Ag Presentation and Cell mediated Immunity

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Objectives

- How do T cells recognize antigens?
- How do T cells get activated?
- What are the functions of different T cell subsets?

Adaptive Immunity

Humoral

By antibodies produced by B cells

Important against extracellular microbes/ toxins

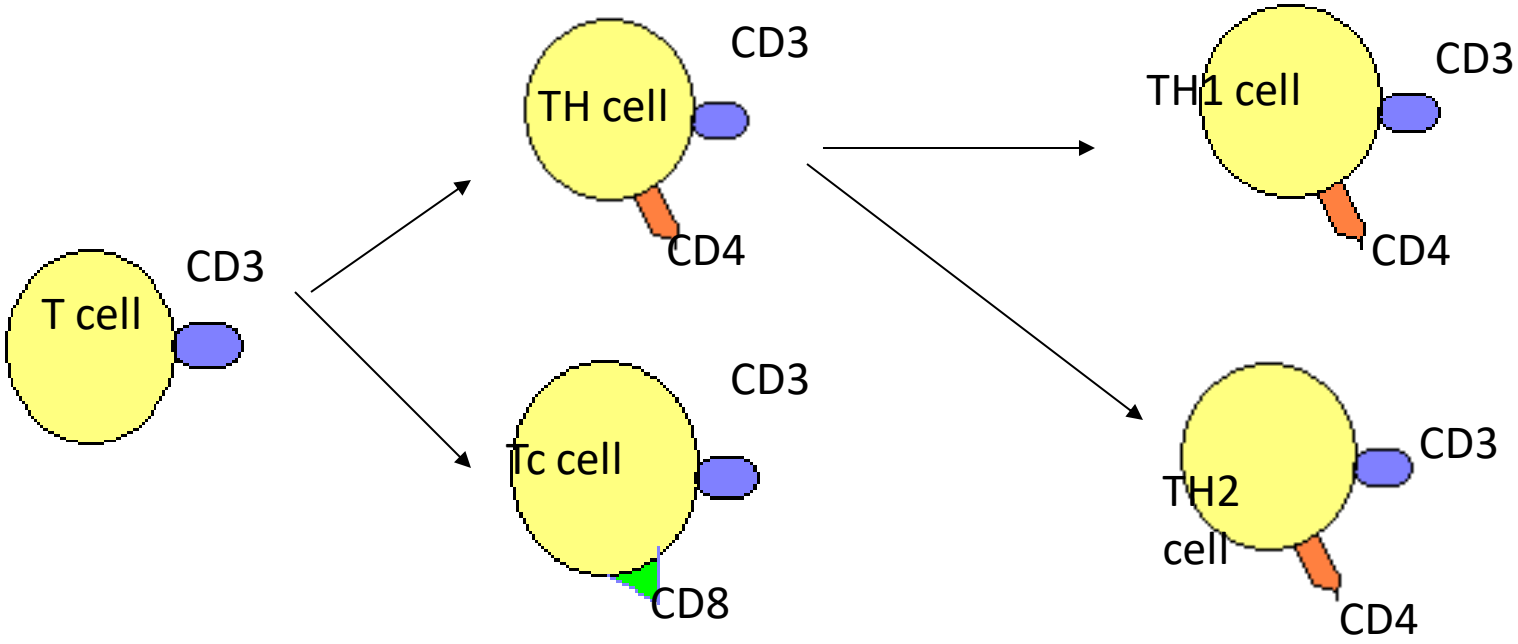
Cell mediated (CMI)

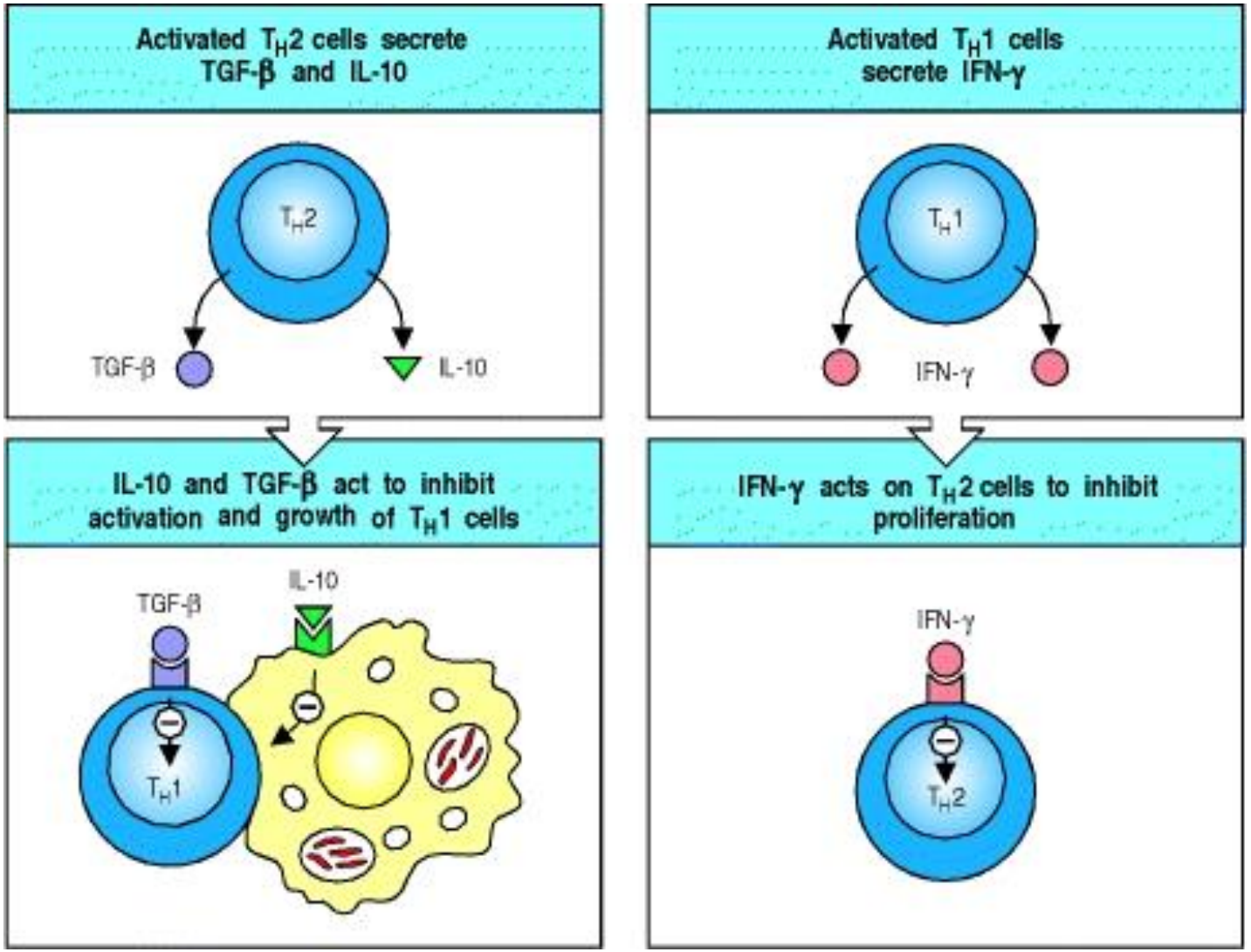
By activated T cells

Important against intracellular microbes(viruses & intra-cellular bacteria)

