

Basic Immunology

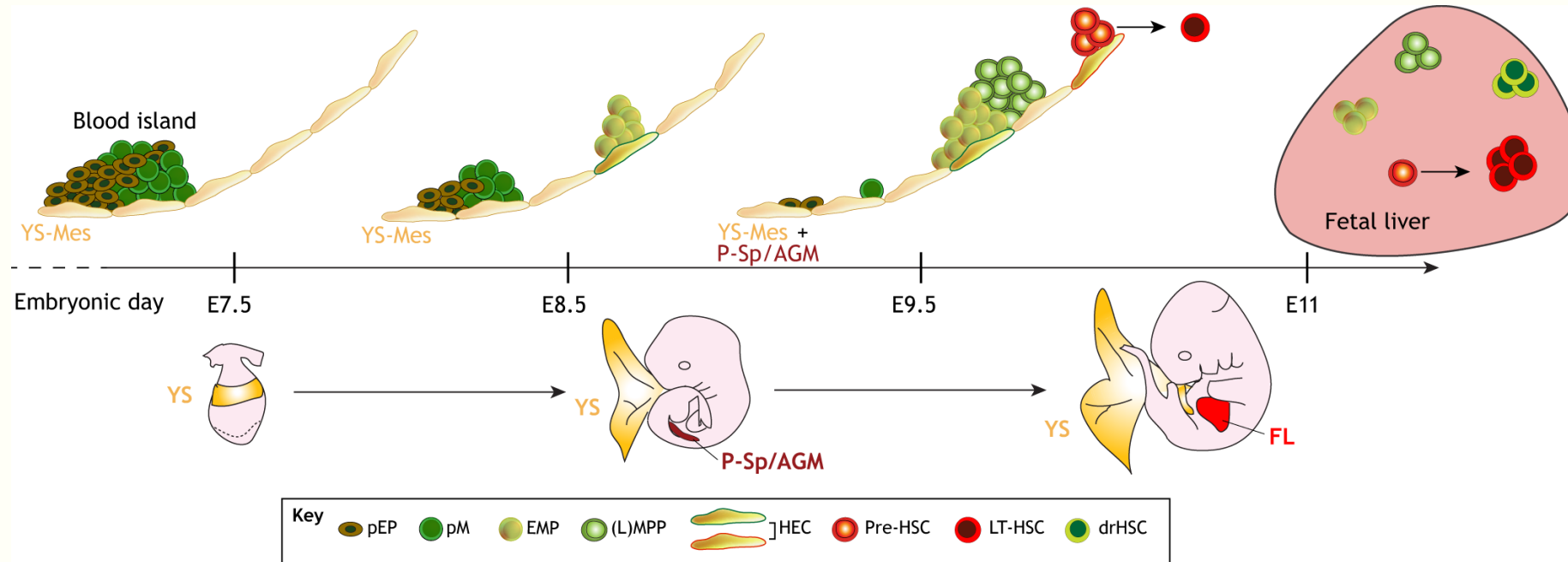
Lecture 10th

**Primary B-cell development:
developmental stages and
checkpoints.**

General issues in blood cell development

- **Ontogeny of hematopoiesis** – *mesodermal differentiation*
- **Maintenance of continuous blood production** – *balance between stem cell differentiation-minority or quiescence - majority*
- **Development of blood cells from hematopoietic stem cells** – *combined individual effect of (a) promoting/inhibitory transcription factors and (b) soluble or cell-bound mediators → **tissue-related differences in product quality***

Ontogeny of hematopoietic tissues in mice



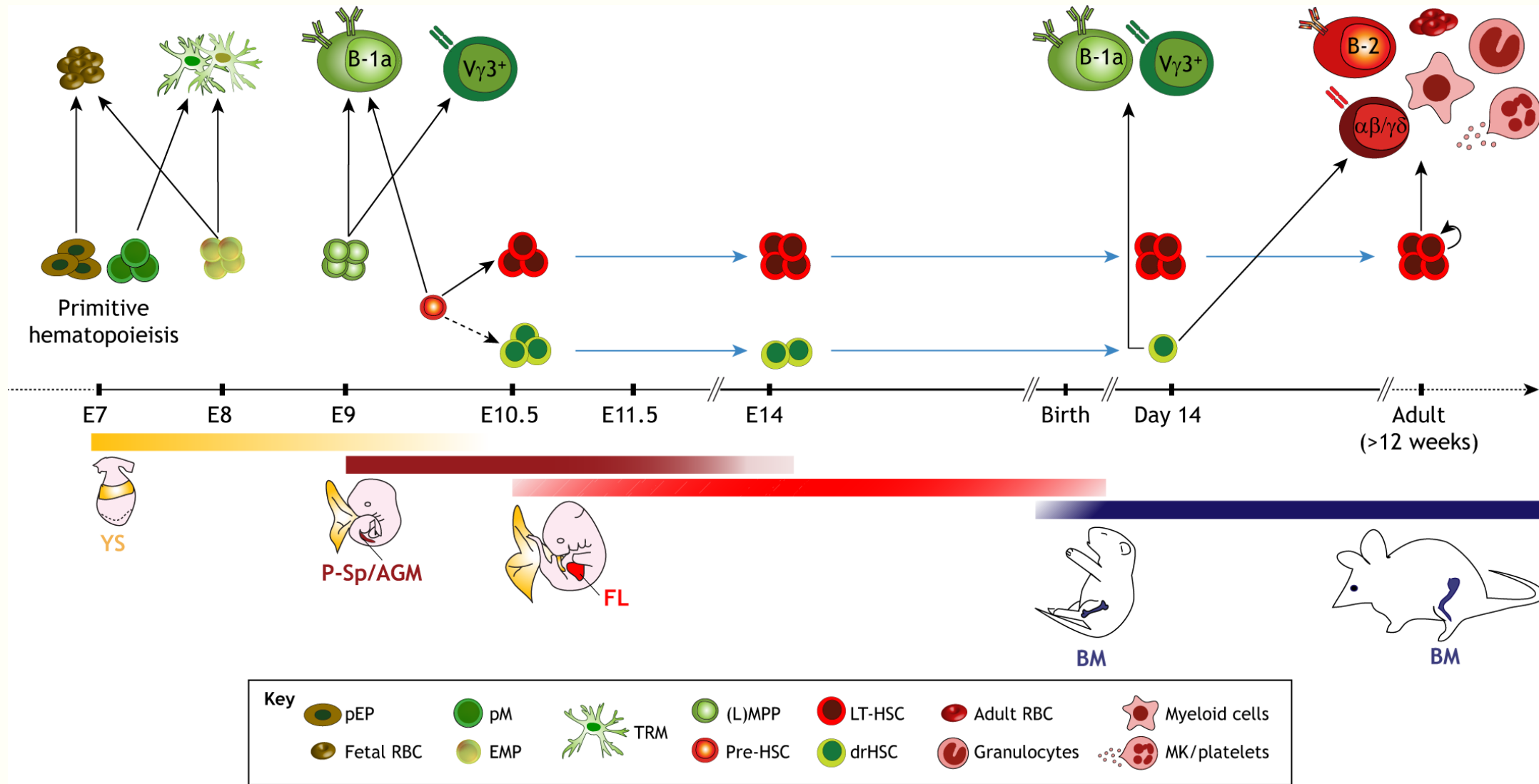
- **EXTRAEMBRYONIC**

- Yolk sac, placenta: erythromyeloid precursors → (adult tissue macrophages)

