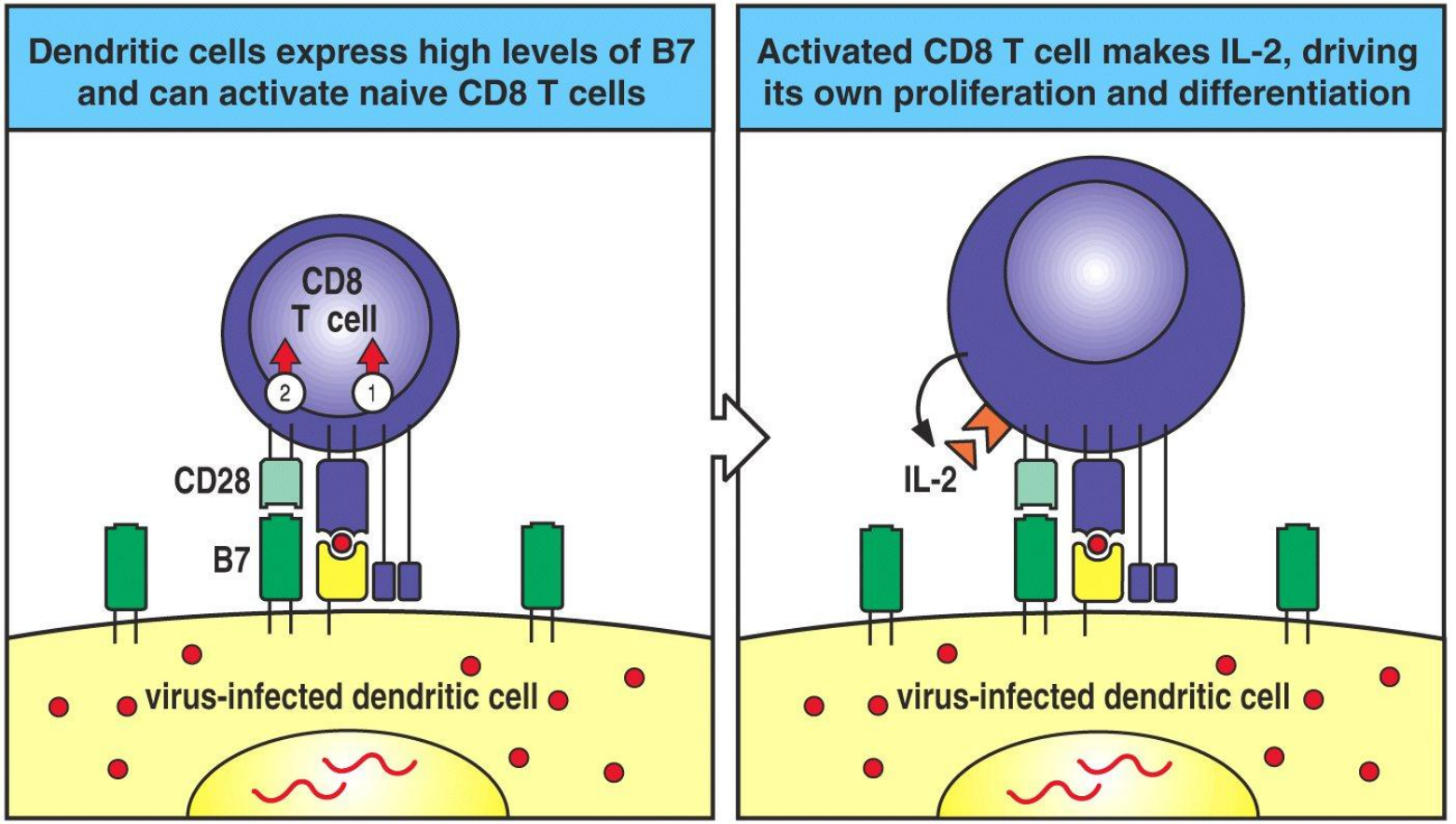


Figure 8-25 Immunobiology, 6/e. (© Garland Science 2005)

Similar process as seen in the activation of naïve CD4+ T cells

-Requires 2 signals

- Produce IL-2 for autocrine stimulation

(II) Some CD8 T-cell responses require help from CD4 T cells → anti-vial or graft

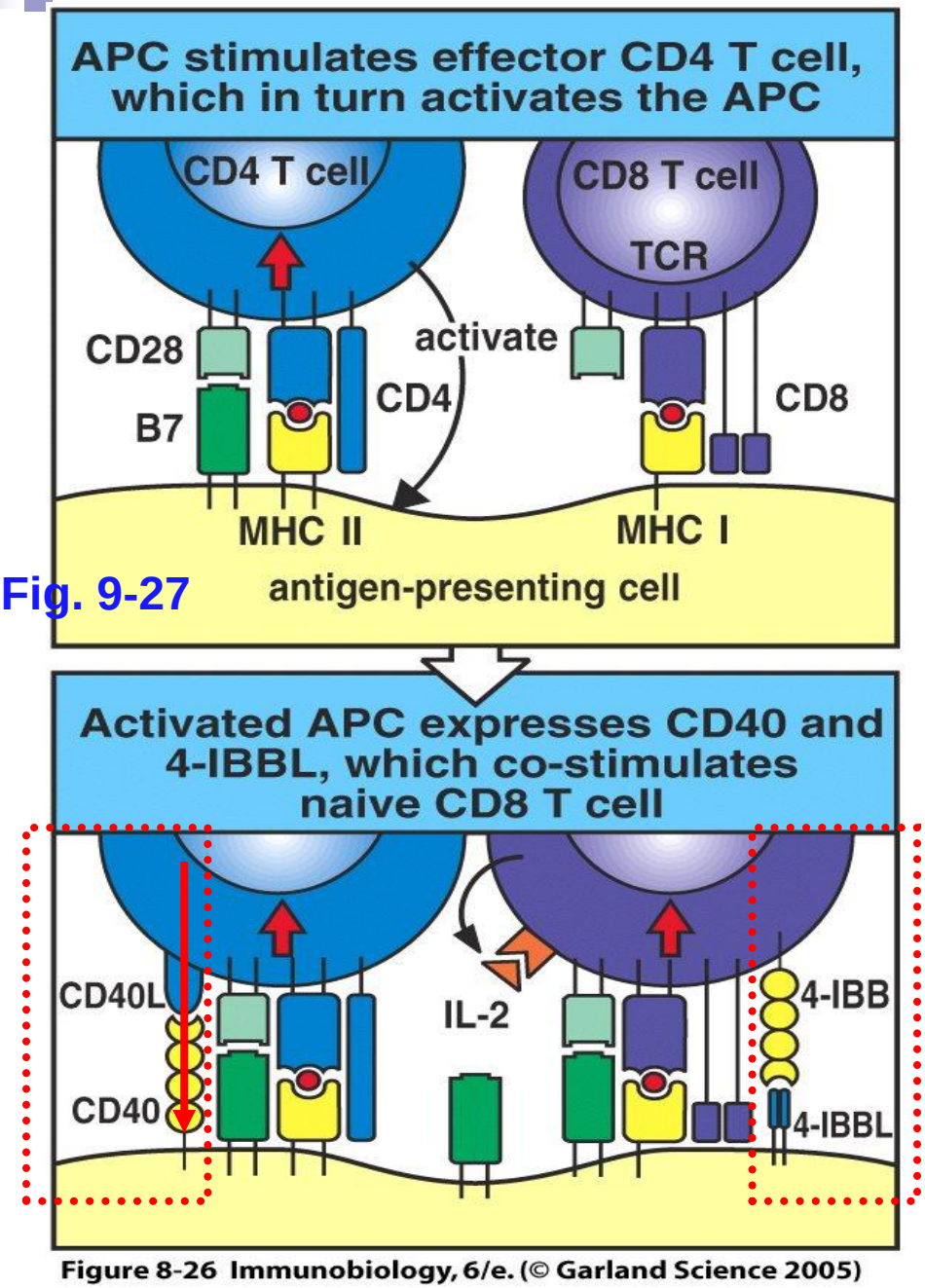


Fig. 9-27

Figure 8-26 Immunobiology, 6/e. (© Garland Science 2005)

1. **Activated CD4 cells express CD40L and IL-2**

2. **CD40L-CD40** interaction stimulates APC to express **higher levels of B7**

3. Then, the APC can activate the CTL (the $CD4^+$ cell "**licenses**" the APC to activate CTLs). This is key when there are few bacterial products to activate the APC (e.g., viral infection).

Both T and APCs receive activating signals from each other (p.329)

→ termed "**T-cell: APC dialogue**"

Summary of Effector Cell Functions

Once activated (acquire their effector function), T cells go to the site where they can carry out their effector function.

1. CTLs go the site of the infection and perform direct killing of self-cells infected with intracellular pathogens (e.g. viruses).

