ΑΝΤΙΓΟΝΑ ΚΑΙ ΑΝΤΙΓΟΝΟΠΑΡΟΥΣΙΑΣΗ

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Ανοσία / Immunity (άνευ νόσου)**:** είναι η προστασία (άμυνα) του οργανισμού έναντι βλαπτικών παραγόντων κυρίως μικροοργανισμών, η οποία επιτυγχάνεται μέσω του ανοσοποιητικού / ανοσολογικού συστήματος (αμυντικό σύστημα)

Ανοσιακή απάντηση / Immune response : είναι η συλλογική και συντονισμένη απάντηση του οργανισμού στην εισαγωγή ξένων ουσιών που επιτυγχάνεται μέσω των κυττάρων και των μορίων του ανοσιακού συστήματος

Phases of the immune response			
Response		**Typical time after infection to start of response**	**Duration of response**
Innate immune response	Inflammation, complement activation, phagocytosis, and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Elimination of pathogen by effector cells and antibody	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Έμφυτη ή φυσική ανοσία (Innate)   **Προσαρμοστική ή ειδική ή επίκτητη ανοσία (adaptive)**
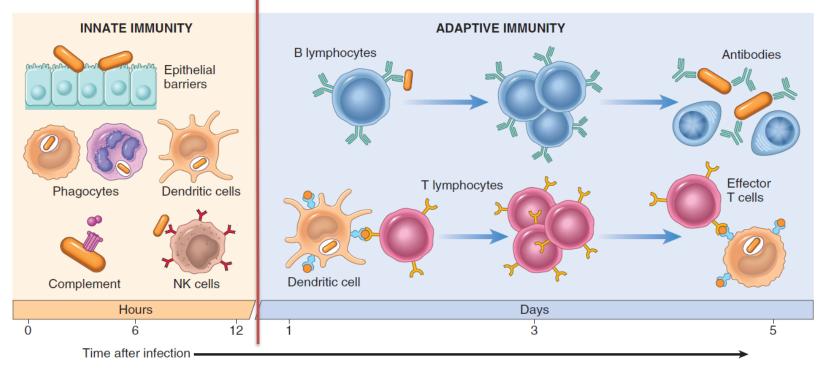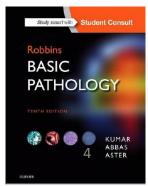

Fig. 5.1 The principal components and kinetics of response of the innate and adaptive immune systems. *NK cells*, Natural killer cells.

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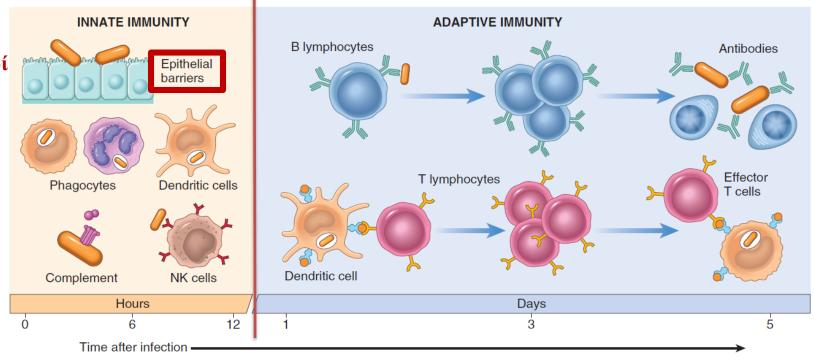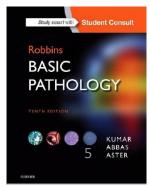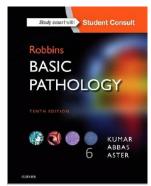
• **Επιθηλιακοί φραγμοί**

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- **Επιθηλιακοί φραγμοί**

- **Φαγοκύτταρα**
- **NK κύτταρα**
- **Συμπλήρωμα**

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18/02/2022

Μακροφάγα

- Τοπικοί φρουροί στις πύλες εισόδου μικροβίων *(δέρμα, πνεύμονες, βλεννογόνοι)*

- Ενεργοποιούνται μετά την αναγνώριση μέσω επιφανειακών υποδοχέων που φέρουν, οι οποίοι καλούνται *pattern recognition receptors* (υπολογίζεται πως υπάρχουν περίπου 100 διαφορετικοί π.χ. LPS receptor, mannose receptor, TLRs), συστατικών του εξωτερικού τοιχώματος των μικροβίων, που καλούνται *pathogen-associated molecular patterns (*υπολογίζεται ότι υπάρχουν περίπου 1000 διαφορετικά *π.χ. LPS, mannose etc).*

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Macrophages express receptors for many microbial constituents

mannose receptor
LPS receptor (CD14)
TLR-2
TLR-4
glucan receptor
scavenger receptor

Figure 1-10 Immunobiology, 7ed.(© Garland Science 2008)

EXTRACELLULAR
Bacterial products
TLR
Microbial polysaccharide
Lectin
Plasma membrane

CYTOSOLIC
NOD-like receptor
Bacterial peptidoglycan; products of damaged cells
Viral RNA
RIG-like receptor

ENDOSOMAL
Nucleic acids of ingested microbes
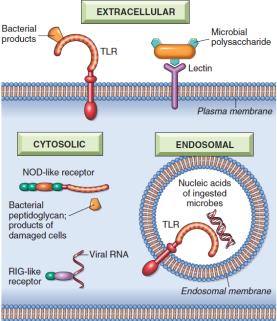TLR
Endosomal membrane

Fig. 5.2 Cellular receptors for microbes and products of cell injury. Phago-cytes, dendritic cells, and many types of epithelial cells express different classes of receptors that sense the presence of microbes and dead cells. Toll-like receptors (TLRs) located in different cellular compartments, as well as other cytoplasmic and plasma membrane receptors, recognize products of different classes of microbes. The major classes of innate immune recep-tors are TLRs, NOD-like receptors in the cytosol (NLRs), C-type lectin receptors, RIG-like receptors for viral RNA, named after the founding member RIG-I, and cytosolic DNA sensors.

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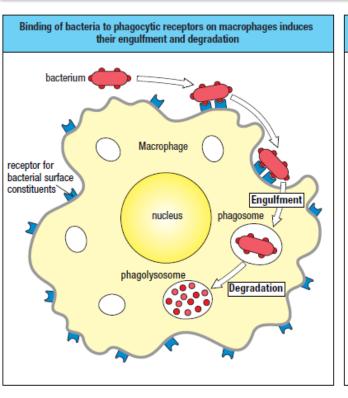
- Στην ενεργοποιημένη μορφή τους καταστρέφουν τον εισβολέα μέσω φαγοκυττάρωσης

- Παράγουν την κυτταροκίνη TNF *(ο TNF καταστρέφει μολυσμένα κύτταρα από ιούς καθώς και καρκινικά κύτταρα και συμβάλλει στη ενεργοποίηση άλλων ανοσολογικών συντελεστών όπως NK κύτταρα)*

- Ενεργοποιούνται και από την IFN-γ

Μακροφάγα

Binding of bacteria to phagocytic receptors on macrophages induces their engulfment and degradation

Binding of bacterial components to signaling receptors on macrophages induces the synthesis of inflammatory cytokines
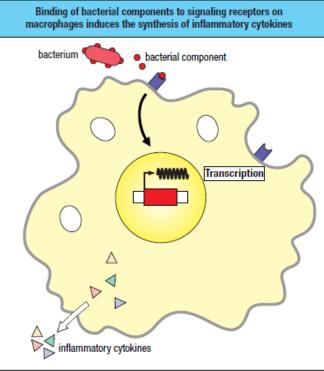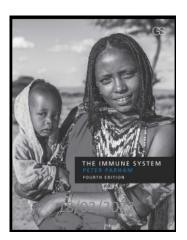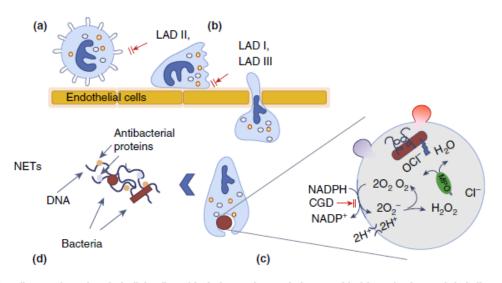
Figure 1.16 Macrophages respond to pathogens by using different receptors to stimulate phagocytosis and cytokine secretion. The left panel shows receptor-mediated phagocytosis of bacteria by a macrophage. The bacterium (red) binds to cell-surface receptors (blue) on the macrophage, inducing engulfment of the bacterium into an internal vesicle called a phagosome within the macrophage cytoplasm. Fusion of the phagosome with lysosomes forms an acidic vesicle called a phagolysosome, which contains toxic small molecules and hydrolytic enzymes that kill and degrade the bacterium. The right panel shows how a bacterial component binding to a different type of cell-surface receptor sends a signal to the macrophage's nucleus that initiates the transcription of genes for inflammatory cytokines. The cytokines are synthesized in the cytoplasm and secreted into the extracellular fluid.

Ουδετερόφιλα πολυμορφοπύρηνα

- Ιδιαίτερα δραστικά φαγοκύτταρα στην ενεργοποιημένη τους μορφή (επιτελεστές), με μικρή διάρκεια ζωής

- Παράγουν και απελευθερώνουν ισχυρές δραστικές ουσίες *(λυσοσωματικά ένζυμα, ρίζες οξυγόνου)* και κυτταροκίνες όπως TNF

- Αναγνώριση βλαπτικών παραγόντων μέσω υποδοχέων PRR (pattern recognition receptors). Σημαντικότεροι οι υποδοχείς τύπου Toll (TLR)

Figure 1 (a) Neutrophils roll on activated endothelial cells, with their attachment being provided by selectins and their ligands (defective in leuko-cyte adhesion deficiencies (LAD) II). (b) Neutrophils adhere firmly to endothelial cells and migrate toward tight junctions (defective in LAD I and III). (c) Neutrophils phagocytize microorganisms, and (*blow-up*) use NADPH oxidase (defective in chronic granulomatous disease (CGD)) to drive forma-tion of hypochlorous acid for killing of microbes and fusion of granules that empty their contents of bactericidal peptides ⚲ to kill microbes. (d) neutrophil extracellular traps (NETs), strands of extracellular DNA with antimicrobial proteins attached, which capture and possibly kill microbes.

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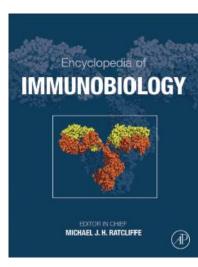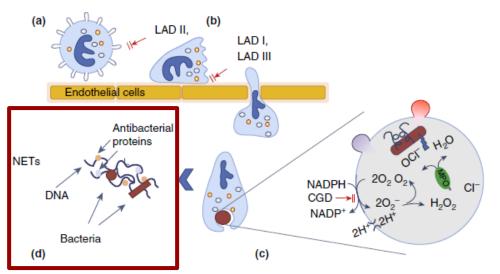

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Fig. 1.10 Infection triggers an inflammatory response. Macrophages encountering bacteria or other types of microorganisms in tissues are triggered to release cytokines (left panel) that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues (center panel). Macrophages also produce chemokines, which direct the migration of neutrophils to the site of infection. The stickiness of the endothelial cells of the blood vessel wall is also changed, so that circulating cells of the immune system adhere to the wall and are able to crawl through it; first neutrophils and then monocytes are shown entering the tissue from a blood vessel (right panel). The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes can also contribute to inflammation.

Bacteria trigger macrophages to release cytokines and chemokines

cytokines

chemokines

Vasodilation and increased vascular permeability cause redness, heat, and swelling

neutrophil

protein

fluids

Inflammatory cells migrate into tissue, releasing inflammatory mediators that cause pain

monocyte

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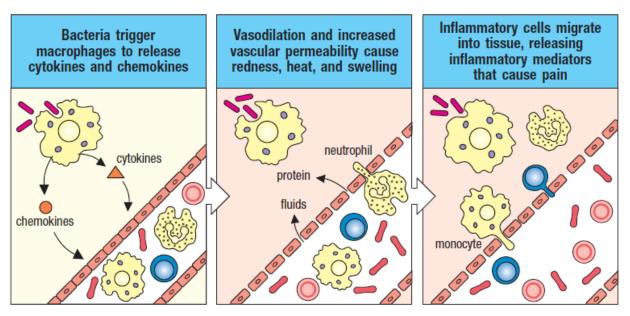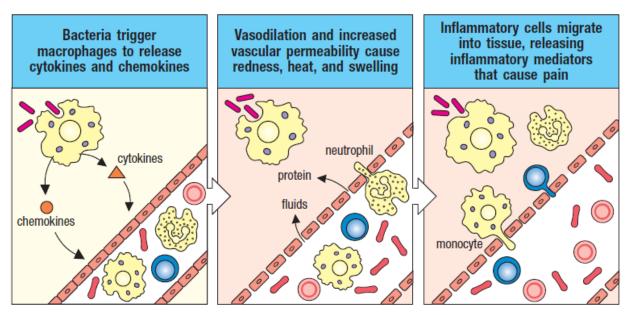

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Inflammation

Pathogens adhere to epithelium	Local infection, penetration of epithelium	Local infection of tissues	Adaptive immunity

tissue macrophage   tissue dendritic cell

blood vessel

Protection against infection

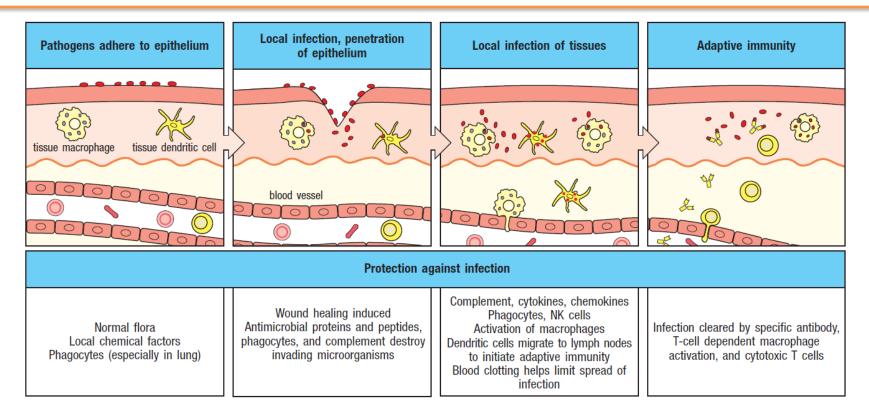|			
Normal flora Local chemical factors Phagocytes (especially in lung)	Wound healing induced Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms	Complement, cytokines, chemokines Phagocytes, NK cells Activation of macrophages Dendritic cells migrate to lymph nodes to initiate adaptive immunity Blood clotting helps limit spread of infection	Infection cleared by specific antibody, T-cell dependent macrophage activation, and cytotoxic T cells

Fig. 2.8 **An infection and the response to it can be divided into a series of stages.** These are illustrated here for an infectious microorganism entering through a wound in the skin. The infectious agent must first adhere to the epithelial cells and then cross the epithelium. A local immune response may prevent the infection from becoming established. If not, it helps to contain the infection and also delivers the infectious agent, carried in lymph and inside dendritic cells, to local lymph nodes. This initiates the adaptive immune response and eventual clearance of the infection.
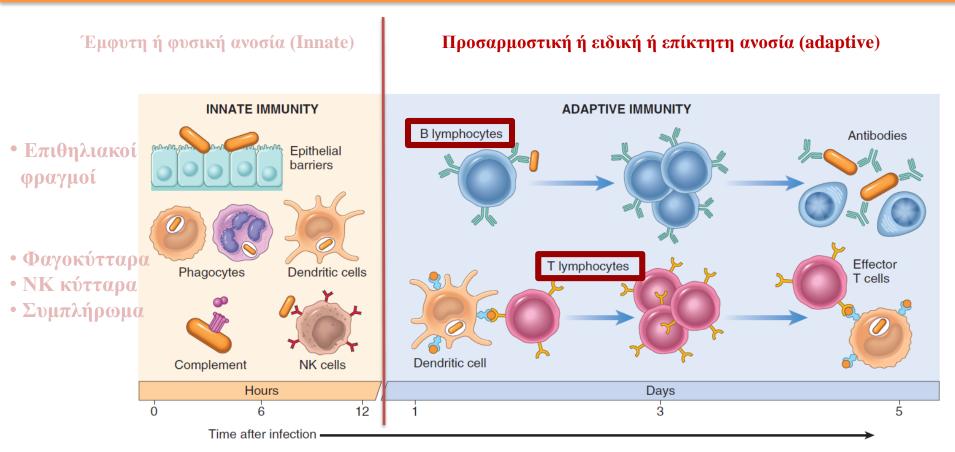
Ανοσιακή απάντηση

Έμφυτη ή φυσική ανοσία (Innate)   **Προσαρμοστική ή ειδική ή επίκτητη ανοσία (adaptive)**

