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

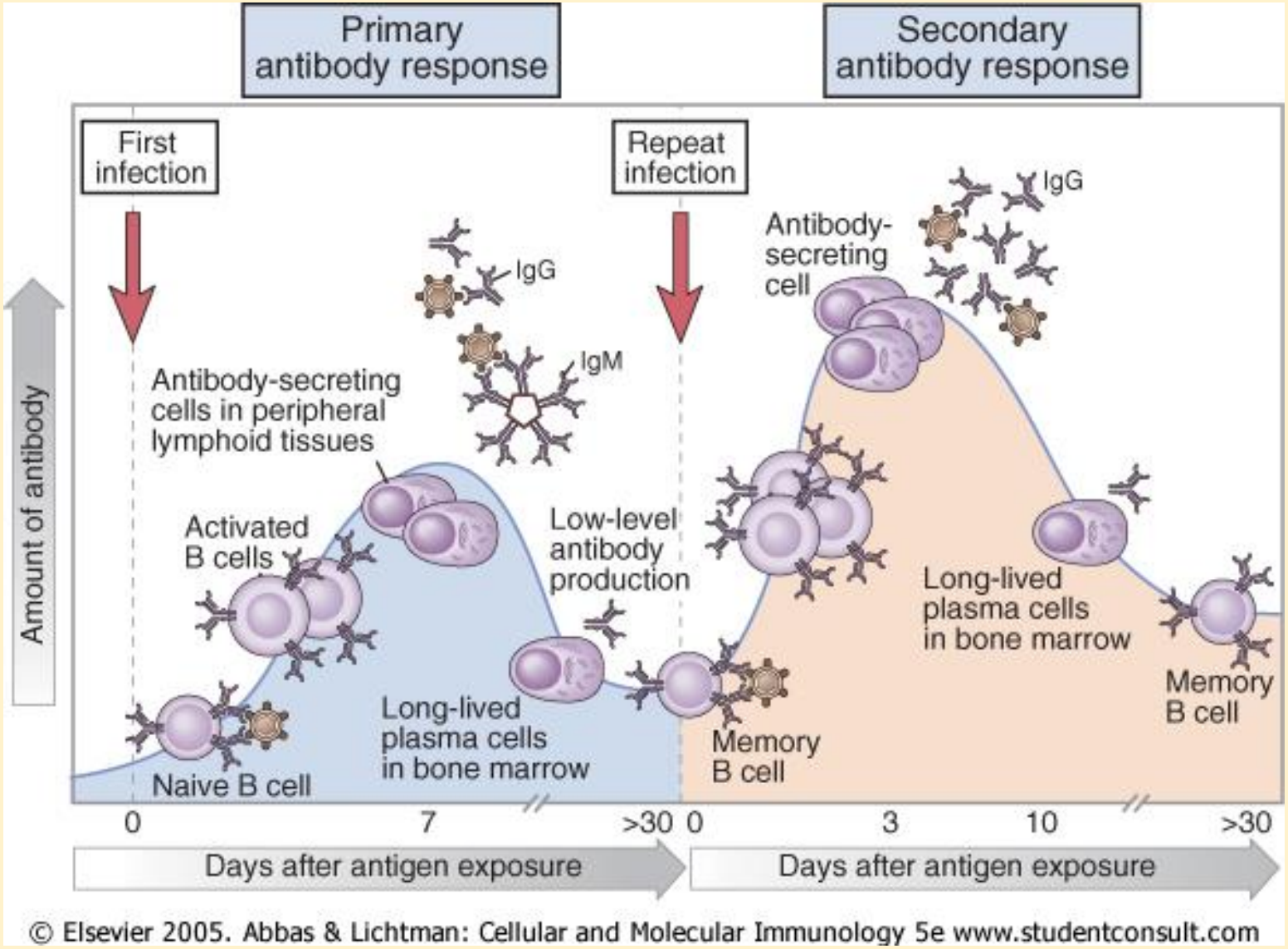
3. Homing behavior of lymphocytes is different

