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T-Cell Development

M1 – Immunology Sequence

Winter 2009

University of Michigan
Medical School

Lineage commitment and TCR gene rearrangement

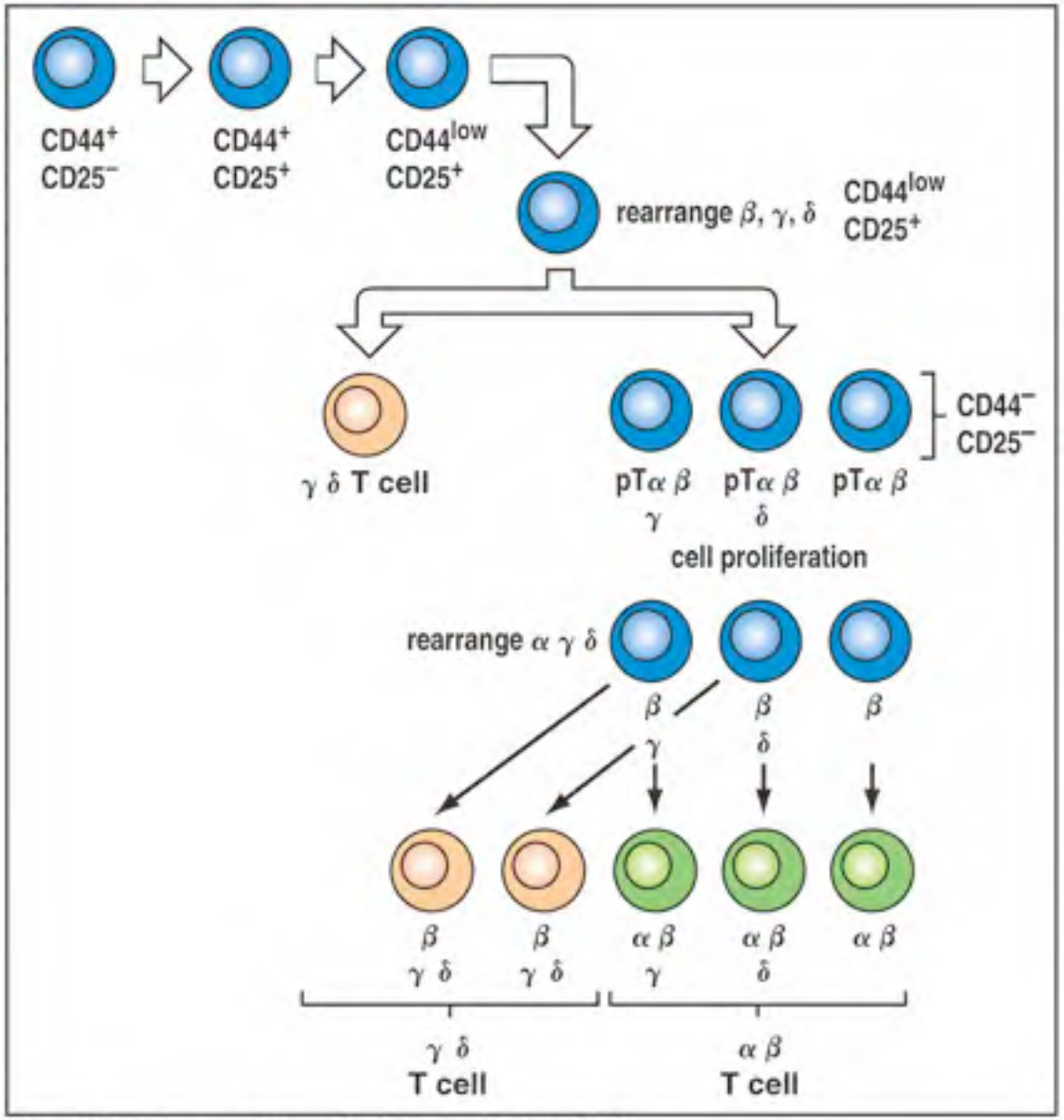


Figure 5-4 The Immune System, 2/e (© Garland Science 2005)

Example

Successful β chain

↓

α chain

↓

αβ T cell

 Immune System, Garland Science 2005

γδ T cell precedes αβ T cell development

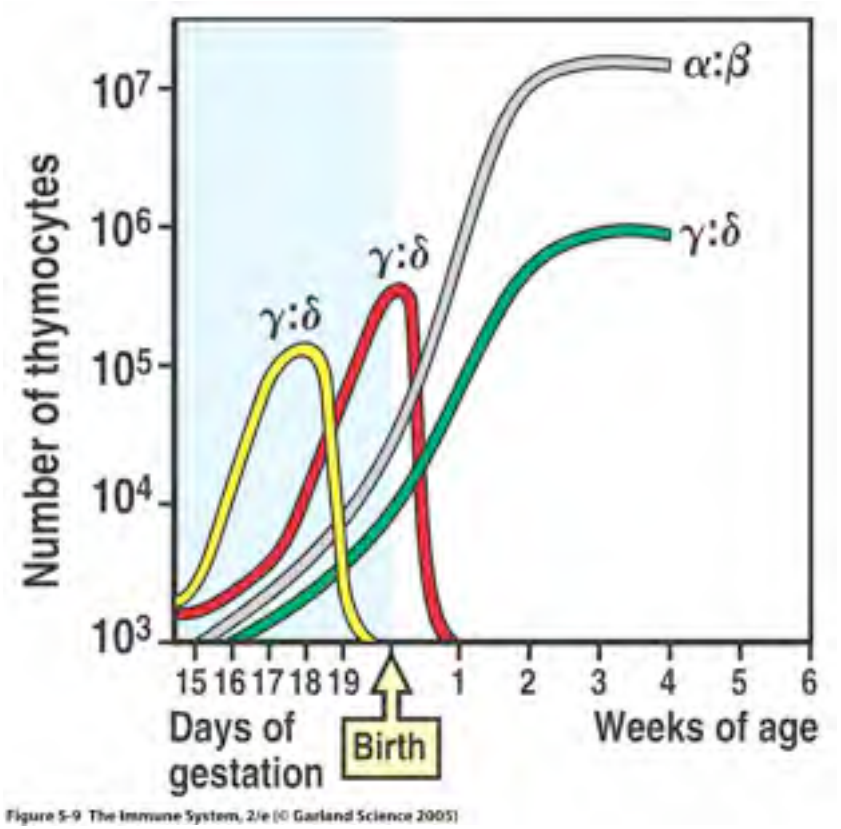


Figure 5-9 The Immune System, 2/e (© Garland Science 2005)

PD-INEL Immune System, Garland Science 2005

Fig. 5.9

1. **The γδ receptor is the first TCR to be expressed during fetal life.**

2. **γδ- and αβ-expressing thymocytes are separate lineages originated from a common precursor**

αβ T cell development

The ultimate goal of selection in the thymus is to produce T cells that are

Self-MHC restricted to recognize foreign antigenic peptides with self-MHC (positive selection)

AND

Self tolerant not to respond to self-peptides (negative selection)

