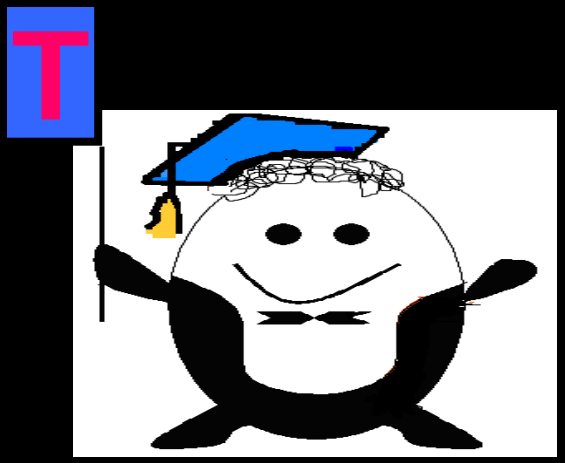
YENİ T HÜCRE ALT GRUPLARI



H. Barbaros Oral

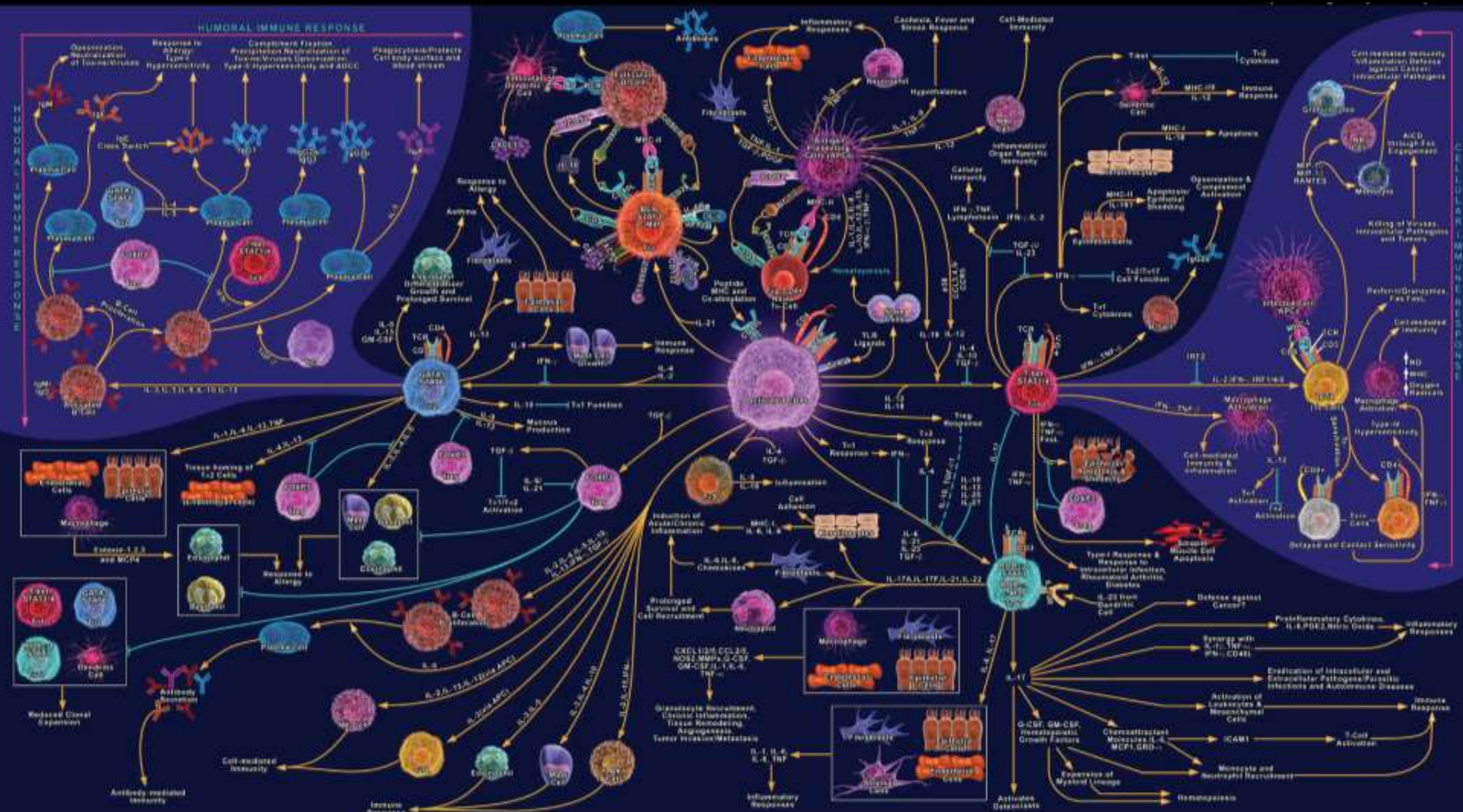
Uludağ Üniversitesi Tıp Fakültesi
Tıbbi Mikrobiyoloji Anabilim Dalı
İmmünoloji Bilim Dalı

1881 - ....

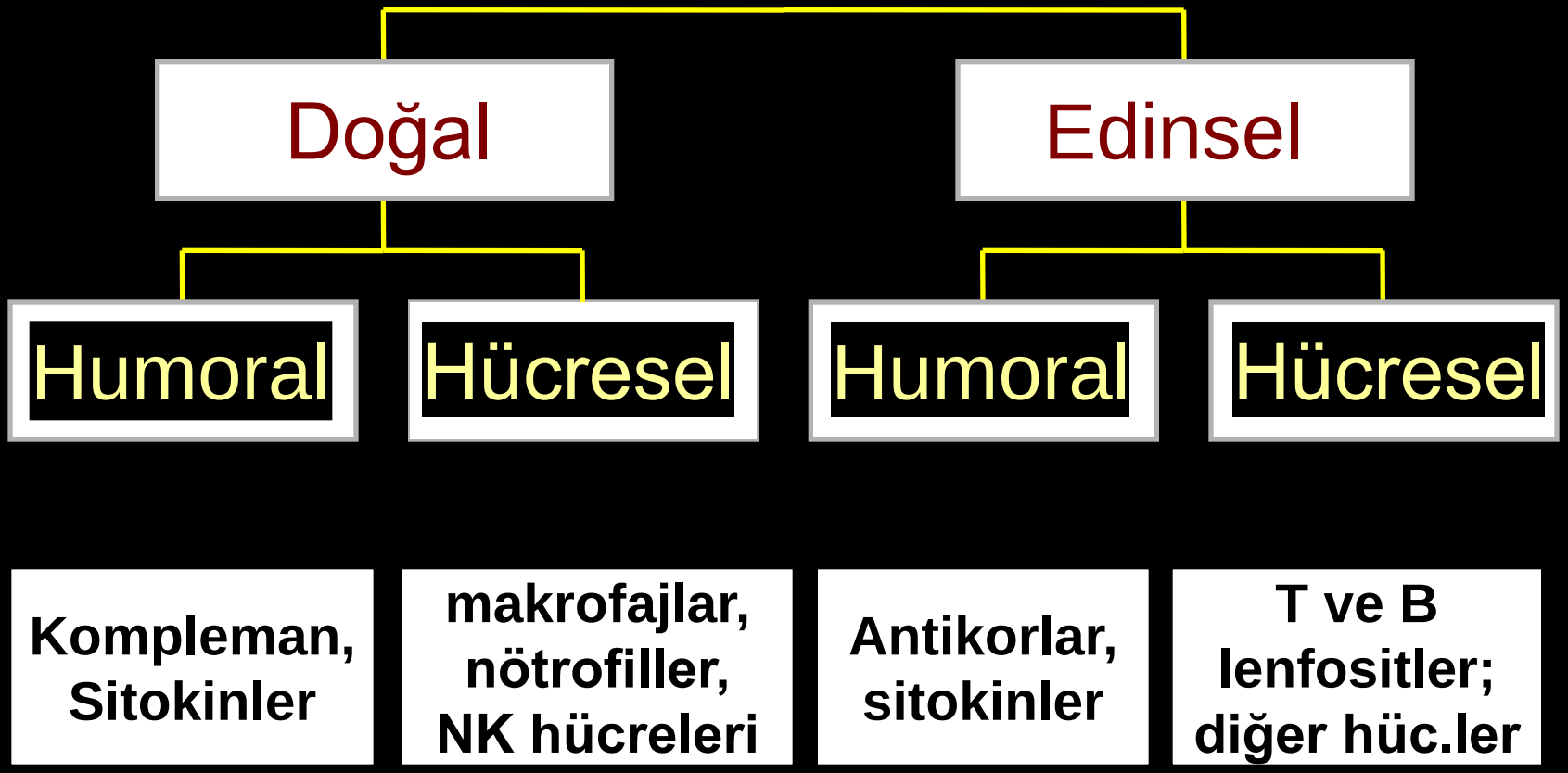
ŞÜKRAN GURUR VE ÖZLEMLE ANIYORUZ

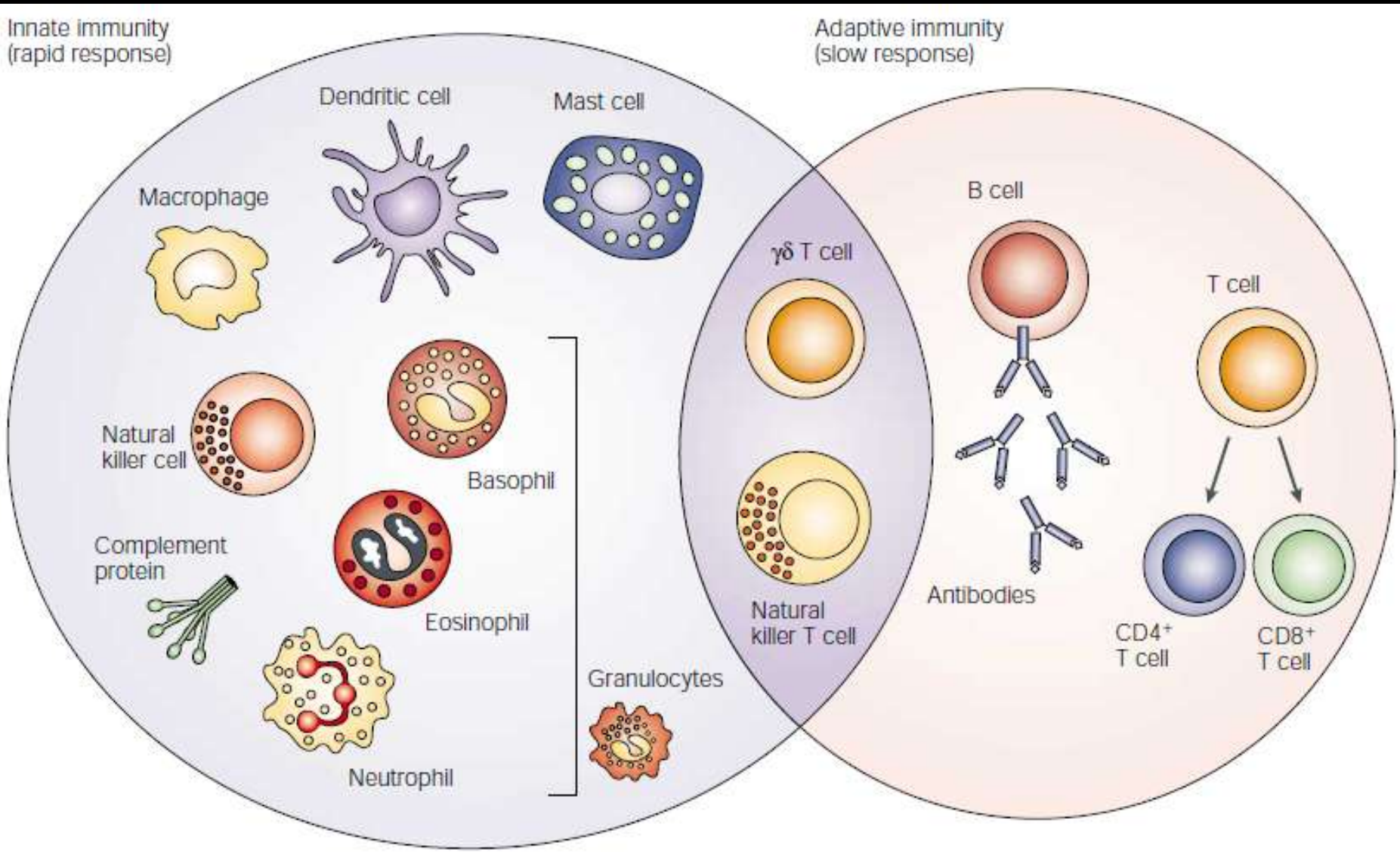
Sunum Planı

- İmmün Sisteme Genel Bakış ve T lenfositler
- Th1 ve Th2 kutuplaşması
- Sitotoksik T lenfositler
- Yeni T hücre alt grupları:
  - T düzenleyici (regülatör)
  - Th17
  - Th22
  - Th9
  - Foliküler T (Tfh)
- T hücre plastisitesi
- Özet


HUMORAL IMMUNE RESPONSE
Inflammatory Responses
Cell-Mediated Immunity
Immune Response
Hematopoiesis
Activates Osteoclasts
Reduced Clonal Expansion
Antibody mediated Immunity
Cell-mediated Immunity
Defense against Cancer?
ICAM1
T-Cell Activation
Monocyte and Neutrophil Recruitment

İmmün Sistemin Komponentleri

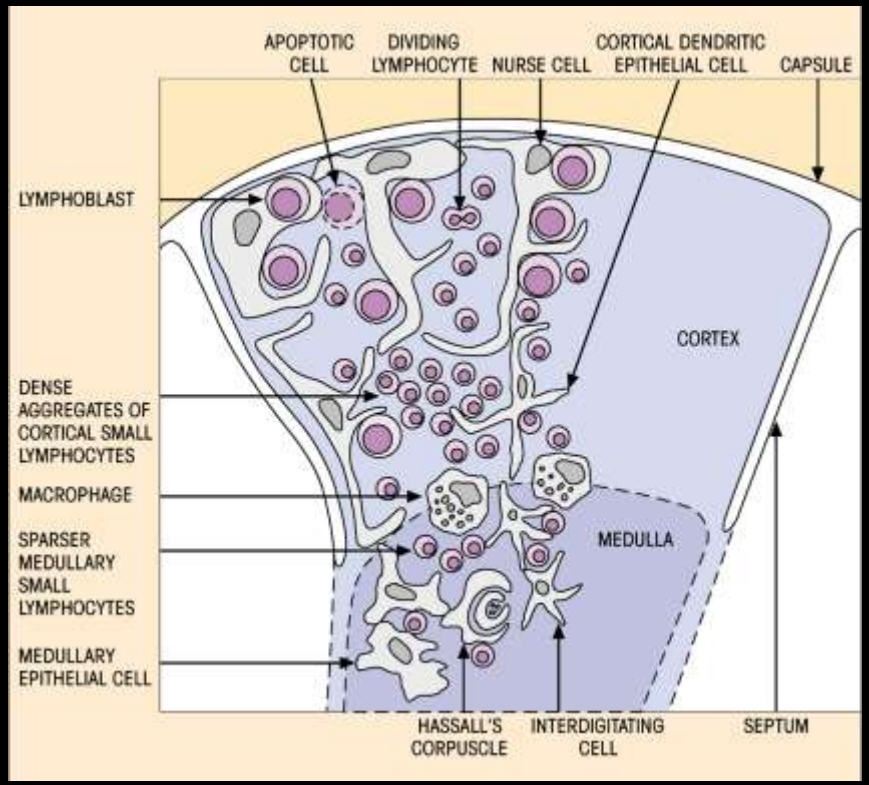



Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
γδ T cell
B cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Antibodies
Natural
killer T cell
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil

T LENFOSİTLER

- Kemikiliğinden göç ederek timus korteksine ulaşan prokürsör hücreler medüllaya doğru hareket ederken timik stroma tarafından yönlendirilen bir seri farklılaşmaya uğrarlar.

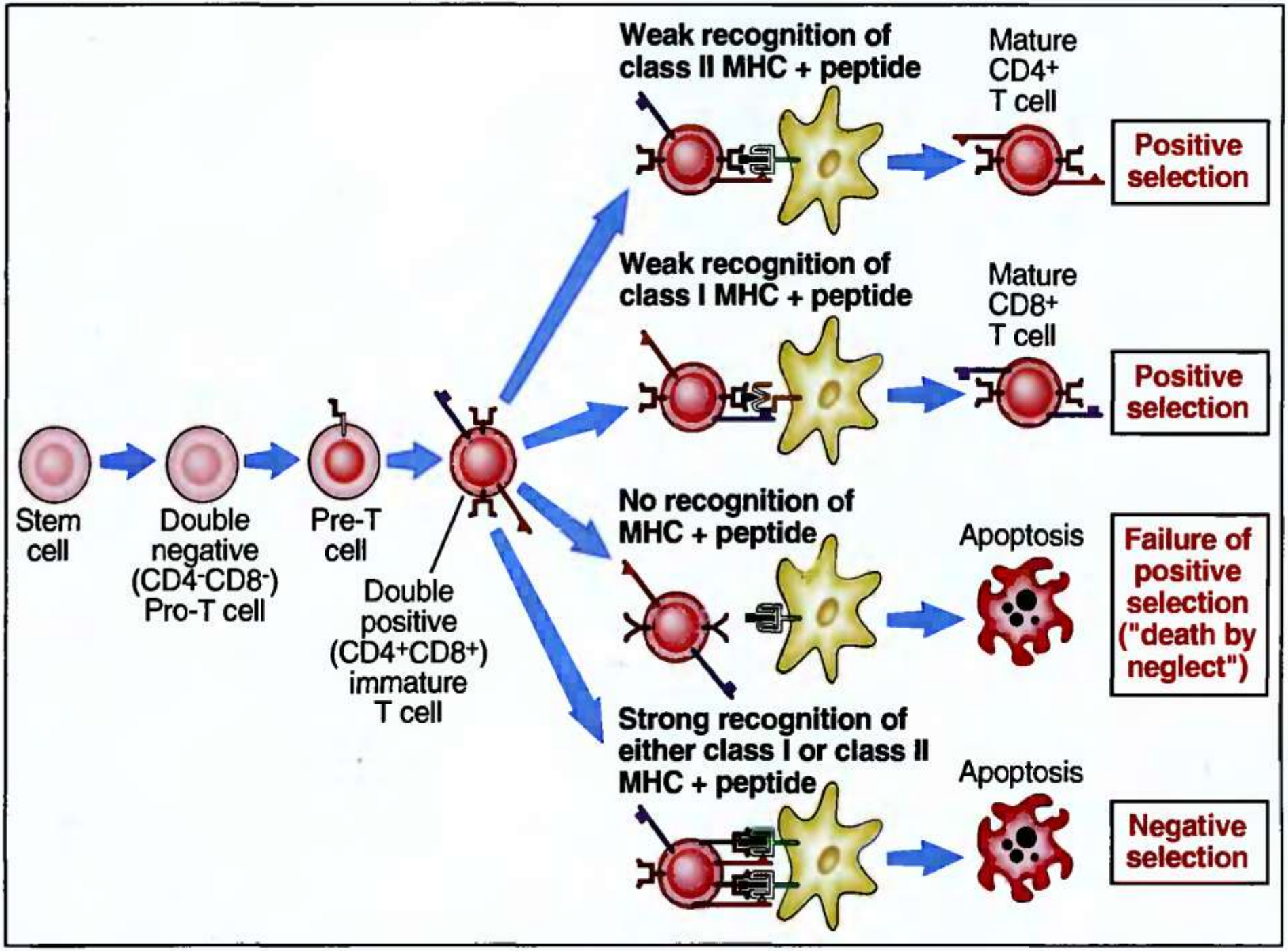
- Timusta T hücre olgunlaşmasına, timik epitel hücreleri, makrofajlar ve dendritik hücreler ortam sağlar.

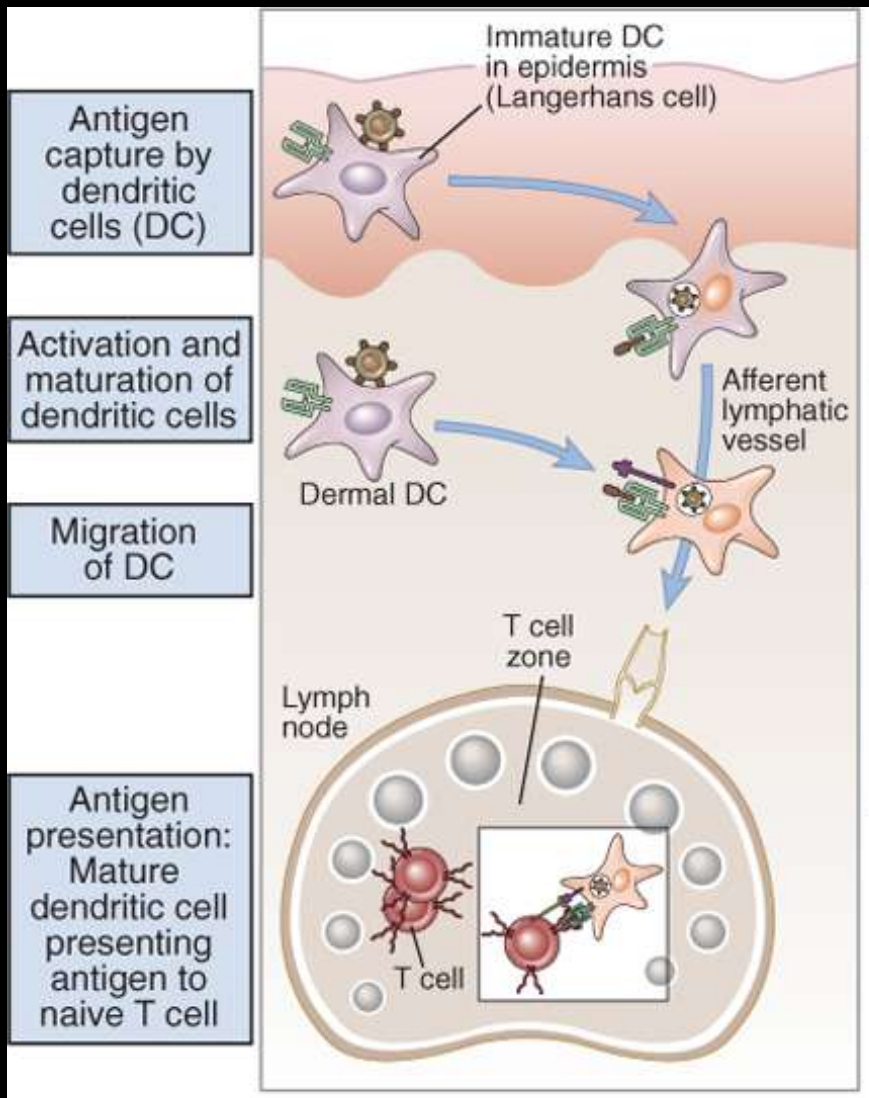


- **Bu farklılaşma sırasında hücreler glikoprotein tabiatında bir takım yüzey antijenlerini kazanırlar veya kaybederler.**

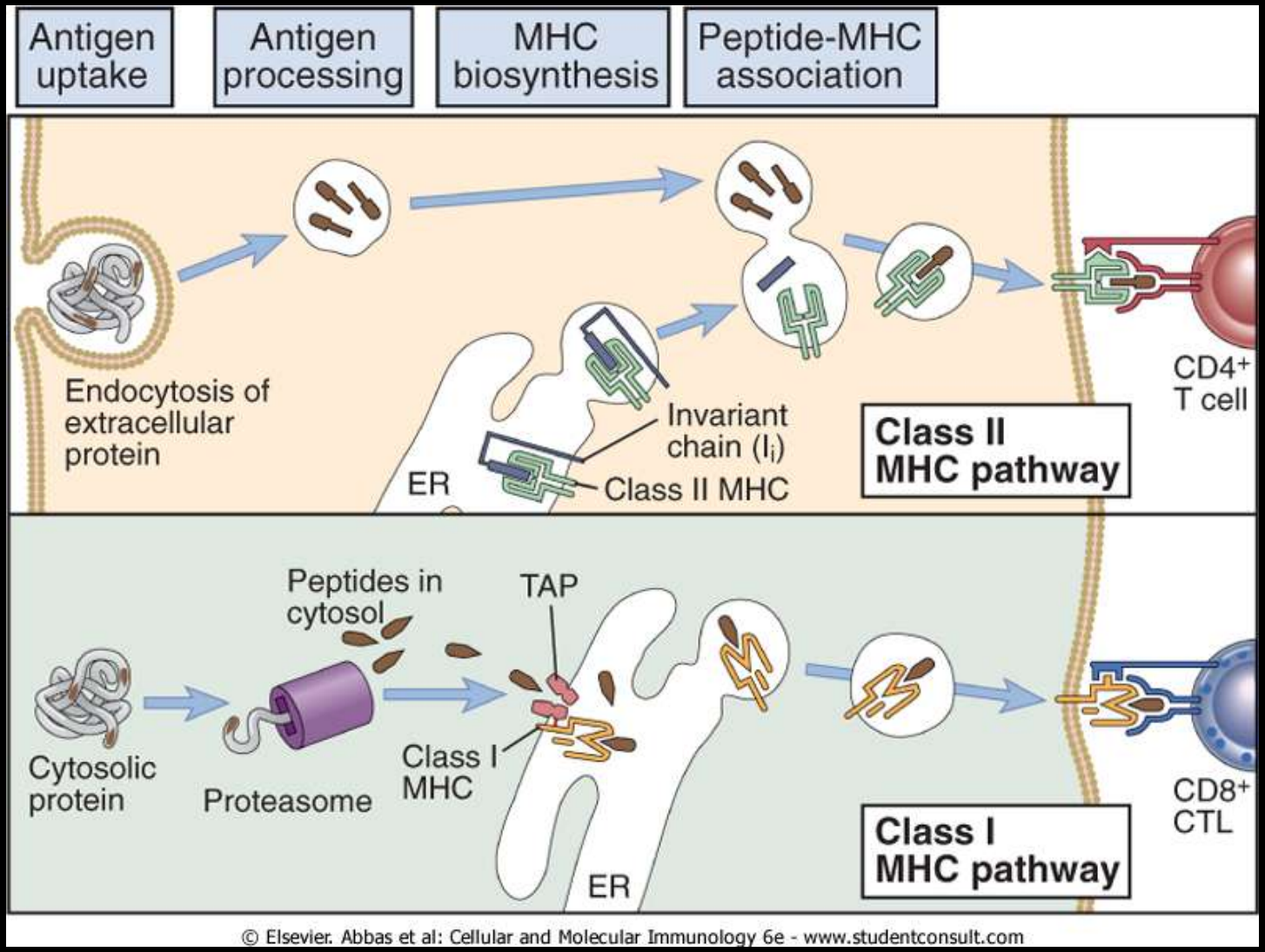
- **Apoptoza uğrayan timositlerin %75'i $CD4^+CD8^+$; %13'ü $CD4^-CD8^-$ hücrelerdir. Sonuçta, self MHC moleküllerine uygun (düşük) afinite gösteren T hücre reseptörü (TCR) eksprese eden timositlerin olgunlaşmasına ve timusu terk etmesine izin verilir. Olgun T hücreleri, kan dolaşımına geçerek sekonder lenfoid organlara ulaşırlar.**

