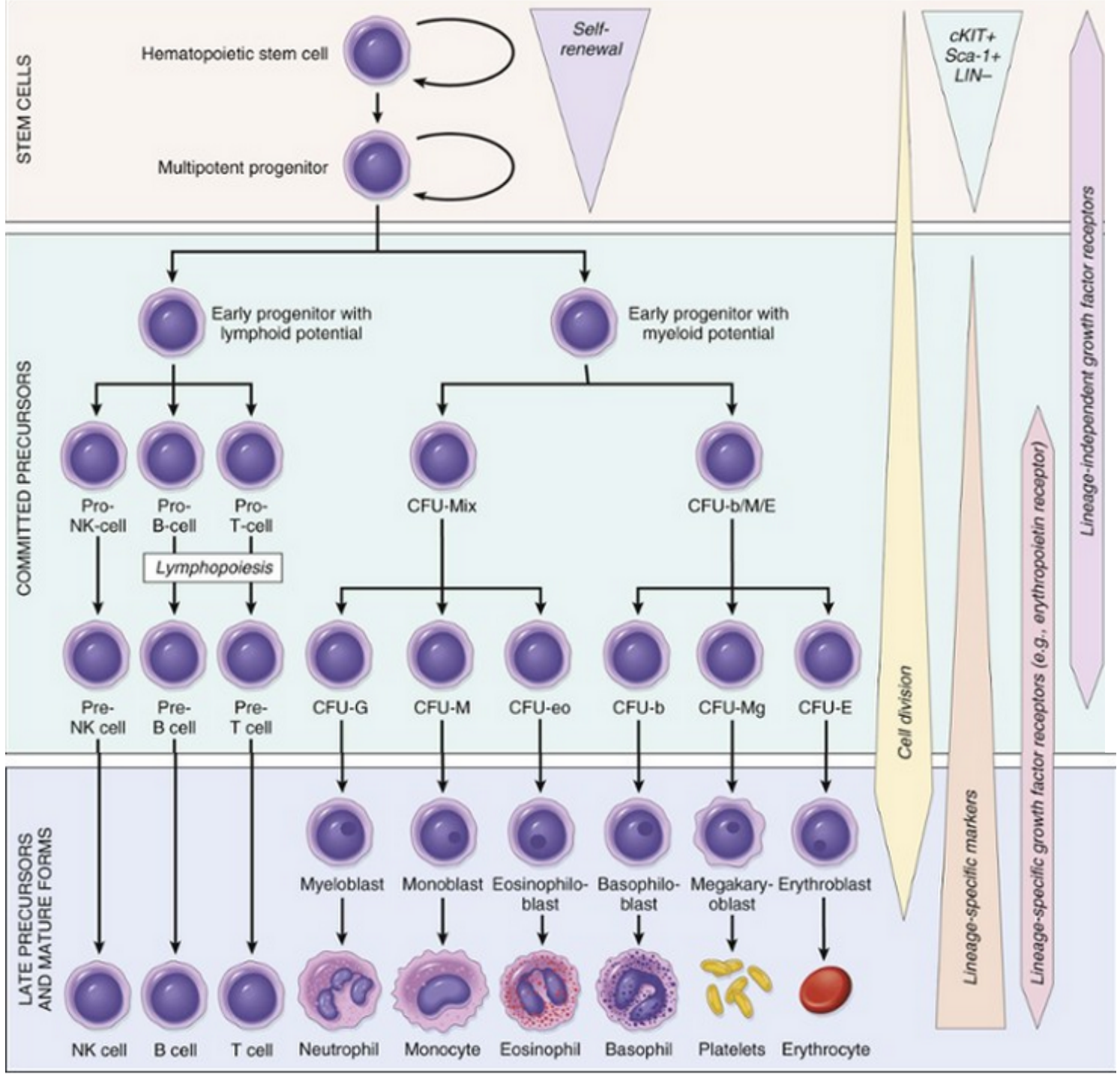
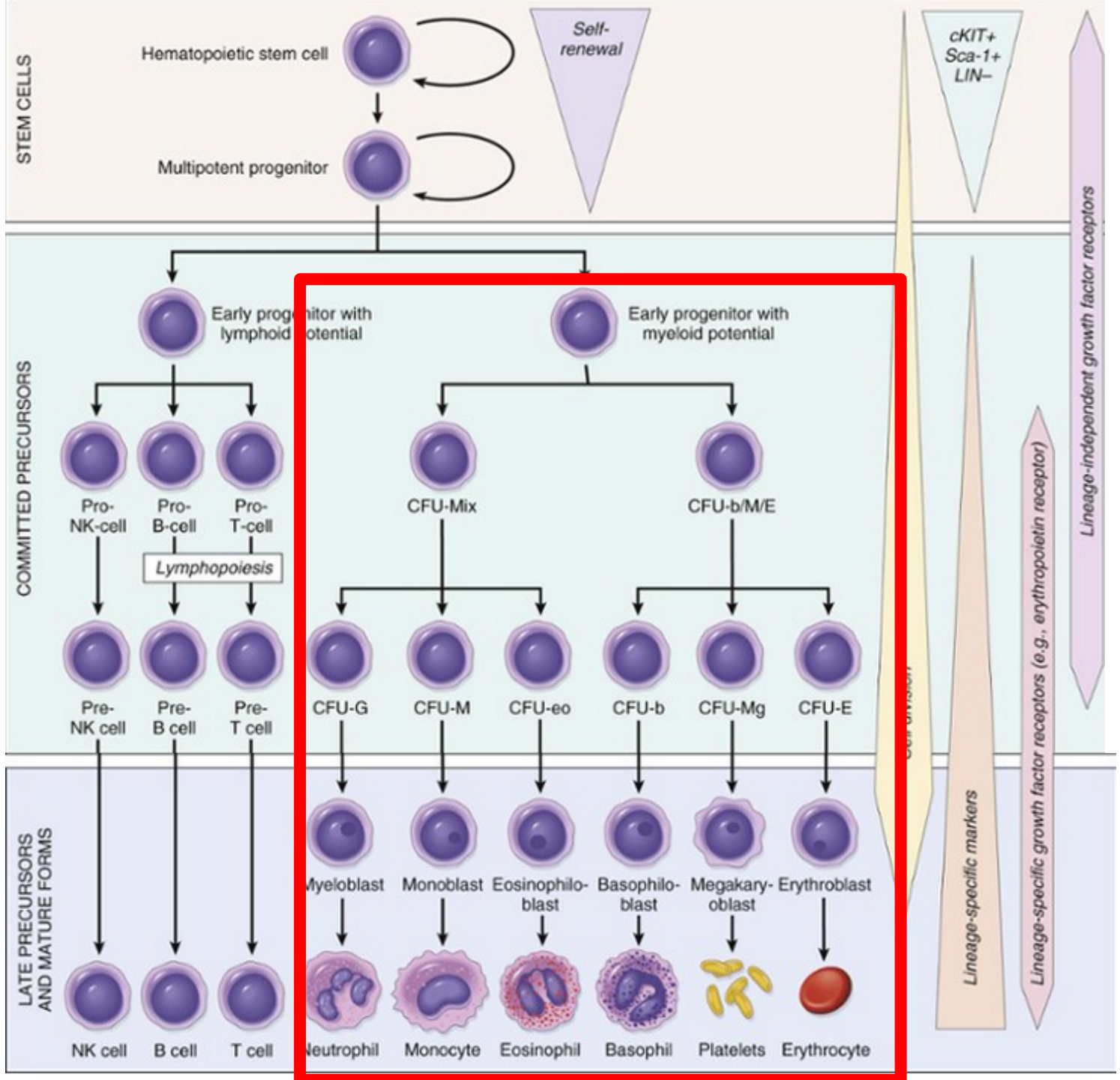
LENFOİD SİSTEME GİRİŞ VE LENFOİD ORGAN PATOLOJİLERİ

Prof. Dr.Işınsu Kuzu
Patoloji Anabilim Dalı
Dönem III Modül IV
13.03.2017



HEMATOPOEZ

Robbins Cotran Kumar

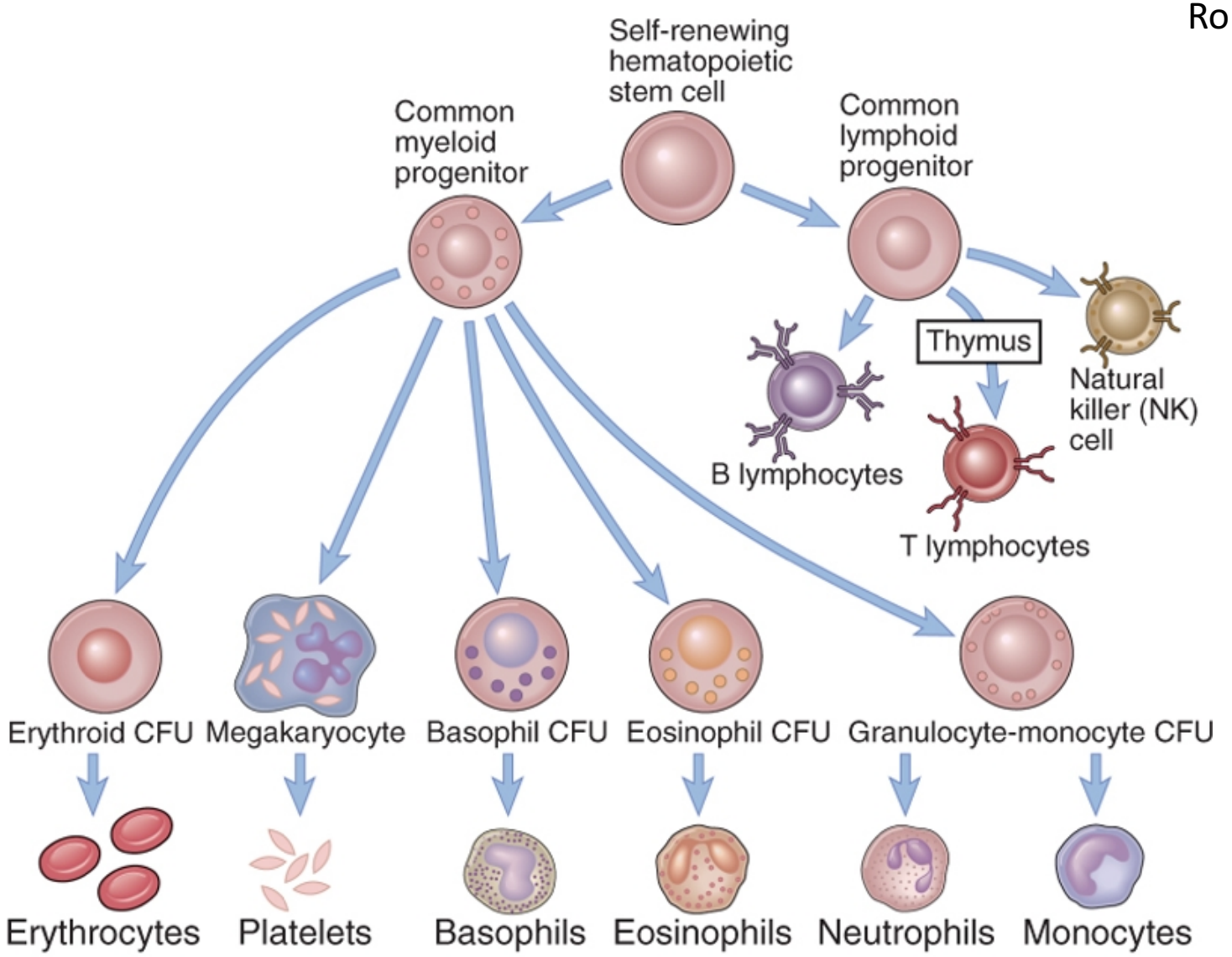


HEMATOPOEZ

Robbins Cotran Kumar

KEMİK İLİĞİ

Robbins Cotran Kumar



ERİTROPOEZ

- Proeritroblast
- Erken eritroblast
- İntermedier eritroblast
- Geç eritroblast
- Retikülosit
- Eritrosit

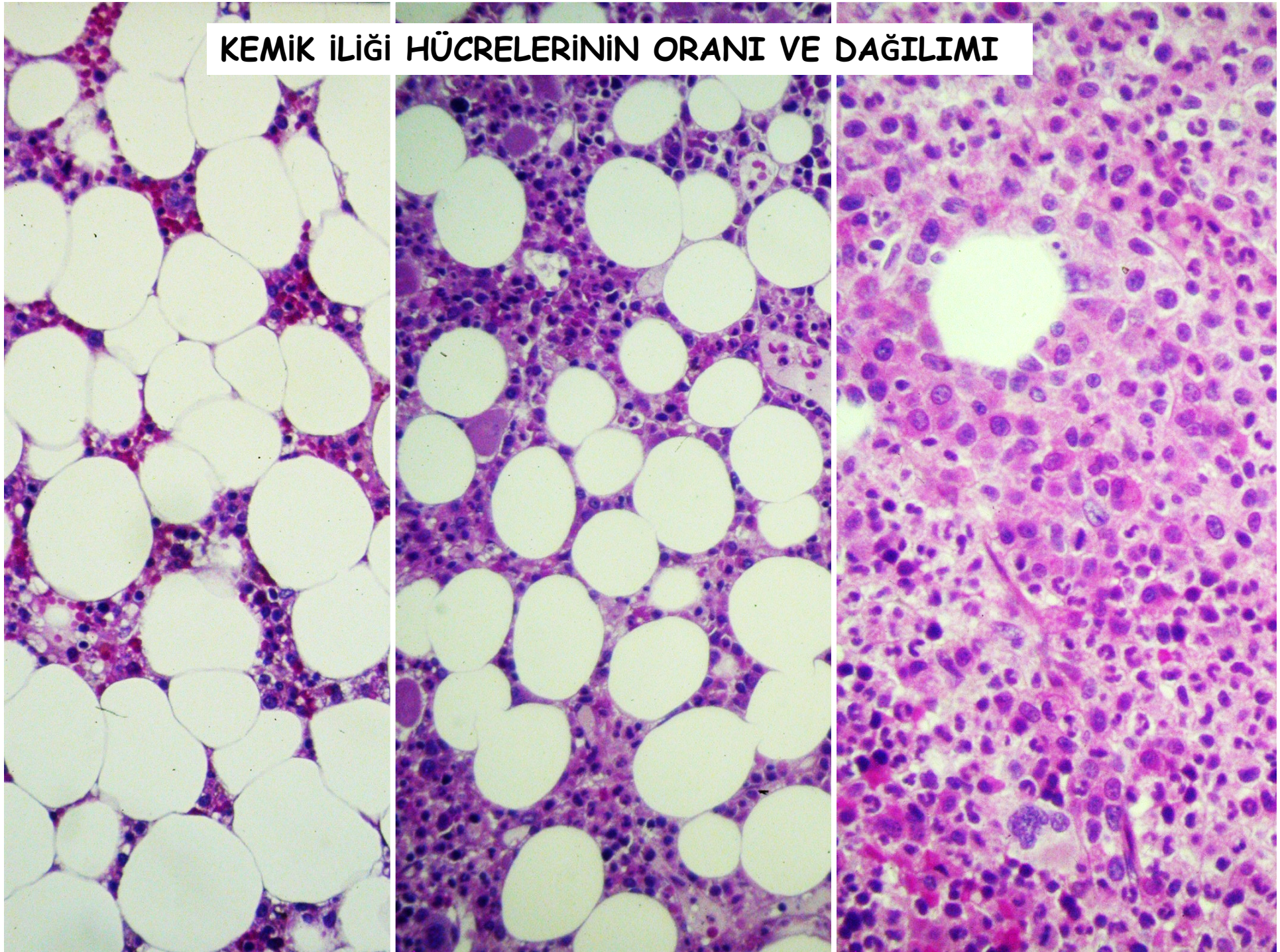
GRANULOPOEZ

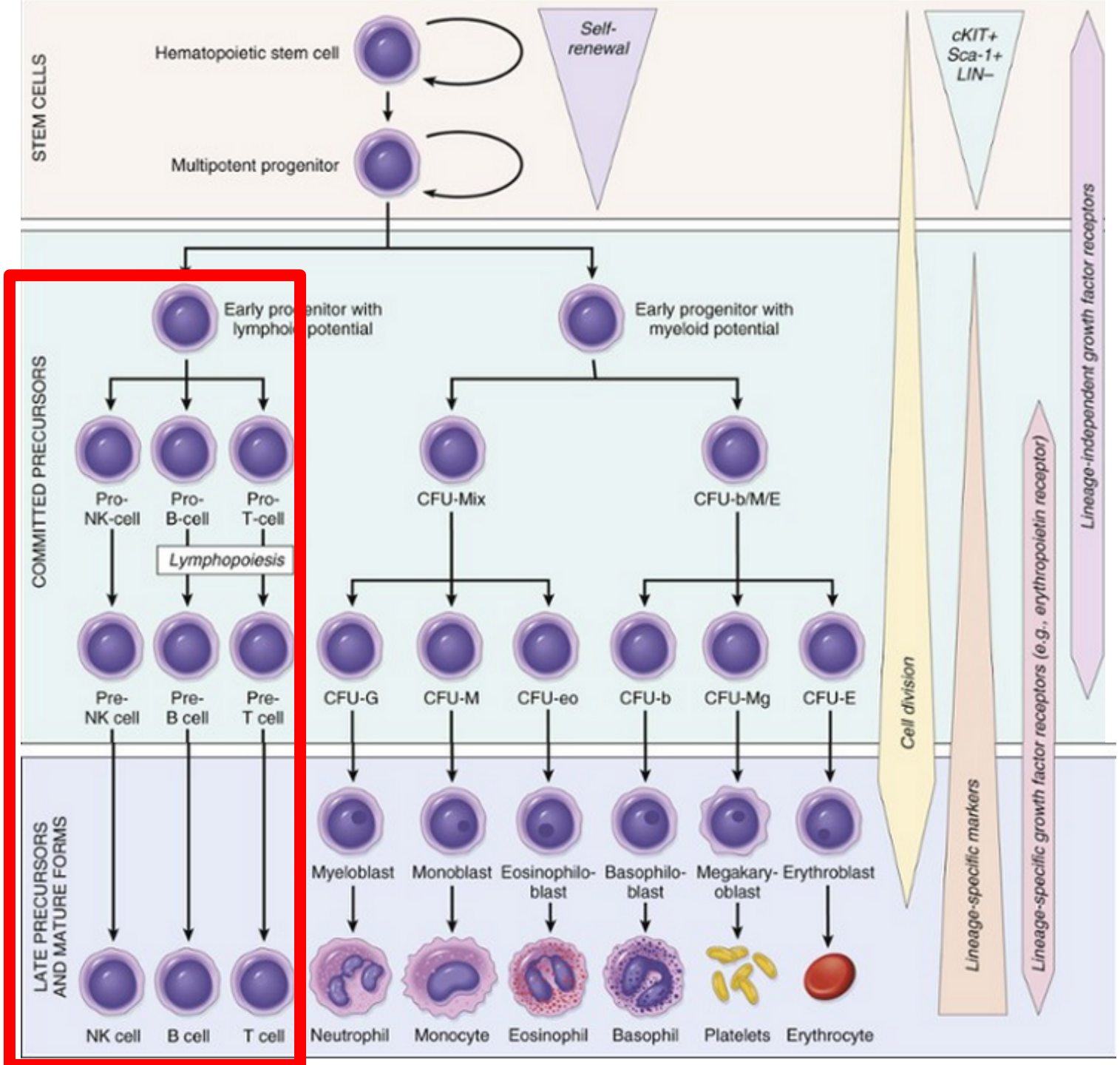
- Myeloblast
- Promyelosit
- Myelosit
- Metamyelosit
- Çomak
- Polimorf nüveli lökosit
  - Bazofil
  - Nötrofil
  - Eosinofil