- **Επιθηλιακοί φραγμοί**

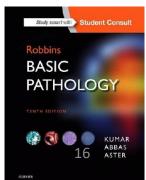- **Φαγοκύτταρα**
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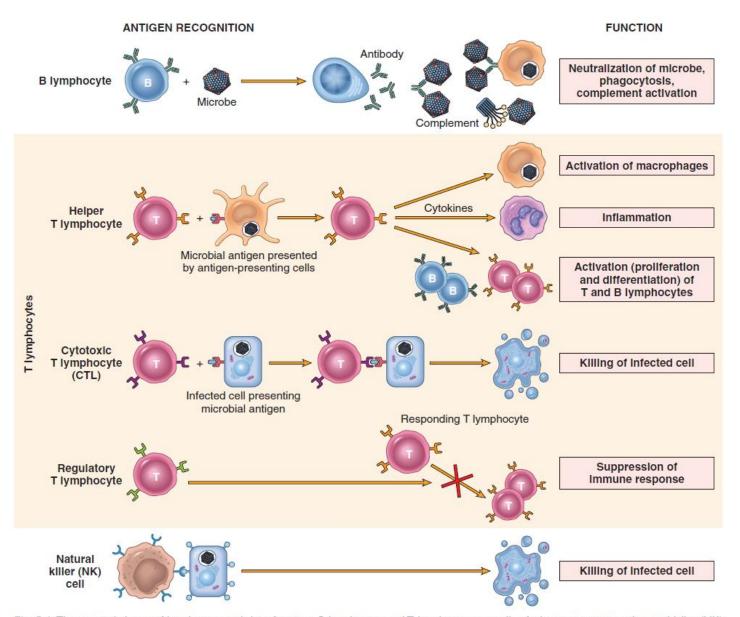
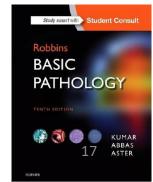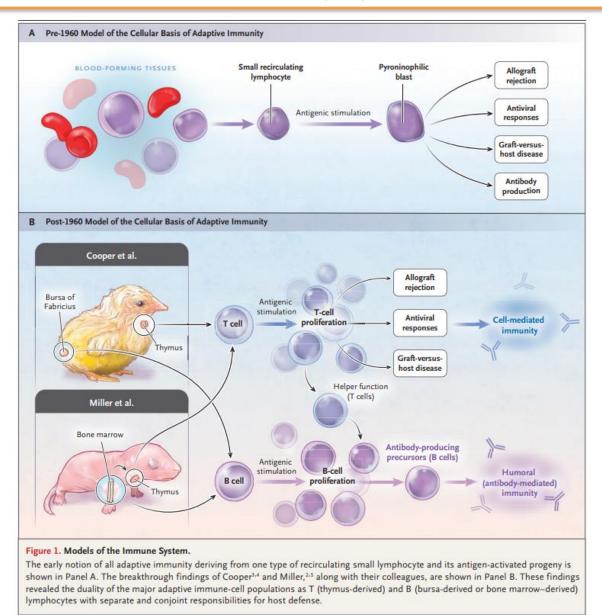**ANTIGEN RECOGNITION**

FUNCTION

Fig. 5.4 The principal classes of lymphocytes and their functions. B lymphocytes and T lymphocytes are cells of adaptive immunity, and natural killer (NK) cells are cells of innate immunity. Several more classes of lymphocytes have been identified, including NK-T cells and so-called "innate lymphoid cells" *(ILCs)*; the functions of these cells are not established.
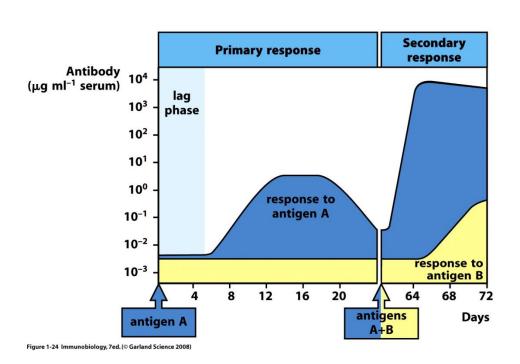
The Cellular Determinants of Adaptive Immunity

Ronald N. Germain, M.D., Ph.D.

Figure 1. Models of the Immune System.

The early notion of all adaptive immunity deriving from one type of recirculating small lymphocyte and its antigen-activated progeny is shown in Panel A. The breakthrough findings of Cooper[3,4] and Miller,[2,5] along with their colleagues, are shown in Panel B. These findings revealed the duality of the major adaptive immune-cell populations as T (thymus-derived) and B (bursa-derived or bone marrow–derived) lymphocytes with separate and conjoint responsibilities for host defense.

Adaptive memory

Figure 1-24 Immunobiology, 7ed. (© Garland Science 2008)

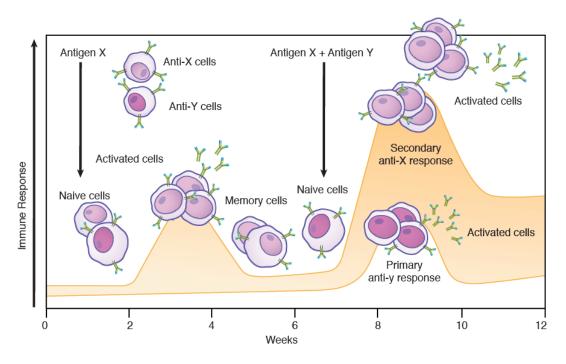**Memory:** The property of the adaptive immune system to respond <u>more rapidly</u>, with <u>greater magnitude</u>, and <u>more effectively</u> to a repeated exposure to an antigen compared with the response to the first exposure.
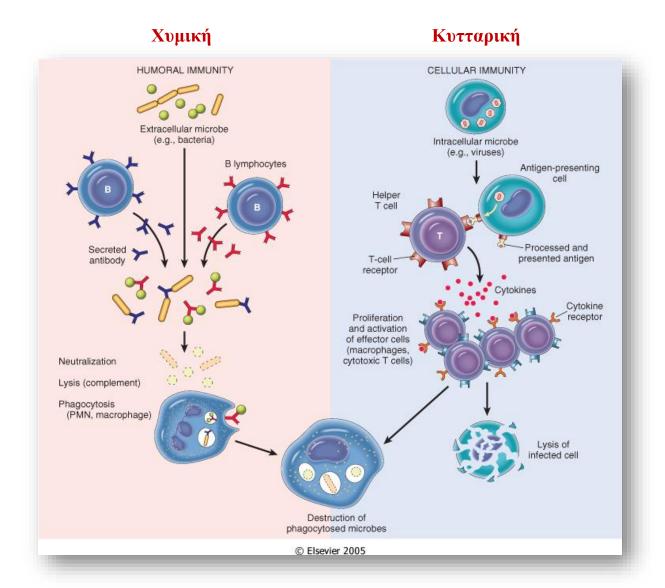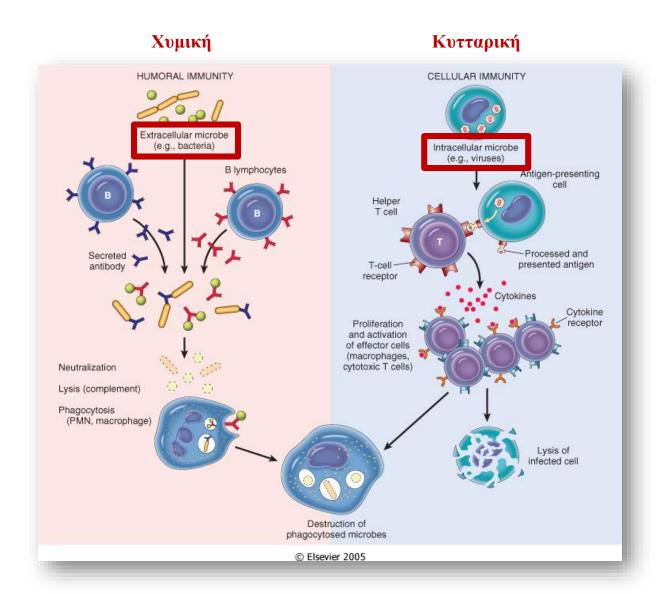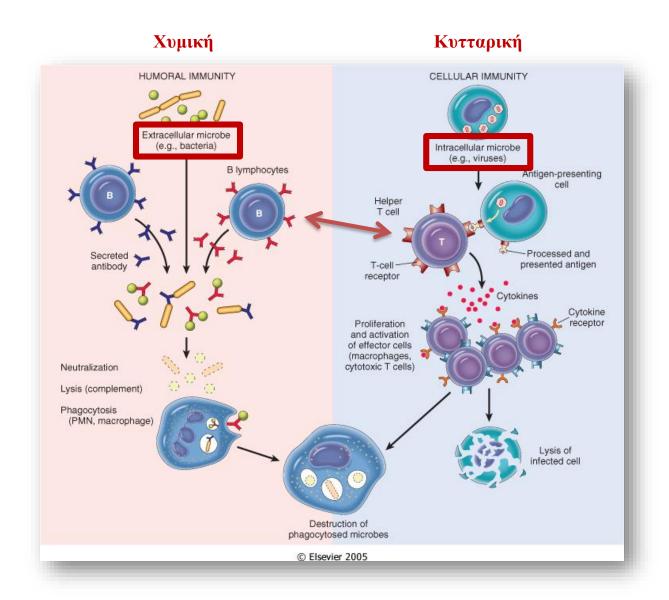
Feature	Primary Response	Secondary Response
Time lag after immunization	5–10 days	1–3 days
Peak response	Small	Large
Antibody isotype	IgM, then IgG	Increasing IgG, IgA, or IgE
Antibody affinity	Variable to low	High (affinity maturation)
Inducing agent	All immunogens	**Protein** antigens
Immunization protocol	High dose of antigen (often with adjuvant)	Low dose of antigen (often without adjuvant)

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▪ Το σύστημα προσαρμοστικής (χυμικής και κυτταρικής) ανοσίας είναι **γενετικά προσχεδιασμένο** για την αναγνώριση και τη στοχευμένη προσβολή του/κάθε ξένου βλαπτικού παράγοντα

▪ Απαντάται μόνο στα σπονδυλωτά ζώα

Χυμική　　　　　　　　**Κυτταρική**

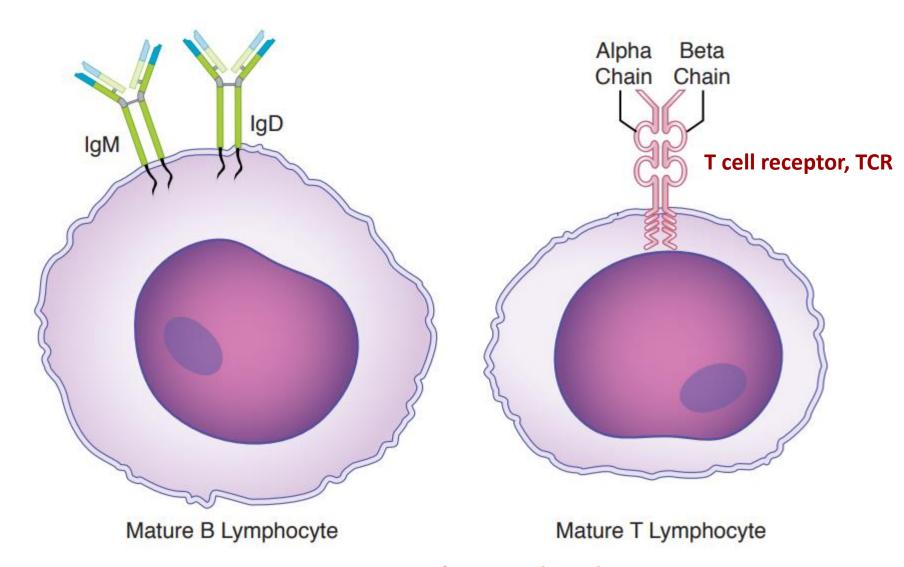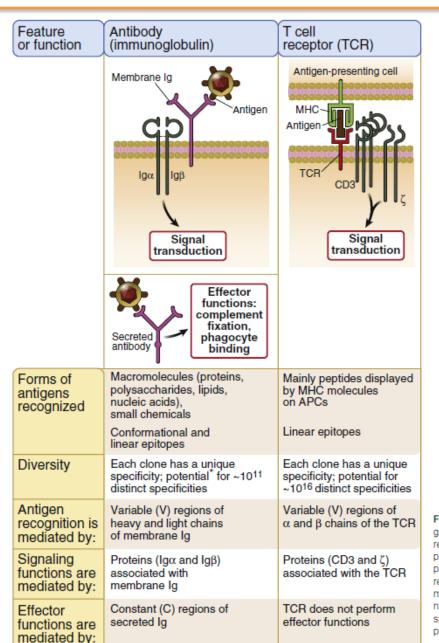**Χυμική** **Κυτταρική**

Χυμική   **Κυτταρική**

Antigen receptors of mature lymphocytes

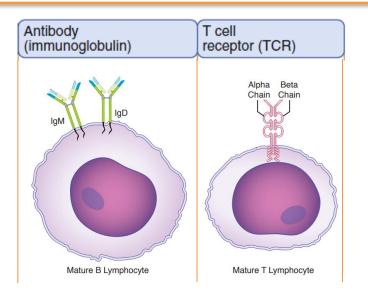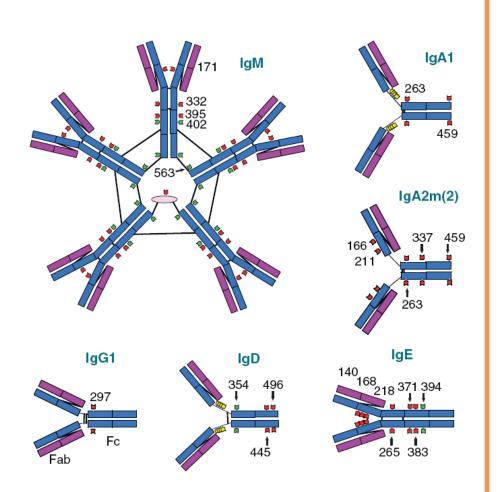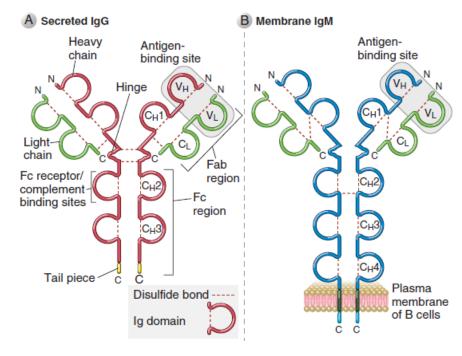| Feature or function	Antibody (immunoglobulin)	T cell receptor (TCR)
Forms of antigens recognized	Macromolecules (proteins, polysaccharides, lipids, nucleic acids), small chemicals Conformational and linear epitopes	Mainly peptides displayed by MHC molecules on APCs Linear epitopes
Diversity	Each clone has a unique specificity; potential* for ~10^{11} distinct specificities	Each clone has a unique specificity; potential for ~10^{16} distinct specificities
Antigen recognition is mediated by:	Variable (V) regions of heavy and light chains of membrane Ig	Variable (V) regions of α and β chains of the TCR
Signaling functions are mediated by:	Proteins (Igα and Igβ) associated with membrane Ig	Proteins (CD3 and ζ) associated with the TCR
Effector functions are mediated by:	Constant (C) regions of secreted Ig	TCR does not perform effector functions

Fig. 4.1 Properties of antibodies and T cell antigen receptors *(TCRs)*. Antibodies (also called immunoglobulins) may be expressed as membrane receptors or secreted proteins; TCRs only function as membrane receptors. When immunoglobulin *(Ig)* or TCR molecules recognize antigens, signals are delivered to the lymphocytes by proteins associated with the antigen receptors. The antigen receptors and attached signaling proteins form the B cell receptor (BCR) and TCR complexes. Note that single antigen receptors are shown recognizing antigens, but signaling typically requires the binding of two or more receptors to adjacent antigen molecules. The important characteristics of these antigen-recognizing molecules are summarized. *The total number of possible receptors with unique binding sites is very large, but only ~10^7–10^9 clones with distinct specificities are present in adults. *APCs*, Antigen-presenting cells; *Ig*, immunoglobulin; *MHC*, major histocompatibility complex.
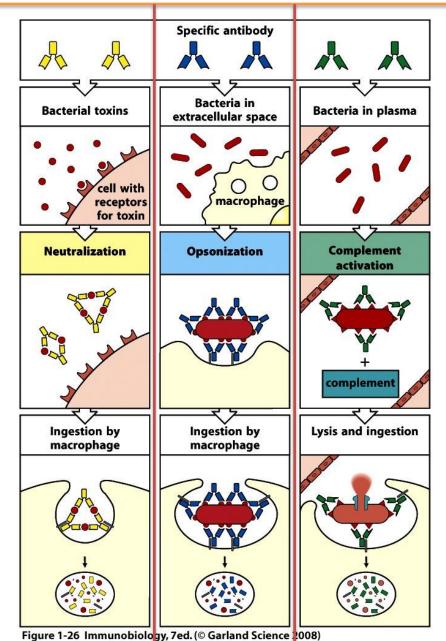
1. Ισότυποι (τάξεις) αντισωμάτων

Immunoglobulin isotypes	All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG. Affinity refers to the individual antibody-antigen interaction, while avidity describes the cumulative binding strength of all antibody-antigen interactions in a multivalent molecule.
IgG	Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). "IgG Greets the Growing fetus."
IgA	Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, *Giardia*). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.
IgM	Produced in the 1° (immediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves.
IgD	Unclear function. Found on surface of many B cells and in serum.
IgE	Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating eosinophils.

