Imunologie virových nákaz

Přednáška 1

Imunitní mechanismy

„ Úvodní přehled“

Financováno Evropskou unií
NextGenerationEU
NÁRODNÍ PLÁN OBNOVY
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

Podstatou imunity je rozpoznání vlastního a cizího

- tato schopnost vyvinuta už u prvoků (potrava x množení)

Mnohobuněční – specializované buňky imunitního systému

- omezení následků kontaktu s alogenními organismy
- obrana proti invadujícím organismům (patogenům)
- zábrana proliferace mutantních buněk

Bezobratlí

- přirozená imunita zejména buněčného typu
- proti povrchovým strukturám

Obratlovci

- mechanismy nespecifické rezistence
- adaptivní imunita
    - diverzita
    - paměť
    - protilátky
- přenos rezistence proti infekci na potomstvo

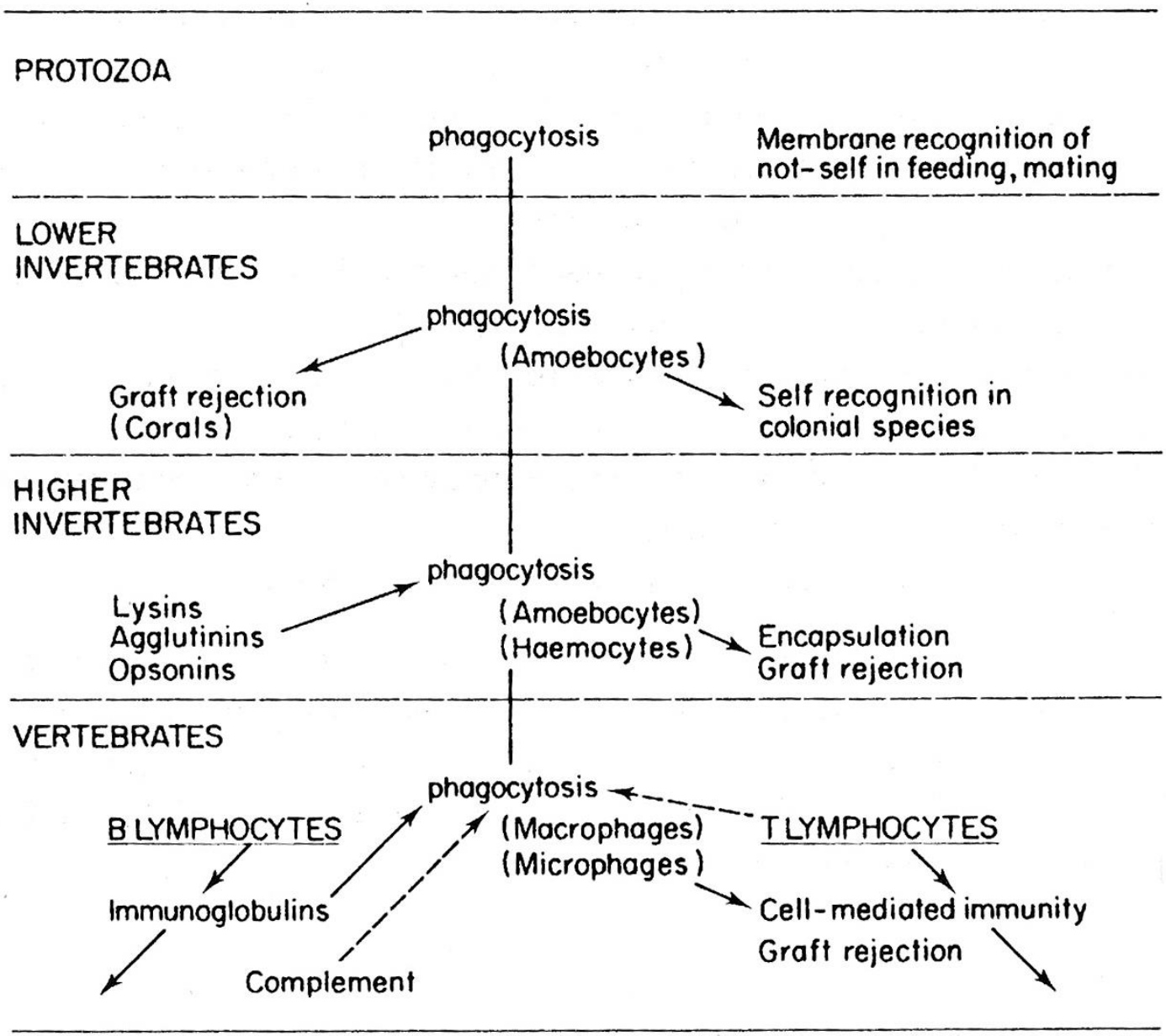


Fig. 2.1 Development of increasingly complex mechanisms of self – not-self discrimination in animal evolution.

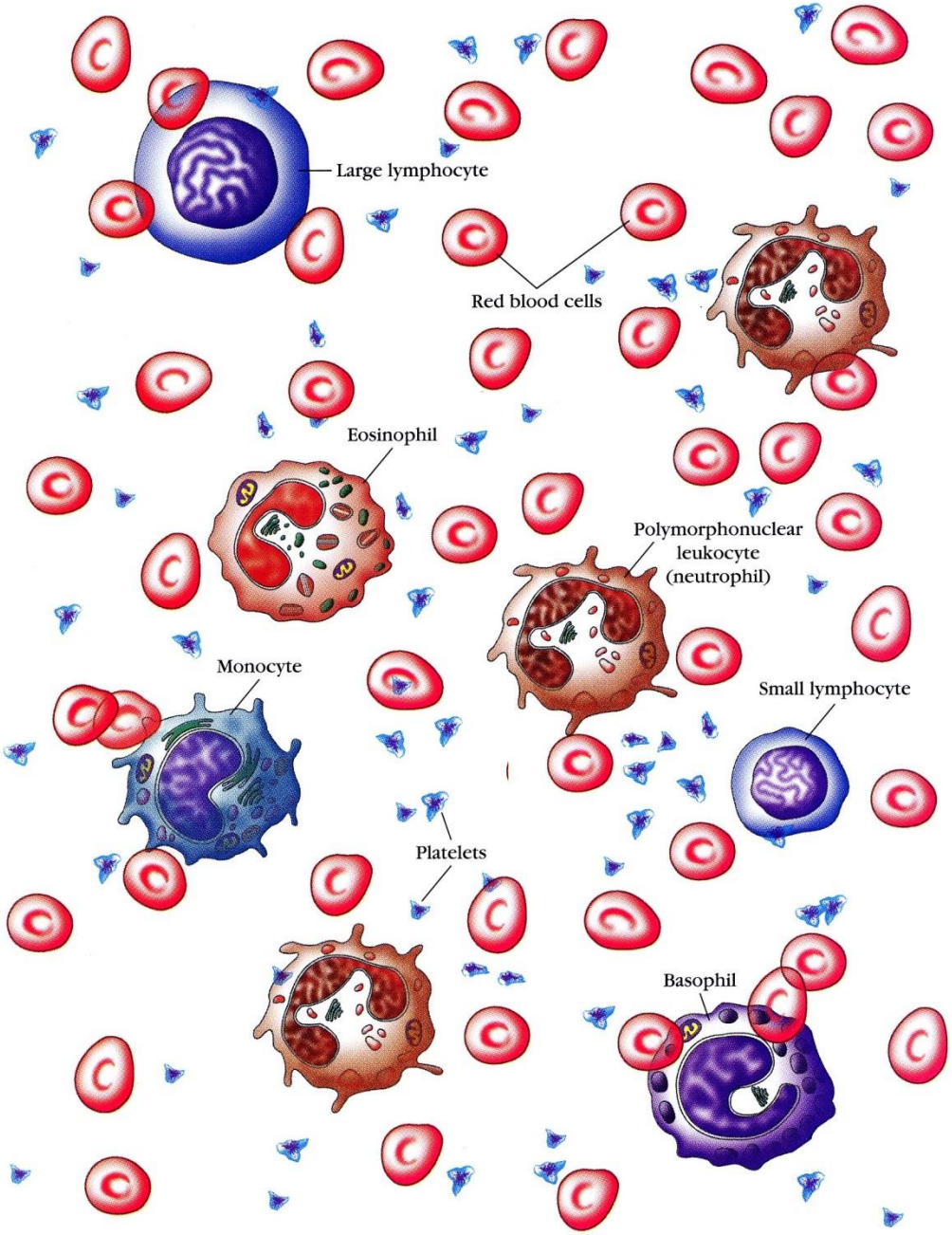
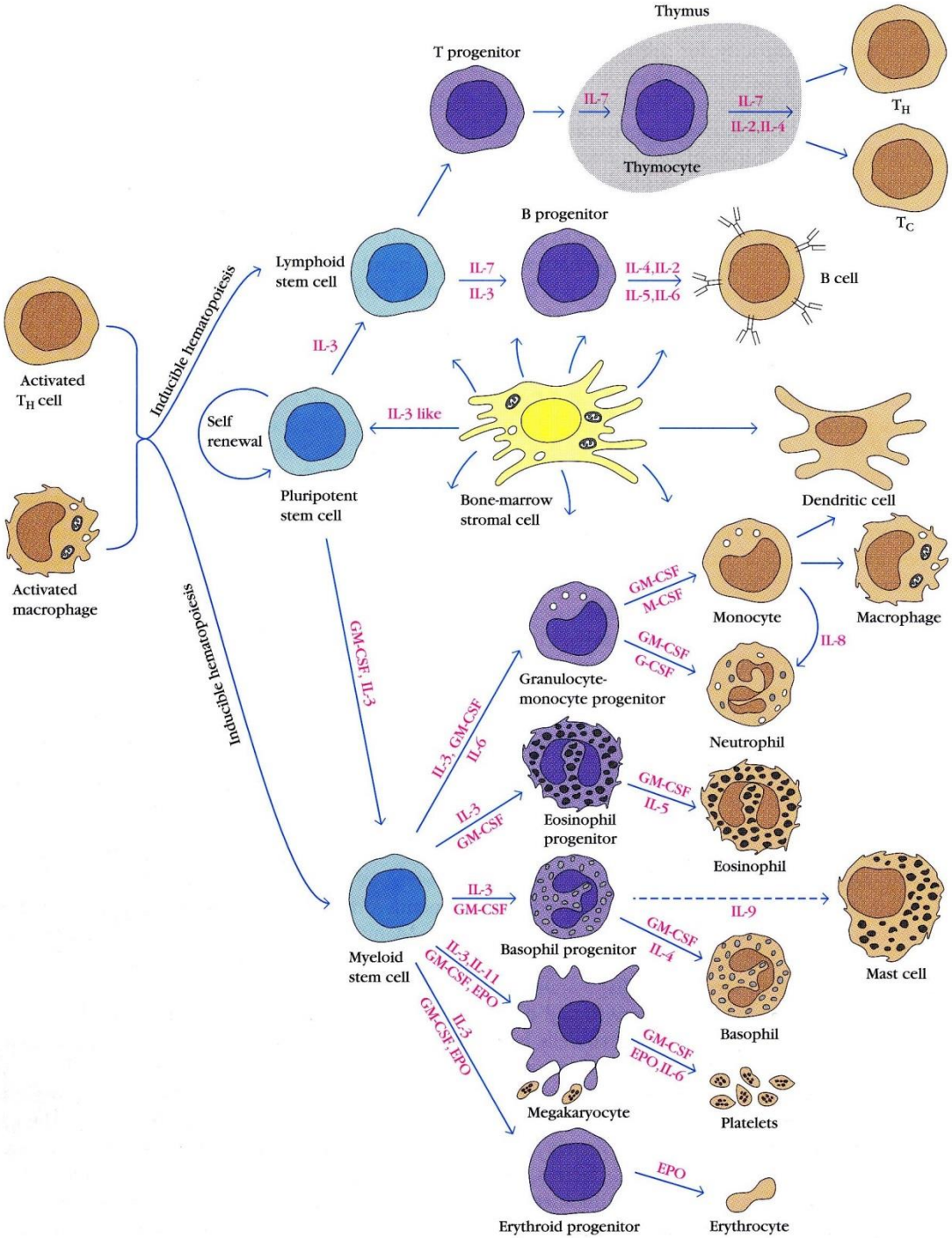
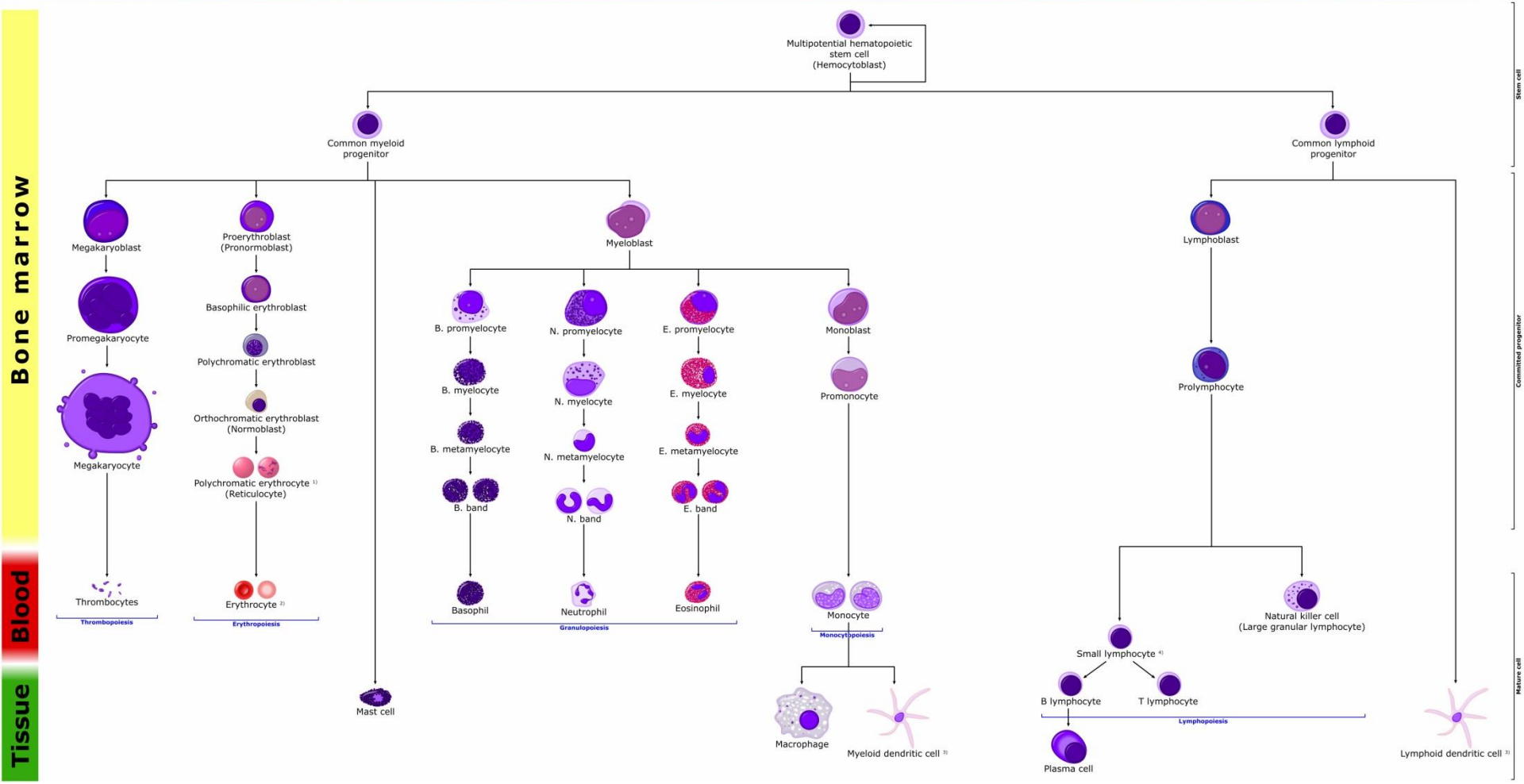


FIGURE 3-1

Morphology and staining characteristics of various types of blood cells. Red blood cells and platelets, which both lack nuclei, are the most numerous. Among the leukocytes responsible for immune responses, the neutrophil is the predominant cell type.