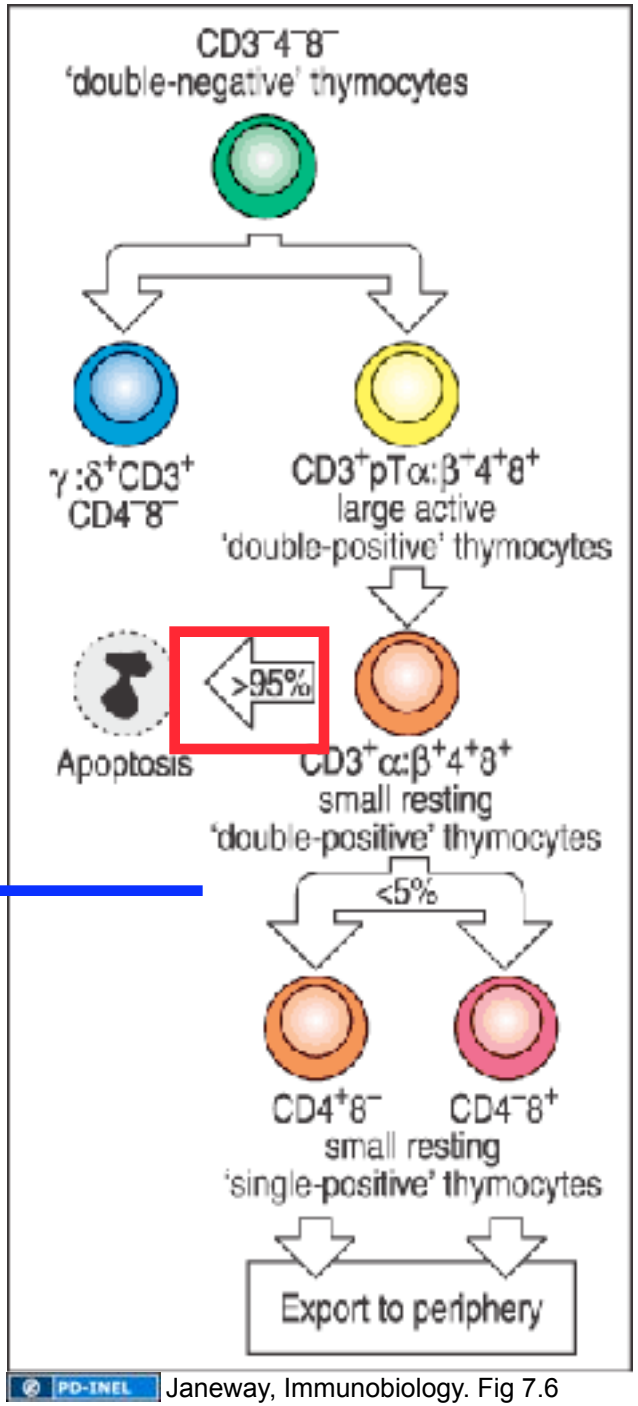
Immature thymocytes

DN: Double Negative
$CD4^-CD8^-$
(<10 %)

DP: Double Positive
$CD4^+CD8^+$
(most abundant, 90%)

Mature T cells

SP: Single Positive
CD4 SP ($CD4^+CD8^-$)
CD8 SP ($CD8^+CD4^-$)
(10 %)

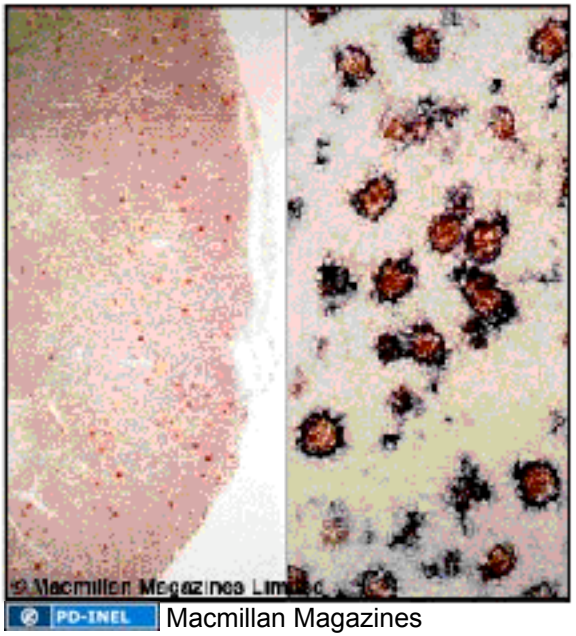


PD-INEL Janeway, Immunobiology. Fig 7.6

Death of immature thymocytes in the thymus by apoptosis

In a young adult mouse:

- **Total; 1-2x10^8 thymocytes**
- **5x10^7 new thymocytes/day**
- **1-2x10^6 will leave thymus**



Macmillan Magazines

Apoptosis (programmed cell death)
Necrosis

Fig 5.6

Apoptosis (Programmed cell death)

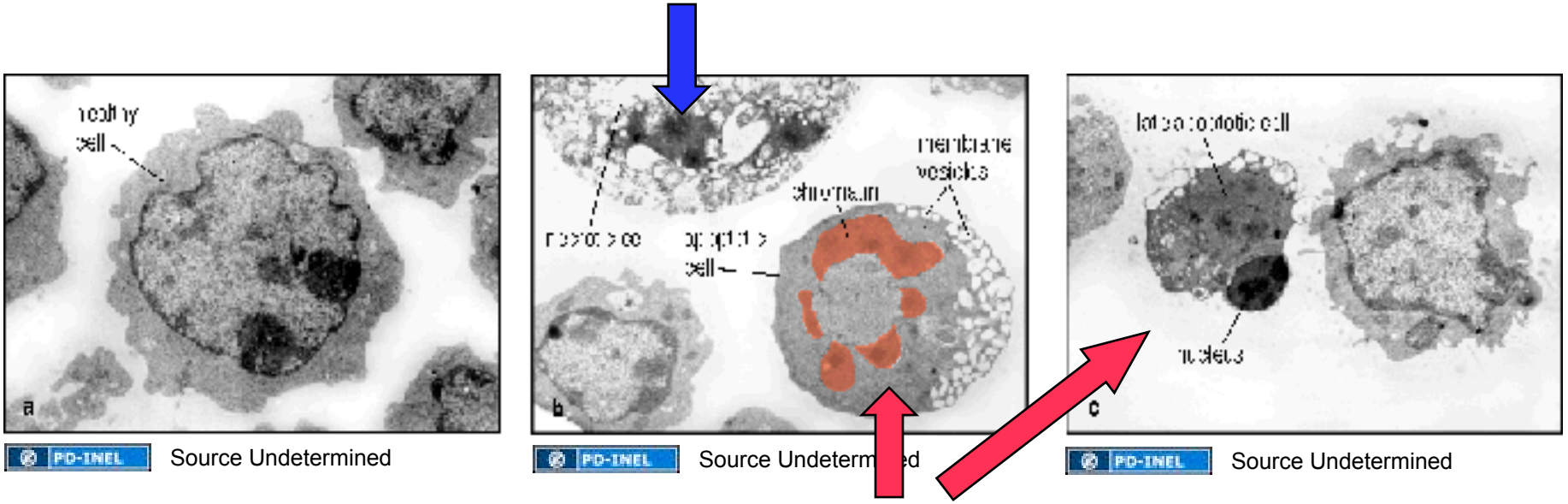
A mechanism of cell death in which the cells to be killed are induced to degrade themselves from within, in a tidy manner

Necrosis

The death of cells by lysis that results from chemical or physical injury. It leaves extensive cellular debris that must be removed by phagocytes.

