Immune Regulation

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Objectives

- What is immune regulation?
- Why we need it?
- What are the mechanisms of immune regulation?
- What is central tolerance?
- What is peripheral tolerance?

Why is immune regulation important?

- If not regulated properly, it can cause harm to host

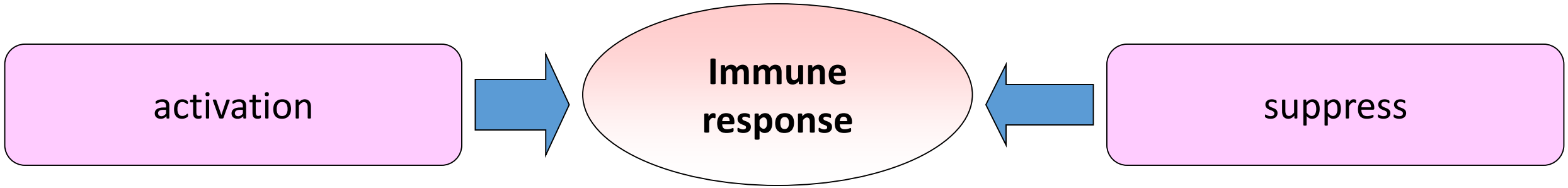
- If defective--------> Immunedeficiency ----> severe infections
  → cancers
- If exaggerated------> Hypersensitivity
  → tissue destruction
- If inappropriate -------> Autoimmunity -----> immune response to self tissues

Immune Regulation

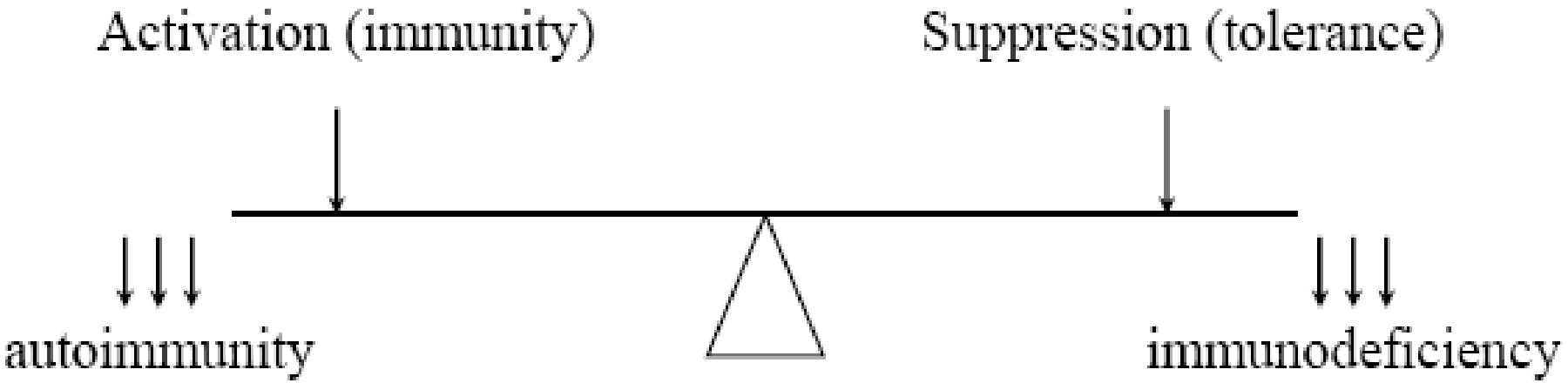
- A balance between
  - activation and
  - suppression

  } of effector cells

- to achieve an efficient immune response without damaging the host.



Immune Regulation



- Natural regulatory mechanisms
- Artificial regulatory mechanisms

Natural Regulatory Mechanisms

Immune Regulation

- Regulatory mechanisms act at all phases of immune response
  - Recognition
  - Activation
  - Effector function

Immune Regulation

- The immune system should react against foreign antigens, But not self antigens
- The activated immune system should be turned off when the foreign antigen is killed
- The immune system should be unresponsive to self antigens

“ immunological tolerance”

Tolerance
Burnet's Hypothesis:(1949)

- During neonatal stage of life, or when immune system is developing, all Ags present are recognized as self.
- Immune system becomes tolerant to these Ags

  - He suggested that if a foreign substance was to be introduced into embryo before its immune system matures, the antigen is accepted as "self"
  - Medawar successfully demonstrated this in lab

Nobel prize for Physiology or Medicine was awarded in 1960 to Macfarlane Burnet and Peter Medawar for " discovery of acquired immunological tolerance"

How does immune system discriminate “self” from “non-self”?

1. Innate immune system
2. Adaptive immune system

Mechanisms of Innate immune system

Cells of innate immune system has receptors (Pattern recognition receptors) to identify broadly expressed molecules shared by broad groups of microbes ("pathogen-associated molecular patterns" PAMPs) e.g. – bac DNA, LPS, teichoic acid

- They are only present on microbes not on self tissues

- Mechanisms of unresponsiveness to self tissues by
  1. Ignorance (lack of recognition) of self cells (unless they change their surface structures)
  2. Presence of inhibitory structures/ receptors

Mechanisms of Adaptive system

- Lymphocytes with receptors capable of recognizing self antigens are constantly being generated in adaptive system

- Immune system is readily accessible to self antigens

? Big problem

How are these cell reactive lymphocytes eliminated?

1)Central tolerance – is induced by “Negative selection”

- T cells in thymus
- B cells in bone marrow

} cells die by “Apoptosis”

2) Peripheral tolerance – is induced by “ Anergy”/”Apoptosis”

T cells - Ag recognition without costimulation (2nd signal)

