Immunology-10

Immunological Tolerance
and
Autoimmunity

Immunological Tolerance: Importance and Mechanisms

- One of the most distinctive features of a healthy immune system is that while it responds to many microbes, the individual does not respond to self-antigens.
- Immunological tolerance can be defined as the non-response of lymphocytes that encounter antigen.

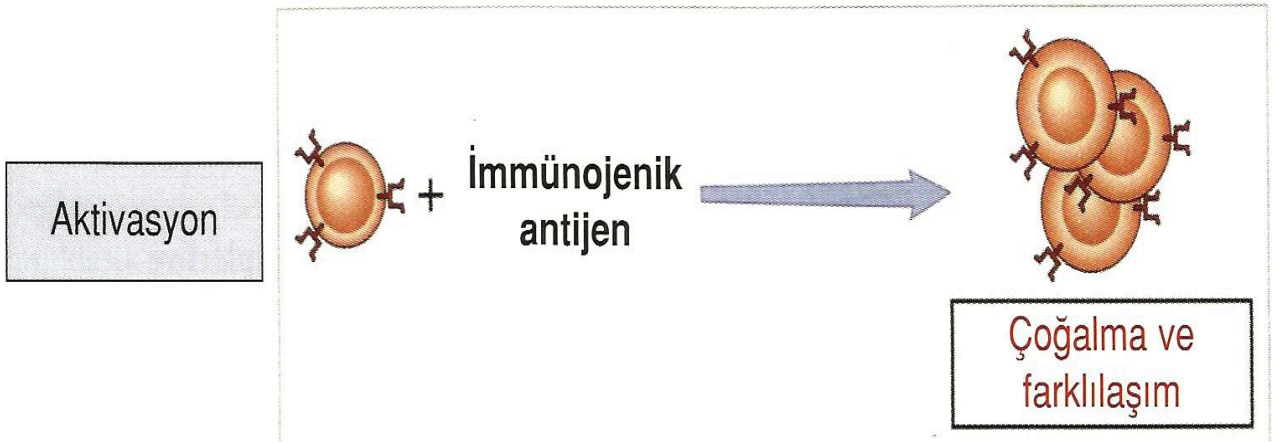
• Immunological tolerance is responsible for distinguishing between self and non-self foreign antigens, which is one of the basic features of the immune system.

• If these mechanisms fail, the immune system may attack the individual's own cells and tissues. Such responses are called "autoimmunity" and the disease they cause is called "autoimmune diseases".

Immunological Tolerance: Importance and Mechanisms

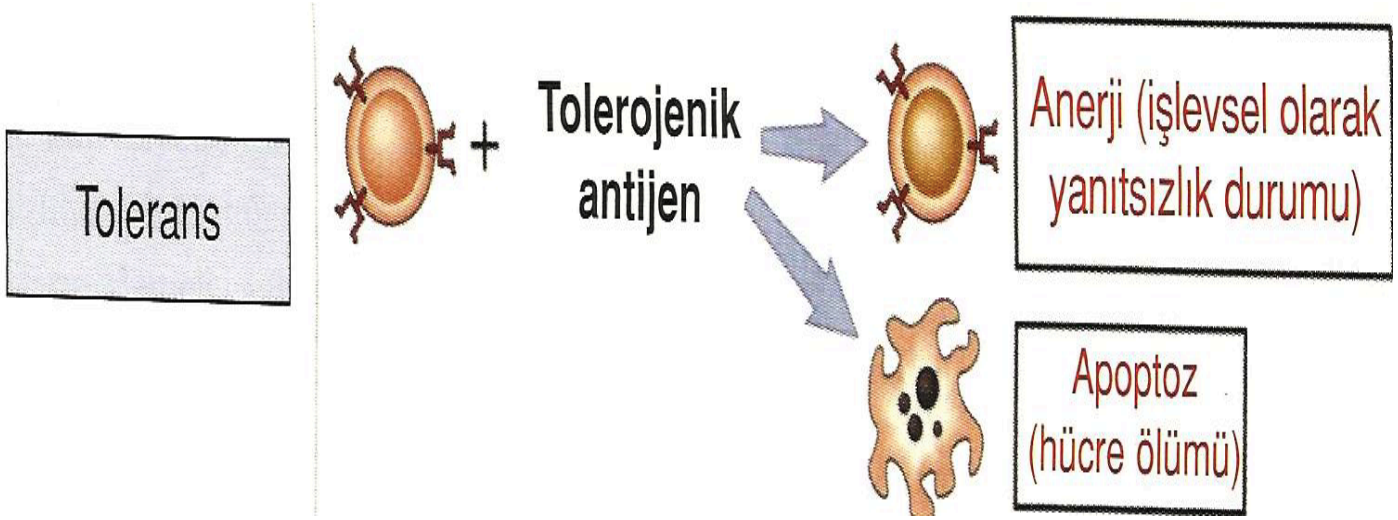
When a lymphocyte with an antigen-specific receptor encounters that antigen, any of three possibilities can develop;

1- Lymphocyte becomes effective and immune response develops; The antigen that elicits such a response is defined as **immunogenic.**



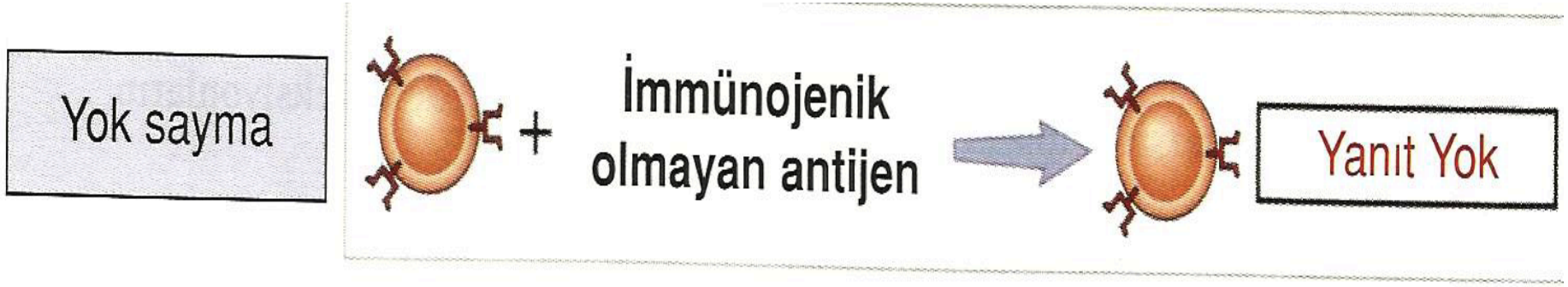
Immunological Tolerance: Importance and Mechanisms

2- Lymphocytes are functionally inactivated or killed, resulting in tolerance to that antigen; The antigen that causes this type of response is defined as **tolerogenic.**



Immunological Tolerance: Importance and Mechanisms

3- In some cases, antigen-specific lymphocytes do not show in the above two cases and **ignore the antigen.**



Immunological Tolerance: Importance and Mechanisms

- Under normal conditions, microorganisms are **immunogenic** and our own antigens are **tolerogenic**, or they are **ignored**.

Activation, tolerance or ignore response;

1. antigen-specific lymphocyte type,

2. the structure of the antigen,

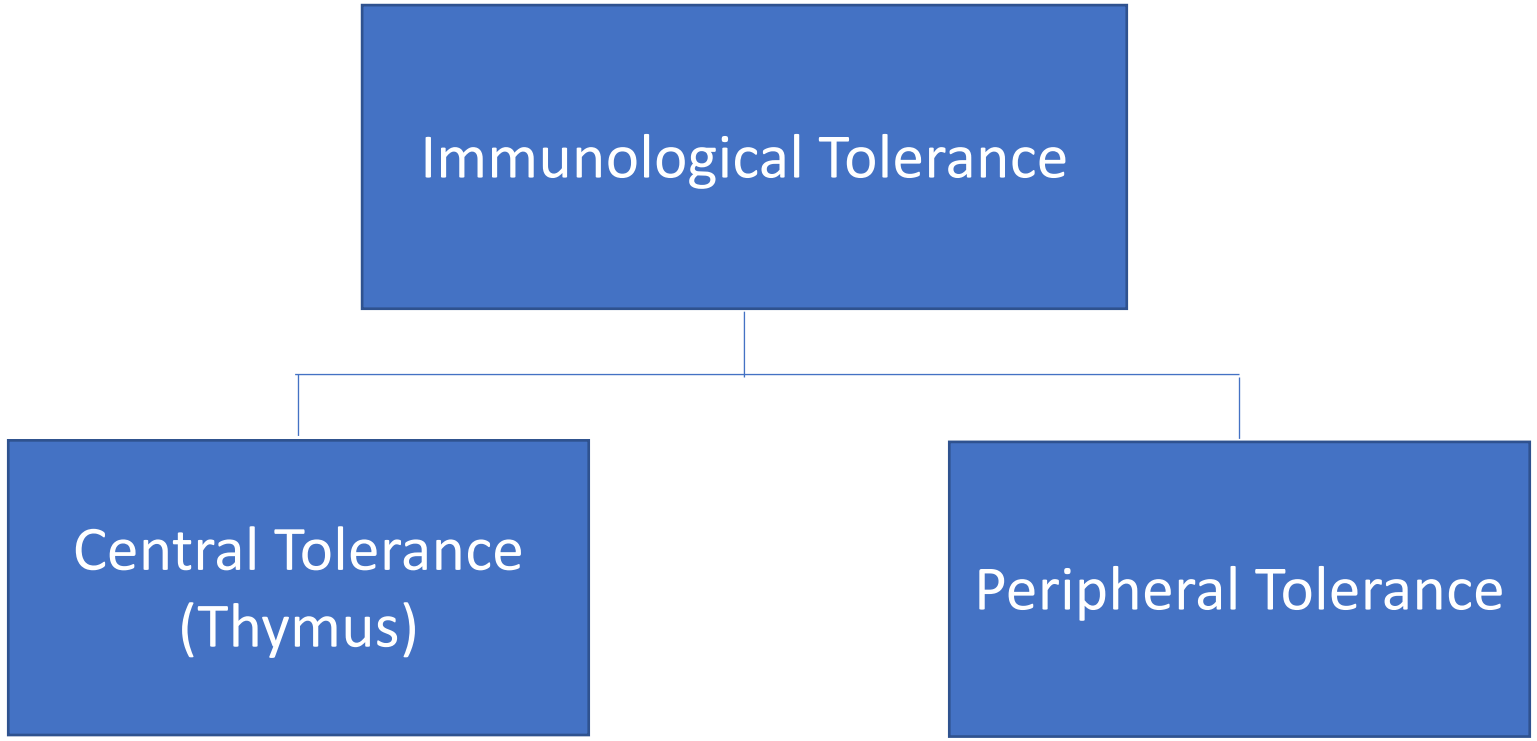
3. It depends on how it is presented to the immune system.

Immunological Tolerance: Importance and Mechanisms

- **The immunological tolerance phenomenon is very important for many reasons.**

❖Self antigens normally initiate tolerance.

❖If we can **learn about the conditions that allow lymphocytes to tolerate a particular antigen**, we can use this knowledge to prevent or control unwanted immune responses.


Immunological Tolerance
Central Tolerance (Thymus)
Peripheral Tolerance

Immunological tolerance

Central tolerance

Thymus

- T-cells
  - Deletion
  - T-regs

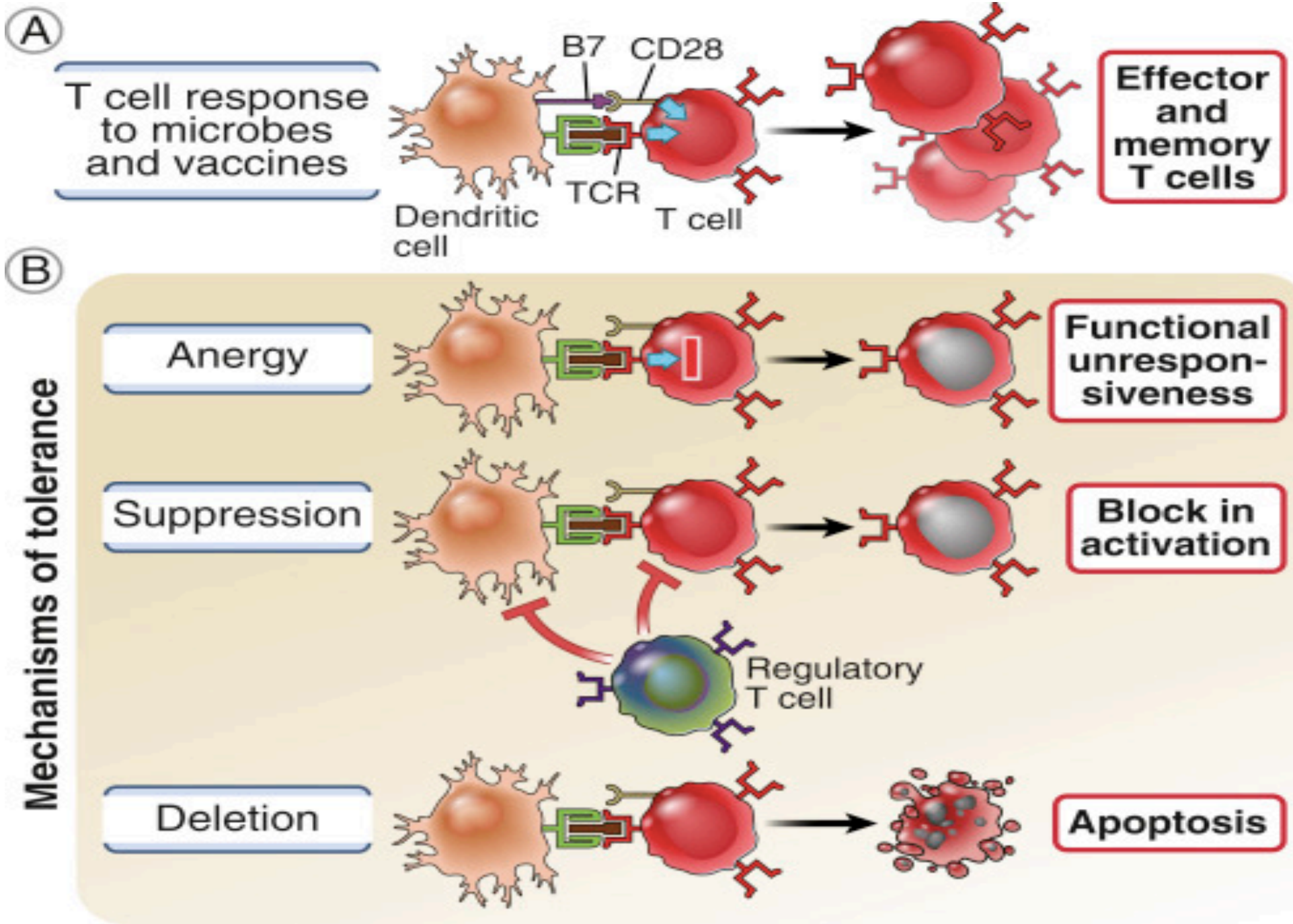
Bone marrow

- B-cells
  - Receptor editing
  - Deletion

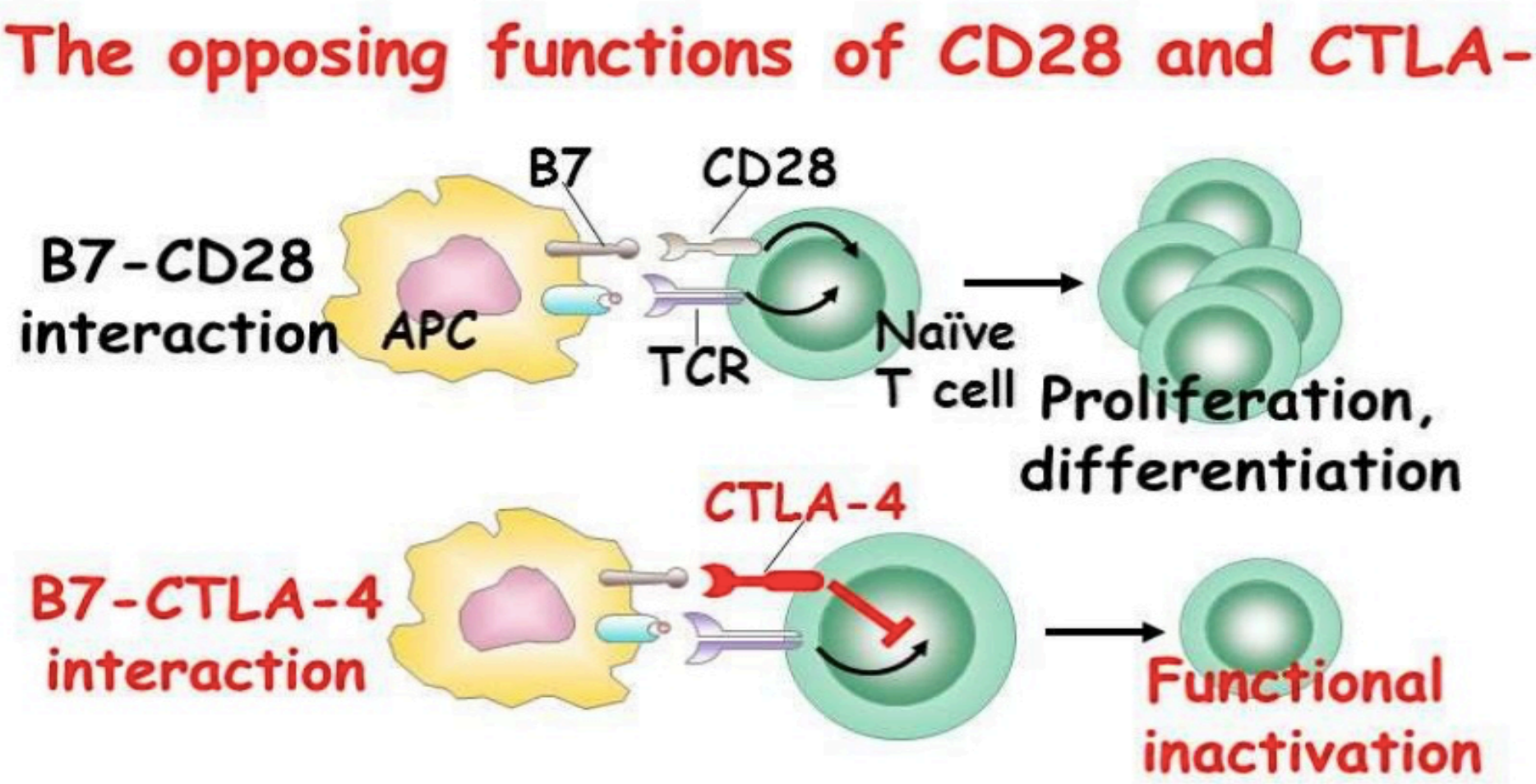
Peripheral tolerance

- Anergy "unresponsiveness"
- Apoptosis
- immunosuppression via
  - T-regulatory cells
  - B-regulatory cells

→ Elimination of self-reactive cells!


