Adaptive immunity
&
Rheumatic diseases

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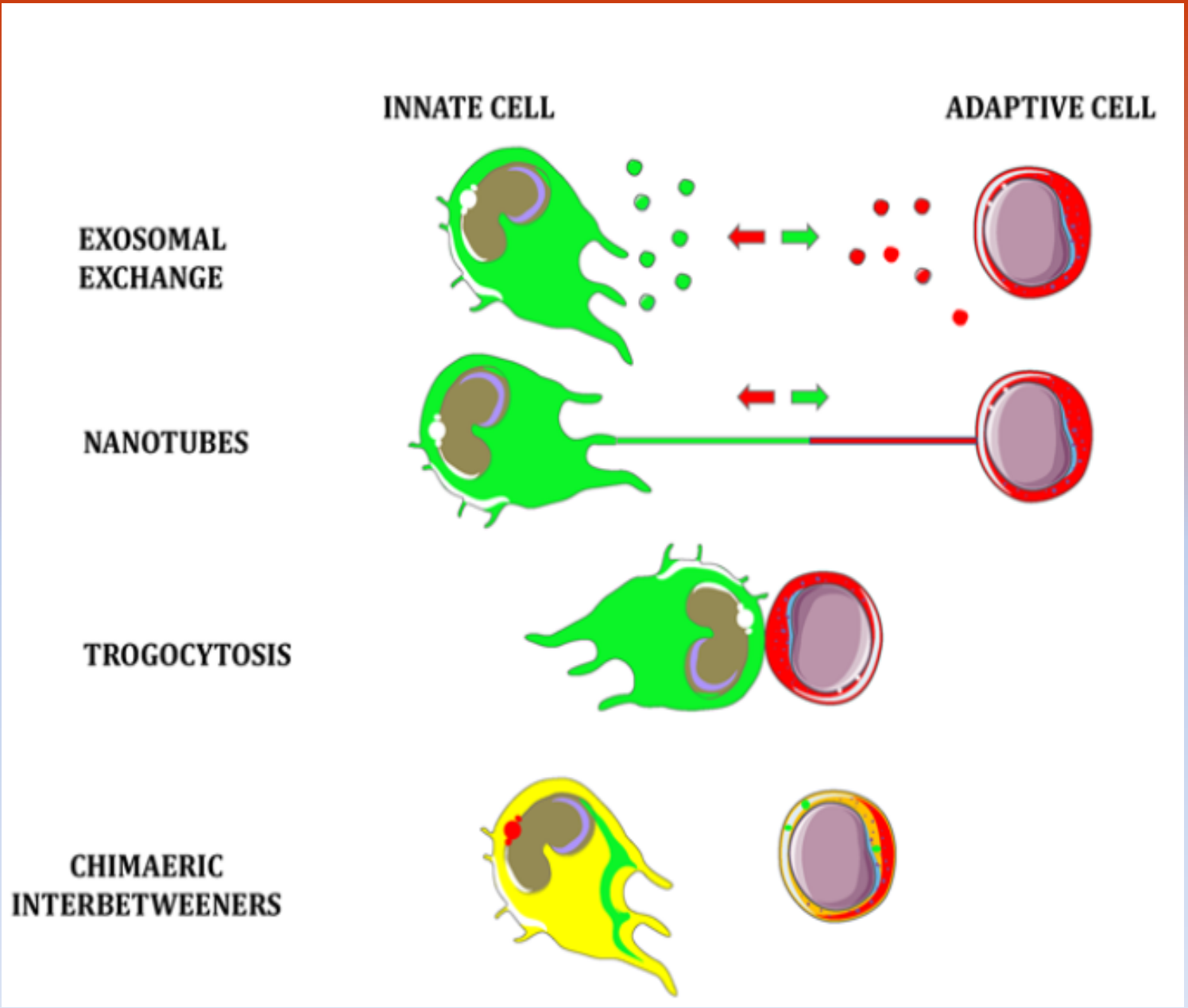
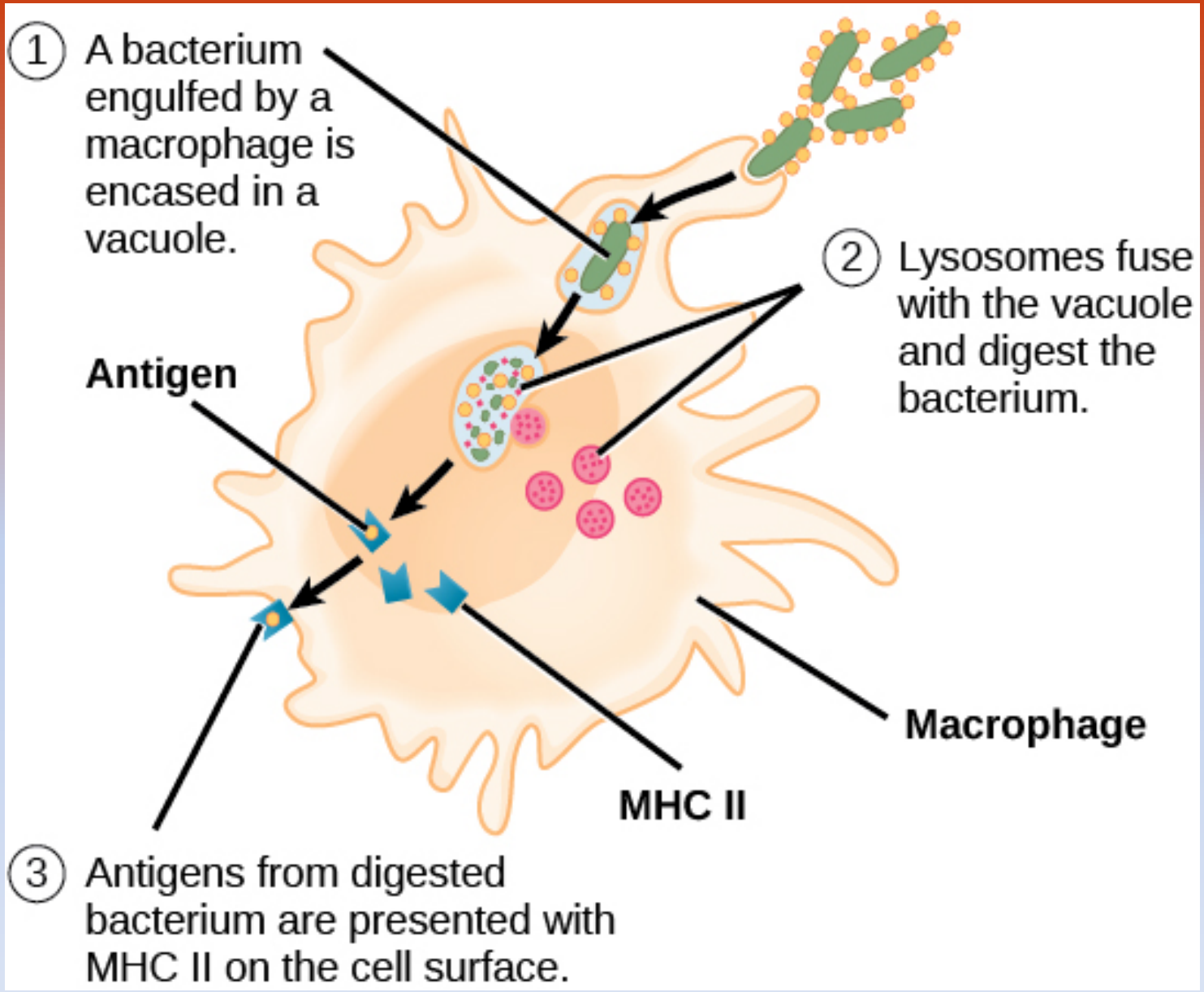
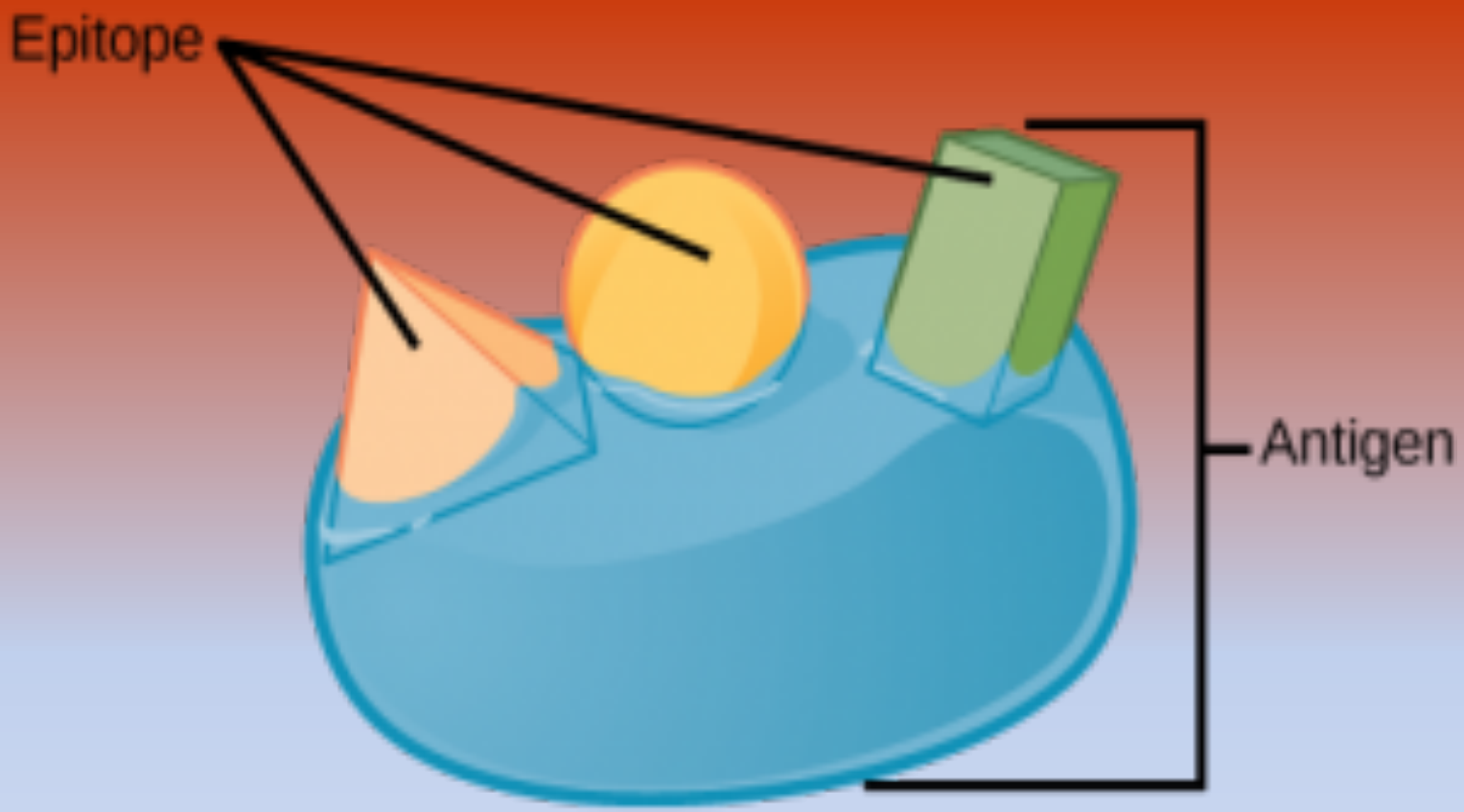
Adaptive Immune Response

- Adaptive immunity is an immunity that occurs after **exposure to an antigen either from a pathogen or a vaccination**.
- This part of the immune system is activated when the innate immune response is insufficient to control an infection. In fact, without information from the innate immune system, **the adaptive response could not be mobilized.**
- There are two types of adaptive responses: **the cell-mediated immune response**, which is carried out by **T cells**, and the **humoral immune response**, which is controlled by **activated B cells** and antibodies.