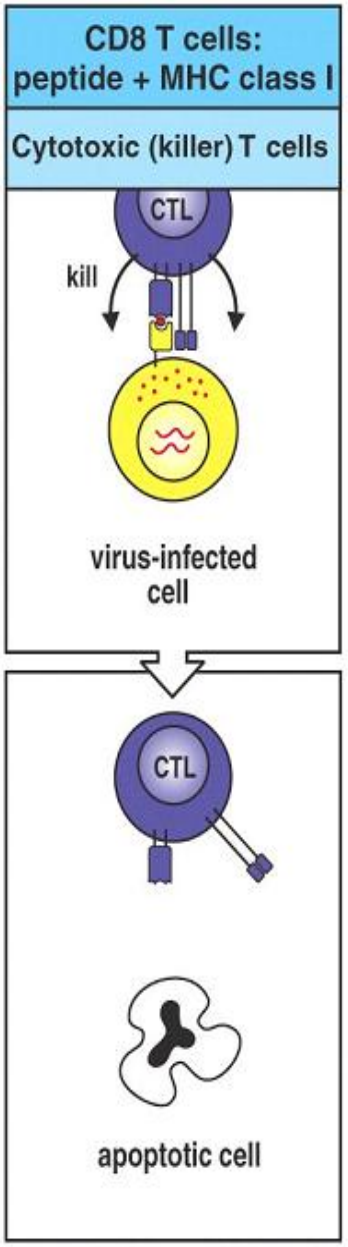


Fig. 9-26

Summary of Effector Cell Functions

Fig. 9-28

2. T_H1 cells can

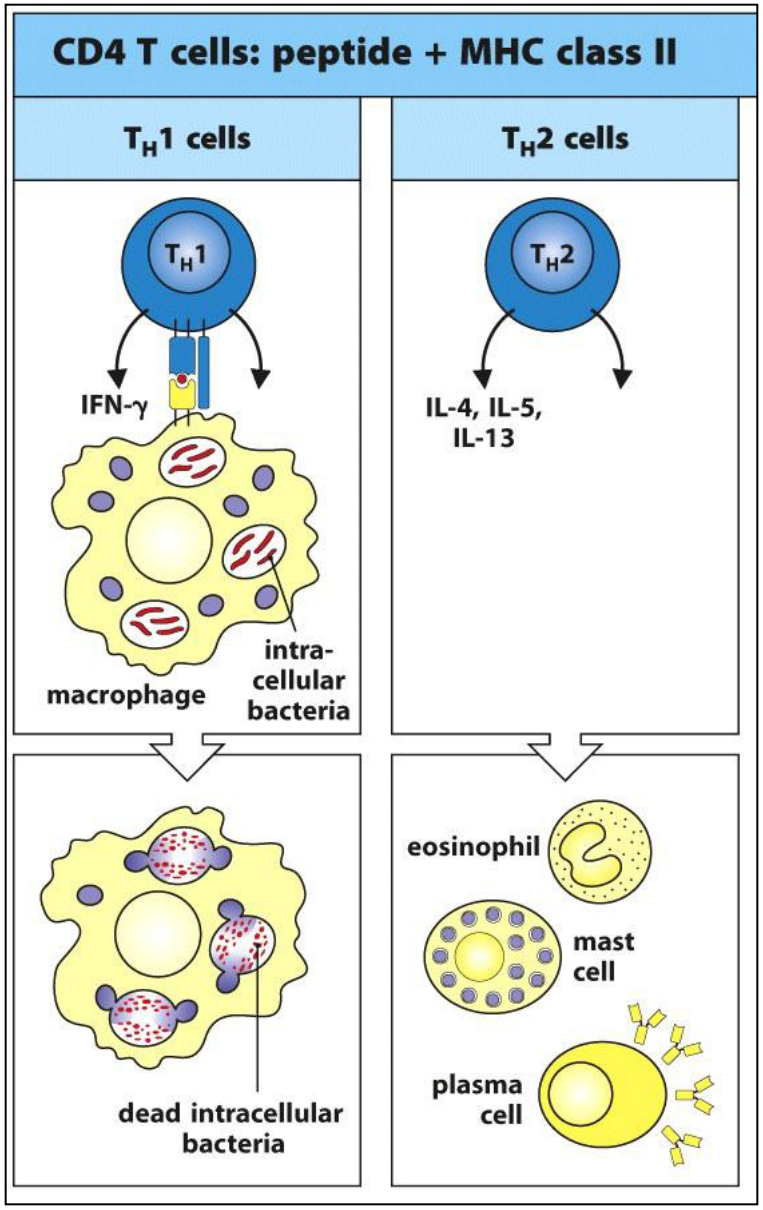
(a) go to the site of the infection ,or

(b) stay in the lymphoid organ to help certain B cell responses

- Macrophage activation (principal role)
- IgG1/G3 production by B cells

3. T_H2 remains in the lymphoid organ to help B cell responses

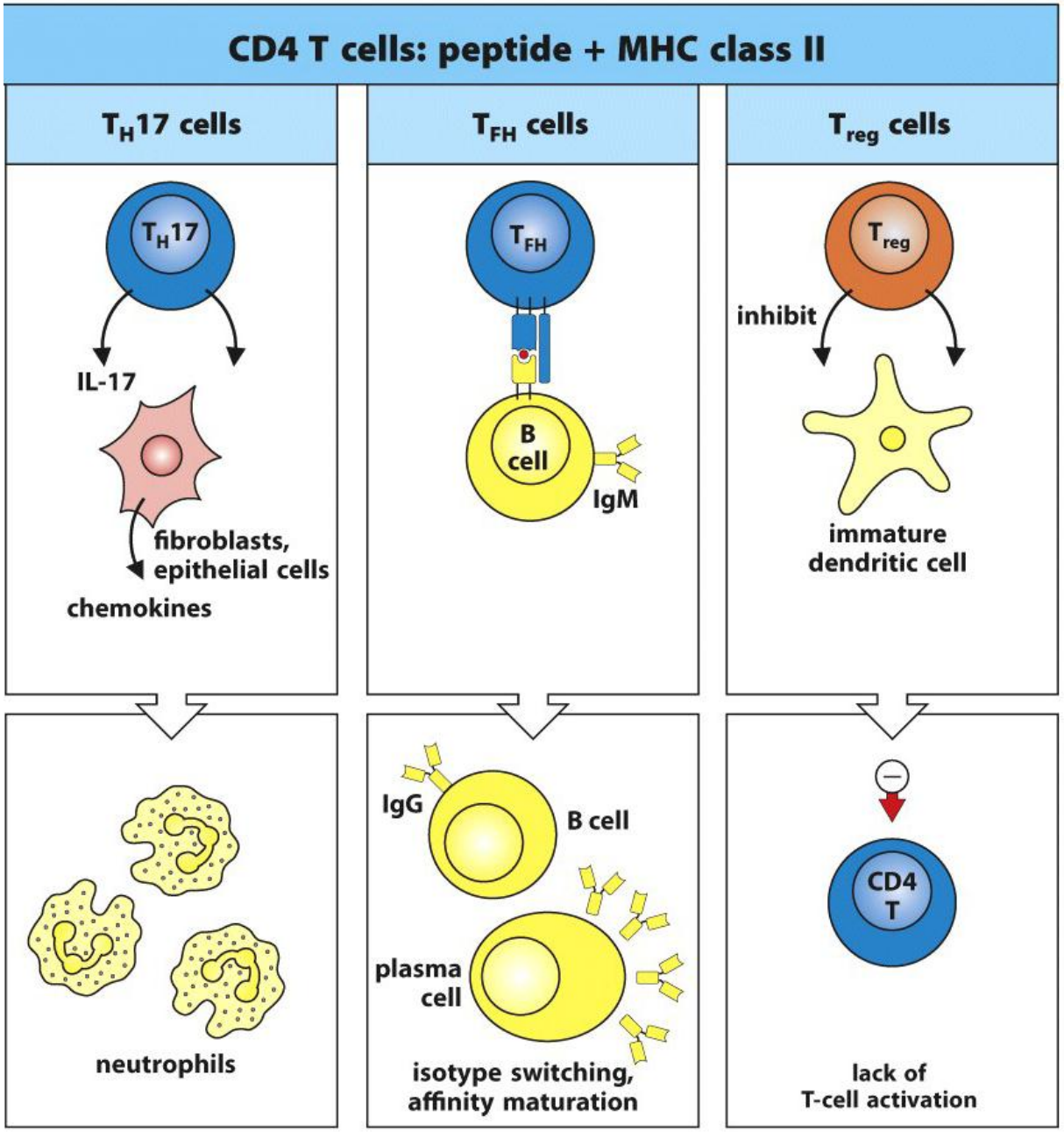
- Ig swtich to classes other than IgG
- Proliferation of naïve B cells



Summary of Effector Cell Functions

Fig. 9-28

4. Other T cell types



General properties of effector T cells and their cytokines

How does CD8 T cell kill target cell?