A
T cell response to microbes and vaccines
B7
CD28
TCR
Dendritic cell
T cell
Effector and memory T cells
B
Mechanisms of tolerance
Anergy
Functional unrespon-siveness
Suppression
Block in activation
Regulatory T cell
Deletion
Apoptosis

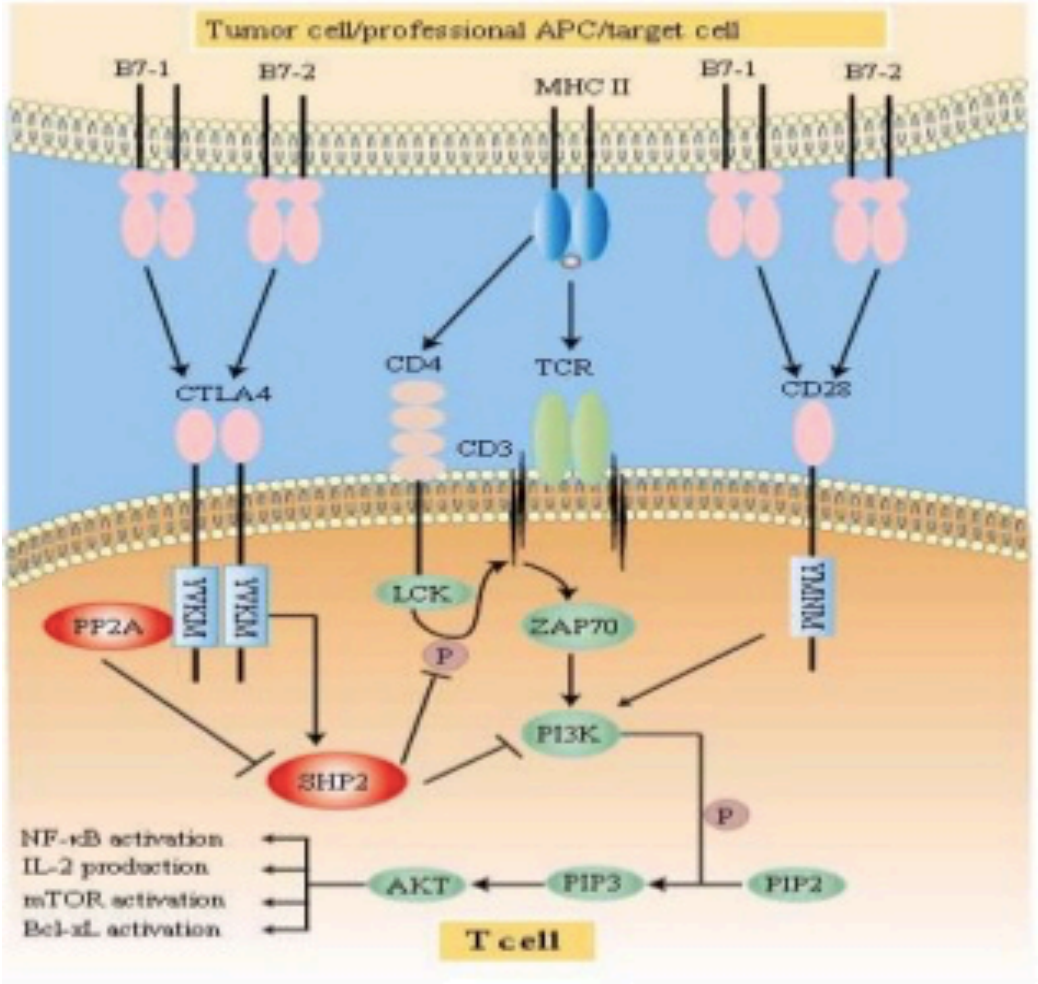
B7 Ligands May Be Activator and Inhibitor



CTLA-4 Regulates T Cell Activation

- B7 interaction with CTLA-4;
- **Prevents CD28 from activating downstream signaling pathways**,
- It causes an increase in intracellular IDO enzyme levels and prevents the production of tryptophan, which is necessary for cell growth,
- Increases the release of TGF-B, which has immunosuppressive properties.

CTLA-4 is a Negative Regulator of T Cells



- When CTLA-4 binds with B7 ligands at the cell membrane, it suppresses MHC-TCR-mediated pathways.

- After all;

✓ IL-2 production,
✓ cellular proliferation,
✓ Immune activity is suppressed.
✓ Apoptosis can also be triggered.

Immunological Tolerance: Importance and Mechanisms

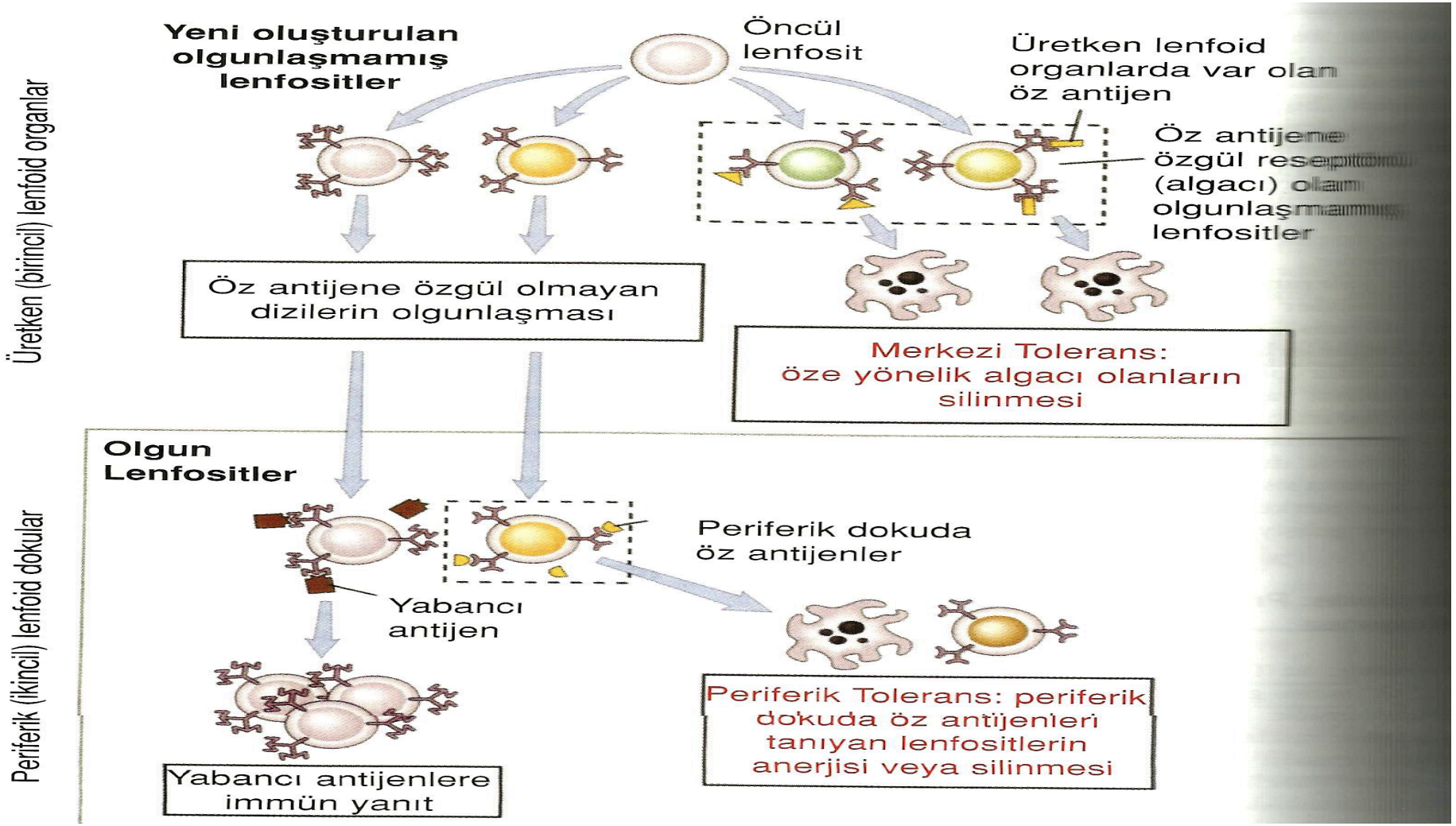
- Immune tolerance can be **achieved with different self-antigens while more lymphocytes are forming in the organs (central tolerance)**, or it can occur as a result of the encounter of mature lymphocytes with self-antigens in peripheral lymphoid organs (peripheral tolerance)

Immunological Tolerance: Importance and Mechanisms

- **Central tolerance** is the mechanism of tolerance only to self-antigens in the bone marrow and thymus, which is responsible for lymphocyte production.

- **Peripheral tolerance;** Tolerance occurs when mature T lymphocytes recognize self-antigens not present (or presented) in the thymus from the periphery.

Immunological Tolerance: Importance and Mechanisms



Primary and Secondary Lymphoid Organs

Primary Lymphoid Organs

- Also called "central lymphoid organs"
- It is where immature lymphocytes develop
- Organs where differentiation, proliferation and maturation of stem cells into immuno competent cells take place.

Includes:

- Thymus
- Bone Marrow

Secondary Lymphoid Organs

- It is where antigen is localized so that it can be effectively exposed to mature lymphocytes.
- initiate adaptive immune response.

Includes:

- Spleen
- Lymph Nodes
- Tonsils
- Appendix
- Peyer's patches

PRIMARY LYMPHOID ORGANS VERSUS SECONDARY LYMPHOID ORGANS

PRIMARY LYMPHOID ORGANS	SECONDARY LYMPHOID ORGANS
Organs of the immune system where lymphocytes are formed and mature	Organs of the immune system which maintain mature naive lymphocytes and initiate an adaptive immune response
Allow lymphoid stem cells to proliferate, differentiate, and mature	Allow lymphoid cells to become functional
Contain either T cells or B cells	Contain both T cells and B cells
Have no contact with antigens	Have contact with antigens
Undergo atrophy with age	Increase size with age

Autoimmunity:
Principles and Pathogenesis

Autoimmunity: Principles and Pathogenesis

- Autoimmunity is the development of an immune activation response to self-antigens and is an important cause of disease.

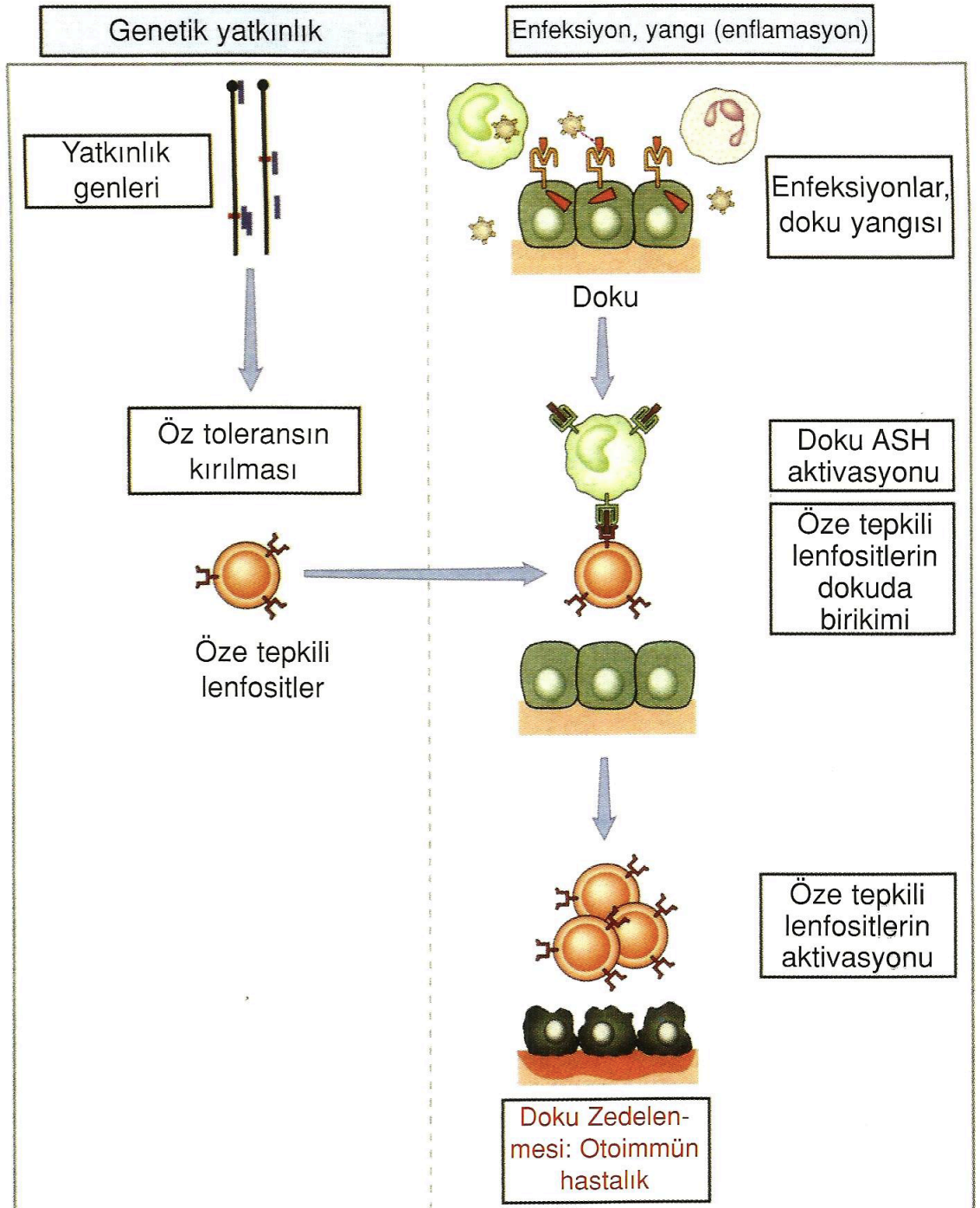
- It is estimated that autoimmune diseases are encountered at a rate of 1-2% in the society.

Autoimmunity: Principles and Pathogenesis

- The main factors in the development of autoimmunity; inheritance of susceptibility genes that may contribute to the lack of self-tolerance, and environmental triggers such as infection that activate autoimmune lymphocytes.

Autoimmunity: Principles and Pathogenesis

- Immunological tolerance has primarily been identified in helper T cells (CD4+).
- If CD4+ T cells are rendered unresponsive to self-antigens, it will be possible to inhibit both cellular and humoral immune responses against antigens.
- Conversely, in case of loss of tolerance in helper T cells, autoimmunity may develop, T cell mediated attack on self antigen or autoimmunity may occur as a result of autoantibodies against self proteins.



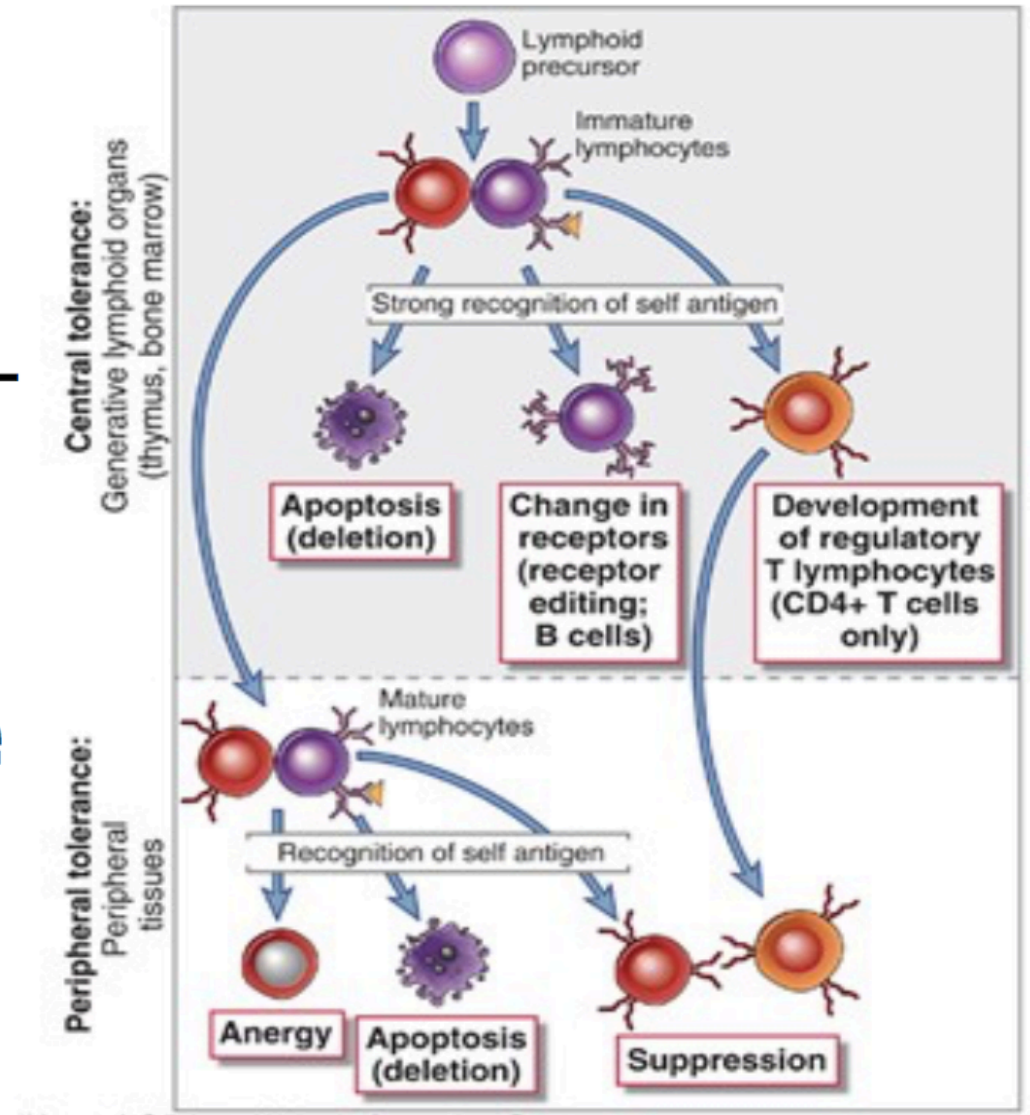
- Many genetic regions that affect the maintenance of self-tolerance may predispose to autoimmunity.

- Environmental triggers such as infections and inflammatory stimuli may be responsible for the accumulation of lymphocytes in the region and the activation of self-responsive T cells and the occurrence of tissue damage.