INNATE CELL
ADAPTIVE CELL
EXOSOMAL EXCHANGE
NANOTUBES
TROGOCYTOSIS
CHIMAERIC INTERBETWEENERS


1 A bacterium engulfed by a macrophage is encased in a vacuole.
2 Lysosomes fuse with the vacuole and digest the bacterium.
Antigen
Macrophage
MHC II
3 Antigens from digested bacterium are presented with MHC II on the cell surface.



An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain **several motifs** that are recognized by immune cells. Each motif is an **epitope**. In this figure, the entire structure is an antigen, and the orange, salmon and green components projecting from it represent potential epitopes.

Key Points

■ Cells of the adaptive **immune system, T and B lymphocytes**, use somatic gene recombination to produce large repertoires of antigen-recognizing T-cell receptors and immunoglobulins.

■ In contrast to the innate immune system, the adaptive repertoire of lymphocytes can recognize and eliminate a broad variety of new antigens not previously encountered by the host or the host's species. Clonal selection preserves and expands the lymphocytes whose products prove useful in protecting the host.

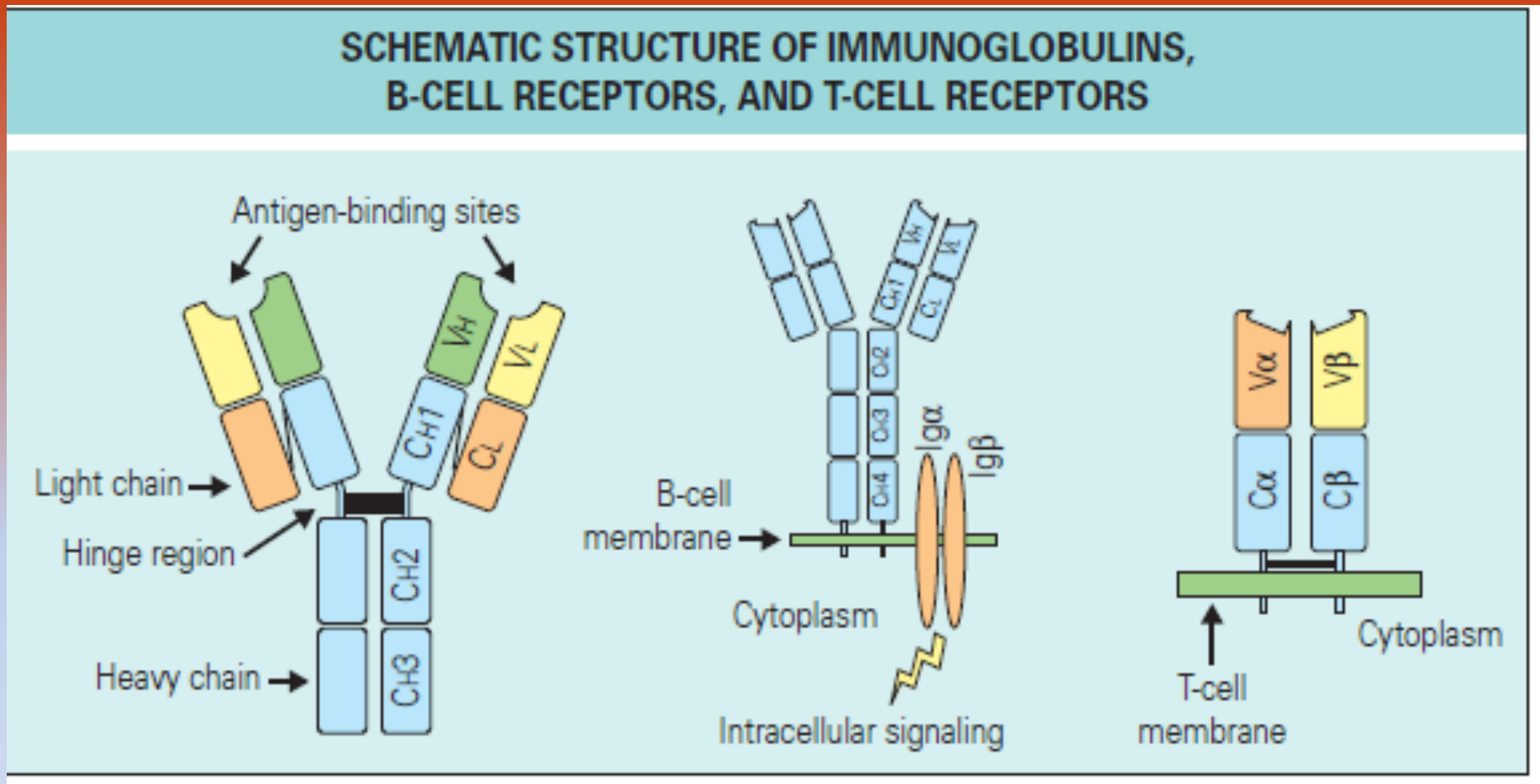
■ The adaptive immune system has an inherent potential for self-reactivity, or autoimmunity. The potential to induce autoimmunity is usually controlled by a combination of deletional and regulatory mechanisms jointly referred to as immune self-tolerance.

■ Triggering of cell-surface receptors activates intracellular signaling cascades controlling lymphocyte differentiation, maturation, immune responsiveness, tolerance, and death.

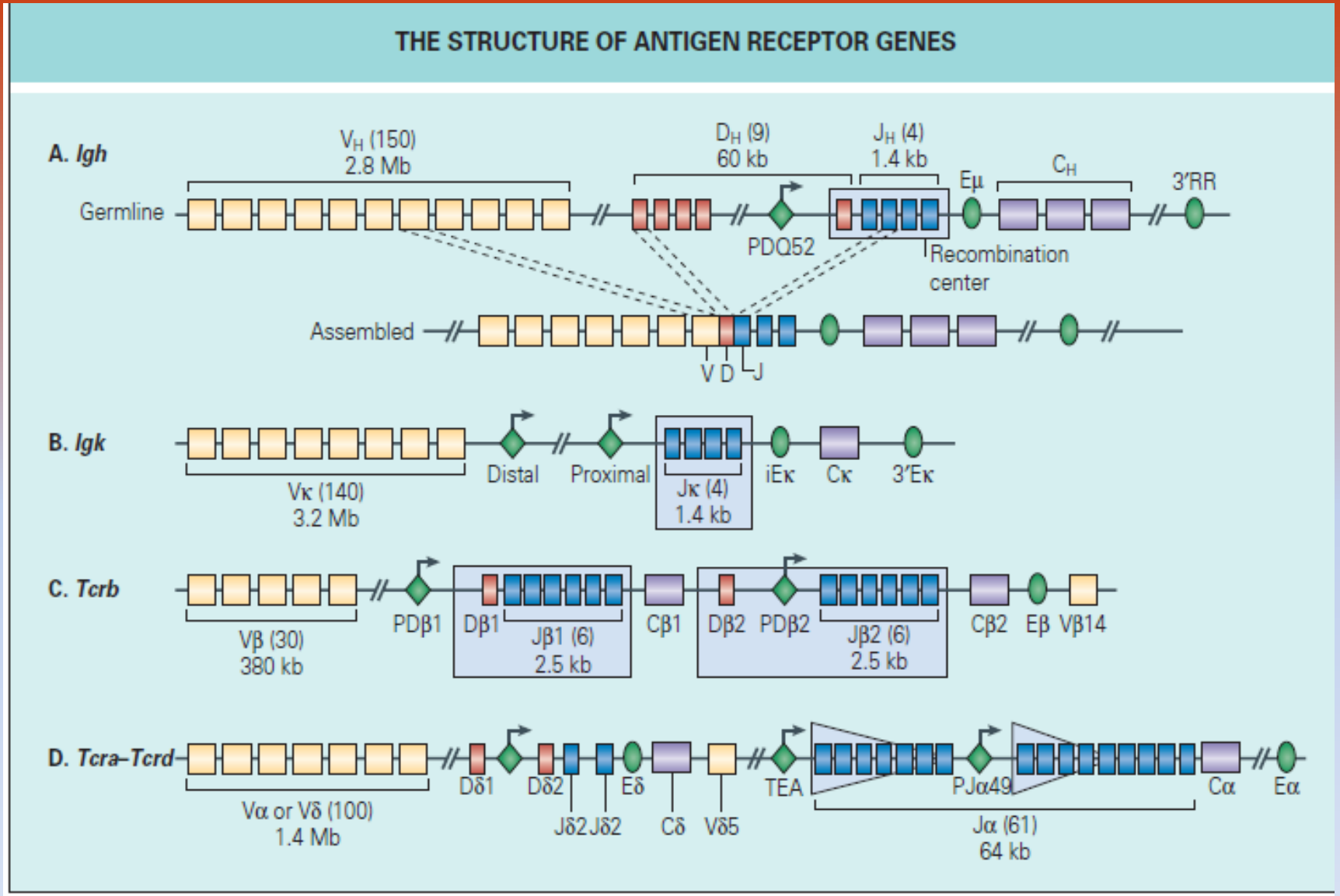
■ Helper T cells of diverse phenotypes coordinate the functioning of the adaptive and innate immune systems.

