T & B Cell Development

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Word/Terms List

- Activation
- Differentiation
- Double negative cells
- Double positive cells
- Effector cells
- Maturation
- Negative selection
- Positive selection

Lymphopoiesis

- T cell progenitors originate in the BM (~50million per day)
- Migrate to thymus
- Characteristic surface marker and genetic/intracellular changes
- 90% never make it to maturity, i.e. only 10% do
- Apoptosis hits those that do not have functional TCR or don’t get ”selected”

Lymphopoiesis

- T cell generation slows down with age
- Mature T cells may divide in secondary lymphoid organs
- What is consequence of that?

T Cell Maturation

- Hematopoietic stem cells(HSC)
- Lymphoid stem cell (progenitor)
- Circulating lymphoid stem cells
- Thymocytes

T cells develop in the thymus

T cells (T-lymphocytes) = thymus-dependent lymphocytes

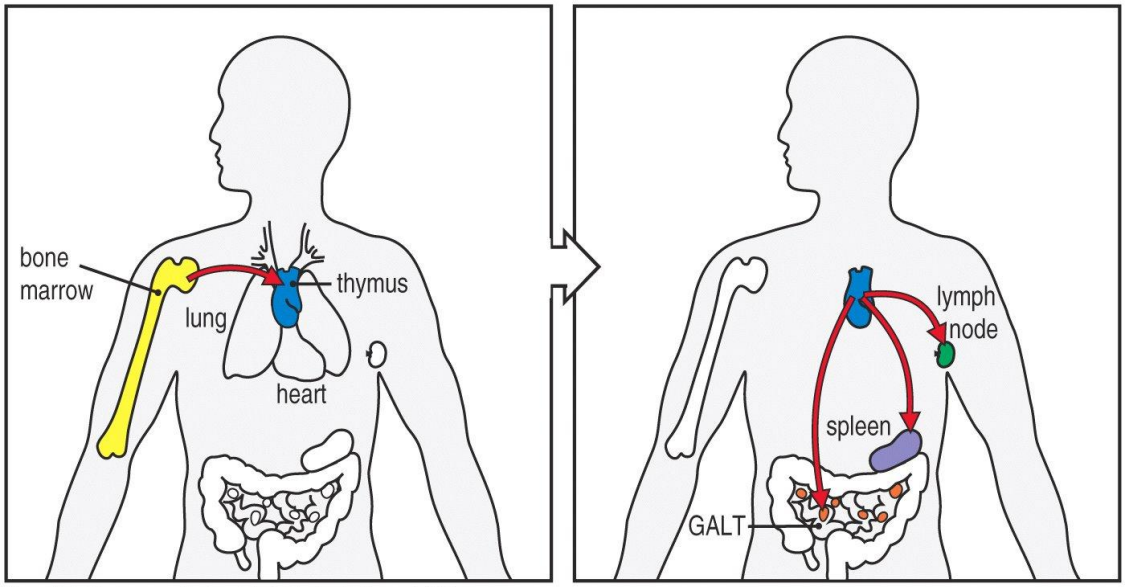


Figure 5-1 The Immune System, 2/e (© Garland Science 2005)

The thymus is a primary lymphoid organ because it is only involved in development, not fighting infection.

The thymus contains

a) Thymocytes (immature T cells)

b) Thymic stroma (epithelial cells)