MEGAKARYOPOEZ VE TROMBOPOEZ

- Megakaryoblast
- Promegakaryosit
- Megakaryosit
- Trombosit

KEMİK İLİĞİ HÜCRELERİNİN ORANI VE DAĞILIMI





HEMATOPOEZ

Robbins Cotran Kumar

KANDAKİ HÜCRELERİN ORANLARI

TABLE 13-1 Adult Reference Ranges for Blood Cells*

Cell Type	
White cells ($\times 10^3/\mu L$)	4.8-10.8
Granulocytes (%)	40-70
Neutrophils ($\times 10^3/\mu L$)	1.4-6.5
Lymphocytes ($\times 10^3/\mu L$)	1.2-3.4
Monocytes ($\times 10^3/\mu L$)	0.1-0.6
Eosinophils ($\times 10^3/\mu L$)	0-0.5
Basophils ($\times 10^3/\mu L$)	0-0.2
Red cells ($\times 10^3/\mu L$)	4.3-5, men; 3.5-5, women
Platelets ($\times 10^3/\mu L$)	150-450

Robbins and Cotran Pathologic Basis of Disease

TABLE 13-2 Mechanisms and Causes of Leukocytosis

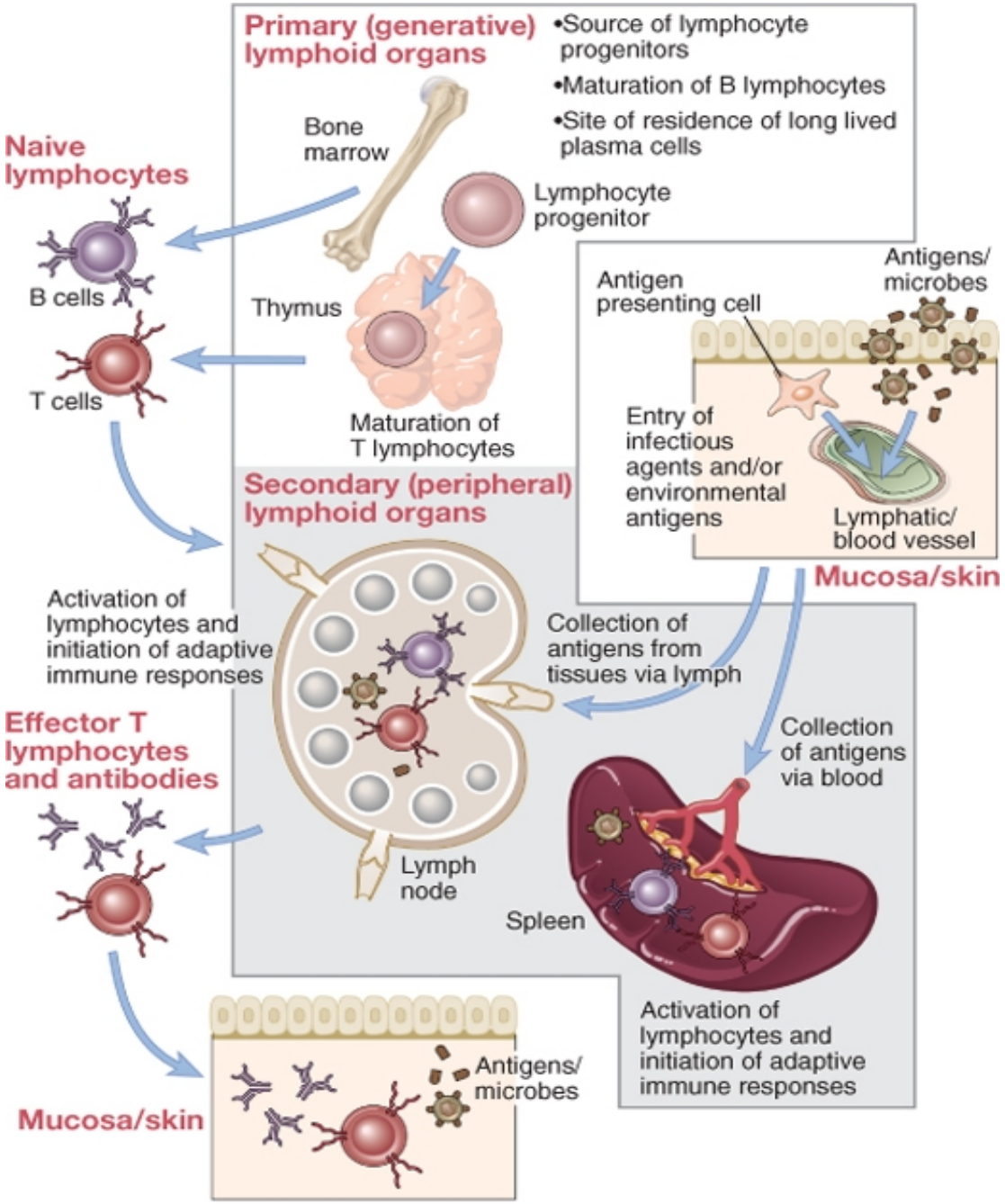
Increased Production in the Marrow
Chronic infection or inflammation (growth factor-dependent) Paraneoplastic (e.g., Hodgkin lymphoma; growth factor-dependent) Myeloproliferative disorders (e.g., chronic myeloid leukemia; growth factor-independent)
Increased Release from Marrow Stores
Endotoxemia Infection Hypoxia
Decreased Margination
Exercise Catecholamines
Decreased Extravasation into Tissues
Glucocorticoids

Robbins and Cotran Pathologic Basis of Disease

LÖKOSİTOZ

Type of Leukocytosis	Causes
Neutrophilic leukocytosis	Acute bacterial infections, especially those caused by pyogenic organisms; sterile inflammation caused by, for example, tissue necrosis (myocardial infarction, burns)
Eosinophilic leukocytosis (eosinophilia)	Allergic disorders such as asthma, hay fever, parasitic infestations; drug reactions; certain malignancies (e.g., Hodgkin and some non-Hodgkin lymphomas); automimmune disorders (e.g., pemphigus, dermatitis herpetiformis) and some vasculitides; atheroembolic disease (transient)
Basophilic leukocytosis (basophilia)	Rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)
Monocytosis	Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; autoimmune disorders (e.g., systemic lupus erythematosus); inflammatory bowel diseases (e.g., ulcerative colitis)
Lymphocytosis	Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

LENFOSİT OLUŞUMU VE BAĞIŞIKLIK YANITI



LENFOSİT AİLESİ

Class	Functions	Antigen receptor and specificity	Selected markers	Percent of total lymphocytes (human)		
				Blood	Lymph node	Spleen
ab T lymphocytes						
$CD4^+$ helper T lymphocytes	B cell differentiation (humoral immunity) Macrophage activation (cell-mediated immunity)	ab heterodimers Diverse specificities for peptide-class II MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	50–60*	50–60	50–60
$CD8^+$ cytotoxic T lymphocytes	Killing of cell infected with microbes, killing of tumor cells	ab heterodimers Diverse specificities for peptide-class I MHC complexes	$CD3^+$, $CD4^-$, $CD8^+$	20–25	15–20	10–15
Regulatory T cells	Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)	ab heterodimers	$CD3^+$, $CD4^+$, $CD25^+$ (Most common, but other phenotypes as well)	Rare	10	10
gd T lymphocytes	Helper and cytotoxic functions (innate immunity)	gd heterodimers Limited specificities for peptide and nonpeptide antigens	$CD3^+$, CD4, and CD8 variable			
B lymphocytes	Antibody production (humoral immunity)	Surface antibody Diverse specificities for all types of molecules	Fc receptors; class II MHC; CD19; CD21	10–15	20–25	40–45
Natural killer cells	Killing of virus-infected or damaged cells (innate immunity)	Various activating and inhibitory receptors Limited specificities for MHC or MHC-like molecules	CD16 (Fc receptor for IgG)	10	Rare	10
NKT cells	Suppress or activate innate and adaptive immune responses	ab heterodimers (Limited specificity for glycolipid-CD1 complexes)	CD16 (Fc receptor for IgG); CD3	10	Rare	10

*In most cases, the ratio of $CD4^+CD8^-$ to $CD8^+CD4^-$ cells is about 2:1.
Abbreviations: IgG, immunoglobulin G; MHC, major histocompatibility complex

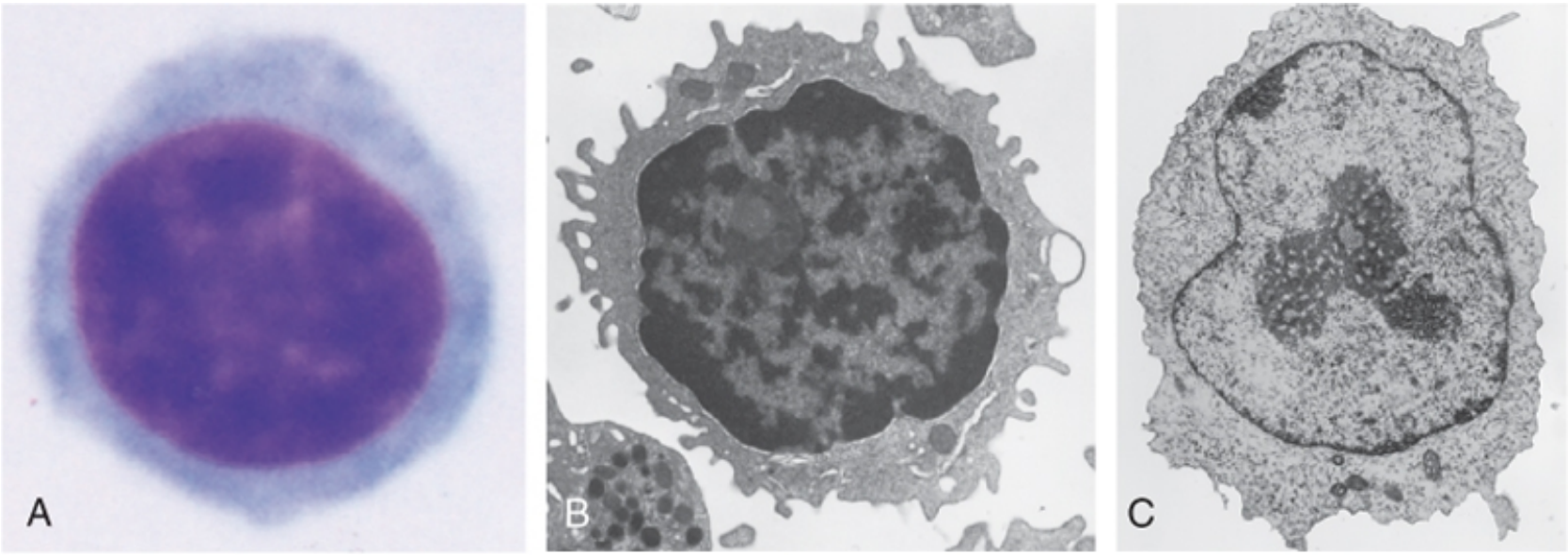
Abbas, Molecular İmmunology

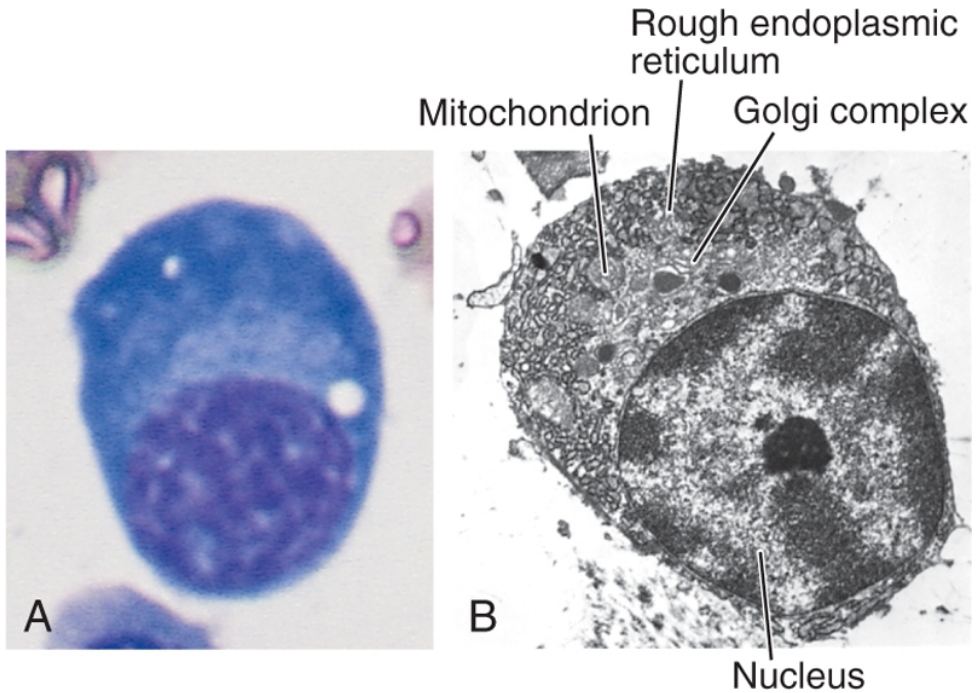
NAİVE EFEKTÖR VE BELLEK LENFOSİT KARAKTERLERİ

	Naive lymphocytes	Activated or effector lymphocytes	Memory lymphocytes
T lymphocytes			
Migration	Preferentially to peripheral lymphoid tissues	Preferentially to inflamed tissues	Preferentially to inflamed tissues, mucosal tissues
Frequency of cells responsive to particular antigen	Very low	High	Low
Effector functions	None	Cytokine secretion; cytotoxic activity	None
Cell cycling	No	Yes	+/–
Surface protein expression			
High-affinity IL-2 receptor	Low	High	Low
Peripheral lymph node homing receptor (L-selectin, CD62L)	High	Low	Low or variable
Adhesion molecules: integrins, CD44	Low	High	High
Chemokine receptor: CCR7	High	Low	Variable
Major CD45 isoform (humans only)	CD45RA	CD45RO	CD45RO; variable
Morphology	Small; scant cytoplasm	Large; more cytoplasm	Small
B lymphocytes			
Membrane immunoglobulin (Ig) isotype	IgM and IgD	Frequently IgG, IgA, IgE	Frequently IgG, IgA, IgE
Affinity of Ig produced	Relatively low	Increases during immune response	Relatively high
Effector function	None	Antibody secretion	None
Morphology	Small; scant cytoplasm	Large; more cytoplasm; some are plasma cells	Small
Chemokine receptor: CXCR5	High	Low	?
CD27	Low	High	High

