Basic Immunology

Lecture 18

Maintenance of the immunological memory and its role in immune response regulation. Comparison of the primary and secondary immune response.

Why is memory important?

- Ability of the adaptive (specific) IR
- Results protection against infections (diseases)
- The phenomenon is used for vaccination
- Ability to respond more rapidly and effectively to the same antigen → secondary, tertiary IR

Why is memory response more effective?

Clonal proliferation of antigen specific cells results a lot of:

-> effector cells -> death by apoptosis

-> memory cells -> survival

-> increase in frequency of antigen specific cells

1. T and B cells with highest affinity BcR and TcR have a chance to contact with the antigen and get signals overcome the apoptotic mechanisms

2. Antigen presenting cells are different

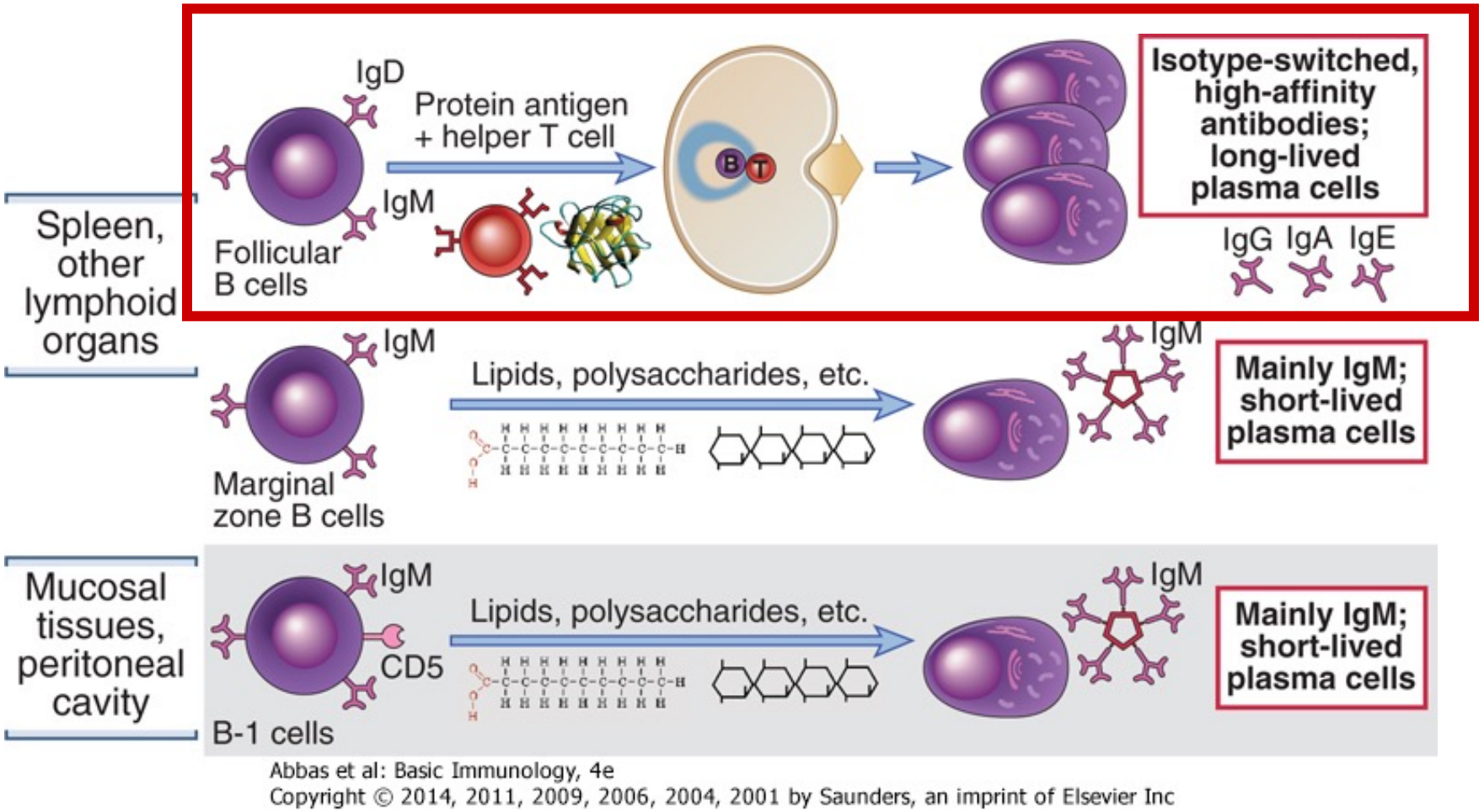
3. Homing behavior of lymphocytes is different

4. Surface adhesion molecules are different

5. CD45 isoform is different

B cell memory

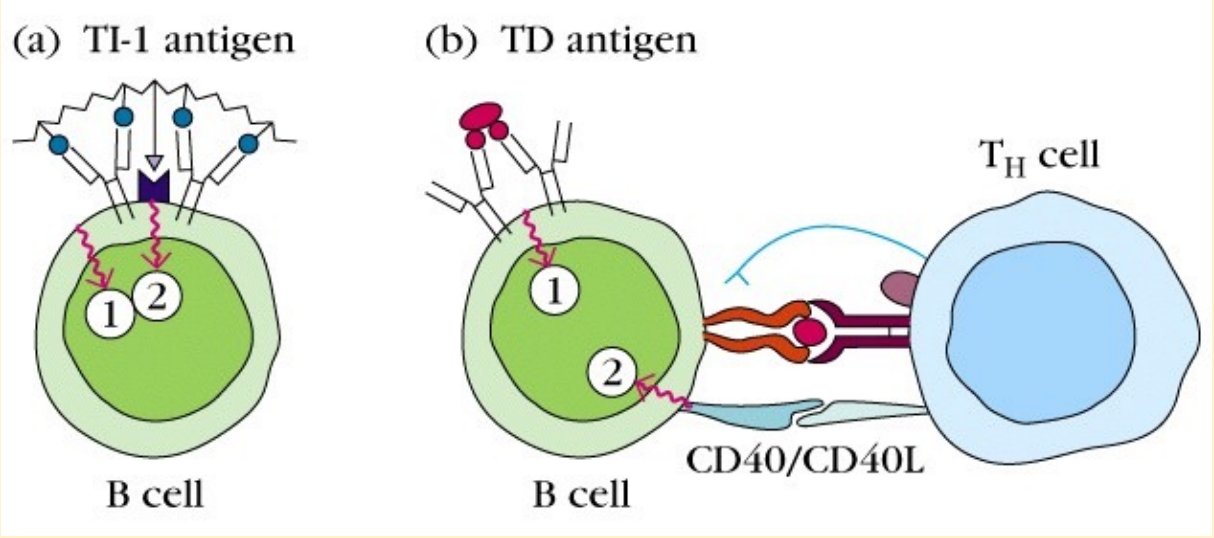
TD and TID antigen response



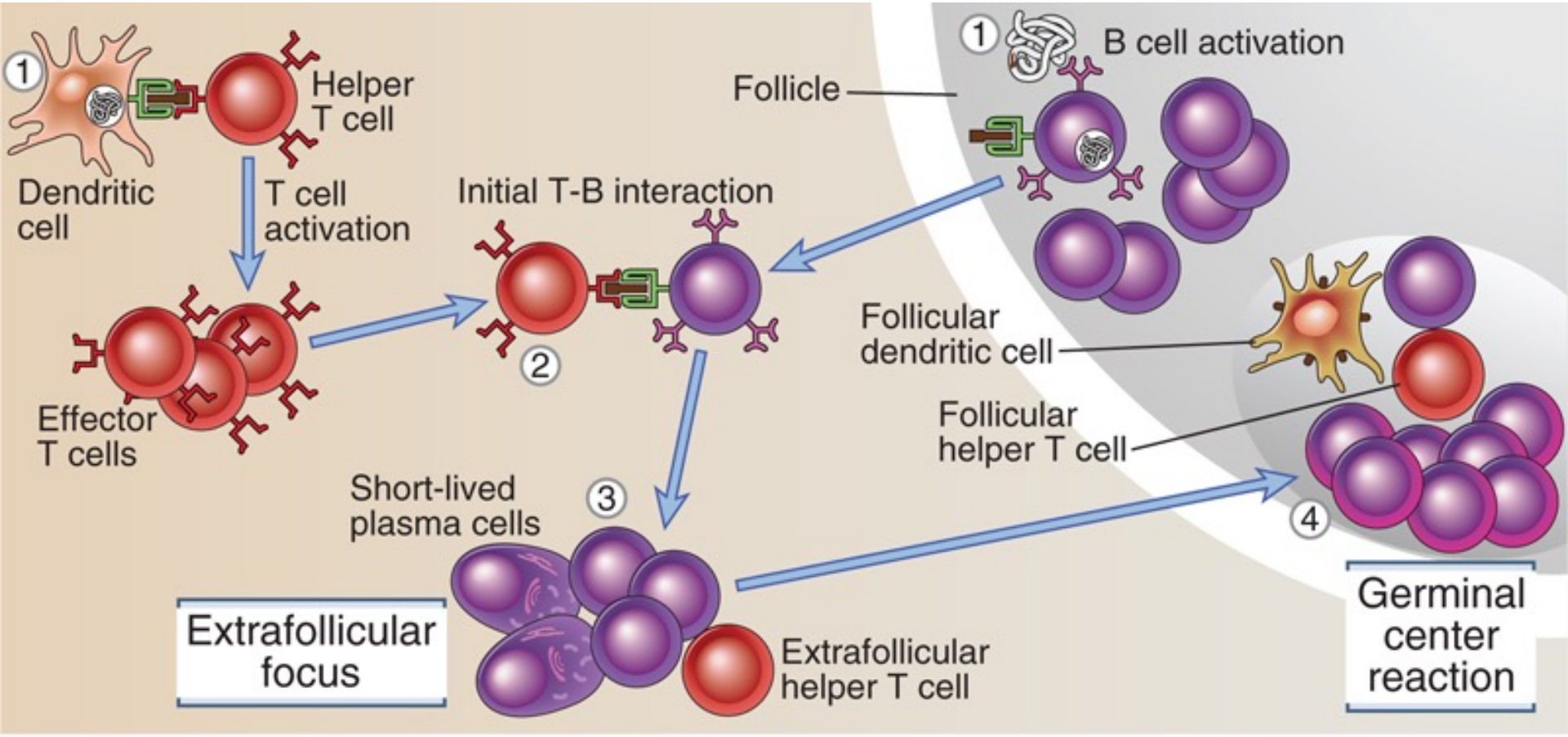
Only T dependent antigens induce immunological memory