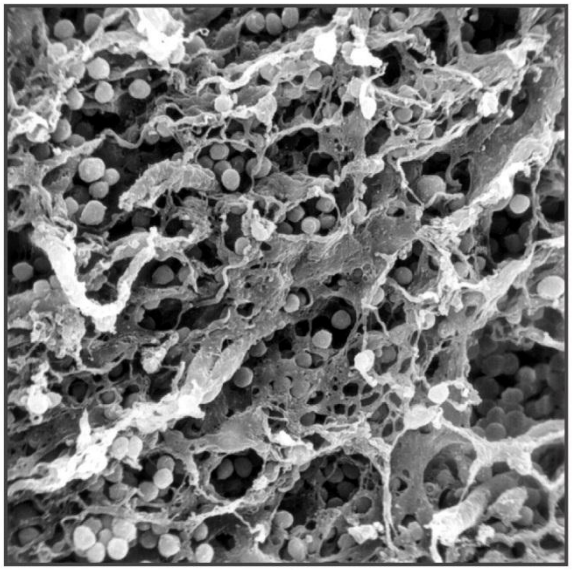


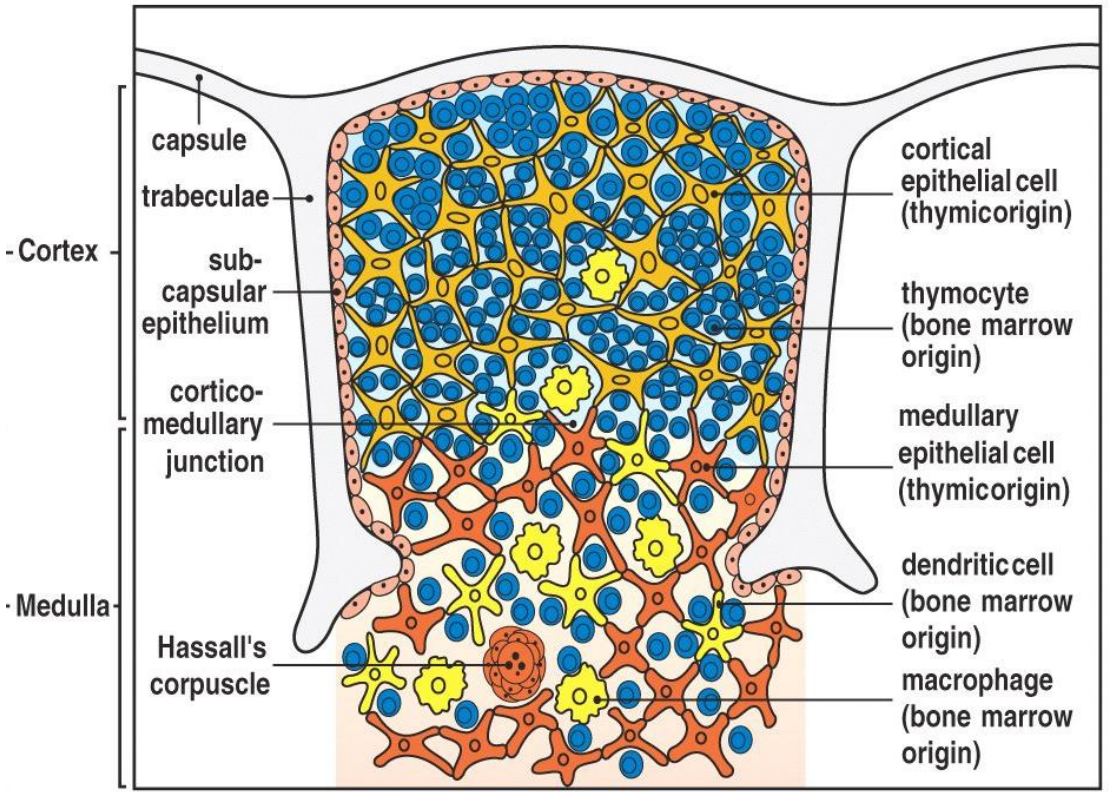
Figure 5-2 The Immune System, 2/e (© Garland Science 2005)

The Thymus

2 areas of the thymus:

Cortex – outer, close-packed consists of ectodermal cells; can contain thymocytes and macrophages

Medulla – inner, less dense consists of endodermal cells; contains thymocytes, dendritic cells, and macrophages



Thymic anlage : The combination of the ectodermal and endodermal cells**,** colonized by progenitor cells from the bone marrow**.**