Abbreviations: IL-2, interleukin-2

Abbas, Molecular İmmunology



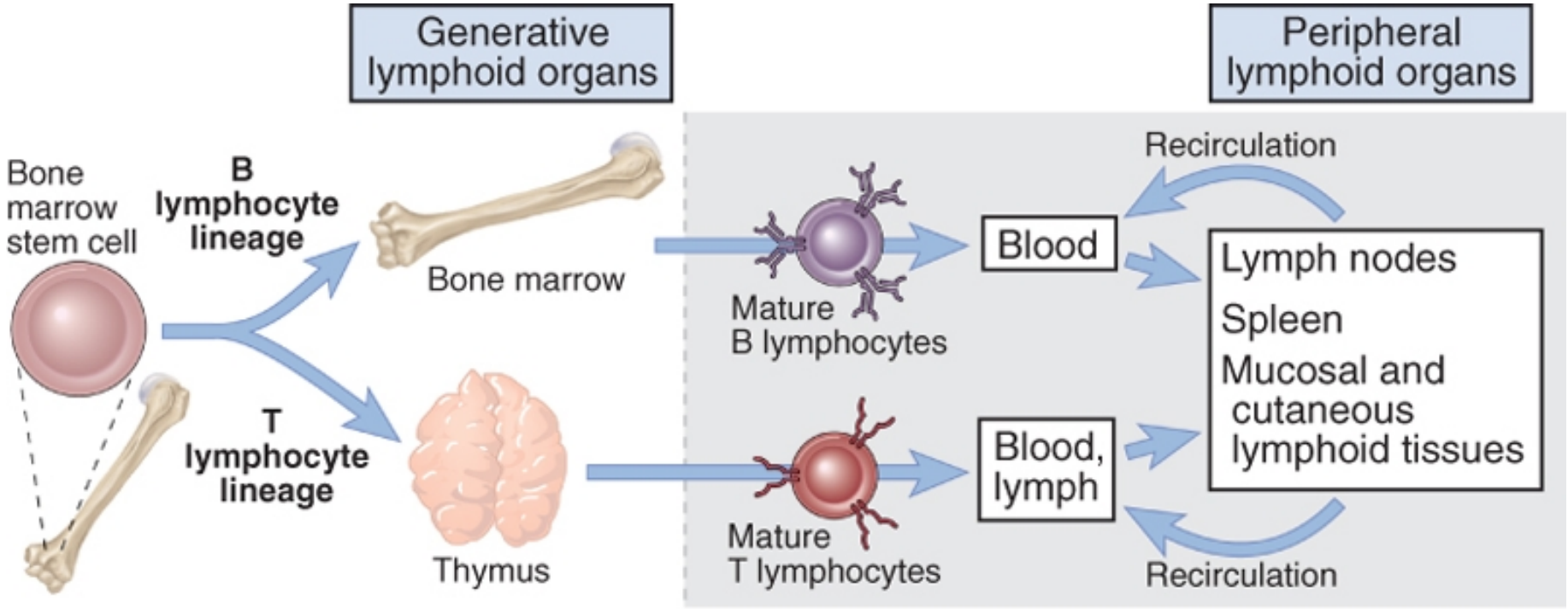


LENFOİD DOKULAR

- LENF NODÜLLERİ VE LENFATİK SİSTEM
- DALAK
- DERİ
- MUKOZAL İMMUN SİSTEM

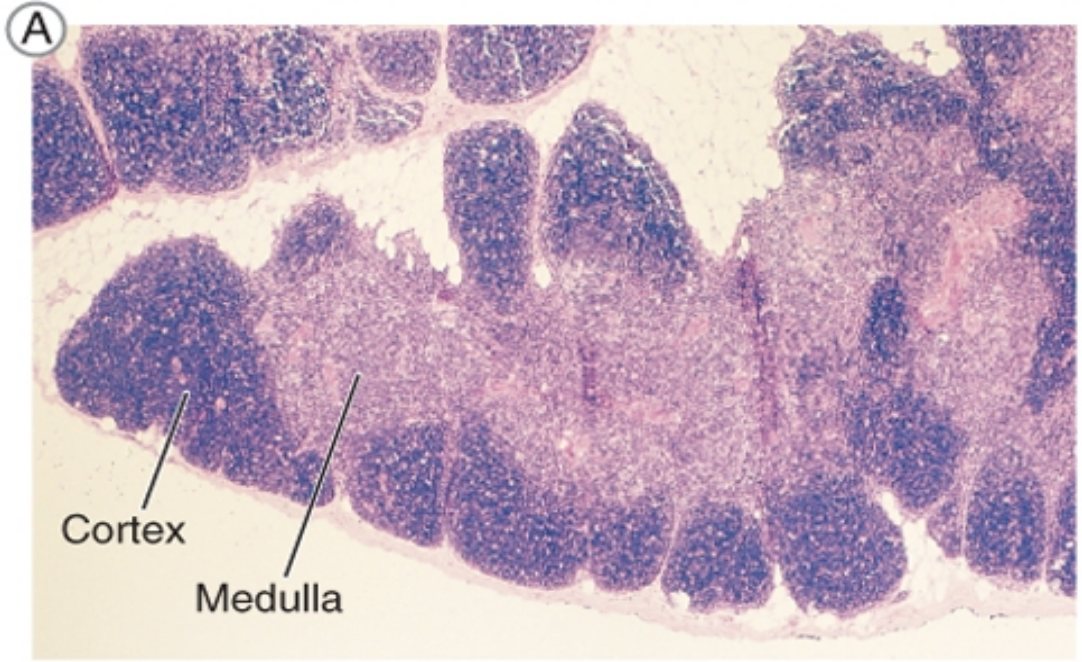
KEMİK İLİĞİ
TİMUS

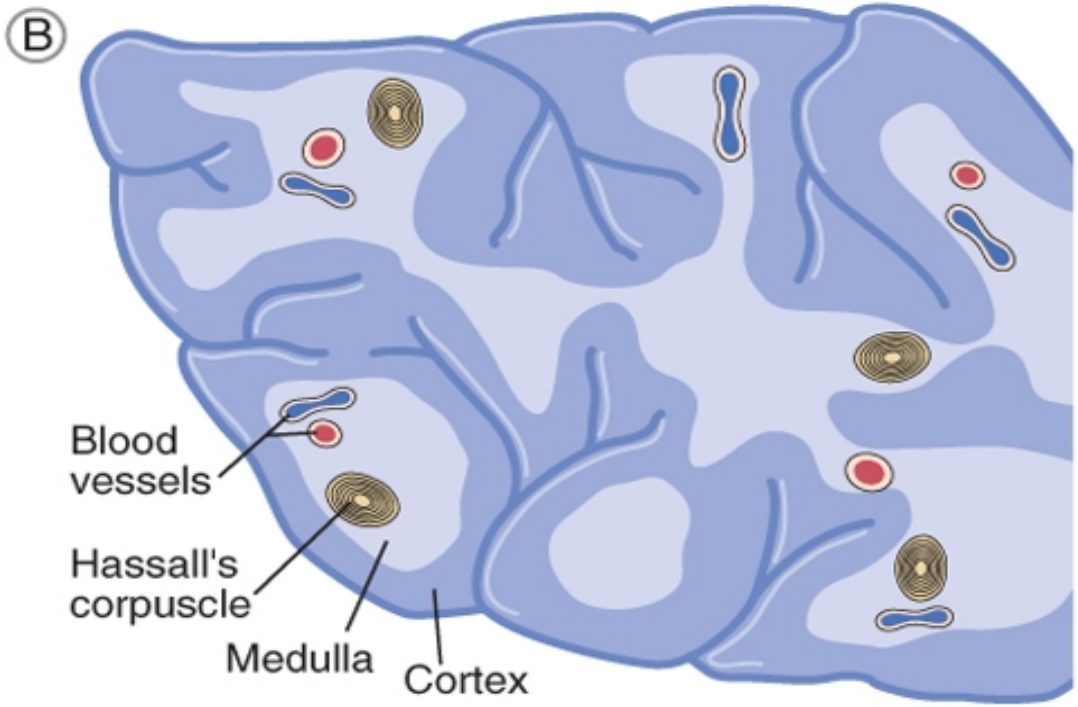
LENF NODÜLLERİ
LENFATİK SİSTEM
DALAK
DERİ
MUKOZAL İMMUN SİSTEM



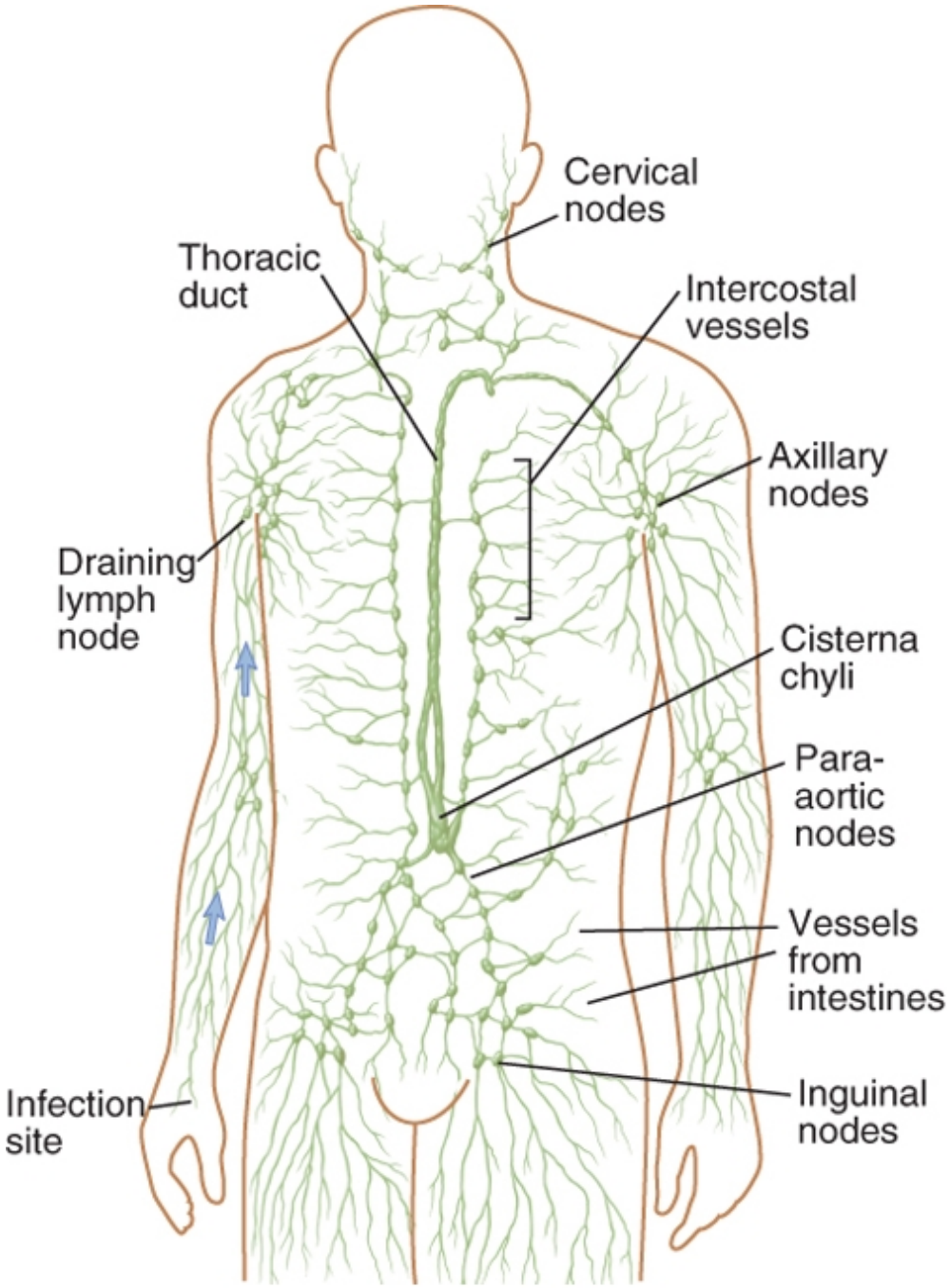
TİMUS

T LENFOSİT OLGUNLAŞMA VE İMMUN TOLERANS GELİŞİMİ





LENF NODÜLLERİ VE LENFATİK SİSTEM



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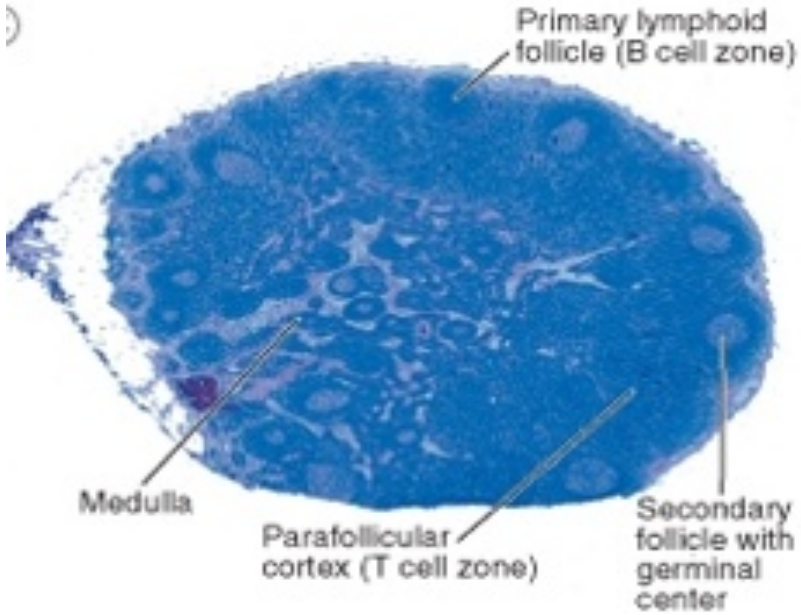
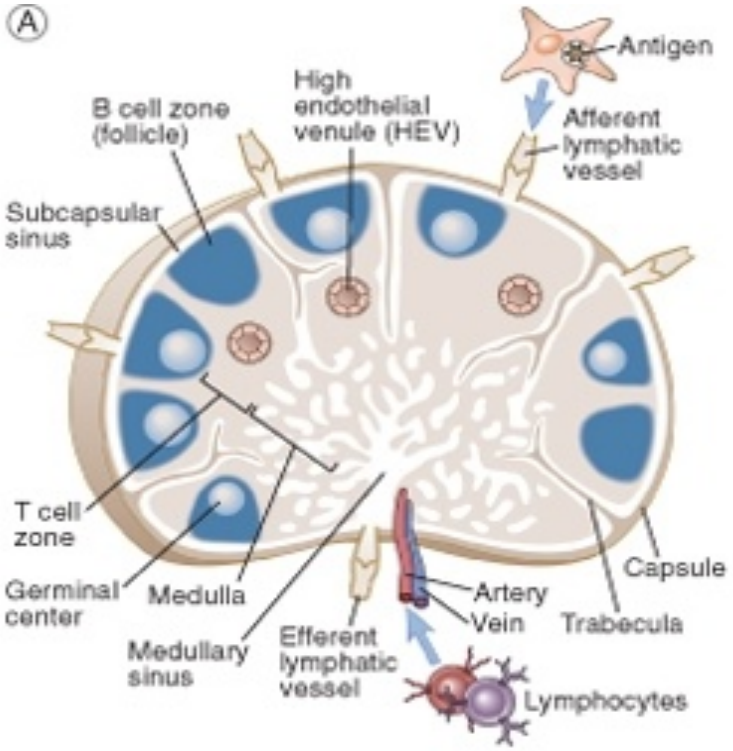
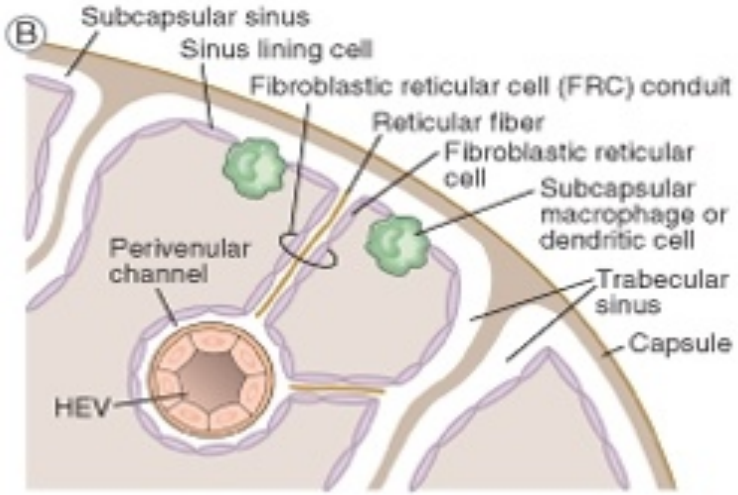
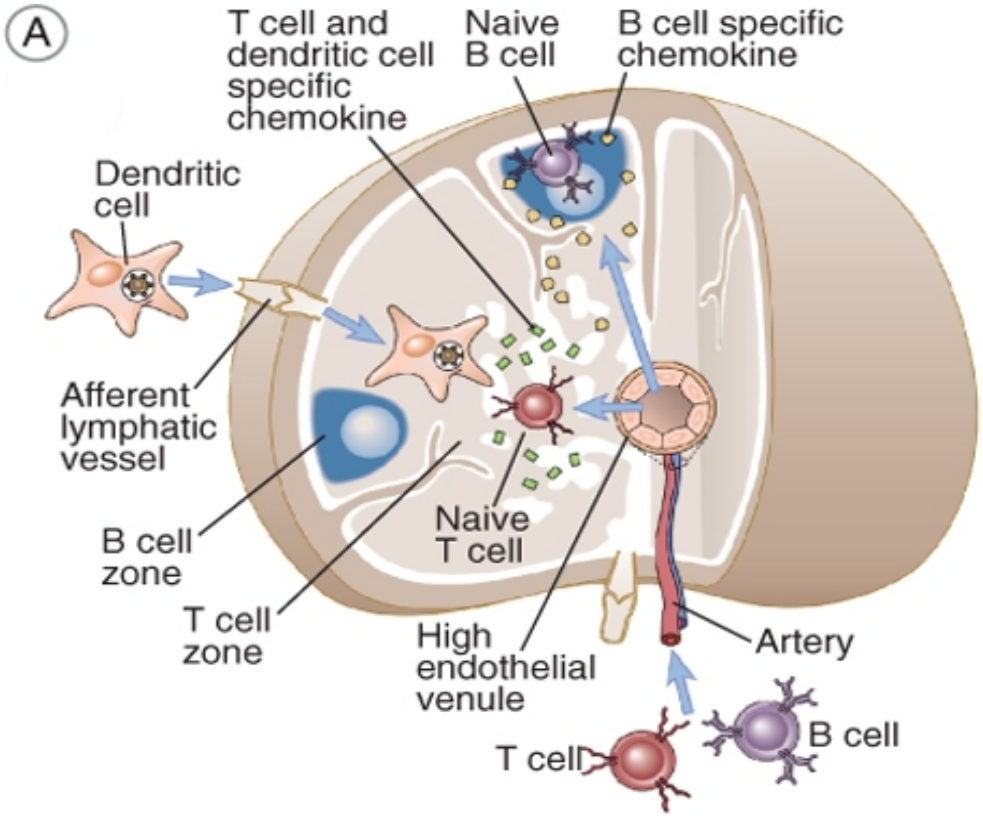


