

Basic Immunology

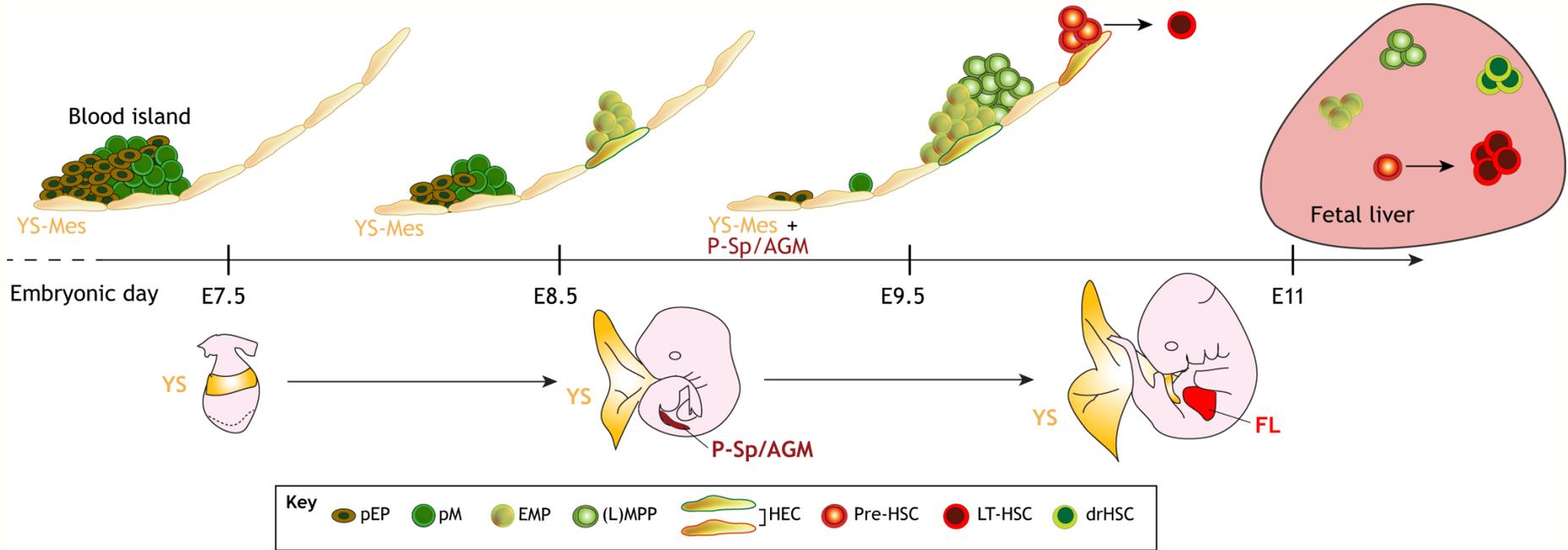
Lecture 10th

**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



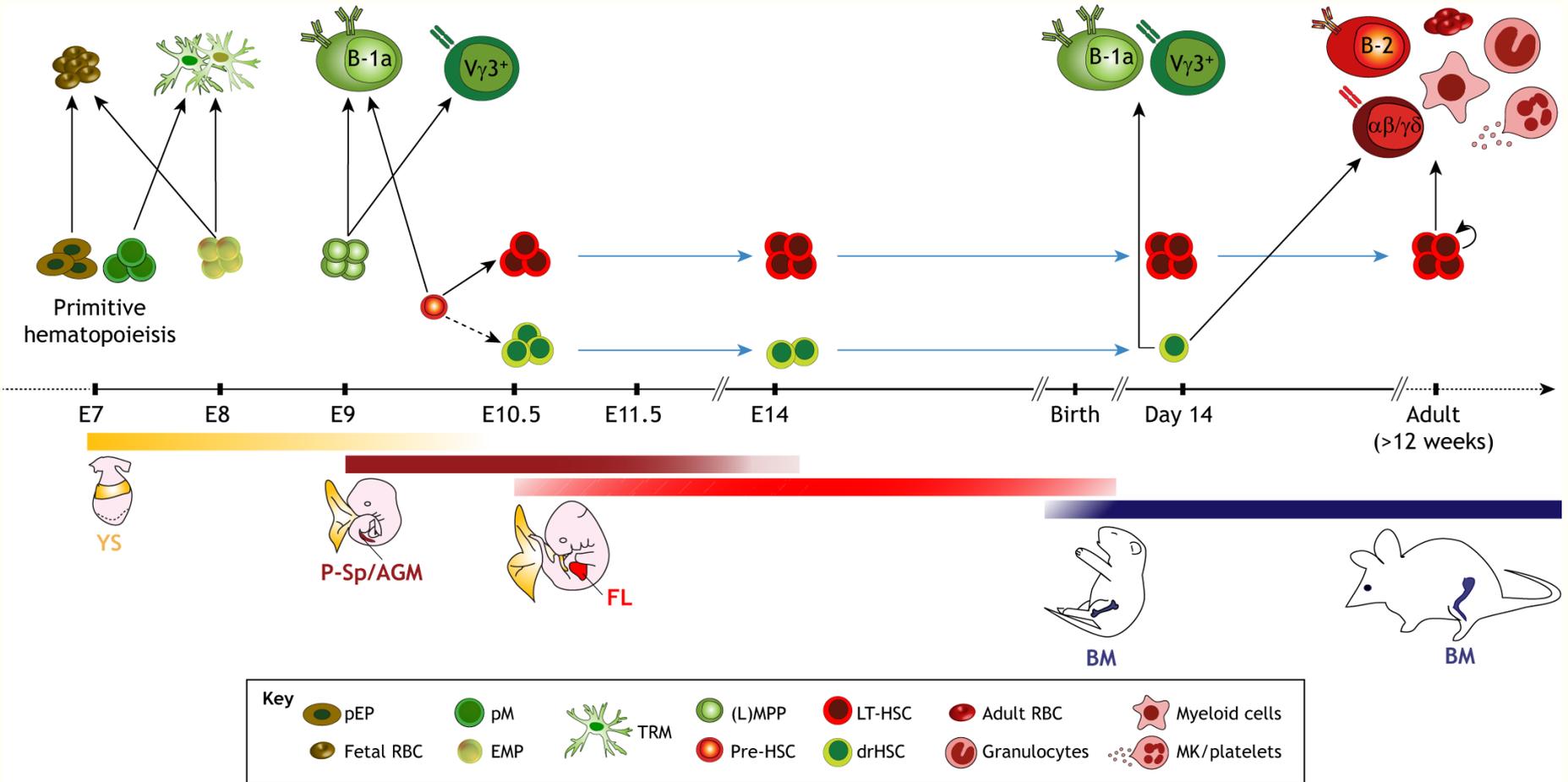
- **EXTRAEMBRYONIC**

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

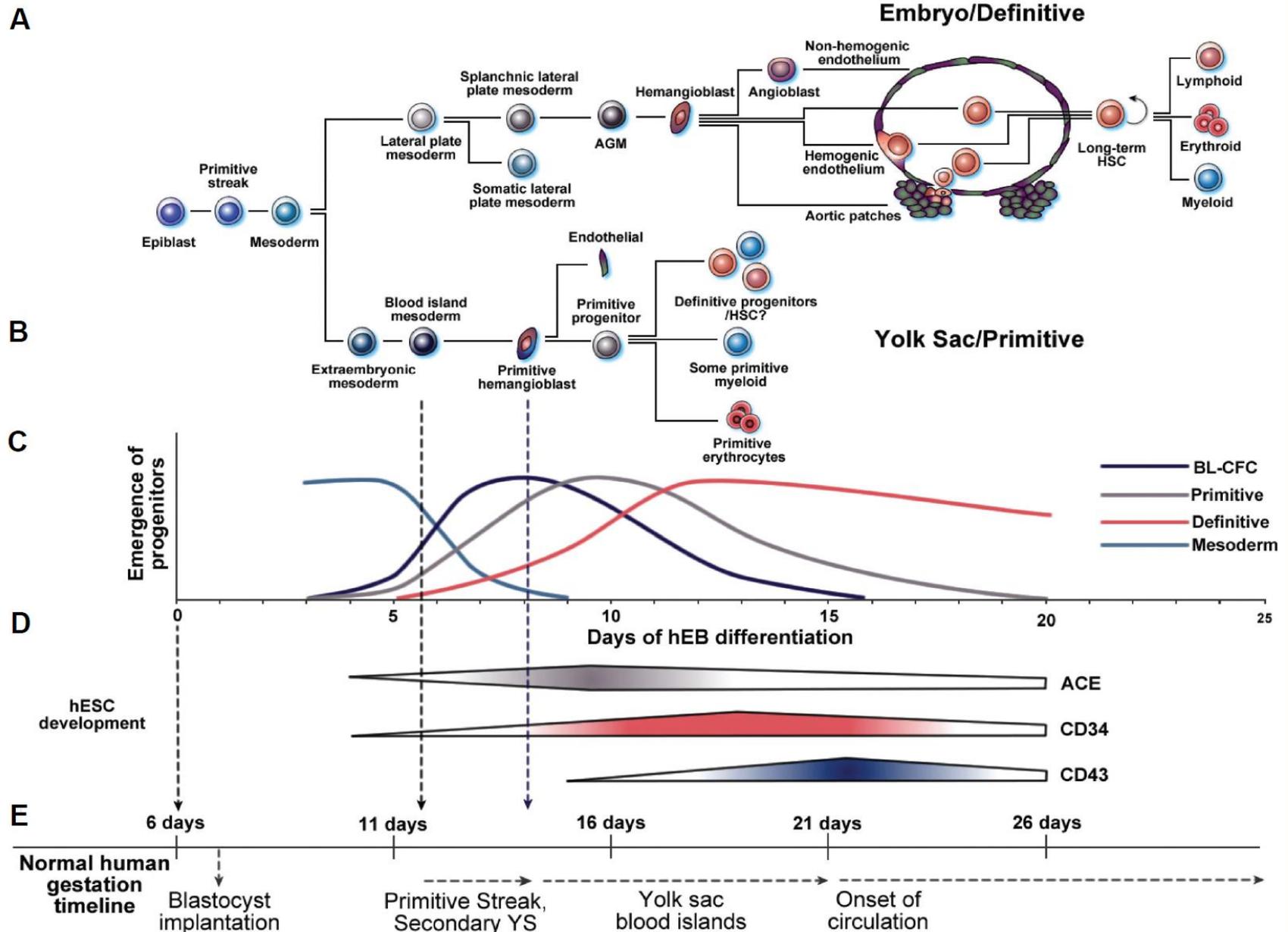
- **INTRAEMBRYONIC**

