Corso di Immunologia - III anno
Prof. Paolini

Lezione 13/11/2026

"I linfociti T citotossici"

Il materiale presente in questo documento viene distribuito esclusivamente ad uso interno e per scopi didattici.

Lymphocyte cytotoxicity

- Effector mechanism of cell-mediated immunity

- Directed against:
  - Infected cells (intracellular pathogens)
  - Tumor cells
  - Allogeneic cells

- 2 major lymphocyte populations:
  - CD8+ T lymphocytes — CTL
  - Natural Killer cells — NK

- Different mechanisms for target cell recognition

- Same lytic mechanisms

Why do exist different cytotoxic lymphocyte populations?

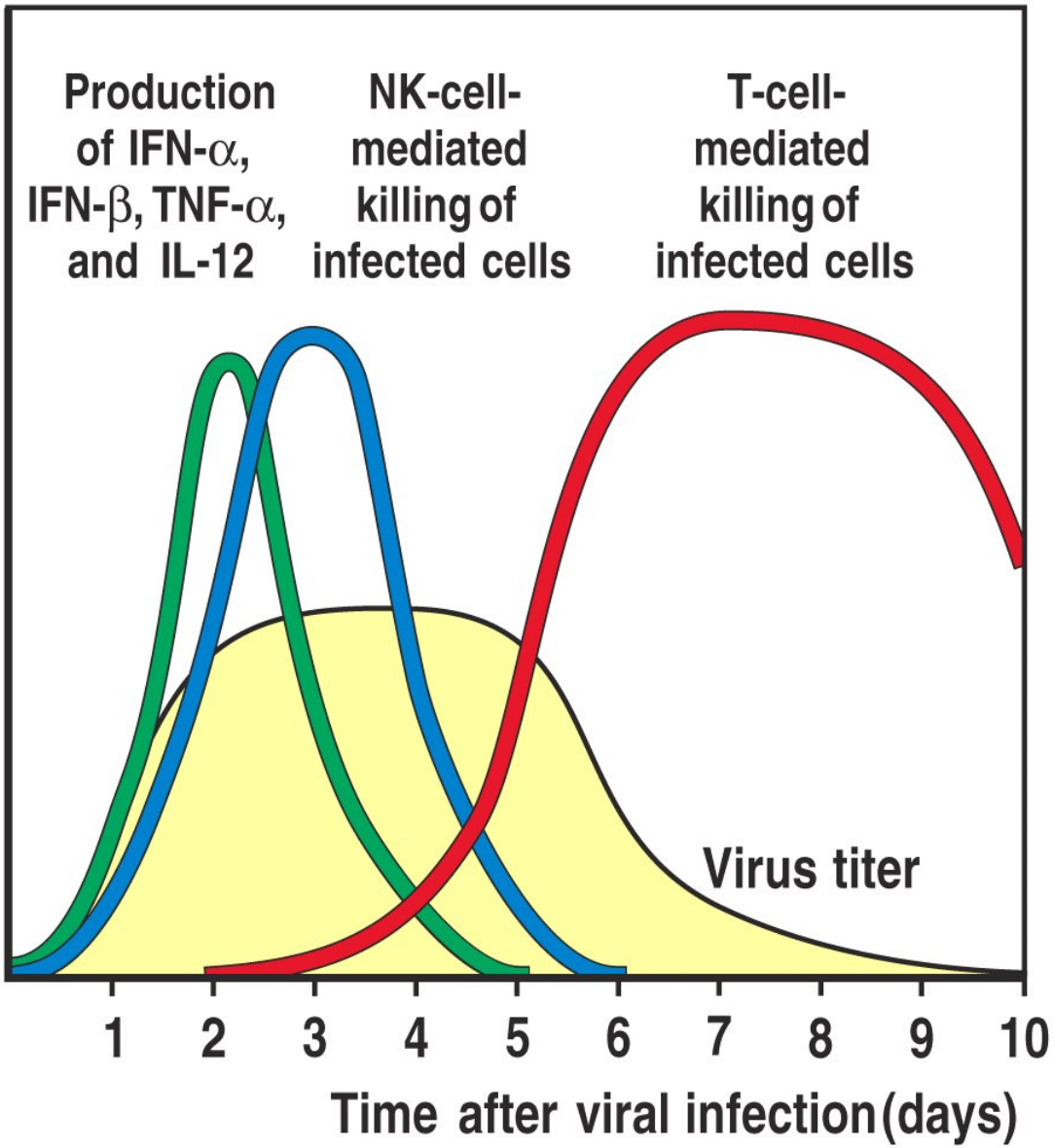
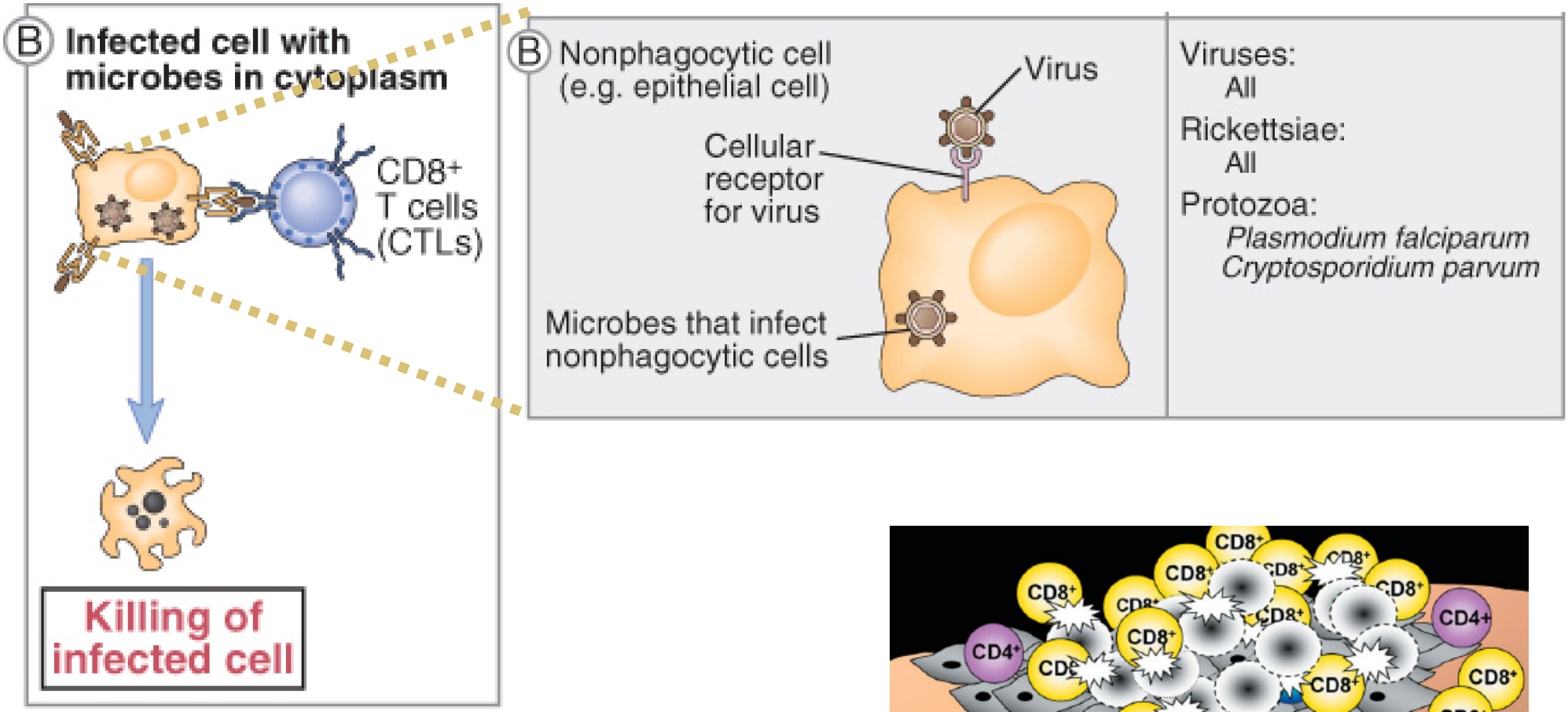


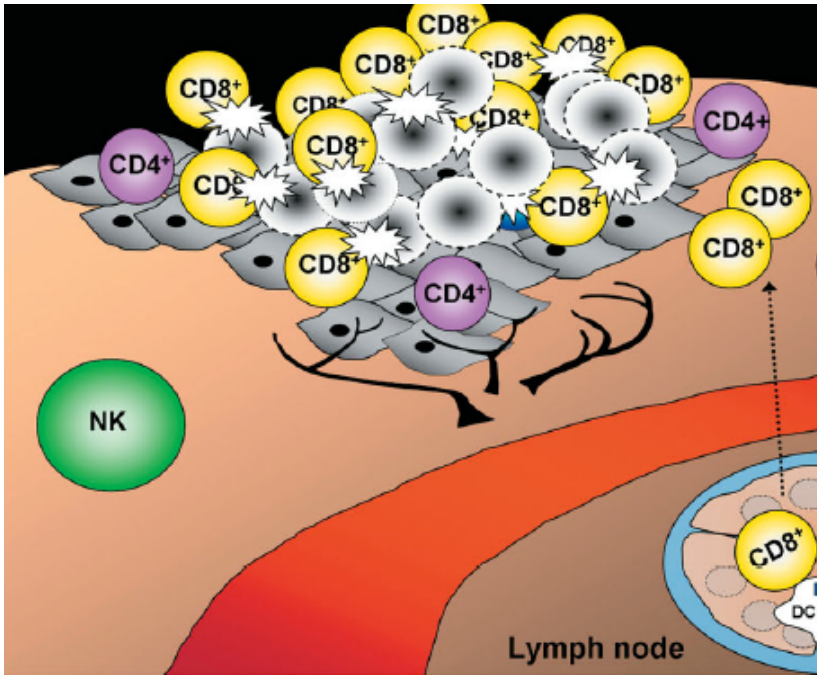
Figure 2-49 Immunobiology, 6/e. (© Garland Science 2005)

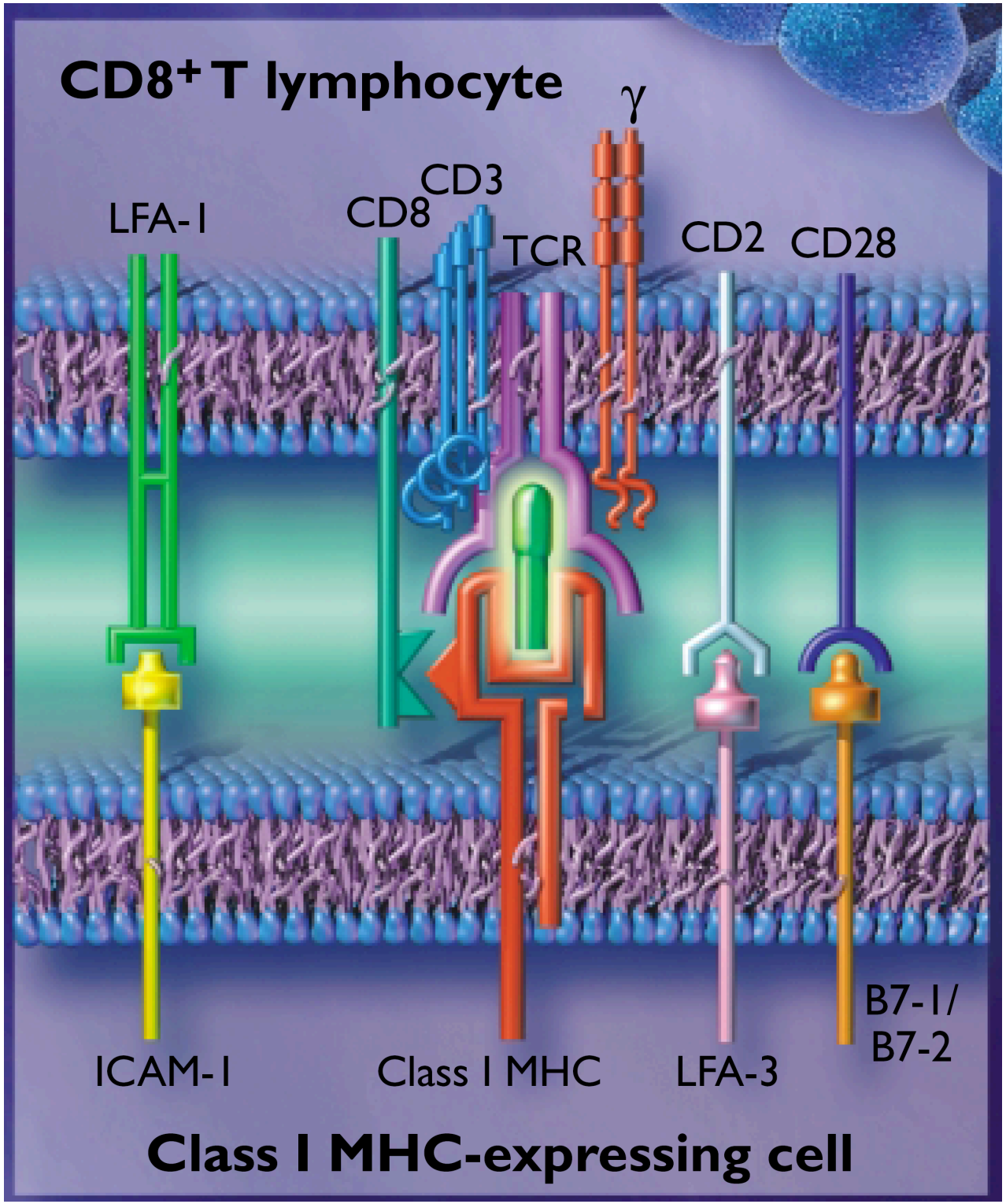
Complementary strategies in the defense against intracellular pathogens!