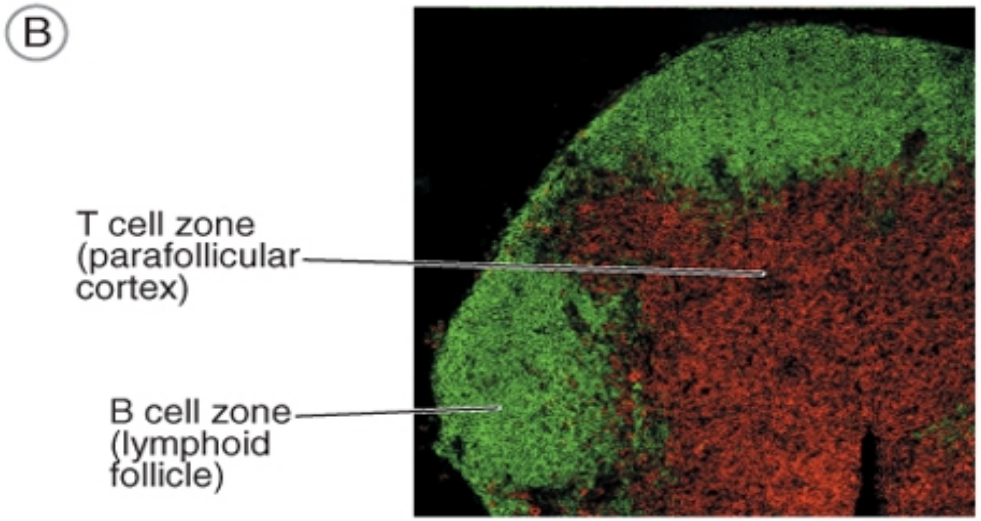




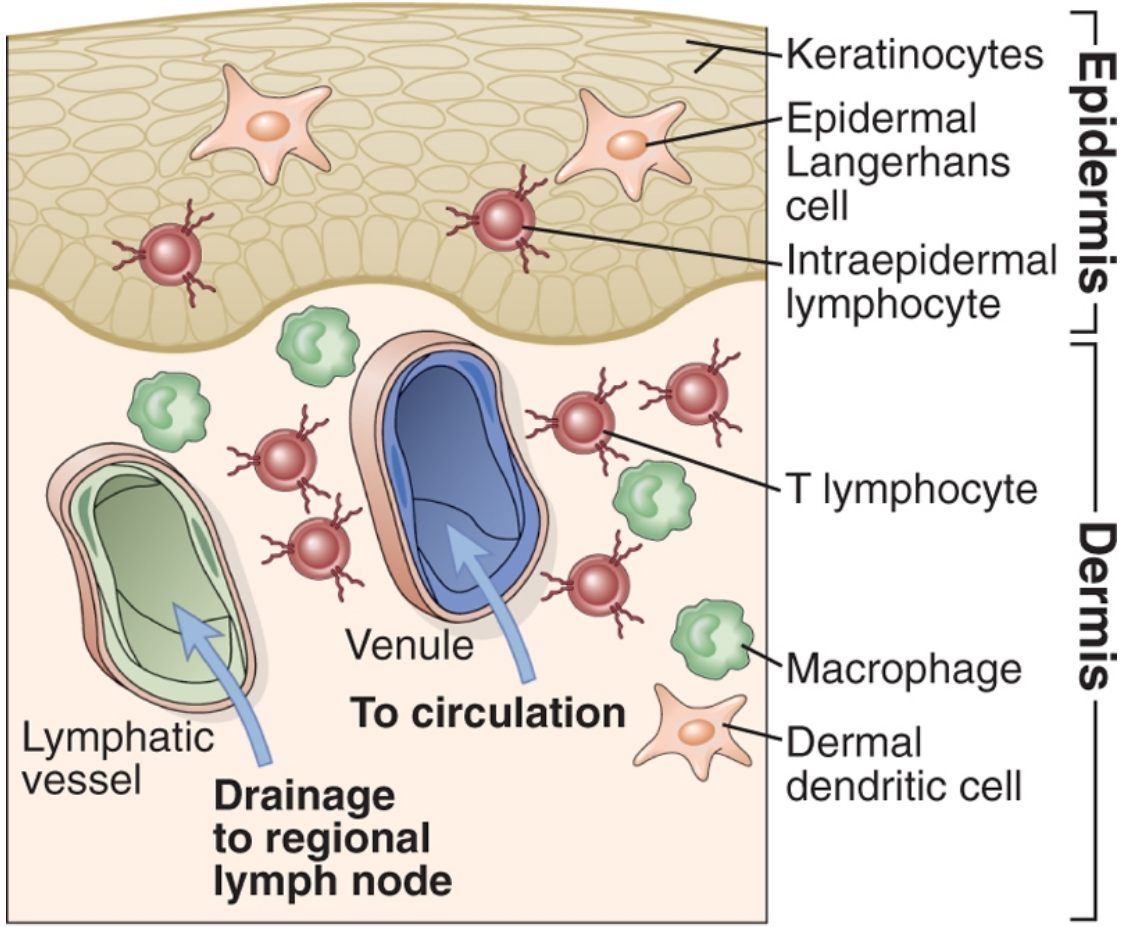
Abbas, Molecular İmmunology

LENF NODÜLLERİ

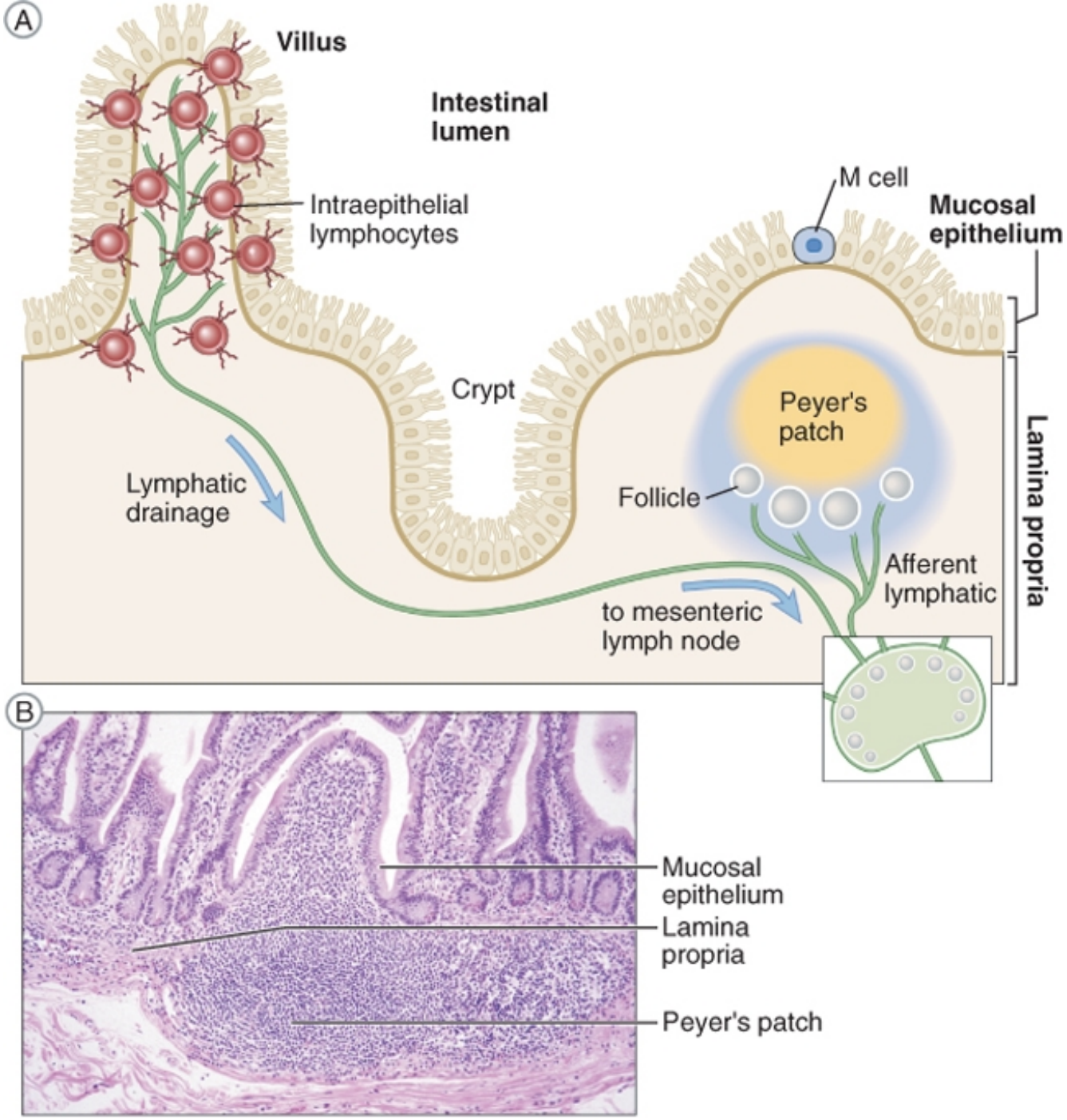




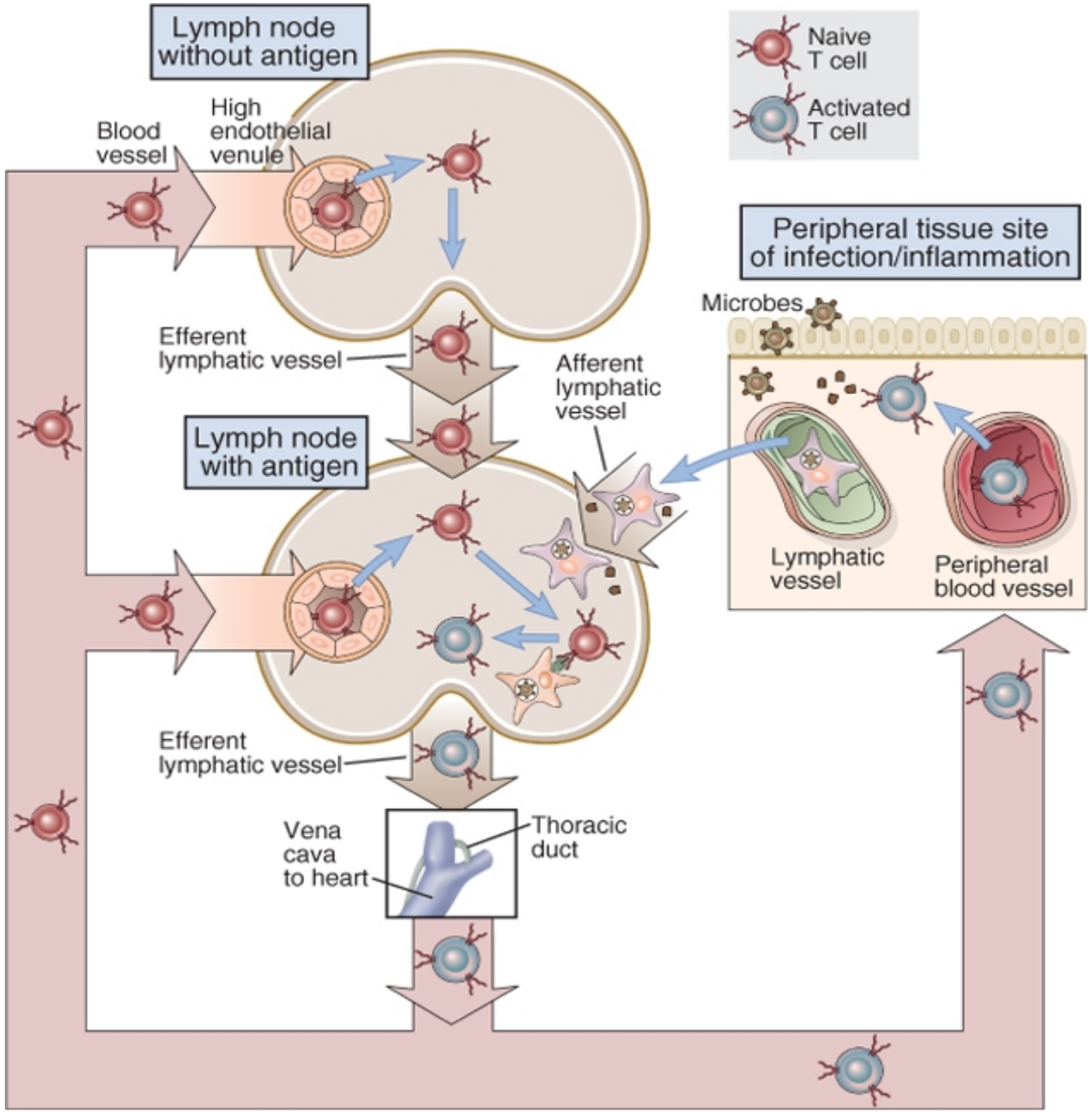
DERİ



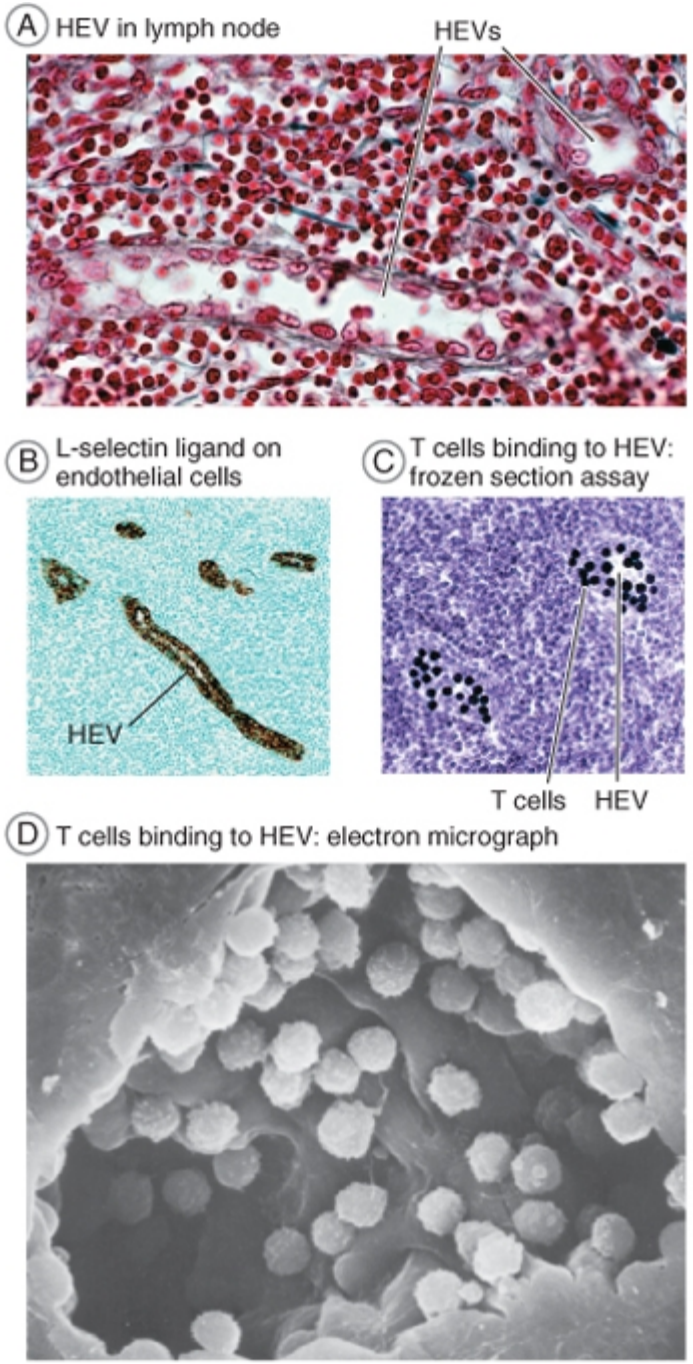
MUKOZAL İMMUN SİSTEM



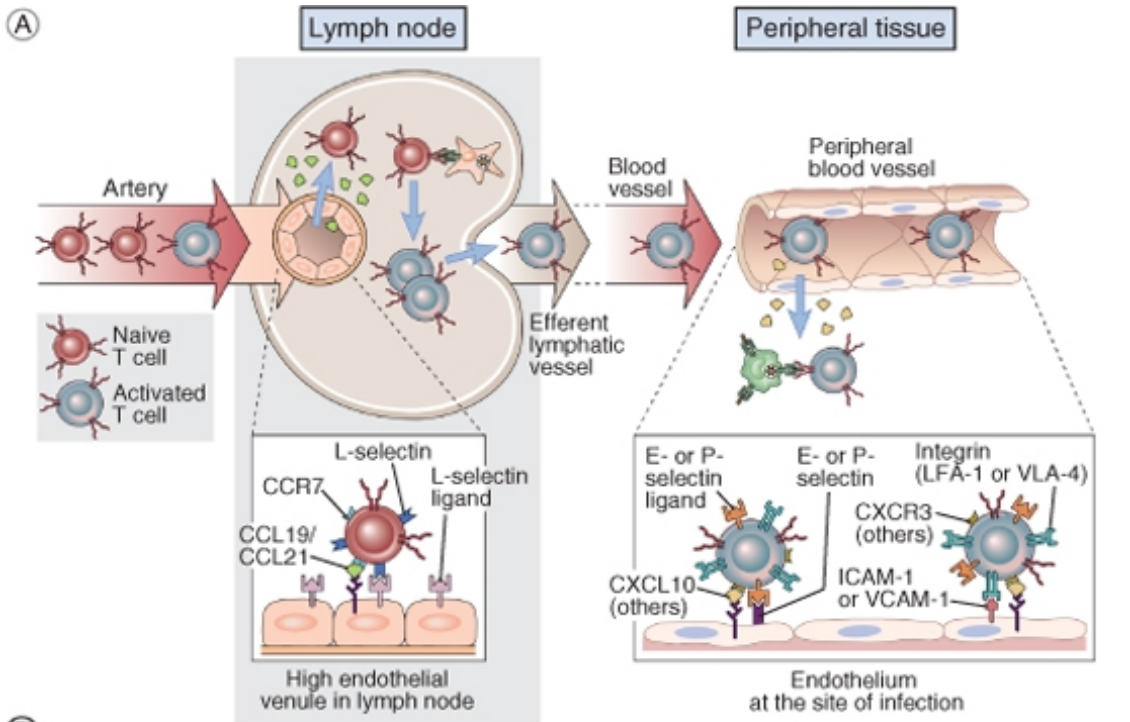
LENFOSİT DOLAŞIMI YOLLARI



HIGH ENDOTELYAL VENÜLLER



NAIVE VE EFEKTÖR T LENFOSİTLERİN GÖÇÜ

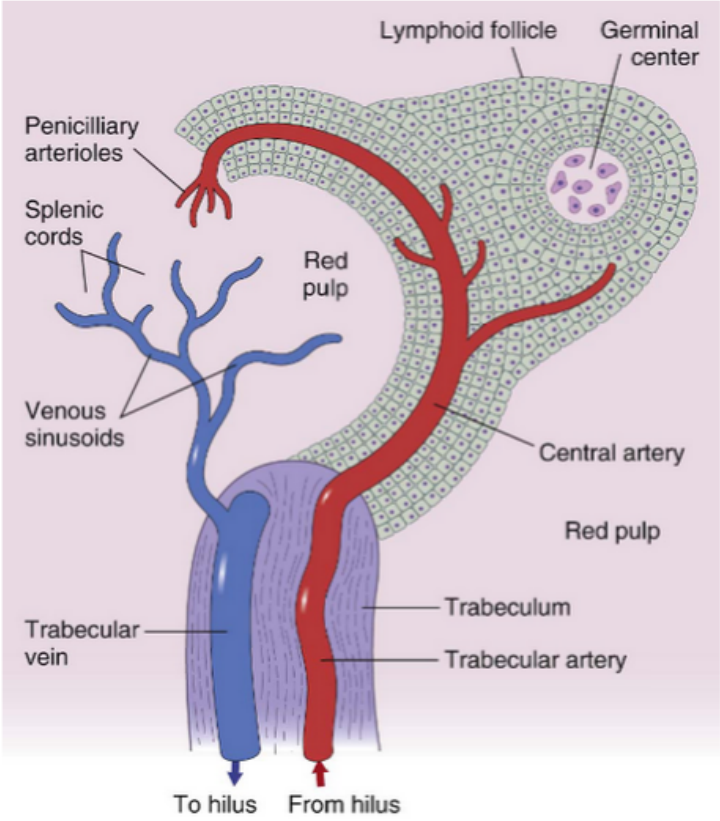


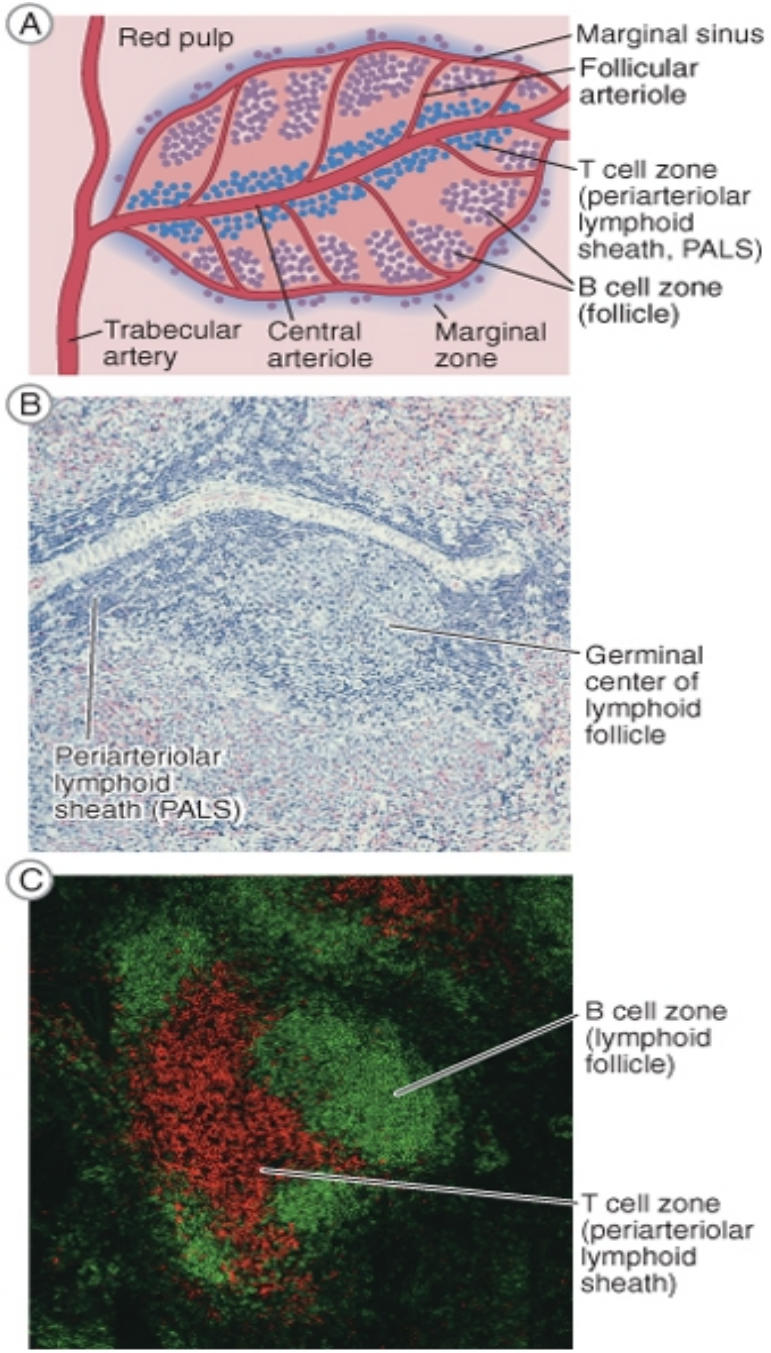
B

T cell homing receptor	Ligand on endothelial cell	Function of receptor: ligand pair
Naive T cells		
L-selectin	L-selectin ligand	Adhesion of naive T cells to high endothelial venule in lymph node
CCR7	CCL19 or CCL21	
Activated (effector and memory) T cells		
E- and P-selectin ligand	E- or P-selectin	Initial weak adhesion of effector and memory T cells to cytokine activated endothelium at peripheral site of infection
LFA-1 (β2-integrin) or VLA-4 (β1 integrin)	ICAM-1 or VCAM-1	Stable arrest on cytokine activated endothelium at peripheral site of infection
CXCR3	CXCL10 (others)	Activation of integrins and chemokinesis
CCR5	CCL4 (others)	Activation of integrins and chemokinesis

