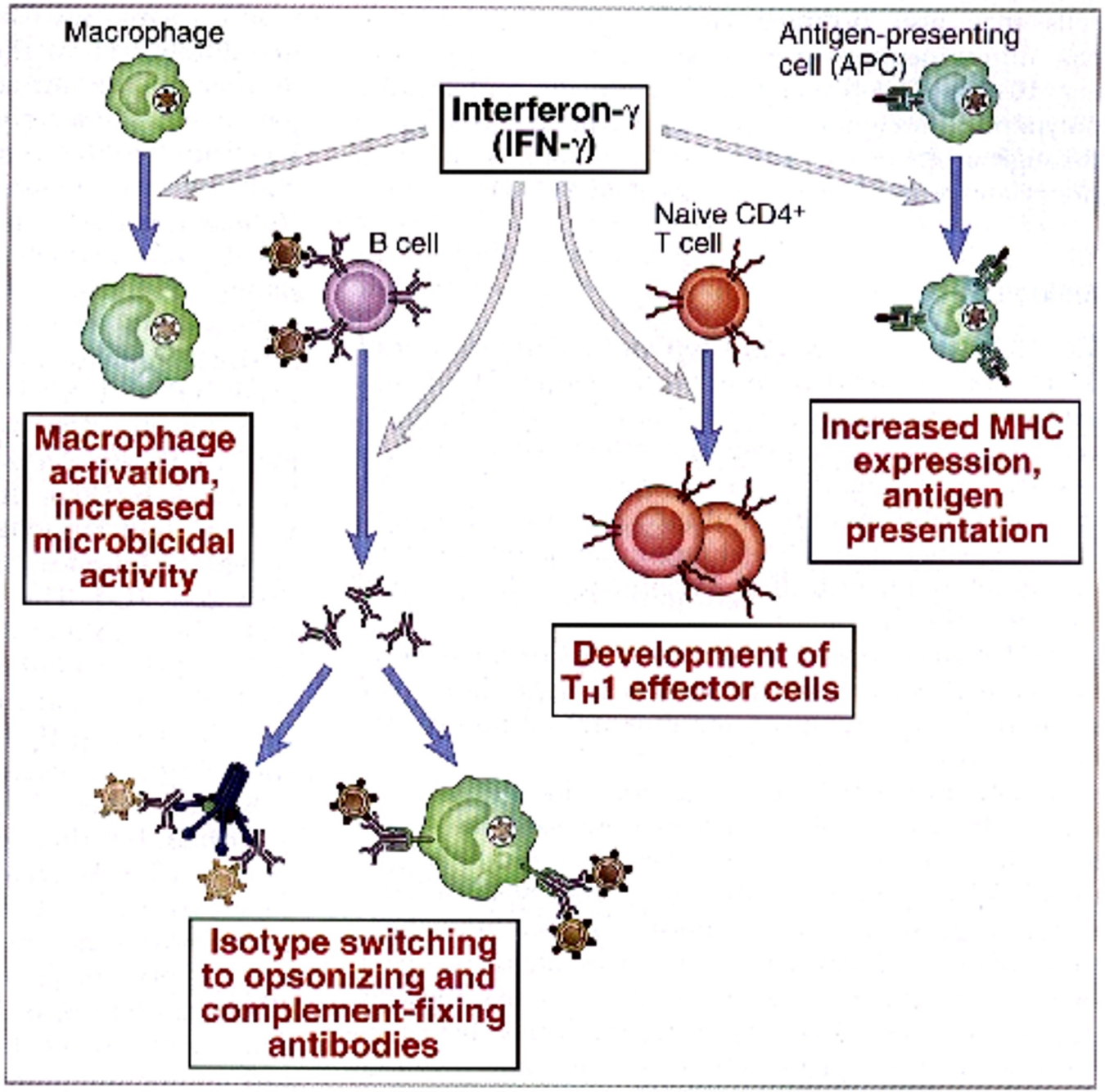
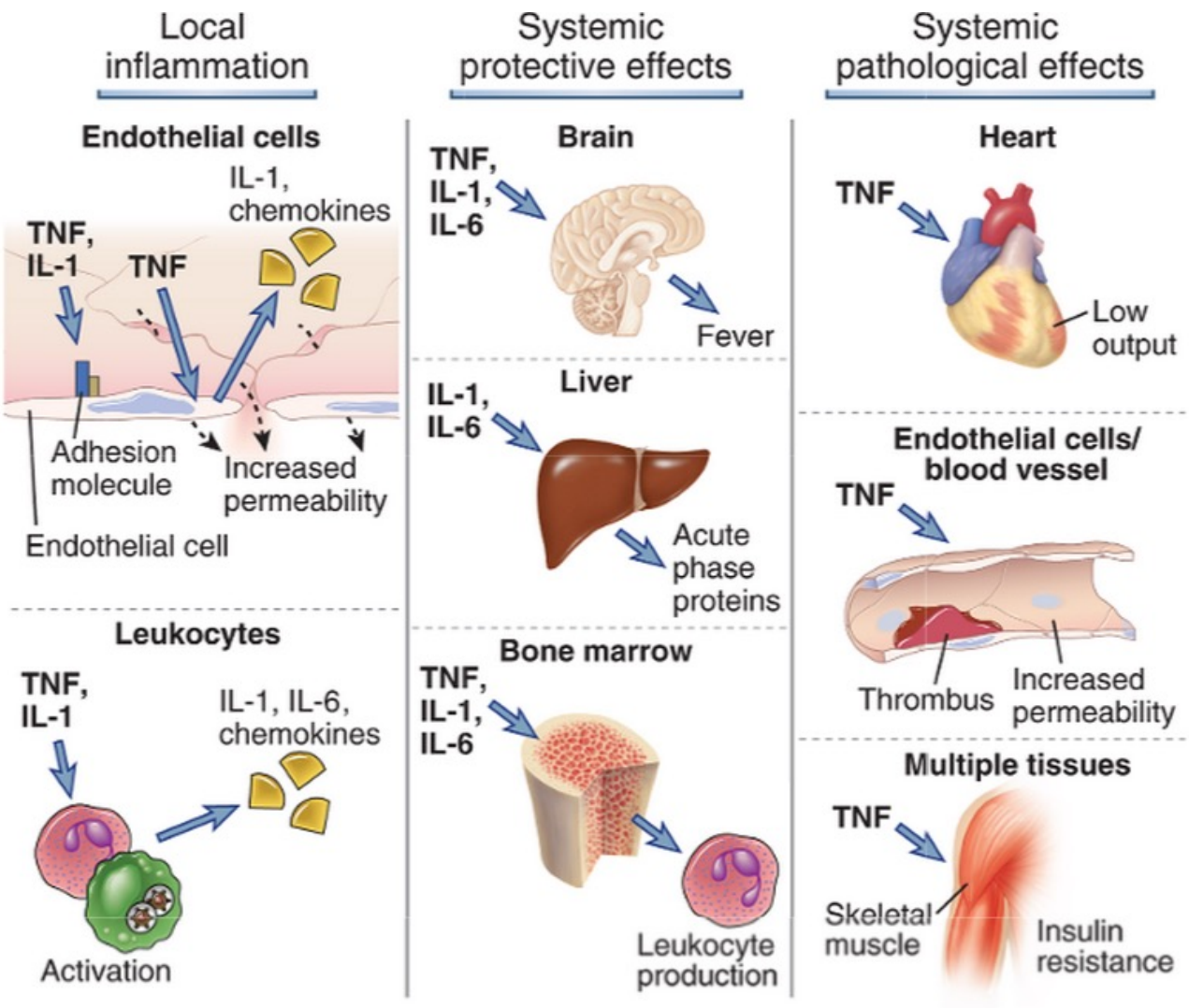
BT 304
Lecture 20
25 Sept 2023

Figure 11–14 Biologic actions of IFN-γ.