B cells - Ag recognition without T cell help, blocking of signaling pw

- partial recognition

3) Regulatory T cells

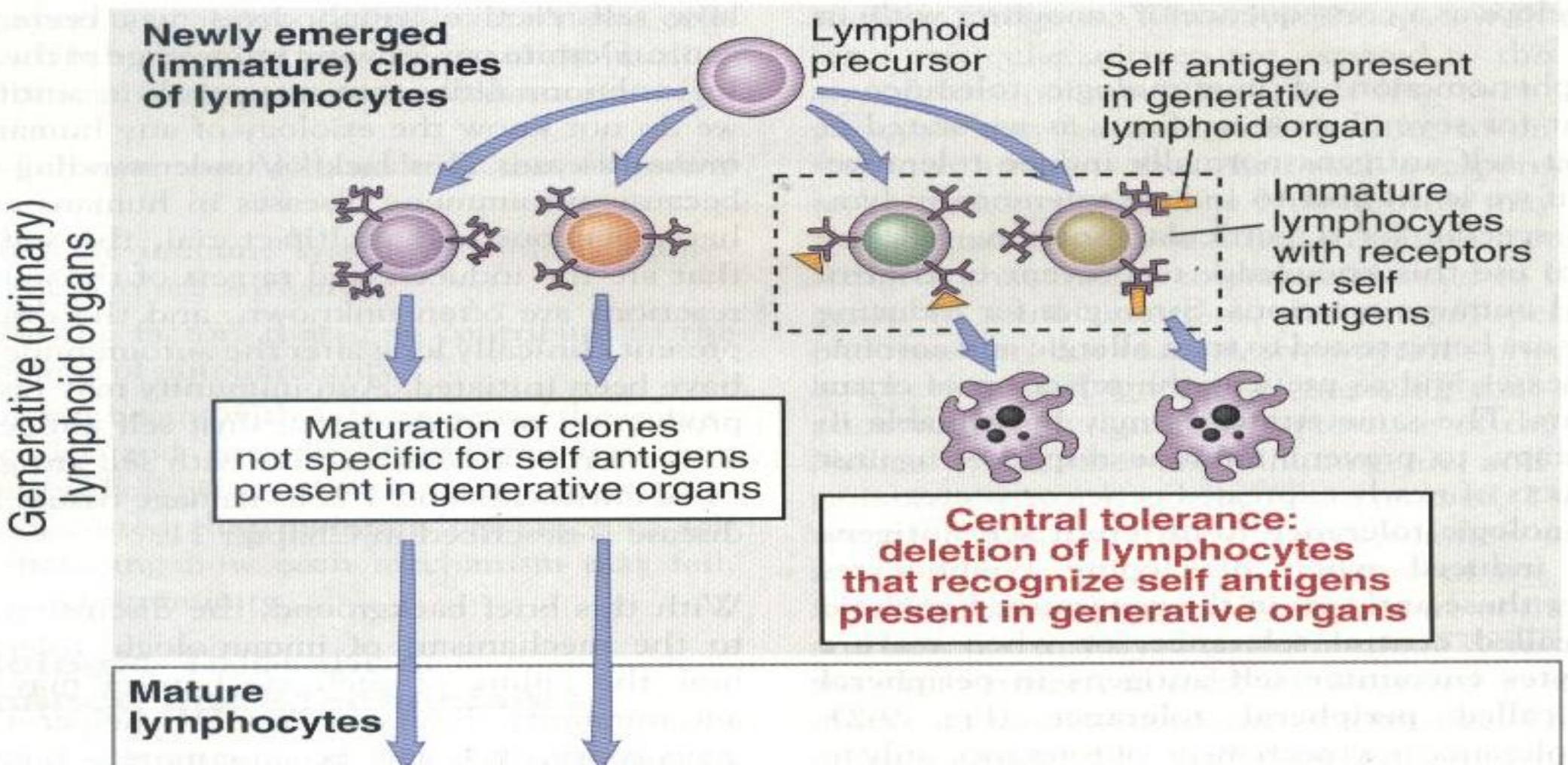
What is central tolerance?

- Process whereby immature T and B cells acquire tolerance to self antigens during maturation in primary lymphoid organs.

- If an immature lymphocyte strongly recognizes and interacts with a self antigen (present in bone marrow and thymus) ---------> dies by a process called apoptosis

  before it can complete its maturation ---**clonal deletion**

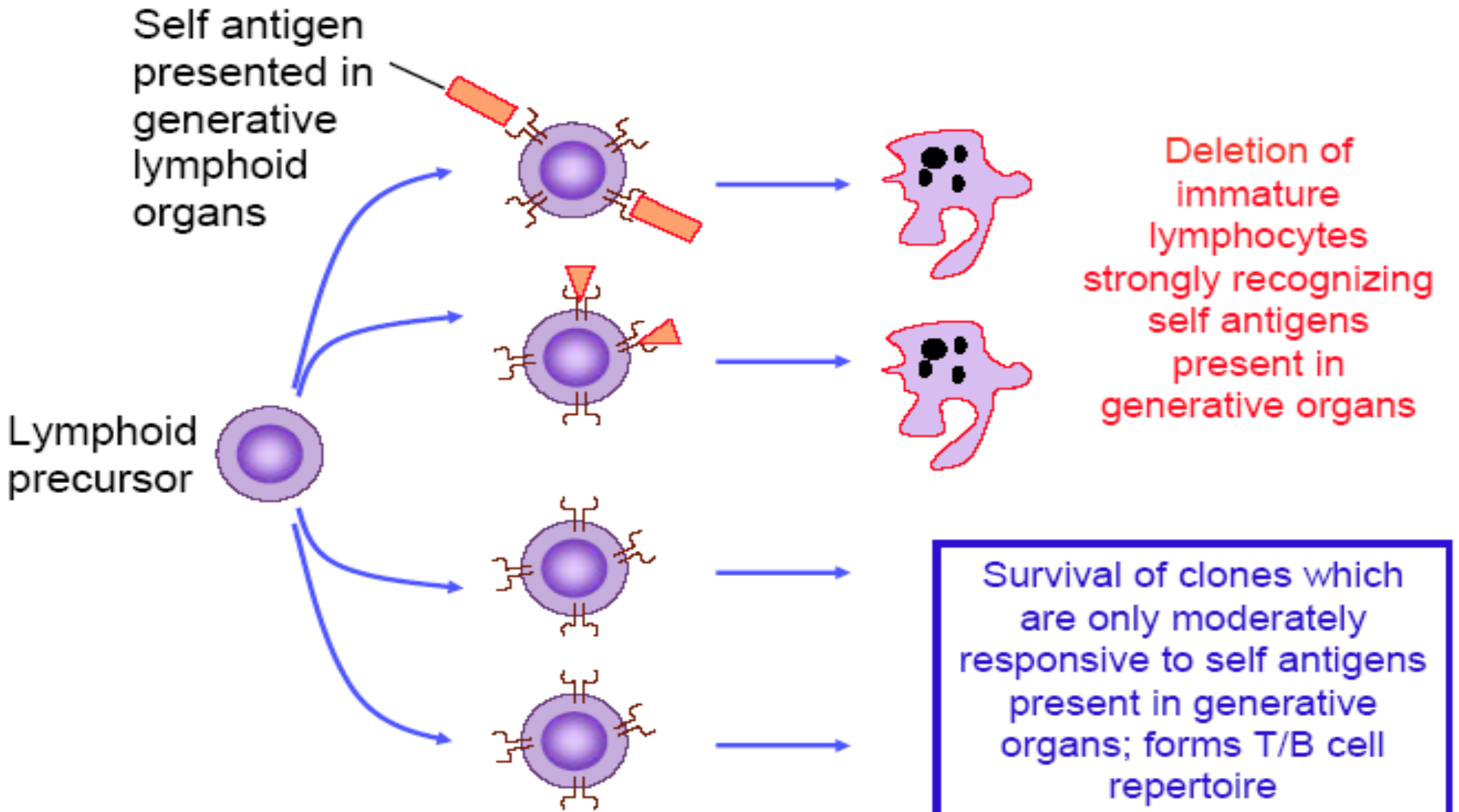
“Negative selection”



lymphocytes that survive negative selection move to peripheral lymphoid organs

Mechanisms of unresponsiveness:

Central tolerance in B and T cells (I): Clonal Deletion



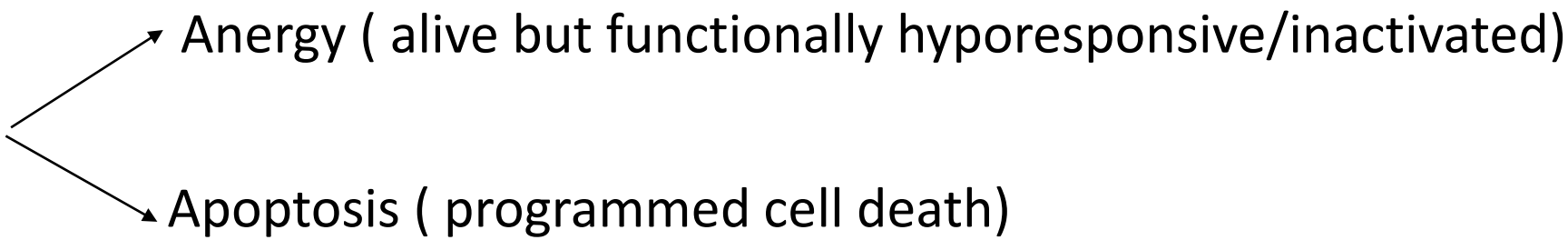
Negative Selection

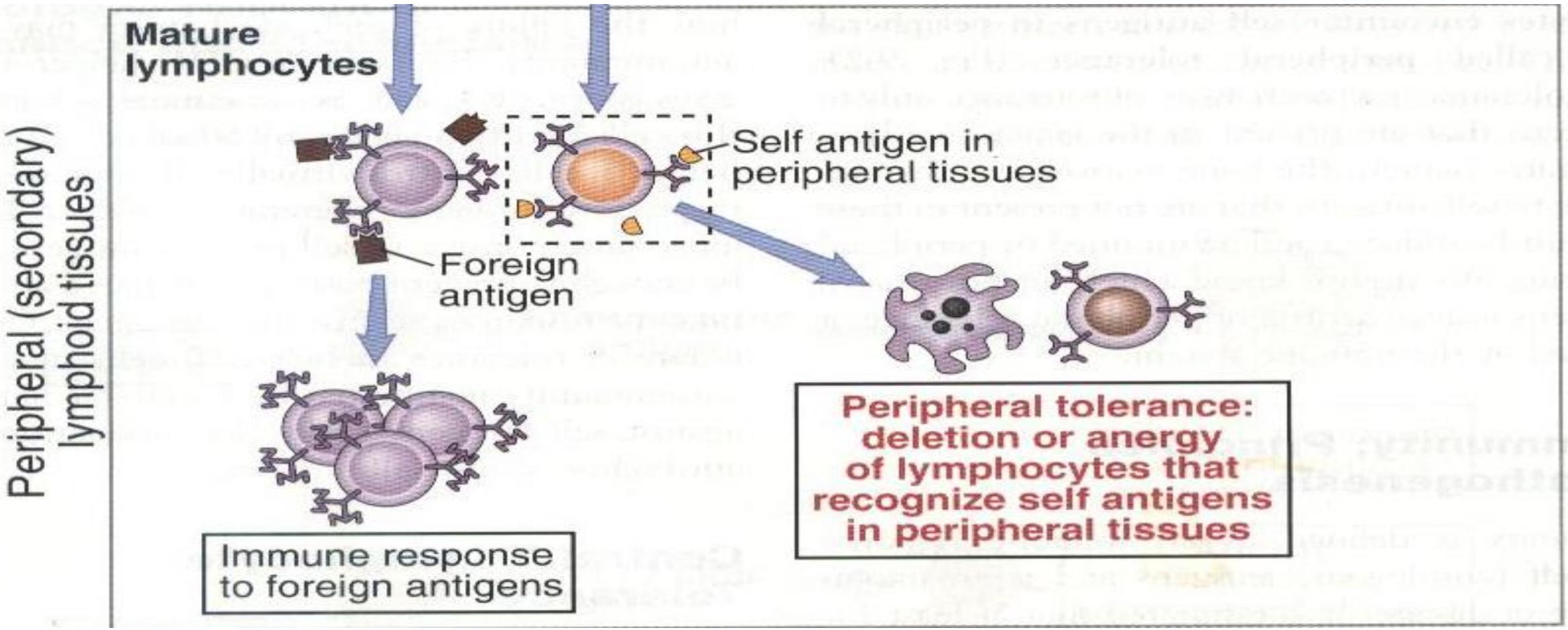
Positive Selection

What is peripheral tolerance?