4. Surface adhesion molecules are different

5. CD45 isoform is different

B cell memory

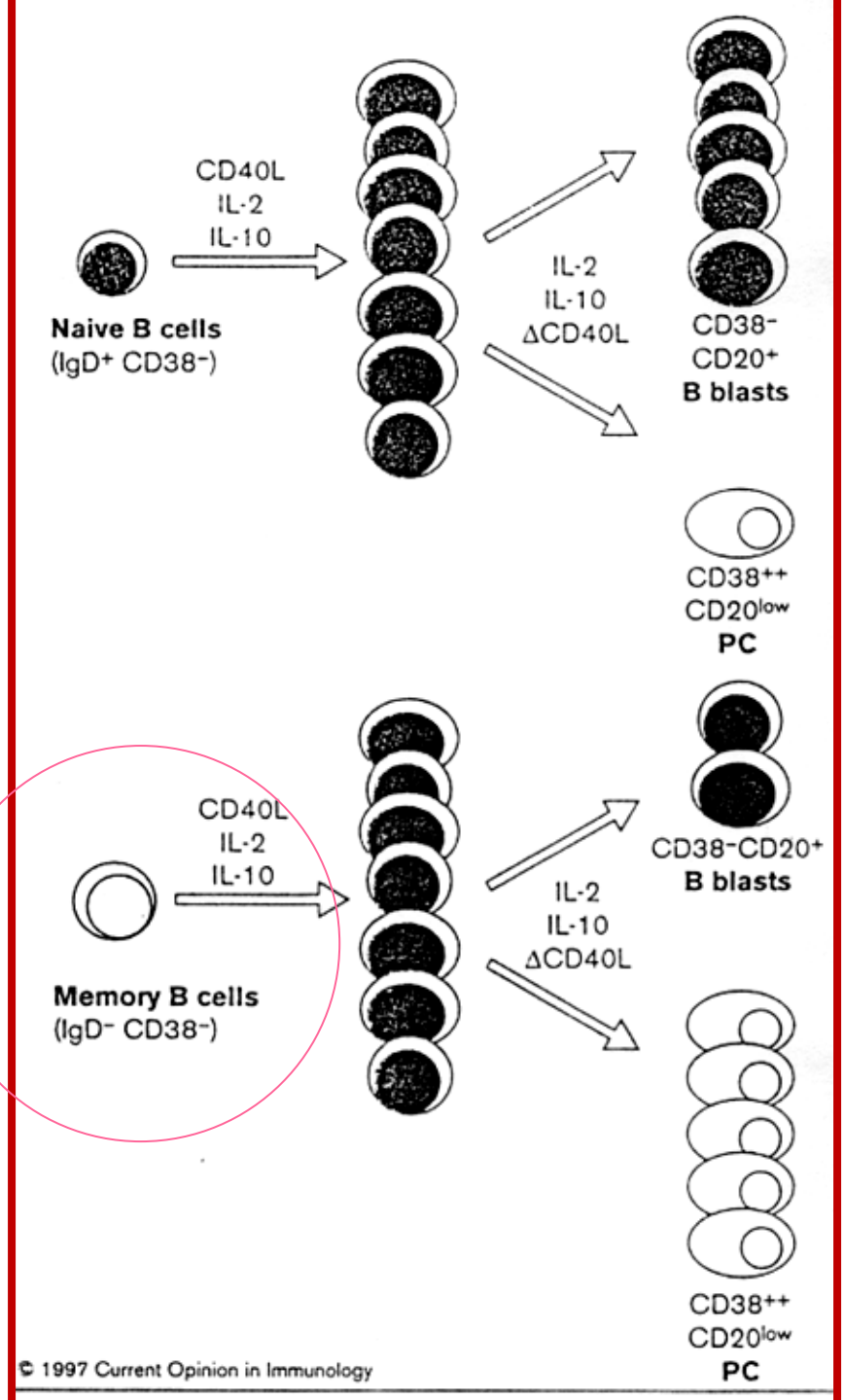
Primary and secondary B cell response



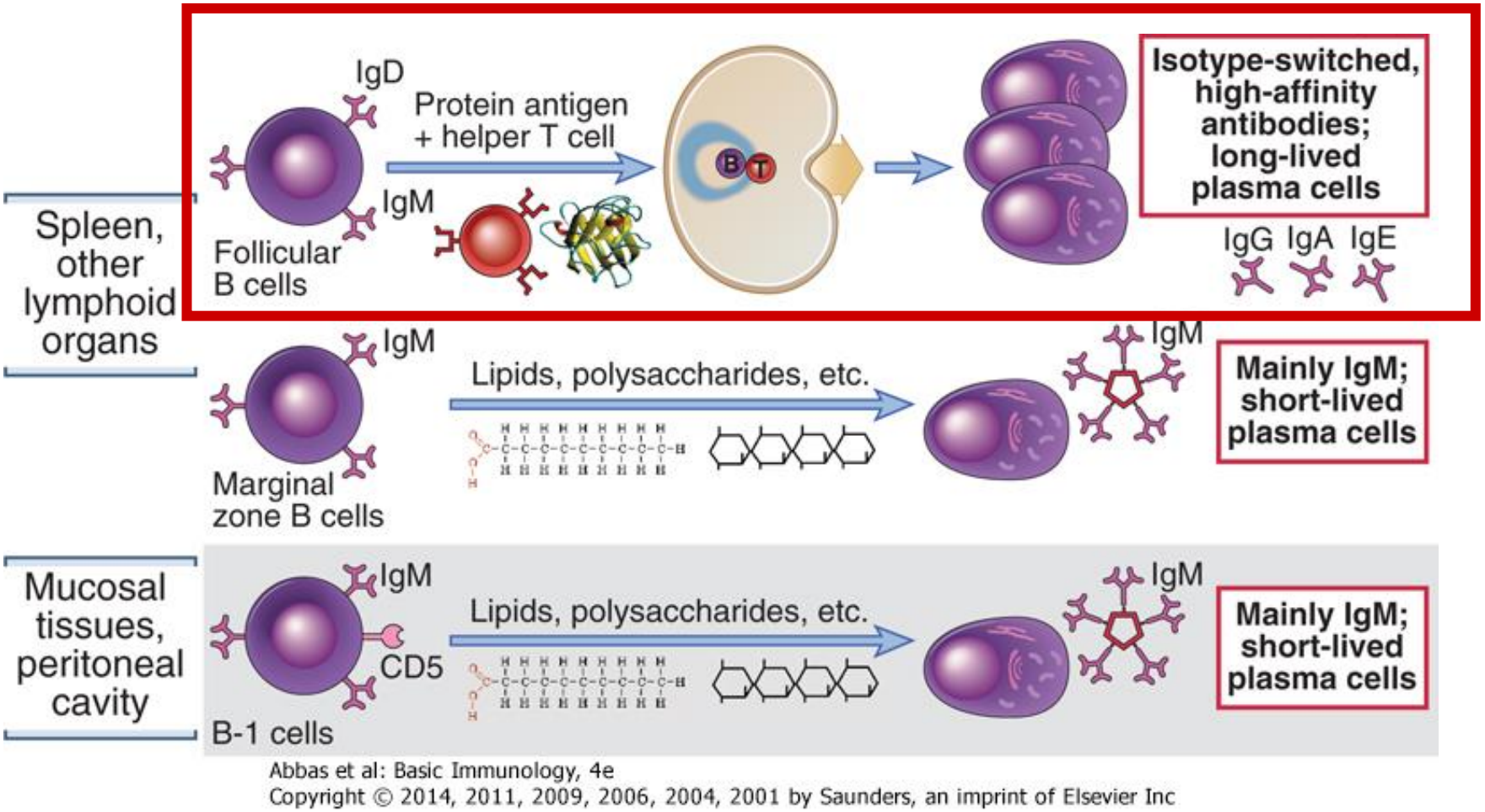
Primary response, naive B cell activation

→ more memory B cells are generated

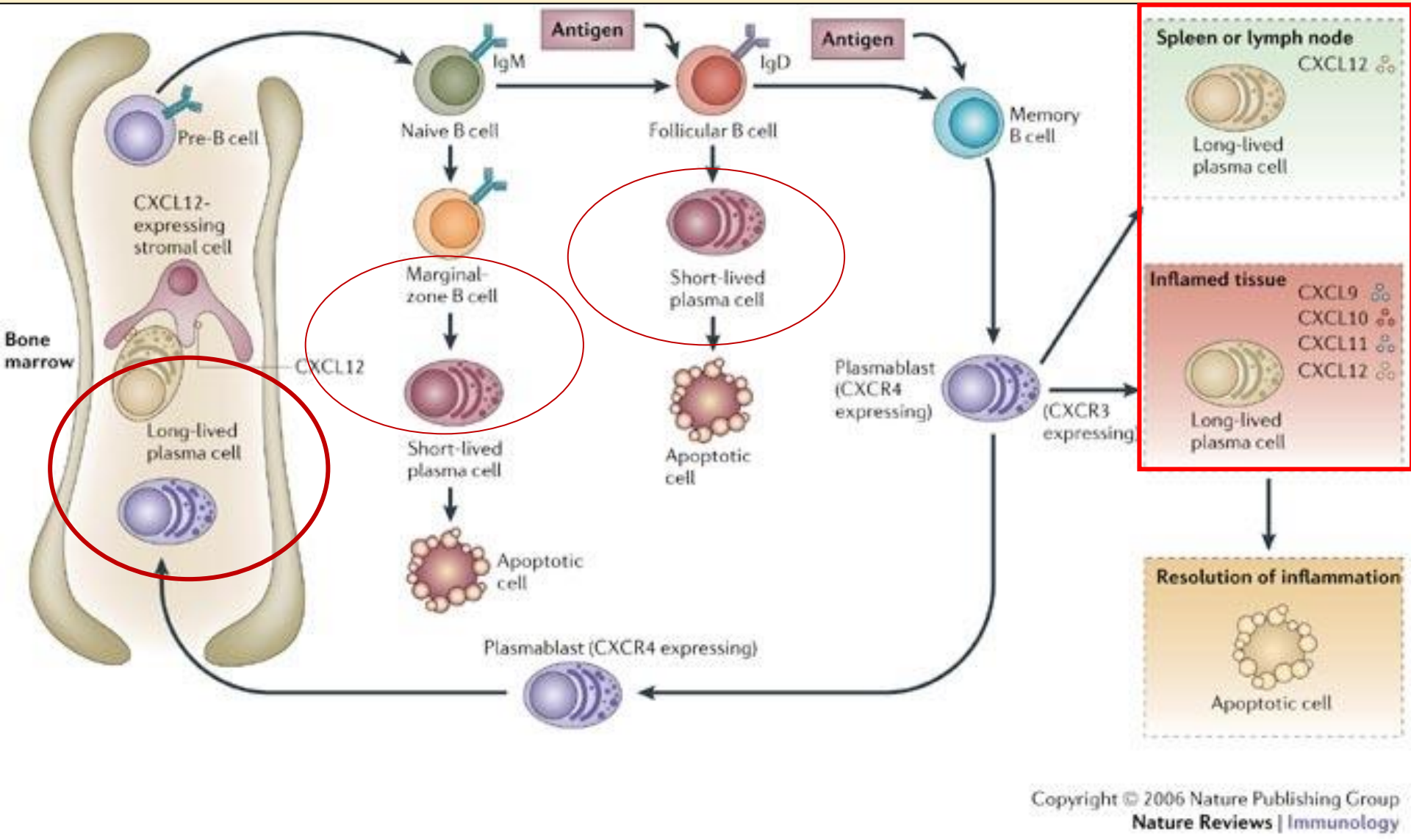
Secondary, memory B cell response → mostly plasma cells are generated (5x more)



