Immunology 7

Ativation of lymphocytes

APC

Effector function of lymphocytes

Characterisation of adaptive immunity

- after 1st exposition to antigen the system reacts slowly and with delay
- even if lymphocytes were screened for self reacting TCR, they test antigens again to prevent false reactions
- to test and balance reactions is allowed by different cells that – recognise, regulate a effect reactions
- Cooperation with innate mechanisme that prepares antigens for adaptive immunity., adaptive immunity influences innate immunity reactions

Antigen processing and presentation

- Phagocyting cells screen (patrol) environment – phagocytosis, macropinocytosis
- ensymatically split engulfed proteins - degradation
- some fragments of proteins are caught and presented by *MHC II* – **presentation of antigens**
- some microbes are not phagocyted, or degraded and are processed and presented by *MHC I* molecules

i.c.pathogens

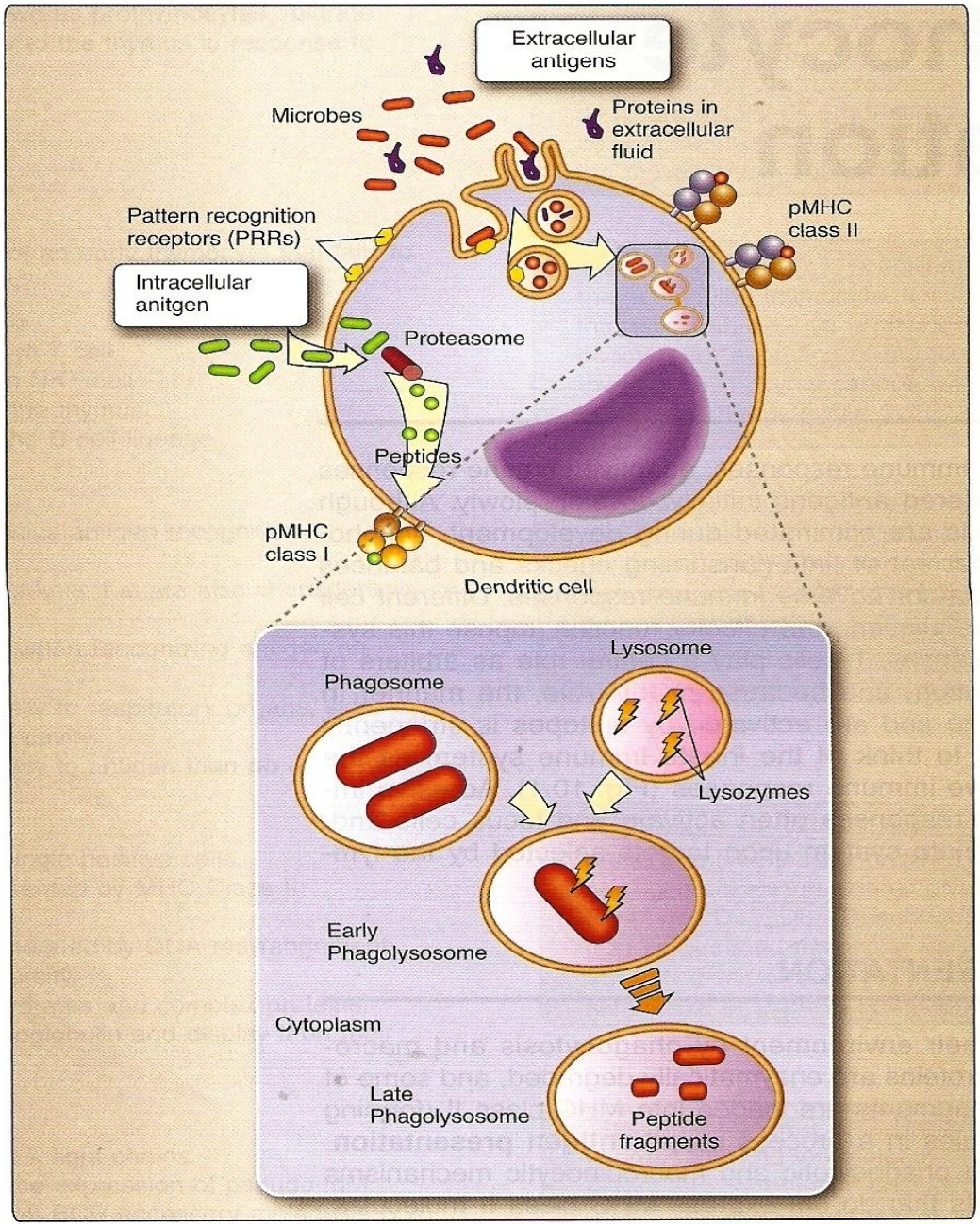
degraded

MHC I

extracelular

processed

MHC II

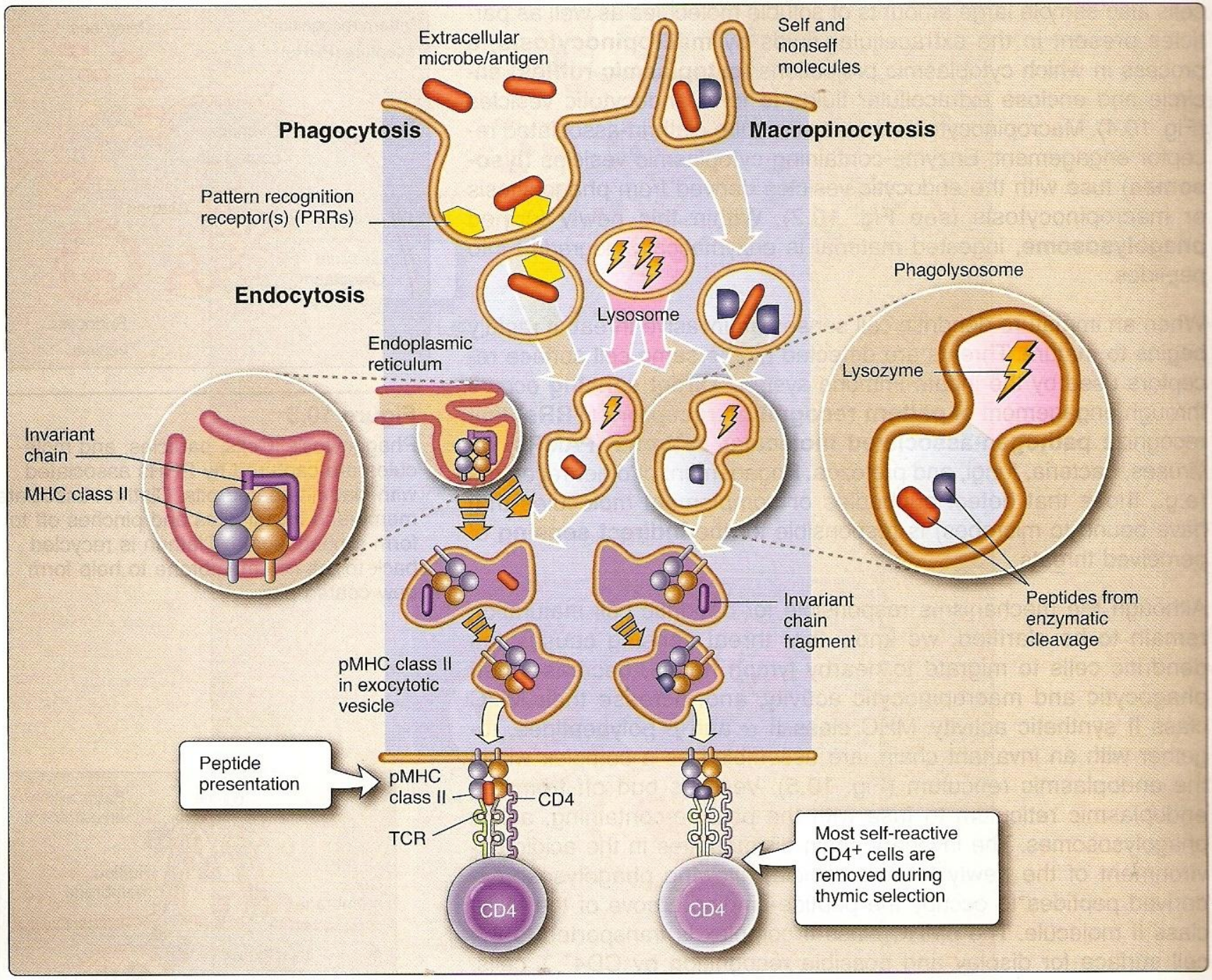


Presentation via MHC II

- *Dendritic cells* – in sites of gate of entry of antigens
- Not mature cell engulf free and bound molecules / antigens – phagocytosis and degradation
- Recognition via PRR receptors – directly (non specific) or indirectly via antibodies(specific)