Apoptosis
(programmed cell death)

Necrotic cell



PD-INEL Source Undetermined

PD-INEL Source Undetermined

PD-INEL Source Undetermined

Apoptotic cell

Fig. 6.25

Positive and negative selection of T cells

Positive selection

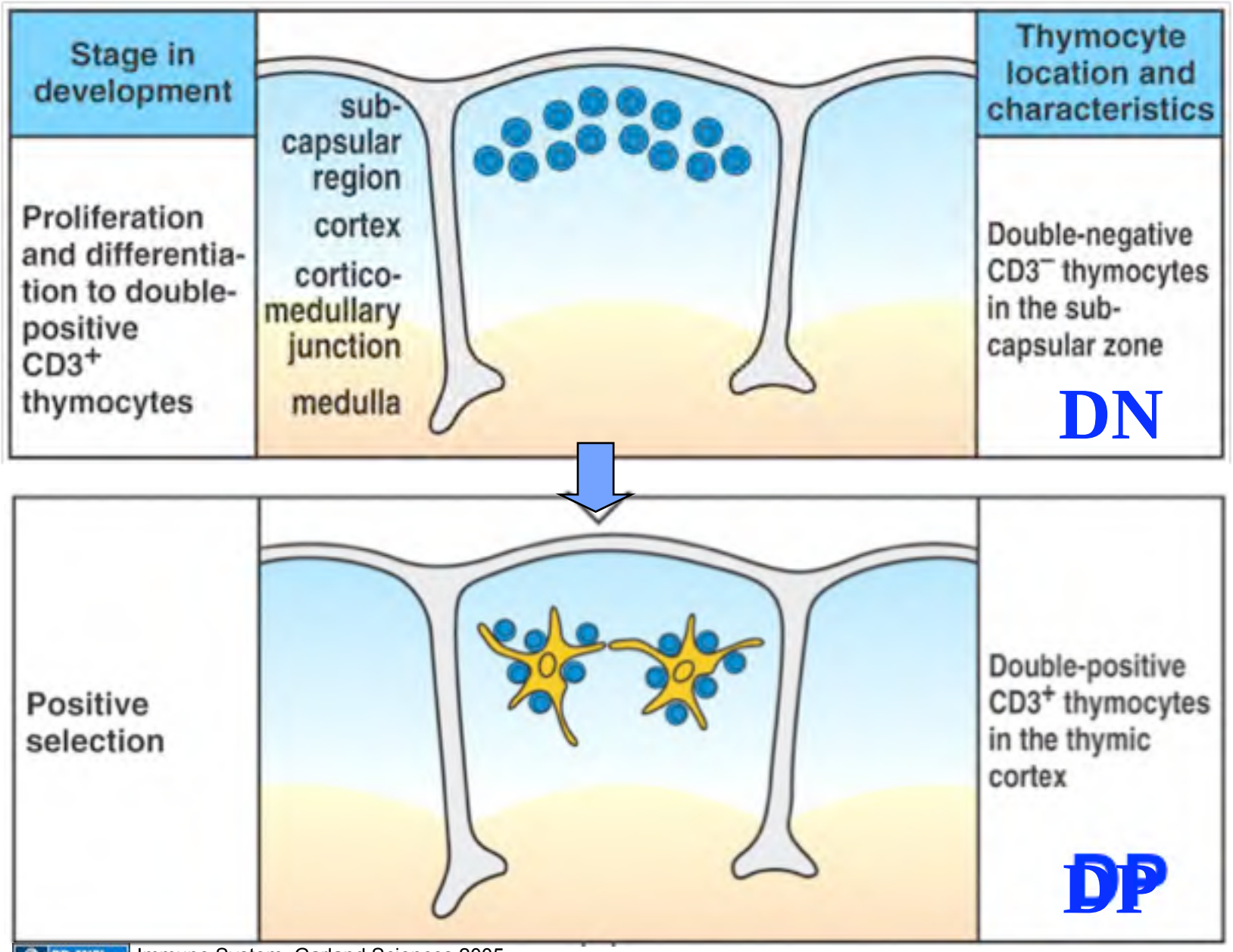
To generate T cells that can recognize foreign or non-self antigens in the context of self MHC (self-MHC restricted)