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

Sequence of lymphoid cell development



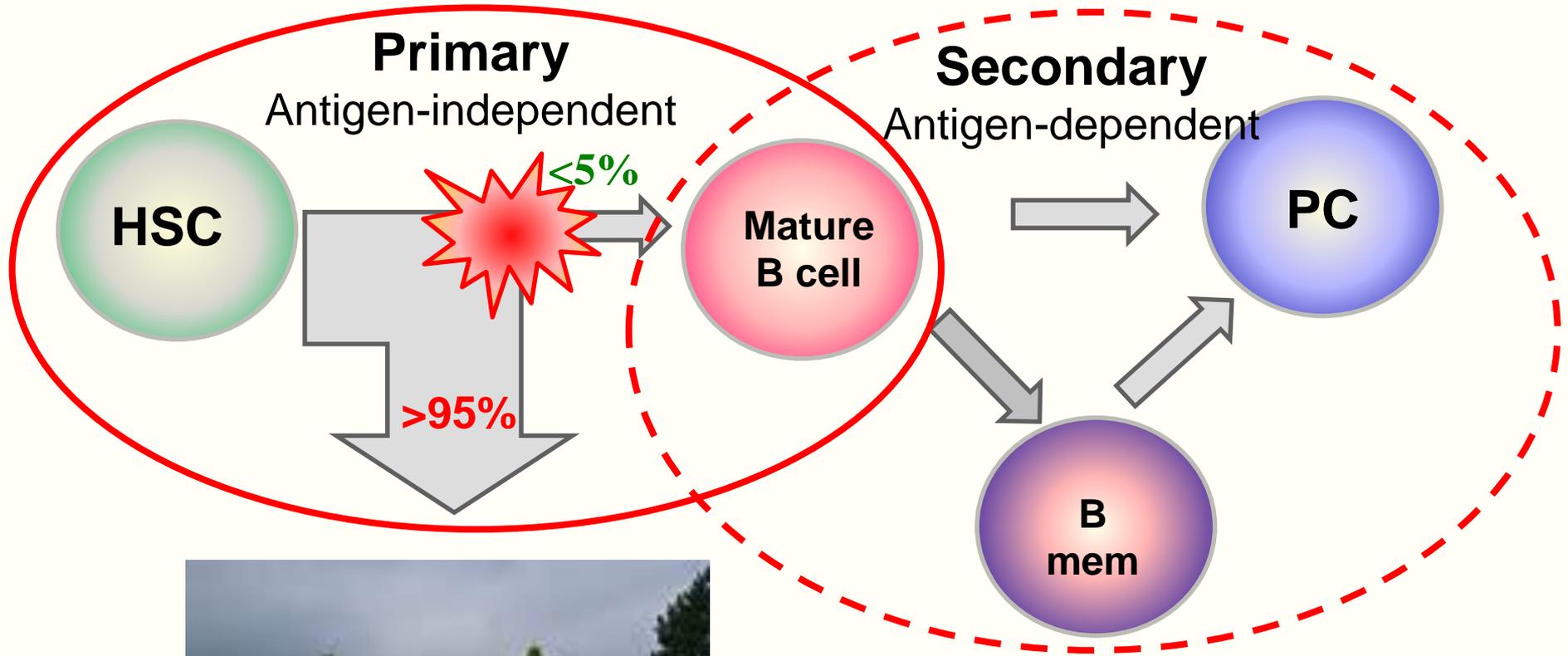
Ontogeny of hematopoiesis in humans



B-cell development: key issues

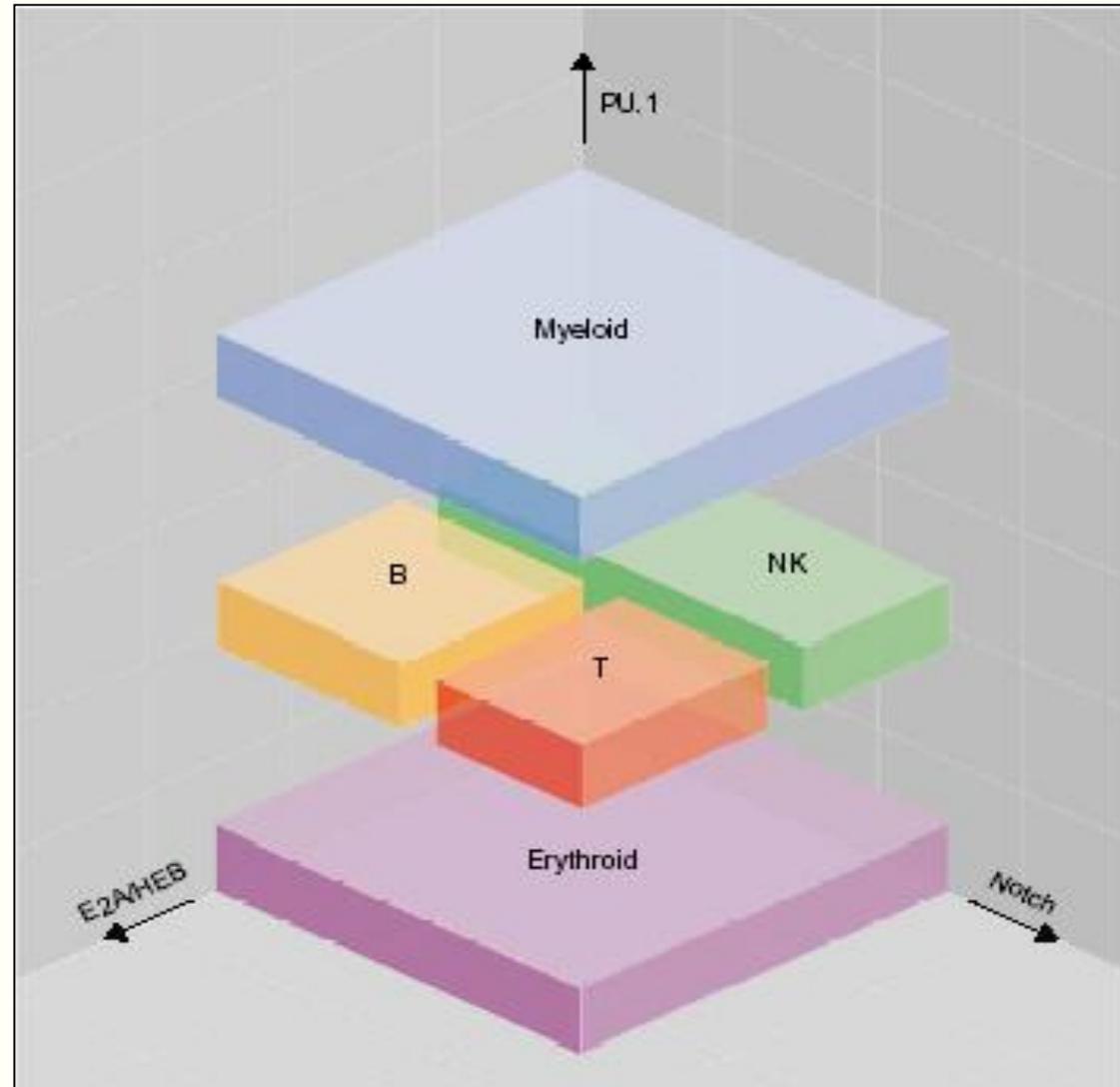
1. **Hematopoietic stem cells**: various locations;
2. **Commitment and survival**: B-lineage specification
3. **Development**: Reactivity without self-reactivity
4. **Components of the pre-immune B-cell society**: as defined by origin, tissue location and phenotype/functions before immunization (secondary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