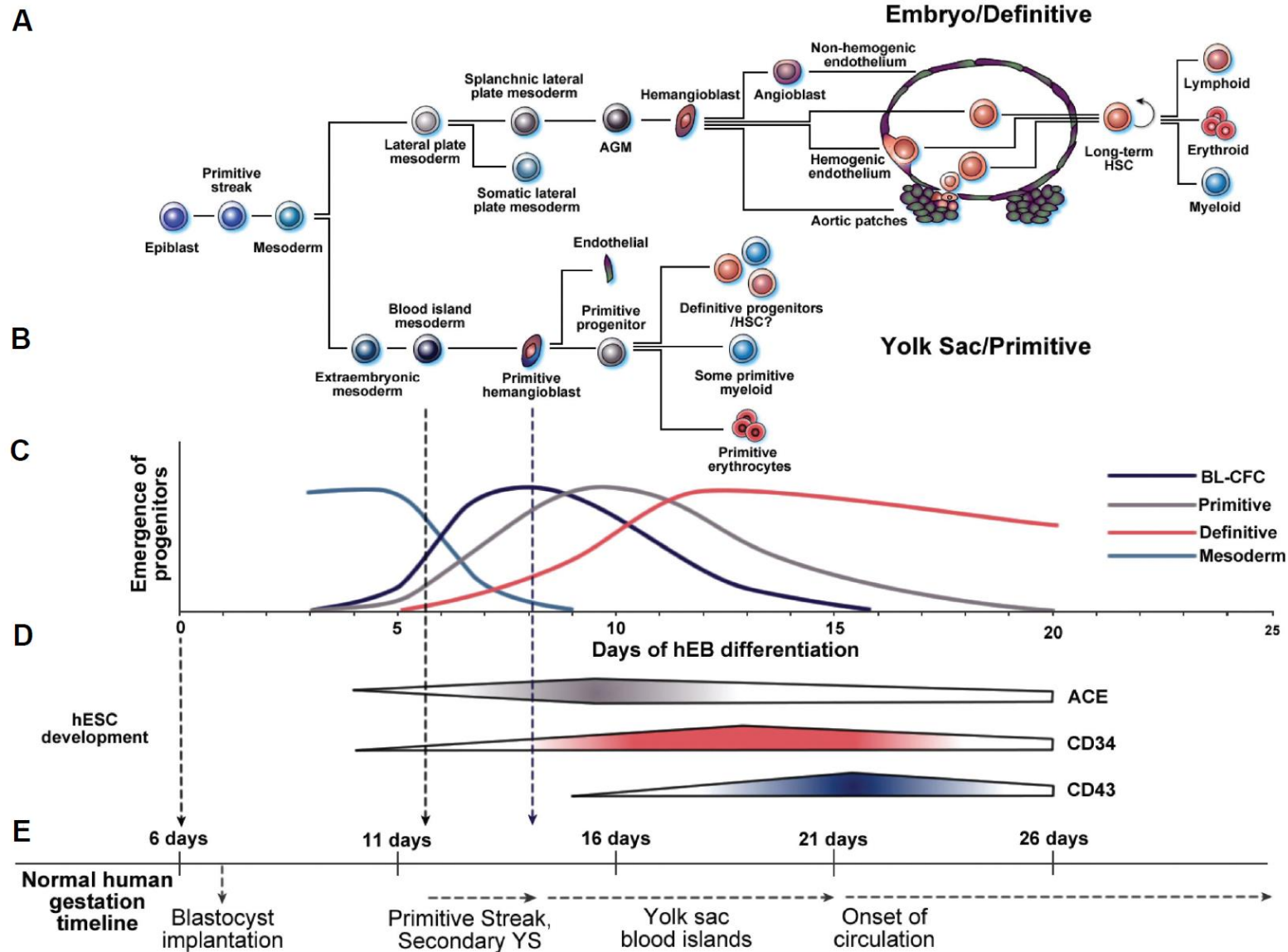
- **INTRAEMBRYONIC**

- AGM → embryonic liver/spleen → bone marrow: definitive

Sequence of lymphoid cell development



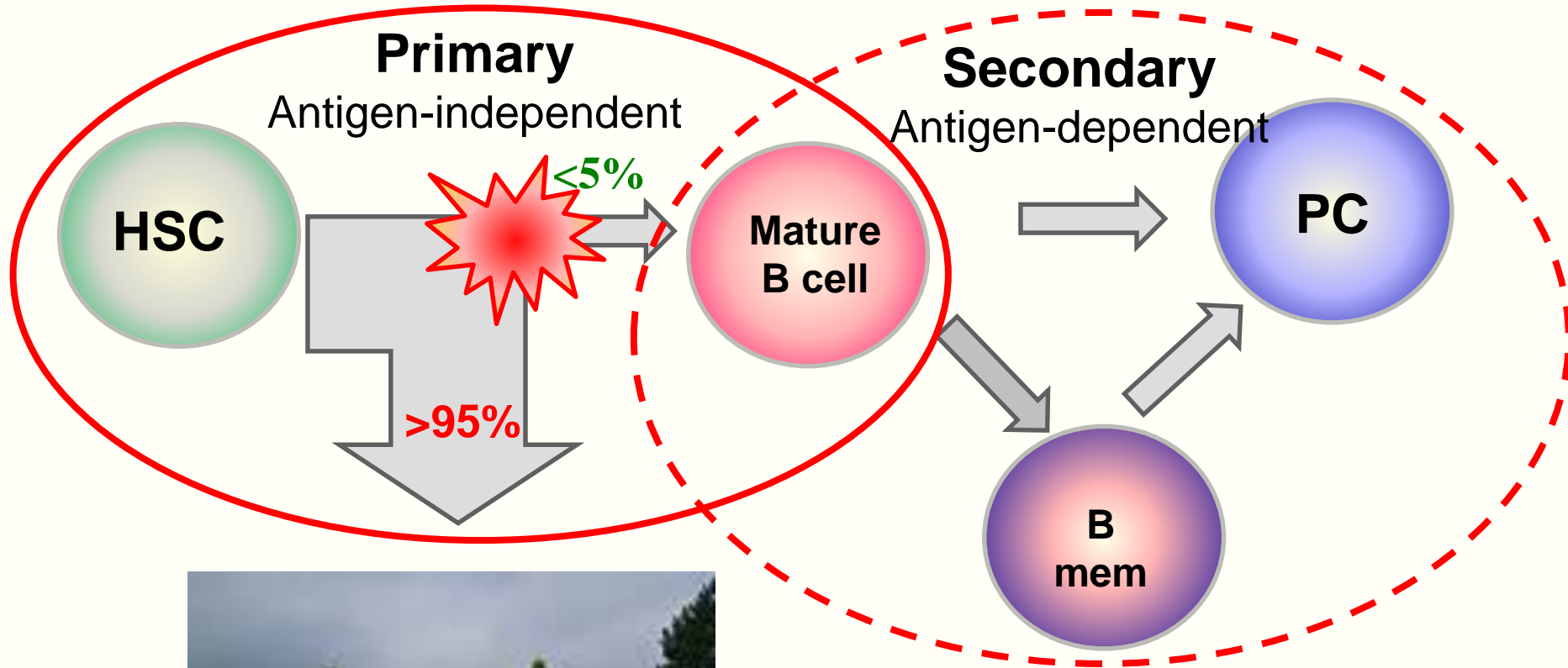
Ontogeny of hematopoiesis in humans



B-cell development: key issues

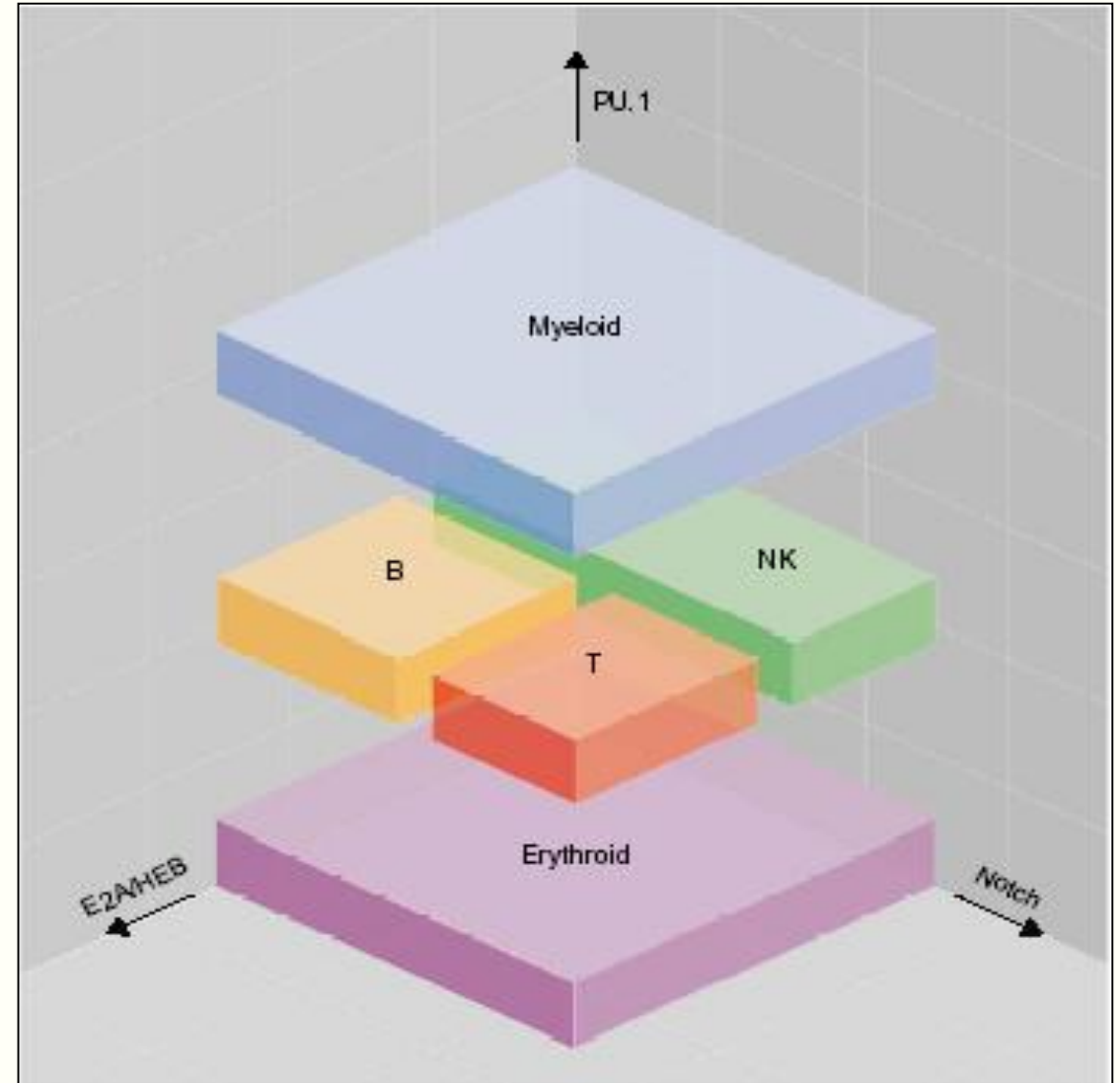
1. **Hematopoietic stem cells:** various locations;
2. **Commitment and survival:** B-lineage specification
3. **Development:** Reactivity without self-reactivity
4. **Components of the pre-immune B-cell society:** as defined by origin, tissue location and phenotype/functions before immunization (secondary differentiation afterwards).
5. **Beyond immunological recognition:** Tissue building