Self tolerance

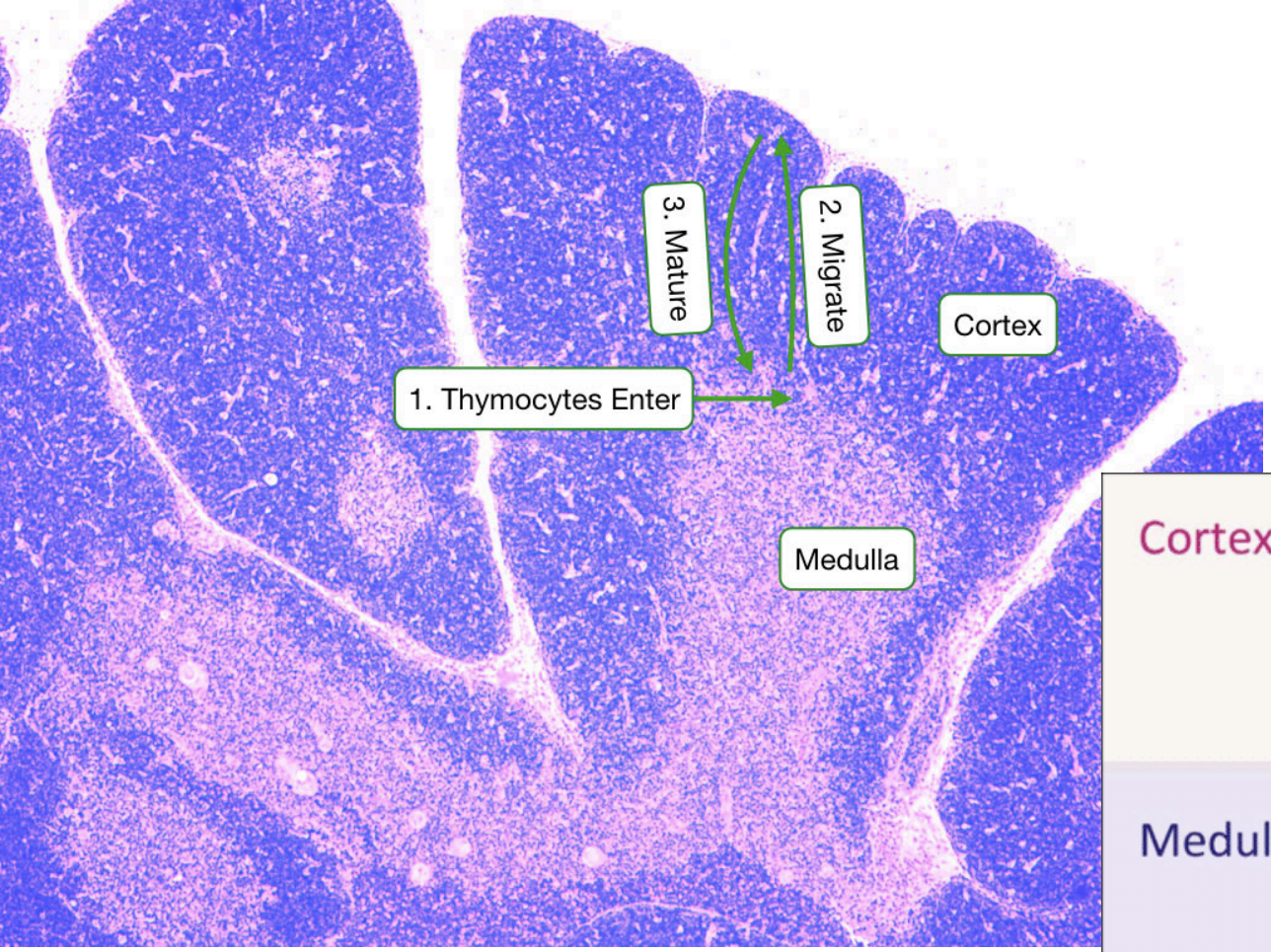
- **Central tolerance**
  - Negative selection
  - Receptor editing
  - Generation of regulatory T cells

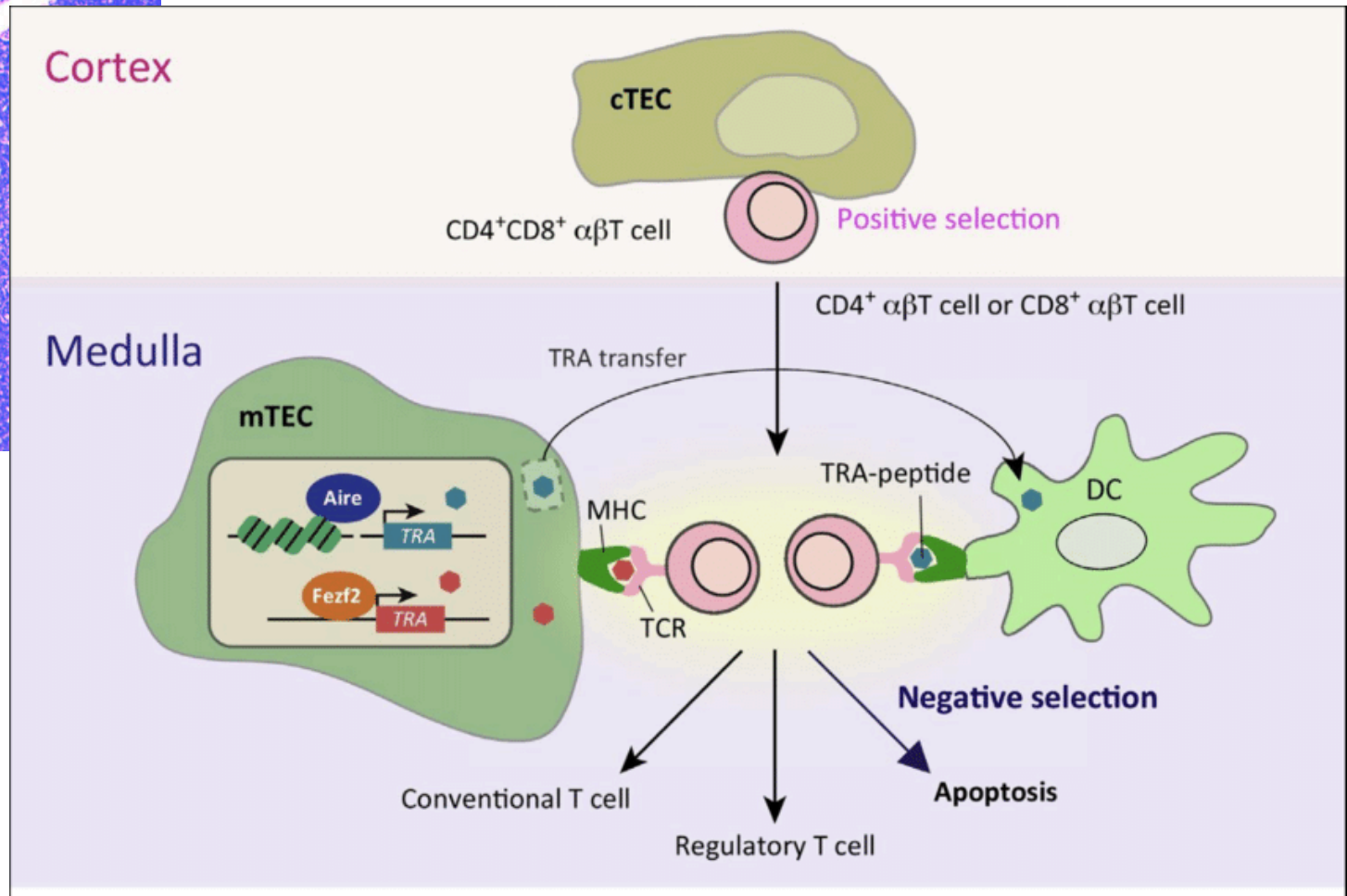
- **Peripheral tolerance**
  - Clonal anergy
  - Clonal deletion
  - Regulatory T cells
  - T-T interaction



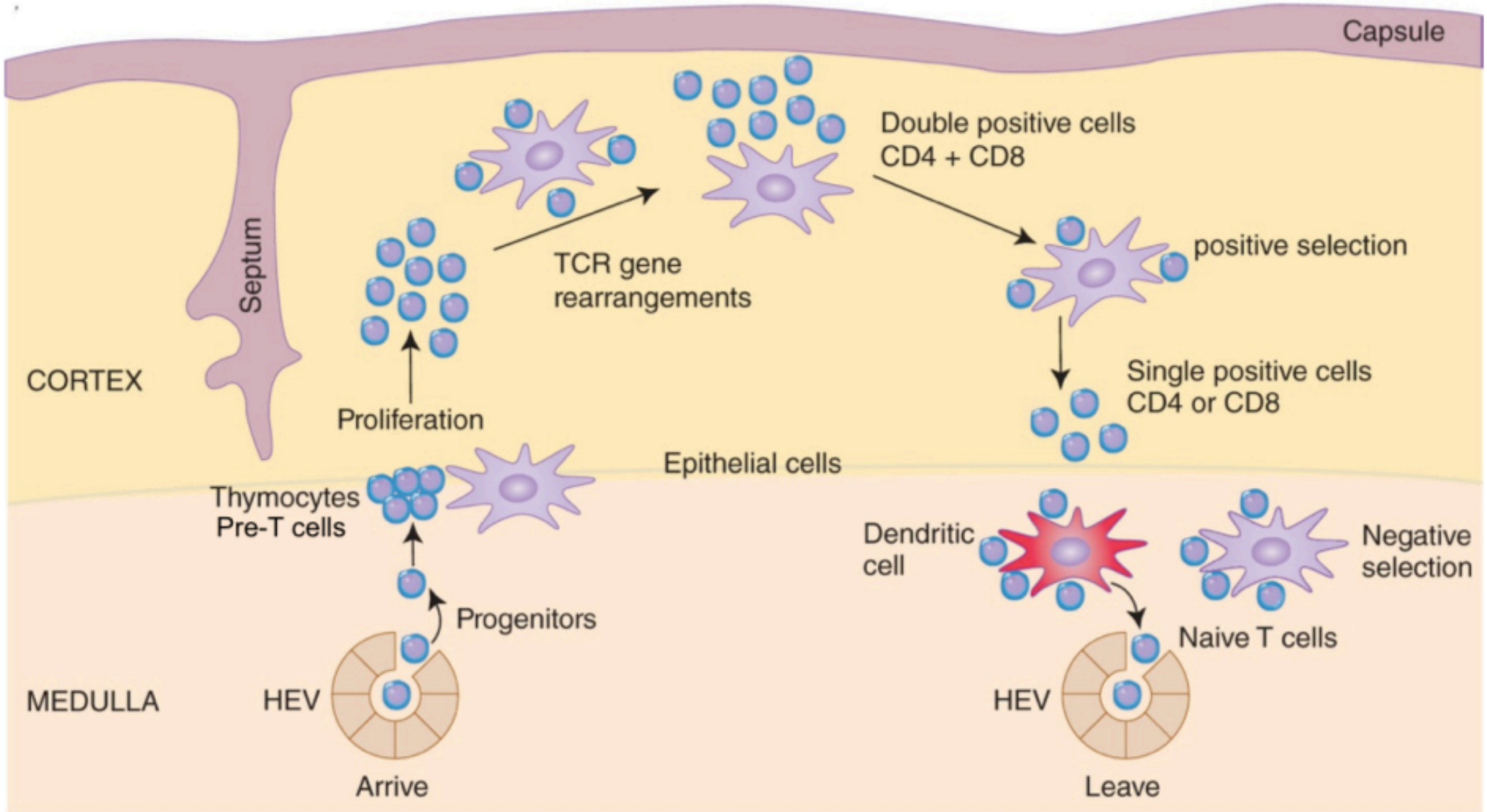
CENTRAL TOLERANCE IN T CELLS

Thymus


3. Mature
2. Migrate
Cortex
1. Thymocytes Enter
Medulla

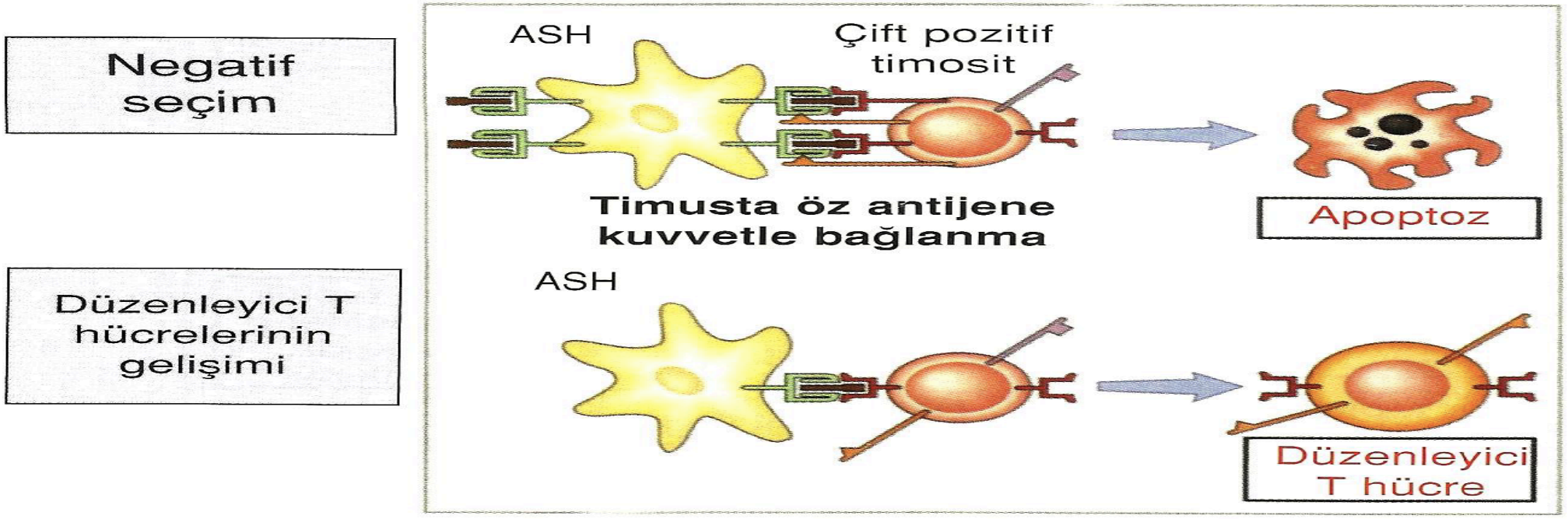

Cortex
cTEC
CD4⁺CD8⁺ αβT cell
Positive selection
CD4⁺ αβT cell or CD8⁺ αβT cell
Medulla
TRA transfer
mTEC
Aire
TRA
Fezf2
TRA
MHC
TCR
TRA-peptide
DC
Negative selection
Conventional T cell
Regulatory T cell
Apoptosis

T cell development



CENTRAL TOLERANCE IN T CELLS

If immature T cells in the thymus recognize self-antigens with high affinity, the lymphocyte dies by apoptosis.



CENTRAL TOLERANCE IN T CELLS

- T cells developing in the thymus have receptors that can recognize many types of self or foreign antigens.
- If immature lymphocytes interact strongly with our own antigens presented by MHC, these lymphocytes receive signals that trigger apoptosis and die before completing their maturation.

CENTRAL TOLERANCE IN T CELLS

- This event is defined as **negative selection** or **elimination**. And this is the main mechanism of central tolerance.
- Immature T lymphocytes may interact strongly with an antigen for two reasons;

✓either that antigen is in high concentration in the thymus

✓or the receptor of the lymphocyte binds to the antigen with **high affinity.**

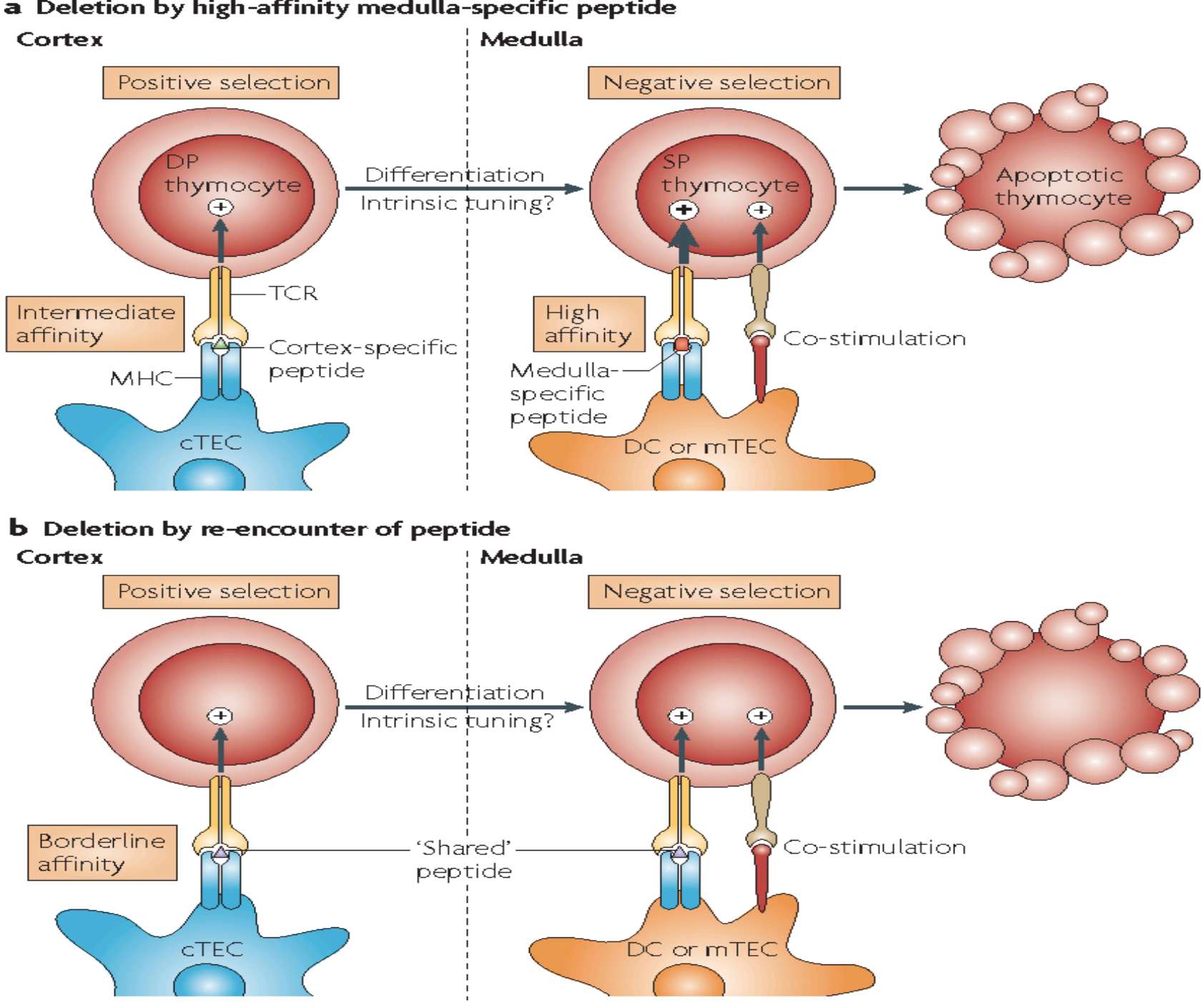
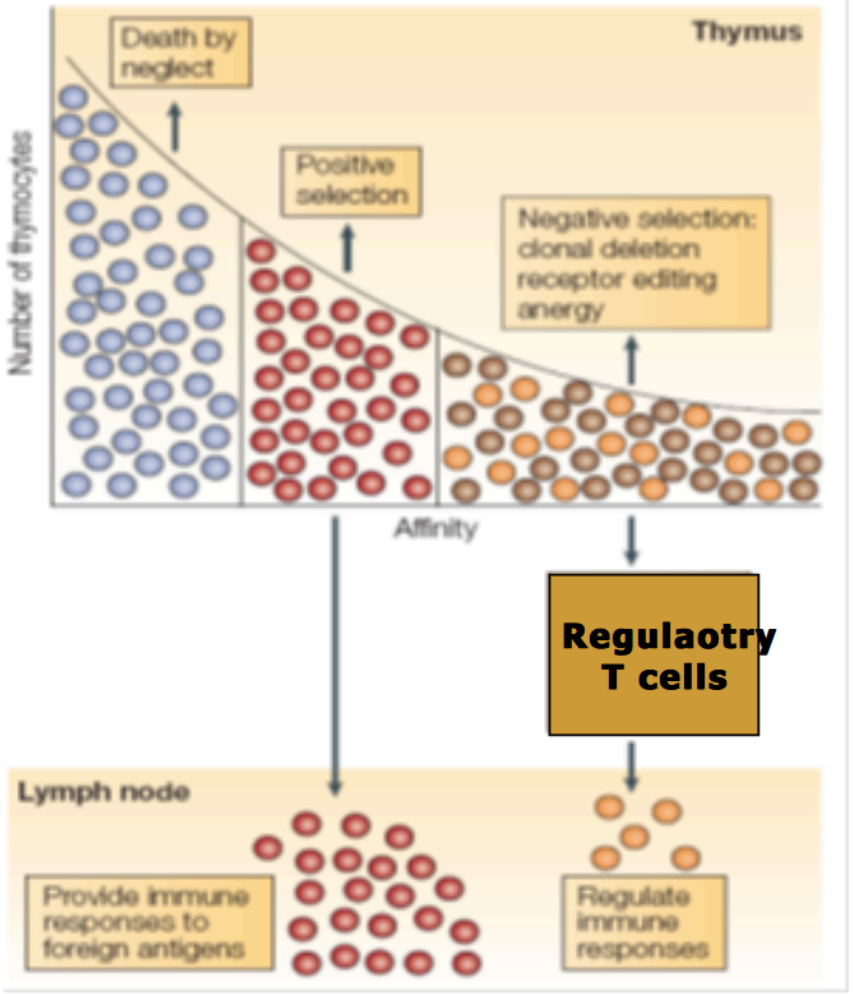
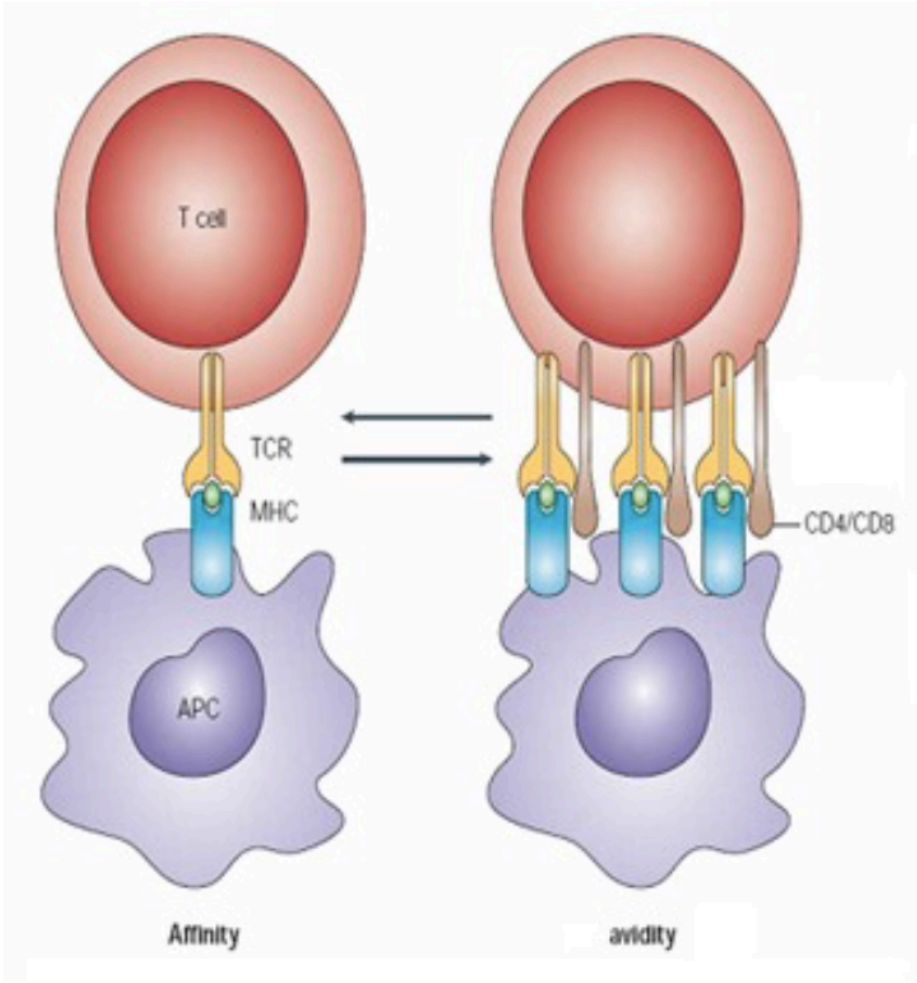