Stages of B-cell differentiation

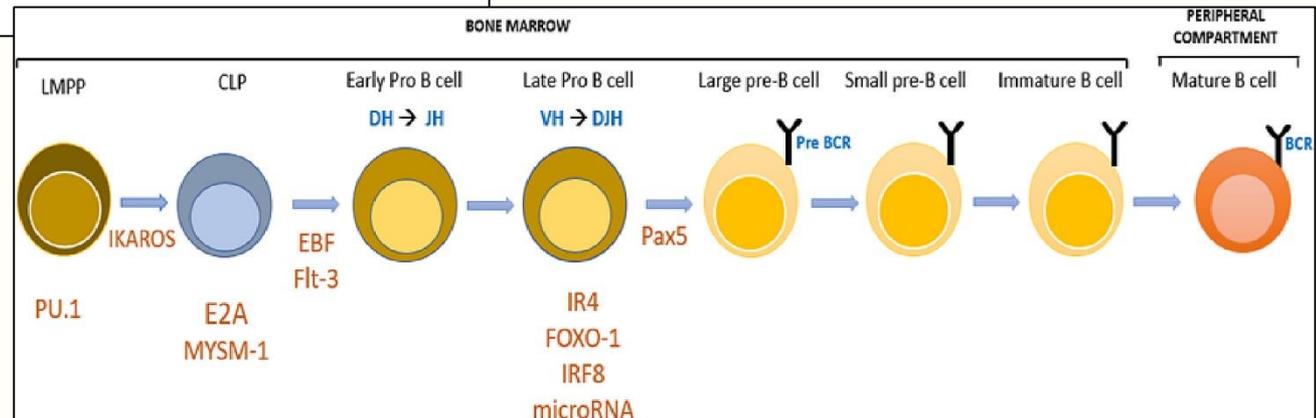
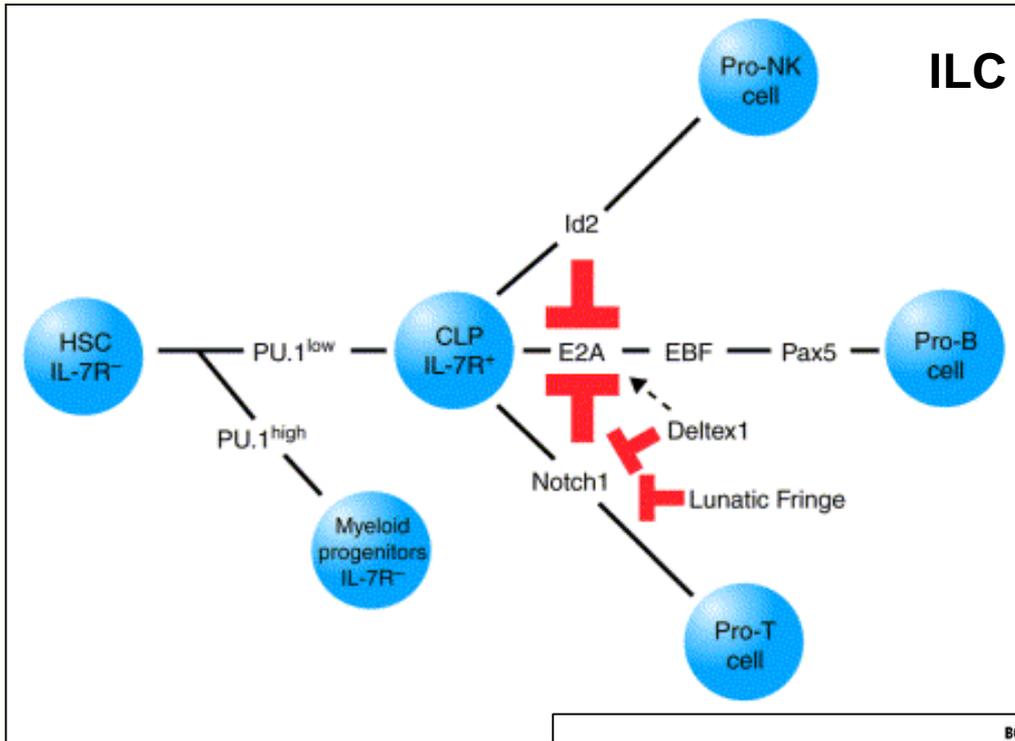


Ly/My commitment – defined by GATA-1 and PU.1 equilibrium

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



B/T/NK commitment – default E2A (B) path 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

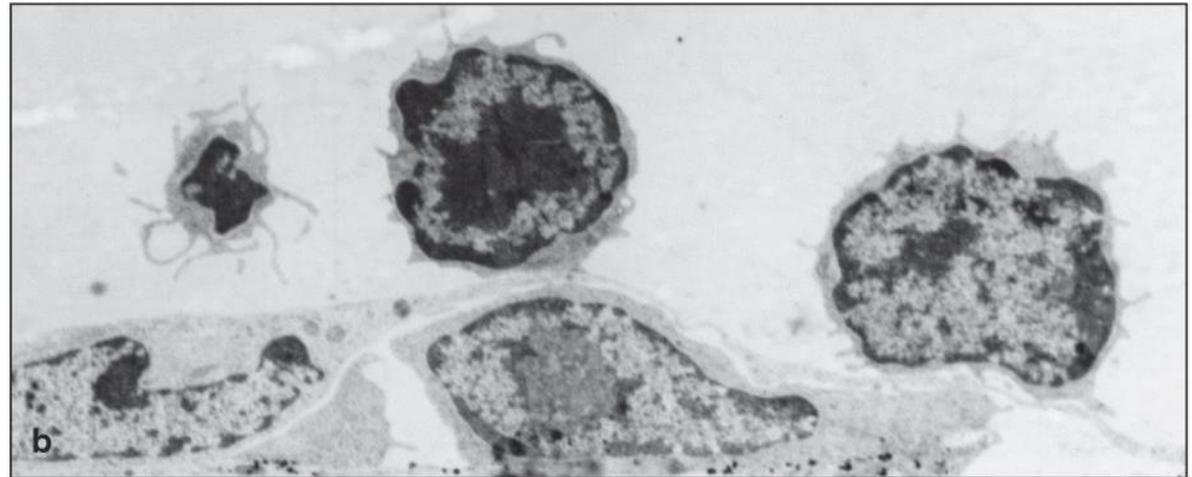
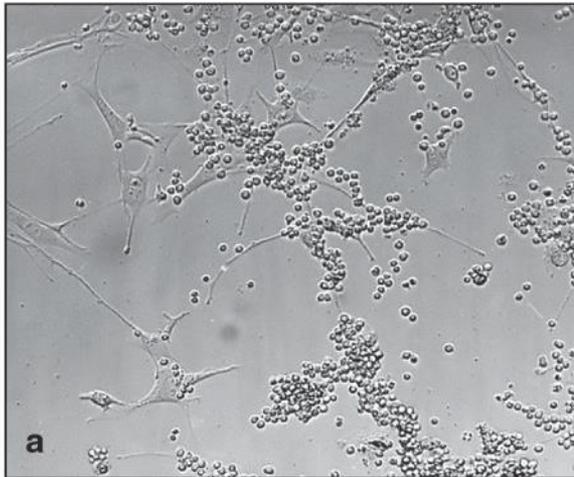
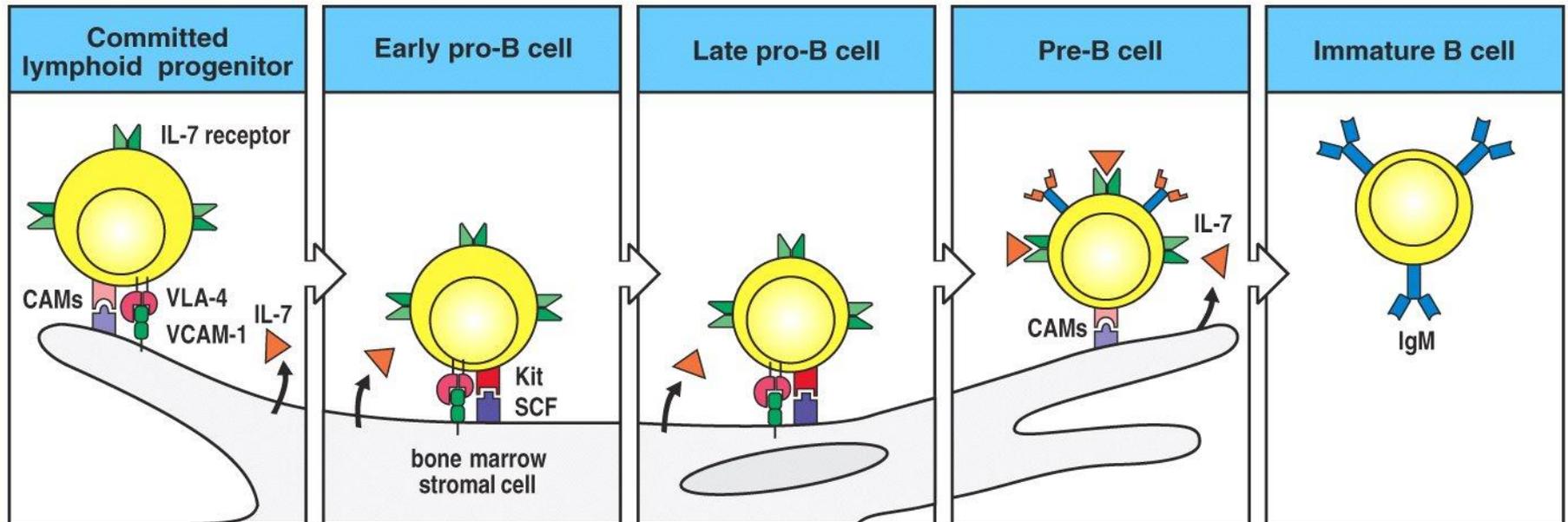