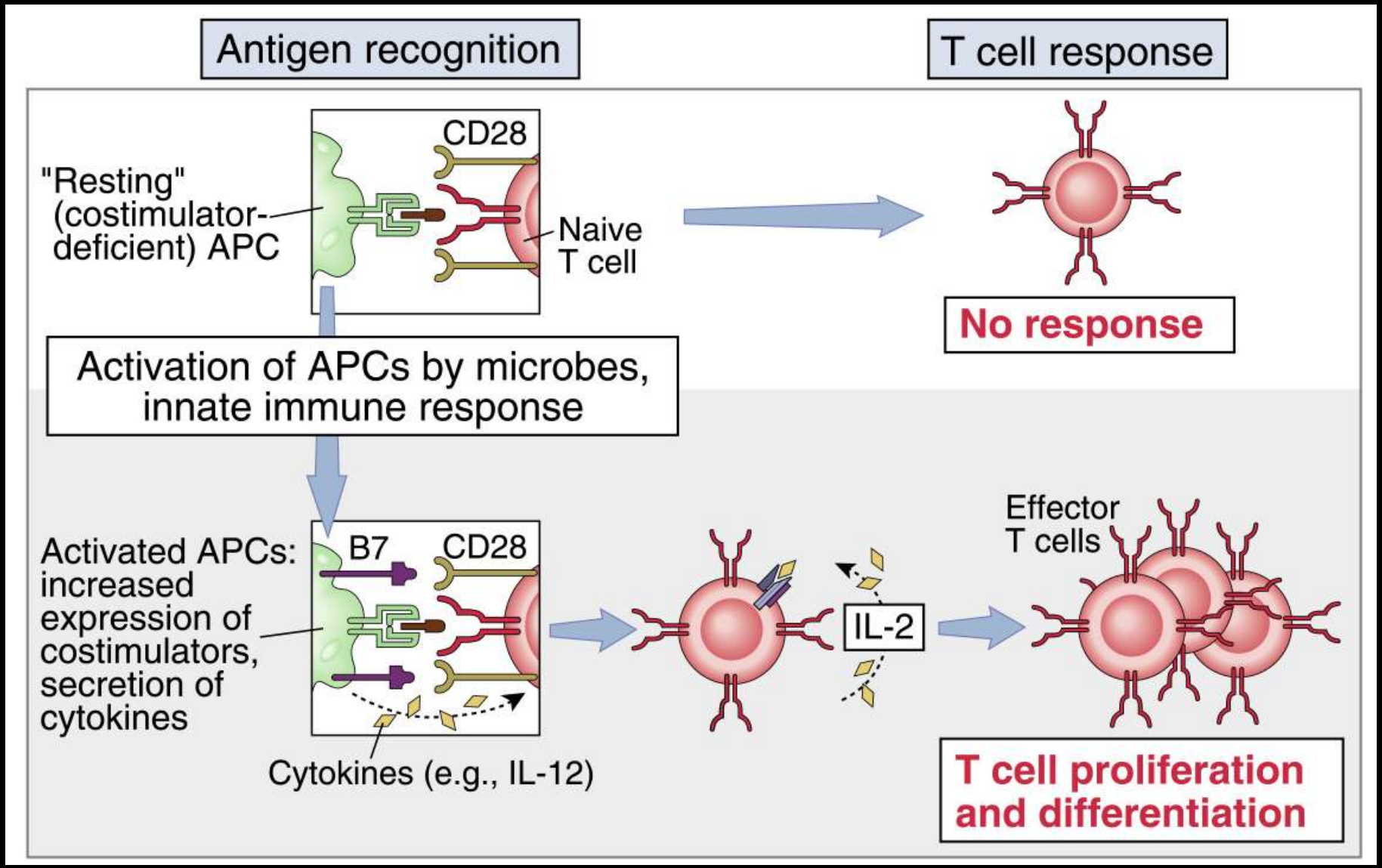
- **Dolaşımda bulunan lenfositlerin %60-80 kadarını T hücreleri oluşturur; bunların üçte ikisi CD4, üçte biri CD8 yüzey markerlerini taşır**


Stem cell
Double negative (CD4-CD8-) Pro-T cell
Pre-T cell
Double positive (CD4+CD8+) immature T cell
Weak recognition of class II MHC + peptide
Mature CD4+ T cell
Positive selection
Weak recognition of class I MHC + peptide
Mature CD8+ T cell
Positive selection
No recognition of MHC + peptide
Apoptosis
Failure of positive selection ("death by neglect")
Strong recognition of either class I or class II MHC + peptide
Apoptosis
Negative selection



	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	–
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	– or low	++
Class II MHC molecules		
Half-life	~10 hr	>100 hr
Number of surface molecules	~10^6	~7×10^6

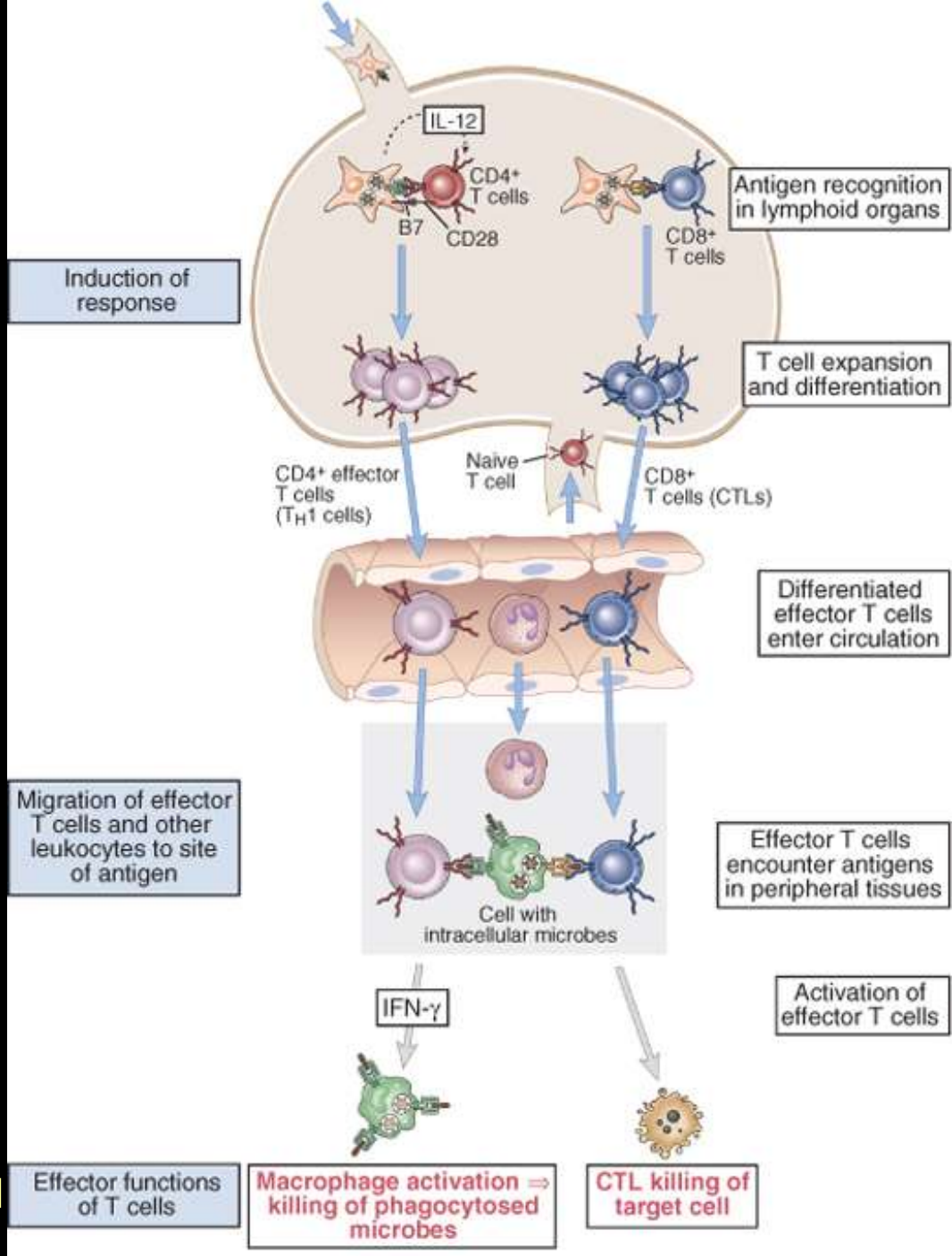


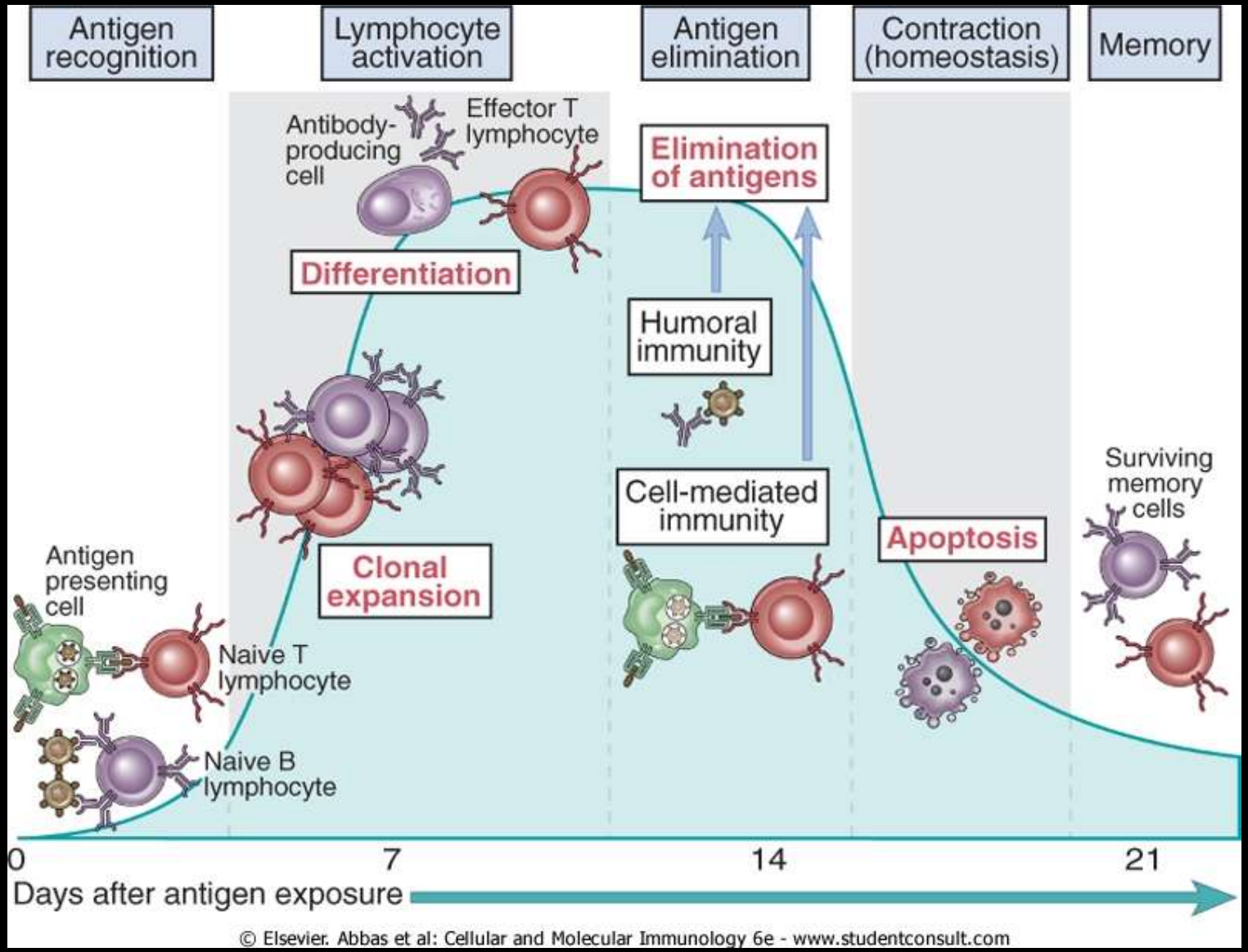

Antigen recognition
T cell response
"Resting" (costimulator-deficient) APC
CD28
Naive T cell
No response
Activation of APCs by microbes, innate immune response
Activated APCs: increased expression of costimulators, secretion of cytokines
B7
CD28
Cytokines (e.g., IL-12)
IL-2
Effector T cells
T cell proliferation and differentiation

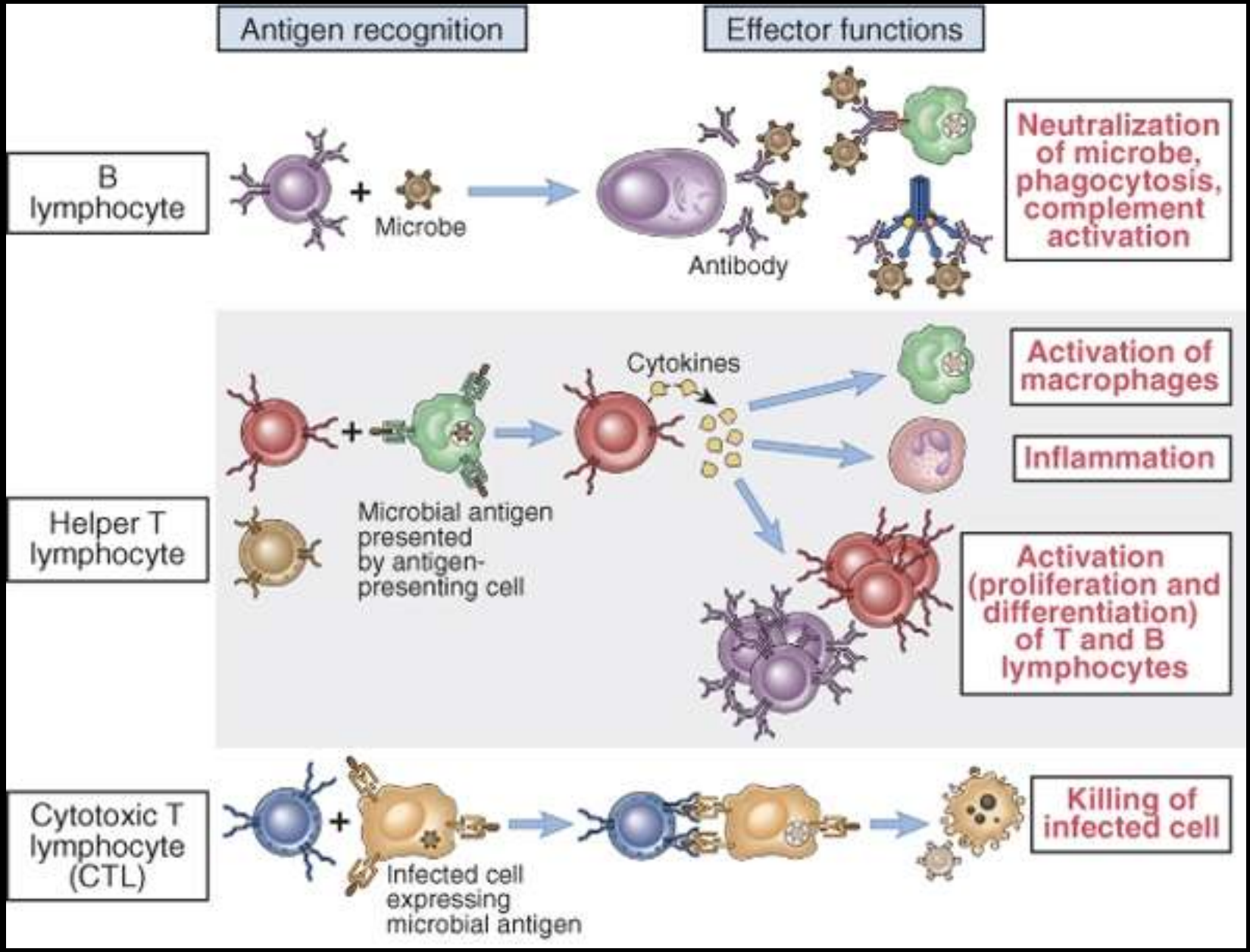
Efektör T hücre gelişimi

Migrasyon

Efektör T hücre aktivasyonu






Antigen recognition
Effector functions
B lymphocyte
Microbe
Antibody
Neutralization of microbe, phagocytosis, complement activation
Helper T lymphocyte
Cytokines
Activation of macrophages
Inflammation
Microbial antigen presented by antigen-presenting cell
Activation (proliferation and differentiation) of T and B lymphocytes
Cytotoxic T lymphocyte (CTL)
Infected cell expressing microbial antigen
Killing of infected cell

Tim Mossman & Robert L. Coffman

Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activiti

Dosya Düzen Görünüm Geçmiş Yer İmleri Araçlar Yardım

Two types of murine helper T cell clone... | Two types of murine helper T cell...

The Journal of Immunology, Vol 136, Issue 7 2348-2357, Copyright © 1986 by American Association of Immunologists

ARTICLES

Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins

TR Mosmann, H Cherwinski, MW Bond, MA Giedlin and RL Coffman

A panel of antigen-specific mouse helper T cell clones was characterized according to patterns of lymphokine activity production, and two types of T cell were distinguished. Type 1 T helper cells (TH1) produced IL 2, interferon-gamma, GM-CSF, and IL 3 in response to antigen + presenting cells or to Con A, whereas type 2 helper T cells (TH2) produced IL 3, BSF1, and two other activities unique to the TH2 subset, a mast cell growth factor distinct from IL 3 and a T cell growth factor distinct from IL 2. Clones representing each type of T cell were characterized, and the pattern of lymphokine activities was consistent within each set. The secreted proteins induced by Con A were analyzed by biosynthetic labeling and SDS gel electrophoresis, and significant differences were seen between the two groups of T cell line. Both types of T cell grew in response to alternating cycles of antigen stimulation, followed by growth in IL 2-containing medium. Examples of both types of T cell were also specific for or restricted by the I region of the MHC, and the surface marker phenotype of the majority of both types was Ly-1+, Lyt-2-, L3T4+, Both types of helper T cell could provide help for B cells, but the nature of the help differed. TH1 cells were found among examples of T cell clones specific for chicken RBC and mouse alloantigens. TH2 cells were found among clones specific for mouse alloantigens, fowl gamma-globulin, and KLH. The relationship between these two types of T cells and previously described subsets of T helper cells is discussed.

Bitti

Th1 ve Th2 Altgruplarının Keşfi

TABLE 1

T_H cell clones: specificities and lymphokine production[a]

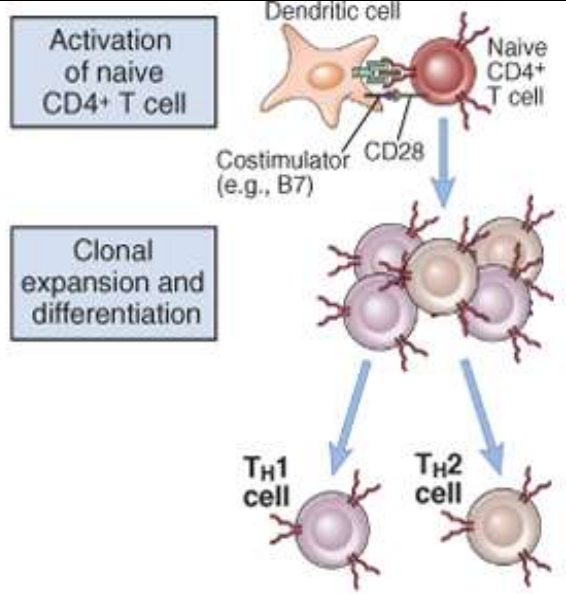
T Cell	Specificity	Strain	MHC Restriction	IL 2	IL 3	IL-4 MCGF2	IL-4 TCGF2	IFN-γ	IL-4 BSF1	IgE & IgG1 Enhancing Activities
T_H1										
LB2-1	CRC-1[b]	C57BL/6	I^b	+	+	−	−	+	−	−
LB19-1	CRC-2[c]	C57BL/6	I^b	+	+	−	ND[e]	+	ND	−
GK15-1	CRC-1	CBA/J	I^k	+	+	−	ND	+	ND	−
GK15-2	CRC-2	CBA/J	I^k	+	+	−	ND	ND	ND	ND
MD13-5	CRC-3[d]	BALB/c	ND	+	+	−	−	+	−	−
MD13-10	CRC-3	BALB/c	I^d	+	+	−	ND	+	−	−
MDK4.1	I^k	BALB/c	NA[f]	+	+	−	ND	+	ND	ND
M264-15	I^d	A.TL	NA	+	+	−	ND	+	−	ND
M264-20	I^d	A.TL	NA	+	+	−	ND	+	−	ND
M264-37	I^d	A.TL	NA	+	+	−	ND	+	−	ND
T_H2										
MI92-1	Spleen	C57BL/6	ND	−	+	+	+	−	+	+
CLLyl/9	Unknown	C57BL/6	ND	−	+	+	+	−	+	+
MDK3.1	I^k	BALB/c	NA	−	+	+	+	ND	+	ND
MDK5.1	$H2^k$	BALB/c	NA	−	+	+	+	ND	ND	ND
HD2-9	I^k	BALB/c	NA	−	+	+	+	ND	+	+
H39-34	Auto	CBA/J	I^k	−	+	+	+	−	+	+
H39-56	FGG	CBA/J	ND	−	+	+	+	−	+	+
H39-72	FGG	CBA/N	I^k	−	+	+	+	−	+	+
H39-119	FGG	CBA/J	ND	−	+	+	+	ND	ND	ND
H39-131	Auto	CBA/J	ND	−	+	+	+	−	+	+
M264-39	I^d	A.TL	NA	−	+	+	+	−	ND	ND
C71G1	$H2^k$	BALB/c	NA	−	+	+	+	−	ND	ND

[a] Lymphokine activities were evaluated by assays described in the text.
[b] CRBC, MHC alleles 2, 14, 15, 19, and 21, but not 13.
[c] CRBC, all MHC alleles.
[d] CRBC, MHC alleles 2, 13, 14, 15, and 19, but not 21.
[e] Not determined.
[f] Not applicable.