IFN-γ activates phagocytes and APCs and induces B cell switching to some immunoglobulin isotypes (that often bind complement and Fc receptors on phagocytes and are distinct from the isotypes induced by IL-4). The T_H1-inducing effect of IFN-γ may be indirect, mediated by increased IL-12 production and receptor expression.





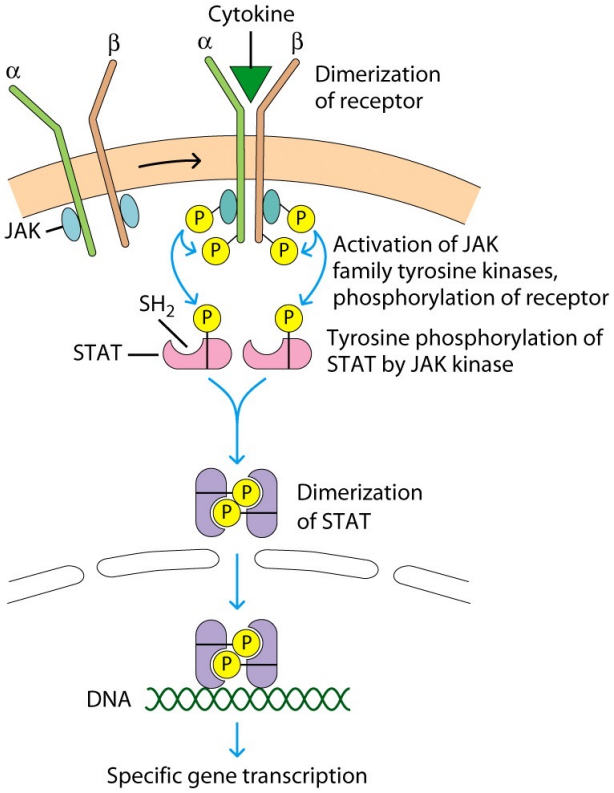
TNF, IL-1, and IL-6 have multiple local and systemic inflammatory effects. TNF and IL-1 act on leukocytes and endothelium to induce acute inflammation, and both cytokines induce the expression of IL-6 from leukocytes and other cell types. TNF, IL-1, and IL-6 mediate protective systemic effects of inflammation, including induction of fever, acute-phase protein synthesis by the liver, and increased production of leukocytes by the bone marrow. Systemic TNF can cause the pathologic abnormalities that lead to septic shock, including decreased cardiac function, thrombosis, capillary leak, and metabolic abnormalities due to insulin resistance.

Cytokine Receptors

- Multimeric receptors
- Common signal-transducing subunits
- Unique high affinity subunits
- High affinity subunits associated with activation of target cell

Signal Transduction

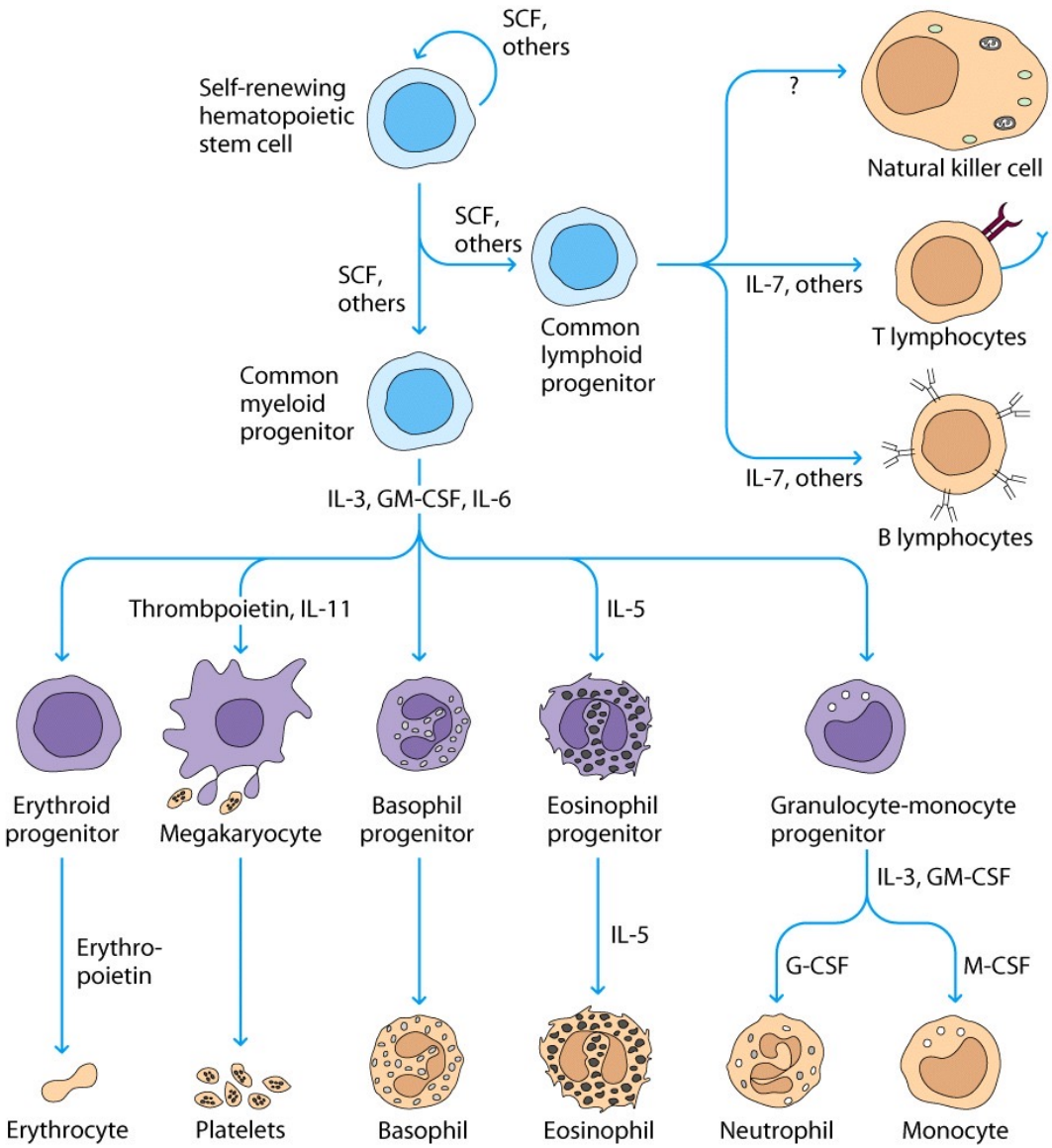
- Initiated by cytokine binding
- Activates JAK (Janus kinase)
- Phosphorylation of tyrosine
- Binding of STAT (Signal transducers and activators of transcription)
- Translocation of STAT to cell's DNA
- Transcription of specific target genes



Role of Cytokines in Hematopoiesis

- SCF (Stem cell factor)
- GM-CSF (Granulocyte-macrophage colony-stimulating factor)
- IL-3 (Interleukin 3)
- IL-5 (Interleukin 5)
- IL-7 (Interleukin 7)
- IL-11(Interleukin 11)