Provides help for development of humoral immunity

T cell subsets




Activated T_H2 cells secrete TGF-β and IL-10
T_H2
TGF-β
IL-10
Activated T_H1 cells secrete IFN-γ
T_H1
IFN-γ
IL-10 and TGF-β act to inhibit activation and growth of T_H1 cells
TGF-β
IL-10
T_H1
IFN-γ acts on T_H2 cells to inhibit proliferation
IFN-γ
T_H2

Ag Recognition

- Ags are recognized by cells in the adaptive immune system by specialized structures on surface

  " Antigen Receptors"

Ag Recognition

- Highly specific and specialized
- B cells can recognize unprocessed Ags
- TCR only identifies peptide fragments of an Ag (processed Ag) displayed by a special unit called MHC molecules on APC/ nucleated cells

B cell receptor

Can identify

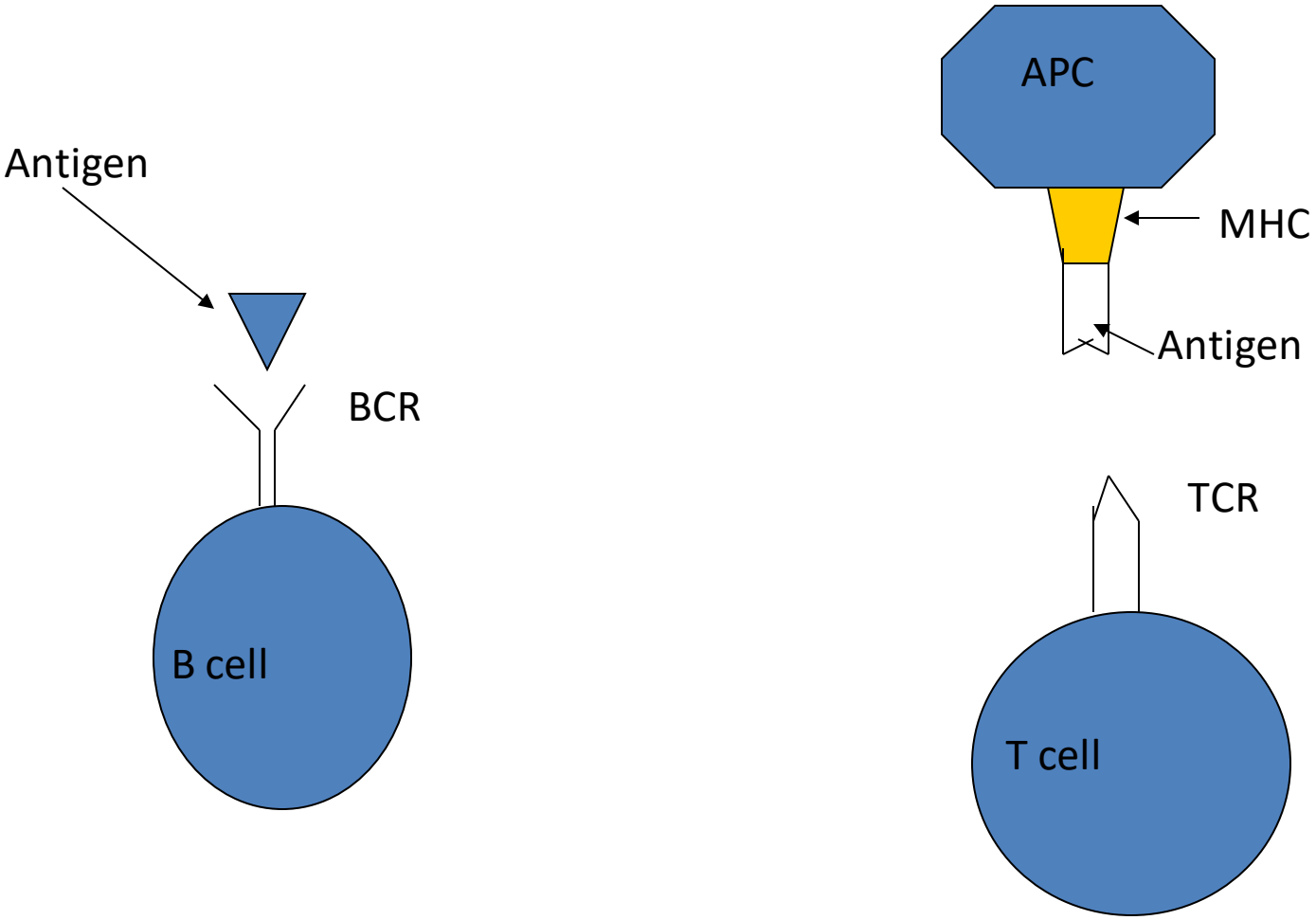
- unprocessed (native) Ags
- Not combined with MHC
- Recognize proteins, CHO, lipids etc

T cell receptor

Recognize Ags that are

- Processed Ags
- Combined with MHC molecules
- Only peptides

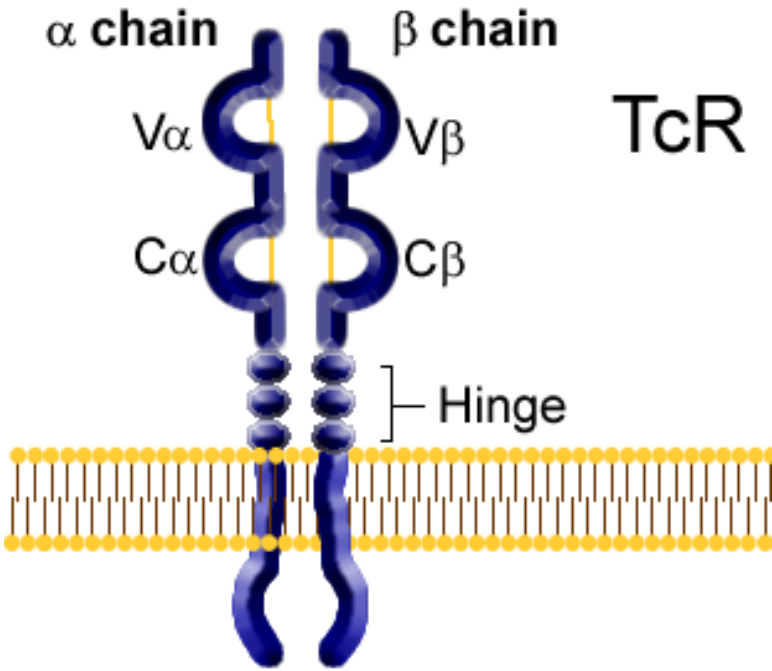
"MHC restricted"


Antigen
BCR
B cell
APC
MHC
Antigen
TCR
T cell

TCR

- Each T lymphocyte clone has TCR specific to a single unique epitope
- Different clones have different TCR
- TCR recognize Ags that are
  - Processed linear peptides
  - Combined with MHC molecules

"MHC restricted"



Ag processing for T cell

- TCR identifies linear peptides only – so processing is needed
- Processed Ags are presented to TCR in conjunction with MHC
- 2 types of Ags
    - Intra cytoplasmic Ags (processed by APC/infected cells) e.g. Viruses----> presented with class I MHC to CD8
    - Vesicular/ phagocytosed Ags (processed by APC) e.g. bacteria ----> presented with class II MHC to CD4

Professional APC

- The immune system contains of three types of antigen presenting cells (APC's).