DALAK

Çevre kanının en önemli antikor kaynağı

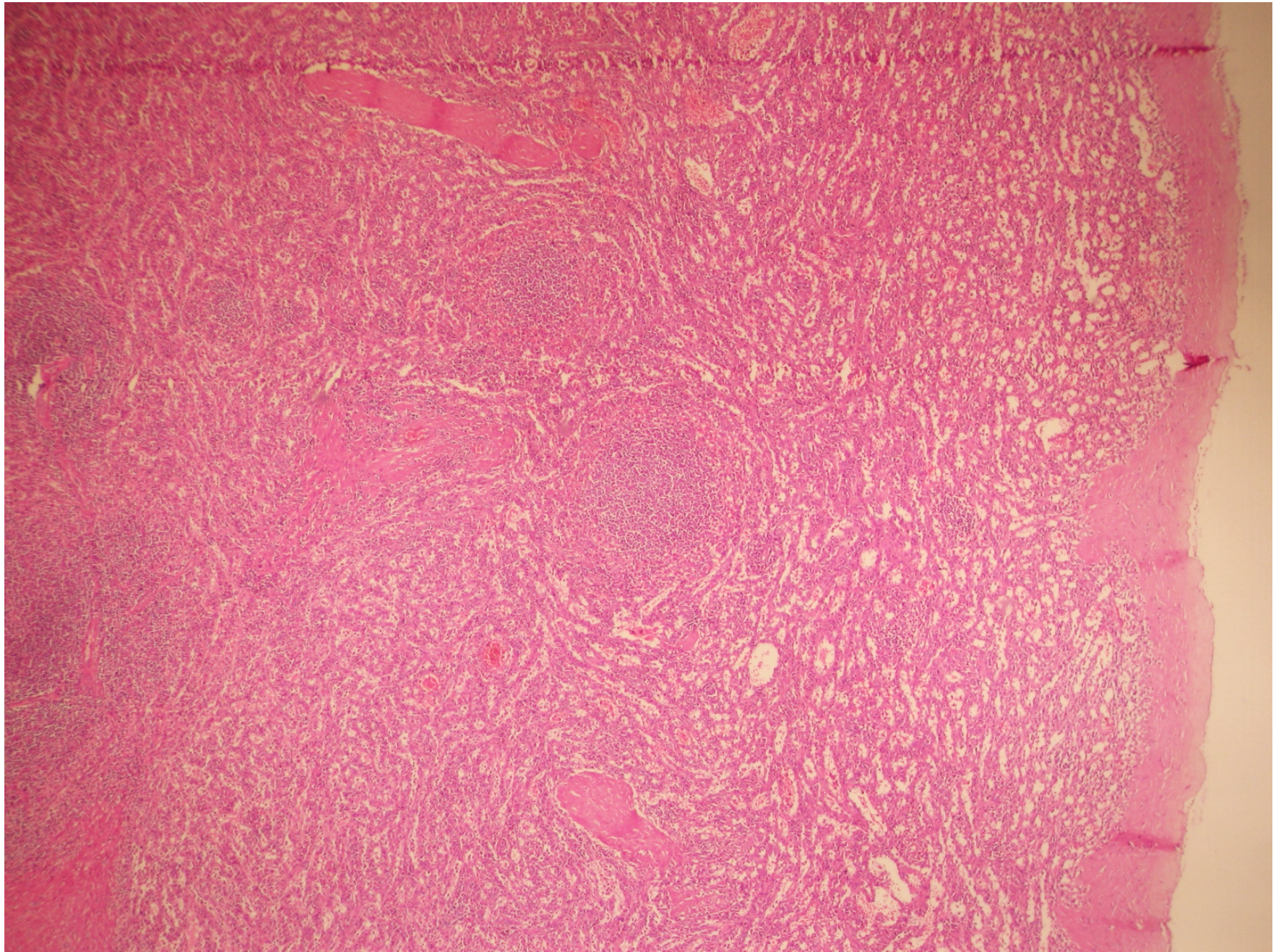




DALAK İŞLEVLERİ

- *Kan hücre ve partiküllerin fagositozu*
- *Antikor yapımı*
- *Hematopoez*
- *Kan hücrelerinin yıkımı (sekestrasyon)*

DALAK



SPLENOMEGALİ

TABLE 13-12 Disorders Associated with Splenomegaly

I. Infections
Nonspecific splenitis of various blood-borne infections (particularly infectious endocarditis)
Infectious mononucleosis
Tuberculosis
Typhoid fever
Brucellosis
Cytomegalovirus
Syphilis
Malaria
Histoplasmosis
Toxoplasmosis
Kala-azar
Trypanosomiasis
Schistosomiasis
Leishmaniasis
Echinococcosis

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SPLENOMEGALİ

II. Congestive States Related to Portal Hypertension
Cirrhosis of the liver Portal or splenic vein thrombosis Cardiac failure
III. Lymphohematogenous Disorders
Hodgkin lymphoma Non-Hodgkin lymphomas and lymphocytic leukemias Multiple myeloma Myeloproliferative disorders Hemolytic anemias
IV. Immunologic-Inflammatory Conditions
Rheumatoid arthritis Systemic lupus erythematosus
V. Storage Diseases
Gaucher disease Niemann-Pick disease Mucopolysaccharidoses
VI. Miscellaneous Disorders
Amyloidosis Primary neoplasms and cysts Secondary neoplasms

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LENFADENOPATİ

1- Reaktif veya infeksiyonlara bağlı

2- Neoplastik büyümeler (Primer – sekonder (metastatik))

Romatolojik – İmmünolojik

Romatoid artrit

Lupus eritematosus

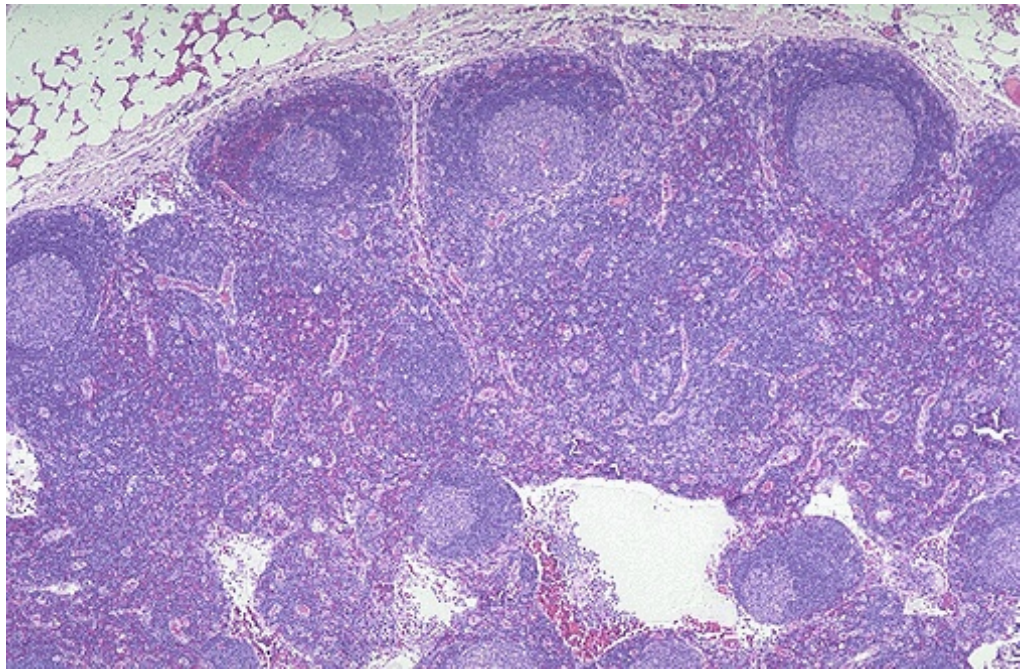
Sjögren sendromu

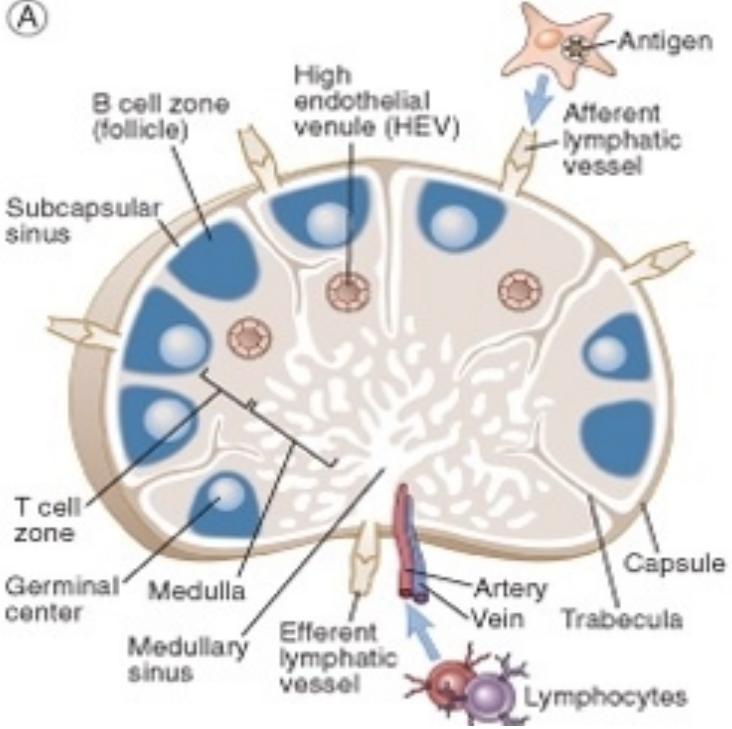
İmmün yetmezlik durumları..

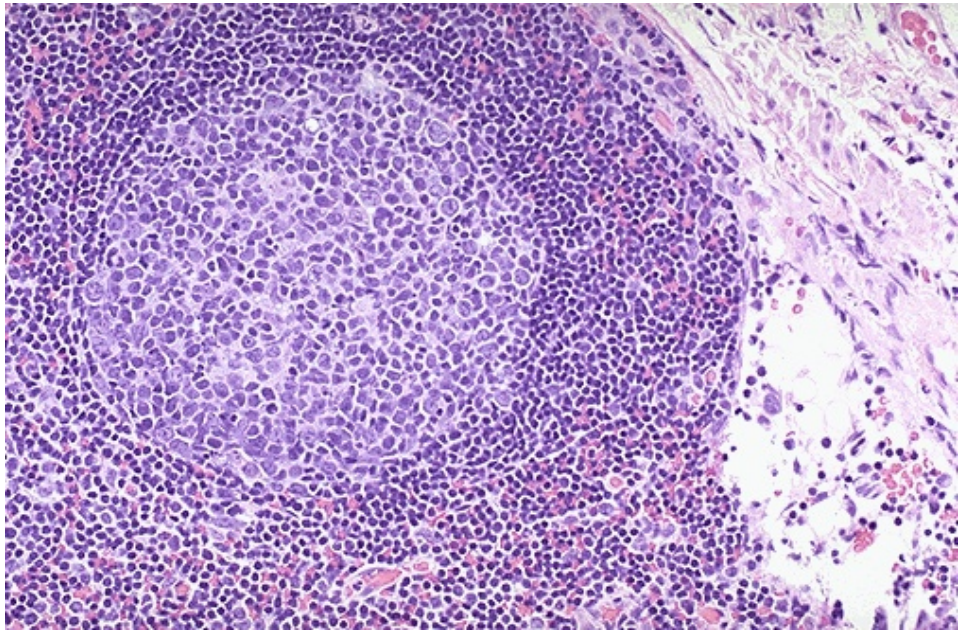
Enfeksiyöz

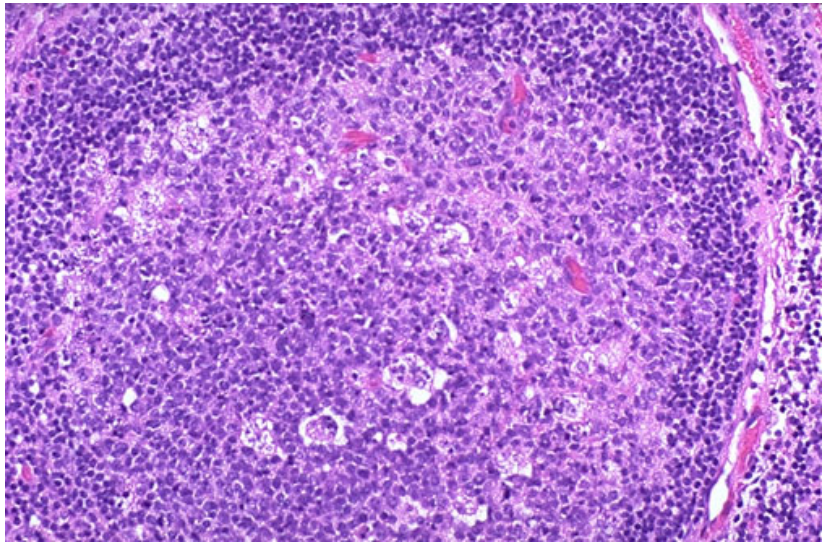
Bakterial

Viral









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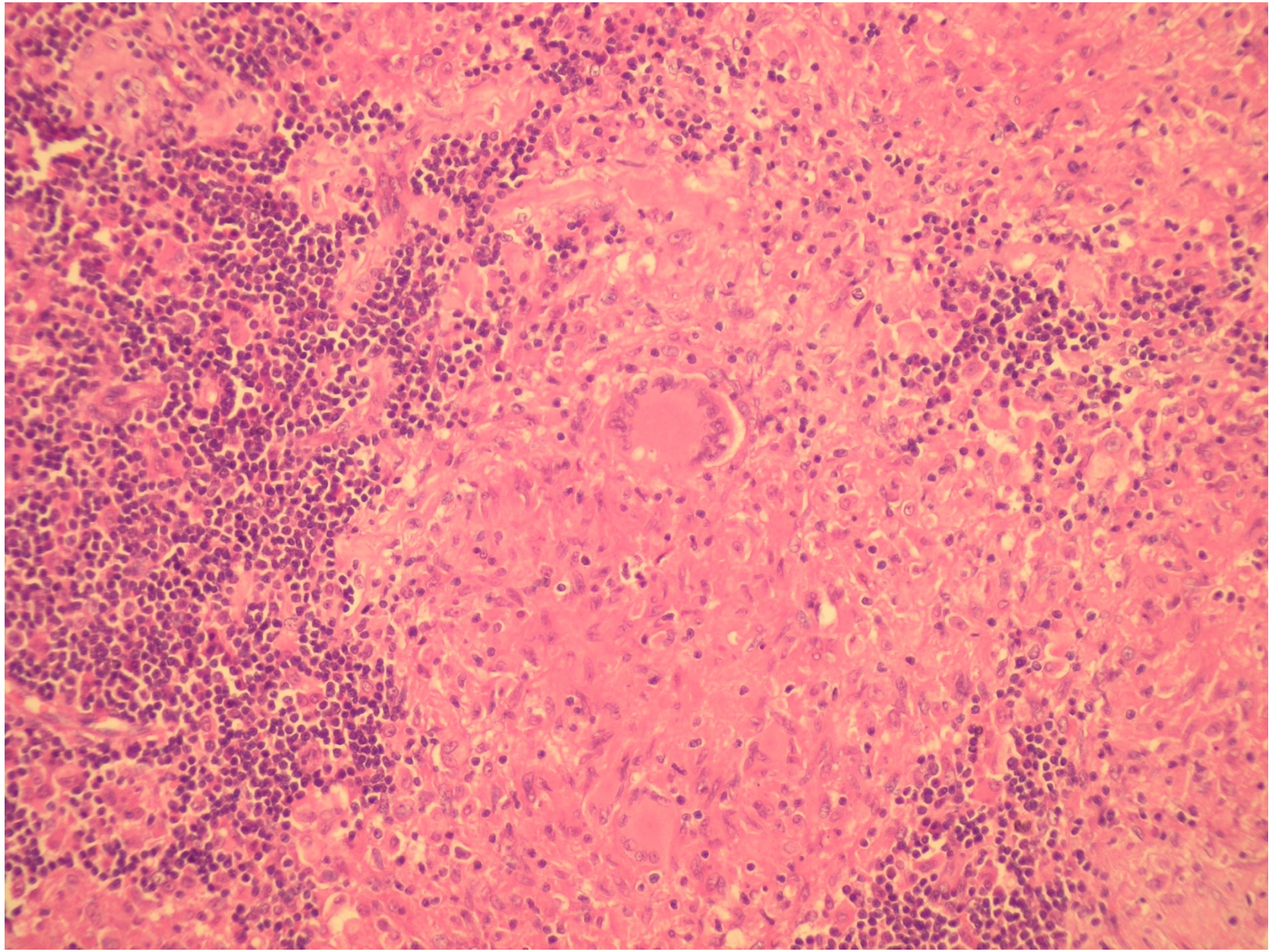
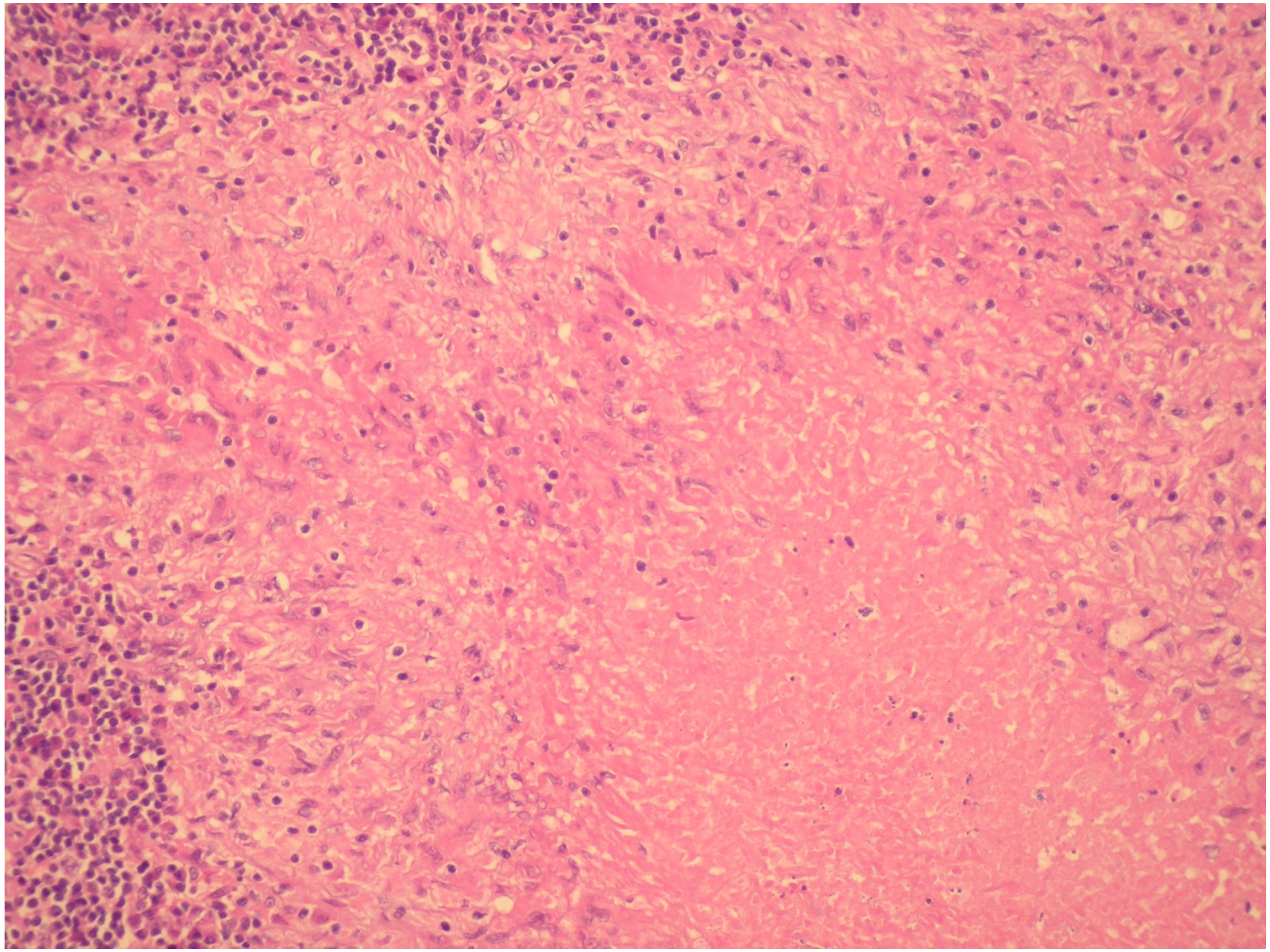
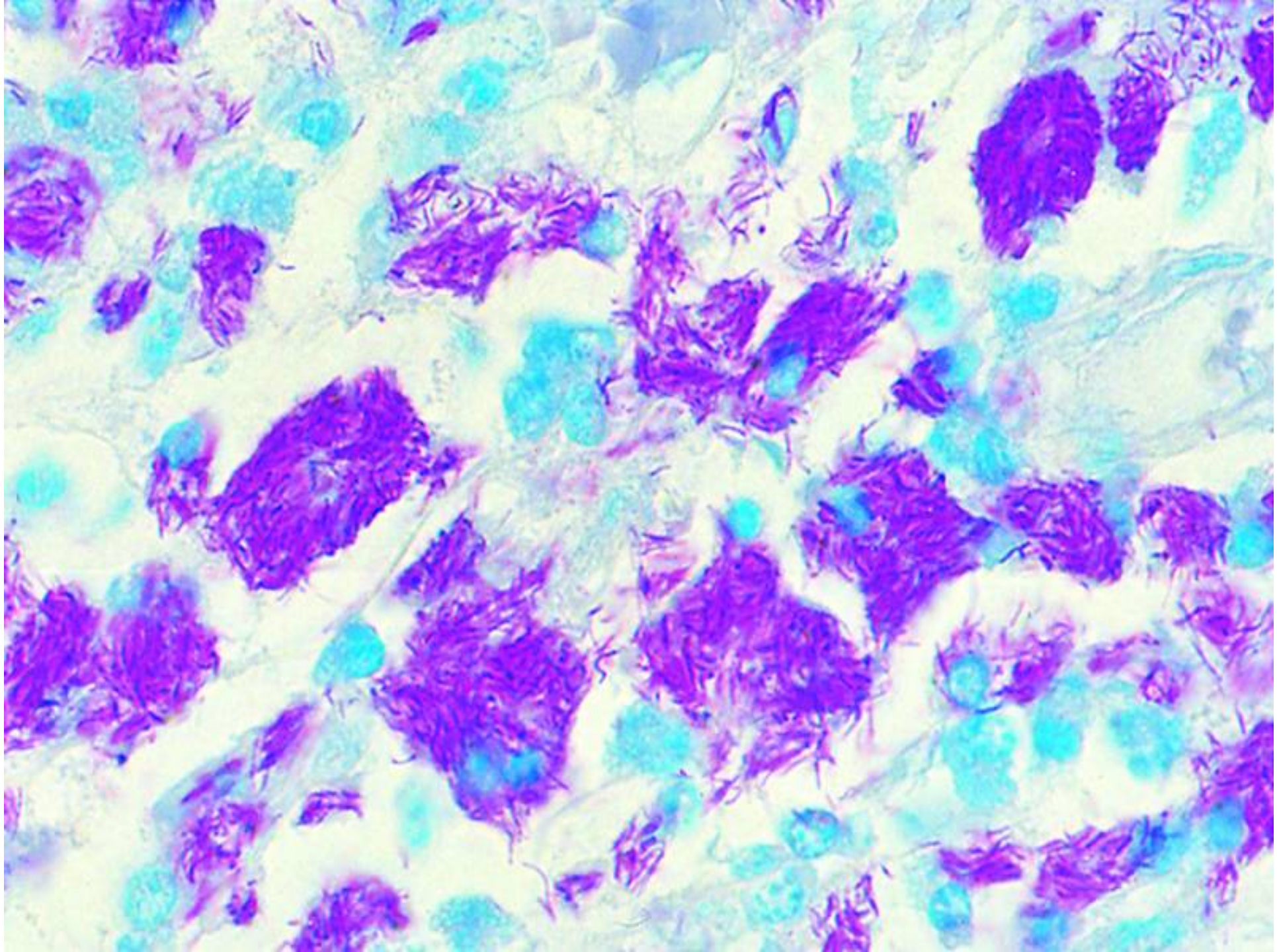
Granülomatöz inflamasyon