Requirements of killing by CTLs

1. Non-specific interaction between LFA-1 (CTL) and ICAM (target)
2. Ag-specific interaction between TCR (CTL) and MHC-I/peptide (target)

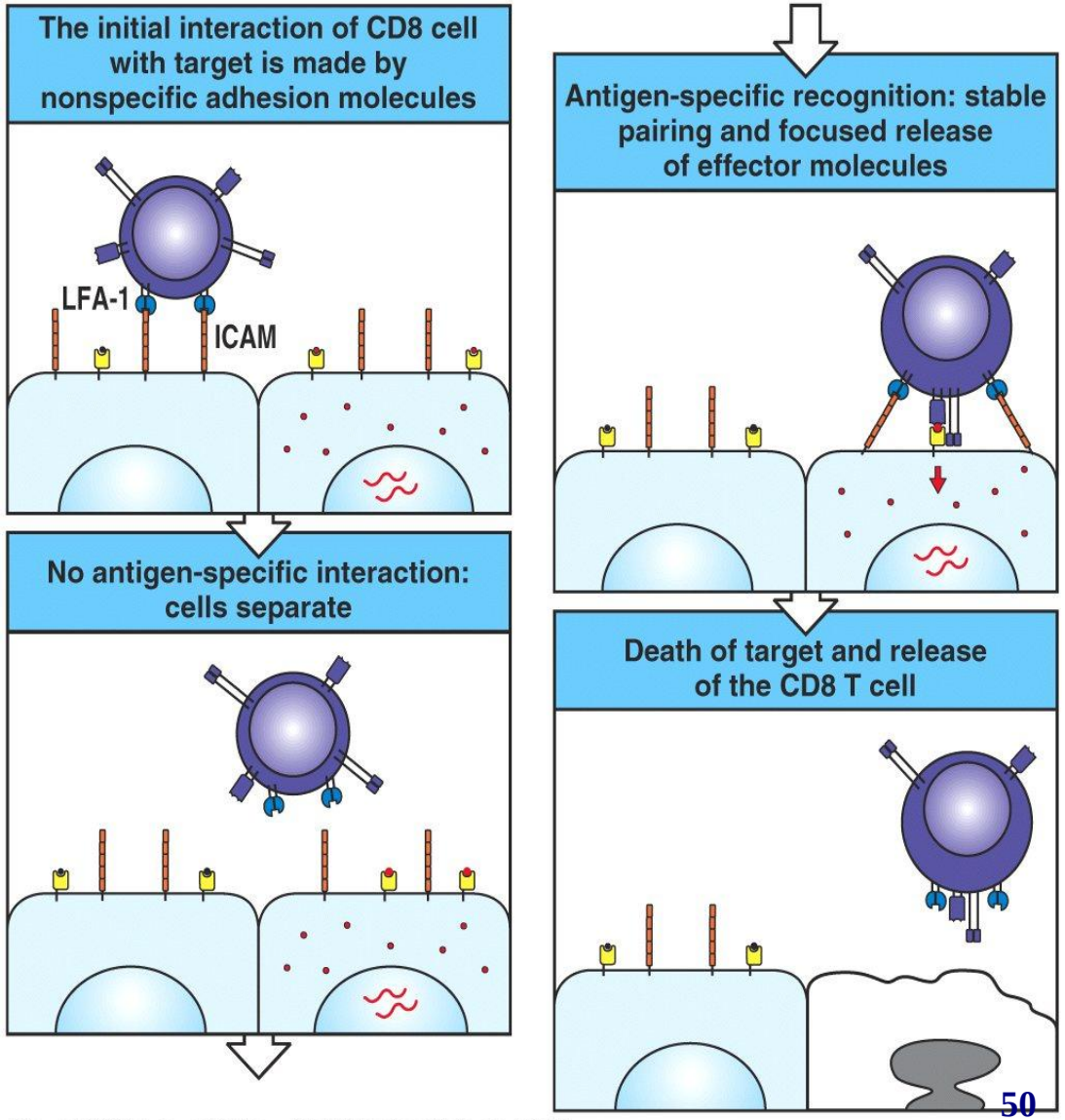


Figure 8-28 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 9-30

Polarization of T cell during Ag-specific recognition of its target

- Allows lytic granules focused on the Ag-bearing cell

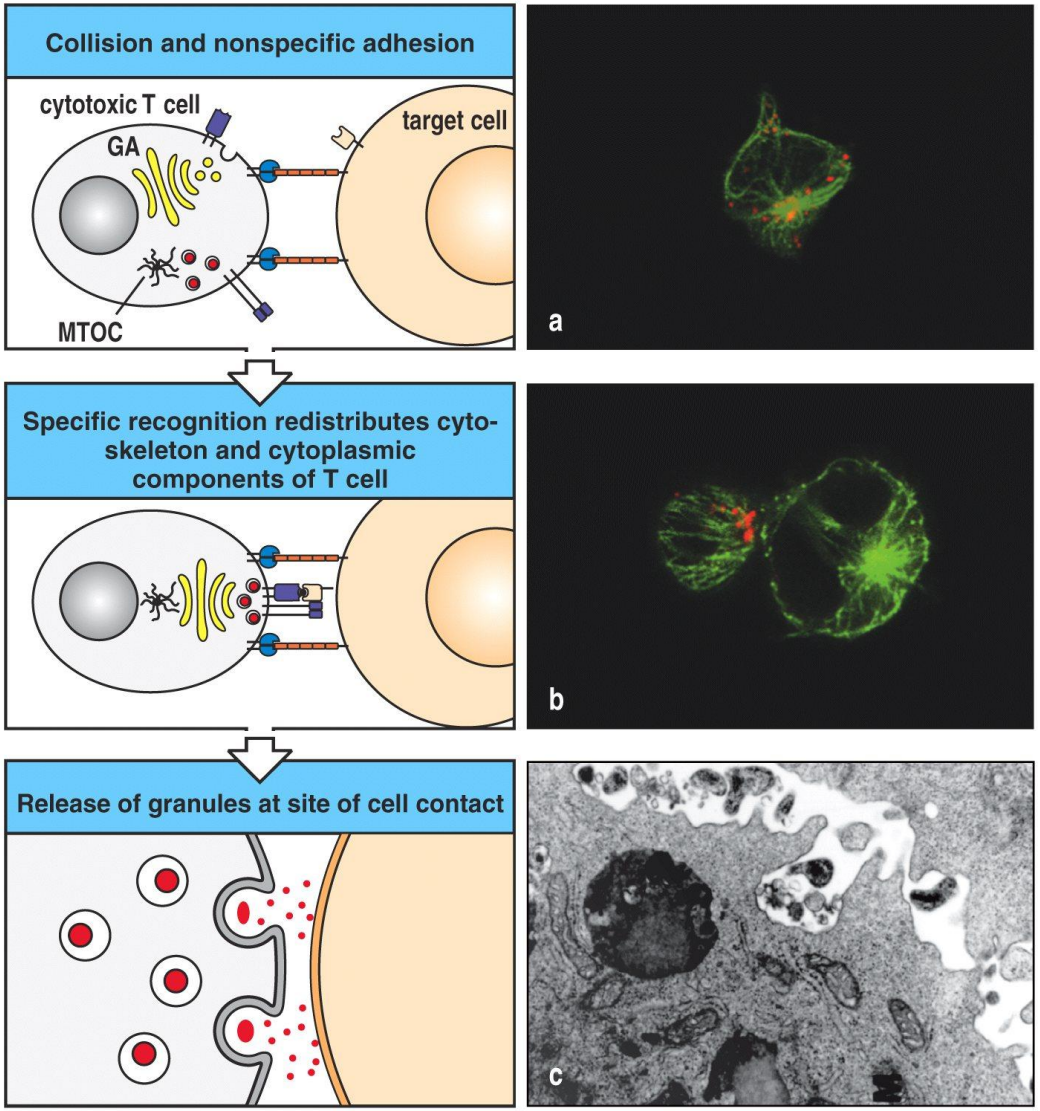


Figure 8-29 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

CTL alone

- Dispersed lytic granules (red)

CTL attacking a target cell

-Reorganization of actin microtubules (green)