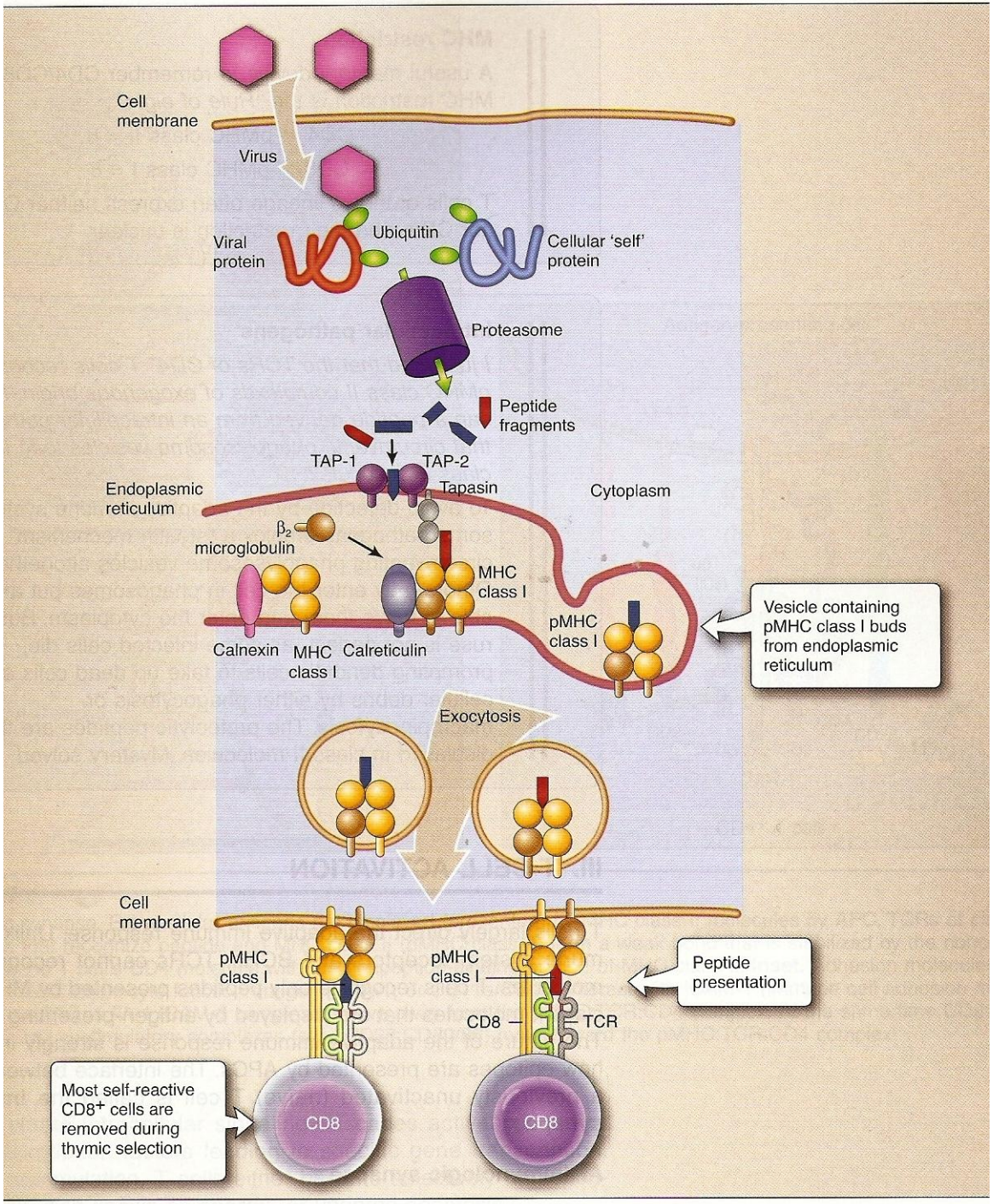
Recognition of threat leads to *maturation of dendritic cells*

- migration closly to lymphatic nodes
- decrease phagocyting activity
- increase synthesis of MHC II
- transport of MHC II with bound peptid = pMHC II to the surface of dendritic cell and presentation of antigen to CD4


Extracellular microbe/antigen
Self and nonself molecules
Phagocytosis
Macropinocytosis
Pattern recognition receptor(s) (PRRs)
Endocytosis
Lysosome
Phagolysosome
Endoplasmic reticulum
Lysozyme
Invariant chain
MHC class II
Invariant chain fragment
Peptides from enzymatic cleavage
pMHC class II in exocytotic vesicle
Peptide presentation
pMHC class II
CD4
TCR
CD4
CD4
Most self-reactive CD4+ cells are removed during thymic selection

Presentation via MHC I

- Not all antigens enter the cell by phagocytosis.
- Some are bound on the surface of target cells that infects
- The cell degrades them by proteasomes and binds them to MHC I – to produce pMHC I, that is exposed and cooperates with CD8

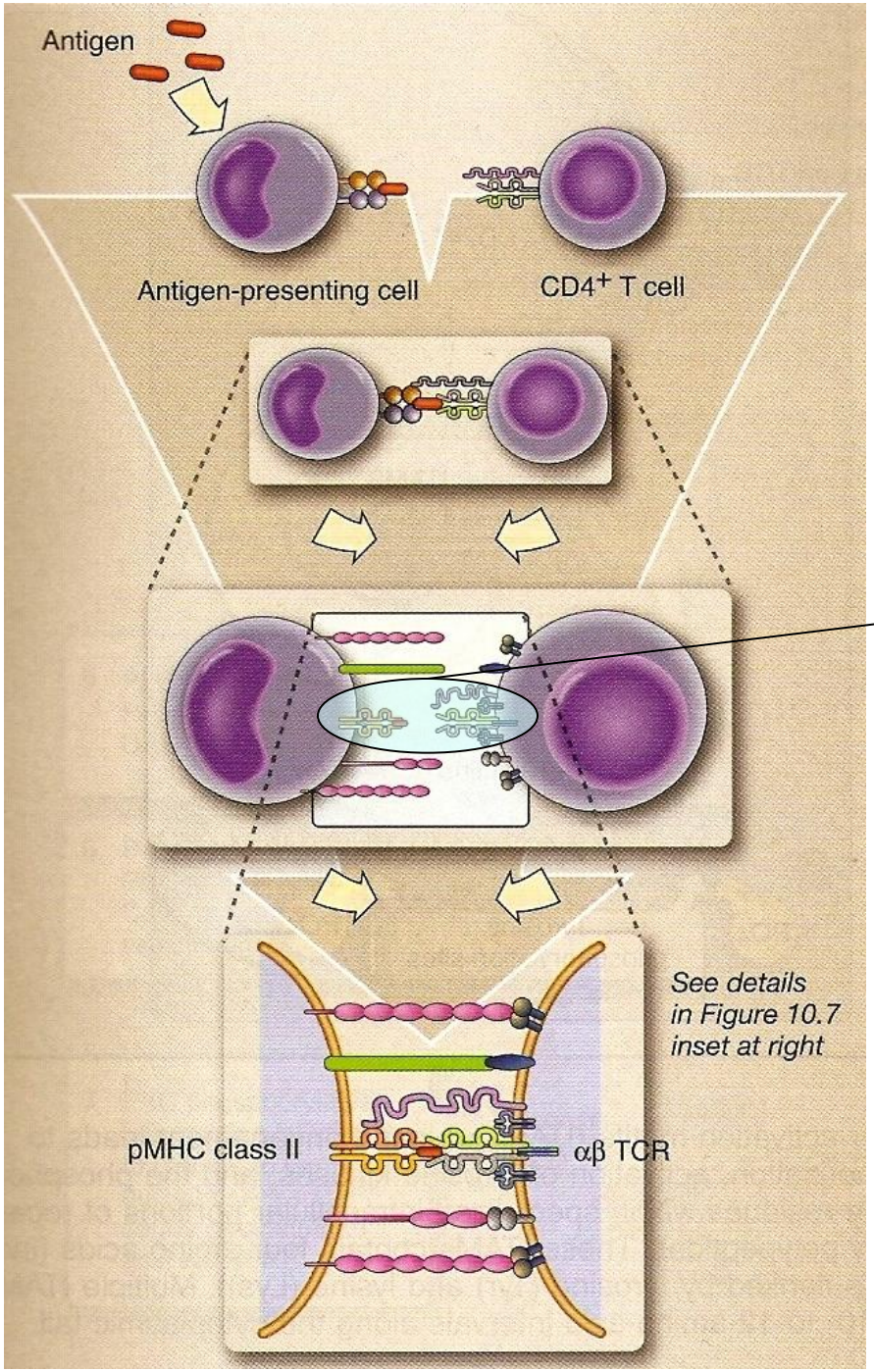

Cell membrane
Virus
Viral protein
Ubiquitin
Cellular 'self' protein
Proteasome
Peptide fragments
TAP-1
TAP-2
Endoplasmic reticulum
Tapasin
Cytoplasm
β2 microglobulin
MHC class I
Calnexin
MHC class I
Calreticulin
pMHC class I
Vesicle containing pMHC class I buds from endoplasmic reticulum
Exocytosis
Cell membrane
pMHC class I
pMHC class I
Peptide presentation
CD8
TCR
Most self-reactive CD8+ cells are removed during thymic selection
CD8
CD8