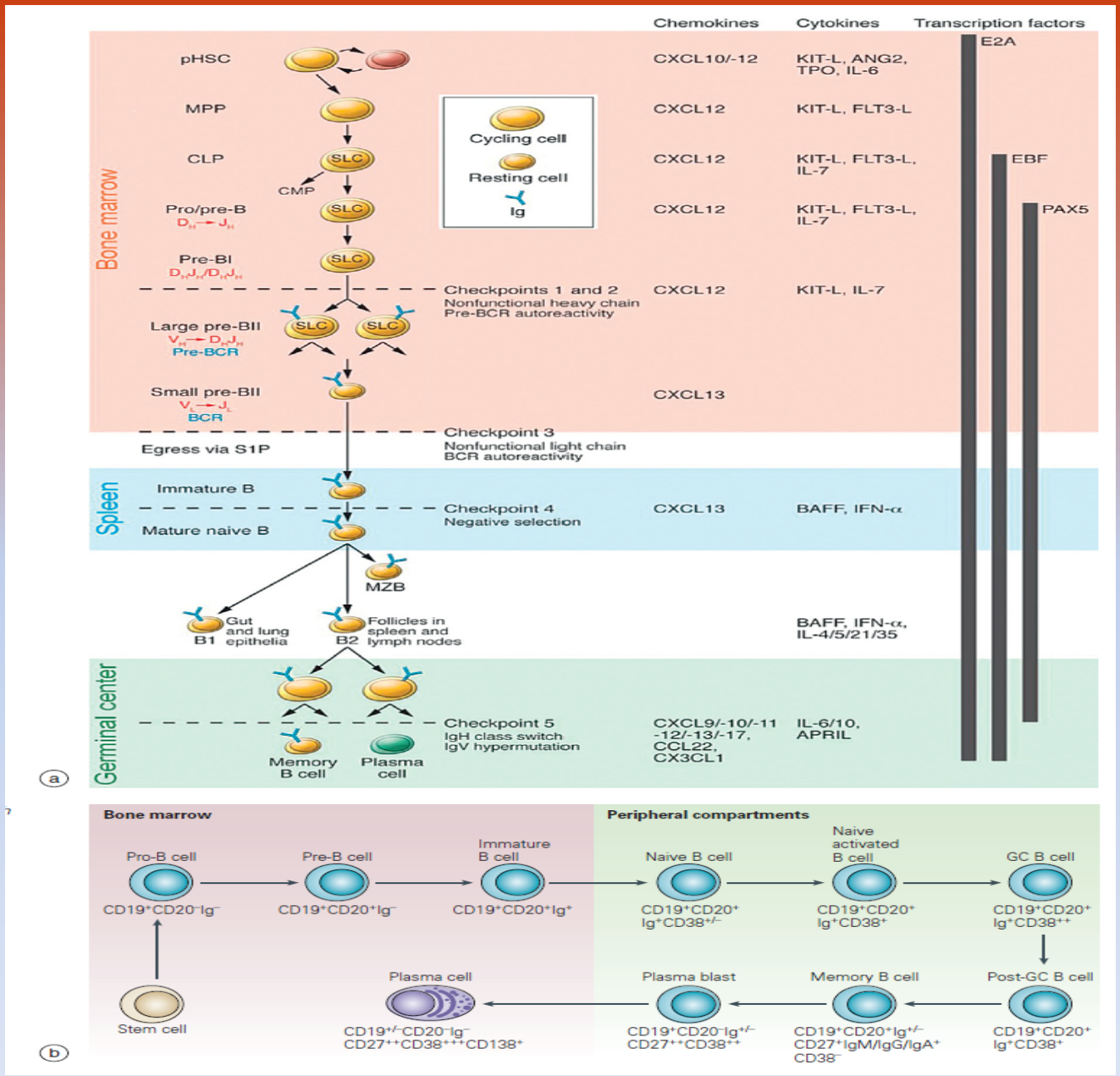
■ All these processes provide targets for therapeutic manipulation in autoimmune rheumatic diseases.

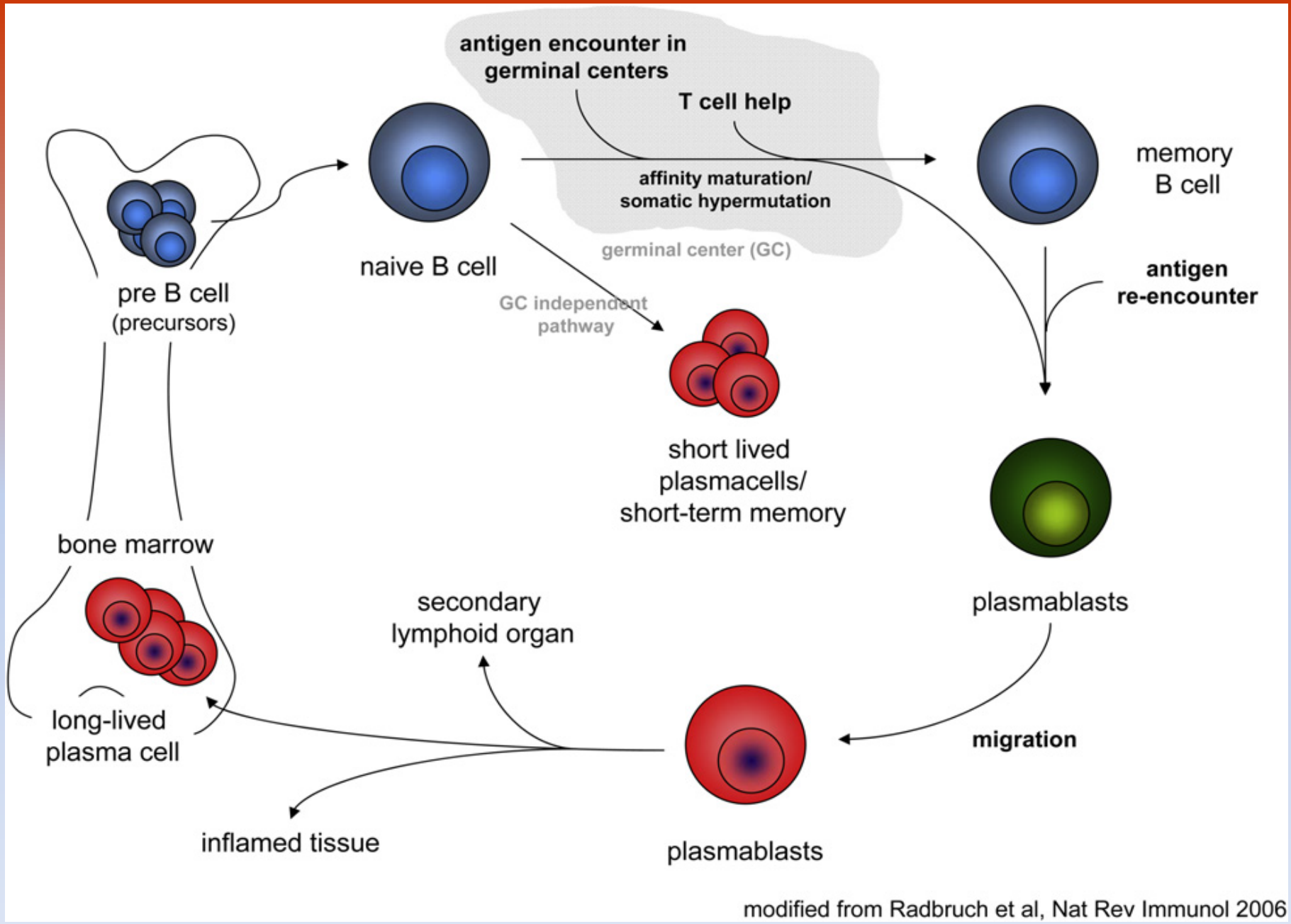
- Both innate and adaptive parts of the immune system must first **recognize their targets**; this process is commonly referred to as the **cognitive phase**. It is followed by **the effector phase**, during which the immune cells respond to the threat.
- **The cognitive phase** defines the central difference between innate and adaptive immunity. In the innate immune system, the PRRs are rather ubiquitously expressed and are ready to bind PAMPs immediately, thus instantly activating the effector phase. In contrast, the adaptive recognition system is constructed to identify and respond effectively to **myriads of unpredictable new foreign molecules (antigens) without confusing them with the body's own molecules**. This process is more complex and less efficient than the functioning of innate immunity, and therefore it is slower.
- To save time during the subsequent encounters with the newly "learned" antigens, adaptive immunity is **capable of retaining specific immunologic memory of previous experiences** and responds much faster and more effectively the next time a previously encountered antigen threatens the host.



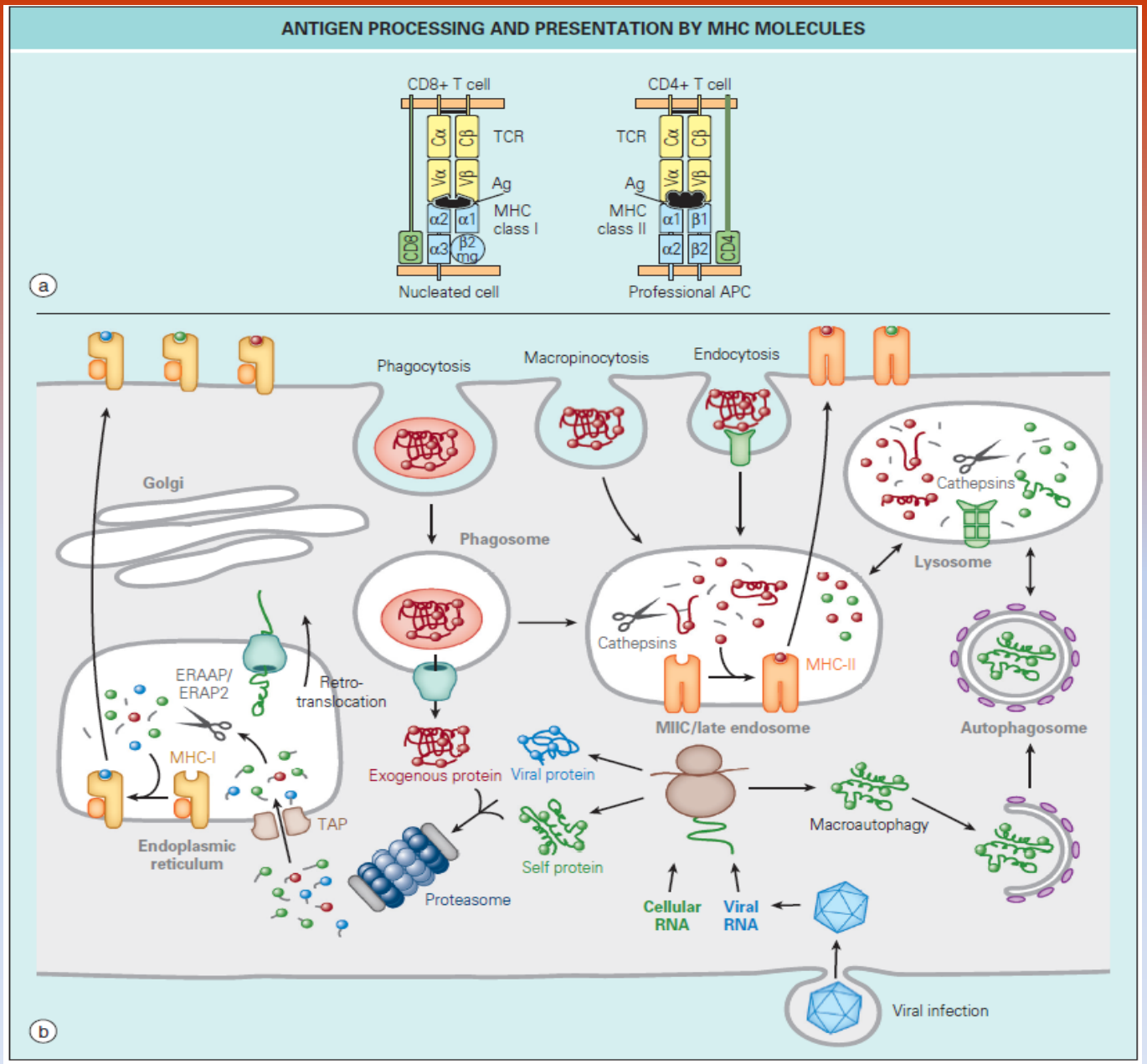
A model of immunoglobulin G (IgG) is shown on the left, a model of surface IgM B-cell receptor is shown in the middle, and a model of T-cell receptor αβ is shown on the right. Constant (C) and variable (V) domains are indicated, as well as heavy (H) and light (L) chains of immunoglobulins.