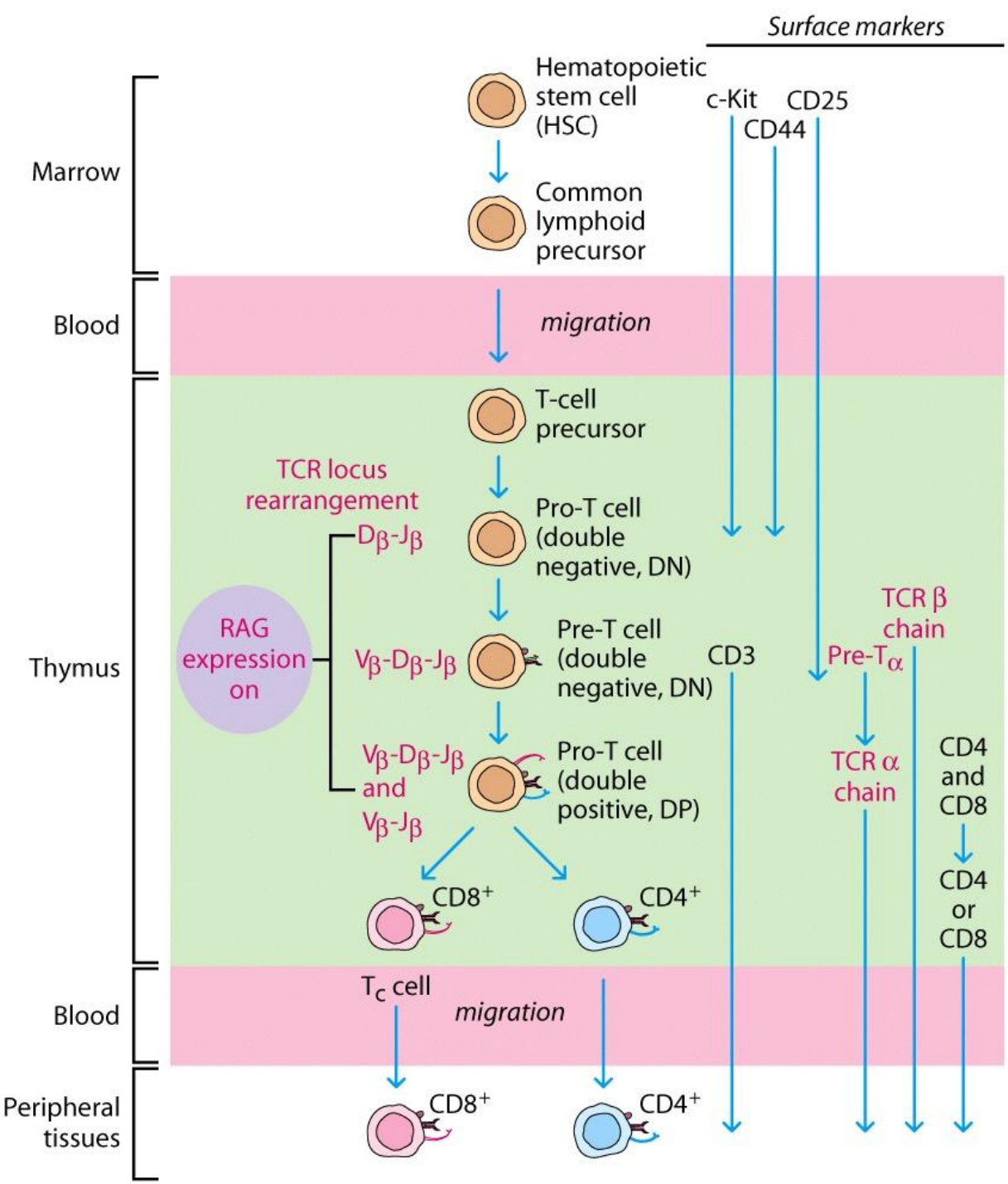
Thymus facts

- Fully developed at birth and increases in size until puberty
- Most active in the young
- Degrades after puberty (involution), being replaced with fat tissue
- Even after involution (~30 yrs. old) or a thymectomy immunity by T cells is not impaired significantly
- Mature T cell repertoire is long-lived and self-renewing

T Cell Maturation

- Young thymocyte (T cell precursor)
- Double negative thymocytes
- Double negative with early TCR expression
- Double positive with TCR expression