Figure 3 | **Unique peptide–MHC complexes on cortical thymic epithelial cells may**

Central tolerance of T cells





CENTRAL TOLERANCE IN T CELLS

- Negative selection for immature T cells is an important mechanism to protect us from autoimmune response to many core proteins.

- **T cells that interact strongly with self antigens are deleted, thus inhibiting responses against peripheral self antigens.**

CENTRAL TOLERANCE IN T CELLS

- Lymphocytes that escape negative selection in the thymus continue to mature and are cleared of self-responsive lymphocytes.

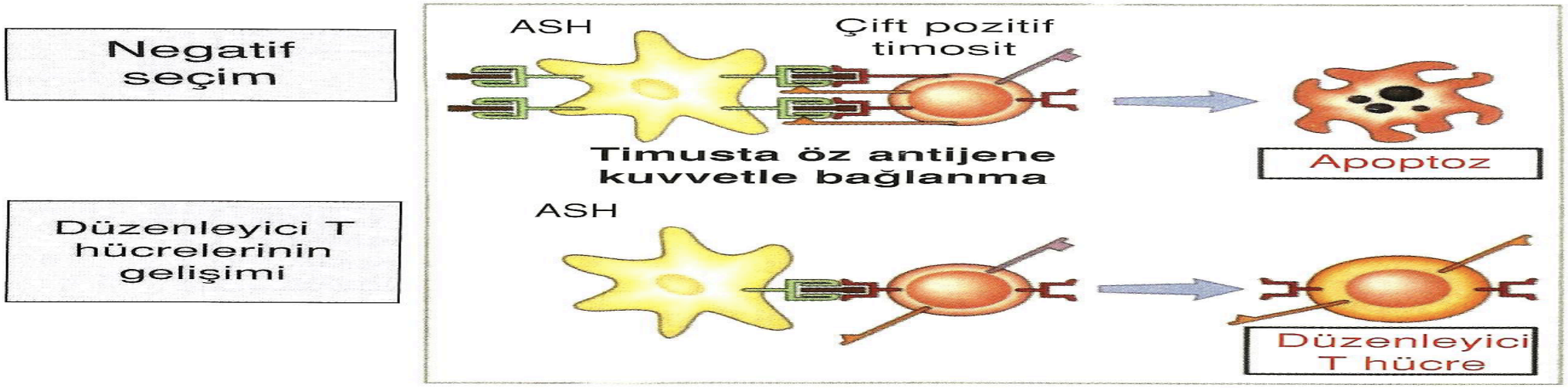
- The central tolerance process is affected by both autoimmune CD8+ that senses the antigenic peptide with MHC class I antigens and autoimmune CD4+ T cells that senses it with MHC class II antigens.

CENTRAL TOLERANCE IN T CELLS

- Some immature T cells that recognize self-antigen in the thymus gain the quality of regulatory cells and enter peripheral tissues.

- It is not yet known what determines that an immature T cell that binds to self antigens is deleted by negative selection or becomes a regulatory T cell.

CENTRAL TOLERANCE IN T CELLS



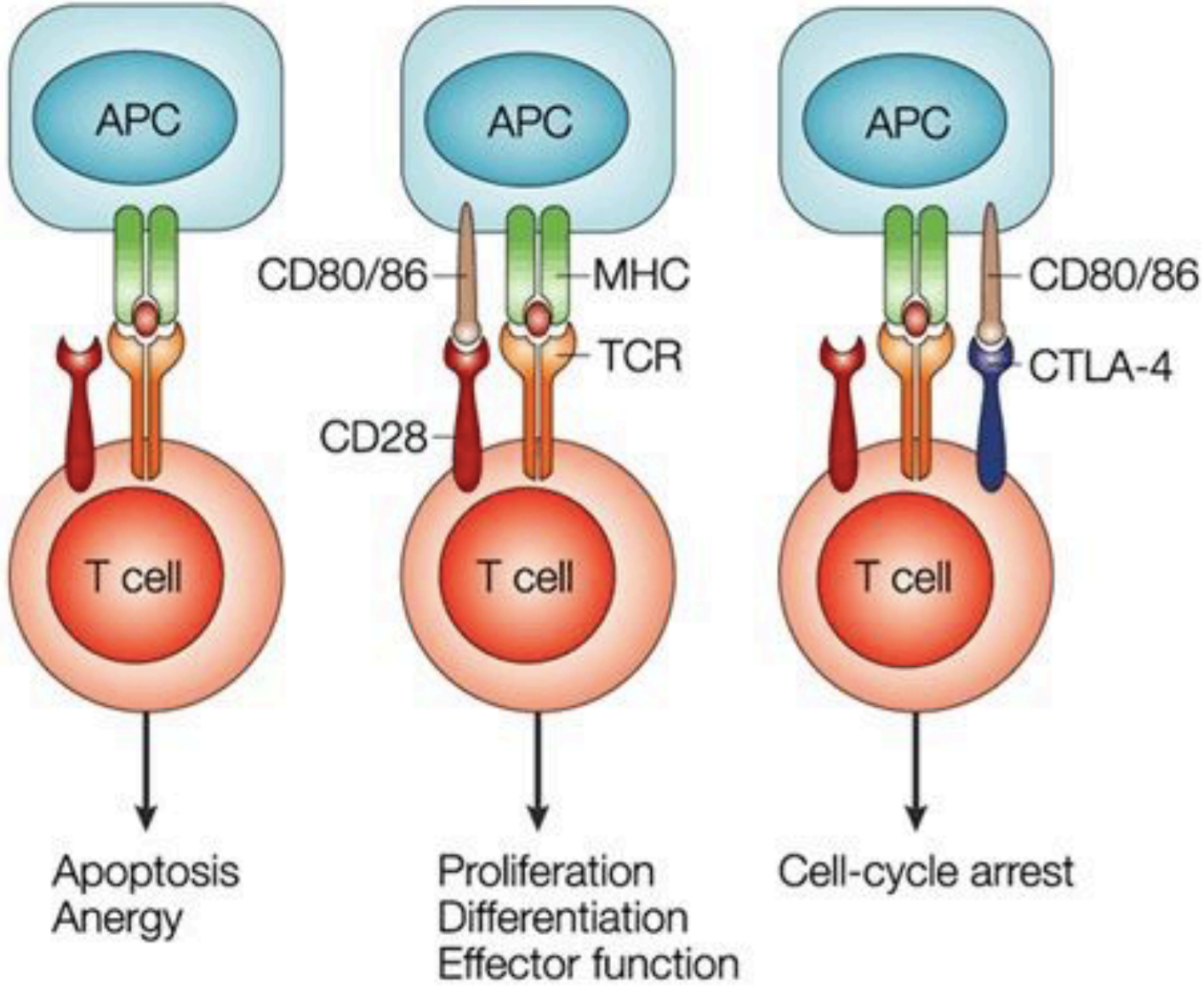
Central T Cell Tolerance; Strong binding of self-antigen with immature T cells in the thymus can lead to cell death (negative selection or deletion). Binding to our self-antigens in the thymus may also lead to the development of regulatory T cells and their migration to the periphery.

Peripheral T Lymphocyte Tolerance

Peripheral T Lymphocyte Tolerance

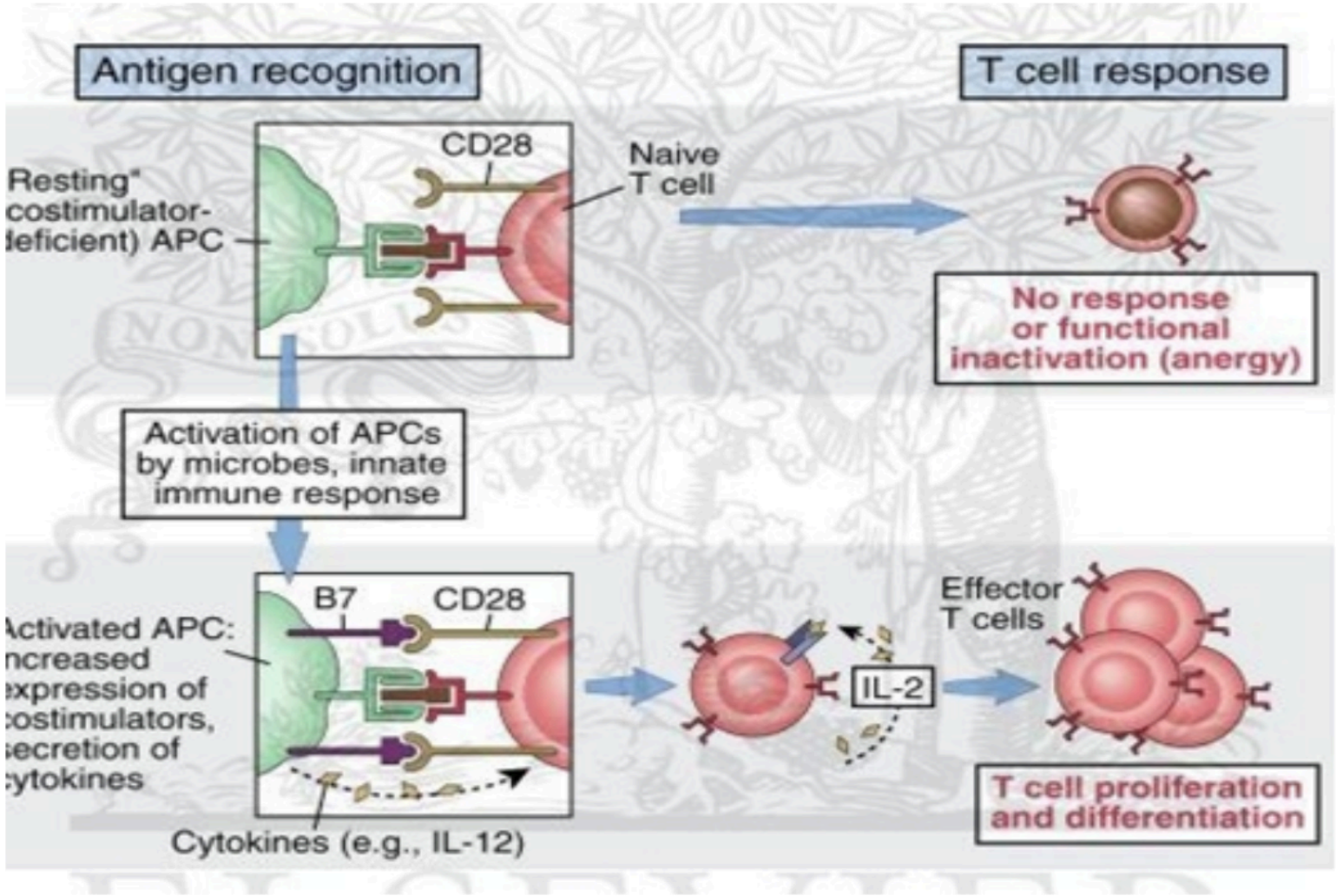
- Peripheral tolerance occurs when mature T cells express self-antigens in the periphery, resulting in functional unresponsiveness (anergy) or death, or suppression of self-reactive lymphocytes by regulatory T cells.

- Peripheral tolerance is important in preventing T cell response to self antigens, which are not found in the thymus, but mainly in peripheral tissues.



T hücre aktivasyonu ve ko-stimülatuvar moleküller

T cell anergy in the absence of co-stimulatory signals



Costimulatory vs. inhibitory moleccules

Costimulation (APC : T cell)	Inhibition (APC : T cell)
B7-2 (CD86) : CD28	B7-2 : CTLA-4
B7-1 (CD80) : CD28	B7-1 : CTLA-4
CD40 : CD40L (CD154)	PD-L1, PD-L2: PD-1
ICOSL : ICOS	
CD70 : CD27	
OX40L (CD134L) : OX40 (CD134)	
4-1BBL : 4-1BB	

Peripheral T Lymphocyte Tolerance

- **Anergy**

• Anergy describes the functional inactivation of the T cell after it encounters an antigen.

• This is usually due to the absence of the second co-stimulus necessary for the full activation of the T cell.

Peripheral T Lymphocyte Tolerance

- **Anergy**

- Two stimuli are required for the complete activation of naive T cells (proliferation and differentiation and transformation into active cells).

➢ The first stimulus is always the antigen.

➢ The second stimulus comes from antigen presenting cells (APC), and the occurrence of this second signal develops in response to microorganisms.

Peripheral T Lymphocyte Tolerance

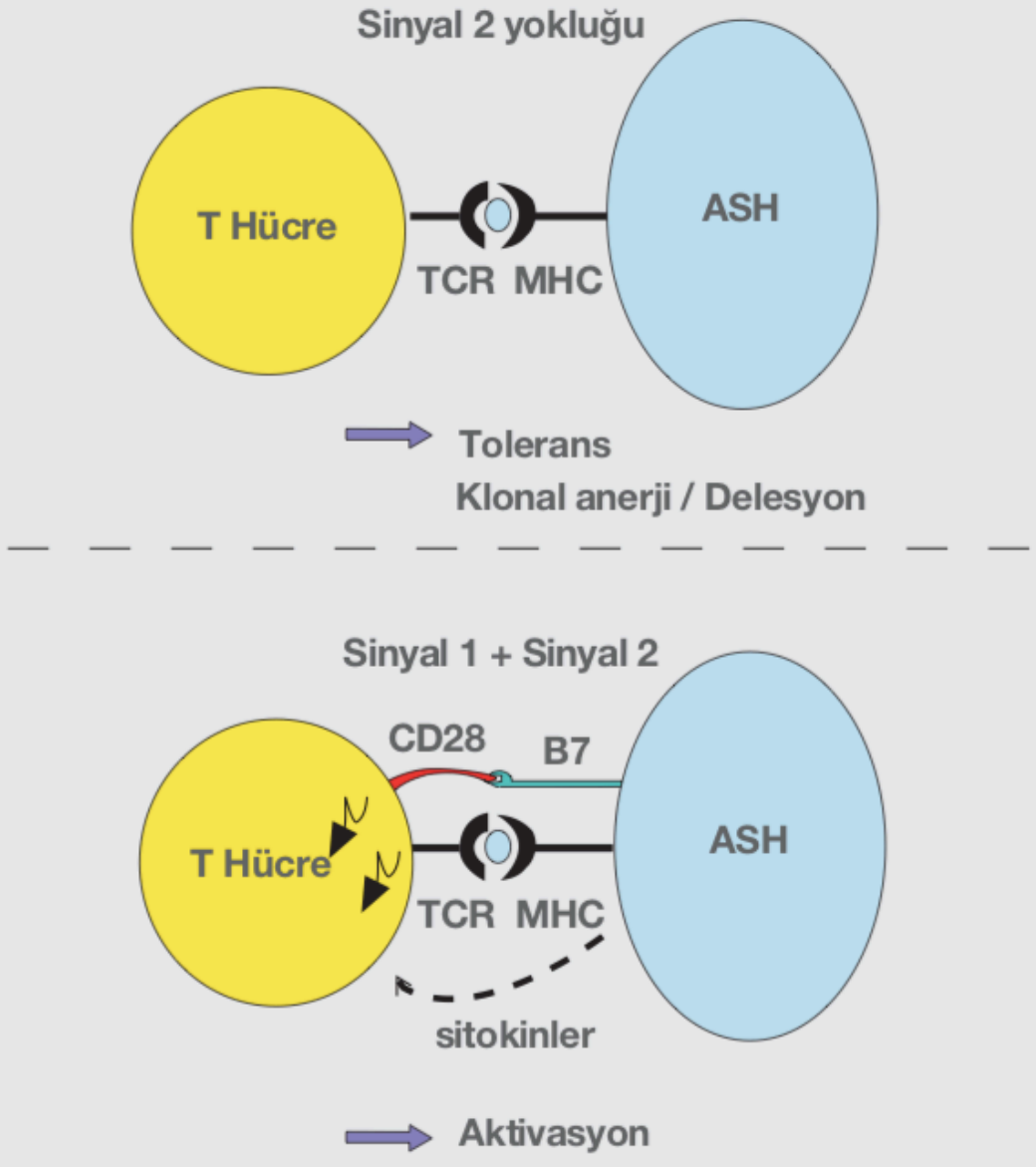
- **Anergy**

➢T lymphocytes that have receptors for self antigens see these antigens.