Role of Cytokines in Hematopoiesis



Cytokines in the Immune Response

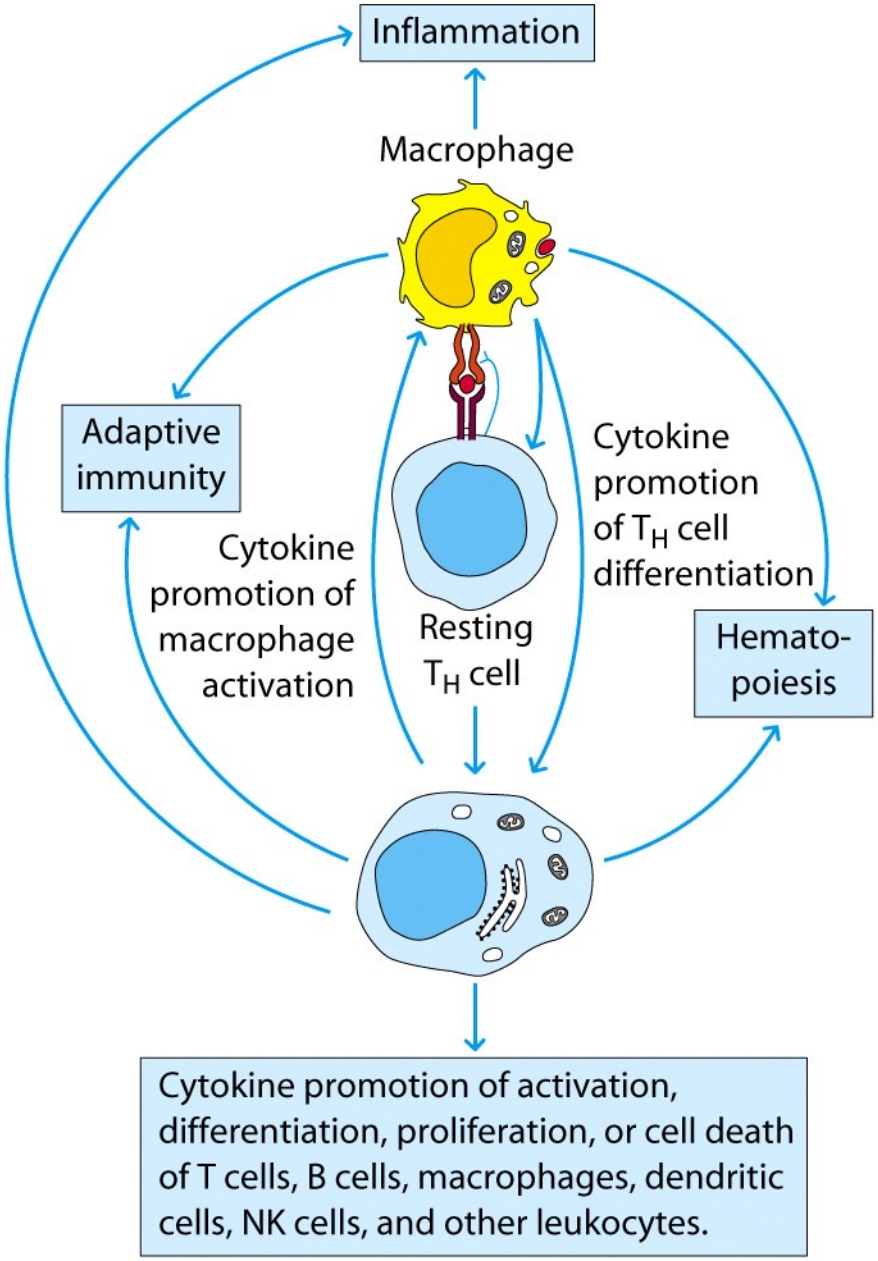
- Innate immune response
  - IL 1-(Macrophage)-fever, capillary effects
  - IL 6-(Macrophage)-adaptive immunity via B cells
  - IL 12(Macrophage)-adaptive immunity via T helper cells
  - TNF (Macrophage)-capillary effects, activates neutrophils
  - IFN *alpha* (Macrophage)-multiple effects
  - IFN *beta* (Fibroblasts)-multiple effects

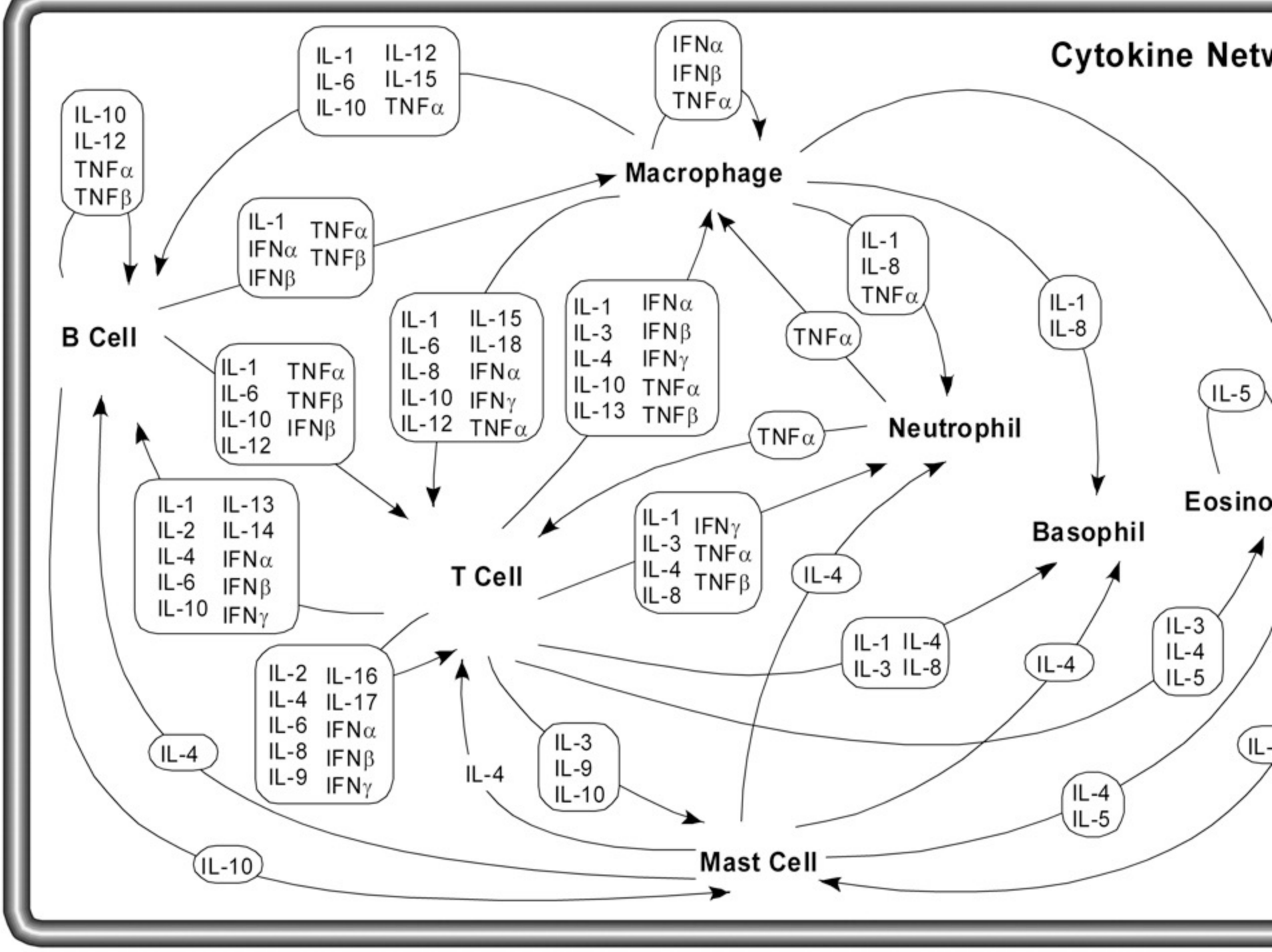
Cytokines in the Immune Response

- Adaptive immune response
  - IL 2-(T cells)-multiple effects
  - IL 4-(T cells & mast cells)-T cell differentiation, IgE production
  - TGF *beta* –(T cells, macrophages)-inhibits adaptive immune response
  - IFN *gamma*-(T cells, NK cells)-Macrophage activation

Cytokine-related Diseases

- **Bacterial septic shock**: endotoxin in cell wall of gram-negative bacteria stimulate macrophages to over produce IL-1 and TNF-a.
- **Bacterial toxic shock**: caused by superantigens that bind simultaneously to MHC class II and TCR Vb domain. 5-25% of total T cells may respond to a single superantigen and result in excessive production of cytokines.