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ΧΥΜΙΚΗ ΑΝΟΣΙΑ

Immunoglobulin								
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	δ	ε
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Serum level (mean adult mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.03	5×10^{-5}
Half-life in serum (days)	21	20	7	21	10	6	6	3	2
Classical pathway of complement activation	++	+	+++	–	++++	–	–	–	–
Alternative pathway of complement activation	–	–	–	–	–	+	–	–	–
Placental transfer	+++	+	++	–/+	–	–	–	–	–
Binding to macrophage and phagocyte Fc receptors	+	–	+	–/+	–	+	+	–	+
High-affinity binding to mast cells and basophils	–	–	–	–	–	–	–	–	+++
Reactivity with staphylococcal Protein A	+	+	–/+	+	–	–	–	–	–

Fig. 5.20 The physical and functional properties of the human immunoglobulin isotypes. IgM is so called because of its size: although monomeric IgM is only 190 kDa, it normally forms pentamers, known as macroglobulin (hence the M), of very large molecular weight (see Fig. 5.23). IgA dimerizes to give an approximate molecular weight of around 390 kDa in secretions. IgE antibody is associated with immediate-type hypersensitivity. When fixed to tissue mast cells, IgE has a much longer half-life than its half-life in plasma shown here. The relative activities of the various isotypes are compared for several functions, ranging from inactive (–) to most active (++++).
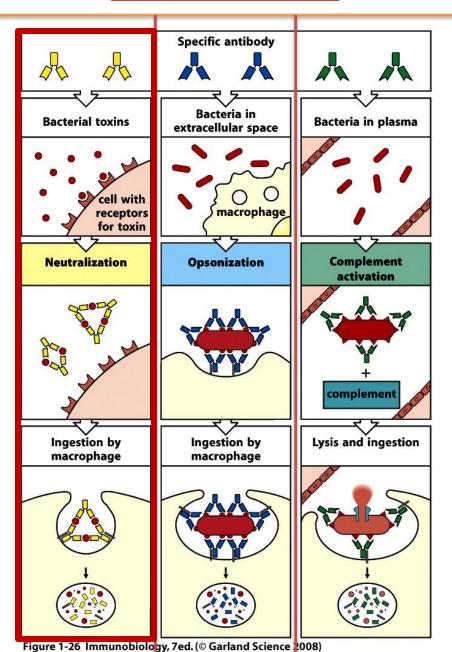
2. Δράση αντισωμάτων

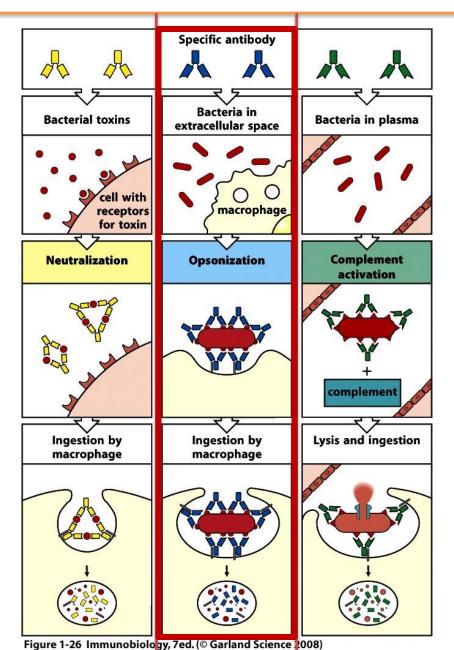Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

2. Δράση αντισωμάτων

▪ **Εξουδετέρωση**

Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)
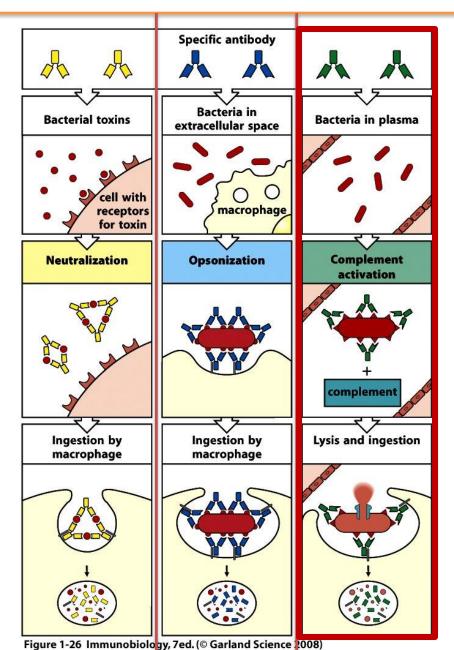
2. Δράση αντισωμάτων

▪ **Οψωνοποίηση**

Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)
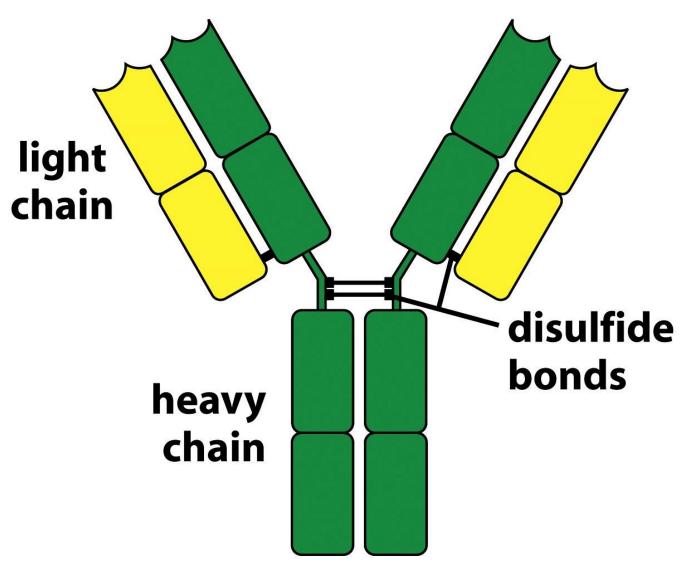
2. Δράση αντισωμάτων

- **Ενεργοποίηση συμπληρώματος**
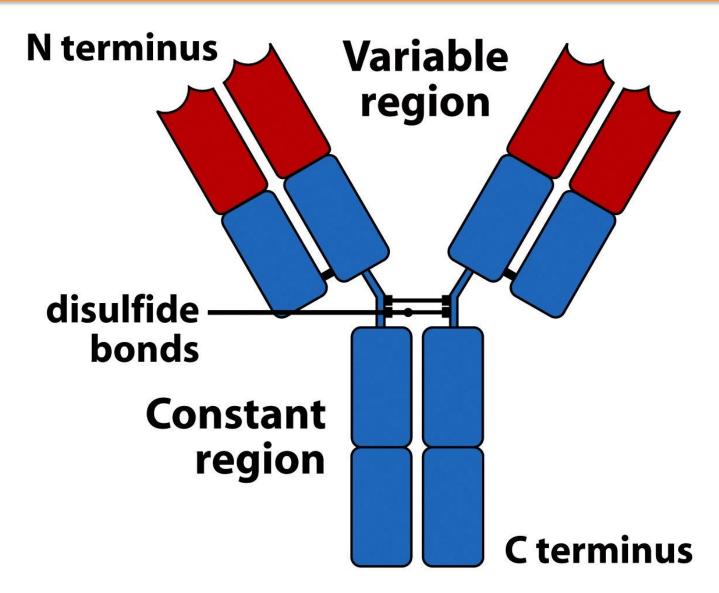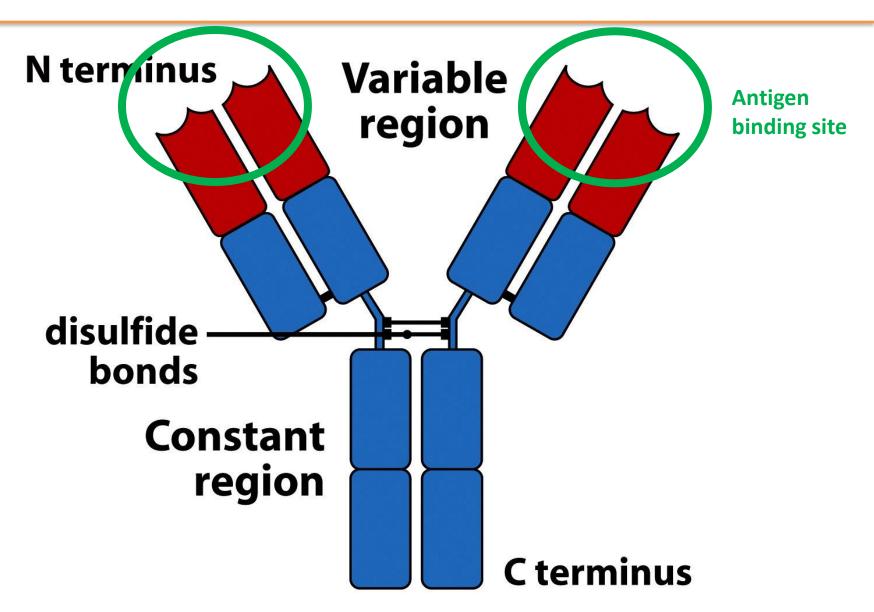
Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

light chain

heavy chain

disulfide bonds

Figure 3-2 Immunobiology, 7ed. (© Garland Science 2008)

Figure 3-1c Immunobiology, 7ed. (© Garland Science 2008)

Figure 3-1c Immunobiology, 7ed. (© Garland Science 2008)

1. Υποδοχέας B λεμφοκυττάρων (BCR, αντίσωμα επιφανείας)

Figure 3-6 Immunobiology, 7ed. (© Garland Science 2008)

1. Υποδοχέας Β λεμφοκυττάρων (BCR, αντίσωμα επιφανείας)
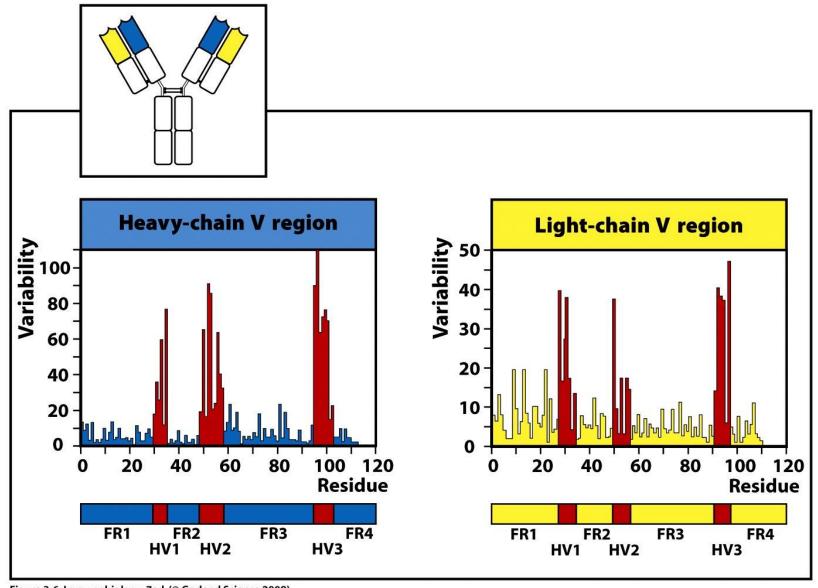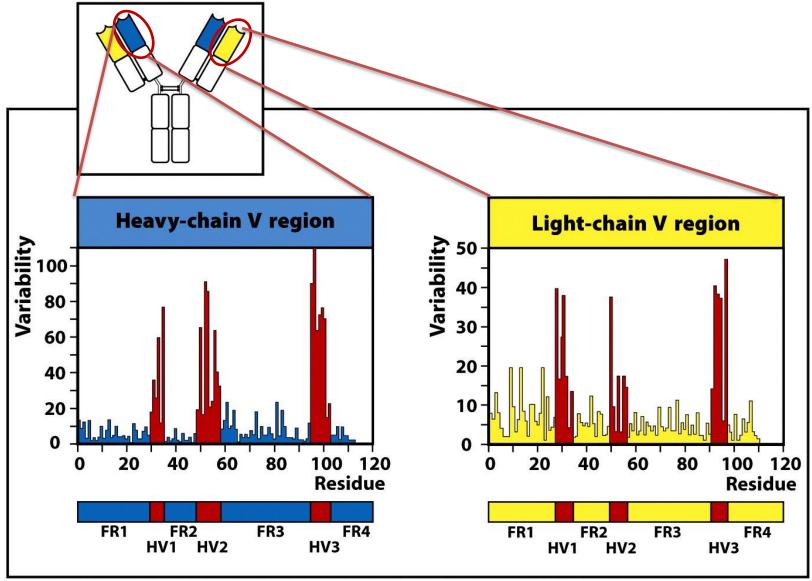
Figure 3-6 Immunobiology, 7ed. (© Garland Science 2008)

Αντιγόνα

Αναγνωρίζονται από τον οργανισμό ως ξένα μόρια και πυροδοτούν μια μη ειδική και μια ειδική ανοσολογική απάντηση

α. Πλήρες αντιγόνο (antigen) / ανοσογόνο (immunogen)

β. Ατελές αντιγόνο (απτίνη, hapten): χαμηλού μοριακού βάρους μόριο *(βραχύ πεπτίδιο ή φαρμακευτική ουσία)* το οποίο δρα σαν αντιγόνο (αναγνωρίζεται από τον υποδοχέα επιφανείας) αλλά για να δράσει σαν ανοσογόνο θα πρέπει να προσδεθεί σε κάποιο μακρομόριο (carrier, φορέας). Αυτό συμβαίνει γιατί προκειμένου να ενεργοποιηθεί το Β λεμφοκύτταρο θα πρέπει πολλοί κοντινοί BCR να ενεργοποιηθούν ταυτόχρονα (cross-linking)

Αντιγόνα
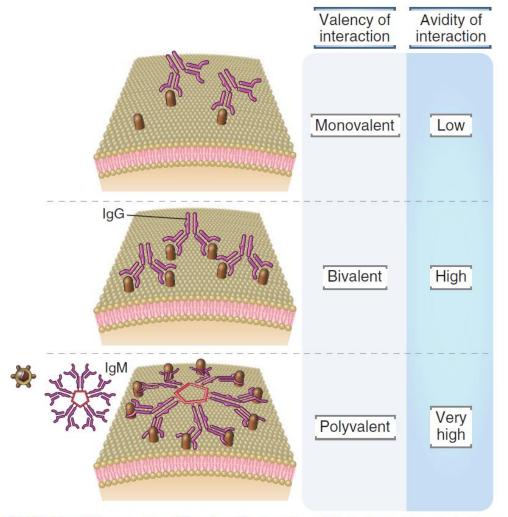
FIGURE 5.14 Valency and avidity of antibody-antigen interactions. Monovalent antigens, or epitopes spaced far apart on cell surfaces, will interact with a single binding site of one antibody molecule. Although the affinity of this interaction may be high, the overall avidity may be relatively low. When repeated determinants on a cell surface are close enough, both the antigen-binding sites of a single IgG molecule can bind, leading to a higher avidity bivalent interaction. The hinge region of the IgG molecule accommodates the shape change needed for simultaneous engagement of both binding sites. IgM molecules have 10 identical antigen-binding sites that can theoretically bind simultaneously with 10 repeating determinants on a cell surface, resulting in a polyvalent, high-avidity interaction.

Αντιγόνα

Cross-linking of B-cell receptors by antigen

bacterial cell

Ag

BCR

B cell

Clustering of antigen receptors allows receptor-associated kinases to phosphorylate the ITAMs
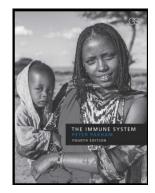
bacterial cell

Ag

BCR

B cell

Blk, Fyn, or Lyn

Syk

Syk binds to doubly phosphorylated ITAMs and is activated on binding

activating signals

Changes in gene expression in nucleus

Figure 9.1 Cross-linking of B-cell receptors by antigens initiates a cascade of intracellular signals. Top panel: the B-cell receptor on a mature, naive B cell is composed of monomeric IgM that binds antigen and associated Igα and Igβ chains, which transduce intracellular signals. The IgM is shown binding repetitive antigens (Ag) on the surface of a bacterium. Center panel: on cross-linking and clustering of the receptors, the receptor-associated tyrosine kinases Blk, Fyn, and Lyn phosphorylate tyrosine residues in the ITAMs of the cytoplasmic tails of Igα (blue) and Igβ (orange). Bottom panel: subsequently, Syk binds to the phosphorylated ITAMs of the B-cell receptor Igβ chains, which are in close proximity within the cluster and activate each other by transphosphorylation, thus initiating further signaling. Ultimately, the signals are relayed to the nucleus of the B cell, where they induce the changes in gene expression that initiate B-cell activation.

18/02/2022

THE IMMUNE SYSTEM
PETER PARHAM
FOURTH EDITION

Αντιγόνα

Αναγνωρίζονται από τον οργανισμό ως ξένα μόρια και πυροδοτούν μια μη ειδική και μια ειδική ανοσολογική απάντηση

α. Πλήρες αντιγόνο (antigen) / ανοσογόνο (immunogen)

β. Ατελές αντιγόνο (απτίνη, hapten): χαμηλού μοριακού βάρους μόριο *(βραχύ πεπτίδιο ή φαρμακευτική ουσία)* το οποίο δρα σαν αντιγόνο (αναγνωρίζεται από τον υποδοχέα επιφανείας) αλλά για να δράσει σαν ανοσογόνο θα πρέπει να προσδεθεί σε κάποιο μακρομόριο (carrier, φορέας). Αυτό συμβαίνει γιατί προκειμένου να ενεργοποιηθεί το Β λεμφοκύτταρο θα πρέπει πολλοί κοντινοί BCR να ενεργοποιηθούν ταυτόχρονα (cross-linking)

γ. Επίτοπος (epitope) ή αντιγονικός καθοριστής (determinant): περιοχή στο αντιγόνο που συνδέεται με το αντίσωμα (πολύ μικρή περιοχή, 5-7 αμινοξέα)

Αντιγονικοί επίτοποι
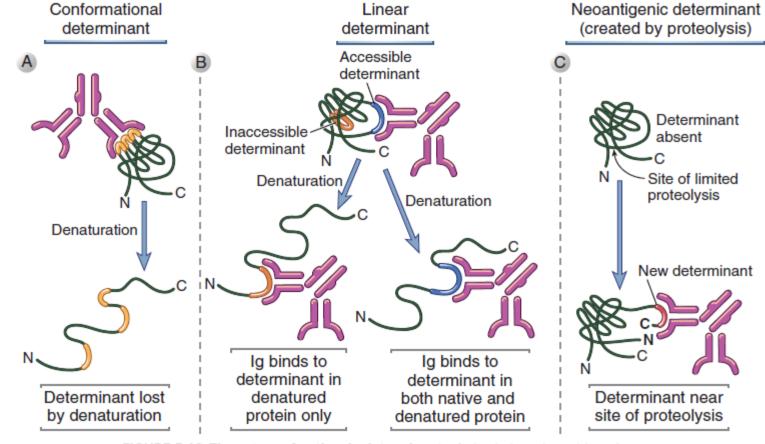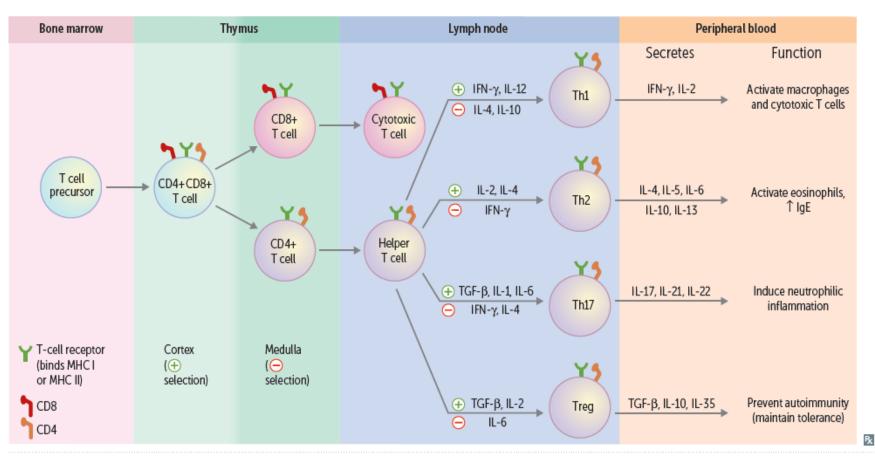
FIGURE 5.13 The nature of antigenic determinants. Antigenic determinants (shown in orange, red, and blue) may depend on protein folding (conformation) as well as on primary structure. Some determinants are accessible in native proteins and are lost on denaturation (**A**), whereas others are exposed only on protein unfolding (**B**). Neodeterminants arise from postsynthetic modifications such as peptide bond cleavage (**C**).