TABLE 11-2 PROPERTIES OF THYMUS-DEPENDENT AND THYMUS-INDEPENDENT ANTIGENS

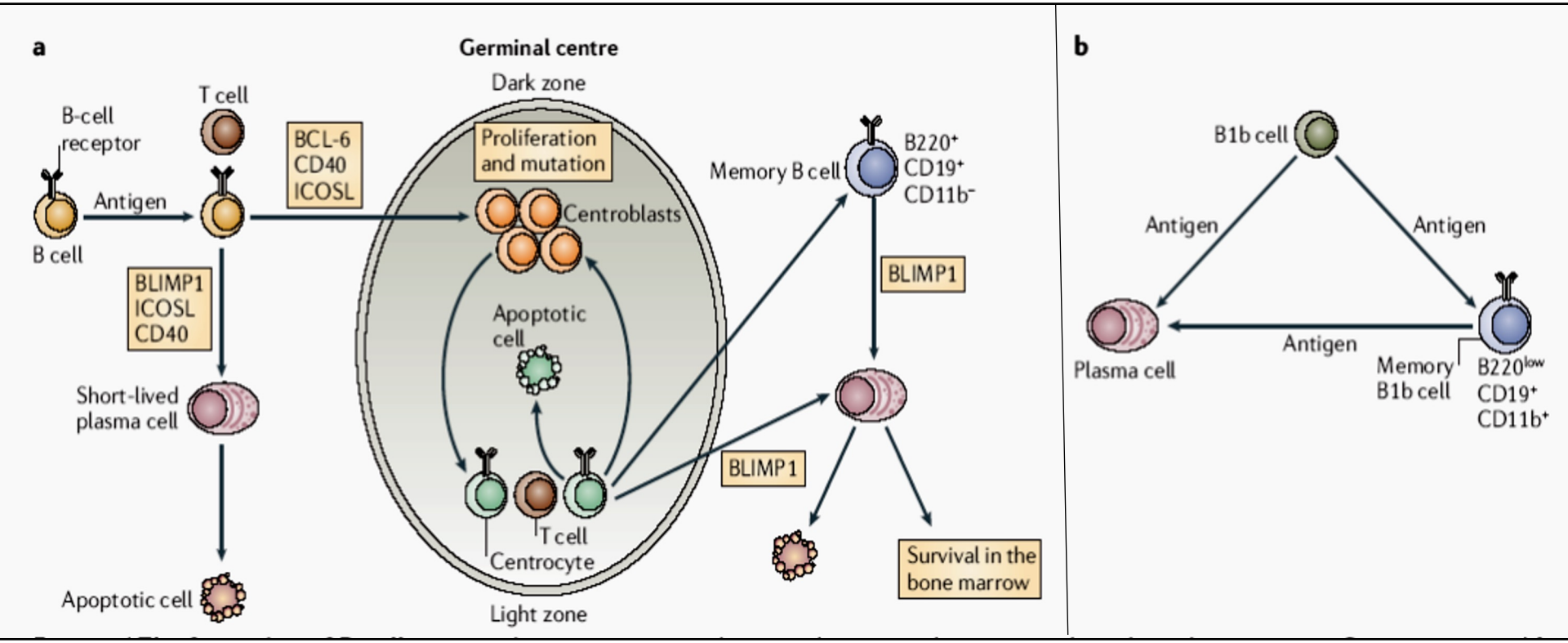
Property	TD antigens	TI antigens	
		Type 1	Type 2
Chemical nature	Soluble protein	Bacterial cell-wall components (e.g., LPS)	Polymeric protein antigens; capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No
Polyclonal activation	No	Yes (high doses)	No



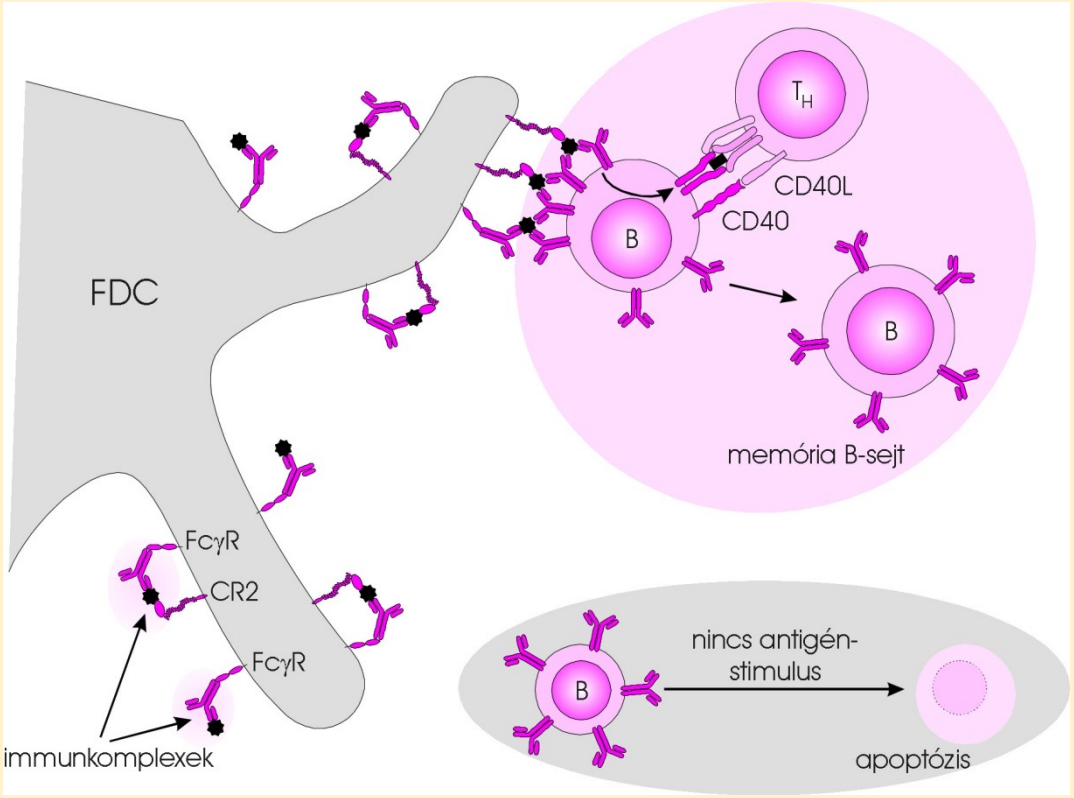
Extrafollicular and GC reaction



Antigen specific B cell memory



1. T and B cells with highest affinity BcR and TcR have a chance to contact with the antigen and get signals overcome the apoptotic mechanisms

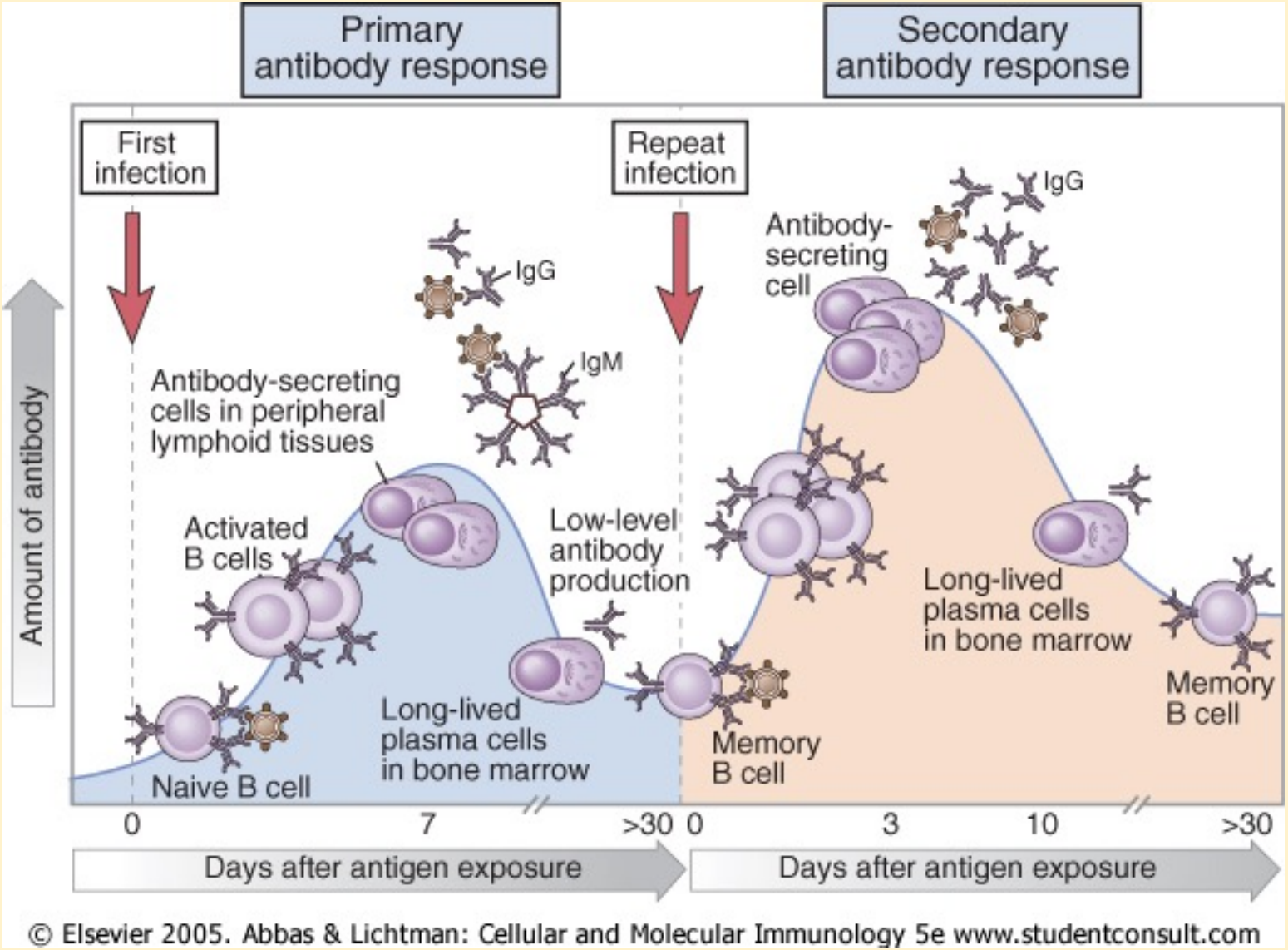


What gives the survival signal?

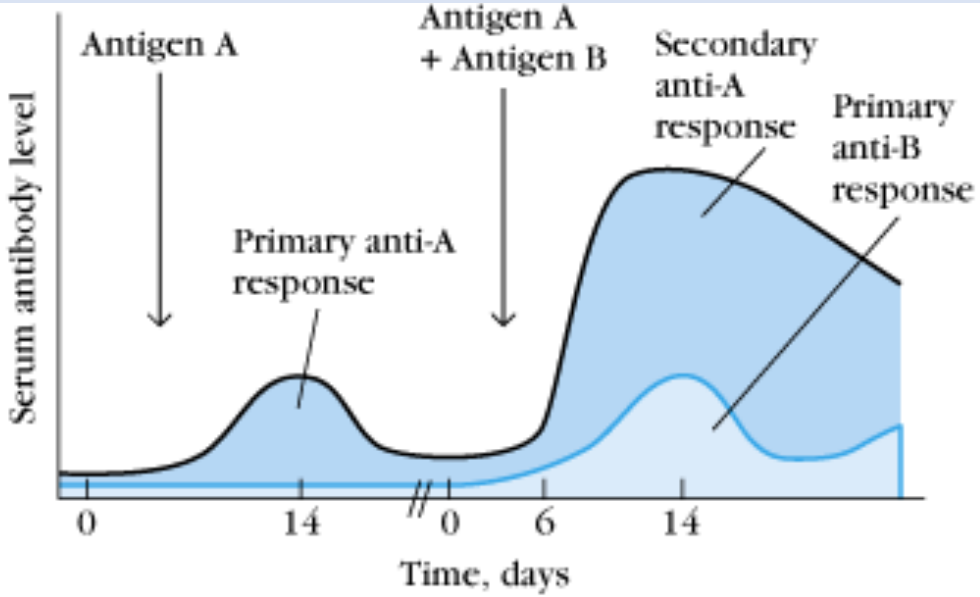
Minute amount of antigen present as IC on FDC or infected cells induce the division and survival of memory cells?