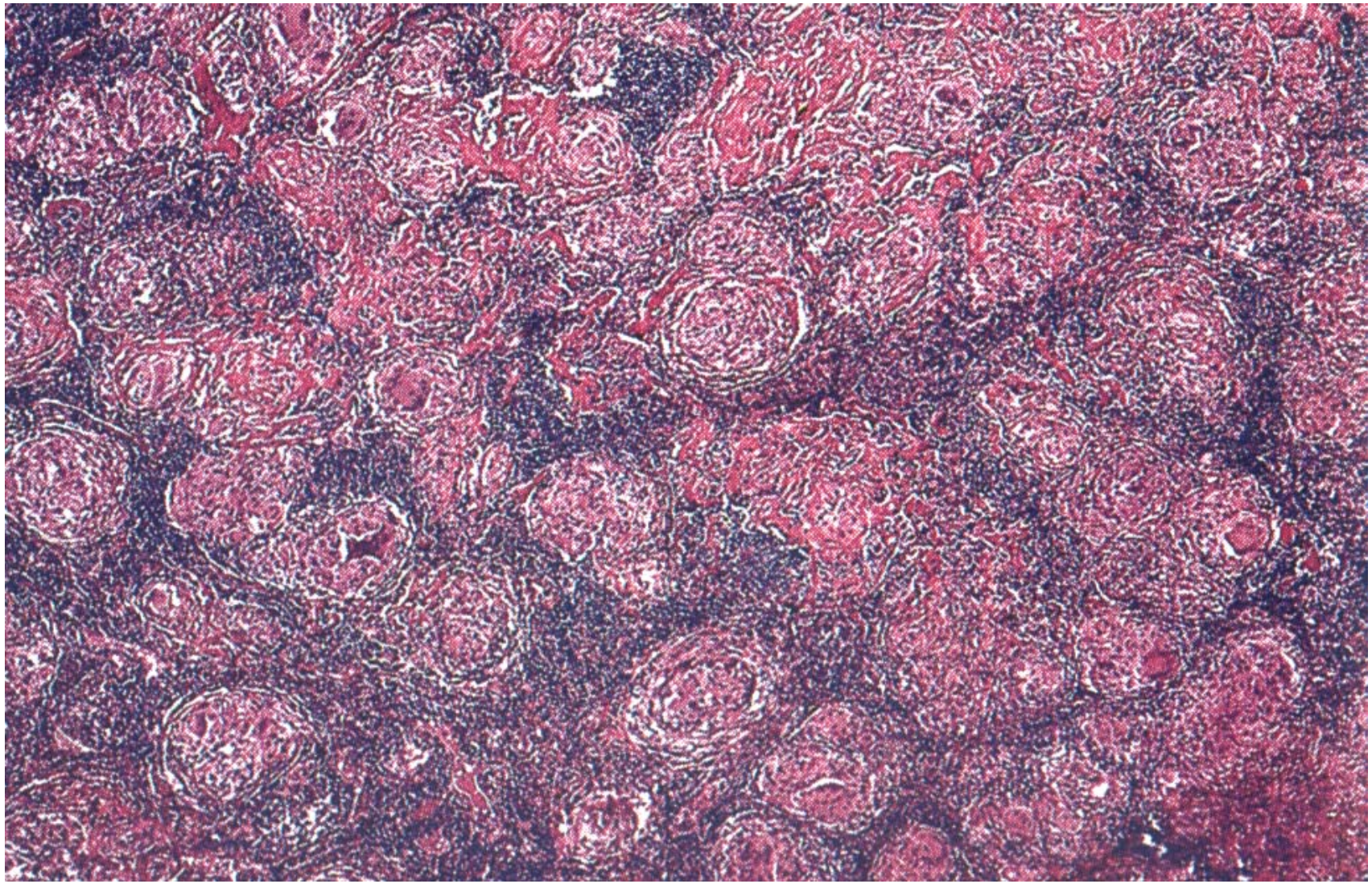


Granülomatöz inflamasyon (nekroz)





Sarkoidozis

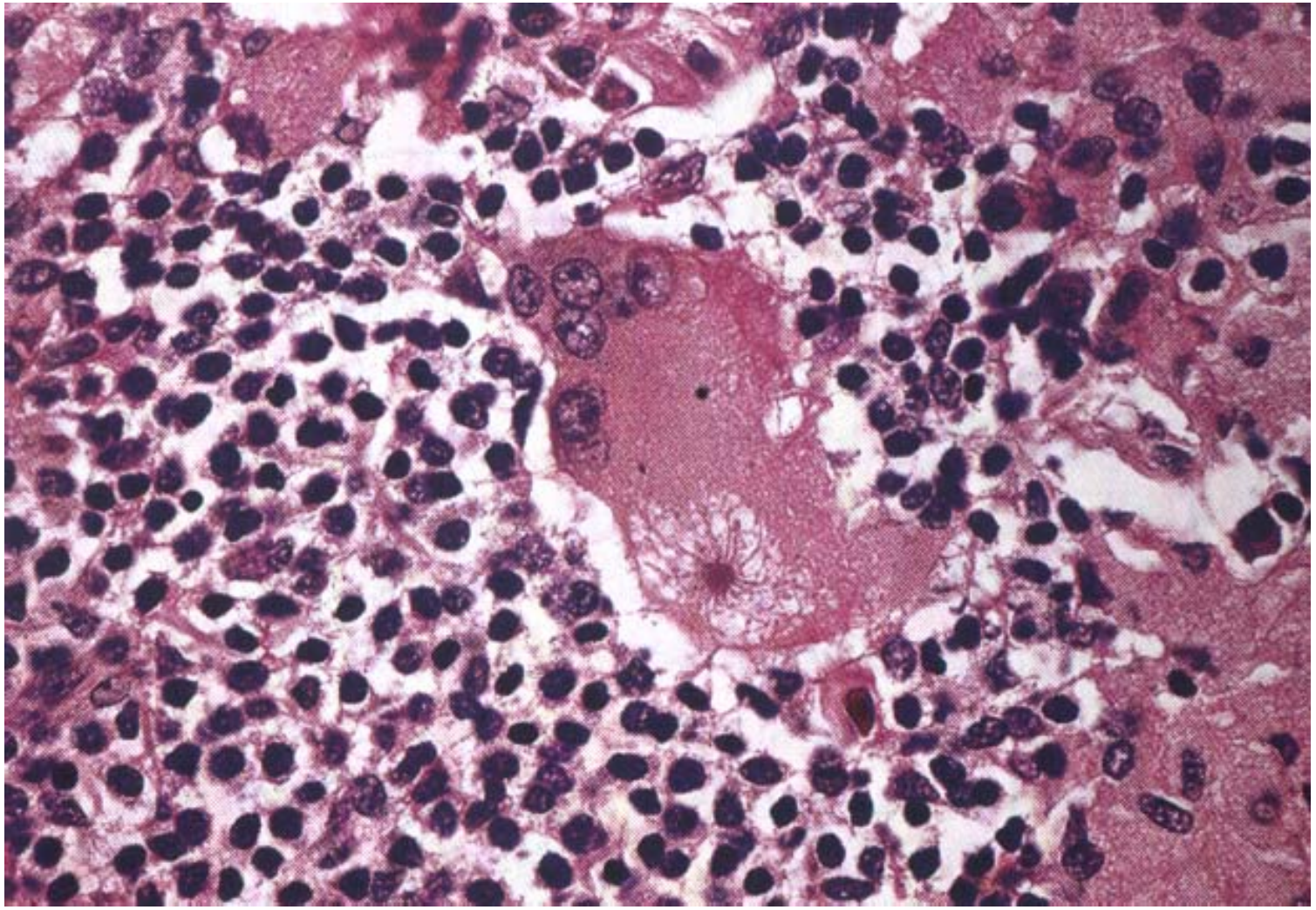


Sarkoidozis nedeni bilinmeyen ve birden fazla sistemi etkileyen, nonkazeöz granülomatöz hastalıktır

Akciğer infiltrasyonları, malignite ile karışabilen hiler lenfadenopati

Lenf düğümünde tüberküloz ile karışabilecek granülomatöz inflmasyon oluşturur.

Sarkoidozis



Süpüratif granülomatöz lenfadenopatiler:

düzensiz kenarlı nekroz alanları ile karakterli, Tüberküloz ile karışabilecek morfolojiye sahip bir grup hastalık

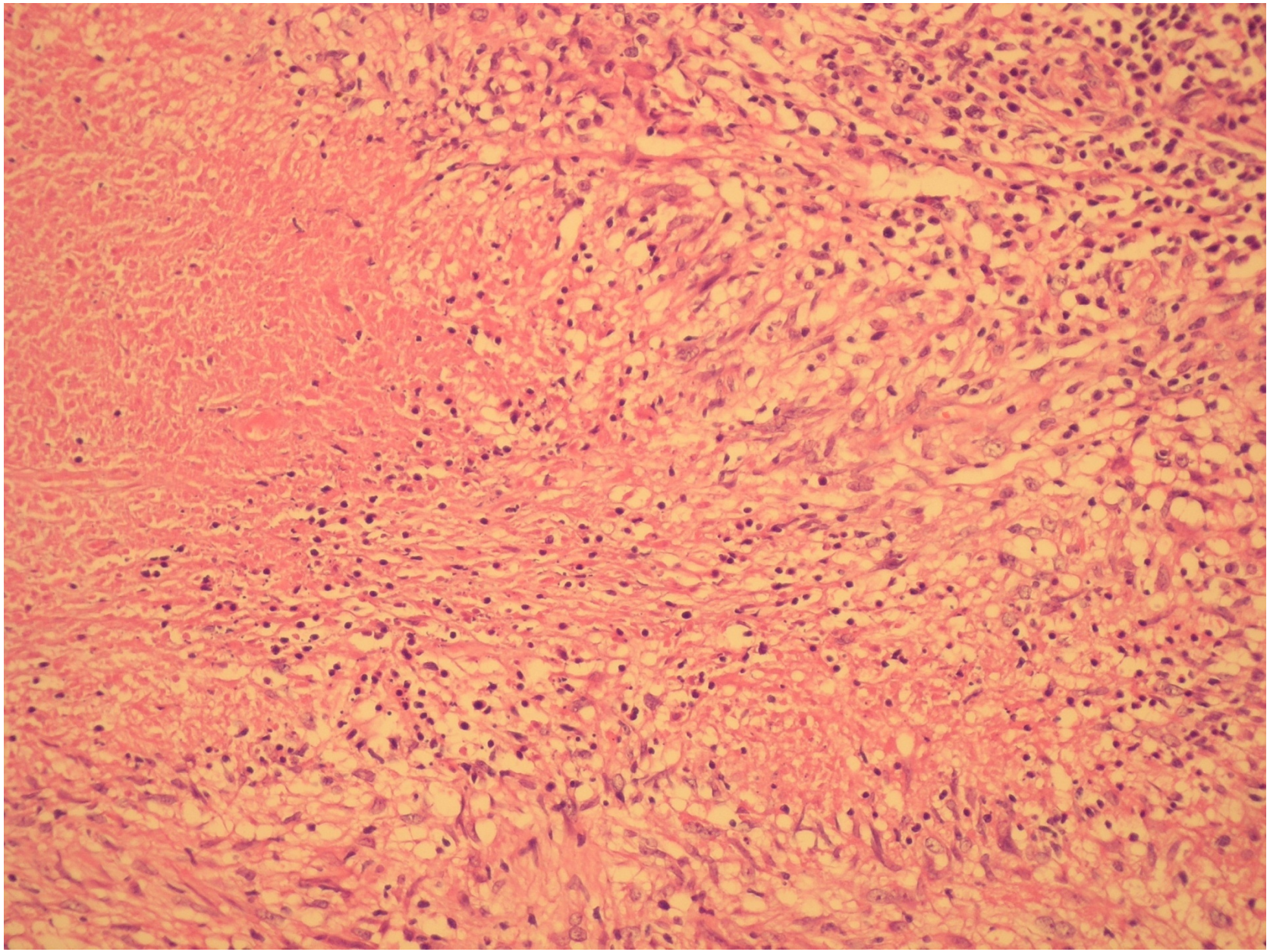
Atipik mikobakteri infeksiyonları,

Kedi tırmığı hastalığı (Bartonella henselae)

Tularemi,

Yersinia,

Lenfogranüloma venereum (Chlamidia trachomatis)

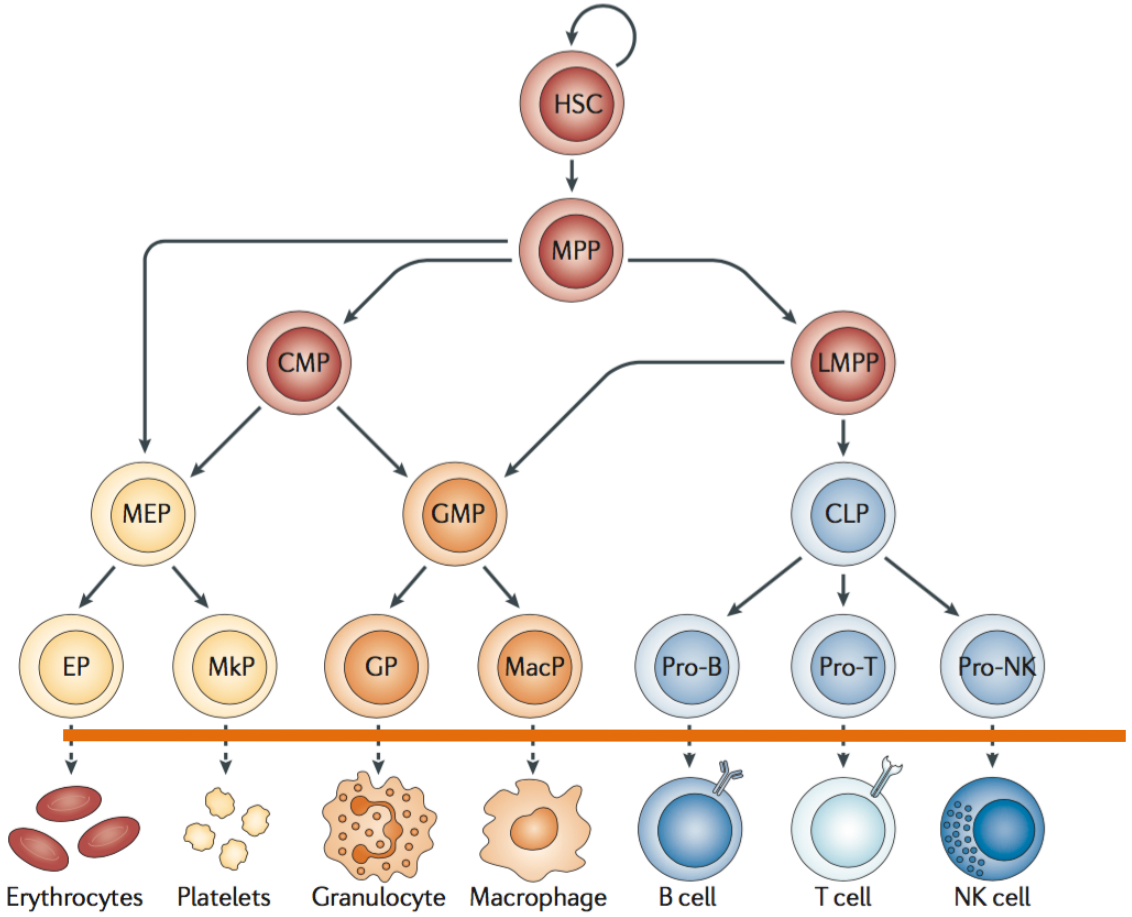


LENFOTROP VİRÜSLER

Human Herpes Virüsler (ds DNA)

- EBV (HHV4) Enfeksiyöz Mononükleozis
- KSV (Kaposi Sarkoma Virus) (HHV8) Castleman Hastalığı
- CMV (Sitomegalovirus) (HHV5)
- HIV (ds RNA)