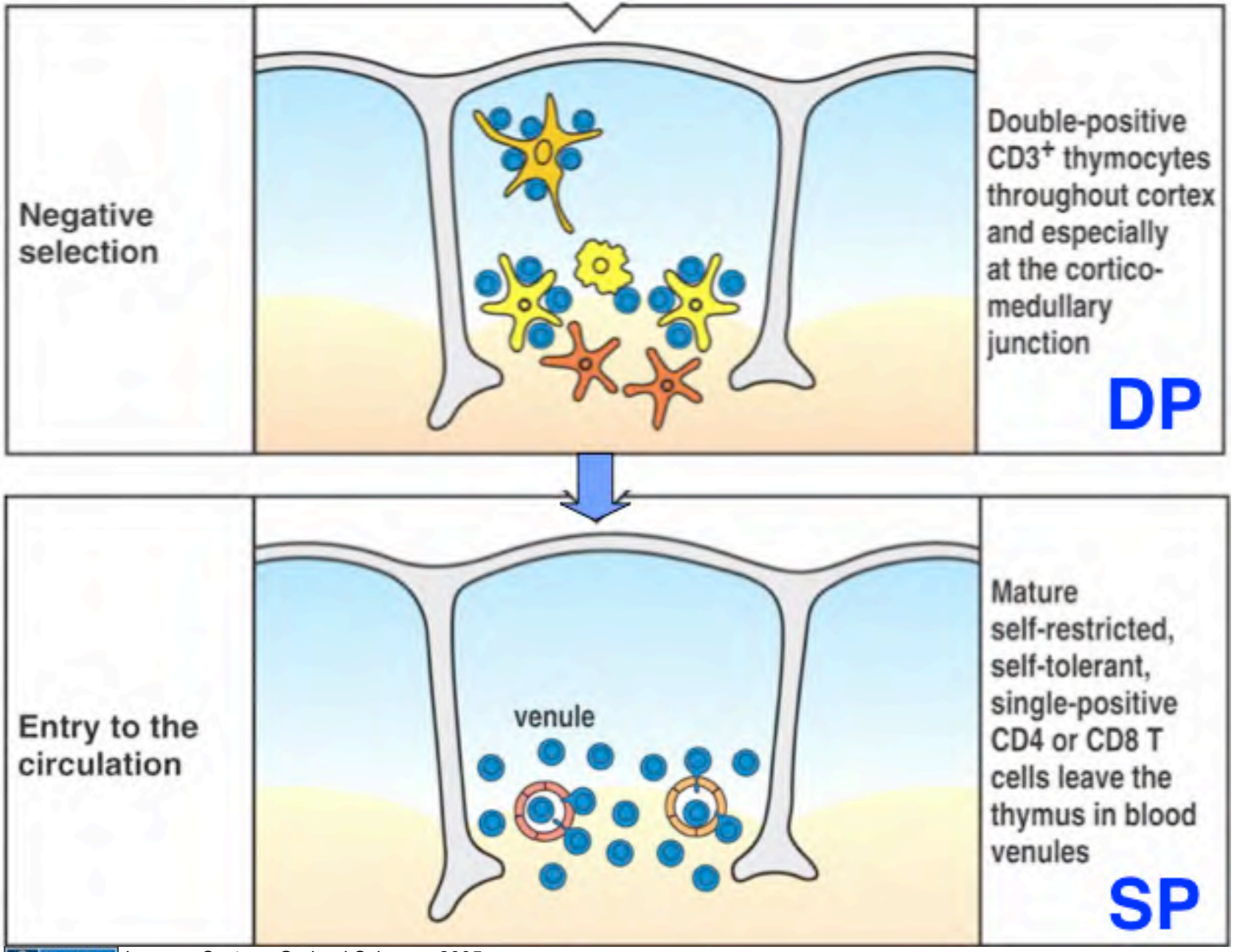
Negative selection

To eliminate potentially self-reactive T cells that recognize self peptide-MHC complexes (tolerized)

Where in the thymus do T cells undergo selection processes?

Development of T cells in the thymus





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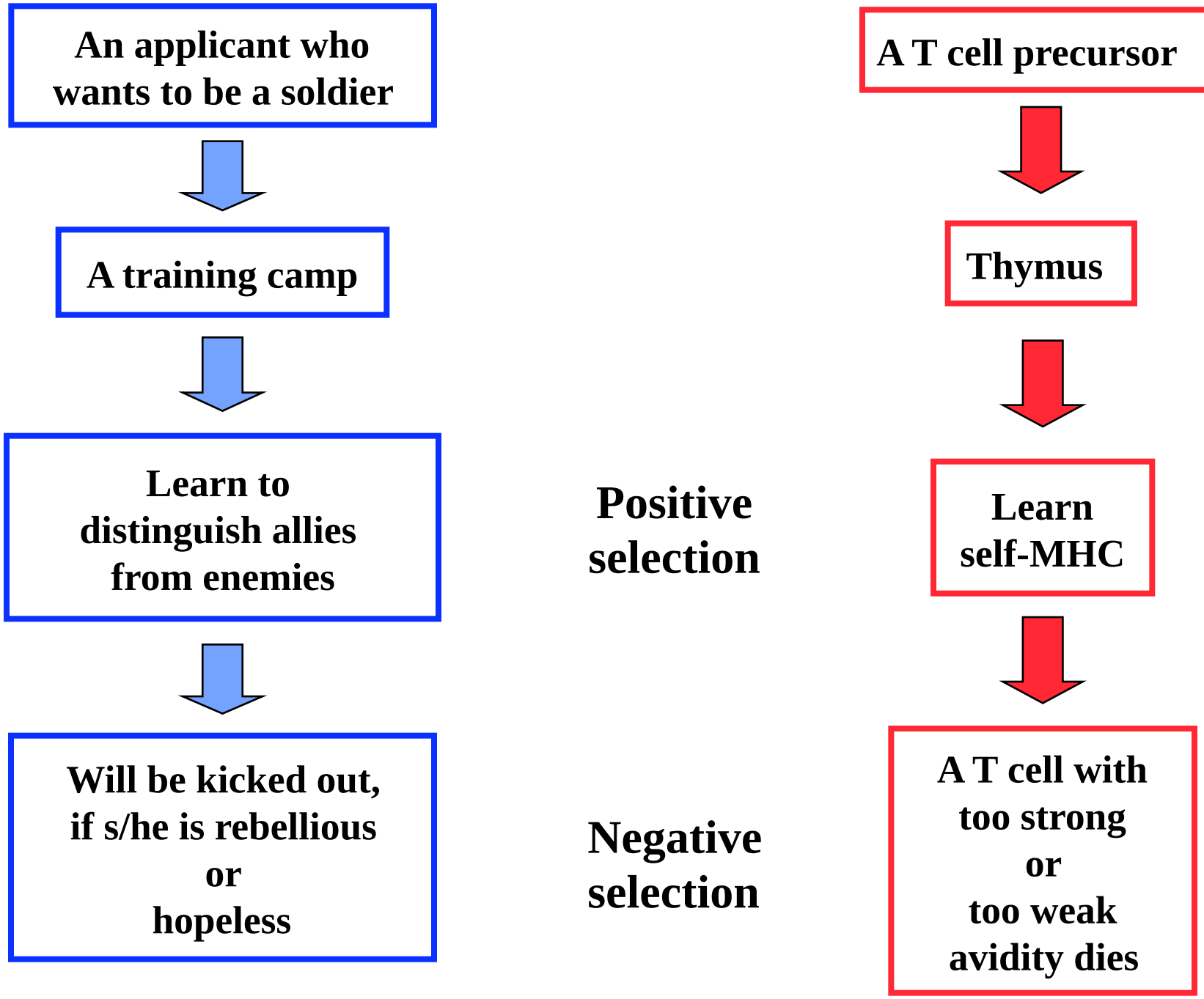
Factors influencing T cell selection

1. **MHC; MHC restriction**
2. **Co-receptors; CD4 and CD8**
3. **Peptides; signaling strength**
4. **Cell type: cells residing in the thymus**

Differential signaling hypothesis

Positive selection of T cells and MHC

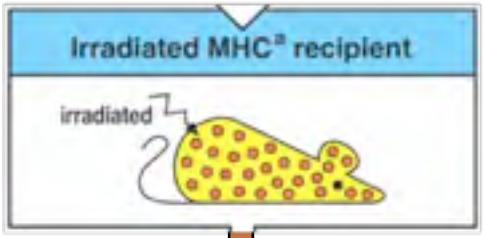
To generate T cells that can discriminate foreign-peptides from self-peptides in the context of self-MHC
(MHC restricted)

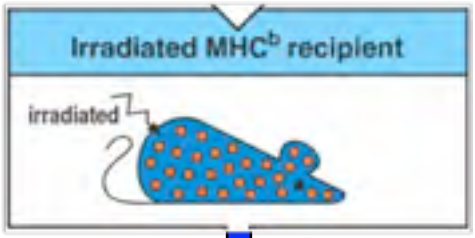

An applicant who wants to be a soldier
A training camp
Learn to distinguish allies from enemies
Will be kicked out, if s/he is rebellious or hopeless
Positive selection
Negative selection
A T cell precursor
Thymus
Learn self-MHC
A T cell with too strong or too weak avidity dies

Positive selection and MHC restriction

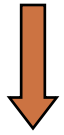
MHC$^{a x b}$ F1 bone marrow cells (T cell precursors)