Inflammation
Macrophage
Adaptive immunity
Cytokine promotion of macrophage activation
Resting T_H cell
Cytokine promotion of T_H cell differentiation
Hemato-poiesis
Cytokine promotion of activation, differentiation, proliferation, or cell death of T cells, B cells, macrophages, dendritic cells, NK cells, and other leukocytes.


Cytokine Netw
Macrophage
B Cell
T Cell
Neutrophil
Basophil
Eosino
Mast Cell
IL-1 IL-12
IL-6 IL-15
IL-10 TNFα
IFNα
IFNβ
TNFα
IL-10
IL-12
TNFα
TNFβ
IL-1
IFNα
IFNβ
TNFα
TNFβ
IL-1 IL-15
IL-6 IL-18
IL-8 IFNα
IL-10 IFNγ
IL-12 TNFα
IL-1 IFNα
IL-3 IFNβ
IL-4 IFNγ
IL-10 TNFα
IL-13 TNFβ
IL-1
IL-8
TNFα
IL-1
IL-8
IL-5
TNFα
IL-1 TNFα
IL-6 TNFβ
IL-10 IFNβ
IL-12
TNFα
IL-1 IL-13
IL-2 IL-14
IL-4 IFNα
IL-6 IFNβ
IL-10 IFNγ
IL-1 IFNγ
IL-3 TNFα
IL-4 TNFβ
IL-8
IL-4
IL-1 IL-4
IL-3 IL-8
IL-4
IL-3
IL-4
IL-5
IL-2 IL-16
IL-4 IL-17
IL-6 IFNα
IL-8 IFNβ
IL-9 IFNγ
IL-4
IL-3
IL-9
IL-10
IL-4
IL-4
IL-5
IL-4
IL-10

Principles of Immunology

T Cell Development

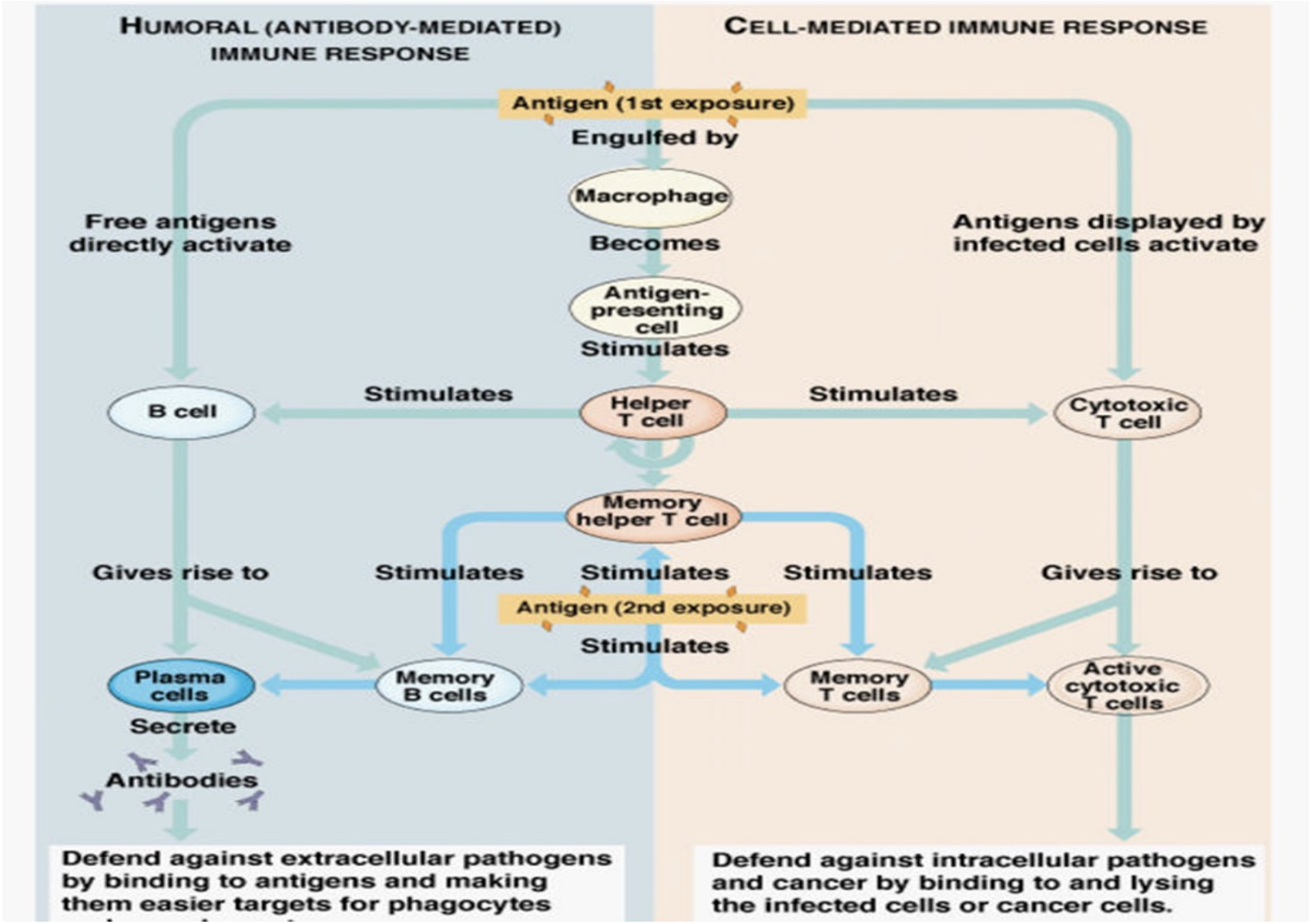
Lecture 21

26 Sept 2023

Word/Terms List

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

Overview of the IMMUNE SYSTEM



Lymphopoiesis

- T cell progenitors originate in the BM (~50 million per day)
- Migrate to thymus
- Characteristic surface marker and genetic/intracellular changes
- 98% never make it to maturity, i.e. only 1 million do
- Apoptosis hits those that do not have functional TCR or don’t get ”selected”