Stages of B-cell differentiation

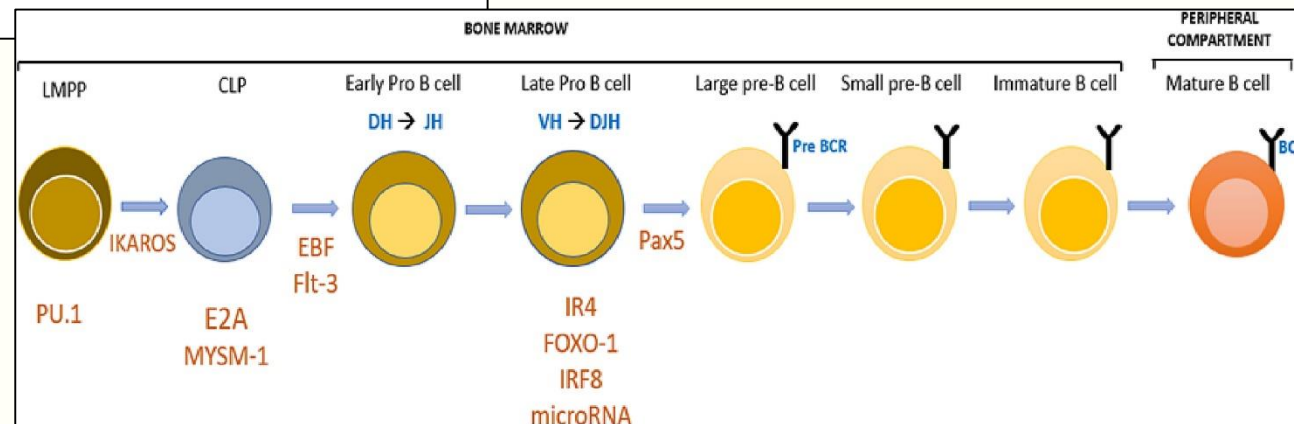
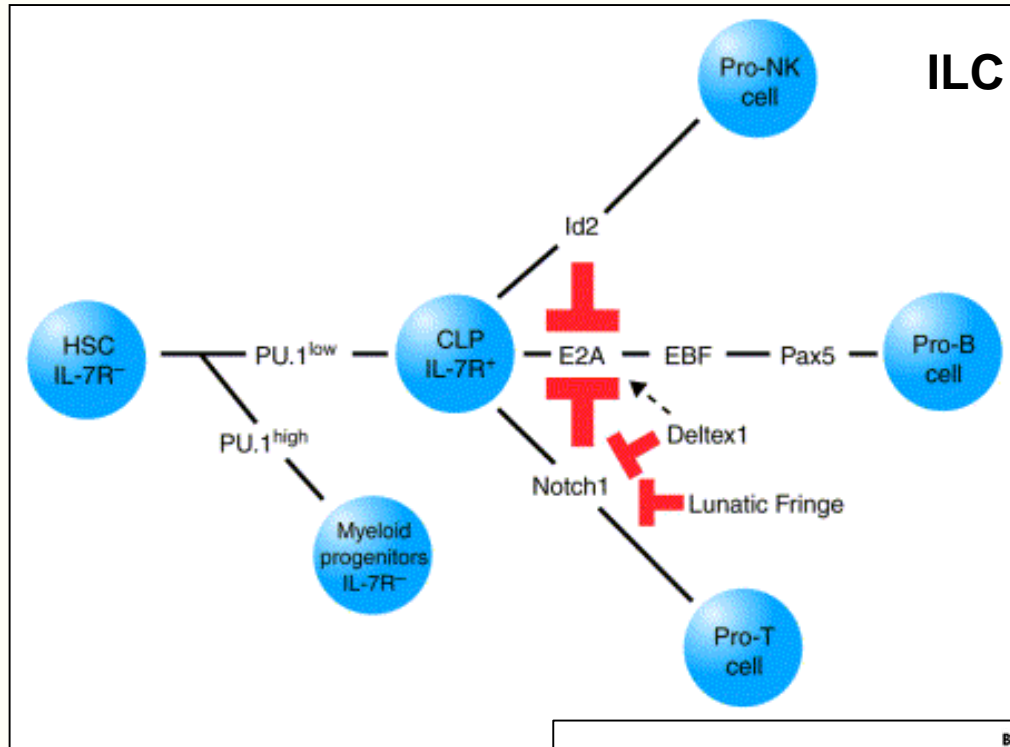


Ly/My commitment – set by GATA-1 and PU.1 equilibrium

Ikaros (Aiolos, Eos, Daedalus & Pegasus):
Maintenance of lymphoid commitment



B/T/NK commitment – E2A (B) overruled by Notch (T) and/or Id2 (NK) signals



Role of BM stroma

1. Adhesion: – CD44, VCAM-1
2. Growth factors: IL-7, IL-3, SCF.
3. Response modifiers: Wnt factors, ECM components.
4. Chemokine-production: SDF-1/CXCR4 ligand.

Elements of B:stromal interactions

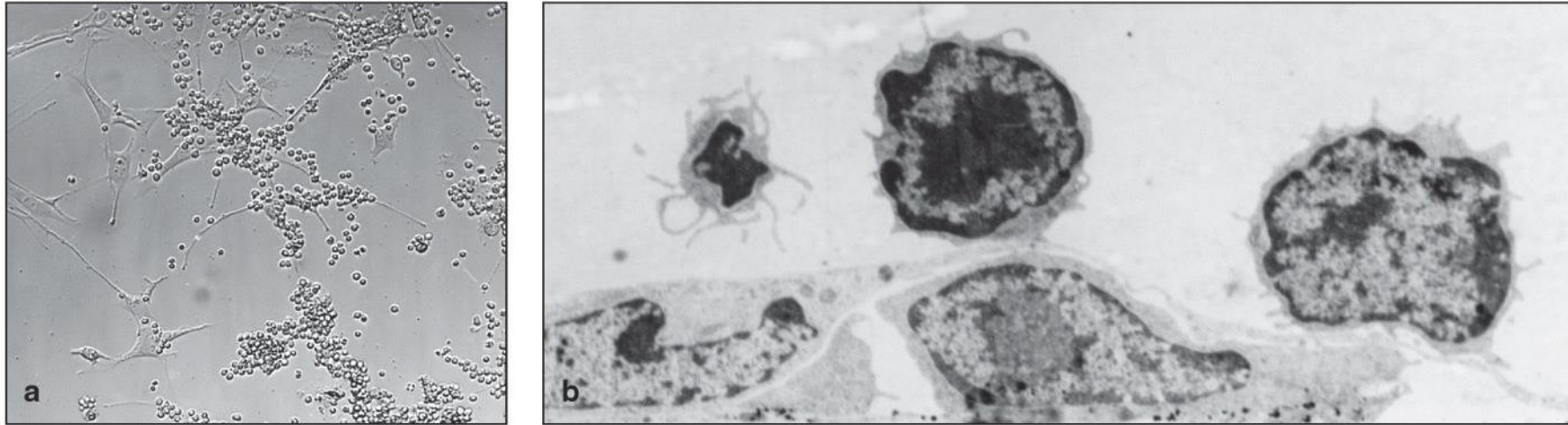
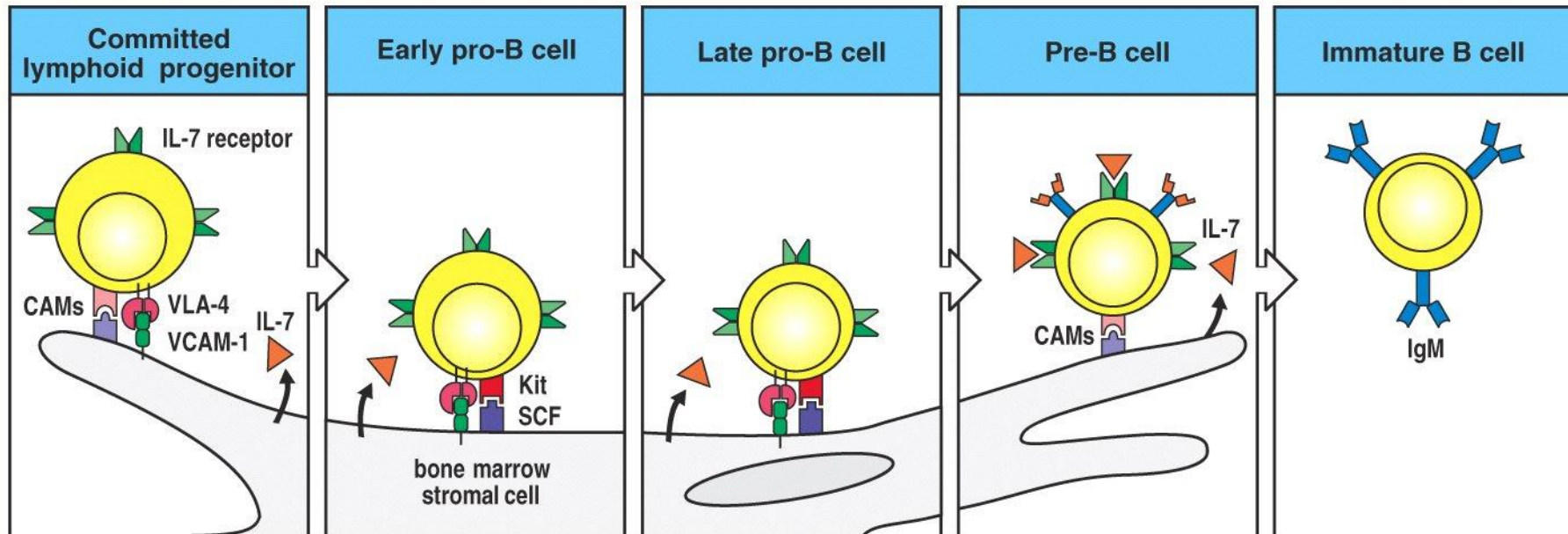