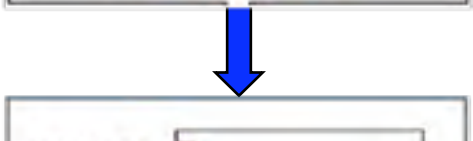
MHC^{a} Recipient



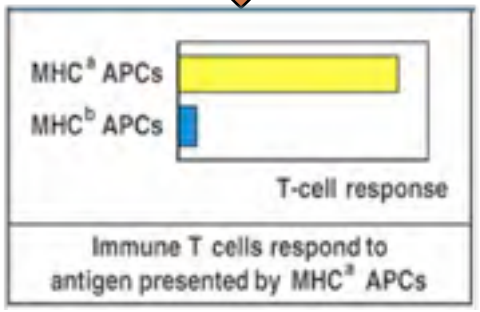


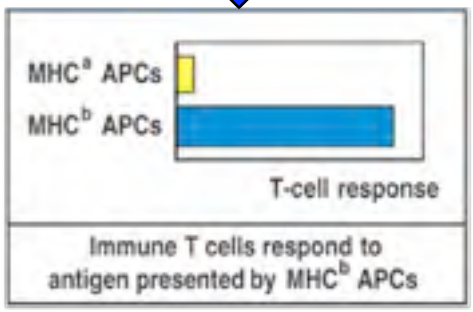
MHC^{b} Recipient





MHC^{a} Restricted

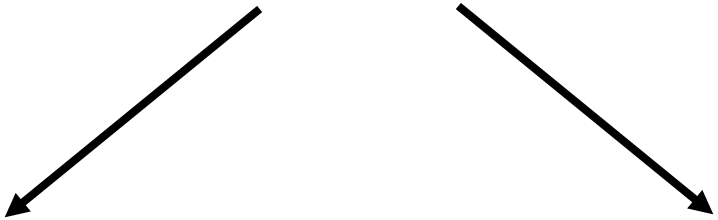




MHC^{b} restricted

PD-INEL Janeway, Immunobiology. Garland Science, 2004. 6th ed. Fig 7.28

MHC (AxB) precursors (thymocytes)



MHC A mouse

MHC B mouse

A restricted T cells

B restricted T cells

Positive selection and co-receptors

Positive selection and co-receptors

MHC class I ⇔ CD8 **MHC class II ⇔ CD4**

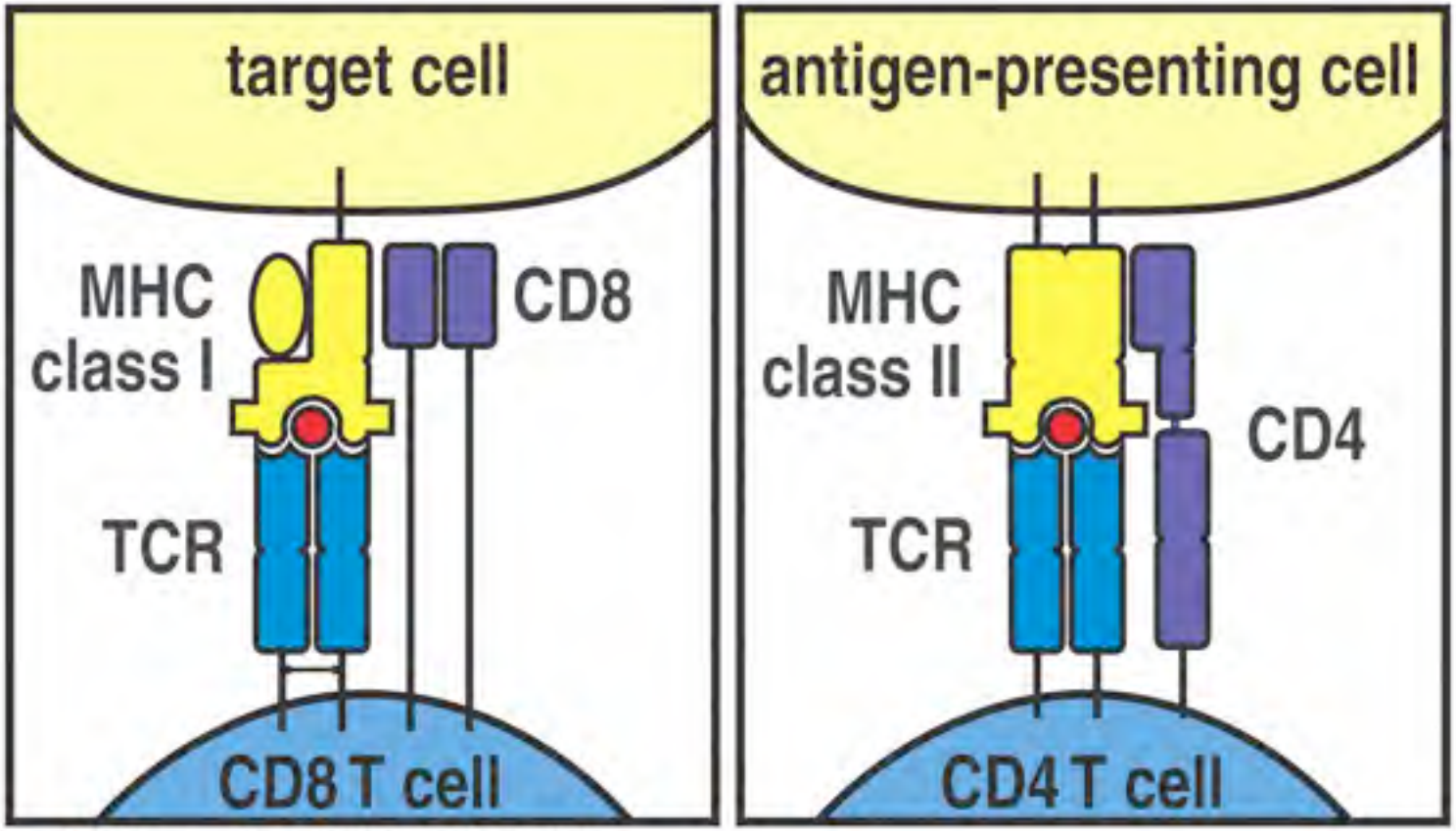
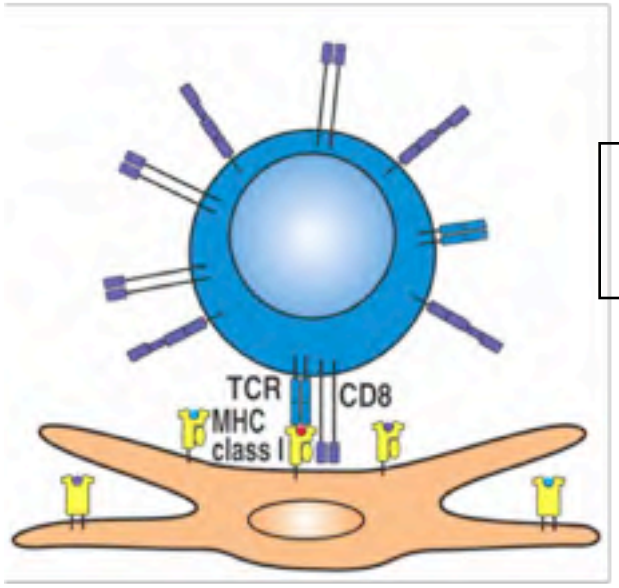


Figure 3-12 The Immune System, 2/e (© Garland Science 2005)