Activation of T lymphocytes
a) immunological synapsis

- T lymphocytes – direct reactions of adaptive immunity
- TCR does not recognise free molecules
- recognise only peptids presented via MHC I or MHC II
- Specific immunity is influenced by the way how the epitopes are presented by Antigen Presenting Cells

Immunological synapsis:

- TCR recognises pMHC
- pMHC + TCR of CD4 or CD8 – stabilisation is done by constant part of TCR =
  TCR:pMHC:CD4(8) = 1st signal via CD3 to Tcell
- 2nd signal – c**ostimulating molecules**
- 1st and 2nd signal = transmission of signal and i.c. activation of transcription of genes for production of cytokines
- Without costimulation the lymphocytes will be selectively non-respondint **(anergy**) or will be submitted for apapotosis

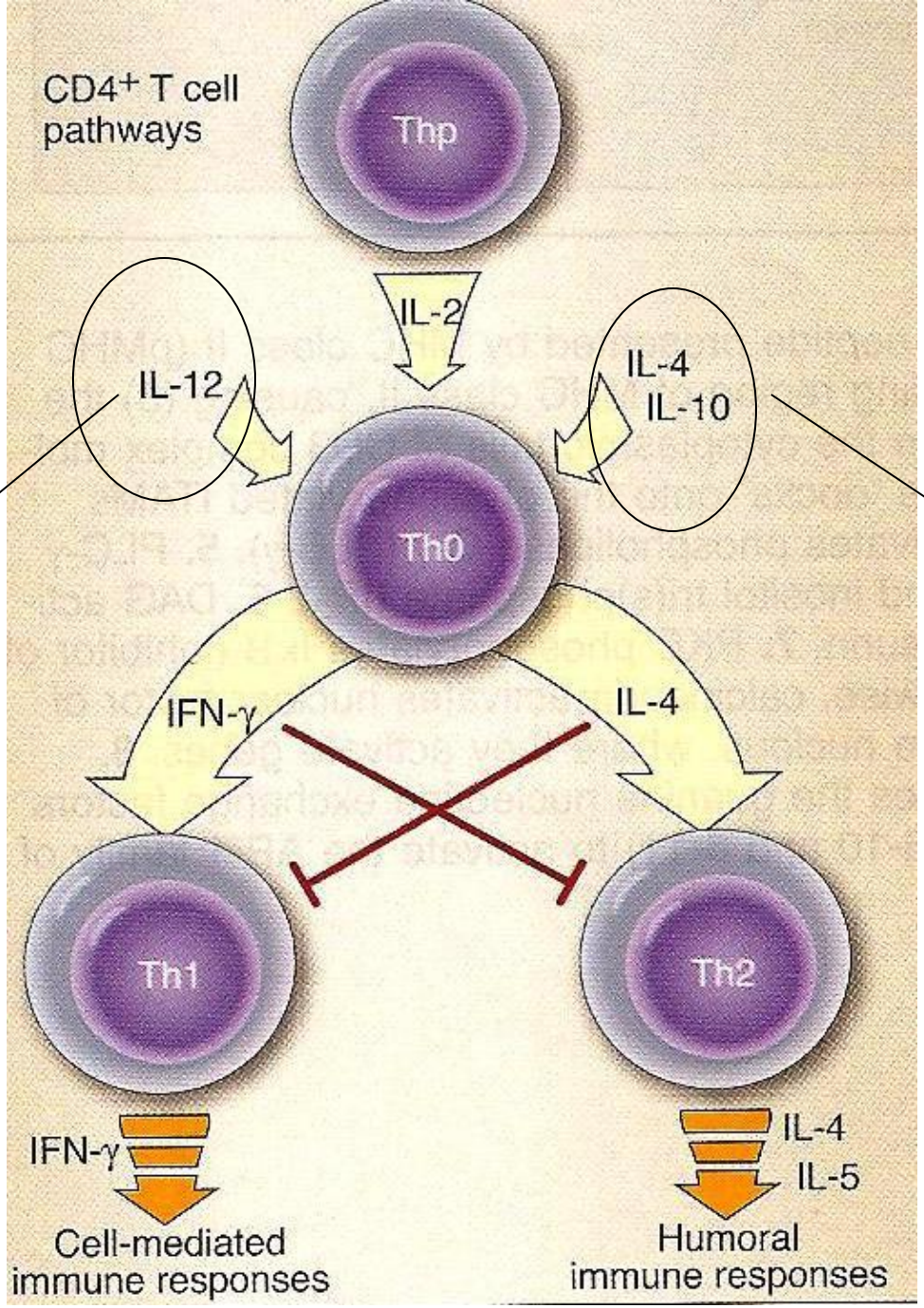


immunological synapsis

CD4 maturation

- T cell + antigen = **priming.**
- Primed CD4 **= T helper**
- **Thp** are precursors of Th **=** stimulated and secretes cytokines
- **Th0 –** developes further by one of 2 functional ways accordinig to the character of contact with APC
- **Th1:** microbial LPS + cytokine from APC(IL12) = activation of phagocytosis and CTL
- **Th2 -** IL 4 leads to Th0 development to Th2 that stimulates B ly to change to plasmatic cells and memory cells

- APC


CD4+ T cell pathways
Thp
IL-2
IL-12
IL-4
IL-10
Th0
IFN-γ
IL-4
Th1
Th2
IFN-γ
IL-4
IL-5
Cell-mediated immune responses
Humoral immune responses