Thymus
T progenitor
IL-7
IL-7
IL-2,IL-4
Thymocyte
T_H
T_C
B progenitor
Lymphoid stem cell
IL-7
IL-3
IL-4,IL-2
IL-5,IL-6
B cell
IL-3
Activated T_H cell
Inducible hematopoiesis
Self renewal
IL-3 like
Pluripotent stem cell
Bone-marrow stromal cell
Dendritic cell
Activated macrophage
GM-CSF, IL-3
GM-CSF
M-CSF
Monocyte
Macrophage
IL-8
GM-CSF
G-CSF
Granulocyte-monocyte progenitor
Neutrophil
IL-3, GM-CSF
IL-6
IL-3
GM-CSF
Eosinophil progenitor
GM-CSF
IL-5
Eosinophil
Inducible hematopoiesis
IL-3
GM-CSF
IL-9
Basophil progenitor
GM-CSF
IL-4
Mast cell
Myeloid stem cell
IL-3,IL-11
GM-CSF,EPO
IL-3
GM-CSF,EPO
Basophil
GM-CSF
EPO,IL-6
Megakaryocyte
Platelets
EPO
Erythroid progenitor
Erythrocyte

Hematopoiesis in humans



Lymfocyty

- vývoj z kmenových buněk kostní dřeně

T lymfocyty – pomocná funkce a buněčná imunita

- rozpoznání vlastních MHC a cizích antigenů
    - T receptor αβ
        - CD4+ T lymfocyty
        - CD8+ T lymfocyty
    - T receptor γδ

B lymfocyty – produkce protilátek

- imunoglobulinový receptor

NK buňky – „natural killer“

- rozpoznávací mechanismy nejsou omezené MHC

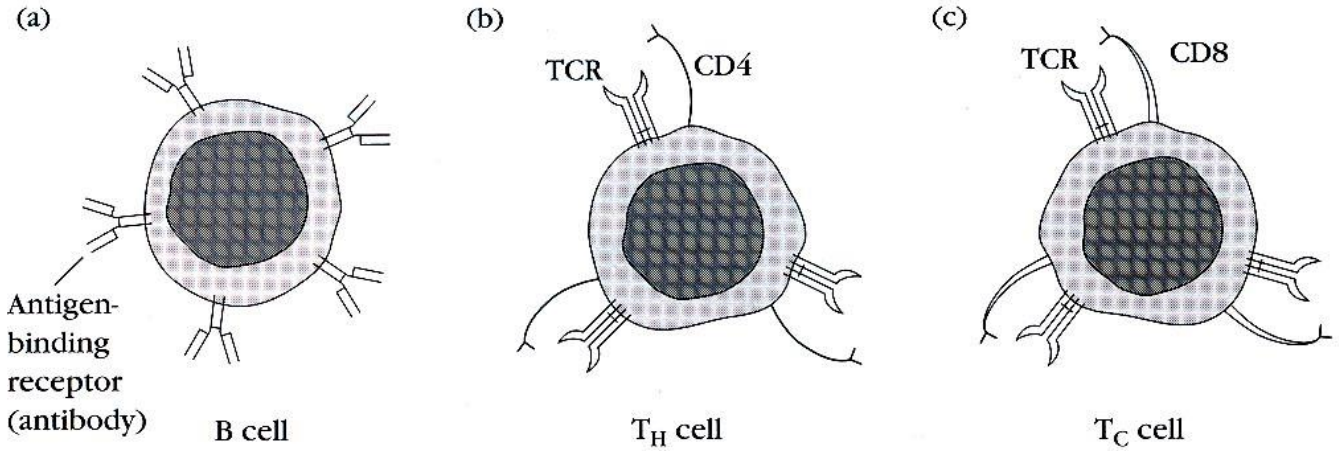


FIGURE 1-6

Distinctive membrane molecules on lymphocytes. (a) B cells have about 10^5 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell exhibit the same antigenic specificity and can interact directly with antigen. (b) T cells bearing CD4 only recognize antigen associated with class II MHC molecules. (c) T cells bearing CD8 only recognize antigen associated with class I MHC molecules. In general, $CD4^+$ T cells function as helper cells and $CD8^+$ cells function as cytotoxic cells. Both types of T cells express about 10^5 identical molecules of the antigen-binding T-cell receptor (TCR) per cell, each with the same antigenic specificity.

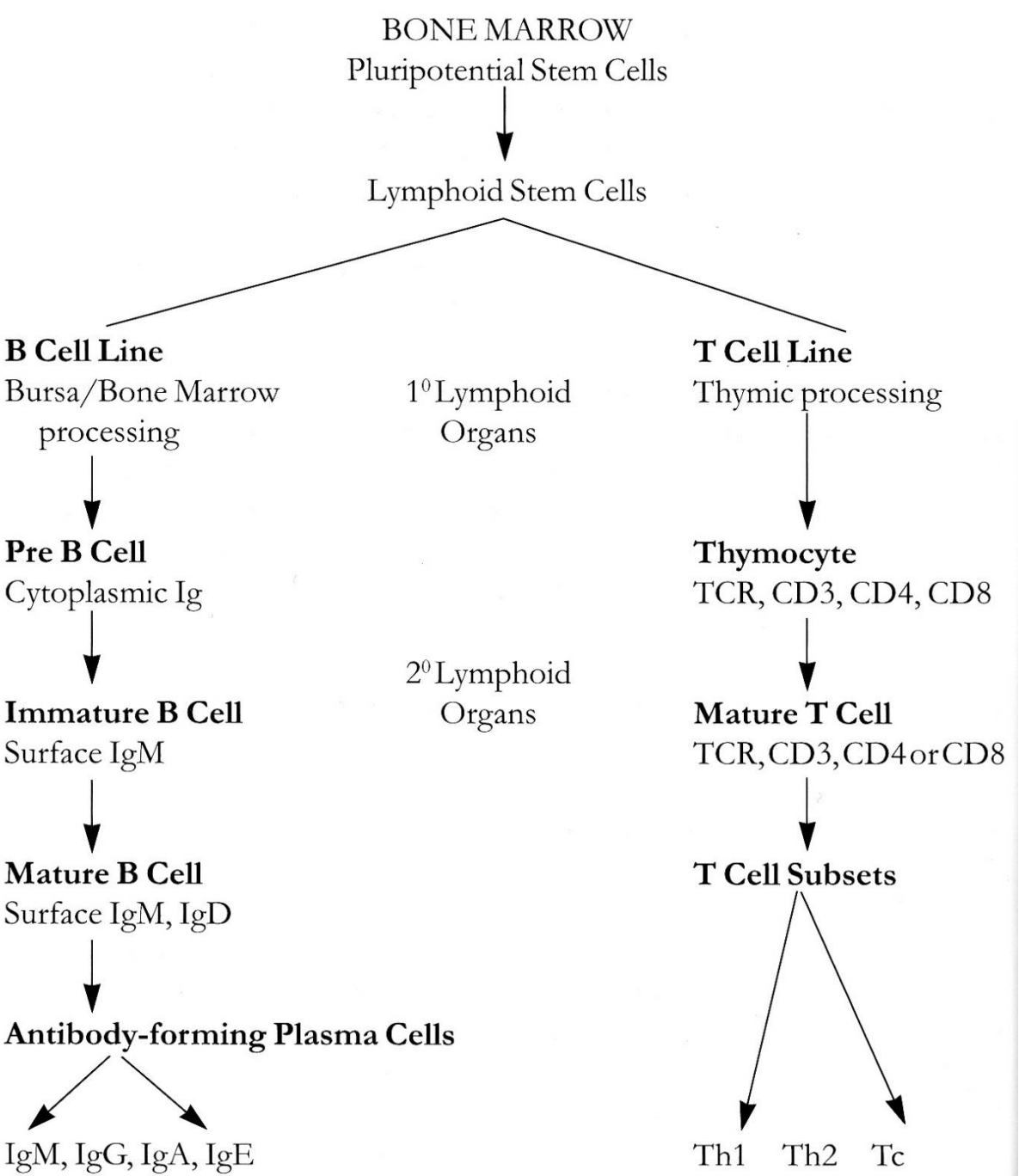
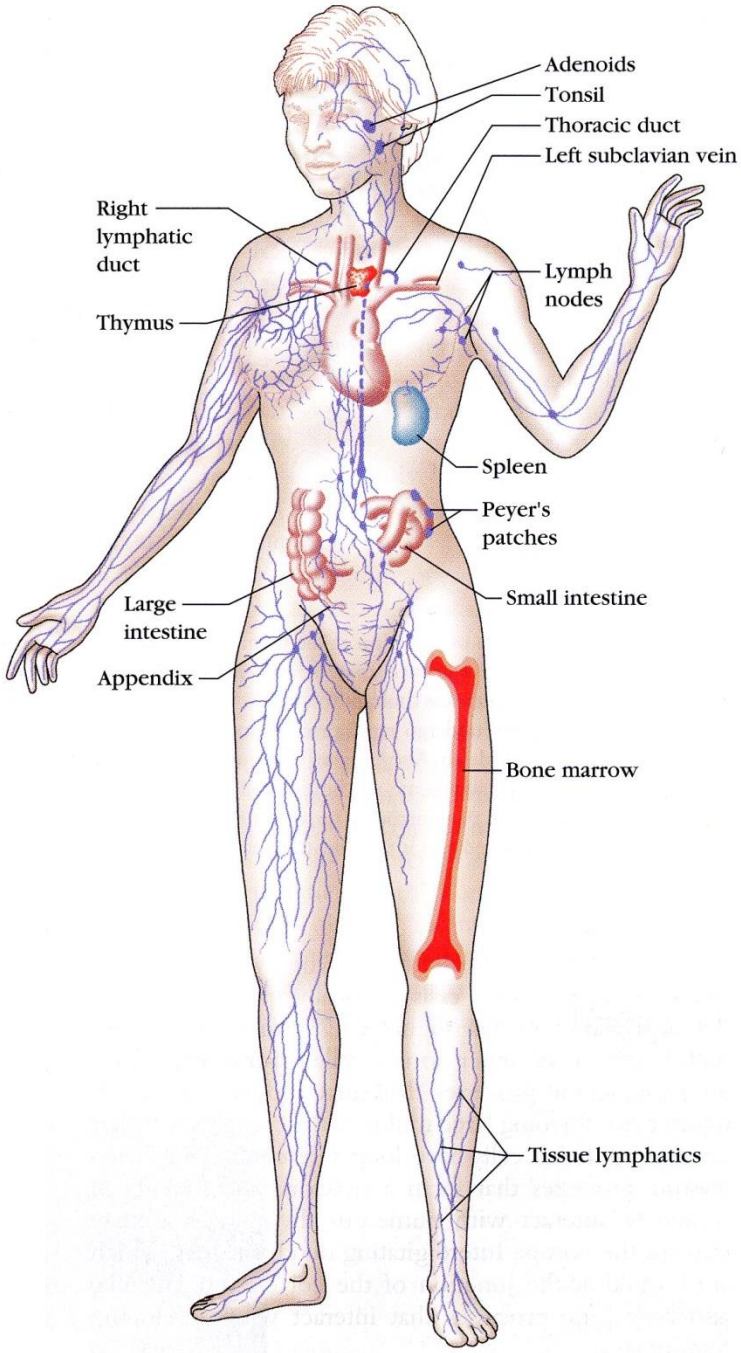


Fig. 2.3 Development and differentiation of lymphocytes. Th, T helper; Tc, T cytotoxic.

FIGURE 3-16

The human lymphoid system. The primary organs (bone marrow and thymus) are shown in red; secondary organs and tissues, in blue. These structurally and functionally diverse lymphoid organs and tissues are interconnected by the blood vessels (not shown) and lymphatic vessels (purple) through which lymphocytes circulate. Only one bone is shown, but all major bones contain marrow and thus are part of the lymphoid system. [Adapted from Harvey Lodish et al., 1995, *Molecular Cell Biology,* 3rd ed., Scientific American Books.]