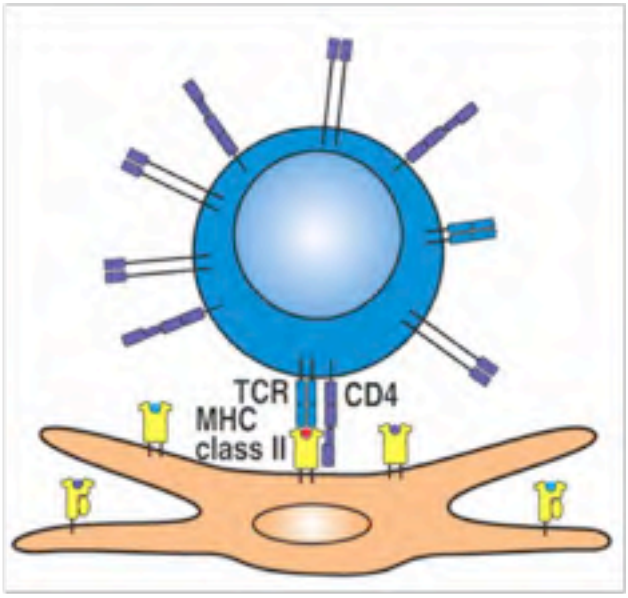
PD-INEL Immune System, Garland Sciences 2005. 2nd ed.

Fig 3.9

Positive selection controls co-receptor expression

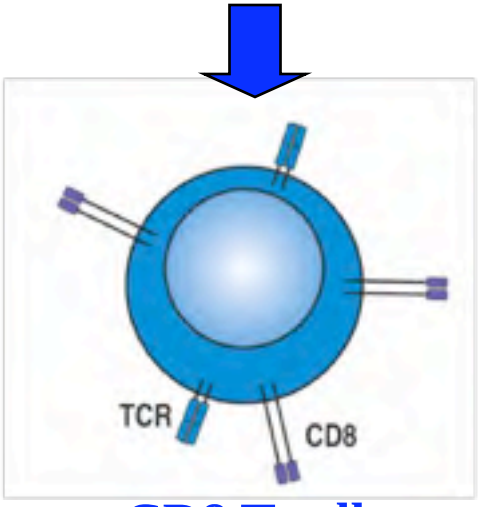


DP thymocytes

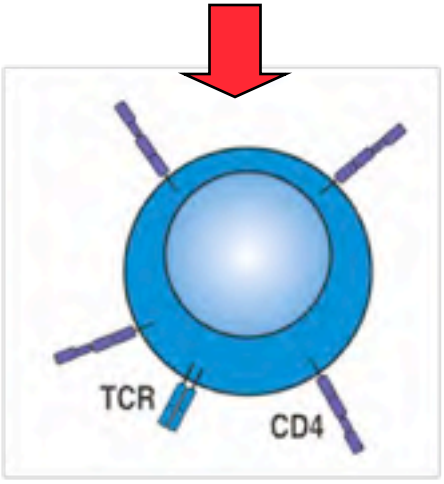


MHC class I

MHC class II



SP thymocytes



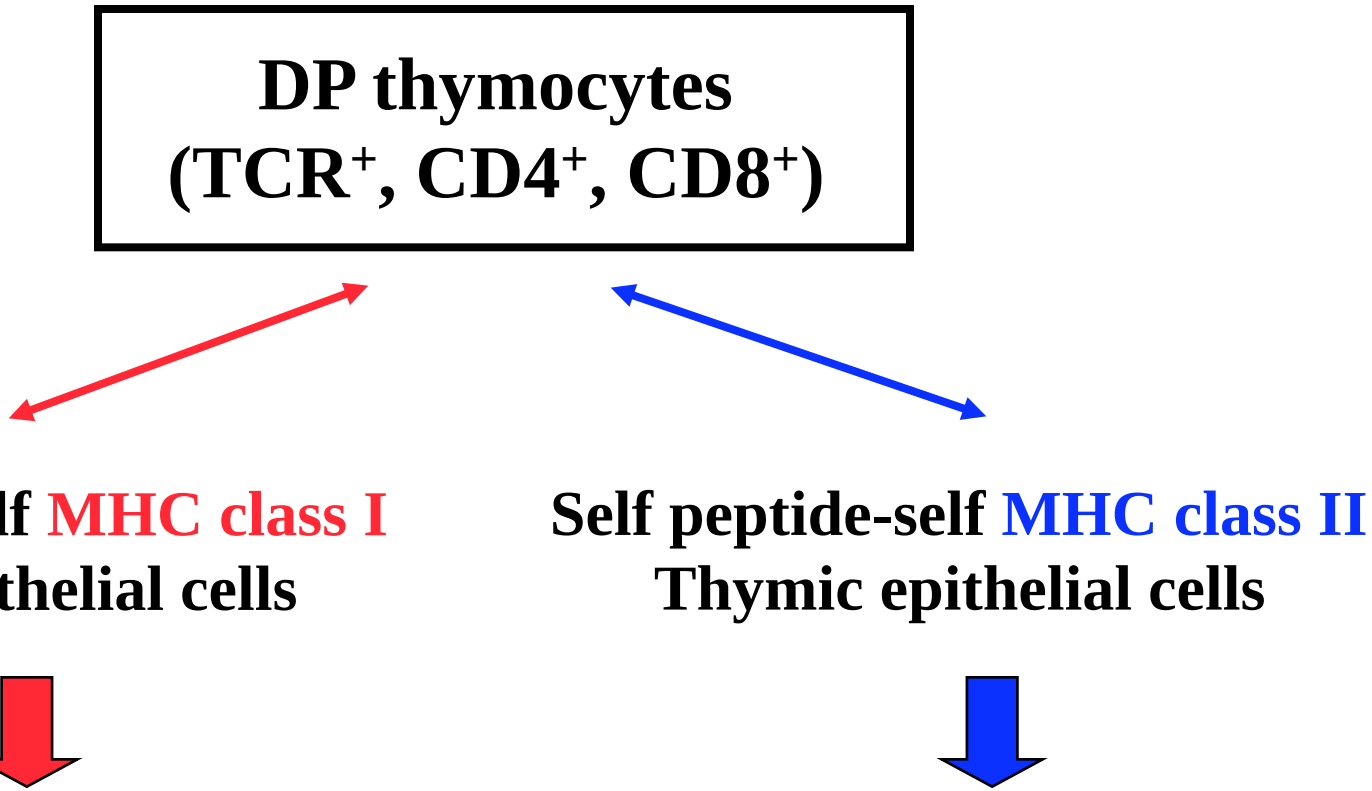
CD8 T cells

CD4 T cells

Fig. 5.13

 Immune System, Garland Sciences 2005. 2nd ed.