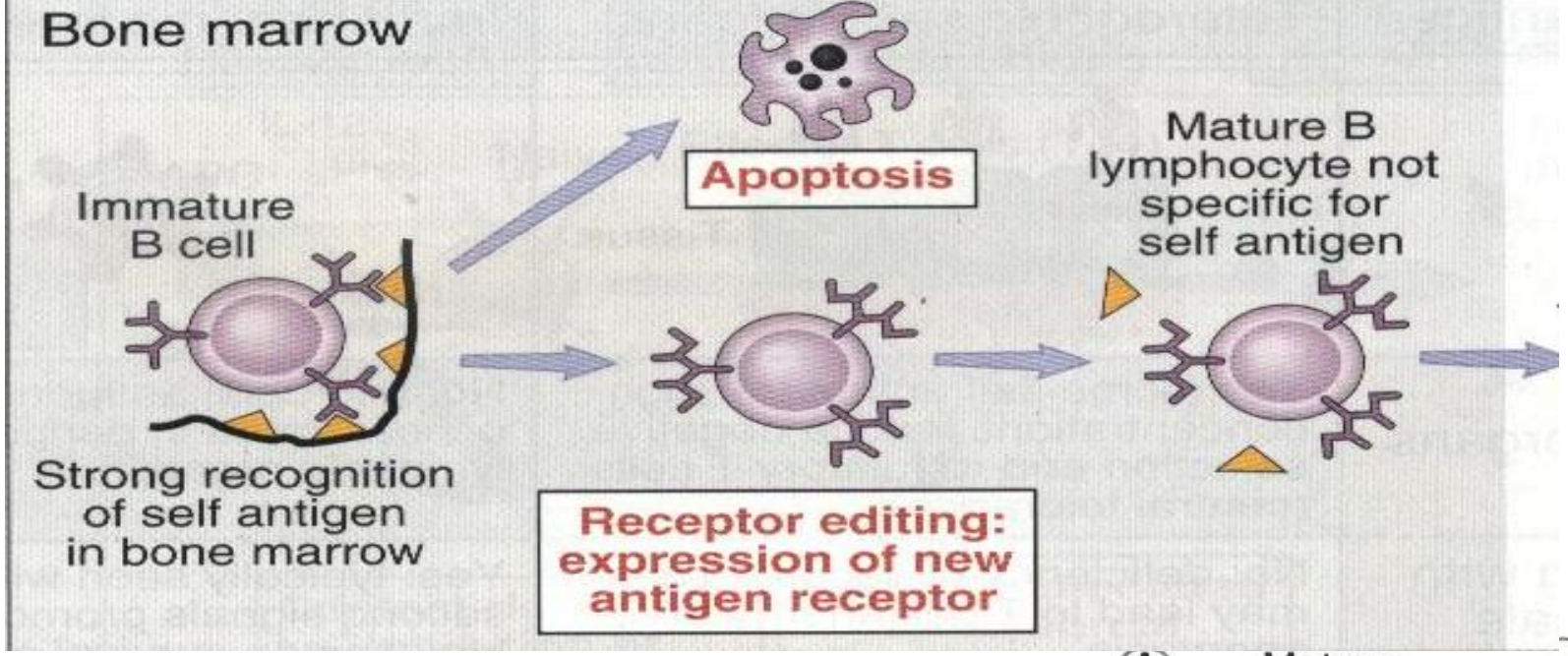
- Process whereby mature T and B cells acquire tolerance to self antigens present in secondary lymphoid organs

- When mature lymphocytes recognize antigens without 2nd signal needed for their full activation

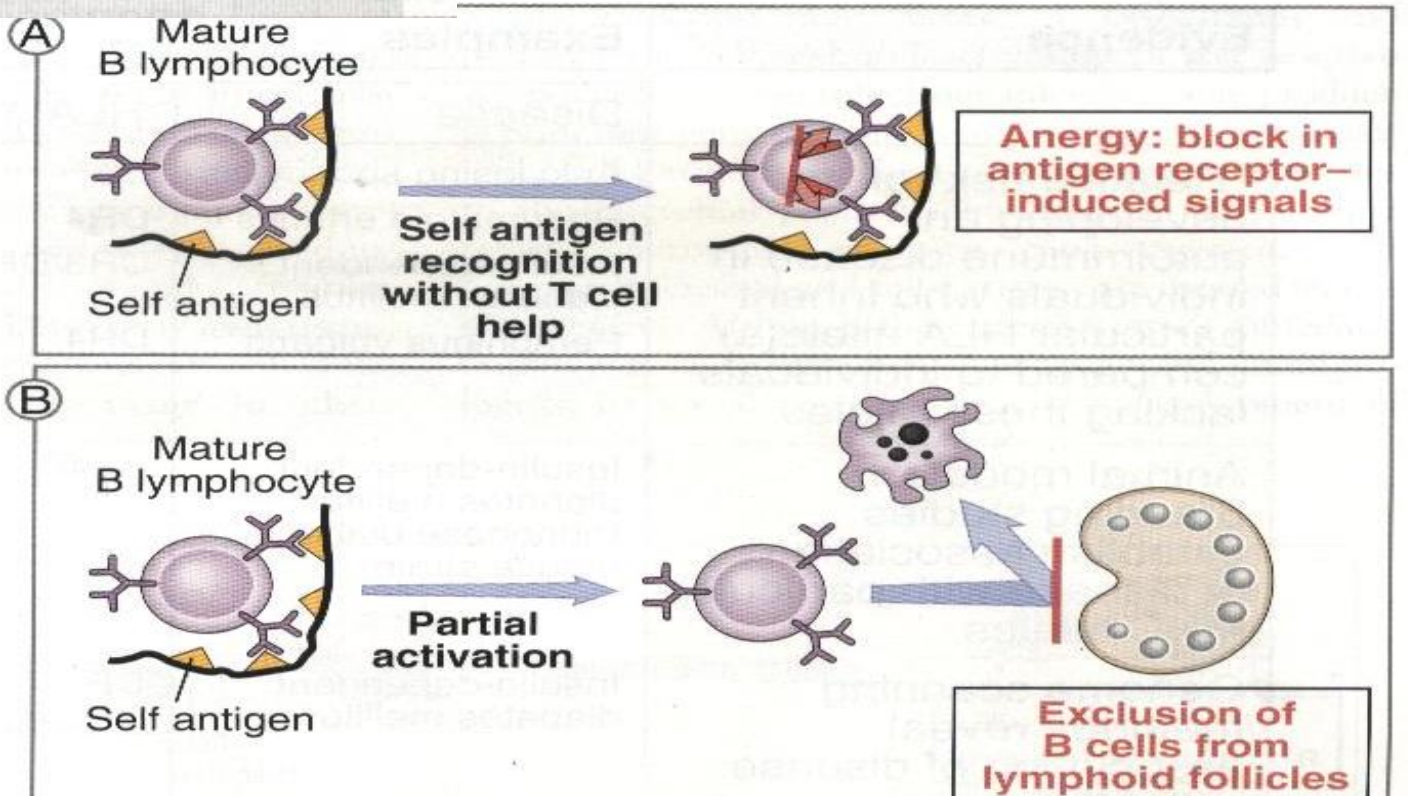



Peripheral (secondary) lymphoid tissues
Mature lymphocytes
Self antigen in peripheral tissues
Foreign antigen
Immune response to foreign antigens
Peripheral tolerance: deletion or anergy of lymphocytes that recognize self antigens in peripheral tissues