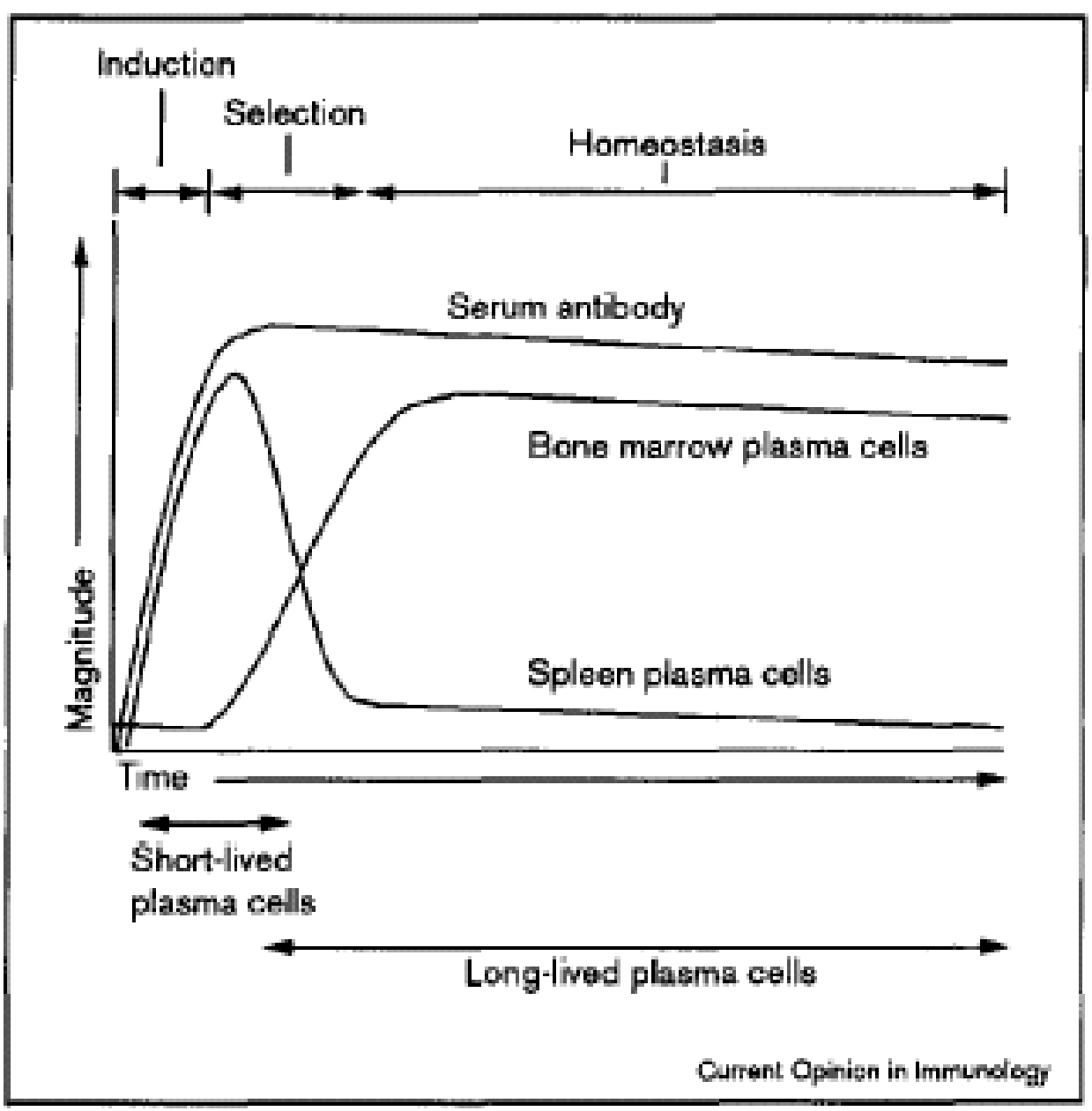
TD and TID antigen response



Plasma cells



Long-lived plasma cells



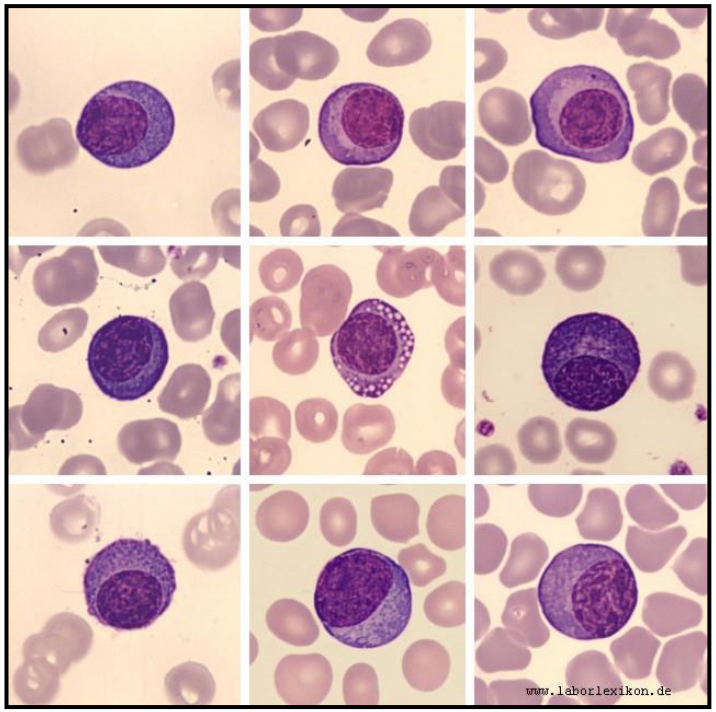
Plazmasejtek

Kialakulásuk függ: citokinek: IL-4, IL-5, IL-6, IL-13…
CD40L-CD40 Szignál

Élettartam:

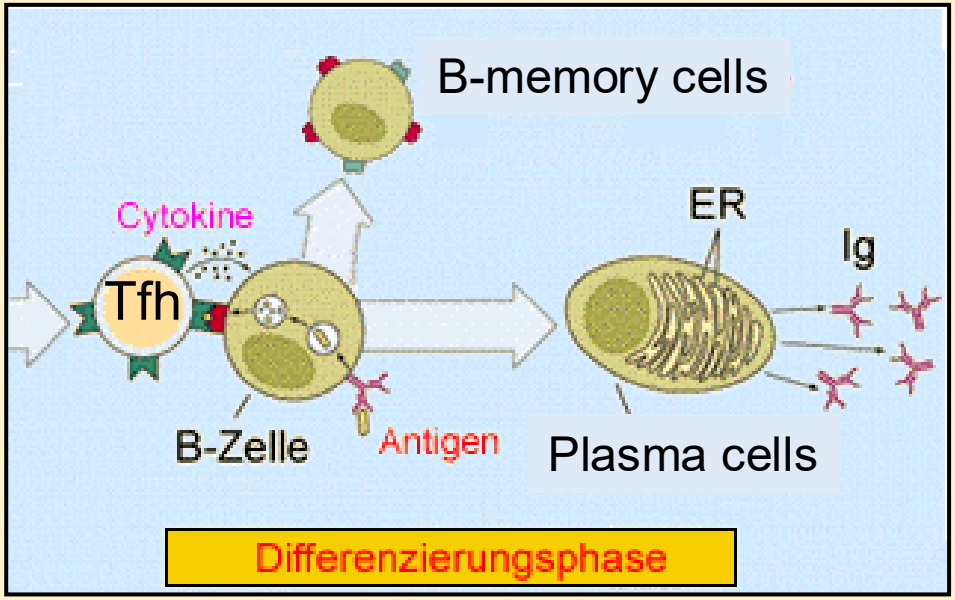
- Rövid életű plazmasejt: nincs hypermutáció

- **Hosszú életű plazmasejtek (LLPCs):**
- évtizedekig termel magas affinitású antitestet,
- Fenotípus: CD19−CD38hi+CD138+
- Csontvelői stróma + megakariocita:
- Túlélést biztosító mikrokörnyezet
- citokinek: IL-6, BAFF és APRIL
- Metabolikus környezet: sok glukóz felvétel, alacsony O2 szint, sok piruvát felvétel
- Pro-apoptotikus molekulák downregulációja, Bcl-2, Bcl-XL uprreguláció



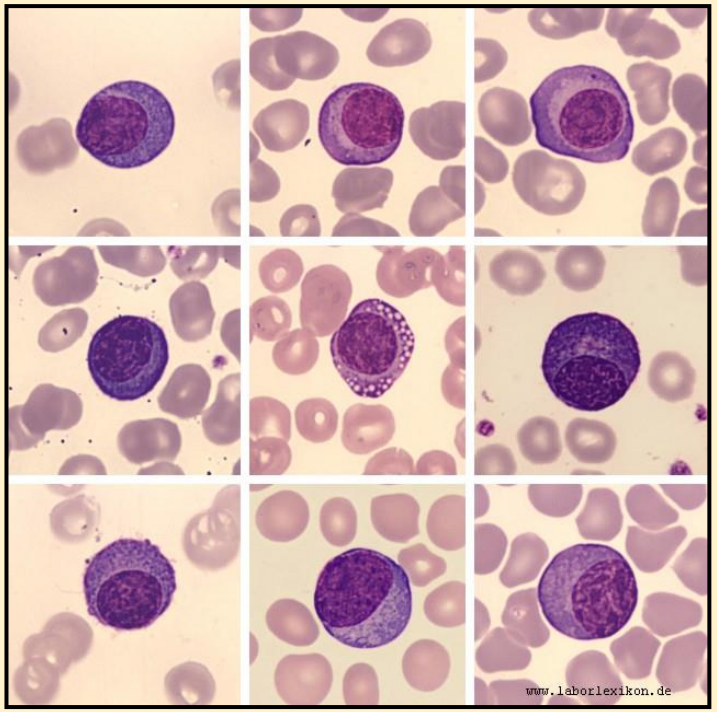
Hol?
Csontvelő perivaskuláris szinusz
Nyálkahártyák Lamina Propria
Lép vörös pulpa
Nyirokcsomó medulla