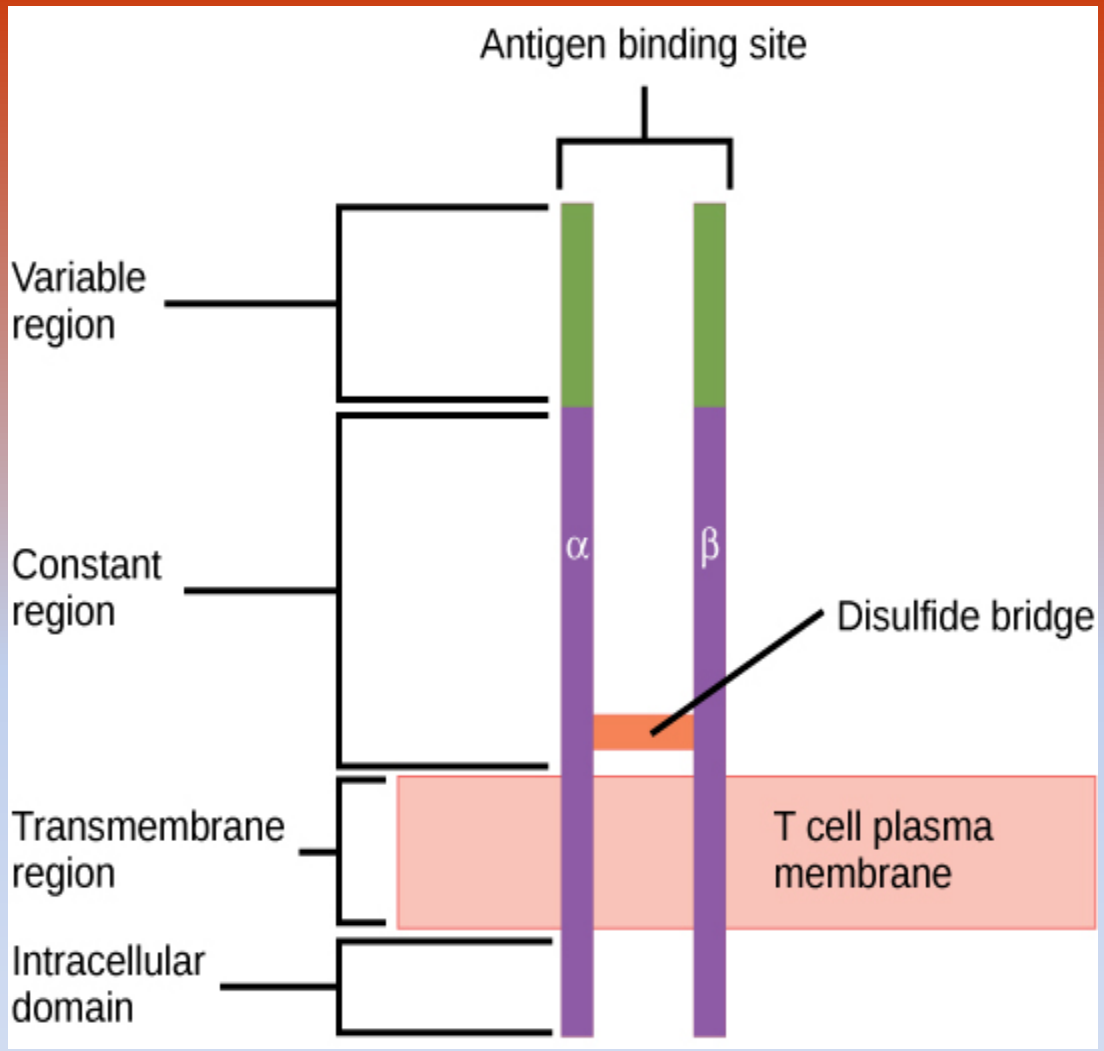

THE STRUCTURE OF ANTIGEN RECEPTOR GENES
A. Igh
VH (150)
2.8 Mb
DH (9)
60 kb
JH (4)
1.4 kb
Eμ
CH
3′RR
Germline
PDQ52
Recombination
center
Assembled
V D J
B. Igk
Distal
Proximal
Jκ (4)
1.4 kb
iEκ
Cκ
3′Eκ
Vκ (140)
3.2 Mb
C. Tcrb
PDβ1
Dβ1
Jβ1 (6)
2.5 kb
Cβ1
Dβ2
PDβ2
Jβ2 (6)
2.5 kb
Cβ2
Eβ
Vβ14
Vβ (30)
380 kb
D. Tcra–Tcrd
Dδ1
Dδ2
Eδ
TEA
PJα49
Cα
Eα
Vα or Vδ (100)
1.4 Mb
Jδ2 Jδ2
Cδ
Vδ5
Jα (61)
64 kb


Chemokines
Cytokines
Transcription factors
E2A
EBF
PAX5
Bone marrow
pHSC
CXCL10/-12
KIT-L, ANG2, TPO, IL-6
MPP
CXCL12
KIT-L, FLT3-L
CLP
CXCL12
KIT-L, FLT3-L, IL-7
CMP
Pro/pre-B
CXCL12
KIT-L, FLT3-L, IL-7
Pre-BI
Cycling cell
Resting cell
Ig
Checkpoints 1 and 2
Nonfunctional heavy chain
Pre-BCR autoreactivity
CXCL12
KIT-L, IL-7
Large pre-BII
Pre-BCR
Small pre-BII
BCR
CXCL13
Checkpoint 3
Nonfunctional light chain
BCR autoreactivity
Egress via S1P
Spleen
Immature B
Checkpoint 4
Negative selection
CXCL13
BAFF, IFN-α
Mature naive B
MZB
B1
Gut and lung epithelia
B2
Follicles in spleen and lymph nodes
BAFF, IFN-α, IL-4/5/21/35
Germinal center
Checkpoint 5
IgH class switch
IgV hypermutation
CXCL9/-10/-11 -12/-13/-17, CCL22, CX3CL1
IL-6/10, APRIL
Memory B cell
Plasma cell
a
Bone marrow
Peripheral compartments
Pro-B cell
CD19+CD20−Ig−
Pre-B cell
CD19+CD20+Ig−
Immature B cell
CD19+CD20+Ig+
Naive B cell
CD19+CD20+ Ig+CD38+/−
Naive activated B cell
CD19+CD20+ Ig+CD38+
GC B cell
CD19+CD20+ Ig+CD38++
Post-GC B cell
CD19+CD20+ Ig+CD38+
Memory B cell
CD19+CD20+Ig+/− CD27+IgM/IgG/IgA+ CD38−
Plasma blast
CD19+CD20−Ig+/− CD27++CD38++
Plasma cell
CD19+/−CD20−Ig− CD27++CD38+++CD138+
Stem cell
b