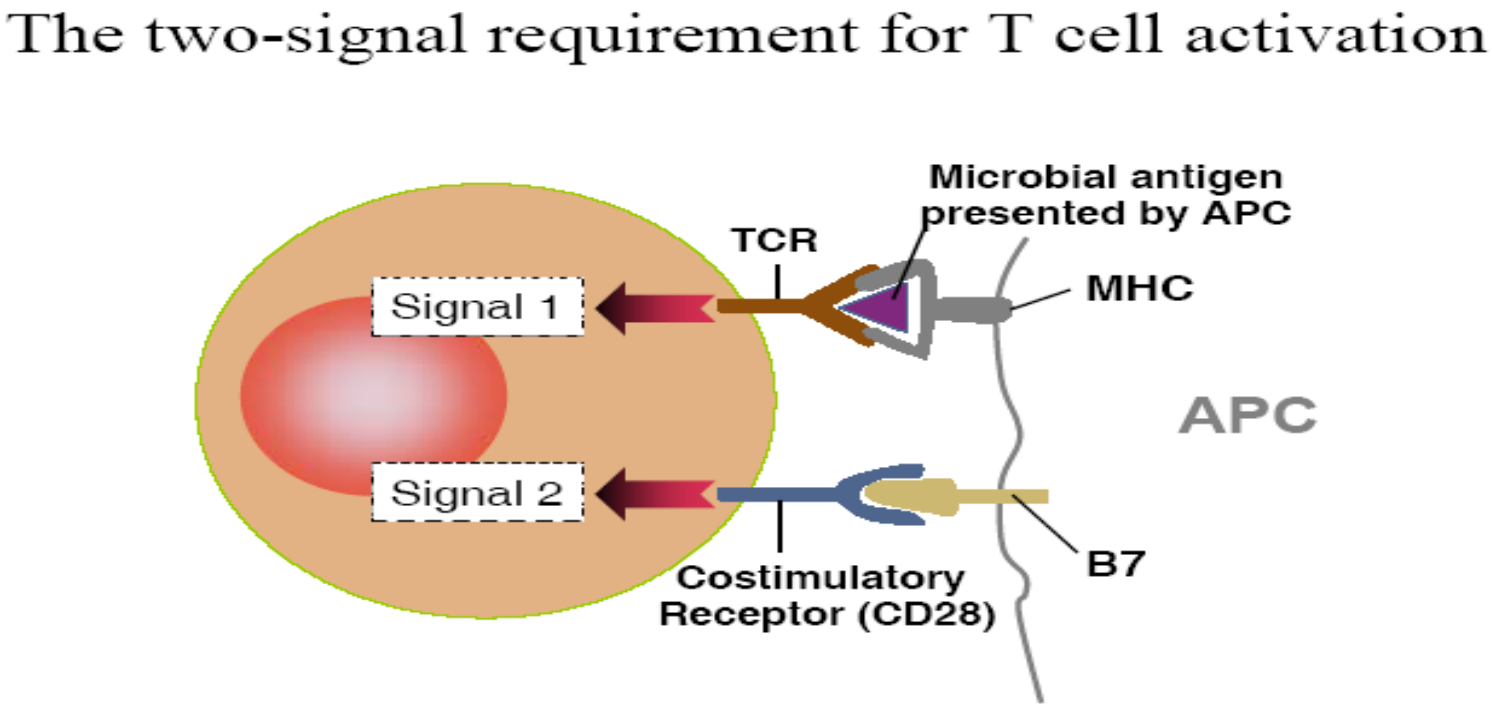
B cell tolerance



peripheral LO



What are the 2 signals required for T cell activation?

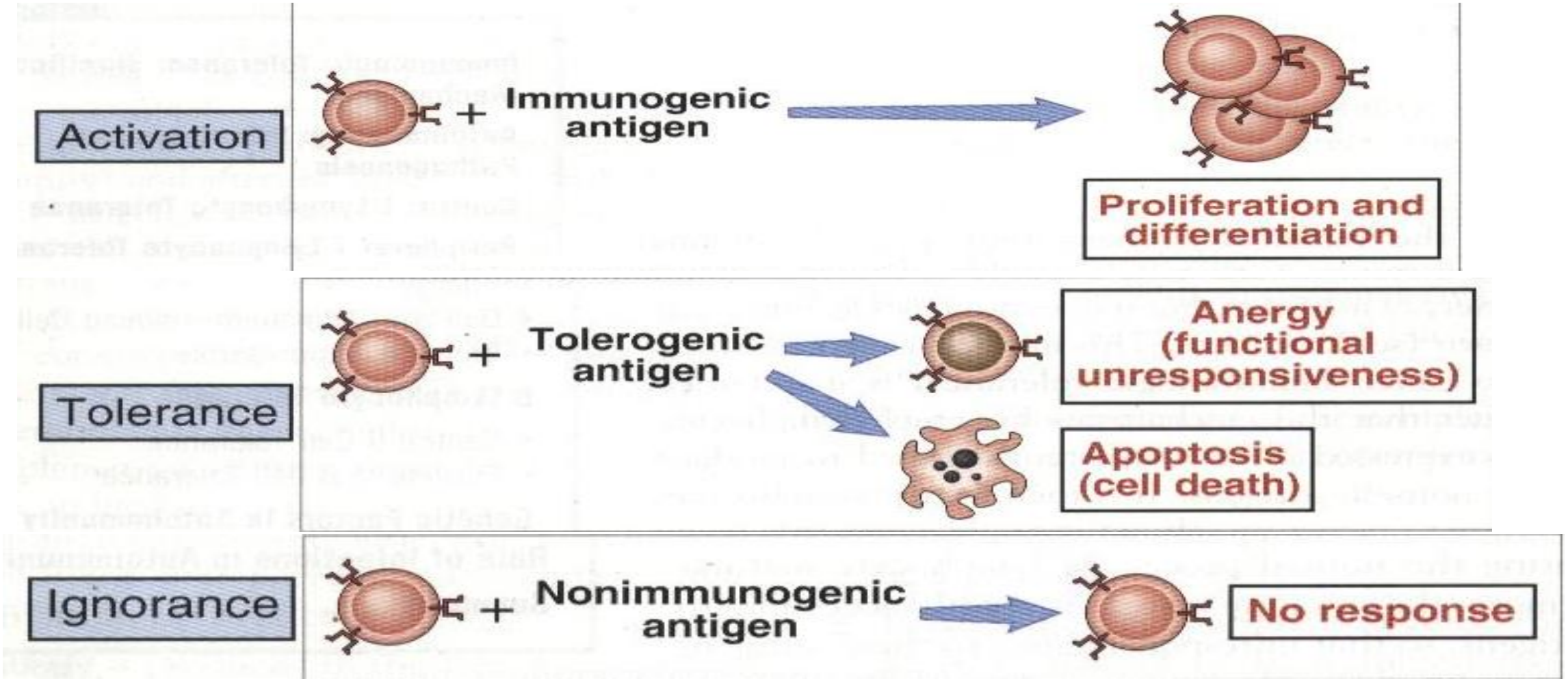


Regulatory T cells

- Some immature T cells that recognize self antigens in thymus develop into regulatory T cells