Plasma cells



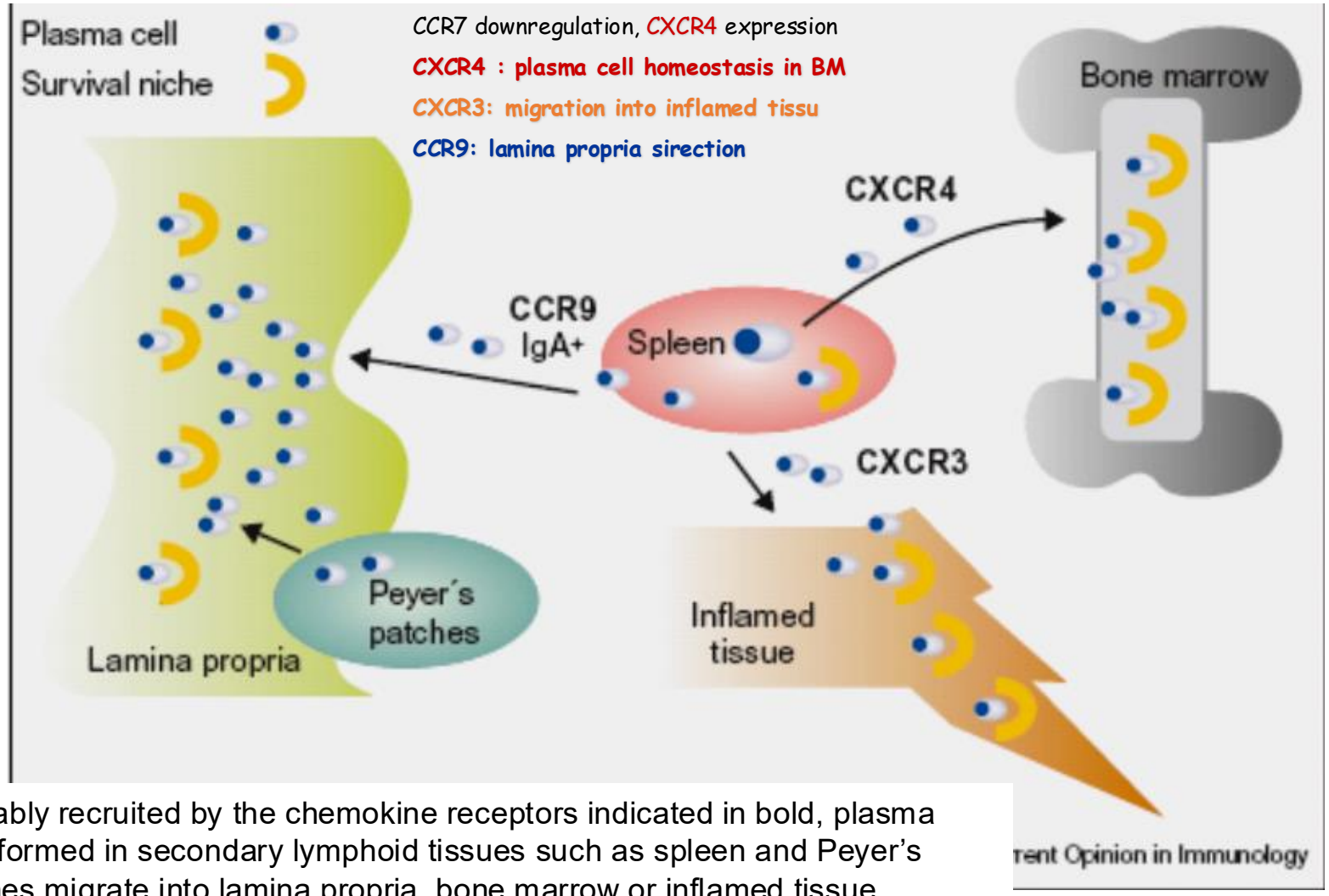
Cytokines: IL-2, IL-4, IL-5, IL-6, IL-10, IL-13…
CD40L-CD40 Signal

Plasma cells: CD38++



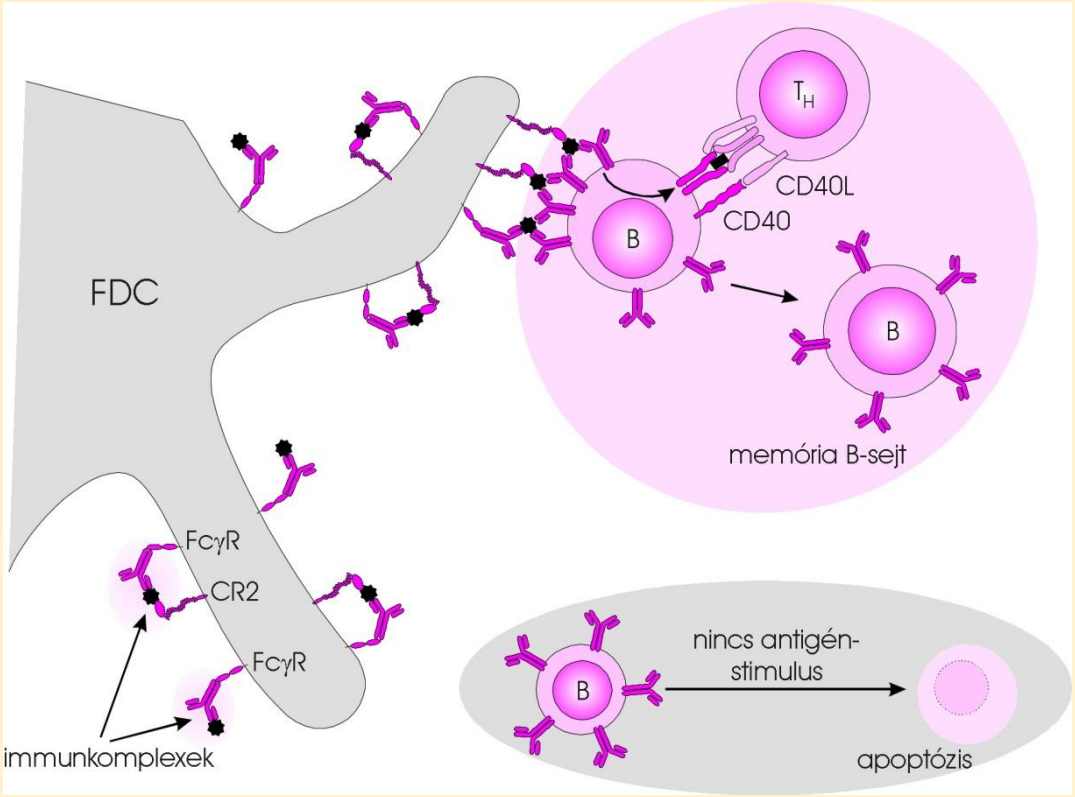
Where?
Bone marrox perivascular sinus
Mucosa Lamina Propria
Spleen red pulp
Lymph node medulla

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.

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

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 !

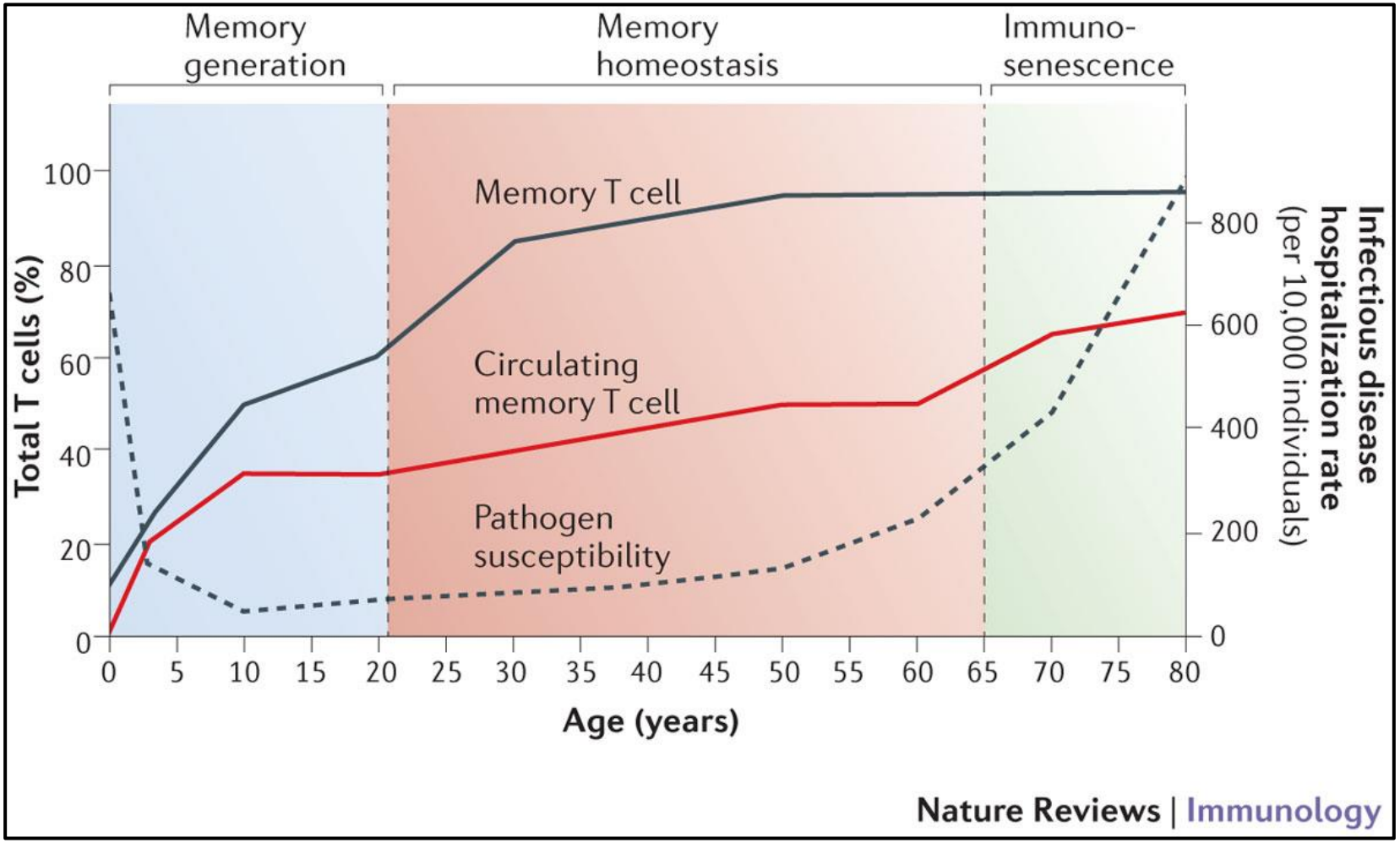
TABLE 11-7 COMPARISON OF NAIVE AND MEMORY B CELLS

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.