-Focused lytic granules on the site of contact

Fig. 9-32

Different T cell effectors produce different effector molecules

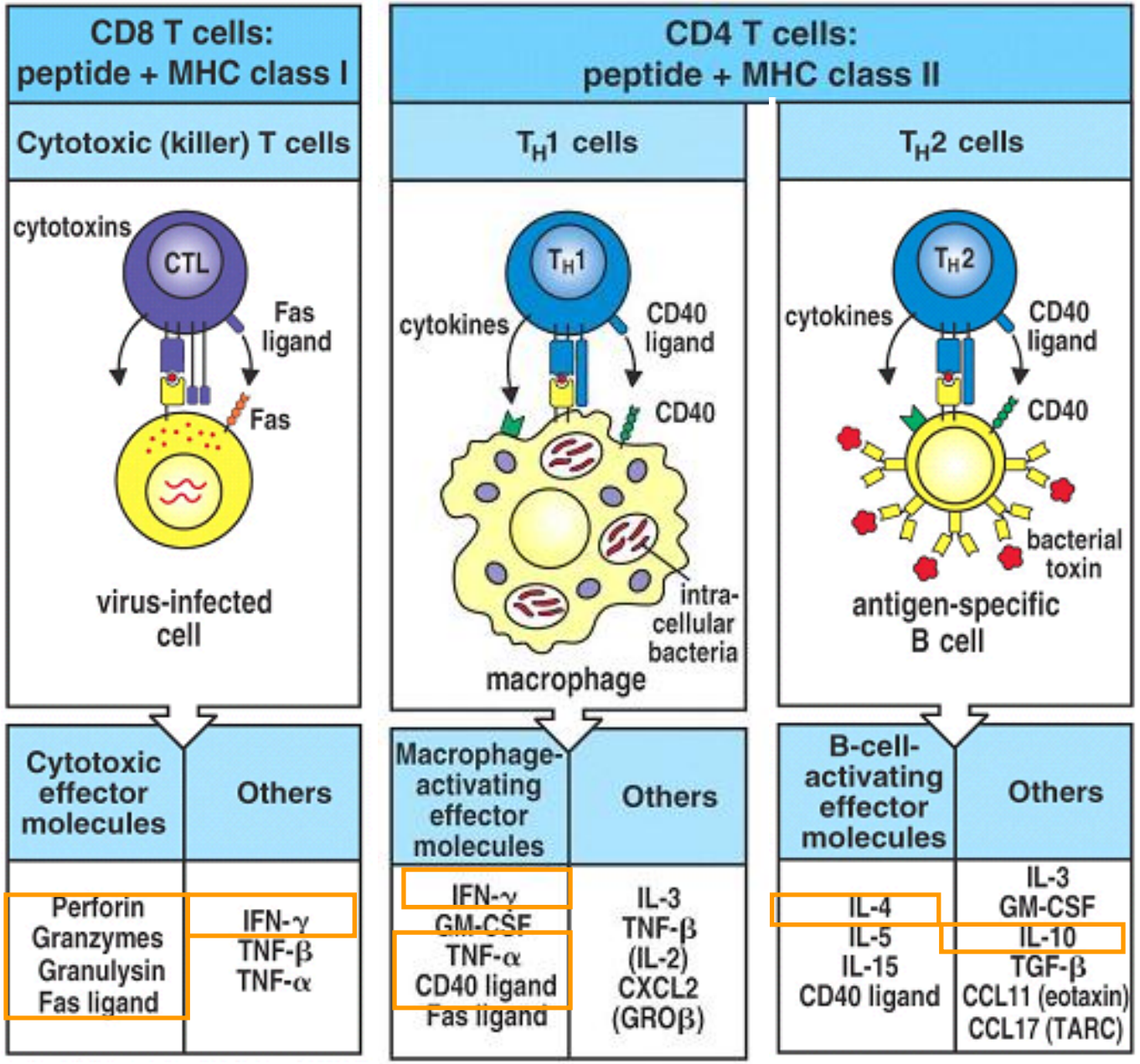
Fig. 9-33

CD8 T cells: peptide + MHC class I	
Cytotoxic (killer) T cells	
Cytotoxic effector molecules	Others
Perforin Granzymes Granulysin Fas ligand	IFN-γ LT-α TNF-α

CD4 T cells: peptide + MHC class II							
T_H1 cells		T_H2 cells		T_H17 cells		T_{reg} cells	
Macrophage-activating effector molecules	Others	Barrier immunity activating effector molecules	Others	Neutrophil recruitment	Others	Suppressive cytokines	Others
IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand	IL-3 LT-α CXCL2 (GROβ)	IL-4 IL-5 IL-13 CD40 ligand	IL-3 GM-CSF IL-10 TGF-β CCL11 (eotaxin) CCL17 (TARC)	IL-17A IL-17F IL-6	TNF CXCL1 (GROα)	IL-10 TGF-β	GM-CSF

Different T cell effectors produce different effector molecules

Similar to Fig. 9-33 (給同學參考用)



T cell cytokines

Fig. 9-34

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hemato-poietic cells	Other tissue cells	
Interleukin-2 (IL-2)	Naive, T_H1, some CD8	Stimulates growth and J-chain synthesis	Growth	–	Stimulates NK cell growth	–	↓ T-cell responses IBD
Interferon-γ (IFN-γ)	T_H1, CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_H2 cell growth	Activation, ↑ MHC class I and class II	Activates NK cells	Antiviral ↑ MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotoxin-α (LT-α, TNF-β)	T_H1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen
Interleukin-4 (IL-4)	T_H2	Activation, growth IgG1, IgE ↑ MHC class II induction	Growth, survival	Inhibits macrophage activation	↑ Growth of mast cells	–	No T_H2
Interleukin-5 (IL-5)	T_H2	Mouse: Differentiation IgA synthesis	–	–	↑ Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-10 (IL-10)	T_H2 (human: some T_H1), T_{reg}	↑ MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD

Figure 9.34 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

IL-4 is also called the '**class-switching factor for IgE synthesis**'.

T_H1 produces **IFNγ** to inhibit TH2. And, **T_H2** produces **IL-10** to inhibit TH1.

Thus, usually, either TH1 or TH2 dominates and the other is very low.

T cell cytokines

Fig. 9-34

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hemato-poietic cells	Other tissue cells	
Interleukin-3 (IL-3)	T_H1, T_H2 some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–	–
Tumor necrosis factor-α (TNF-α)	T_H1, some T_H2 some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium	Susceptibility to Gram –ve sepsis
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T_H1, some T_H2 some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	↑ Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–	–
Transforming growth factor-β (TGF-β)	CD4 T cells (T_{reg})	Inhibits growth IgA switch factor	Inhibits growth, promotes survival	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-17 (IL-17)	CD4 T cells (T_H17) macrophages	–	–	–	Stimulates neutrophil recruitment	Stimulates fibroblasts and epithelial cells to secrete chemokines	–

Figure 9.34 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

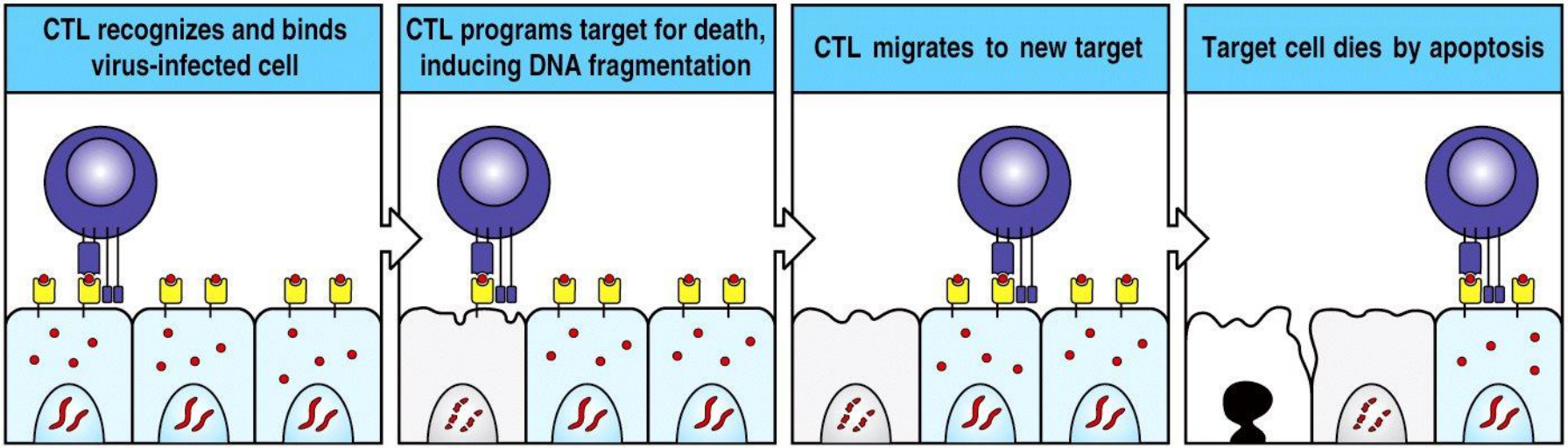
TH1 produces IFNγ to inhibit TH2. And, TH2 produces IL-10 to inhibit TH1.

Thus, usually, either TH1 or TH2 dominates and the other is very low.

T cell-mediated cytotoxicity

CTLs are serial killers!!!

Fig. 9-35



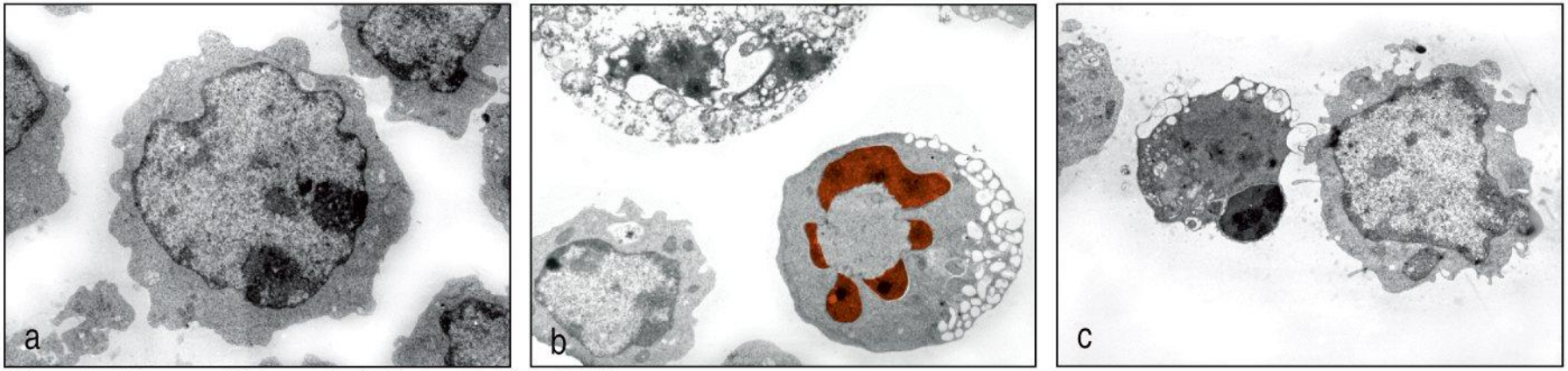
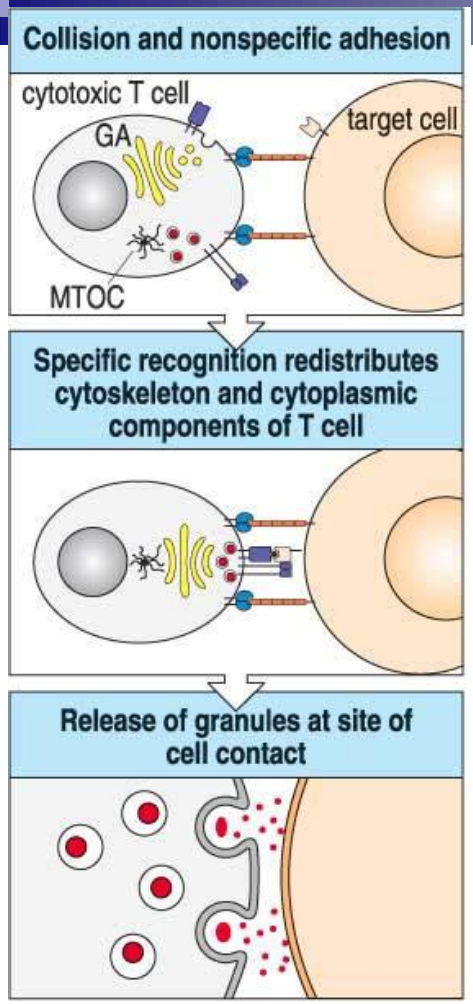


