THE UNIVERSITY OF MELBOURNE

Faculty of Veterinary and Agricultural Sciences

Functions of the Adaptive Immune System

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VETS30015 / VETS90121

Intended learning outcomes

- Describe the role of the adaptive immune system
- Describe how B lymphocytes and T lymphocytes both recognise and respond to pathogens
- Explain how the adaptive and innate immune systems work in conjunction to eliminate infections

Summary so far

There are three types of host resistance to microbial infection:

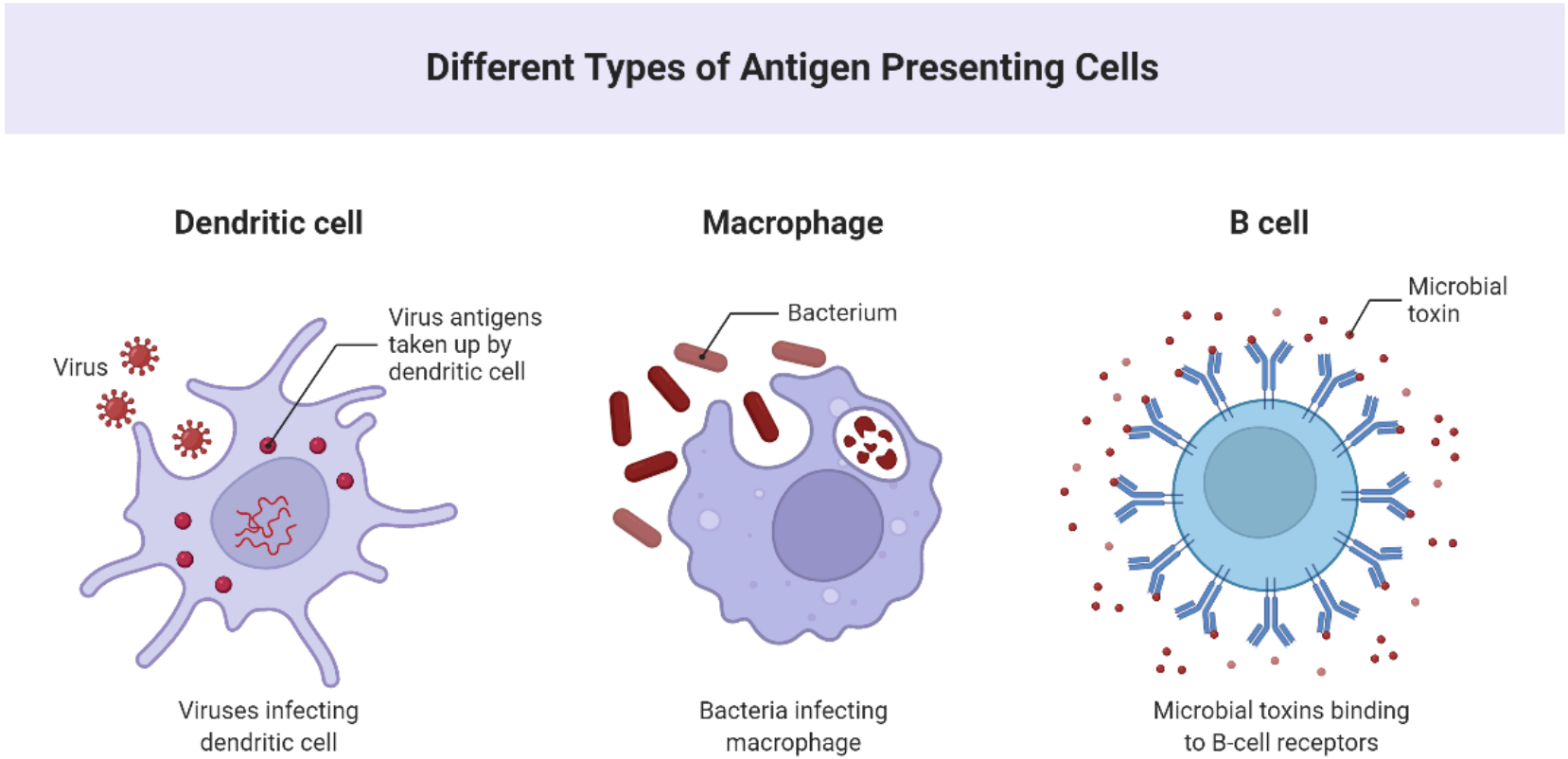
1. Physical barriers
   - Skin barrier & mucous membranes
   - Normal bacterial flora

2. Innate: *non-specific immunity*
   - Circulating messengers (complement, cytokines, etc)
   - Phagocytes & Inflammation

3. Adaptive – *specific immunity*
   - Target specific defence against microbial antigens

Antigen recognition – innate → adaptive immune system

- Antigen presenting cells

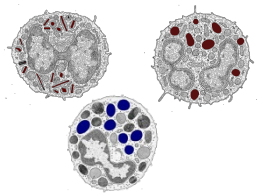


Concept of “self” & “non-self”

- Innate system relies on a broad defence against “non-self” invaders
- BUT – it is energetically expensive & the innate system can be easily avoided by clever rapidly evolving pathogens
  - Protective surfaces e.g. capsules made of slime
  - Chemical mimicry pretending to be “host”
  - Ability to survive intracellularly

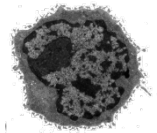
Leukocytes – white blood cells

- Polymorphonuclear cells - involved in inflammation
  - Non-discriminating self destructing suicide missions
  - Release damaging enzymes that destroy invaders



- APCs, macrophages & dendritic cells
  - Phagocytose, process & present Ag to T cells

- Lymphocytes
  - T cells - killers/helpers (T cell receptors on cell surface interact with antigen presented on another cell surface)
  - B cells - produce soluble antibody which interacts with antigen
  - NK-cells, seek & destroy tumour cells & virus-infected cells via receptor recognition

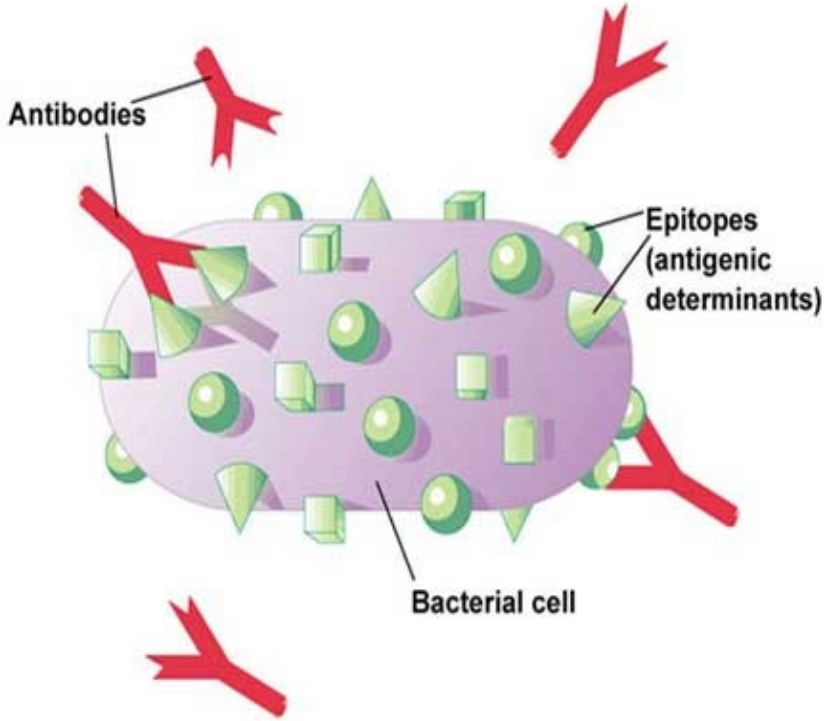


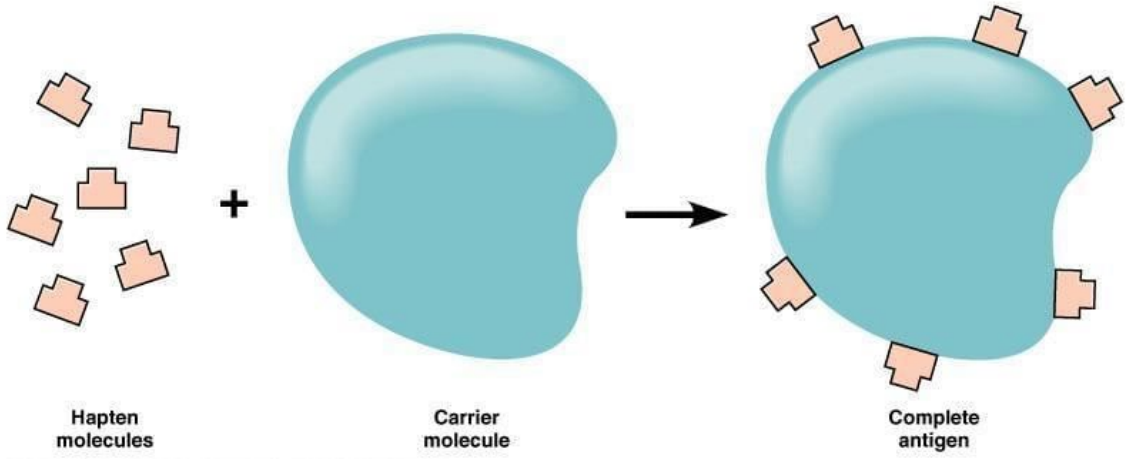
Features of Adaptive Immune Response

- Adaptability
  - Recognition of novel antigens - *emerging viruses have never been seen before!*
- Specificity
  - Recognition of self versus non-self – not just to avoid autoimmune disease
- Diversity
  - Capacity to produce a large array of antibodies & T cell receptors - gene recombination
- Memory
  - Secondary response to re-exposure (principles of vaccination)

Antigens

- What is an antigen?
  - A molecule that can be recognised by receptors on immune cells
  - Small chemical structures through to highly complex molecules
- Recognition usually only small part of antigen = epitope
- Not all antigens are immunogenic
  - Haptens (e.g. drugs)
  - Carbohydrates

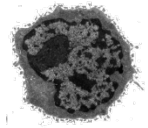




Cells of the Adaptive Immune System

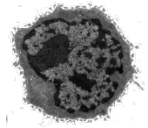
Adaptive immune responses are Ag specific & involve B & T cell responses