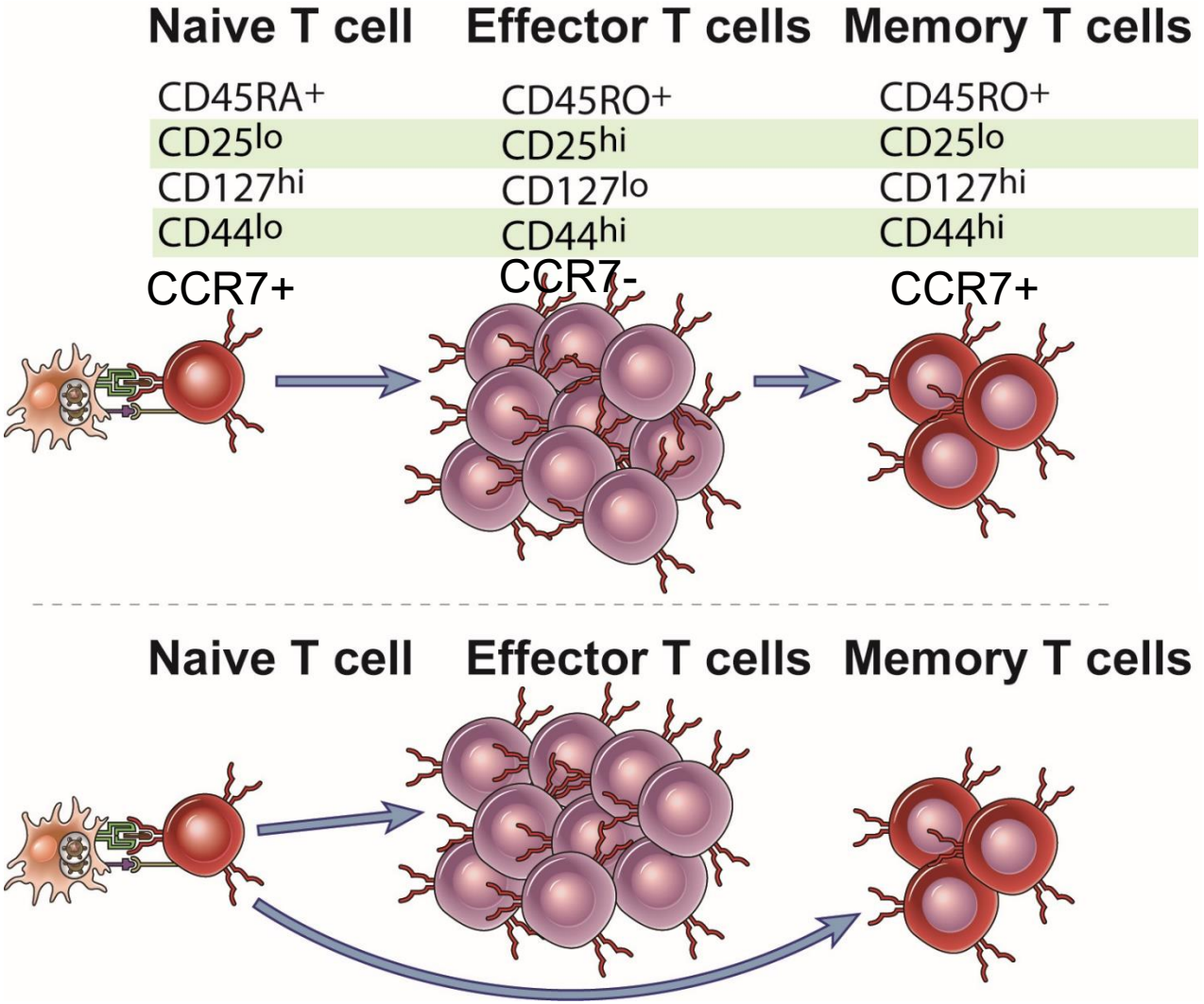
T cell memory

A memória-T-sejt életszakaszai: a memória kialakulása, fenntartása és az immun-öregedés



A pubertás végére a limfoid szövetekben, a nyálkahártyákban és a bőrben túlnyomórészt memória-T-sejtek találhatók, amelyek a felnőttkorban is megmaradnak, és a szervezetben a legnagyobb számban előforduló limfocita-populációt alkotják

Development of memory T cells

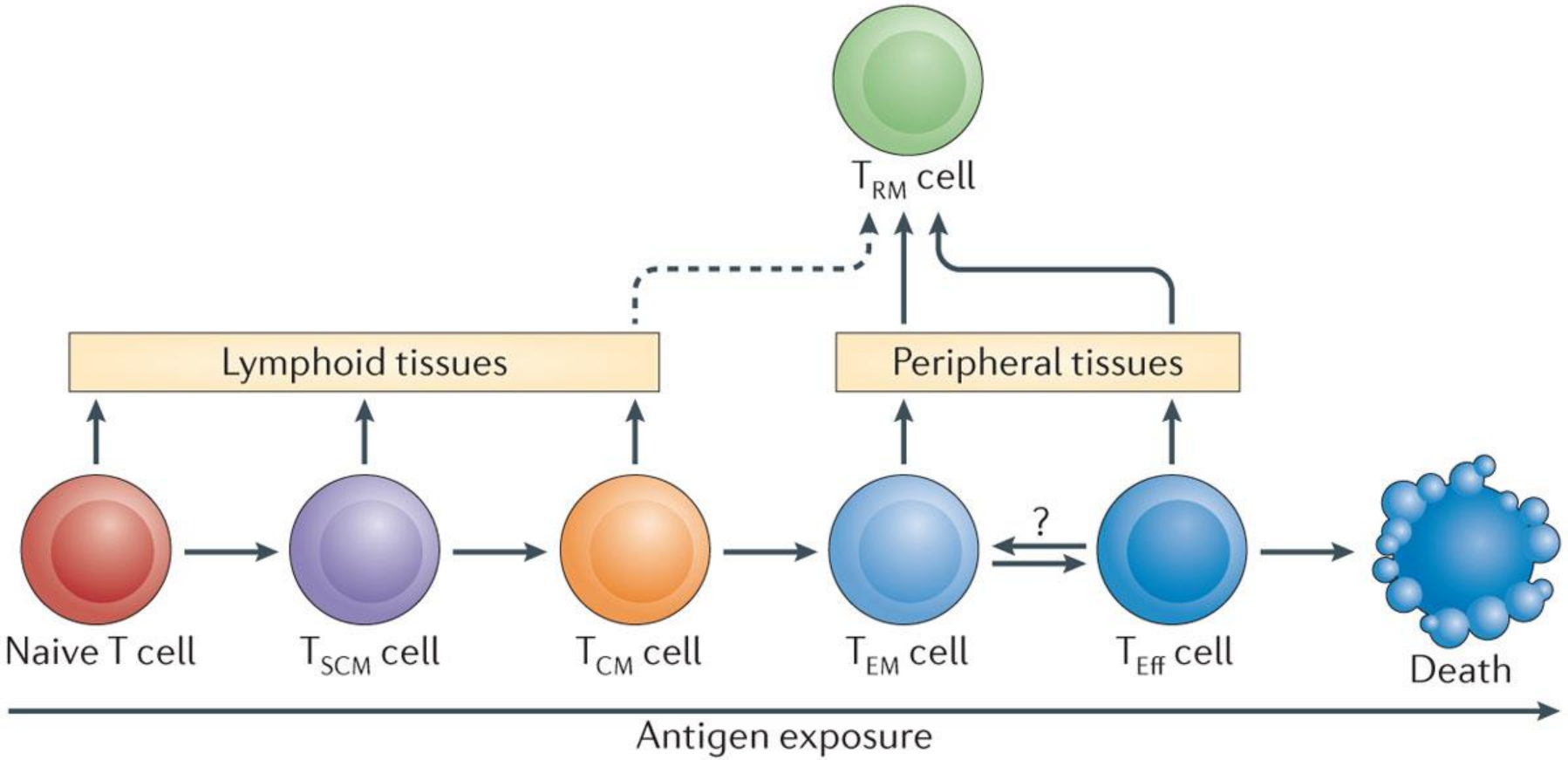


Stem cell memory T (T_{SCM}) cells,
CD45RA+
CD27+, CD28+
IL7R+
CCR7+

Multipotens,
Önmegújító
Nagy
osztódóképességű

Fig. 9-19

Szöveti T_{RM} sejtek képződése és eloszlása



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A CD103-at expresszáló CD4+ és CD8+ (CCR7−CD69+) TRM-sejtek a tüdőben, a belekben, a bőrben és a csontvelőben előforduló T-sejt-alcsoportok közül a leggyakoribbak

Survival of central memory T cells (T_{CM})