➢Thus, T cells receive signals from the antigen receptor **(signal-1)** but do not receive the necessary secondary signals.

➢Signal-1 may cause prolonged living **T cell anergy** in the absence of appropriate **signal-2.**

Lenfosit Aktivasyonu



Peripheral T Lymphocyte Tolerance

- **Anergy**

• In some cases, the T cell that encounters the self-antigen expresses a molecule called **CTLA-4** (CD152), this molecule is the high-affinity binder of the B7 molecule and the activation of the T cell is inhibited.

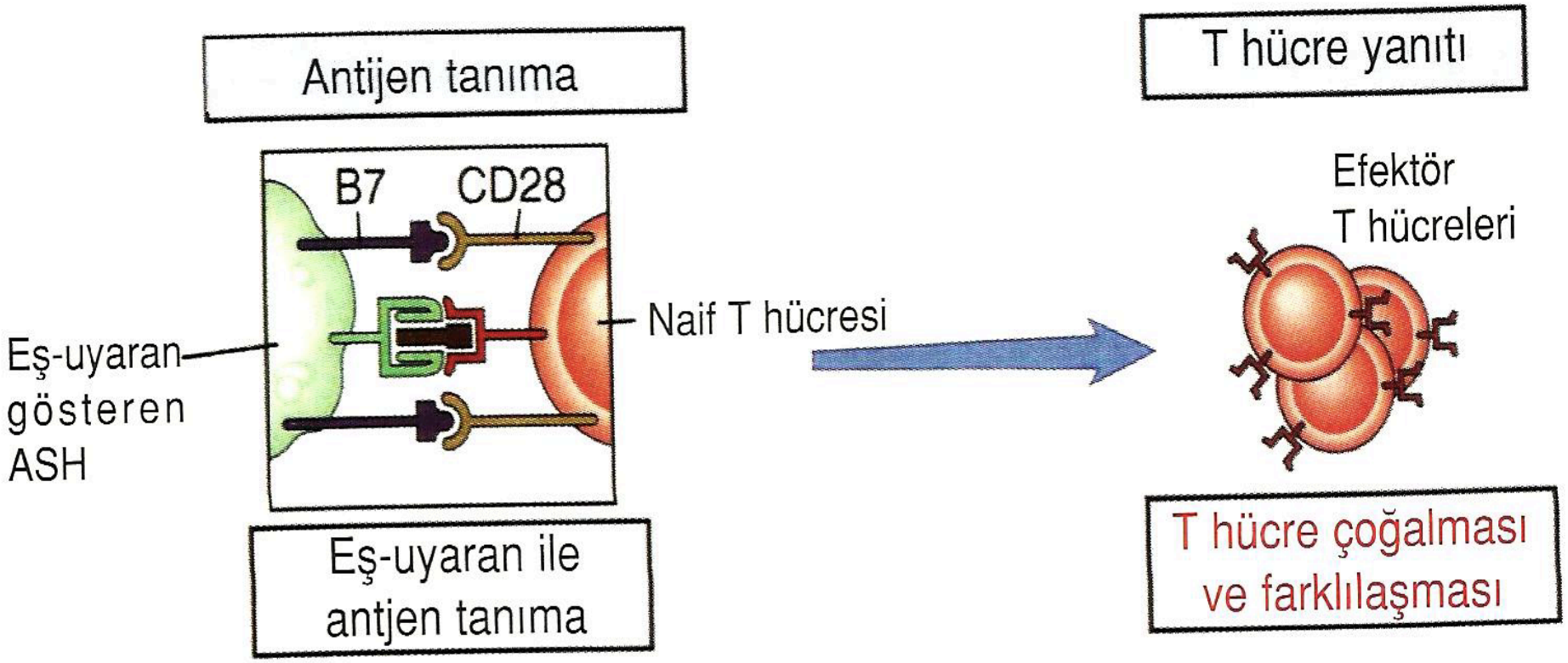
• In summary, the T cell that sees the self-antigen on ASH binds to B7 with CTLA-4 and eventually creates T cell inactivation.

Peripheral T Lymphocyte Tolerance

- **Anergy**

- Antigen presentation to the T cell by ASH expressing co-stimuli results in a normal T cell response.

Normal Response

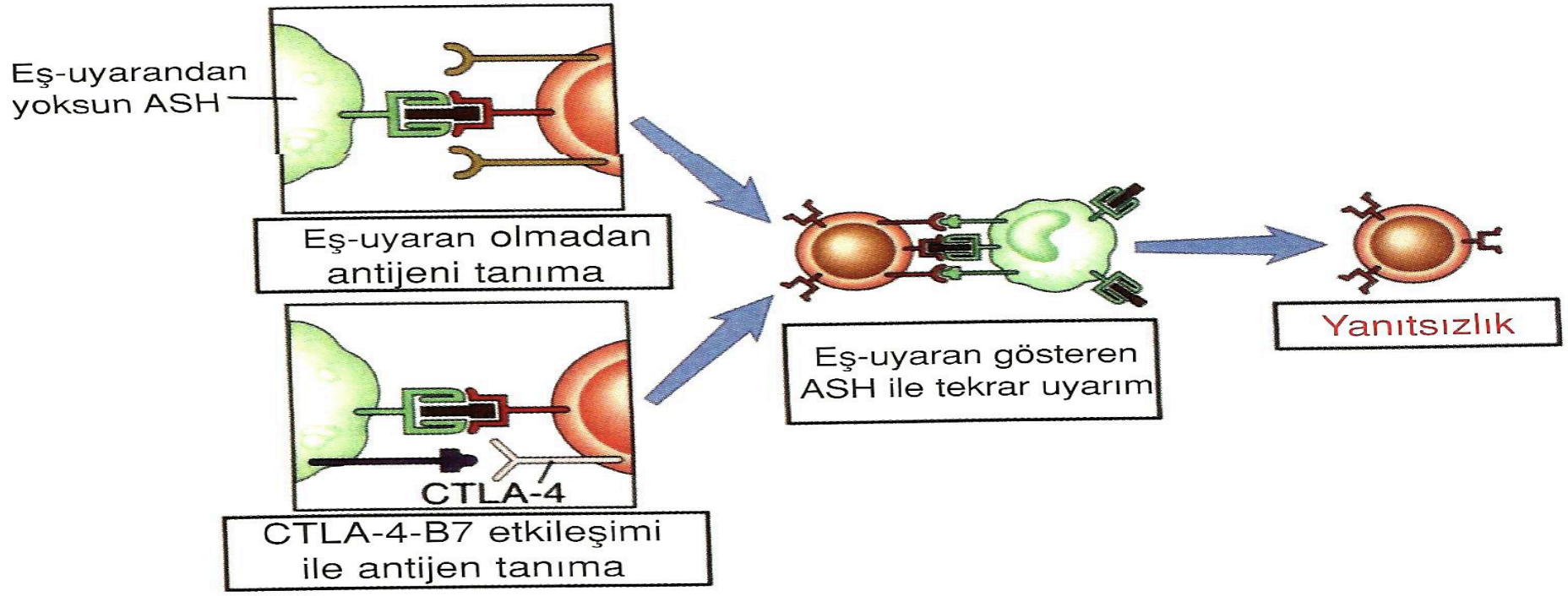


Peripheral T Lymphocyte Tolerance

- **Anergy**

- If the T cell sees the antigen without co-stimulus or with CTLA-4-B7 interaction, it cannot become active and remains unresponsive. The T cell does not respond even if it encounters the same antigen and then with ASH, which also shows the co-stimulus.

Anergy



Functions of Costimulators in T Cell Activation

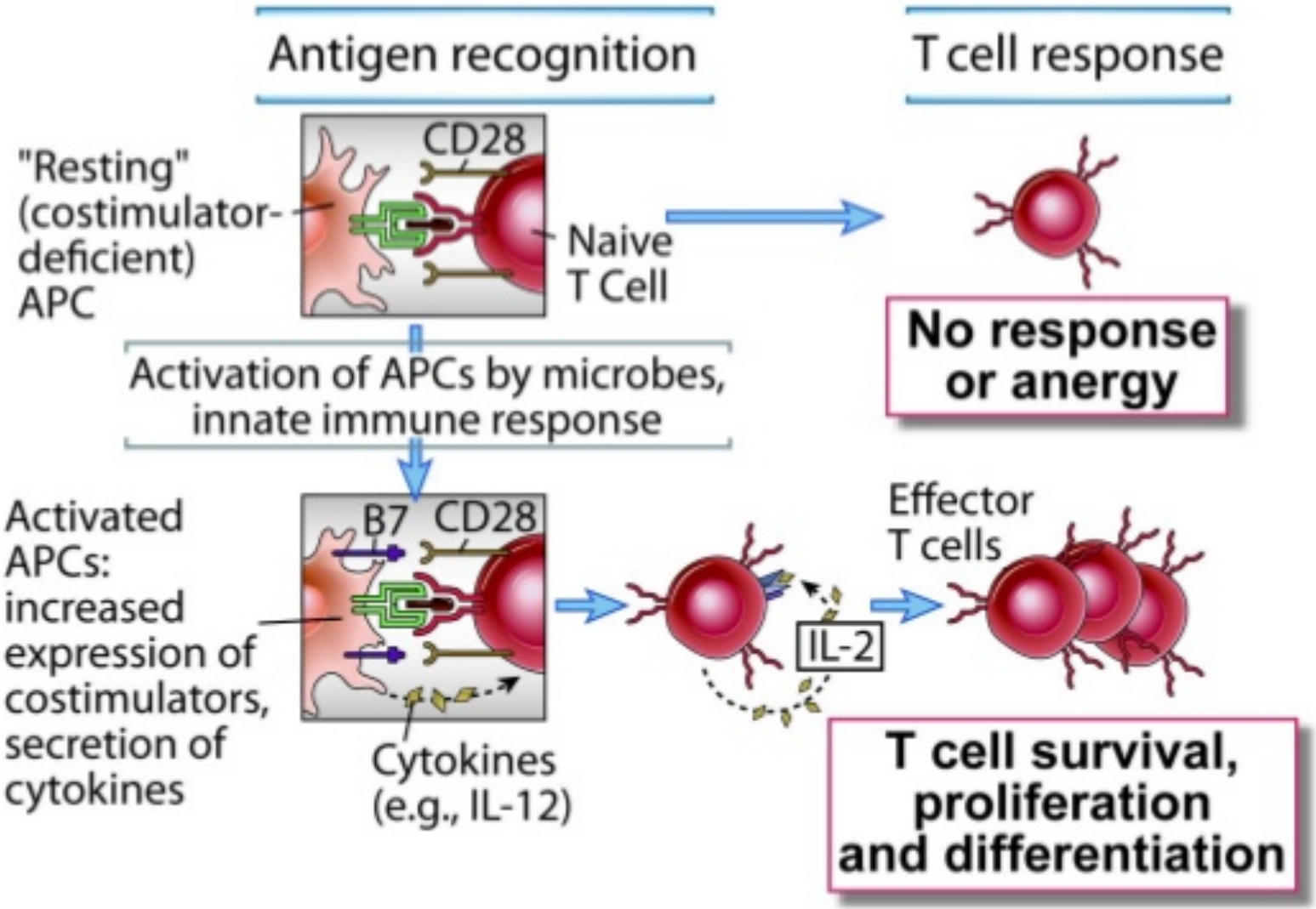
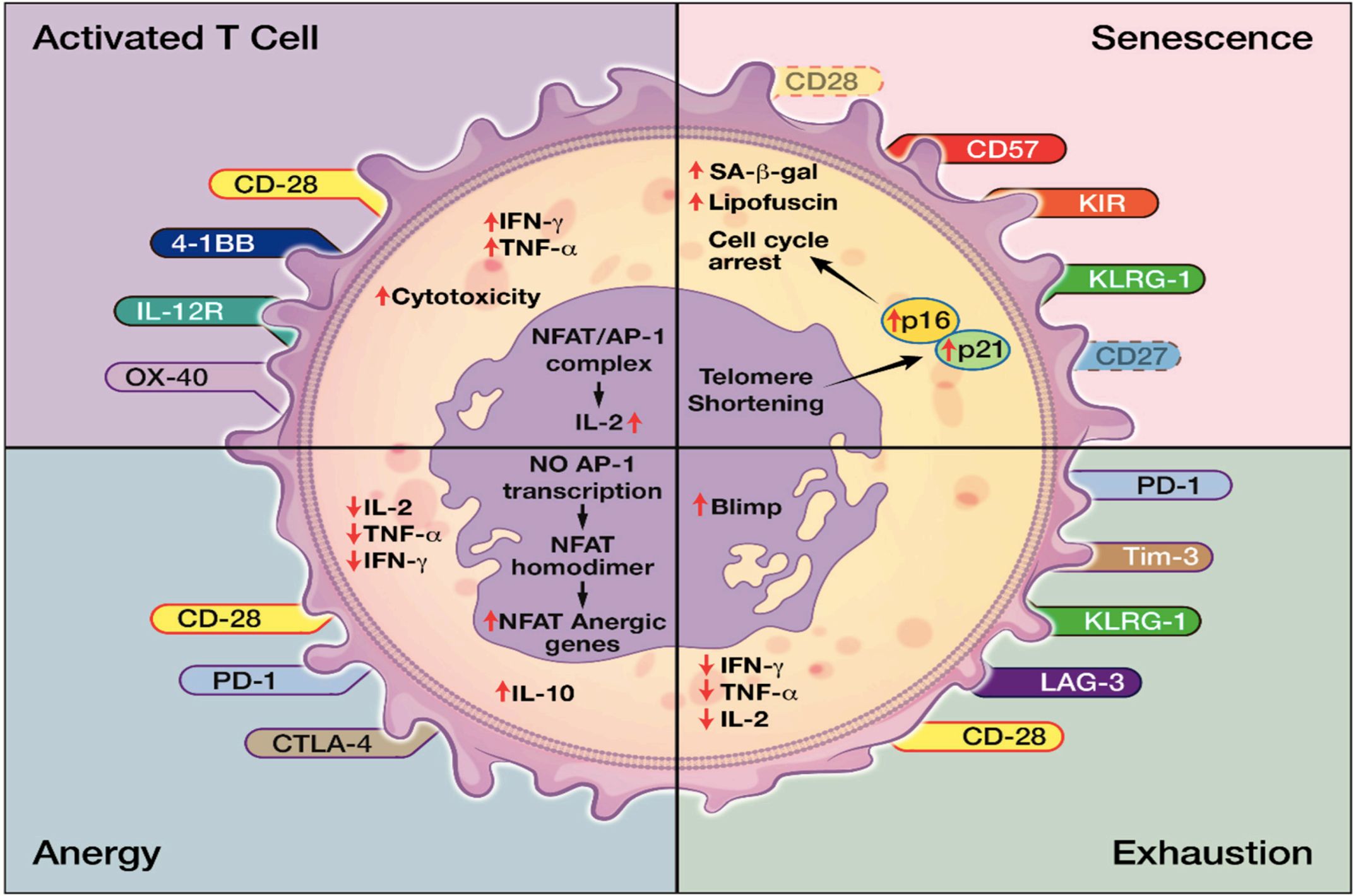


Fig. 9-3


Activated T Cell
Senescence
CD-28
4-1BB
IL-12R
OX-40
↑IFN-γ
↑TNF-α
↑Cytotoxicity
NFAT/AP-1 complex
IL-2↑
CD28
CD57
KIR
KLRG-1
CD27
↑SA-β-gal
↑Lipofuscin
Cell cycle arrest
↑p16
↑p21
Telomere Shortening
↓IL-2
↓TNF-α
↓IFN-γ
NO AP-1 transcription
NFAT homodimer
↑NFAT Anergic genes
↑IL-10
↑Blimp
PD-1
Tim-3
KLRG-1
LAG-3
CD-28
↓IFN-γ
↓TNF-α
↓IL-2
CD-28
PD-1
CTLA-4
Anergy
Exhaustion

Peripheral T Lymphocyte Tolerance

• Deletion: Activation-Induced Cell Death

- Repetitive stimulation of mature T cells with self-antigens or recognition of self-antigen without a second signal triggers the apoptosis pathway, and elimination **(deletion)** of these self-responsive lymphocytes occurs.
- This process is defined as activation-induced cell death.