Differentiation of T cells

Positive selection — Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.

Negative selection — Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-1 (Chronic mucocutaneous candidiasis, Hypoparathyroidism, Adrenal insufficiency, Recurrent Candida infections). "Without AIRE, your body will CHAR".

45
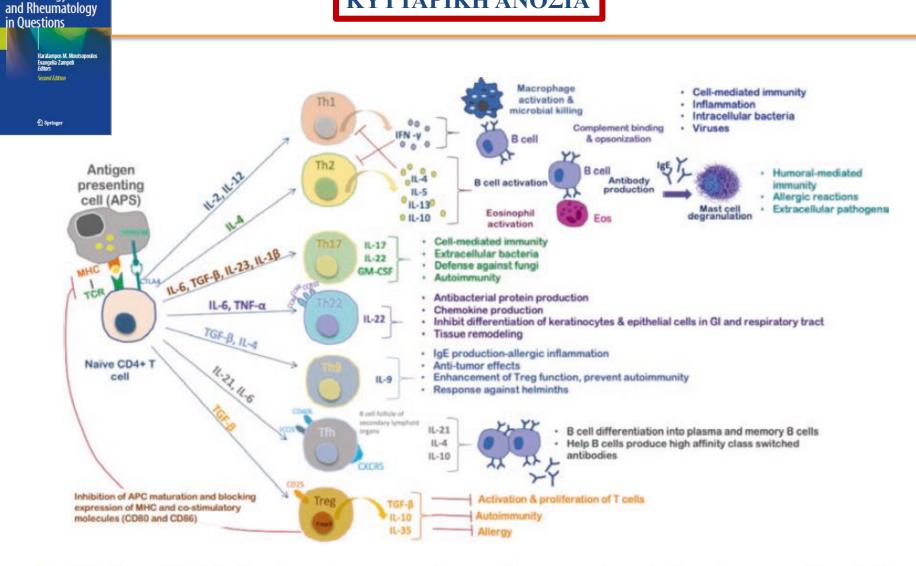
Fig. 1.2 Naïve CD4⁺ T cells, after antigen presentation, depending on the cytokine milieu, differentiate to distinct types of T helper (Th) cells. Each of these subsets of Th cells has different functions implicated in adaptive immune responses. On the other hand, regulatory T (T_reg) cells use several mechanisms to suppress the activation, proliferation, and cytokine production of T cells thereby promoting homeostasis and self-tolerance, essential for preventing autoimmunity (*Figure created by Evangelia Zampeli, MD*)

• **Βοηθητικά (T helper, Th)**
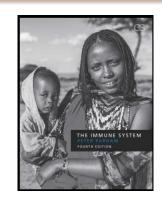
	TH1 cells	TH17 cells	TH2 cells	TFH cells	T regulatory cells (Treg)
Effector CD4 T cell	TH1	TH17	TH2	TFH	Treg
Cytokines that induce differentiation	IL-12 IFN-γ	IL-6 IL-21	IL-4	IL-16 TGF-β IL-23	TGF-β
Defining transcription factor	T-bet	RORγT	GATA3	Bcl6	FoxP3
Characteristic cytokines	IL-12 IFN-γ	IL-17 IL-6	IL-4 IL-5	IL-21	TGF-β IL-10
Function	Activate macrophages	Enhance neutrophil response	Activate cellular and antibody response to parasites	Activate B cells Maturation of antibody response	Suppress other effector T cells

Figure 8.14 Five functional classes of effector CD4 T cell are produced by activation and differentiation in different cytokine environments. Summarized here are the cytokines that induce the different pathways of differentiation, the transcription factors uniquely associated with each pathway, the cytokines made by each type of effector CD4 T cell, and the roles of these cells in the immune response.

• **Βοηθητικά (T helper, Th)**

	TH1 cells	TH17 cells	TH2 cells	TFH cells	T regulatory cells (Treg)
Effector CD4 T cell					
Cytokines that induce differentiation	IL-12 IFN-γ	IL-6 IL-21	IL-4	IL-16 TGF-β IL-23	TGF-β
Defining transcription factor	T-bet	RORγT	GATA3	Bcl6	FoxP3
Characteristic cytokines	IL-12 IFN-γ	IL-17 IL-6	IL-4 IL-5	IL-21	TGF-β IL-10
Function	Activate macrophages	Enhance neutrophil response	Activate cellular and antibody response to parasites	Activate B cells Maturation of antibody response	Suppress other effector T cells

Ανοσοϊστοχημική ανίχνευσή Τους στους ιστούς με την χρήση αντισωμάτων

Figure 8.14 Five functional classes of effector CD4 T cell are produced by activation and differentiation in different cytokine environments. Summarized here are the cytokines that induce the different pathways of differentiation, the transcription factors uniquely associated with each pathway, the cytokines made by each type of effector CD4 T cell, and the roles of these cells in the immune response.

1. Υποδοχέας Β λεμφοκυττάρων (BCR, αντίσωμα επιφανείας)

Αναγνωρίζει εξωκυττάρια αντιγόνα
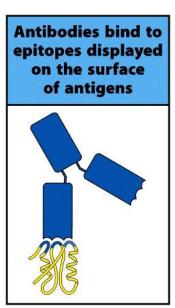
Figure 1-16 Immunobiology, 7ed. (© Garland Science 2008)

2. Υποδοχέας Τ λεμφοκυττάρων (TCR)

Αναγνωρίζει ενδοκυττάρια αντιγόνα με την μορφή σπασμένων μικρών πεπτιδίων τα οποία παρουσιάζονται στην επιφάνεια των κυττάρων με την βοήθεια των αντιγόνων ιστοσυμβατότητας (MHC μόρια)

Figure 1-16 Immunobiology, 7ed. (© Garland Science 2008)
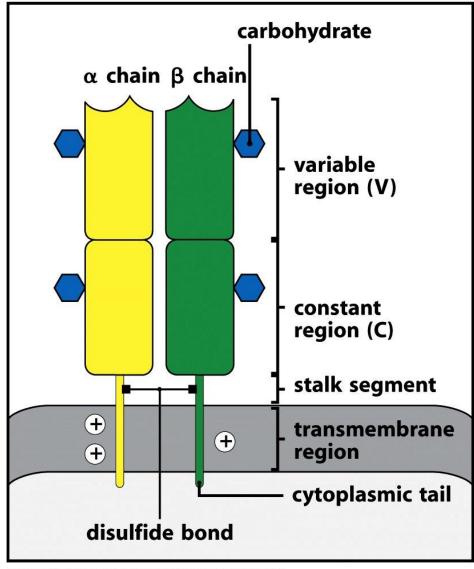
Figure 3-12 Immunobiology, 7ed. (© Garland Science 2008)
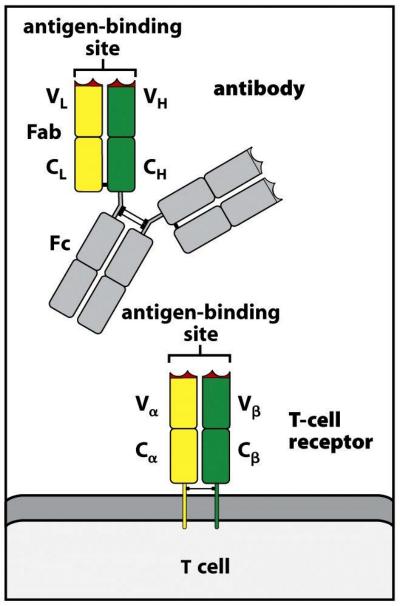
Figure 3-11 Immunobiology, 7ed. (© Garland Science 2008)

Αντιγονική παρουσίαση στον Τ κυτταρικό υποδοχέα

Figure 5-20 Immunobiology, 7ed. (© Garland Science 2008)

Αντιγονική παρουσίαση στον T κυτταρικό υποδοχέα
μέσω των μορίων του μείζονος συμπλέγματος ιστοσυμβατότητας (=αντιγόνα ιστισυμβατότητας)
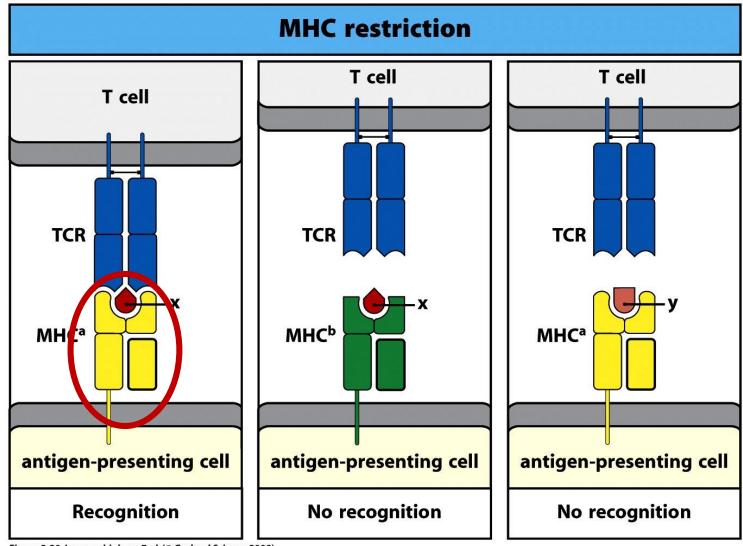
Figure 5-20 Immunobiology, 7ed. (© Garland Science 2008)

Ανοσορυθμιστικά αντιγόνα κυτταρικής επιφάνειας

Συνώνυμα

- Αντιγόνα μείζονος συμπλέγματος ιστοσυμβατότητας (MHC)
- Ανθρώπινα λευκυτταρικά αντιγόνα (HLA)
- Αντιγόνα μεταμοσχεύσεων

- **Βασικοί συντελεστές της ειδικής κυτταρικής ανοσο-αντίδρασης** μέσω της **παρουσίασης αντιγονικών πεπτιδίων ως σύμπλεγμα στα Τ λεμφοκύτταρα**

- **Ιδιαίτερα πολυμορφικό σύστημα** λόγω μεγάλου αριθμού εναλλακτικών γονιδιακών αλληλιών, ο συνδυασμός των οποίων καθορίζει την **ιστική ταυτότητα** κάθε ατόμου

- **Ιδιαίτερα ανοσογόνα**, υπεύθυνα για την απόρριψη αλλομοσχευμάτων

- **HLA Τάξης Ι** : **υπάρχουν σε όλα τα κύτταρα.** Παρουσιάζουν ξένες προς τον οργανισμό πρωτεΐνες ενδο-κυττάριας προέλευσης *(παθολογικές πρωτεΐνες, ιικές πρωτεΐνες και πρωτεΐνες καρκινικών κυττάρων)*

- **HLA Τάξης ΙΙ** : **υπάρχουν κυρίως στα αντιγονοπαρουσιαστικά κύτταρα (antigen presenting cells) δηλ. στα μακροφάγα, στα κύτταρα Langerhans του δέρματος, στα διαπλεκόμενα και δενδριτικά κύτταρα του λεμφικού ιστού και στα Β λεμφοκύτταρα.** Παρουσιάζουν κλάσματα πεπτιδίων (προϊόντα φαγοκυττάρωσης εξωγενών πρωτεϊνών π.χ. *βακτηριακών)*

- **HLA Τάξης ΙΙΙ** : συστατικά συμπληρώματος, κυτταροκίνες (TNFα και β), πρωτεΐνες οξείας φάσης.

Feature	Significance	
Polymorphic genes: Many different alleles are present in the population	Different individuals are able to present and respond to different microbial peptides	
Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	T cells / MHC molecules / Parental chromosomes
MHC-expressing cell types: Class I: All nucleated cells	CD8+ CTLs can kill any type of virus-infected cell	Leukocytes / Epithelial cells / Mesenchymal cells
Class II: Dendritic cells, macrophages, B cells	CD4+ helper T lymphocytes interact with dendritic cells, macrophages, B lymphocytes	Dendritic cell / Macrophage / B cell

Fig. 3.9 Properties of major histocompatibility complex (MHC) molecules and genes. Some of the important features of MHC molecules and their significance for immune responses. *CTLs,* Cytotoxic T lymphocytes.
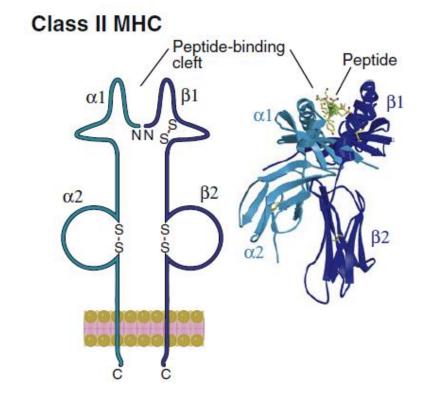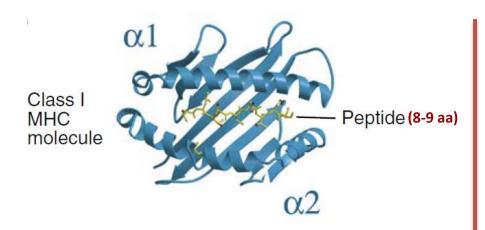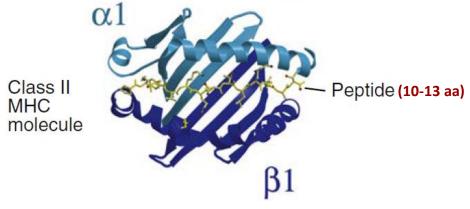
Fig. 3.8 Structure of class I and class II major histocompatibility complex (MHC) molecules. Schematic diagrams *(at left)* and models of the crystal structures *(at right)* of class I MHC and class II MHC molecules illustrate the domains of the molecules and the fundamental similarities between them. Both types of MHC molecules contain peptide-binding clefts and invariant portions that bind CD8 (the α3 domain of class I) or CD4 (the α2 and β2 domains of class II). *Ig,* Immunoglobulin; *β2m,* β2-microglobulin. (Crystal structures courtesy Dr. P. Bjorkman, California Institute of Technology, Pasadena, CA.)

Ταξινόμηση των μορίων HLA

Class I MHC molecule — α1, α2 — Peptide **(8-9 aa)**

Class II MHC molecule — α1, β1 — Peptide **(10-13 aa)**

Ενδογενή αντιγόνα

↓

CD8+ κυτταροτοξικά T λεμφοκύτταρα

Εξωγενή αντιγόνα

↓

CD4+ βοηθητικά T λεμφοκύτταρα

Ταξινόμηση των μορίων HLA

α1

Class I
MHC
molecule

Peptide **(8-9 aa)**

α2

Class II
MHC
molecule

α1

Peptide **(10-13 aa)**

β1

Ενδογενή αντ...   ...ωγενή αντιγόνα

CD8+ κυτταρο...
Τ λεμφοκύττ...

...D4+ βοηθητικά
...λεμφοκύτταρα

T cell contact
residue of
peptide

T cell receptor

Polymorphic
residue
of MHC

Peptide

Anchor
residue
of peptide

MHC

"Pocket" of MHC

FIGURE 6.1 A model for T cell recognition of a peptide-major histocompatibility complex. This schematic illustration shows an MHC molecule binding and displaying a peptide and a T cell receptor recognizing the complex of peptide and MHC molecule. As discussed later in the text, MHC-associated peptides contain some residues that anchor them into pockets in the cleft of the MHC molecule and other residues that are recognized by T cell antigen receptors. MHC residues that may vary among individuals (polymorphic residues) are also recognized by the T cell receptor. Thus, T cells see both peptide antigens and MHC molecules.