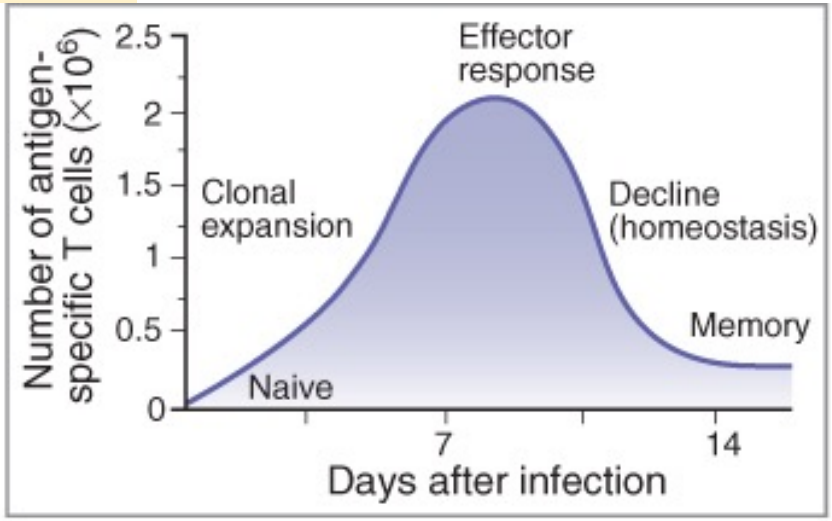
Cross-reactive antigens?

Idiotype-specific antibodies

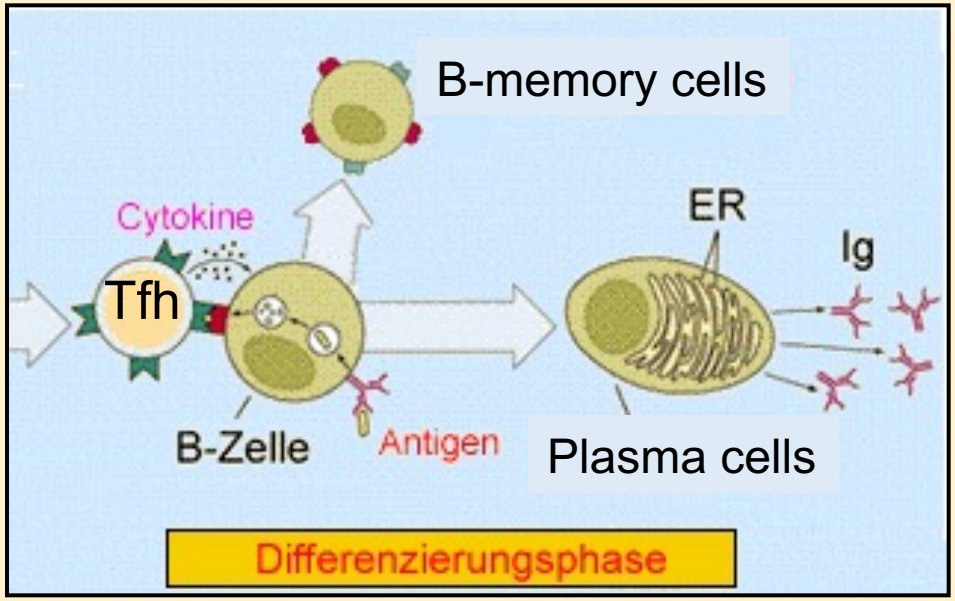


Serum Ig level and T cell number after infection



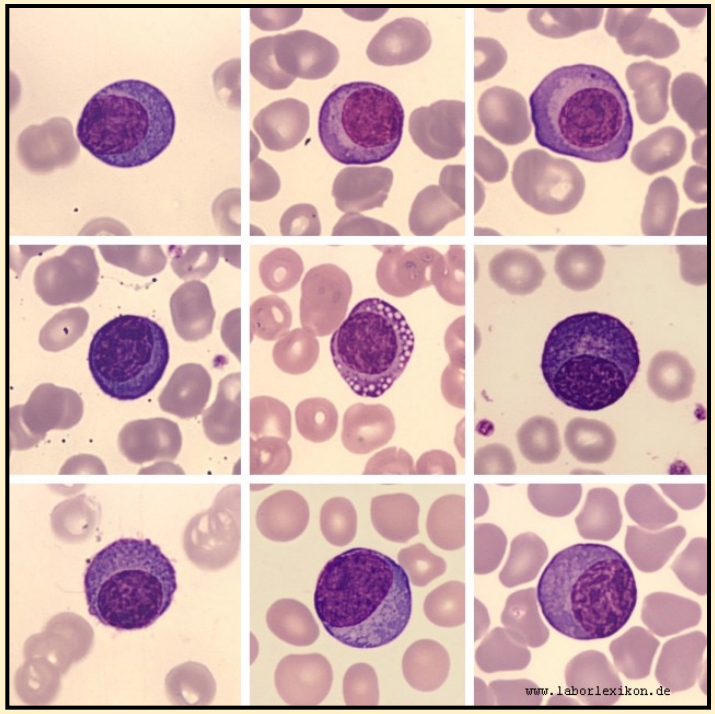


Plasma cells

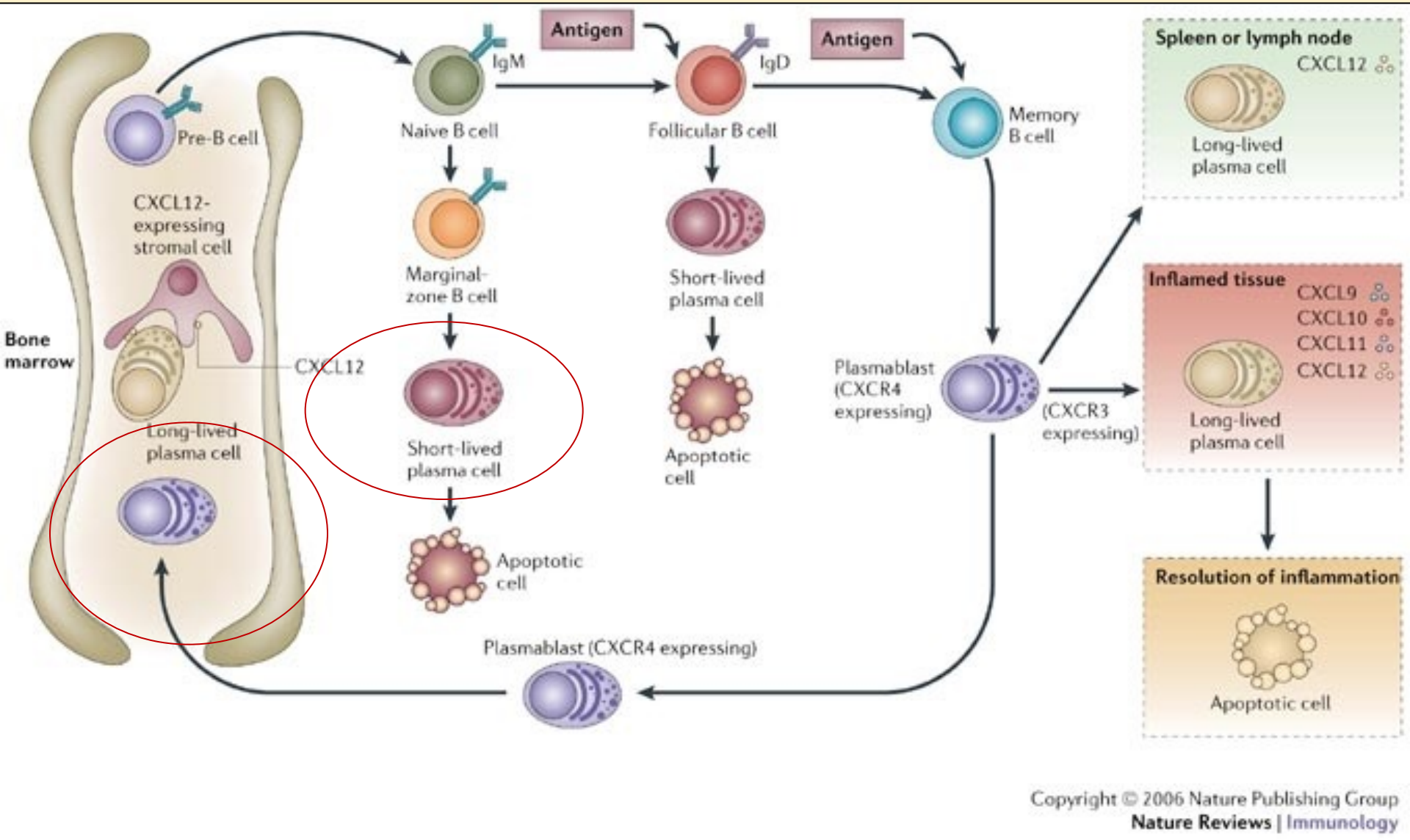


Cytokines: IL-2, IL-4, IL-5, IL-6, IL-10, IL-13…
CD40L-CD40 Signal

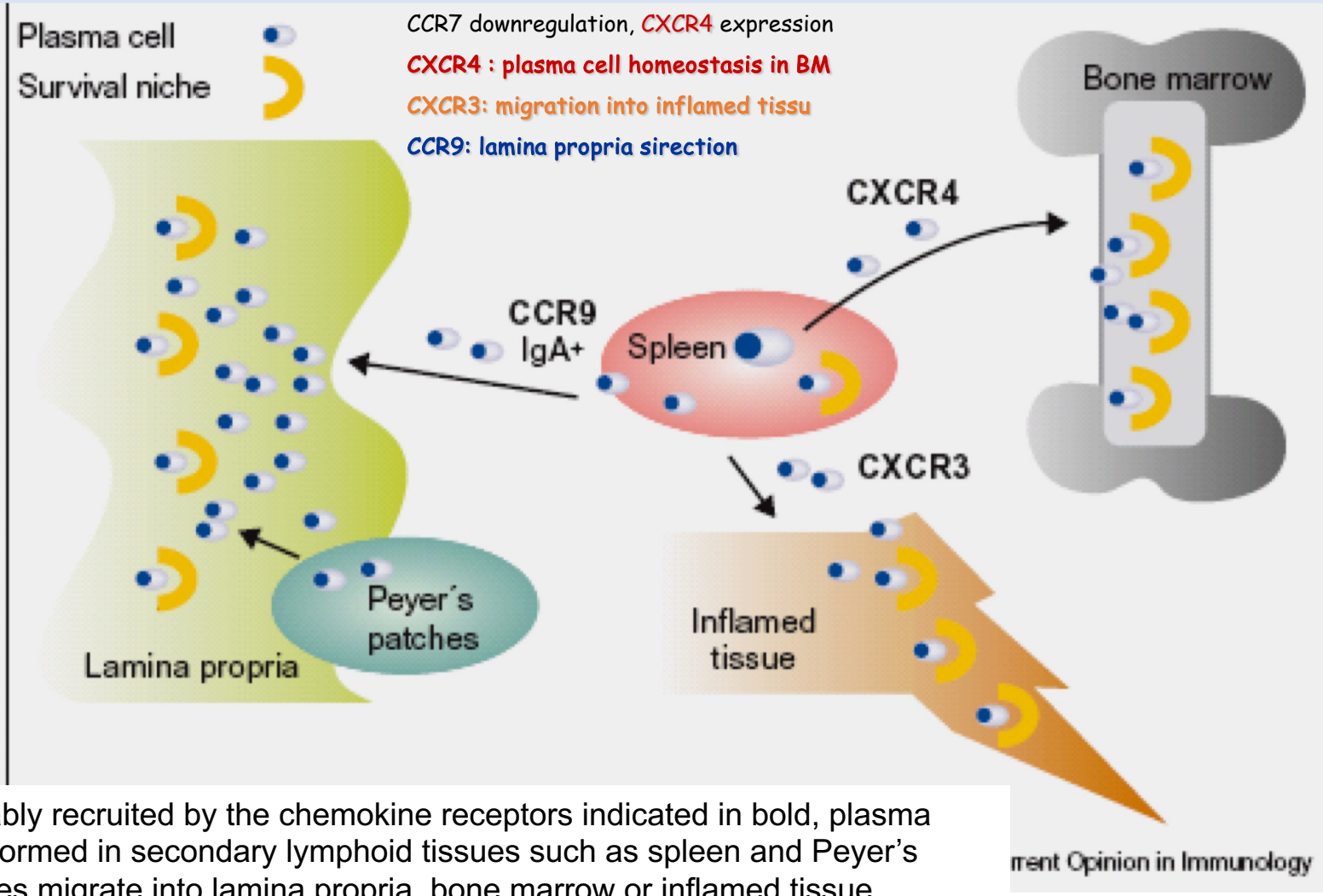
Plasma cells: CD38++



Where?
Bone marrox perivascular sinus
Mucosa Lamina Propria
Spleen red pulp
Lymph node medulla