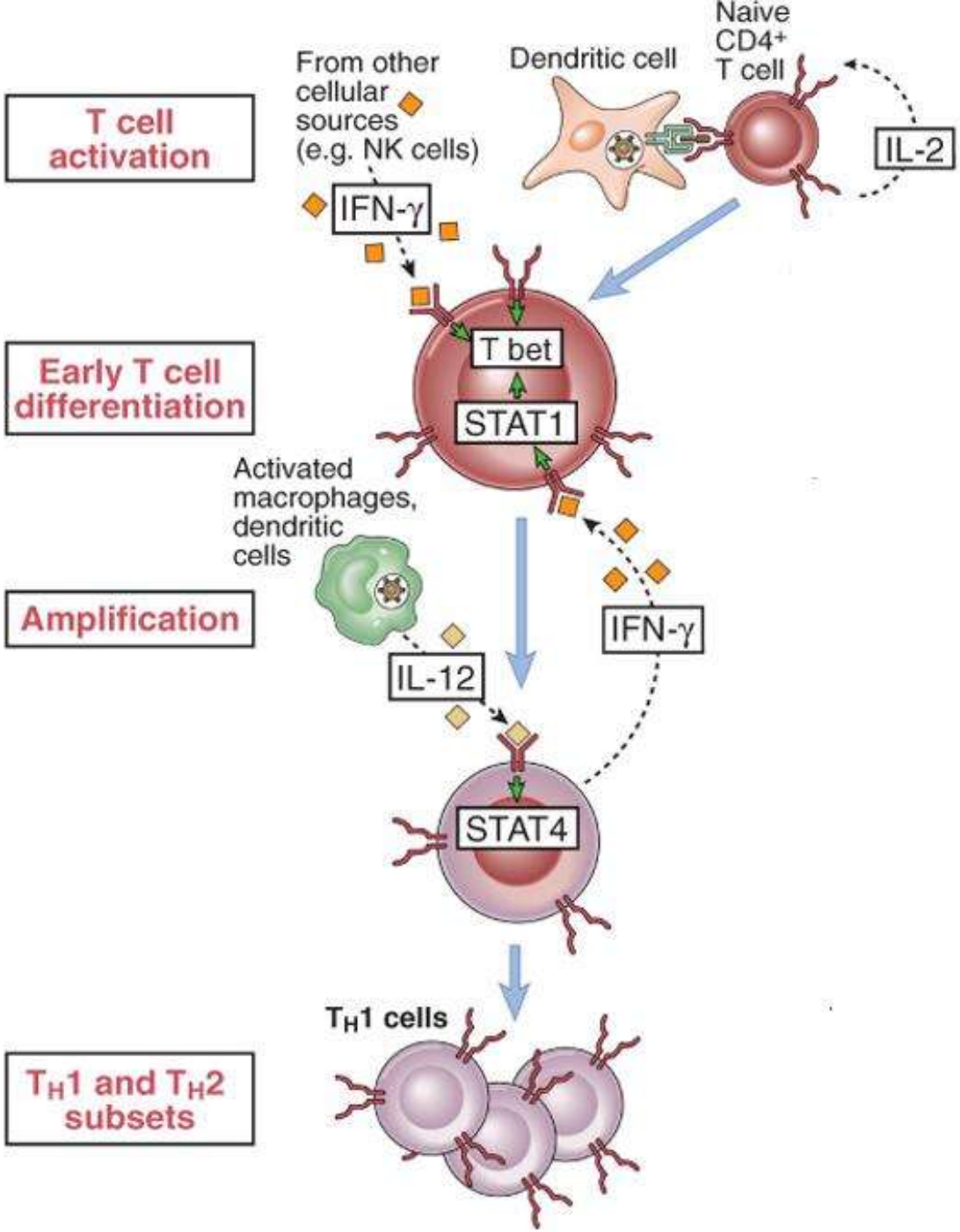
Mosmann TR etal. J. Immunol. 1986:13, 2348-57.

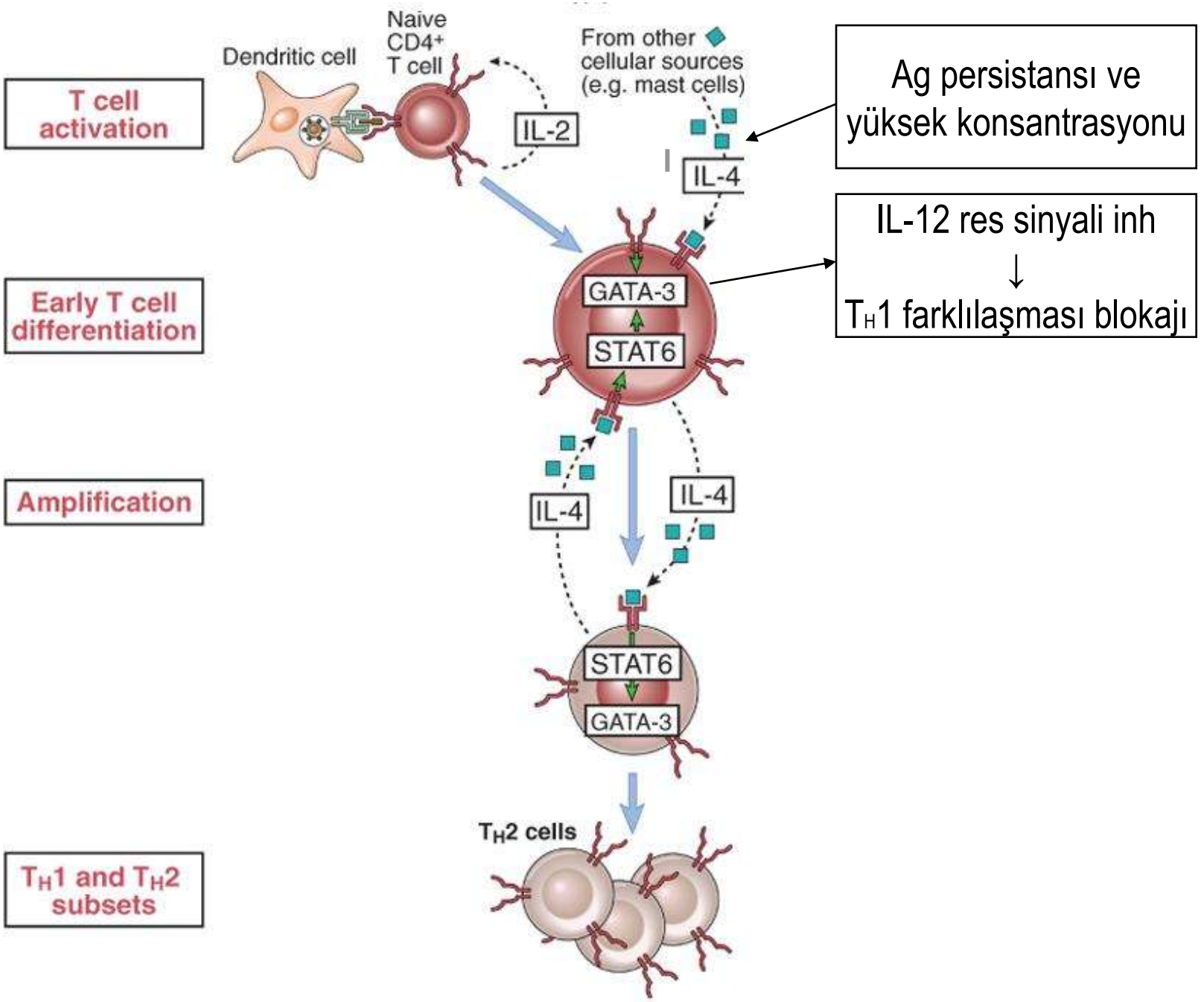
Differential Expression of Cytokines by Th1 and Th2 cells

Cytokine	Th1	Th2	Th0	Thp
IFN-γ	+	-	+	-
LT (TNFβ)	+	-		-
IL-2	+	-	+	+
IL-3	+	+	+	-
GM-CSF	+	+	+	-
TNF-α	+	+		
MIP-1α	+	+		
MIP-1β	+	+		
TCA-3	+	+		
IL-4	-	+	+	-
IL-5	-	+	+	-
IL-6	-	+		
IL-9	-	+		
IL-10	-	+		-
IL-13	-	+		



Property	T_H1 subset	T_H2 subset
Cytokines produced		
IFN-γ	+++	–
IL-4, IL-5, IL-13	–	+++
IL-10	+/–	++
IL-3, GM-CSF	++	++
Cytokine receptor expression		
IL-12R β chain	++	–
IL-18R	++	–
Chemokine receptor expression		
CCR4, CCR8, CXCR4	+/–	++
CXCR3, CCR5	++	+/–
Ligands for E- and P-selectin	++	+/–
Antibody isotypes stimulated	IgG2a (mouse)	IgE, IgG1 (mouse)/IgG4 (humans)
Macrophage activation	Classical	Alternative


T cell activation
From other cellular sources (e.g. NK cells)
IFN-γ
Dendritic cell
Naive CD4+ T cell
IL-2
Early T cell differentiation
T bet
STAT1
Activated macrophages, dendritic cells
Amplification
IL-12
IFN-γ
STAT4
TH1 and TH2 subsets
TH1 cells


T cell activation
Early T cell differentiation
Amplification
TH1 and TH2 subsets
Dendritic cell
Naive CD4+ T cell
IL-2
From other cellular sources (e.g. mast cells)
IL-4
GATA-3
STAT6
IL-4
IL-4
STAT6
GATA-3
TH2 cells
Ag persistansı ve yüksek konsantrasyonu
IL-12 res sinyali inh
↓
TH1 farklılaşması blokajı

Th1 hücre farklılaşması

3-12 gün (ort.7 gün) inkübasyon

- IL-12
- Anti-IL-4
- Anti-CD2, anti-CD3 ve anti-CD28

Th2 hücre farklılaşması

3-12 gün (ort.7 gün) inkübasyon

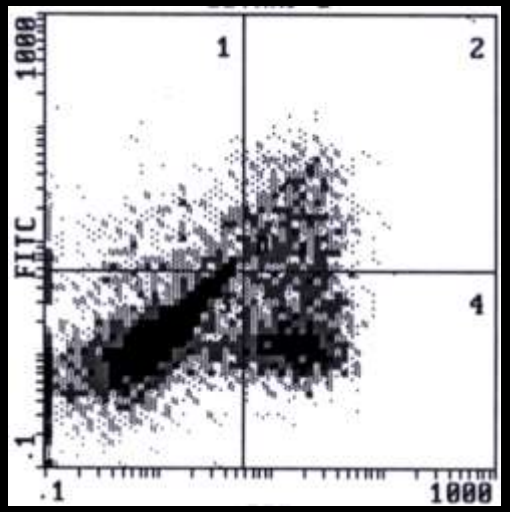
- IL-4
- Anti-IL-12
- Anti-CD2, anti-CD3 ve anti-CD28