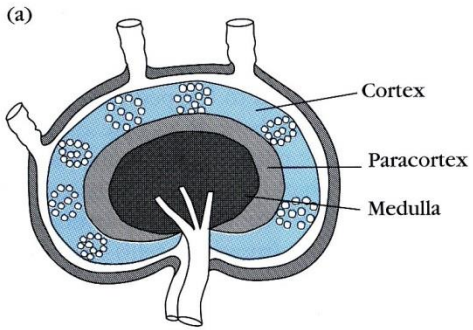
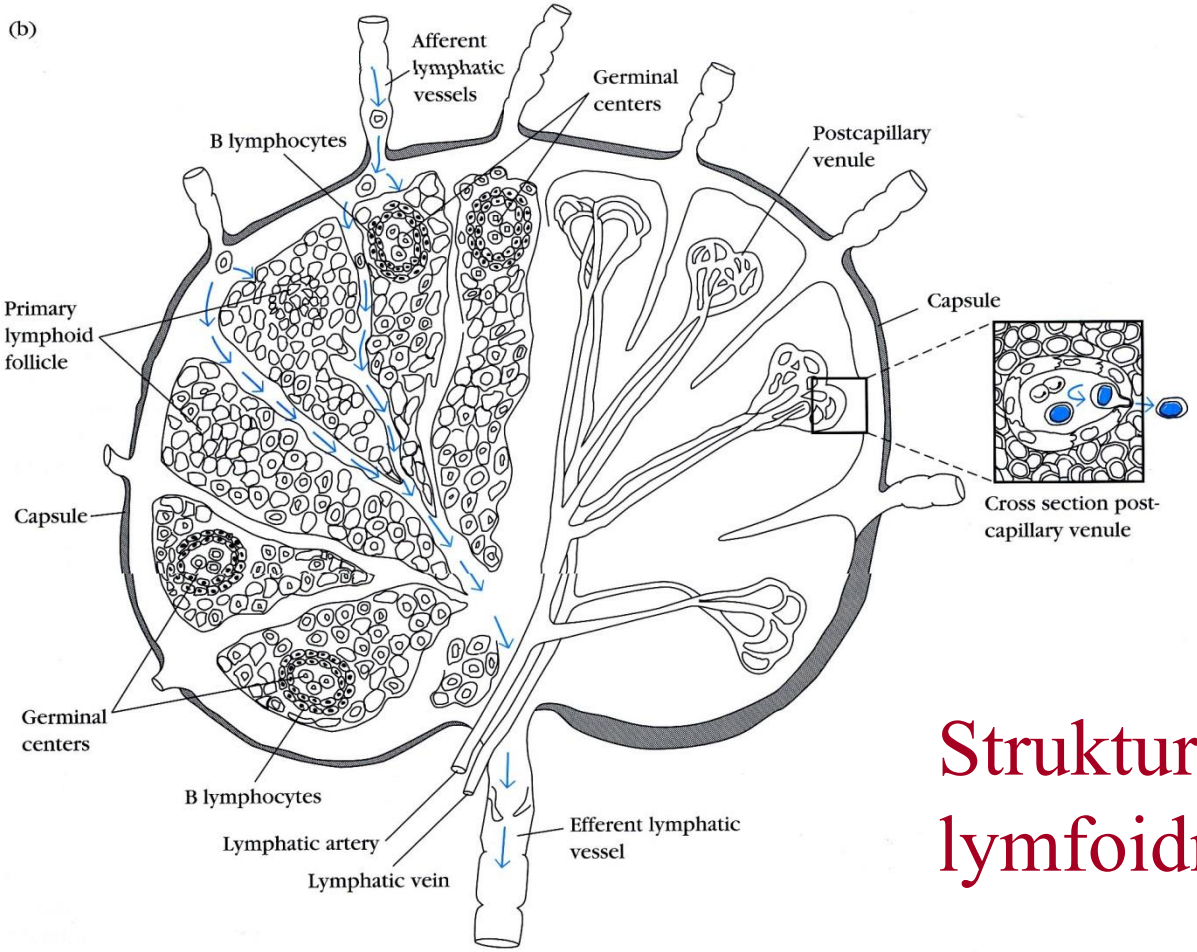


FIGURE 3-21

Structure of a lymph node. (a) The three layers of a lymph node provide distinct microenvironments. (b) The left side depicts the arrangement of reticulum and lymphocytes within the various regions of a lymph node. Macrophages and dendritic cells, which trap antigen, are present in the cortex and paracortex. T_H cells are concentrated in the paracortex; B cells are located primarily in the cortex within follicles and germinal centers. The medulla is populated largely by antibody-producing plasma cells. Lymphocytes circulating in the lymph are carried into the node via afferent lymphatics; they either enter the reticular matrix of the node or pass through it and leave via the efferent lymphatic vessel. The right side of (b) depicts the lymphatic artery and vein and the postcapillary venules. Lymphocytes in the circulation can pass into the node from the postcapillary venules by a process called extravasation (*inset*).



Struktura sekundárních lymfoidních orgánů

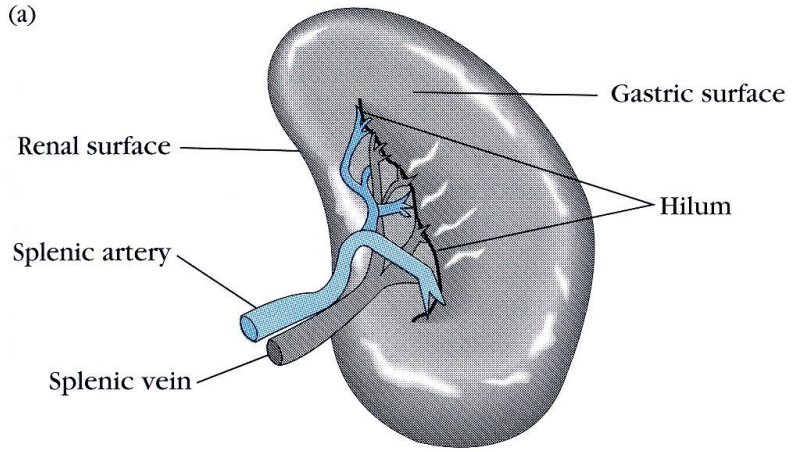
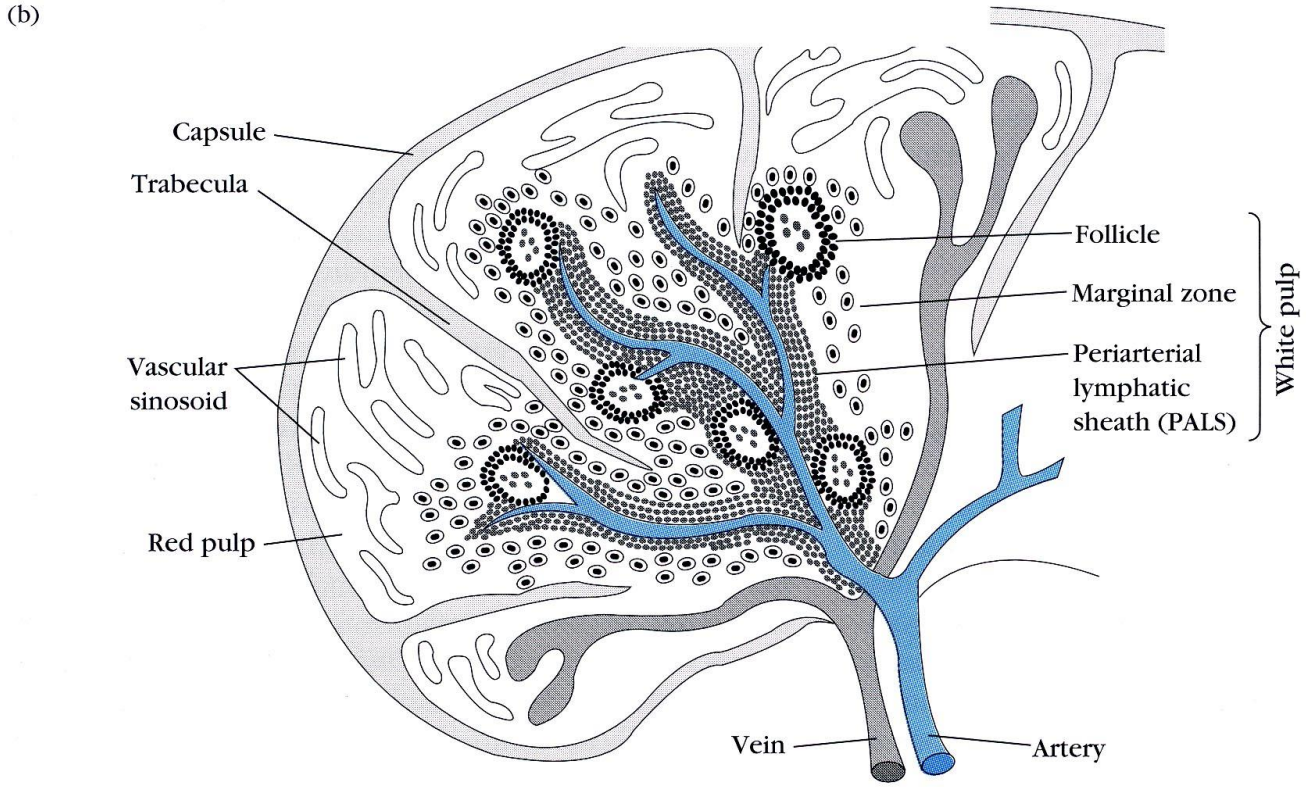


FIGURE 3-22

Structure of the spleen. (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens. (b) Diagrammatic cross section of the spleen. The arteriole blood supply pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarteriolar lymphoid sheath (PALS) around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, a B-cell–rich area containing lymphoid follicles that can develop into germinal centers.



Hlavní histokompatibilní komplex

- rozpoznání cizího a vlastního
- HLA antigeny u lidí na šestém chromozomu
- H-2 komplex u myší na 17. chromozomu

MHC antigeny I a II třídy

- MHC I - na všech jaderných buňkách
  - α řetězec + β_2 mikroglobulin
- MHC II - na antigen prezentujících buňkách
  - α a β řetězec

- variabilní a konstantní domény, štěrbina pro antigen

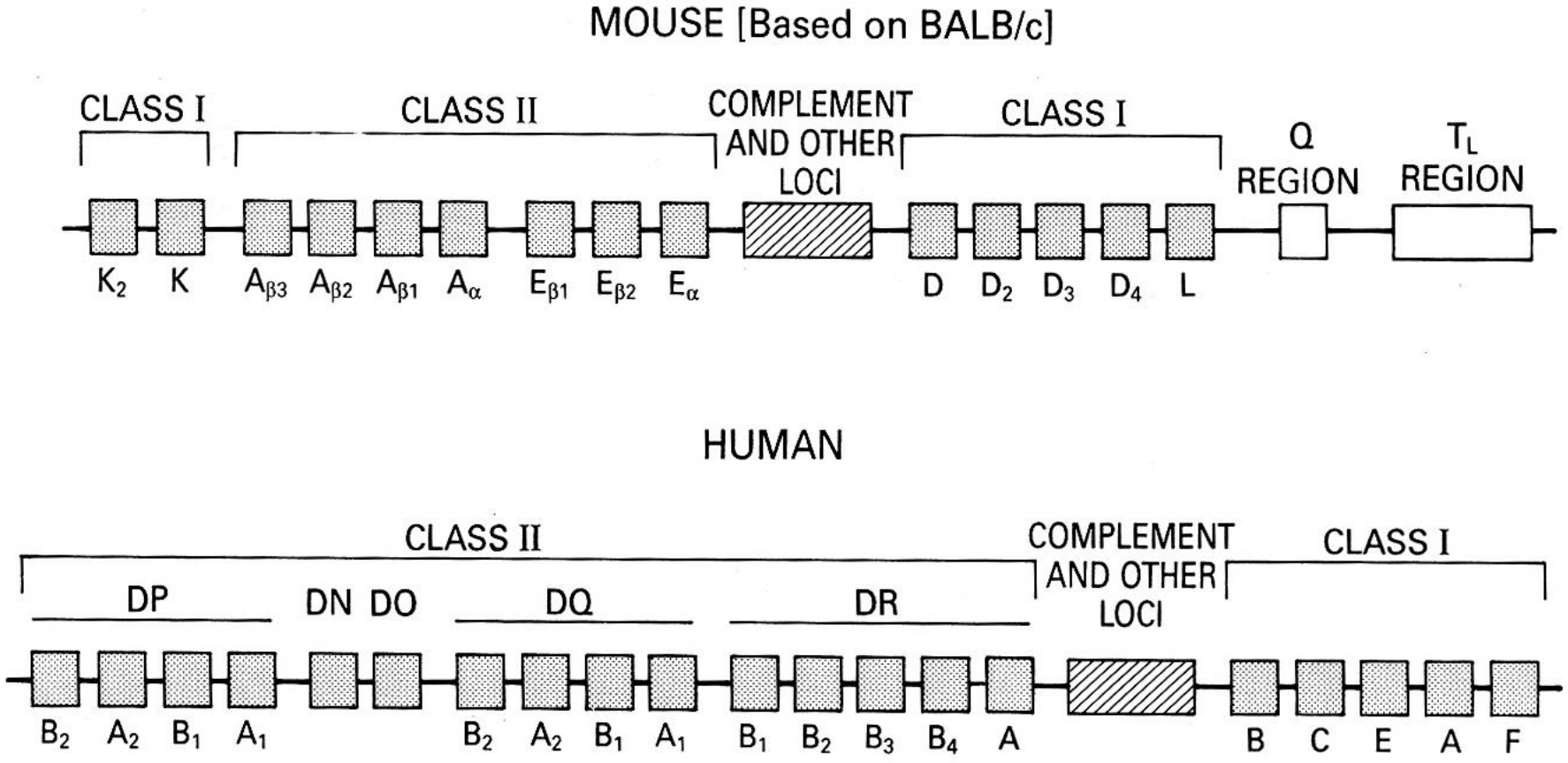


Fig. 2.2 Major histocompatibility complexes (MHC) of mice and humans. Many more genes have been identified in the MHC than are expressed. The figure shows some of the loci that are most important in immune responses. Class I gene products, the classical transplantation antigens, are expressed on almost all cells. Expression of Class II products is much more restricted (e.g. macrophages, dendritic cells, B cells). (Based on Klein, 1990, *Immunology*, Blackwell Scientific Publications).