- recognise specific Ag through cell surface receptors & need to be **activated** before they function as **effector** cells
- need to be able to tell the difference between self & non-self



T cells

- T helper cells (T_H) orchestrate the response with cytokines
- T cytotoxic cells (T_C) kill pathogen-infected cells or cancer cells
- "Cell mediated immunity"



B cells produce antibodies (Ag-specific)

- "Humoral immunity"

Lymphocytes patrol the body through lymph, blood & tissues

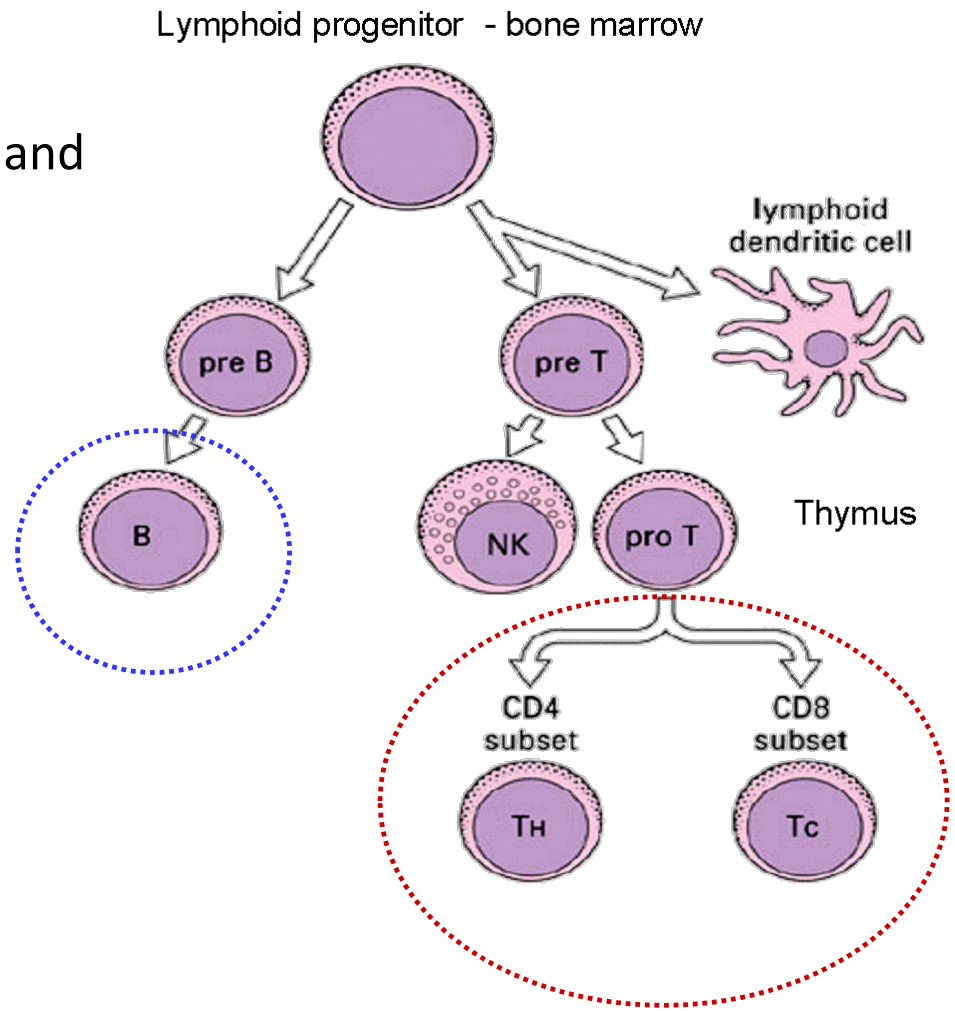
Lymphocyte - development

T cell precursors come from the bone marrow and develop in the **T**HYMUS

T cells only develop in the thymus; nowhere else in the body.

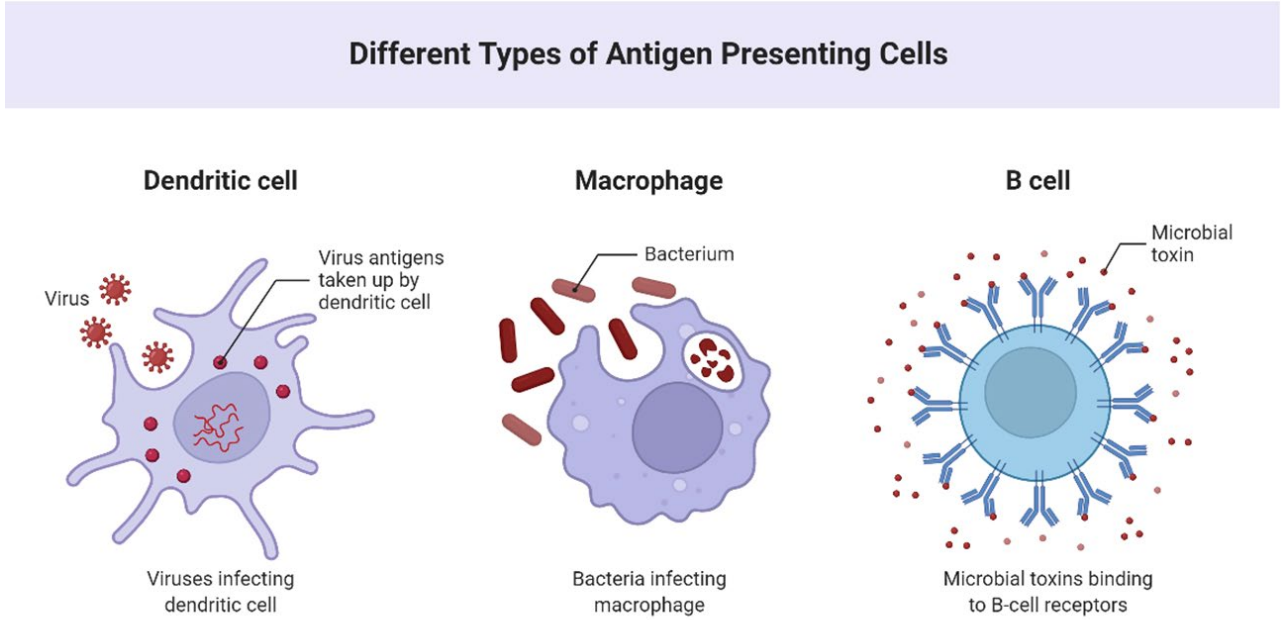
B cell precursors come from the bone marrow & develop in the **B**ursa of Fabricius (birds)

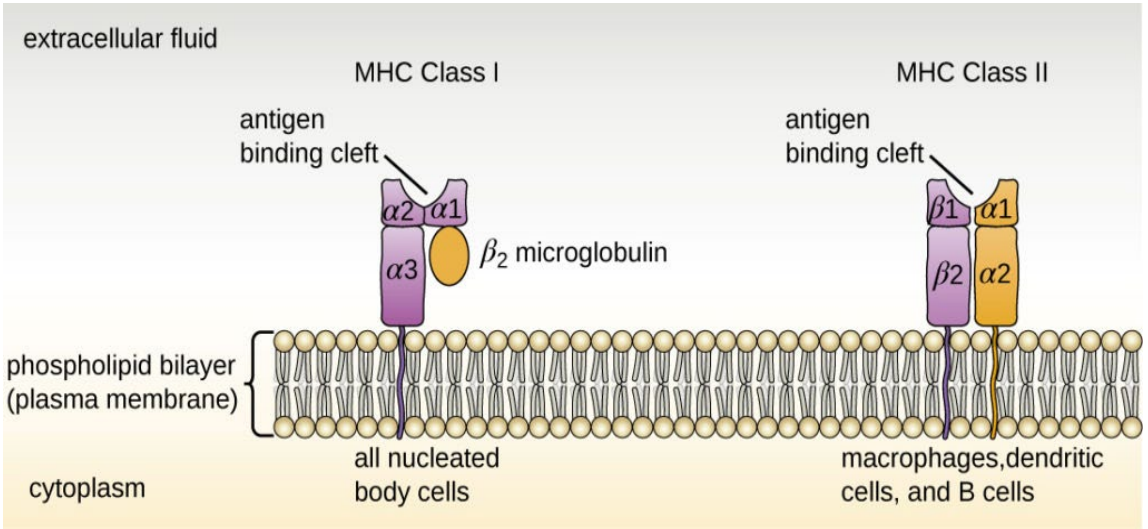
& the **B**one marrow in mammals



MHC

- Major histocompatibility complex
- Structure used by cells to present antigens
- Two classes: MHC-I and MHC-II
- All nucleated cells express MHC-I
- Antigen-presenting cells express MHC-II as well
- MHC is specific to “self”