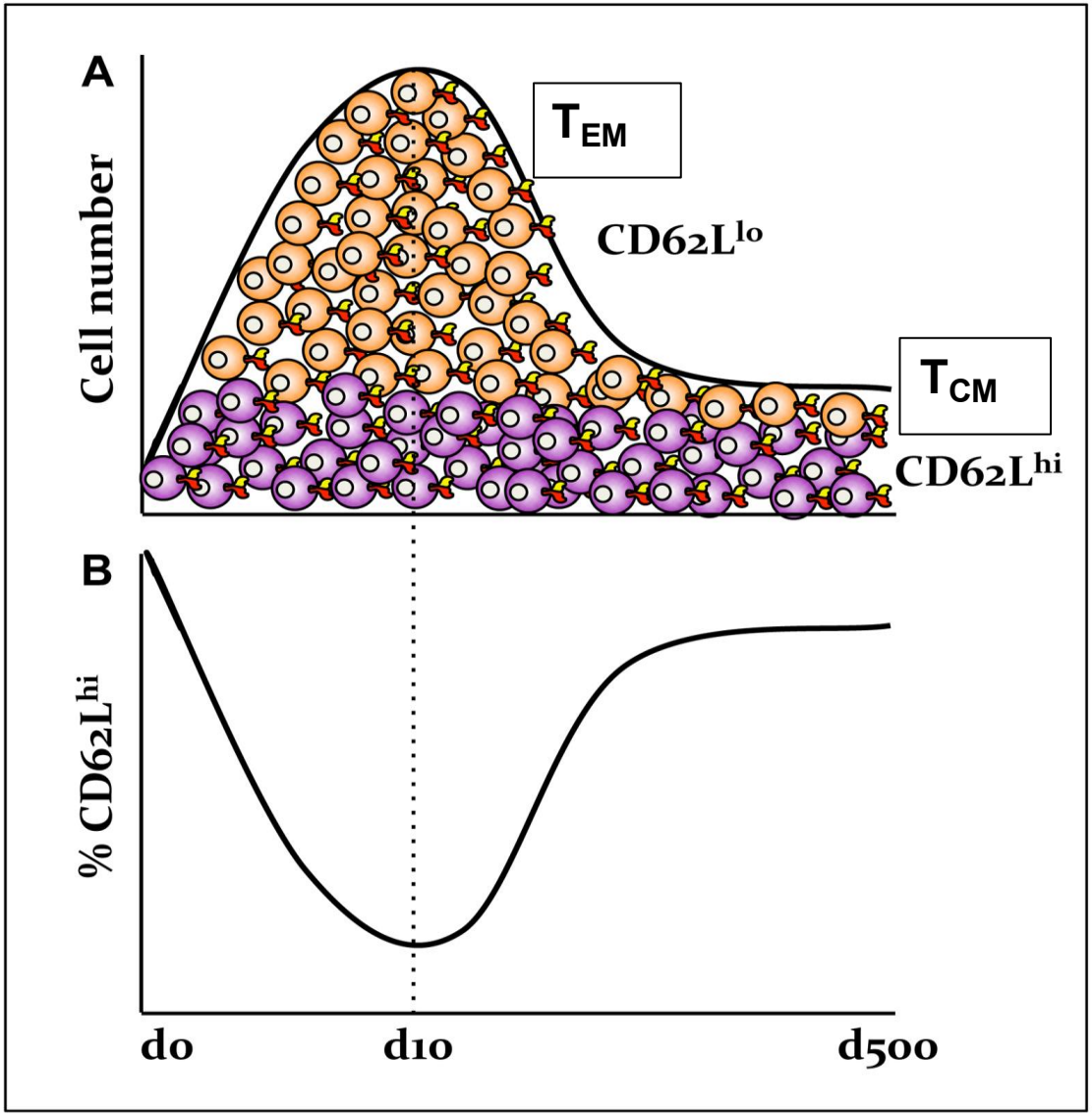


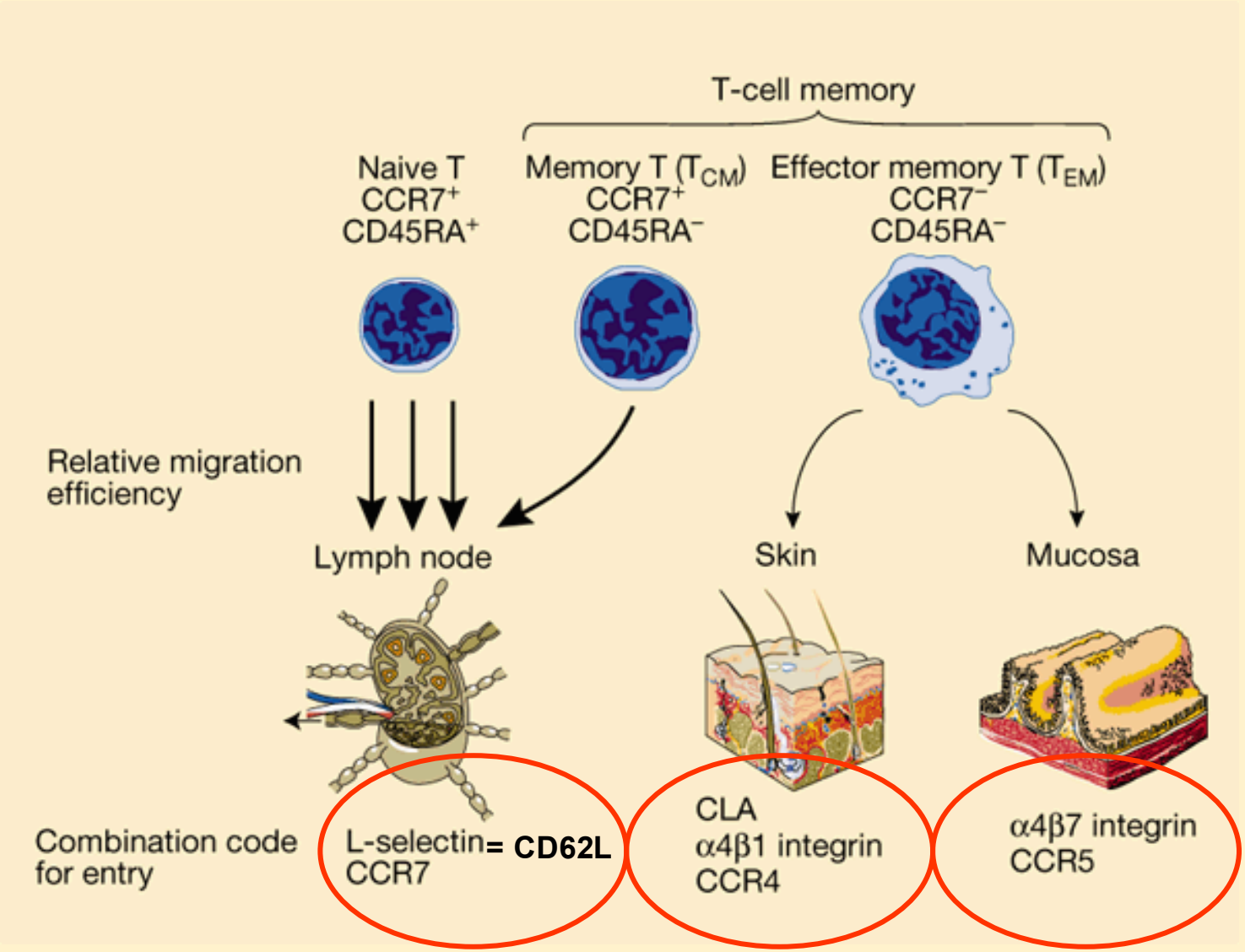
Figure 1 Kedzierska et al

Effector memory T cells: T_{EM}

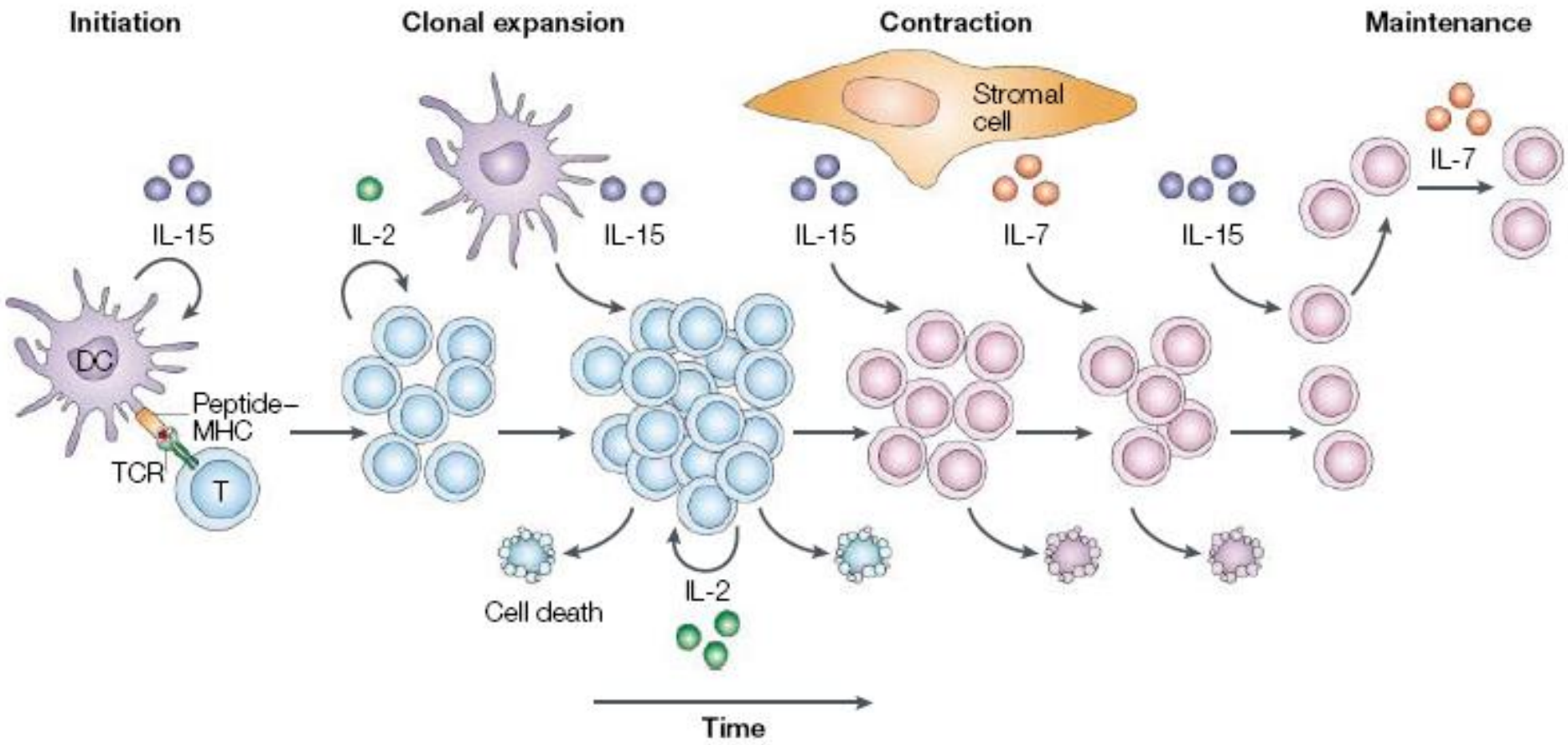
Central memory T cells: T_{CM}

Preferential survival of antigen-specific central memory CD62Lhi+CD8+ T cells following influenza virus infection.