1) Macrophages
2) Dendritic cells
3) B cells

- In addition to antigen presentation, they provide co-stimulatory signals via B7 co-stimulators – provide 2nd signal for T cell activation

- They have both MHC class I and MHC class II molecules

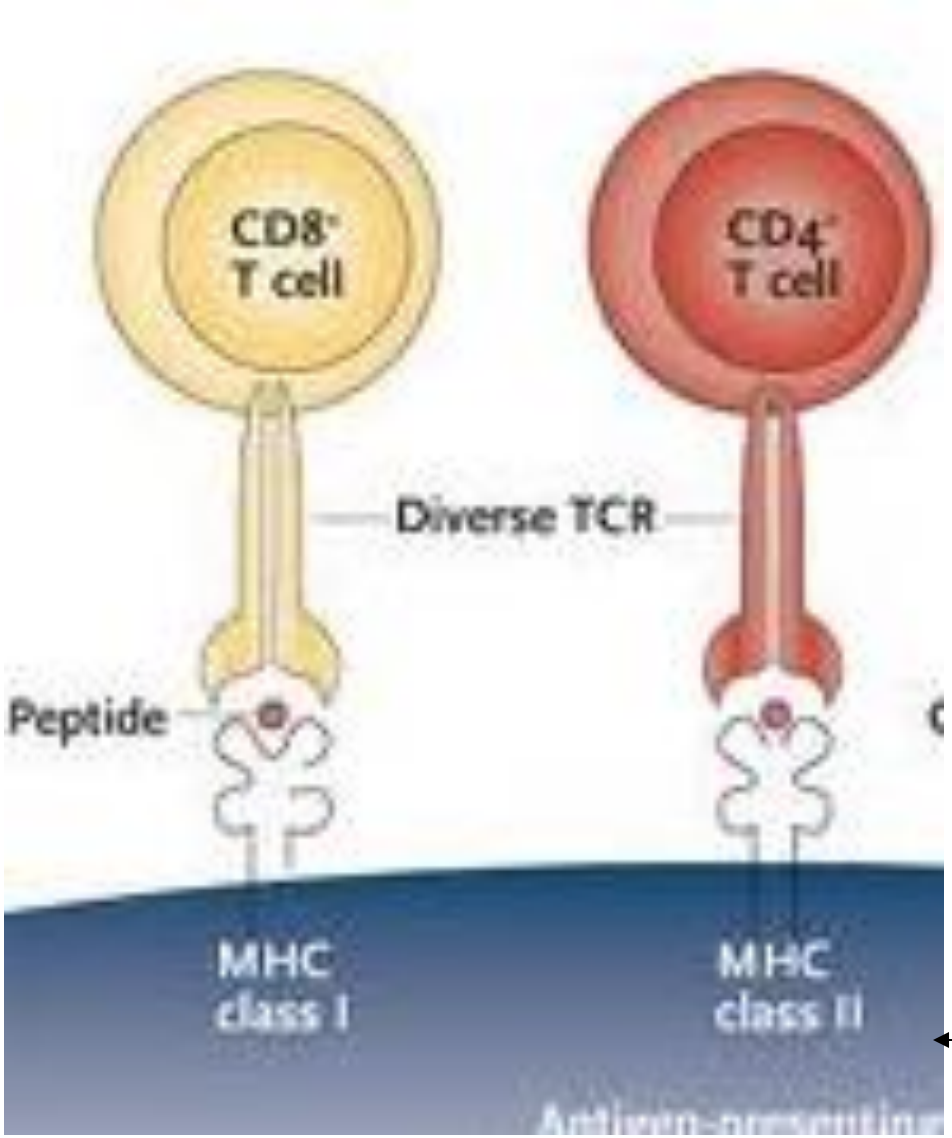
- They identify PAMPs of microbes by pattern recognition molecules

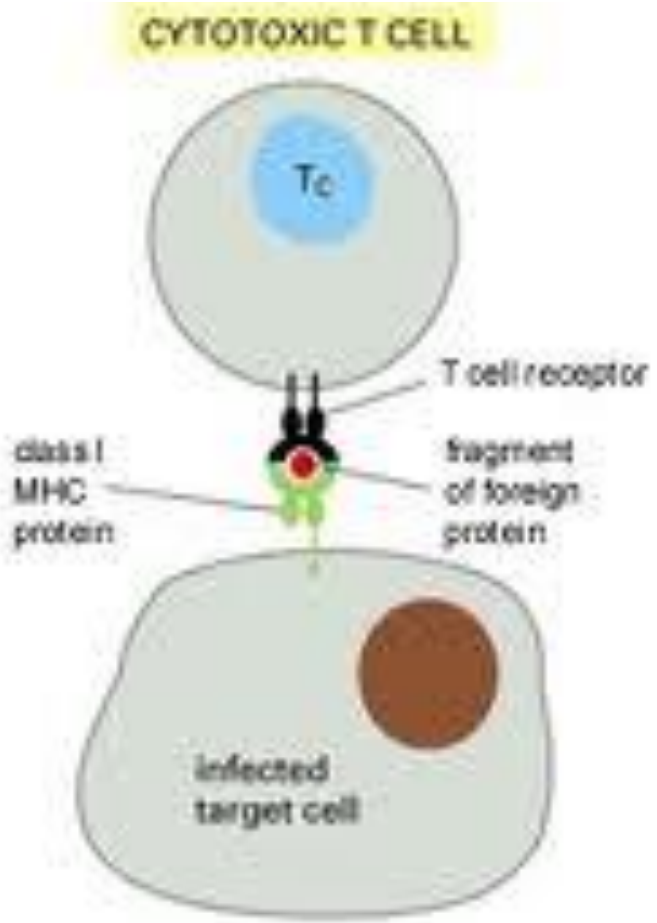
Ag recognition

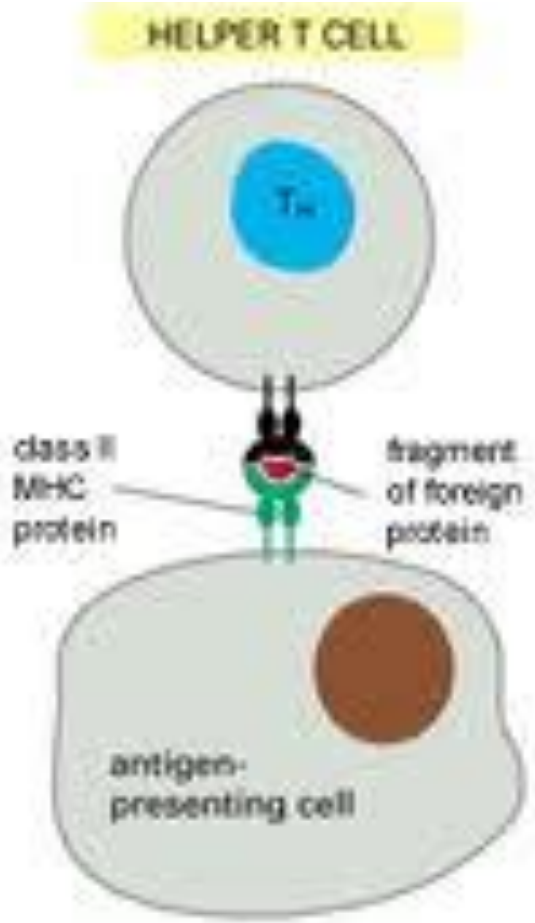
- Macrophages - process intra-vesicular Ags (intra cellular bac- e.g.TB)
- Dendritic cells – process viral Ags
- B cells – process extra cellular bac. Ags, toxins