Positive selection controls expression of the CD4 or CD8 co-receptor



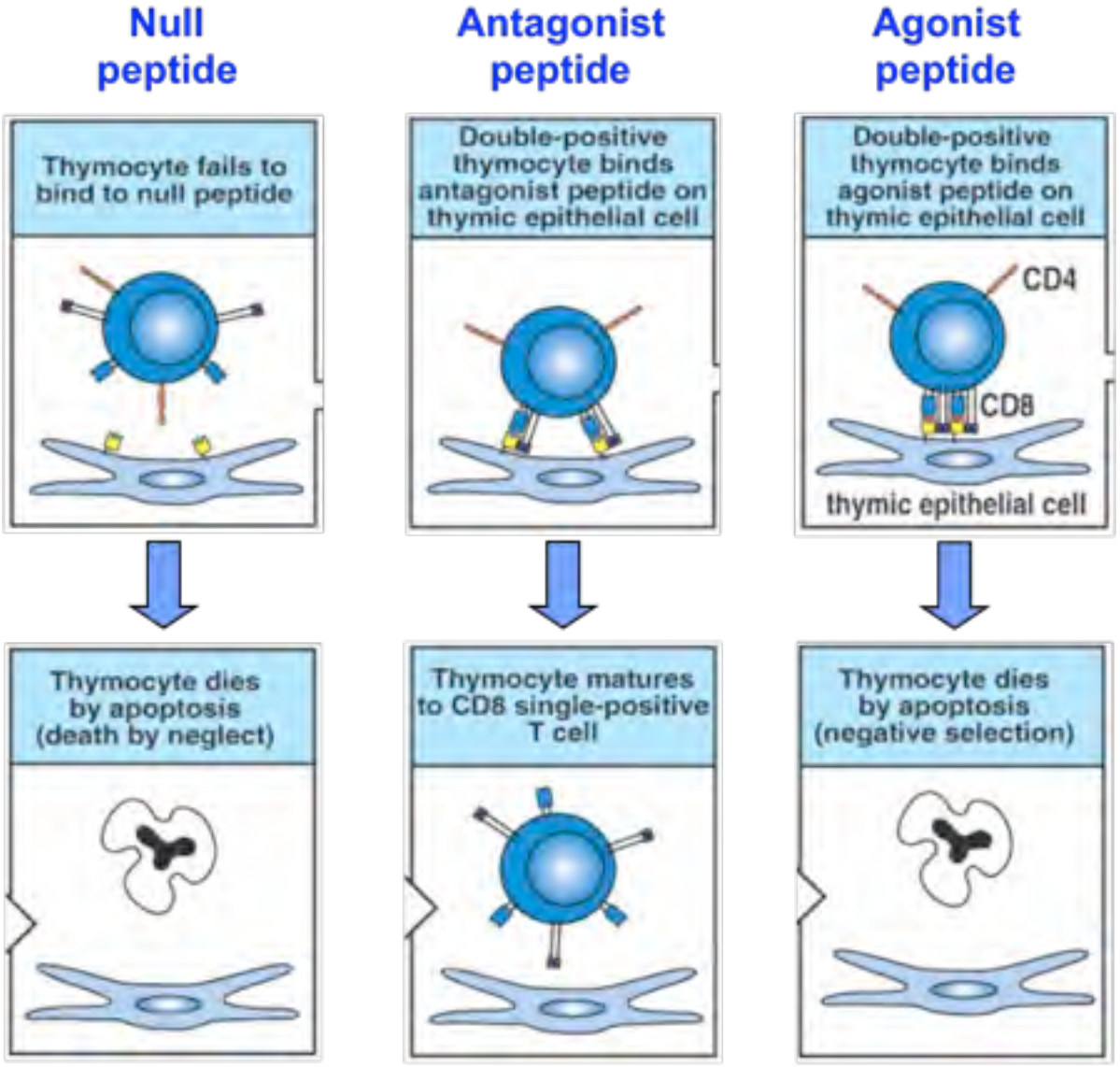
Negative selection

1. **Thymocytes die, if TCRs bind too strongly to MHC-peptide (self-peptides) complexes in the thymus.**

2. **The strength of signals received by TCRs is determined by peptides and the type of antigen presenting cells.**

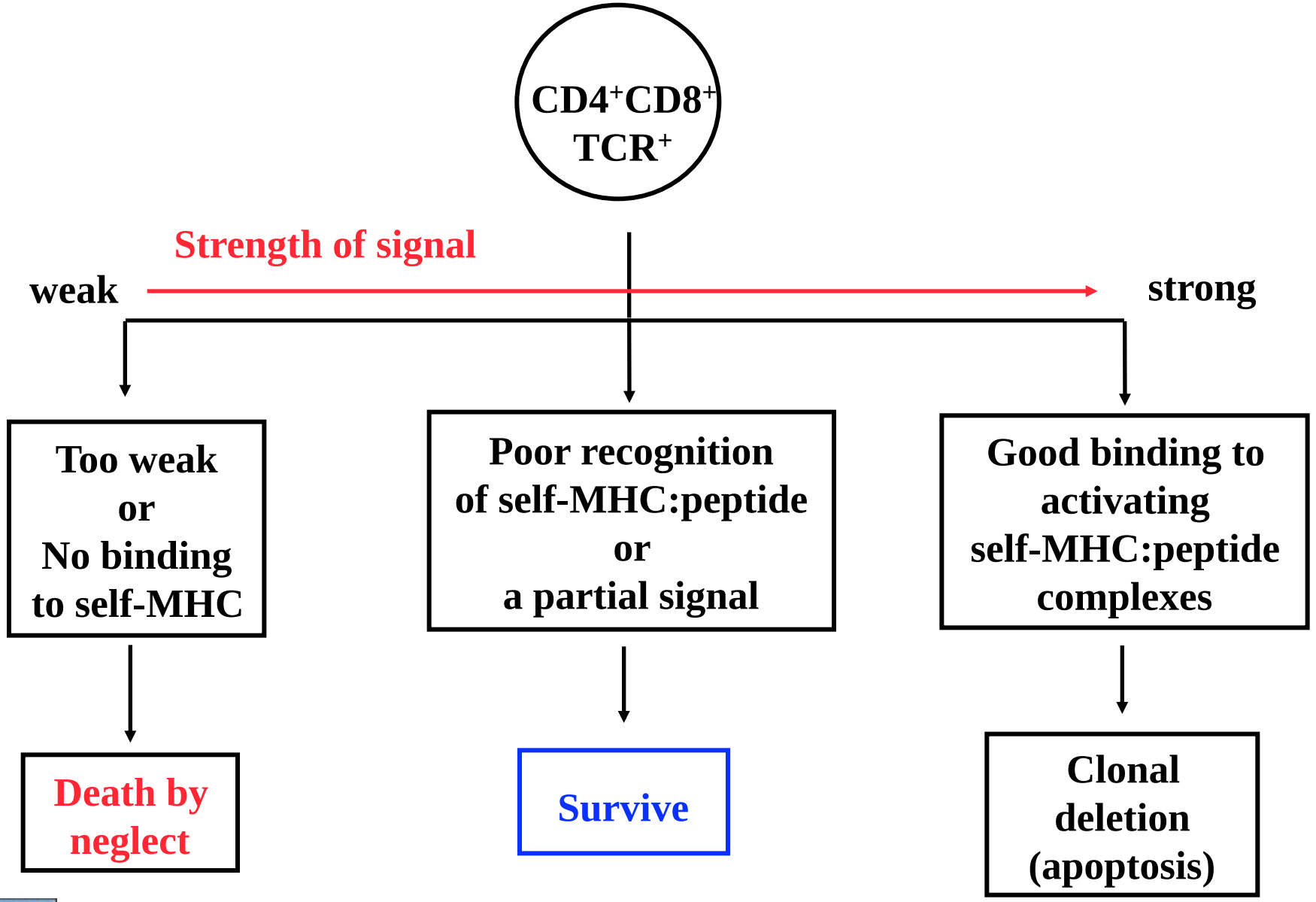
Differential signaling hypothesis

Effect of different peptides on thymic selection



 Janeway, Immunobiology. Garland Science, 2004.