- Naïve CD4 and CD8 T cells

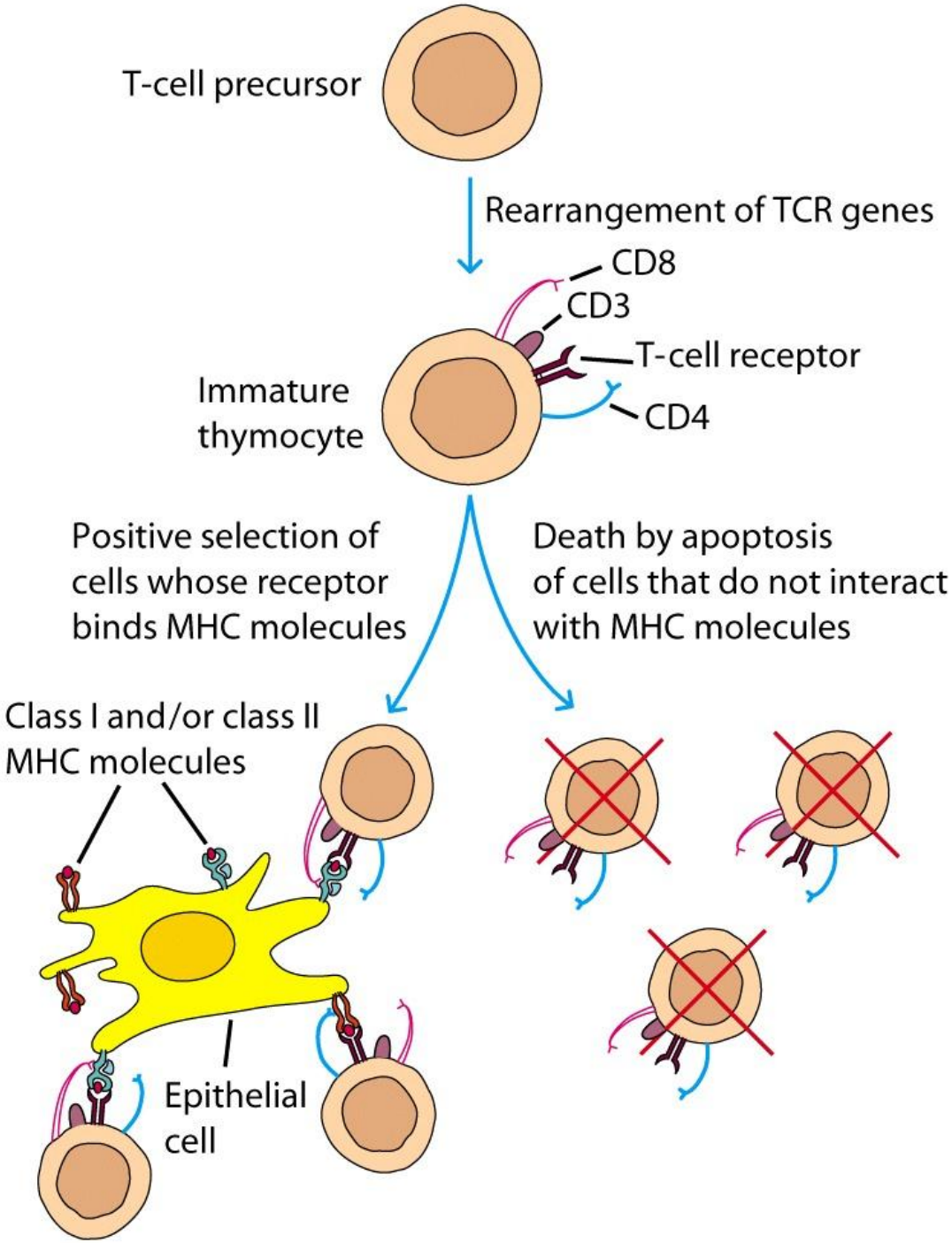

Surface markers
Marrow
Blood
Thymus
Blood
Peripheral tissues
Hematopoietic stem cell (HSC)
Common lymphoid precursor
c-Kit
CD25
CD44
migration
T-cell precursor
TCR locus rearrangement
Dβ-Jβ
Pro-T cell (double negative, DN)
RAG expression on
Vβ-Dβ-Jβ
Pre-T cell (double negative, DN)
CD3
TCR β chain
Pre-Tα
Vβ-Dβ-Jβ and Vβ-Jβ
Pro-T cell (double positive, DP)
TCR α chain
CD4 and CD8
CD4 or CD8
CD8+
CD4+
Tc cell
migration
CD8+
CD4+