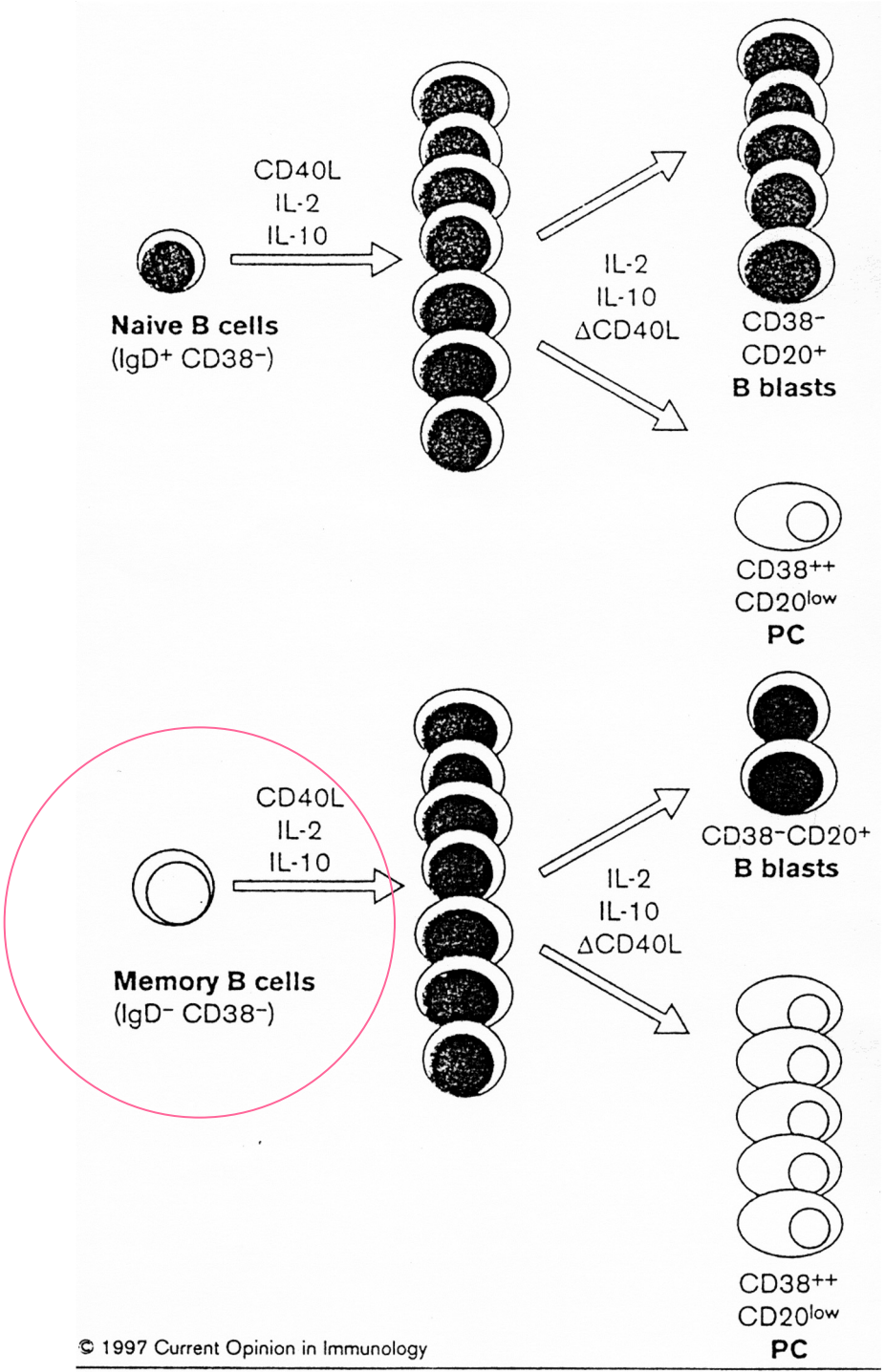


Possible regulation of plasma cell homeostasis by survival niches



Probably recruited by the chemokine receptors indicated in bold, plasma cells formed in secondary lymphoid tissues such as spleen and Peyer's patches migrate into lamina propria, bone marrow or inflamed tissue.

In the secondary, memory response mostly plasma cells differentiate form memory B cells (5x). In the primary response more B blasts and memory B cells are formed



Long-lived plasma cells

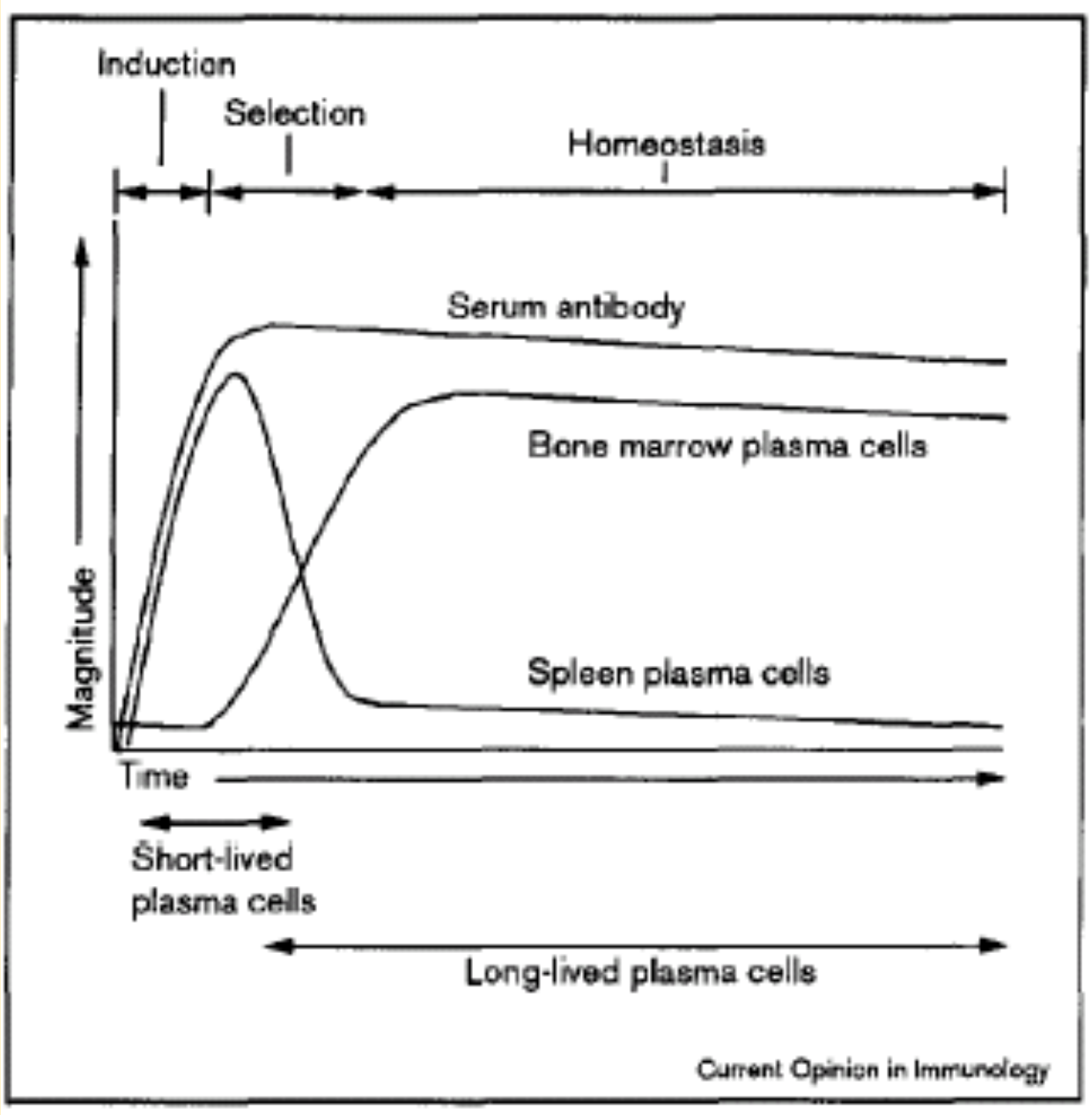


TABLE 11-4 COMPARISON OF PRIMARY AND SECONDARY ANTIBODY RESPONSES

Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher

BcR changes during memory formation !

TABLE 11-7 COMPARISON OF NAIVE AND MEMORY B CELLS

Properties	Naive B cell CD27- IgD+	Memory B cell CD27+ IgD-
Membrane markers		
Immunoglobulin	IgM, IgD	IgM, IgD(?), IgG, IgA, IgE
Complement receptor	Low	High
Anatomic location	Spleen	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation*
Adhesion molecules	Low ICAM-1	High ICAM-1

*Affinity maturation results from somatic mutation during proliferation of centroblasts and subsequent antigen selection of centrocytes bearing high-affinity mIg.

TcR does not change

TABLE 14-1 COMPARISON OF NAIVE AND EFFECTOR T CELLS

Property	Naive T cells	Effector T cells
Co-stimulatory signal (CD28-B7 interaction)	Required for activation	Not required for activation
CD45 isoform	CD45RA	CD45RO
Cell-adhesion molecules (CD2 and LFA-1)	Low	High
Trafficking patterns	HEVs* in secondary lymphoid tissue	Tertiary lymphoid tissues; inflammatory sites

*HEV = high endothelial venules, sites in blood vessel used by lymphocytes for extravasation.