CD8 - maturation

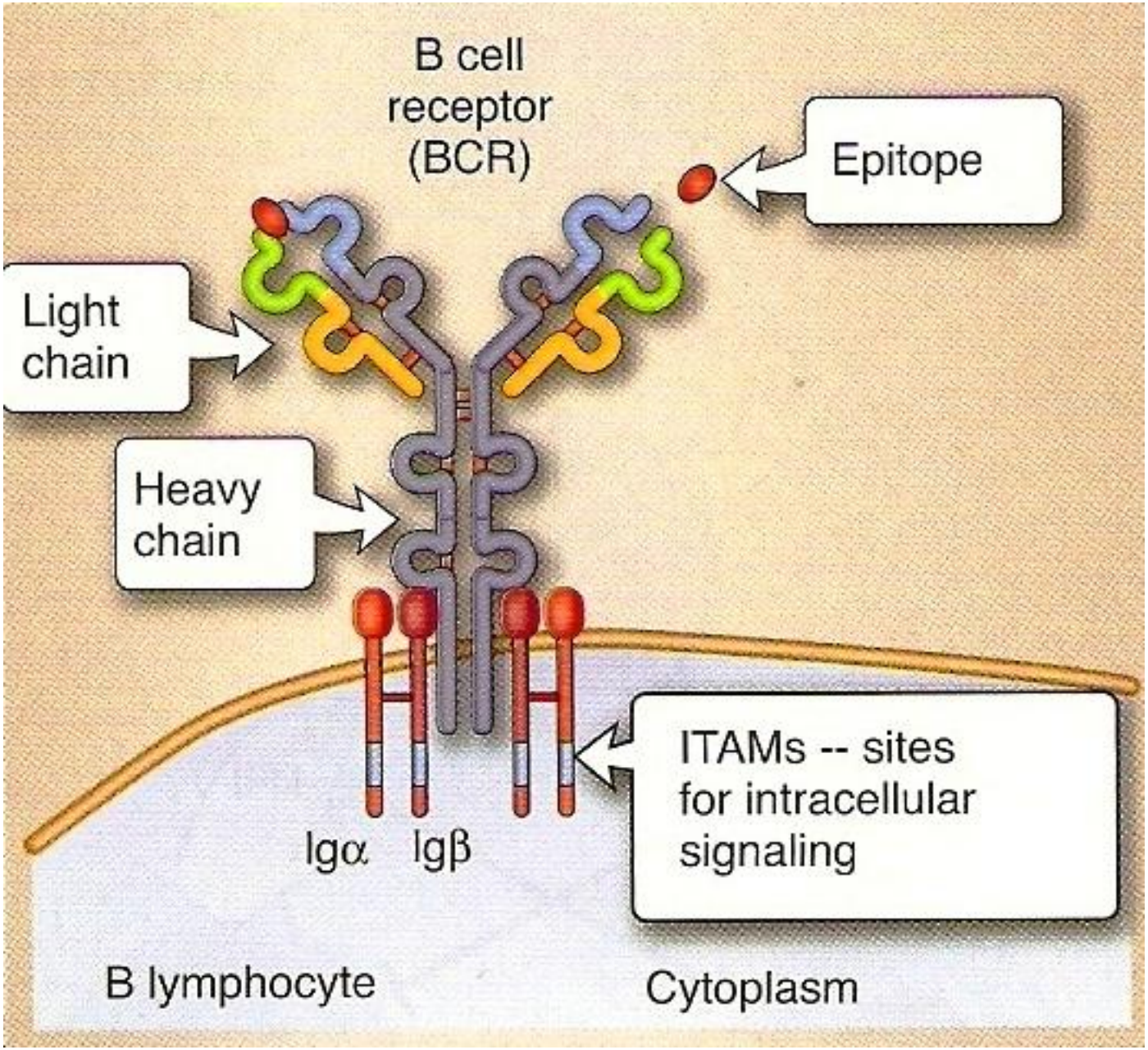
- Recognition of pMHC I on the surface of (APC, infected or other) cells by CD8 – formation of **IL-2 receptor**
- IL 2 is produced by CD4, that communicated with the same antigen in MHC II on APC (phagocyted fragments of microbe body)
- IL 2 **stimulates CD8** to differenciate to CTL – cytotoxic T cells – containing cytolytical granules (perforins and granzymes), that kill cell with specific pMHC I

Memory cells

- TCR + pMHC II (**first signal**)
- CD 28 on Tly + APC (CD80/86) **2nd signal** that leads to
  - production of IL 2 by CD4 Tly
  - to formation of IL 2 receptor on CD8 and
  - to proliferation (negative stimulation – selfregulation to stop if prolifer too much)
- Some CD4 become memory cells – have more CD 28 – react much faster to APC and migrate to the place of infection (do not stay at LNodes)

Activation of B cells

- BCR recognise and process free and bound antigens
- BCR has the shape of monomer of IgD and/or IgM
- Cytoplasmatic part of Ig – play the role of CD3 of Tcells
- Binding of epitop on Ig leads to transmission of signal and to transsduction and transcription and activation of genes, endocytosis, ensymatic degradation amd exposition of fragments by pMHC II and to production of costimulationg molecules
- B cells can act as APC


B cell
receptor
(BCR)
Epitope
Light
chain
Heavy
chain
Igα
Igβ
ITAMs -- sites
for intracellular
signaling
B lymphocyte
Cytoplasm

T independent antigens
T independent activation

TI activates B lymphocytes without T cell

- TI-1 antigens – polyclonal activators of proliferation and Ig production = **mitogens of B cells**
- T1-2 antigens – contain repeated epitopes (polysacharides), activate mature B cells (transmission of signals) – in minimal quantity activates also T cells

2nd signal – other bindings of B cell – coreceptors on B cells (C3b, CD 21= CR2, CR1...)