Immunological memory is systemic



The checkpoints of memory T cell survival



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

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)

Homing of memory T cells

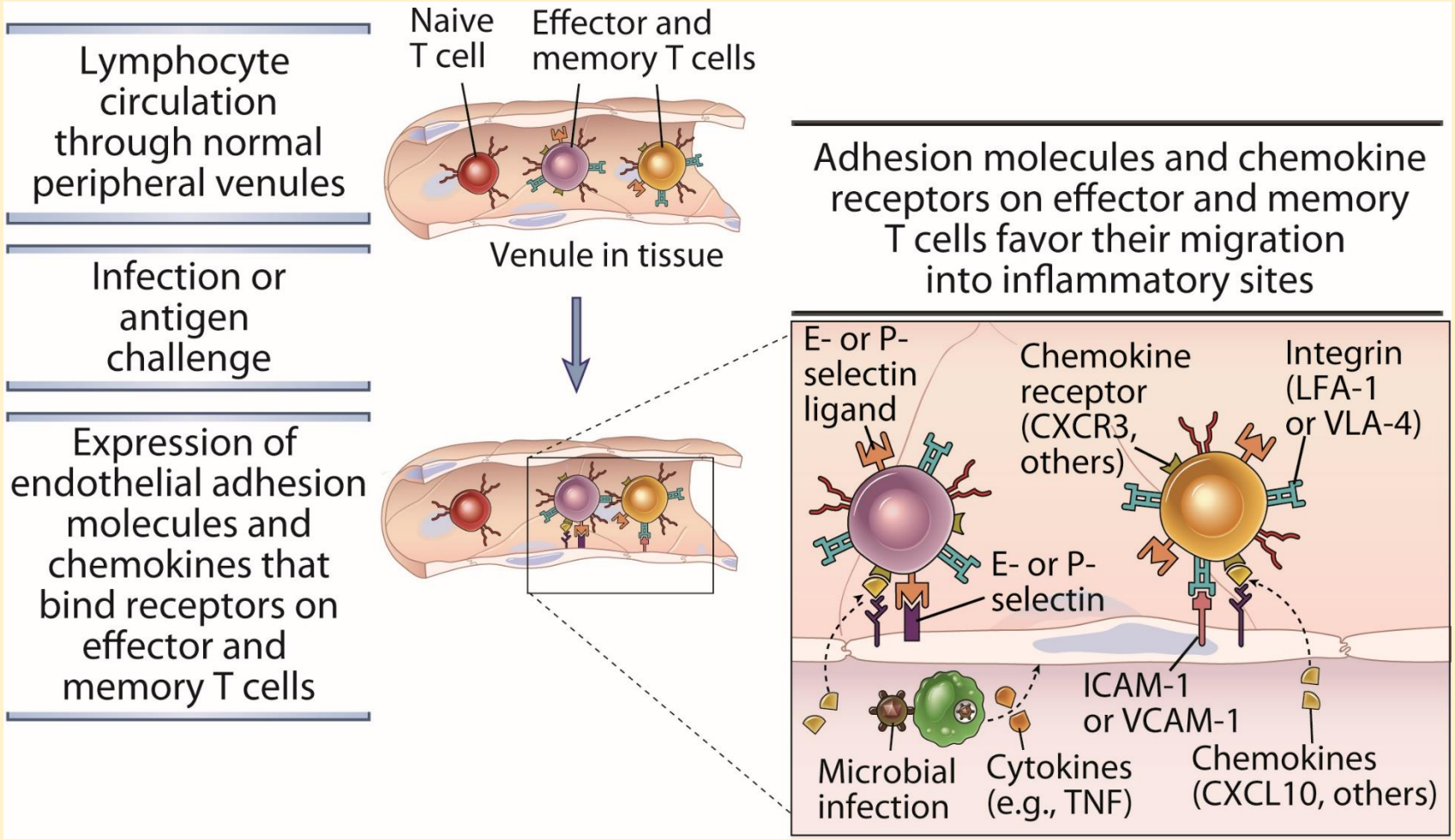
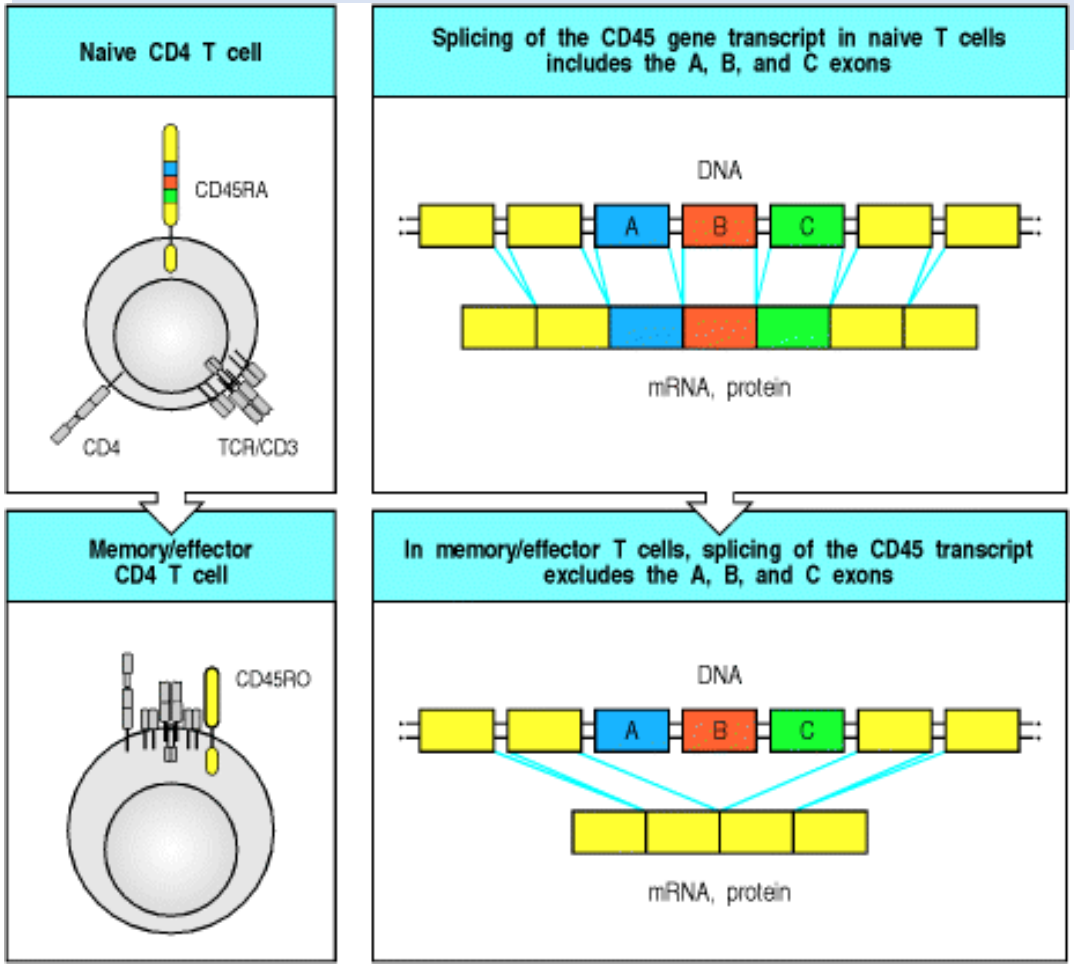