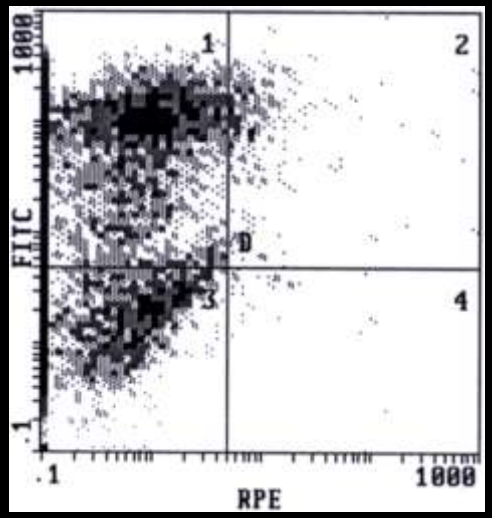
Th

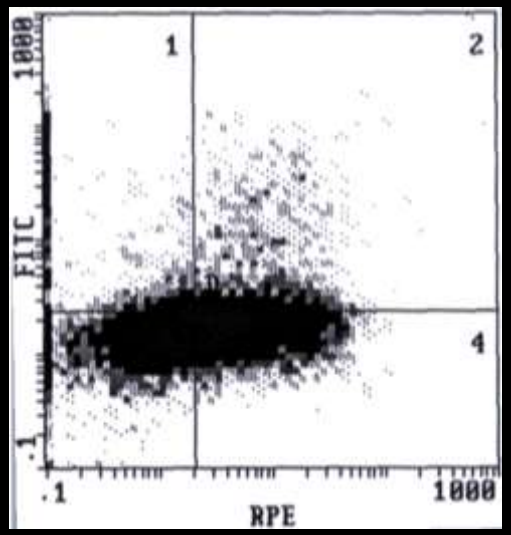
Th1

Th2

IFN-γ



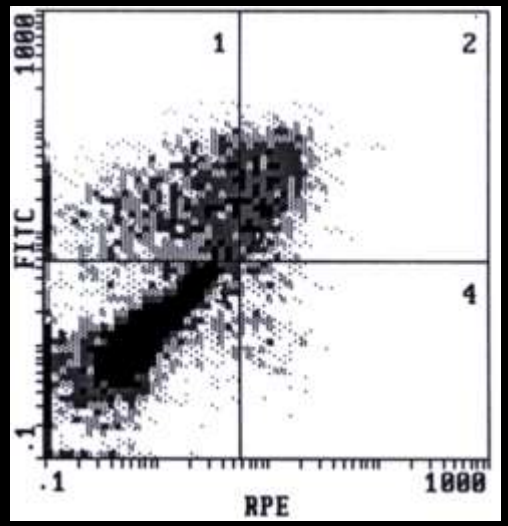


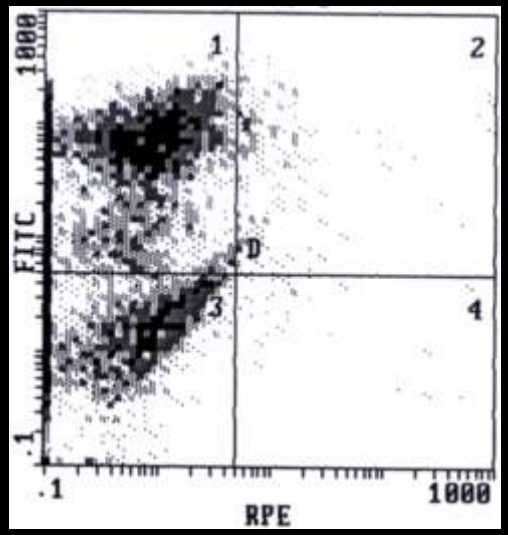


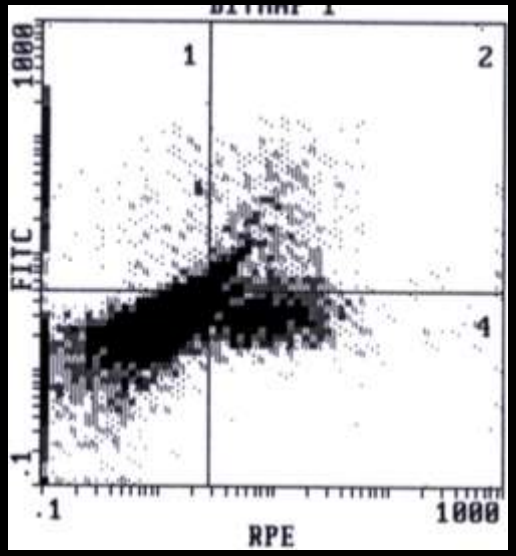
Tc

Tc1

Tc2







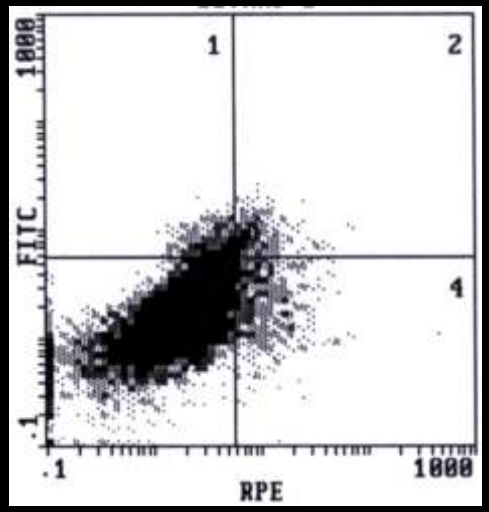
IL-13

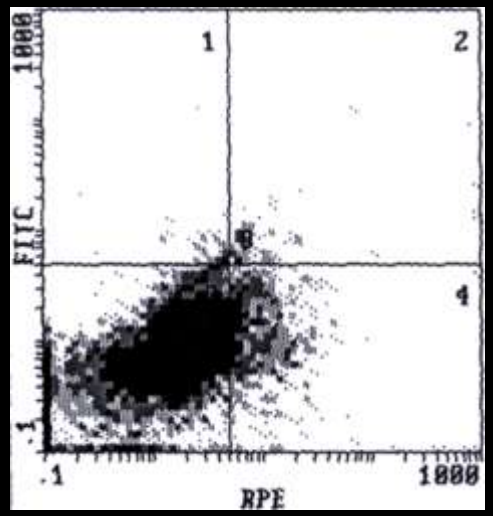
Th

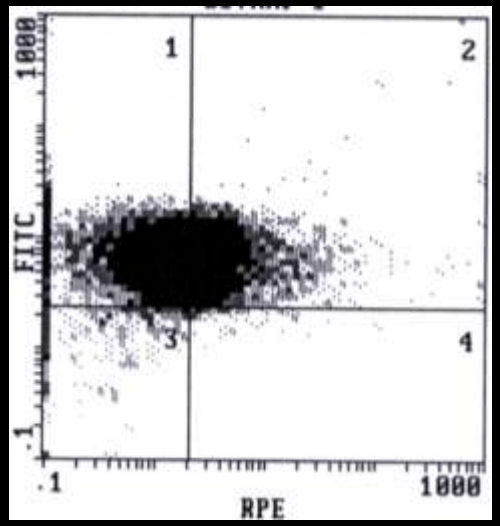
Th1

Th2

IL-4



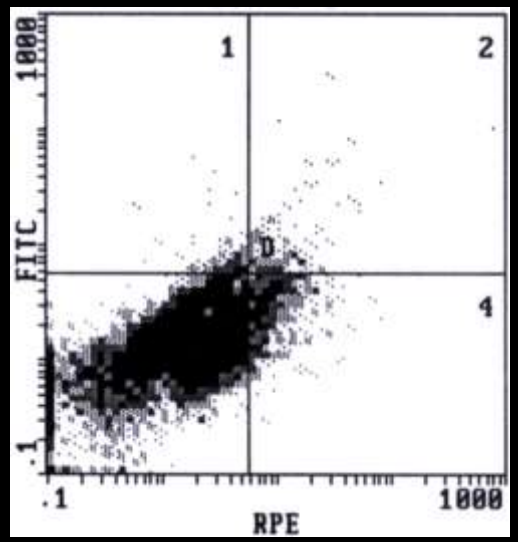


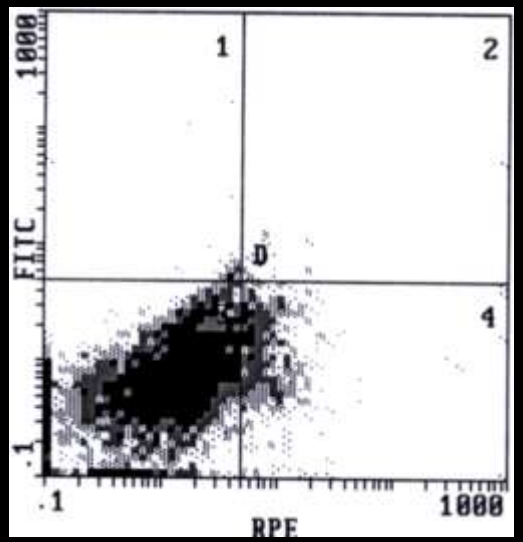


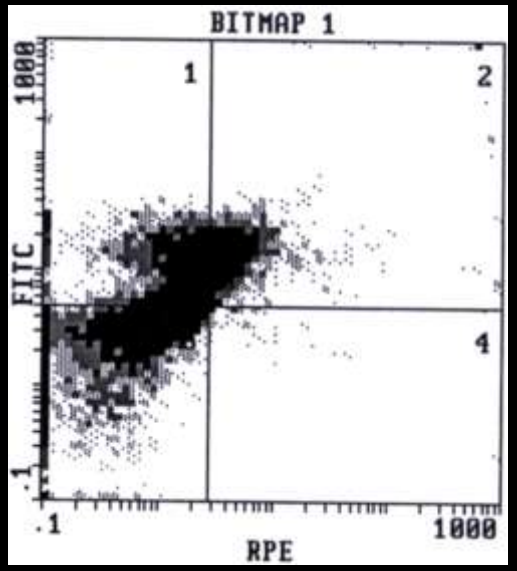
Tc

Tc1

Tc2



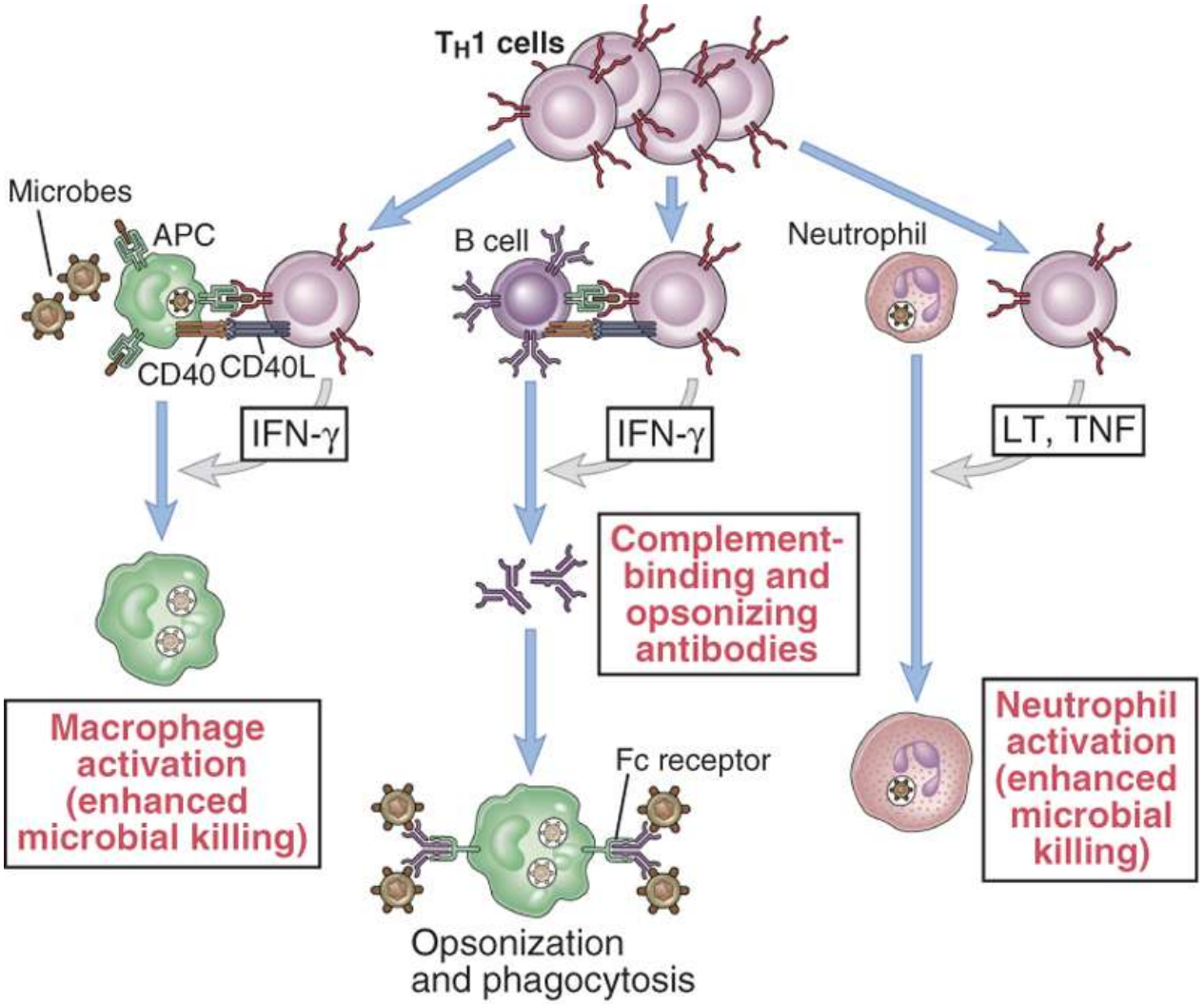




IL-10

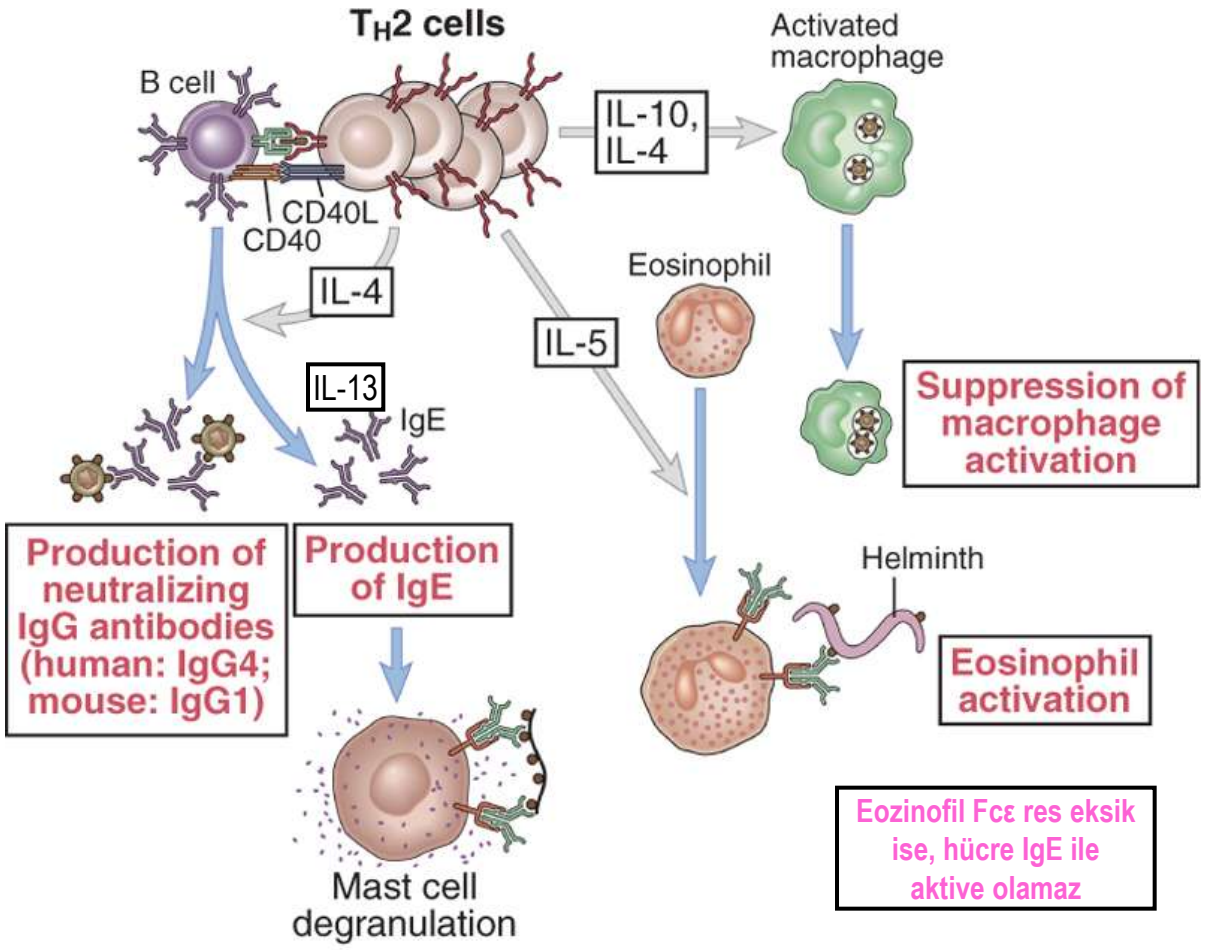
Th1 aracılı immün yanıt

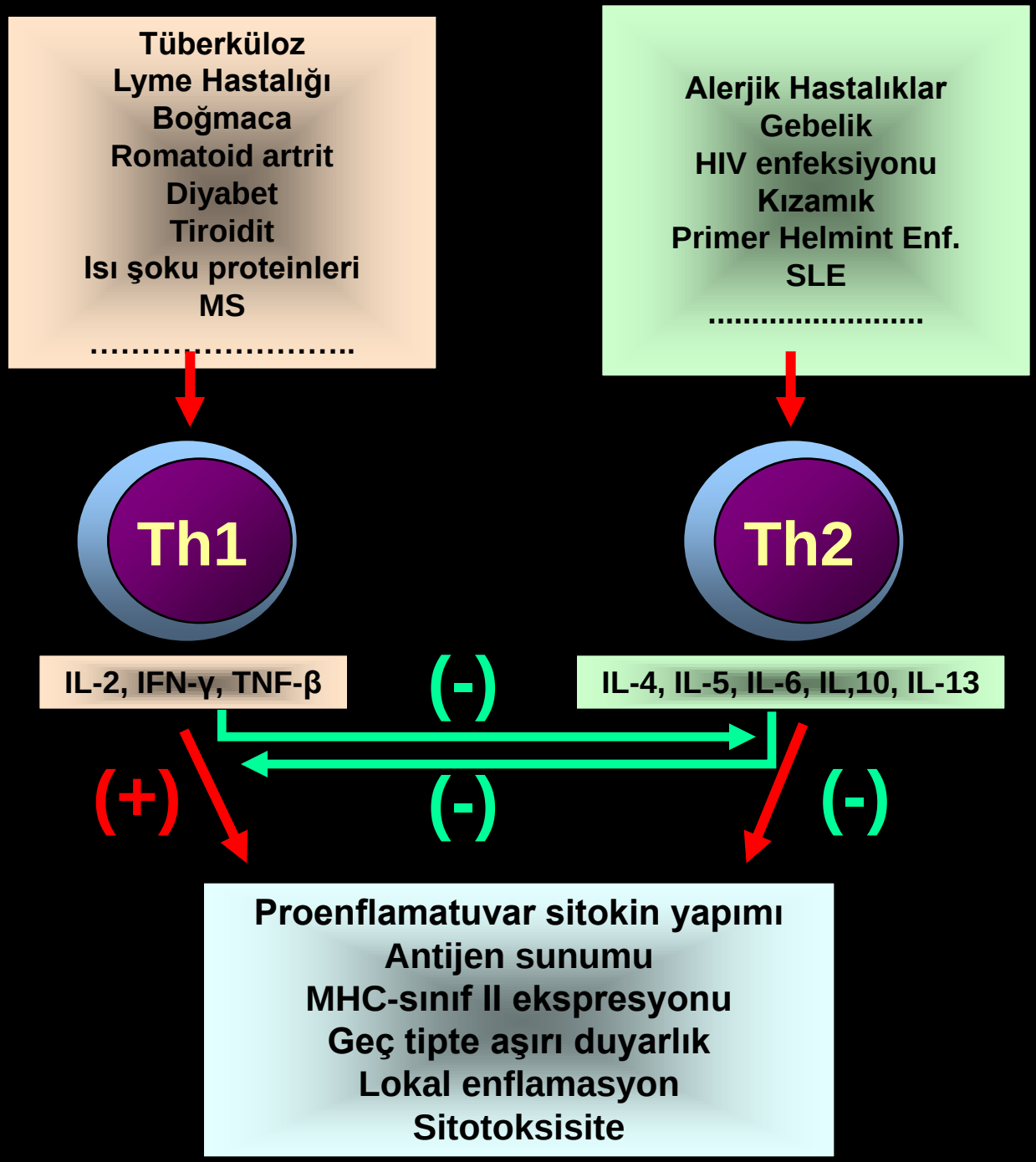
Temel işlevi; hücre içi mikroplara karşı fagosit aracılı savunma



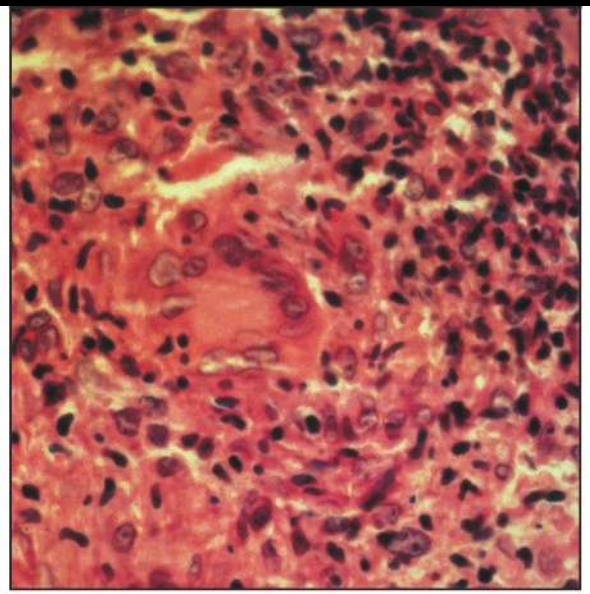
Th2 aracılı immün yanıt

Temel fonksiyonu, helmintik enfeksiyonlara karşı, IgE ve eozinofil/mast hücresi aracılı immün yanıtı güçlendirmek

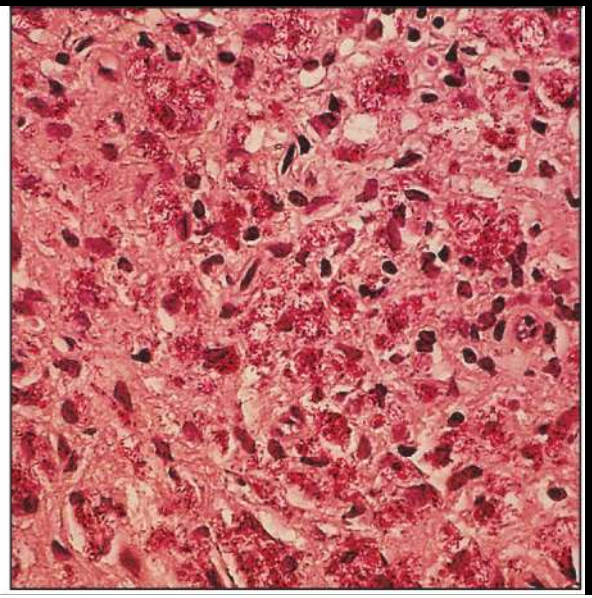


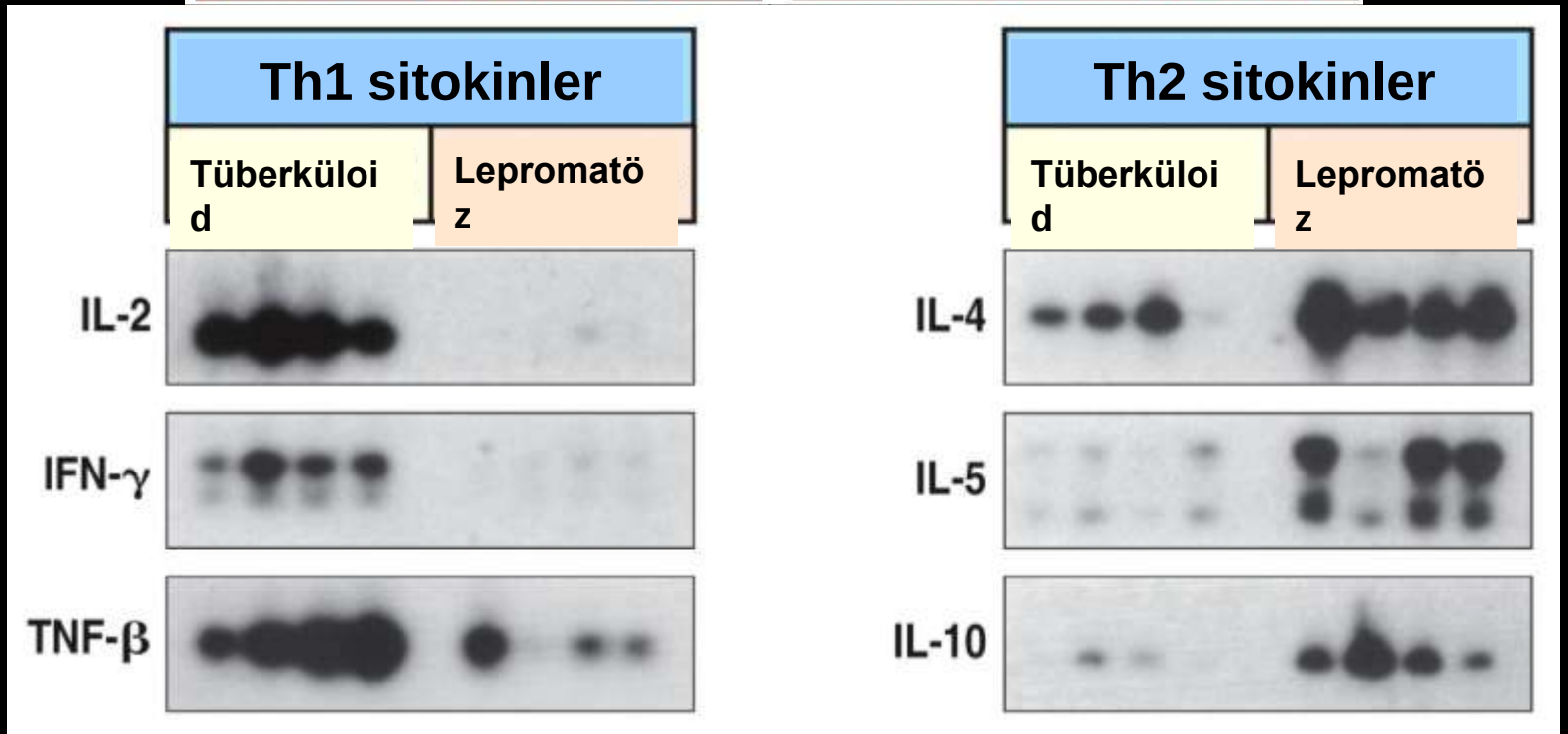

Tüberküloz
Lyme Hastalığı
Boğmaca
Romatoid artrit
Diyabet
Tiroidit
Isı şoku proteinleri
MS
.....
Alerjik Hastalıklar
Gebelik
HIV enfeksiyonu
Kızamık
Primer Helmint Enf.
SLE
.....
Th1
Th2
IL-2, IFN-γ, TNF-β
IL-4, IL-5, IL-6, IL,10, IL-13
(-)
(+)
(-)
(-)
Proenflamatuvar sitokin yapımı
Antijen sunumu
MHC-sınıf II ekspresyonu
Geç tipte aşırı duyarlık
Lokal enflamasyon
Sitotoksisite

Tüberküloid lepra



Lepromatöz lepra





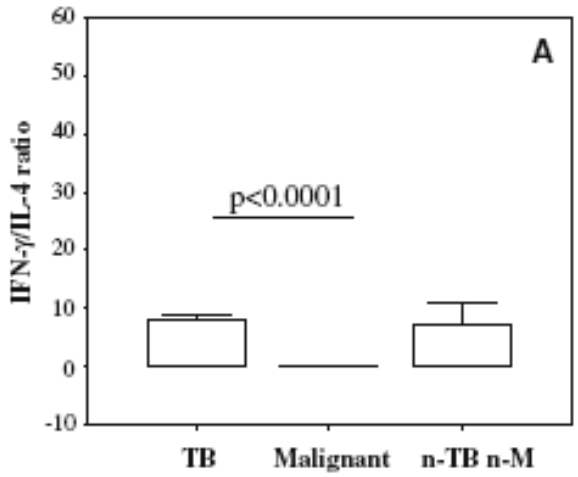
Lung (2008) 186:337–343
DOI 10.1007/s00408-008-9107-5

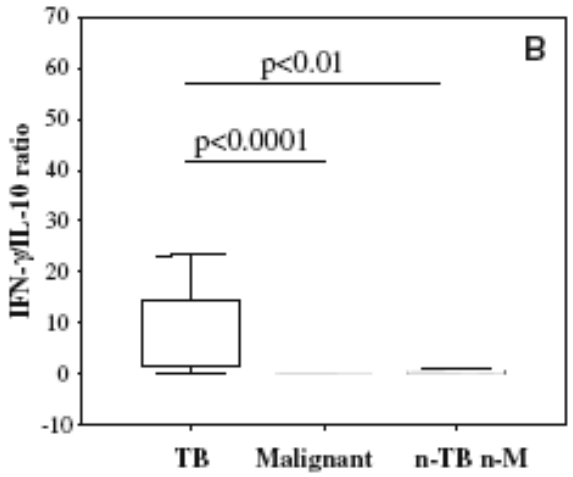
TUBERCULOSIS

Increased Pleural Soluble Fas Ligand (sFasL) Levels in Tuberculosis Pleurisy and Its Relation with T-helper Type 1 Cytokines

Ferah Budak · Esra Kunt Uzaslan · Şengül Cangür · Güher Göral · Haluk Barbaros Oral

Cytokines (pg/ml)	TB pleurisy	Malignant pleurisy	n-TB n-M pleurisy
IFN-γ	156.1 ± 32.4	1.2 ± 0.1***	47.5 ± 46.2***
IL-12p40	1053.6 ± 137.6	482.7 ± 81.5***	35.4 ± 16.2***
IL-18	1312.0 ± 124.2	1200.3 ± 112.1	726.1 ± 146.2*
IL-8	621.7 ± 121.3	295.0 ± 121.3**	173.4 ± 90.3*
TNF-α	40.1 ± 13.3	34.3 ± 14.4	5.3 ± 0.8***
IL-4	19.3 ± 9.8	38.0 ± 7.2***	25.4 ± 12.8
IL-10	22.2 ± 5.1	23.9 ± 4.3	15.3 ± 7.1





Brucella abortus L7/L12 Recombinant Protein Induces Strong Th1 Response in Acute Brucellosis Patients

Esra Kazak[1], Sergio Costa Oliveira[2], Güher Goral[3], Halis Akalin[1], Emel Yilmaz[1], Yasemin Heper[1], Haluk Barbaros Oral[3*]

[1]Department of Infectious Diseases and Clinical Microbiology, Uludağ University Faculty of Medicine, Bursa,Turkey, [2]Department of Biochemistry and Immunology, Federal University of Minas Gerais, Brazil, [3]Department of Medical Microbiology, Immunology Unit, Uludağ University Faculty of Medicine, Bursa,Turkey

ABSTRACT

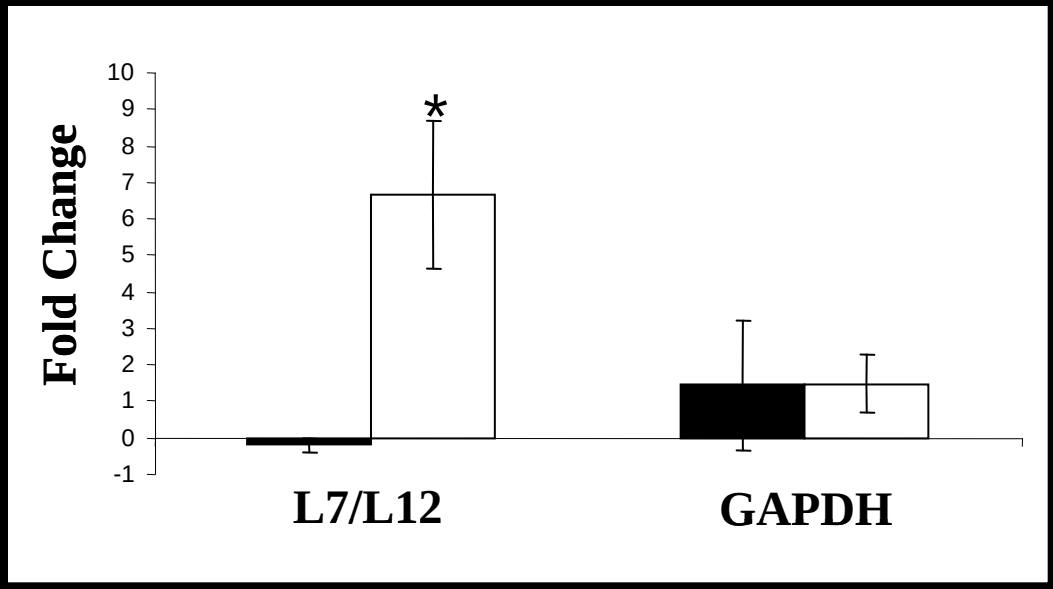
Background: Because of high morbidity of the brucellosis in humans and the potential use of the microorganism as an agent of biologic warfare, protection of effective vaccines and specific diagnostic reagents become necessary to eradicate brucellosis. **Objective:** In this study we aimed to investigate the cytokine responses and changes in peripheral blood lymphocyte subgroups of acute brucellosis patients in response to L7/L12 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) recombinant proteins derived from *Brucella abortus*. **Methods:** levels of IFN-γ, IL-4 and IL-10 secreted from PBMCs of 25 acute brucellosis patients and 15 healthy controls, stimulated with Phytohemagglutinin (PHA), L7/L12 or GAPDH were measured by ELISA. Furthermore alterations in lymphocyte subgroups in response to these *Brucella* antigens were determined by flow cytometry. **Results:** Extracellular IFN-γ levels were found to be elevated after stimulation with L7/L12 in patients with acute brucellosis, whereas no significant changes were found in IL-4 and IL-10 levels. Similar data was also obtained with GAPDH, but the stimulation of IFN-γ production was not observed in all patients and was not as strong as that observed for L7/L12. Moreover, when the distribution of lymphocytes subgroups ($CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD4^+CD25^+$, $CD3^+CD69^+$ and $CD3^+CD152^+$) was evaluated, it was found that the stimulation with L7/L12 and GAPDH only led to an increase in the percentage of $CD3^+CD69^+$ lymphocytes. **Conclusion:** These data indicate that *Brucella abortus* L7/L12 or GAPDH induce a Th1 type of immune response in acute brucellosis patients. Additionally, these recombinant proteins, especially L7/L12, may be used in new vaccine preparations and diagnostic tests.

Keywords: Brucellosis, Cytokine, Recombinant Proteins, T Lymphocytes

---

*Corresponding Author: Dr. Haluk Barbaros Oral, Department of Medical Microbiology, Immunology Unit, Uludağ University Faculty of Medicine, Bursa, TÜRKİYE, Tel: (+) 90 224 295 41 14, Fax: (+) 90 224 442 49 41, e-mail: oralb@uludag.edu.tr

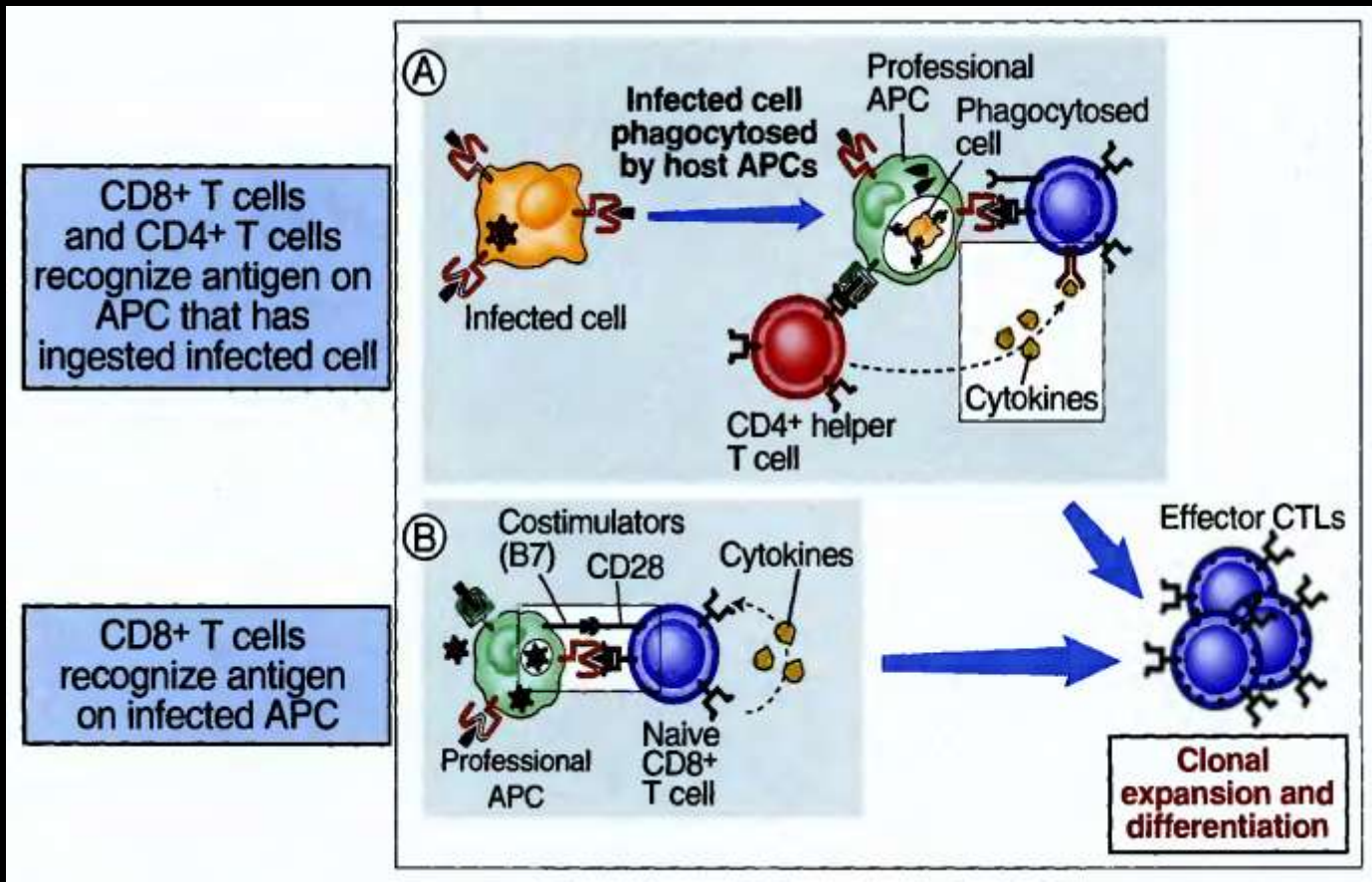
	IFN–γ (pg/ml)		IL-4 (pg/ml)		IL-10 (pg/ml)	
	Patients	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**
US	58.3±28,4	637.4±274.6	U	U	292.1±65.3	276.9±31.4
PHA	5273.8±869.8*	4618.3±1236.2***	71.7±7.8	96.9±8.3	579.3±31.8 **	585.1±44.5**
L7/L12	776.9±200.1**	418.4 ±113.7	U	U	638.6±48.5*	552.8±72.3*
GAPDH	274.0±84.5*	568.0±314.8	U	U	718.8±72.6*	696.9±70.8*

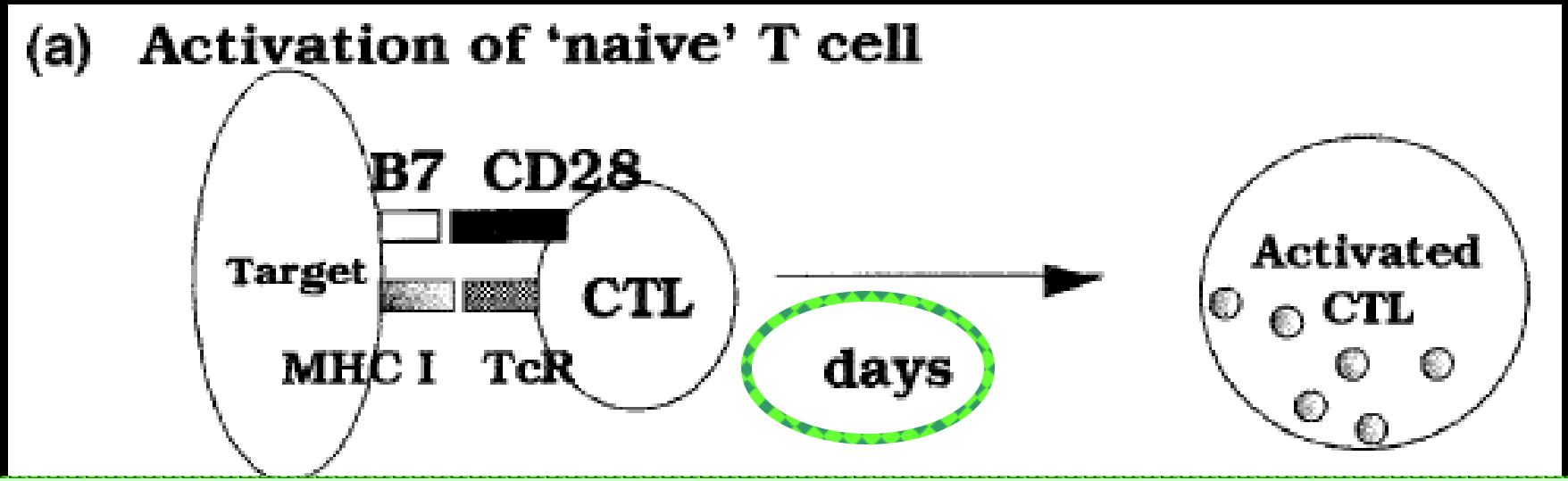


Kazak E et al. Iran. J. Immunol. 2010: 7, 132-9.