T cell memory

Memory T-cell types

Naive T cell	Effector T cells	Memory T cells
CD45RA+	CD45RO+	CD45RO+
CD25lo	CD25hi	CD25lo
CD127hi	CD127lo	CD127hi
CD44lo	CD44hi	CD44hi

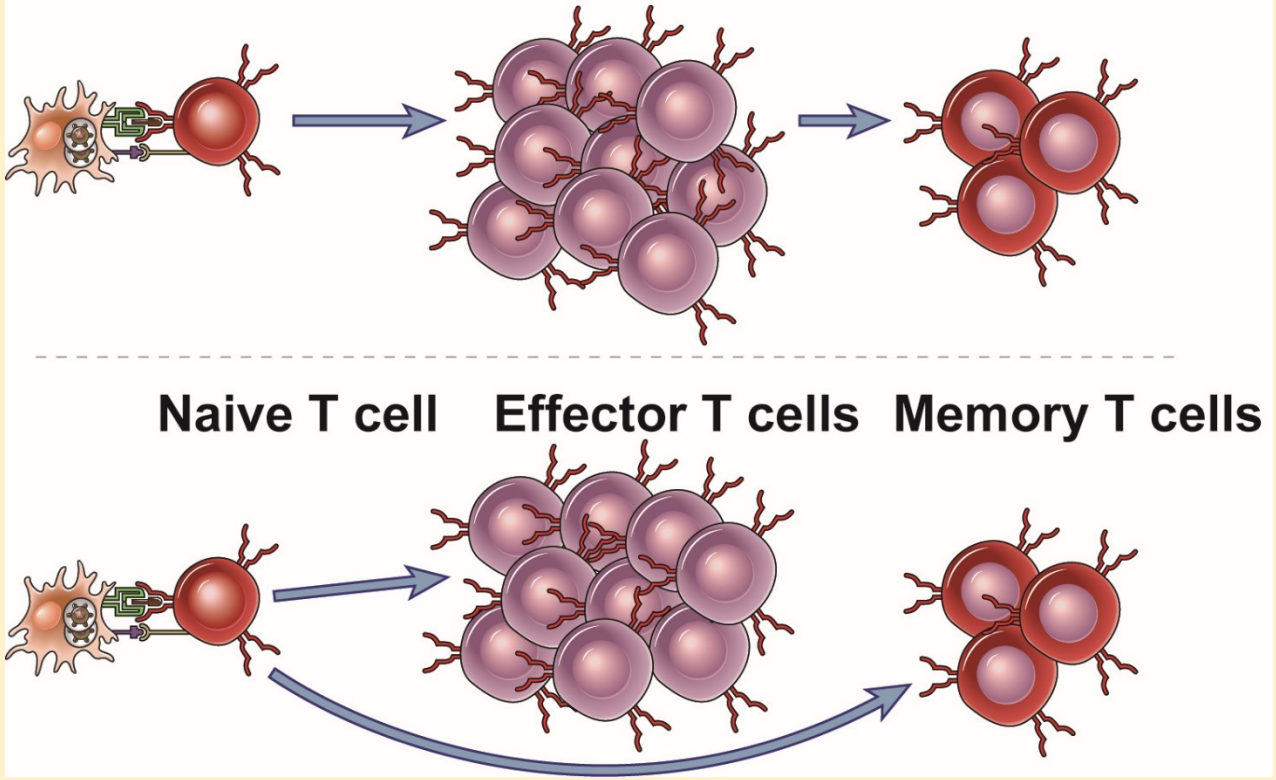


Fig. 9-19

Preferential survival of antigen-specific memory CD62LhiCD8+ T cells following influenza virus infection.

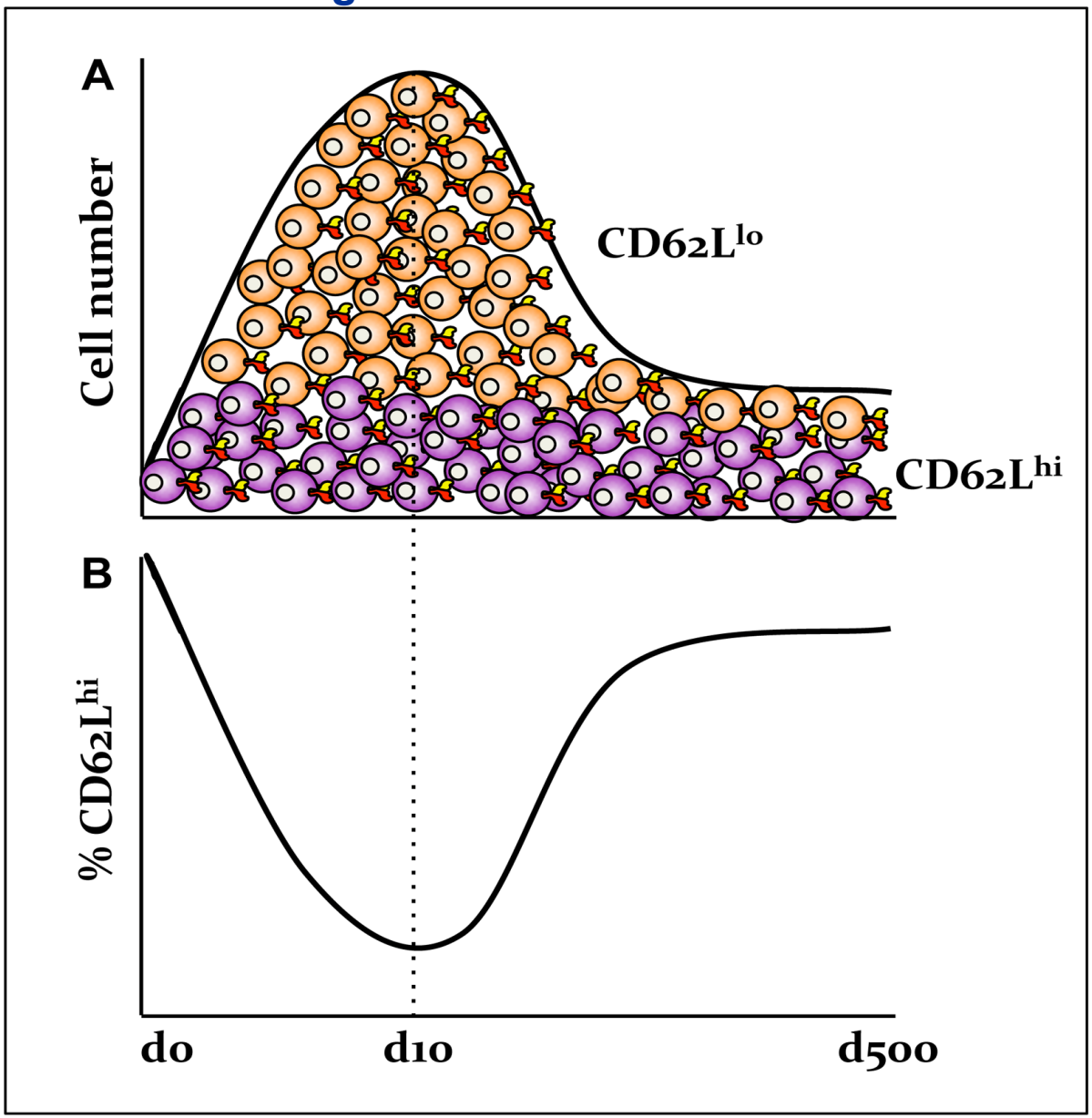
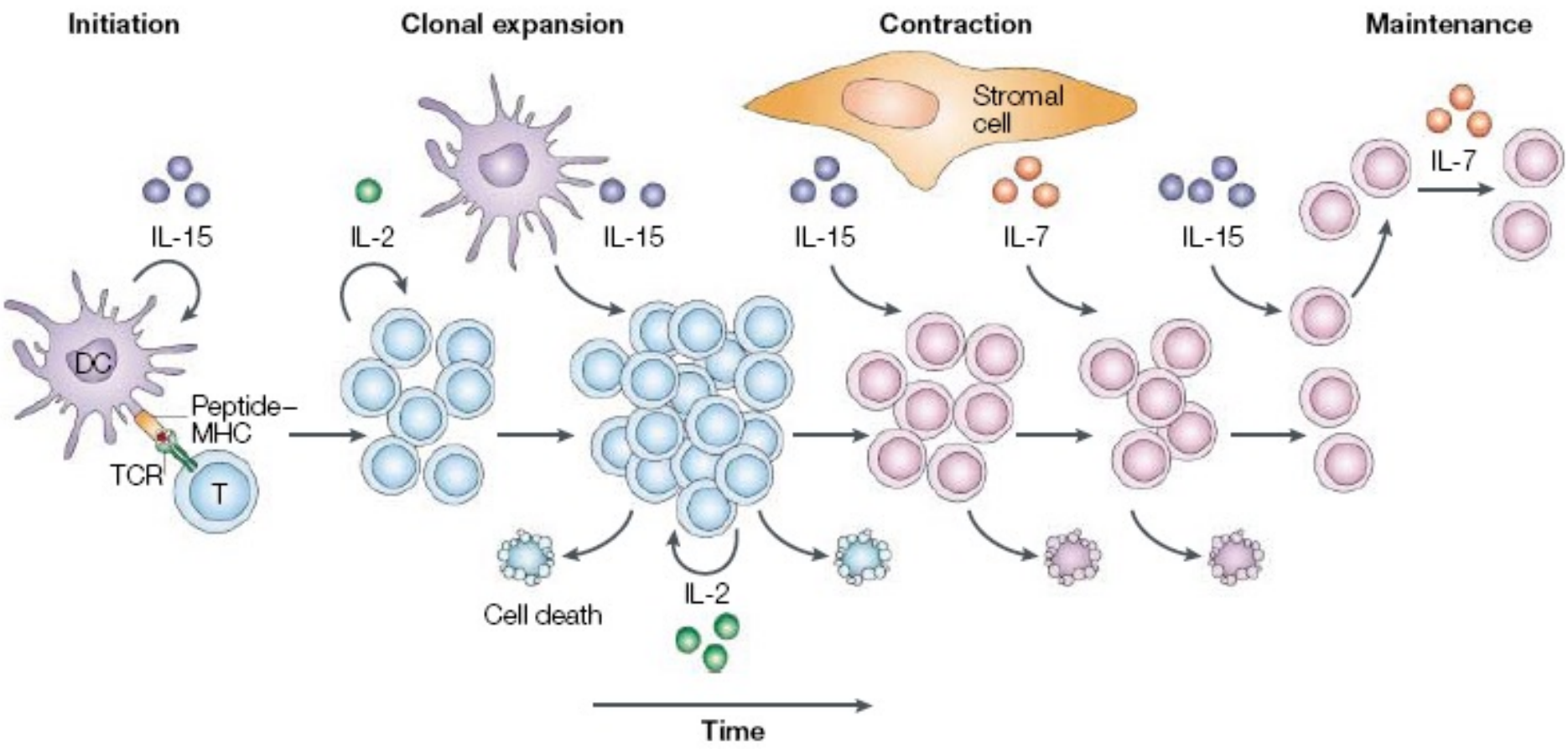


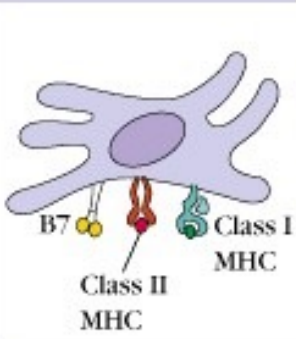
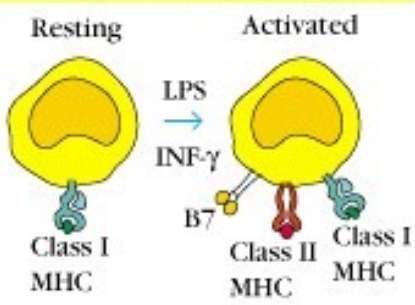
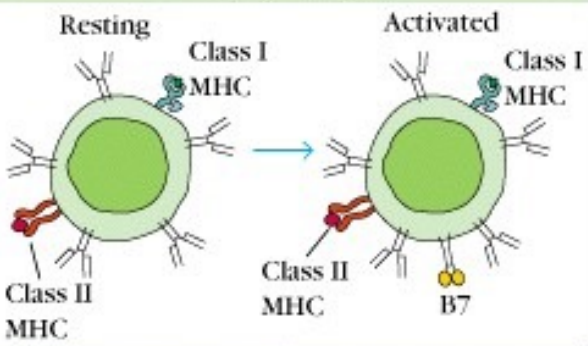
Figure 1 Kedzierska et al