B cell
+ TI antigen

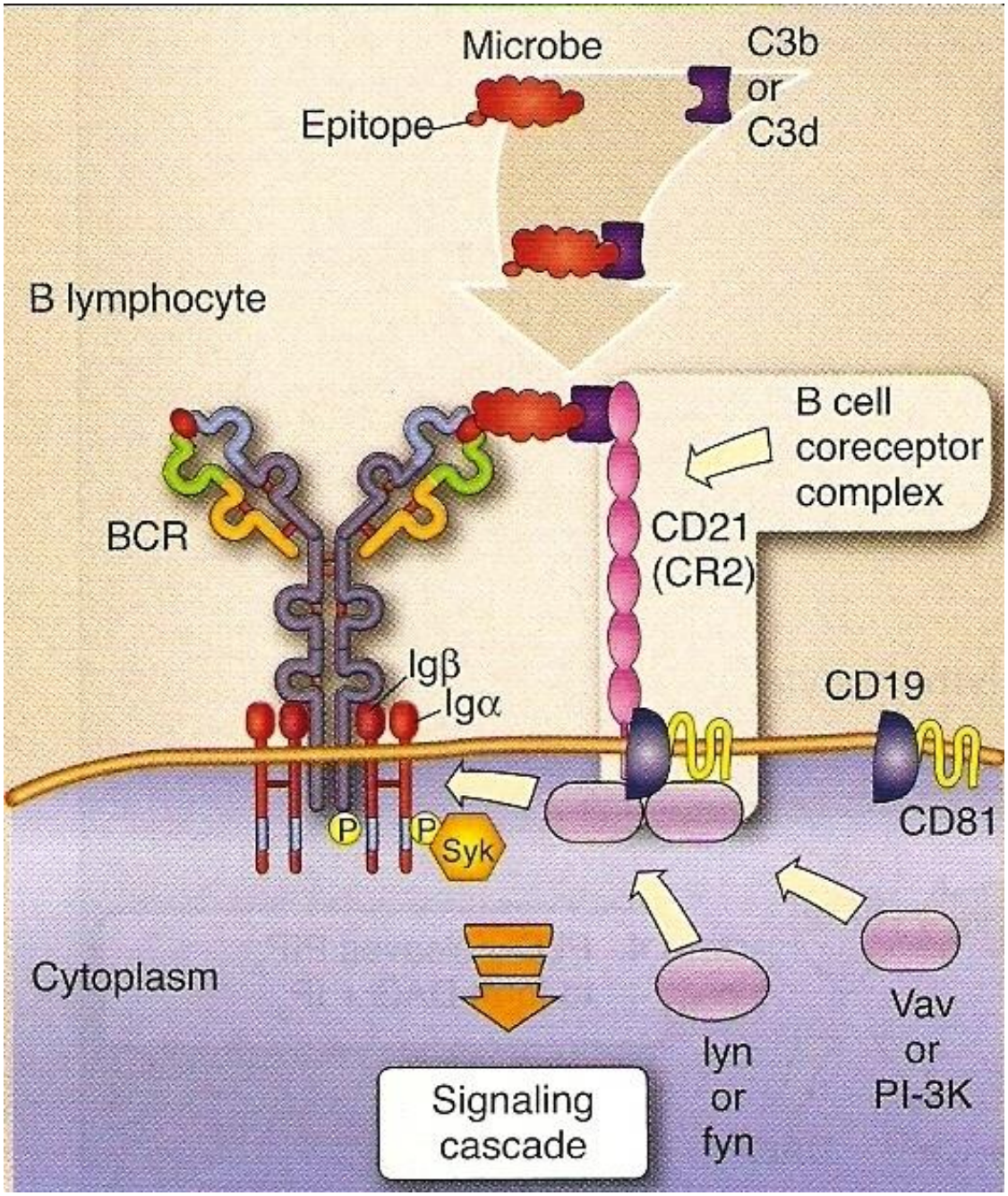
BCR

siganlising cascade

transformation to plasmatic cells

production of IgM

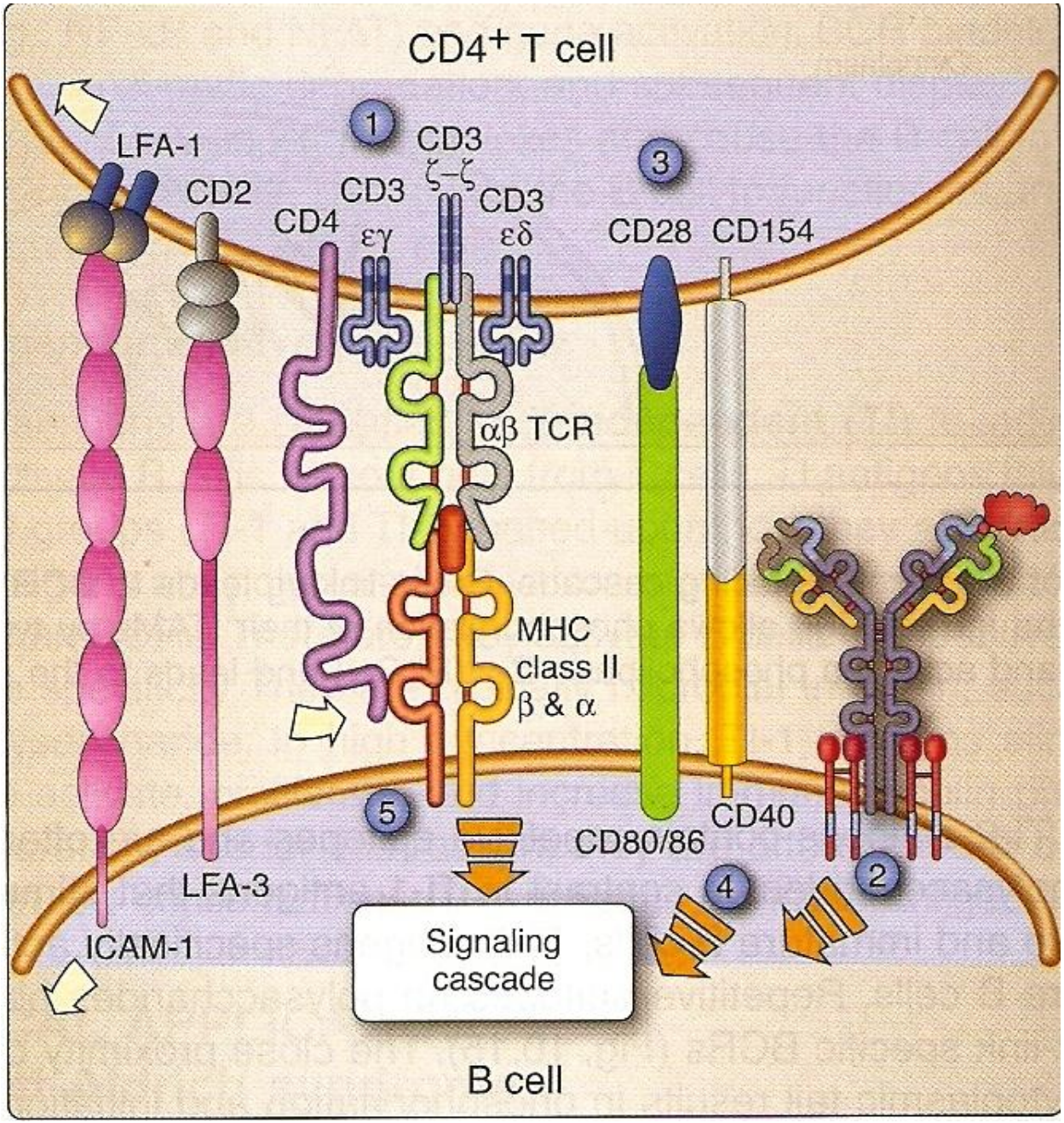
+ correceptors on B cell



T dependent antigens and activation

- Antigens bound via MHC II (on APC or B cells) – first signal
- 2nd signal to B lymphocyte is given by CD4 helper cell
- MHC II + TCR CD4 cells = production of cytokines (IL4) and formation of IL4 receptore on B cells – proliferation of B cells, differenciation to plasmatic cell

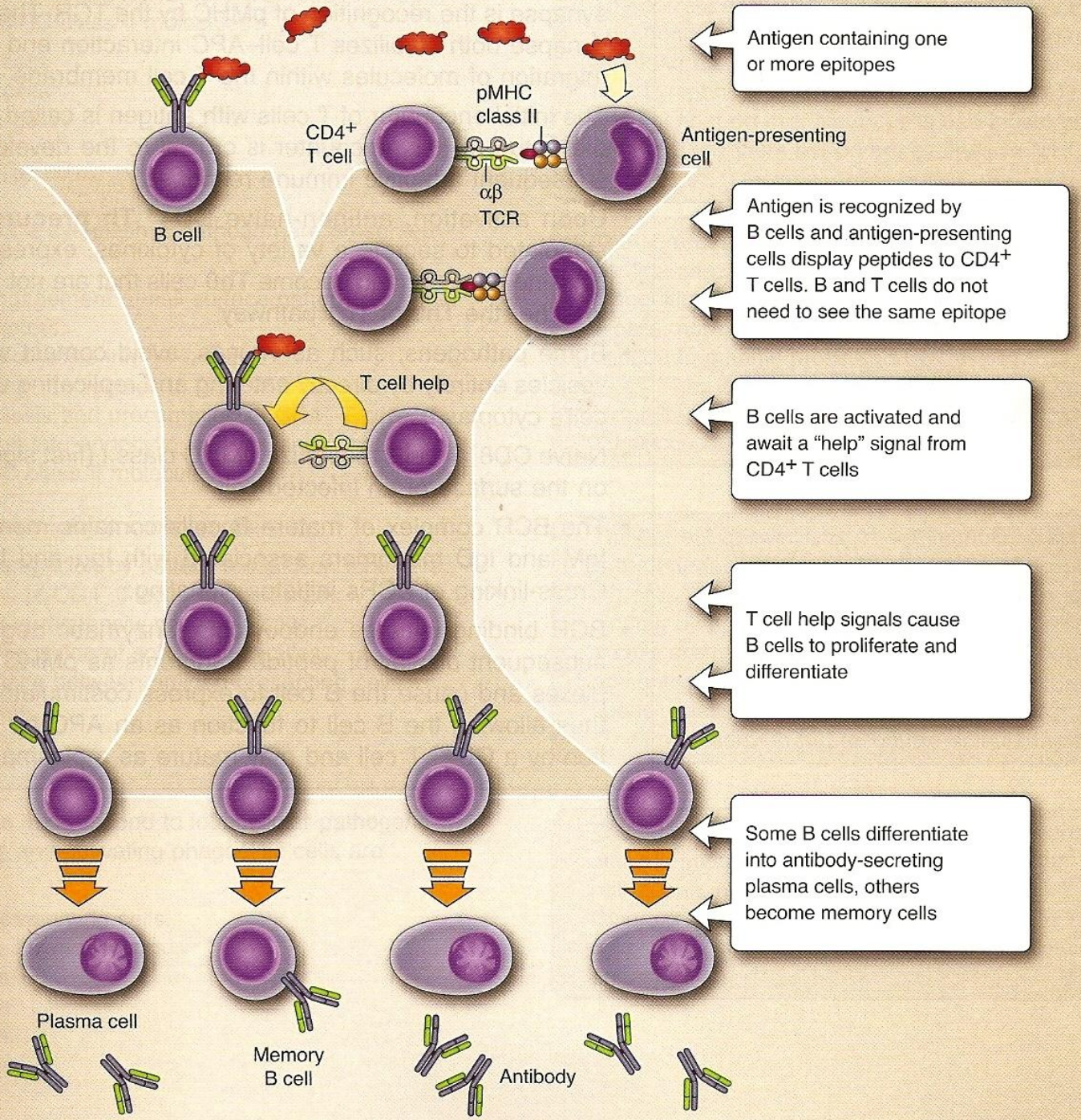
B cell (APC)
TD antigen
CD4



Plasmatic cells and memory B cells

- Plasmatic cells – terminally differenciated B cells
- the same epitope on BCR as on secreted Ig