- APC's present Ags to T cells in peripheral lymphoid organs in conjunction with MHC molecules

MHC class I	MHC classII
Membrane proteins	Membrane proteins
Coded by class I MHC genes	Coded by class II MHC genes
Expressed on all nucleated cells	Expressed on APC's only
Cytoplasmic peptides are presented to CD8 cells	Intra-vesicular peptides are presented to CD4 cells


CD8+
T cell
CD4+
T cell
Diverse TCR
Peptide
MHC
class I
MHC
class II
APC


CYTOTOXIC T CELL
Tc
T cell receptor
class I
MHC
protein
fragment
of foreign
protein
infected
target cell

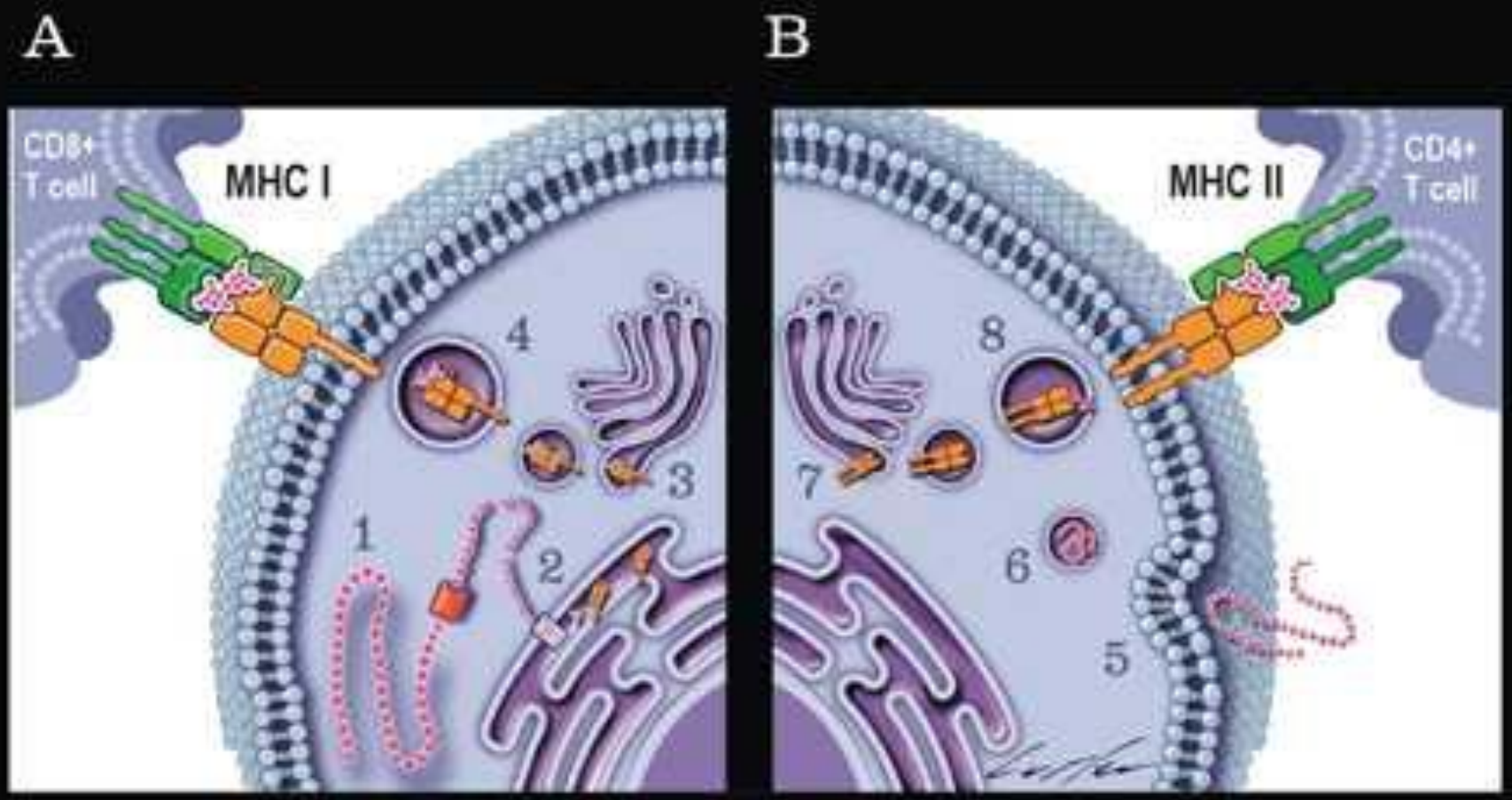

HELPER T CELL
TH
class II
MHC
protein
fragment
of foreign
protein
antigen-
presenting cell

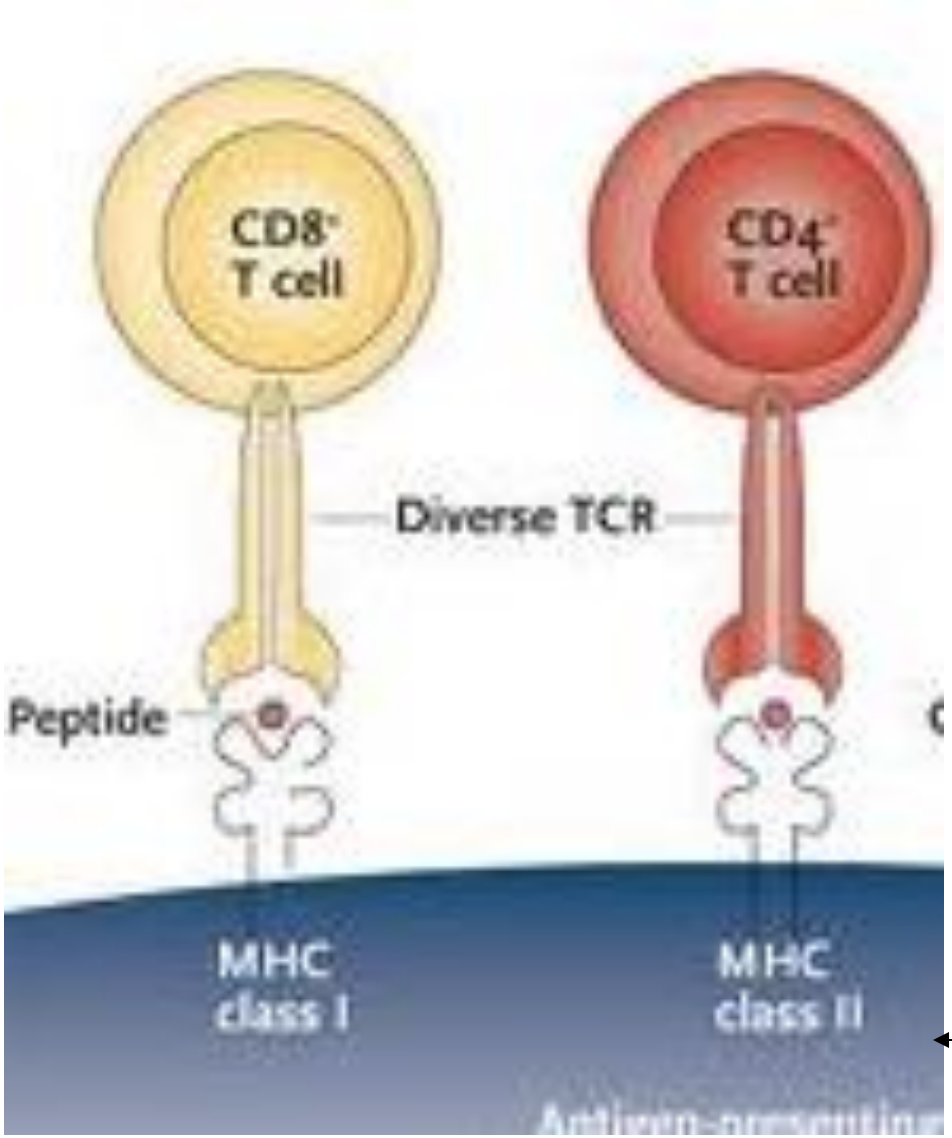
Phases of immune response

Recognition	TCR identifies processed peptides in conjunction with MHC molecules on APC
Activation	Clonal expansion and differentiation into armed effector T cells amd memory cells
Effector phase	By- cytotoxic T cells (T_C) - helper T cells (T_H)