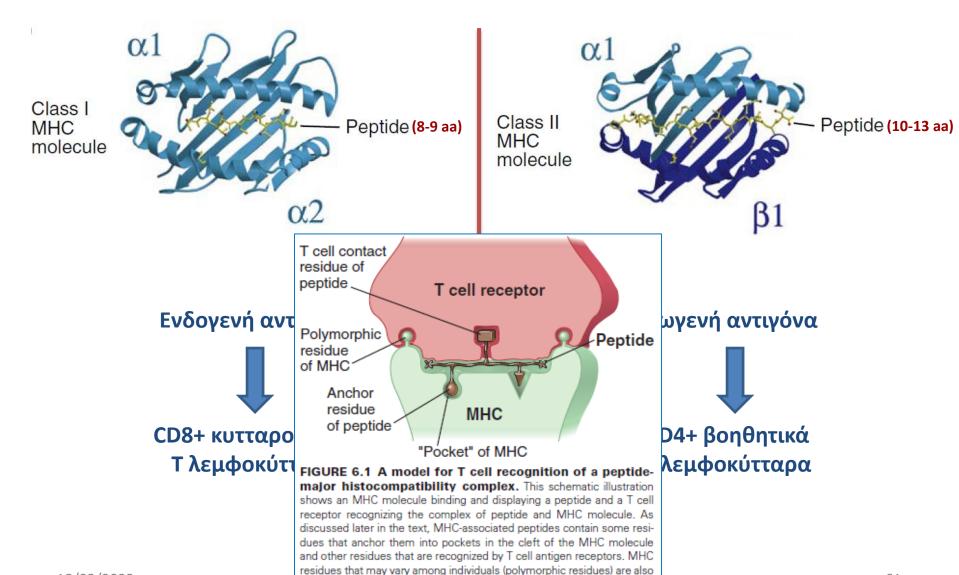| Feature	Significance	
Broad specificity	Many different peptides can bind to the same MHC molecule	
Each MHC molecule displays one peptide at a time	Each T cell responds to a single peptide bound to an MHC molecule	
MHC molecules bind only peptides	MHC-restricted T cells respond mainly to protein antigens*	Proteins → Peptides → Lipids → Carbohydrate sugars → Nucleic acids →
Class I and class II MHC molecules display peptides from different cellular compartments	Class I and class II MHC molecules provide immune surveillance for microbes in different locations	Peptides from proteins in cytosol Cytosolic protein → Proteasome → Class I MHC Endosome/lysosome → Peptides from internalized proteins in endocytic vesicles Endocytosis of extracellular protein → Class II MHC
Stable surface expression of MHC molecule requires bound peptide	Only peptide-loaded MHC molecules are expressed on the cell surface for recognition by T cells	→ MHC molecule with bound peptide → "Empty" MHC molecule
Very slow off-rate	MHC molecule displays bound peptide for long enough to be located by T cell	β2-microglobulin + α + Peptide → → Days

Fig. 3.11 Features of peptide binding to MHC molecules. Some of the important features of peptide binding to MHC molecules, with their significance for immune responses. *ER*, Endoplasmic reticulum; *I*ᵢ, invariant chain.
*Some small chemicals and heavy metal ions may directly alter MHC molecules and are recognized by T cells.

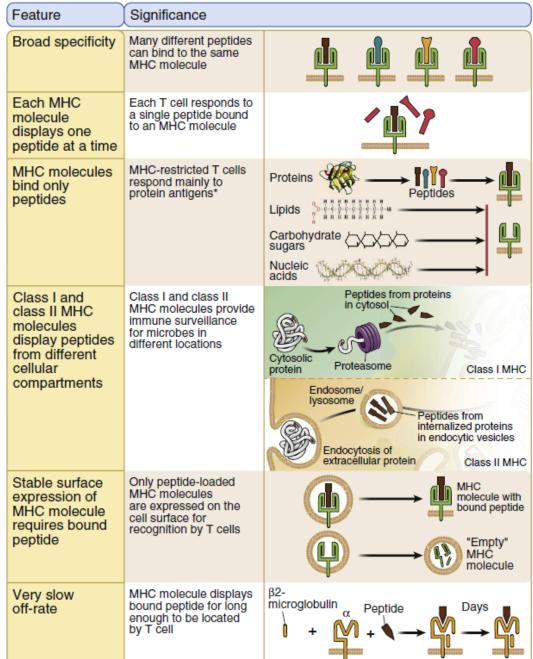| Feature	Significance	
Broad specificity	Many different peptides can bind to the same MHC molecule	
Each MHC molecule displays one peptide at a time	Each T cell responds to a single peptide bound to an MHC molecule	
MHC molecules bind only peptides	MHC-restricted T cells respond mainly to protein antigens*	Proteins → Peptides Lipids Carbohydrate sugars Nucleic acids
Class I and class II MHC molecules display peptides from different cellular compartments	Class I and class II MHC molecules provide immune surveillance for microbes in different locations	Peptides from proteins in cytosol — Cytosolic protein — Proteasome — Class I MHC Endosome/lysosome — Peptides from internalized proteins in endocytic vesicles — Endocytosis of extracellular protein — Class II MHC
Stable surface expression of MHC molecule requires bound peptide	Only peptide-loaded MHC molecules are expressed on the cell surface for recognition by T cells	MHC molecule with bound peptide "Empty" MHC molecule
Very slow off-rate	MHC molecule displays bound peptide for long enough to be located by T cell	β2-microglobulin + α + Peptide → Days

Fig. 3.11 Features of peptide binding to MHC molecules. Some of the important features of peptide binding to MHC molecules, with their significance for immune responses. *ER*, Endoplasmic reticulum; *I*i, invariant chain.
*Some small chemicals and heavy metal ions may directly alter MHC molecules and are recognized by T cells.

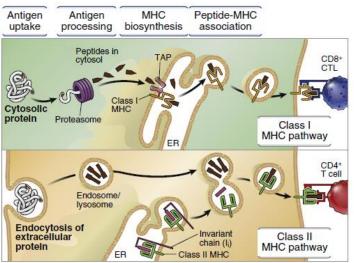| Antigen uptake	Antigen processing	MHC biosynthesis	Peptide-MHC association

Fig. 3.12 Pathways of intracellular processing of protein antigens. The class I MHC pathway converts proteins in the cytosol into peptides that bind to class I MHC molecules for recognition by CD8+ T cells. The class II MHC pathway converts protein antigens that are endocytosed into vesicles of antigen-presenting cells into peptides that bind to class II MHC molecules for recognition by CD4+ T cells. *CTL*, Cytotoxic T lymphocyte; *ER*, endoplasmic reticulum; *TAP*, transporter associated with antigen processing.
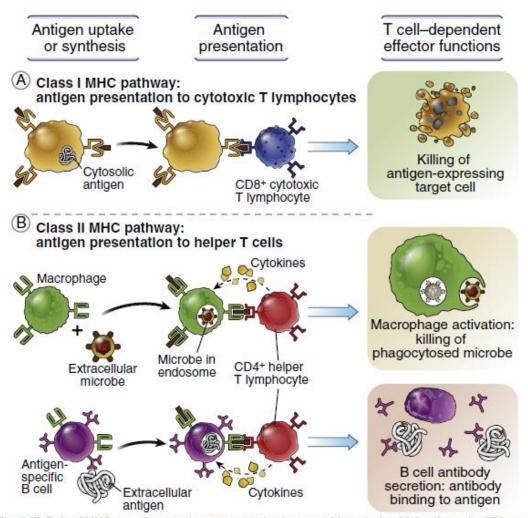
63

Fig. 3.17 Role of MHC-associated antigen presentation in recognition of microbial antigens by CD8+ and CD4+ effector T cells. **A,** Protein antigens of microbes that live in the cytoplasm of infected cells enter the class I MHC pathway of antigen processing. As a result, these proteins are recognized by CD8+ cytotoxic T lymphocytes, whose function is to kill infected cells. **B,** Protein antigens of microbes that are endocytosed from the extracellular environment by macrophages and B lymphocytes enter the class II MHC pathway of antigen processing. As a result, these proteins are recognized by CD4+ helper T lymphocytes, whose functions are to activate macrophages to destroy phagocytosed microbes and activate B cells to produce antibodies against extracellular microbes and toxins.

Tolerance in the Age of Immunotherapy

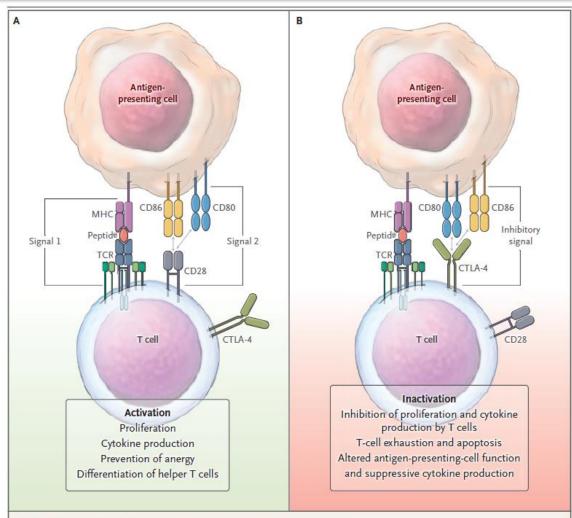Jeffrey A. Bluestone, Ph.D., and Mark Anderson, M.D., Ph.D.

Figure 1. Two-Signal Models of Costimulatory and Inhibitory Pathways.

Initiation of a productive T-cell response involves integration of a primary signal delivered through the T-cell receptor (TCR) and major histocompatibility complex (MHC)–peptide, followed by a second signal delivered through the CD28–CD80 or CD28–CD86 pathway (Panel A). After initiation of T-cell activation, other inhibitory checkpoint interactions can shut down T-cell activity (Panel B). Pathways that may be affected as a consequence of both positive and negative second signals are listed at the bottom of the figure. CTLA-4 denotes cytotoxic T-lymphocyte–associated protein 4.
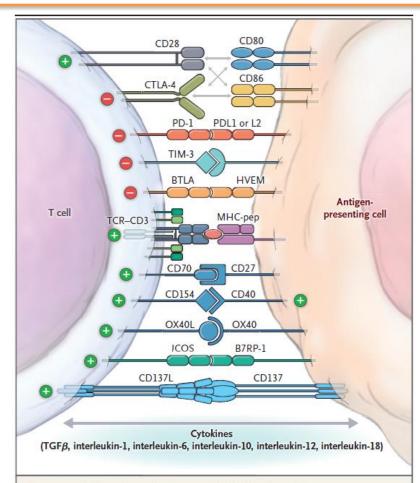
Tolerance in the Age of Immunotherapy

Jeffrey A. Bluestone, Ph.D., and Mark Anderson, M.D., Ph.D.

Figure 2. Additional Costimulatory and Checkpoint Pathways.

In addition to the two-signal models of costimulatory and checkpoint pathways, additional stimulatory and inhibitory pathways (indicated by plus and minus signs, respectively) influence the immune response, including molecules of the tumor necrosis factor (TNF)—related family, other members of the CD28 family, adhesion molecules, and T-cell immunoglobulin and mucin (TIM) molecules. The various stimulatory and inhibitory pathways can influence and be influenced by cytokines. Pep denotes peptide, and TGF-β transforming growth factor β.

Tolerance in the Age of Immunotherapy

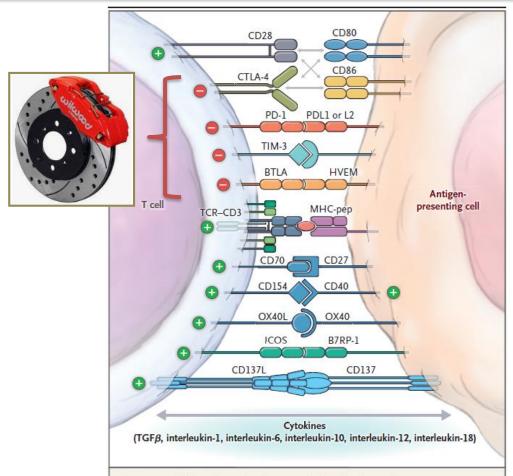Jeffrey A. Bluestone, Ph.D., and Mark Anderson, M.D., Ph.D.

Figure 2. Additional Costimulatory and Checkpoint Pathways.

In addition to the two-signal models of costimulatory and checkpoint pathways, additional stimulatory and inhibitory pathways (indicated by plus and minus signs, respectively) influence the immune response, including molecules of the tumor necrosis factor (TNF)—related family, other members of the CD28 family, adhesion molecules, and T-cell immunoglobulin and mucin (TIM) molecules. The various stimulatory and inhibitory pathways can influence and be influenced by cytokines. Pep denotes peptide, and TGF-β transforming growth factor β.

Fundamental Mechanisms of Immune Checkpoint Blockade Therapy

Spencer C. Wei[1], Colm R. Duffy[1], and James P. Allison[1,2]

Fundamental Mechanisms of Immune Checkpoint Blockade Therapy
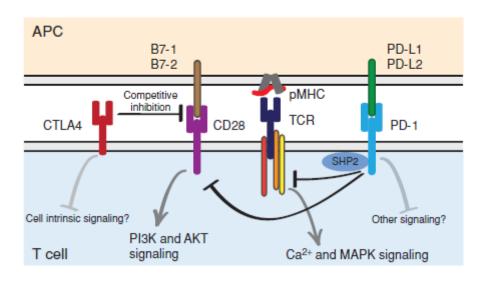
Figure 1. Molecular mechanisms of CTLA4 and PD-1 attenuation of T-cell activation. Schematic of the molecular interactions and downstream signaling induced by ligation of CTLA4 and PD-1 by their respective ligands. The possibility of additional downstream cell-intrinsic signaling mechanisms is highlighted for both CTLA4 and PD-1.
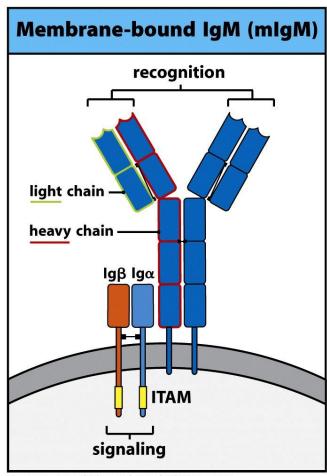
Figure 6-9 Immunobiology, 7ed. (© Garland Science 2008)
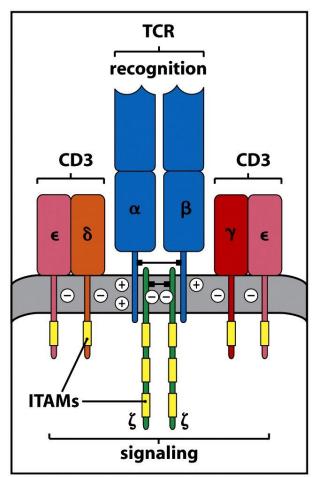
Figure 6-10 Immunobiology, 7ed. (© Garland Science 2008)

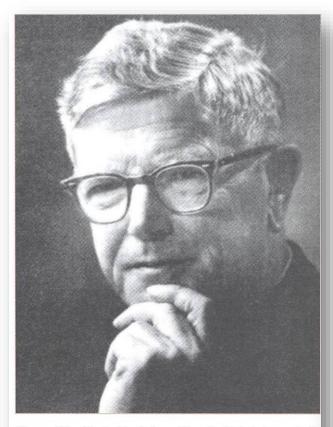**Figure 48** Burnet and Fenner's famous monograph

Figure 13 Sir F. Macfarlane Burnet, Nobel Laureate in Medicine, who described the clonal selection theory of acquired immunity

From: *Historical Atlas of Immunology*

Antibody Production by Single Cells

FAGREUS[1] and others[2,3] have shown that certain tissues from pre-sensitized animals can form antibody *in vitro*. This communication describes a technique whereby antibody production by single cells isolated in microdroplets can be detected. The technique is based on specific immobilization of *Salmonella* serotypes by anti-flagellar antibody. It was observed that single cells from a rat, simultaneously stimulated with two antigens, formed detectable amounts of one or the other antibody.

Two monophasic *Salmonellae* were used : *S. adelaide*, flagellar antigen H_1^{fg}, and *S. typhi*, H_1^d. They were maintained at maximum motility by frequent passages through a semi-solid nutrient gelatin agar medium[4]. A formalinized broth culture containing about 10^9 organisms per ml. was used as the antigen. Adult Wistar rats were injected with 0·25 ml. of a mixture of equal parts of both antigens into both hind foot-pads. Usually the animals were given three pairs of injections at three weekly intervals. Three days after the tertiary injections, they were killed by exsanguination under anæsthesia. Both popliteal lymph nodes were removed, pooled, and processed[6] to give dispersed cell suspensions in Earle's saline buffered to pH 7·0 with *tris*, and supplemented with 20 per cent normal rat serum. The cells were sedimented by gentle centrifugation, and washed three times to remove free soluble antibody. Single cells were then isolated in microdroplets by a simple modification[4,5] of de Fonbrune's oil chamber method[7]. This consisted essentially of depositing tiny droplets (volume 10^{-7}–10^{-6} ml.) on the surface of a coverslip and immersing them in paraffin oil. The coverslip was then inverted over a chamber filled with oil. The easiest method for preparing droplets containing one cell was to dispense a large number of droplets by free-hand manipulation from a suspension containing 1 : 400 by volume of lymph node cells. These droplets contained from nought to six cells ; each droplet was later recorded for its cell content. Larger droplets containing up to 100 cells could also be prepared. Alternatively, droplets containing exactly one cell each could be prepared by micromanipulation, but this was more tedious, due to the adhesion of the cells to the micropipette. The oil chamber was then incubated at 37° C. for 4 hr. At the end of this time, the chamber was placed on a microscope and the droplets surveyed at one hundred-fold magnification, dark ground. With a micropipette controlled by de Fonbrune micromanipulator, about ten bacteria were introduced into each droplet. Half the droplets were inoculated with *S. adelaide*, and the other half with *S. typhi*. After twenty minutes at room temperature, the droplets were observed for motility of the organisms. Total loss of motility of all the organisms was recorded as 'inhibition'. If even one organism in the droplet remained motile, this was recorded as 'no inhibition'. For control purposes, the suspending medium, the final supernatant from the washings, and the whole cell suspension prior to incubation were all shown to be free of inhibitory activity. Droplets prepared from the final cell suspension but containing no cells were also scored and found to lack inhibitory activity. Cells from several untreated rats were tested and these failed to elaborate a factor inhibiting the motility of the bacteria. Antisera against each serotype showed negligible cross-reaction with the other.