Fig. 10-3

CD45 isoforms on naive and memory T cells



Naive T cells: CD45-RA

Memory T cells: CD45-RO

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

CD45 is important in cell activation, regulation of signal transduction - ***tyrosine –foszfatase*** ***domain -dephosphorylation***

Components of immunological memory

The result of antigen-specific cell proliferation:

- **effector cells → apoptosis**
- **memory cells → survival TEM, TCM, BMEM +PLASMA CELLS**
- **memory cell with increased frequency (M/E)**

1. **T/B cells with the highest affinity can bind to residual or re-entrant antigen with the highest chance of survival. Cells/clones?**
2. **Different CD45 isoform**
3. **Altered cell surface adhesion molecule composition.**
4. **B cell becomes the main antigen-presenting cell.**
5. **Lymphocyte recirculation pattern differs.**

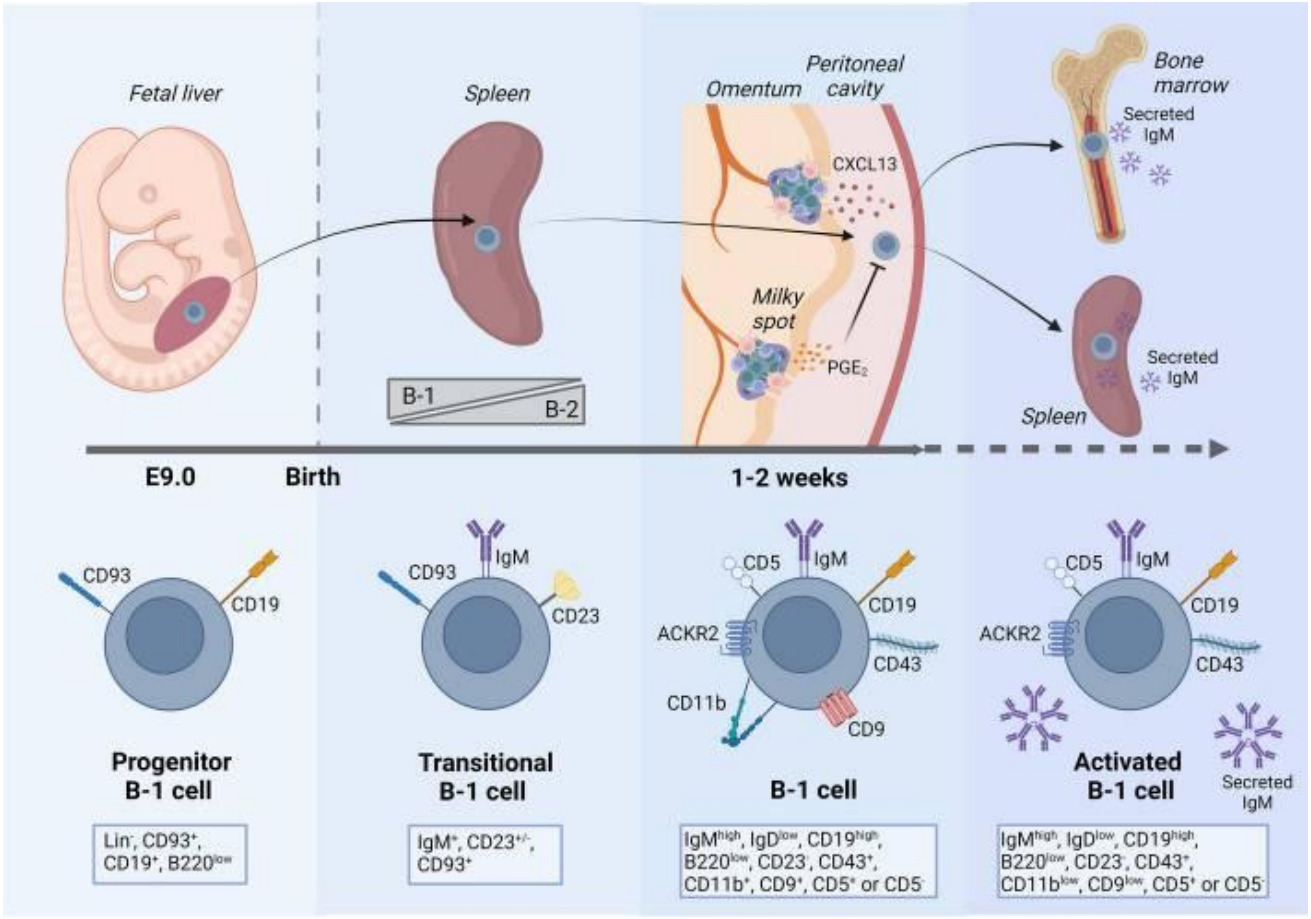
Memory of natural immunity: long lived B1 and invariant T cells

- **CD5-positive (B-1) B cells**: continuous production of low-affinity polyreactive antibodies without antigen stimulation against common bacterial polysaccharide antigens and apoptotic self molecules;

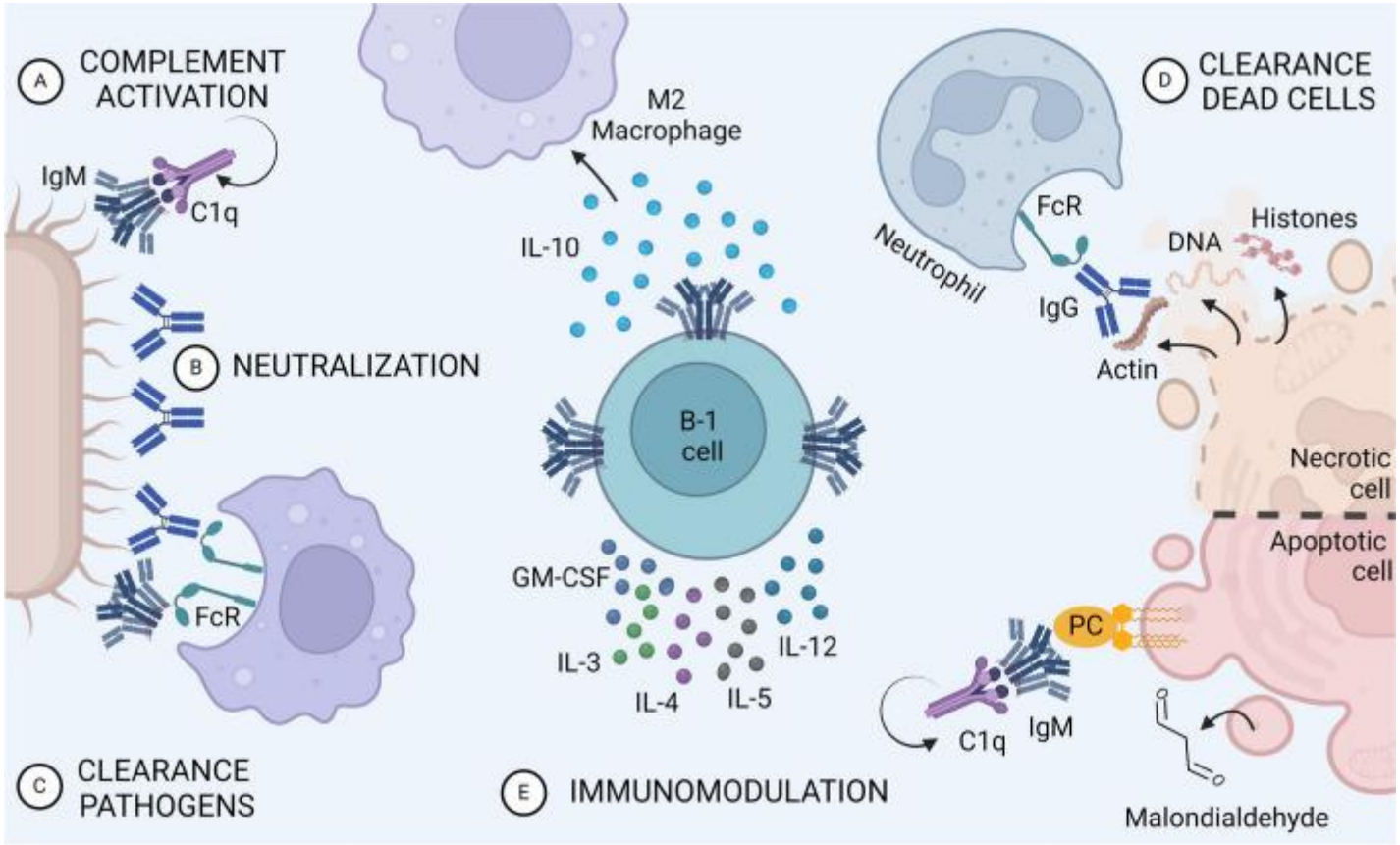
self-renewal; dominant B cell type in newborn, tissue resident cells

- 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

B-1 cell migration and tissue distribution



Homeostatic B-1 cell functions



B-1 cells secrete IgM and/or IgG Natural antibodies (Nabs) that act as first-line defense against invading pathogens and tissue damage by promoting: **A** complement cascade activation; **B** pathogen neutralization; **C** NAbs-dependent phagocytosis of invading pathogens; **D** opsonization and NAbs-dependent phagocytosis of dead cells; **E** modulation the immune system by secreting cytokines. PC: phosphorylcholine