CTL participate to the response against intracellular pathogens



…and tumor cells





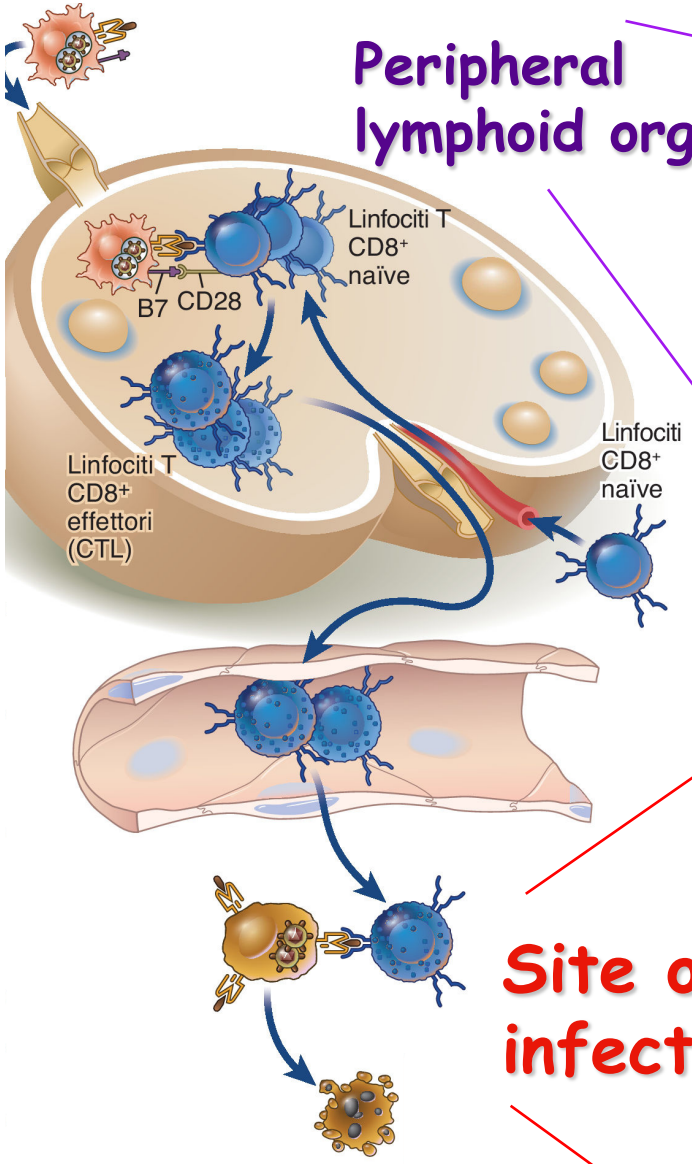
CD8 T cell recognition is

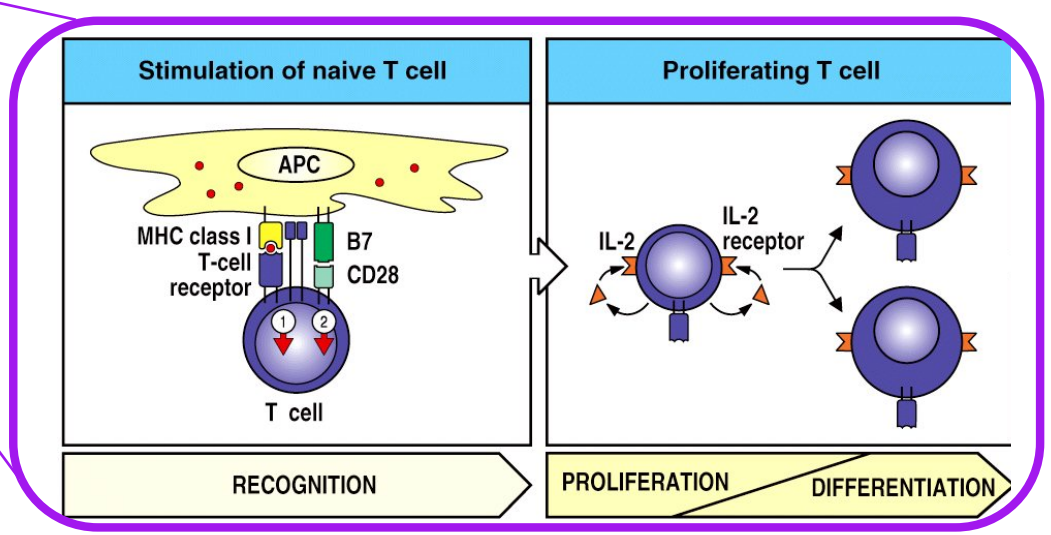
specific

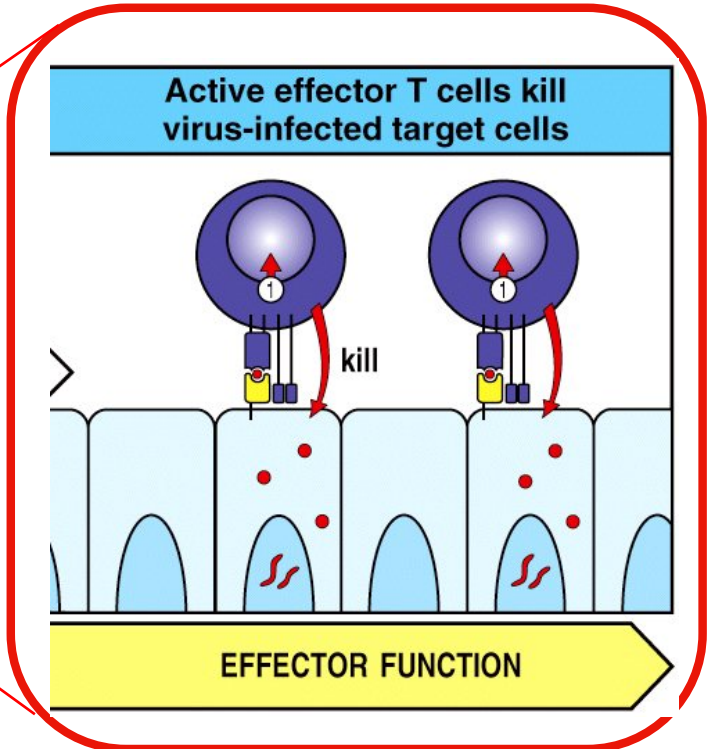
and

MHC class I-restricted

Differentiation of pre-CTL to effector cells





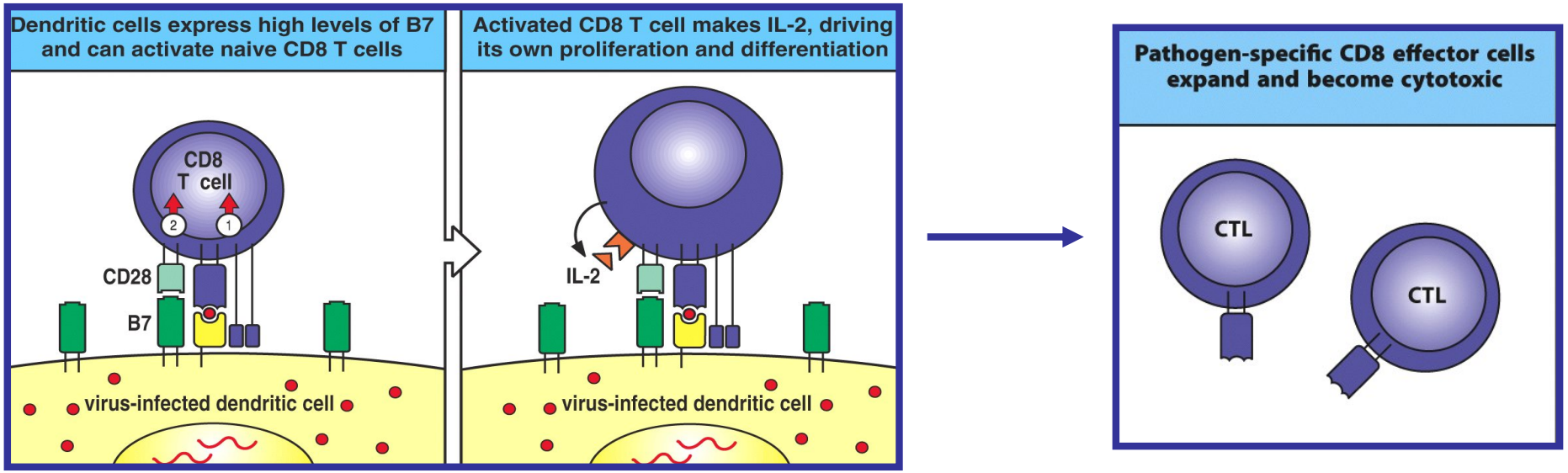


CD8 T CELLS MATURE IN THE THYMUS
AND ARE PRE-CTLs,
ABLE TO RECOGNIZE ANTIGENS BUT NOT TO KILL
INFECTED TARGET CELLS

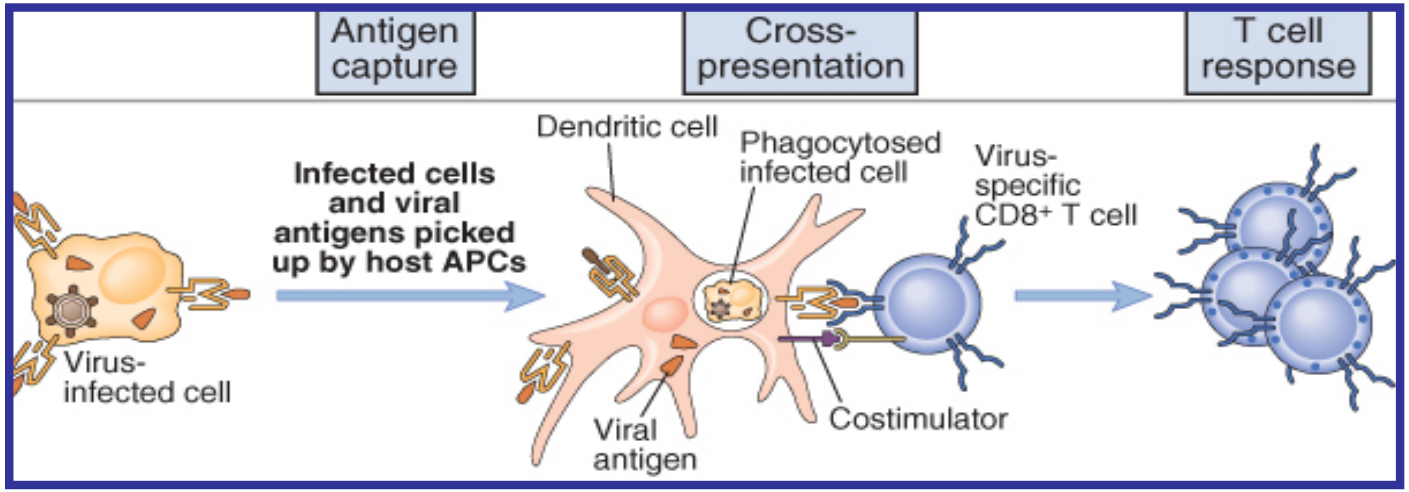
HOW ARE THEY ACTIVATED AND HOW DO THEY
BECOME CTLs?

Different mechanisms for CTL differentiation

I° Naive CD8+ lymphocytes are activated by a dendritic cell infected by an intracellular pathogen

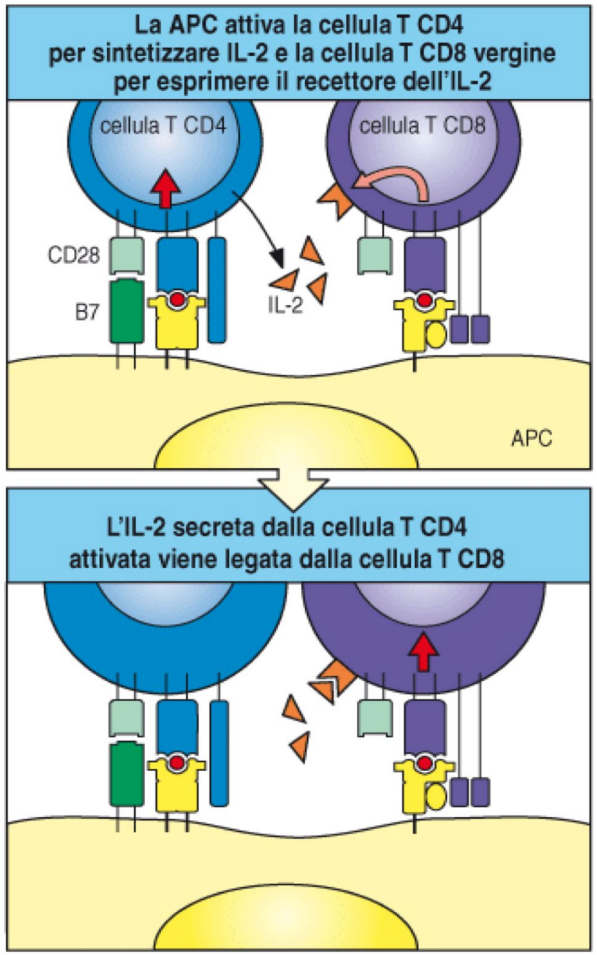


… or from an uninfected dendritic cell that cross-presents viral antigens



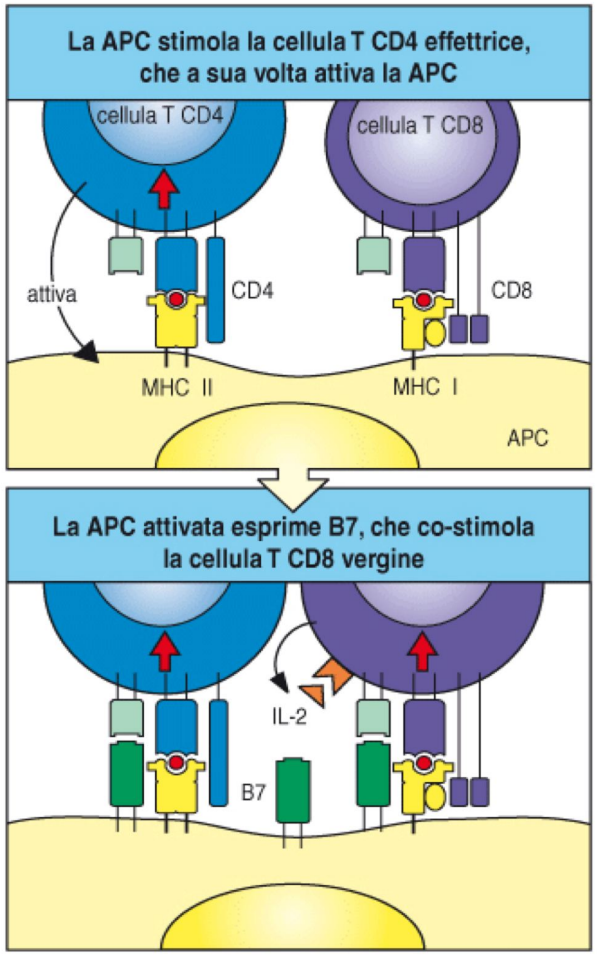
Alternative mechanisms require help from CD4+ T cells

II°



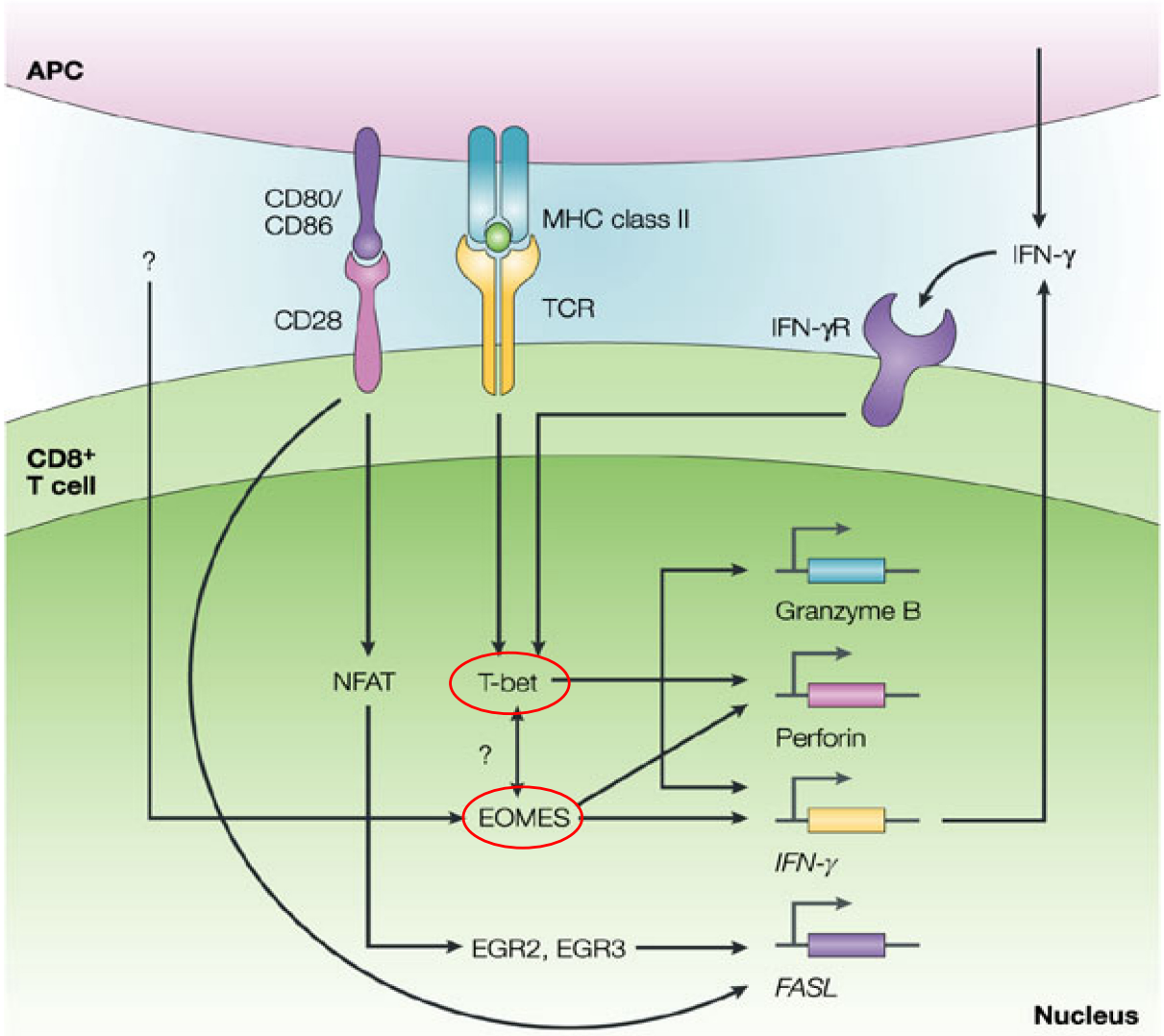
CD4 produces IL-2
which activates CD8

III°



CD4 activates DC to express
ligands that induce CD8 to produce
IL-2 driving its own proliferation

Cytotoxic mediators are acquired during differentiation: CTLs acquire the ability to kill!!

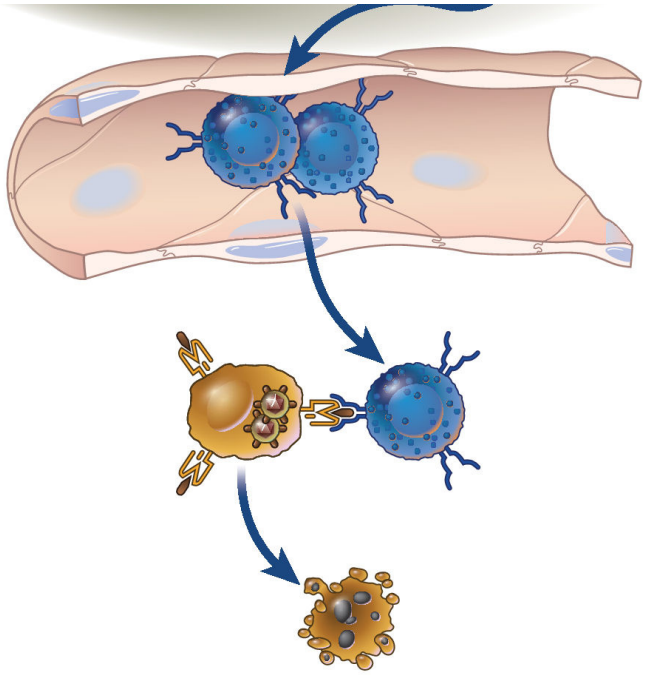


EOMES = Eomesodermin
EGR2 = early growth response 2

The synthesis of mediators is induced:

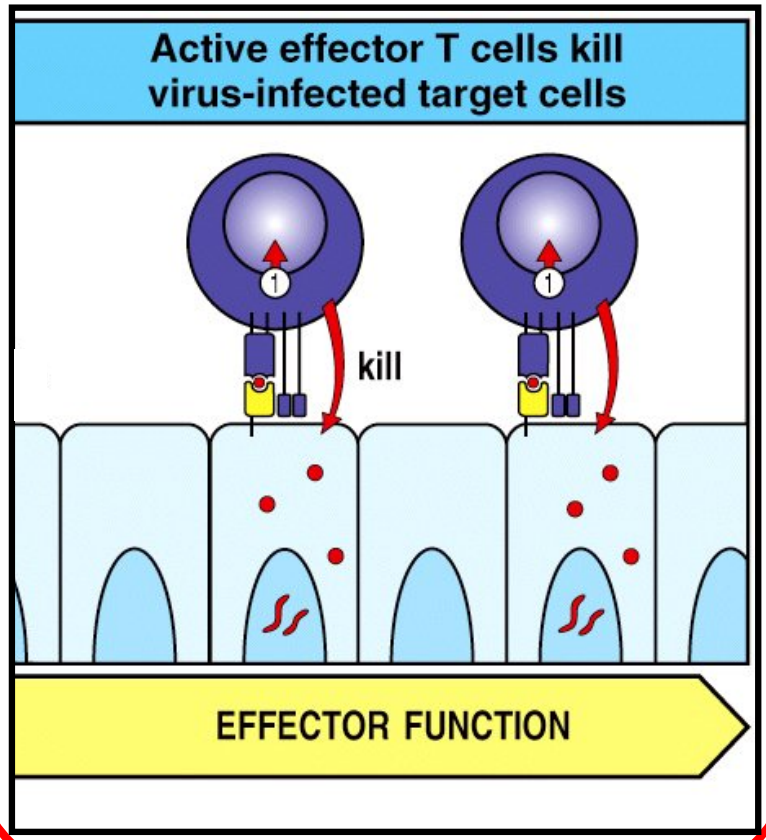
- Cytotoxic granules (perforin and granzymes)
- Cytokines (IFNγ e TNFβ)
- Expression of FasL

CTLs migrate to the site of infection…



…. where they are activated by antigen recognition and kill the infected cell!