Prezentace antigenu

- exogenní antigen je zpracován a prezentován s MHCII antigeny na antigen prezentujících buňkách.
- fragmenty antigenu cca 10 AK vázané v MHC II jsou rozpoznány T receptorem na Th lymfocytech CD4+
- klonální expanze lymfocytů rozpoznávajících antigen
- produkce cytokinů

- endogenní antigen je prezentován spolu s MHC I
- CTL – specifické ničení napadených buněk

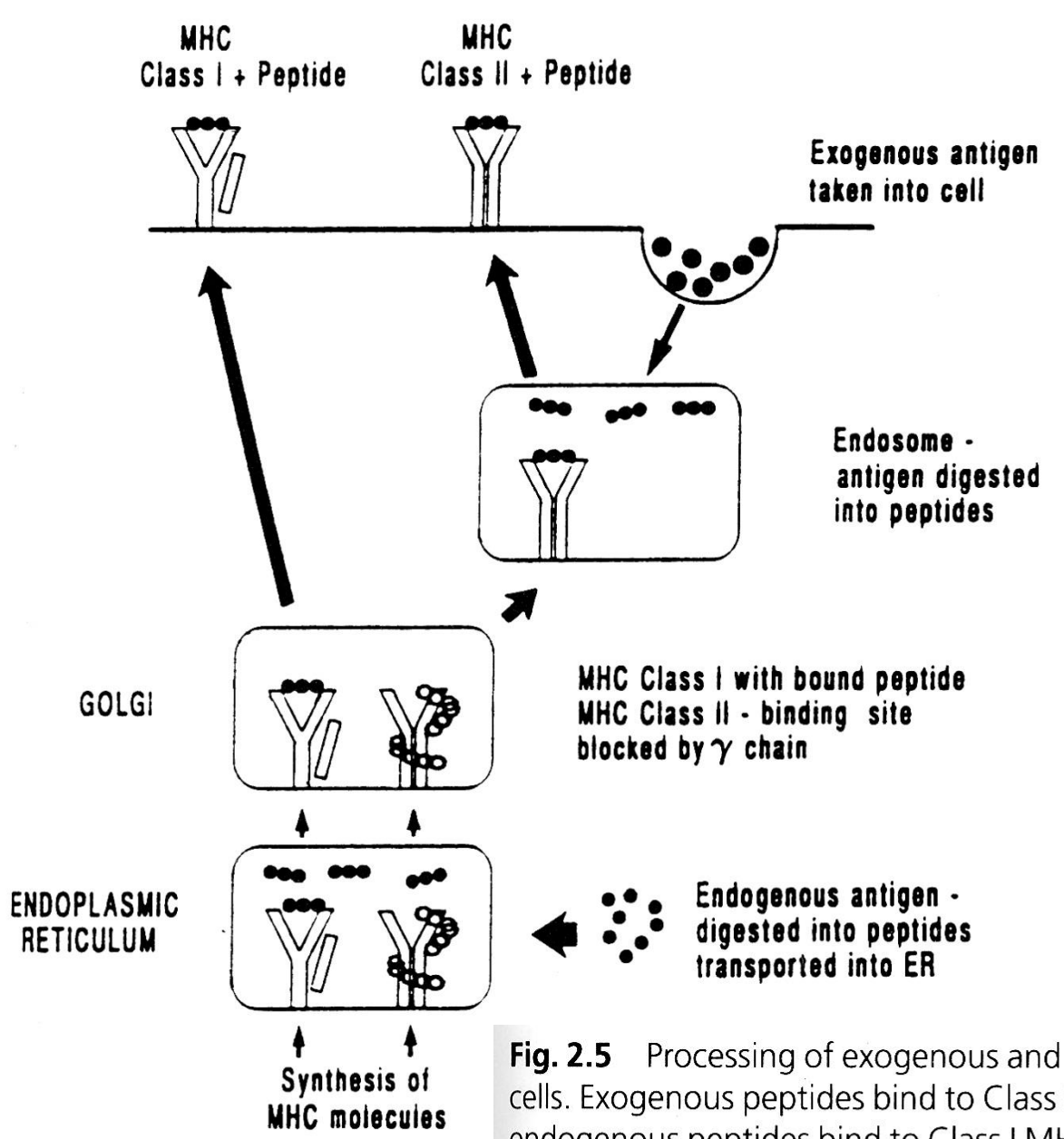


Fig. 2.5 Processing of exogenous and endogenous antigens in antigen presenting cells. Exogenous peptides bind to Class II MHC molecules in the endosomes, endogenous peptides bind to Class I MHC molecules in the endoplasmic reticulum. Binding of peptides to Class II molecules is blocked until the gamma chain is removed. (Taken from Smyth, 1994, *Introduction to Animal Parasitology*, Cambridge University Press.)

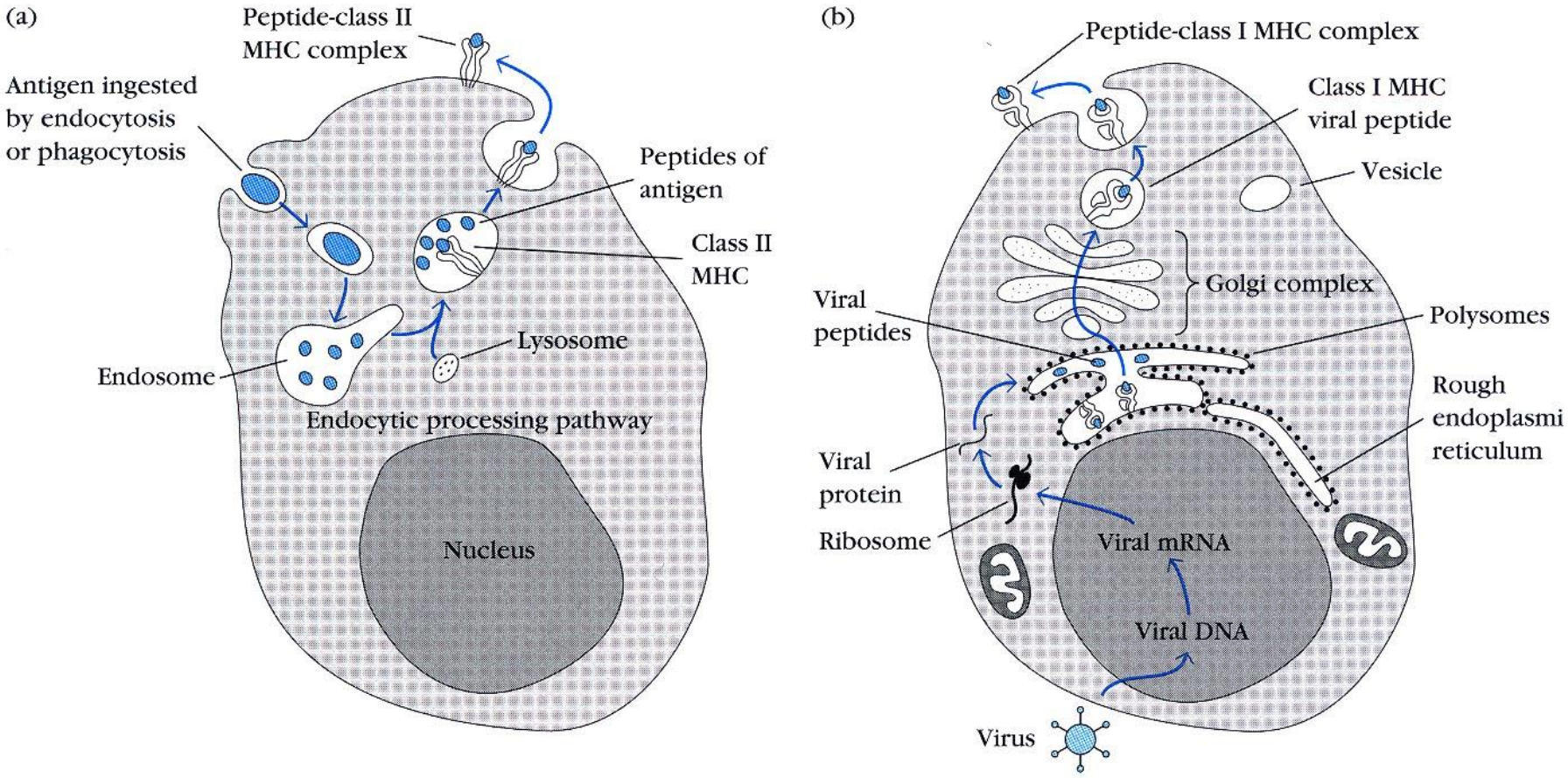


FIGURE 1-10

Processing and presentation of exogenous and endogenous antigens. (a) Exogenous antigen is ingested by endocytosis or phagocytosis and then enters the endocytic processing pathway. Here, within an acidic environment, the antigen is degraded into small peptides, which then are presented with class II MHC molecules on the membrane of the antigen-presenting cell. (b) Endogenous antigen, which is produce within the cell itself (e.g., in a virus-infected cell), is degraded withi the cytoplasm into peptides, which move into the endoplasmic reticu lum where they bind to class I MHC molecules. The peptide–class MHC complexes then move via the Golgi complex to the cell surface

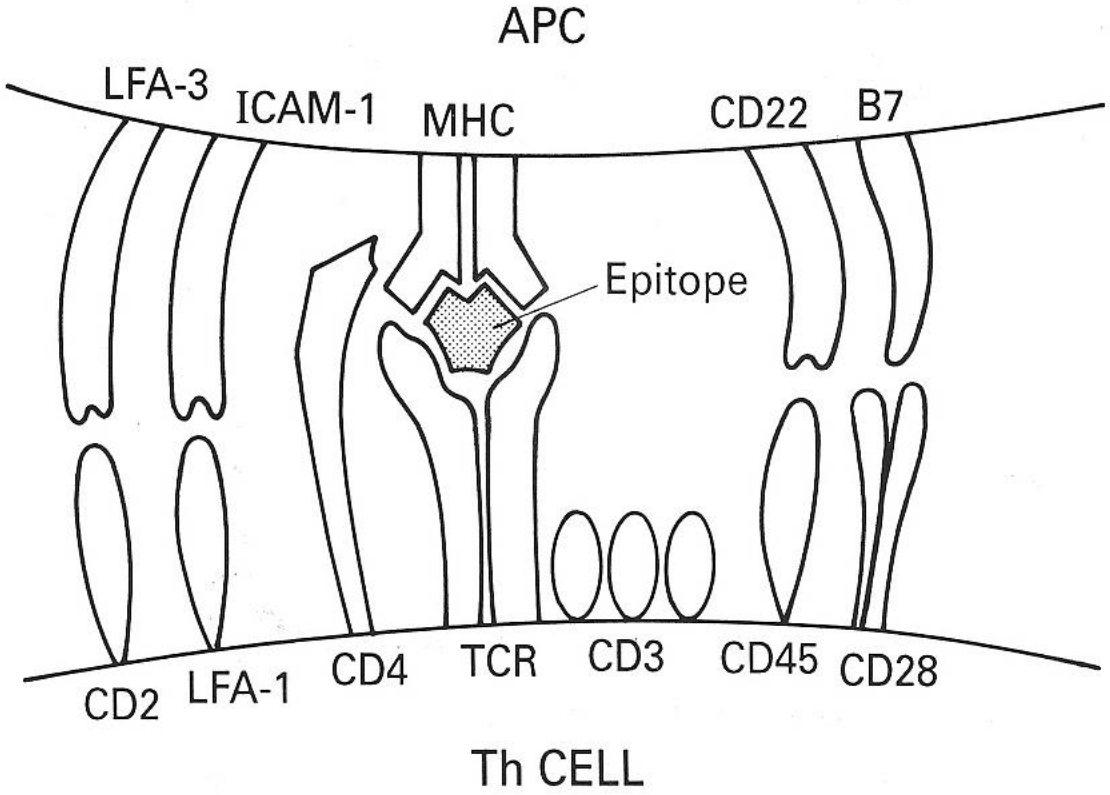


Fig. 2.6 Schematic representation of molecular interactions between antigen presenting cell (APC) and T helper cell (Th) during antigen recognition. The epitope is presented by the Class II MHC molecule and recognized by the T cell receptor (TCR). Signal transduction involves the CD3 and CD4 molecules. A number of additional ligand–receptor interactions facilitate the APC–Th cell interaction.

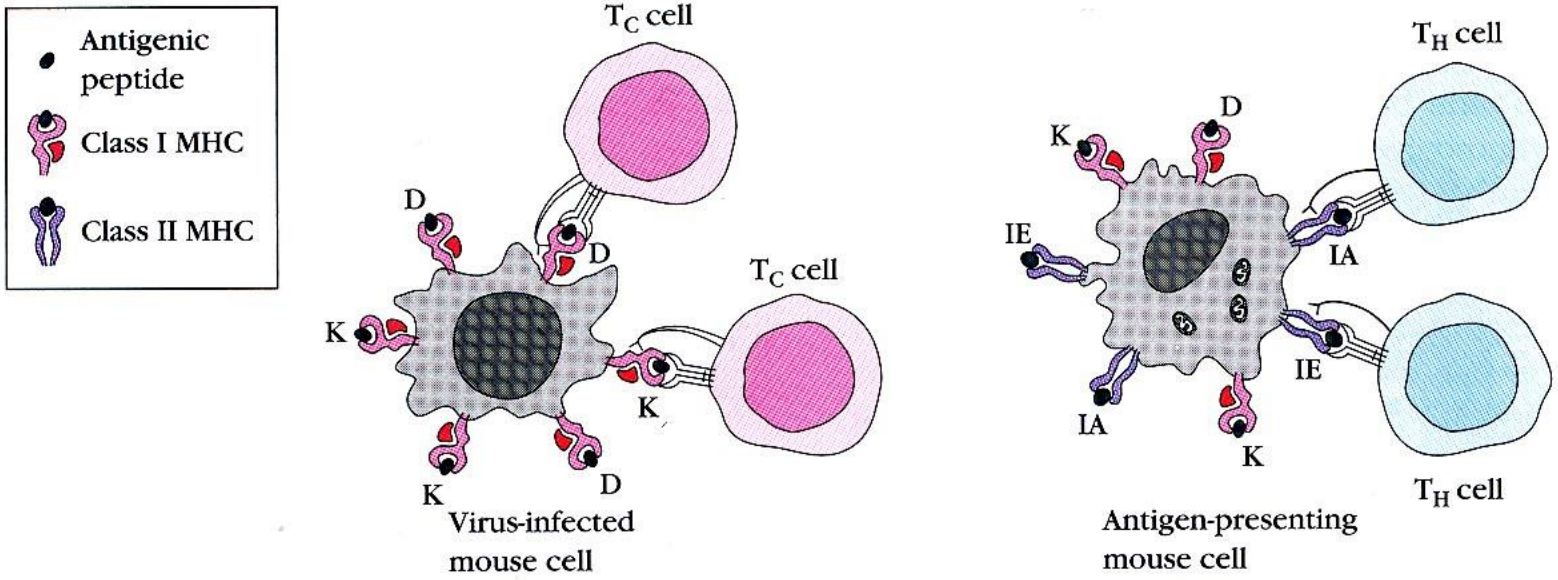


FIGURE 1-9

Role of MHC molecules in antigen recognition by T cells. Class I MHC molecules are encoded by the *K* and *D* loci in mice (*A*, *B*, and *C* loci in humans) and are expressed on nearly all nucleated cells. Class II MHC molecules are encoded by the *IA* and *IE* loci in mice (*DP*, *DQ*, and *DR* loci in humans) and are expressed only on antigen-presenting cells. $CD4^+$ T cells only recognize antigenic peptides displayed with a class II MHC molecule; they generally function as T helper (T_H) cells. $CD8^+$ T cells only recognize antigenic peptides displayed with a class I MHC molecule; they generally function as T cytotoxic (T_C) cells.