Figure 8-34 Immunobiology, 6/e. (© Garland Science 2005)



Polarized release of cytotoxic granules by CTLs

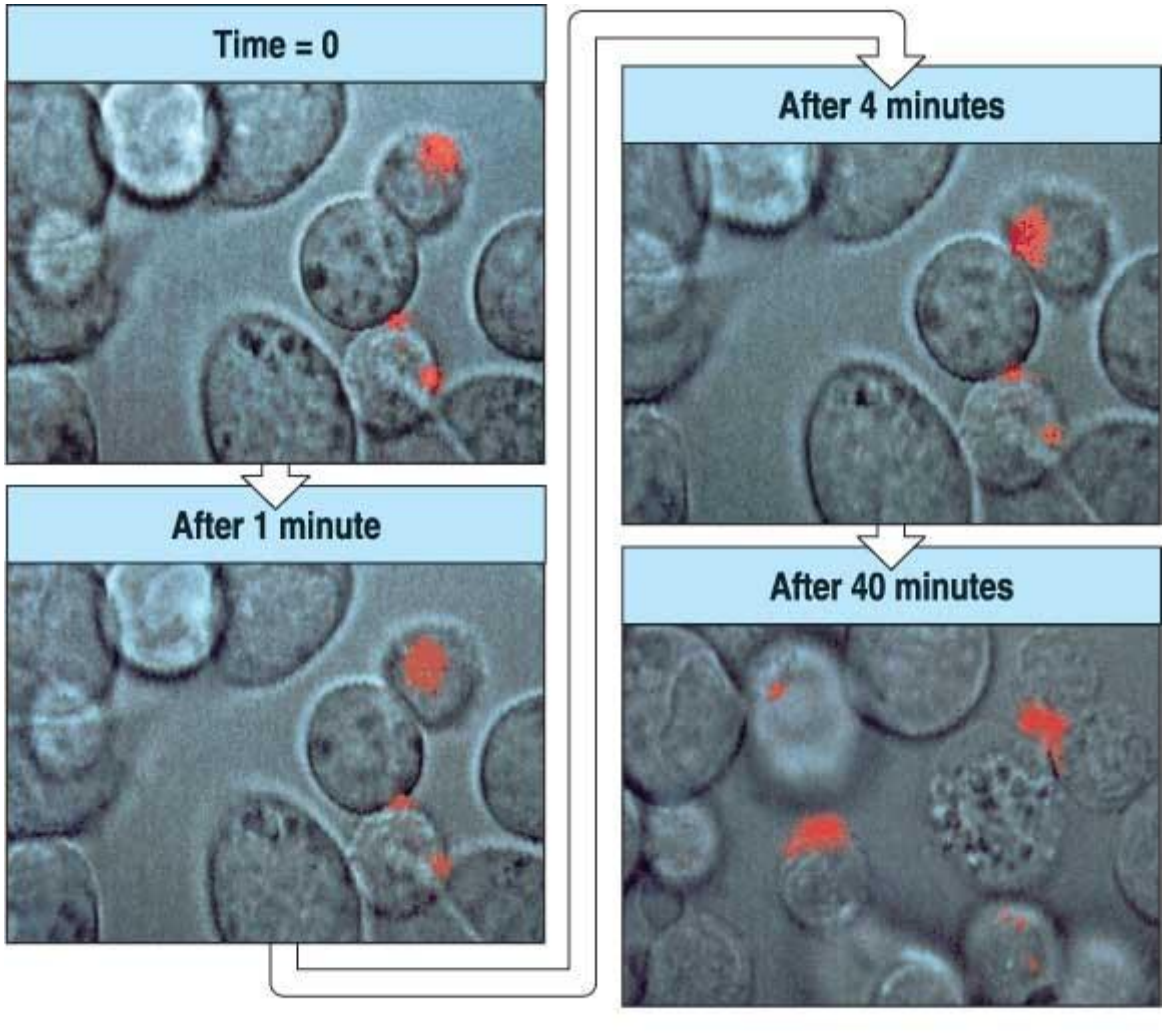


Fig 8.38 © 2001 Garland Science

CTL are susceptible to being killed by other CTLs but they do not kill themselves

Fig. 9-38

Protein in lytic granules of cytotoxic T cells	Actions on target cells
Perforin	Polymerizes to form a pore in target membrane
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
Granulysin	Induces apoptosis
Fas ligand on the surface	Induces apoptosis in cells expressing Fas on their surface

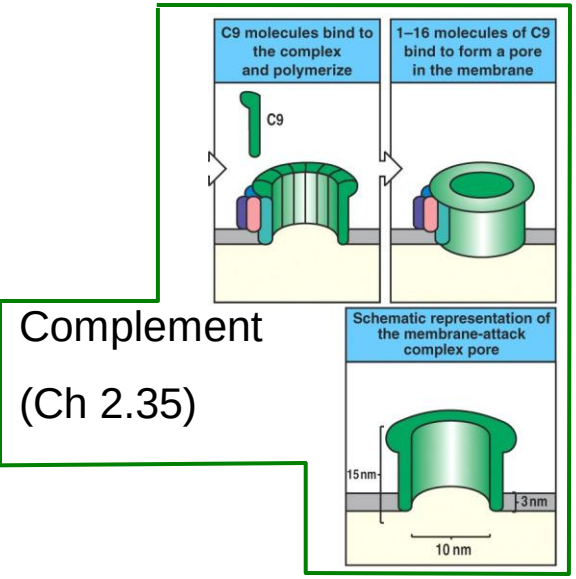
Fig. 9-36

Also, CTLs release IFN-γ to

1. attract and activate macrophages, and
2. inhibit viral replication.
3. IFNγ is also made by T_H1 cells

Endonucleases that degraded host DNA during apoptosis may also degrade viral DNA

Perforin



Complement

(Ch 2.35)

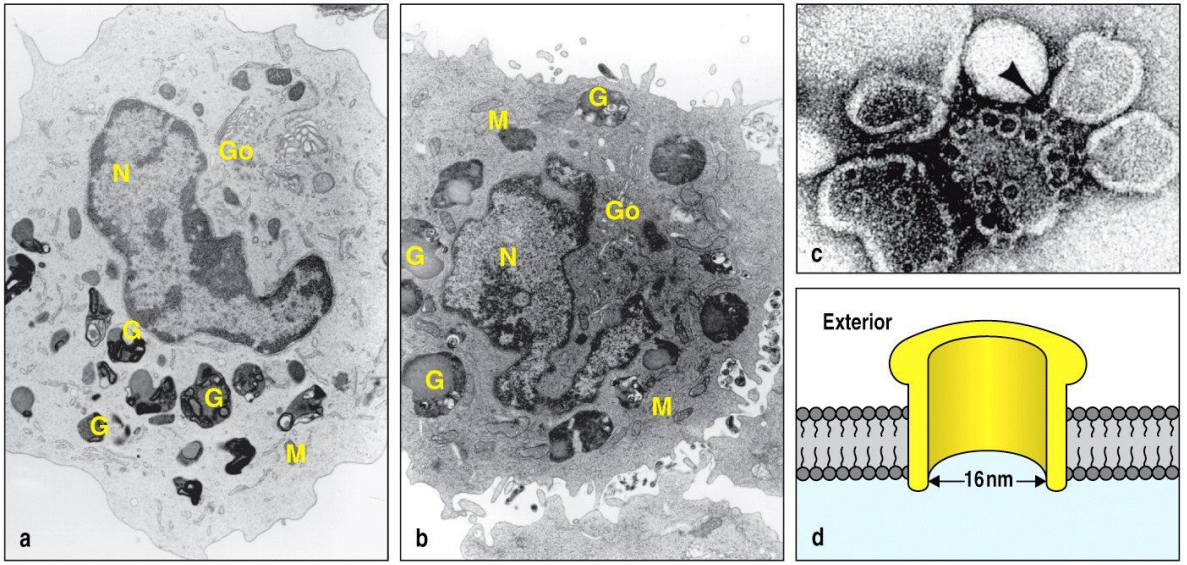


Figure 8-36 Immunobiology, 6/e. (© Garland Science 2005)