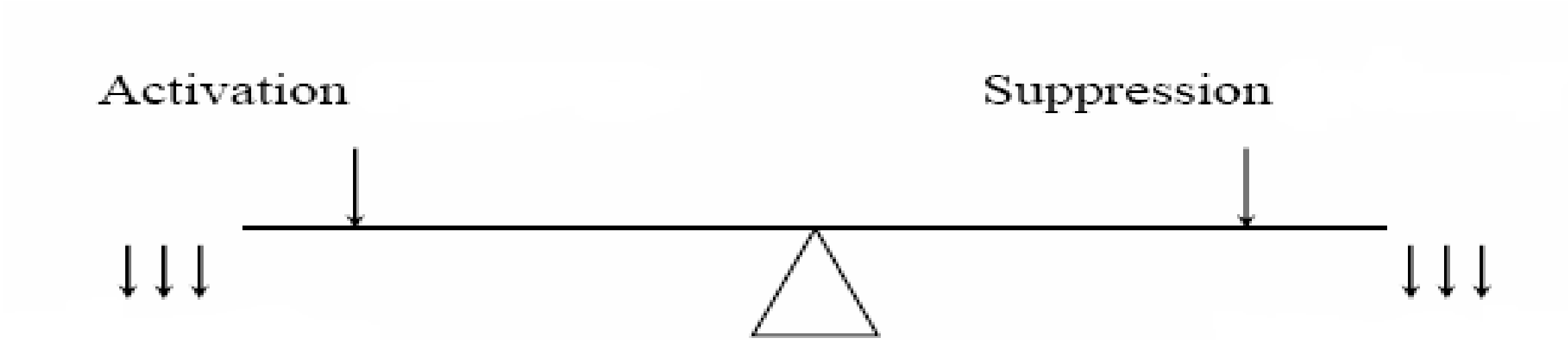
- They enter peripheral tissues and produce cytokines that block the activation of self reactive lymphocytes

Consequences of encounter of lymphocytes with Ags



Artificial Regulatory Mechanisms

Artificial Regulatory Mechanisms (Immune-modulation)



Immuno-potentiaition

Immuno-suppression

Given For –

Prevention of infection

Treatment for infection/ca

Patients with immune deficiency

Given For –

Prevention of graft rejection

Treatment of Autoimmunity

Autoimmunity

Objectives

- Mechanisms of autoimmune diseases
- Mechanisms of breaking of tolerance
- Factors affecting autoimmune diseases

- Organ-specific and non organ-specific AD

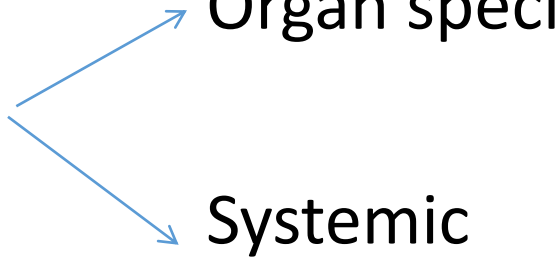
Autoimmunity

- The response of the adaptive immune system to self antigens that occurs when mechanisms of self tolerance fails.

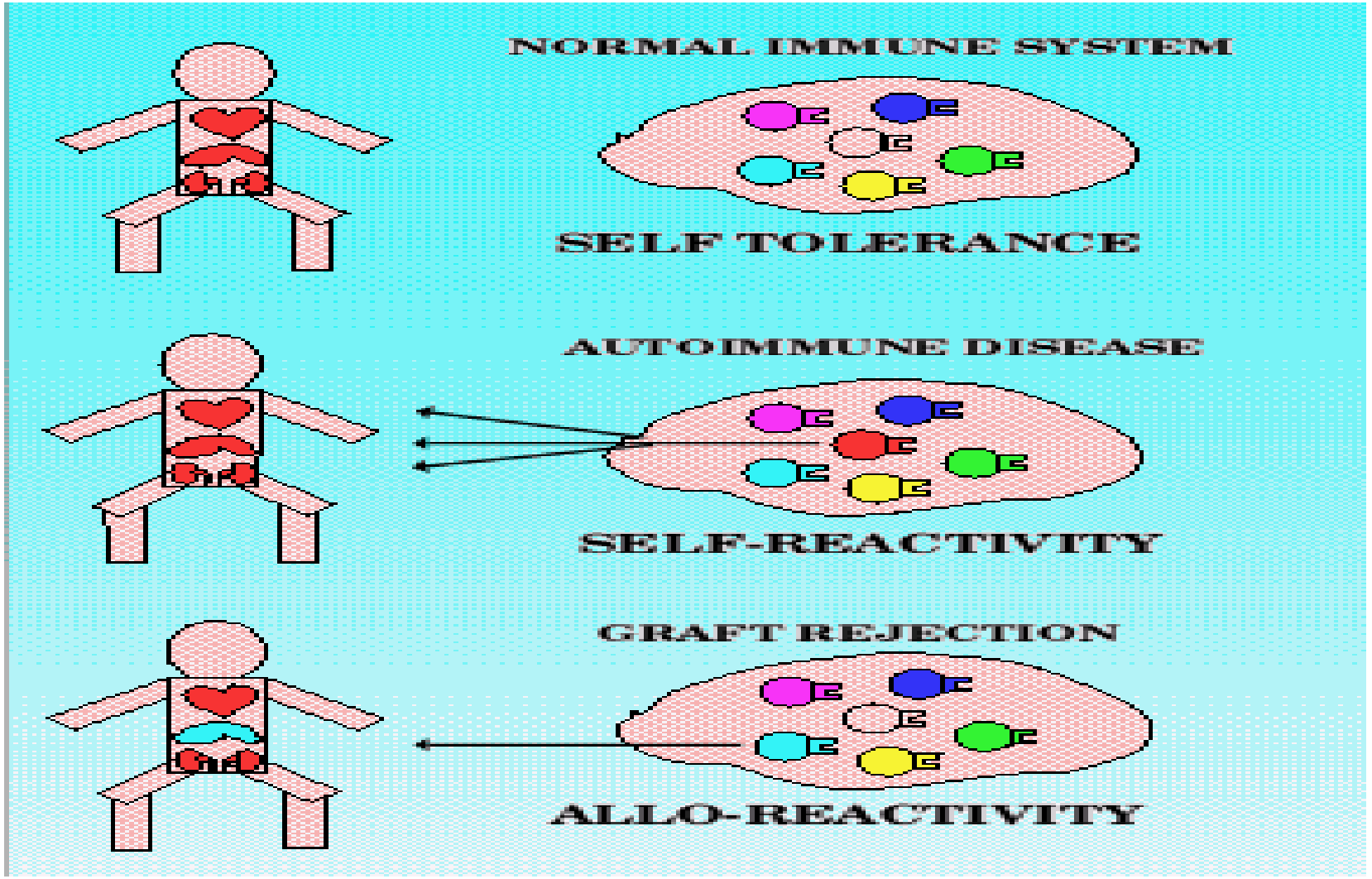
"acquired immune reactivity to self antigens"