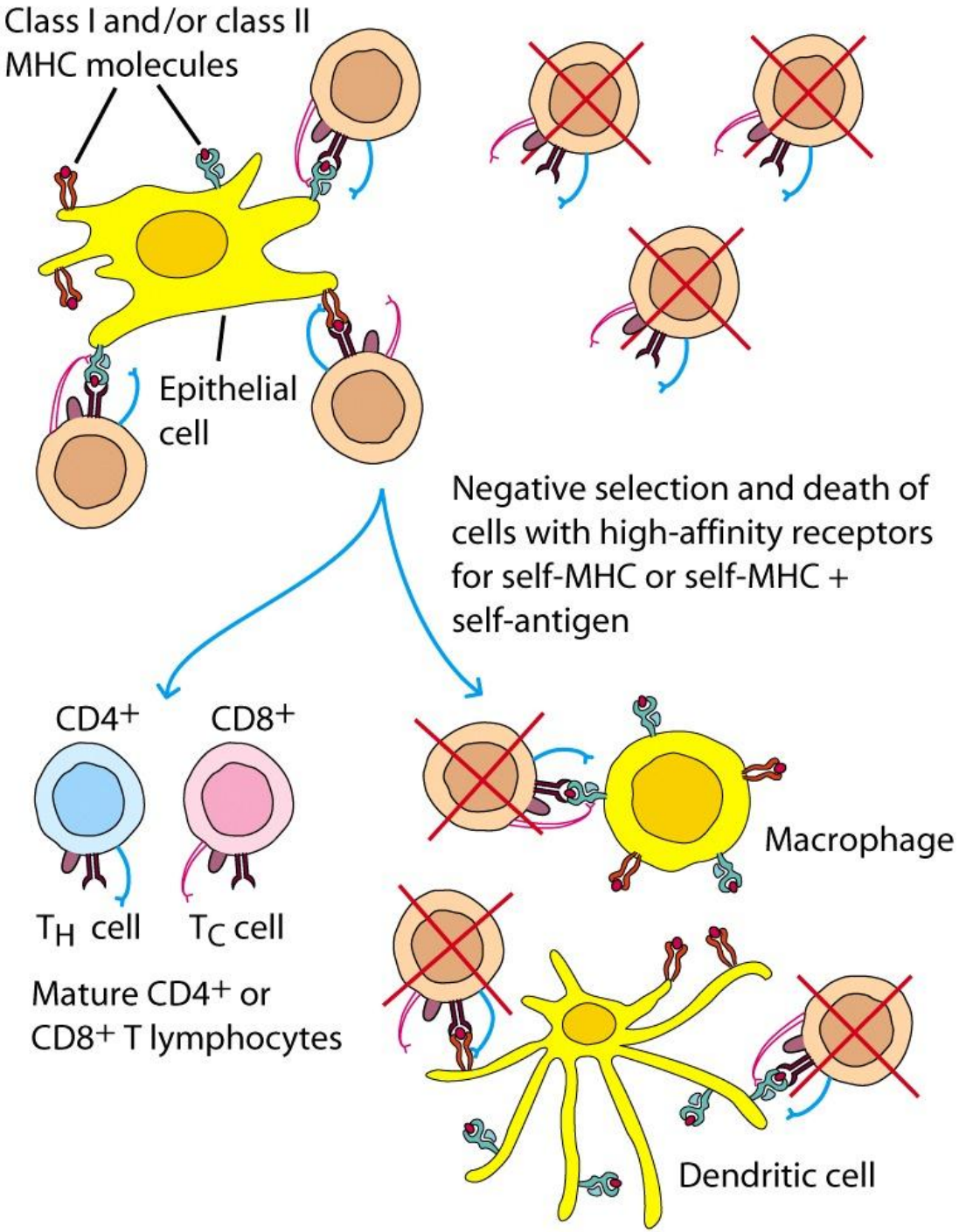
Thymic Selection

- Positive selection
  - Double positives bind MHC molecules
  - Nonbinders die
  - Binders become single positives

Thymic Selection

- Negative selection
  - CD4 or CD8 cells that survive positive selection may react or bind to self MHC alone with high affinity or with Self MHC-self Ag complexes
  - These cells are programmed to die
  - Nonbinders survive


T-cell precursor
Rearrangement of TCR genes
CD8
CD3
T-cell receptor
CD4
Immature
thymocyte
Positive selection of
cells whose receptor
binds MHC molecules
Death by apoptosis
of cells that do not interact
with MHC molecules
Class I and/or class II
MHC molecules
Epithelial
cell


Class I and/or class II
MHC molecules
Epithelial
cell
Negative selection and death of
cells with high-affinity receptors
for self-MHC or self-MHC +
self-antigen
CD4+
CD8+
TH cell
TC cell
Mature CD4+ or
CD8+ T lymphocytes
Macrophage
Dendritic cell