Cytokiny

- glykoproteiny ovlivňující vývoj imunitní odpovědi
- produkovány různými buňkami organismu
- nejvýznamnějšími producenty jsou buňky přímo zapojené v imunitní odpovědi

Kaskádovitý efekt

- váží se na membránové receptory a způsobují produkci dalších cytokinů či expresi dalších receptorů
- autokrinní x parakrinní účinek

- Th1 x Th2 odpověď

Table 2.1 *Major cytokines relevant to immunoparasitology*

Cytokine	Main Source	Functions
IL-1	Many cells	Activation, regulation, inflammation
IL-2	T cells	Stimulates T cells, B cells, macrophages, T cell proliferation
IL-3	T cells	Stimulates B cells; multi-potential CSF for many cell types in bone marrow
IL-4	T cells	Stimulates T and B cells; induces IgE; mast cell development; enhances MHC expression; down-regulates Th1 cells
IL-5	T cells	Stimulates B cells; induces IgA; eosinophil development
IL-6	Many cells	Stimulates T cells, B cells and granulocytes; induces acute phase proteins
IL-9	T cells	Mast cell development
IL-10	T cells	Down-regulates Th1 cells
IL-12	Macrophages	Stimulates release of IFN and B cells
IL-13	T cells	Suppresses macrophage cytotoxicity, down-regulates production of IFN-γ and IL-12
IFN–γ	T cells, NK cells	Activates macrophages; enhances MHC expression; stimulates B cells; induces acute phase proteins, down-regulates Th2 cells
TNF-α	Macrophages	Inflammation, cytotoxicity, cytokine release
TNF-β	T cells	Inflammation, cytotoxicity, cytokine release
CSF	Many cells	Control production of myeloid cell colonies in bone marrow. (e.g. GM-CSF, granulocyte /macrophage; G-CSF, granulocyte)

Notes:
IL, interleukin; IFN, interferon; TNF, tumour necrosis factor; CSF, colony stimulating factor.

Table 2.2 *Major cytokines associated with T helper cell subsets (based on data from* in vivo *and* in vitro *studies with mice)*

	Type 1		Type 2					Type 3		
	IFN-γ	IL-2	IL-4	IL-5	IL-6	IL-10	IL-13	IL-3	GM-CSF	TNF-β
T helper 1	+	+	–	–	–	–	–	+	+	+
T helper 2	–	–	+	+	+	+	+	+	+	+
T helper 0	+	+	+	+	+	+	+	+	+	+

(Interleukins IL-1, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15 are produced by non-T cells)

Protilátky

- vazba antigenu
- B lymfocyty
    - plazmatické B lymfocyty
    - paměťové B lymfocyty

- produkce většinou závislá na Th buňkách
- na thymu nezávislé antigeny pomoc nepotřebují (karbohydráty se sériově se opakujícími epitopy).
- neutralizace patogenů, nebo jejich toxinů či enzymů
- opsonizace (fagocytóza, ADCC)
- aktivace komplementu

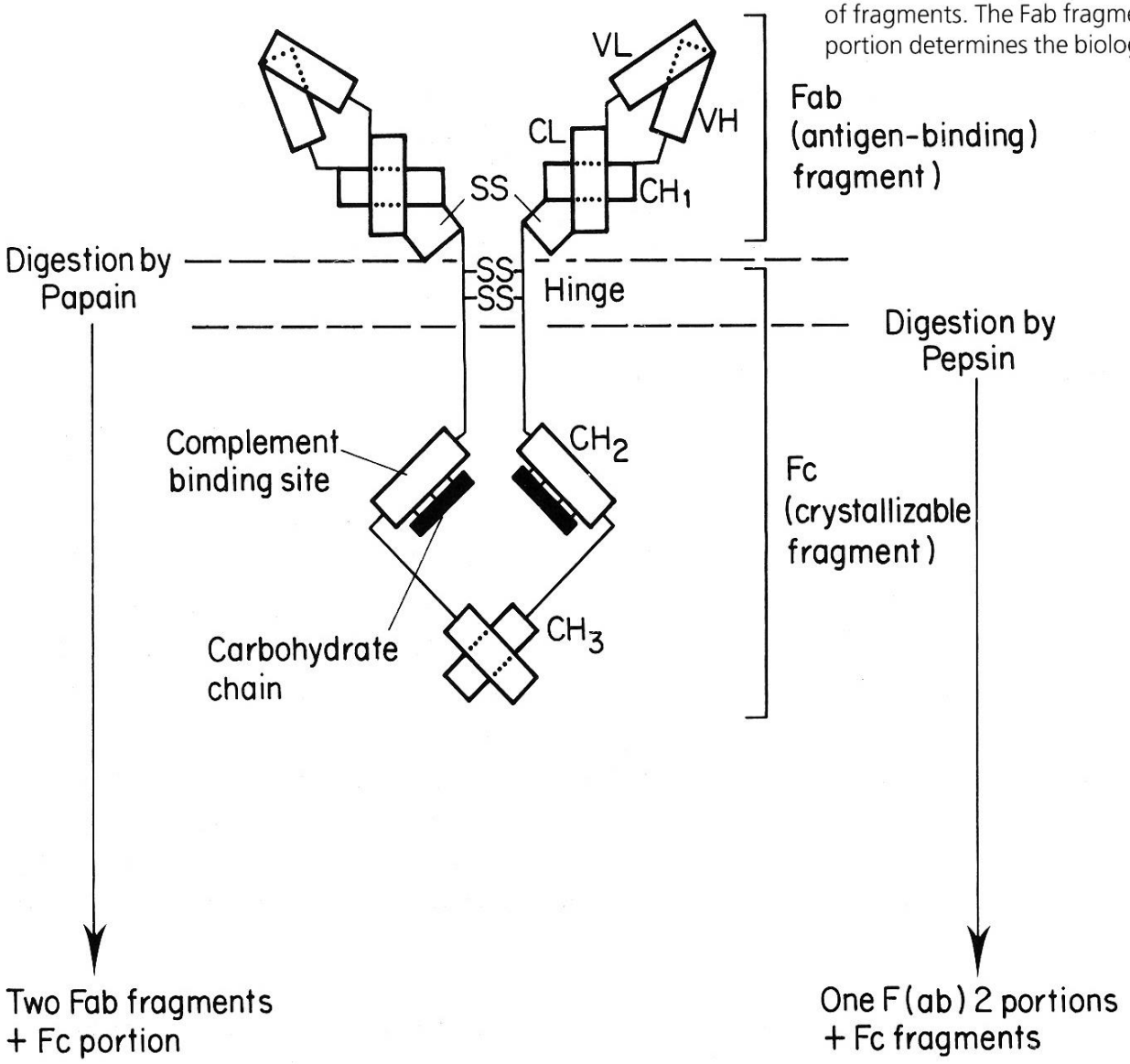


Fig. 2.7 Representation of an IgG_1 molecule, based on the Edelman and Porter model. The molecule is formed of two identical light chains (MW 25kDa) and two identical heavy chains (MW50 kDa) held together by disulphide bridges. The light chains are folded into two domains VL and CL, the heavy chains into four domains VH, CH_1, CH_2 and CH_3, and all except CH_2 are arranged in pairs held together by non-covalent forces. The amino acid sequences of the domains are variable (V) or constant (C) and the antigen binding sites are associated with hypervariable regions in the VL and VH domains. Digestion by proteolytic enzymes breaks the molecule into a variety of fragments. The Fab fragments contain the active antigen-binding sites, the Fc portion determines the biological characteristics of the molecule.

Table 2.3 *Characteristics of immunoglobulins*

Isotype	Structure	MW (kDa)	% total serum Ig	Characteristics
IgM	Pentamer	900	6	First isotype in response, good agglutinator, fixes complement, secreted across mucosal surfaces
IgG	Monomer	150	80	Major isotype in body fluids, fixes complement, binds to macrophages and polymorphs, facilitates ADCC, crosses placenta,several subclasses
IgA	Monomer Dimer (+ secretory piece)	160 400	13	Major isotype at mucosal surfaces, secreted across epithelial cells, secreted in milk, binds to eosinophils, can activate complement by alternative pathway
IgE	Monomer	200	0.002	Binds to mast cells and basophils, involved in immediate hypersensitivity, binds to eosinophils, facilitates ADCC

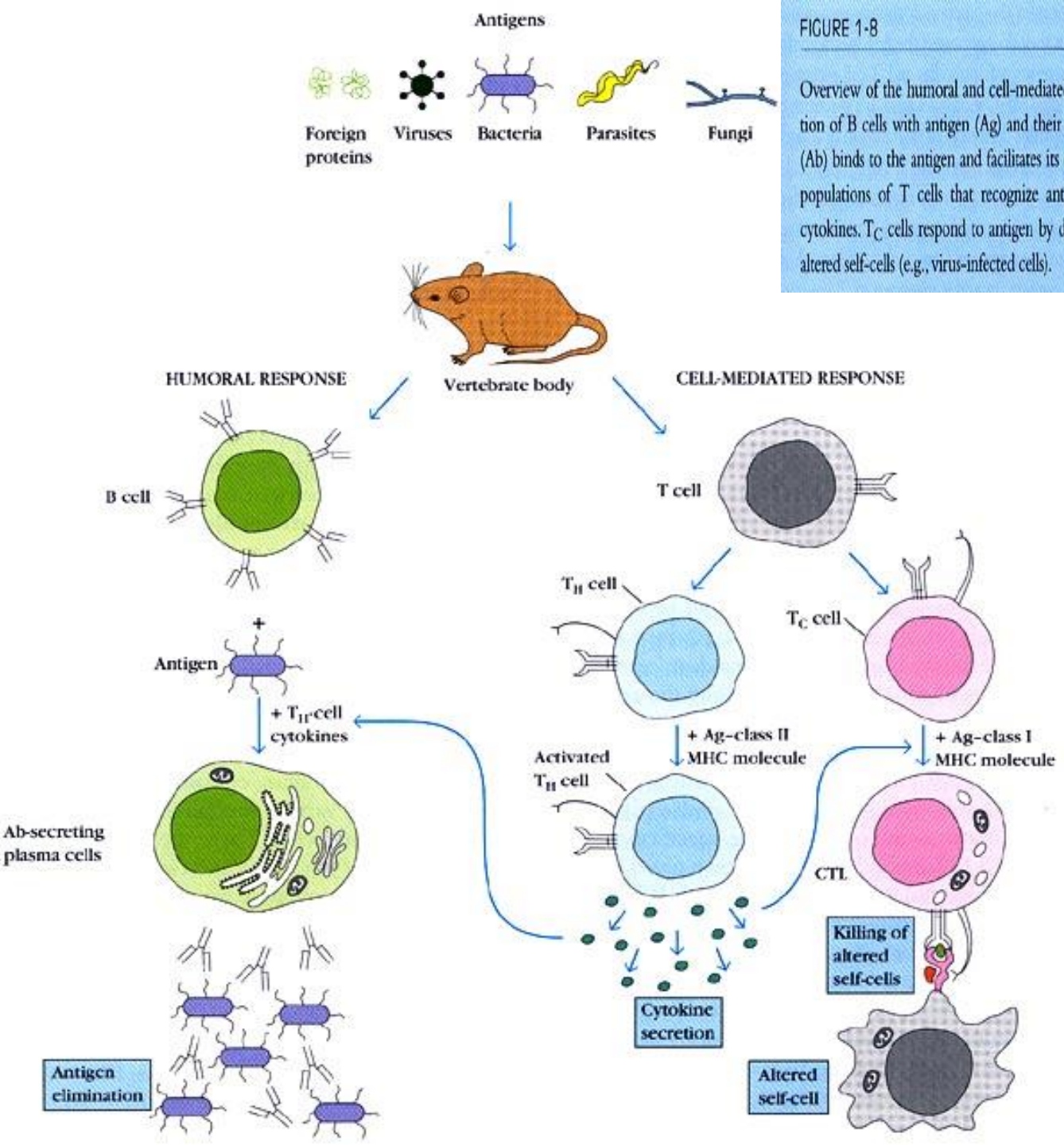


FIGURE 1-8

Overview of the humoral and cell-mediated branches of the immune system. The humoral response involves interaction of B cells with antigen (Ag) and their differentiation into antibody-secreting plasma cells. The secreted antibody (Ab) binds to the antigen and facilitates its clearance from the body. The cell-mediated response involves various subpopulations of T cells that recognize antigen presented on self-cells. T_H cells respond to antigen by producing cytokines. T_C cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).