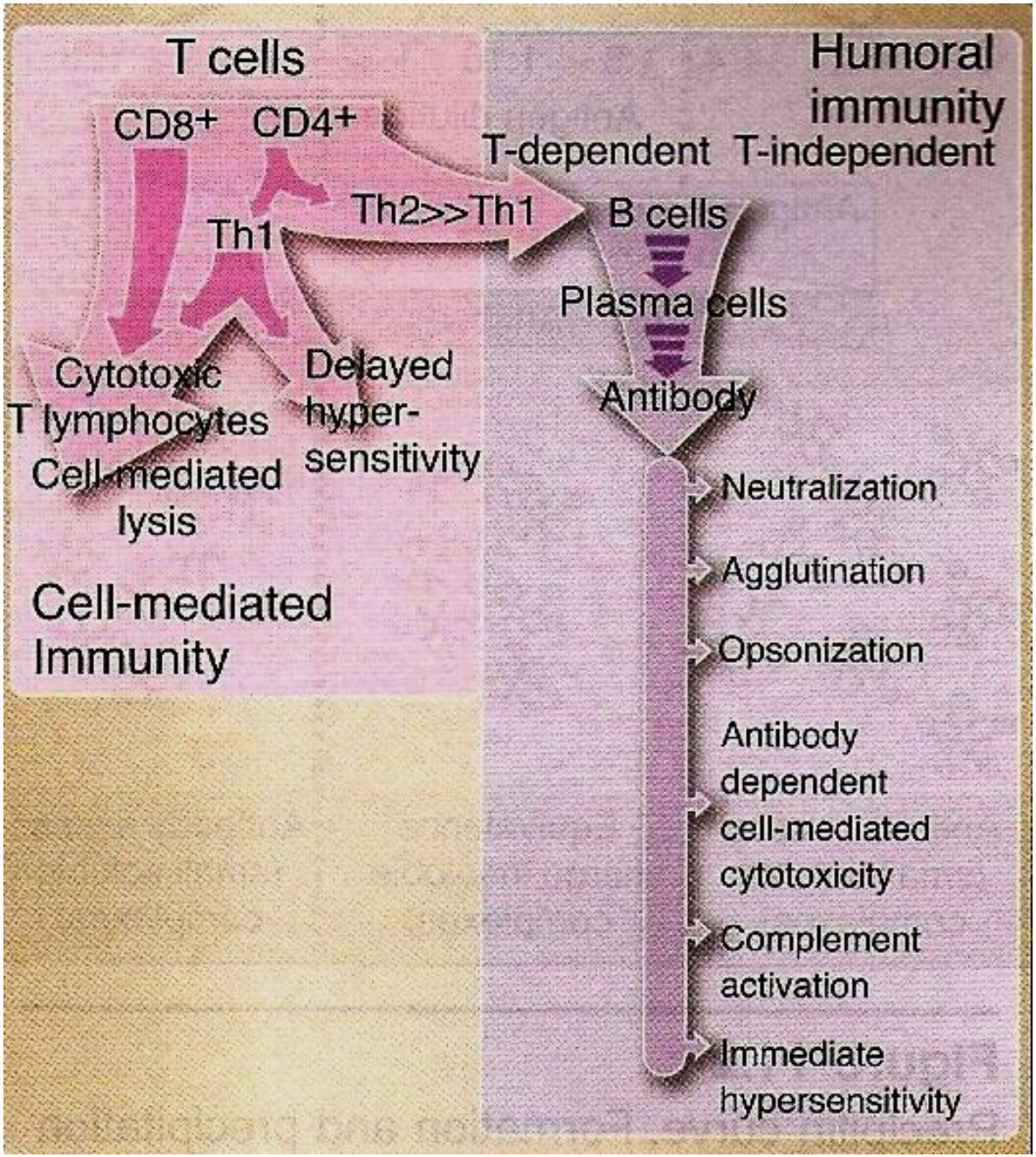
- Not all B cells differentiate to plasma cells
- Some stay for B memory cells


Antigen containing one or more epitopes
pMHC class II
CD4+ T cell
Antigen-presenting cell
αβ TCR
B cell
Antigen is recognized by B cells and antigen-presenting cells display peptides to CD4+ T cells. B and T cells do not need to see the same epitope
T cell help
B cells are activated and await a "help" signal from CD4+ T cells
T cell help signals cause B cells to proliferate and differentiate
Some B cells differentiate into antibody-secreting plasma cells, others become memory cells
Plasma cell
Memory B cell
Antibody

Effector function of lymphocytes

- Innate immunity – cell and humoral
- Adaptive immunity – cell and humoral

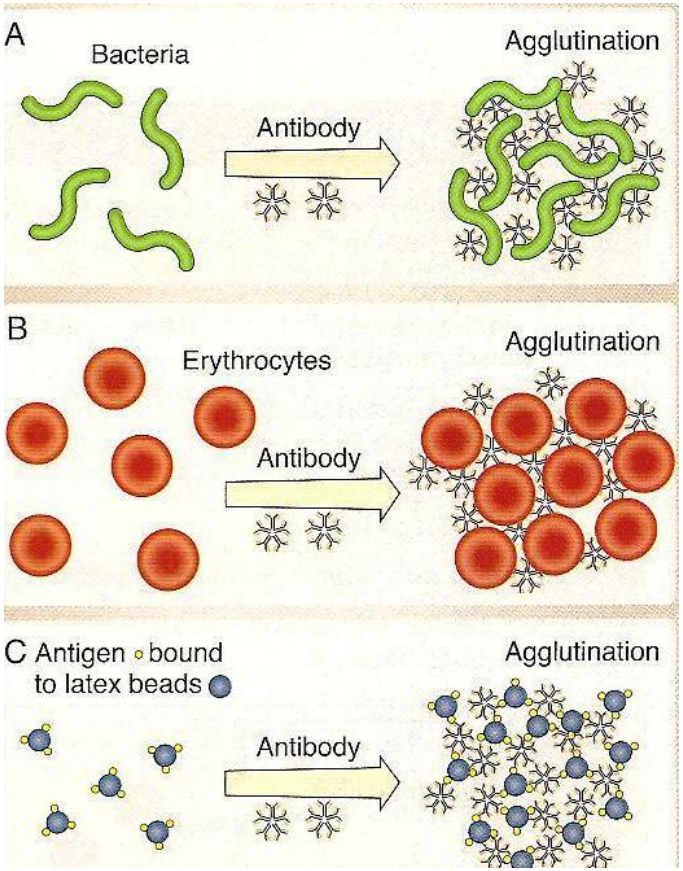
- humoral – free molecules in liquid (humors = liquid) – antibodies...
- cellulas – T cells


T cells
CD8+ CD4+
Th1
Th2>>Th1
Cytotoxic T lymphocytes
Cell-mediated lysis
Delayed hyper-sensitivity
Cell-mediated Immunity
Humoral immunity
T-dependent
T-independent
B cells
Plasma cells
Antibody
Neutralization
Agglutination
Opsonization
Antibody dependent cell-mediated cytotoxicity
Complement activation
Immediate hypersensitivity

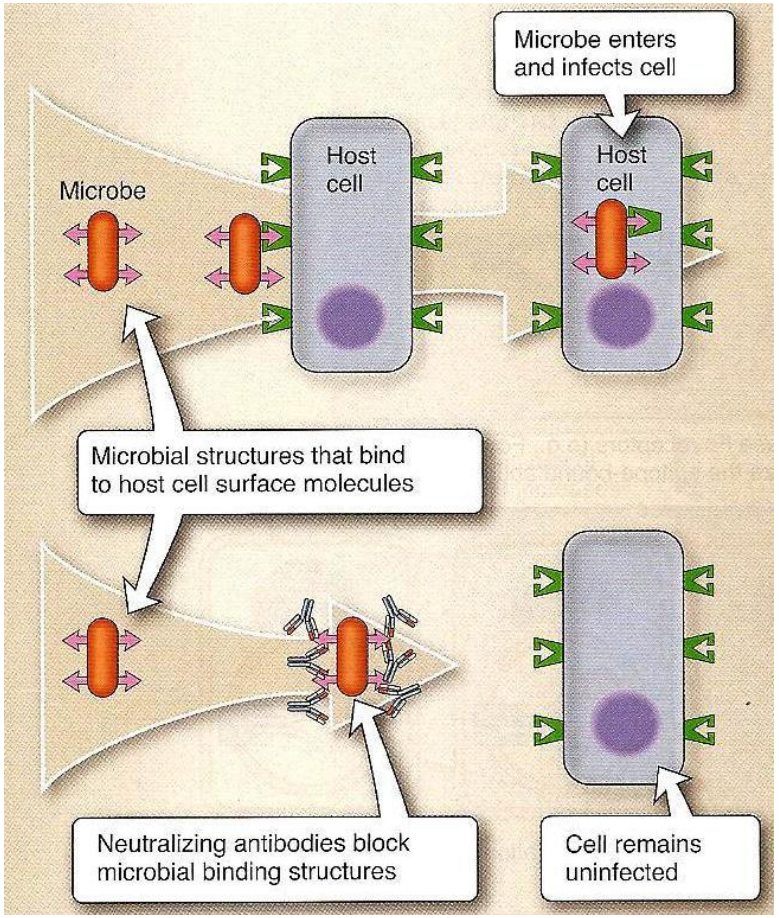
Humoral immunity - adaptive

- Reaction of antigen and antibodyg
- Agglutination, neutralisation, opsonisation
- ADCC – antibody dependent cell cytotoxicity – (NK cells, eosinofils) – antibodies bound on microbes bind by Fc fragment on cytolytical cell (eosinofils), that will then produce the lysis of microbe
- Activation of complement
- Hypersensitivity of the Ist type