A proportion of the cells from immunized animals developed a factor immobilizing the test bacteria, and this was presumed to be antibody. All droplets containing single cells which were seen to immobilize the first serotype were then inoculated with about ten organisms from the second. After a further twenty minutes at room temperature, they were again observed for motility. The results of a typical experiment are recorded in Table 1. They indicate that none of the single cells was able to immobilize the organisms of both strains. To date 456 single cells have been tested for antibody production, 228 against each of the two organisms. Out of these, 33 were active against *S. adelaide* and 29 against *S. typhi*, but none of the 62 immobilized both strains.

Table 1. ANTIBODY PRODUCTION BY ISOLATED CELLS

No. of cells in drop	No. of drops inhibitory	No. of drops tested
First tested versus *S. adelaide*		
1	6*	39
2	5	25
3	7	24
4	6	21
5	6	10
6–10	17	33
First tested versus *S. typhi*		
1	3*	18
2	6	26
3	0	14
4	3	14
5	1	8
6–10	22	42

Lymph node cells from rats presensitized to *S. adelaide* plus *S. typhi* were dispensed in micro droplets and incubated for 4 hr. They were then tested by the introduction of motile bacteria.
* These droplets were also tested for activity against the alternative serotype and were negative.

These results imply that when an animal is stimulated with two contrasting antigens, individual cells tend to form one species of antibody. We cannot exclude a residual production of other antibodies at lower rates. The experiments were provoked by current hypotheses on the role of clonal individuation in antibody formation[8,9], with which they are consistent so far as they go. However, further studies will be needed to determine whether the assortment of antibody-forming phenotypes reflects a genotypic restriction or whether it is more akin to such phenotypic effects as interference between related viruses, or diauxie and competition in enzyme formation.

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JOSHUA LEDERBERG*

Walter and Eliza Hall Institute
of Medical Research,
Melbourne.
March 25.

* Fulbright Visiting Professor of Bacteriology, University of Melbourne ; from Department of Medical Genetics, University of Wisconsin, Madison.

[1] Fagreus, A., *J. Immunol.*, **58**, 1 (1948).
[2] Thorbecke, G. J., and Keuning, F. J., *J. Immunol.*, **70**, 129 (1953).
[3] Wesslen, T., *Acta Dermato-Venerol.*, **32**, 265 (1952).
[4] Lederberg, J., *Genetics*, **41**, 845 (1956).
[5] Lederberg, J., *J. Bacteriol.*, **68**, 258 (1954).
[6] Harris, S., Harris, T. N., and Farber, M. B., *J. Immunol.*, **72**, 148 (1954).
[7] De Fonbrune, P., "Technique de micromanipulation" (Masson, Paris 1949).
[8] Burnet, F. M., *Austral. J. Sci.*, **20**, 67 (1957).
[9] Talmage, D. W., "Ann. Rev. Med.", **8**, 239 (1957).

THE CLONAL
SELECTION THEORY OF
ACQUIRED IMMUNITY

BY

SIR MACFARLANE BURNET
O.M., F.R.S.

THE
ABRAHAM FLEXNER LECTURES OF
VANDERBILT UNIVERSITY
1958

CAMBRIDGE
AT THE UNIVERSITY PRESS
1959

PUBLISHED IN U.S.A. BY
VANDERBILT UNIVERSITY PRESS
NASHVILLE, TENNESSEE

Figure 14 Dr Burnet's famous book describing clonal selection, for which he was awarded the Nobel Prize in Medicine

Figure 13 Sir F. Macfarlane Burnet, Nobel Laureate in Medicine, who described the clonal selection theory of acquired immunity

From: *Historical Atlas of Immunology*   72

Clonal selection theory, Burnet F.M.,1959

1. Κάθε λεμφοκύτταρο φέρει στην επιφάνειά του πολυάριθμα αντίγραφα ενός μοναδικού υποδοχέα ειδικό για κάποιο ξένο αντιγόνο

2. Αναγνώριση μέσω του επιφανειακού υποδοχέα και ενδοκυττάρια μεταφορά του σήματος αποτελεί το εναρκτήριο γεγονός της ανοσολογικής απάντησης

3. Τα λεμφοκύτταρα των οποίων ο επιφανειακός υποδοχέας αναγνωρίζει ίδια (self) αντιγόνα εξαλείφονται πρώιμα στη ζωή

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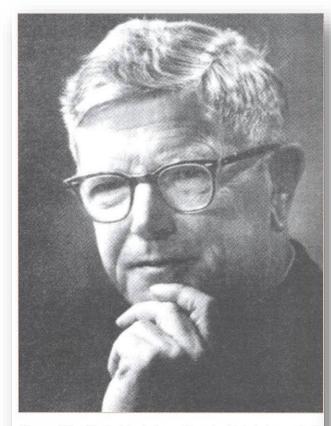**Figure 14** Dr Burnet's famous book describing clonal selection, for which he was awarded the Nobel Prize in Medicine

73

Clonal selection theory, Burnet F.M.,1959

1. Κάθε λεμφοκύτταρο φ... ...λυάριθμα αντίγραφα ενός μοναδικού υποδοχέα... ...ντιγόνο

2. Αναγνώριση μέσω του... ...αι ενδοκυττάρια μεταφορά του σήματος α... ...ονός της ανοσολογικής απάντησης

3. Τα λεμφοκύτταρα των... ...οδοχέας αναγνωρίζει ίδια (self) αντιγόνα εξαλε...

Figure 14 Dr Burnet's famous book describing clonal selection, for which he was awarded the Nobel Prize in Medicine

Figure 58 Susumu Tonegawa

From: *Historical Atlas of Immunology*

Evidence for somatic rearrangement of immunoglobulin genes coding for variable and constant regions

(κ-chain mRNA/restriction enzymes/RNA·DNA hybridization)

NOBUMICHI HOZUMI AND SUSUMU TONEGAWA

Basel Institute for Immunology, 487, Grenzacherstrasse, CH-4058 Basel, Switzerland
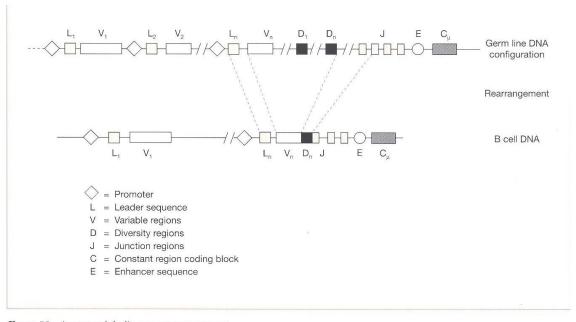
Figure 59 Immunoglobulin gene rearrangement
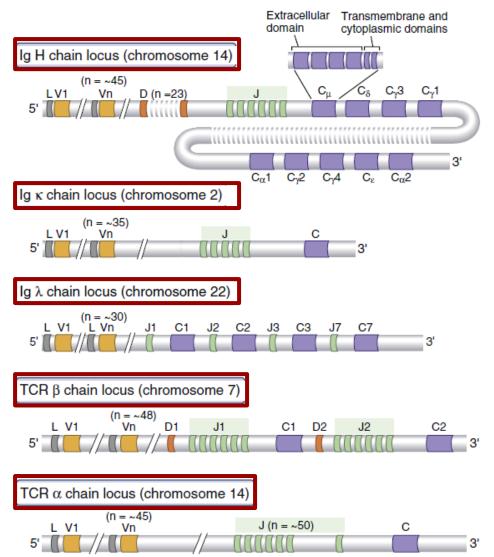
Fig. 4.11 Germline organization of antigen receptor gene loci. In the germline, inherited antigen receptor gene loci contain coding segments (exons, shown as colored blocks of various sizes) that are separated by segments that are not expressed (introns, shown as *gray* sections). Each immunoglobulin *(Ig)* heavy-chain constant *(C)* region and T cell receptor *(TCR)* C region consists of multiple exons, which are not shown, that encode the domains of the C regions; the organization of the C_μ exons in the Ig heavy-chain locus is shown as an example. The diagrams illustrate the antigen receptor gene loci in humans; the basic organization is the same in all species, although the precise order and number of gene segments may vary. The numbers of V, D, and J gene segments are estimates of functional gene segments (those that can code for proteins). The sizes of the segments and the distances between them are not drawn to scale. *D*, Diversity; *J*, joining; *L*, leader sequence (a small stretch of nucleotides that encodes a peptide that guides proteins through the endoplasmic reticulum and is cleaved from the mature proteins); *V*, variable.
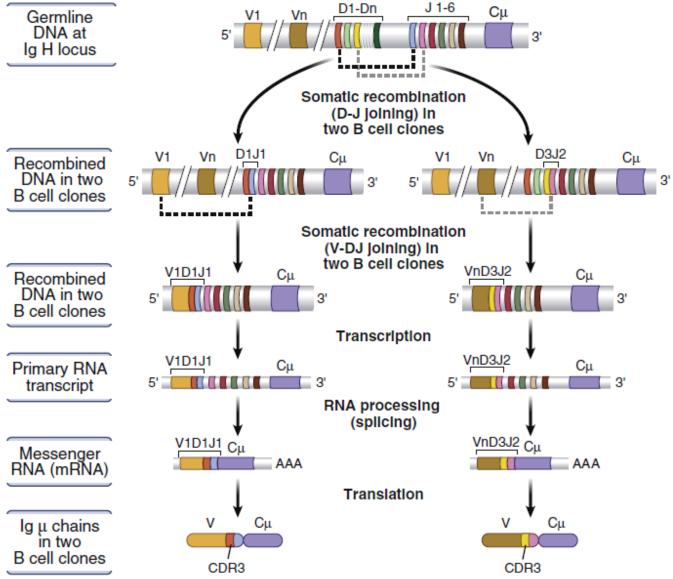
Fig. 4.12 Recombination and expression of immunoglobulin (Ig) genes. The expression of an Ig heavy chain involves two gene recombination events (D-J joining, followed by joining of a V region to the DJ complex, with deletion of intervening gene segments). The recombined gene is transcribed, and the VDJ complex is spliced onto the C region exons of the first heavy-chain RNA (which is μ), to give rise to the μ messenger RNA (mRNA). The mRNA is translated to produce the μ heavy-chain protein. The recombination of other antigen receptor genes—that is, the Ig light chain and the T cell receptor (TCR) α and β chains—follows essentially the same sequence, except that in loci lacking D segments (Ig light chains and TCR α), a V gene recombines directly with a J gene segment.

	Immunoglobulin			T cell receptor	
	Heavy chain	κ	λ	α	β
Number of variable (V) gene segments	~45	35	30	45	48
Number of diversity (D) gene segments	23	0	0	0	2
Number of joining (J) gene segments	6	5	4	50	12

Mechanism

Combinatorial diversity:	
Number of possible V(D)J combinations	Ig: ~3x10^6 TCR: ~6x10^6
Junctional diversity:	Removal of nucleotides Addition of nucleotides (N-region or P-nucleotides)
Total potential repertoire with junctional diversity	Ig: ~10^{11} TCR: ~10^{16}

Fig. 4.13 Mechanisms of diversity in antigen receptors. Diversity in immunoglobulins and T cell receptors is produced by random combinations of V, D, and J gene segments, which is limited by the numbers of these segments and by removal and addition of nucleotides at the V-J or V-D-J junctions, which is almost unlimited. The numbers of gene segments refer to the average numbers of functional genes (which are known to be expressed as RNA or protein) in humans. Junctional diversity maximizes the variations in the CDR3 regions of the antigen receptor proteins, because CDR3 includes the junctions at the site of V-J and V-D-J recombination. The diversity is further enhanced by the juxtaposition of the V regions of the two types of chains in Ig or TCRs to form the complete antigen binding sites, and thus the total diversity is theoretically the product of the total diversity of each of the juxtaposed V regions. The estimated contributions of these mechanisms to the total possible numbers of distinct B and T cell antigen receptors are shown. Although the upper limit on the number of immunoglobulin (Ig) and TCR proteins that may be expressed is extremely large, each individual contains on the order of only 10^7–10^9 clones of B cells and T cells with distinct specificities and receptors; in other words, only a fraction of the potential repertoire may actually be expressed. (Modified from Davis MM, Bjorkman PJ: T-cell antigen receptor genes and T-cell recognition, *Nature* 334:395–402, 1988.)

	HSC	Pro-B	Large Pre-B	Small Pre-B	Immature B	Mature B
Ig H chain gene	Germline	D to J rearrangement	V to DJ rearrangement	Rearranged VDJ	Rearranged VDJ	Rearranged VDJ
Ig L chain gene	Germline	Germline	Germline	V to J rearrangement	Rearranged VJ	Rearranged VJ
Ig protein	None	None	pre-BCR	Intracellular μ	IgM	IgM, IgD

Fig. 4.14 Steps in the maturation and selection of B lymphocytes. The maturation of B lymphocytes proceeds through sequential steps, each of which is characterized by particular changes in immunoglobulin (*Ig*) gene expression and in the patterns of Ig protein expression. Pro-B cells begin to rearrange Ig heavy-chain genes and large pre-B cells are selected to survive and proliferate if they successfully rearrange an Ig heavy-chain gene and assemble a pre-BCR. The pre-BCR consists of a membrane-associated Ig μ protein attached to two other proteins called surrogate light chains because they take the place of the light chain in a complete Ig molecule. Small pre-B cells initiate Ig light-chain gene rearrangement, immature B cells assemble a complete membrane IgM receptor, and mature B cells coexpress IgD, with the same V regions and specificity as in the first Ig produced. *BCR*, B cell receptor; *HSC*, hematopoietic stem cell; *mRNA*, messenger RNA.
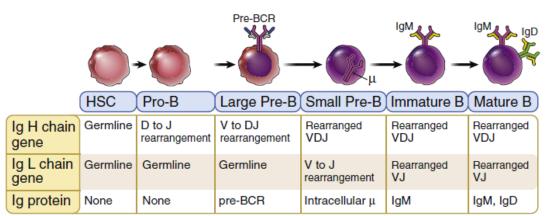
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RAG1/2 → VDJ rearrangement

AID → SHM

AID → CSR

precursor B-cell → naïve B-cell → circulating naïve B-cell → GC B-cell "centroblast" → GC B-cell "centrocyte" → memory B-cell / plasma cell

Pre-BCR

IgM

IgM IgD

μ

	HSC	Pro-B	Large Pre-B	Small Pre-B	Immature B	Mature B
Ig H chain gene	Germline	D to J rearrangement	V to DJ rearrangement	Rearranged VDJ	Rearranged VDJ	Rearranged VDJ
Ig L chain gene	Germline	Germline	Germline	V to J rearrangement	Rearranged VJ	Rearranged VJ
Ig protein	None	None	pre-BCR	Intracellular μ	IgM	IgM, IgD

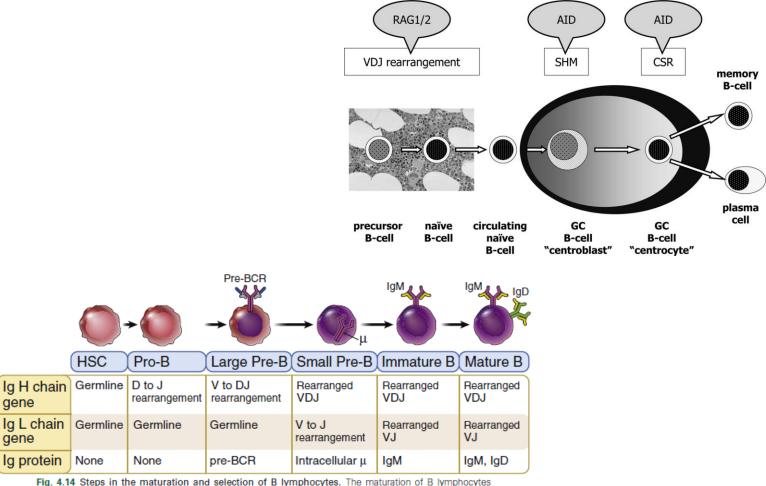a Somatic hypermutation   b Class-switch recombination

Fig. 4.14 Steps in the maturation and selection of B lymphocytes. The maturation of B lymphocytes proceeds through sequential steps, each of which is characterized by particular changes in immunoglobulin (Ig) gene expression and in the patterns of Ig protein expression. Pro-B cells begin to rearrange Ig heavy-chain genes and large pre-B cells are selected to survive and proliferate if they successfully rearrange an Ig heavy-chain gene and assemble a pre-BCR. The pre-BCR consists of a membrane-associated Ig μ protein attached to two other proteins called surrogate light chains because they take the place of the light chain in a complete Ig molecule. Small pre-B cells initiate Ig light-chain gene rearrangement, immature B cells assemble a complete membrane IgM receptor, and mature B cells coexpress IgD, with the same V regions and specificity as in the first Ig produced. BCR, B cell receptor; HSC, hematopoietic stem cell; mRNA, messenger RNA.
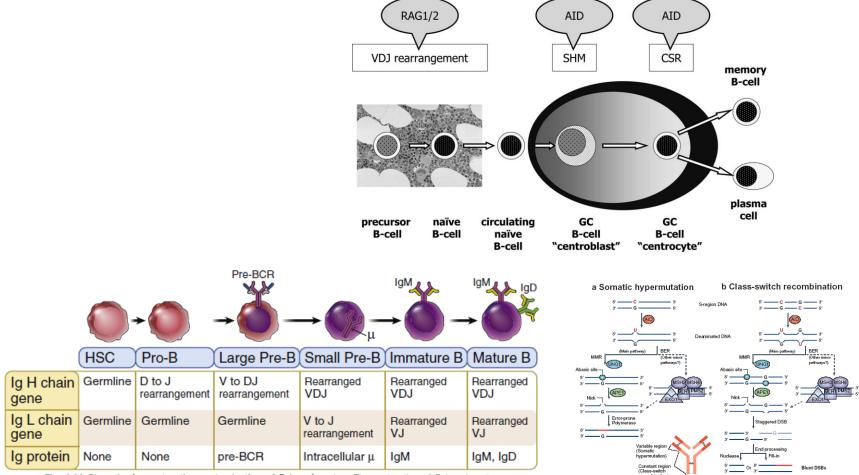
Figure 8.1 Dendritic cells take up antigens at a site of wounding and infection in the skin and carry them to the draining lymph node for presentation to naive T cells. Dendritic cells in the skin are immature and specialized in the uptake of pathogens and their antigens (red dots). On migration to the lymph node, they settle in the T-cell areas and differentiate into mature dendritic cells that are specialized in activating naive T cells. The immature dendritic cells in the skin, also known as Langerhans cells, are distinguished morphologically by their Birbeck granules (not shown), which are part of the system of endosomal vesicles.