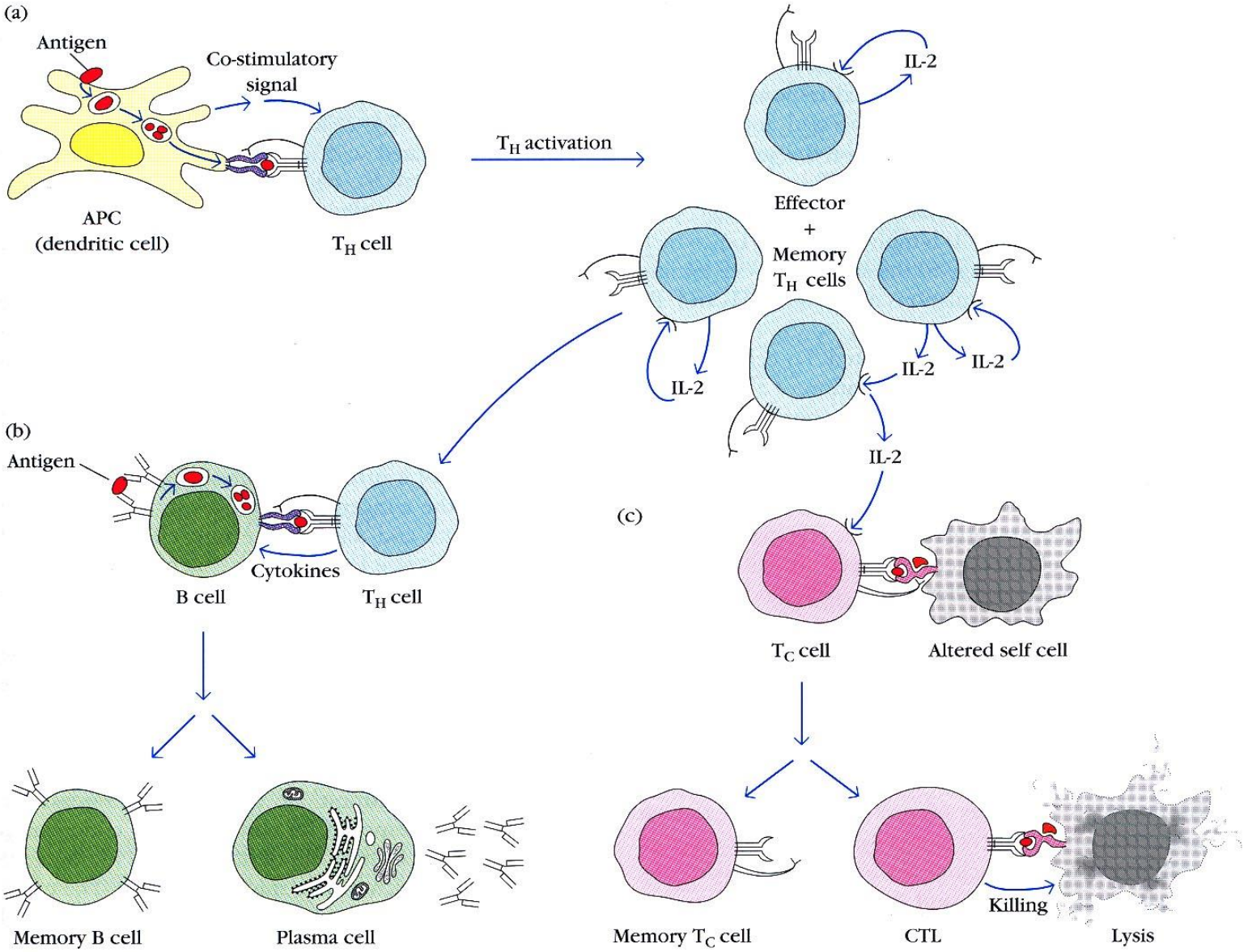


FIGURE 1-14

Cellular interactions involved in induction of immune responses. Activation and proliferation of T_H cells (a) is required for generation of a humoral response (b) and a cell-mediated response to altered self-cells (c). APC = antigen-presenting cell; Ag = antigen. See text for discussion.

Mechanisms by which specific antibody controls some parasitic infections

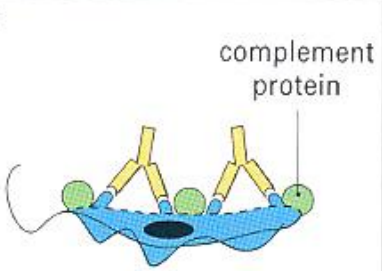
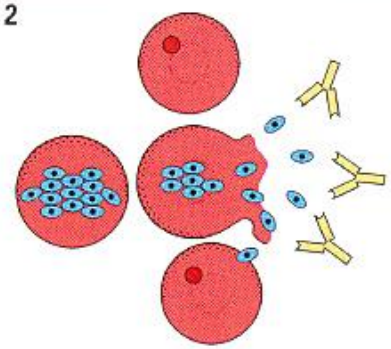
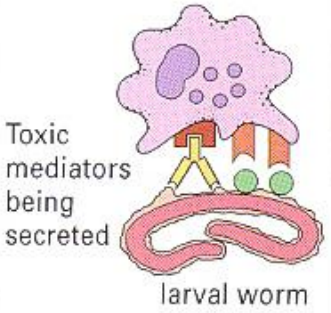
	1	2	3	4
parasite	*Plasmodium* spp. sporozoite, intestinal worms, trypanosome	*Plasmodium* spp. sporozoite and merozoite, *T. cruzi*, *T. gondii*	*Plasmodium* spp. trypanosome	schistosomes, *T. spiralis*, filarial worm larvae
mechanism				
effect	direct damage or complement-mediated lysis	prevents spread by neutralizing attachment site, prevents escape from lysosomal vacuole, prevents inhibition of lysosomal fusion	enhancement of phagocytosis	antibody-dependent cell-mediated cytotoxicity (ADCC)

Fig. 15.12 (**1**) Direct damage. Antibody activates the classical complement pathway, causing damage to the parasite membrane and increasing susceptibility to other mediators. (**2**) Neutralization. Parasites such as *Plasmodium* spp. spread to new cells by specific receptor attachment; blocking the merozoite binding site with antibody prevents attachment to the receptors on the erythrocyte surface and prevents further multiplication. (**3**) Enhancement of phagocytosis. Complement C3b deposited on the parasite membrane opsonizes it for phagocytosis by cells with C3b receptors (e.g. macrophages). Macrophages also have Fc receptors. (**4**) Eosinophils, neutrophils, platelets, and macrophages may be cytotoxic for some parasites when they recognize the parasite via specific antibody (ADCC). The reaction is enhanced by complement.

Myeloidní buňky

- APC - monocyty
- makrofágy
- dendritické buňky

- granulocyty
  - neutrofily
  - eozinofily
  - bazofily

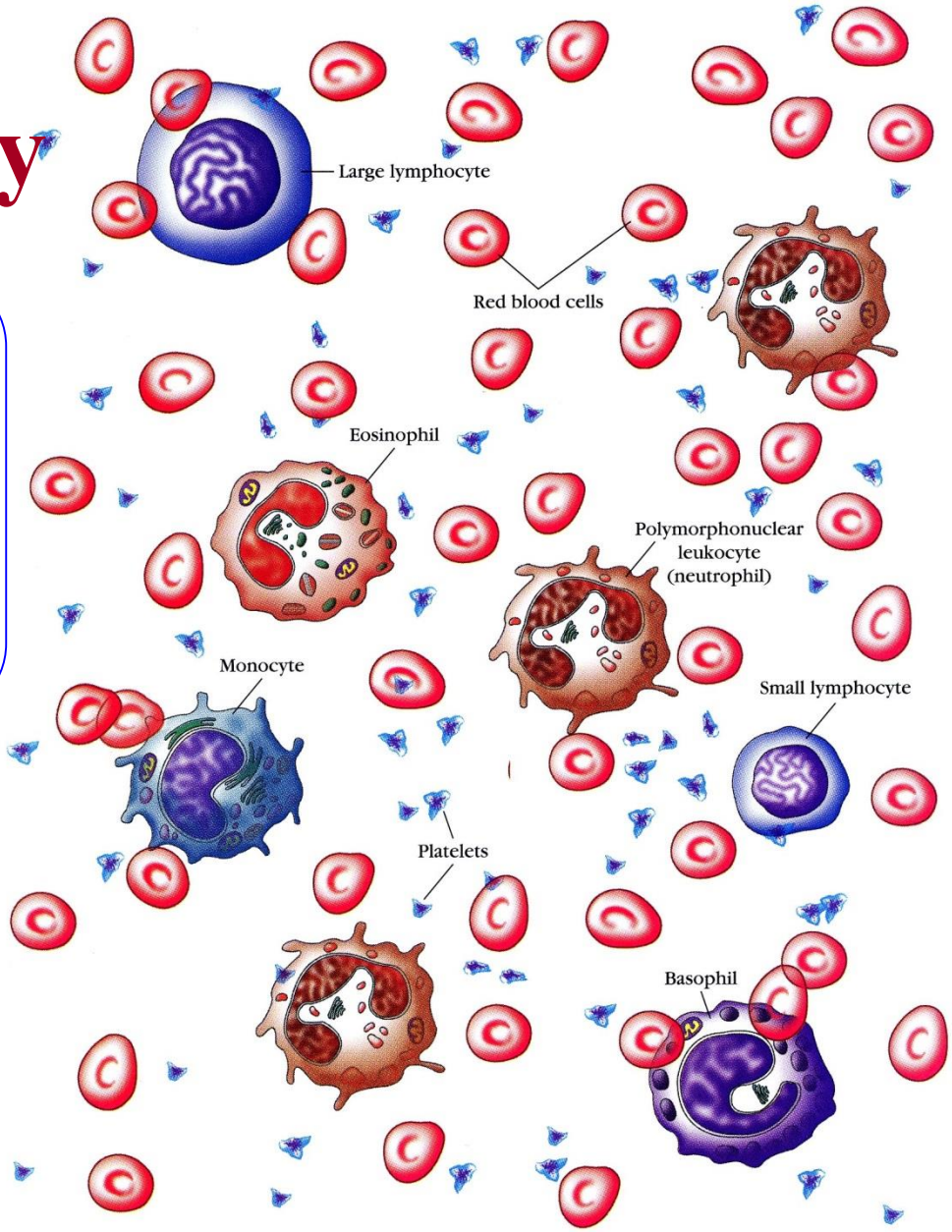


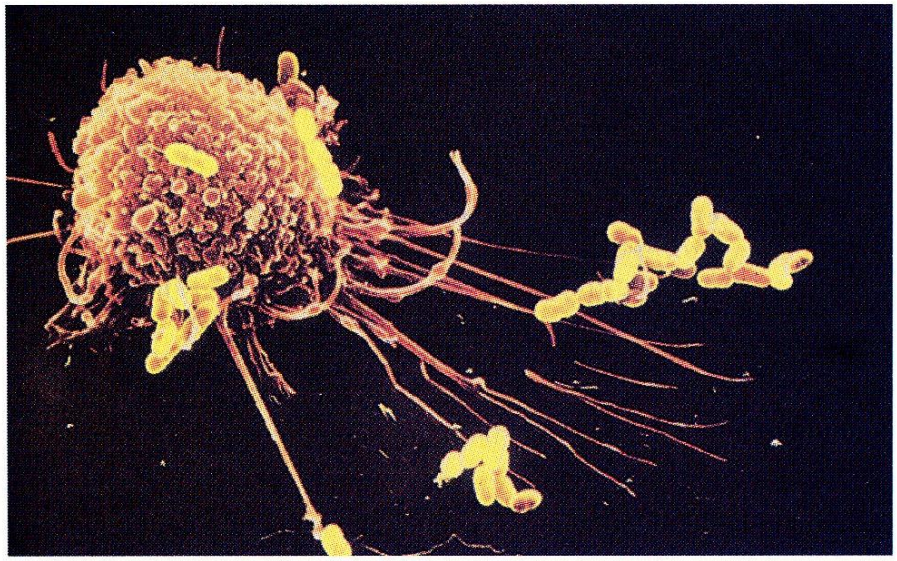
FIGURE 3-1

Morphology and staining characteristics of various types of blood cells. Red blood cells and platelets, which both lack nuclei, are the most numerous. Among the leukocytes responsible for immune responses, the neutrophil is the predominant cell type.

Makrofágy (MFs)

- monocyty
- indukce a regulace imunitní odpovědi
- prezentace antigenu, produkce cytokinů
- množství receptorů (Fc, C3b) - ADCC
- aktivace MF cytokiny a antigeny patogenů (LPS)
- nespecifická x specifická imunita

(a)



(b)

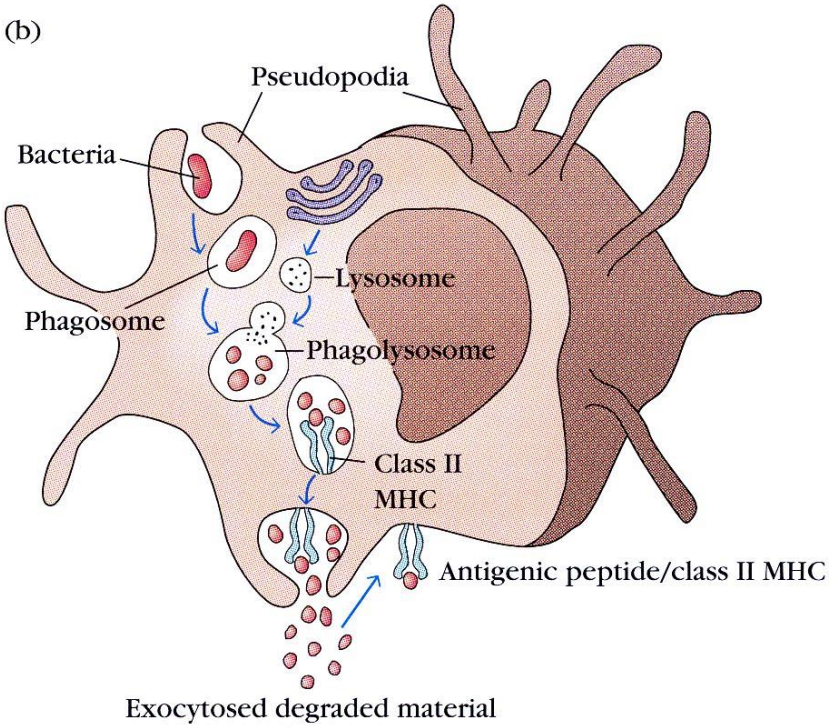


FIGURE 3-12

Macrophages can ingest and degrade particulate antigens, including bacteria. (a) Scanning electron micrograph of a macrophage. Note the long pseudopodia extending toward and making contact with bacterial cells, an early step in phagocytosis. (b) Phagocytosis and processing of exogenous antigen by macrophages. Most of the products resulting from digestion of ingested material are exocytosed, but some peptide products interact with class II MHC molecules, forming complexes that move to the cell surface where they are presented to T_H cells. See text for details. [Photograph by Lennart Nilsson; courtesy of Boehringer Ingelheim International GmbH.]