Ag recognition

- TCR recognizes peptides that have been processed in APC
- APC's present peptides with MHC class I to cytotoxic T cell
- APC's present peptides with MHC class II to helper T cell


A
B
CD8+
T cell
MHC I
MHC II
CD4+
T cell
1
2
3
4
5
6
7
8


CD8+
T cell
CD4+
T cell
Diverse TCR
Peptide
MHC
class I
MHC
class II
APC

T cell Activation

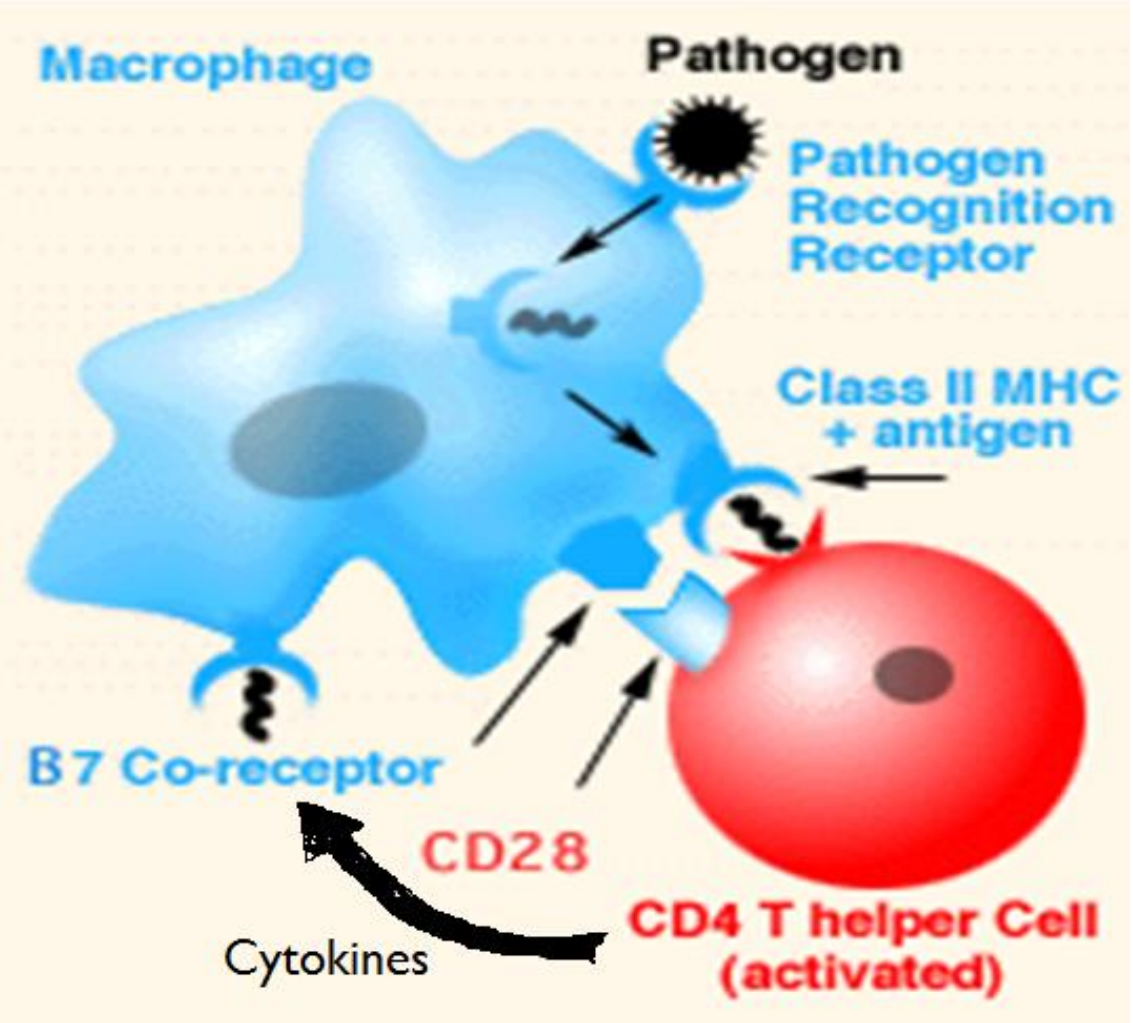
After recognition T cells need 2 signals for activation

Signal 1 -Binding of Ag to TCR

Signal 2- APC's provide 2nd signal to activate T cells via B7 co-stimulators + cytokines

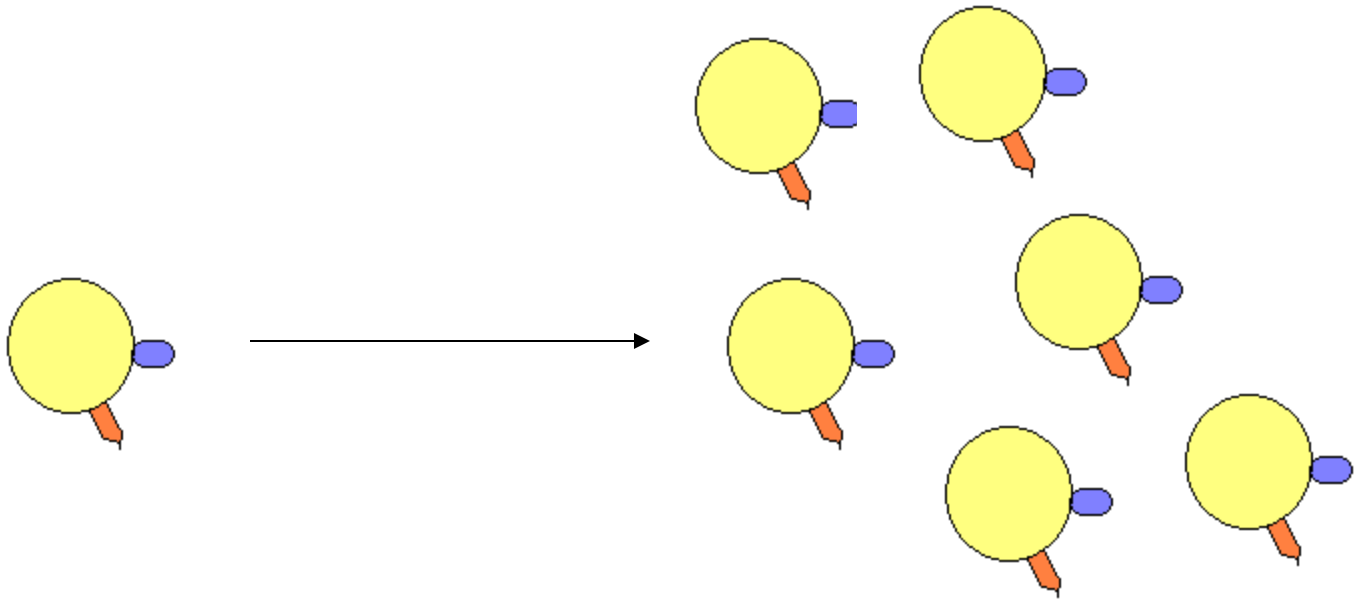
T cell Activation

- In addition to Ag presentation, APC's provide 2nd signal to activate T cells via B7 co-stimulators---> activated T cells