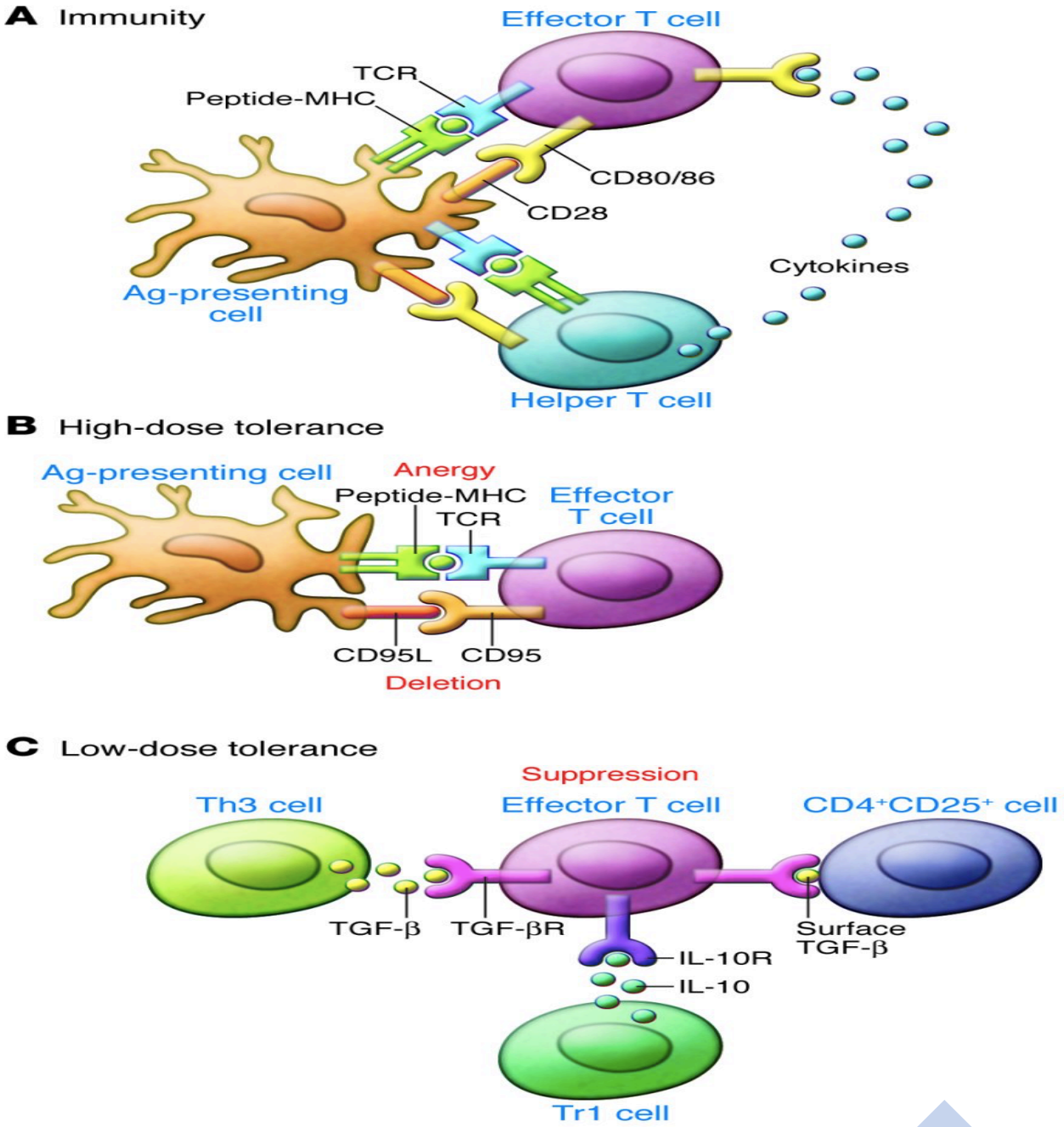
Peripheral T Lymphocyte Tolerance

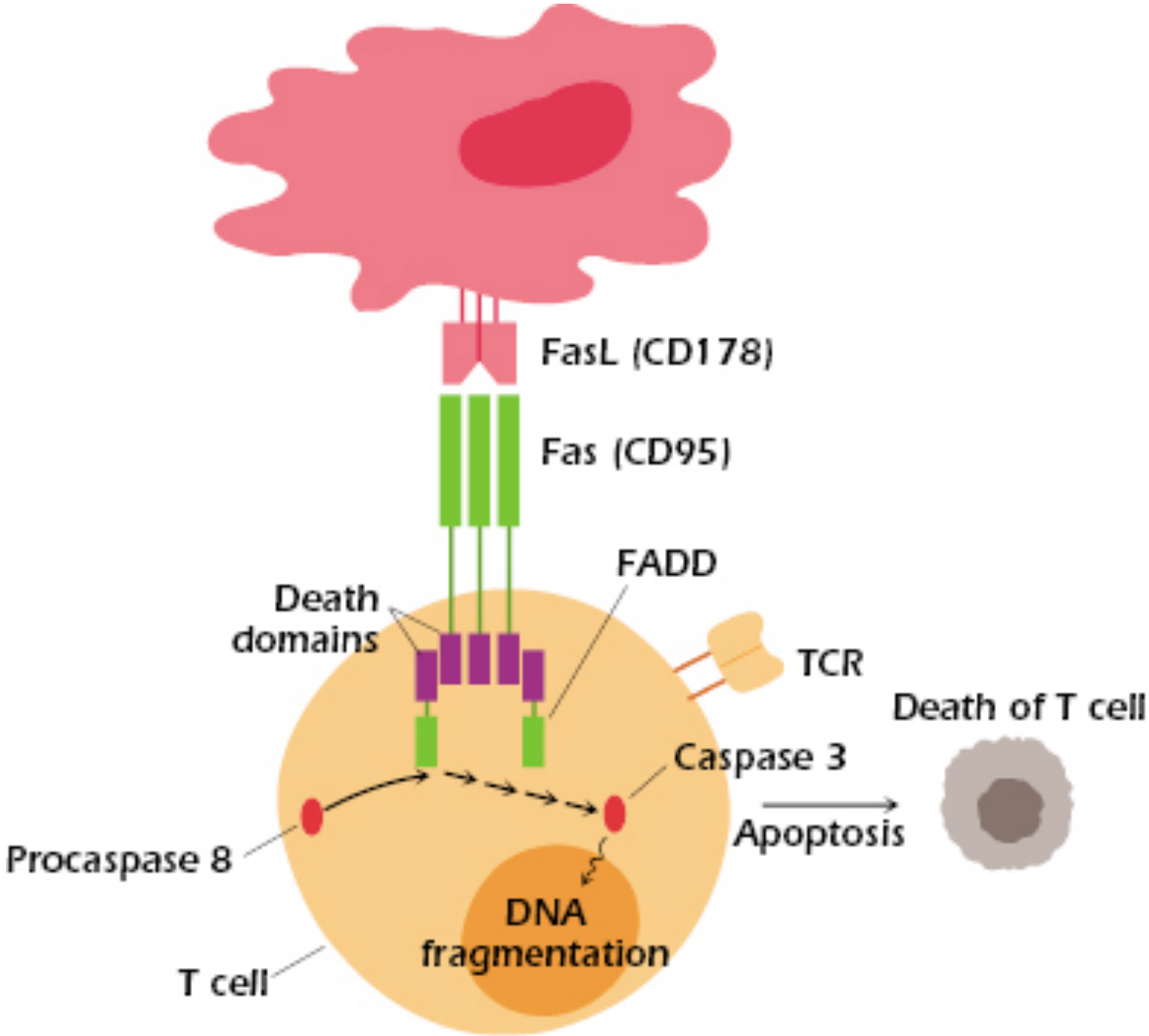
- **Deletion: Activation-Induced Cell Death**

There are two possible mechanisms for activation-induced cell death:

- First, CD4+ T cells express, by repeated activations, a death receptor Fas (CD95) and its binding Fas Ligand (FasL).

- The binding of Fas with FasL is transmitted intracellularly by the Fas death algae, and apoptosis develops with the activation of caspases and cytosolic enzymes


A Immunity
Effector T cell
TCR
Peptide-MHC
CD80/86
CD28
Cytokines
Ag-presenting cell
Helper T cell
B High-dose tolerance
Ag-presenting cell
Anergy
Peptide-MHC
TCR
Effector T cell
CD95L
CD95
Deletion
C Low-dose tolerance
Suppression
Th3 cell
Effector T cell
CD4+CD25+ cell
TGF-β
TGF-βR
Surface TGF-β
IL-10R
IL-10
Tr1 cell


FasL (CD178)
Fas (CD95)
FADD
Death domains
TCR
Death of T cell
Caspase 3
Apoptosis
Procaspase 8
DNA fragmentation
T cell

Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**

- **Thus, in case of repeated activation, the T cell activates its own internal death program and prevents a continuous immune activation.**

- Self antigens can cause the destruction of T cells specific to them, because these antigens persist throughout life and repeatedly stimulate those lymphocytes

Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**

The second mechanism proposed for activation-induced cell death is

- It is based on the formation of proto-apoptotic proteins in the antigen-stimulated T cell.

- If the T cell is stimulated by microorganisms, especially the anti-apoptotic proteins formed during the innate immune response prevent this effect. If the stimulus is self-antigen, these anti-apoptotic molecules do not form and the cell goes to apoptosis.

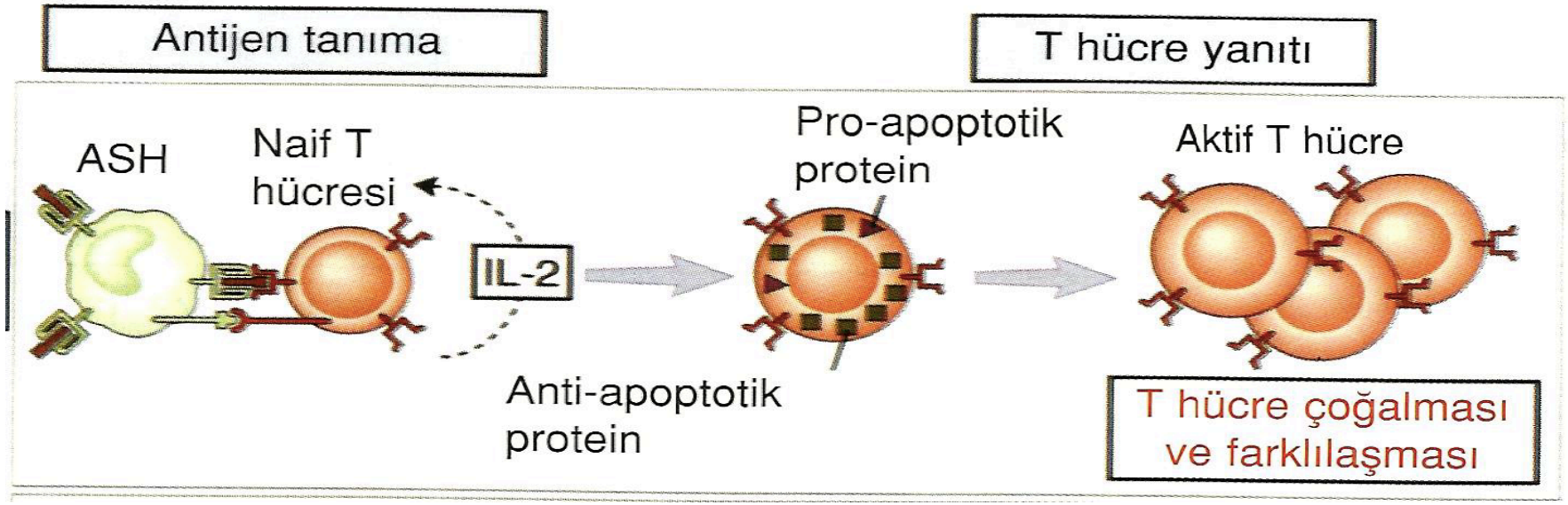
Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**
  - Thus, the activated T cell for self-antigens is destroyed by apoptosis. Fas death receptors have no role in this pathway.
  - It has been observed that lymphocyte accumulation and autoimmune diseases develop in mice with mutations in Fas or Fas L genes and in children with mutations in fas gene.

Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**

Normal Response

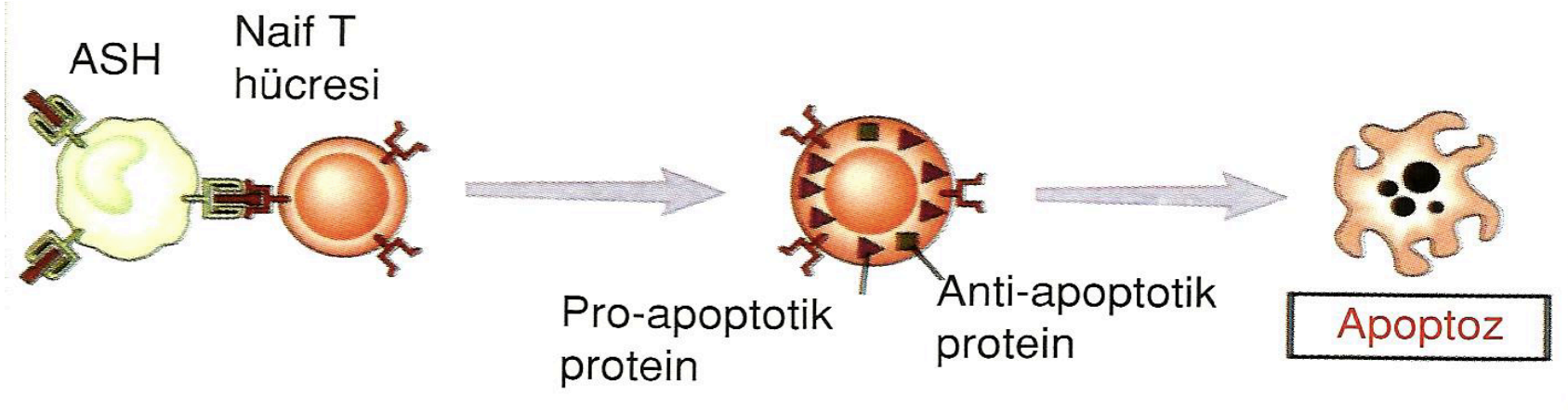


- T cell responds normally with proliferation and differentiation by producing IL-2 and anti-apoptotic proteins against the antigen presented by normal APCs.

Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**

Activation-initiated death: The role of pro–apoptotic proteins

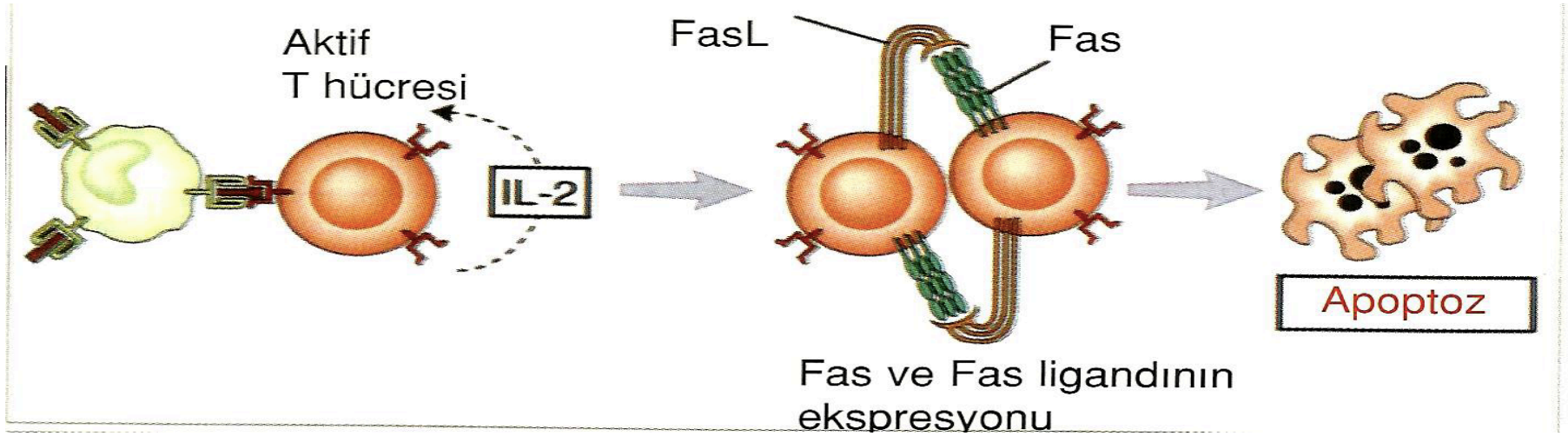


In the second mechanism, which is not dependent on Fas, in the absence of co-stimulus and innate immunity, the formation of pro-apoptotic proteins inside the cell, which cannot be balanced with anti-pro-apoptotic proteins, leads to cell death.

Peripheral T Lymphocyte Tolerance

- **Deletion: Activation-Induced Cell Death**

Activation-initiated death: role of death receptors



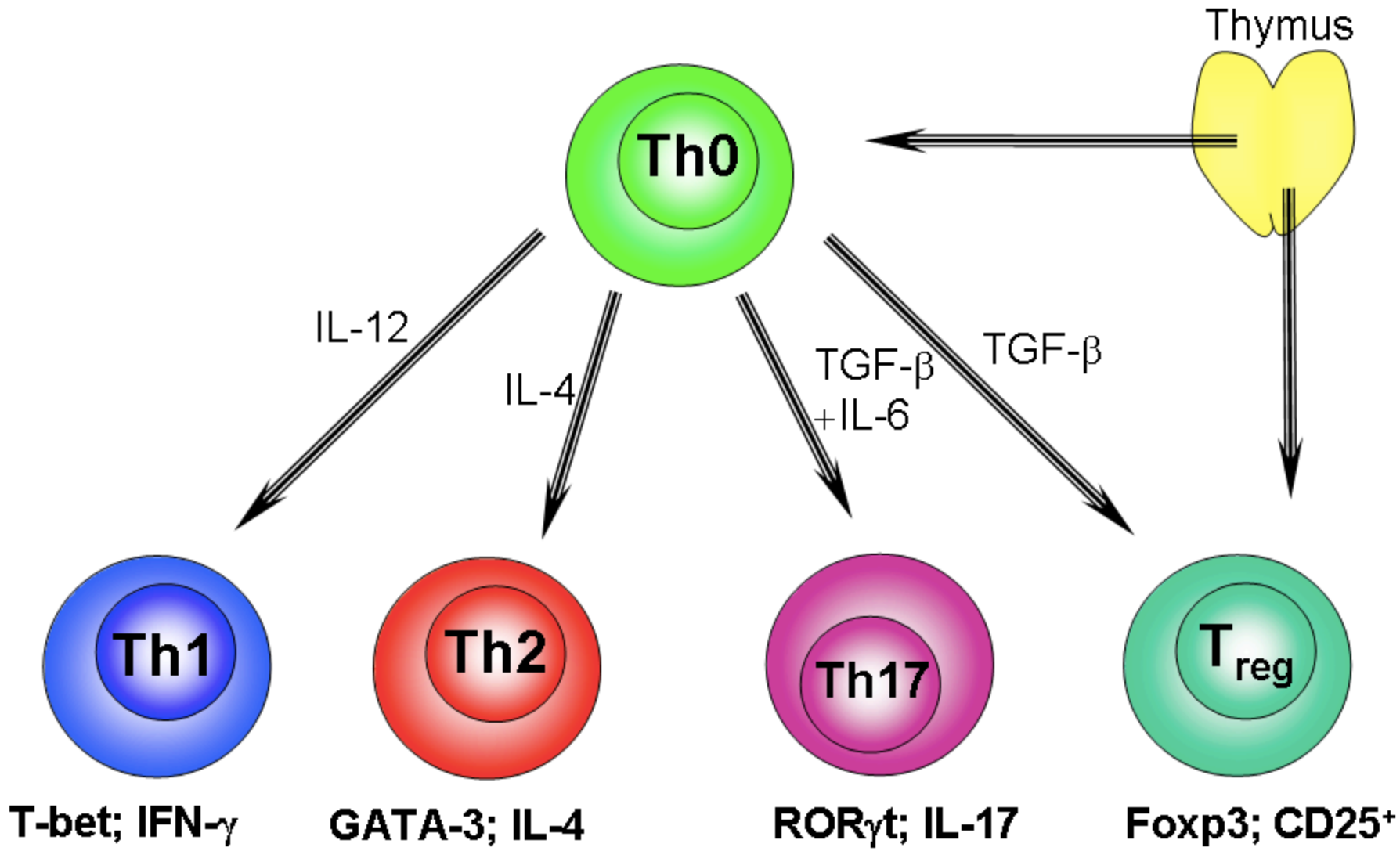
- In one embodiment of death initiated by activation; When the newly stimulated activated T cell is re-stimulated with the same antigen, it begins to express Fas and FasL simultaneously, Fas-FasL expression results in apoptotic death of the T cell.