Lymphopoiesis

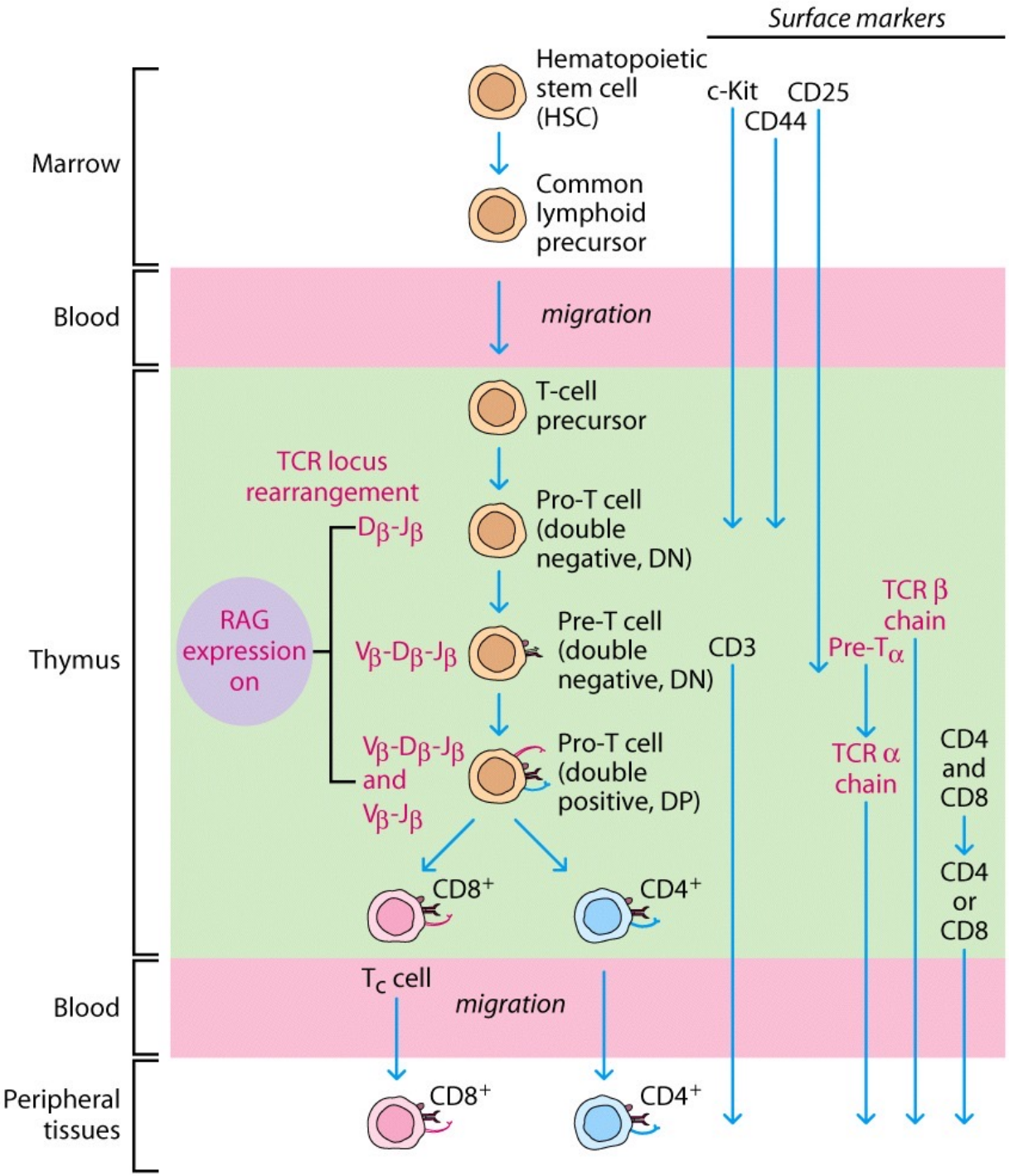
- T cell generation slows down with age
- Mature T cells may divide in secondary lymphoid organs
- What is consequence of that?

T Cell Maturation

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

T 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+

Thymocyte Changes

- Double negative cells
  - No expression of CD4 or CD8
  - Rearrangement of TCR *beta* genes (V,D,J)
  - Loss of stem cell markers (c-Kit, CD 44)
  - Expression of Pre TCR (*Beta* chain plus pre *alpha* chain)
  - Suppression of further *beta* chain changes
  - Signal to initiate *alpha* chain

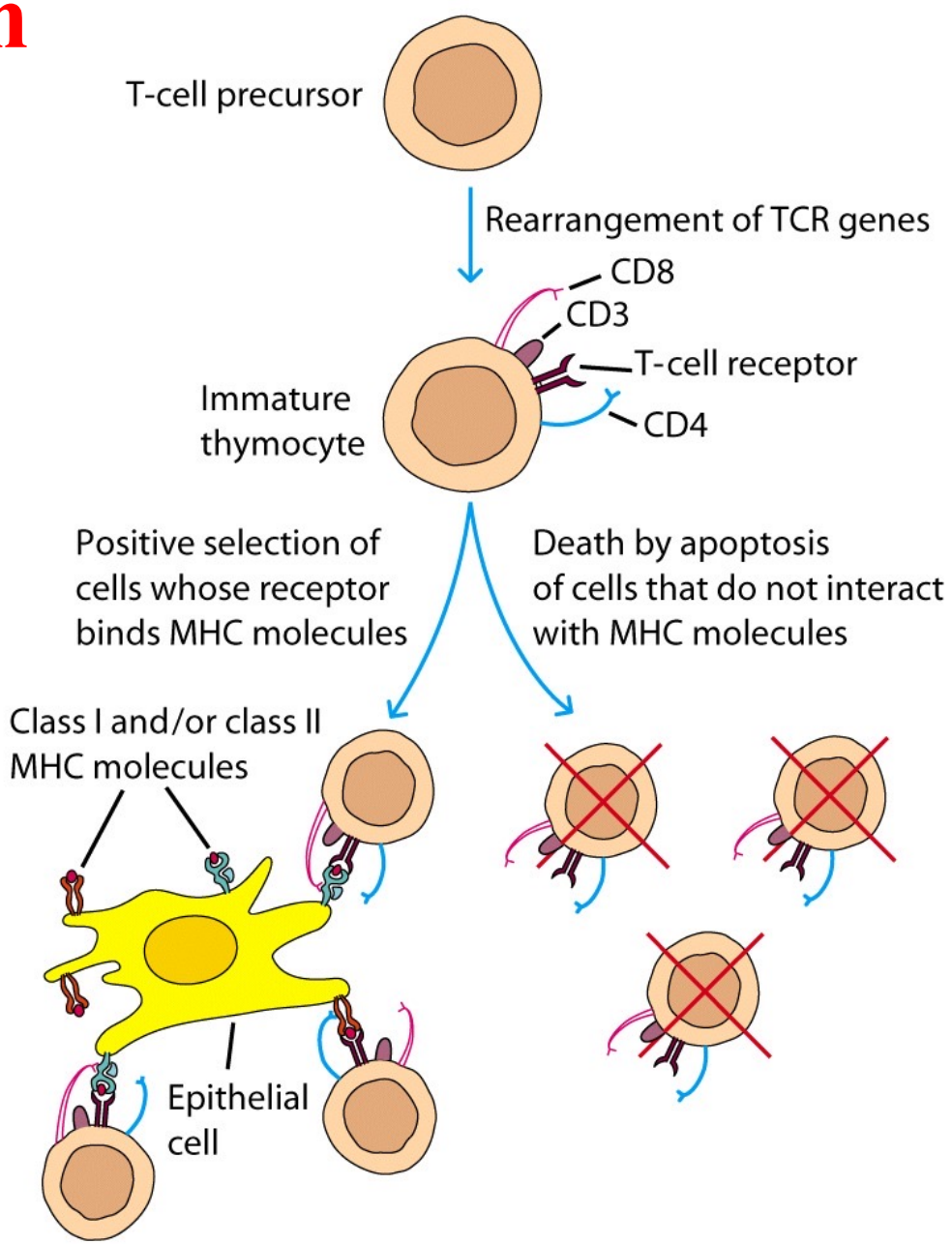
Thymocyte Changes

- Double negative to double positive cells
  - Expression of CD? (Associated with TCR)
  - Expression of CD4 and CD8
  - Proliferation of double negatives
  - Contributes to diversity of *alpha* chains and ultimately T cells
  - Population of T cells with defined TCRs and single CD4 or CD8 expression