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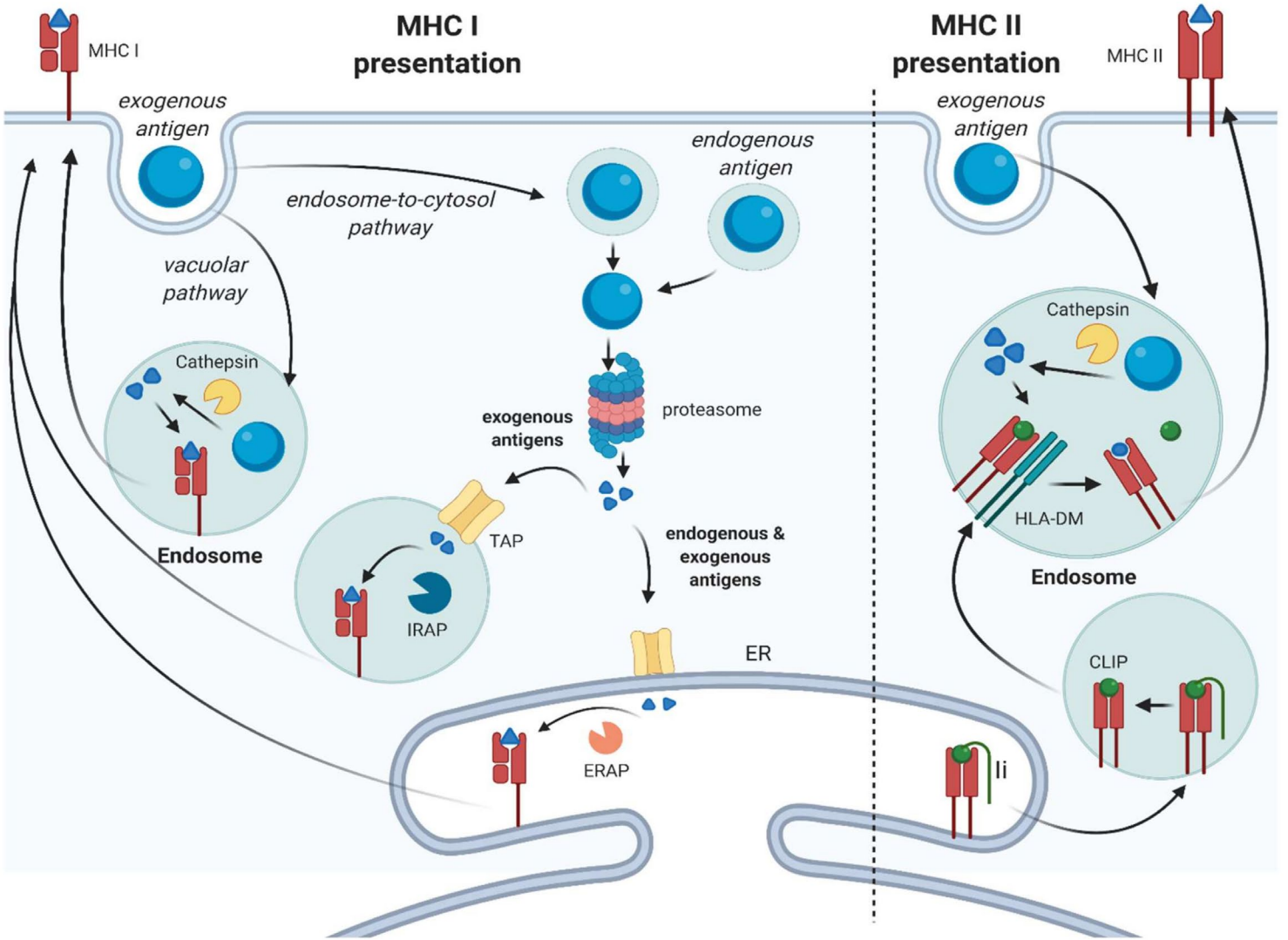
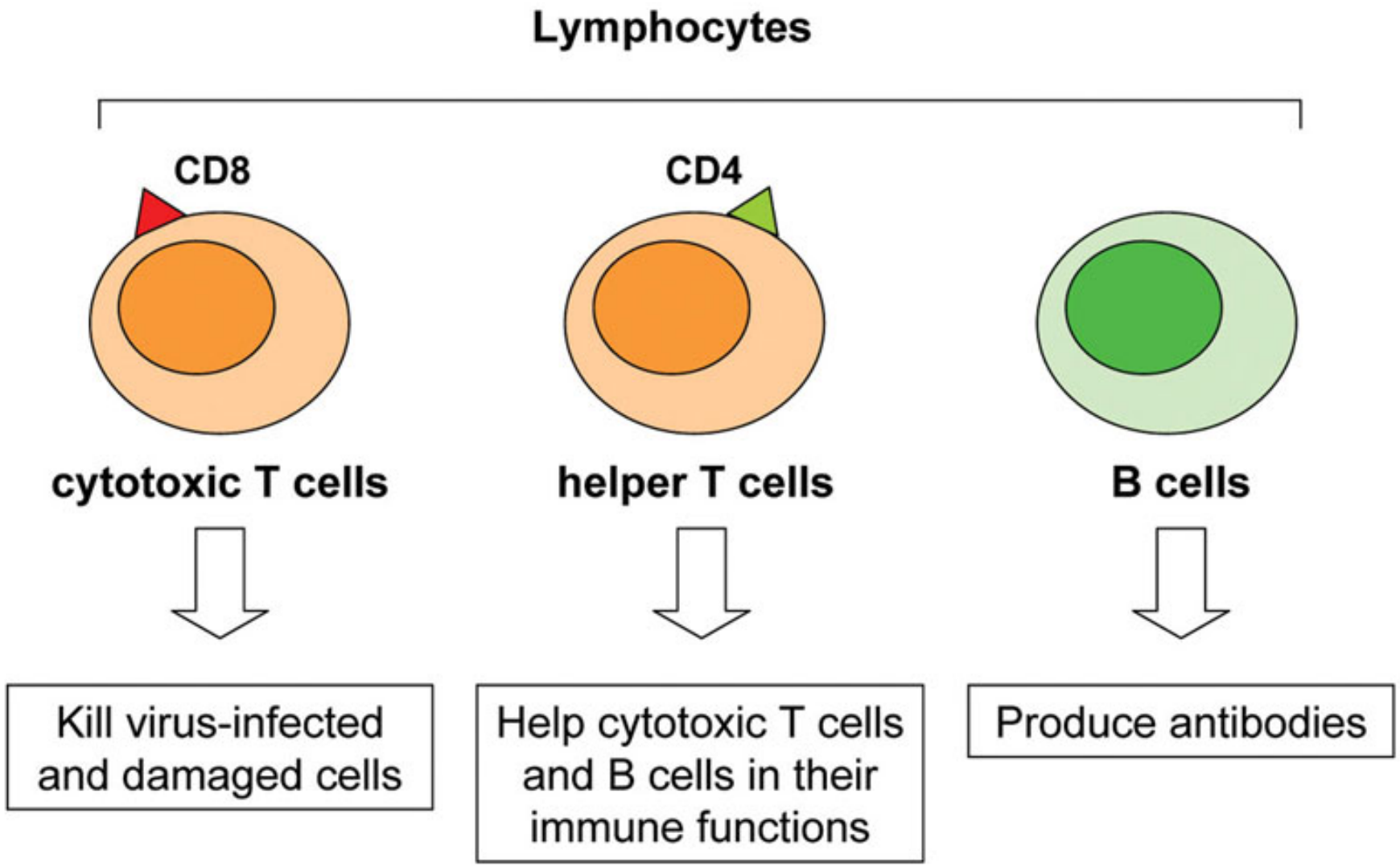
Antigen processing

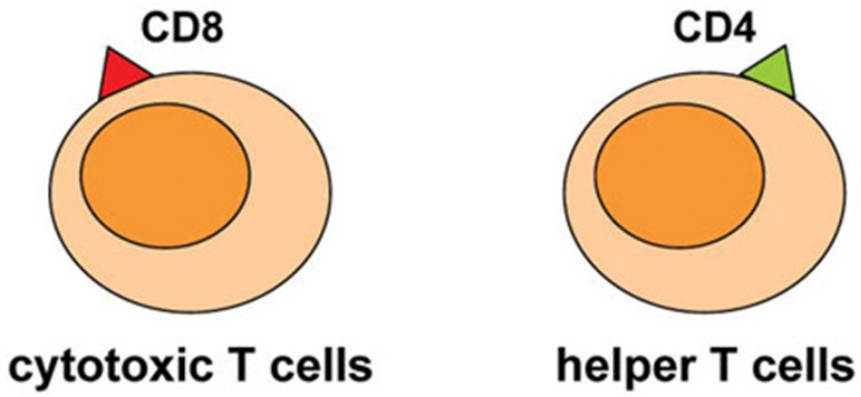


Harryvan et al., 2022


Lymphocytes
CD8
CD4
cytotoxic T cells
helper T cells
B cells
Kill virus-infected and damaged cells
Help cytotoxic T cells and B cells in their immune functions
Produce antibodies

T cell receptors

- T cells only recognise peptide antigens when presented by MHC
- T cell receptors bind antigen presented by MHC
- Made of glycoprotein chains
  - α/β (most species) or γ/δ (ruminants)
  - Form a complex with CD3
- Additional proteins can be found in close association with TCRs
  - CD4 proteins are found on helper T cells
  - CD8 proteins are found on cytotoxic T cells
- CD4 binds to MHC-II
- CD8 binds to MHC-I

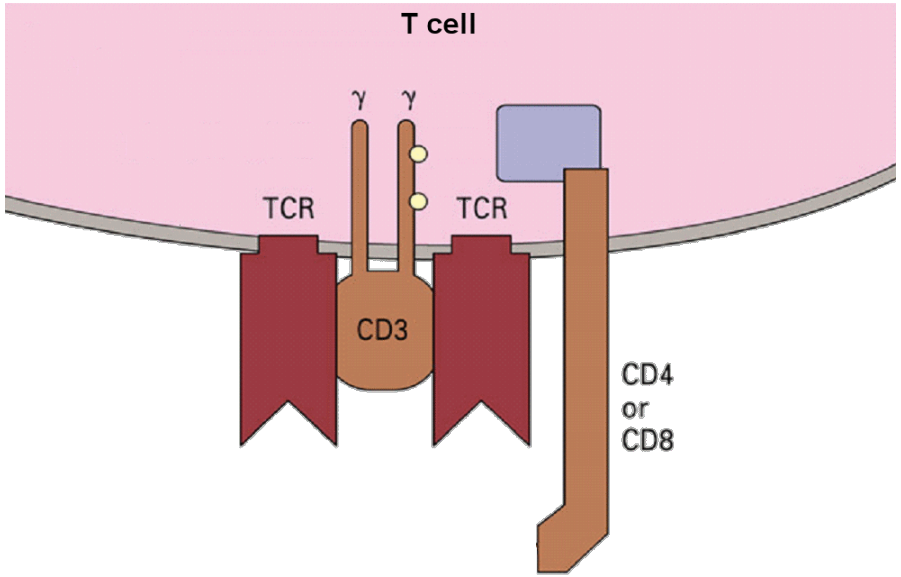


T cell receptors – γ/δ

- Most γ/δ T cell receptors don’t recognise MHC-antigen complexes
  - Most don’t have CD4 or CD8
- Activation of γ/δ T cells results in production of cytokines, lysis of infected cells, interaction with other cells

T cell receptor (TCR)