Site of infection



MECHANISMS OF CTL-MEDIATED LYSIS

CYTOTOXICITY DEPENDENT ON:

Direct contact:

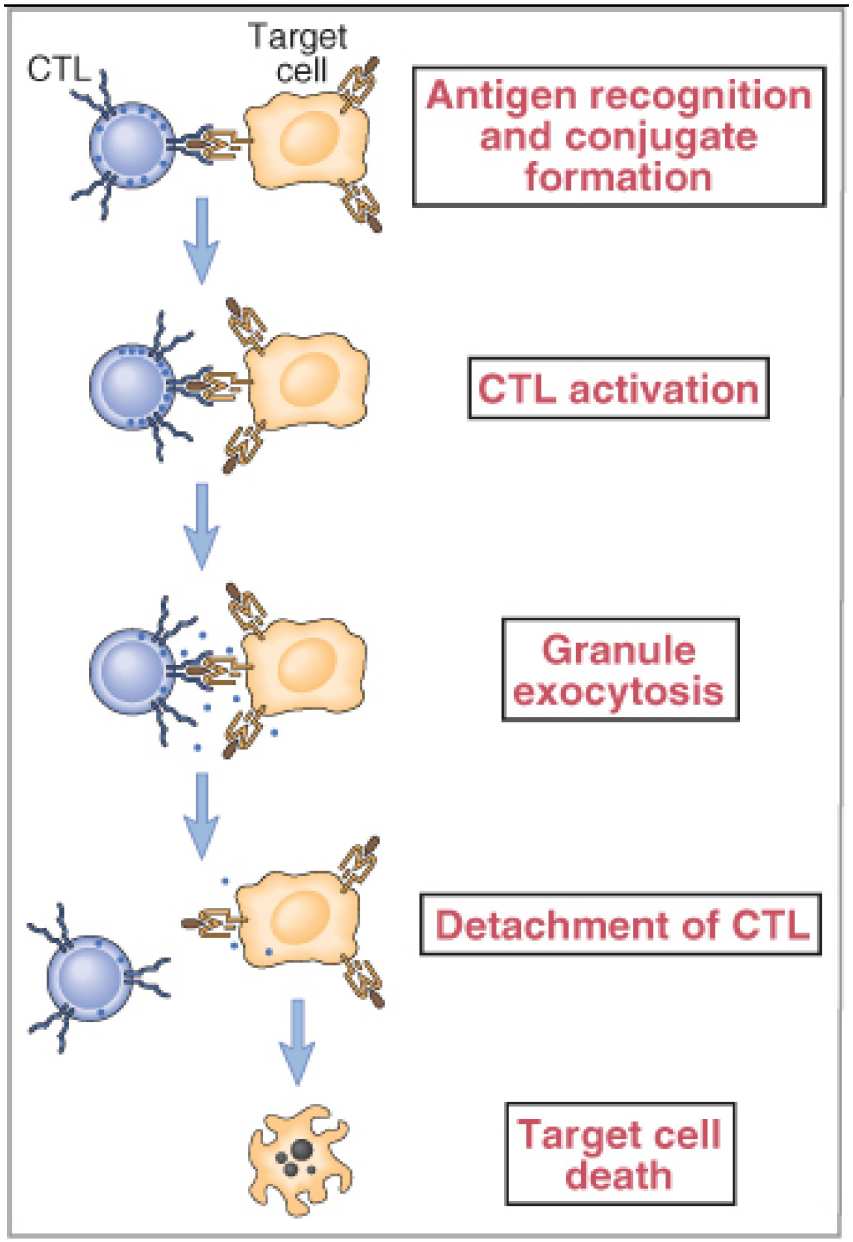
Secretory Mechanism
- Calcium-Dependent
- Granule Exocytosis

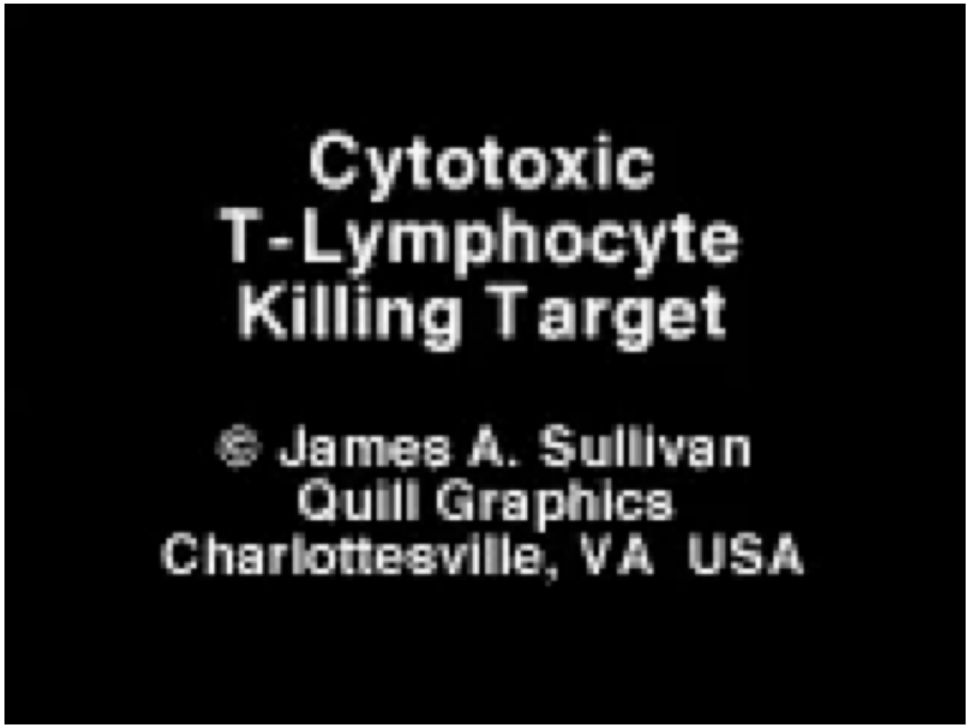
Non secretory mechanism
- Calcium-Independent
- Fas-FAsL

Cytokine secretion: IFN γ TNF α/β

TARGET CELL DEATH
- Osmotic lysis
- Apoptosis

1° CELL-CONTACT-DEPENDENT CYTOTOXICITY: SECRETORY MECHANISM





Antigen recognition augments LFA-1 affinity & avidity: Formation of a stable effector/target conjugate

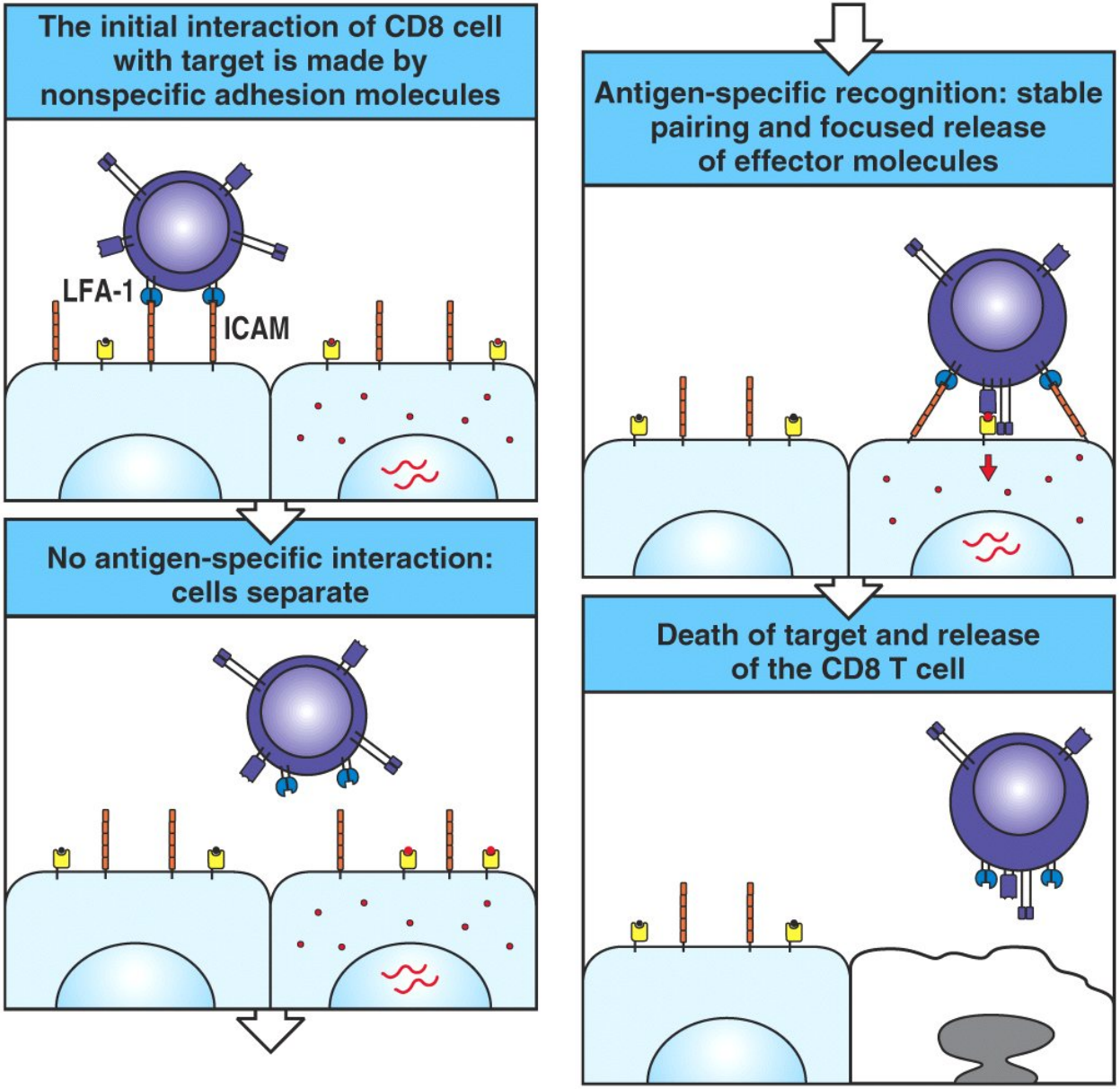


Figure 8-28 Immunobiology, 6/e. (© Garland Science 2005)

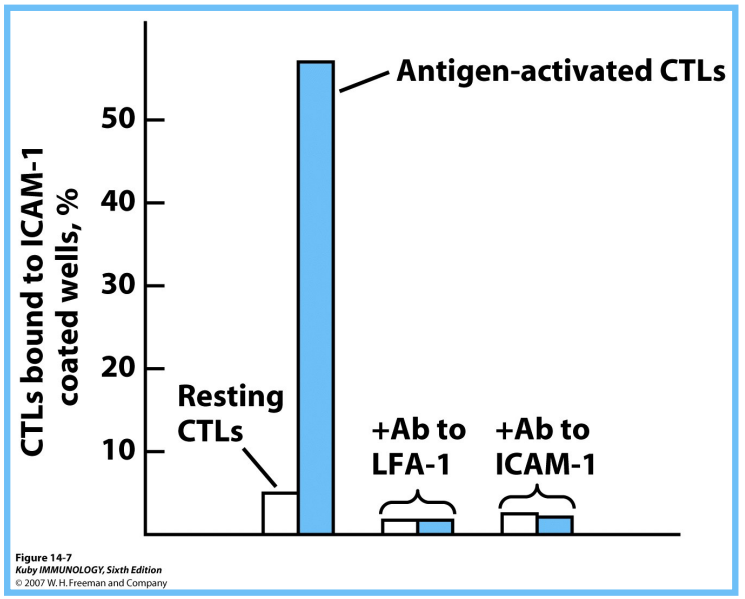
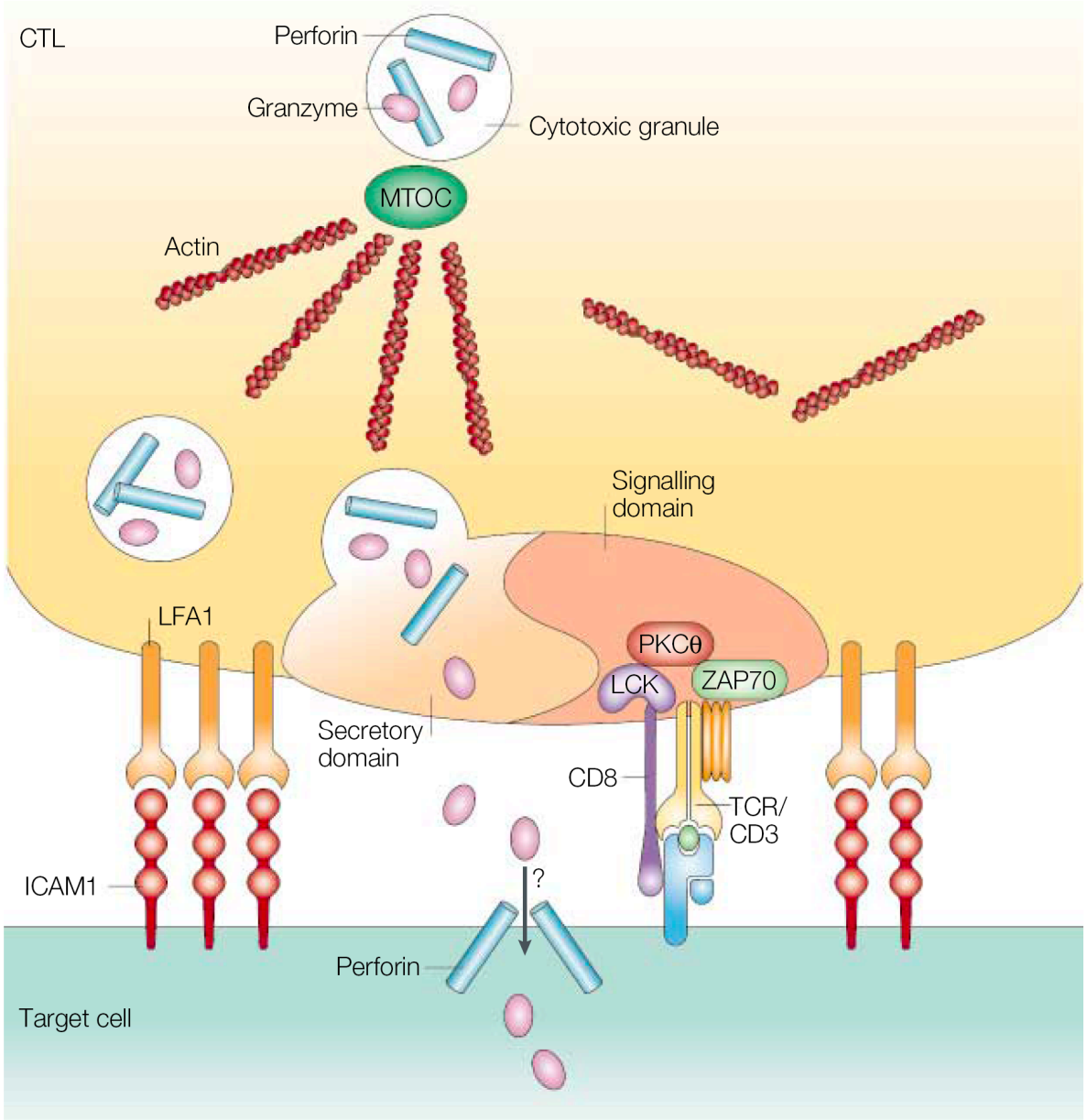
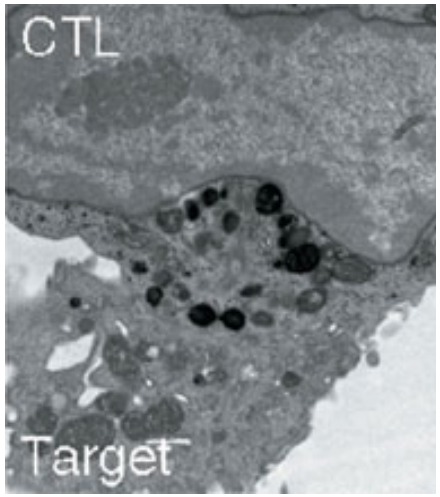


Figure 14-7
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

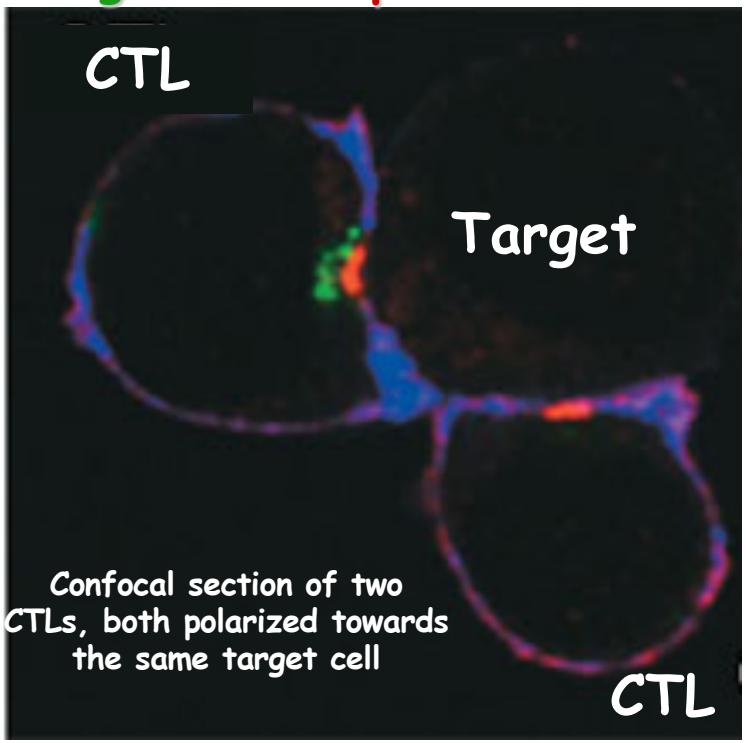
The secretory synapse:

Immunological synapse formed by CTL and target cell



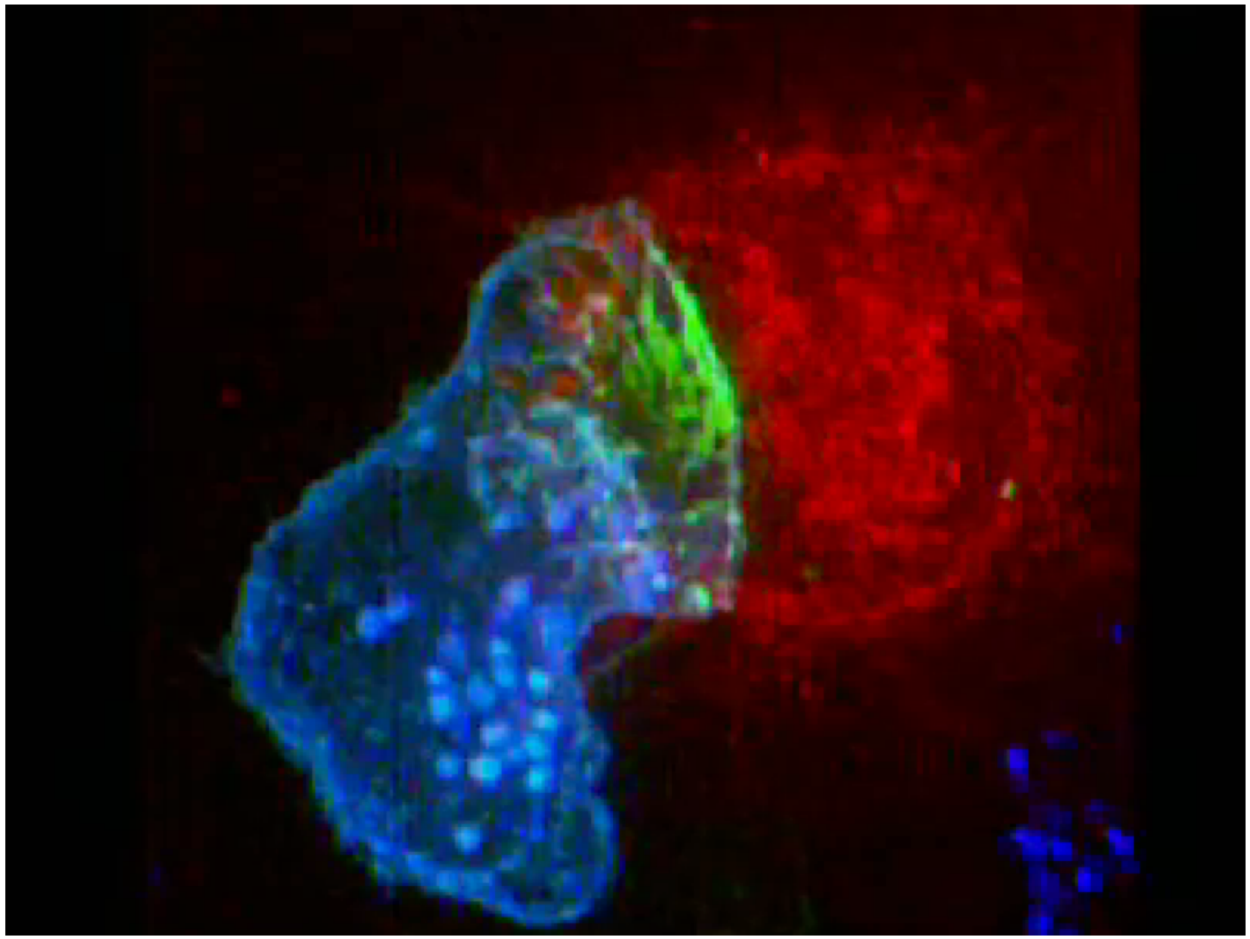


granules p56Lck actin



Confocal section of two CTLs, both polarized towards the same target cell

The secretory synapse



The different phases of the secretory mechanism

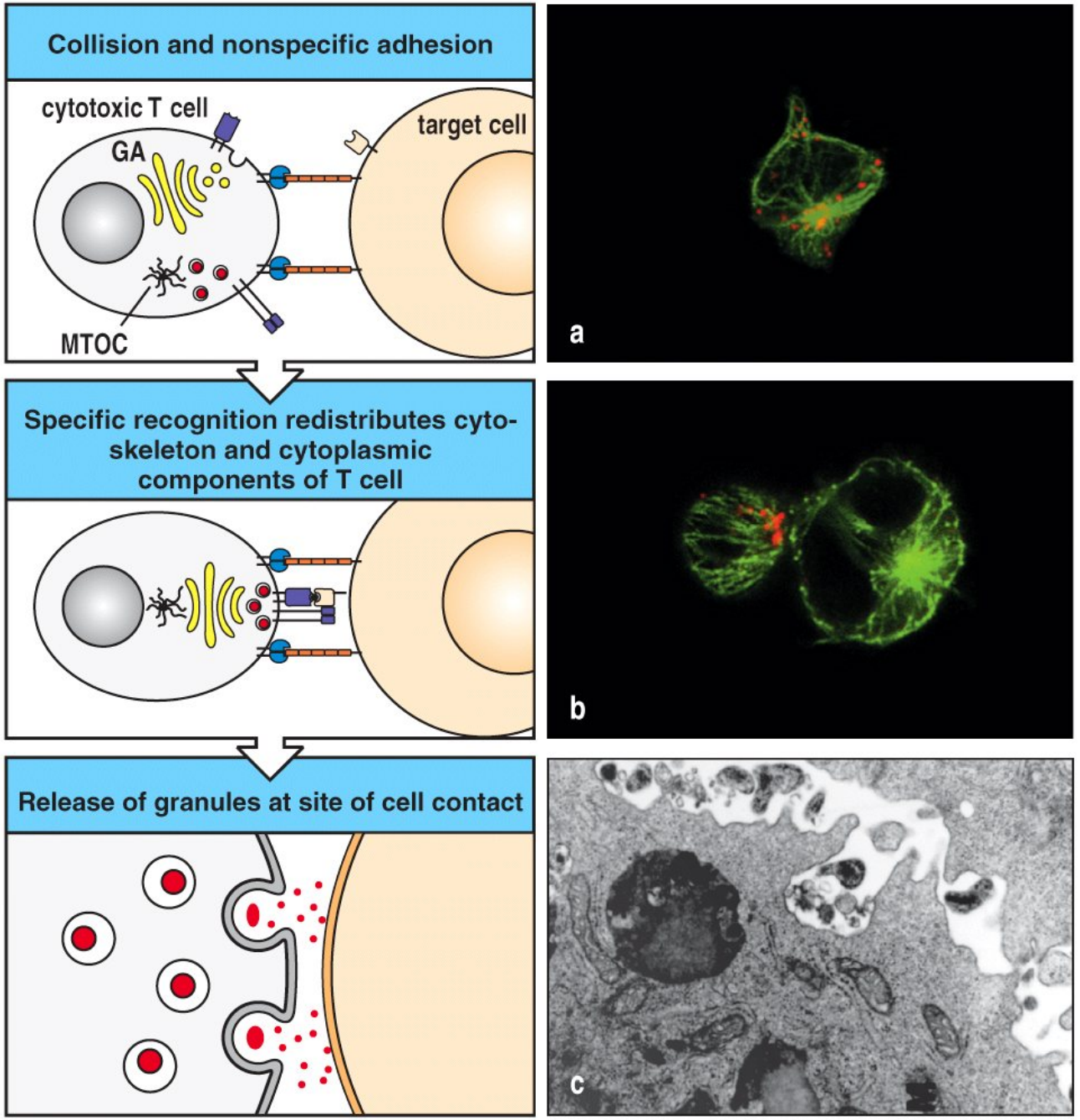
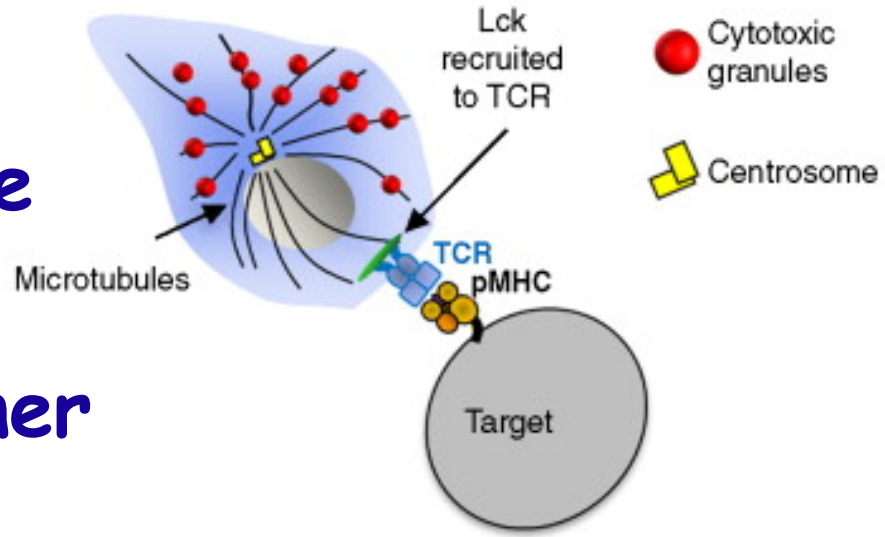
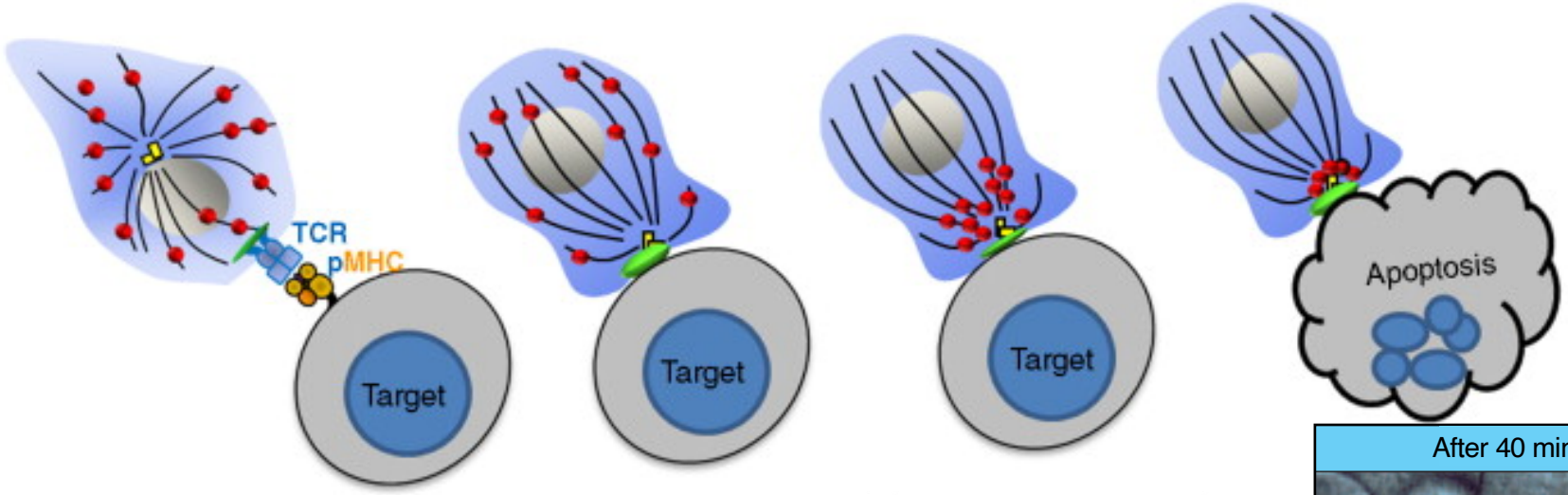
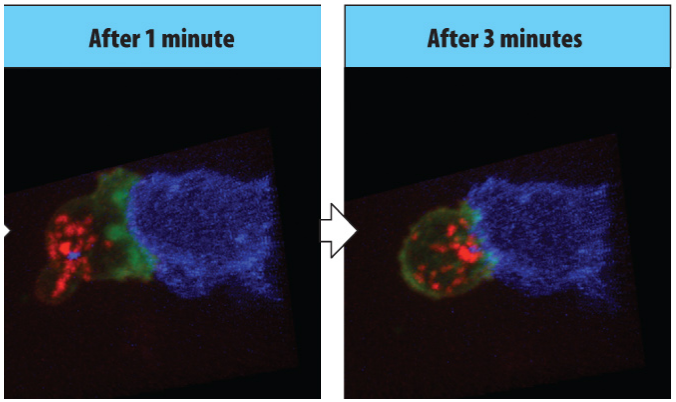


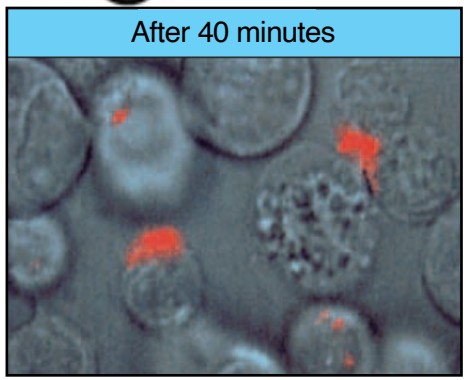
Figure 8-29 Immunobiology, 6/e. (© Garland Science 2005)

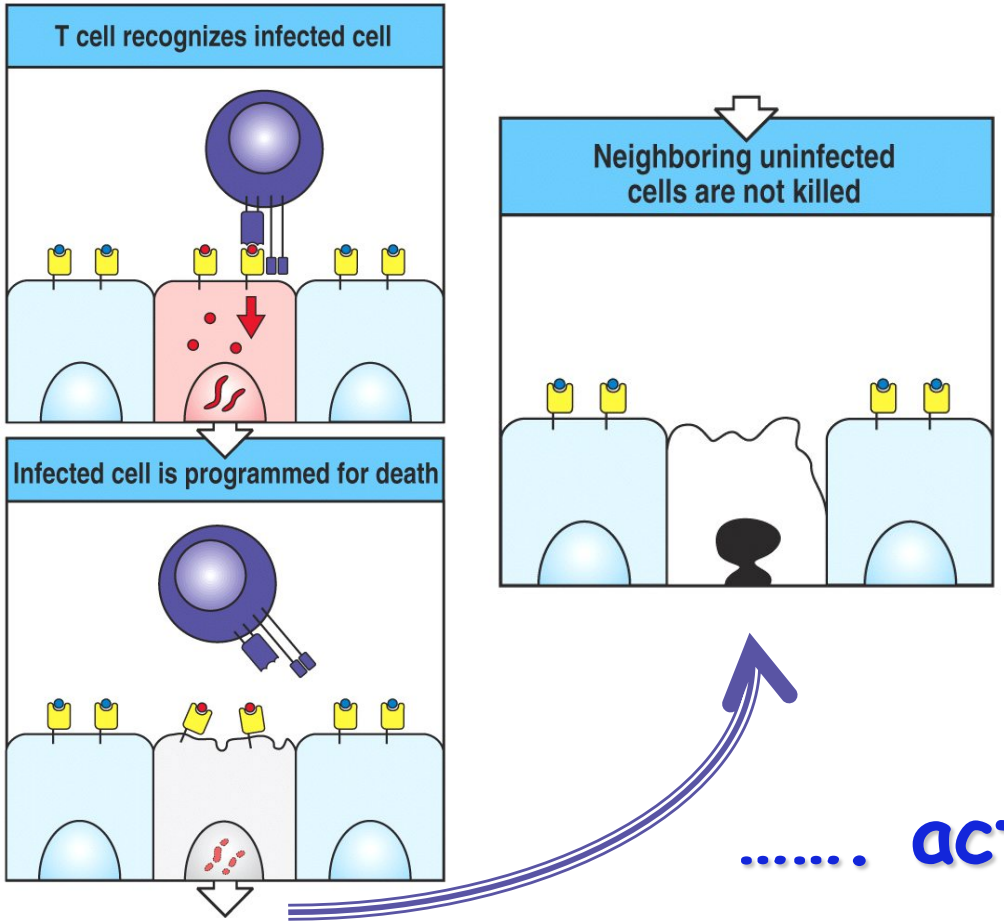
The granules are secreted in a POLARIZED manner





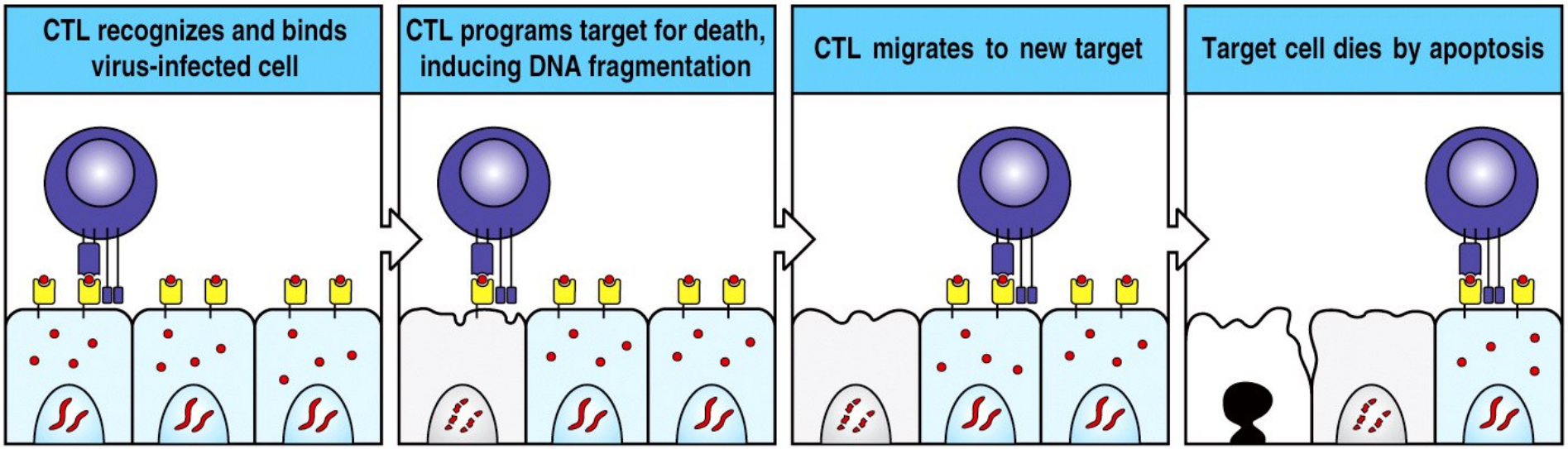






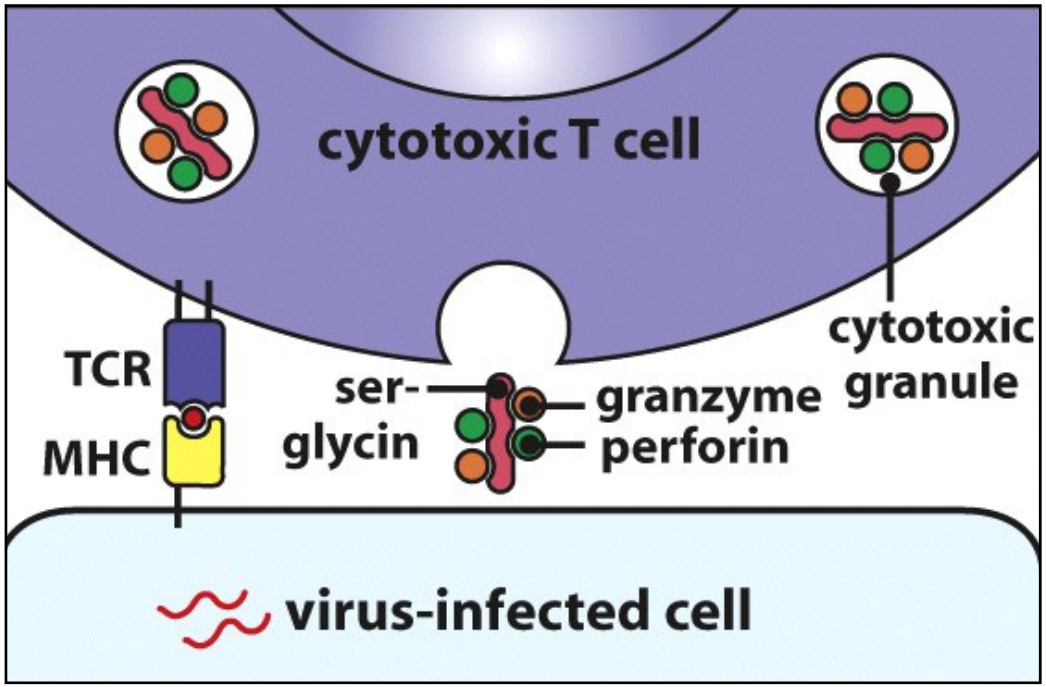
CTL exerts a selective cytotoxic activity…..