dermis

epidermis

Dendritic cells take up bacterial antigens in the skin and then move to enter a draining lymphatic vessel

Dendritic cells bearing antigen enter the draining lymph node, where they settle in the T-cell areas
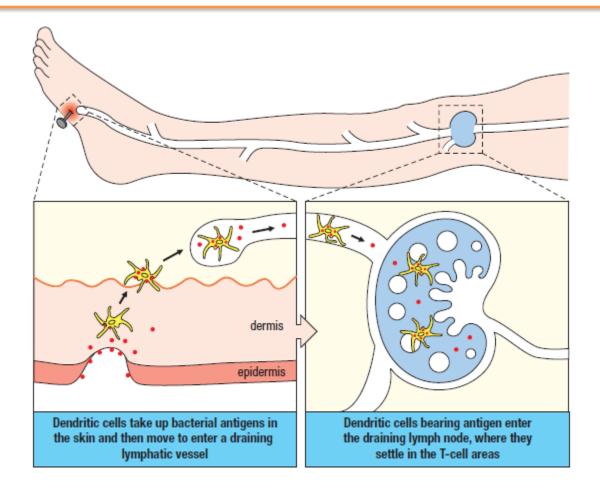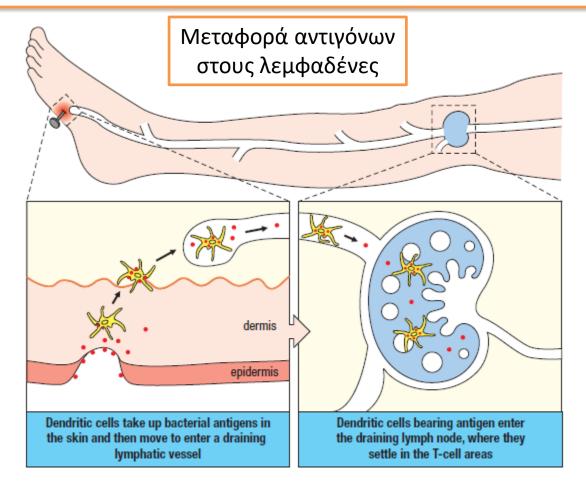
Μεταφορά αντιγόνων στους λεμφαδένες

Figure 8.1 Dendritic cells take up antigens at a site of wounding and infection in the skin and carry them to the draining lymph node for presentation to naive T cells. Dendritic cells in the skin are immature and specialized in the uptake of pathogens and their antigens (red dots). On migration to the lymph node, they settle in the T-cell areas and differentiate into mature dendritic cells that are specialized in activating naive T cells. The immature dendritic cells in the skin, also known as Langerhans cells, are distinguished morphologically by their Birbeck granules (not shown), which are part of the system of endosomal vesicles.

dermis

epidermis

Dendritic cells take up bacterial antigens in the skin and then move to enter a draining lymphatic vessel

Dendritic cells bearing antigen enter the draining lymph node, where they settle in the T-cell areas

Μέσω της λέμφου και των προσαγωγών λεμφαγγείων είτε ως διαλυτά μόρια / αντιγόνα, είτε με δενδριτικά κύτταρα, τα οποία φαγοκυτταρώνουν τα αντιγόνα, τα επεξεργάζονται / διασπούν και παρουσίαζουν τα πεπτίδιά τους, όταν φτάσουν στους επιχώριους λεμφαδένες, με τα αντιγόνα ιστοσυμβατότητας τάξης I και II στα κυτταροτοξικά και βοηθητικά T λεμφοκύτταρα, αντίστοιχα.

CD21

Δενδριτικά κύτταρα των λεμφοζιδίων (Follicular Dendritic Cells, FDC)
= CD21+, CD23+, CD35+

CD21

High endothelial venules

CD21

18/02/2022

High endothelial venules

Φλεβίδια με υψηλό ενδοθήλιο (HEVs) = Pnad+ (MECA-79)

CD21

18/02/2022

10.000 lymphocytes/sec/lymph node

T cells

B cells

High endothelial venules

CD21

18/02/2022

10.000 lymphocytes/sec/lymph node

DCs
CCL19
CCL21

FDCs
CXCL13

T cells

B cells

High endothelial venules

CD21

Μεταφορά αντιγόνων στους λεμφαδένες

Dendritic cells

Διαλυτά αντιγόνα

T cells

B cells

High endothelial venules

Μεταφορά αντιγόνων στους λεμφαδένες

Figure 8.1 Dendritic cells take up antigens at a site of wounding and infection in the skin and carry them to the draining lymph node for presentation to naive T cells. Dendritic cells in the skin are immature and specialized in the uptake of pathogens and their antigens (red dots). On migration to the lymph node, they settle in the T-cell areas and differentiate into mature dendritic cells that are specialized in activating naive T cells. The immature dendritic cells in the skin, also known as Langerhans cells, are distinguished morphologically by their Birbeck granules (not shown), which are part of the system of endosomal vesicles.
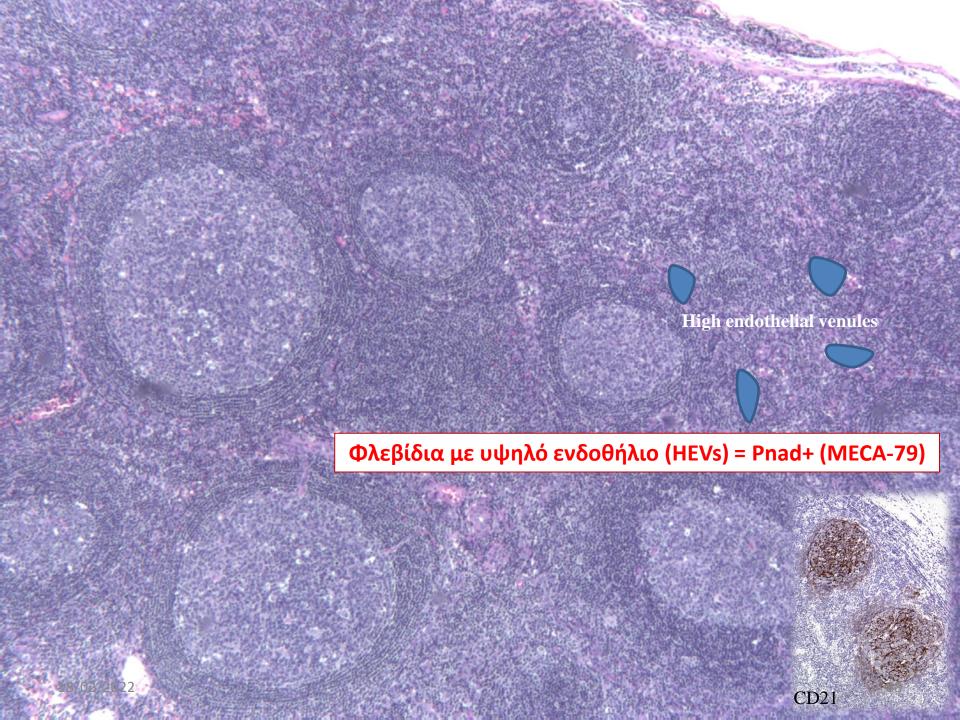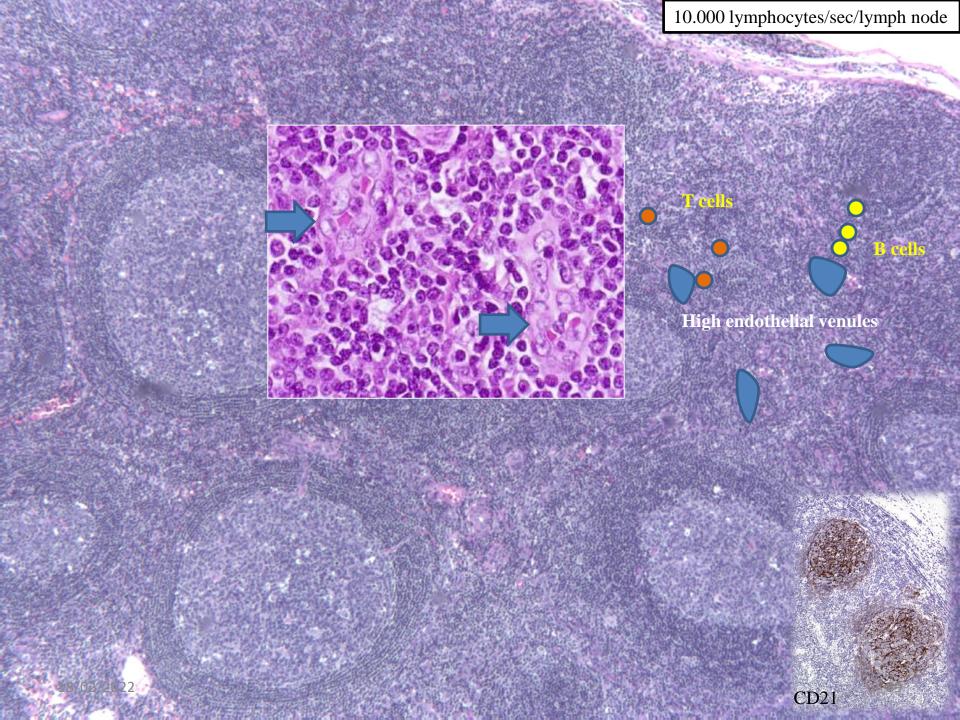
CD21

Dendritic cells

Ενεργοποίηση Τ λεμφοκυττάρων

T cells

B cells

High endothelial venules

CD21

28/02/2022

Antigen capture

Antigen capture by dendritic cells (DC)

Inflammatory cytokines

Loss of DC adhesiveness

Immature DC in epidermis (Langerhans cell)

Maturation of migrating DC

Migration of DC

Afferent lymphatic vessel

Antigen presentation

Lymph node

T cells

Mature dendritic cell presenting antigen to naive T cell

C

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Subcapsular sinus

'Ag-trapping' cells

No Ag engagement; B cell leaves node in lymph

Engages Ag via FcR + CR2 and transports it to FDC

Engages Ag via BCR, inducing interaction with primed T cells

Recirculating B cell migrates from blood to follicular mantle

Ag enters node in afferent lymph

Dendritic cells

Ενεργοποίηση Τ λεμφοκυττάρων

T cells

B cells

High endothelial venules

CD21

18/02/2022

Ενεργοποίηση Β λεμφοκυττάρων

Διαλυτά αντιγόνα

Subcapsular sinus

'Ag-trapping' cells

Ag enters node
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High endothelial venules

FDC

Ag

CD21

Subcapsular sinus

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from blood to follicular mantle

Διαλυτά αντιγόνα

T cells

B cells

High endothelial venules

FDC

Ag

Ενεργοποίηση Β λεμφοκυττάρων

1.

Surveillance

Foreign antigen

Lymph node

1 in 10⁴-10⁶
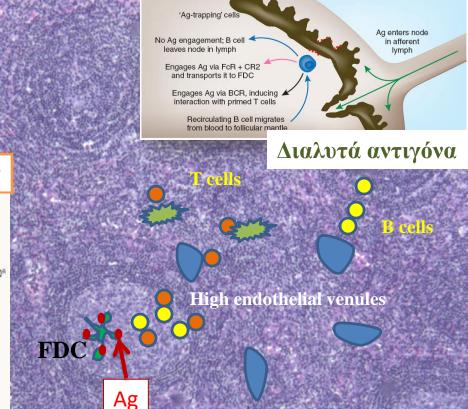
Encounter
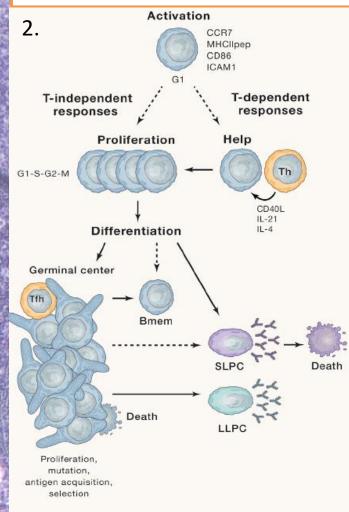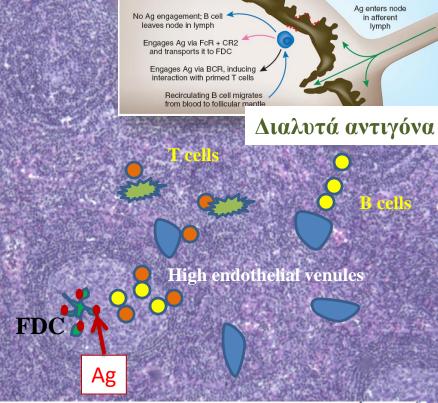
Follicular dendritic cell

CR2   BCR

B cell

G0

Activation

Circulating antigen-specific B cells (blue) that are as rare as 1 in 10^4 to 1 in 10^6 enter and survey an antigen-draining lymph node (LN). A B cell encounters an opsonized (complement coated) antigen displayed on a follicular dendritic cell (FDC) process and receives B cell receptor (BCR) and complement receptor-2 (CR2) signals. Activation involves upregulation of surface molecules, antigen internalization processing and (in the case of protein-containing antigens) presentation as MHC class II peptide (MHCIIpep) complexes, and entry into G1 of cell cycle. If the antigen engages multiple BCRs and/or coreceptors on the B cell, a T-independent (TI) proliferative response ensues. Lower valency protein-containing antigens drive T-dependent (TD) responses, where the B cell depends on signals from helper T cells to undergo proliferation. The proliferative phase is followed by differentiation into short-lived plasma cells (SLPCs), germinal center (GC) B cells, and/or memory B cells (Bmem). The relative differentiation to these distinct states varies and depends on the integration of signals received by the B cell including via the BCR, co-receptors, and T cell help. GC B cells take on a dendritic morphology that may facilitate antigen encounter and affinity discrimination. GCs give rise to more SLPCs, to Bmems, and to long-lived plasma cells (LLPCs).

'Ag-trapping' cells

No Ag engagement; B cell leaves node in lymph

Ag enters node in afferent lymph

Engages Ag via FcR + CR2 and transports it to FDC

Engages Ag via BCR, inducing interaction with primed T cells

Recirculating B cell migrates from blood to follicular mantle

Διαλυτά αντιγόνα

Ενεργοποίηση Β λεμφοκυττάρων

2.

Activation

CCR7
MHCIIpep
CD86
ICAM1

G1

T-independent responses

T-dependent responses

Proliferation

Help

G1-S-G2-M

Th

CD40L
IL-21
IL-4

Differentiation

Germinal center

Tfh

Bmem

SLPC

Death

Death

LLPC

Proliferation, mutation, antigen acquisition, selection

T cells

B cells

High endothelial venules

FDC

Ag

Circulating antigen-specific B cells (blue) that are as rare as 1 in 10^4 to 1 in 10^6 enter and survey an antigen-draining lymph node (LN). A B cell encounters an opsonized (complement coated) antigen displayed on a follicular dendritic cell (FDC) process and receives B cell receptor (BCR) and complement receptor-2 (CR2) signals. Activation involves upregulation of surface molecules, antigen internalization processing and (in the case of protein-containing antigens) presentation as MHC class II peptide (MHCIIpep) complexes, and entry into G1 of cell cycle. If the antigen engages multiple BCRs and/or coreceptors on the B cell, a T-independent (TI) proliferative response ensues. Lower valency protein-containing antigens drive T-dependent (TD) responses, where the B cell depends on signals from helper T cells to undergo proliferation. The proliferative phase is followed by differentiation into short-lived plasma cells (SLPCs), germinal center (GC) B cells, and/or memory B cells (Bmem). The relative differentiation to these distinct states varies and depends on the integration of signals received by the B cell including via the BCR, co-receptors, and T cell help. GC B cells take on a dendritic morphology that may facilitate antigen encounter and affinity discrimination. GCs give rise to more SLPCs, to Bmems, and to long-lived plasma cells (LLPCs).
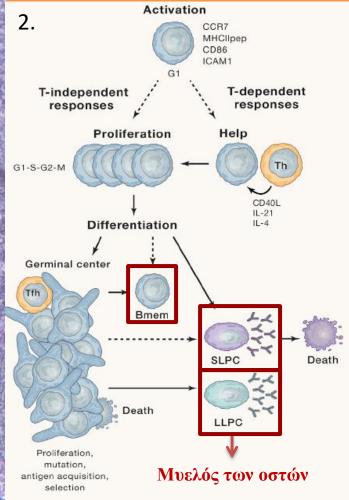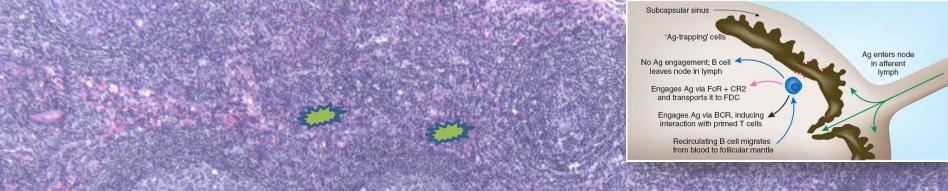
Διαλυτά αντιγόνα

Ενεργοποίηση Β λεμφοκυττάρων

2.