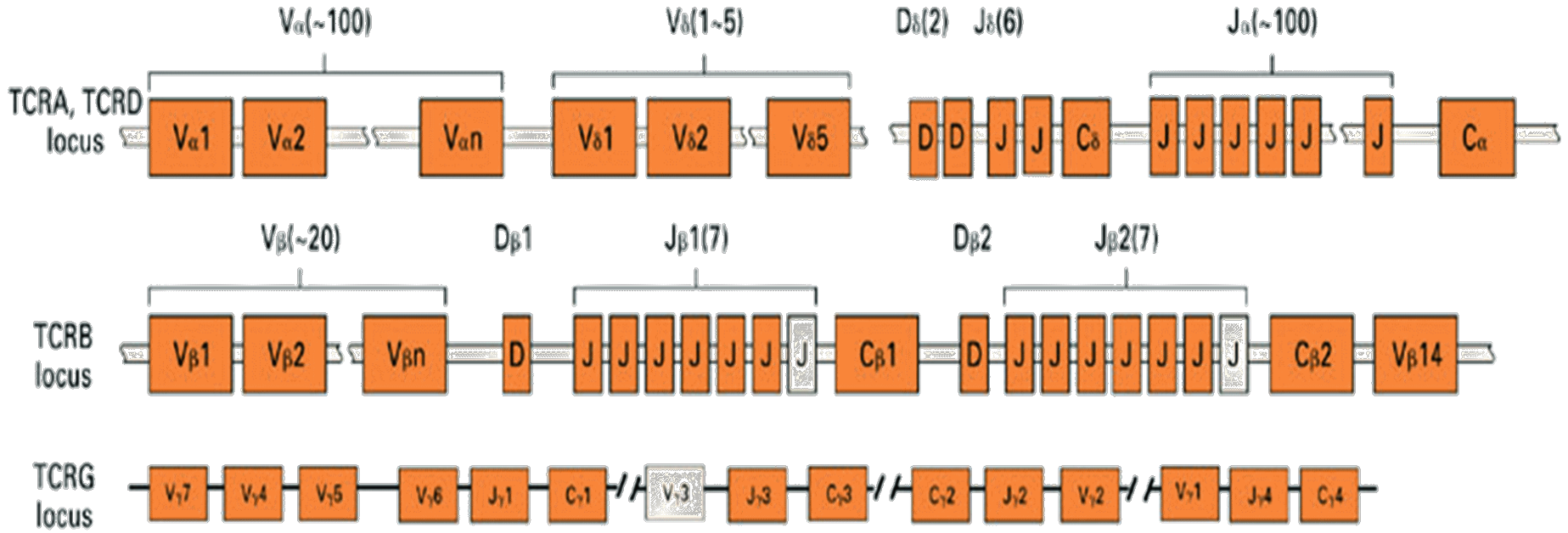
- Highly variable protein that recognises specific Ag presented to them
- TCR is anchored into the cell by a conserved transmembrane domain complexed to CD3 protein
- CD3 is required for cell surface expression of TCR and is involved in signal transduction
- TCR:CD3 complex is present on all T-cells
- TCR binding site is <u>different</u> for each Ag
- APCs seek out a TCR that matches



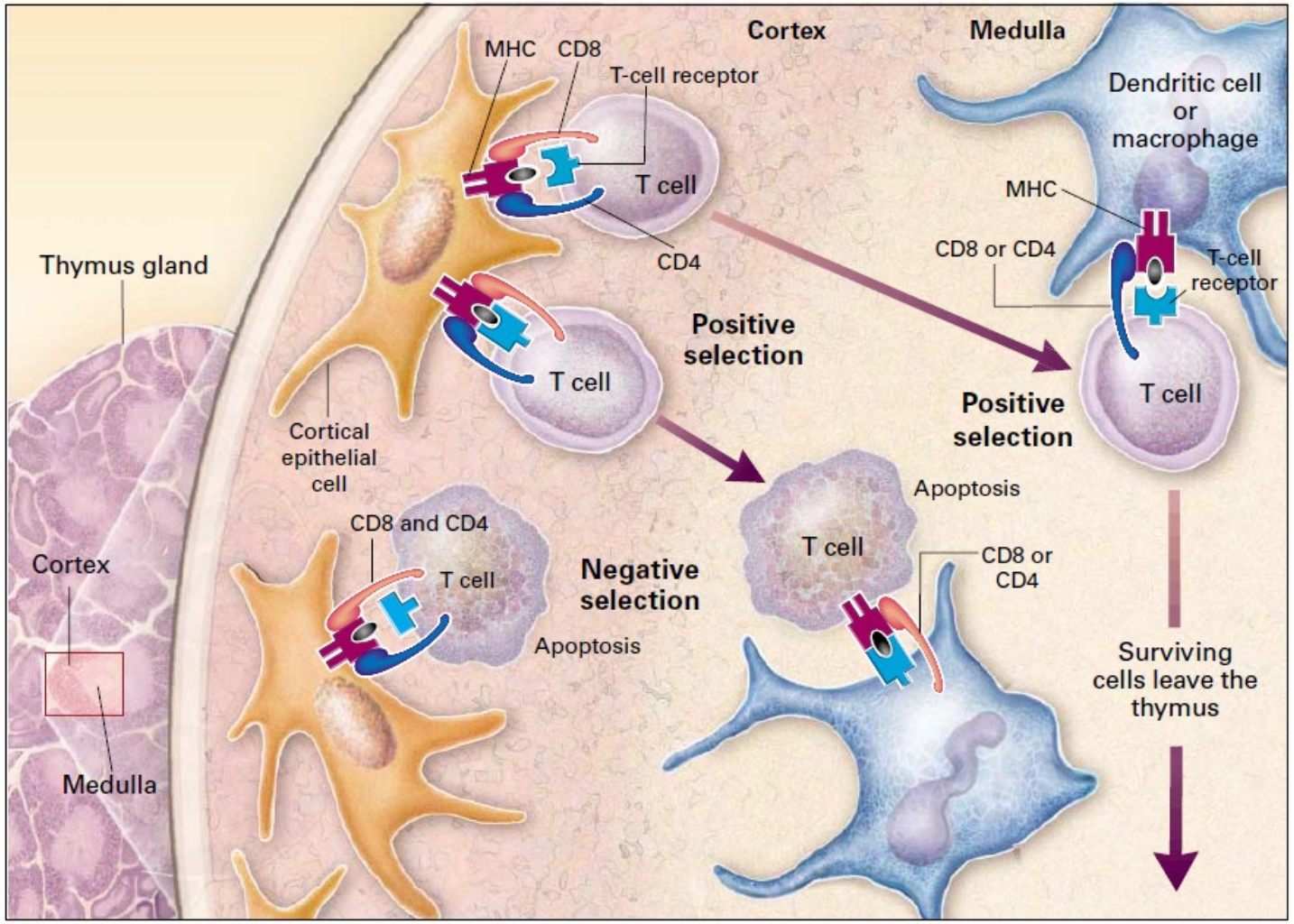
CD4 (or CD8) is also required to recognise the type of cell that is presenting Ag

Why?

TCR genes


Vα(~100)
Vδ(1~5)
Dδ(2)
Jδ(6)
Jα(~100)
TCRA, TCRD locus
Vα1
Vα2
Vαn
Vδ1
Vδ2
Vδ5
D
D
J
J
Cδ
J
J
J
J
J
J
Cα
Vβ(~20)
Dβ1
Jβ1(7)
Dβ2
Jβ2(7)
TCRB locus
Vβ1
Vβ2
Vβn
D
J
J
J
J
J
J
Cβ1
D
J
J
J
J
J
J
Cβ2
Vβ14
TCRG locus
Vγ7
Vγ4
Vγ5
Vγ6
Jγ1
Cγ1
Vγ3
Jγ3
Cγ3
Cγ2
Jγ2
Vγ2
Vγ1
Jγ4
Cγ4

T cell development in thymus



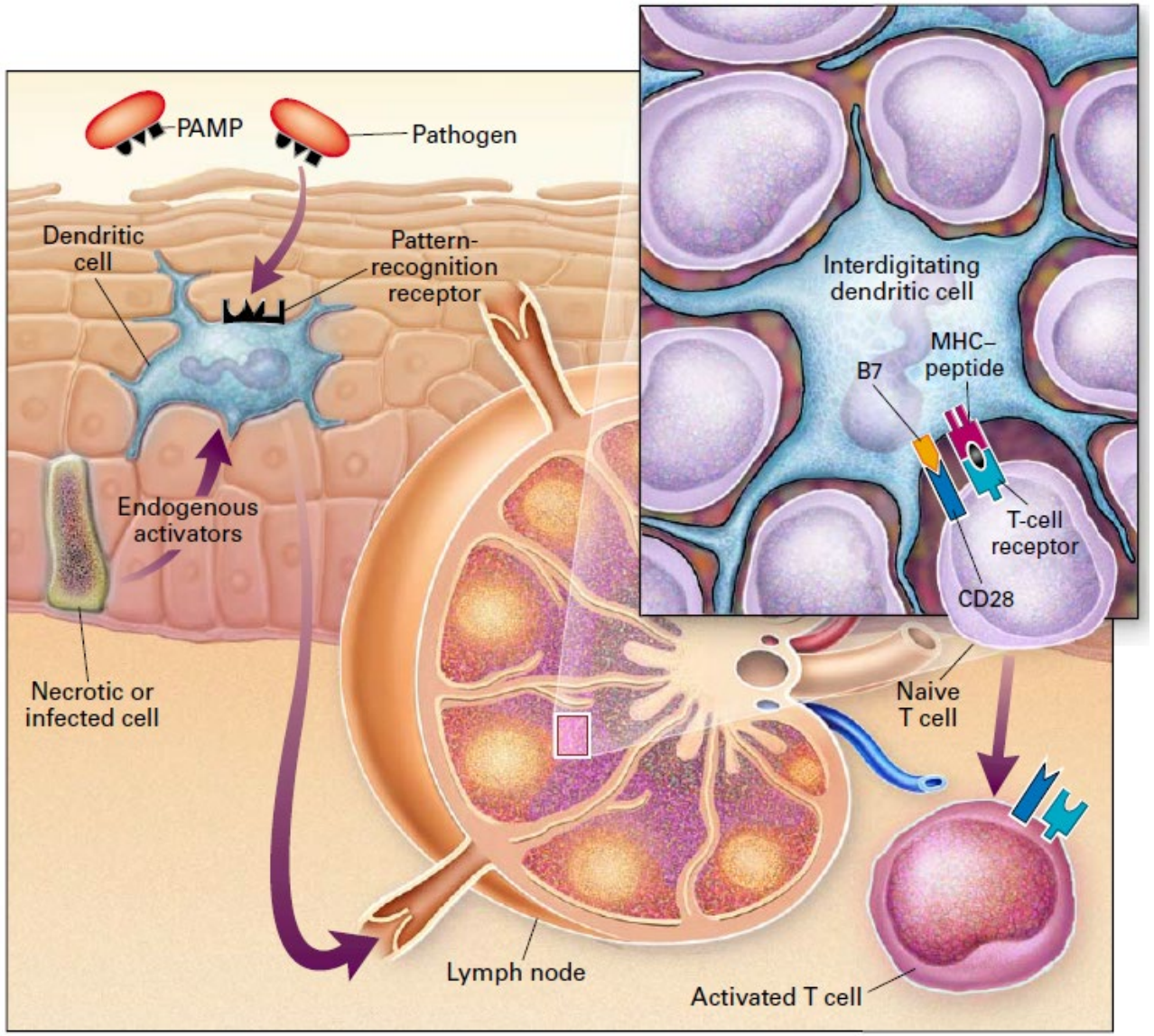
Delves & Roitt, *NEJM*, 2000

T cell receptors (α/β)