Figure 7-4 Immunobiology, 6/e. (© Garland Science 2005)



B-cell development I: HSC > "Large pre-B"

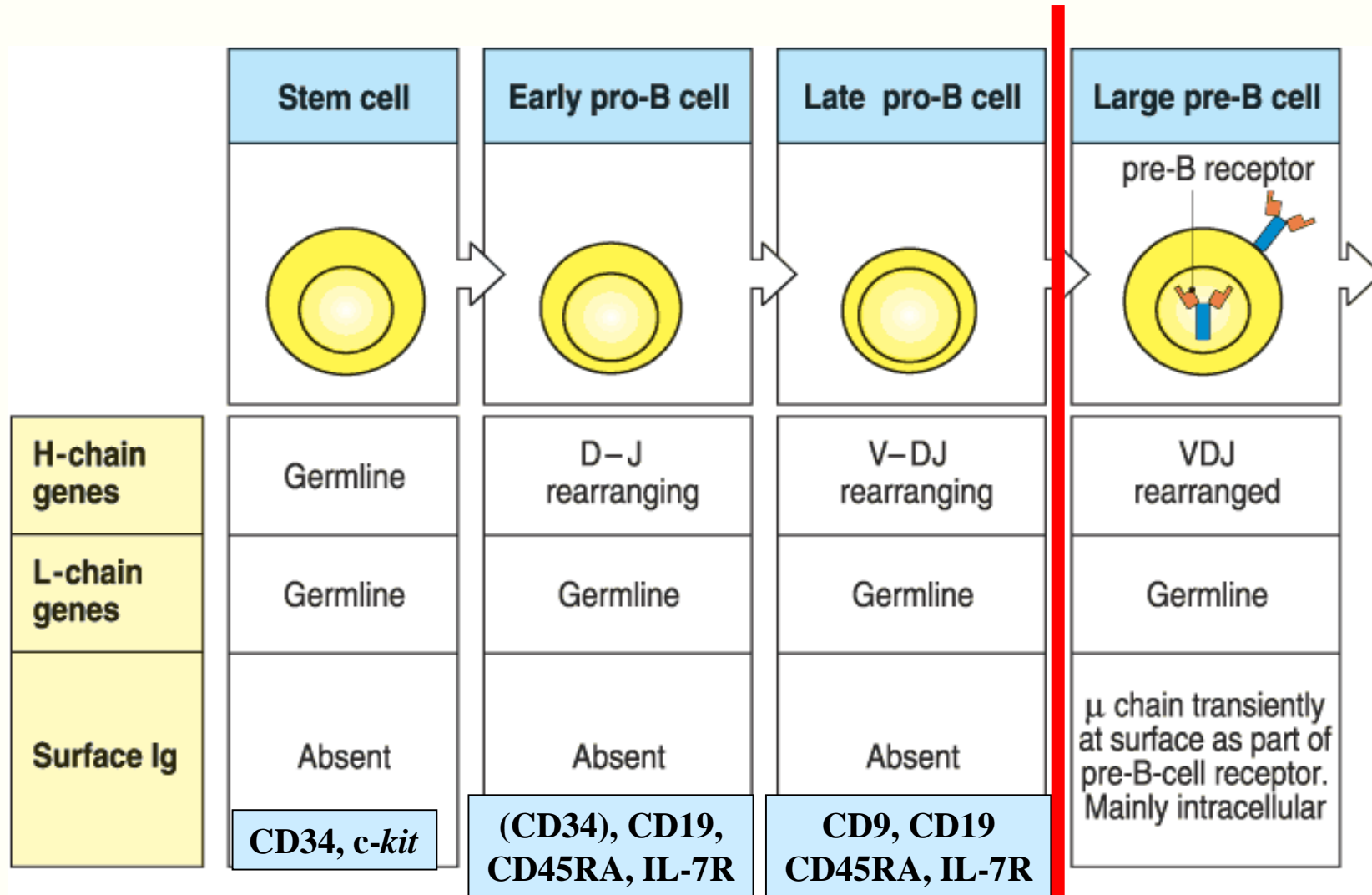


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B-cell development II “Small pre-B” > “mature B”