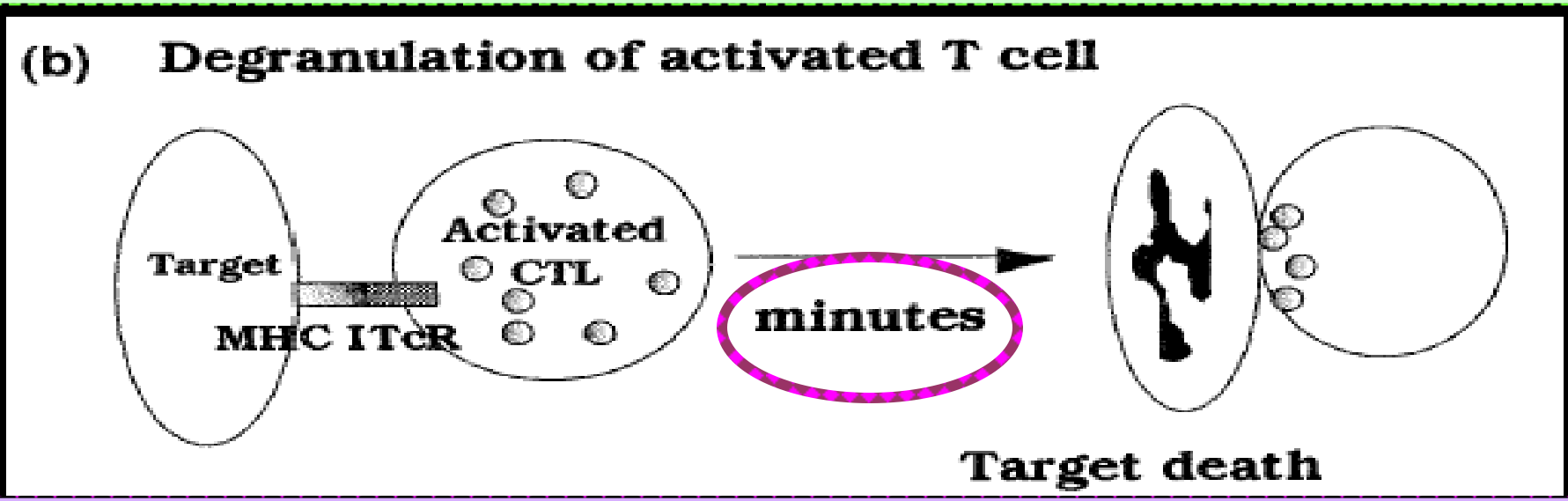
Sitotoksik T lenfositler

- **CTL'ler MHC sınıf I molekülleri ile ilişkili yabancı peptit Ag'leri eksprese eden hedef hücreleri tanıyan ve öldüren T hücreleridir.**

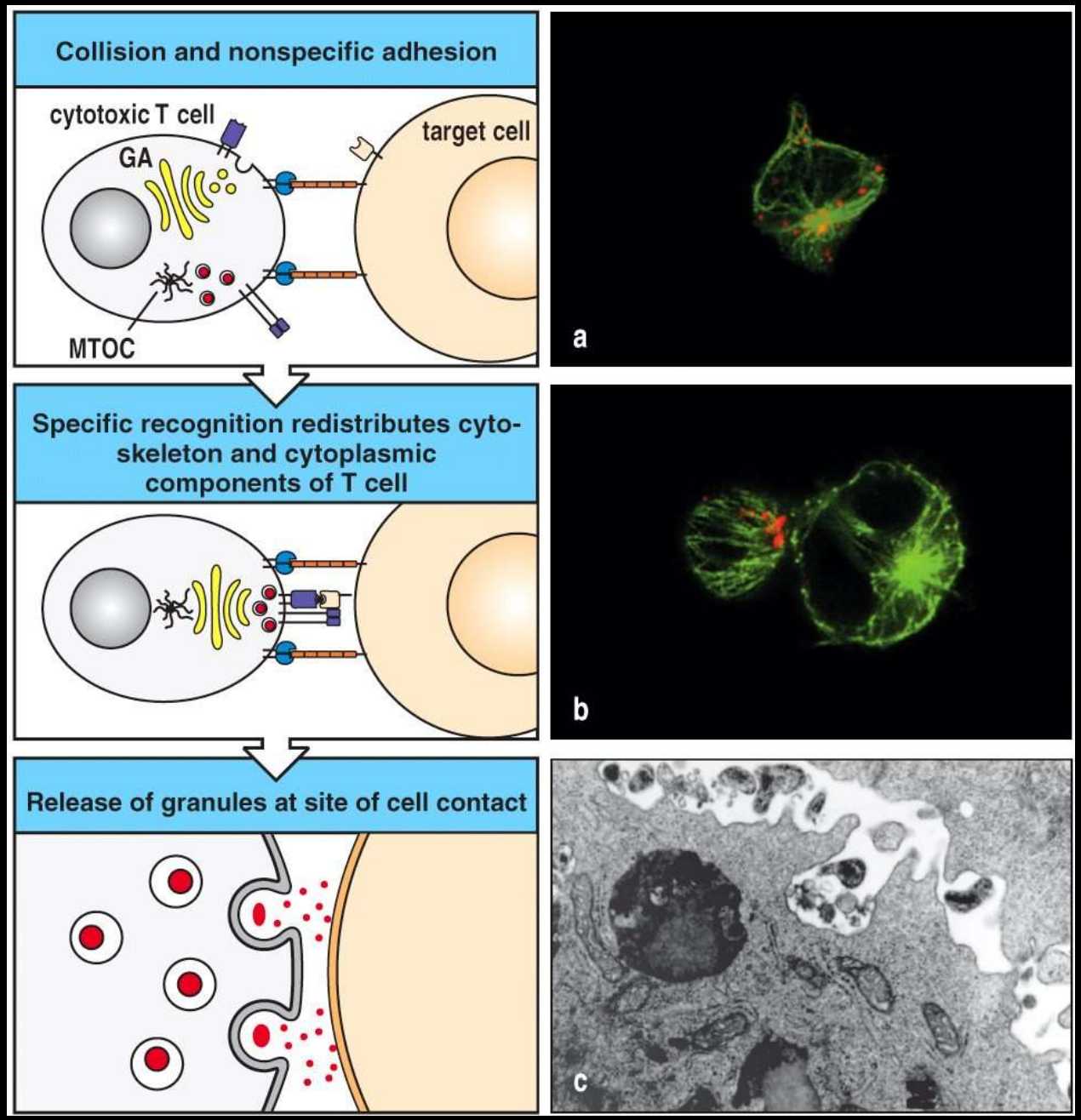


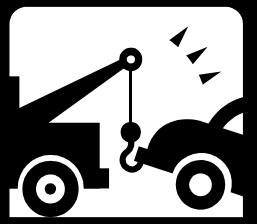


(a) Lenf Nodlarında: Naif $CD8^+$ T lenfositlerin APC tarafından ilk aktivasyonu : Yabancı Ag+MHC+kostimülasyon---- TCR



(b) Periferde: Aktive CTL'ler hedefleri "öldürür". Yabancı Ag+MHC---- TCR

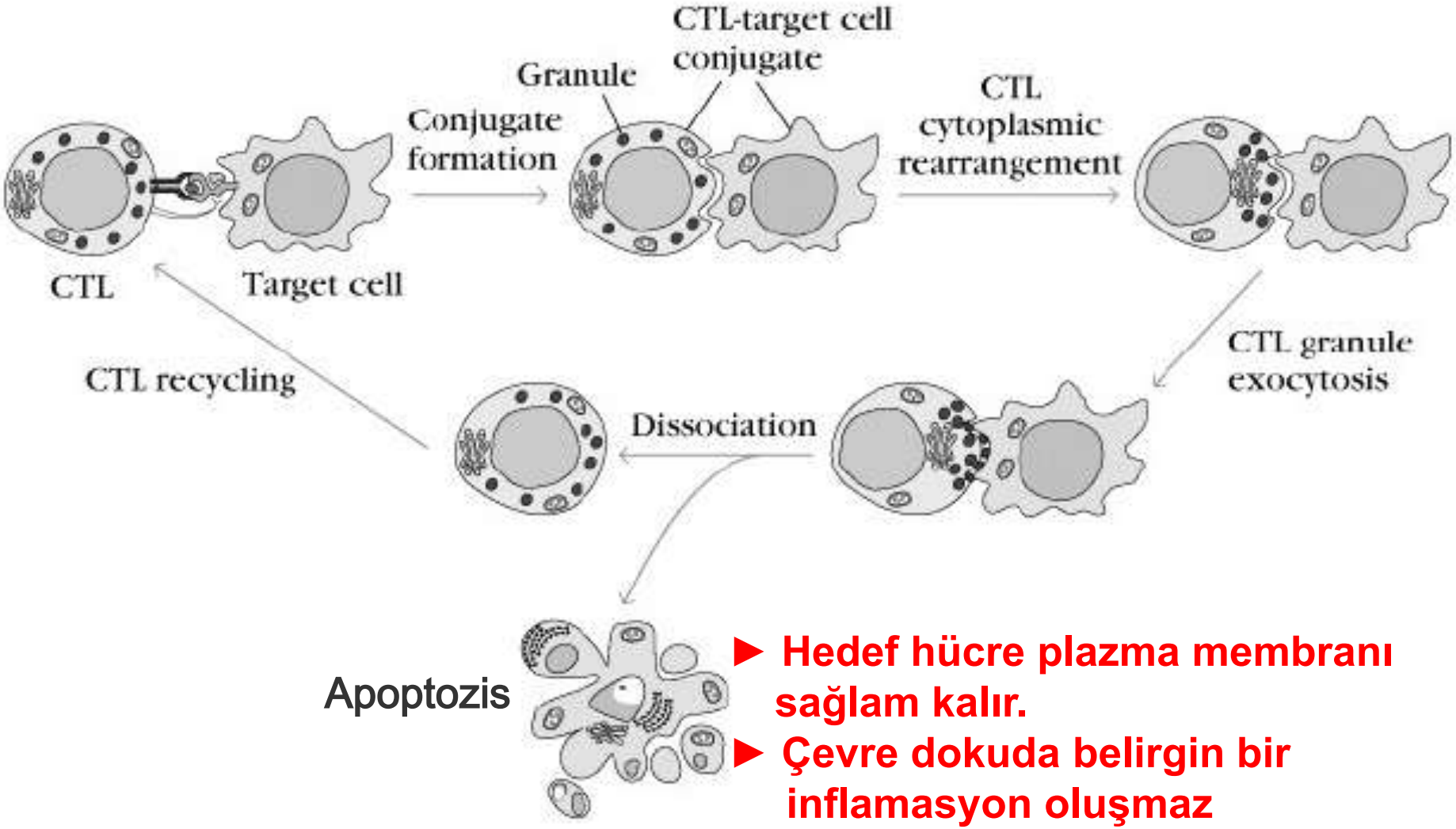




TCR ile Ag'nin tanınmasından sonra "perforin granzim" yolu aktive olur

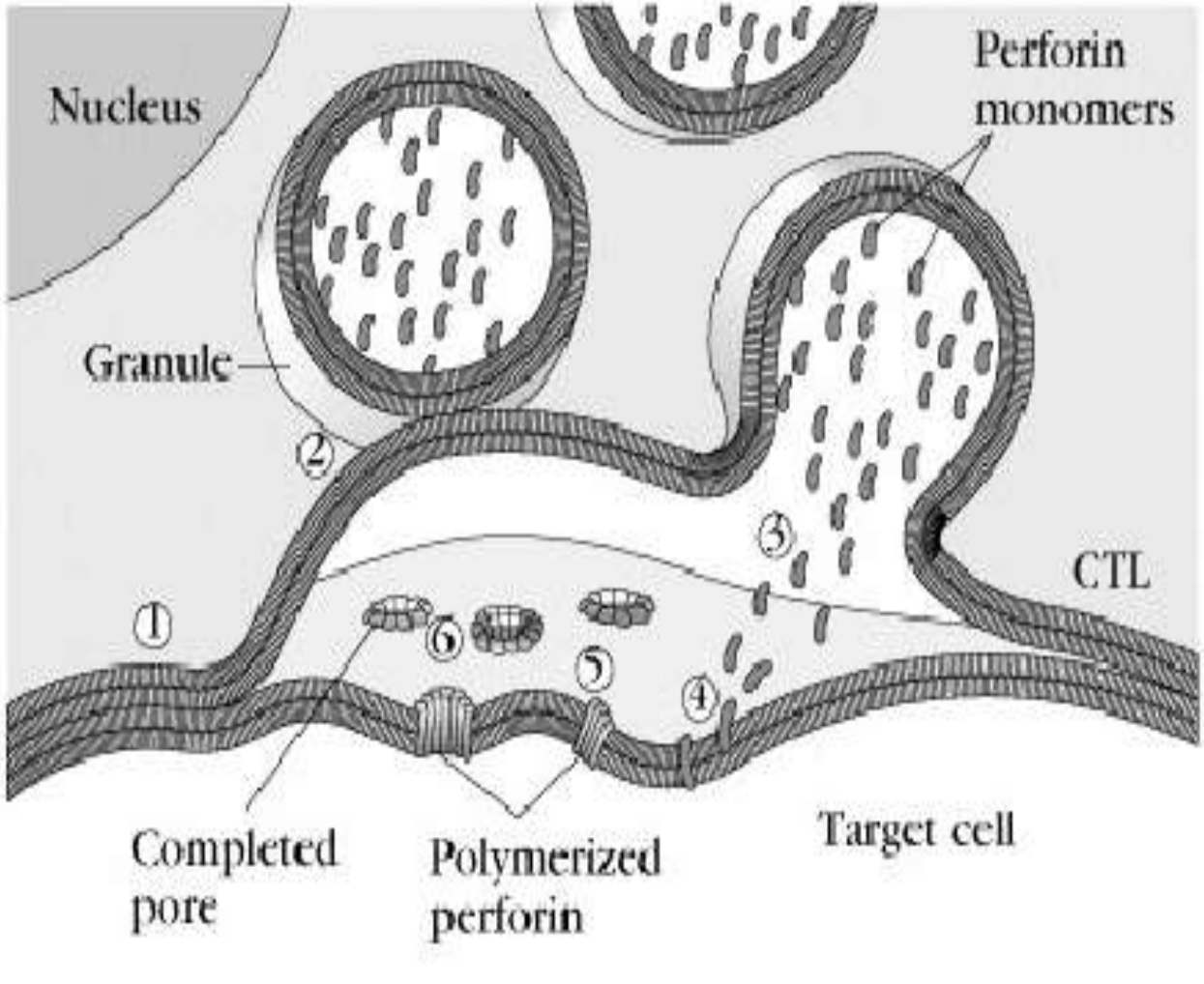
Granüller, yönlendirildikleri alana salınır

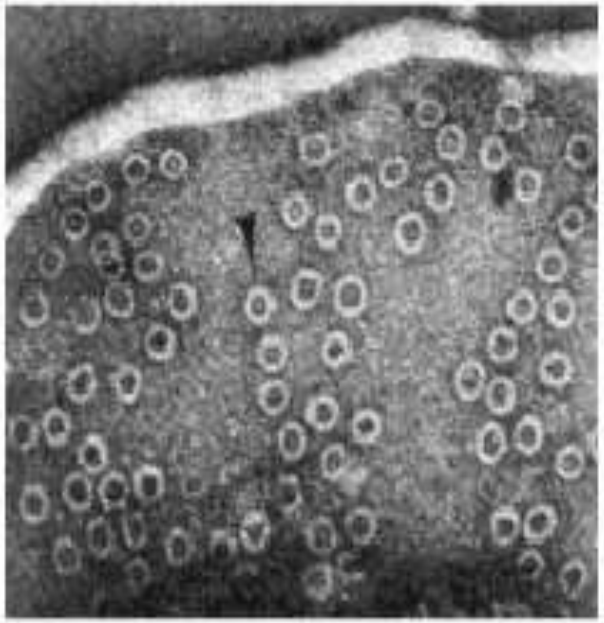
Ag spesifik öldürme dk'lar içinde gerçekleşir. CTL'ler "seri katil" gibi işlev görür.

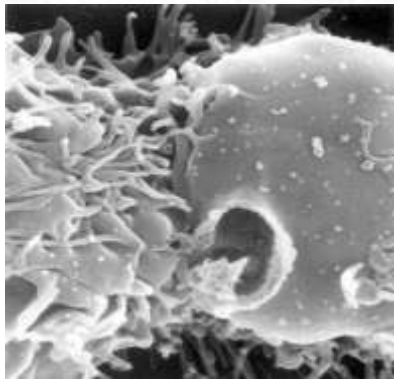


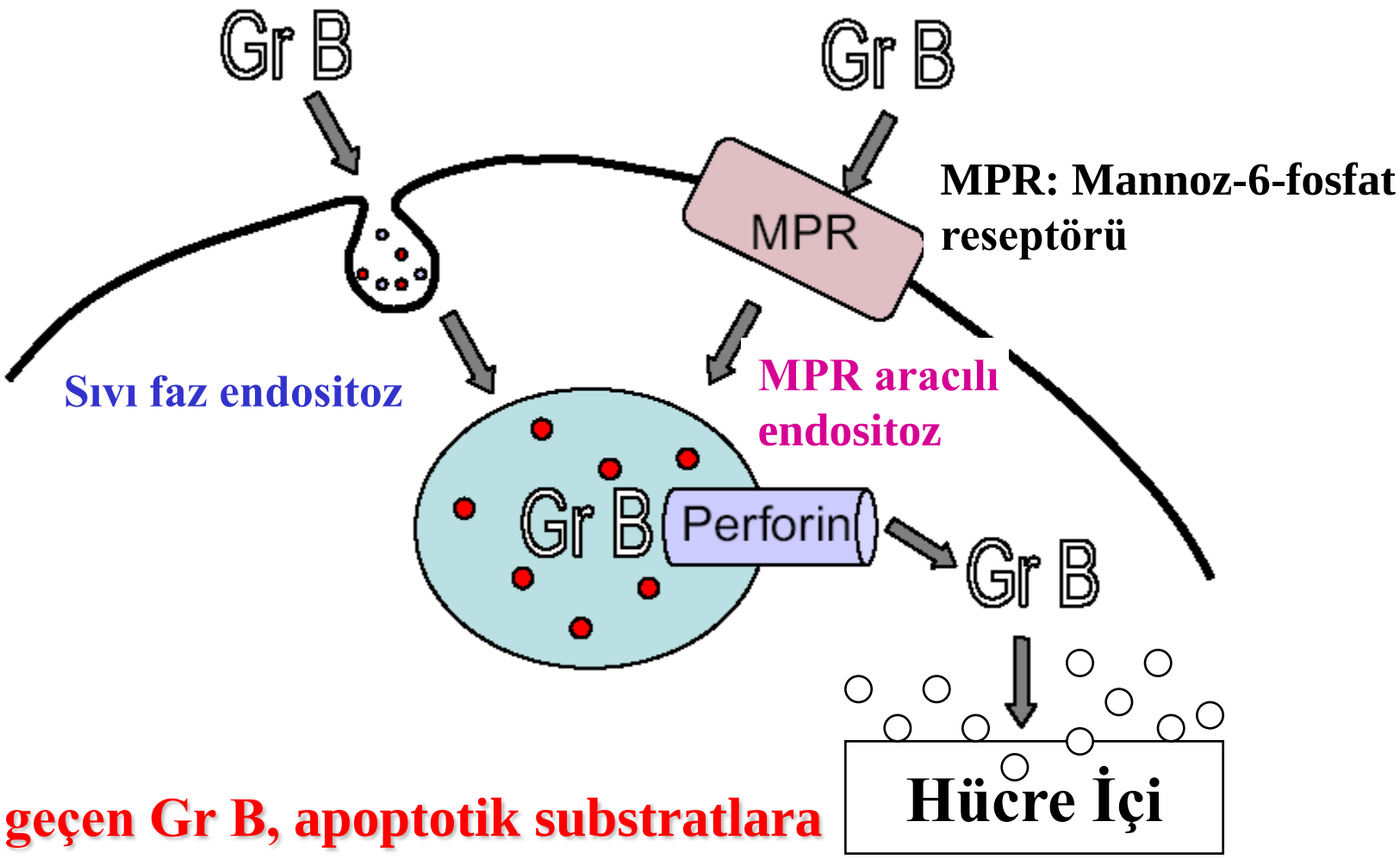
- Hedef hücre plazma membranı sağlam kalır.
- Çevre dokuda belirgin bir inflamasyon oluşmaz

“Perforin” hedef hücre membranında delikler açar.



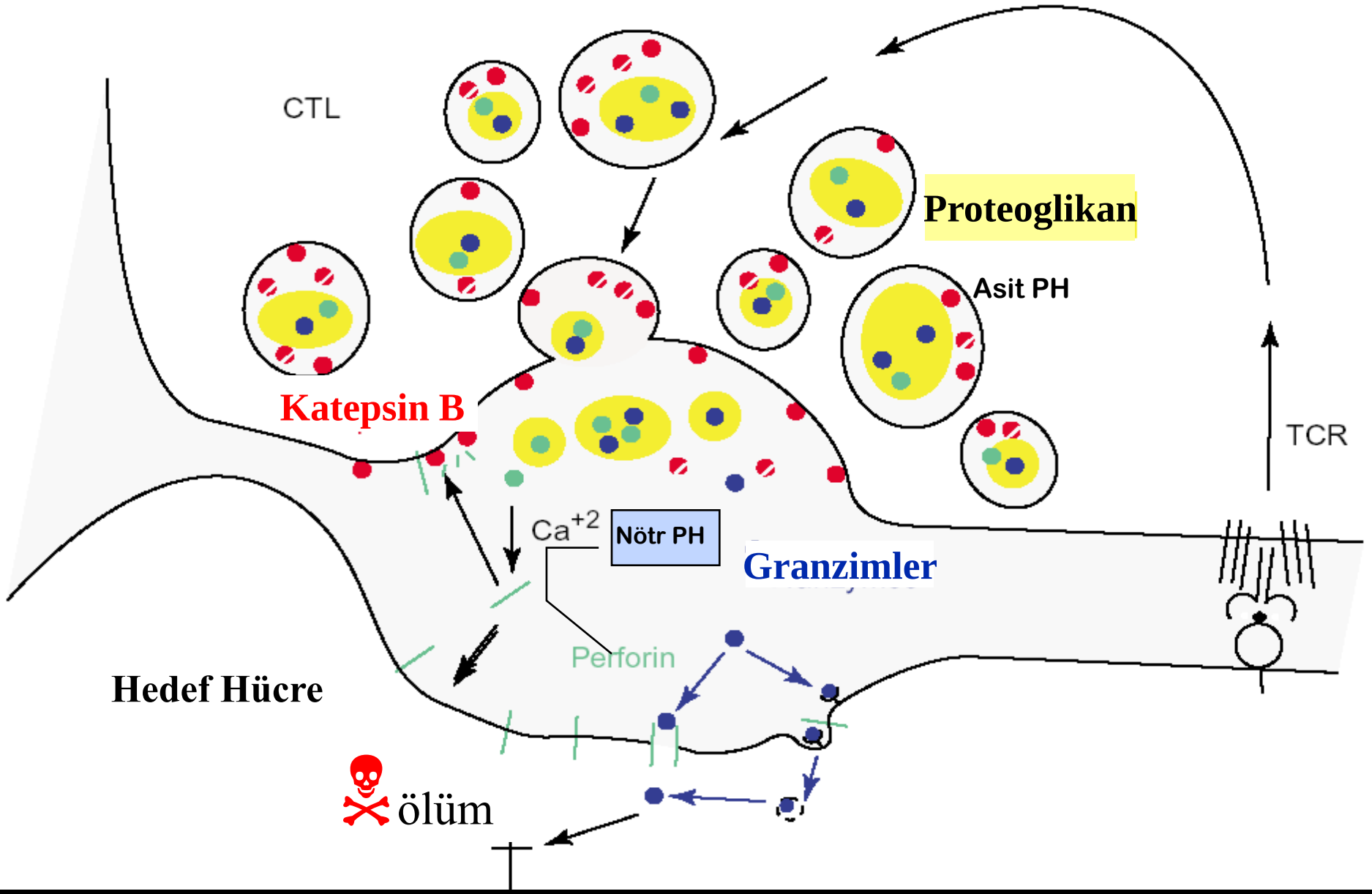




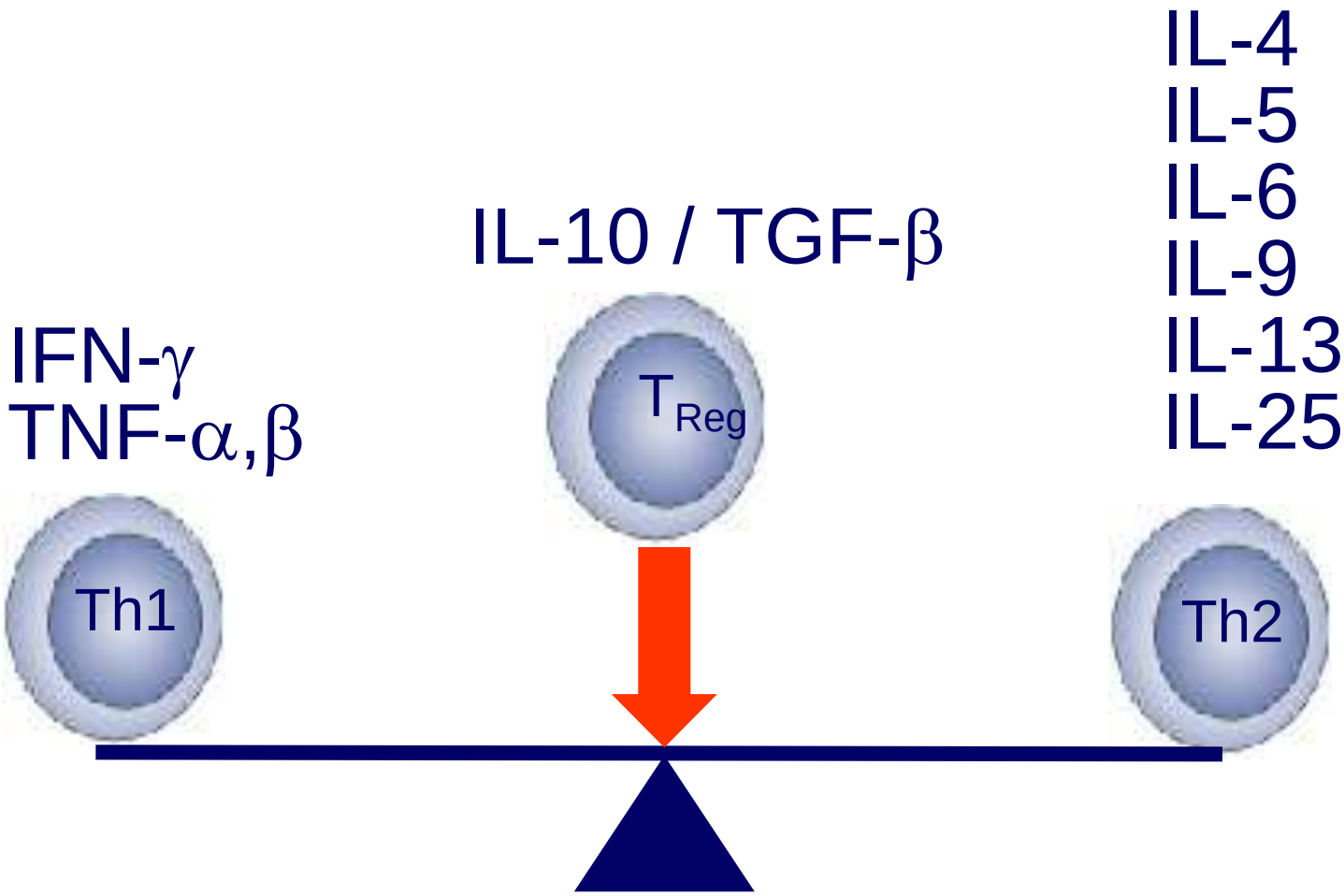


Sitozole geçen Gr B, apoptotik substratlara ulaşarak ölüm sinyallerini başlatır.