- **DON'T** recognise own MHC with no antigen bound
  - This is considered "self"
- **DO** recognise self MHC + bound antigen
  - = "altered self"
  - Occasionally non-peptide antigens can alter self MHC and elicit a T cell response
- **DO** recognise foreign MHC

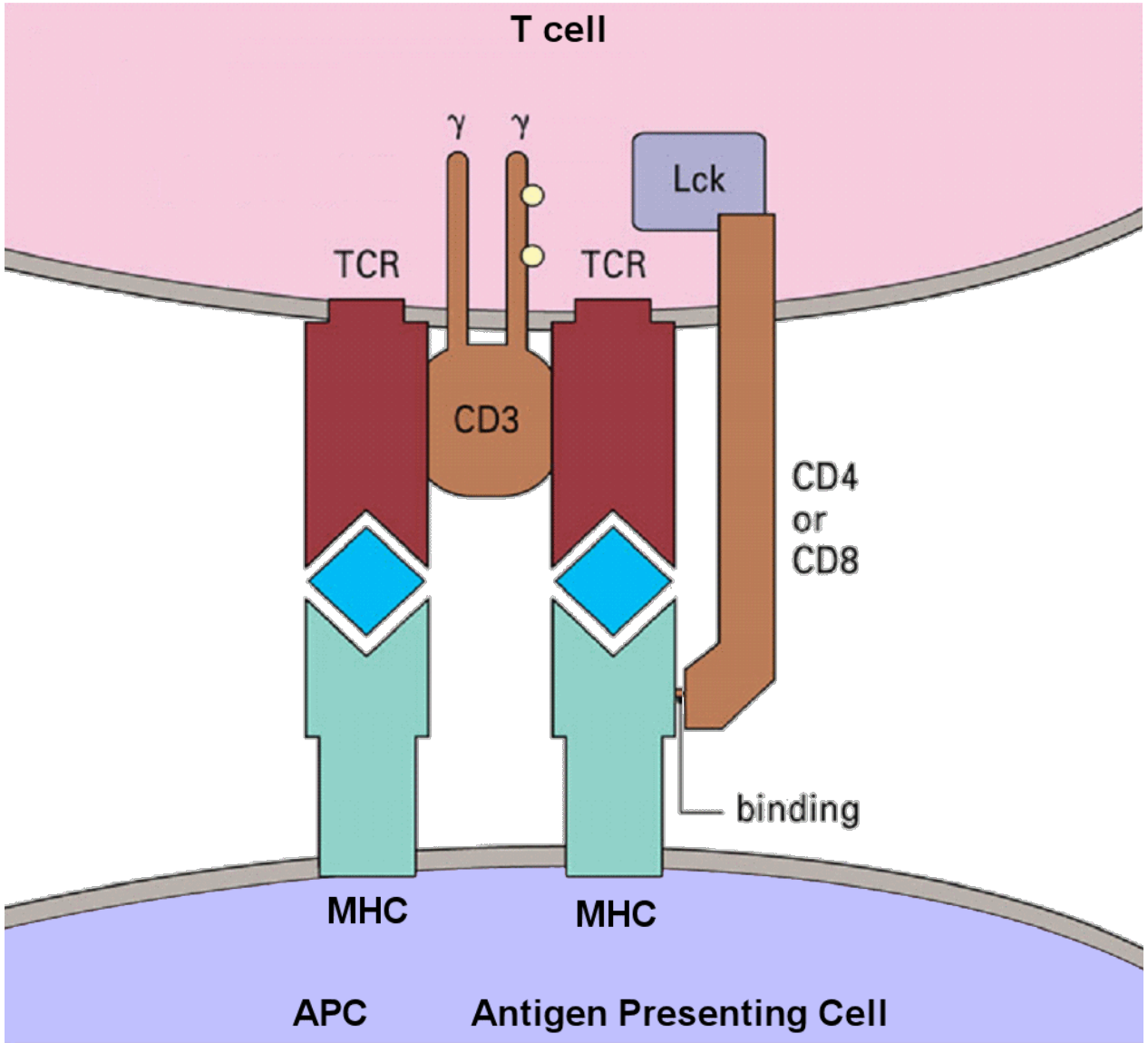
Antigen presentation

- Activated dendritic cells migrate to local draining lymph node
- Process antigen
- Present antigen to T cells
  - MHC molecules
  - Costimulatory molecules