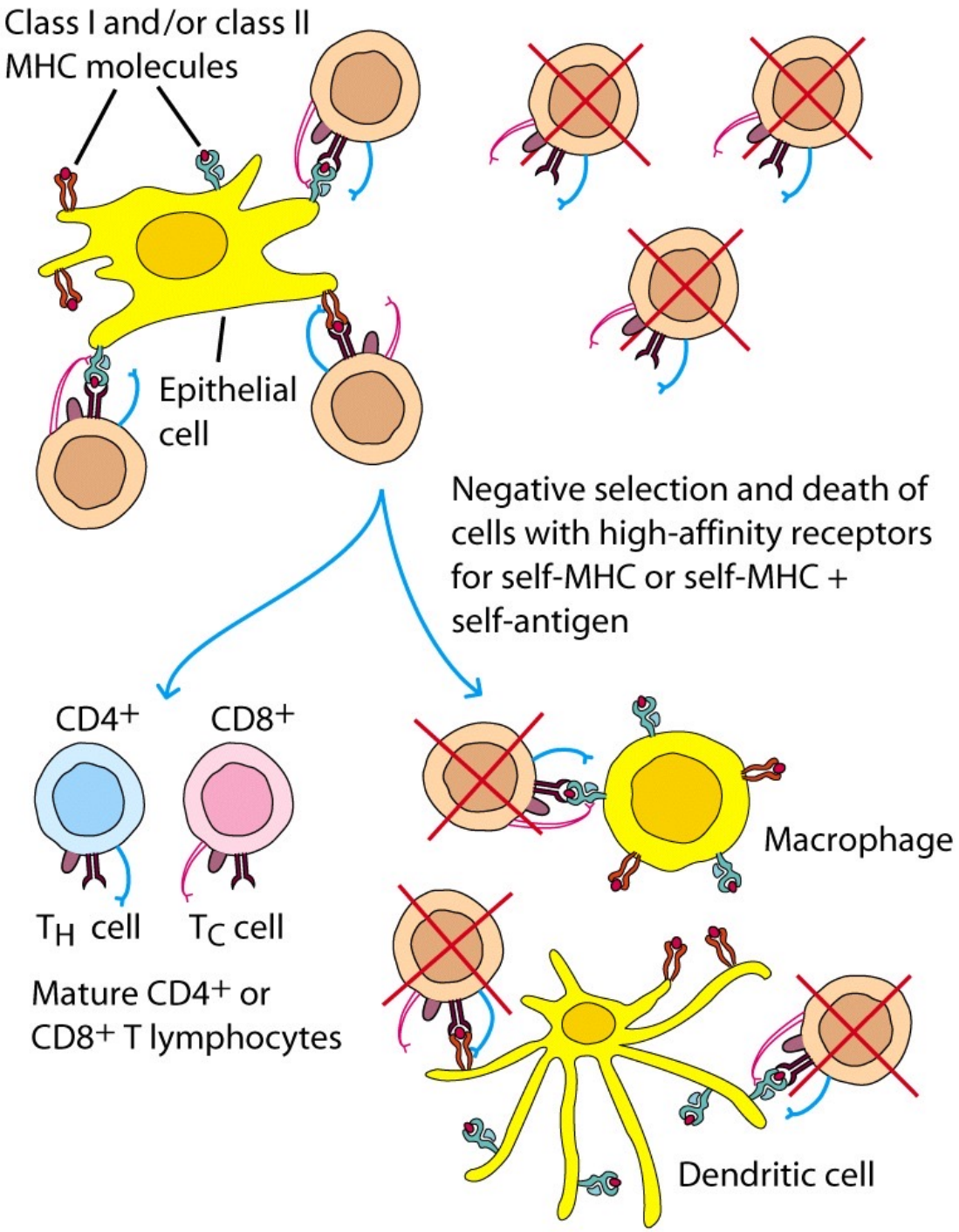
Thymic Selection

- Self MHC restricted
  - Only T cells with TCRs that recognize same haplotype are "selected" for further maturation
- Positive selection
  - Double positives bind MHC molecules
  - Nonbinders die
  - Possible that binding counters programmed apoptosis
  - Binders become single positives
- 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

Thymic Selection

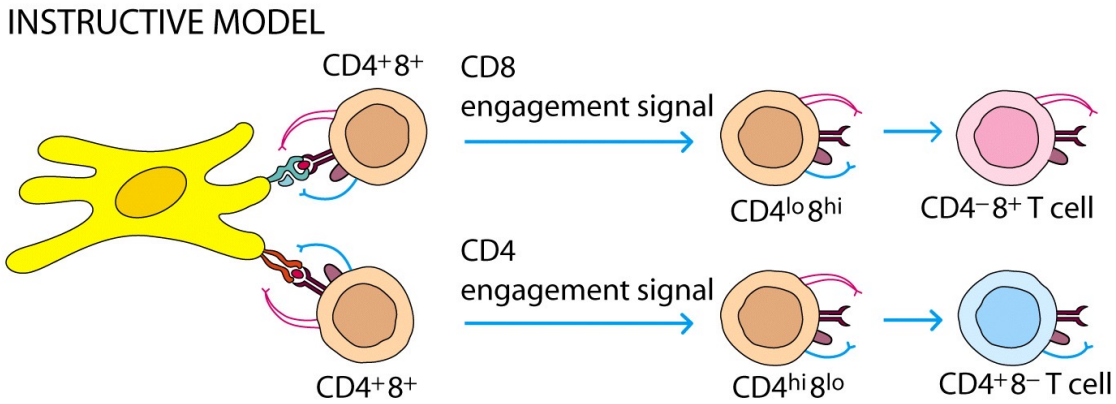


Thymic Selection

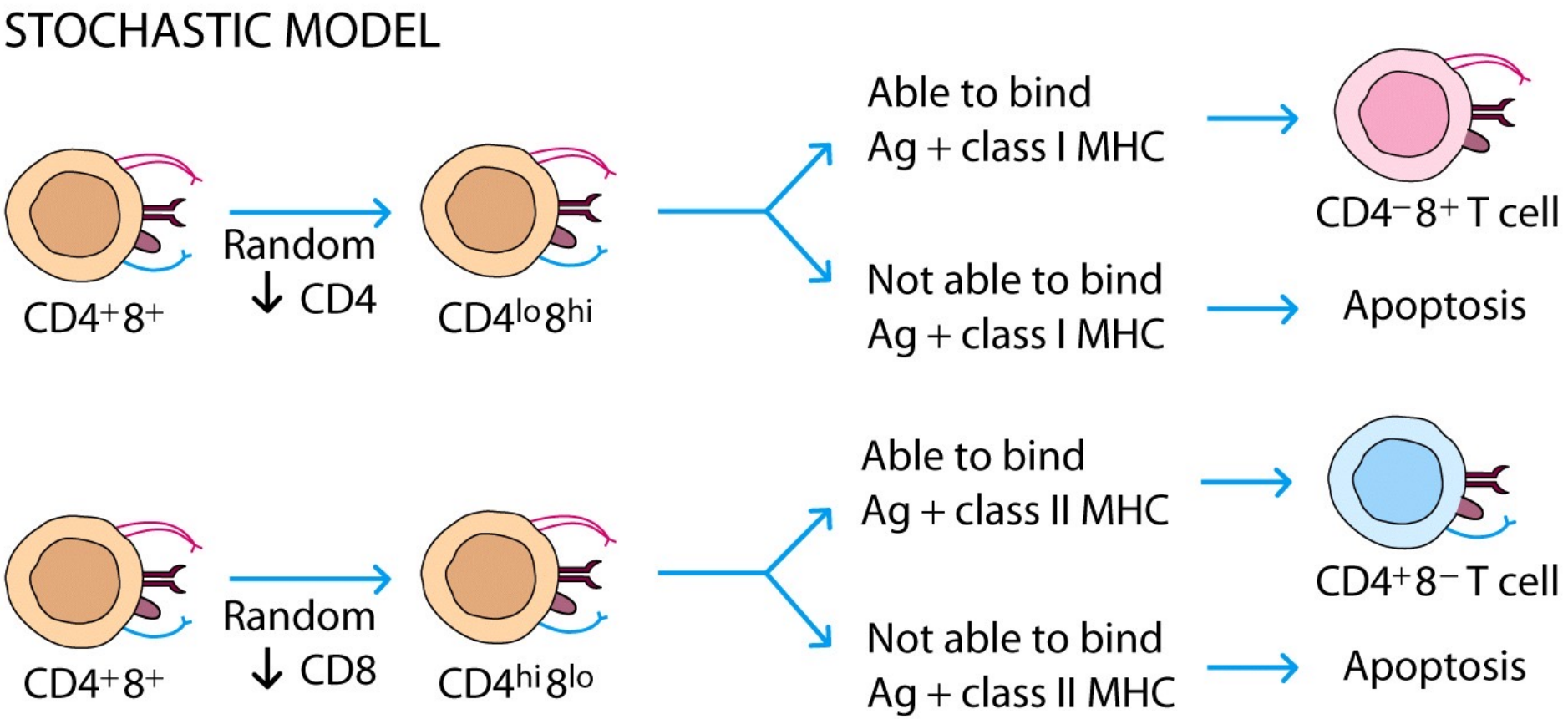


Double to Single Positive

- Two theories
- **Instructive model**
  - Binding precedes down regulation of non dominant marker