Neden CTL'ler kendilerine zarar vermezler ?

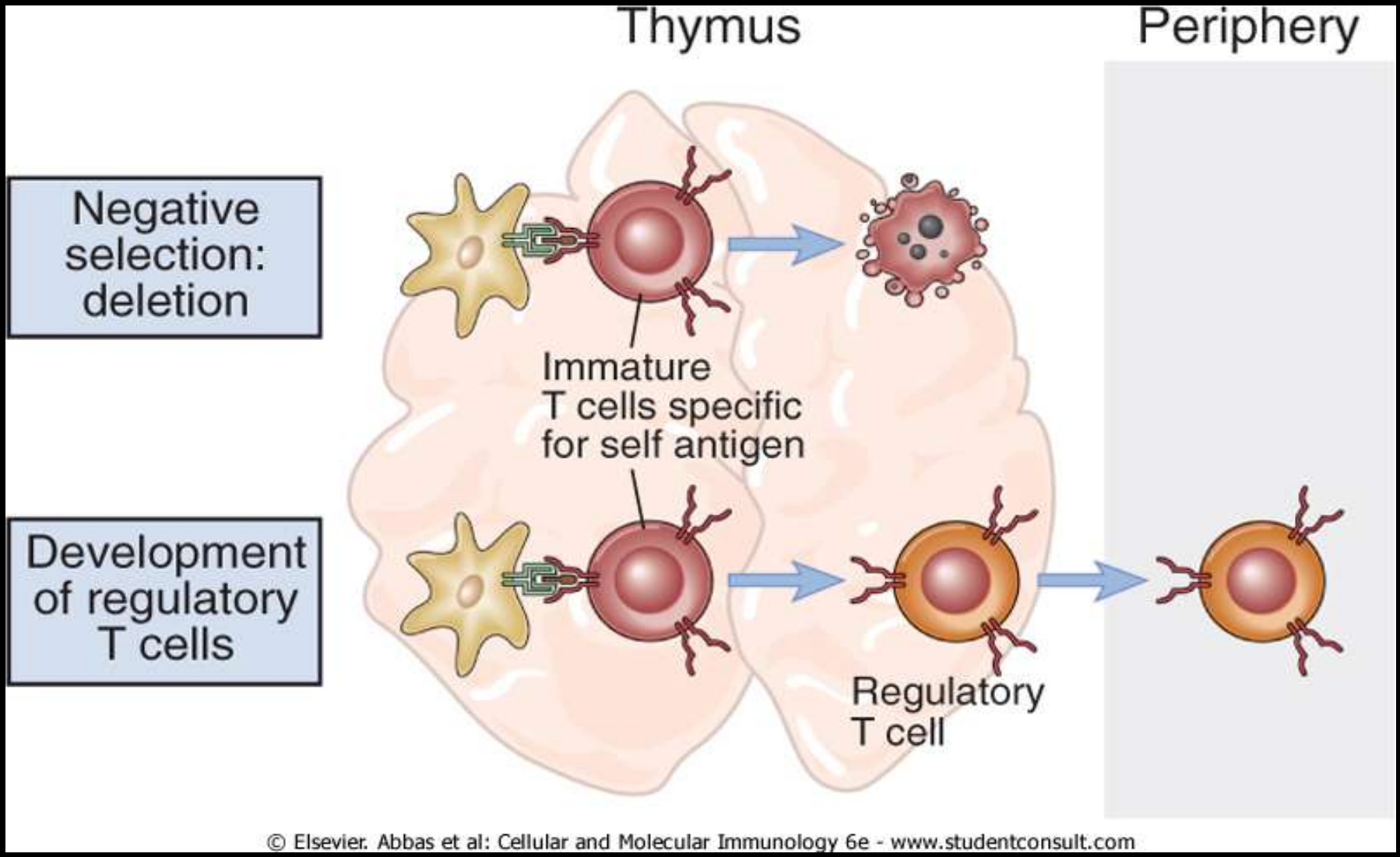


Th1 ve Th2 hücre dengesi: homeostasis

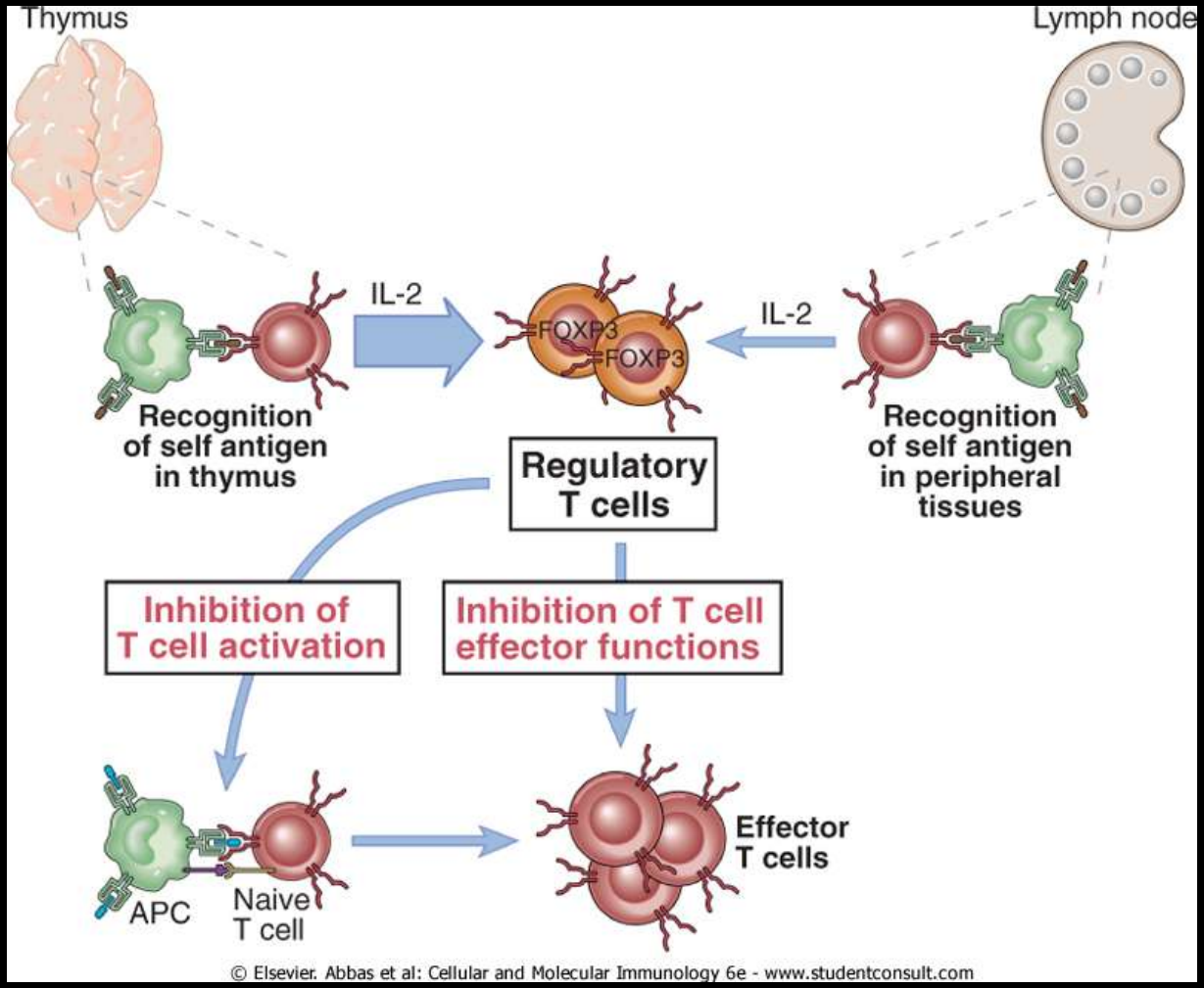


Regülatör T hücreleri

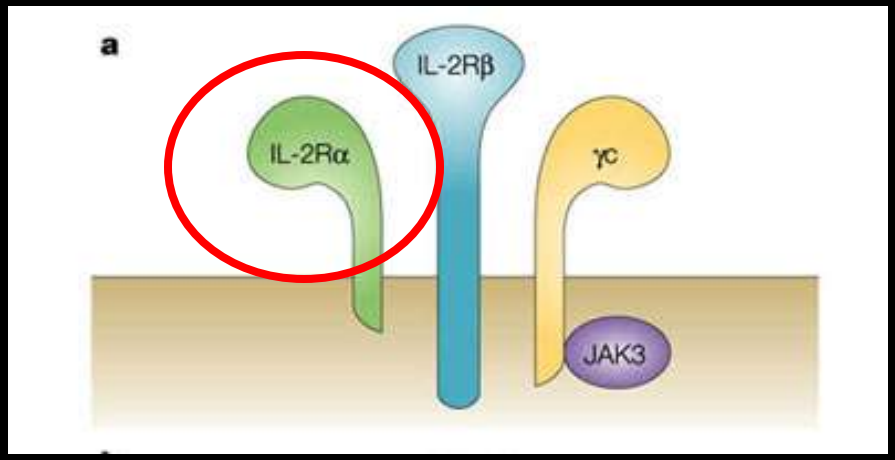
Regülatör T hücreleri	Baskılayıcı mekanizma
Tr1	IL-10, TGF-ß
Th3	TGF-ß
$CD4^+$ $CD25^{yüksek}$ T_{Reg}	IL-10, TGF-ß, CTLA-4, PD-1, GITR, FoxP3
$CD8^+$ $CD25^+$	$CD4^+$ $CD25^+$ gibi
$CD28^-$ T_{Reg}	
Qa-1-dependent $CD8^+$	Qa-1-specific TCR induction of apoptosis
$CD4^-$ $CD8^-$ T_{Reg}	
TCR$\gamma\delta$ T_{Reg}	IL-10, TGF-ß

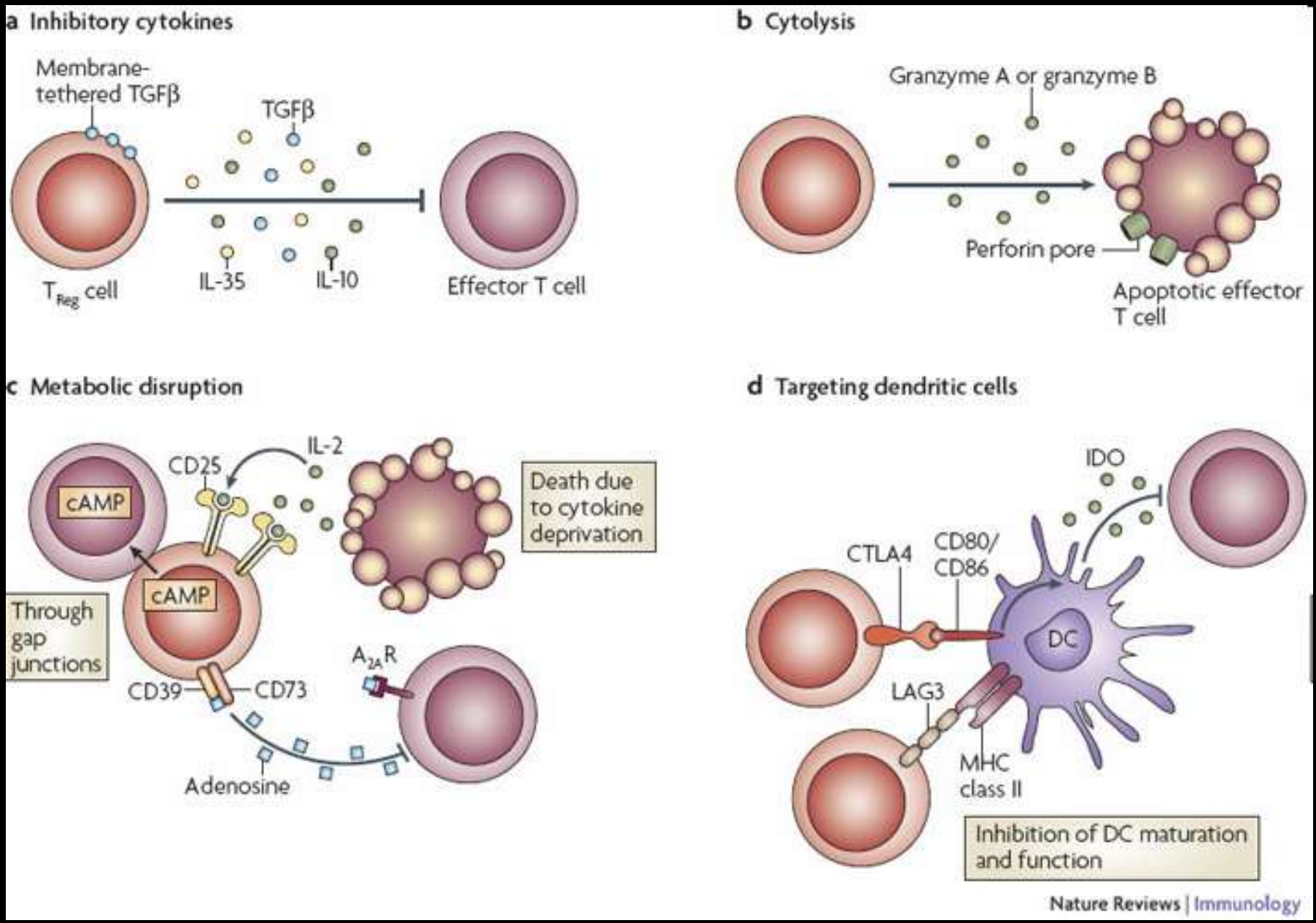


Self reaktif lenfositlerin T regülatör hücreler tarafından baskılanması



- Treg'ler yüksek seviyede IL-2Rα zinciri (CD25) eksprese eder
  - Gelişimi ve yaşamını sürdürebilmesi; TGF-β, IL-2 ve CD28:B7 yolu
  - Bir T hücresinin efektör/hafıza/regülatuvar h olacağını belirleyen sinyal??
    - FoxP3; transkripsiyon faktörü
      - RTL'lerin çoğunun gelişimi ve fonksiyonu için kritik rol
      - Mutasyonu → otoimmünite



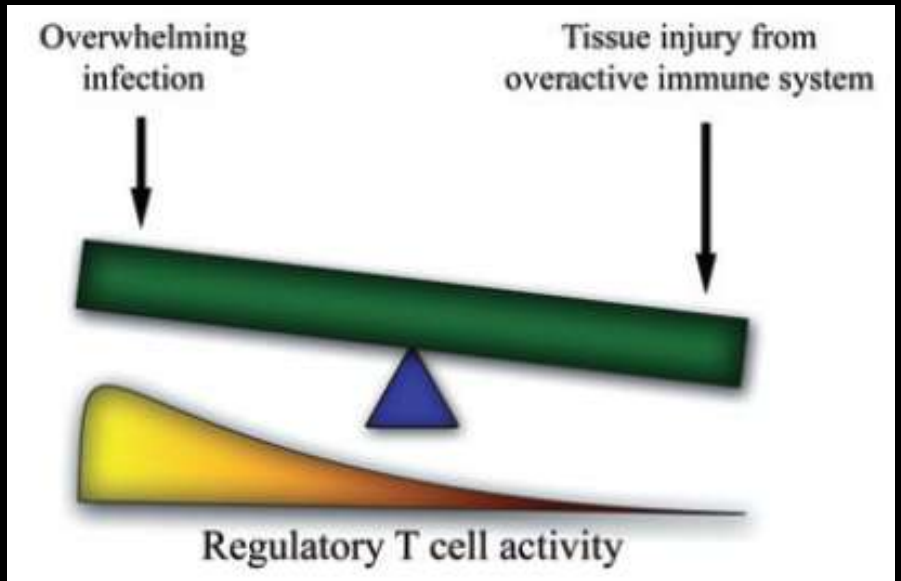


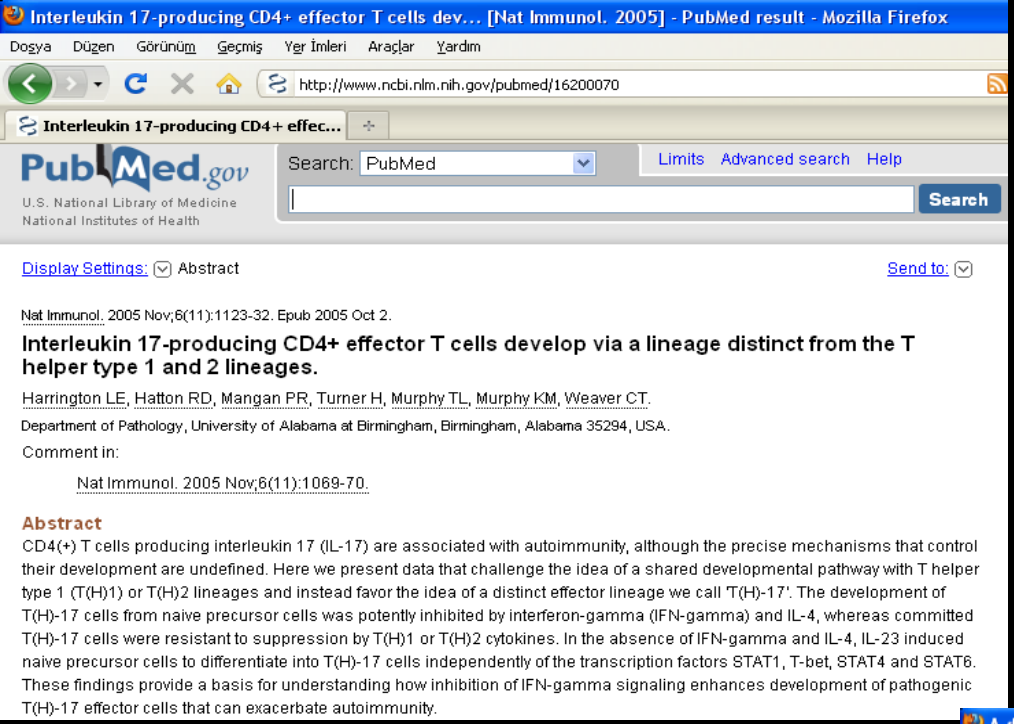
Vignali DAA et al. Nat. Rev. Immunol. 2008: 8, 523-32.

• Otoimmüniteyi, alerjiyi ve transplant rejeksiyonunu önlemede etkili

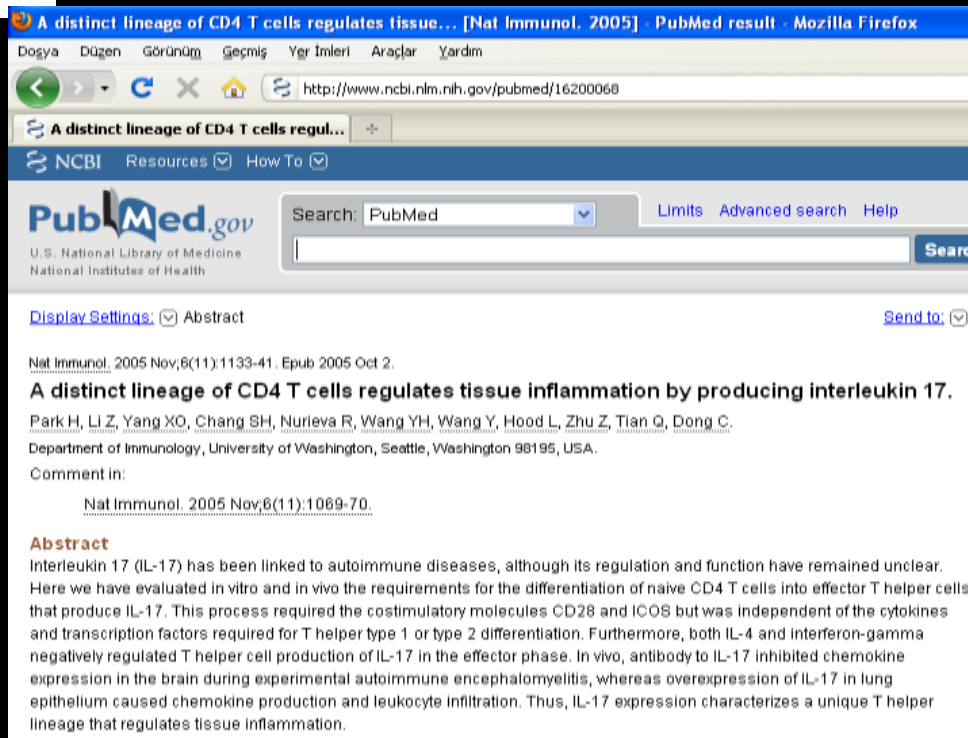
• Enfeksiyonların kronisiteye gidişinden ve sistemik enfeksiyonların ciddi seyrinden sorumlu faktörlerden biri

• İmmünoterapide kullanılmasıyla ilgili en önemli sorun **PLASTİSİTE**



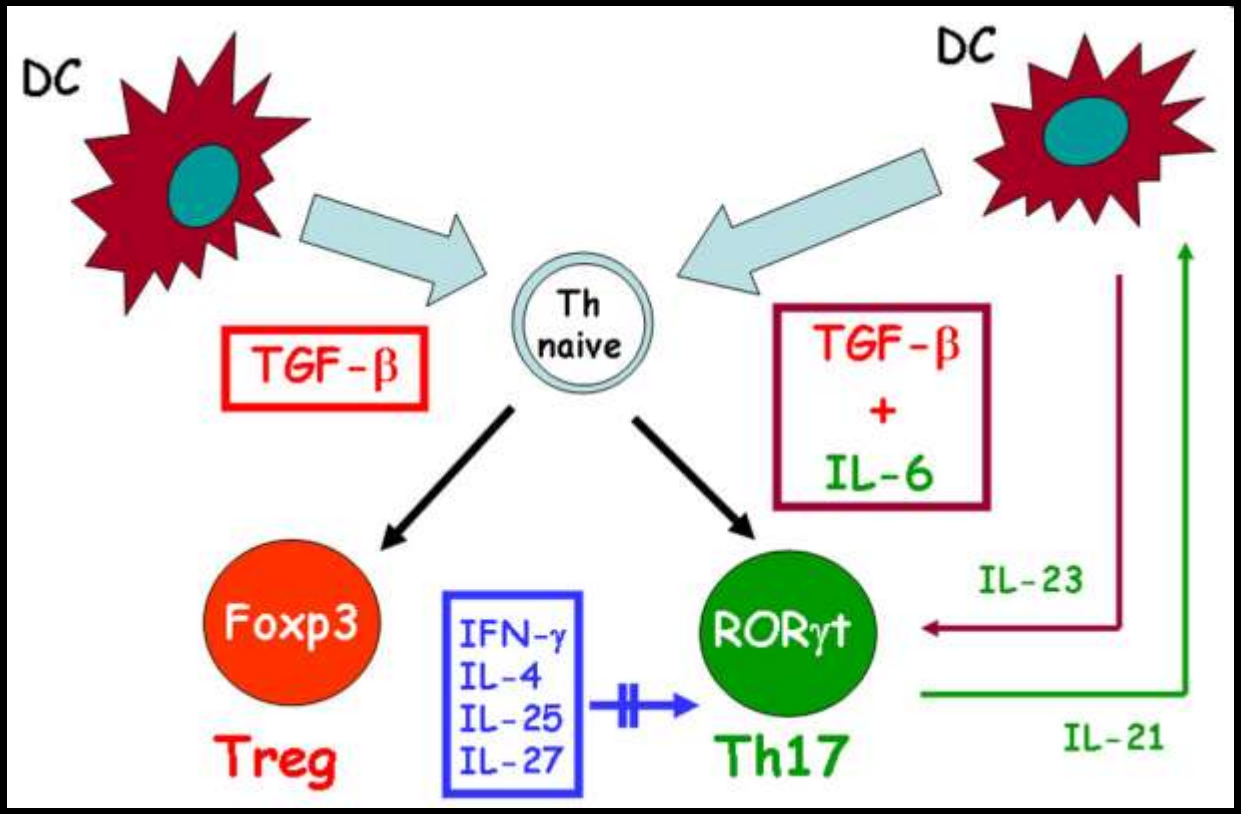

Interleukin 17-producing CD4+ effector T cells dev... [Nat Immunol. 2005] - PubMed result - Mozilla Firefox
Dosya Düzen Görünüm Geçmiş Yer İmleri Araçlar Yardım
http://www.ncbi.nlm.nih.gov/pubmed/16200070
Interleukin 17-producing CD4+ effec...
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
Search: PubMed
Limits Advanced search Help
Search
Display Settings: Abstract
Send to:
Nat Immunol. 2005 Nov;6(11):1123-32. Epub 2005 Oct 2.
Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages.
Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT.
Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.
Comment in:
Nat Immunol. 2005 Nov;6(11):1069-70.
Abstract
CD4(+) T cells producing interleukin 17 (IL-17) are associated with autoimmunity, although the precise mechanisms that control their development are undefined. Here we present data that challenge the idea of a shared developmental pathway with T helper type 1 (T(H)1) or T(H)2 lineages and instead favor the idea of a distinct effector lineage we call 'T(H)-17'. The development of T(H)-17 cells from naive precursor cells was potently inhibited by interferon-gamma (IFN-gamma) and IL-4, whereas committed T(H)-17 cells were resistant to suppression by T(H)1 or T(H)2 cytokines. In the absence of IFN-gamma and IL-4, IL-23 induced naive precursor cells to differentiate into T(H)-17 cells independently of the transcription factors STAT1, T-bet, STAT4 and STAT6. These findings provide a basis for understanding how inhibition of IFN-gamma signaling enhances development of pathogenic T(H)-17 effector cells that can exacerbate autoimmunity.