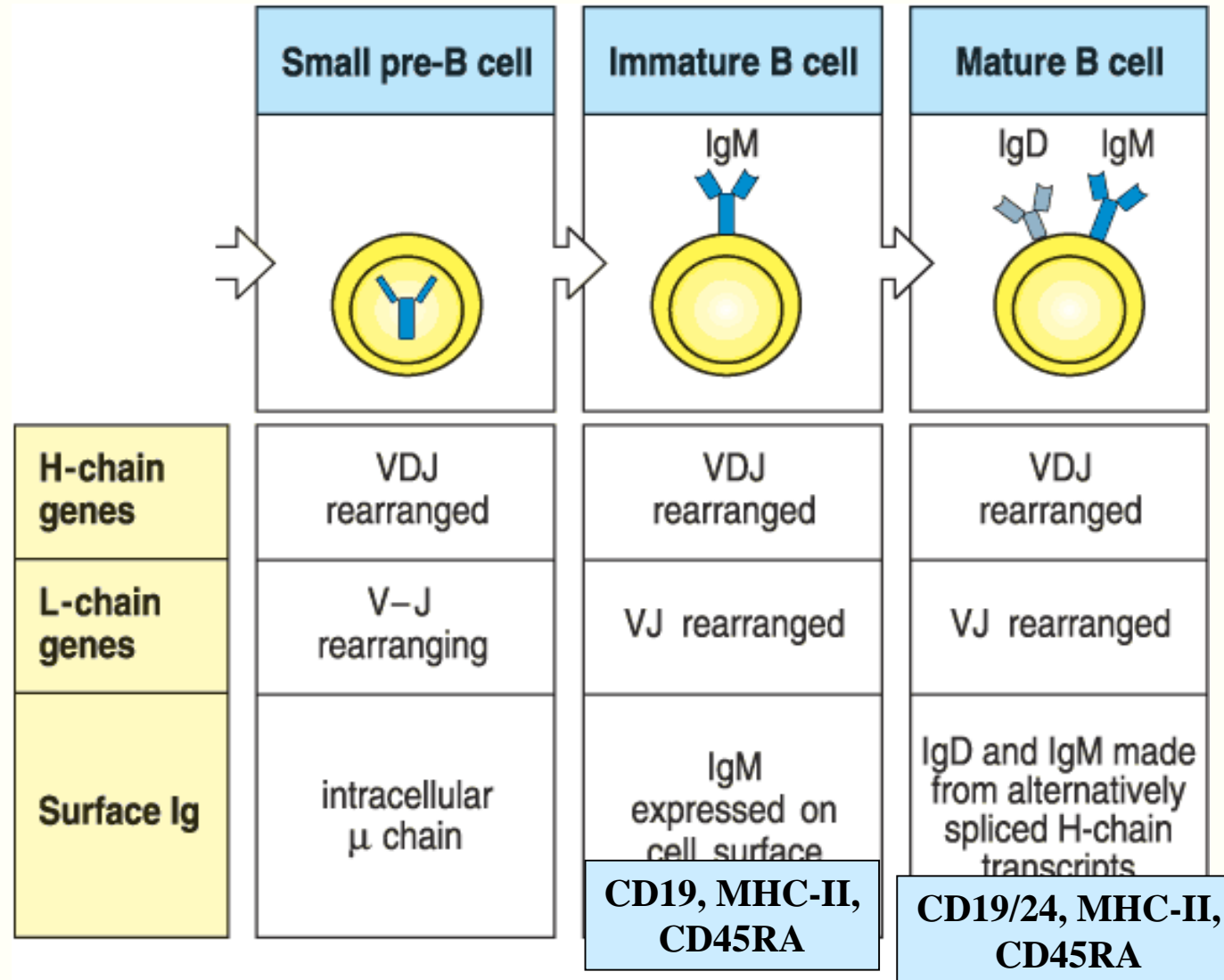
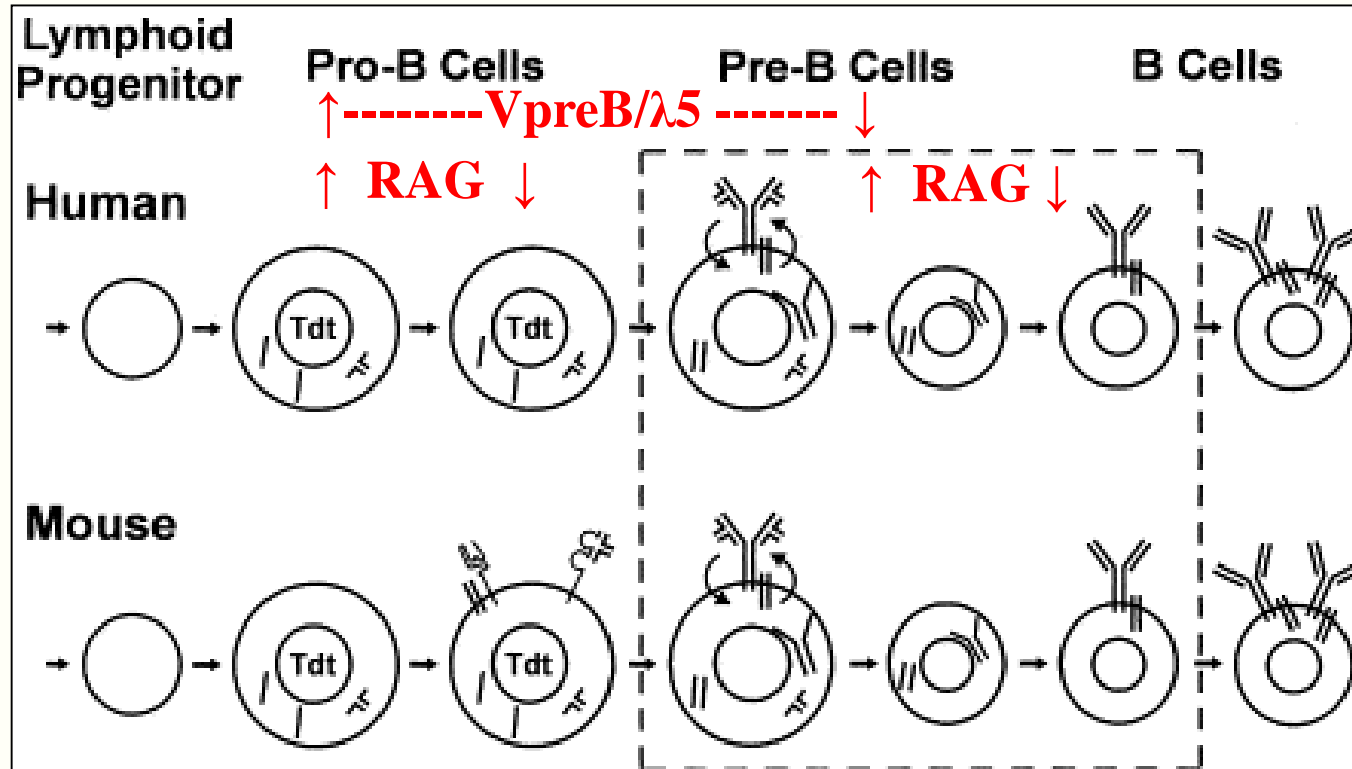


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preBcR – BcR switch



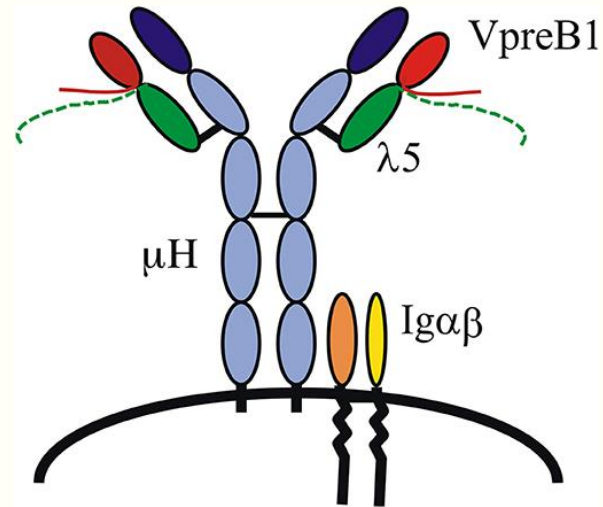
Regulatory elements:

preBcR: IgH(tm)/VpreB/λ5 → Their absence leads to severe B-cell development blockade;

Function: binding a stromal ligand (?)