B Cell Production and development

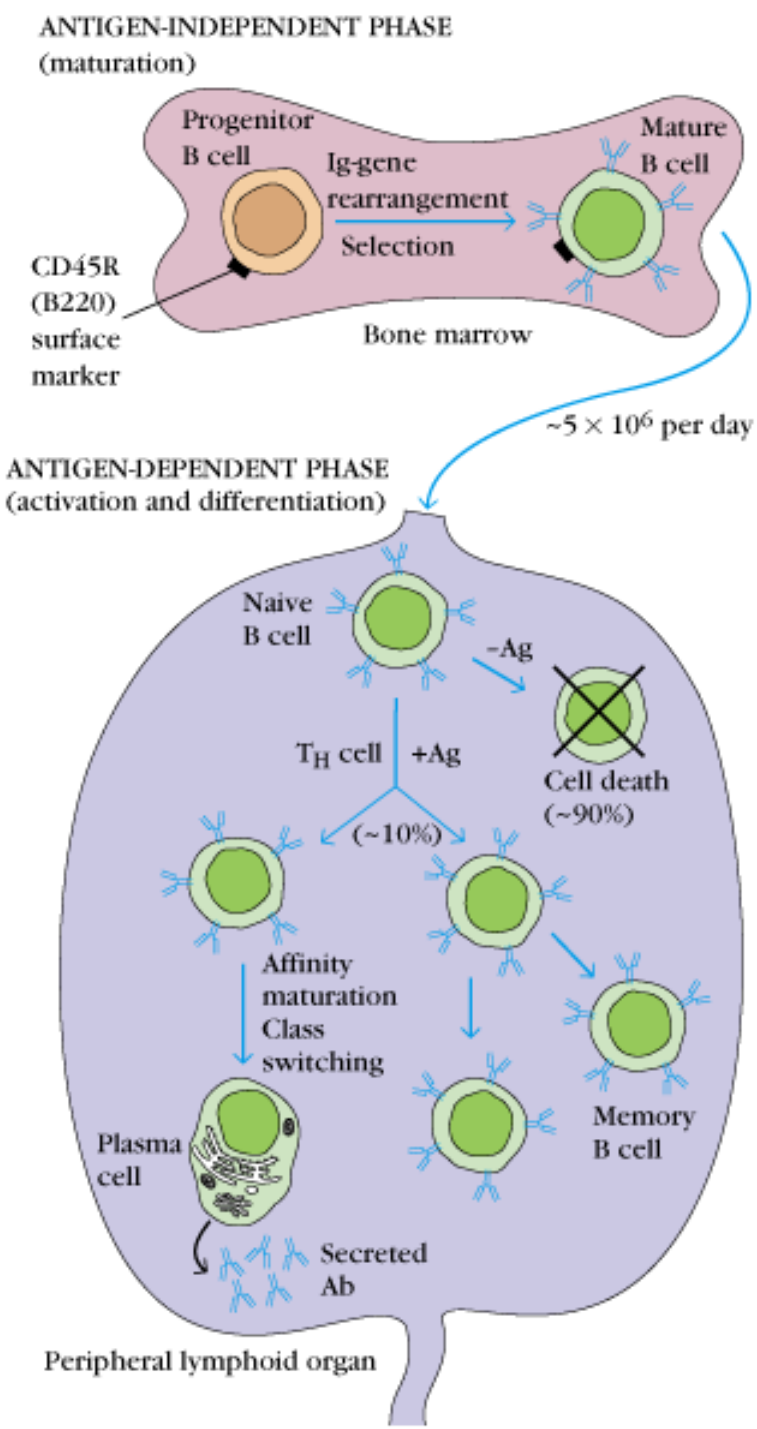
B-CELLS…

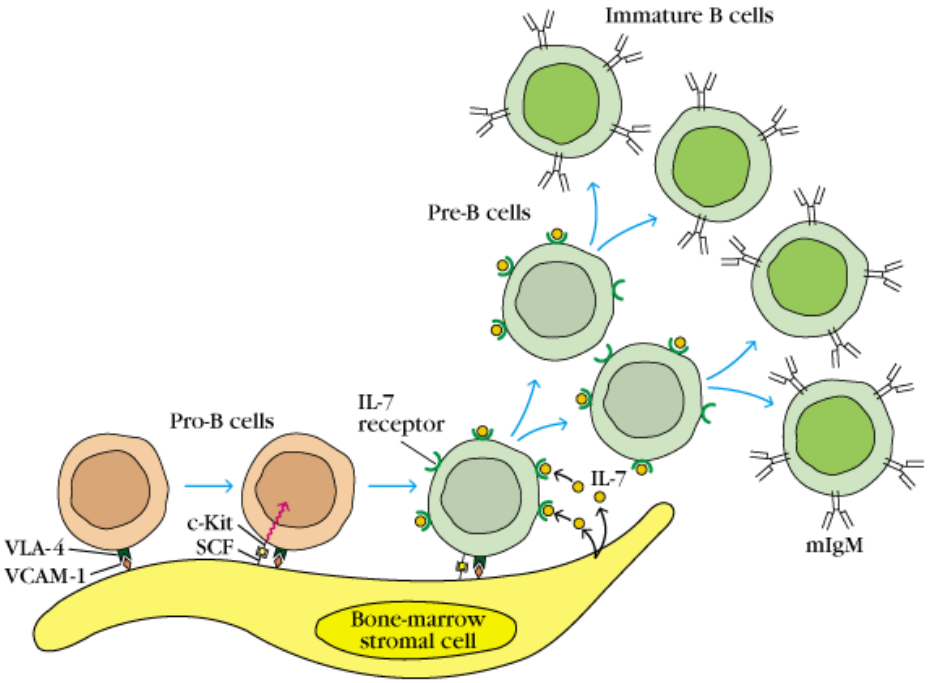
- Origin…
- Development…
- Selection**S**
- Activation**S**

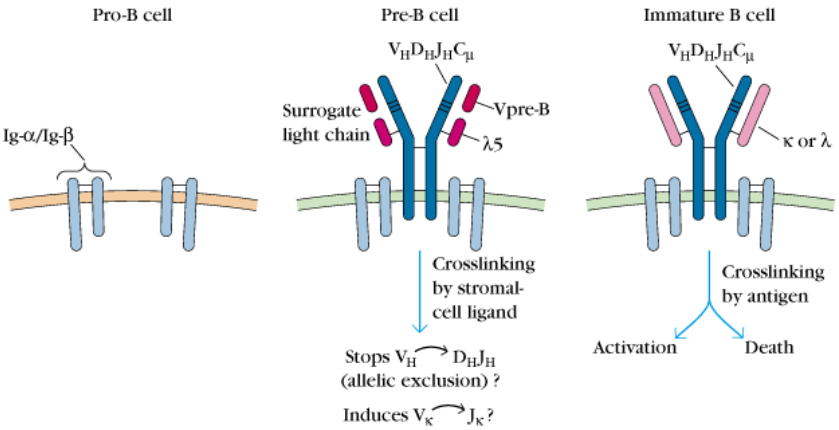
•Progenitor B cells (pro-B-cells) bearing a CD45R marker develop – in the bone marrow – into immature and then mature B cells.