Th17

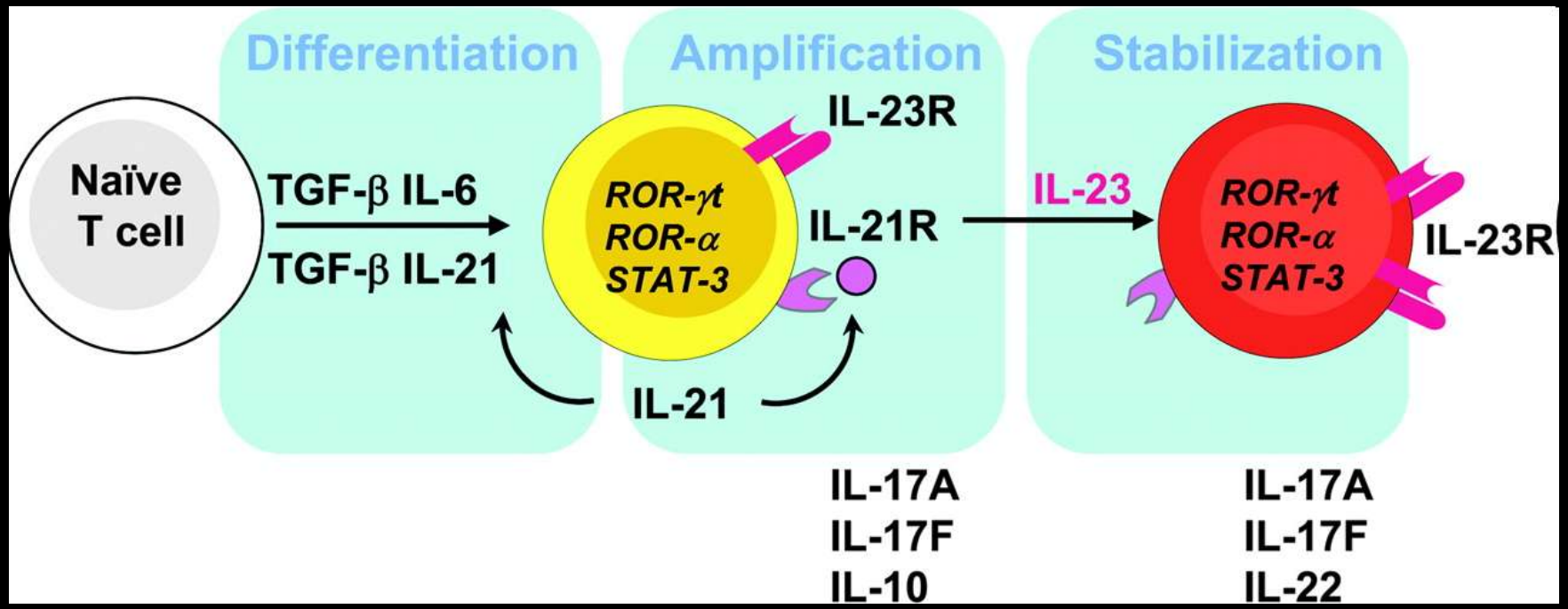

A distinct lineage of CD4 T cells regulates tissue... [Nat Immunol. 2005] - PubMed result - Mozilla Firefox
Dosya Düzen Görünüm Geçmiş Yer İmleri Araçlar Yardım
http://www.ncbi.nlm.nih.gov/pubmed/16200068
A distinct lineage of CD4 T cells regul...
NCBI Resources How To
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
Search: PubMed
Limits Advanced search Help
Display Settings: Abstract
Send to:
Nat Immunol. 2005 Nov;6(11):1133-41. Epub 2005 Oct 2.
A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17.
Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C.
Department of Immunology, University of Washington, Seattle, Washington 98195, USA.
Comment in:
Nat Immunol. 2005 Nov;6(11):1069-70.
Abstract
Interleukin 17 (IL-17) has been linked to autoimmune diseases, although its regulation and function have remained unclear. Here we have evaluated in vitro and in vivo the requirements for the differentiation of naive CD4 T cells into effector T helper cells that produce IL-17. This process required the costimulatory molecules CD28 and ICOS but was independent of the cytokines and transcription factors required for T helper type 1 or type 2 differentiation. Furthermore, both IL-4 and interferon-gamma negatively regulated T helper cell production of IL-17 in the effector phase. In vivo, antibody to IL-17 inhibited chemokine expression in the brain during experimental autoimmune encephalomyelitis, whereas overexpression of IL-17 in lung epithelium caused chemokine production and leukocyte infiltration. Thus, IL-17 expression characterizes a unique T helper lineage that regulates tissue inflammation.

Th17 : Ayrı bir alt grup

- Th17 farklılaşması TGF-β ve IL-6 bağımlıdır



Th17 farklılaşmasındaki adımlar



Awasthi A & Kuchroo VK, Int. Immunol. 2009: 21, 489-98.

- **Th17'nin ana sitokini IL-17 : akut inflamatuvar sürecin mediatörleri olan TNF-α, IL-1β, IL-6, IL-8 v.b. Sitokinleri; kemokinlerden CXCL1,2 yapımını uyarır.**

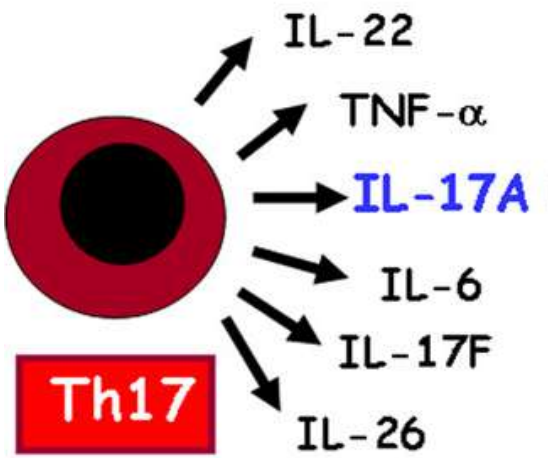
- **Kemokinler nötrofil hareketini uyarır ki, nötrofil birikimi Th17 aracılı inflamasyonun ana patolojik bulgusudur**

- Bakterilere karşı koruyucu immün yanıt

- Otoimmün hastalıklarda patojenik rol

KRONİK ENFLAMASYON

Granülosit ve monosit birikimi



Endotel hücreleri
Fibroblastlar
Epitel hücreleri
Makrofajlar

CXCL1, CXCL2, CXCL5, CCL2, CCL5

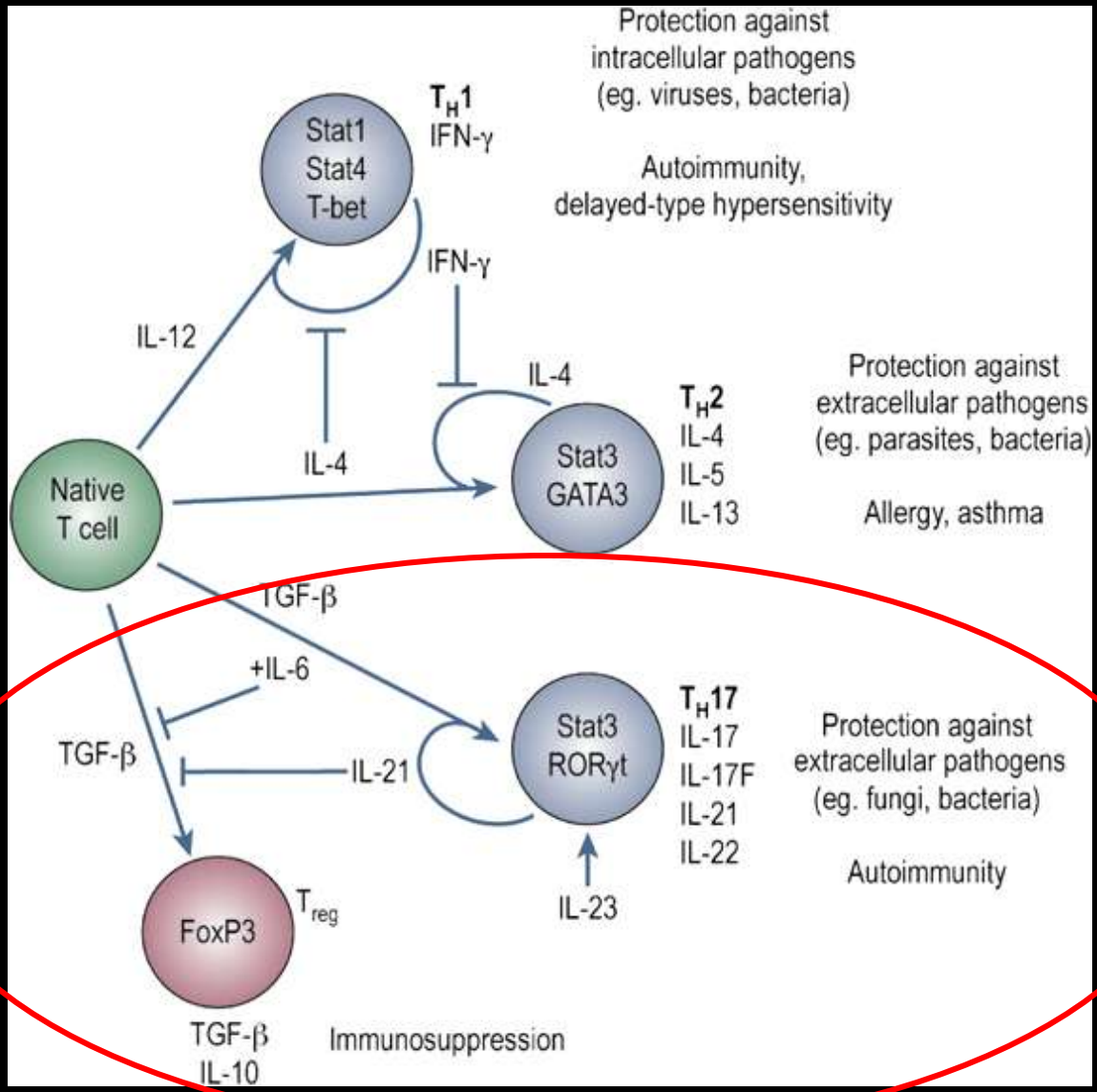
NOS-2

MMP3

G-CSF, GM-CSF

IL-1, IL-6, TNF-α

Th17 ve Treg



Deenick EK & Tangye SG, Immunol. Cell Biol. 2007: 85, 503-5.

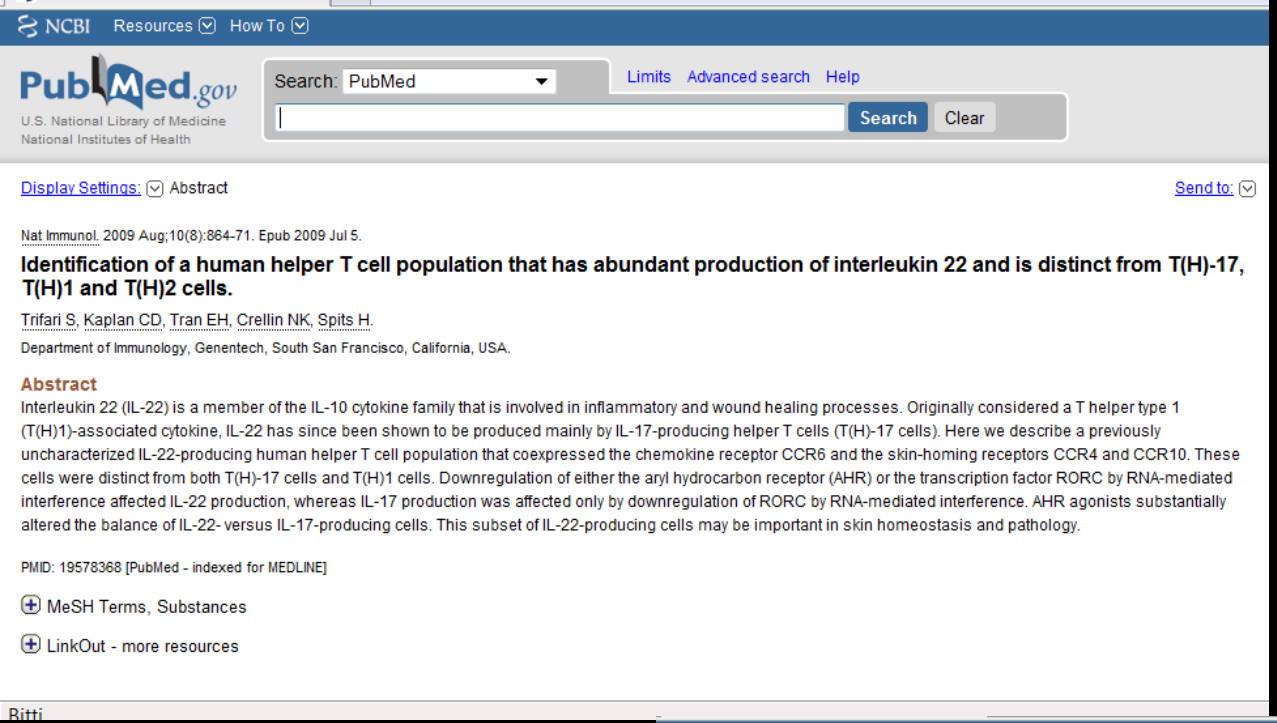
Th17 ve Hastalıklar

• **Otoimmün hastalıklar:**
Romatoid artrit (CIA), Multiple scleroz (EAE), İnflamatuvar barsak hastalıkları, Psoriasis

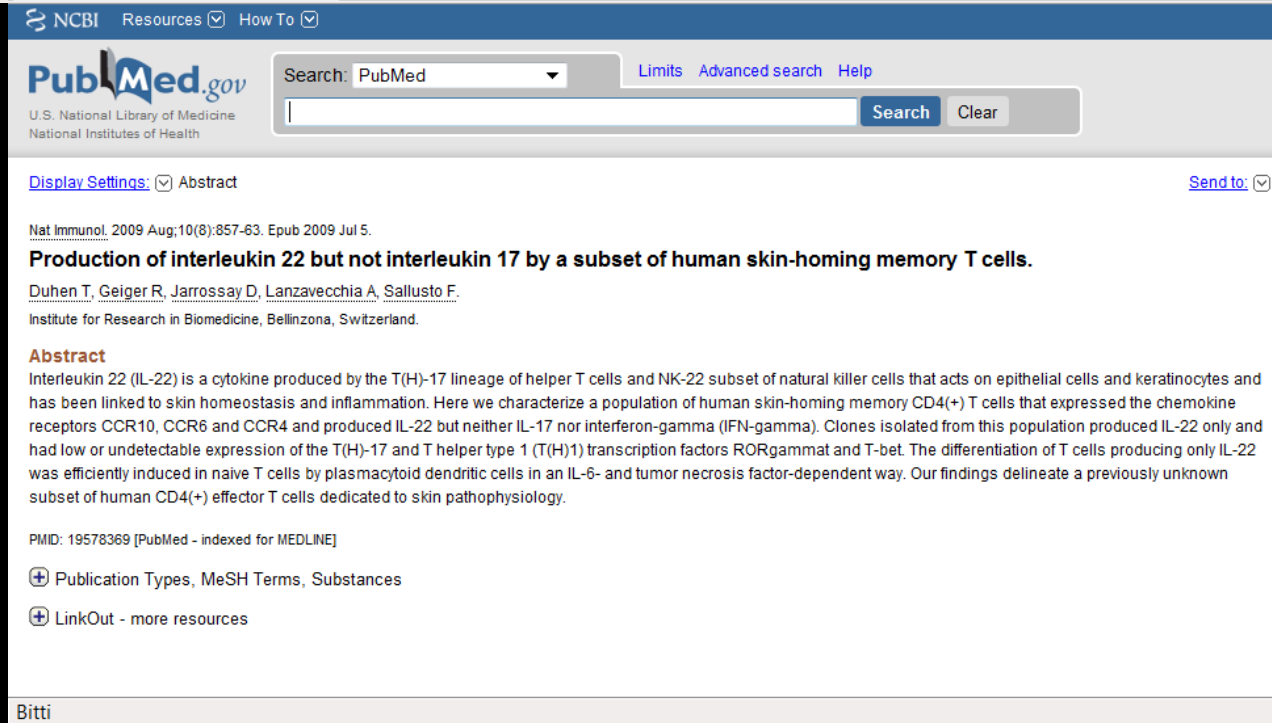
IL-17 proinflamatuvar stikoinlerin yapımına ve nötrofillerin aktivasyonuna yol açar

• **Enfeksiyonlar:**
Hem hücre içi hem de hücre dışı mikroplar için önemli
IL-17 özel kemokinleri, proinflamatuvar sitokinlerin ve koloni uyarıcı faktörlerin
Yapımına yol açar; nötrofiller ve diğer miyeloid hücrelerin enfeksiyon alanında
toplanmasına katkıda bulnur

Bakteriyel: *Mycobacteria* tuberculosis ve *Pneumocystis jirovechii*
Fungal: candida
Viral: HIV ve diğerleri


NCBI Resources How To
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
Search: PubMed
Limits Advanced search Help
Search Clear
Display Settings: Abstract
Send to:
Nat Immunol. 2009 Aug;10(8):864-71. Epub 2009 Jul 5.
Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells.
Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H.
Department of Immunology, Genentech, South San Francisco, California, USA.
Abstract
Interleukin 22 (IL-22) is a member of the IL-10 cytokine family that is involved in inflammatory and wound healing processes. Originally considered a T helper type 1 (T(H)1)-associated cytokine, IL-22 has since been shown to be produced mainly by IL-17-producing helper T cells (T(H)-17 cells). Here we describe a previously uncharacterized IL-22-producing human helper T cell population that coexpressed the chemokine receptor CCR6 and the skin-homing receptors CCR4 and CCR10. These cells were distinct from both T(H)-17 cells and T(H)1 cells. Downregulation of either the aryl hydrocarbon receptor (AHR) or the transcription factor RORC by RNA-mediated interference affected IL-22 production, whereas IL-17 production was affected only by downregulation of RORC by RNA-mediated interference. AHR agonists substantially altered the balance of IL-22- versus IL-17-producing cells. This subset of IL-22-producing cells may be important in skin homeostasis and pathology.
PMID: 19578368 [PubMed - indexed for MEDLINE]
MeSH Terms, Substances
LinkOut - more resources
Bitti

Th22

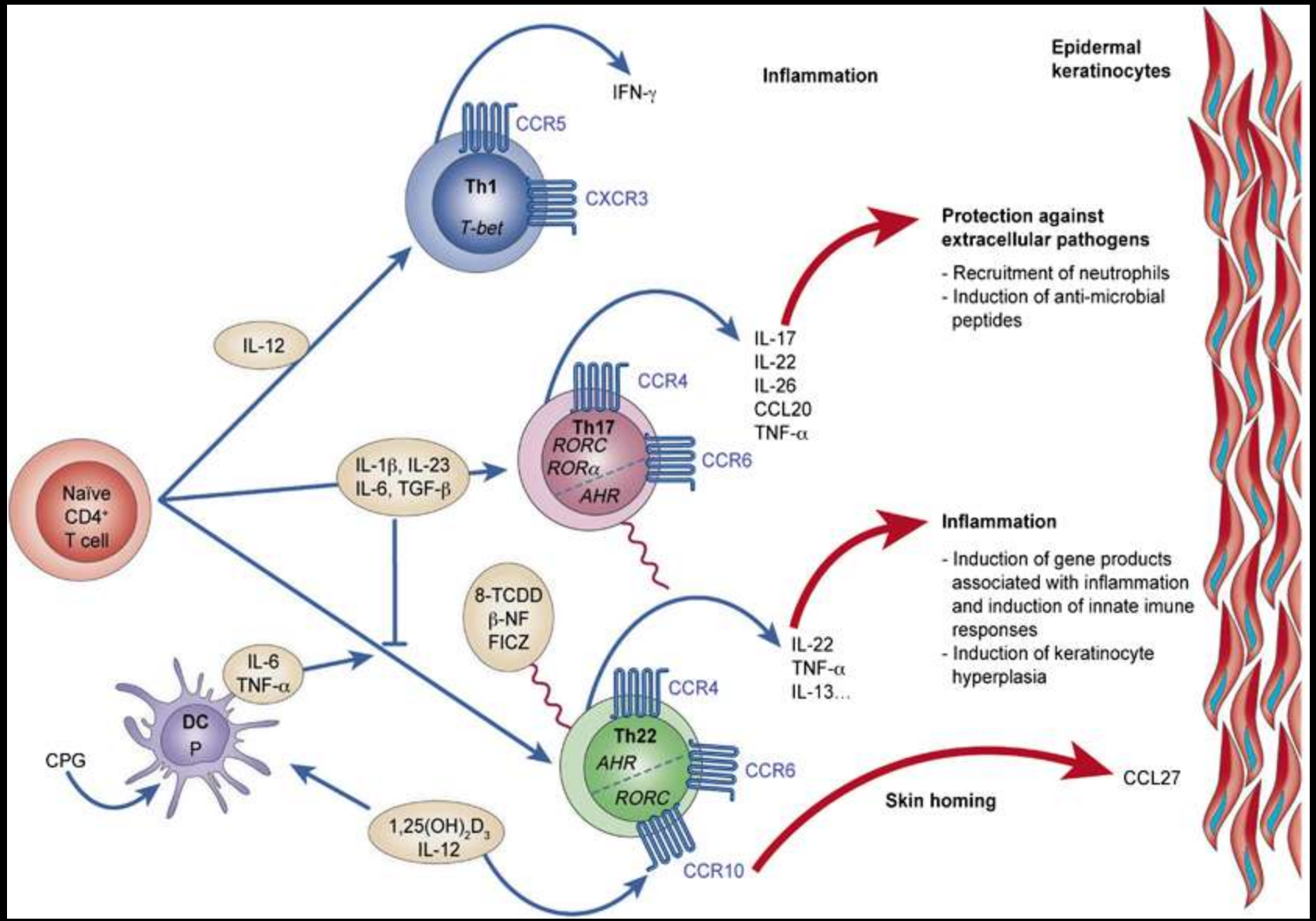

NCBI Resources How To
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
Search: PubMed
Limits Advanced search Help
Search Clear
Display Settings: Abstract
Send to:
Nat Immunol. 2009 Aug;10(8):857-63. Epub 2009 Jul 5.
Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells.
Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F.
Institute for Research in Biomedicine, Bellinzona, Switzerland.
Abstract
Interleukin 22 (IL-22) is a cytokine produced by the T(H)-17 lineage of helper T cells and NK-22 subset of natural killer cells that acts on epithelial cells and keratinocytes and has been linked to skin homeostasis and inflammation. Here we characterize a population of human skin-homing memory CD4(+) T cells that expressed the chemokine receptors CCR10, CCR6 and CCR4 and produced IL-22 but neither IL-17 nor interferon-gamma (IFN-gamma). Clones isolated from this population produced IL-22 only and had low or undetectable expression of the T(H)-17 and T helper type 1 (T(H)1) transcription factors RORgammat and T-bet. The differentiation of T cells producing only IL-22 was efficiently induced in naive T cells by plasmacytoid dendritic cells in an IL-6- and tumor necrosis factor-dependent way. Our findings delineate a previously unknown subset of human CD4(+) effector T cells dedicated to skin pathophysiology.
PMID: 19578369 [PubMed - indexed for MEDLINE]
Publication Types, MeSH Terms, Substances
LinkOut - more resources
Bitti

Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling

Stefanie Eyerich,[1] Kilian Eyerich,[2] Davide Pennino,[2] Teresa Carbone,[2] Francesca Nasorri,[2] Sabatino Pallotta,[3] Francesca Cianfarani,[4] Teresa Odorisio,[4] Claudia Traidl-Hoffmann,[5] Heidrun Behrendt,[5] Stephen R. Durham,[6] Carsten B. Schmidt-Weber,[1] and Andrea Cavani[2]

[1]Molecular Immunology, Department of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College, London, United Kingdom. [2]Laboratory of Immunology, [3]Division of Dermatology, and [4]Laboratory of Cellular and Molecular Biology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy. [5]Division of Environmental Dermatology and Allergy, Helmholtz Center Munich/Technische Universität Munich and ZAUM — Center for Allergy and Environment, Technische Universität Munich, Munich, Germany. [6]Upper Respiratory Medicine, Department of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College, London, United Kingdom.