TdT: in its absence no N-insertion → B-1 cell dominance

Developmental role(s) of preBcR



Proliferation – *around 5 division cycles*

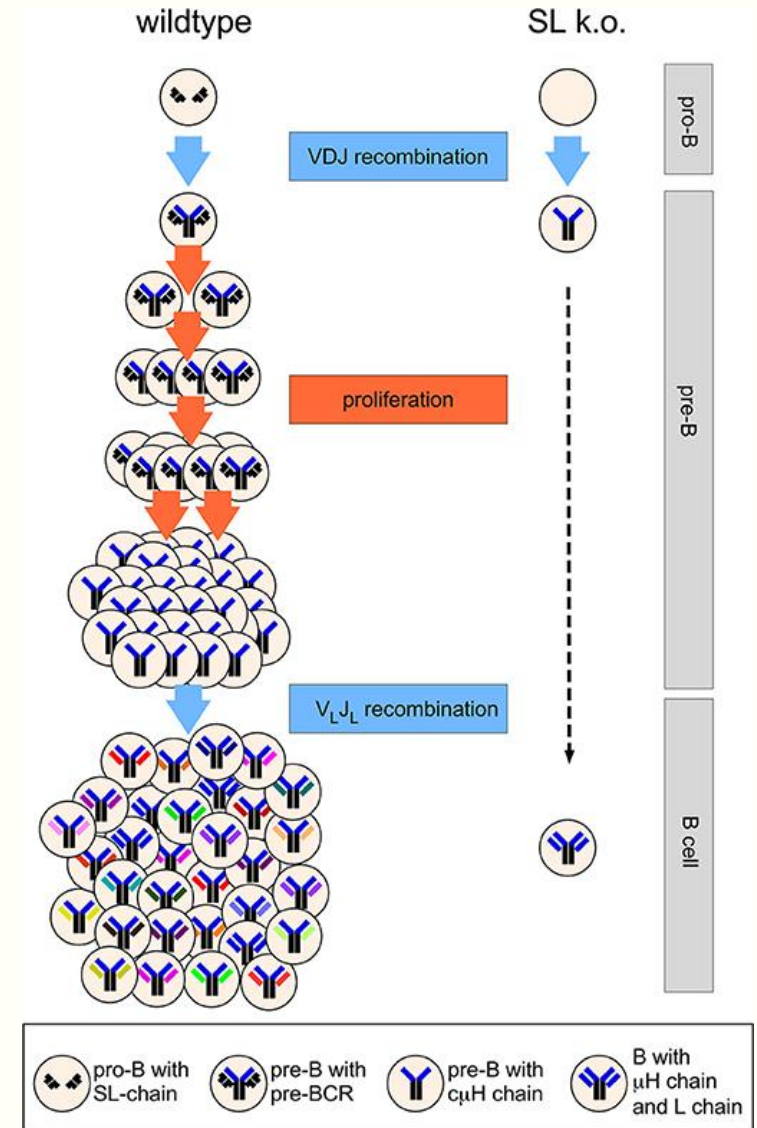
Survival – *via putative ligands*

Positive selection of pre-B cells

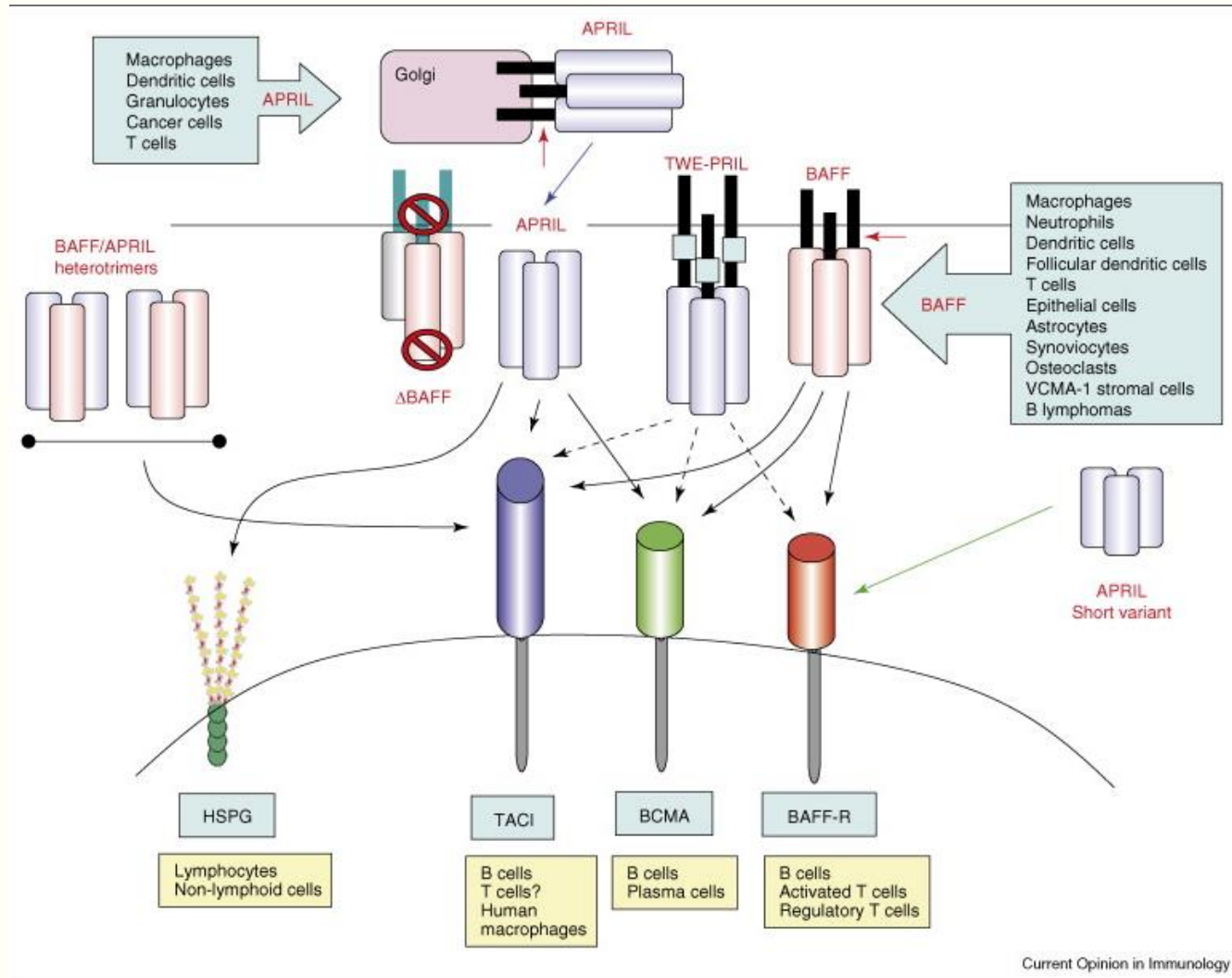
Downregulation of the RAG recombinases - *IgH allelic exclusion*