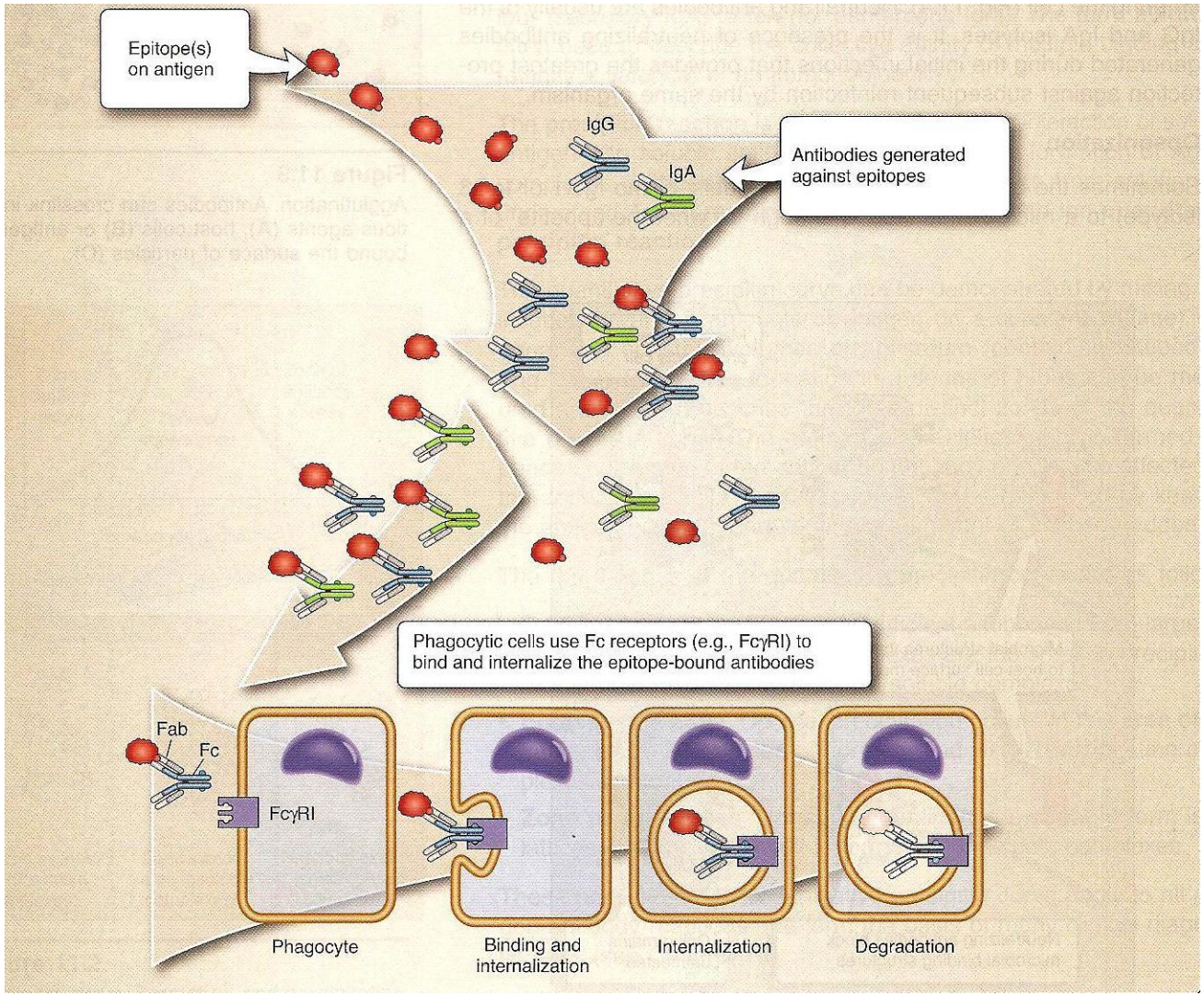
agglutination

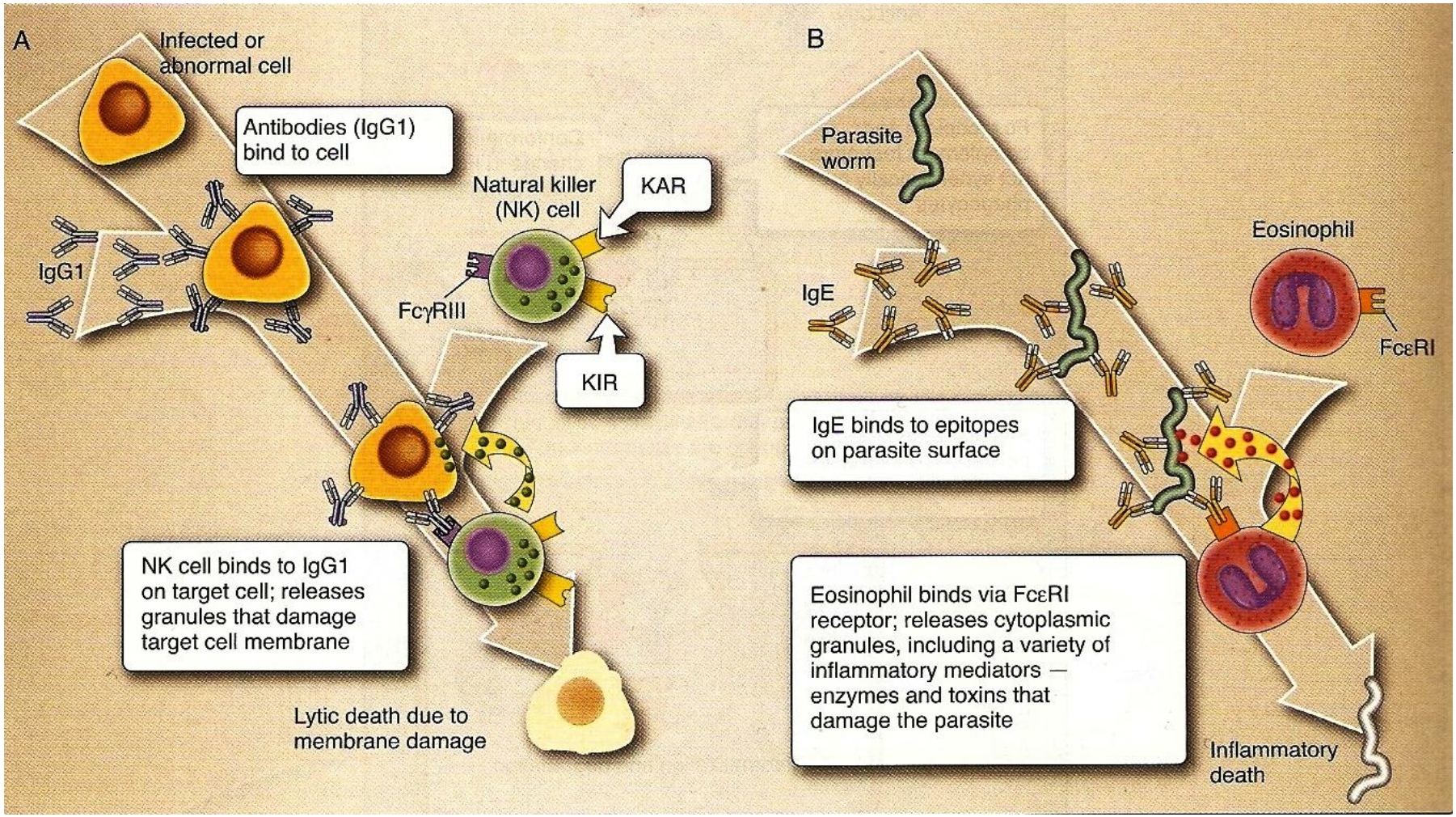


neutralisation



Opsonisation




A
Infected or abnormal cell
Antibodies (IgG1) bind to cell
IgG1
Natural killer (NK) cell
KAR
FcγRIII
KIR
NK cell binds to IgG1 on target cell; releases granules that damage target cell membrane
Lytic death due to membrane damage
B
Parasite worm
IgE
Eosinophil
FcεRI
IgE binds to epitopes on parasite surface
Eosinophil binds via FcεRI receptor; releases cytoplasmic granules, including a variety of inflammatory mediators — enzymes and toxins that damage the parasite
Inflammatory death