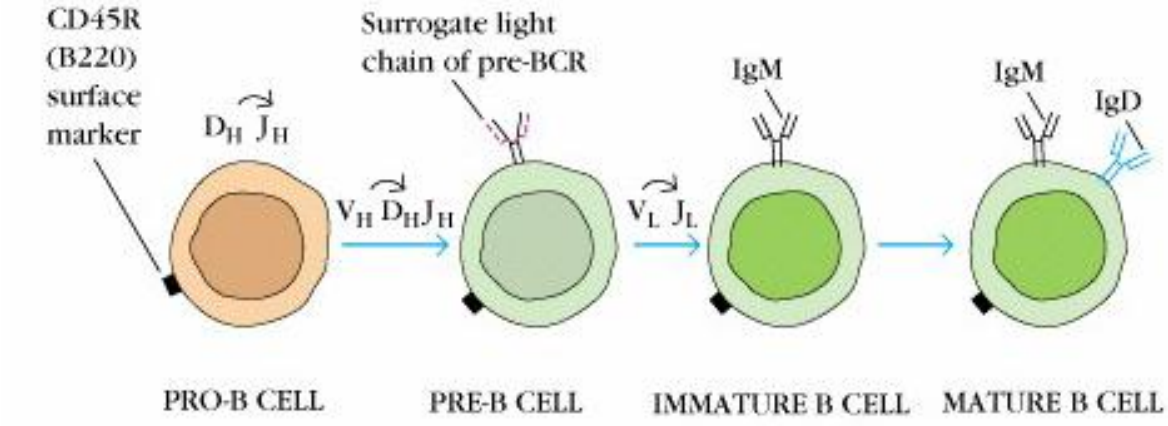
•Then, they migrate to peripheral lymph nodes.

•Those developmental events are physically and physiologically distinct; the former are antigen *in*dependent; the latter are antigen *de*pendent.