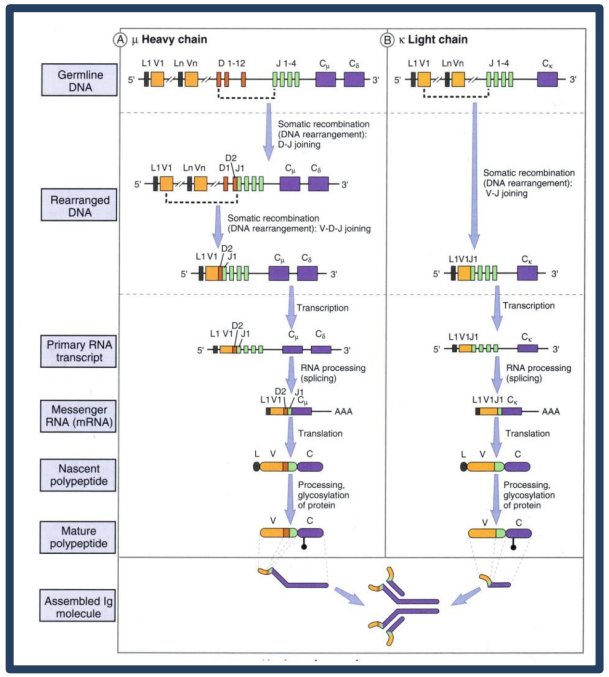
Lenfoid Hücreler

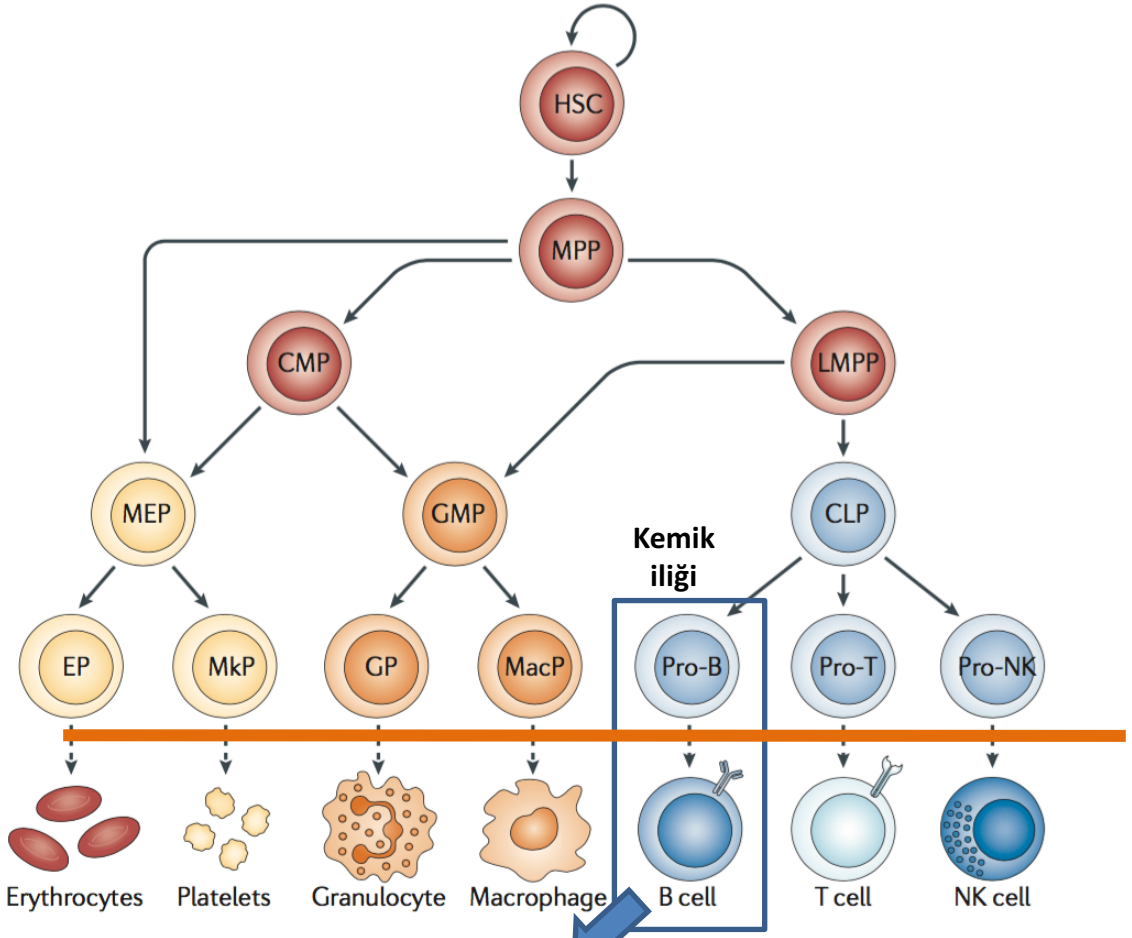


Cedar, Nat Rev Immunol 2015

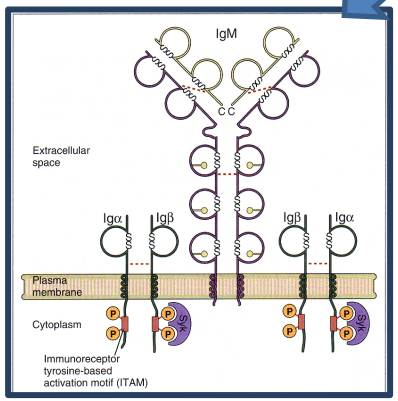
Lenfoid Hücreler

Hümoral Bağışıklık





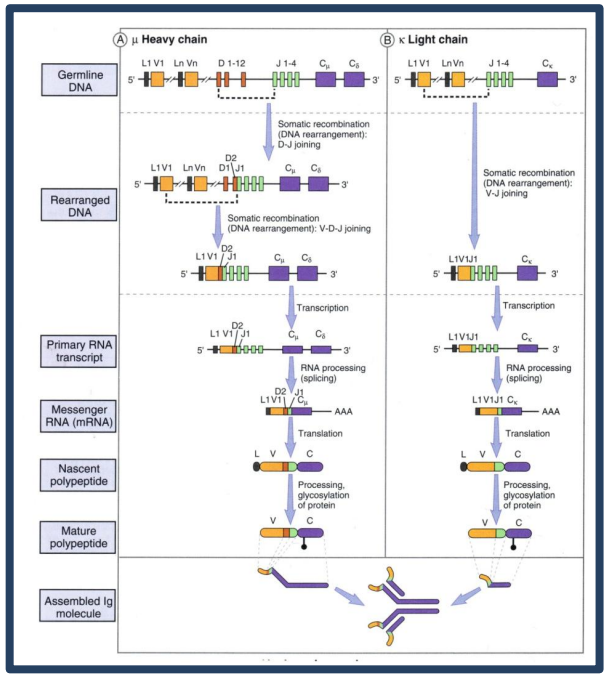
B hücre Reseptörü
İmmunglobulin (Ig) Molekülü

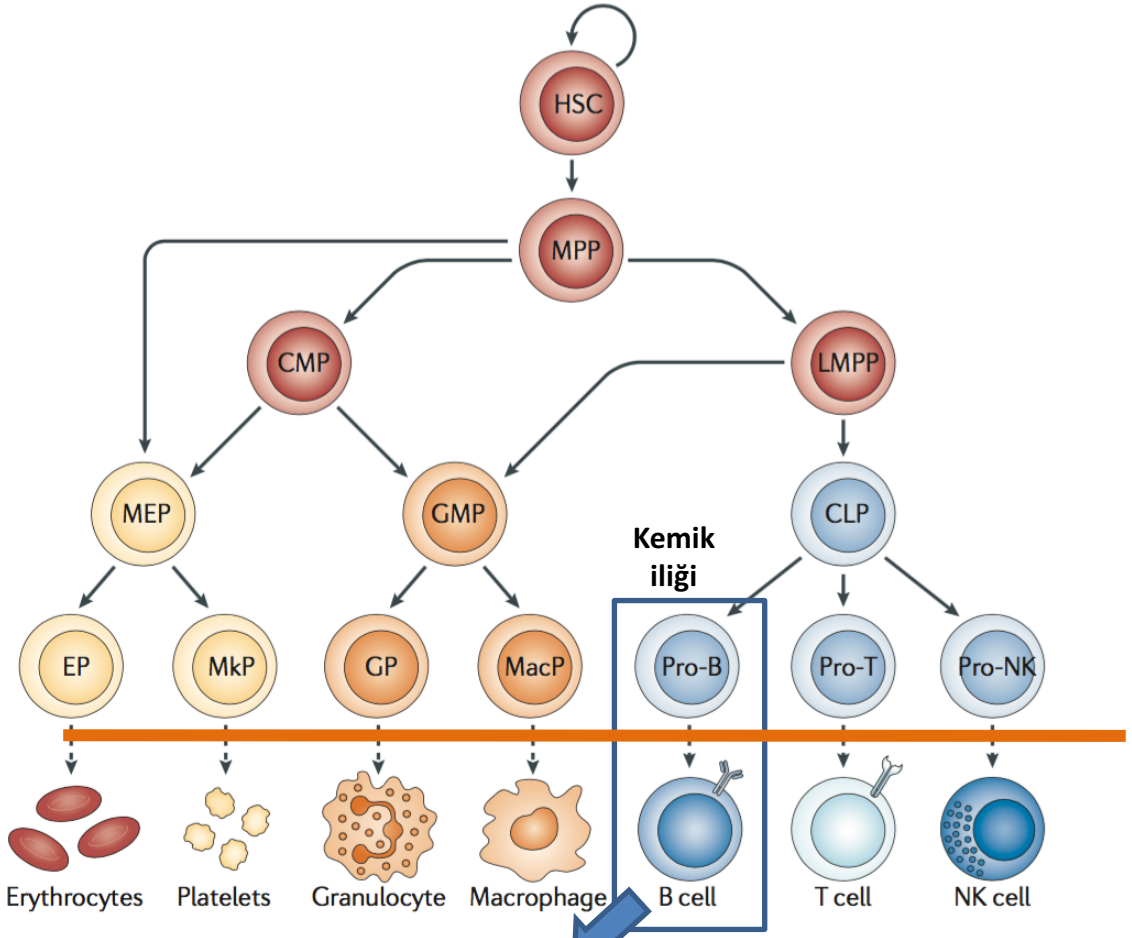


Cedar, Nat Rev Immunol 2015
Abbas, Cellular &Molecular Immunology

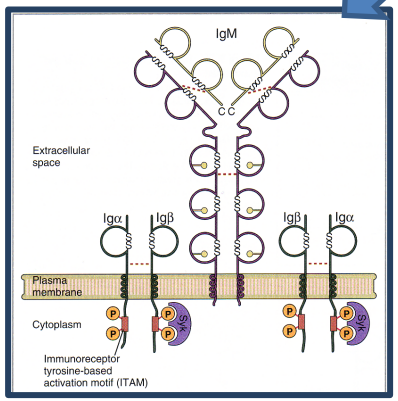
Lenfoid Hücreler

Hümoral Bağışıklık



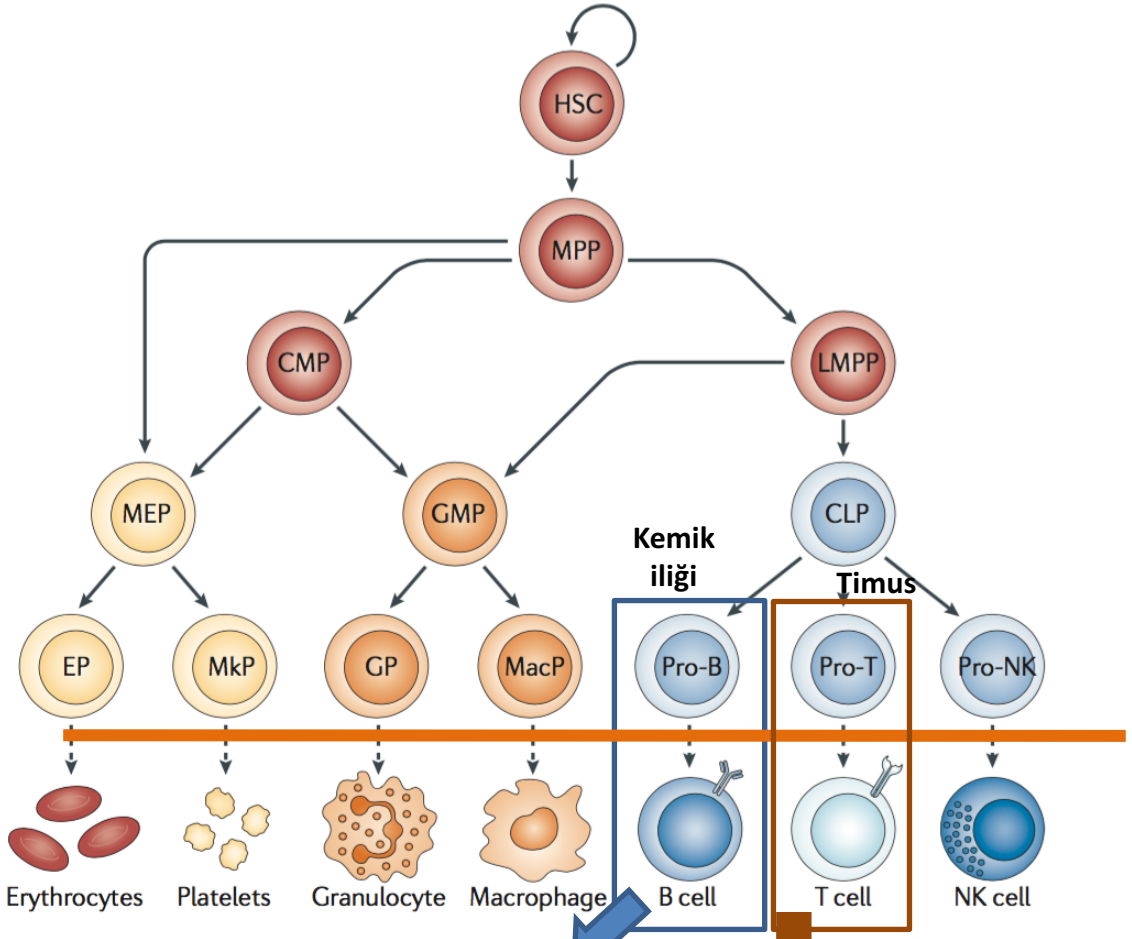


B hücre Reseptörü
İmmunglobulin (Ig) Molekülü

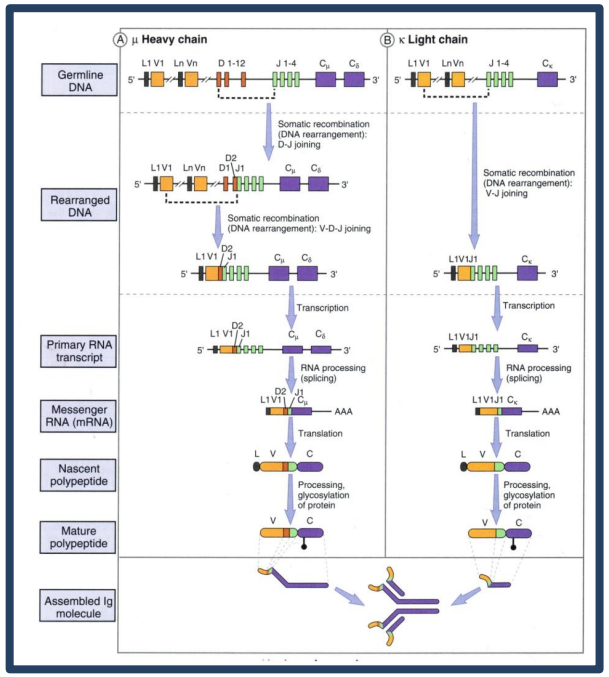


Cedar, Nat Rev Immunol 2015
Abbas, Cellular &Molecular Immunology

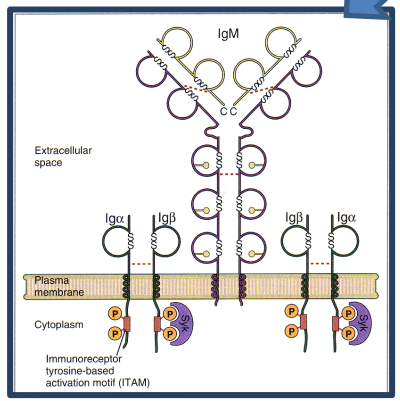
Lenfoid Hücreler

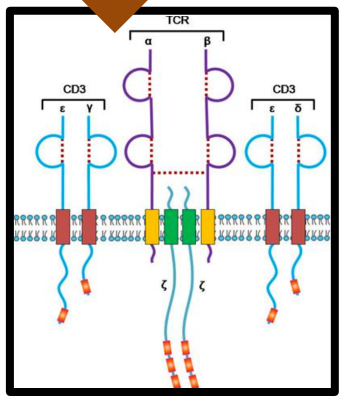


Hümoral Bağışıklık



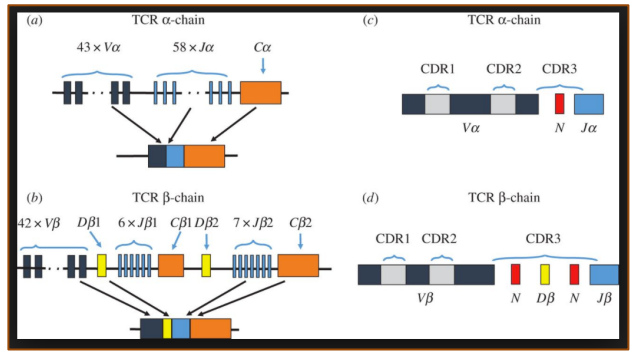
B hücre Reseptörü İmmunglobulin (Ig) Molekülü





T Hücre reseptörü TCR Molekülü

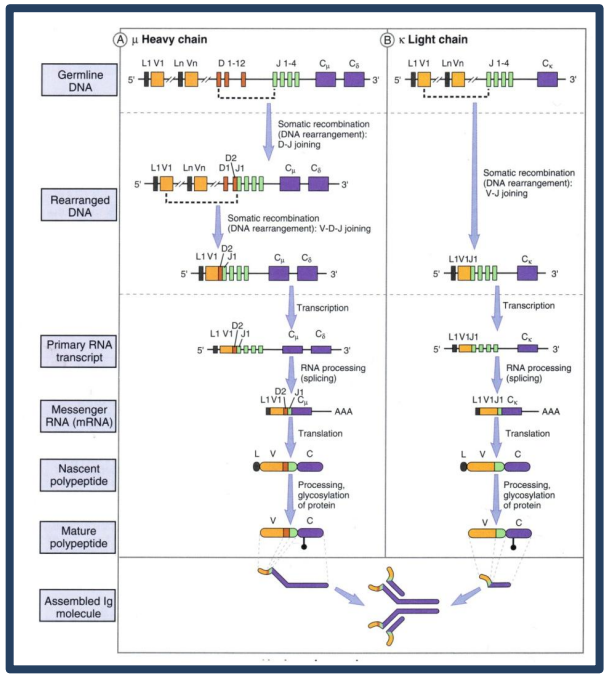
Hücresel immunite



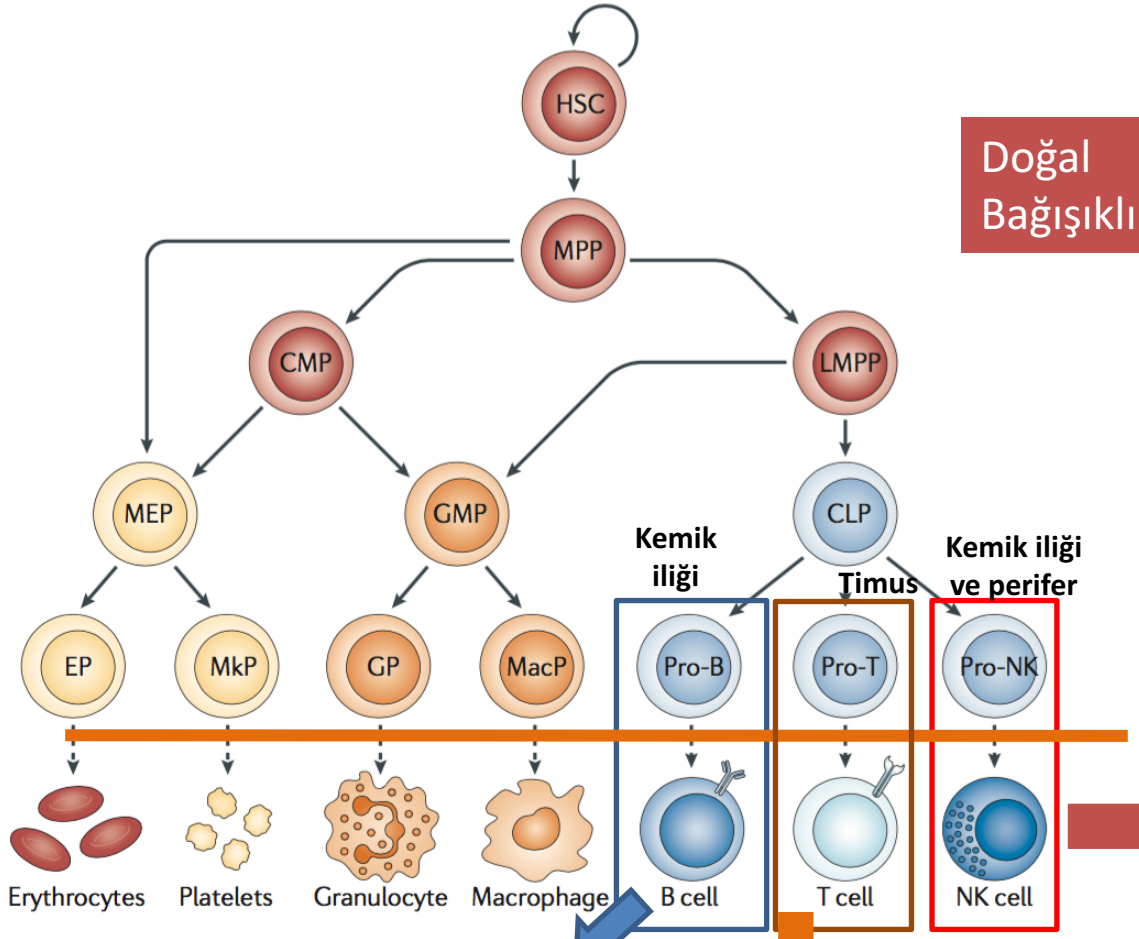
Cedar, Nat Rev Immunol 2015
Abbas, Cellular &Molecular Immunology