The checkpoints of memory T cell formation



Memory T cells: IL-15-dependent proliferation, IL-7 dependent survival

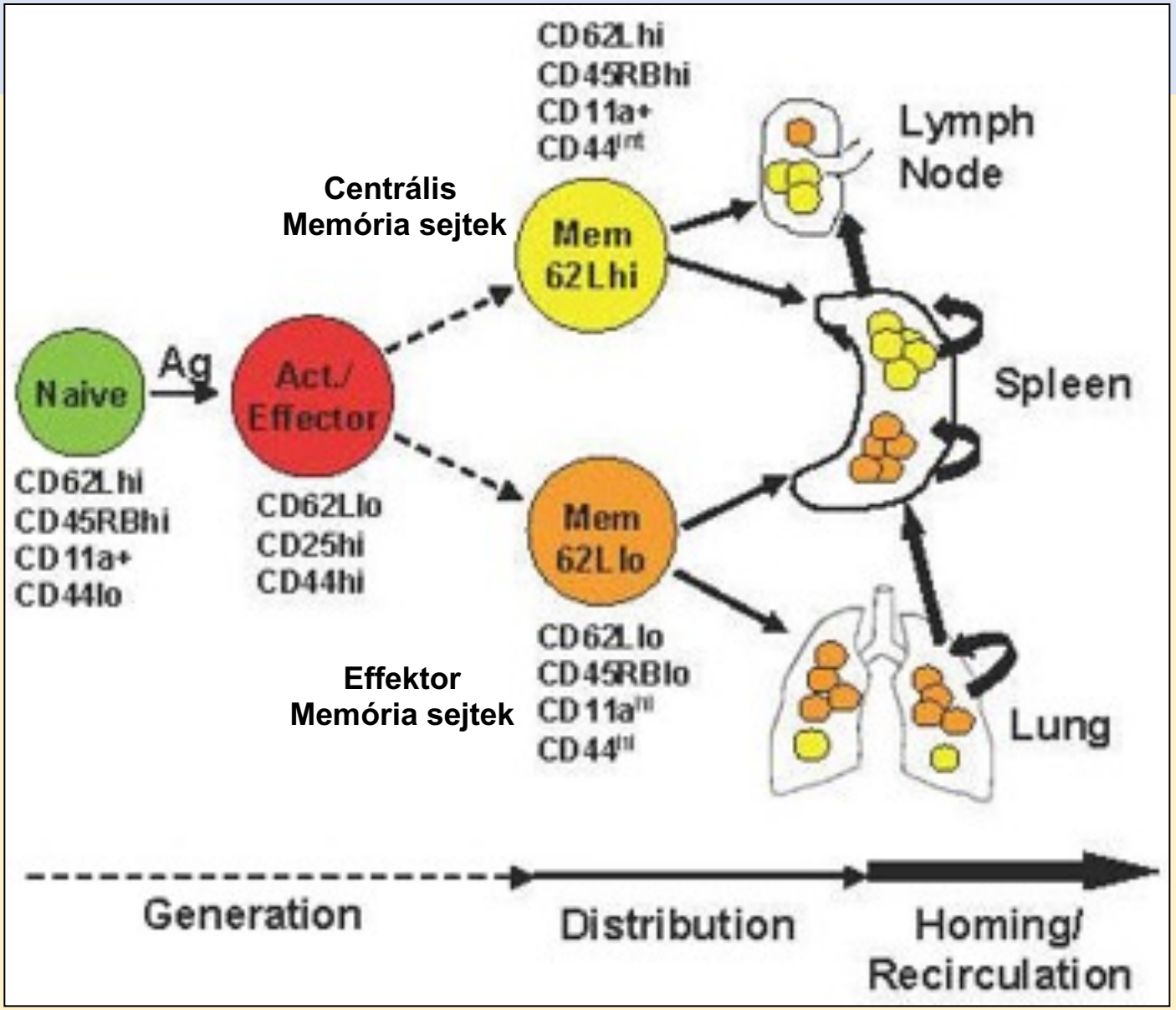
2. Antigen presenting cells are different

	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (−)	Inducible (++)	Constitutive (++)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (−)	Inducible B7 (++)	Inducible B7 (−)	Inducible B7 (++)
T-cell activation	Naive T cells Effector T cells Memory T cells	(−)	Effector T cells Memory T cells	Effector T cells Memory T cells	Naive T cells Effector T cells Memory T cells

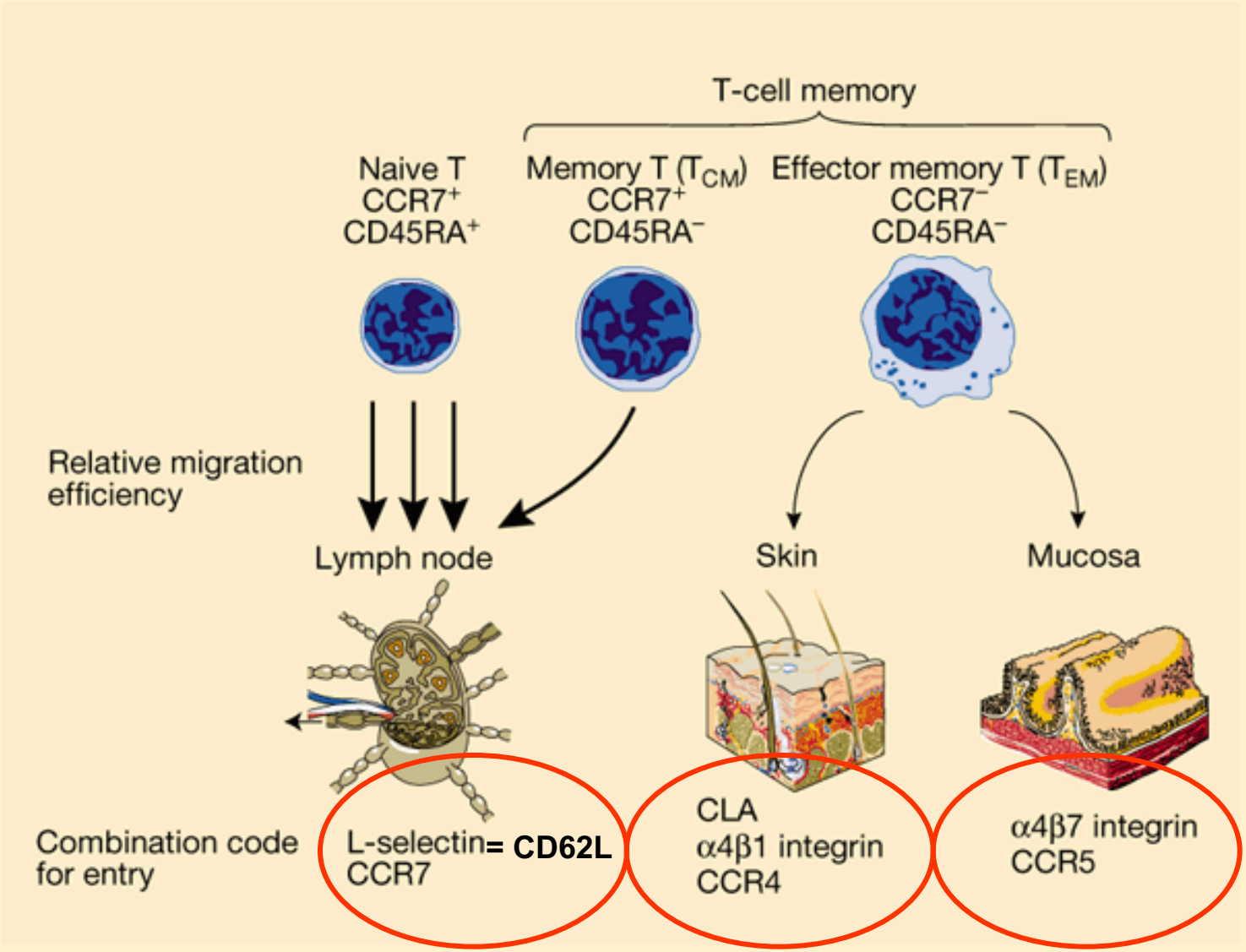
Activation of effector and memory T cells does not require the co-stimulatory B7

Antigen specific memory B cells with high affinity surface Ig take up low dose antigen and present it to memory T cells -> more effective APC

Memory T cell types



Immunological memory is systemic



4. Surface adhesion molecules are different

- Downregulation of: L-selectin
- Upregulation of:
  - VLA-4 (ligand of VCAM)
  - LFA-1, CD2, LFA-3
  - CD44 (hyaluronic acid receptor)

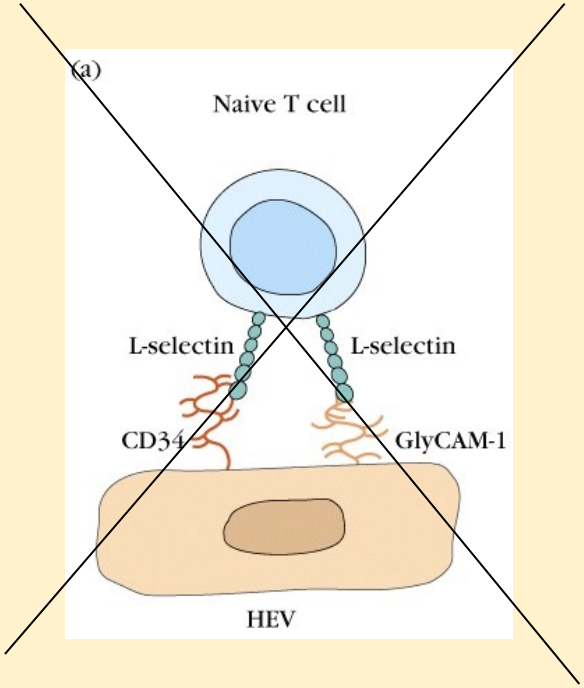
Table 1 | **Comparison of effector and memory cell phenotypes**