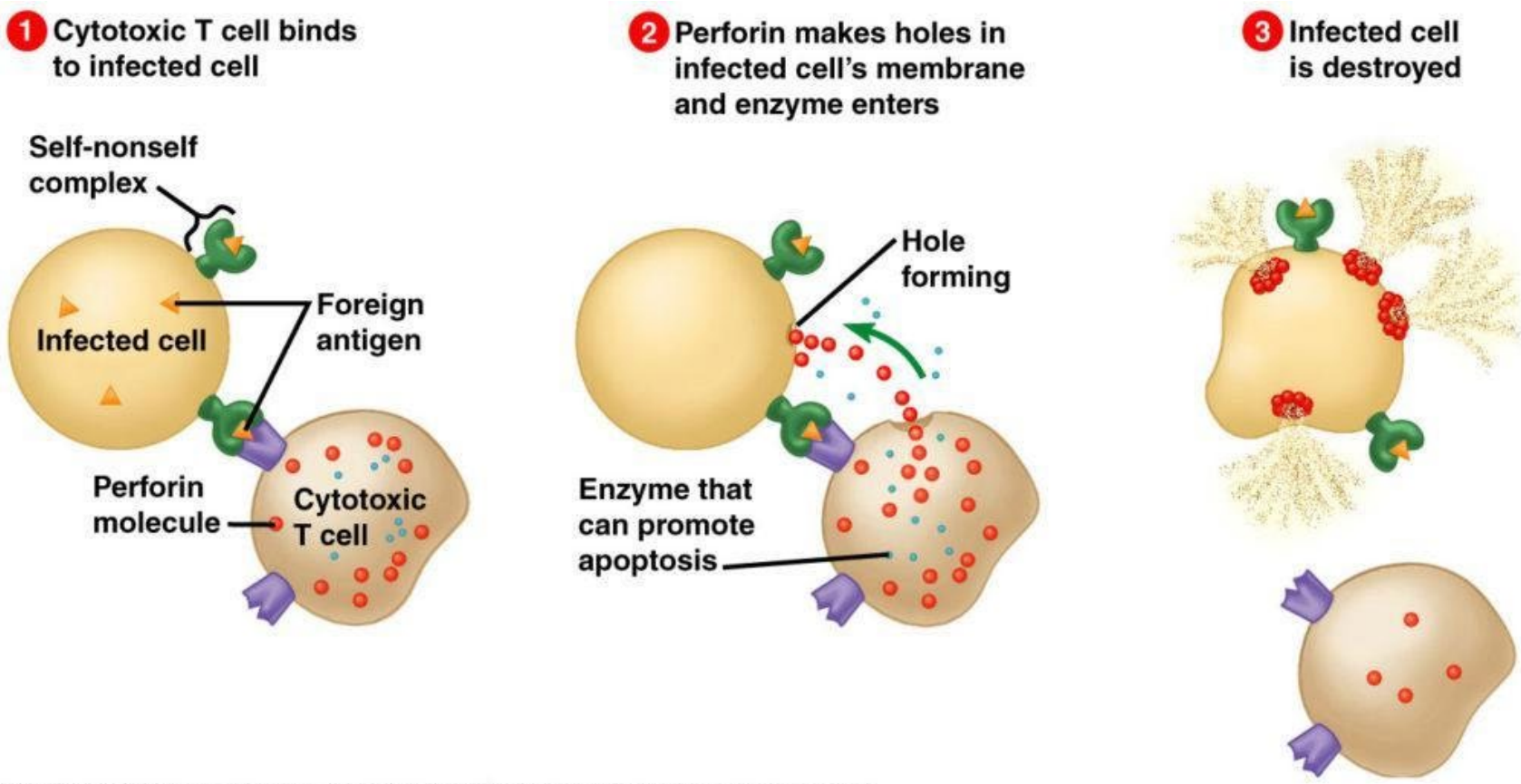


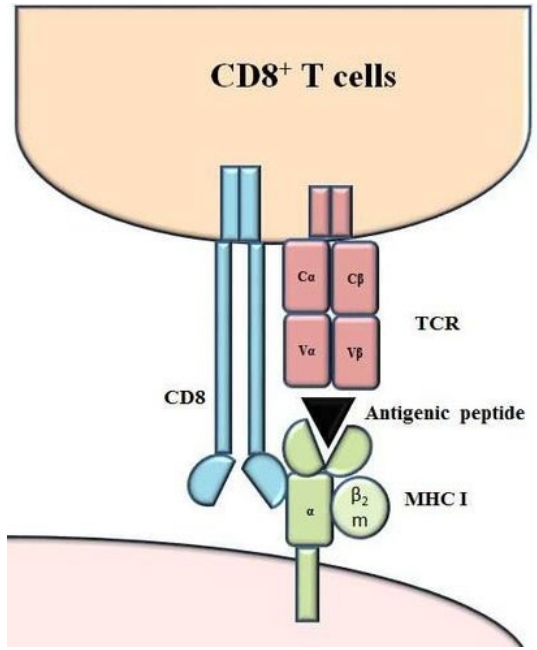
Delves & Roitt, *NEJM*, 2000

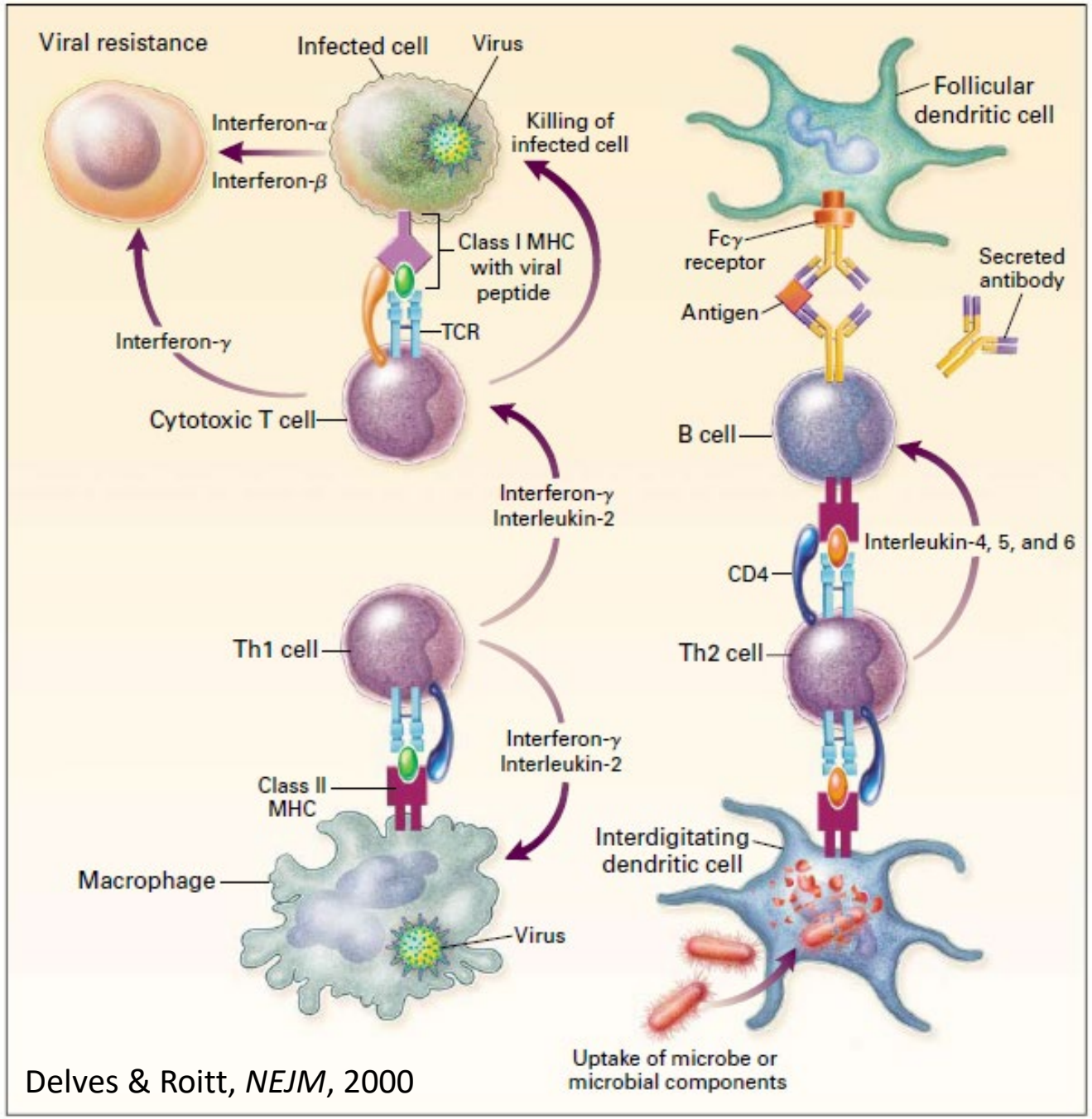
Interaction of T cell & APC



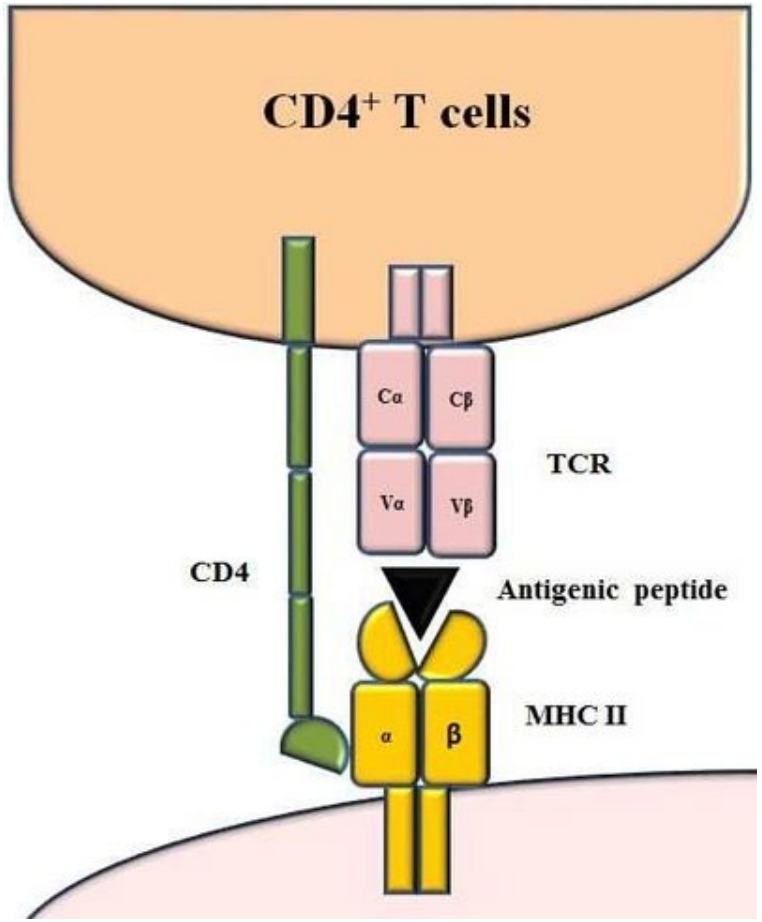
Antigen presentation → T cell activation

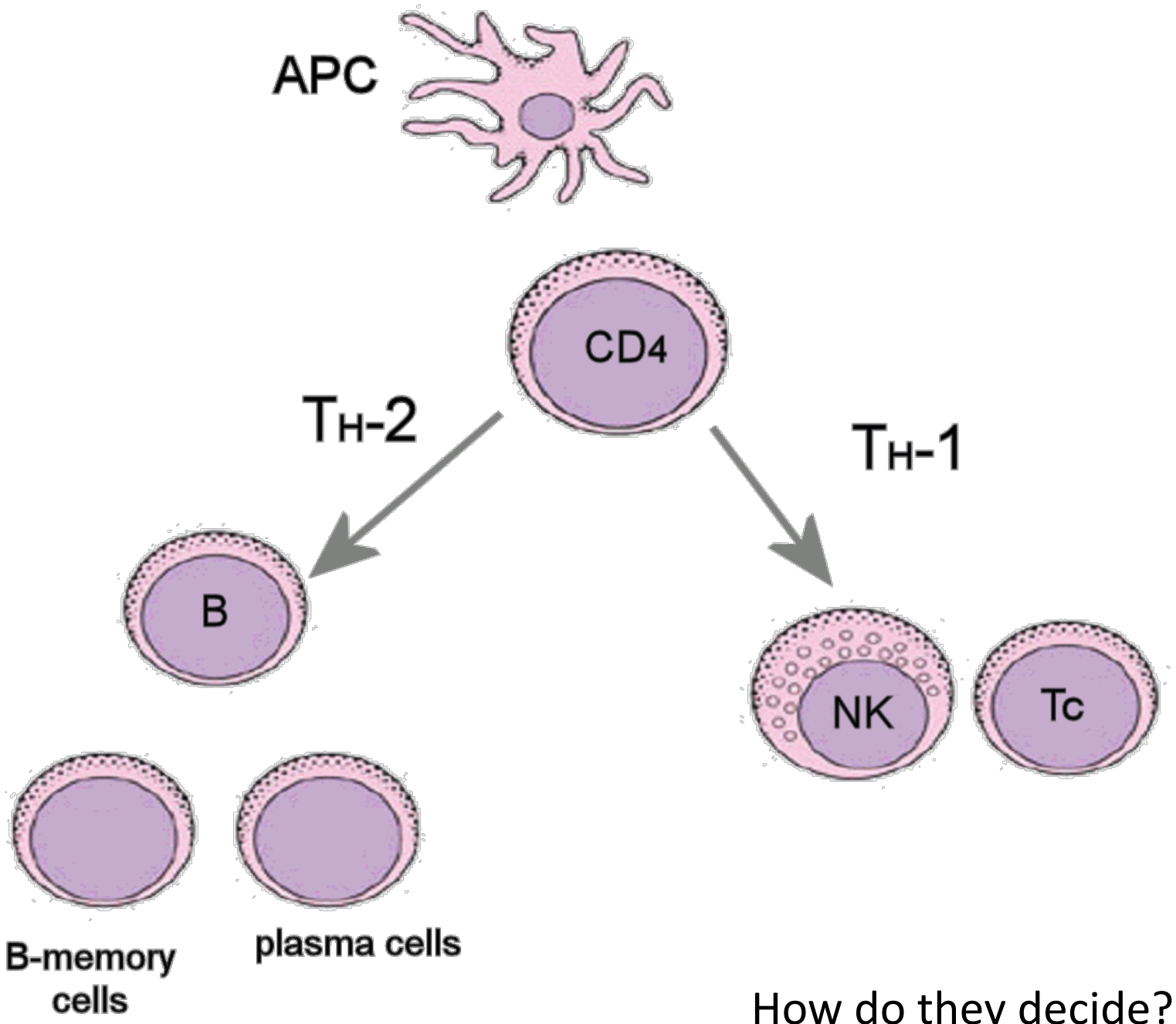






Delves & Roitt, *NEJM*, 2000





How do they decide?