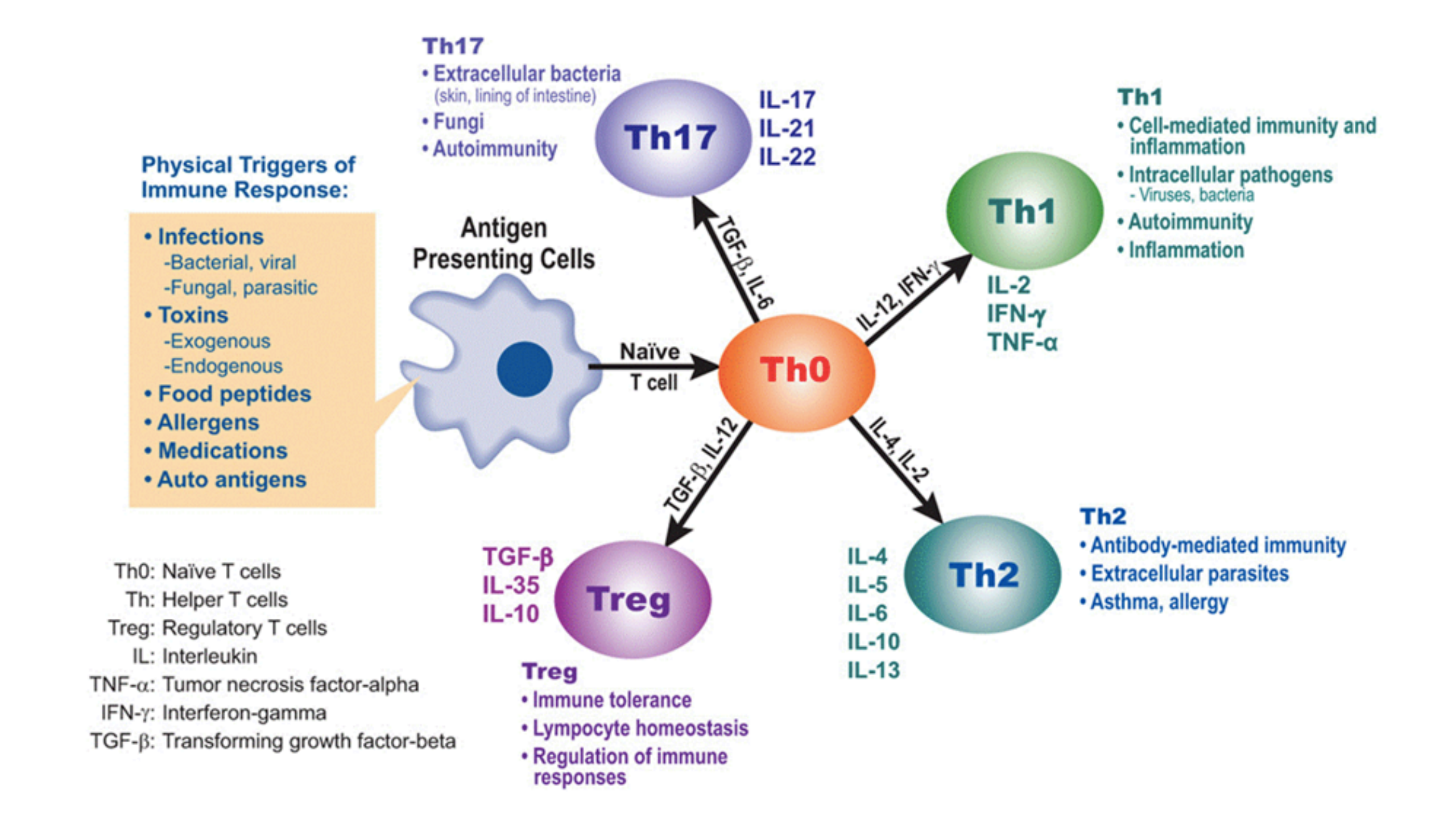
Peripheral T Lymphocyte Tolerance

• Immune Suppression

• After encountering with self-antigen, some self-responsive T lymphocytes can transform into regulatory cells and exert a suppressive or inhibitory effect on other autoimmune response cells.

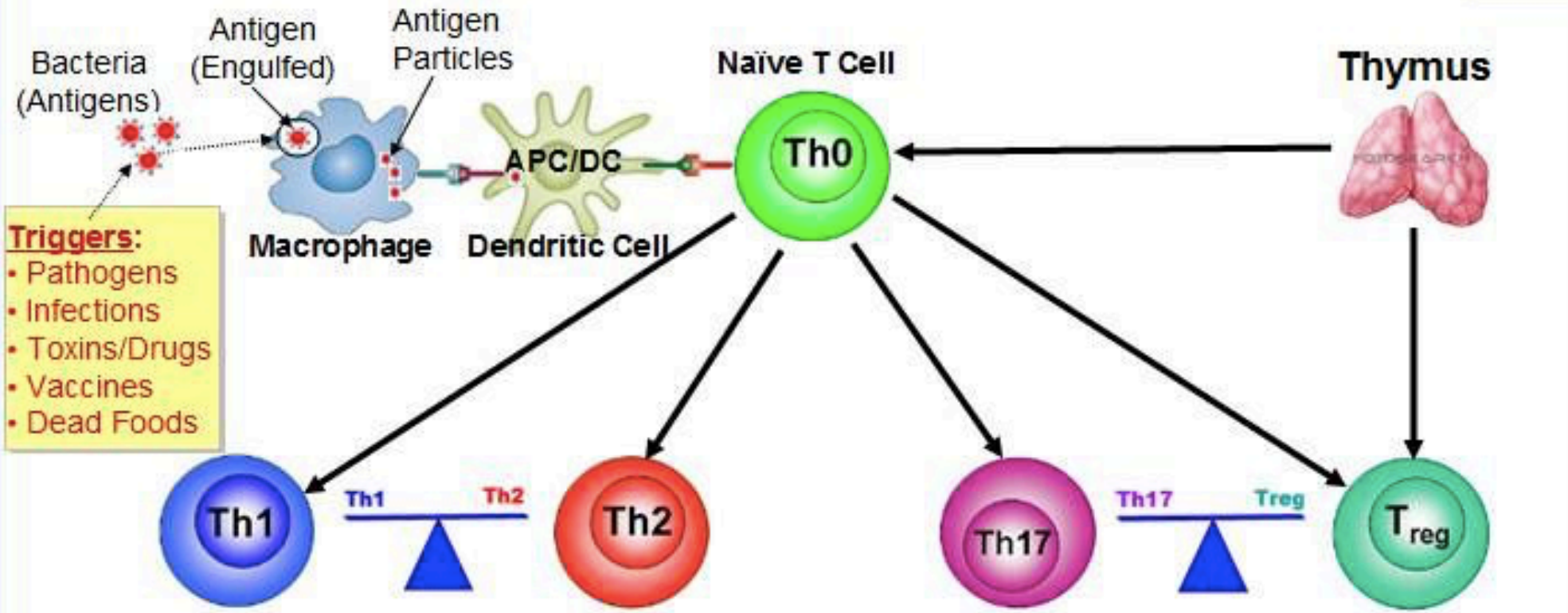
• Regulatory T cells can occur in the thymus or in the peripheral lymphoid organ.


Thymus
Th0
IL-12
IL-4
TGF-β
+IL-6
TGF-β
Th1
Th2
Th17
Treg
T-bet; IFN-γ
GATA-3; IL-4
RORγt; IL-17
Foxp3; CD25+


Th17
• Extracellular bacteria
(skin, lining of intestine)
• Fungi
• Autoimmunity
Th17
IL-17
IL-21
IL-22
Th1
• Cell-mediated immunity and inflammation
• Intracellular pathogens
- Viruses, bacteria
• Autoimmunity
• Inflammation
Th1
IL-2
IFN-γ
TNF-α
Physical Triggers of Immune Response:
• Infections
-Bacterial, viral
-Fungal, parasitic
• Toxins
-Exogenous
-Endogenous
• Food peptides
• Allergens
• Medications
• Auto antigens
Antigen Presenting Cells
TGF-β, IL-6
IL-12, IFN-γ
Naïve T cell
Th0
TGF-β, IL-12
IL-4, IL-2
TGF-β
IL-35
IL-10
Treg
Treg
• Immune tolerance
• Lympocyte homeostasis
• Regulation of immune responses
IL-4
IL-5
IL-6
IL-10
IL-13
Th2
Th2
• Antibody-mediated immunity
• Extracellular parasites
• Asthma, allergy
Th0: Naïve T cells
Th: Helper T cells
Treg: Regulatory T cells
IL: Interleukin
TNF-α: Tumor necrosis factor-alpha
IFN-γ: Interferon-gamma
TGF-β: Transforming growth factor-beta

T Helper Cells

Death to Diabetes



Th1 Cells
- Cell-mediated immunity
- Intracellular pathogens (Viruses, bacteria)
- Inflammation
- Drives autoimmunity
- NKs, Neutrophils

Th2 Cells
- Antibody-mediated immunity
- Extracellular parasites
- Allergy
- Asthma
- Antibodies

Th17 Cells
- Cell-mediated immunity
- Extracellular bacteria (Skin, intestinal lining)
- Inflammation
- Fungi
- Autoimmunity

Treg Cells
- Immune tolerance
- Immune suppression
- Immune response regulation

Reference: DTD Autoimmune Diseases Book, Chapter 4

Peripheral T Lymphocyte Tolerance

- **Immune Suppression**

  - Some regulatory cells **make cytokines such as TGF β and IL-10 that inhibit the activation of lymphocytes and macrophages.**

  - Apart from secreting cytokines, these cells are also likely to interact and act directly with lymphocytes or APCs.

Peripheral T Lymphocyte Tolerance

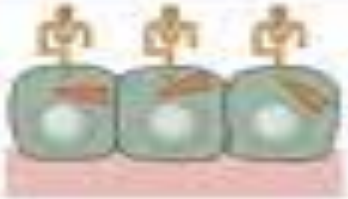
- **Immune Suppression**

  • Self antigens are different from the antigens of micro-organisms in many ways, **these differences cause tolerance in the encounter with the self-antigen and activation in the encounter with the micro-organism.**

  • Self antigens are located in the thymus and form central tolerance, whereas microbial antigens are transported to peripheral organs and concentrated in these areas.

Peripheral T Lymphocyte Tolerance

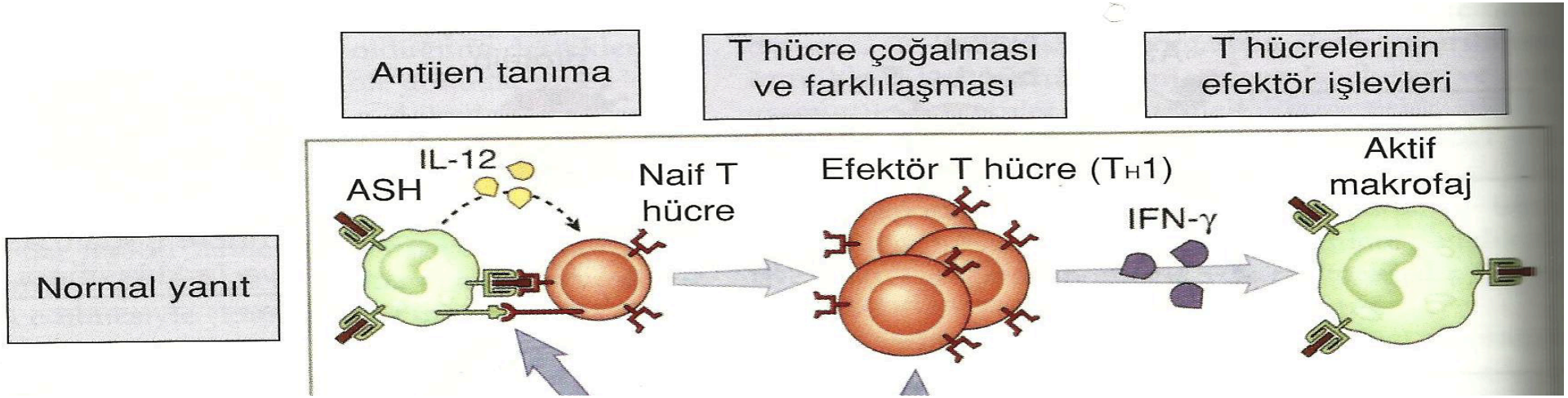
- **Immune Suppression**

Feature of antigen	Tolerogenic self antigens	Immunogenic foreign antigens
		
Presence in generative organs	Yes (some self antigens): high concentrations induce negative selection and regulatory T cells (central tolerance)	No: microbial antigens are concentrated in peripheral lymphoid organs
Presentation with second signals (costimulation, innate immunity)	No: deficiency of second signals may lead to T cell anergy or apoptosis	Yes: typically seen with microbes; second signals promote lymphocyte survival and activation
Persistence of antigen	Long-lived (throughout life); prolonged TCR engagement may induce anergy and apoptosis	Usually short lived; immune response eliminates antigen

Important features in the selection of T-cell tolerance or effective response development of protein antigens

Peripheral T Lymphocyte Tolerance

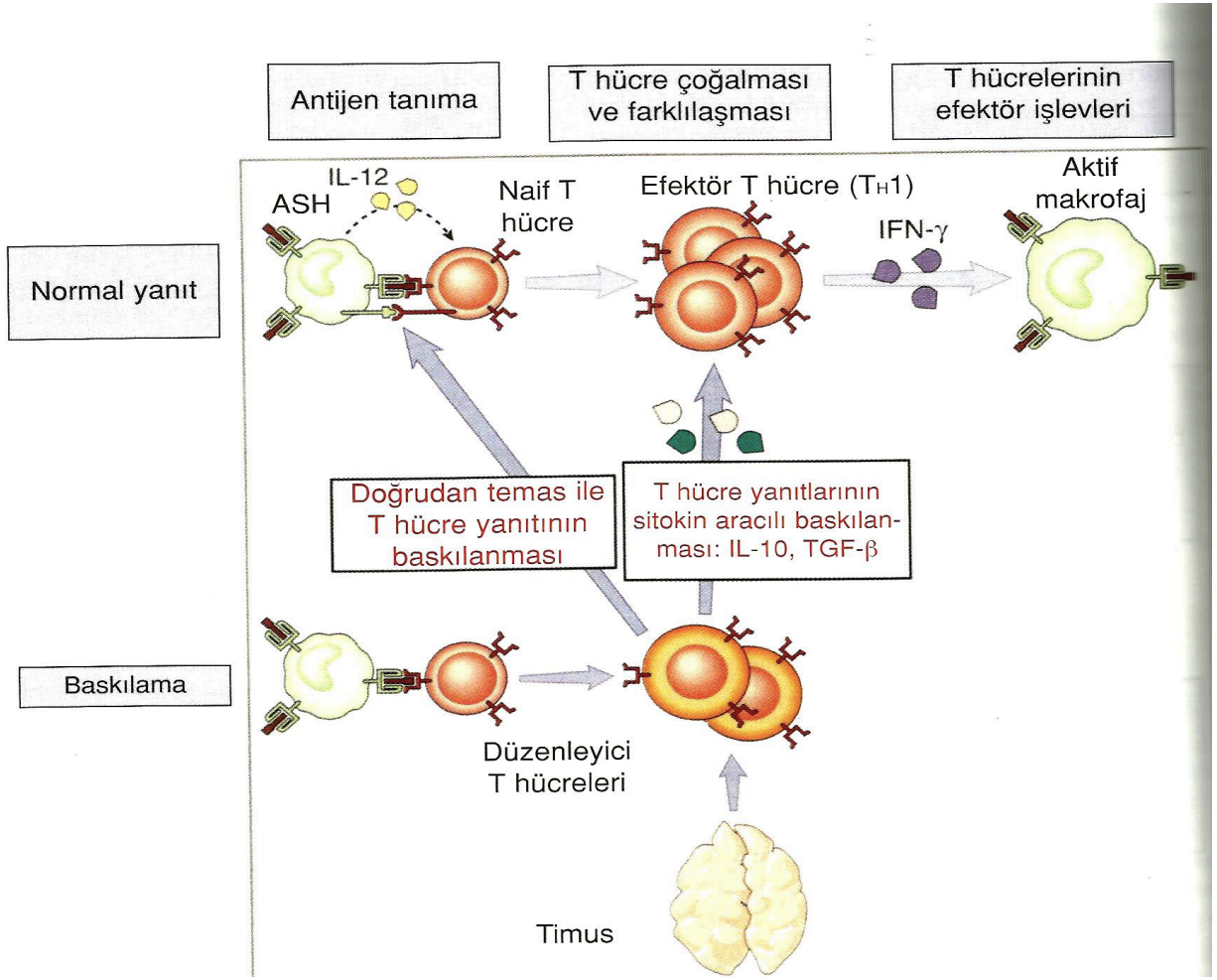
- **Immune Suppression**



- In a normal response, the T cell recognizes the antigen, proliferates and differentiates into effector cells. The figure shows a normal typical TH1 response. It has been shown that the naive T cell, stimulated by APCs in the presence of co-stimulus and IL-2, transforms into an active TH1 cell and activates macrophages by releasing IFN-γ.

Peripheral T Lymphocyte Tolerance

- **Immune Suppression**



- Some T cells can transform into regulatory T cells in the thymus or peripheral tissues, and the T-cell response can be suppressed by direct cell-cell interaction or by released cytokines.

B Lymphocyte Tolerance

B Lymphocyte Tolerance

- Core polysaccharides, lipids and nucleic acids are T-independent antigens that T cells do not recognize.
- These antigens must establish B lymphocyte tolerance in order to prevent autoantibody production.
- Central and peripheral B lymphocyte tolerance are basically similar to T cell tolerance mechanisms.

B Lymphocyte Tolerance

• Central B Lymphocyte Tolerance

• If immature B lymphocytes bind strongly to self antigens in the bone marrow, they are either **killed by negative selection** or change the **specificity of their receptors.**

• The deletion process is similar to the negative selection of immature T cells.

B Lymphocyte Tolerance

• Central B Lymphocyte Tolerance

• As with T cells, the negative selection mechanism of B cells results in the elimination of immature B cells that bind to widely expressed cell membrane or soluble self-antigens with high affinity algae.

• **Immature B lymphocytes use a second mechanism to inhibit autoimmunity.**

B Lymphocyte Tolerance

• Central B Lymphocyte Tolerance

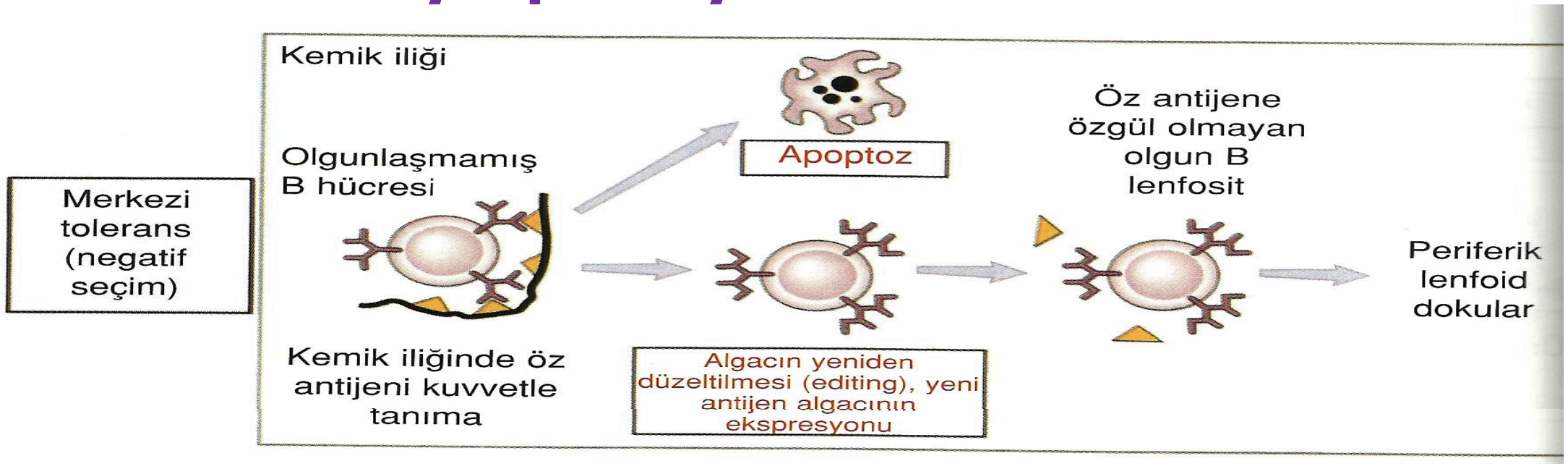
• When B cells recognize self antigens in the bone marrow, the immunoglobulin genes can be rearranged to make a new Ig light chain.

• Thus, this light chain can combine with previously regulated heavy chains to transform into a new algae that is not specific for the previous self antigen.

• Change of receptor specificity is **called receptor editing.**

B Lymphocyte Tolerance

- **Central B Lymphocyte Tolerance**



B Lymphocyte Tolerance

• Peripheral B Lymphocyte Tolerance

• The B cell, which encounters high concentrations of self-antigens in peripheral tissues, becomes anergic and does not respond to that antigen again.

• According to another assumption, if the B lymphocyte recognizes an antigen but does not receive the necessary help message from the T cell (T cells may have developed tolerance to that antigen), it becomes anergic.