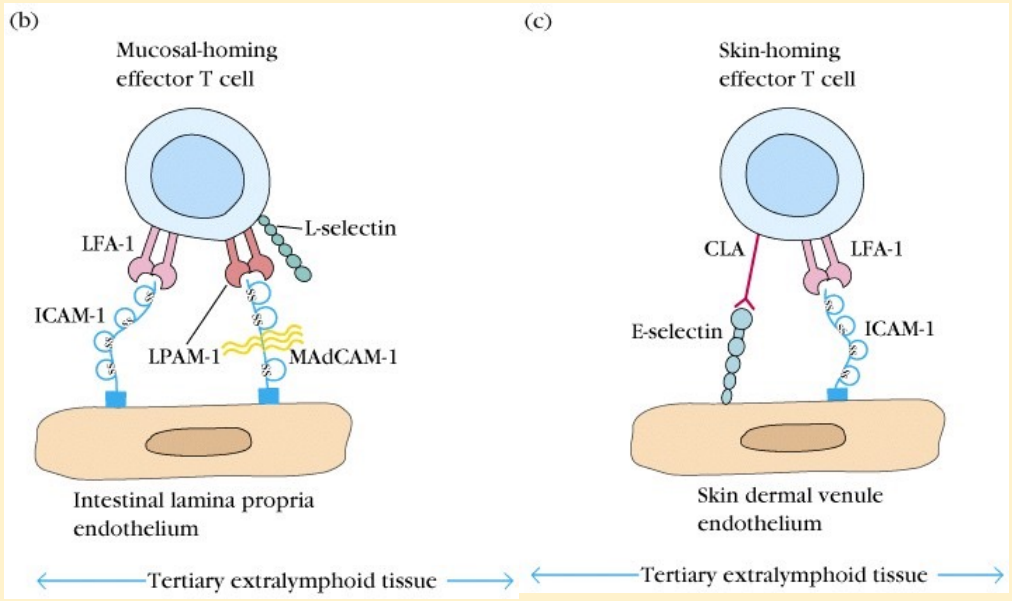
Cell type	Markers	
	Effector cell	**Memory cell**
$CD8^+$ T cell	$CD44^{hi}$ $IL\text{-}7R\alpha^{low}$ $IL\text{-}2R\beta^{low}$ $KLRG1^{hi}$ $LY6C^{low/-}$	$CD44^{hi}$ $IL\text{-}7R\alpha^{hi}$ $IL\text{-}2R\beta^{hi}$ $KLRG1^{low}$ $LY6C^{hi}$
$CD4^+$ T cell	$CD44^{hi}$ $IL\text{-}7R\alpha^{low}$ $IL\text{-}2R\beta^{low}$ $CD49b^+$ $LY6C^{low/-}$	$CD44^{hi}$ $IL\text{-}7R\alpha^{hi}$ $IL\text{-}2R\beta^{hi}$ $CD49b^+$ $LY6C^{hi}$
B cell*	$B220^+$ $CD138^-$ $GL7^+$ sIg^+ $LY6C^{low/-}$	$B220^+$ $CD138^-$ $GL7^-$ sIg^+ $LY6C^{low/-}$
Plasma cell‡	$B220^{+/-}$ $CD138^{hi}$ $GL7^-$ $sIg^{low/-}$ $LY6C^{hi}$	$B220^-$ $CD138^{hi}$ $GL7^-$ $sIg^{low/-}$ $LY6C^{hi}$

IL, interleukin; KLRG1, killer cell lectin-like receptor subfamily G, member 1; R, receptor; sIg, surface immunoglobulin. *The effector B cell is a germinal centre B cell. ‡The effector plasma cell is a plasmablast.

3. Homing behavior of memory lymphocytes is different

- **Naive cells** migrate – „home” - into secondary lymphoid organs → primary immune response is **local**
- **Memory cells** migrate (extravasate) into the place of inflammation→ **memory is systemic**





Tissue homing specificity:

- CLA-1: cutaneous carbohydrate antigen
- LPAM-1 ($\alpha 4\beta 7$) integrin: mucosal homing

Homing of memory T cells

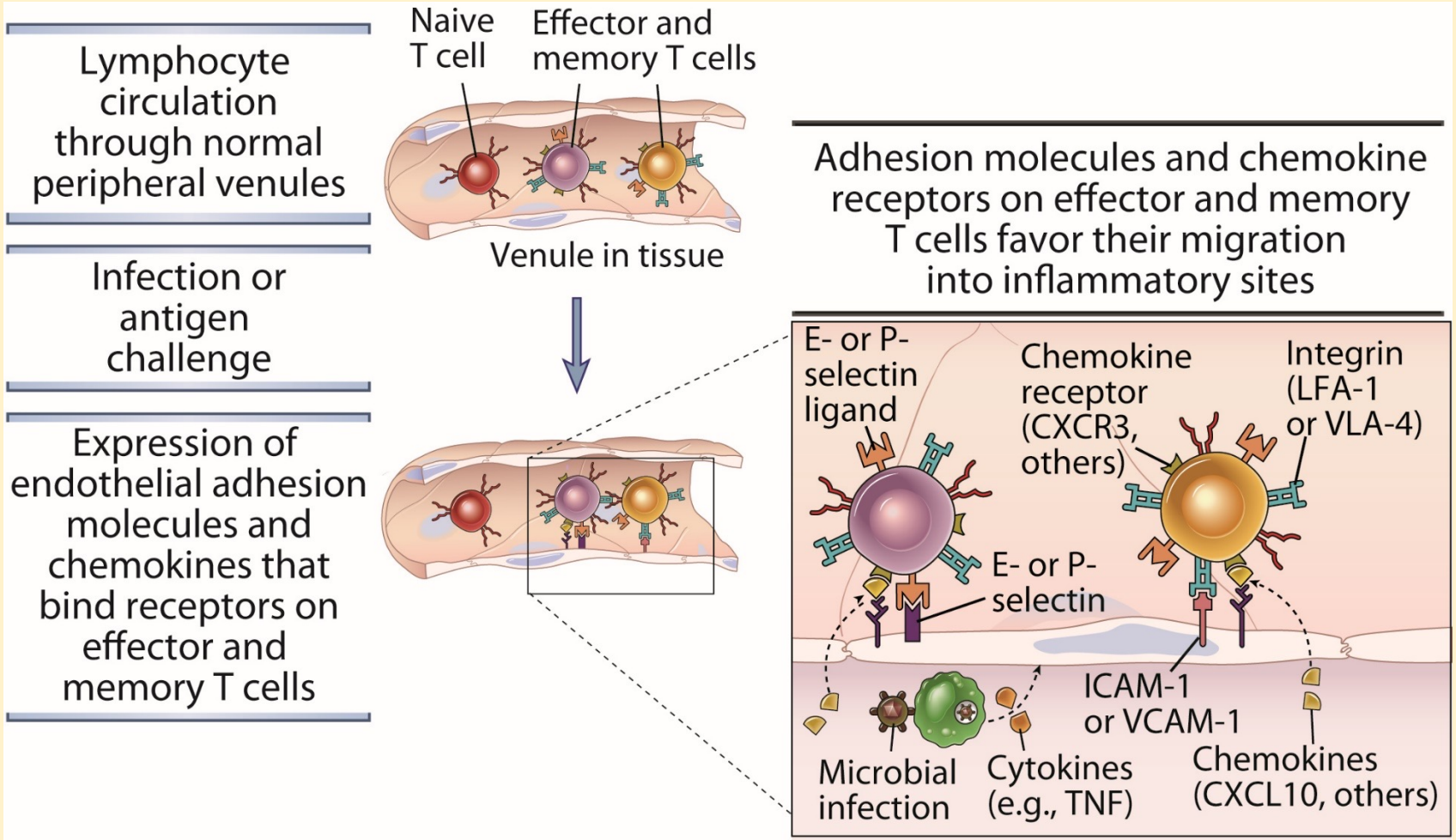
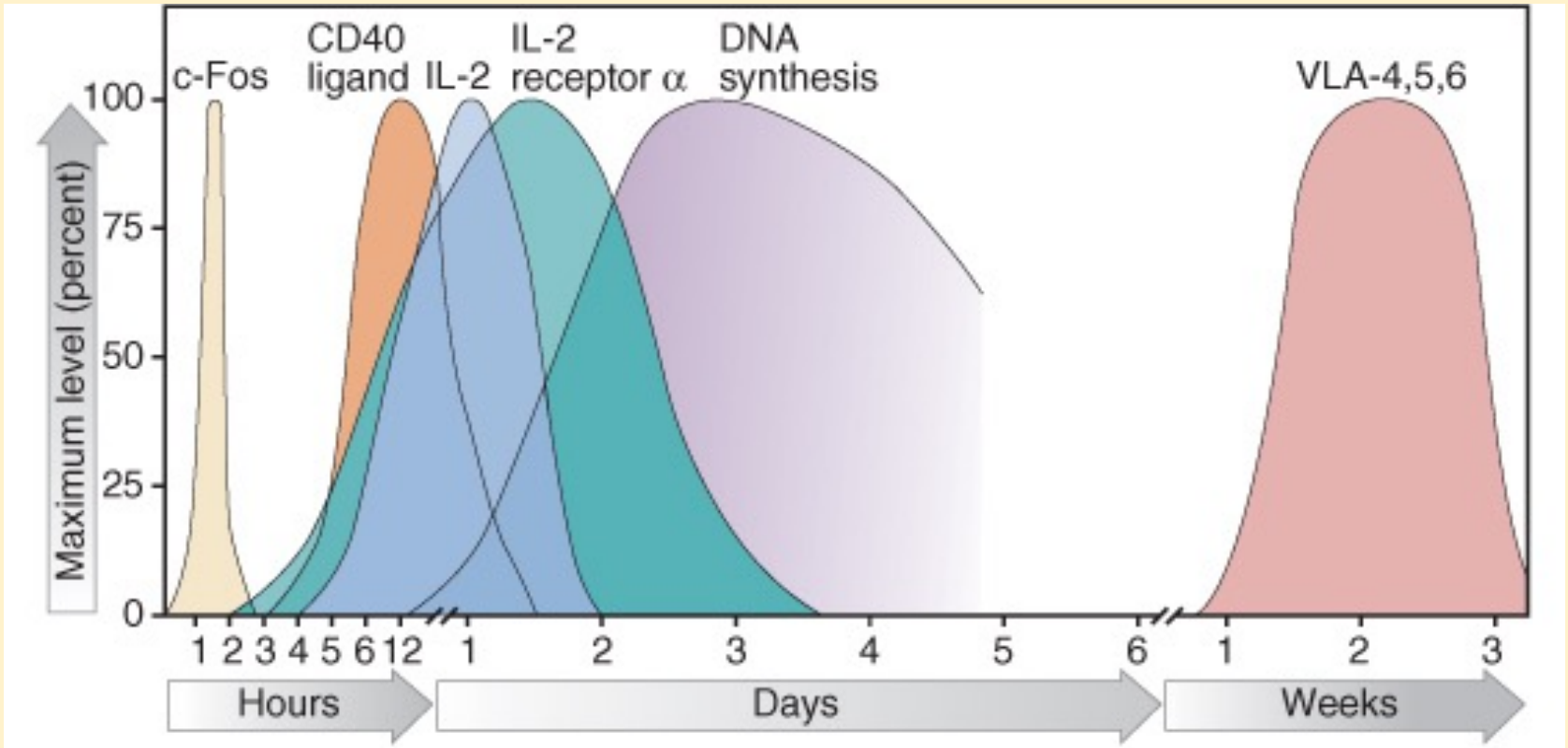


Fig. 10-3

VLA molecules appear after 1 week



5. CD45 isoform is different

-Naive T cells: CD45-RA

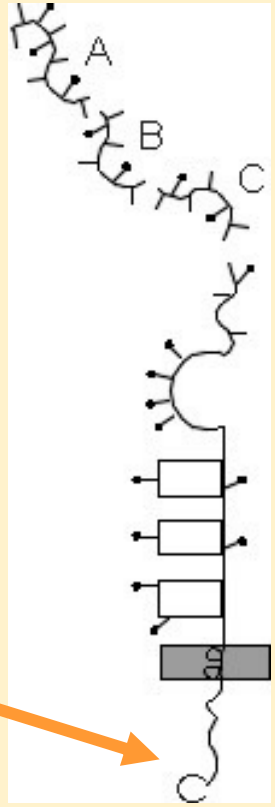
-Memory T cells: CD45-RO

→shorter extracellular domain→ can associate much better to TcR → more effective signal transduction