Principle cytokines of Th responses

IL-2 → B cell proliferation & differentiation

IL-4 → IgE production

IL-5 → IgA production Th2

IL-6 → plasma cell differentiation

IL-10 → downregulates Th1 cytokines

= **<u>antibody production</u>**

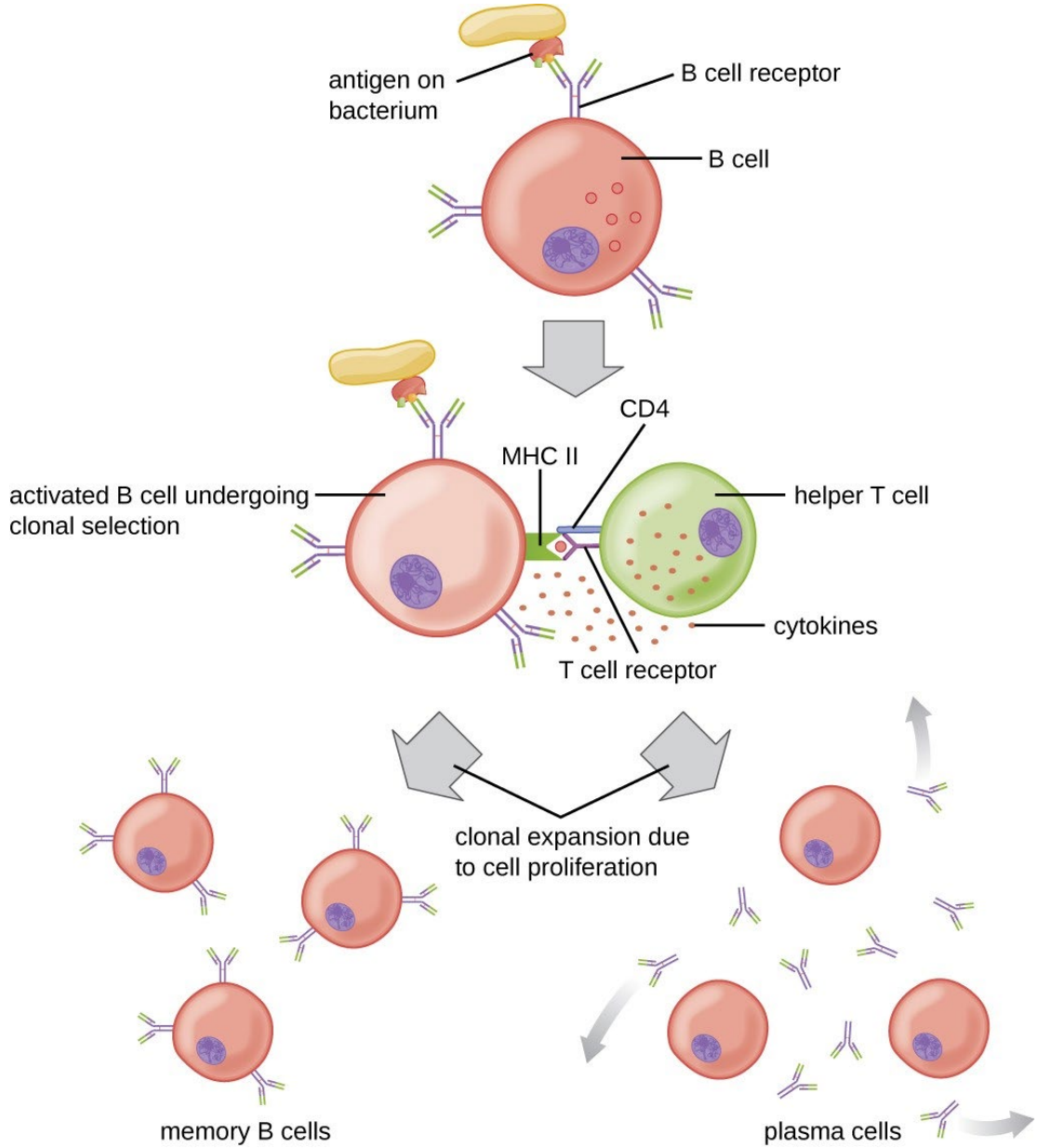
IFNγ → macrophages, NK cells, Th1

downregulates Th2 activation

= **<u>Cytotoxic T cells</u> & cell-mediated immunity**

B cells

- Surface receptors & soluble receptors (= antibodies)
- Act as APCs
  - Antigen binds to B cell receptor
  - Internalised, processed, and expressed on MHC-II
  - BCRs are specific for one particular type of antigen
- Helper T cells co-stimulate B cells



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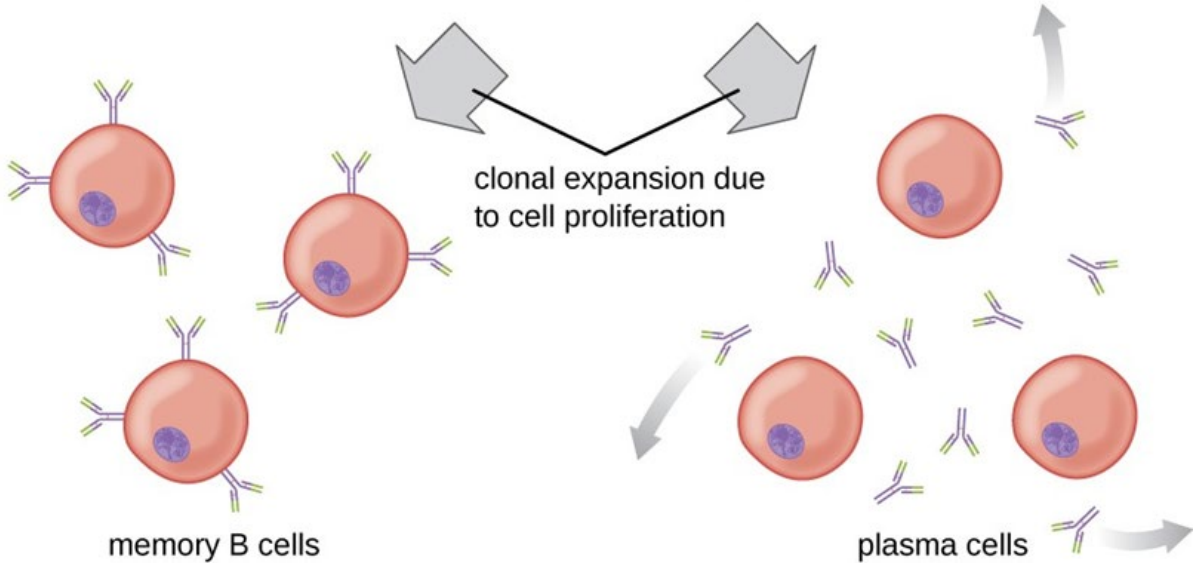
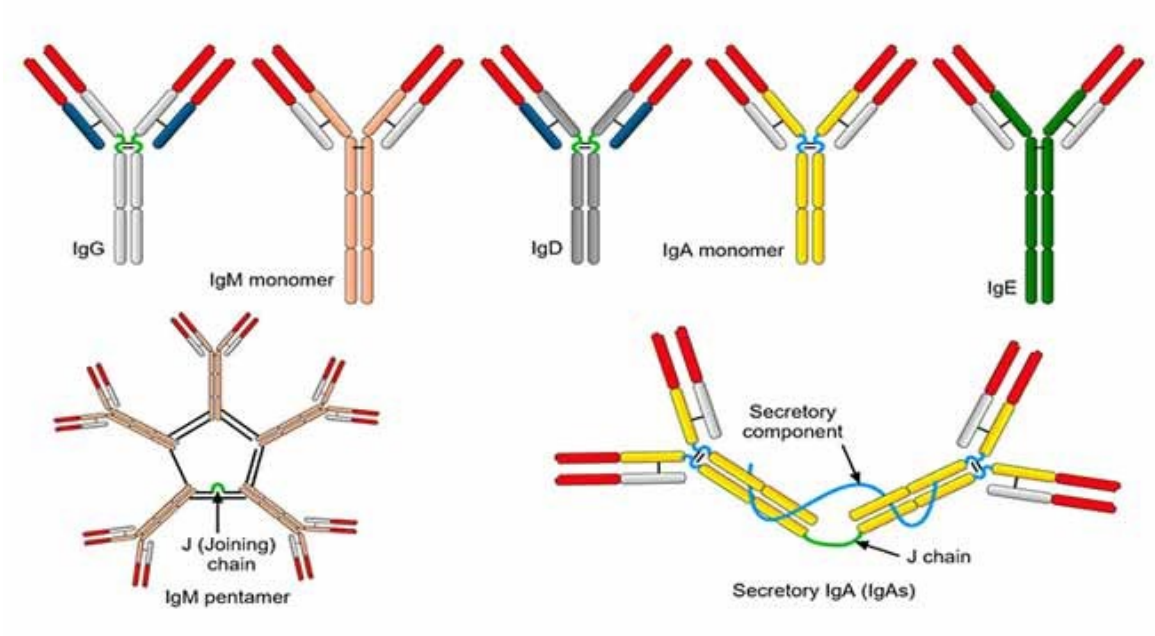
Activated B cells

- Clonal proliferation
  - Plasma cells (produce LOTS of antibodies)
  - Memory B cells