Clonal Expansion

- Once activated, T cell proliferate
- Generate thousands of progeny cells in selected clone with the same Ag specificity
- Differnetiate into armed effector T cells and memory cells



Effector Phase

- Activated T cells move to site of infection
- Different types of T cell subsets are activated according to the type of Ag
- Different T cell subsets have different actions

Armed effector CD4 T cells

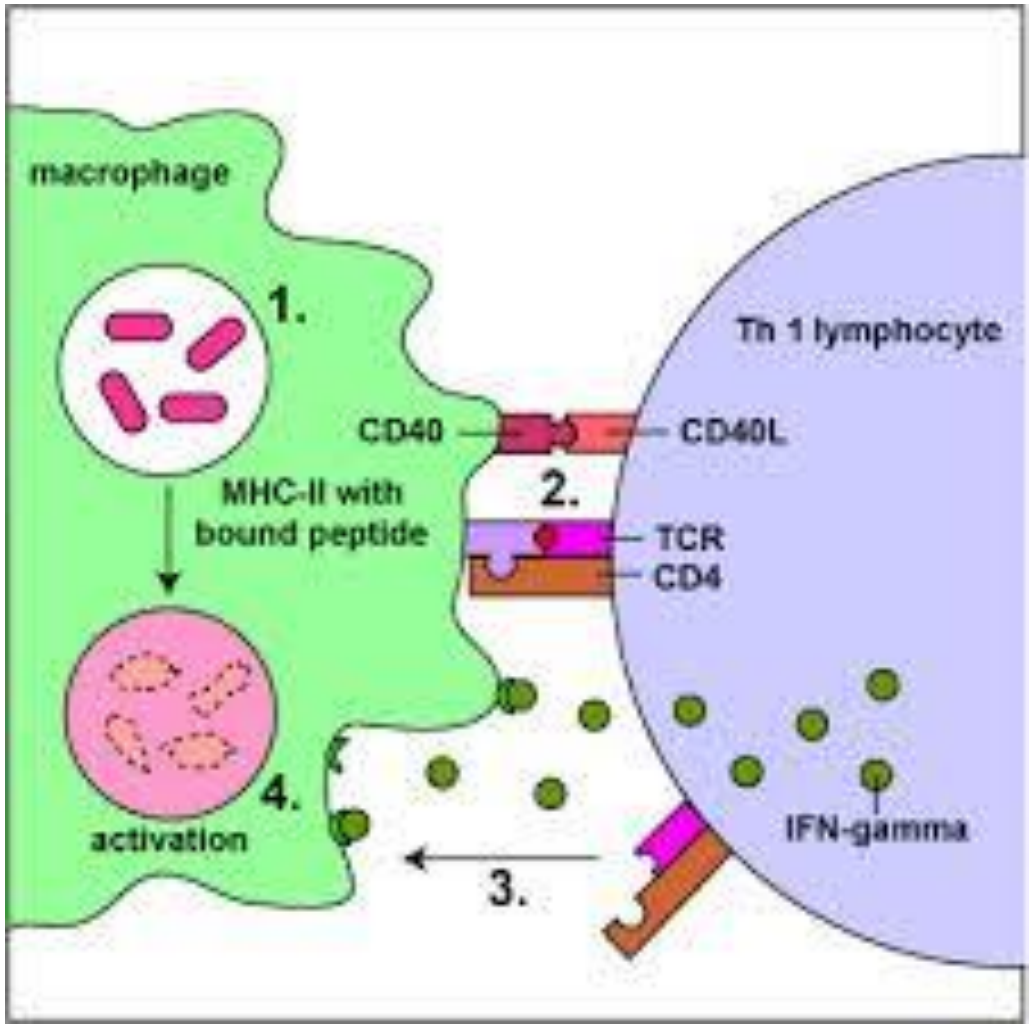
- 2 types of CD4 T cells (T helper cells)
  - Th1
  - TH2
- Type depends on
  - Type of APC
  - Cytokines

Th1 cells

- Produce several types of cytokines
- Help in activating

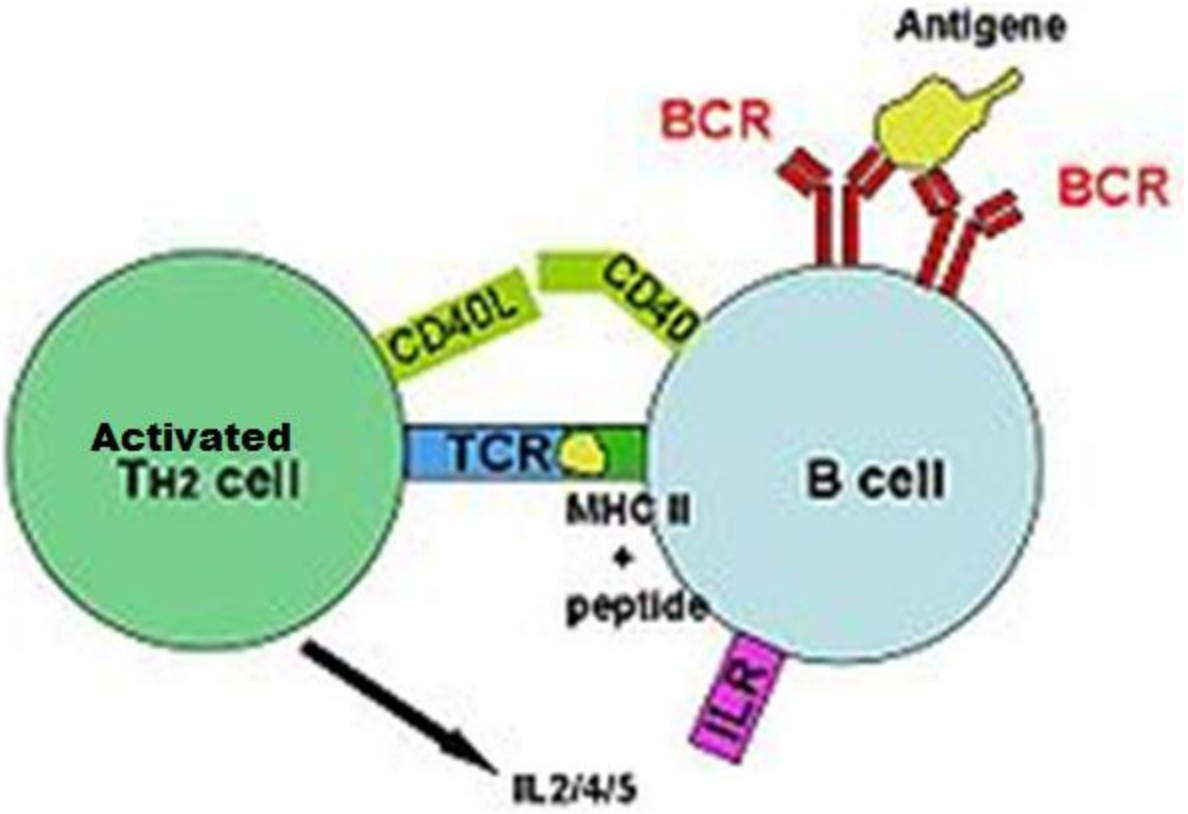
1. Macrophages – important in killing intra-vesicular m.o.
2. CD8 cells – important in killing virally infected cells
3. B cells- opsonizing Abs