Figure 7-4 Immunobiology, 6/e. (© Garland Science 2005)



B-cell development I: HSC > “Large pre-B”

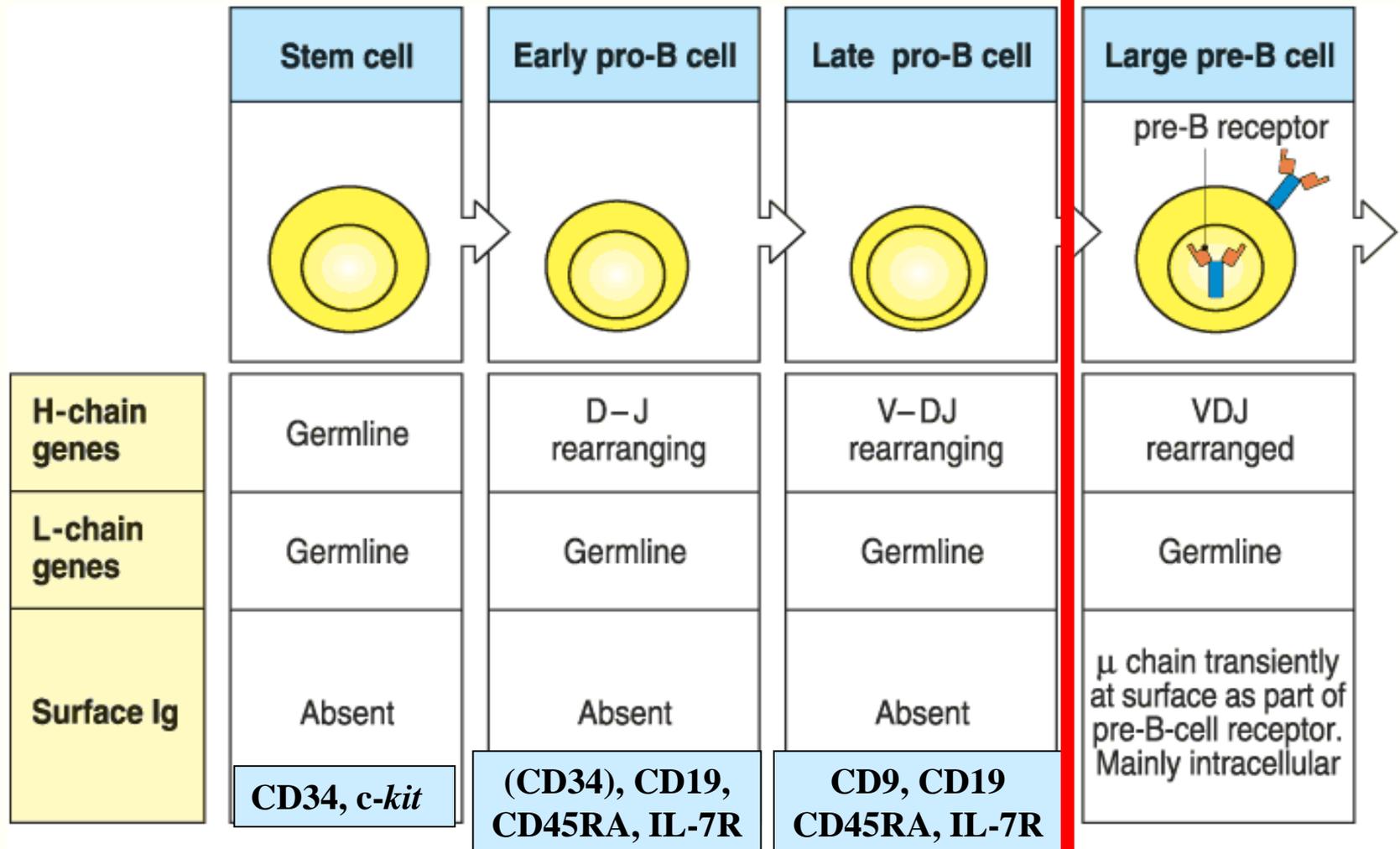


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B-cell development II

“Small pre-B” > “mature B”