Table 2.4 *Factors released from macrophages that interact with components of the immune and inflammatory systems*

Coagulation factors
Complement components
Cytokines (e.g. IL-1, IFN-γ, TNF-α)
Enzymes (acid and neutral hydrolases, lysozyme)
Enzyme inhibitors
Fibronectin
Inflammatory mediators (leukotrienes, prostaglandins, PAF)
Reactive metabolites (nitric oxide, oxygen radicals)

Dendritické buňky (DCs)

APCs – prezentace antigenu

- Langerhansovy buňky
- Interdigitující DCs
- Folikulární DCs

- pattern recognition receptors (PRR)

- pathogen associated molecular patterns (PAMPs)

- **VÝVOJ IMUNITNÍ ODPOVĚDI**

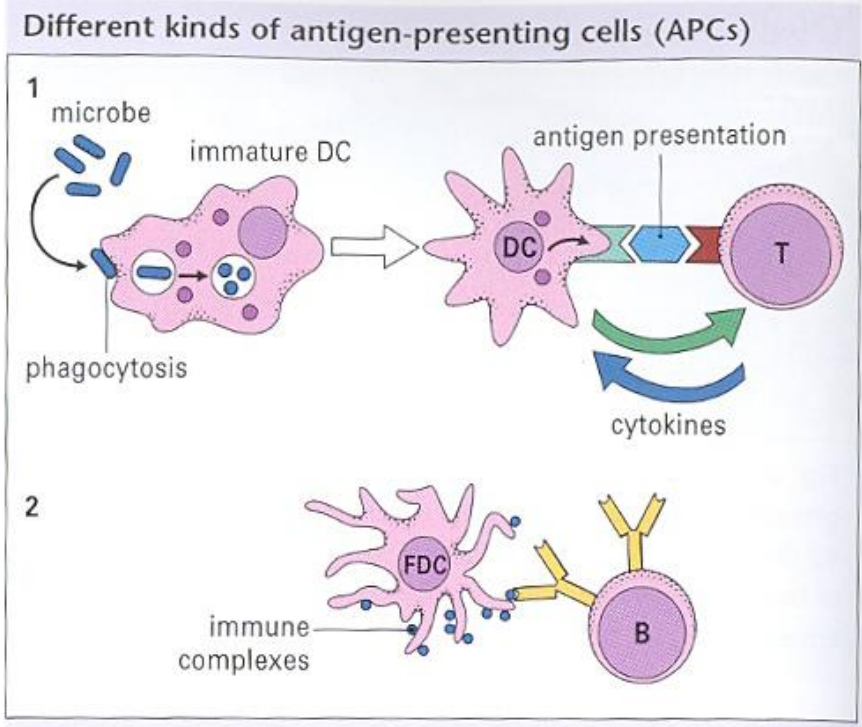


Fig. 2.14 There are two main types of specialized APCs – dendritic cells (DCs) and follicular dendritic cells (FDCs). (1) Immature DCs are derived from bone marrow and interact mainly with T cells. They are highly phagocytic, take up microbes, process the foreign microbial antigens, and become mature APCs carrying the processed antigen on their surface with specialized MHC molecules. Specific T cells recognize the displayed antigen and, in the presence of cytokines produced by the mature DC, proliferate and also produce cytokines. (2) FDCs are not bone marrow derived and interact with B cells. In the B cell follicles of lymphoid organs and tissues they bind small immune complexes (IC, called iccosomes). Antigen contained within the IC is presented to specific B cells in the lymphoid follicles. This protects the B cell from cell death. The B cell then proliferates and with T cell help can leave the follicle and become a plasma cell or memory cell (see Fig. 2.48)

Ultrastructure of an interdigitating dendritic cell (IDC) in the T cell area of a rat lymph node

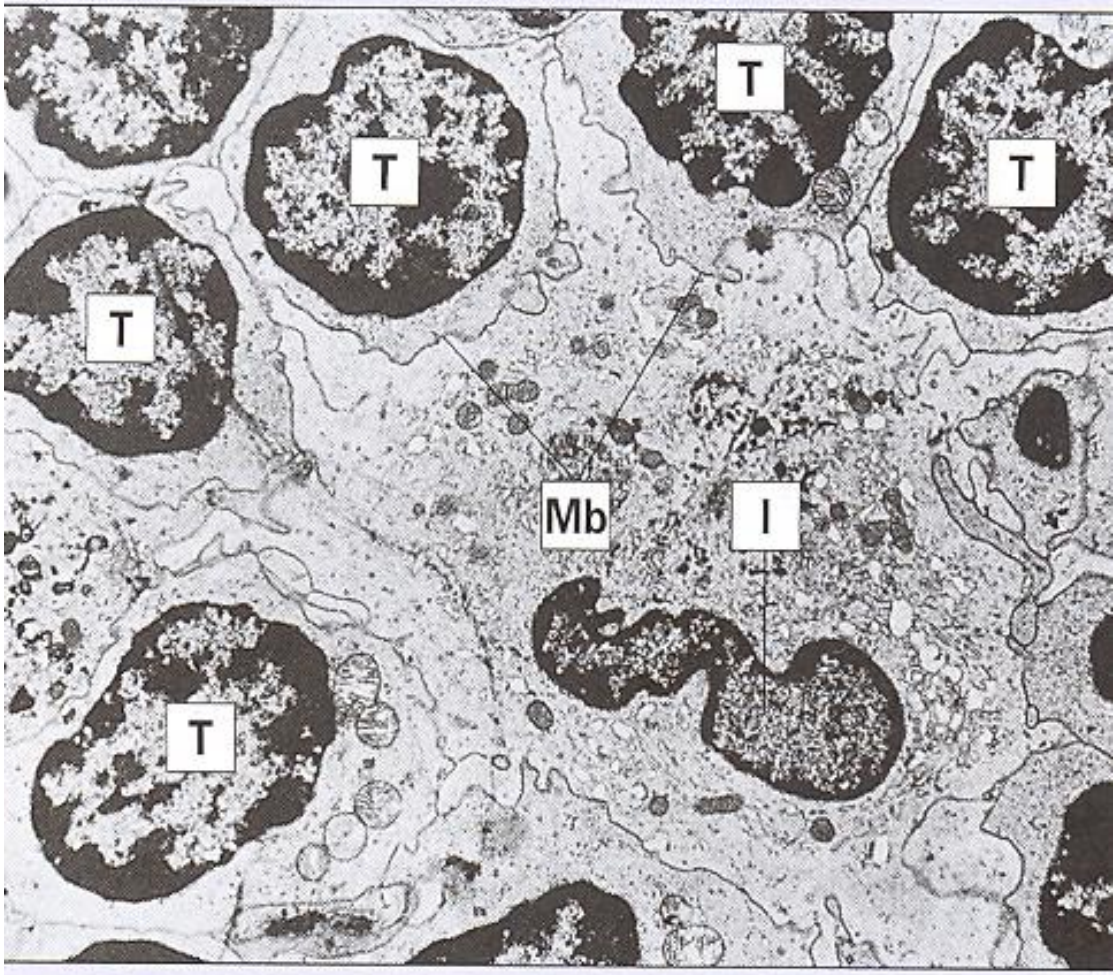


Fig. 2.16 Intimate contacts are made with the membranes of the surrounding T cells. The cytoplasm contains a well-developed endosomal system and does not show the Birbeck granules characteristic of skin Langerhans' cells. × 2000. (I, IDC nucleus; Mb, IDC membrane; T, T cell nucleus) (Courtesy of Dr BH Balfour)

Follicular dendritic cell

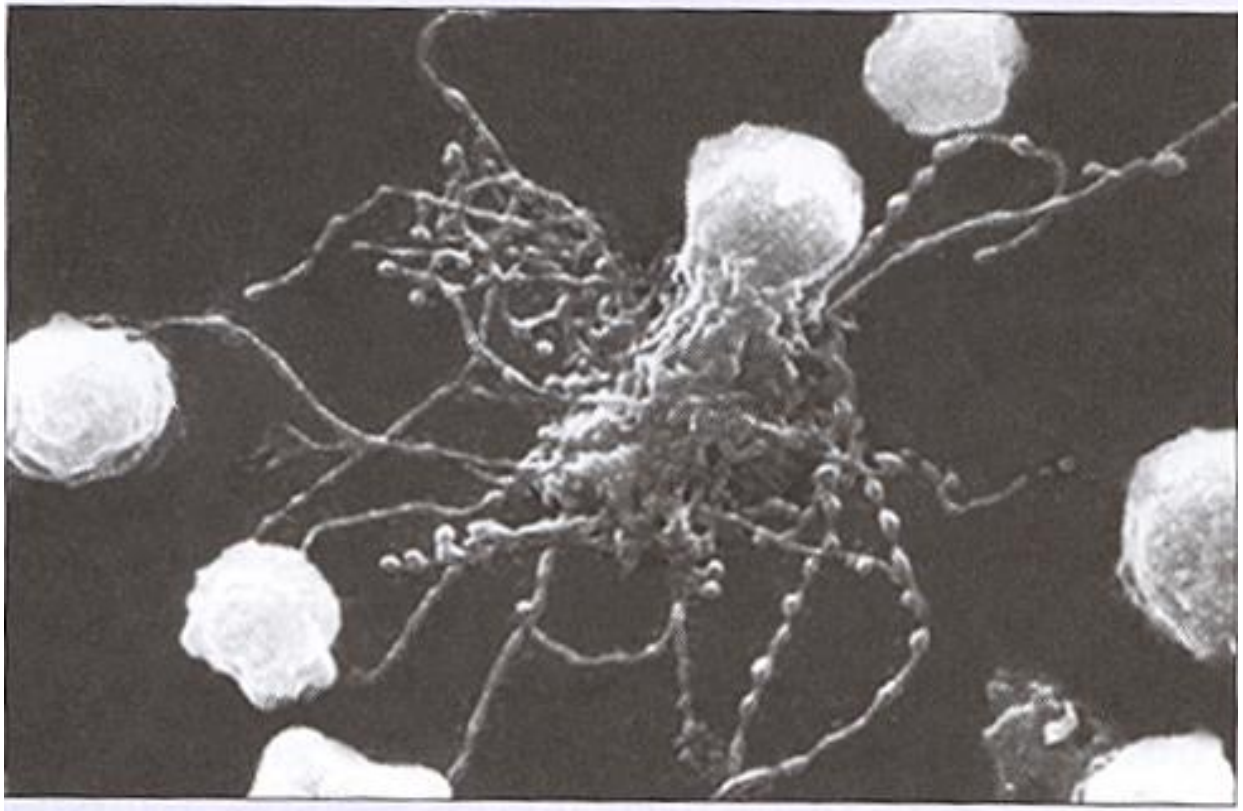


Fig. 2.18 An isolated follicular dendritic cell (FDC) from the lymph node of an immunized mouse 24 hours after injection of antigen. The FDC is of intermediate maturity with smooth filiform dendrites typical of young FDCs, and beaded dendrites, which participate in the formation of iccosomes (immune complexes) in mature FDCs. The adjacent small white cells are lymphocytes. (Electron micrograph kindly provided by Dr Andras Szakal; reproduced by permission of the Journal of Immunology)

Neutrofily (mikrofágy)

- fagocytóza a destrukce mikroorganismů
- lysozomální enzymy, kyslíkové radikály
- Fc a C3b receptor (ADCC)
- atrahovány C3a
- akumulace neutrofilů indukovaná imunními koplexy- hypersenzitivita třetího typu

Eozinofily

- hydrolytické enzymy (peroxidáza)
- Fc a C3b receptor (ADCC)
- adheze k povrchu parazita, vylití obsahu granul
- aktivace regulována T lymfocyty (IL-5) a bazofily (ECF-A)
- produkce cytokinů

Bazofily a žírné buňky

- granula obsahují histamin, serotonin, heparin a chemotaktické faktory
- vysoce afinní receptor pro IgE
- přemostění na membránu vázaných Ig molekul antigenem vede k exocytóze granul
- velmi důležitý antiparazitární mechanismus
x časná hypersenzitivita I typu

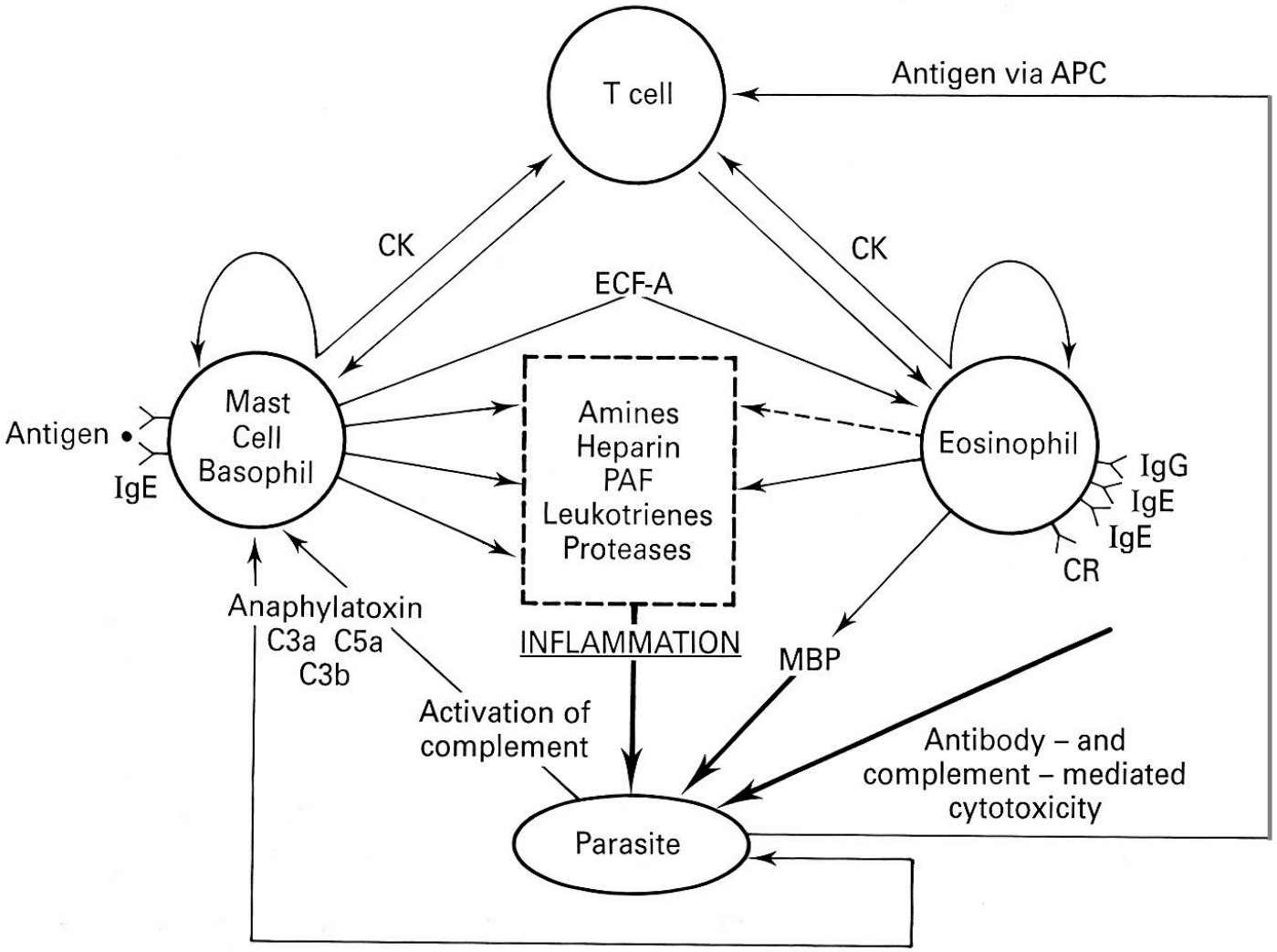


Fig. 2.10 Interactions between lymphocytes, amine-containing cells, eosinophils and parasites. →, factors released by cells; –––→, inactivating factors released by eosinophils; ➔, anti-parasite responses; APC, antigen presenting cell; C3 etc., complement components; CK, cytokines; CR, complement receptor; ECF-A, eosinophil chemotactic factor of anaphylaxis; Ig, immunoglobulin; PAF, platelet activating factor.