Autoimmune disease

- Autoimmune response → tissue damage -----> disease



Autoimmunity



Mechanisms of autoimmune diseases

- Immunological autoreactivity
- Defective mechanisms of immunological tolerance (unresponsiveness to self antigens)

Immunological Auto-reactivity

- Auto-reactive T cells
- Auto-antibodies

Mechanisms of Immunological Autoreactivity

- Polyclonal activation by microbial Ags
  - EBV, endotoxin
- Availability of normally sequestered self antigens
  - Lens of eyes, thyroid, testes
- Dysregulation of idiotype network – SDL

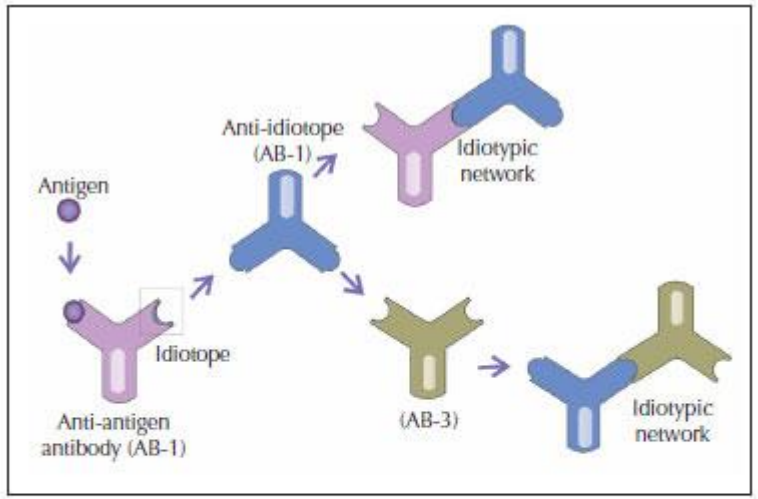


Figure 5
Schematic representation of the idiotypic network. The domain formed by hypervariable regions of the immunoglobulin molecule (AB-1) characterizes the antigenic specificity of a given antibody, which is known as idiotope. Each idiotope is, in turn, recognized by an anti-idiotope antibody (AB-2), therefore forming an idiotype recognition network.

- Immunological autoreactivity alone is not sufficient for the development of the disease

- **Defects in mechanisms of tolerance play an important role.**

Mechanisms of tolerance

1)Central toerance

2) Peripheral tolerance

3) Regulatory T cells (formerly called suppressor T cells)

MECHANISMS OF BREAKING OF SELF-TOLERANCE

- Infections
  - Molecular mimicry
    - Eg. Cross reactive Ags b/w heart muscle and grp. A Strep leads to rheumatic fever
  - Disruption of cell or tissue barrier
  - Infection of antigen presenting cell
  - Modification of cell surface by microbes
  - Superantigen
- Failure of negative selection
- Presence of self reactive T cells
  - Extrathymic T cell development

Infections Break Tolerance

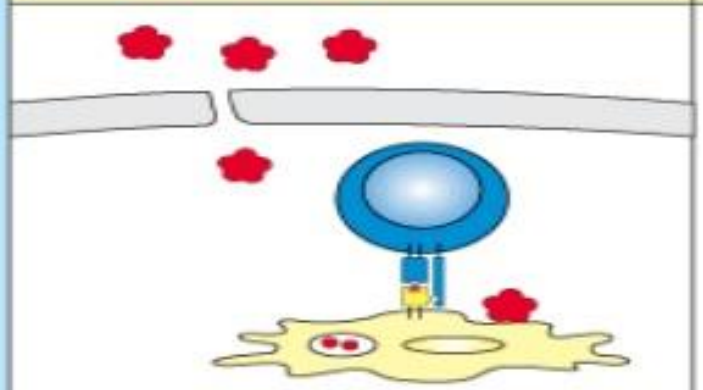
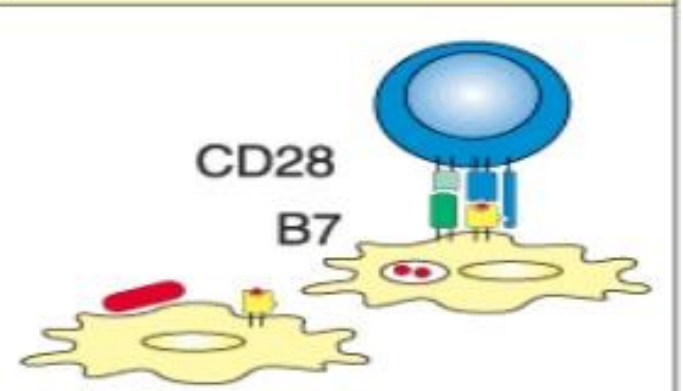
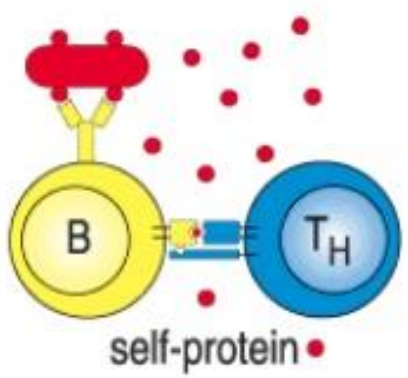
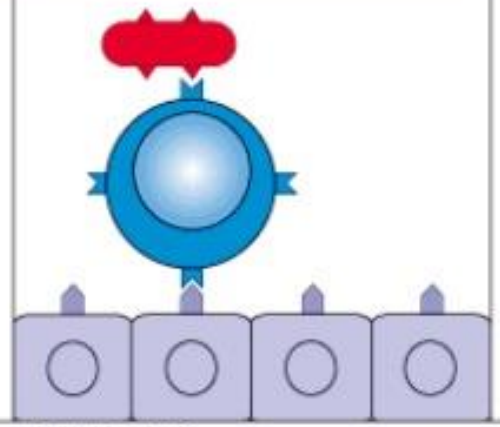
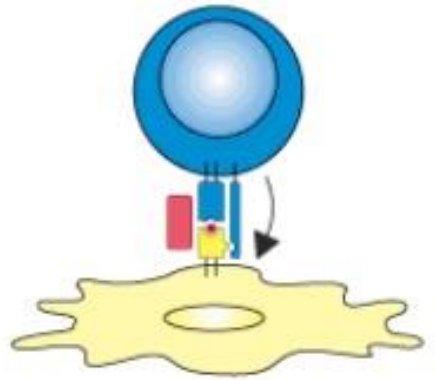
Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell
Effect	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells
Example	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE
		