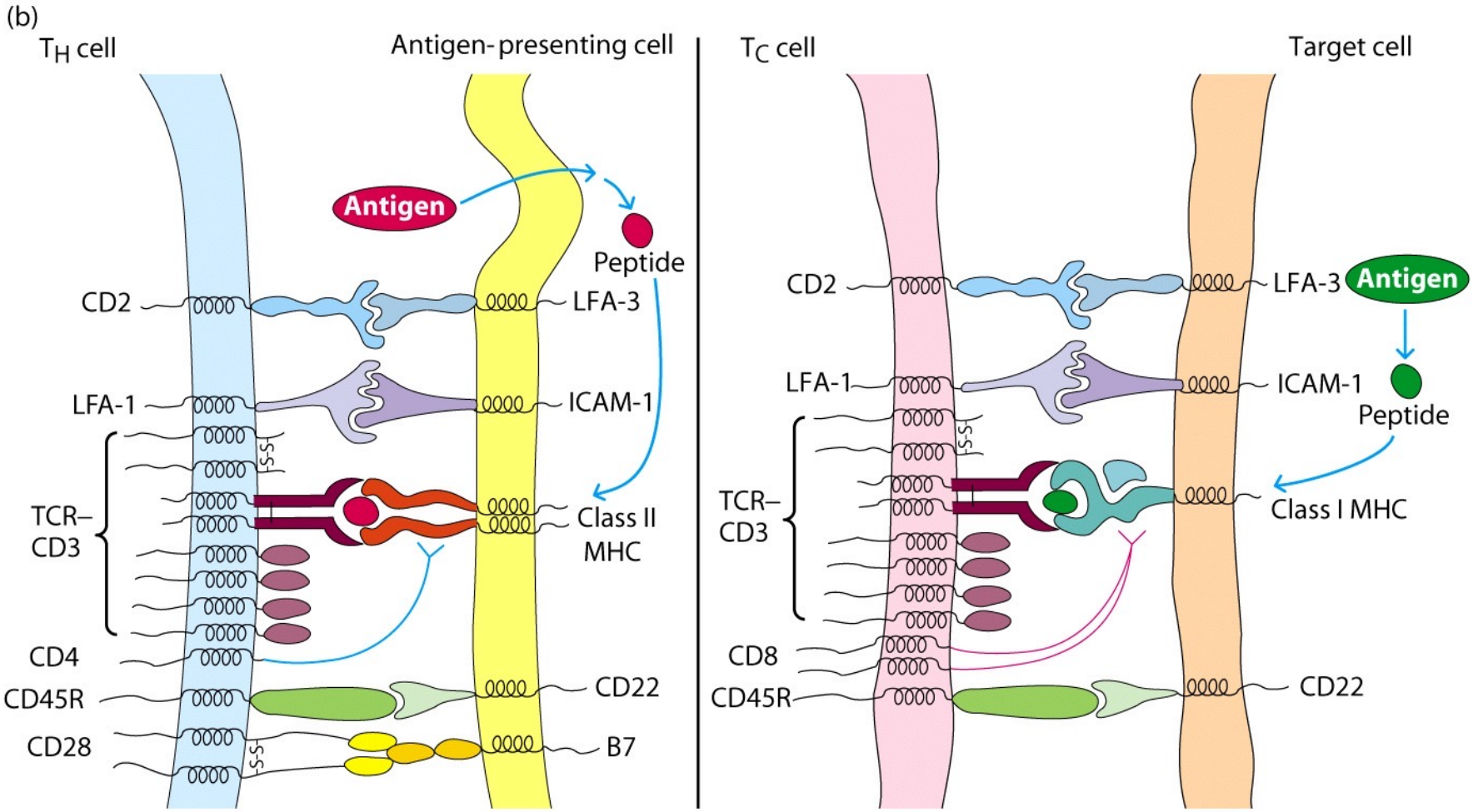


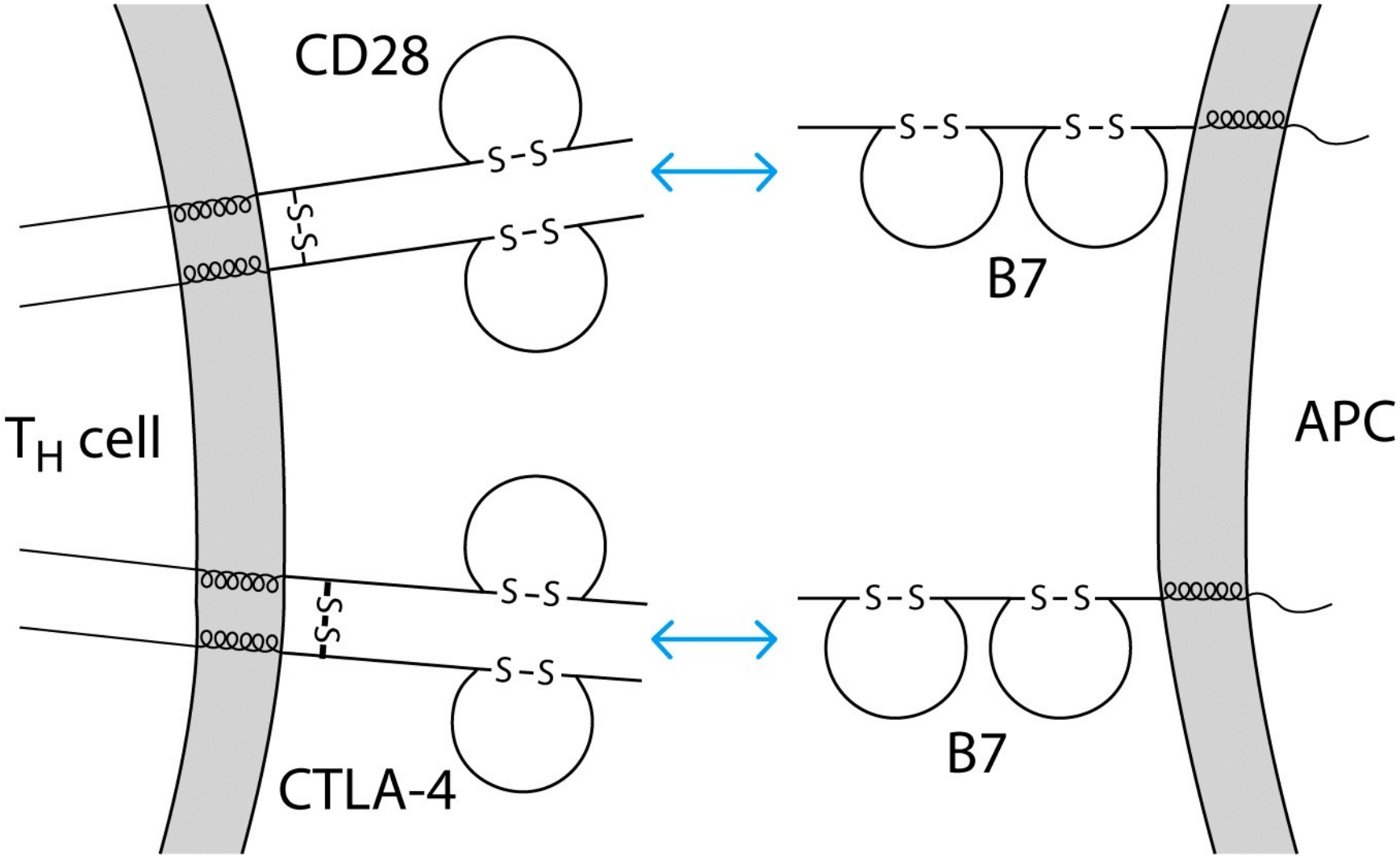
- **Stochastic model**
  - Random down regulation occurs before binding
  - Nonbinders die via apoptosis