T cells

B cells

High endothelial venules

FDC

Ag

Μυελός των οστών

Circulating antigen-specific B cells (blue) that are as rare as 1 in 10⁴ to 1 in 10⁶ enter and survey an antigen-draining lymph node (LN). A B cell encounters an opsonized (complement coated) antigen displayed on a follicular dendritic cell (FDC) process and receives B cell receptor (BCR) and complement receptor-2 (CR2) signals. Activation involves upregulation of surface molecules, antigen internalization processing and (in the case of protein-containing antigens) presentation as MHC class II peptide (MHCIIpep) complexes, and entry into G1 of cell cycle. If the antigen engages multiple BCRs and/or coreceptors on the B cell, a T-independent (TI) proliferative response ensues. Lower valency protein-containing antigens drive T-dependent (TD) responses, where the B cell depends on signals from helper T cells to undergo proliferation. The proliferative phase is followed by differentiation into short-lived plasma cells (SLPCs), germinal center (GC) B cells, and/or memory B cells (Bmem). The relative differentiation to these distinct states varies and depends on the integration of signals received by the B cell including via the BCR, co-receptors, and T cell help. GC B cells take on a dendritic morphology that may facilitate antigen encounter and affinity discrimination. GCs give rise to more SLPCs, to Bmems, and to long-lived plasma cells (LLPCs).
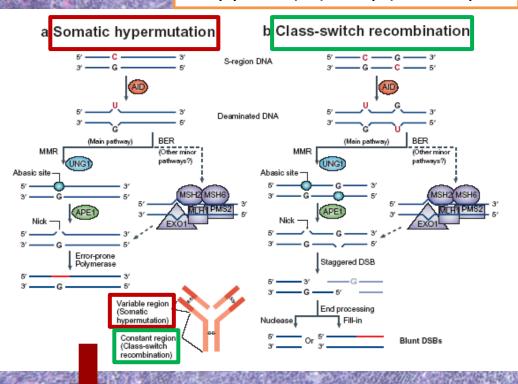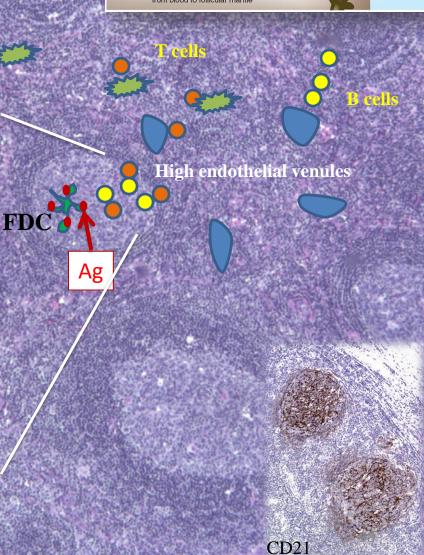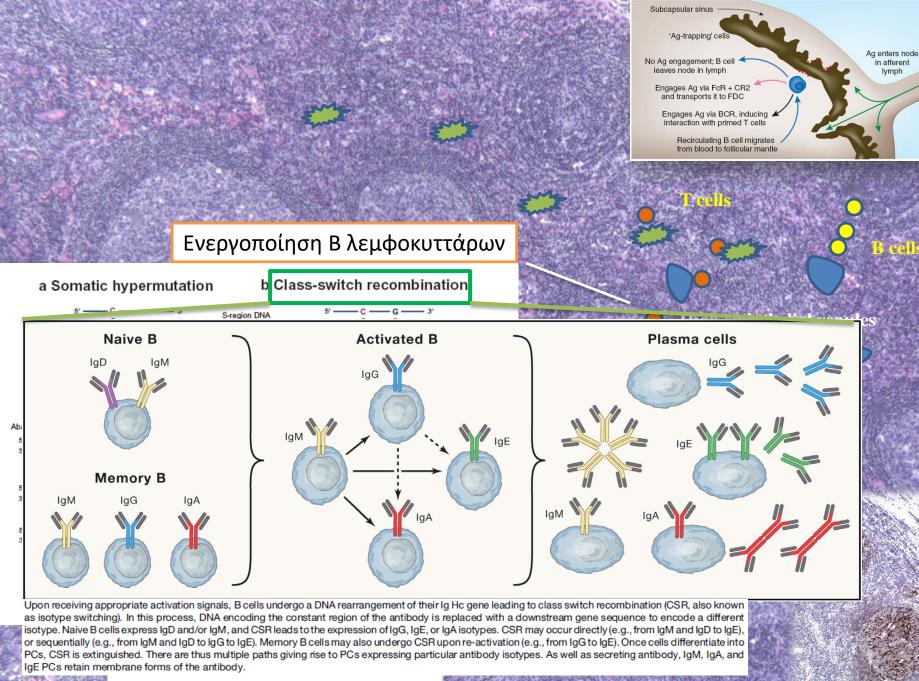
18/02/2022

Subcapsular sinus

'Ag-trapping' cells

Ag enters node in afferent lymph

No Ag engagement; B cell leaves node in lymph

Engages Ag via FcR + CR2 and transports it to FDC

Engages Ag via BCR, inducing interaction with primed T cells

Recirculating B cell migrates from blood to follicular mantle

Ενεργοποίηση Β λεμφοκυττάρων

T cells

B cells

High endothelial venules

FDC

Ag

CD21

a **Somatic hypermutation**

b **Class-switch recombination**

S-region DNA

5′ —— C —— 3′
3′ —— G —— 5′

AID

5′ —— U —— 3′
3′ —— G —— 5′

Deaminated DNA

(Main pathway) | BER (Other minor pathways?)

MMR

UNG1

Abasic site

5′ 3′
3′ —— G —— 5′

APE1

Nick

5′ 3′
3′ —— G —— 5′

MSH2 MSH6
MLH1 PMS2
EXO1

Error-prone Polymerase

5′ 3′
3′ —— G —— 5′

Variable region (Somatic hypermutation)

Constant region (Class-switch recombination)

5′ —— C —— G —— 3′
3′ —— G —— C —— 5′

AID

5′ —— U —— G —— 3′
3′ —— G —— U —— 5′

(Main pathway) | BER (Other minor pathways?)

MMR

UNG1

Abasic site

5′ —— G —— 3′
3′ —— G —— 5′

APE1

Nick

5′ —— G —— 3′
3′ —— G —— 5′

MSH2 MSH6
MLH1 PMS2
EXO1

Staggered DSB

5′ —— 3′
3′ —— G —— 5′

End processing

Nuclease | Fill-in

5′ —— 3′ Or 5′ —— G —— 3′
3′ —— G —— 5′   3′ —— 5′

Blunt DSBs

Βελτίωση της χημικής συγγένειας της ανοσοσφαιρίνης προς το αντιγόνο

Ενεργοποίηση Β λεμφοκυττάρων

a Somatic hypermutation   **b** Class-switch recombination

T cells

B cells

Upon receiving appropriate activation signals, B cells undergo a DNA rearrangement of their Ig Hc gene leading to class switch recombination (CSR, also known as isotype switching). In this process, DNA encoding the constant region of the antibody is replaced with a downstream gene sequence to encode a different isotype. Naive B cells express IgD and/or IgM, and CSR leads to the expression of IgG, IgE, or IgA isotypes. CSR may occur directly (e.g., from IgM and IgD to IgE), or sequentially (e.g., from IgM and IgD to IgG to IgE). Memory B cells may also undergo CSR upon re-activation (e.g., from IgG to IgE). Once cells differentiate into PCs, CSR is extinguished. There are thus multiple paths giving rise to PCs expressing particular antibody isotypes. As well as secreting antibody, IgM, IgA, and IgE PCs retain membrane forms of the antibody.

Αλλαγή της λειτουργίας του Ab

CD21

FIGURE 5.16 Changes in antibody structure during humoral immune responses. The illustration depicts the changes in the structure of antibodies that may be produced by the progeny of activated B cells (one clone) and the related changes in function. During affinity maturation, mutations in the V region (indicated by yellow dots) lead to changes in fine specificity without changes in C region–dependent effector functions. Activated B cells may shift production from largely membrane-bound antibodies containing transmembrane and cytoplasmic regions to secreted antibodies. Secreted antibodies may or may not show V gene mutations (i.e., secretion of antibodies occurs before and after affinity maturation). In isotype switching, the C regions change (indicated by color change from purple to green, yellow, or pink) without changes in the antigen-binding V region. Isotype switching is seen in membrane-bound and secreted antibodies. We will discuss the molecular basis for these changes in Chapter 12.

B cell lymphomas (~90%)

T cell lymphomas (~10%)

COVID-19: immunopathology, pathophysiological mechanisms, and treatment options
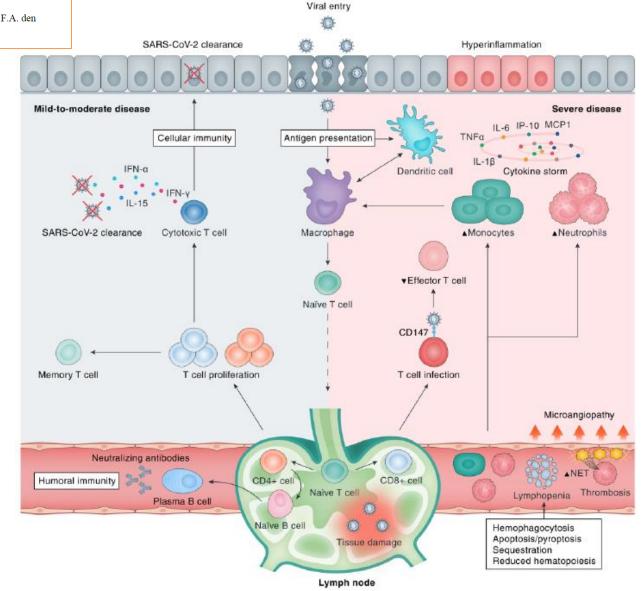
Larissa E. van Eijk[1,*], Mathijs Binkhorst[2,*], Arno R. Bourgonje[3,†], Annette K. Offringa[4,†], Douwe J. Mulder[5], Eelke M. Bos[6], Nikola Kolundzic[7], Amaal E. Abdulle[5], Peter H.J. van der Voort[8], Marcel G.M. Olde Rikkert[9], Johannes G. van der Hoeven[10], Wilfred F.A. den Dunnen[1], Jan-Luuk Hillebrands[1,‡], Harry van Goor[1,‡]

18/02/2022

Lymphoid tissue fibrosis is associated with impaired vaccine responses

Cissy Kityo,[1] Krystelle Nganou Makamdop,[2] Meghan Rothenberger,[3] Jeffrey G. Chipman,[3] Torfi Hoskuldsson,[3] Gregory J. Beilman,[3] Bartosz Grzywacz,[3] Peter Mugyenyi,[1] Francis Ssali,[1] Rama S. Akondy,[4] Jodi Anderson,[3] Thomas E. Schmidt,[3] Thomas Reimann,[3] Samuel P. Callisto,[3] Jordan Schoephoerster,[3] Jared Schuster,[3] Proscovia Muloma,[1] Patrick Ssengendo,[1] Eirini Moysi,[2] Constantinos Petrovas,[2] Ray Lanciotti,[5] Lin Zhang,[3] Maria T. Arévalo,[6] Benigno Rodriguez,[7] Ted M. Ross,[6] Lydie Trautmann,[8,9] Rafick-Pierre Sekaly,[7] Michael M. Lederman,[7] Richard A. Koup,[10] Rafi Ahmed,[4] Cavan Reilly,[3] Daniel C. Douek,[2] and Timothy W. Schacker[3]

Figure 1. Increased immune activation in HIV⁻ Ugandans. Prevaccination plasma samples demonstrated elevated levels of TGF-β (**A**) and IL-6 (**B**) in a group from Uganda compared with a group from the U.S. LN sections stained for Ki67 also demonstrated increased immune activation when compared with LN tissues obtained from people in the U.S. (**C**). Representative sections of LN stained with Ki67 antibodies from an HIV negative person in Minnesota (**D**) and an HIV negative Ugandan (**E**) are shown. Scale bars indicate 100 µm and magnification is ×10.

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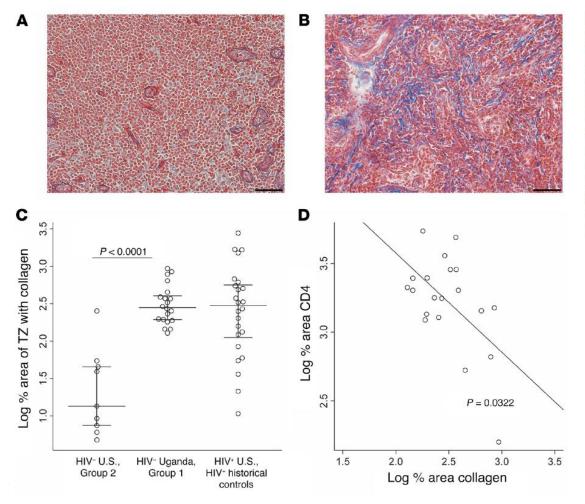
Figure 2. Increased T cell zone fibrosis in people from Uganda. A representative section of LNs stained with trichrome from a person from the U.S. (**A**) was compared with one from a person from Uganda (**B**). There was an increase in the amount of collagen (blue fibers) in the Ugandan sample. LN tissues from the Ugandan participants in Group 1 have a similar amount of collagen as LN tissues from HIV$^-$ people from the U.S. in Group 2 (**C**). We see the expected inverse relationship between TZ collagen and the size of the resident CD4$^+$ T cell population in the HIV$^-$ Ugandans (**D**). Scale bar indicates 50 μm and magnification is ×20.

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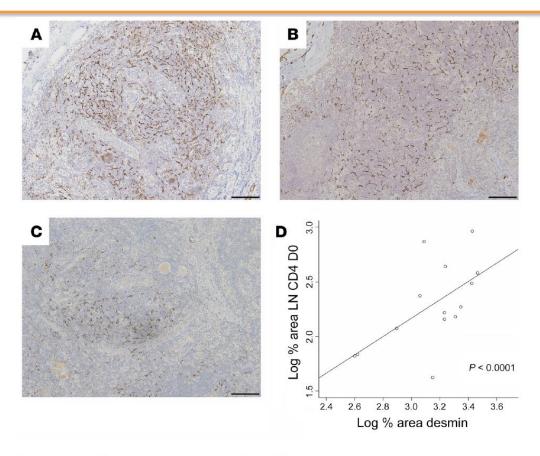
Figure 3. The fibroblastic reticular cell network (FRCn) is depleted in Ugandans. We used QIA to identify TZ desmin in HIV⁻ people in the U.S. (Group 2, A) and people from Uganda (Group 1, B and C) and then used quantitative image analysis to compare the amount of desmin in the section to the size of the CD4⁺ T cell population in the LN (D), showing the significant and direct relationship. Scale bar indicates 100 μm and magnification is ×20.

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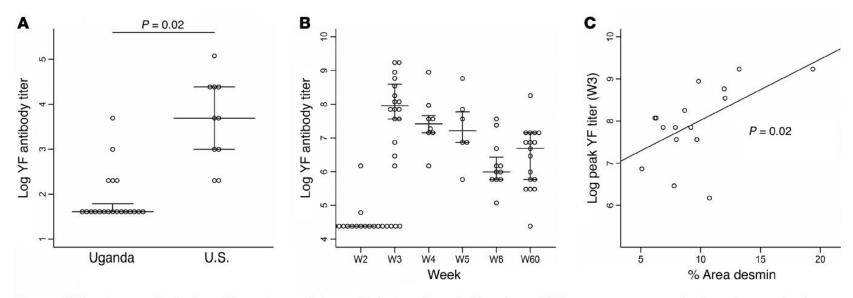
Figure 6. Yellow fever antibody titers. Titers of neutralizing antibody titers from the Ugandan and U.S. groups are compared using a plaque reduction neutralization assay with a starting dilution of 1:20 (**A**), demonstrating that by week 2 all of the U.S. participants had detectable antibodies but only 5 of 20 people from Uganda did. In (**B**) we show the peak titer of the Ugandan participants at day 21 (week 3) and the decline through month 14. In (**C**) we show that measures of desmin in LNs correlate to peak antibody titer.

Lymph node fibrosis: a structural barrier to unleashing effective vaccine immunity

Boris Julg and Galit Alter

Ragon Institute of MGH, MIT and Harvard, Cambridge, Massachusetts, USA. Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
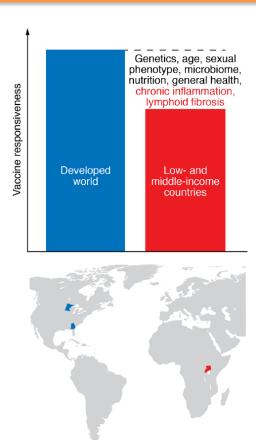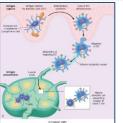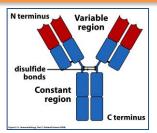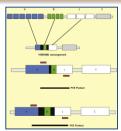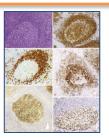
Figure 1. Factors driving lower vaccine responsiveness around the globe. The cartoon bar graph depicts the observed differences in vaccine responsiveness around the globe, and highlights factors that have been associated with vaccine immunogenicity. Factors listed in black have been previously published. Factors listed in red represent the findings in the manuscript by Kityo et al., which evaluated differences in vaccine response in subjects from the U.S. (Minnesota and Georgia, blue) and subjects from Uganda (red).
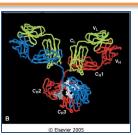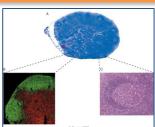
ΑΝΤΙΓΟΝΑ ΚΑΙ ΑΝΤΙΓΟΝΟΠΑΡΟΥΣΙΑΣΗ

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