Lenfoid Hücreler

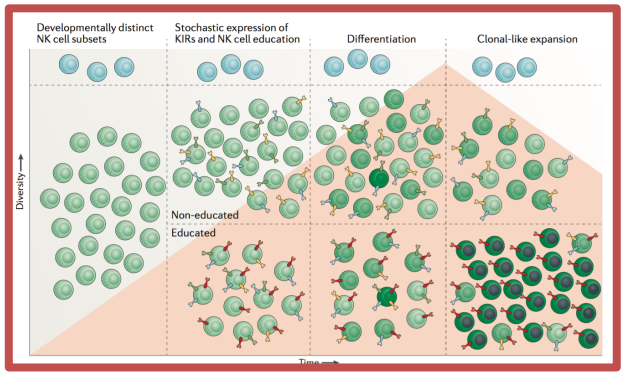
Hümoral Bağışıklık

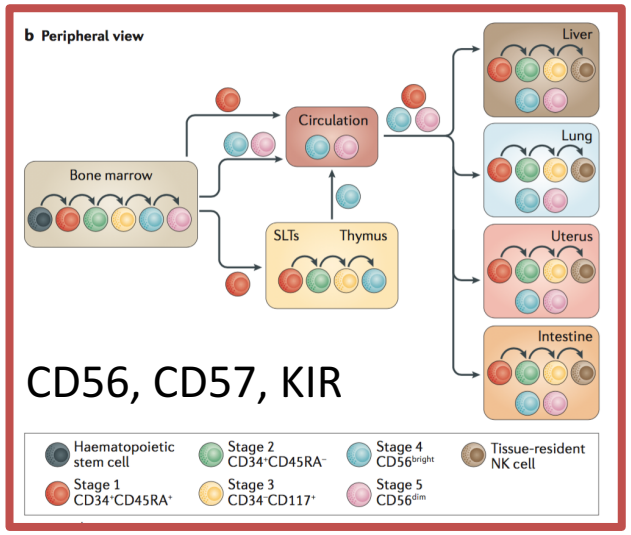


Cedar, Nat Rev Immunol 2015
Björkström Nat Rev Immunol 2016
Abbas, Cellular &Molecular Immunology



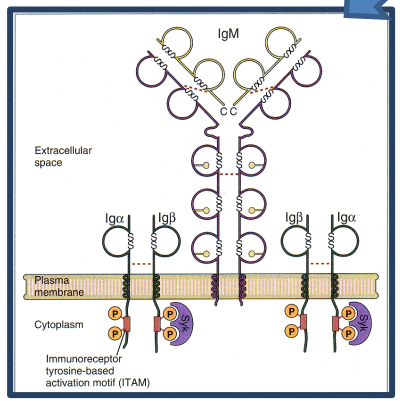
Doğal Bağışıklık

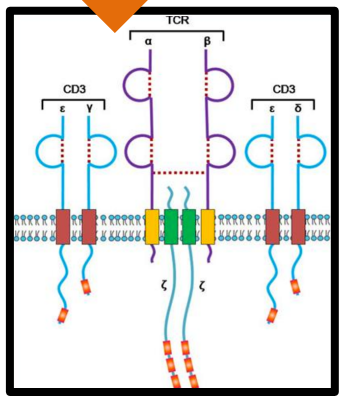




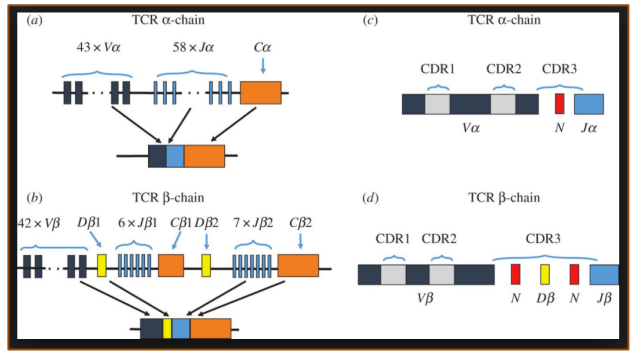
Hücresel Bağışıklık

B hücre Reseptörü İmmunglobulin (Ig) Molekülü



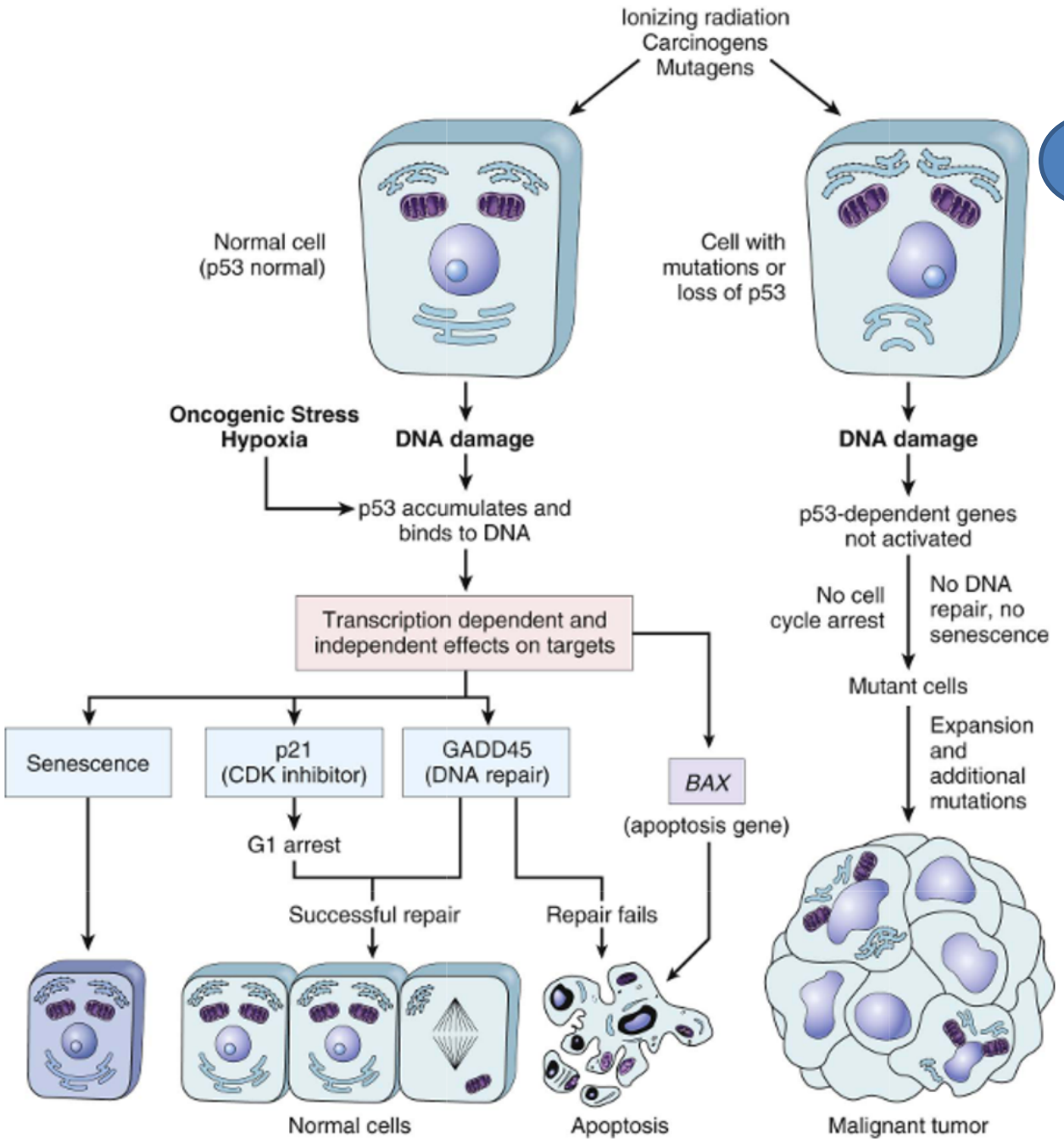


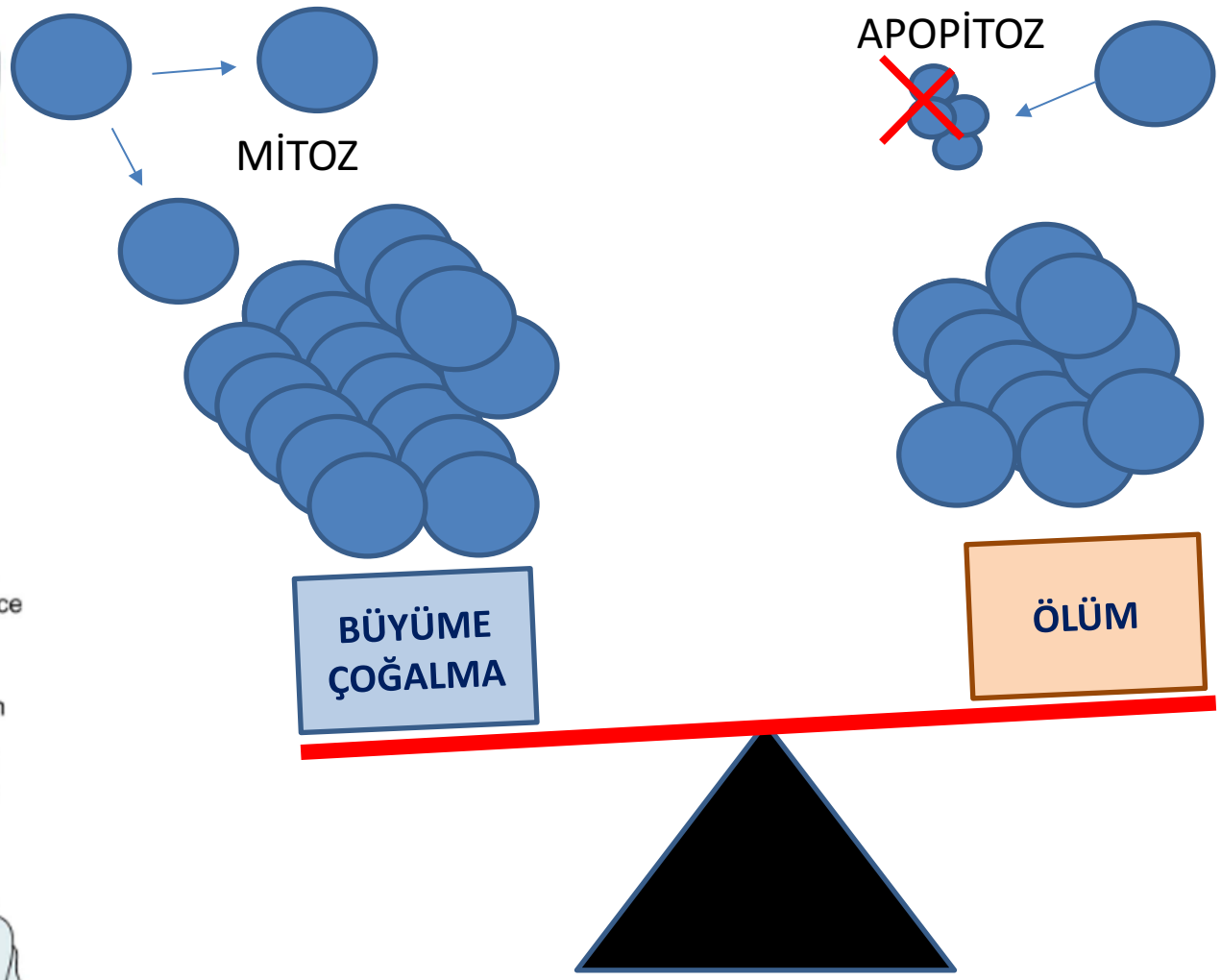
T Hücre reseptörü TCR Molekülü



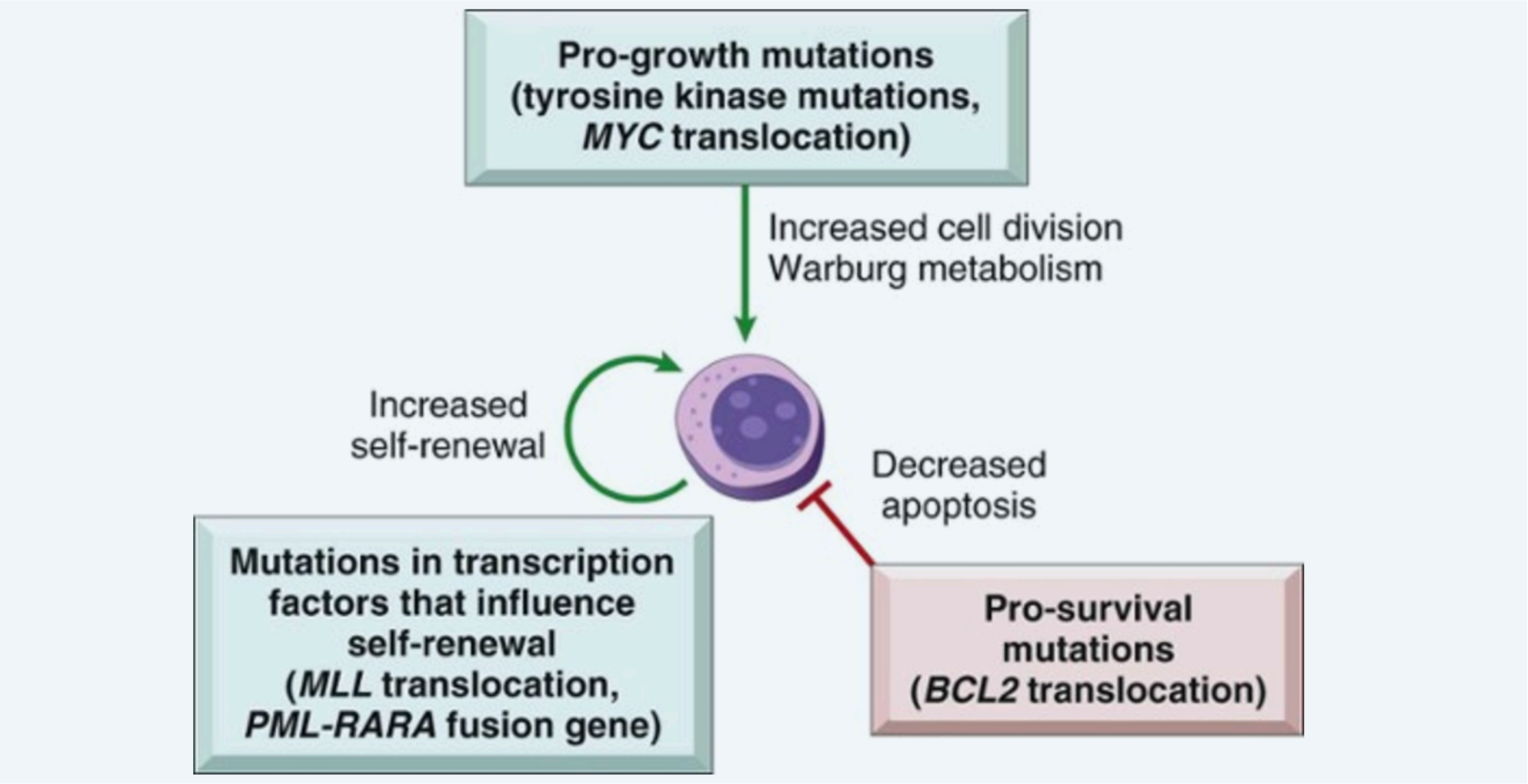
HEMATOLOJİK NEOPLAZİLERİN GELİŞME MEKANİZMALARI

- NORMAL HÜCRELERİN OLGUNLAŞMA, BÜYÜME, YAŞAMA VE ÖLÜM İŞLEVLERİYLE İLGİLİ MOLEKÜLLER (SİTOKİN – BÜYÜME FAKTÖRLERİ)
- HIZLI ÇOĞALMA GEREKLİLİĞİ
- KALITSAL FAKTÖRLER
- ENFEKSİYONLAR
- KRONİK İNFLAMASYONLAR
- KİMYASAL VE FİZİKSEL KARSİNOJENLER (İlaçlar, radyasyon, sigara, çeşitli diğer kimyasal karsinojenler)





Robbins Cotran Kumar. Pathological Basis of Disease



Robbins Cotran Kumar. Pathological Basis of Disease

Tümör gelişimi ile ilişkili onkogenler

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
Growth Factors			
PDGF-β chain	*PDGFB*	Overexpression	Astrocytoma
Fibroblast growth factors	*HST1*	Overexpression	Osteosarcoma
	FGF3	Amplification	Stomach cancer
			Bladder cancer
			Breast cancer
			Melanoma
TGF-α	*TGFA*	Overexpression	Astrocytomas
HGF	*HGF*	Overexpression	Hepatocellular carcinomas
			Thyroid cancer
Growth Factor Receptors			
EGF-receptor family	*ERBB1 (EGFR)* *ERBB2 (HER)*	Mutation Amplification	Adenocarcinoma of lung Breast carcinoma
FMS-like tyrosine kinase 3	*FLT3*	Point mutation	Leukemia

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Overexpression, translocation	Gliomas, leukemias
Receptor for KIT ligand	*KIT*	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	*ALK*	Translocation, fusion gene formation	Adenocarcinoma of lung, certain lymphomas
		Point mutation	Neuroblastoma
Proteins Involved in Signal Transduction			
GTP-binding (G) proteins	*KRAS*	Point mutation	Colon, lung, and pancreatic tumors
	HRAS	Point mutation	Bladder and kidney tumors
	NRAS	Point mutation	Melanomas, hematologic malignancies
	GNAQ	Point mutation	Uveal melanoma
	GNAS	Point mutation	Pituitary adenoma, other endocrine tumors
Nonreceptor tyrosine kinase	*ABL*	Translocation	Chronic myelogenous leukemia
		Point mutation	Acute lymphoblastic leukemia

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
RAS signal transduction	*BRAF*	Point mutation, Translocation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	*NOTCH1*	Point mutation, Translocation Gene rearrangement	Leukemias, lymphomas, breast carcinoma
JAK/STAT signal transduction	*JAK2*	Translocation	Myeloproliferative disorders
			Acute lymphoblastic leukemia
Nuclear Regulatory Proteins			
Transcriptional activators	*MYC*	Translocation	Burkitt lymphoma
	NMYC	Amplification	Neuroblastoma
Cell Cycle Regulators			
Cyclins	*CCND1* (Cyclin D1)	Translocation	Mantle cell lymphoma, multiple myeloma
		Amplification	Breast and esophageal cancers
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma

Robbins Cotran Kumar. Pathological Basis of Disease

HEMATOLOJİK NEOPLAZİLER

MİYELOİD NEOPLAZİLER

- MİYELODİSPLASTİK SENDROMLAR
- AKUT MİYELOİD LÖSEMİLER
- KRONİK MİYELOPROLİFERATİF NEOPLAZİLER

LENFOMALAR

- LENFOBLASTİK LÖSEMİLER (T ve B Hücreli)
- HODGKİN DIŞI LENFOMALAR :
  1- OLGUN B HÜCRELİ LENFOMALAR - PLAZMA HÜCRELİ NEOPLAZİLER
  2- OLGUN T HÜCRELİ LENFOMLAR
- HODGKİN LENFOMA

HİSTİYOSİTİK NEOPLAZİLER