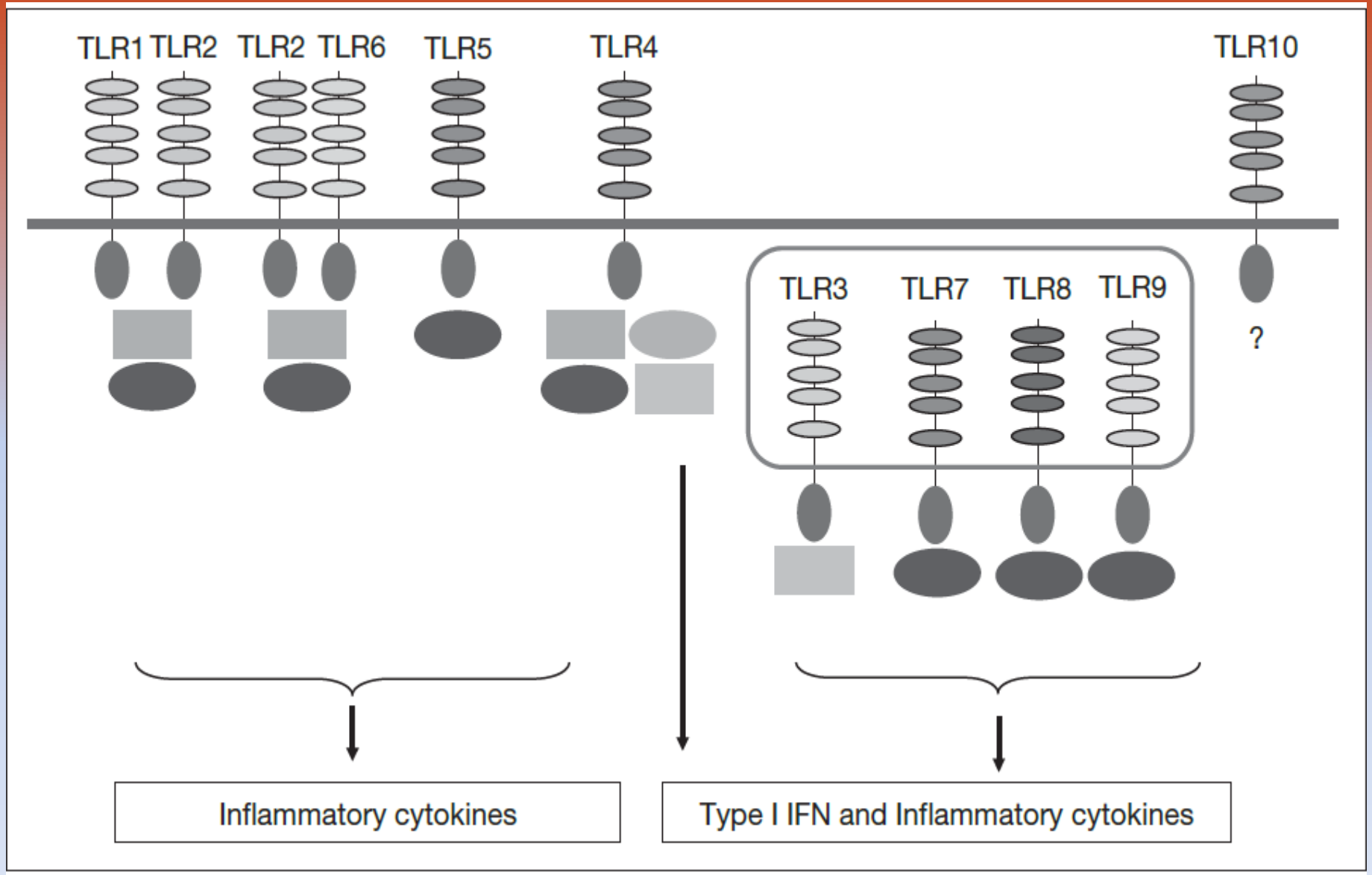


modified from Radbruch et al, Nat Rev Immunol 2006

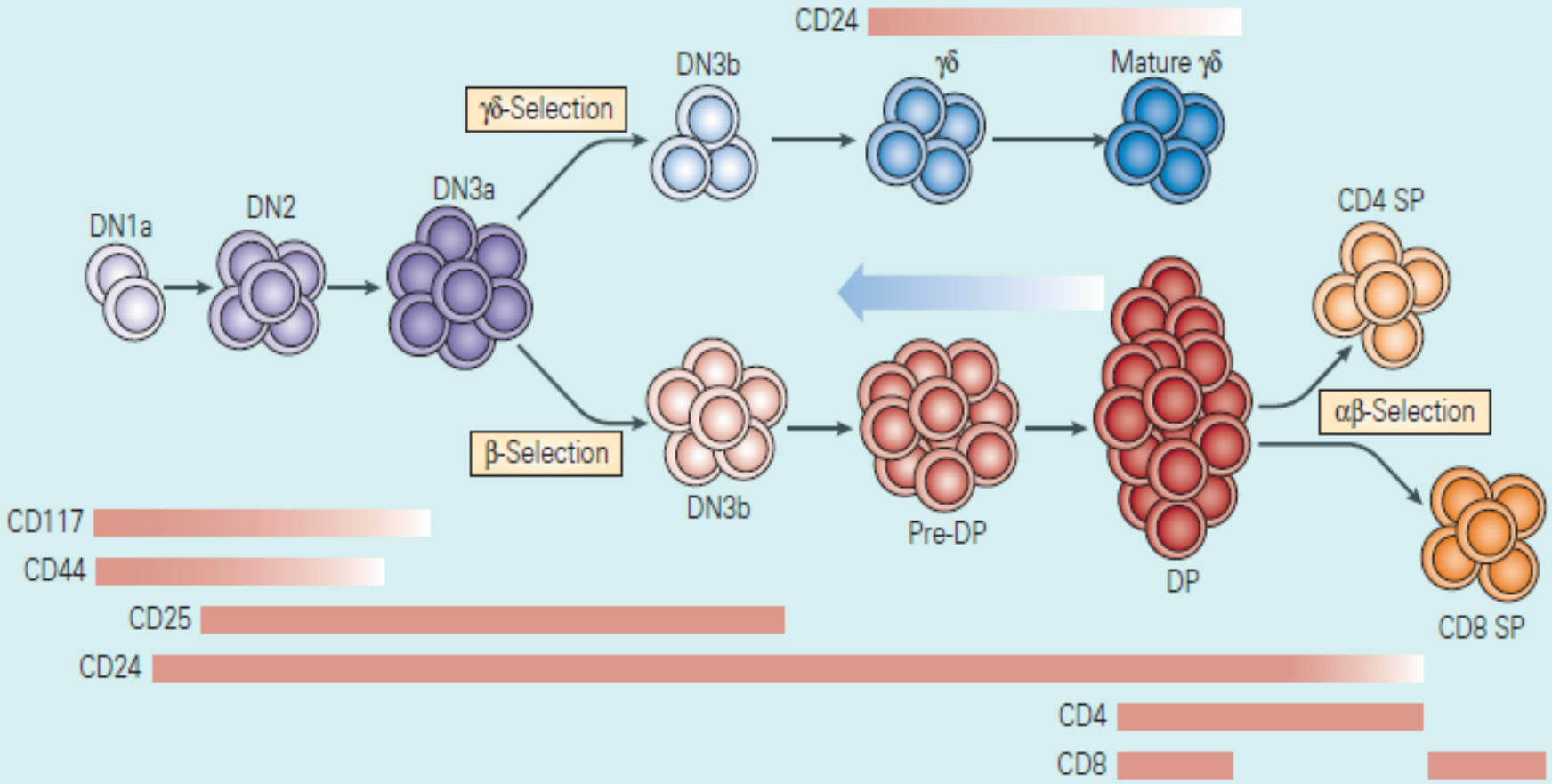

ANTIGEN PROCESSING AND PRESENTATION BY MHC MOLECULES
CD8+ T cell
CD4+ T cell
TCR
Ag
MHC class I
MHC class II
Nucleated cell
Professional APC
a
Phagocytosis
Macropinocytosis
Endocytosis
Golgi
Phagosome
Cathepsins
Lysosome
ERAAP/ ERAP2
Retro-translocation
MHC-I
MHC-II
MIIC/late endosome
Autophagosome
Exogenous protein
Viral protein
Self protein
TAP
Endoplasmic reticulum
Proteasome
Macroautophagy
Cellular RNA
Viral RNA
Viral infection
b



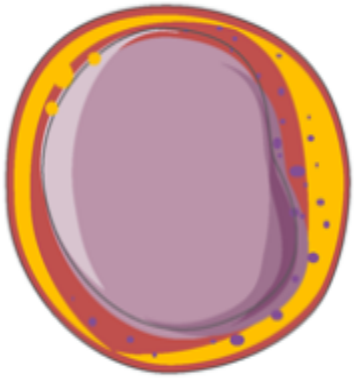
A T cell receptor spans the membrane and projects variable binding regions into the extracellular space to bind processed antigens via MHC molecules on APCs.


TLR1
TLR2
TLR2
TLR6
TLR5
TLR4
TLR10
TLR3
TLR7
TLR8
TLR9
?
Inflammatory cytokines
Type I IFN and Inflammatory cytokines

STAGES OF γδ AND αβ T-CELL DEVELOPMENT



γδT cell



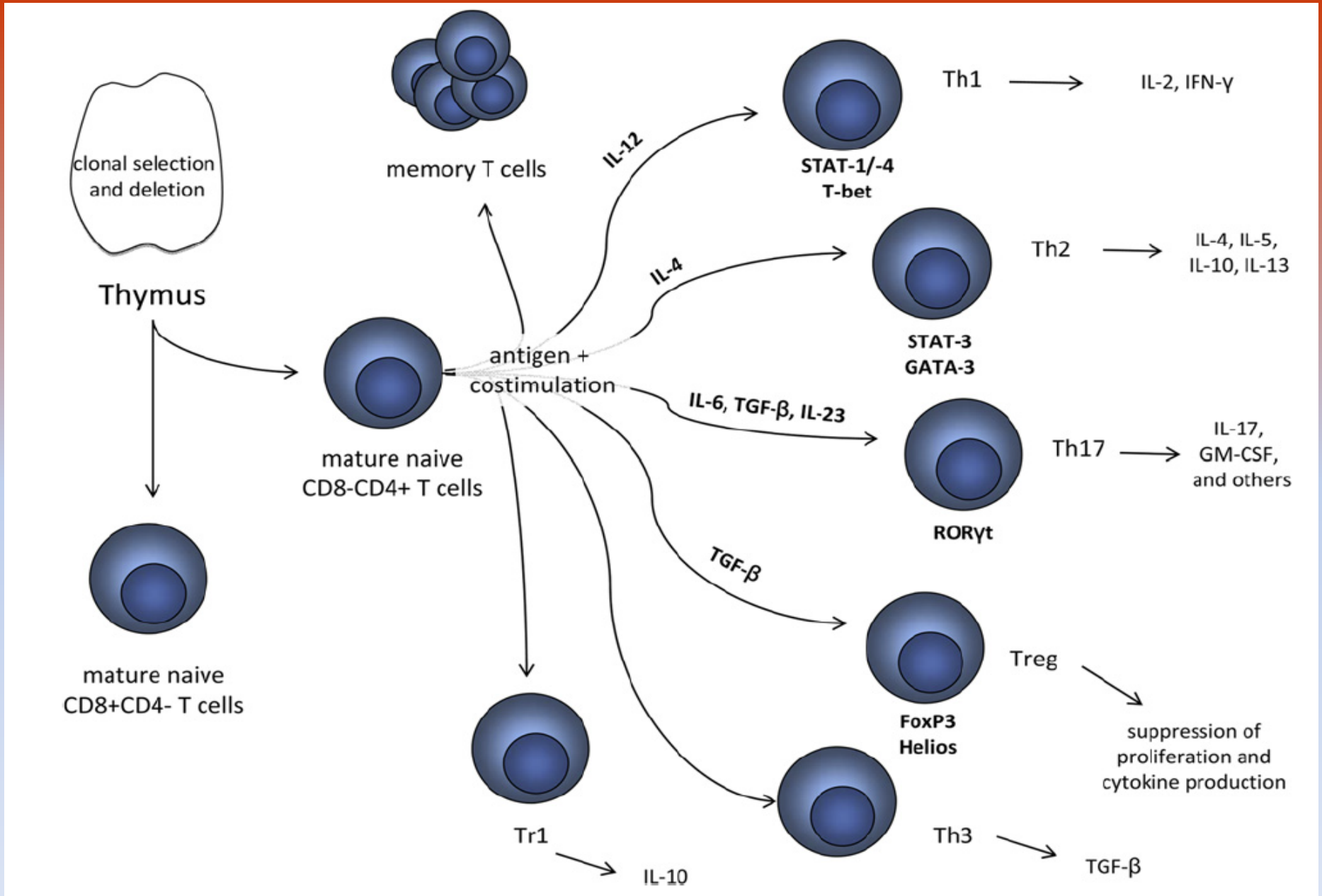
REGULATION OF IMMUNE RESPONSE
pro- and anti-inflammatory cytokines IFN-γ, TGF-β, TNFα, IL-4, IL-10, IL-17, IL-23…

RECOGNITION OF NON-SELF
synthetic alkyl phosphates, isopentenyl pyrophosphate and prenyl pyrophosphate derivatives, myelin-derived glycosphingolipid sulfatide, phycoerythrin, tetanus toxin, listeriolysin O