……. acting as a serial killer

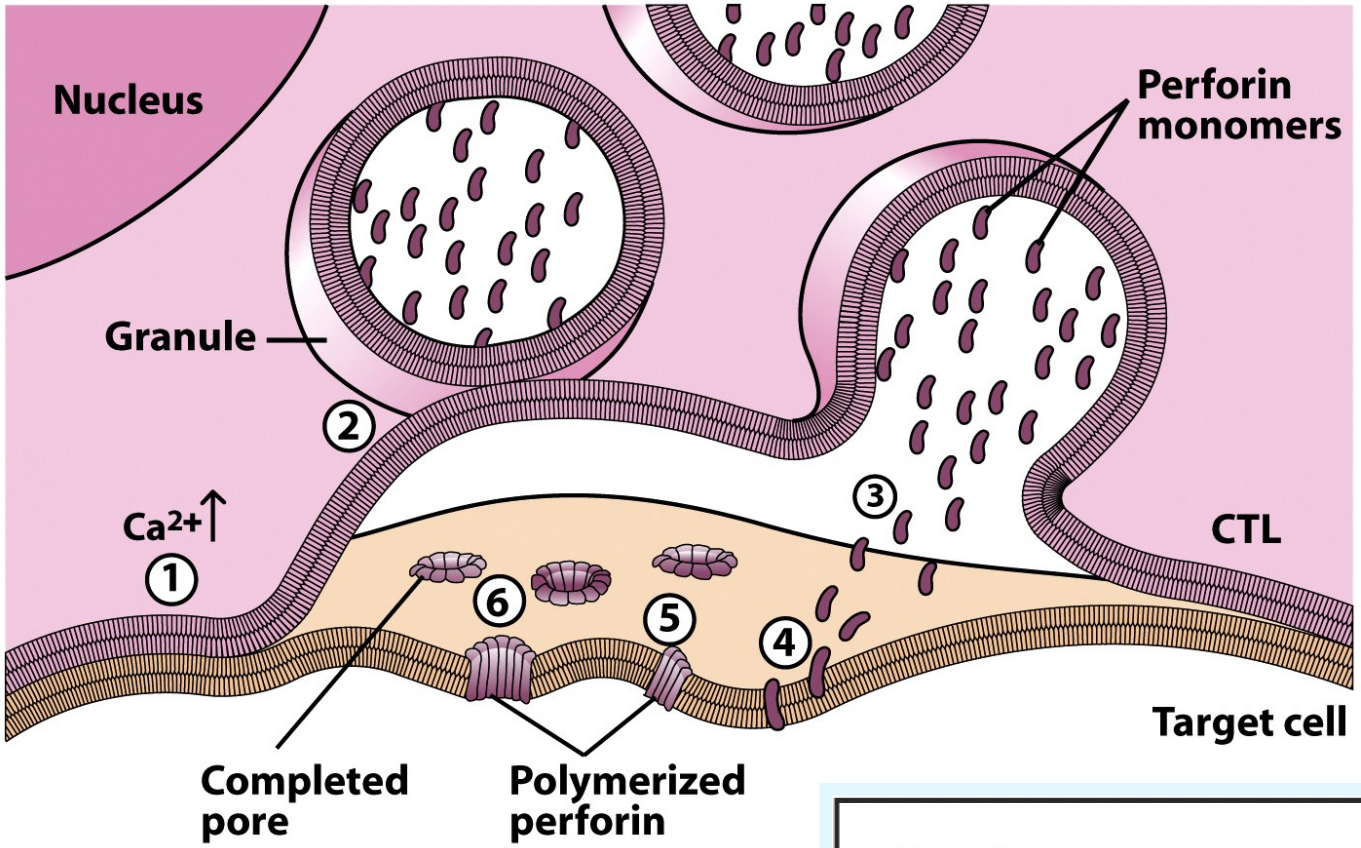


What's in CTL cytotoxic granules?

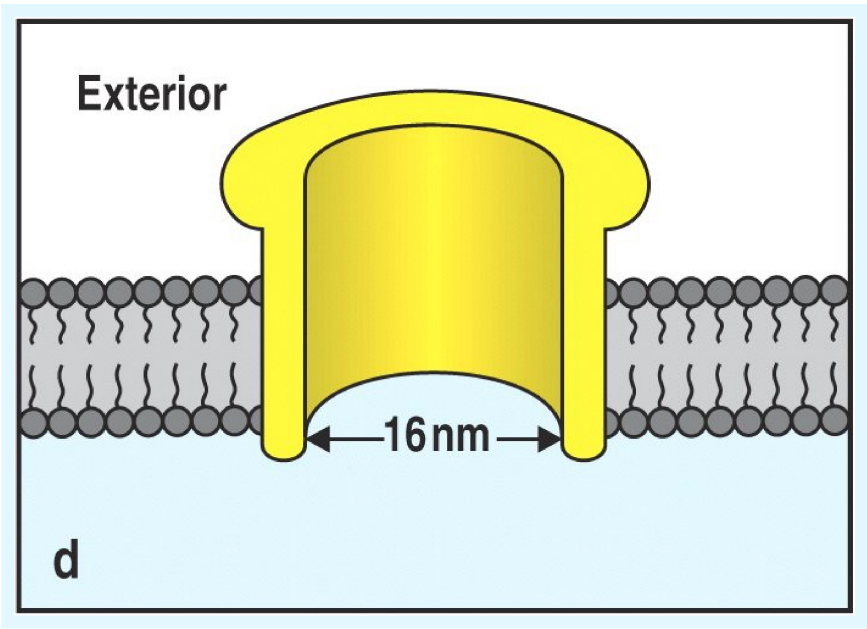
Protein in granules of cytotoxic T cells	Actions on target cells
Perforin	Aids in delivering contents of granules into the cytoplasm of target cell
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
Granulysin	Has antimicrobial actions and can induce apoptosis
Proteoglycans	a structural role and a protective function



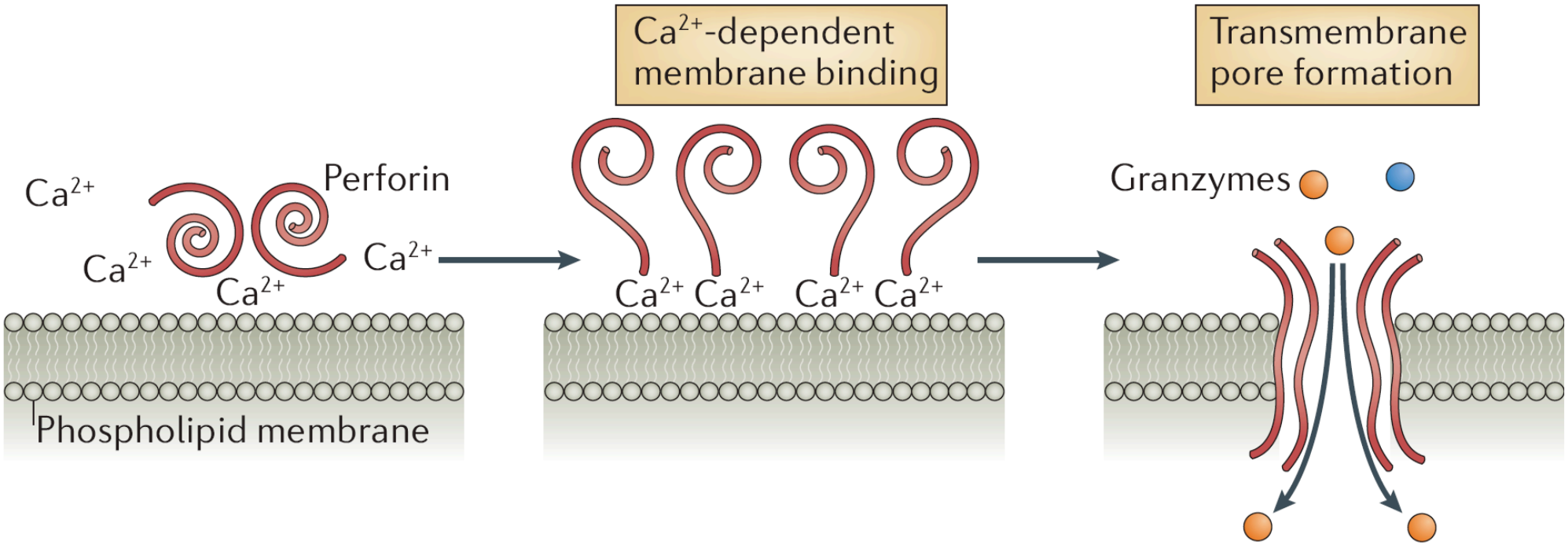
Perforin polymerization creates pores on target cell membrane







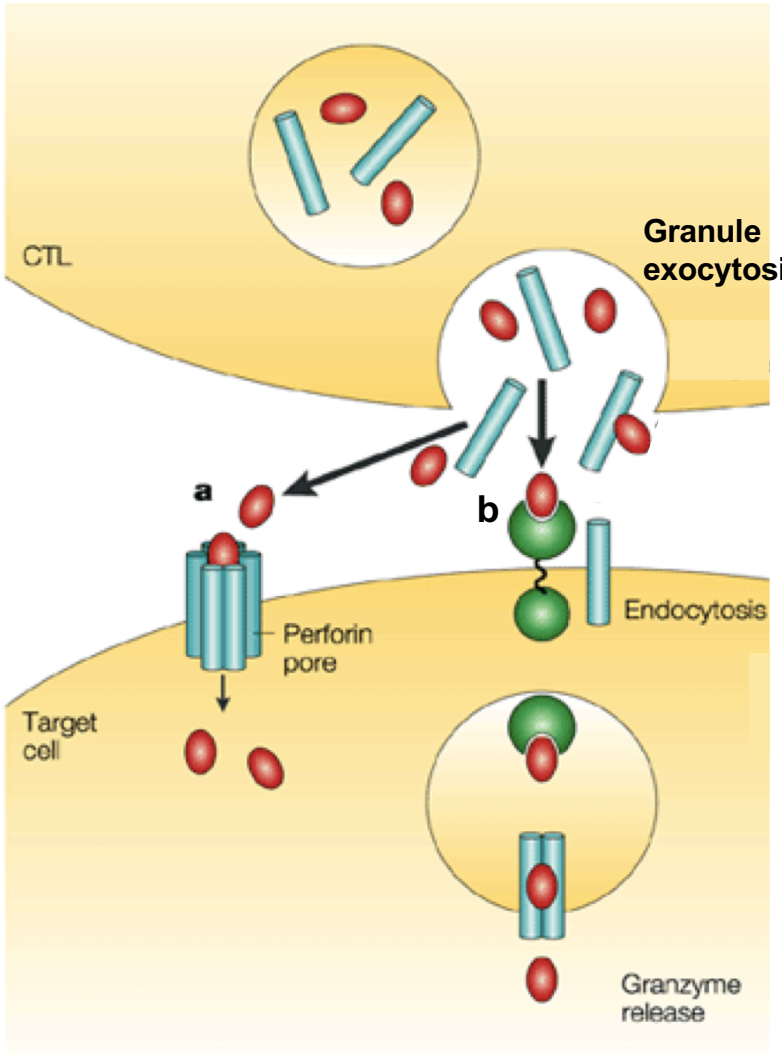
Model of perforin and granzyme synergy in target-cell death



Perforin polymerizes into transmembrane pores (Ca^{++}- and pH-dependent), through which granzymes might diffuse into the cell

Models of granzyme entry into the target cell

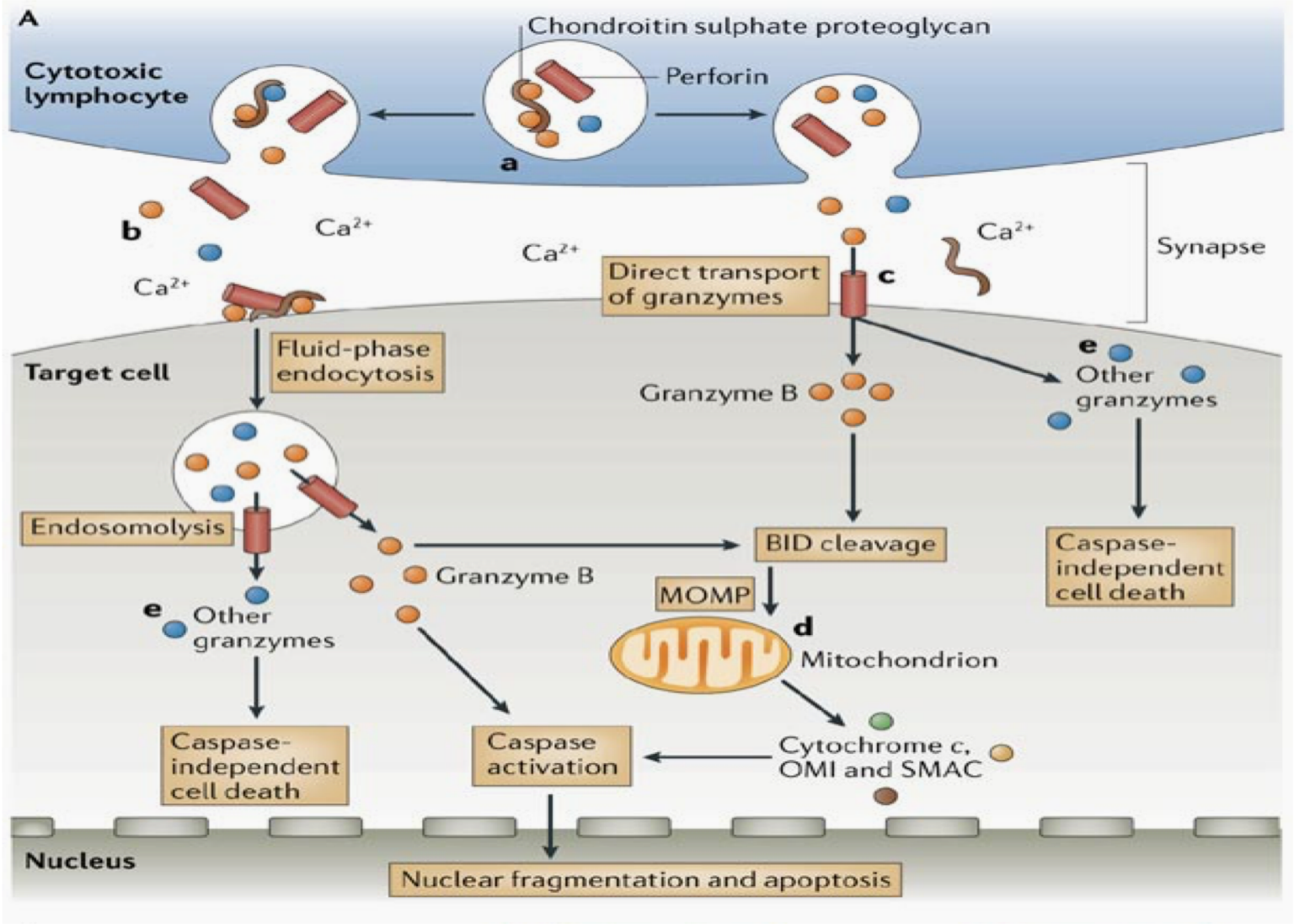
Perforin allows the diffusion of granzymes into the cytoplasm of the target cell by creating pores on its plasma membrane



Granzymes are recognized by specific receptors and internalized along with perforin.

Inside endosomes, perforin allows granzymes to escape into the cytosol.

Perforin-Granzyme mediated target-cell death

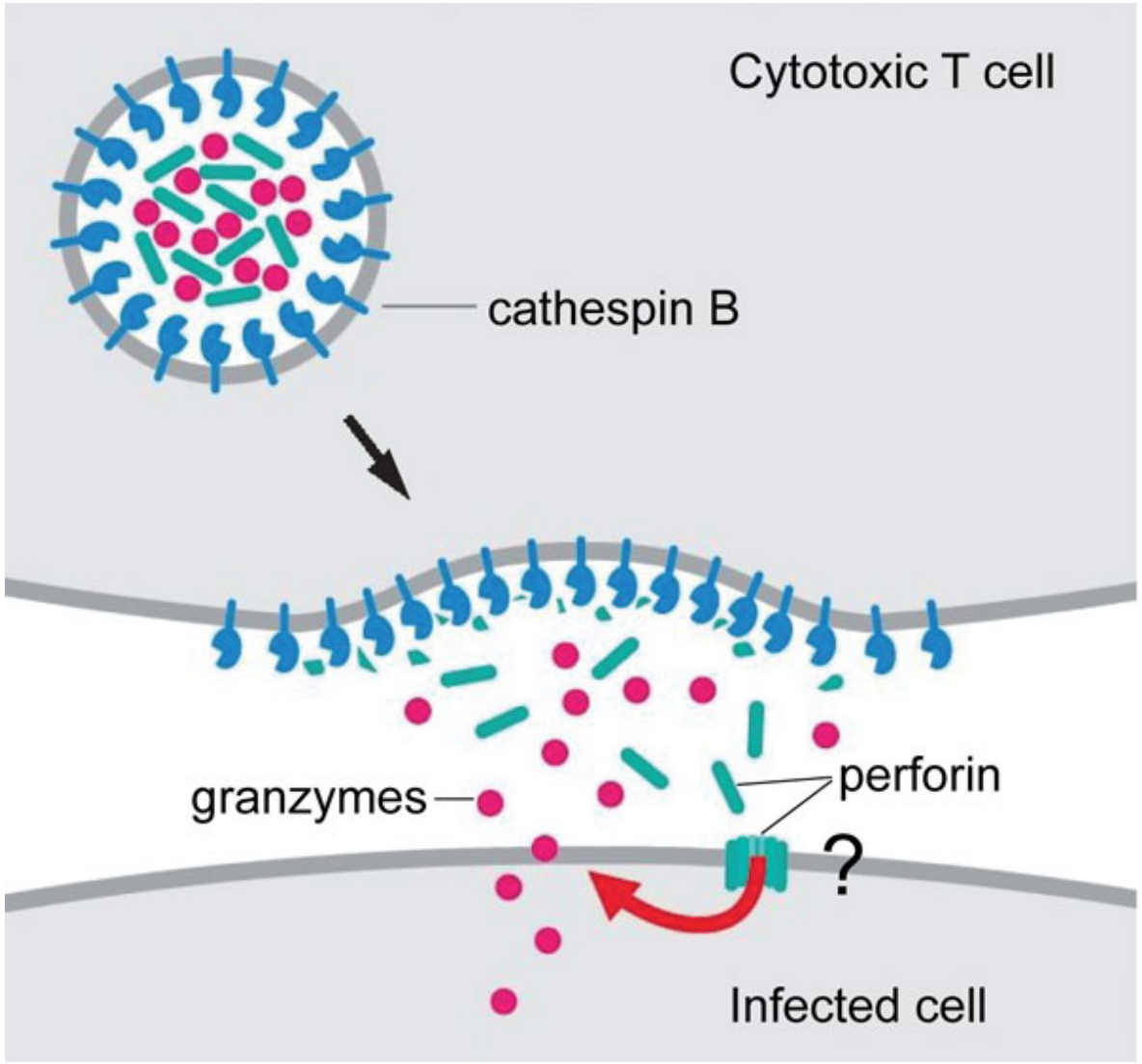


Perforin induces pores and osmotic death!!

Granzyme B activates caspases and causes apoptotic death!!!