STOCHASTIC MODEL
CD4+8+
Random
↓ CD4
CD4lo8hi
Able to bind
Ag + class I MHC
CD4−8+ T cell
Not able to bind
Ag + class I MHC
Apoptosis
CD4+8+
Random
↓ CD8
CD4hi8lo
Able to bind
Ag + class II MHC
CD4+8− T cell
Not able to bind
Ag + class II MHC
Apoptosis

T Cell Activation

- Initiation
  - TCR-CD3/MHC peptide complex interact
  - Involvement of coreceptor
    - CD4 to MHC II
    - CD8 to MHC I
  - Co-stimulatory signal
    - CD 28 to B7 (T_H Cells/APCs)
  - Inhibitory role of CTLA-4


(b)
TH cell
Antigen-presenting cell
Antigen
Peptide
CD2
LFA-3
LFA-1
ICAM-1
TCR–
CD3
Class II
MHC
CD4
CD45R
CD22
CD28
B7
TC cell
Target cell
CD2
LFA-3
Antigen
LFA-1
ICAM-1
Peptide
TCR–
CD3
Class I MHC
CD8
CD45R
CD22


CD28
S-S
S-S
S-S
S-S
S-S
B7
T_H cell
APC
S-S
S-S
S-S
S-S
S-S
B7
CTLA-4

Gene Expression

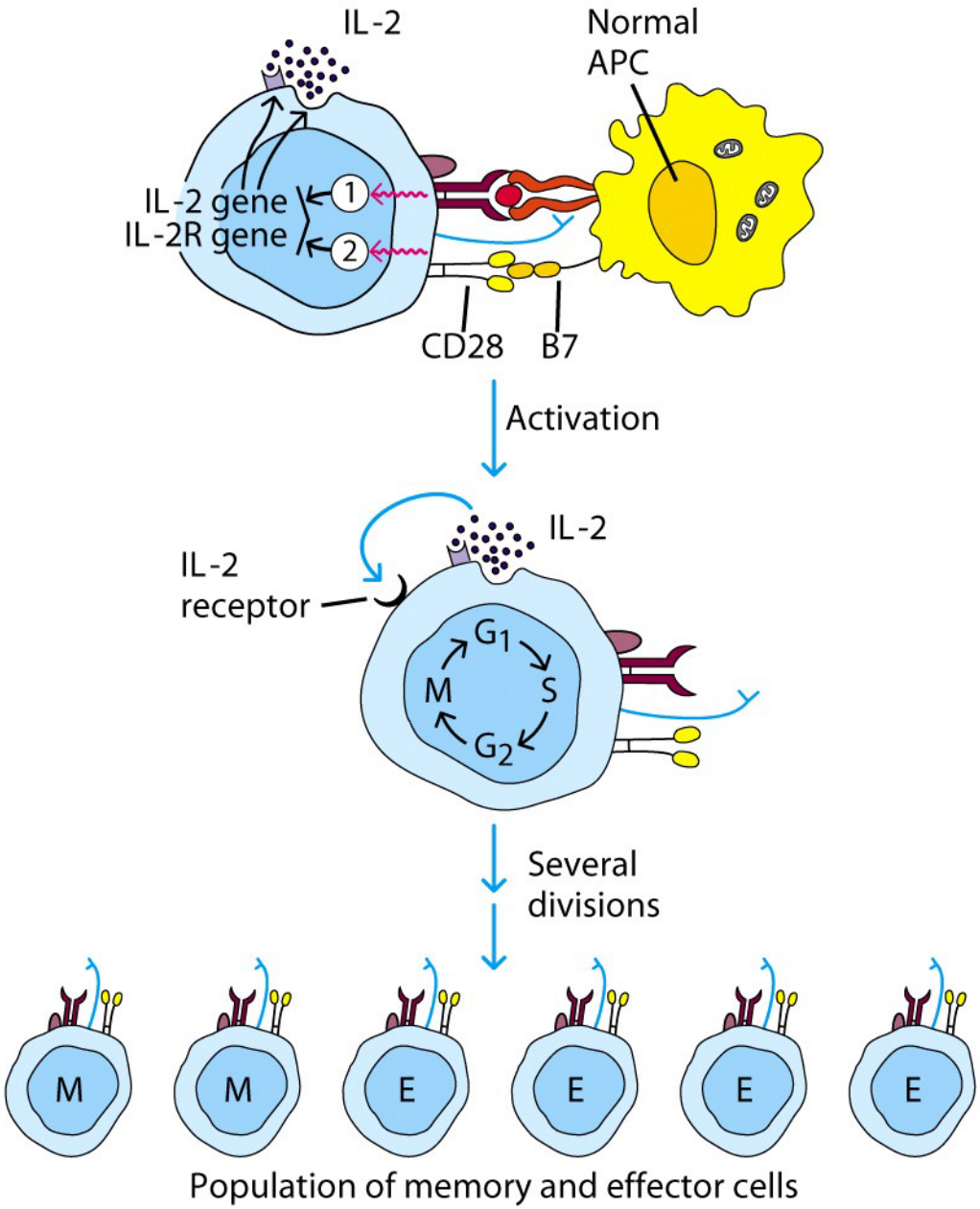
- Immediate
  - C-Fos, c-Jun
  - Influence transcription
  - Produced within 30 min
- Early
  - Cytokines (IL-2, 3, 4, 5, 6, IFN *gamma*)
  - Secreted
  - Produced within 1-2 hours
- Late
  - Adhesion molecules
  - Produced within days

Results of Signaling Pathways

- Gene expression changes
- Functional changes
- Differentiation

✓ Occurs in secondary lymphoid tissue
✓ Activated cell becomes a blast cell
✓ IL-2 levels are increased 100 times
✓ Binds to IL-2 receptor on producing cell
✓ Takes several days to occur
✓ Effector cells and memory cells are produced

- Functions of effectors
  - B cell helper
  - Cytotoxicity
- Characteristics of memory cells
  - Last months to years vs. effector cells that last days to weeks
  - Memory cells more easily activated by all APCs then naïve T cells


IL-2
Normal
APC
IL-2 gene
IL-2R gene
1
2
CD28
B7
Activation
IL-2
IL-2
receptor
G1
S
G2
M
Several
divisions
M
M
E
E
E
E
Population of memory and effector cells

Naive T cells: They become activated on antigen recognition which is presented by APC (e.g. dendritic cells).

Effector cells: cells which having short life with special functions such as cytokine secretion , helps B-cell and cytotoxic killing activity.
Effector cells are derived from naïve or memory cells after antigen activation (e.g. CTLs)

Memory cells: long-lived resting cells that are derived from naïve and effector cells.
They respond faster and stronger to a subsequent challenge with the same antigen.

Regulatory T cells: cells that can inhibit the proliferation of other T cell population which cause problem to host body.
(e.g. CD4,CD25)