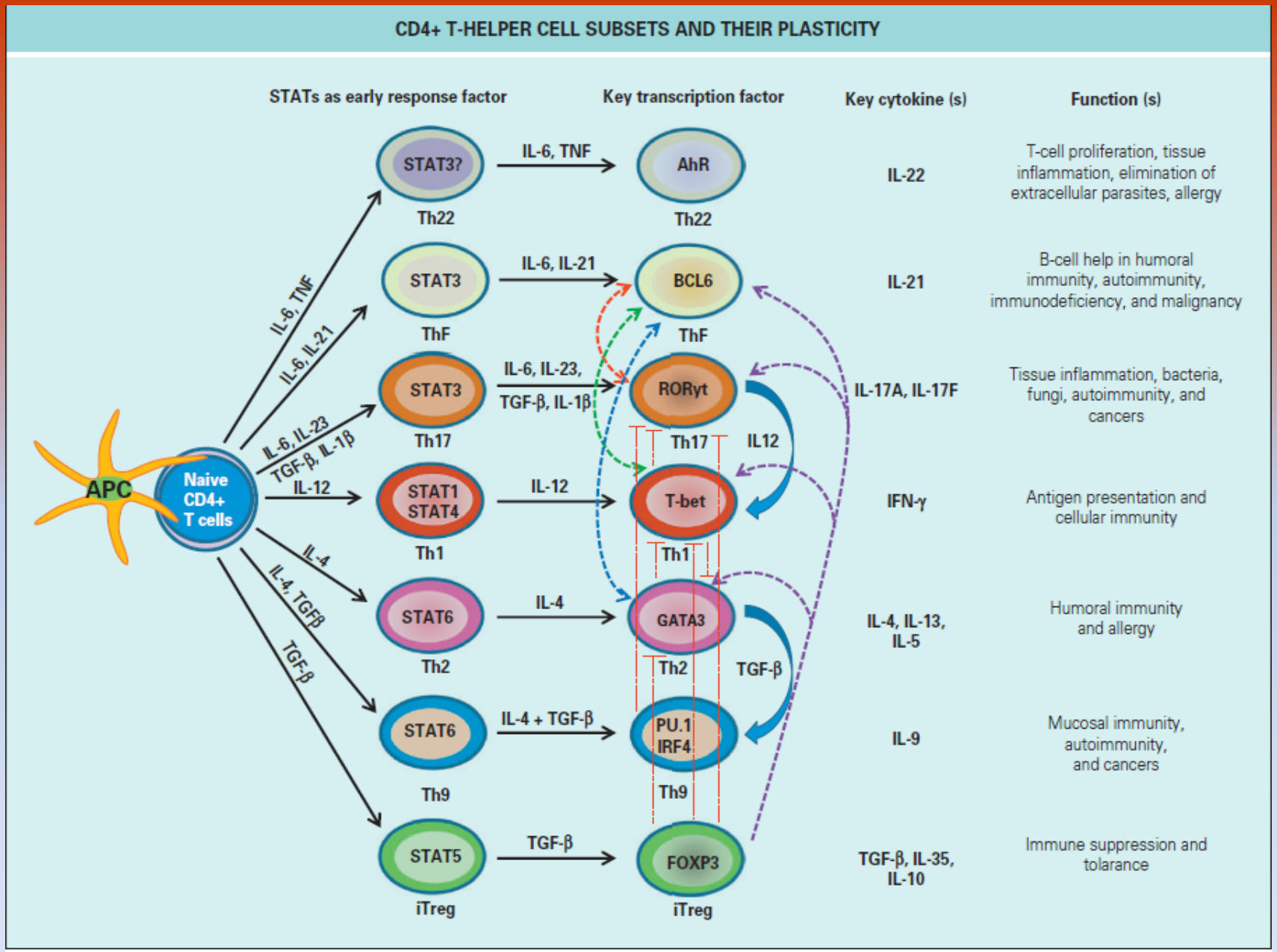
RECOGNITION OF ALTERED/STRESSED SELF
MICA/B, Hsp60, annexin A2, EPCR, BTN3A1, F1-ATPase/ApoI, T10/T22, Qa-1, Skint-1, BTN3A1…

WOUND HEALING/ANGIOGENESIS
production of KGF, IGF-1, EGF, FGF-9, ANG, PDGF or VEGF.

REGULATION OF THERMOGENESIS
IL-17 control ST2+ Treg cells producing IL-33 modulating activity and differentiation of brown and beige adipose tissue

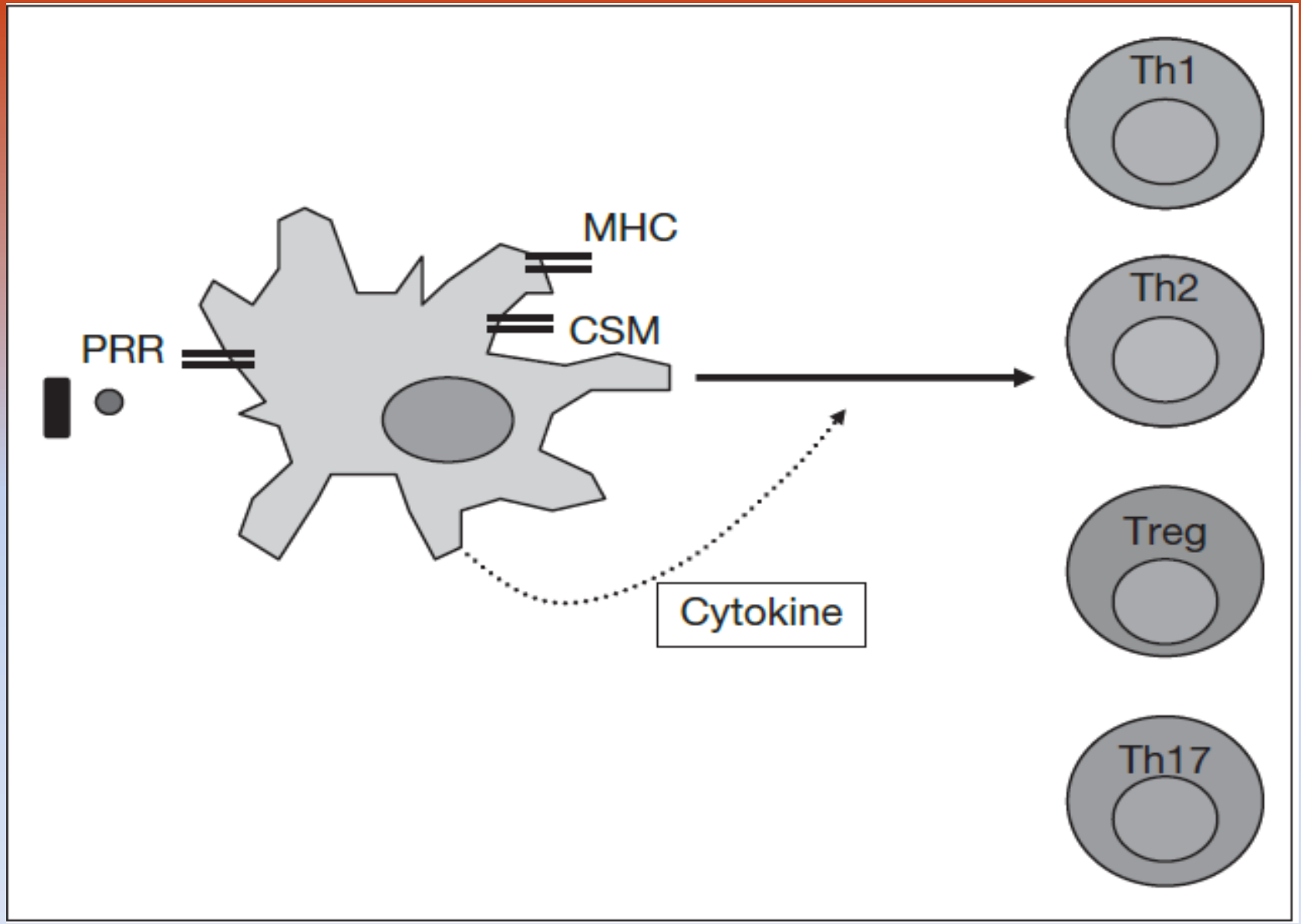

clonal selection and deletion
Thymus
memory T cells
IL-12
Th1
IL-2, IFN-γ
STAT-1/-4
T-bet
IL-4
Th2
IL-4, IL-5, IL-10, IL-13
STAT-3
GATA-3
antigen + costimulation
mature naive CD8-CD4+ T cells
IL-6, TGF-β, IL-23
Th17
IL-17, GM-CSF, and others
RORγt
mature naive CD8+CD4- T cells
TGF-β
Treg
FoxP3
Helios
suppression of proliferation and cytokine production
Tr1
IL-10
Th3
TGF-β

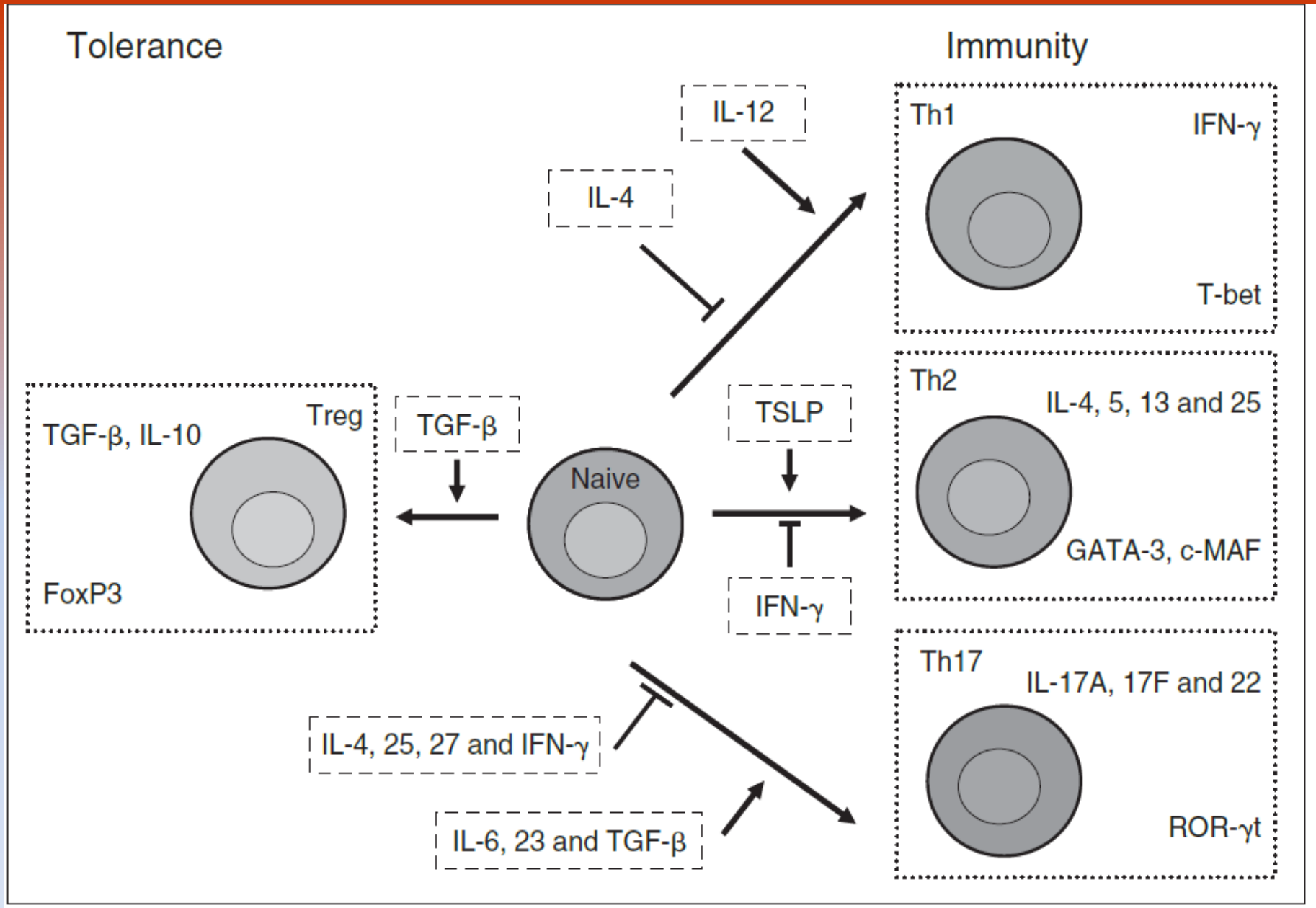
Main targets	T lymphocytes		Cytokines	ILCs	
viruses, bacteria autoimmunity	Th1		IFNγ		ILC1
helminths allergy	Th2		IL-4, IL-5, IL-13		ILC2
fungi, bacteria autoimmunity	Th17		IL-17, IL-22		ILC3
tumors, viruses alloreactivity	Tc		IFNγ perforin, granzymes		NK
downregulation of immune responses	Treg		IL-10,TGFβ		ILCreg