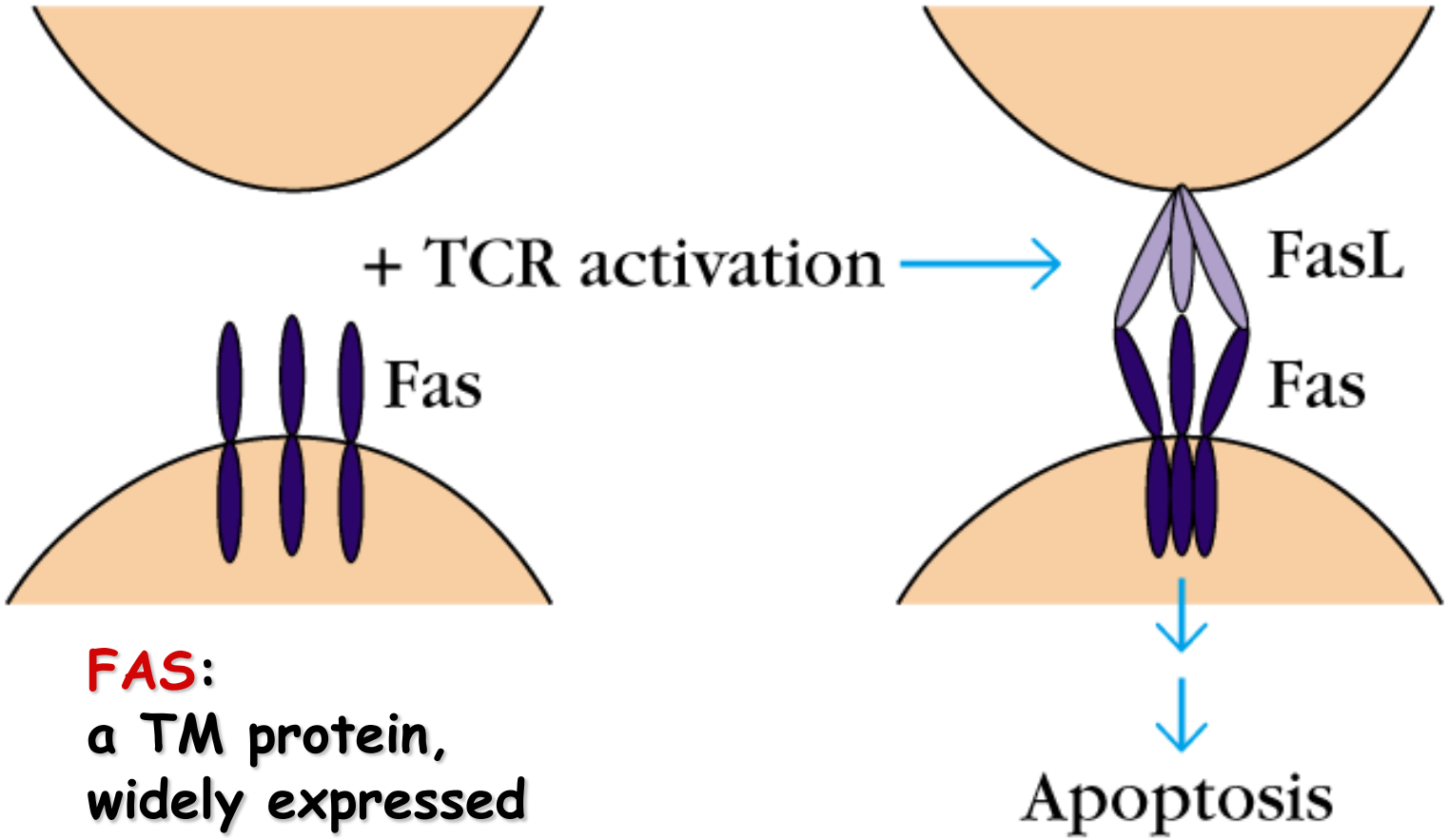
Granzyme A releases an endonuclease that cuts DNA and induces apoptosis

Why isn't the CTL killed?



2° CELL-CONTACT DEPENDENT CTL CYTOTOXICITY: NON-SECRETORY MECHANISM (FAS/FASL)

FAS ligand (FASL):
- a TM protein induced on activated T cells (CD8, Th1) and released from cell surface in soluble form



FAS:
a TM protein, widely expressed

FAS engagement initiates a cascade of caspases

1.Caspase 8

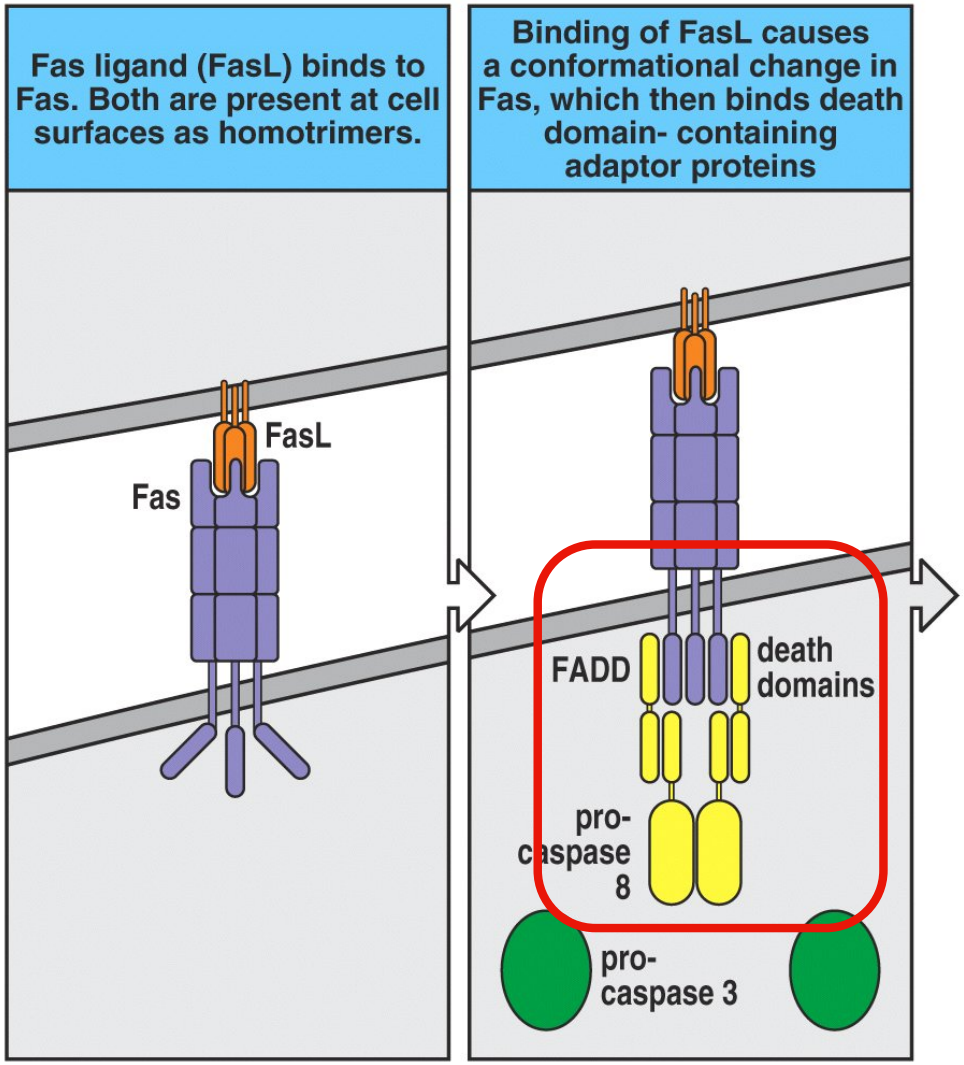


Figure 6-24 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

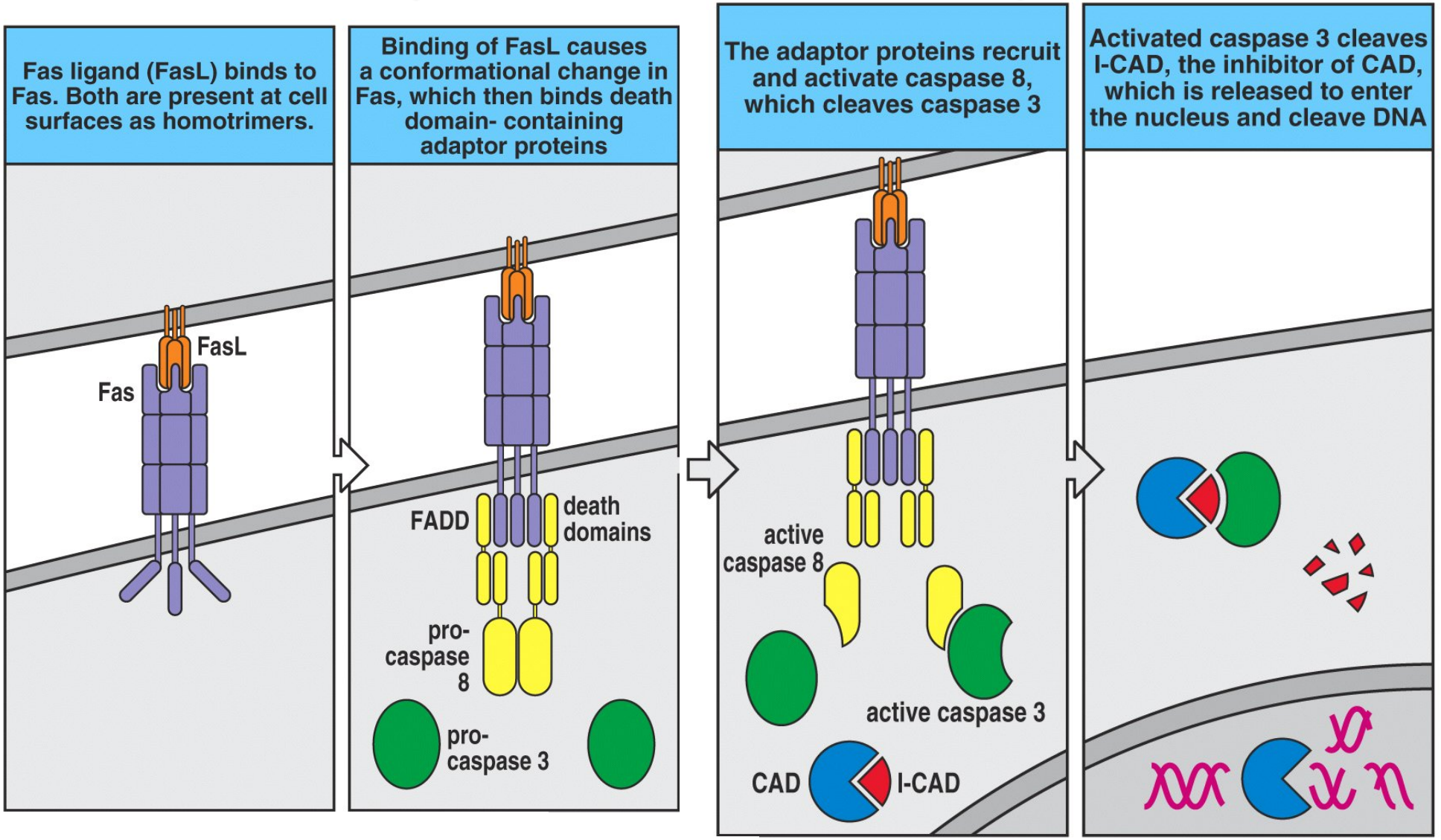
FAS belongs to the death receptor family (with TNF-RI), and expresses a death domain (DD)

Trimeric FAS
FADD
Caspase 8

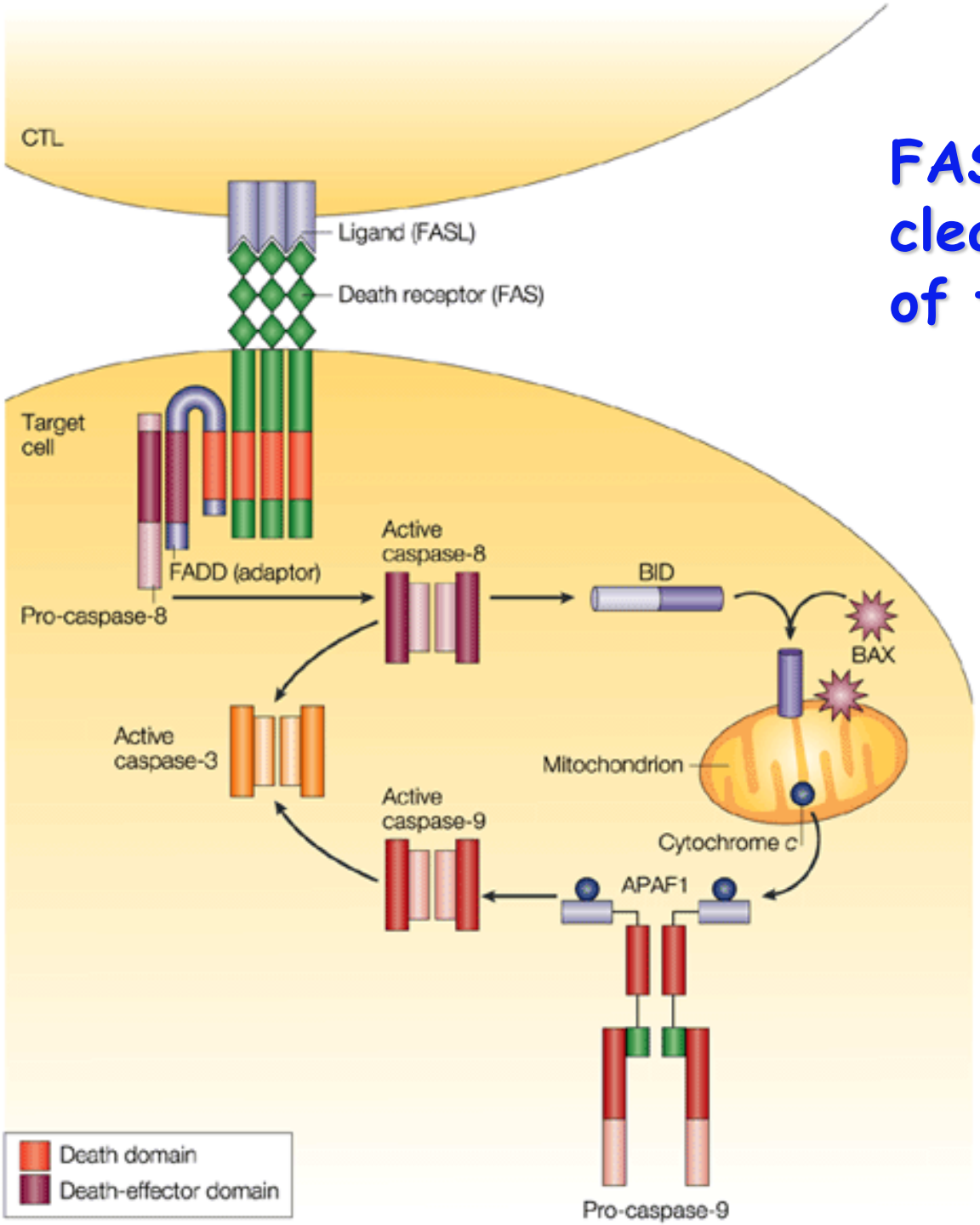
DISC complex

FAS engagement initiates a cascade of caspases

1.Caspase 8 → 2.Caspase 3

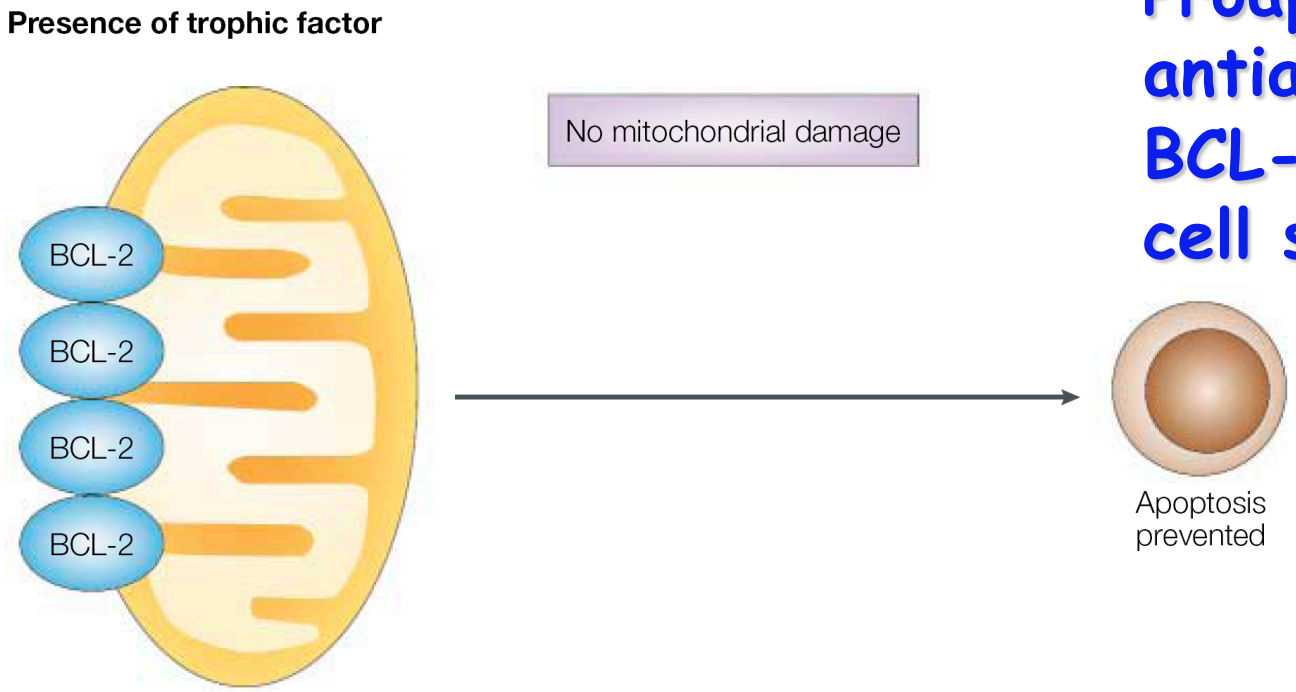


Multiple caspase 3 substrates lead to:
cell shrinkage, and membrane blebbing
DNA degradation, and block of DNA repair



FAS-activated caspase 8 cleaves BID, a member of the BCL-2 family

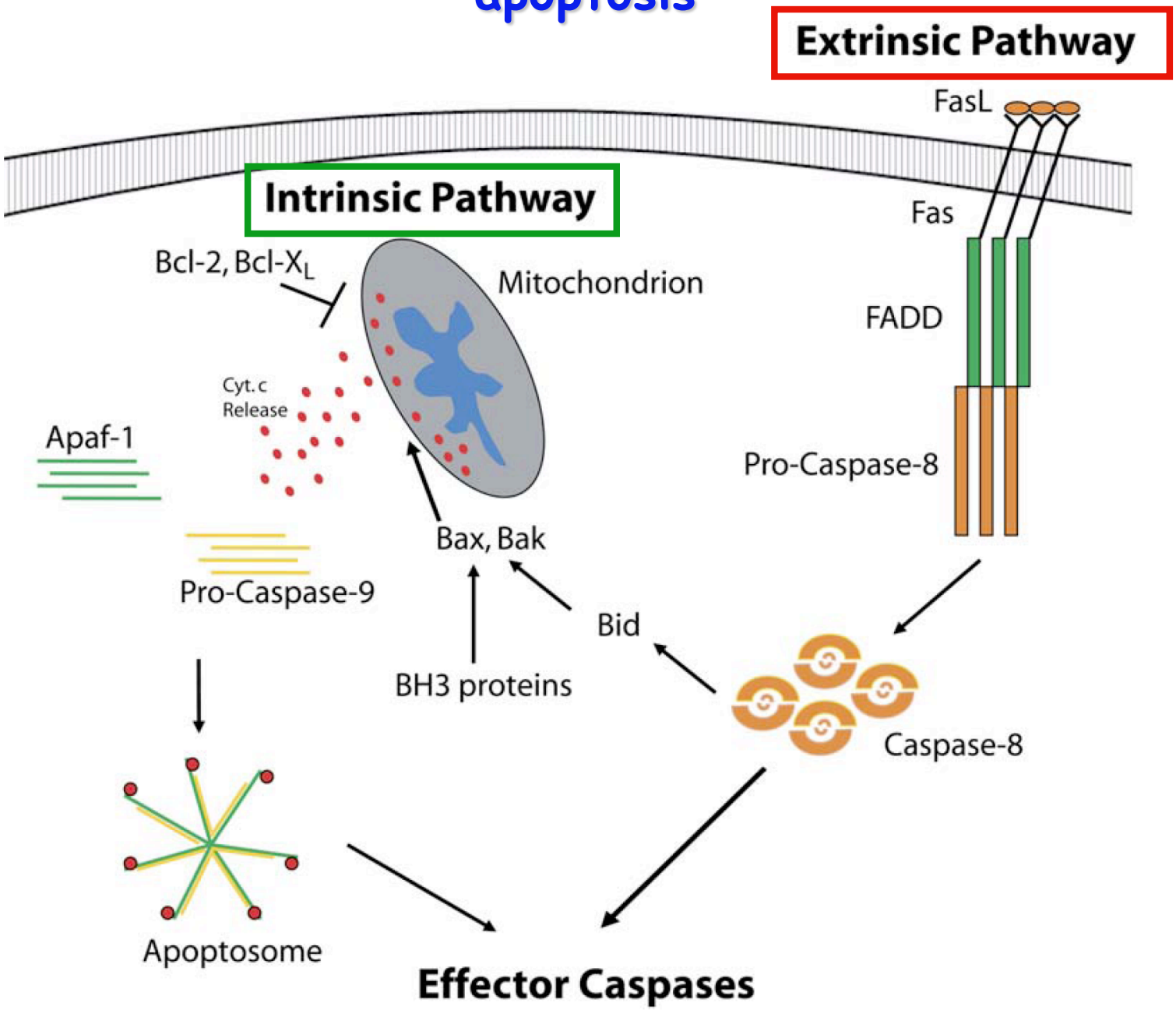
Proapoptotic and antiapoptotic members of BCL-2 family regulate cell survival