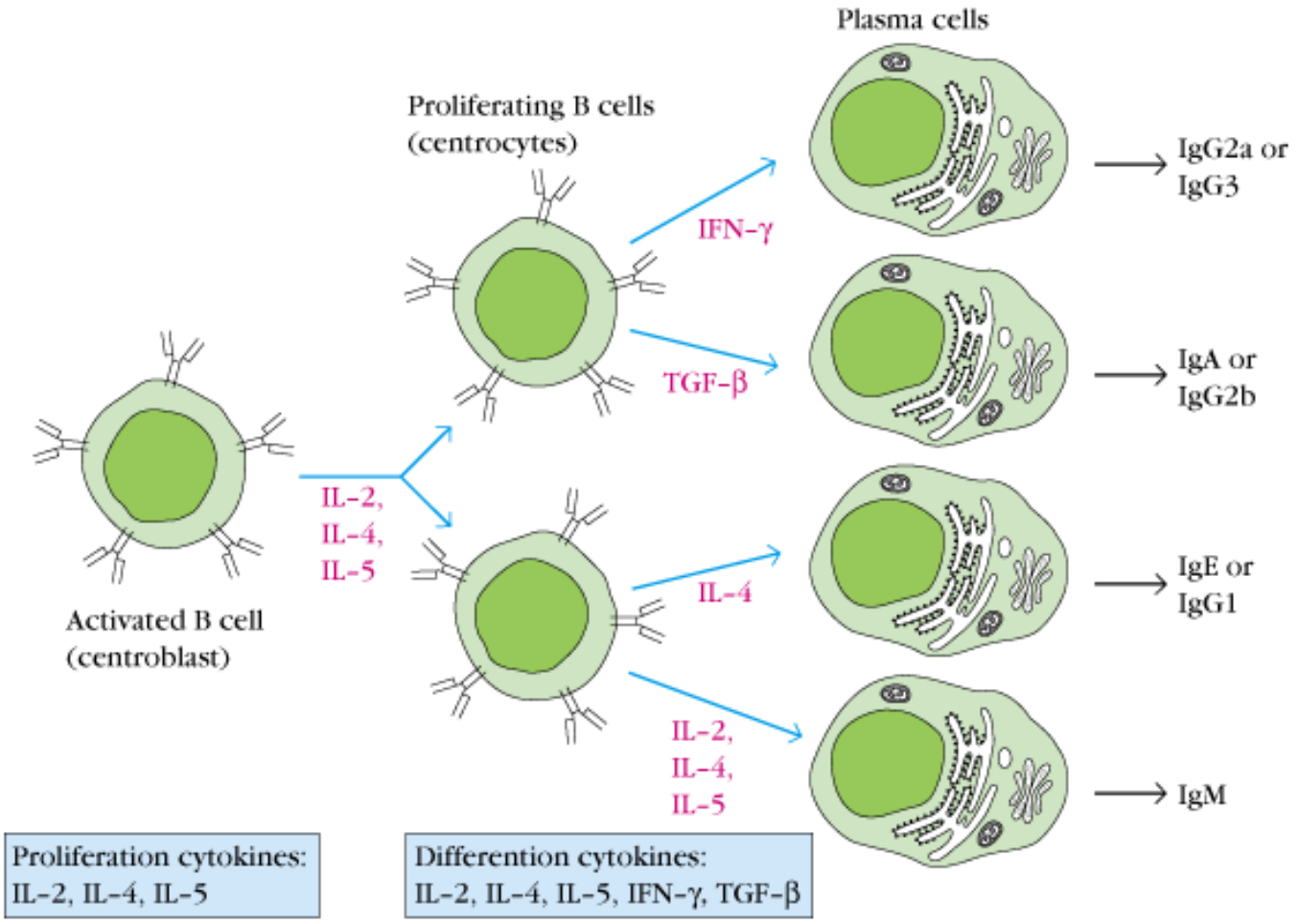



Immature B cells
Pre-B cells
Pro-B cells
IL-7 receptor
IL-7
c-Kit
SCF
VLA-4
VCAM-1
mIgM
Bone-marrow stromal cell

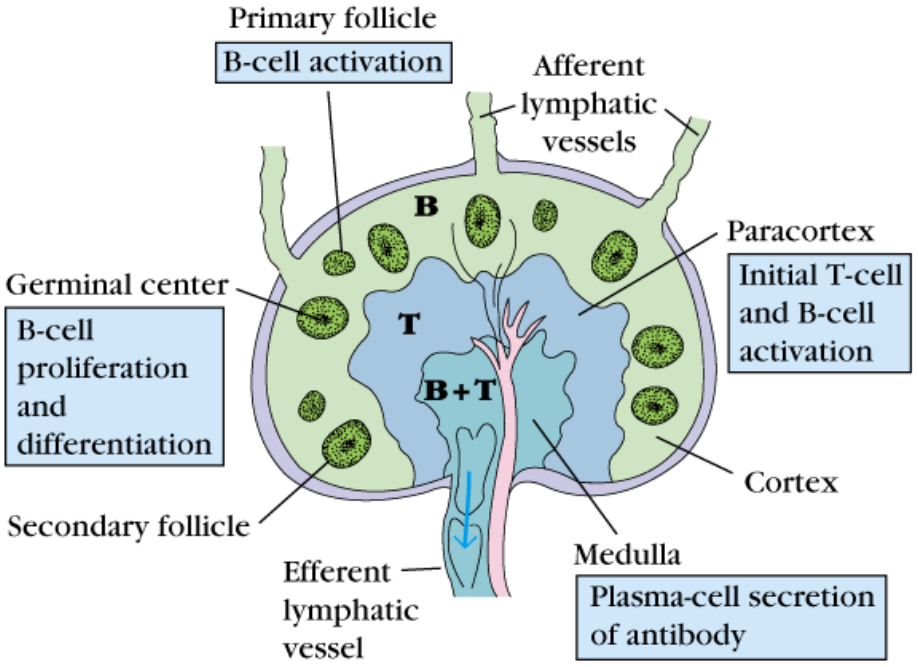

Pro-B cell
Pre-B cell
Immature B cell
Ig-α/Ig-β
$V_HD_HJ_HC_\mu$
Surrogate light chain
Vpre-B
λ5
κ or λ
Crosslinking by stromal-cell ligand
Crosslinking by antigen
Stops $V_H \rightarrow D_HJ_H$ (allelic exclusion) ?
Induces $V_\kappa \rightarrow J_\kappa$?
Activation
Death


CD45R (B220) surface marker
$D_H J_H$
Surrogate light chain of pre-BCR
$V_H D_H J_H$
$V_L J_L$
IgM
IgM
IgD
PRO-B CELL
PRE-B CELL
IMMATURE B CELL
MATURE B CELL

- Cytokines of various types are secreted by T-helper cell and are received by differentiating B-cells.
- The various cytokines affect what immunoglobulin isotypes will be produced by plasma cells.



Where is activation happening? And *what* is happening?



The primary response is initiated in the paracortex.

T-cells respond to processed antigen that is typically delivered from a site of origin by dendritic cells.

B-cells see the same antigen in an *un*processed form in the lymph.