Selection of the IgH repertoire

Negative selection - *tolerance*

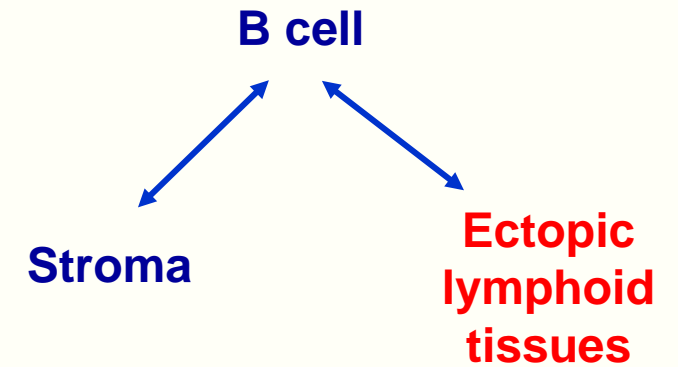
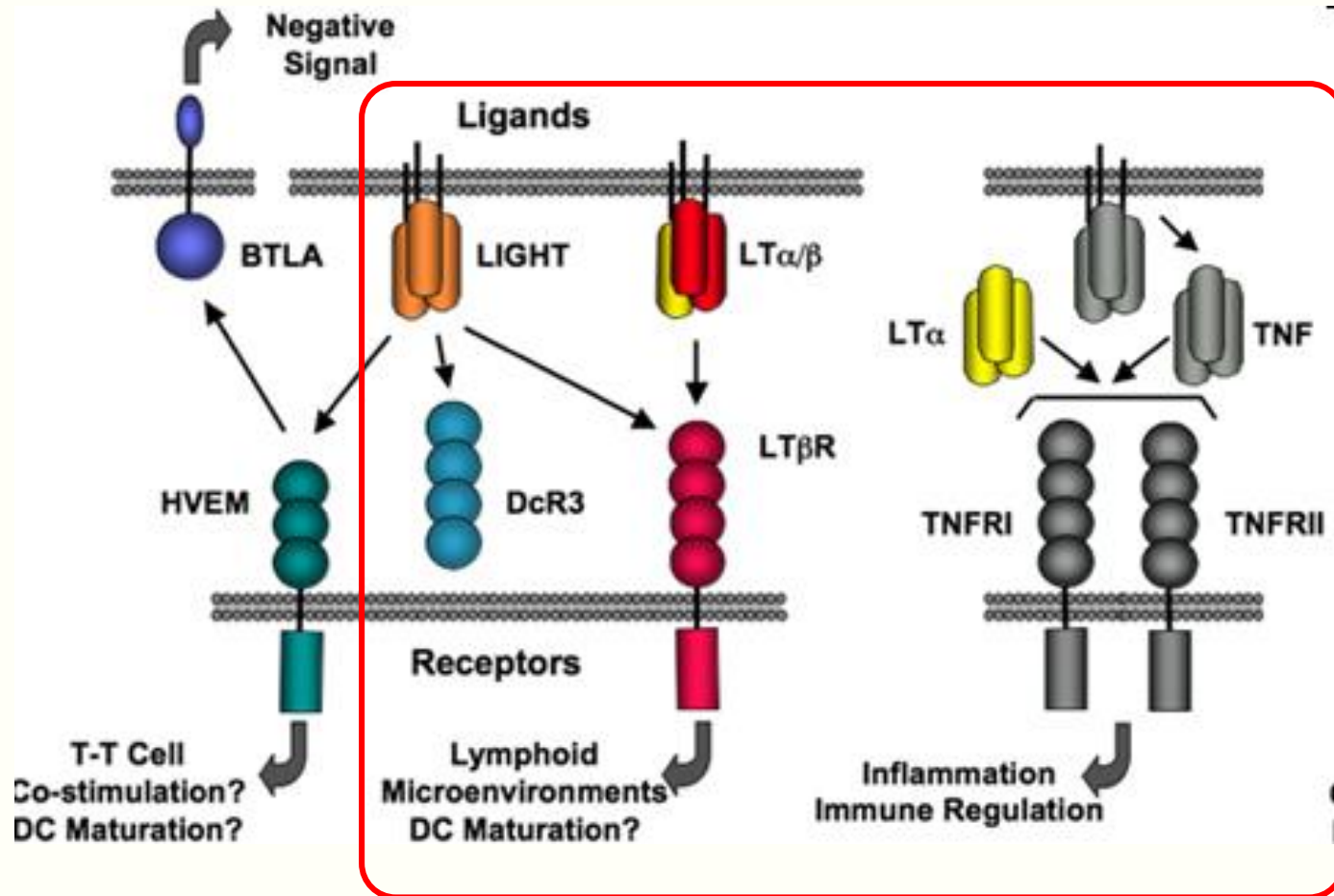


Pre-immune survival of peripheral B cells



Increased BAFF/BAFF-R expression in autoimmune diseases and B-cell malignancies

Tissue-building roles of B cells in the peripheral lymphoid organs



Organization of the naive B-cell pool

| Type of difference | Subset | Characteristics |
|--------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Developmental origin | B-1 | Fetal hematopoietic stem cell; self-renewal, low-affinity autoantibody production (TdT-independent BcR), dominance in neonates and CLL, located in body cavities. (CD5+, CD43+, IgM++/IgD+) |
| | B-2 | Postnatal bone marrow-derived |
| Tissue compartmentalization (within the B-2 subset) | Follicular B cell (FoB) | Distributed in peripheral lymphoid tissues, recirculate (IgM+/IgD++, CD21+, CD23++). |
| | Marginal zone B cells (MZB) | Located in the splenic MZ (in humans also in MALT) with Ig phenotype similar to B-1 B cells, adult BM origin, distinct developmental regulation to Fo B cells, relatively sessile. (IgM++/IgD+, CD21++, CD23+/-) |
| Functional specialization | Regulatory and other B cells (Bregs) | Production of IL-10 and GM-CSF |
| Age-related appearance | Ageing-associated B cells (ABC) | Increased presence in elderly and with autoimmune diseases (T-bet/CD11c) |

Essentials – B-cell development

B cells originate from various primary sources

the site of origin defines their lineage subset affiliation (B-1 vs. B-2)

B-cell development progresses through sequential stages:

lymphoid/B-lineage commitment: transcriptional control

selection for rearrangement efficiency – role of preBcR

tolerance/clonal deletion/silencing: based on BcR/preBcR affinity

Other factors shaping B-cell repertoire

BAFF and homologues promoting B-cell survival

Non-BcR/Ig-related functions of B cells:

induction of follicular stroma via their LT/TNF receptors

B-cell subsets:

defined by origin, tissue location, phenotype and cytokine secretion capacity