A simple view of the thymic selection



Cells mediating positive and negative selection

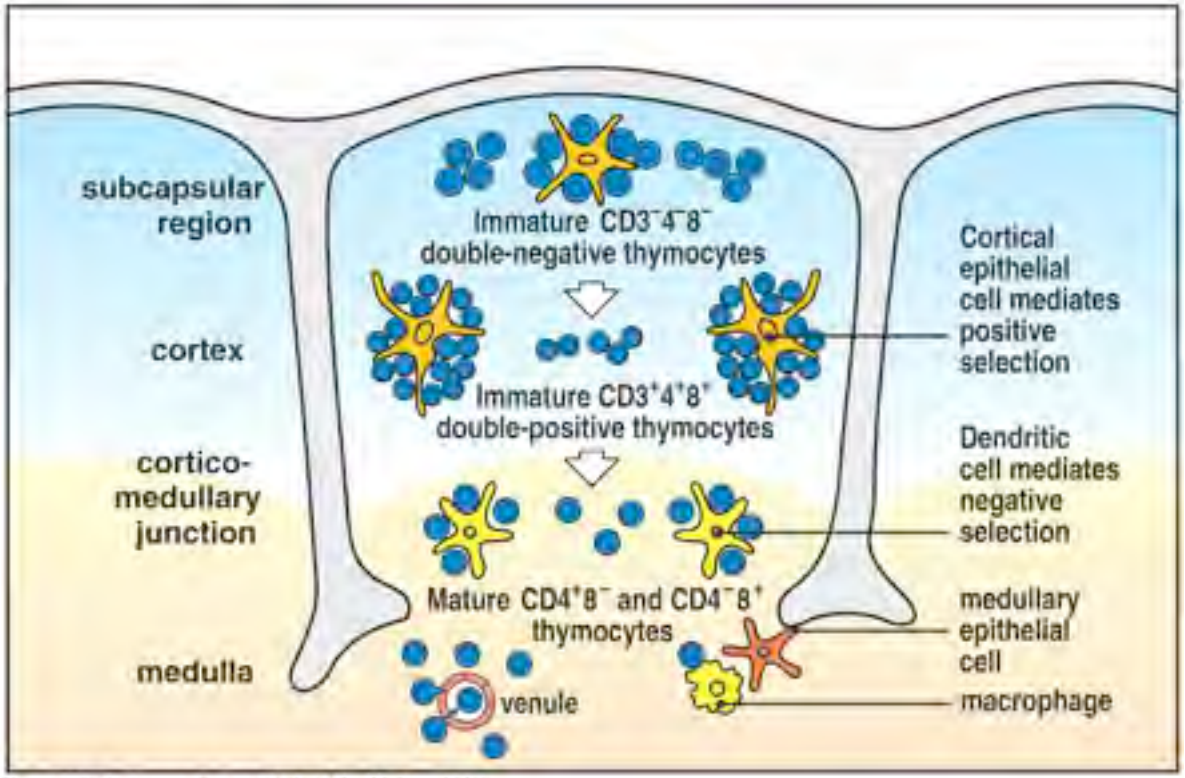


Figure 5-13 The Immune System, 2/e (© Garland Science 2005)

PD-INEL Immune System, Garland Science 2005

Positive selection by cortical epithelial cells

Negative selection by dendritic cells and macrophages

Fig 5.14

Expression pattern of MHC

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Other antigen-presenting cells (e.g., dendritic cells)	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	–†
Non-nucleated cells		
Red blood cells	–	–

Figure 3-22 The Immune System, 2/e (© Garland Science 2005)

Professional Antigen Presenting Cells

Cells that can express MHC class II

 Immune System, Garland Science 2005

Factors influencing T cell selection

1. **MHC; MHC restriction**
2. **Co-receptors; CD4 and CD8**
3. **Peptides; signaling strength**
4. **Cell type: cells residing in the thymus**

Differential signaling hypothesis

If T cells escape from selection processes in the thymus, what would be the consequences?

1. Failure of positive selection;

   Lack of functional T cells

2. Failure of negative selection;

   Self-reactive T cells in the periphery resulting in autoimmunity

The ultimate goal of selection is to produce T cells that are

- **Self-MHC restricted to recognize foreign antigenic peptides with self-MHC**

AND

- **Self tolerant not to respond to self-peptides**

T cell repertoire

Highly personalized as a result of positive and negative selection

This is due to the diversity of HLA types in the human population.

Summary #1

1. **What do T cells require to become mature T cells in the thymus?**

   CD4 T cells require MHC class II-peptide complexes expressed on thymic stromal cells.

   CD8 T cells require MHC class I-peptide complexes expressed on thymic stromal cells.

2. **What is the developmental pathway of thymocytes?**

   DN ($CD4^-CD8^-$); most immature thymocytes
   DP ($CD4^+CD8^+$); intermediate stage and the most abundant population of thymocytes
   SP ($CD4^+$ or $CD8^+$); matured and exit to the periphey

Summary #2

3. What is positive and negative selection of T cells?

Positive selection: T cells bearing TCR that are partially signaled by self-MHC with peptides are rescued from apoptosis and matures.

Negative selection: T cells recognizing self-peptide bound to self-MHC with high affinity are deleted by apoptosis.

4. Why is T cell selection important?

To generate T cells that are not self-reactive (tolerant) and recognize foreign peptides with self-MHC.

5. What is the consequence of dysregulated T cell development?

Lack of functional T cells (immunodeficiencies) or production of autoreactive T cells (autoimmune diseases)

Why does an individual express a limited number of different MHC molecules?

To educate developing T cells

A T cell repertoire of an individual is diverse enough to mediate a whole array of different immune reactions.

How can we achieve the diversity of T cells with a limited number of HLA?

A possible maximum number of peptides that can be bound by one MHC allele

In theory

- Let's take MHC class I that binds a 9 aa long peptide
- Each position can have 20 different amino acid residues

Total peptides presentable by one MHC allele

20x20x20x20x20x20x20x20x20= **5.12×10^{11}**

In reality

- Anchor residues; Both the position and identity restriction
- A smaller number of total MHC-peptide complexes

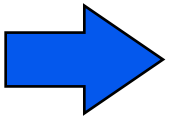
???

What would happen to the T cell repertoire, if you have a defect in the following molecules ?

MHC class I
MHC class II
β2m
TAP
Ii

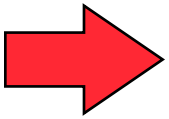
Phenotype of the T cell repertoire

Any defect in proper expression of MHC class I on the cell surface



No CD8 T cells

Any defect in proper expression of MHC class II expression on the cell surface



No CD4 T cells

A defect in	Results in the lack of
MHC class I	CD8
MHC class II	CD4
β2m	CD8
TAP	CD8
Ii	CD4

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Slide 27: Wesley Dunnick
Slide 28: Immune System, Garland Science 2005
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