Activation of Macrophage by Th_1 cells



Th2 cells

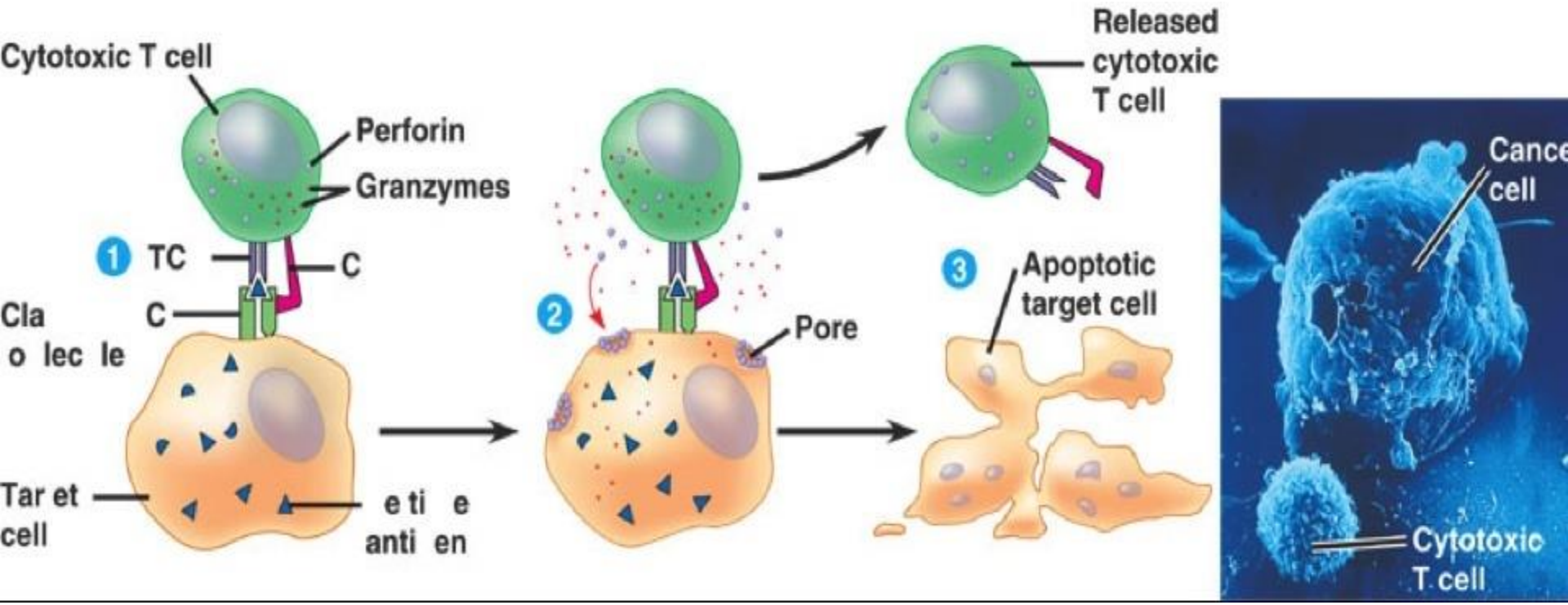
- Mainly help B cells
- Helps in
    - Class switching
    - Affinity maturation
    - Memory cells

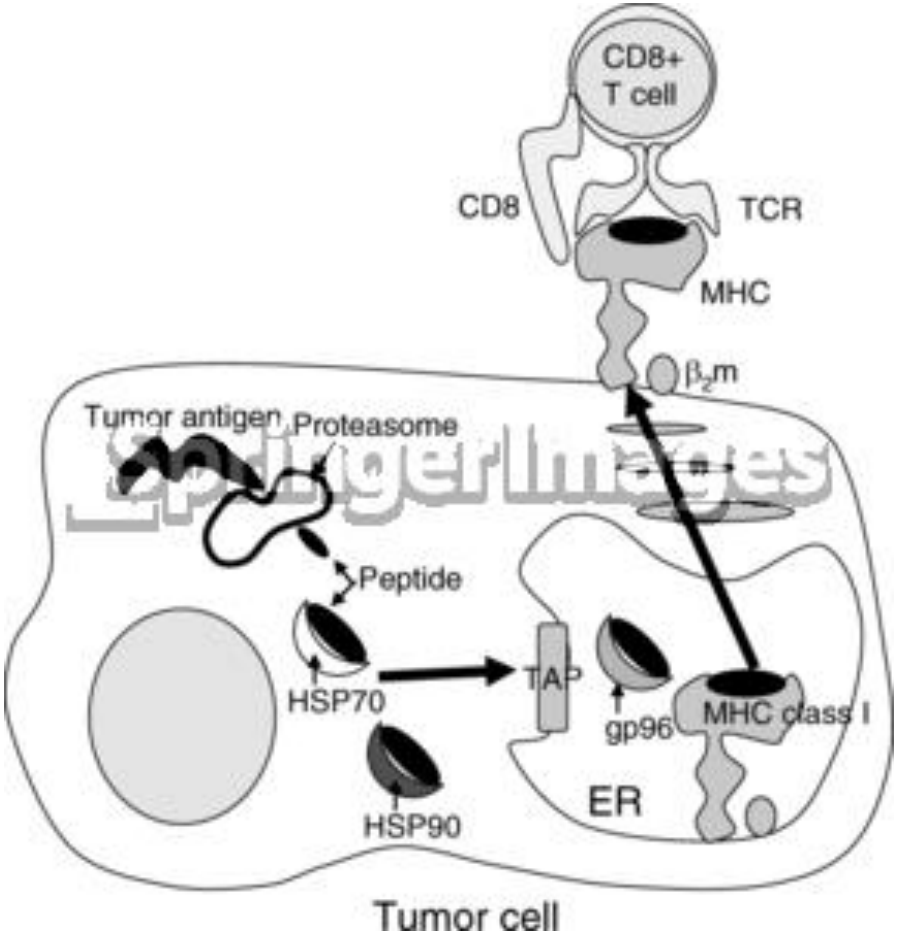

Antigene
BCR
BCR
CD40L
CD40
Activated
TH2 cell
TCR
MHC II
+
peptide
B cell
ILR
IL2/4/5

Cytotoxic T cells (Tc)

- Activated Tc cells circulate
- Can attack virally infected cells and tumor cells by identifying Ags present on cell surface of these cells in conjunction with MHC 1 molecules
- Important for killing of
  - Viral infected cells
  - Tumor cells

Cytotoxic T cells (Tc)




CD8+
T cell
CD8
TCR
MHC
β_2m
Tumor antigen
Proteasome
Peptide
HSP70
TAP
gp96
MHC class I
ER
HSP90
Tumor cell