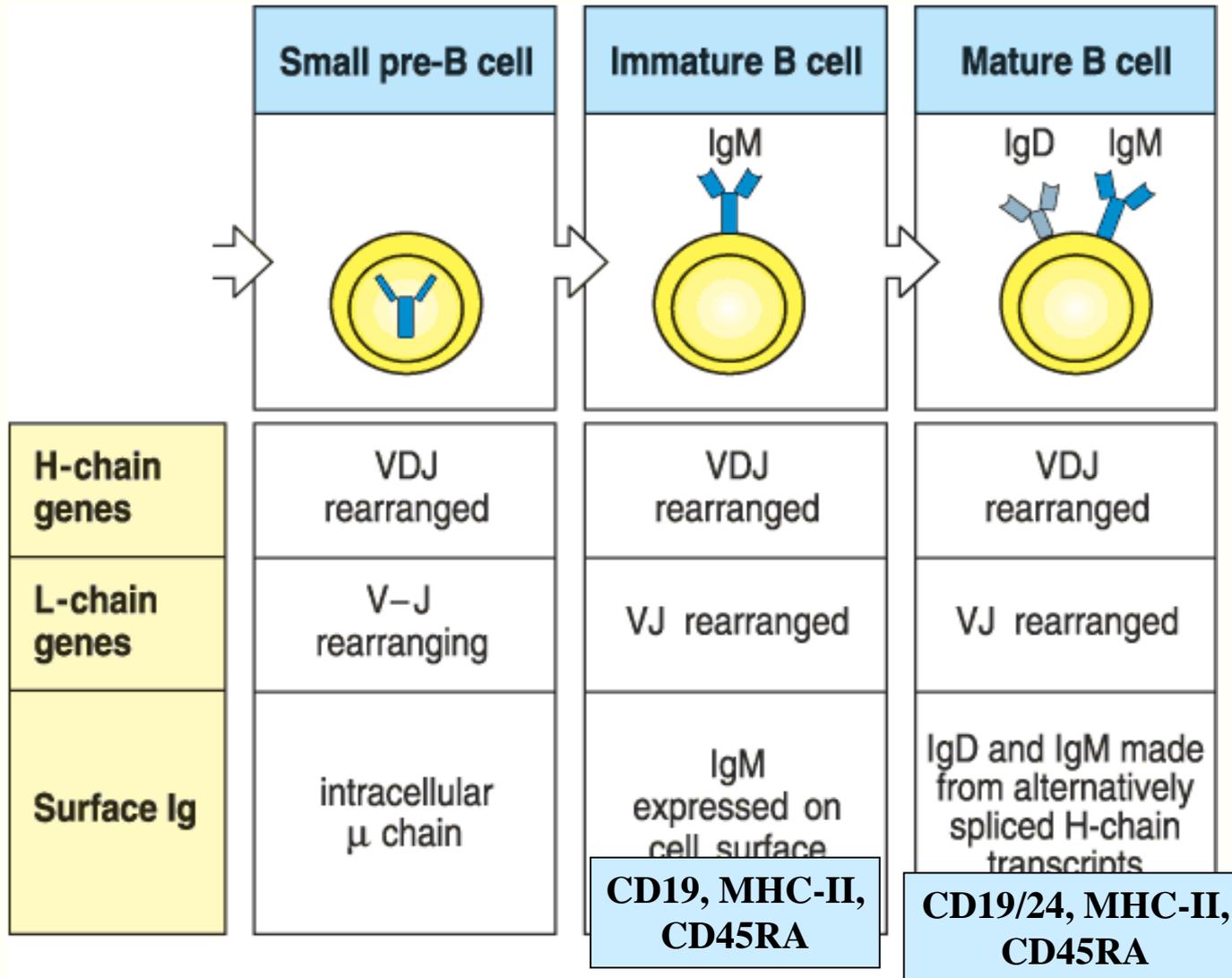
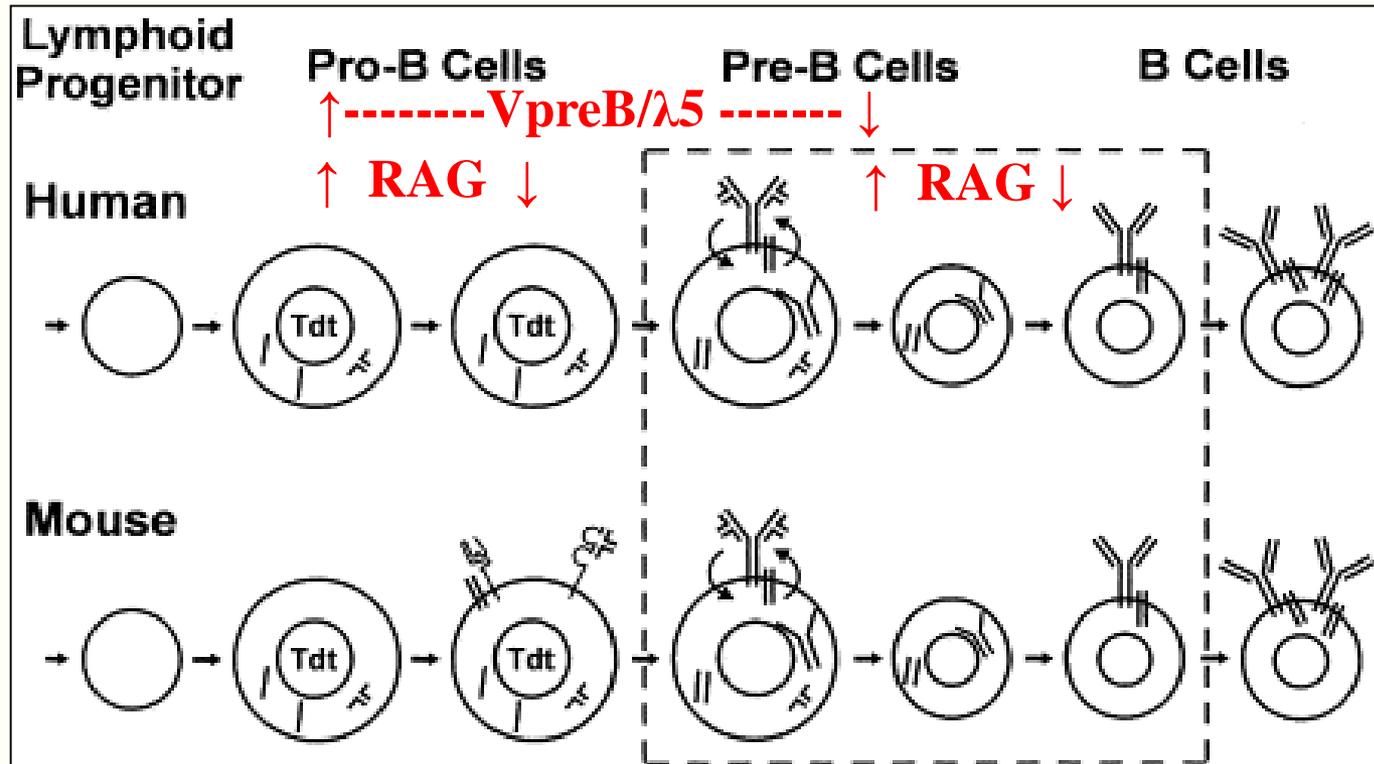