CD4+ T-HELPER CELL SUBSETS AND THEIR PLASTICITY
STATs as early response factor
Key transcription factor
Key cytokine (s)
Function (s)
APC
Naive CD4+ T cells
IL-6, TNF
IL-6, IL-21
IL-6, IL-23
TGF-β, IL-1β
IL-12
IL-4
IL-4, TGFβ
TGF-β
STAT3?
Th22
IL-6, TNF
AhR
Th22
IL-22
T-cell proliferation, tissue inflammation, elimination of extracellular parasites, allergy
STAT3
ThF
IL-6, IL-21
BCL6
ThF
IL-21
B-cell help in humoral immunity, autoimmunity, immunodeficiency, and malignancy
STAT3
Th17
IL-6, IL-23, TGF-β, IL-1β
RORγt
Th17
IL-17A, IL-17F
Tissue inflammation, bacteria, fungi, autoimmunity, and cancers
IL12
STAT1 STAT4
Th1
IL-12
T-bet
Th1
IFN-γ
Antigen presentation and cellular immunity
STAT6
Th2
IL-4
GATA3
Th2
IL-4, IL-13, IL-5
Humoral immunity and allergy
TGF-β
STAT6
Th9
IL-4 + TGF-β
PU.1 IRF4
Th9
IL-9
Mucosal immunity, autoimmunity, and cancers
STAT5
iTreg
TGF-β
FOXP3
iTreg
TGF-β, IL-35, IL-10
Immune suppression and tolarance

Mechanisms that control TLR activity in epithelial cells of the gastrointestinal tract

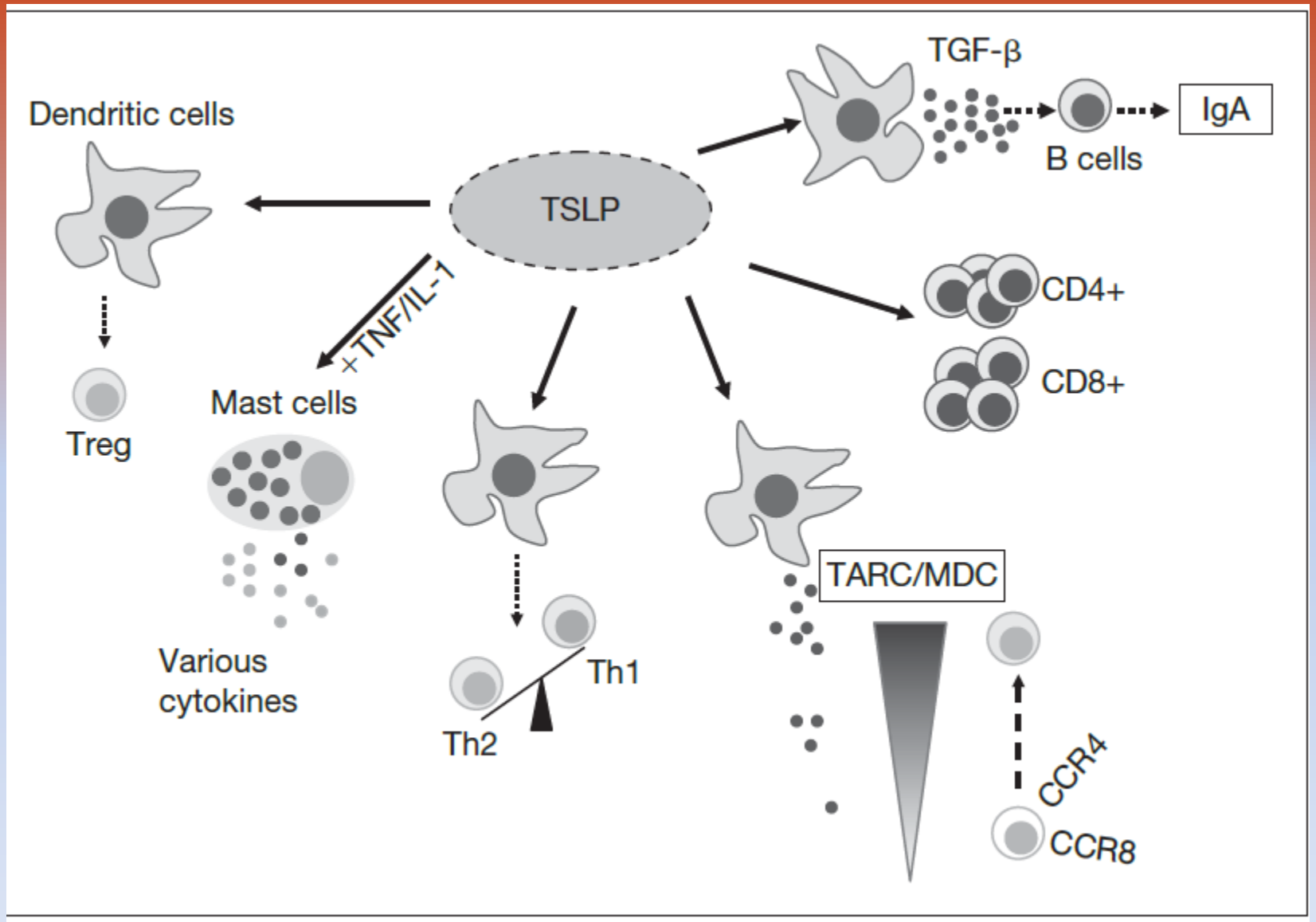
Reduced expression in areas of higher bacterial load – e.g. colon vs. small intestine
Preferential expression on basal surface of epithelium (e.g. TLR5)
Limited TLR repertoire
Endotoxin (and other PAMPs) tolerance
Expression of inhibitory molecules
Physiological role in gut immune homeostasis


Th1
MHC
Th2
CSM
PRR
Treg
Cytokine
Th17


Tolerance
Immunity
IL-12
IL-4
Th1
IFN-γ
T-bet
Th2
IL-4, 5, 13 and 25
GATA-3, c-MAF
TSLP
IFN-γ
TGF-β
Treg
TGF-β, IL-10
FoxP3
Naive
Th17
IL-17A, 17F and 22
ROR-γt
IL-4, 25, 27 and IFN-γ
IL-6, 23 and TGF-β

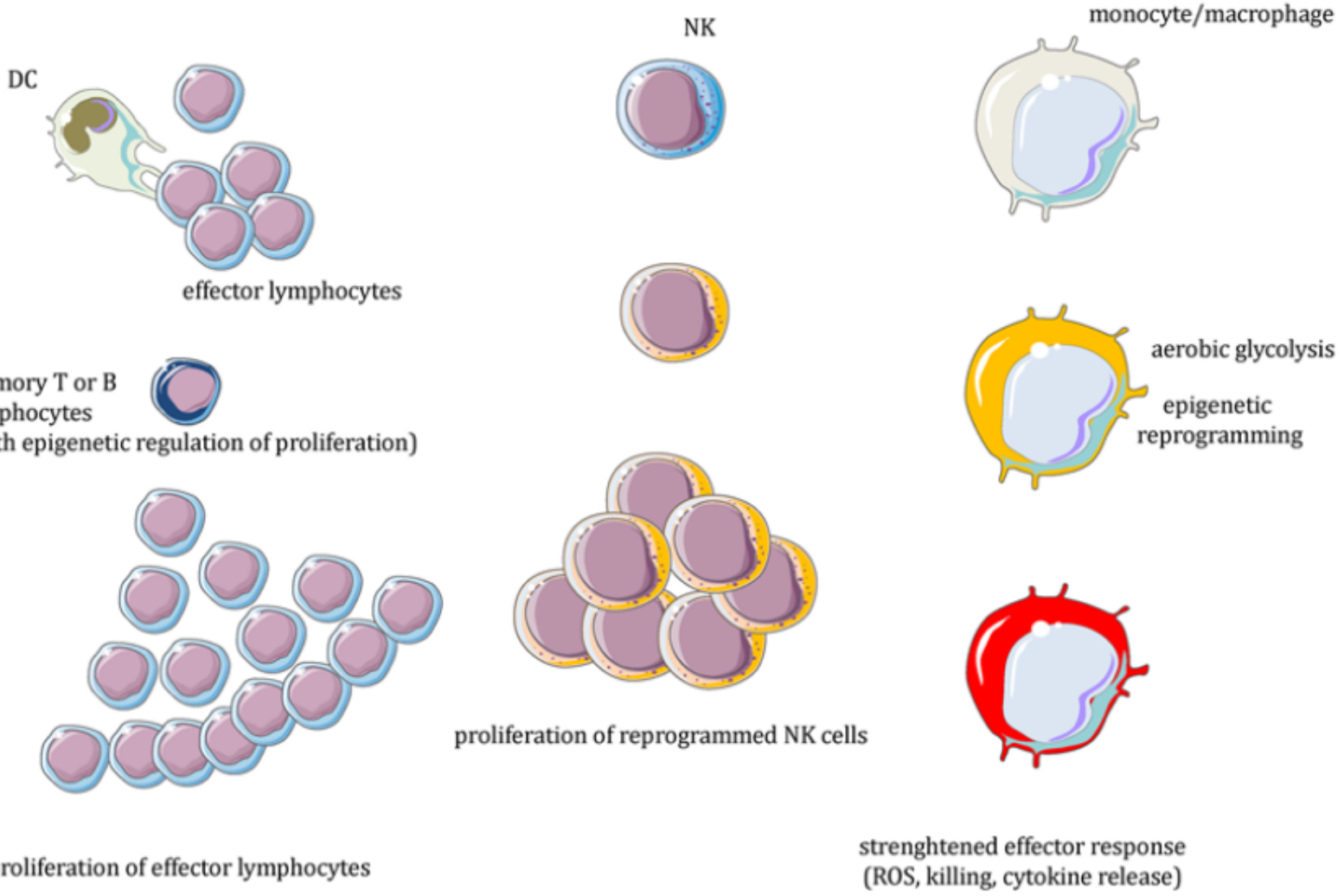
IgA-mediated mechanisms with a role in non-inflammatory immune protection