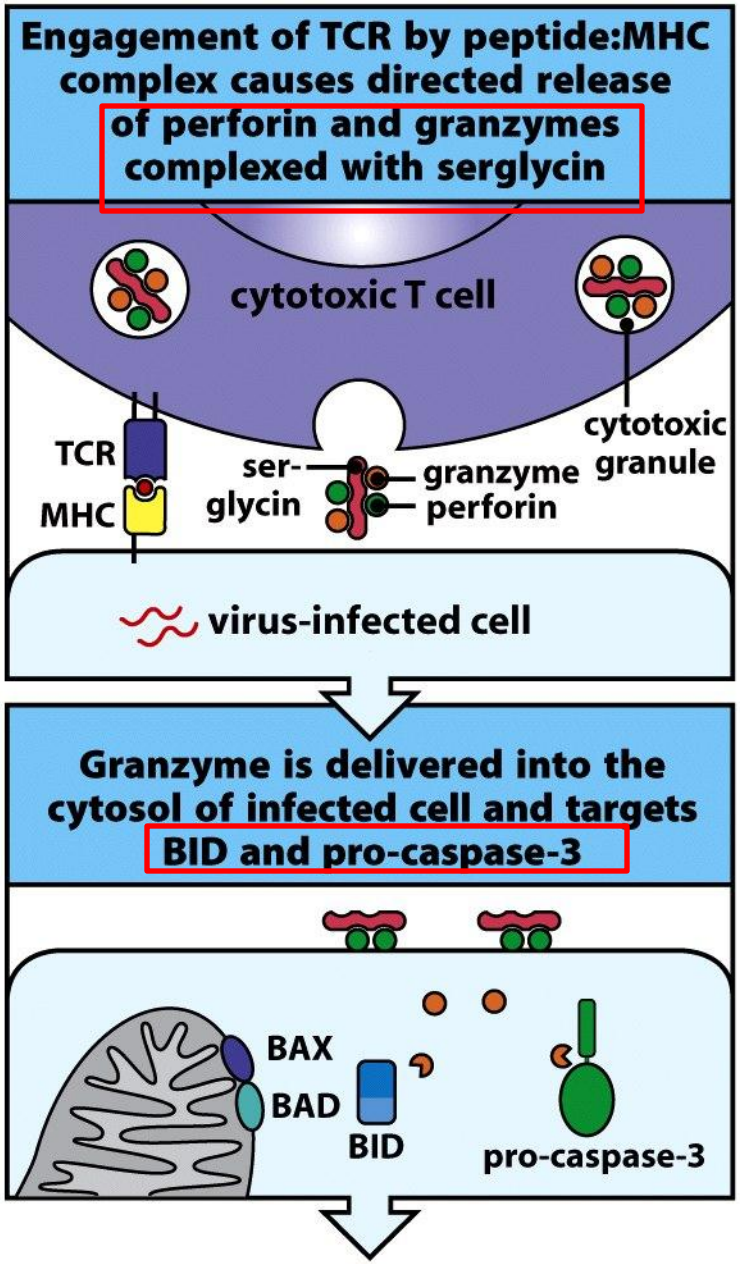


Figure 8-38 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)

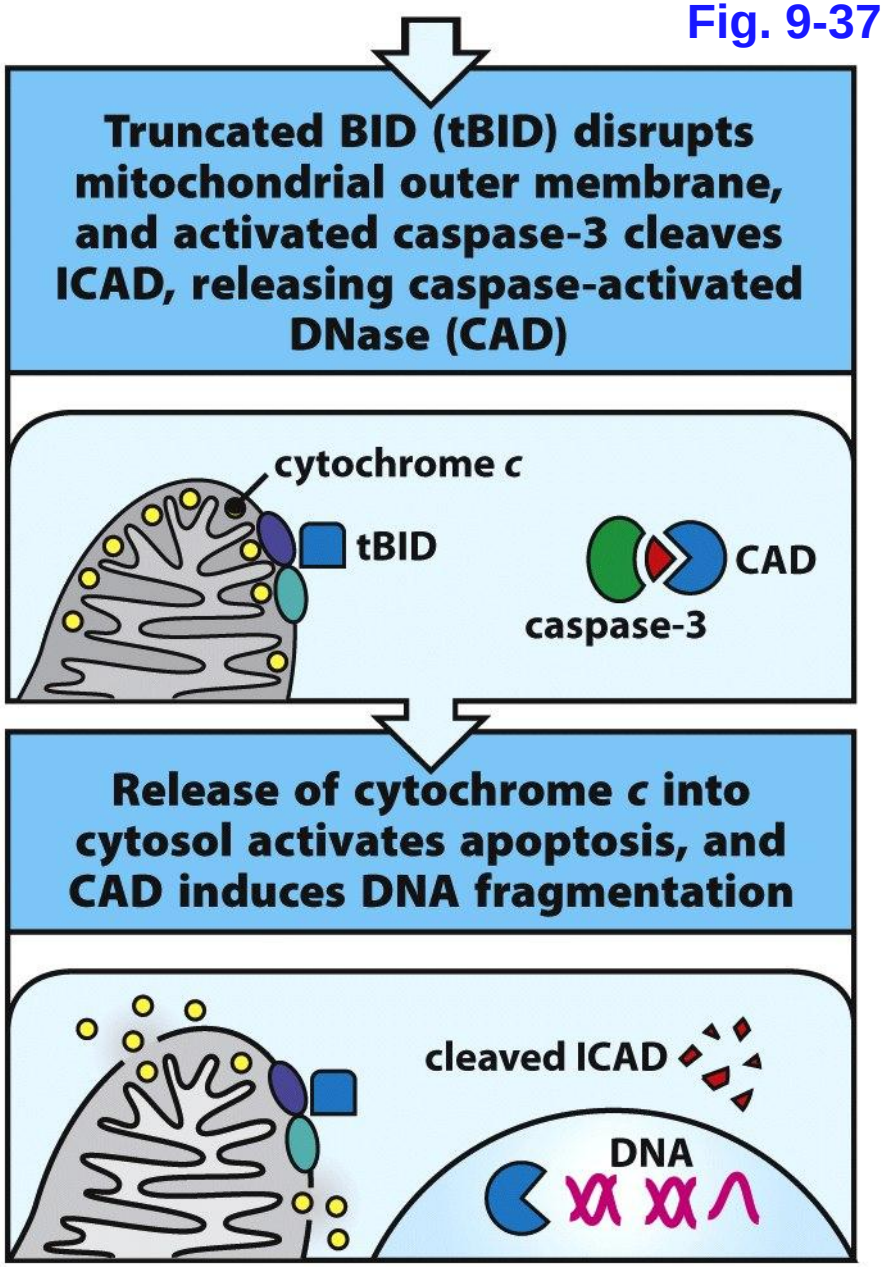


Figure 8-38 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

CTLs

Can kill with no bystander killing (不濫殺無辜)

Can be proficient serial killer

(熟練的連續殺手)