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preBcR – BcR switch



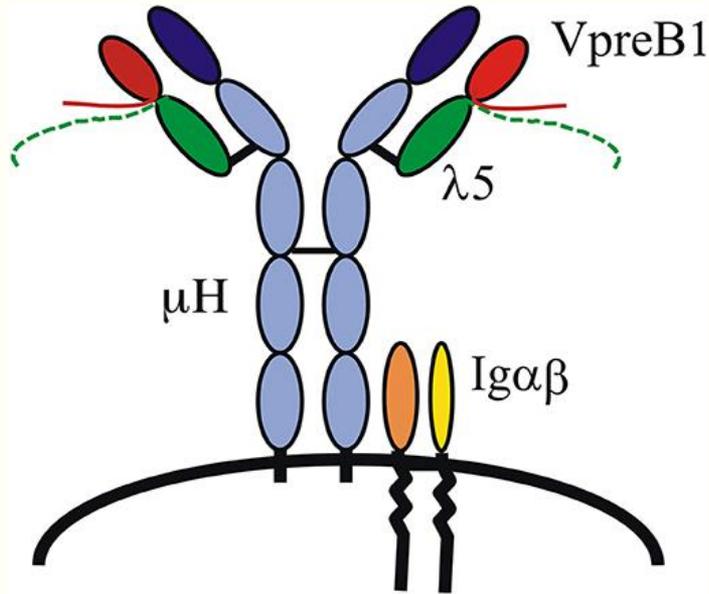
Regulatory elements:

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

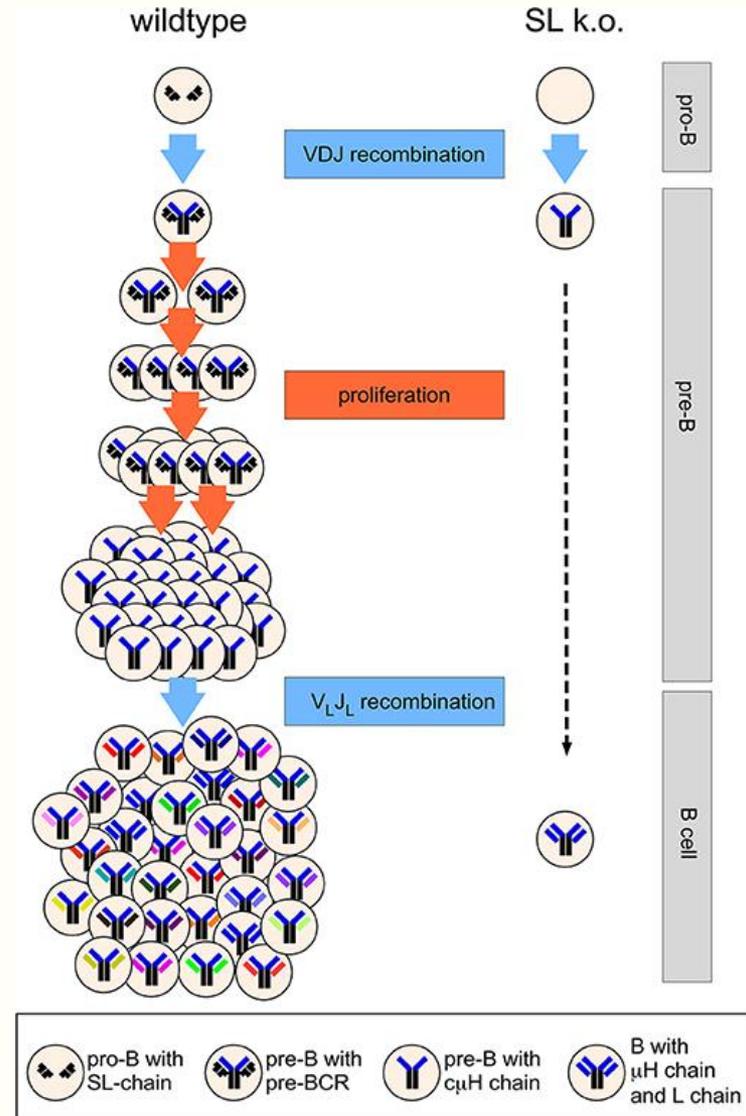
Survival – via putative ligands

Positive selection of pre-B cells

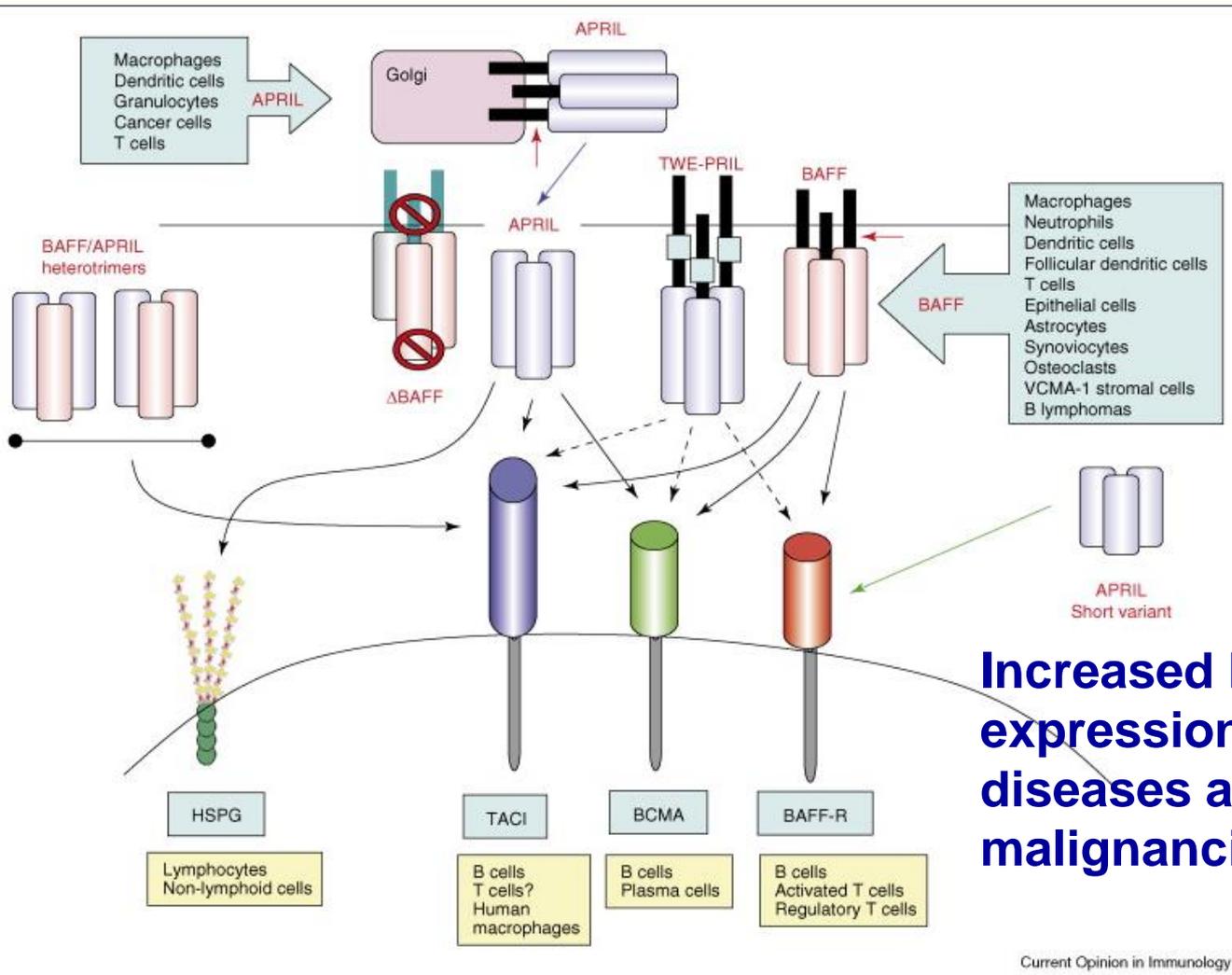
Downregulation of the RAG recombinases - *IgH allelic exclusion*

Selection of the IgH repertoire

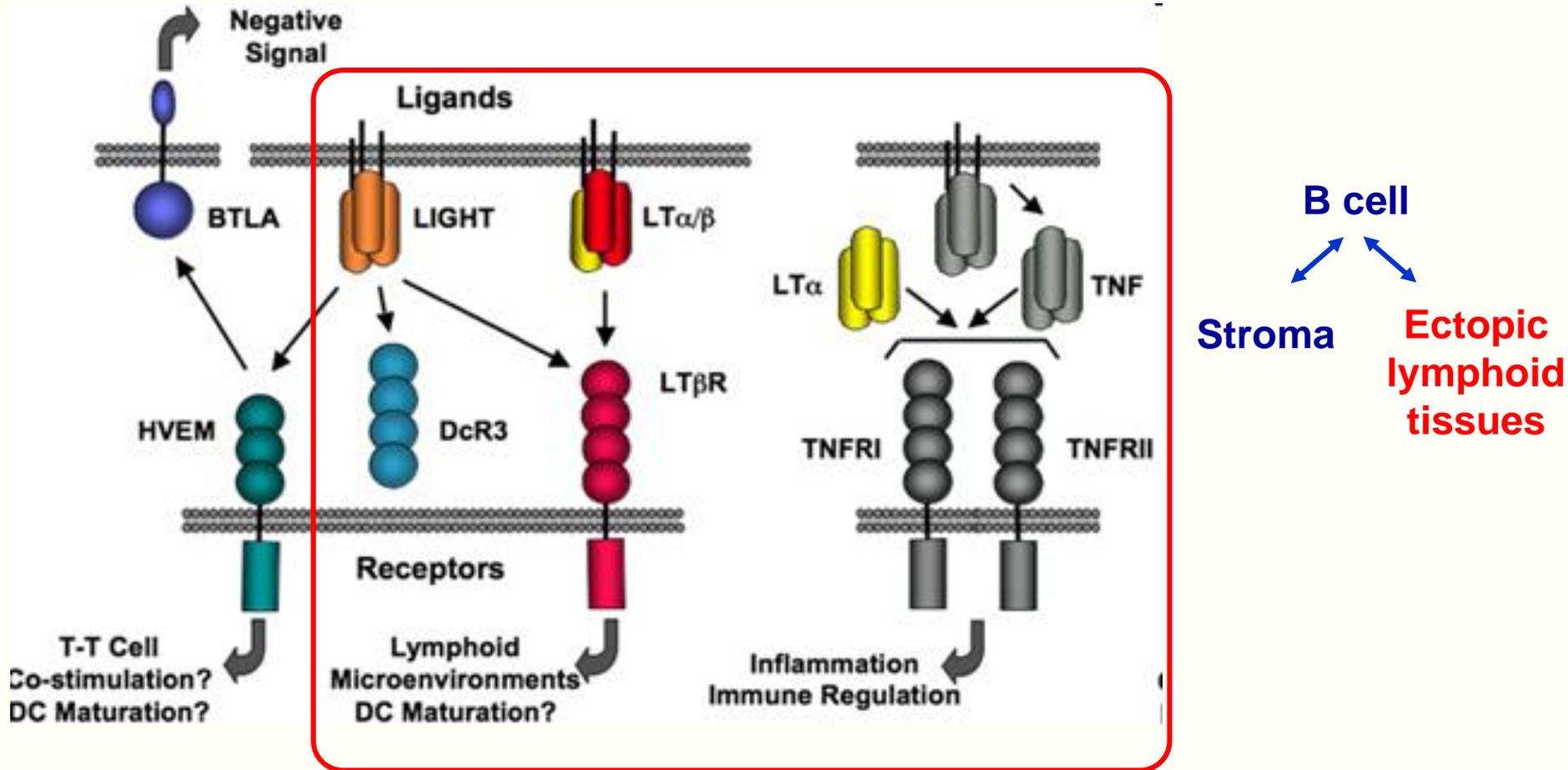
Negative selection - *tolerance*



Pre-immune survival of peripheral B cells



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	Aging-associated B cells (ABC)	Increased presence in elderly and with autoimmune diseases (T-bet/CD11c)

Essentials – B-cell development

B cells may 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