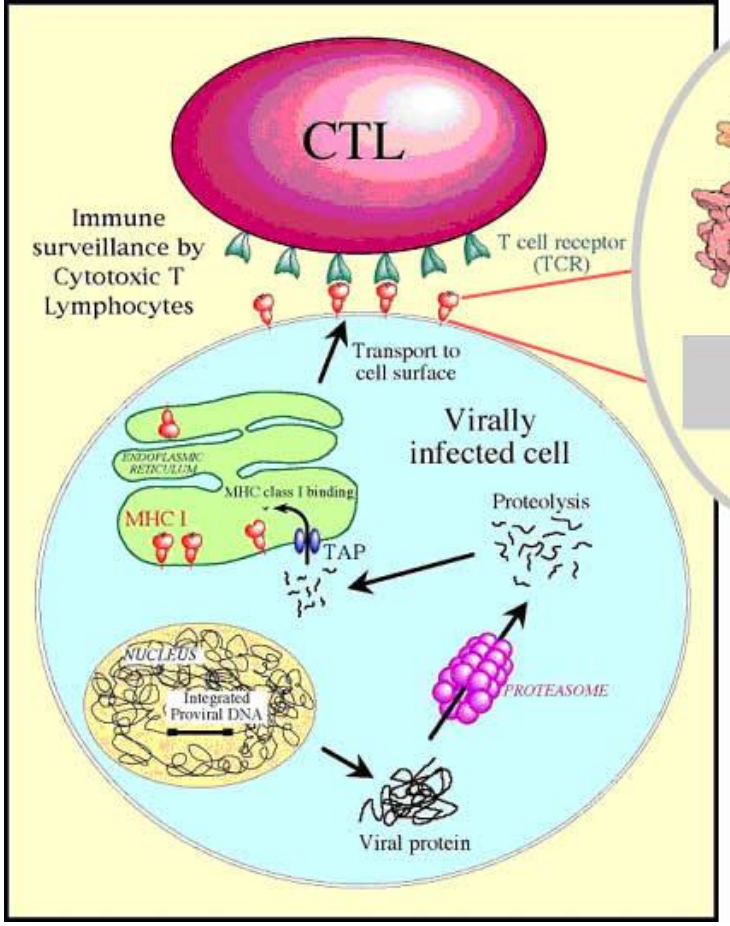
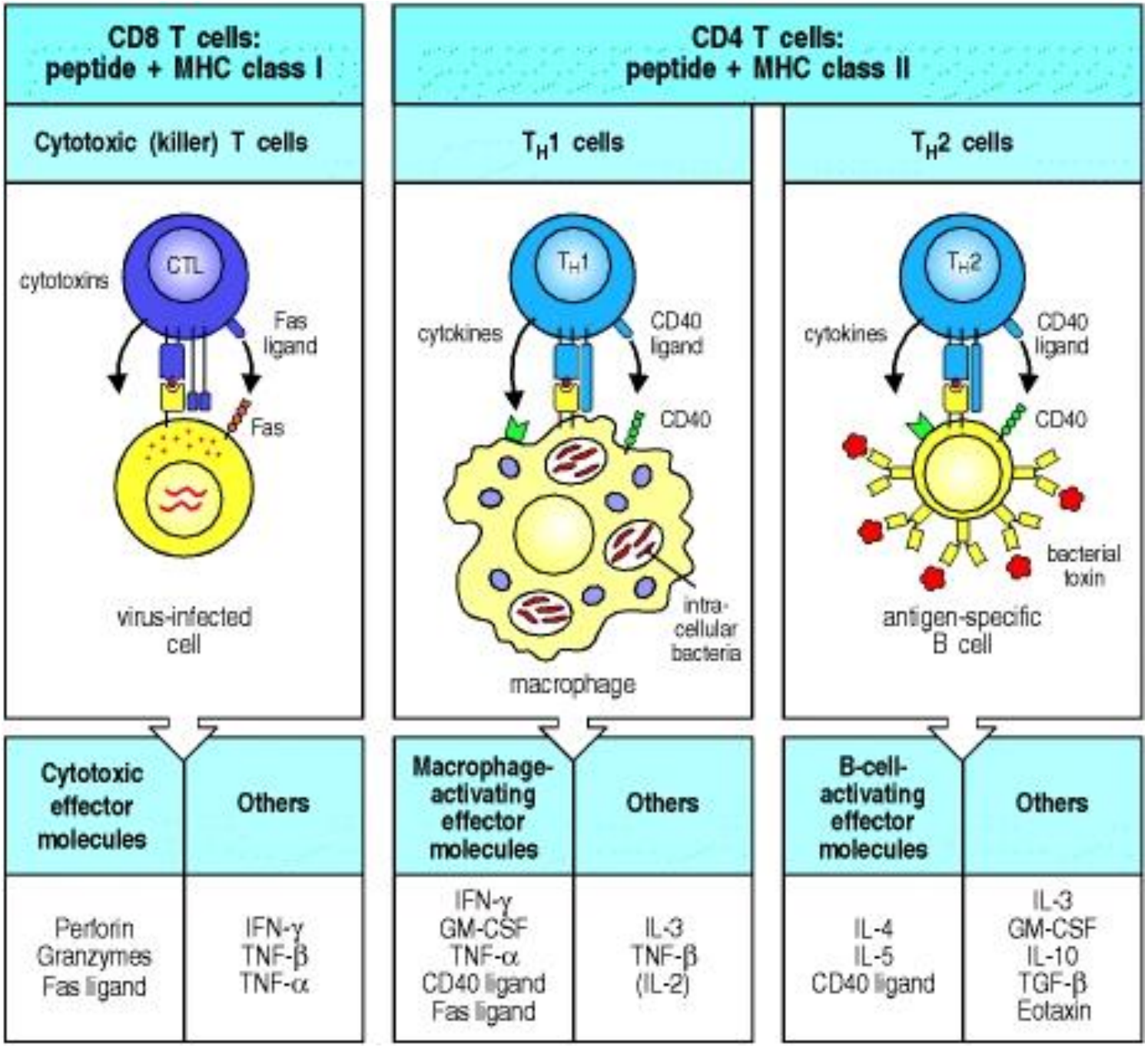

CTL
Immune surveillance by Cytotoxic T Lymphocytes
T cell receptor (TCR)
Transport to cell surface
Virally infected cell
ENDOPLASMIC RETICULUM
MHC class I binding
MHC I
TAP
Proteolysis
NUCLEUS
Integrated Proviral DNA
PROTEASOME
Viral protein

Fig. 2b


CD8 T cells:
peptide + MHC class I
CD4 T cells:
peptide + MHC class II
Cytotoxic (killer) T cells
TH1 cells
TH2 cells
cytotoxins
CTL
Fas ligand
Fas
virus-infected cell
TH1
cytokines
CD40 ligand
CD40
intra-cellular bacteria
macrophage
TH2
cytokines
CD40 ligand
CD40
bacterial toxin
antigen-specific B cell
Cytotoxic effector molecules
Others
Perforin
Granzymes
Fas ligand
IFN-γ
TNF-β
TNF-α
Macrophage-activating effector molecules
Others
IFN-γ
GM-CSF
TNF-α
CD40 ligand
Fas ligand
IL-3
TNF-β
(IL-2)
B-cell-activating effector molecules
Others
IL-4
IL-5
CD40 ligand
IL-3
GM-CSF
IL-10
TGF-β
Eotaxin

Summary

- How do T cells recognize antigens?
- How do T cells get activated?
- What are the functions of different T cell subsets?