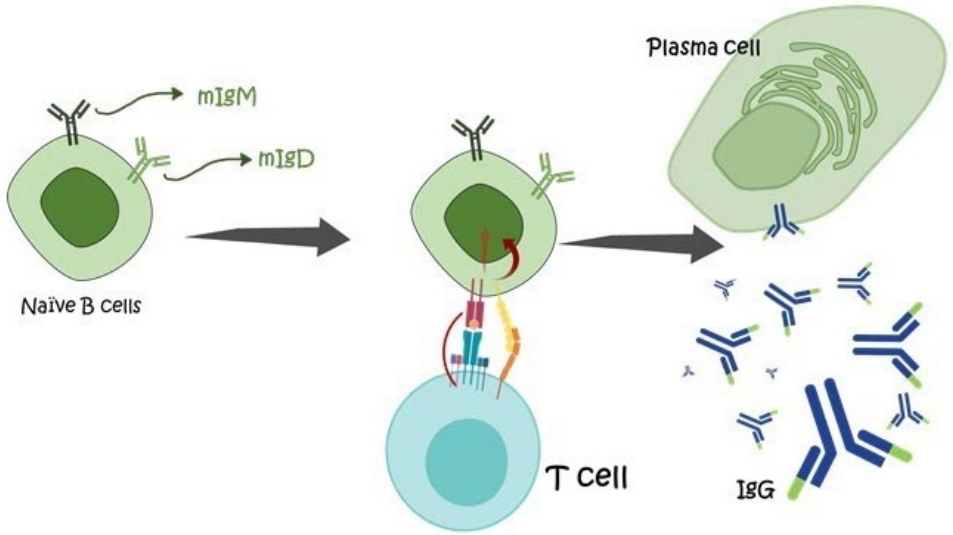


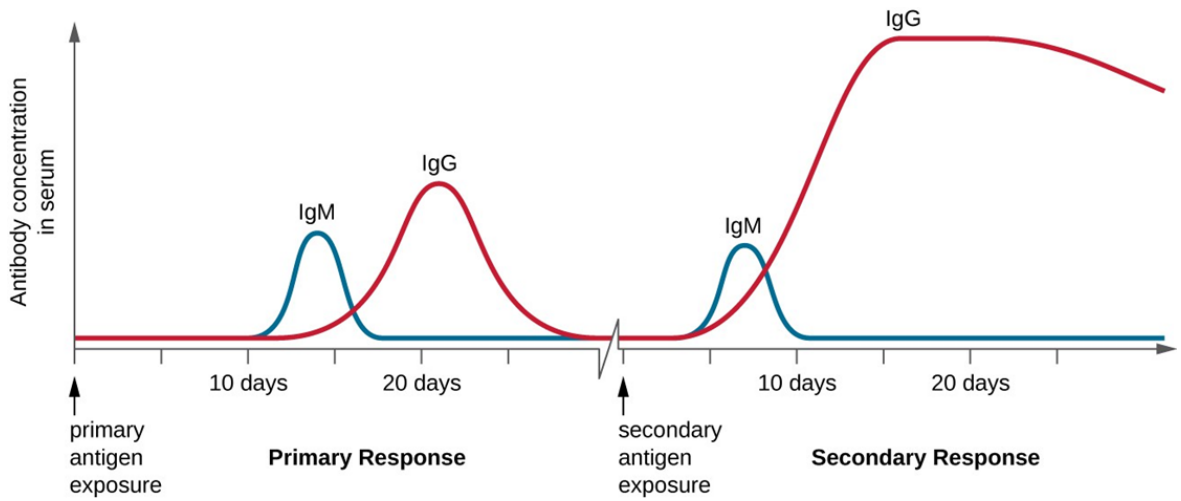
Antibodies



- 5 classes of antibody (immunoglobulins)
  - IgG
  - IgA
  - IgM
  - IgE
  - IgD
- All based on a Y-shaped molecule that matches a specific antigen
- Secreted into body fluids, can also bind to surface receptors on certain cells to facilitate antigen recognition and/or presentation

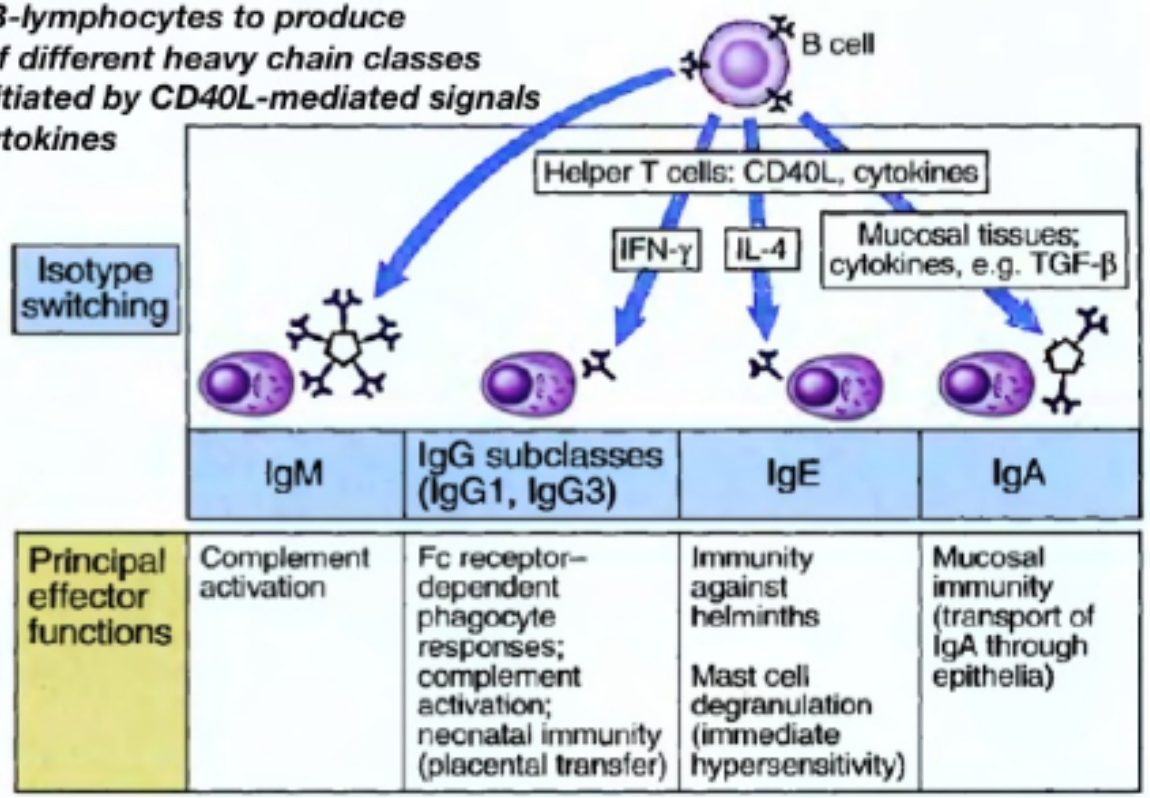
Antibody class switching by B cells

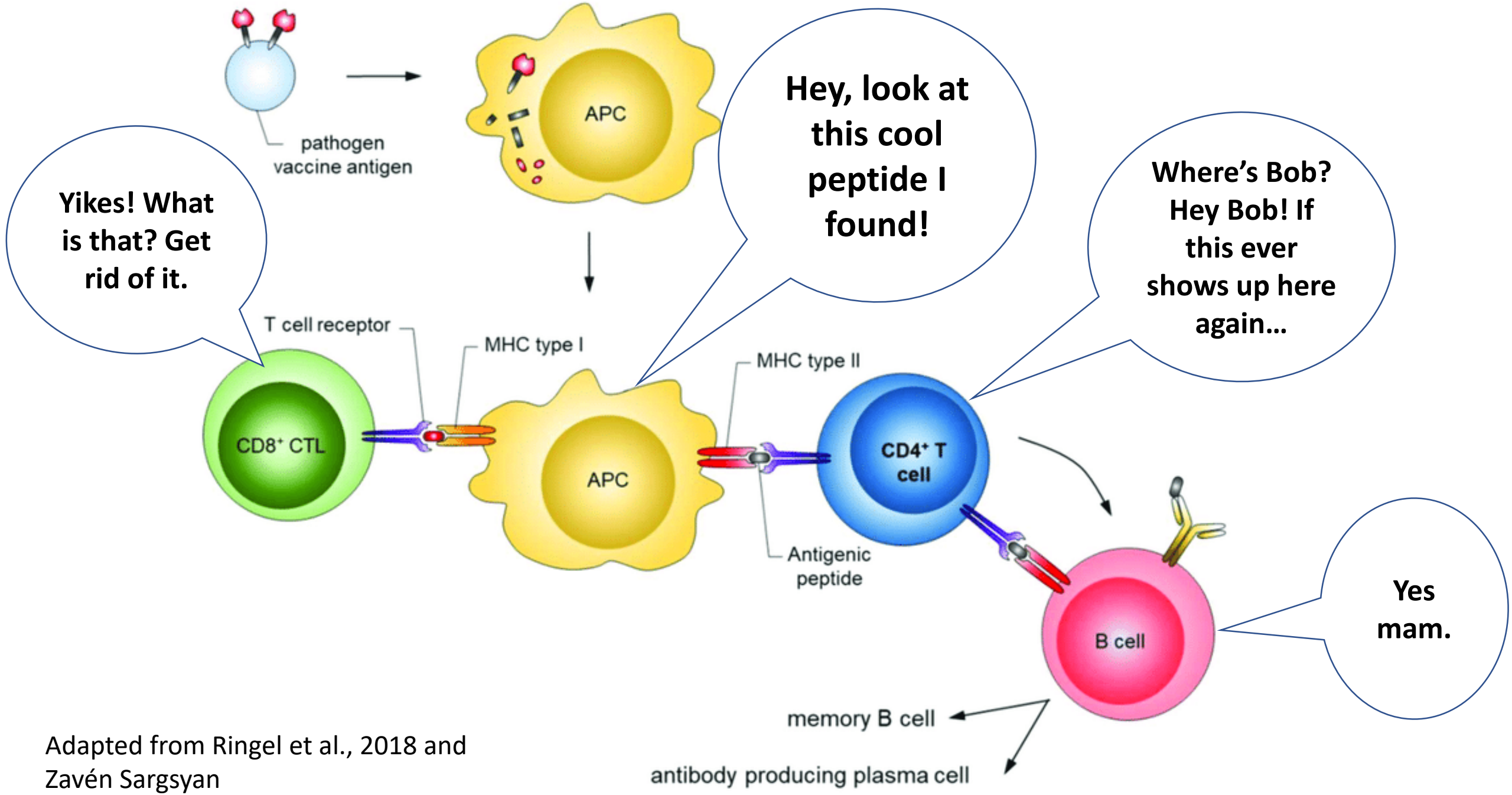




ISOTYPE SWITCHING

Helper T-cells stimulate the progeny of IgM+ IgD expressing B-lymphocytes to produce antibodies of different heavy chain classes (isotypes) initiated by CD40L-mediated signals and other cytokines





Adapted from Ringel et al., 2018 and Zavén Sargsyan

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