B Lymphocyte Tolerance

• Peripheral B Lymphocyte Tolerance

• T-independent antigens are probably only able to activate B lymphocytes when they are strongly stimulated.

• Anergic B lymphocytes may leave the lymphoid follicle or are subsequently excluded from the lymphoid follicle. These excluded B cells die because they do not receive the necessary stimulation to survive.

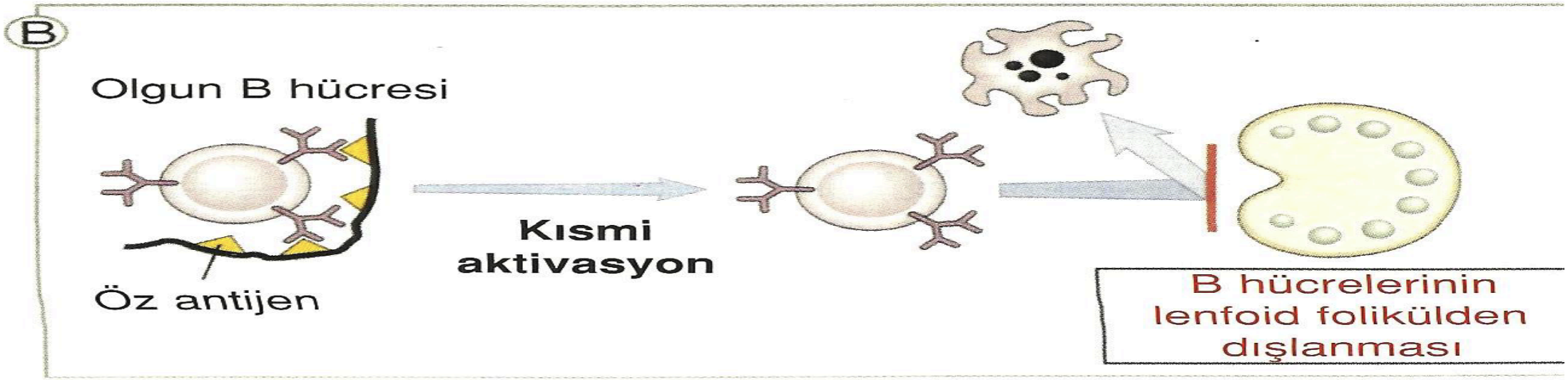
B Lymphocyte Tolerance

- **Peripheral B Lymphocyte Tolerance**

If the mature B cell recognizes a self-antigen without the help of peripheral T cells, it is functionally stopped and cannot respond to that antigen.

B Lymphocyte Tolerance

- **Peripheral B Lymphocyte Tolerance**



B cells that partially respond without T cell help may be excluded from the follicle and die because they cannot receive vital stimuli.

Genetic Factors in Autoimmunity

Genetic Factors in Autoimmunity

- Many genes predispose to autoimmune disease, but the most important of these are MHC genes.
- The important role of autoimmunity genetic factors has attracted attention in studies conducted with twins.
- When an autoimmune disease develops in one of the twins, the probability of development in the other twin is much higher than expected in the society. Moreover, this increased frequency is higher in identical twins than in fraternal twins.

Genetic Factors in Autoimmunity

- Many autoimmune diseases in humans and co-lineages are associated with certain **MHC alleles.**

- The relationship between HLA alleles and autoimmune diseases has been known for a long time, and this information was perceived as primary evidence that T cells also play an important role in these diseases (because the main task of MHC molecules is to present peptide antigens to T cells).

Genetic Factors in Autoimmunity

- The frequency of some autoimmune diseases is observed to be much higher in those who carry a certain HLA allele than in those who do not.
- This increased frequency is defined as the "relative risk" in the HLA-disease association. It should be noted here that carrying a particular HLA allele increases the risk of developing that autoimmune disease, but the allele itself is not the cause of the disease.

Genetic Factors in Autoimmunity

Certain MHC antigens can cause the development of autoimmunity by:

- Inability to present self antigens effectively
- Causing false negative selection
- failure of the peptide presented by these MHCs to stimulate the development of regulatory T cells

Genetic Factors in Autoimmunity

Kanıt	Örnekler		
	Hastalık	HLA alleli	Göreceli risk
Belirli bir HLA allelini taşıyan bireylerde, taşımayanlara göre otoimmün hastalığın gelişmesinde "göreceli risk"	Ankilozan Spondilit Romatoid Artrit İnsüline bağımlı diabetes mellitus Pemphigus vulgaris	B27 DR4 DR3/DR4 DR4	90 4 25 14
Hayvan modelleri: Seçici çiftleştirmelerle belirli bir MHC alleli ile birlikteliğin gösterilmesi	İnsüline bağımlı diabetes mellitus (non-obez diyabetik fare suşu)	$I\text{-}A^{g7}$	
Genom tarama yöntemi ile MHC bölgesinin hastalıkla ilişkisi	İnsüline bağımlı diabetes mellitus	DR	

- Association of autoimmune diseases with MHC locus alleles. In many ways, data support the link between certain MHC alleles and some autoimmune diseases.

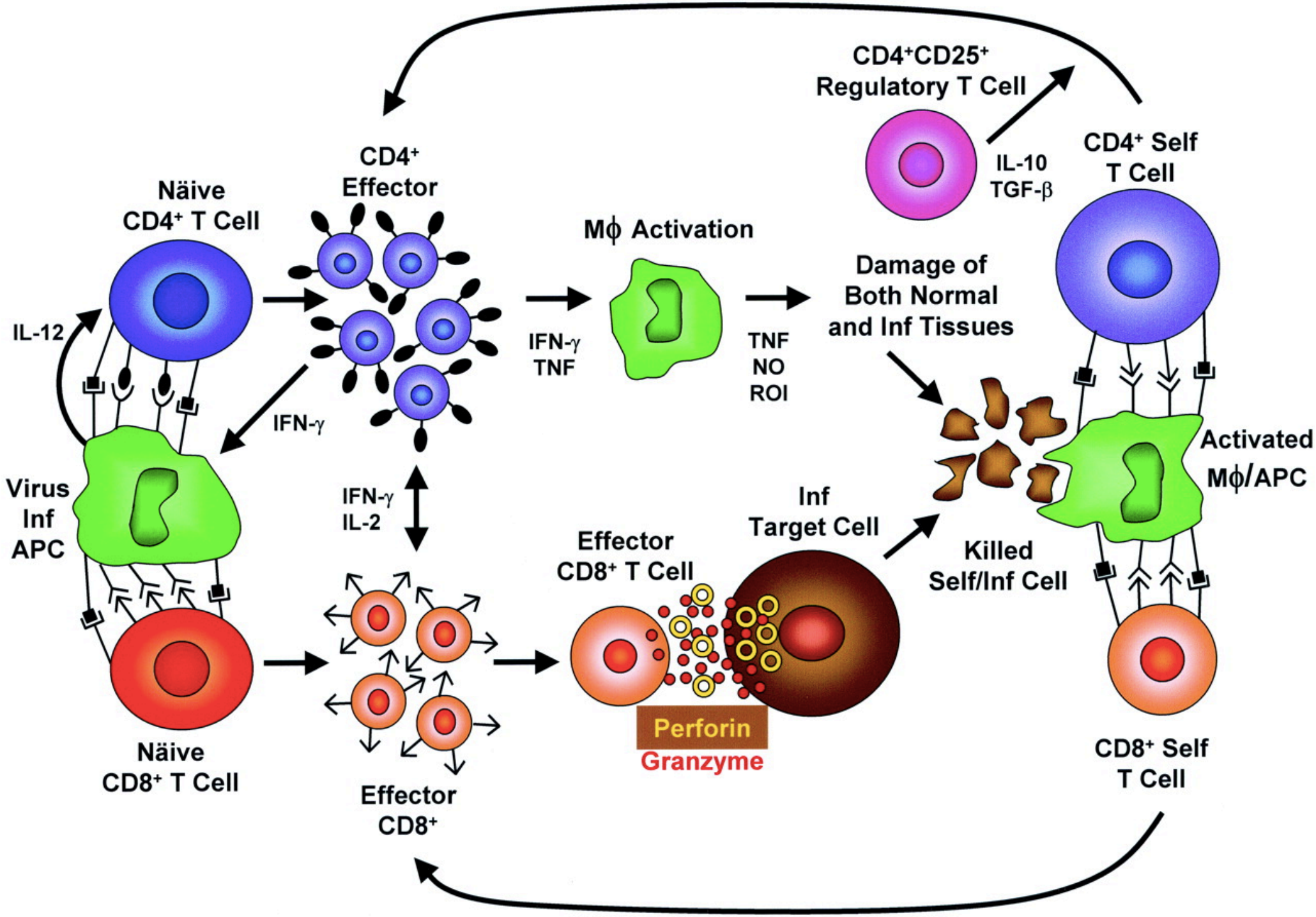
Genetic Factors in Autoimmunity

Gen(ler)	Hastalıkla ilişki	Mekanizma
Kompleman proteinleri (C2, C4)	Lupus benzeri hastalık	İmmün komplekslerin etkin bir şekilde temizlenememesi? B hücre toleransında hata?
Fas, FasL	Lpr, gld sıçan suşları insanda ALPS	Öze tepkili T ve B lenfositlerinin aktivasyonla ortaya çıkan hücre ölümü (AICD) ile elenememesi
AIRE	Kandidiazis ve ektodermal displazi ile seyreden otoimmün poliendokrinopati	Timusta öze tepkili T hücrelerinin elenme yetersizliği

- The role of some non-MHC genes in autoimmunity: here are examples of genes involved in the development of non-MHC autoimmunity.

Lpr: lymphoproliferation in the rat, gld: diffuse lymphoproliferative disease, AICD activation-induced cell death; ALPS, autoimmune lymphoproliferative syndrome.

Role of Infections in Autoimmunity


CD4+CD25+
Regulatory T Cell
IL-10
TGF-β
CD4+ Self
T Cell
CD4+
Effector
Näive
CD4+ T Cell
Mϕ Activation
Damage of
Both Normal
and Inf Tissues
IL-12
IFN-γ
TNF
IFN-γ
TNF
NO
ROI
Activated
Mϕ/APC
Virus
Inf
APC
IFN-γ
IL-2
Inf
Target Cell
Effector
CD8+ T Cell
Killed
Self/Inf Cell
Perforin
Granzyme
Näive
CD8+ T Cell
Effector
CD8+
CD8+ Self
T Cell

Role of Infections in Autoimmunity

- Infections can activate self-directed lymphocytes and lead to the development of autoimmune diseases.
- Clinicians have observed for years that the symptoms of autoimmune diseases appear or increase in the early stages of infectious diseases.
- The association of infections with autoimmune tissue injury has also been demonstrated in animal models.

Role of Infections in Autoimmunity

- Infections can contribute to the development of autoimmunity in many ways.
- Infection in a tissue leads to activation of innate immunity in that area, thus increasing the expression and production of co-stimulatory messages and cytokines in APC.
- As a result, activated APCs also stimulate self-responsive T cells in that tissue.

Role of Infections in Autoimmunity

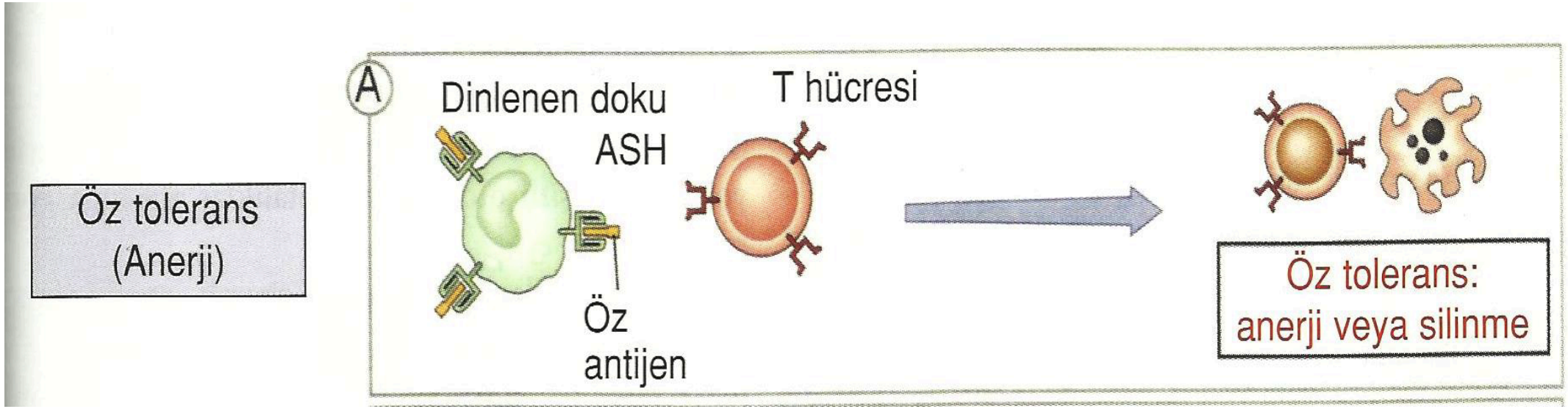
- Infections may break T cell anergy and cause the survival and activation of self-reactive lymphocytes.
- Some **microorganisms contain or produce peptides that are very similar to or cross-react with our antigens.**
- In this case, the immune response and attack against this peptide will be self-directed.

Role of Infections in Autoimmunity

- This cross-reaction between the peptides of microorganisms and our antigens is defined as **"molecular affinity".**

- The actual role of the molecular affinity event in the development of autoimmune diseases is unknown.

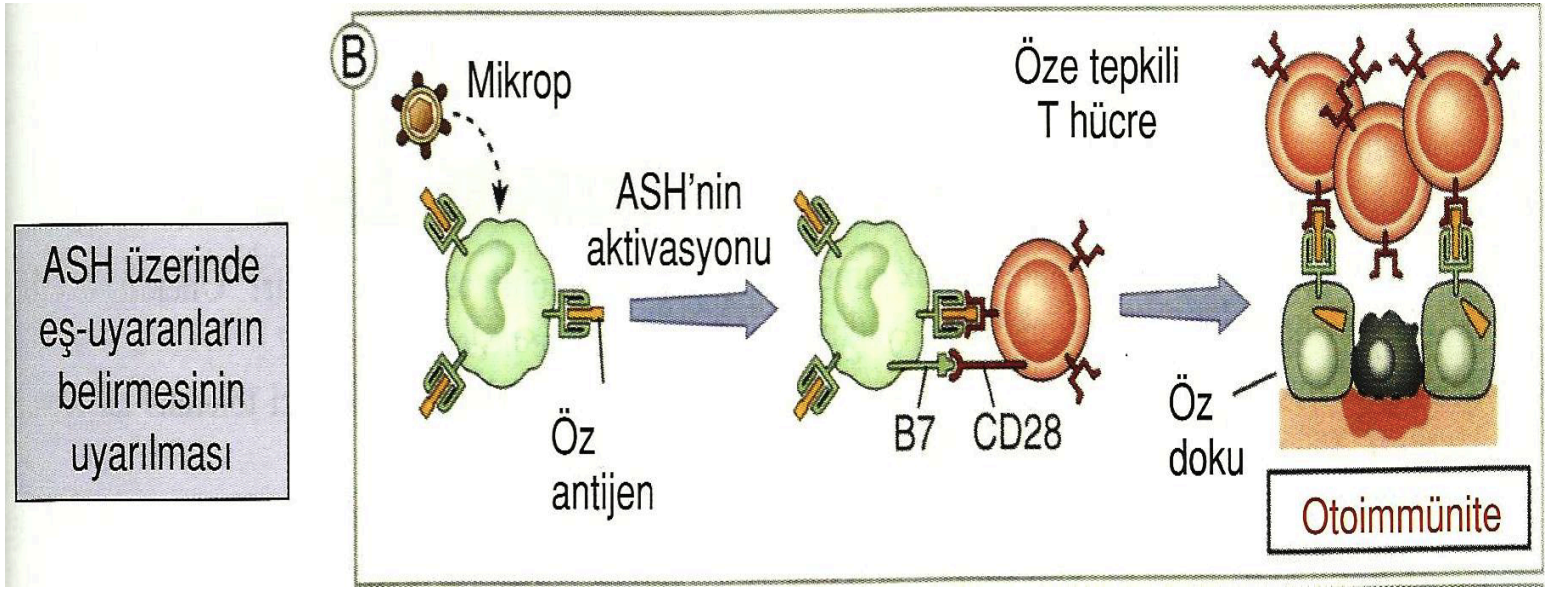
Role of Infections in Autoimmunity



- Normally, anergy or deletion occurs when mature T cells see self-antigens on unactivated APCs.

Role of Infections in Autoimmunity

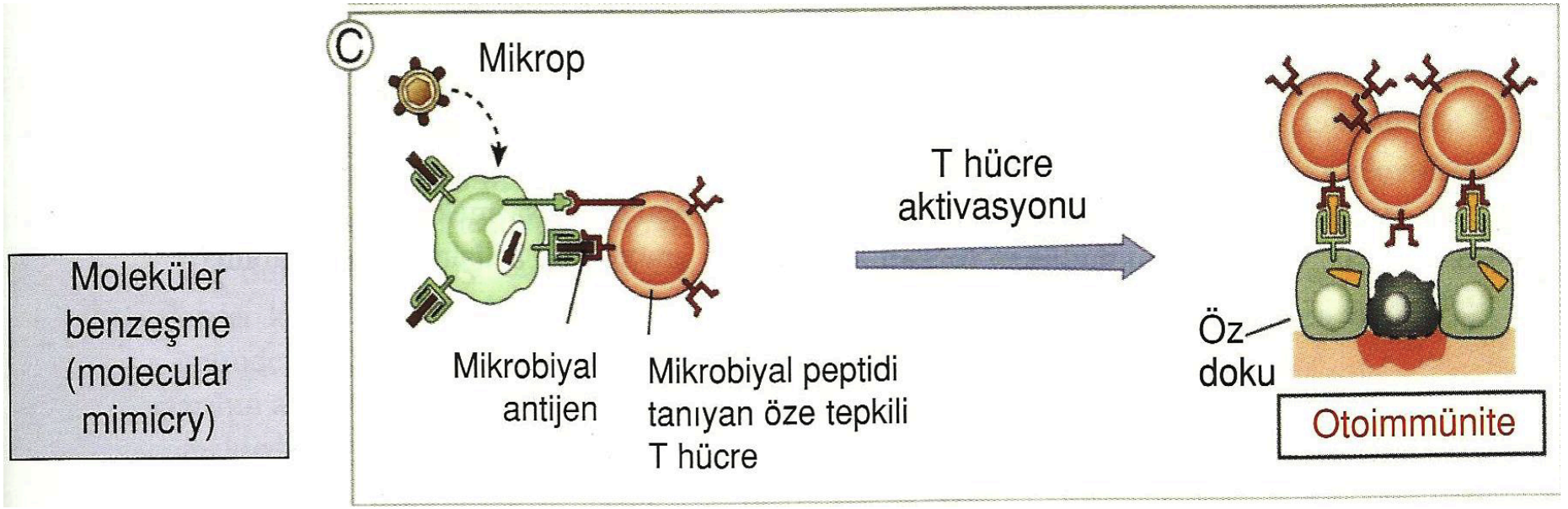
Mechanisms of microorganisms causing autoimmunity



- Microorganisms activate APCs, causing them to display secondary messages and co-stimuli, in which case response-responsive T cells tend to interact instead of tolerance.

Role of Infections in Autoimmunity

Mechanisms of microorganisms causing autoimmunity



- **Some microbial antigens are similar to self antigens and therefore T cells activated for this peptide will also target our self antigens.** Molecular affinity is also valid for B lymphocytes.