Trapping dietary antigen and microorganisms in mucus
Limiting commensal flora from breaching the epithelium
Down-modulating proinflammatory epitopes on commensal bacteria
Blocking epithelial attachment by microorganisms
Facilitating antigen sampling by M (microfold) cells
Promoting clearance of microorganisms via IgA receptor expressed on dendritic cells, neutrophils and other cell types


TGF-β
Dendritic cells
IgA
B cells
TSLP
TNF/IL-1
CD4+
CD8+
Treg
Mast cells
TARC/MDC
Various
cytokines
Th1
Th2
CCR4
CCR8

Imunological memory based on clonal expansion of antigen-specific cells

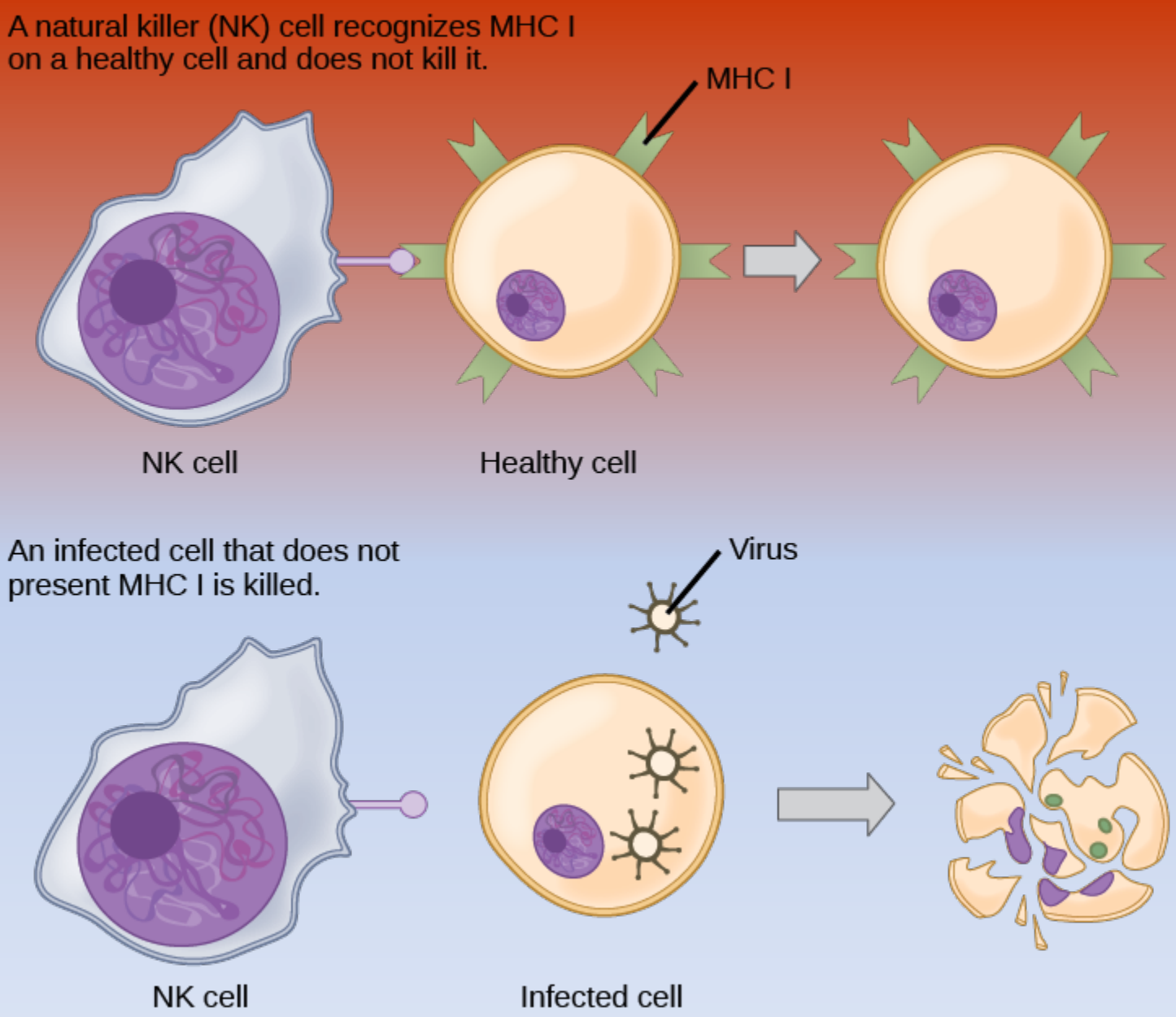
Immunological memory based on metabolic and epigenetic changes



TLRs represent one of the major families of PRRs used by immune cells for sensoring microbial motifs and molecular patterns of tissue injury

Receptor	CD	Location	Major ligands	Target
TLR1	CD281	Plasma membrane	Triacylated lipopeptides	Bacteria
TLR2	CD282	Plasma membrane	Multiple glycolipids, lipopeptides and lipoproteins	Bacteria, fungi
TLR3	CD283	Endolysosomal compartment	dsRNA	Viruses
TLR4	CD284	Plasma membrane	LPS, HSPs, low-density lipoproteins	Bacteria, endogenous proteins
TLR5	CD285	Plasma membrane	Flagellin, profilin	Bacteria, *Toxoplasma gondii*
TLR6	CD286	Plasma membrane	Multiple diacylated lipopeptides, lipoteichoic acid, zymosan	Bacteria, mycoplasma
TLR7	CD287	Endolysosomal compartment	ssRNA	Viruses, bacteria, self RNA
TLR8	CD288	Endolysosomal compartment	ssRNA	Viruses, bacteria, self RNA
TLR9	CD289	Endolysosomal compartment	Unmethylated CpG-containing DNA	Bacteria, DNA viruses
TLR10	CD290	Plasma membrane	Unknown, dsRNA?	Unknown
Mouse TLR11	*Gm287*	*Endolysosomal compartment*	*Profilin*	*T. gondii*
Mouse TLR12	*Gm1365*	*Endolysosomal compartment*	*Profilin*	*T. gondii*
Mouse TLR13	*Gm713*	*Endolysosomal compartment*	*Bacterial ribosomal RNA*	*Bacteria*

Natural killer (NK) cells recognize the MHC I receptor on healthy cells. If MHC I is absent, the cell is lysed.



Exercises

1- Which of the following statements about T cells is false?

A-Helper T cells release cytokines while cytotoxic T cells kill the infected cell.

Helper

B-T cells are CD4+, while cytotoxic T cells are CD8+.

C-MHC II is a receptor found on most body cells, while MHC I is a receptor found on immune cells only.

D- The T cell receptor is found on both CD4+ and CD8+ T cells.

2- Based on what you know about MHC receptors, why do you think an organ transplanted from an incompatible donor to a recipient will be rejected?

3- The Rh antigen is found on Rh-positive red blood cells. An Rh-negative female can usually carry an Rh-positive fetus to term without difficulty. However, if she has a second Rh-positive fetus, her body may launch an immune attack that causes hemolytic disease of the newborn. Why do you think hemolytic disease is only a problem during the second or subsequent pregnancies?

4- **Which of the following is both a phagocyte and an antigen-presenting cell?**

A- NK cell

B-eosinophil

C-neutrophil

D-macrophage

5- **Which immune cells bind MHC molecules on APCs via CD8 coreceptors on their cell surfaces?**

A-TH cells

B-CTLs

C-mast cells

D-basophils

6-What "self" pattern is identified by NK cells?

A-altered self

B-missing self

C-normal self

D-non-self

7-The acquired ability to prevent an unnecessary or destructive immune reaction to a harmless foreign particle, such as a food protein, is called _____.

A-the TH2 response
B-allergy
C-immune tolerance
D-autoimmunity

8-A memory B cell can differentiate upon re-exposure to a pathogen of which cell type?

A-CTL
B-naïve B cell
C-memory T cell
D-plasma cell

9-Foreign particles circulating in the blood are filtered by the _____.

A-spleen
B-lymph nodes
C-MALT
D-lymph

10-Explain the difference between an epitope and an antigen.

11-What is a naïve B or T cell?

12-How does the TH1 response differ from the TH2 response?

13-In mammalian adaptive immune systems, T cell receptors are extraordinarily diverse. What function of the immune system results from this diversity, and how is this diversity achieved?

14-How do B and T cells differ with respect to antigens that they bind?

15- Why is the immune response after reinfection much faster than the adaptive immune response after the initial infection?

1- C

2- MHC receptors differ from person to person. Thus, MHC receptors on an incompatible donor are considered “non-self” and are rejected by the immune system.

3- If the blood of the mother and fetus mixes, memory cells that recognize the Rh antigen can form late in the first pregnancy. During subsequent pregnancies, these memory cells launch an immune attack on the fetal blood cells. Injection of anti-Rh antibody during the first pregnancy prevents the immune response from occurring.

4- D

5- B

6- B

7- C

8- D

9- A

10- An antigen is a molecule that reacts with some component of the immune response (antibody, B cell receptor, T cell receptor). An epitope is the region on the antigen through which binding with the immune component actually occurs.

11- A naïve T or B cell is one that has not been activated by binding to the appropriate epitope. Naïve T and B cells cannot produce responses.

12- The TH1 response involves the secretion of cytokines to stimulate macrophages and CTLs and improve their destruction of intracellular pathogens and tumor cells. It is associated with inflammation. The TH2 response is involved in the stimulation of B cells into plasma cells that synthesize and secrete antibodies.

13- The diversity of TCRs allows the immune system to have millions of different T cells, and thereby to be specific in distinguishing antigens. This diversity arises from mutation and recombination in the genes that encode the variable regions of TCRs.

14- T cells bind antigens that have been digested and embedded in MHC molecules by APCs. In contrast, B cells function themselves as APCs to bind intact, unprocessed antigens.

15- Upon reinfection, the memory cells will immediately differentiate into plasma cells and CTLs without input from APCs or TH cells. In contrast, the adaptive immune response to the initial infection requires time for naïve B and T cells with the appropriate antigen specificities to be identified and activated.

Practice points

- The most important characteristics of the **adaptive immune** system are **specificity for antigen**, the ability to modulate and enhance this specificity and the ability to **generate life-long memory**.
- Both central and peripheral control mechanisms are crucial to prevent reactivity to self.
- Rheumatic diseases comprise a wide spectrum of conditions, of which some are caused by the **adaptive immune system**, while others develop because of **defects of the innate immune system**.
- The potential of the adaptive immune system to induce autoimmunity is usually controlled by a combination of **deletional and regulatory tolerance mechanisms**. Regulatory T cells play a central role in maintaining immune tolerance.
- **Failure of tolerance** leads to **autoimmunity**, in which the immune system attacks its **own tissues**. Autoimmunity commonly occurs in and contributes to mechanisms of rheumatic diseases. By its nature, the **adaptive immune system** potentially represents the **most specific target for therapy in autoimmune diseases**.