CD45 - pan-leukocyte marker

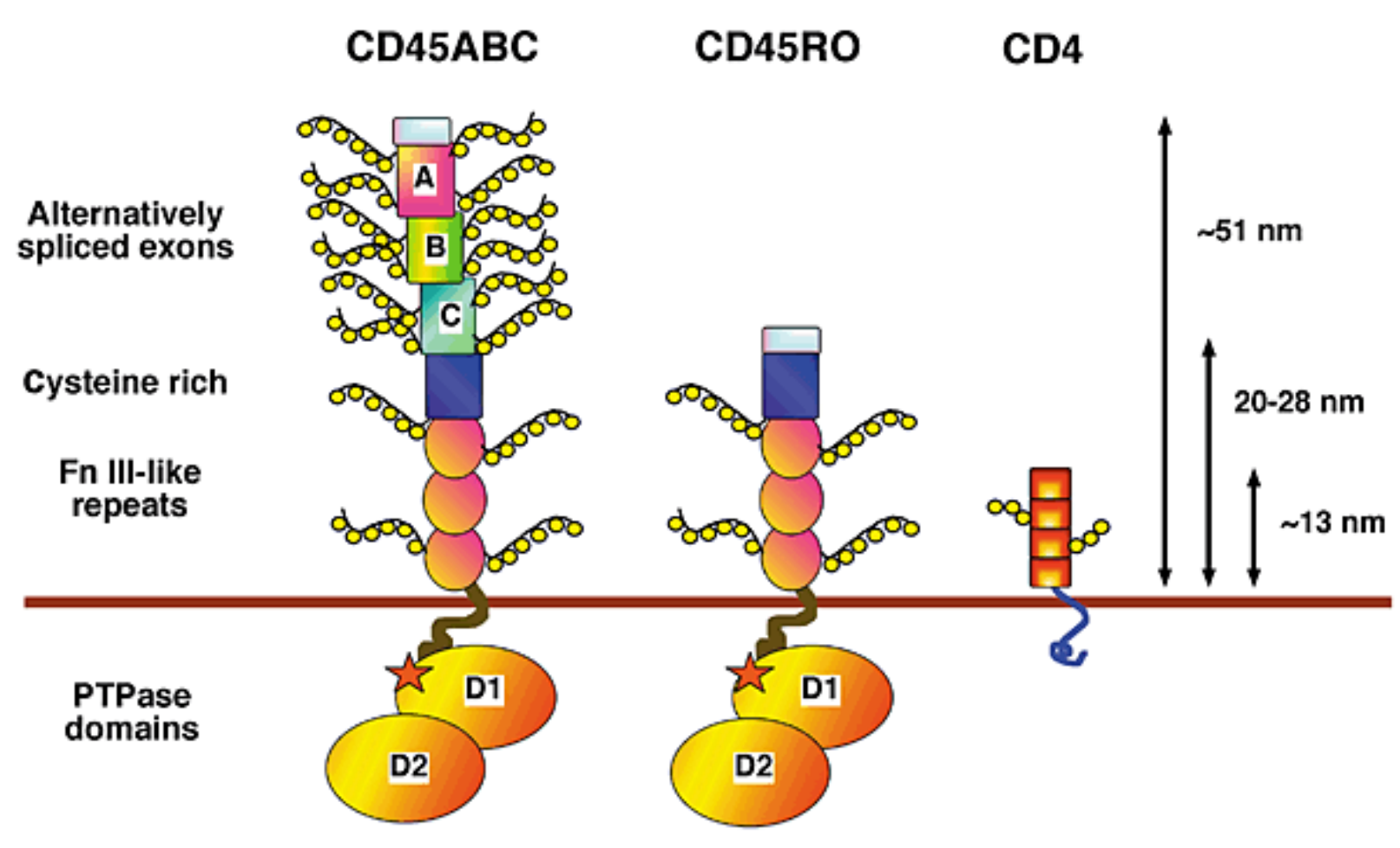
Expressed on each leukocyte
- Highly glycosylated,
- More isoforms (180, 190, 200, 205, 220 kDa)
- alternate splicing: CD45RA, CD45RO, CD45RB

Important in cell activation, regulation of signal transduction
- ***tyrosine –foszfatase*** ***domain - dephosphorylation***

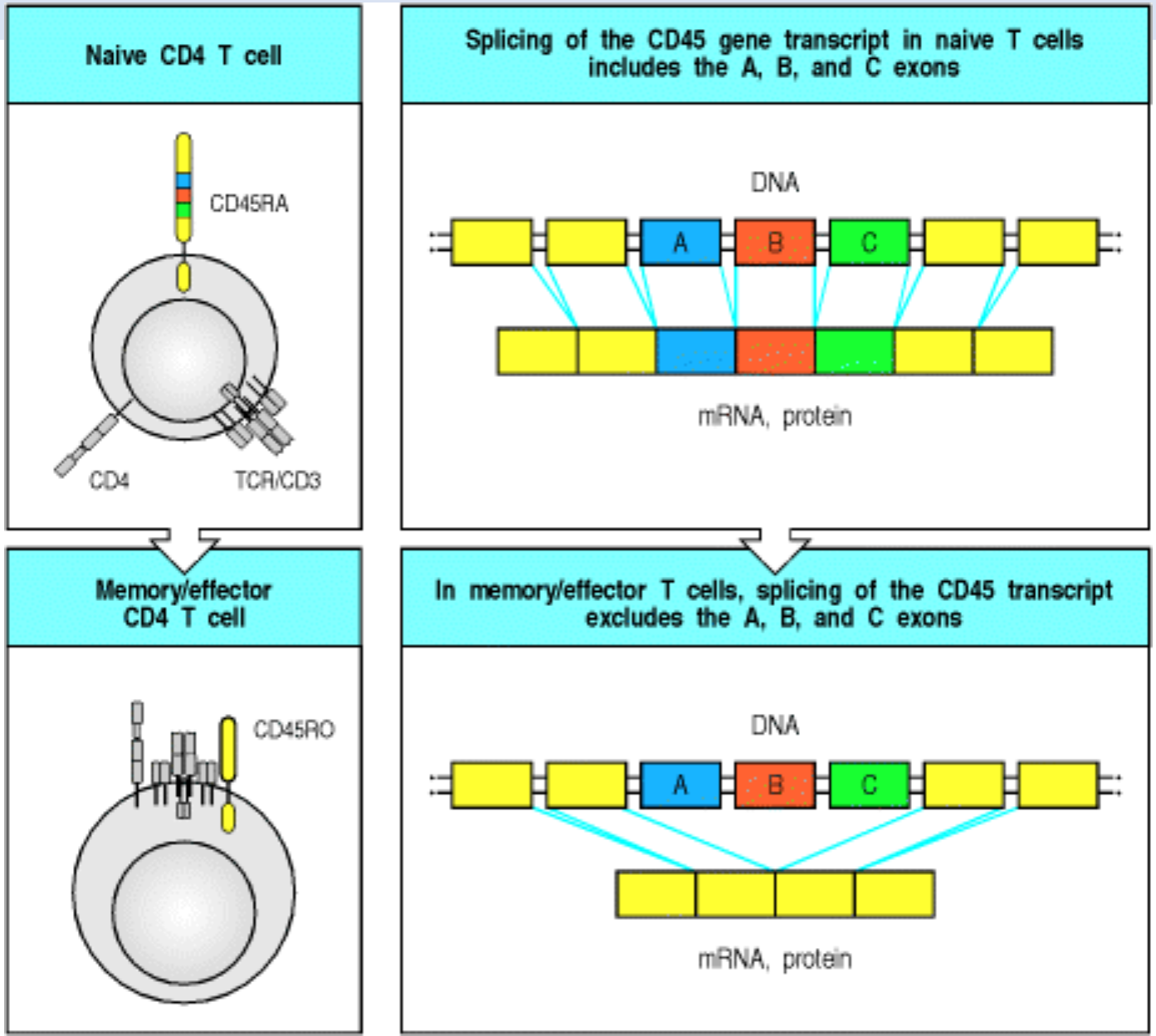


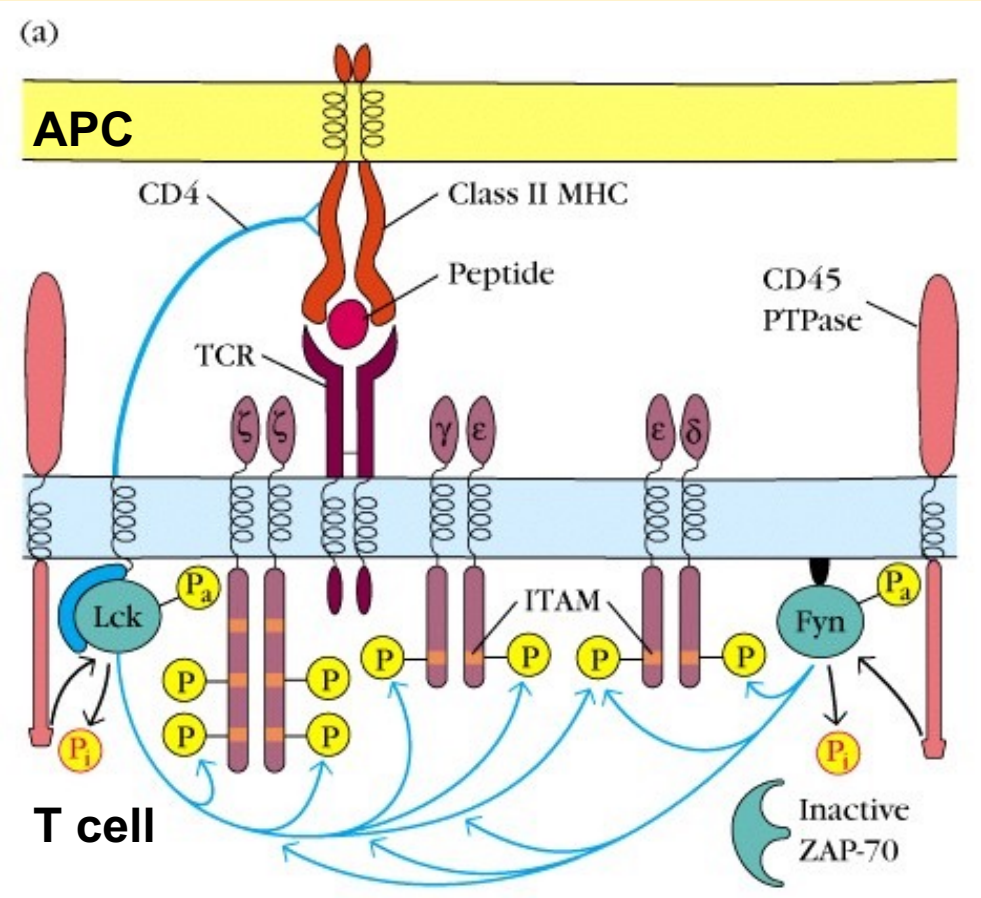
CD45

CD45 isoforms



CD45 isoforms on naive and memory T cells





ITAM: immunoreceptor tyrosine-based activation motif

1. TCR crosslinking results the association of co-receptors (CD4, CD3, CD45) closer to TcR
2. **Protein tyrosine kinase (PTK) Lck and Fyn activation: CD45 phosphatase removes an inhibitory phosphate (Pi) + addition of a phosphate (Pa)**
3. Fyn and Lck phosphorylate ITAMs of CD3 complex
4. Docking of ZAP-70 PTK to ζ-chain ITAMs and its phosphorylation

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Cells of the evolutional (species specific) memory: NATURAL IMMUNITY

- **CD5-positive (B-1) B cells**: production of low-affinity polyreactive antibodies against common bacterial polisaccharide antigens; autonom self-renewal; dominant B cell type in newborn
- **γ/δ T cells, NKT cells**: restricted TcR specificity, bacterial glycolipid antigen recognition with non-conventional MHC-like molecules: CD1, MR. Effector and memory phenotype