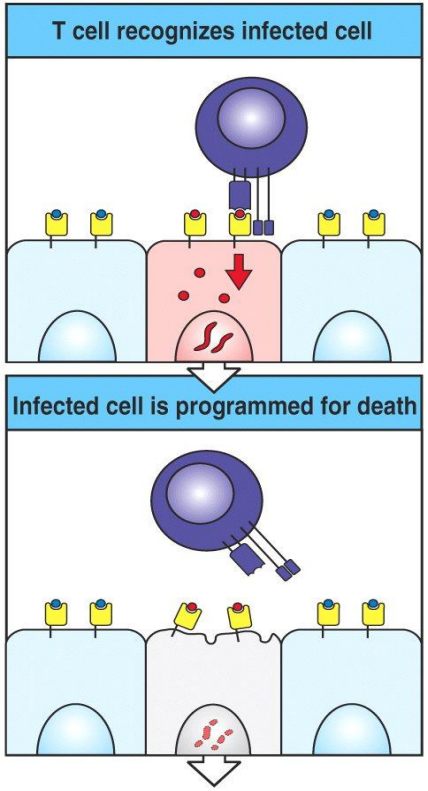


Fig. 9-39

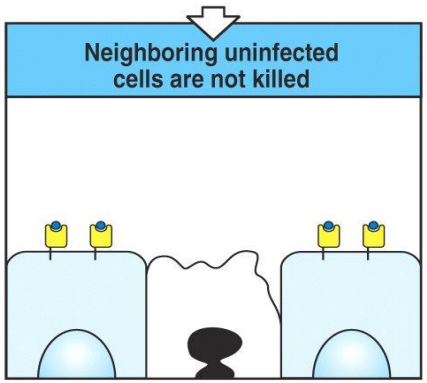
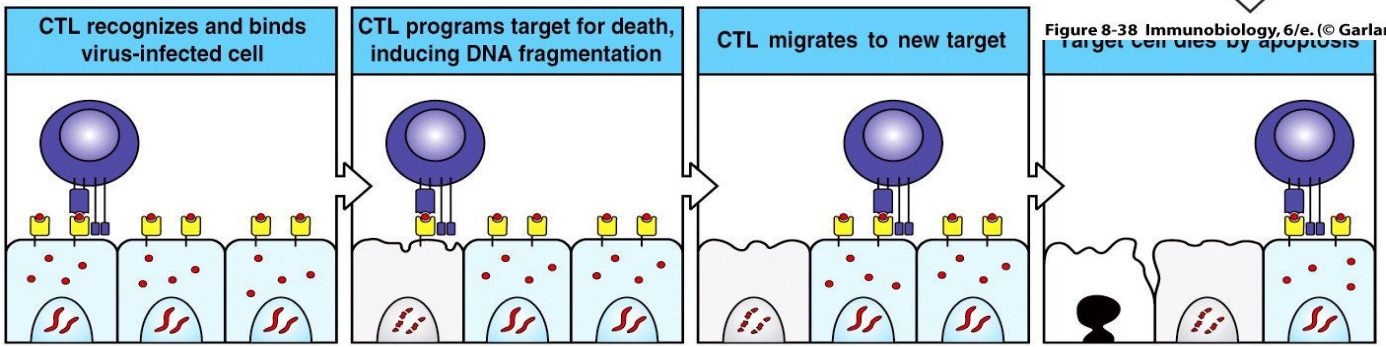


Figure 8-38 Immunobiology, 6/e. (© Garland Science 2005)



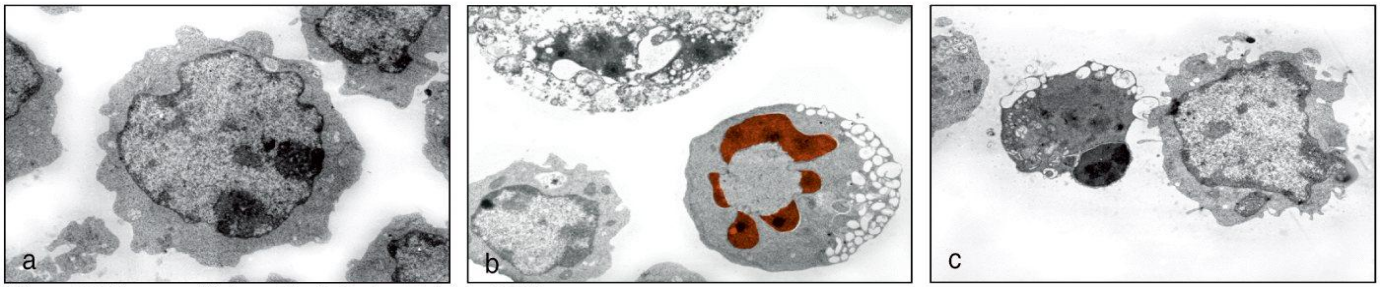


Figure 8-34 Immunobiology, 6/e. (© Garland Science 2005)

•Macrophages can kill most bacteria w/o the help of antibodies or TH1 cells.

•Abs serve as opsonins to aid in phagocytosis

•TH1 provide IFN-γ to activate macrophages

•Certain bacteria, such as *Mycobacterium tuberculosis* and *M. laprae* can live in macrophage vesicles. TH1 helps lysosomes fuse with vesicles containing bacteria.

Macrophages activation by TH1 requires IFN-γ and CD40L

Once activated, macrophages are highly microbicidal!!

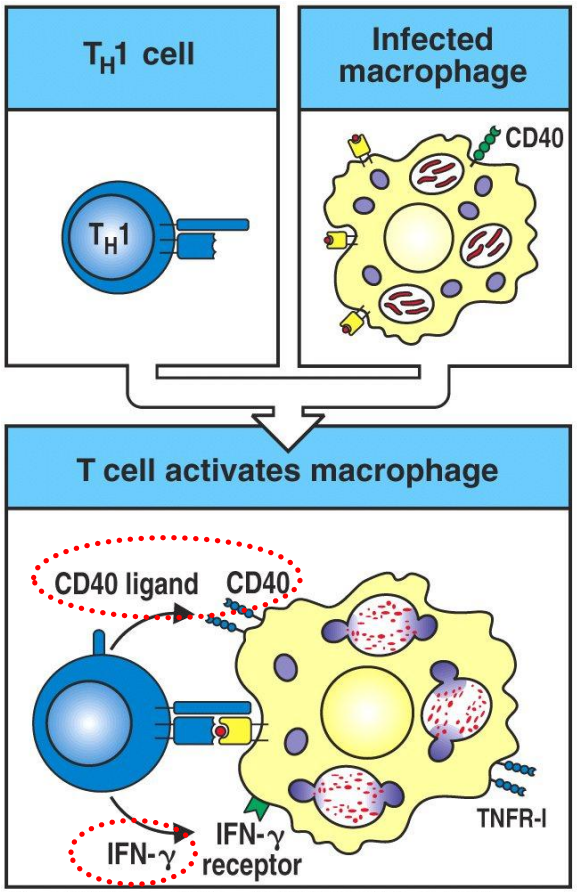


Figure 8-39 Immunobiology, 6/e. (© Garland Science 2005)

$O2^{\cdot}$ = superoxides and other reactive oxygen species

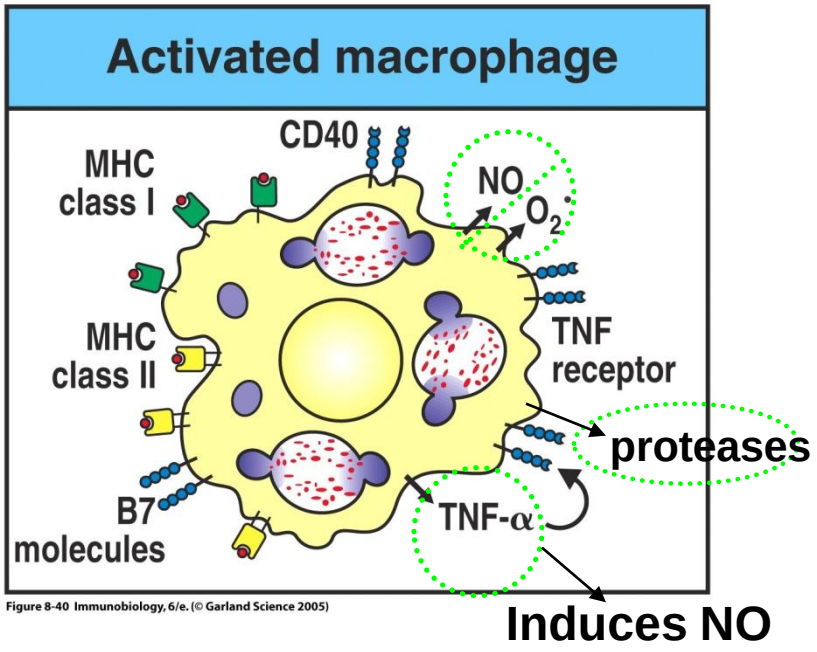


Figure 8-40 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 9-40, 41

Macrophage activation by TH1 requires IFN-γ and CD40L

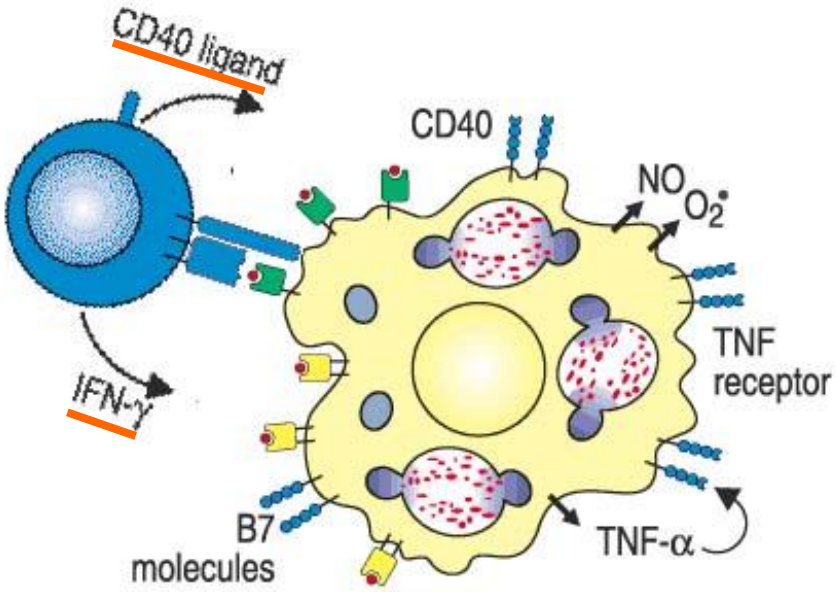


Fig. 9-40, 41

- IFN-γ from the TH1 or from CTL. Therefore, **IFN-γ is characteristic of cell-mediated immunity (CMI)**
- IFN-γ increases macrophage expression of CD40
- LPS and other bacterial products make macrophage more responsive to IFN-γ
- Macrophage activation is a typical TH1-mediated immunity
  - Inhibited by IL-10 inactivates macrophages (IL-10 made by TH2 cells)

TH1 **does not** store IFNγ so it must synthesize it upon contact with macrophage.