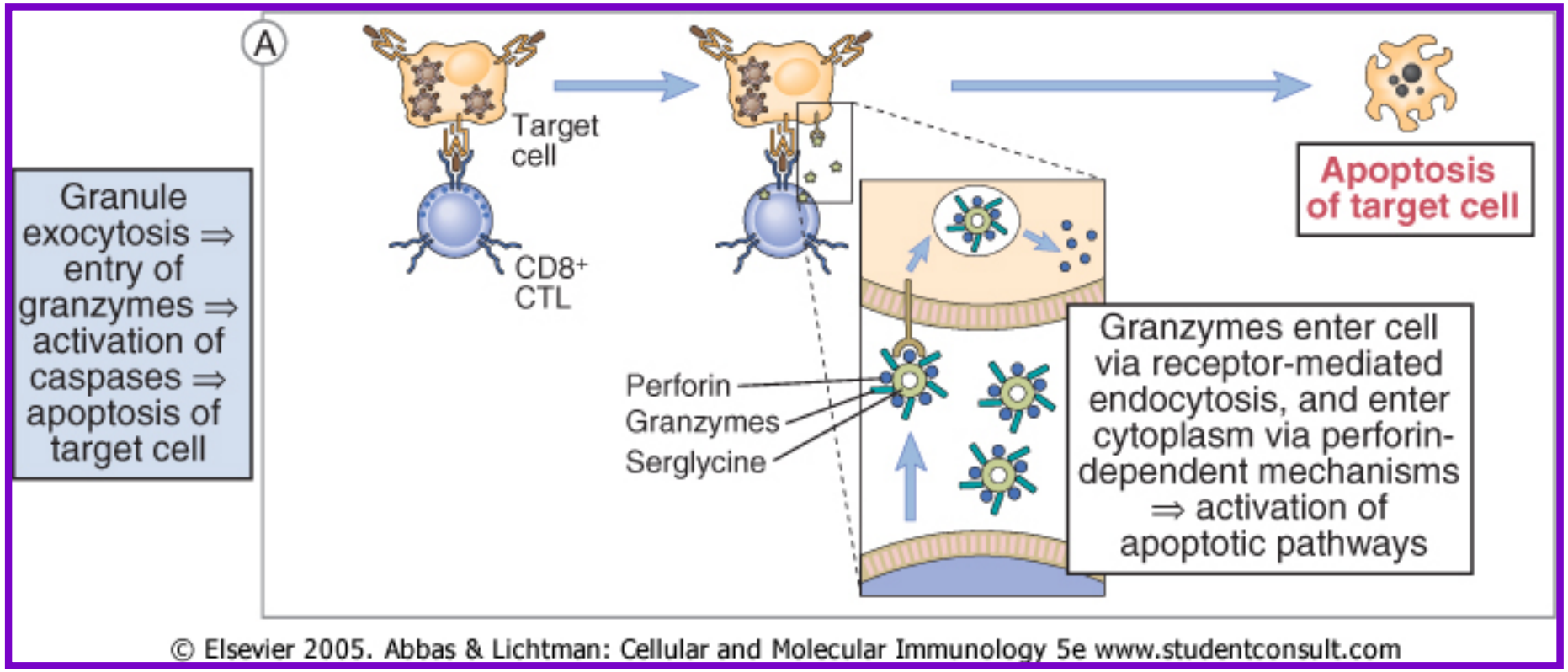
BCL-2
BCL-XL
(anti-apoptotic)

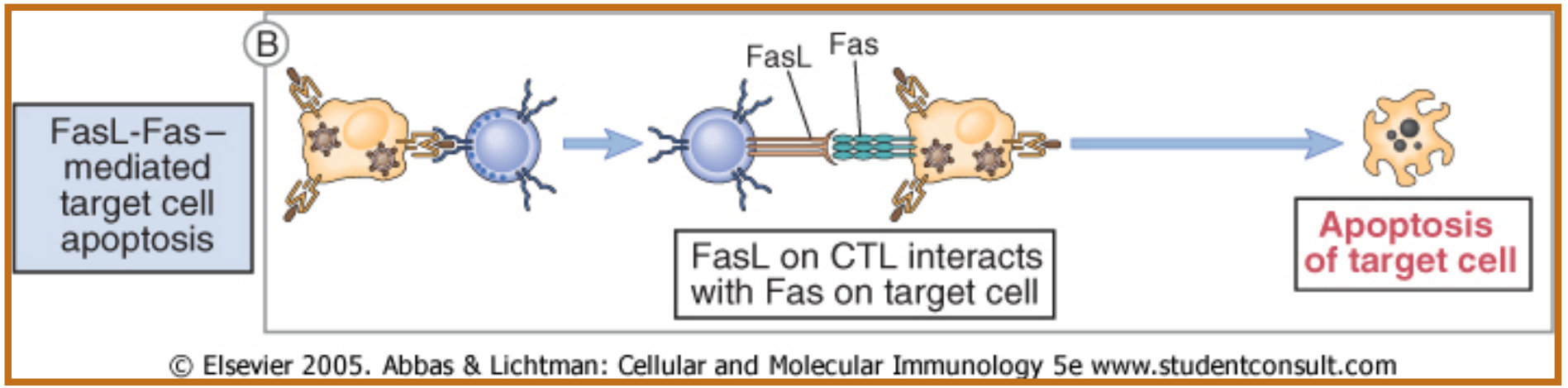
Bax, Bad
Bim, Bak
(pro-apoptotic)

Cooperation between the extrinsic (death receptor-mediated) and the intrinsic (mitochondrion-mediated) pathways to cell apoptosis

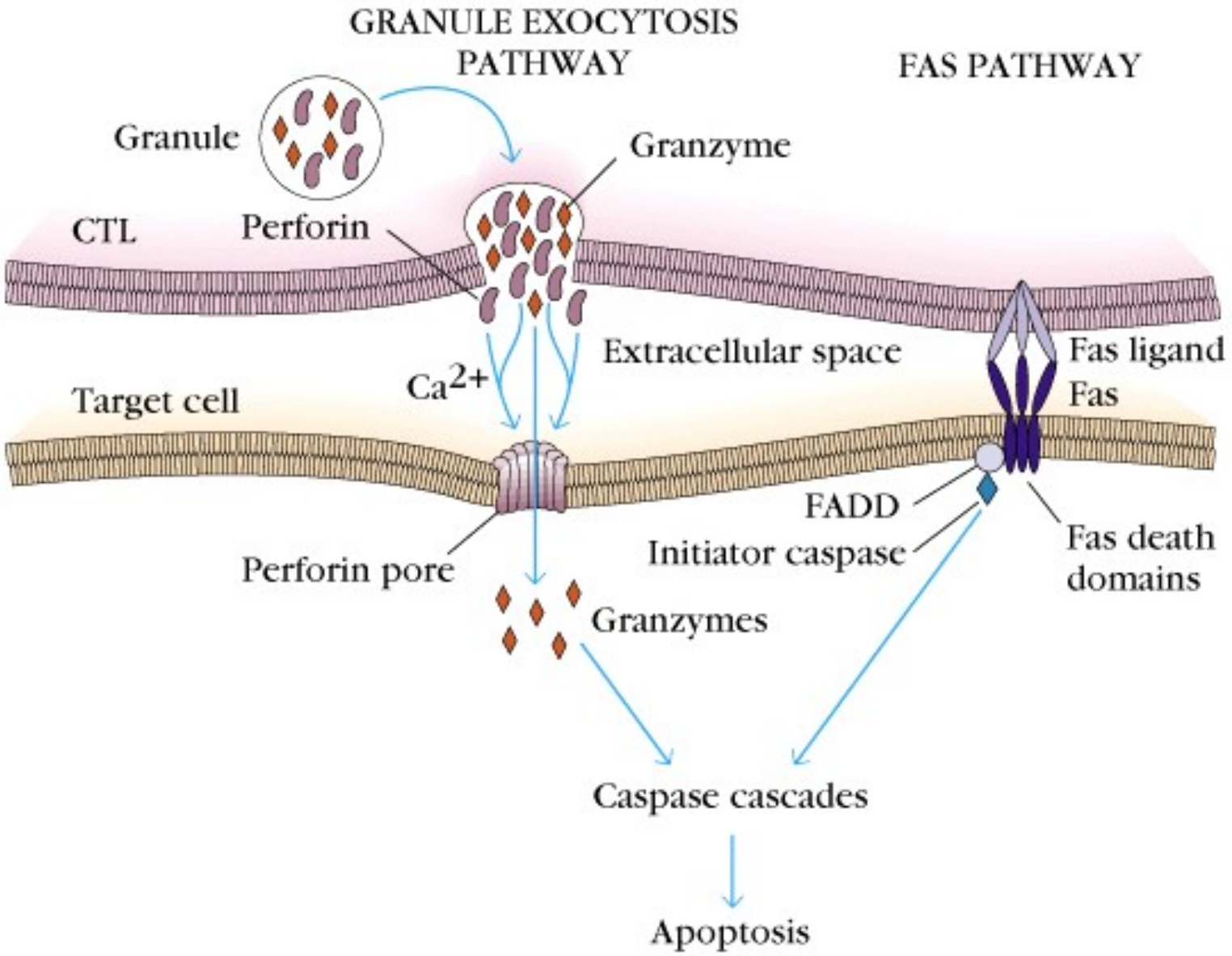


Two major lytic mechanisms of lymphocytes

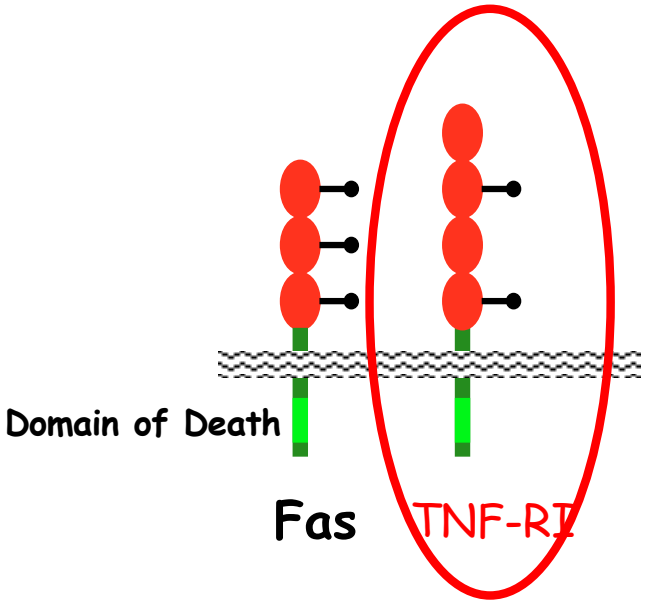


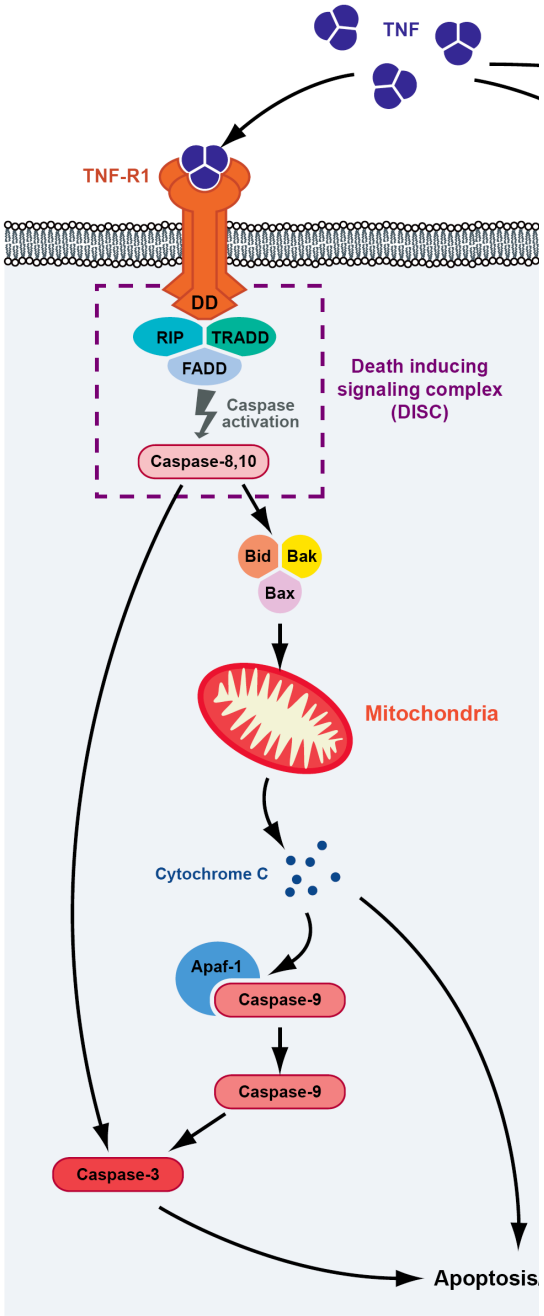


Cooperation between the granule-dependent and the FAS-mediated mechanism of cytotoxicity



3° CTL also produce CYTOTOXIC cytokines





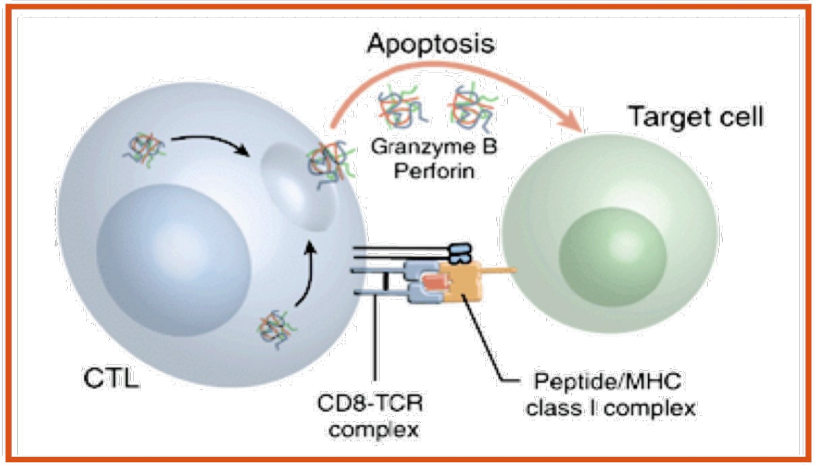
Tumor **N**ecrosis **F**actor

TNF α

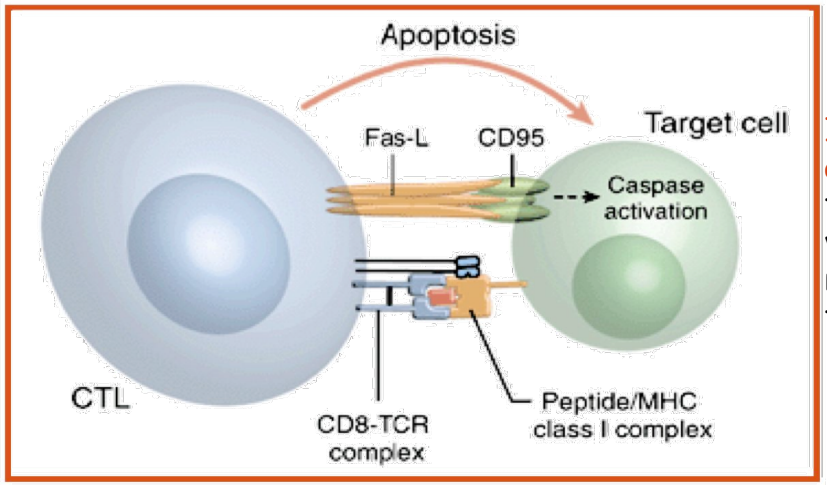
TNF β (LT)

that can induce apoptosis (through TNF-RI)

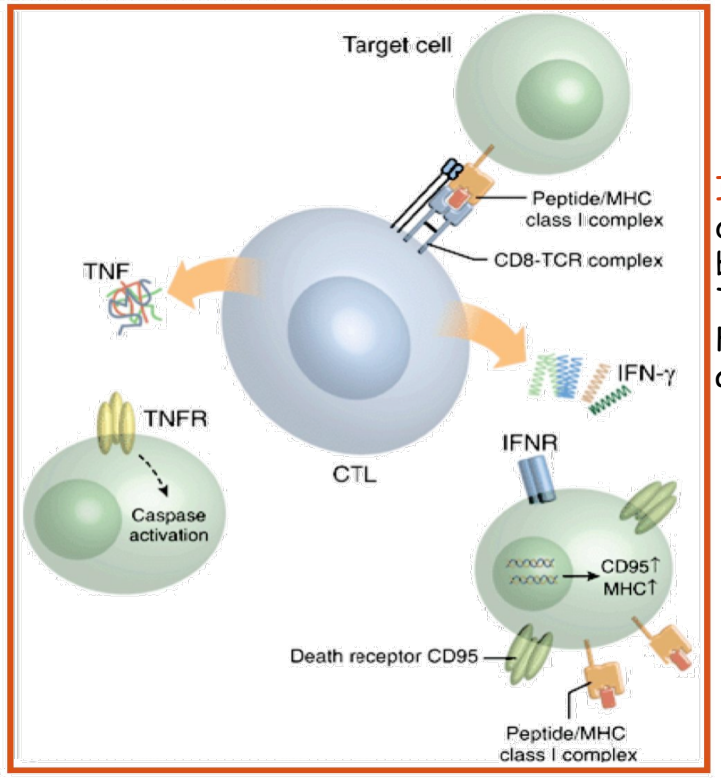
CTL-mediated cytotoxicity



Direct killing by release of granzyme B and perforin into the intercellular space between CTL and target cell