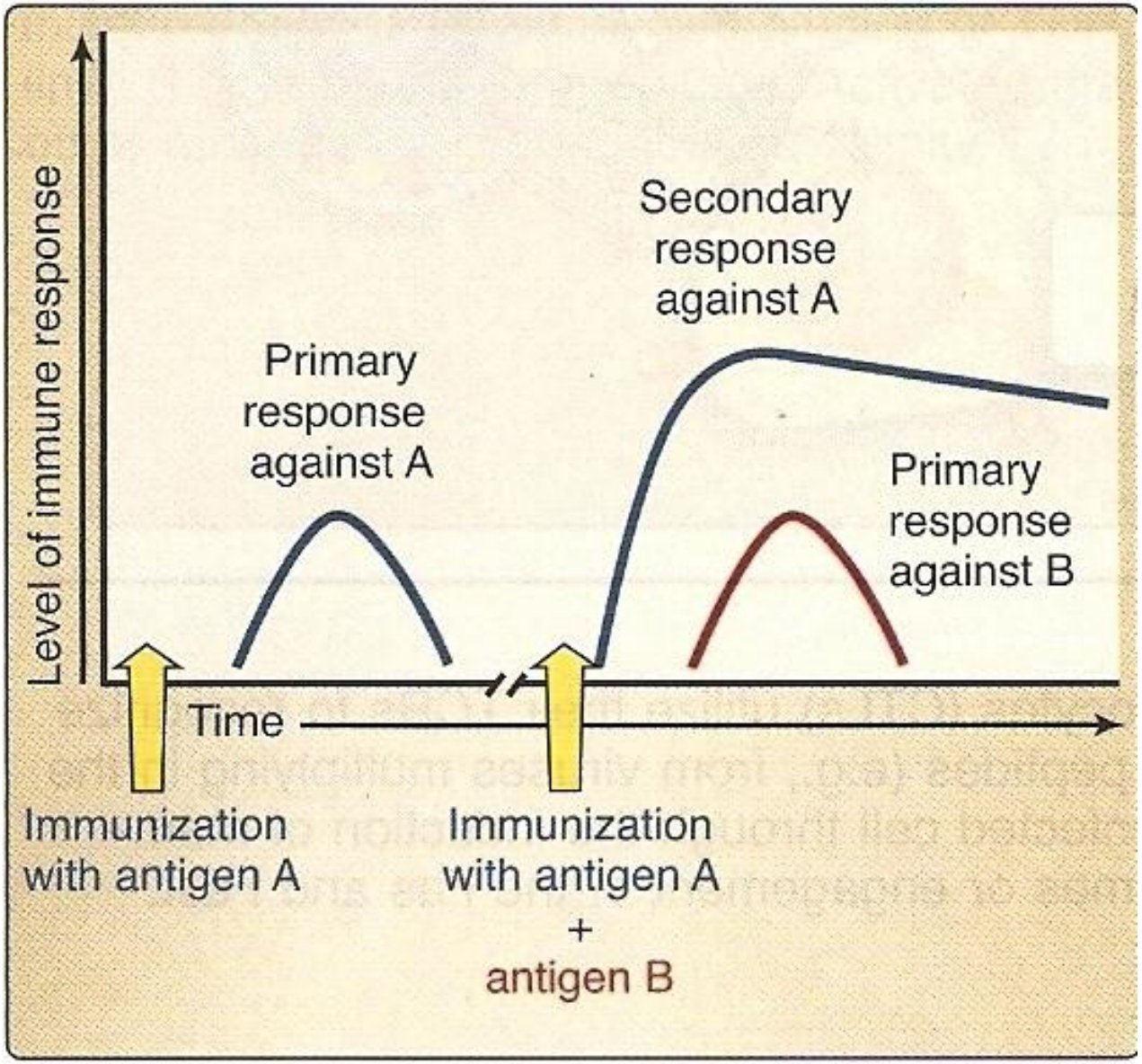
T cell mediated immunity

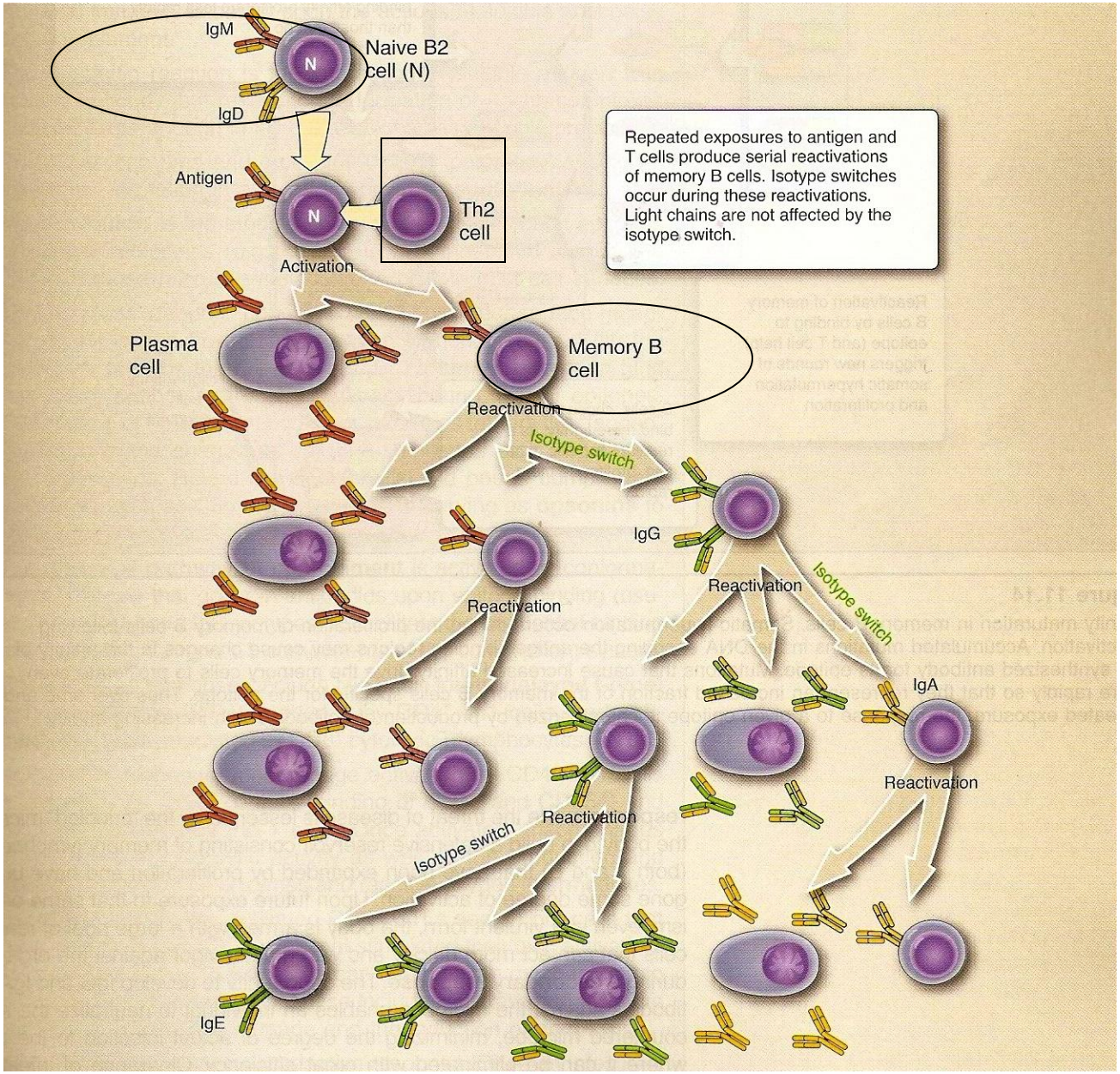
2 forms to eliminate microbes (antigen)

- DTH –delayed type of hypersensitivity – via CD4 Th1 (activation of macrophages via Th1) *Mycobycterium tbc*
- cell mediated lysis via CD8 Tly - CTL - lysis of infected, changed or foreing cells

Immunological memory

- primary answer to ag
- secondary answer by stimulation of memory cells – faster,isotype switch
- Vaccination


Level of immune response
Secondary response against A
Primary response against A
Primary response against B
Time
Immunization with antigen A
Immunization with antigen A + antigen B


IgM
N
Naive B2 cell (N)
IgD
Antigen
N
Th2 cell
Activation
Repeated exposures to antigen and T cells produce serial reactivations of memory B cells. Isotype switches occur during these reactivations. Light chains are not affected by the isotype switch.
Plasma cell
Memory B cell
Reactivation
Isotype switch
IgG
Reactivation
Isotype switch
Reactivation
IgA
Reactivation
Isotype switch
Reactivation
IgE