It may take hours to make the IFNγ and to activate the macrophage.

The TH1 cell stays engaged with the macrophage for the entire process.

Summary of TH1 effector mechanisms

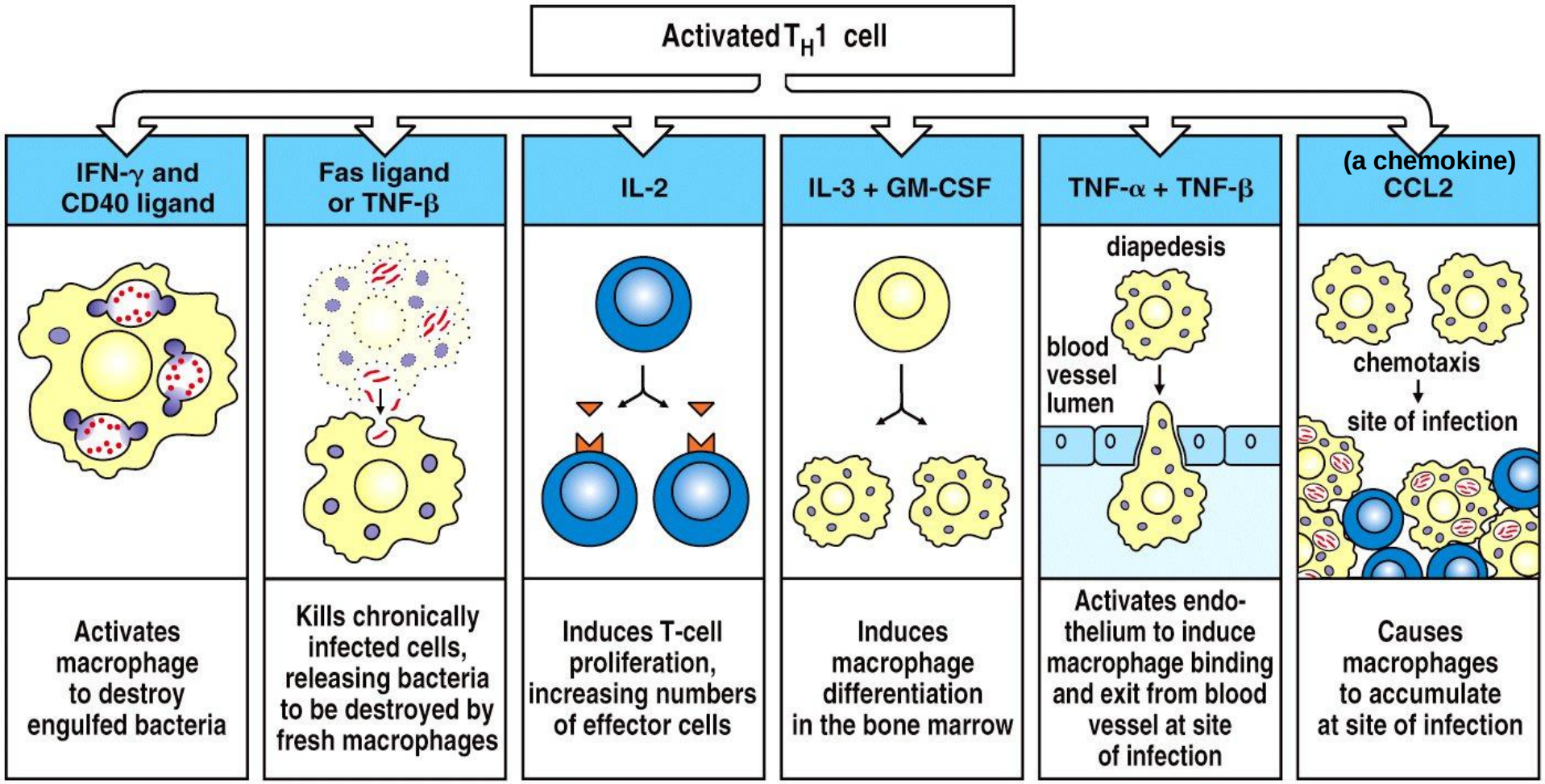


Figure 8-41 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 9-42

When the macrophages are *incapable* of killing intracellular bacteria (or there is chronic inflammation from an agent that cannot be removed), a **granuloma** may form to **protect against further spreading of the pathogens**.

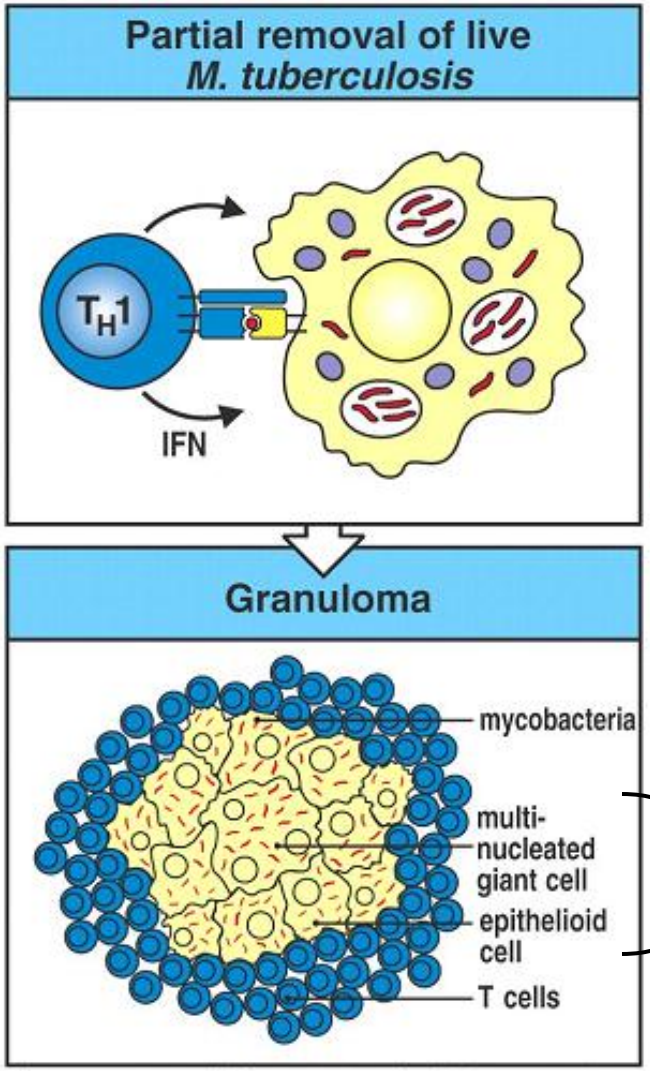


Figure 8-42 Immunobiology, 6/e. (© Garland Science 2005)

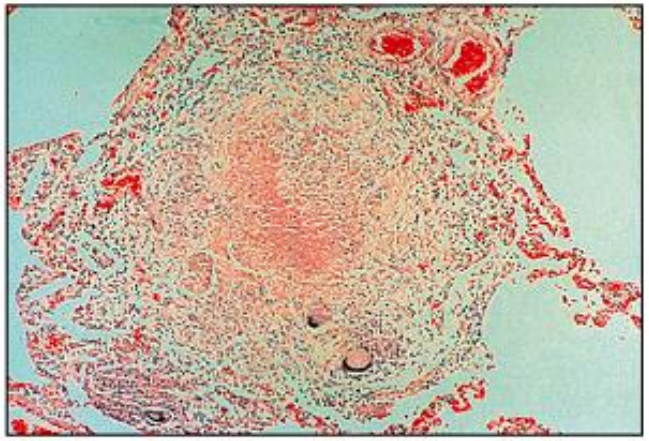
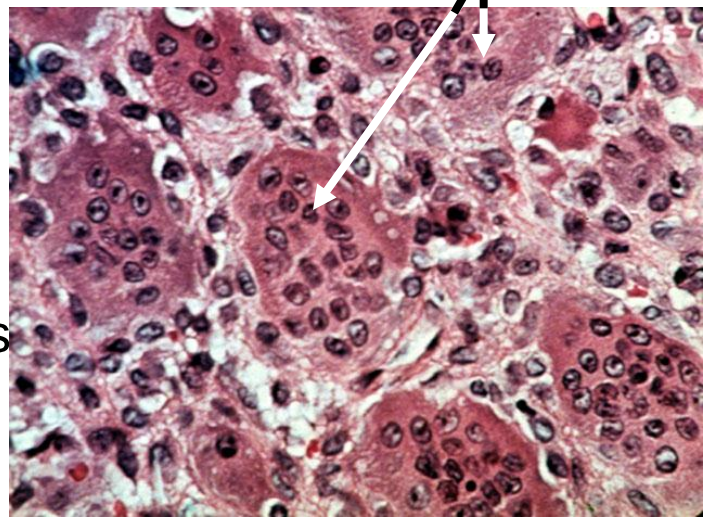


Fig. 9-43

Multinucleated giant cell



Derived from macrophages

Summary

- Initiation of adaptive immunity begins when naïve T cell encounter APCs + Ag and requires co-stimulatory signals.
- Activated T cells produce IL-2 and drive themselves to proliferate and differentiate into armed effector T cells.
- Armed effector T cells can be triggered to destroy infected cells, independently of co-stimulatory signals.

End of Chapter