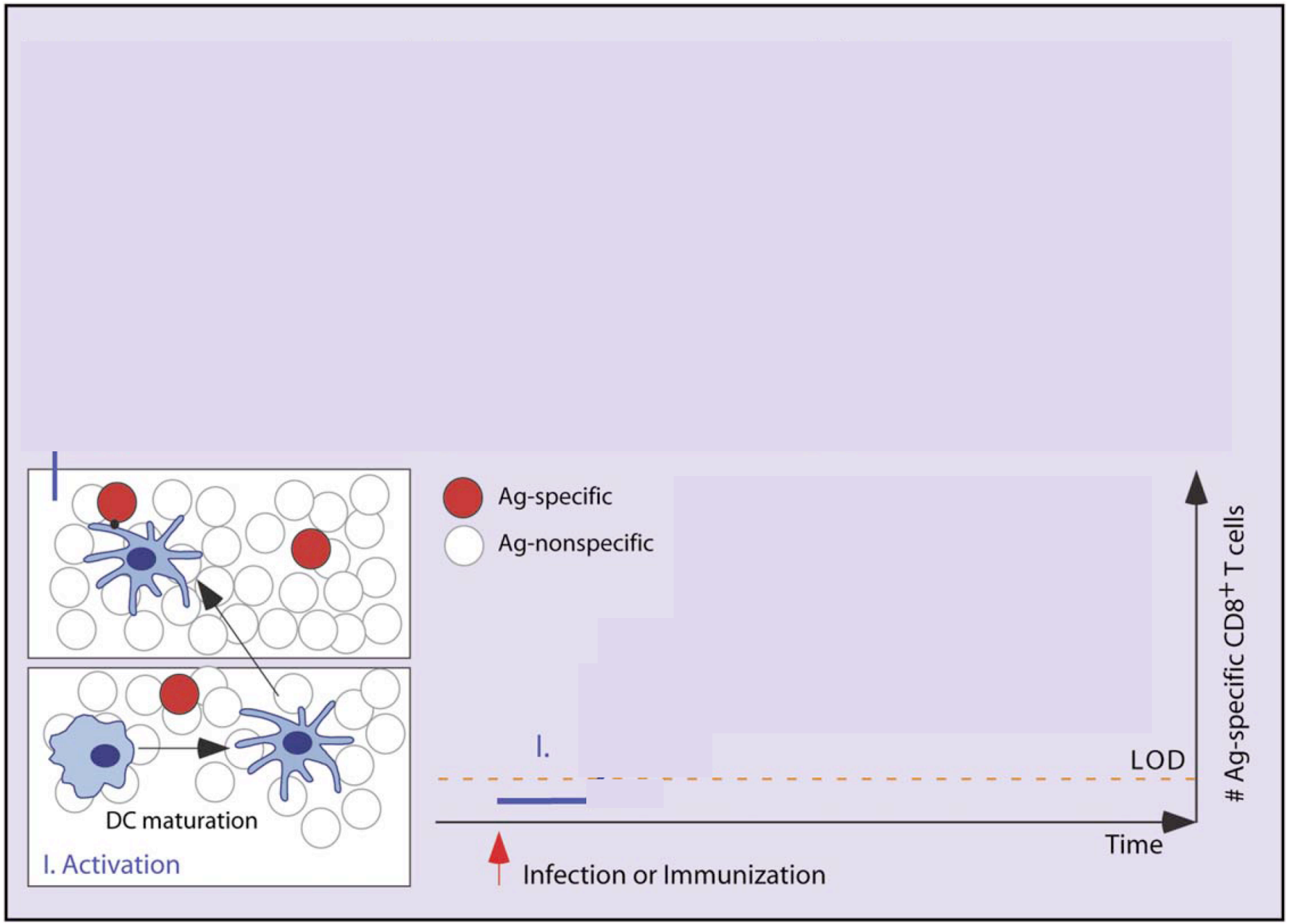


Induction of apoptosis in target cells via death receptor triggering

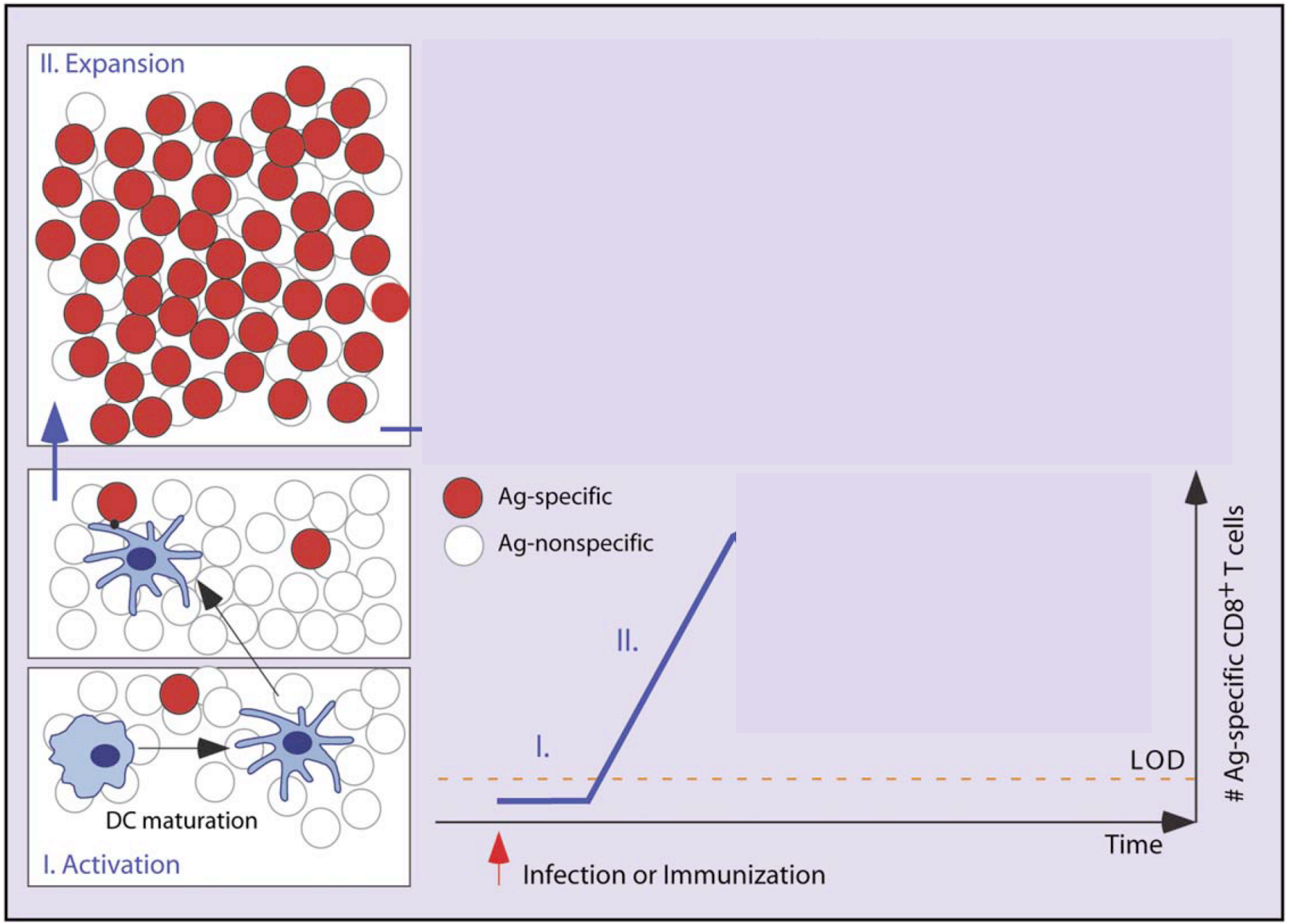


Indirect killing of target cells by release of Tumor Necrosis Factor-alpha and IFN-gamma

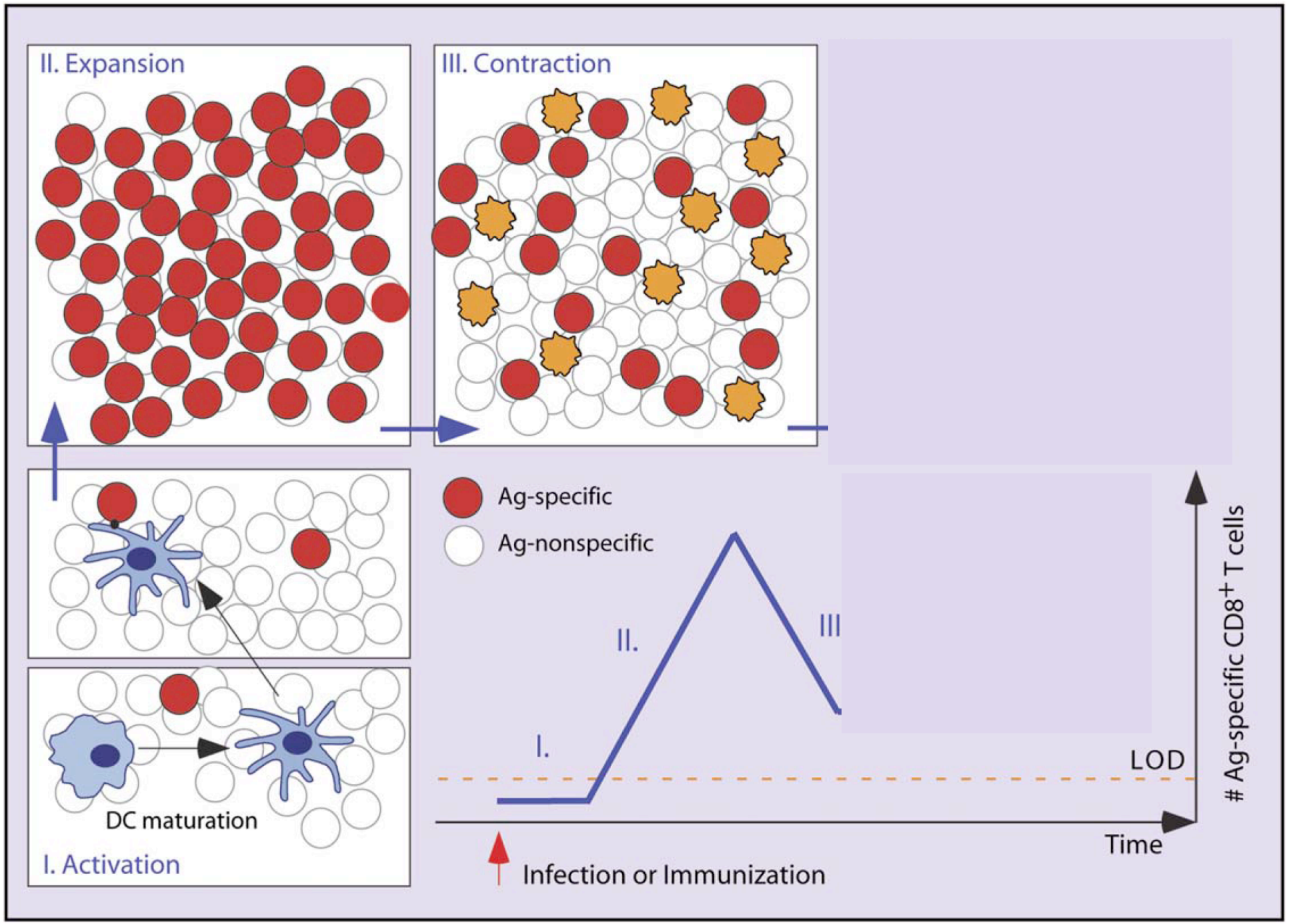
Naive-to-memory progression after acute infection



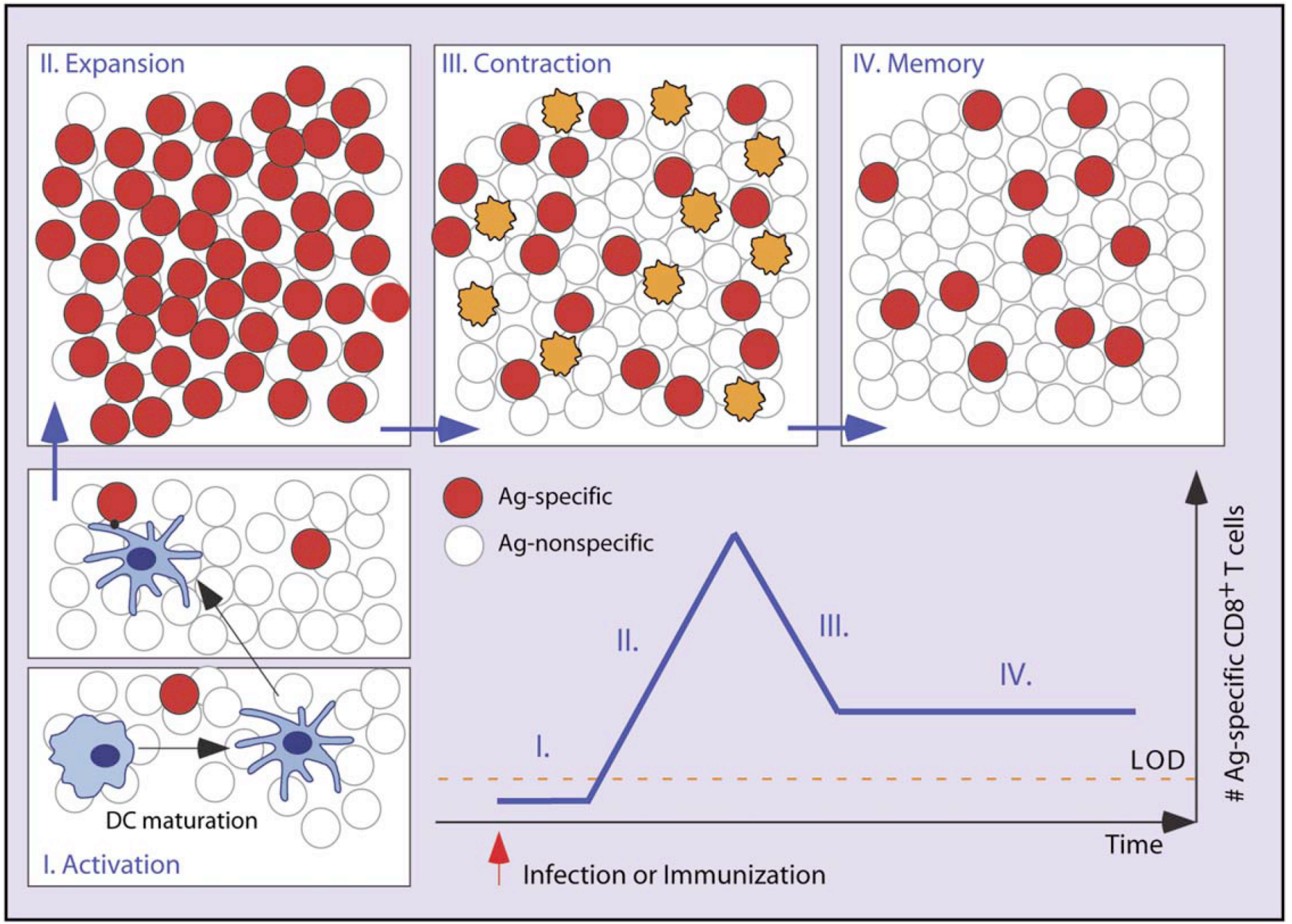
Naive-to-memory progression after acute infection or vaccinati



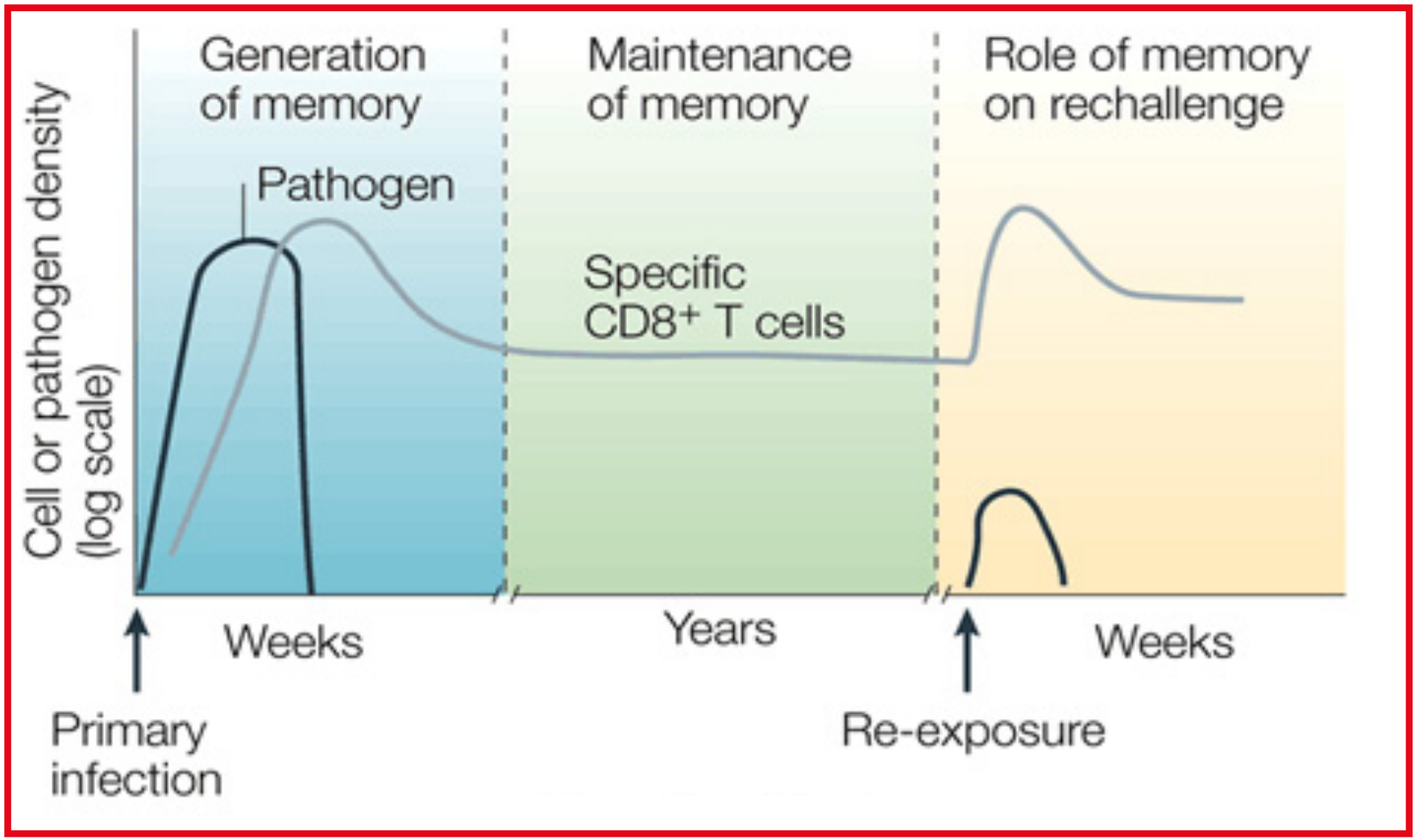
Naive-to-memory progression after acute infection or vaccinati



Naive-to-memory progression after acute infection or vaccinati

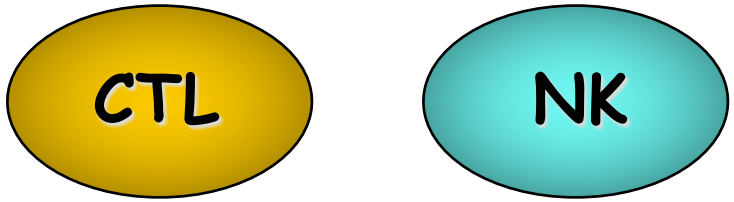


Memory CTL can be maintained for many years



ogical memory can be divided into distinct phases with different time-scales. Primary infection hogen results in the clonal expansion and contraction of pathogen-specific CD8+ T cells and the

Two types of cytotoxic lymphocytes



- Different recognition strategies
- Distinct activation mechanisms
- Common lytic mechanisms

They use complementary defense strategies against intracellular pathogens and tumor cells!