Fig 13.42 part 1 of 2

Infections Break Tolerance

Mechanism	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
			

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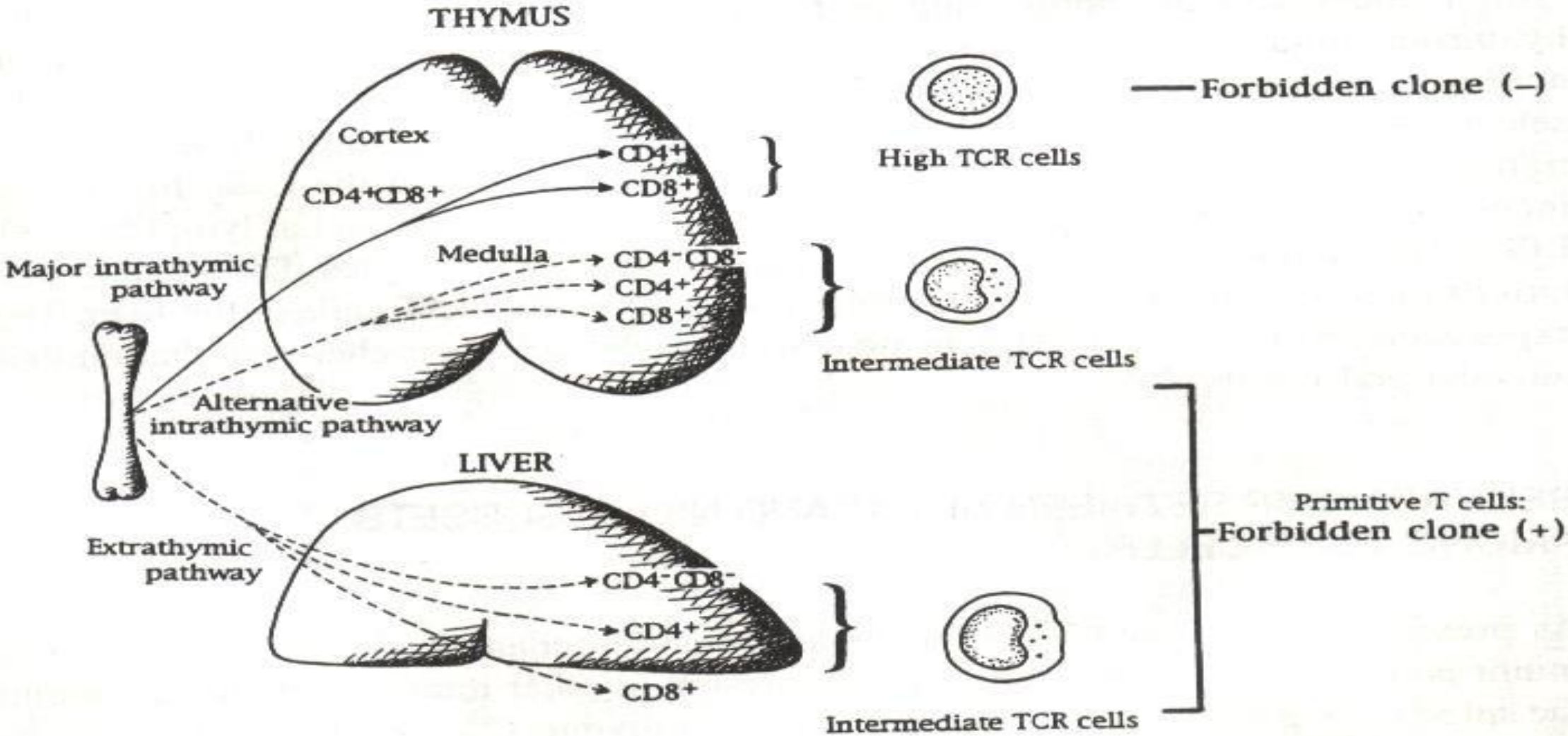

Figure 4.4. Pathways of T cell differentiation. There is a major pathway of T cell differentiation in the thymus, which produce TCR^{high} cells (i.e., the mainstream in the thymus). TCR^{int} cells (i.e., primitive or primordial T cells) are generated by the primordial pathways in the liver and thymic medulla. The primordial pathway in the thymus (mainly in the thymic medulla) is also referred to as an alternative intrathymic pathway of T cell differentiation.

Effector mechanisms in the pathogenesis of autoimmune diseases

- Autoantibodies directly mediate cell destruction
  - Eg; AIHA and ITP, haemolytic disease of new borne
- Autoantibodies modulate function
  - Eg; Myasthenia gravis, Graves
- Autoantibodies form immune-complexes
  - Eg; SLE
- Cell-mediated destruction
  - Eg; Type I diabetes mellitus

Other factors contributing to development of autoimmune diseases

- Age – higher incidence in aged population
- Gender – women have a greater risk than men
- Immunodeficiency – complement and IgA
- Genetic – HLA
    - Eg. HLA -DR3 in SLE
- Environmental

OTHER FACTORS FAVORING AUTOIMMUNITY

1. Overproduction and/or dysregulation of cytokines
2. Disturbances of apoptosis
3. Pre-existing defects in the target organ
4. Direct stimulation of autoreactive cells by foreign antigen

Examples of organ specific and systemic autoimmune diseases

Organ-specific

- Hashimoto thyroiditis
- Thyrotoxicosis
- Addison's disease
- Atrophic gastritis
- Juvenile diabetes mellitus
- Multiple sclerosis
- Guillain Barre synd
- Grave's dis.

Systemic

- Systemic lupus (SLE)
- Rheumatoid arthritis (RA)
- Scleroderma
- Dermatomyositis
- Mixed connective tissue disease (MCTD)
- Sjögren's syndrome

Summary

- What is immune regulation?
- Why we need it?
- What are the mechanisms of immune regulation?
- What is central tolerance?
- What is peripheral tolerance?

Any Questions?

Thank you