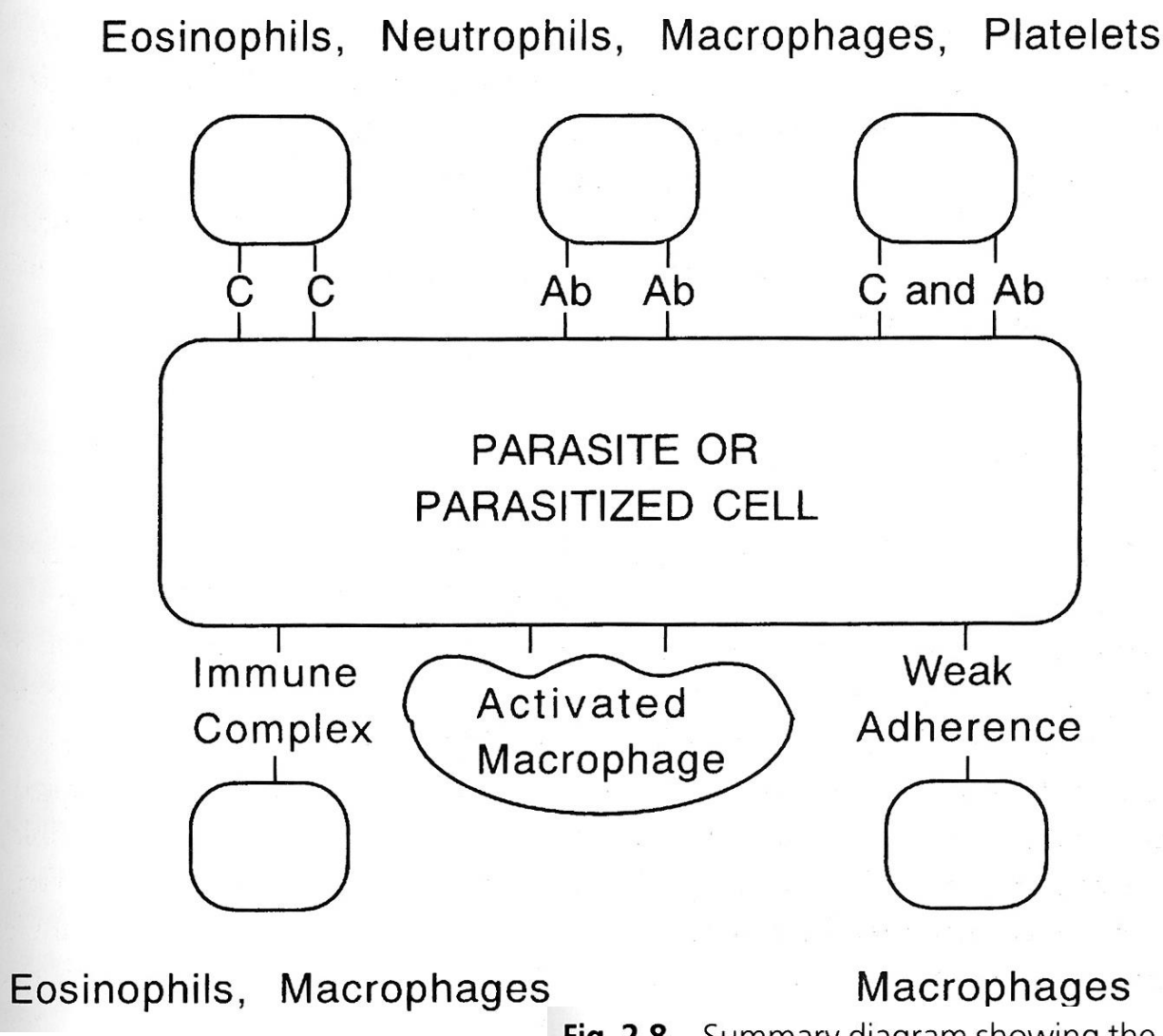


Fig. 2.8 Summary diagram showing the variety of interactions that are possible between the surfaces of parasites or parasitized cells and myeloid cells (eosinophils, macrophages, neutrophils, platelets). Cells may bind to the target by their complement (C) or antibody (Ab – IgM, IgG, IgA, IgE) receptors after complement activation and/or antibody binding; bound immune complexes allow antigen-specific binding. Binding also occurs by intermolecular interactions (e.g. sugars–lectins) the strength of which is increased when cells are activated. Interactions may result in phagocytosis, if the target is small, or ADCC if it is large.

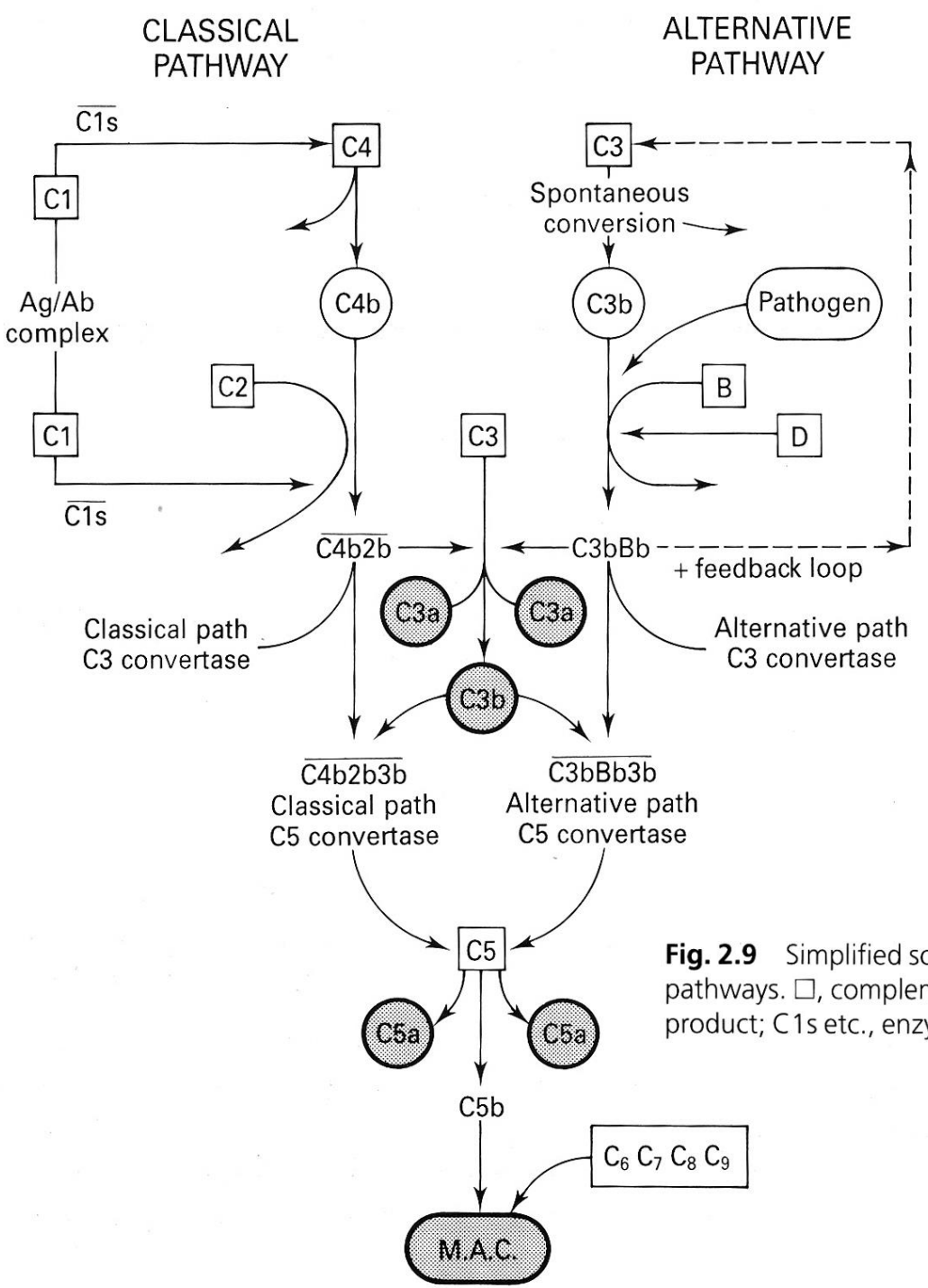


Fig. 2.9 Simplified scheme of complement activation by the classical and alternative pathways. □, complement component; ○, cleavage product; ●, biologically active product; C1s etc., enzymatically active form; M.A.C., membrane attack complex.

Komplement

- proteázový systém
- lýza patogenů
- opsonizace
- chemotaxe a adherence efektorových buněk
- C3a a C5a – anafilatoxiny vážící se na bazofily

Hypersenzitivita

časný typ přecitlivělosti

přecitlivělost závislá na protilátkách vedoucí k lýze buněk

přecitlivělost z imunních komplexů

DTH (aktivace Th1, migrace makrofágů, bazofilů – granulom)

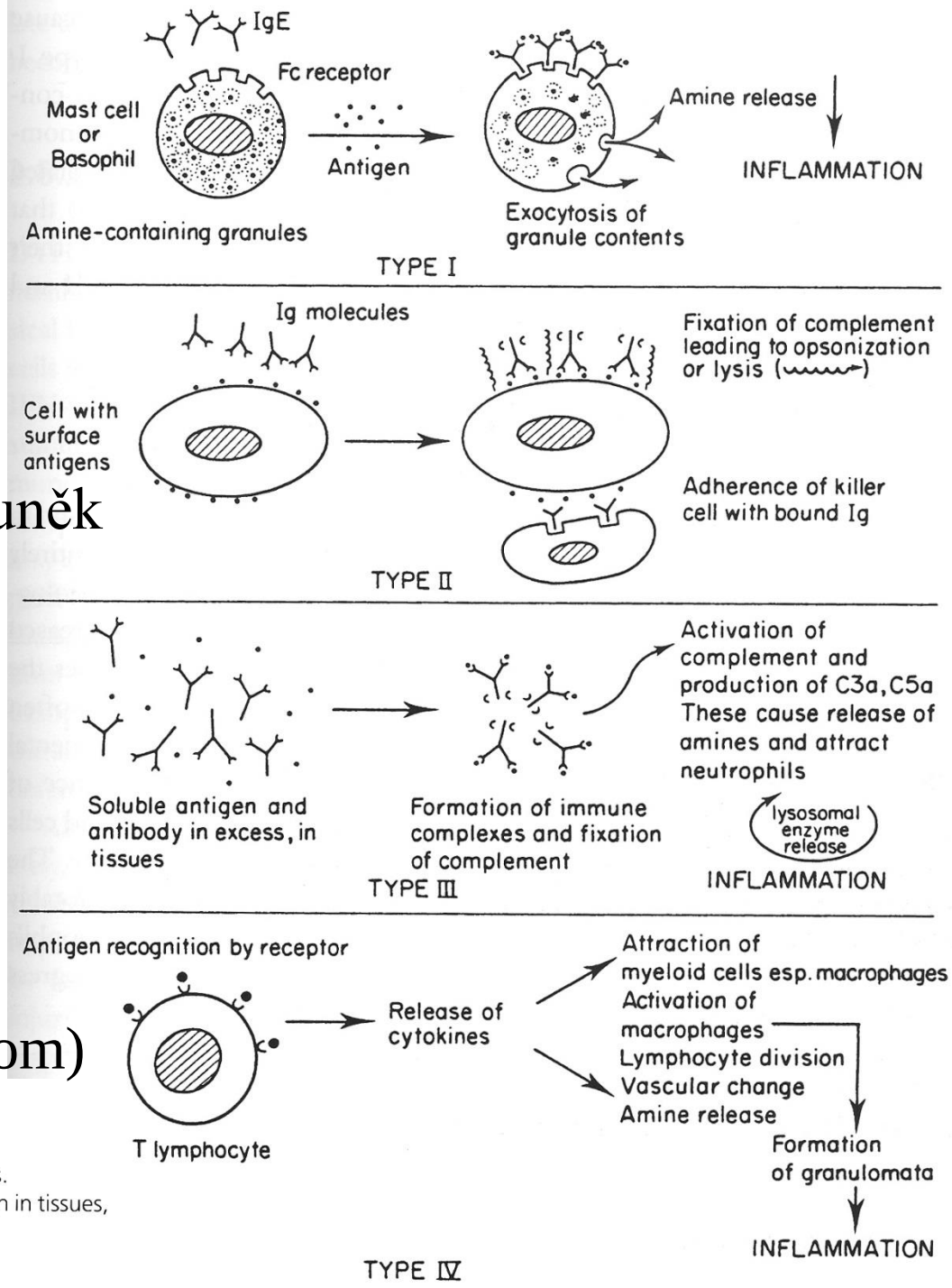


Fig. 2.11 Summary of hypersensitivity reactions.
Type I: Immediate-type hypersensitivity, initiated by IgE antibody.
Type II: Antibody-dependent cytotoxic hypersensitivity, resulting in cell lysis.
Type III: Complex-mediated hypersensitivity, resulting in the Arthus reaction in tissues, or in serum sickness.
Type IV: Delayed-type hypersensitivity: resulting in granuloma formation.

GELL AND COOMBS CLASSIFICATION OF HYPERSENSITIVE REACTIONS

TYPE	DESCRIPTIVE NAME	INITIATION TIME	MECHANISM	TYPICAL MANIFESTATIONS
			IMMEDIATE REACTIONS	
Type 1	IgE-mediated hypersensitivity	2–30 min	Ag induces cross-linkage of IgE bound to mast cells and basophils with release of vasoactive mediators	Systemic anaphylaxis Localized anaphylaxis: Hay fever Asthma Hives Food allergies Eczema
Type II	Antibody-mediated cytotoxic hypersensitivity	5–8 h	Ab directed against cell-surface antigens mediates cell destruction via complement activation or ADCC	Blood-transfusion reactions Erythroblastosis fetalis Autoimmune hemolytic anemia
Type III	Immune complex–mediated hypersensitivity	2–8 h	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response	Localized Arthus reaction Generalized reactions: Serum sickness Glomerulonephritis Rheumatoid arthritis Systemic lupus erythematosus
			DELAYED REACTIONS	
Type IV	Cell-mediated hypersensitivity	24–72 h	Sensitized T_{DTH} cells release cytokines that activate macrophages or T_C cells, which mediate direct cellular damage	Contact dermatitis Tubercular lesions Graft rejection