Th subsets are defined according to their production of lineage-indicating cytokines and functions. In this study, we have identified a subset of human Th cells that infiltrates the epidermis in individuals with inflammatory skin disorders and is characterized by the secretion of IL-22 and TNF-α, but not IFN-γ, IL-4, or IL-17. In analogy to the Th17 subset, cells with this cytokine profile have been named the Th22 subset. Th22 clones derived from patients with psoriasis were stable in culture and exhibited a transcriptome profile clearly separate from those of Th1, Th2, and Th17 cells; it included genes encoding proteins involved in tissue remodeling, such as FGFs, and chemokines involved in angiogenesis and fibrosis. Primary human keratinocytes exposed to Th22 supernatants expressed a transcriptome response profile that included genes involved in innate immune pathways and the induction and modulation of adaptive immunity. These proinflammatory Th22 responses were synergistically dependent on IL-22 and TNF-α. Furthermore, Th22 supernatants enhanced wound healing in an in vitro injury model, which was exclusively dependent on IL-22. In conclusion, the human Th22 subset may represent a separate T cell subset with a distinct identity with respect to gene expression and function, present within the epidermal layer in inflammatory skin diseases. Future strategies directed against the Th22 subset may be of value in chronic inflammatory skin disorders.



Yssel H & Pene J, Immunol. Cell Biol. 2009, 87, 574–6

NCBI Resources How To

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed Limits Advanced search Help

Search

Display Settings: Abstract Send to:

Nat Immunol. 2008 Dec;9(12):1341-6. Epub 2008 Oct 19.

Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset.

Veldhoen M, Uyttenhove C, van Snick J, Helmby H, Westendorf A, Buer J, Martin B, Wilhelm C, Stockinger B.

Division of Molecular Immunology, Medical Research Council National Institute for Medical Research, London NW7 1AA, UK.

Abstract

Since the discovery of T helper type 1 and type 2 effector T cell subsets 20 years ago, inducible regulatory T cells and interleukin 17 (IL-17)-producing T helper cells have been added to the 'portfolio' of helper T cells. It is unclear how many more effector T cell subsets there may be and to what degree their characteristics are fixed or flexible. Here we show that transforming growth factor-beta, a cytokine at the center of the differentiation of IL-17-producing T helper cells and inducible regulatory T cells, 'reprograms' T helper type 2 cells to lose their characteristic profile and switch to IL-9 secretion or, in combination with IL-4, drives the differentiation of 'T(H)-9' cells directly. Thus, transforming growth factor-beta constitutes a regulatory 'switch' that in combination with other cytokines can 'reprogram' effector T cell differentiation along different pathways.

Th9

oMed Limits Advanced search Help

U.S. National Library of Medicine
National Institutes of Health

Search

Display Settings: Abstract Send to:

Nat Immunol. 2008 Dec;9(12):1347-55. Epub 2008 Nov 9.

IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(-) effector T cells.

Dardalhon V, Awasthi A, Kwon H, Galileos G, Gao W, Sobel RA, Mitsdoerffer M, Strom TB, Elyaman W, Ho IC, Khoury S, Oukka M, Kuchroo VK.

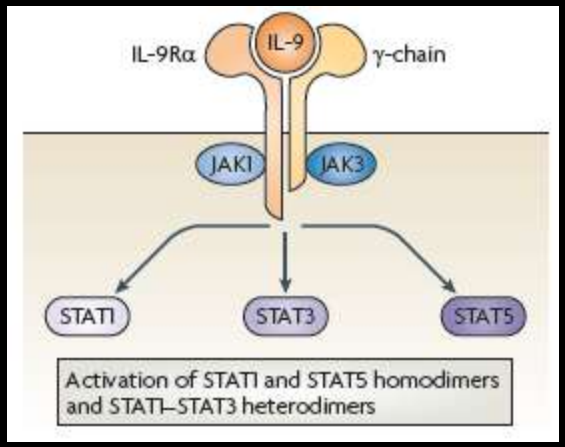
Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Cambridge, Massachusetts 02139, USA.

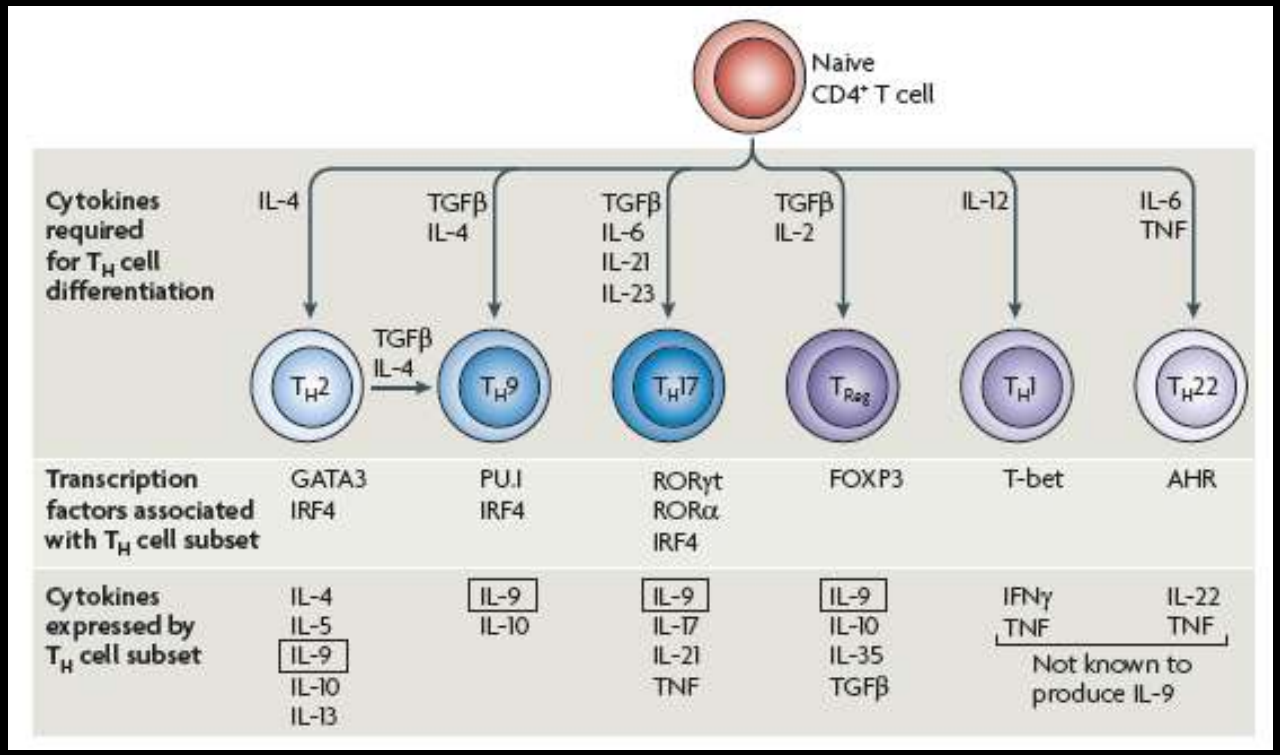
Erratum in:

Nat Immunol. 2009 May;10(5):551.

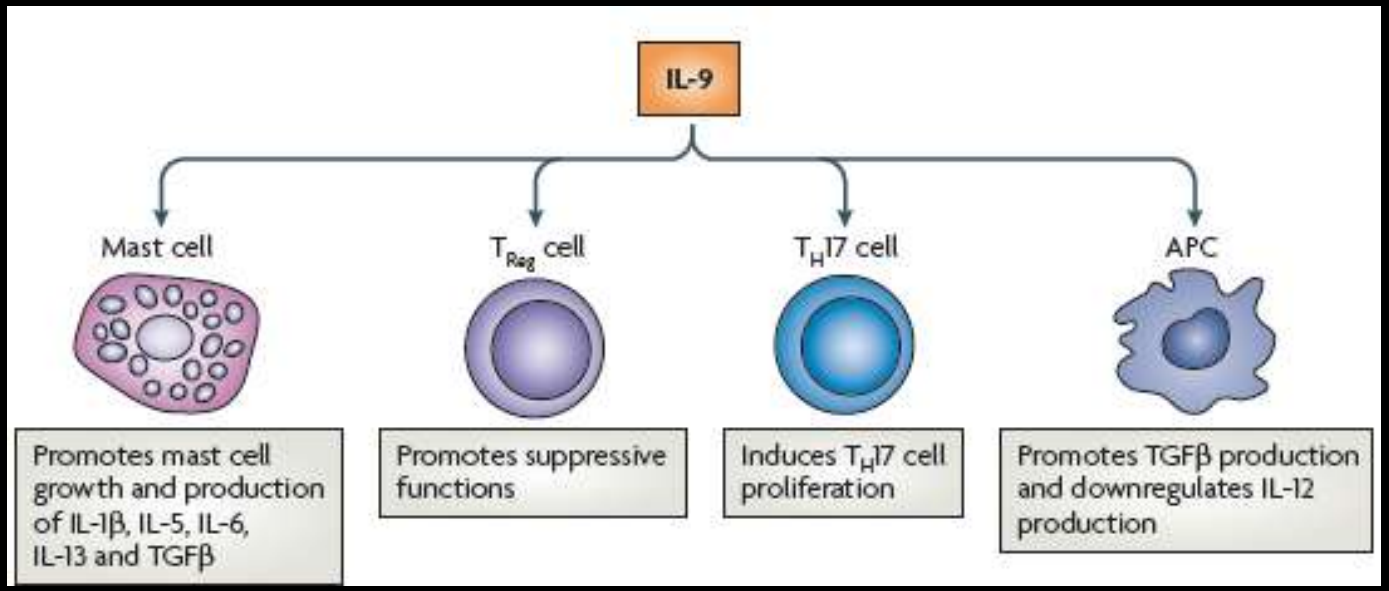
Abstract

Transcription factor Foxp3 is critical for generating regulatory T cells (T(reg) cells). Transforming growth factor-beta (TGF-beta) induces Foxp3 and suppressive T(reg) cells from naive T cells, whereas interleukin 6 (IL-6) inhibits the generation of inducible T(reg) cells. Here we show that IL-4 blocked the generation of TGF-beta-induced Foxp3(+) T(reg) cells and instead induced a population of T helper cells that produced IL-9 and IL-10. The IL-9(+)IL-10(+) T cells demonstrated no regulatory properties despite producing abundant IL-10. Adoptive transfer of IL-9(+)IL-10(+) T cells into recombination-activating gene 1-deficient mice induced colitis and peripheral neuritis, the severity of which was aggravated if the IL-9(+)IL-10(+) T cells were transferred with CD45RB(hi) CD4(+) effector T cells. Thus IL-9(+)IL-10(+) T cells lack suppressive function and constitute a distinct population of helper-effector T cells that promote tissue inflammation.

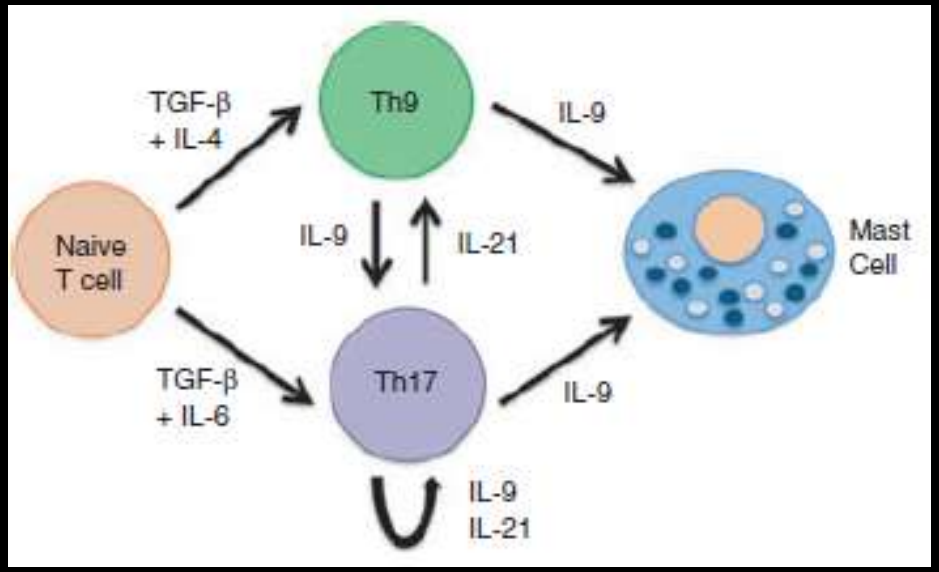




Noelle RJ & Nowak EC, Nat. Rev. Immunol. 2010:10, 683-7.c



Noelle RJ & Nowak EC, Nat. Rev. Immunol. 2010:10, 683-7.



Nowak EC & Noelle RJ. Immunology 2010:131, 169-73.

NCBI Resources How To

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed
Breitfeld D CXC
RSS Save search Limits Advanced search Help
Search Clear

Display Settings: Abstract

Send to:

J Exp Med. 2000 Dec 4;192(11):1545-52.

Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production.

Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M, Förster R.

Molecular Tumor and Immunogenetics, Max-Delbrück Center for Molecular Medicine, 13092 Berlin, Germany.

Comment in:

J Exp Med. 2000 Dec 4;192(11):F31-4.

Abstract

Chemokines and their receptors have been identified as major regulators controlling the functional organization of secondary lymphoid organs. Here we show that expression of CXC chemokine receptor 5 (CXCR5), a chemokine receptor required for B cell homing to B cell follicles, defines a novel subpopulation of B helper T cells localizing to follicles. In peripheral blood these cells coexpress CD45RO and the T cell homing CC chemokine receptor 7 (CCR7). In secondary lymphoid organs, CD4(+)CXCR5(+) cells lose expression of CCR7, which allows them to localize to B cell follicles and germinal centers where they express high levels of CD40 ligand (CD40L), a costimulatory molecule required for B cell activation and inducible costimulator (ICOS), a recently identified costimulatory molecule of the CD28 family. Thus, when compared with CD4(+)CD45RO(+)CXCR5(-) cells, CD4(+)CD45RO(+)CXCR5(+) tonsillar T cells efficiently support the production of immunoglobulin (Ig)A and IgG. In contrast, analysis of the memory response revealed that long-lasting memory cells are found within the CD4(+)CD45RO(+)CXCR5(-) population, suggesting that CXCR5(+)CD4 cells represent recently activated effector cells. Based on the characteristic localization within secondary lymphoid organs, we suggest to term these cells "follicular B helper T cells" (T(FH)).

PMID: 11104797 [PubMed - indexed for MEDLINE] PMCID: PMC2193094 Free PMC Article

Bitti

Tfh

NCBI Resources How To

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed
Limits Advanced search Help
Search Clear

Display Settings: Abstract

Send to:

J Exp Med. 2000 Dec 4;192(11):1553-62.

CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function.

Schaerli P, Willimann K, Lang AB, Lipp M, Loetscher P, Moser B.

Theodor-Kocher Institute, University of Bern, CH-3000 Bern 9, Switzerland. patrick.schaerli@tki.unibe.ch

Comment in:

J Exp Med. 2000 Dec 4;192(11):F31-4.

Abstract

Leukocyte traffic through secondary lymphoid tissues is finely tuned by chemokines. We have studied the functional properties of a human T cell subset marked by the expression of CXC chemokine receptor 5 (CXCR5). Memory but not naive T cells from tonsils are CXCR5(+) and migrate in response to the B cell-attracting chemokine 1 (BCA-1), which is selectively expressed by reticular cells and blood vessels within B cell follicles. Tonsillar CXCR5(+) T cells do not respond to other chemokines present in secondary lymphoid tissues, including secondary lymphoid tissue chemokine (SLC), EBV-induced molecule 1 ligand chemokine (ELC), and stromal cell-derived factor 1 (SDF-1). The involvement of tonsillar CXCR5(+) T cells in humoral immune responses is suggested by their localization in the mantle and light zone germinal centers of B cell follicles and by the concomitant expression of activation and costimulatory markers, including CD69, HLA-DR, and inducible costimulator (ICOS). Peripheral blood CXCR5(+) T cells also belong to the CD4(+) memory T cell subset but, in contrast to tonsillar cells, are in a resting state and migrate weakly to chemokines. CXCR5(+) T cells are very inefficient in the production of cytokines but potently induce antibody production during coculture with B cells. These properties portray CXCR5(+) T cells as a distinct memory T cell subset with B cell helper function, designated here as follicular B helper T cells (T(FH)).

PMID: 11104798 [PubMed - indexed for MEDLINE] PMCID: PMC2193097 Free PMC Article

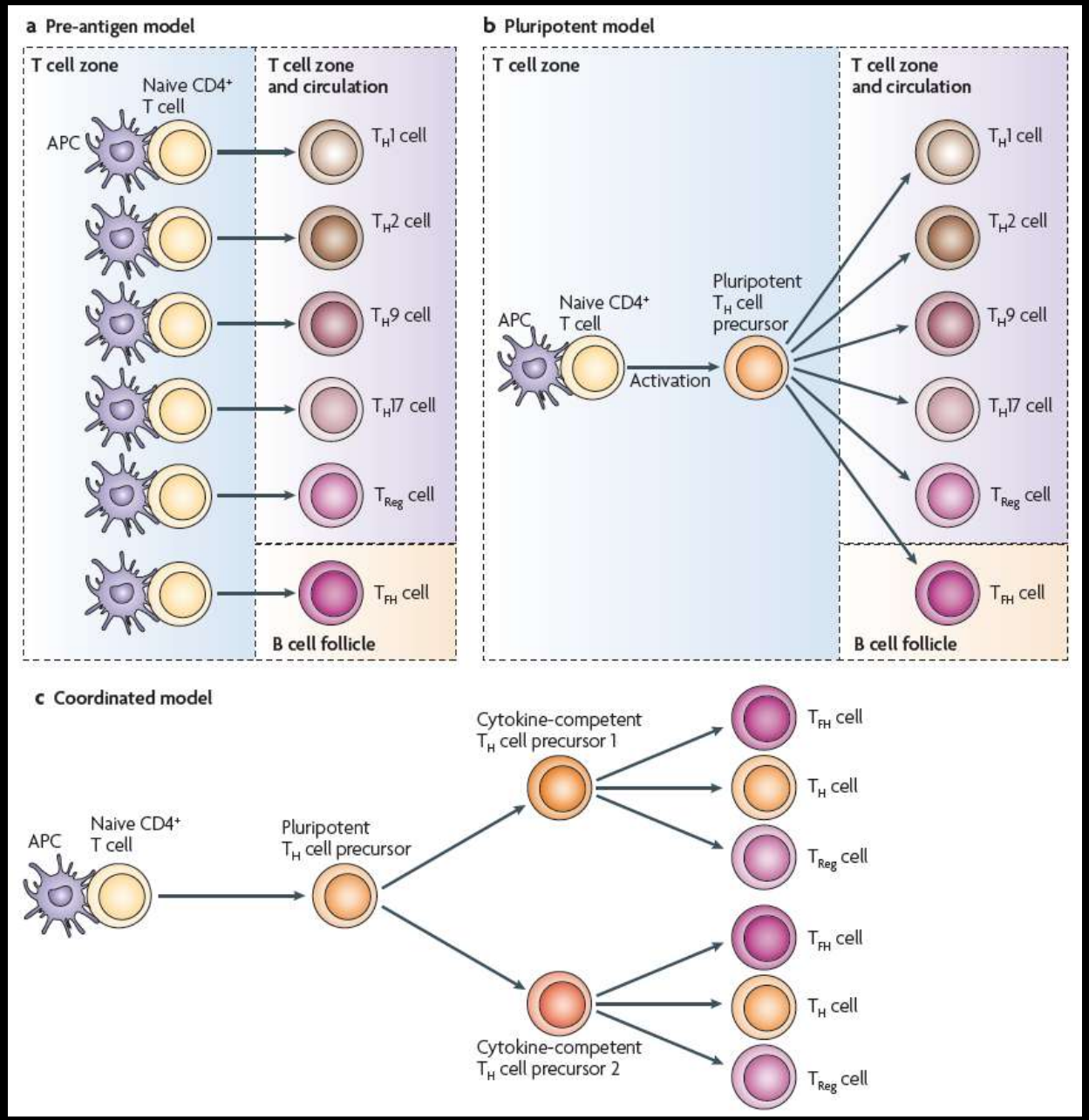
T foliküler yardımcı (Tfh) hücreler

- Kutuplaşmamış CD4+ T hücreleri ??

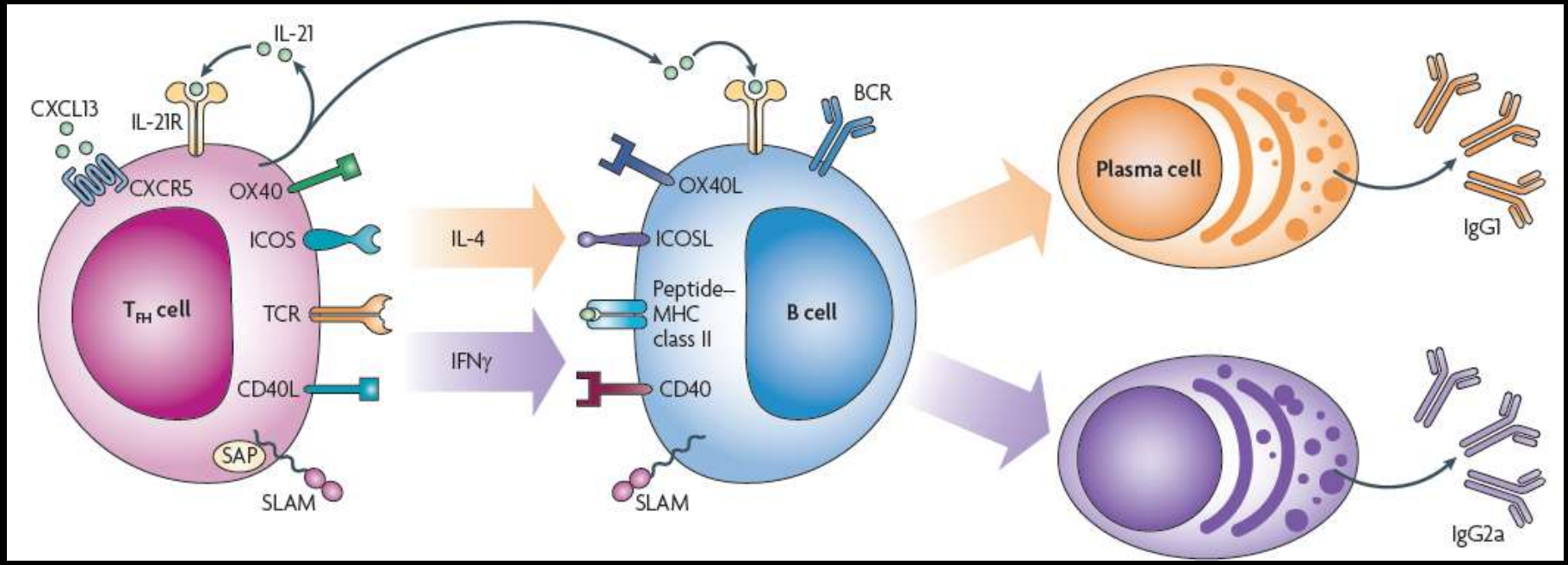
- B hücre foliküllerine yuvalanan yegane T hücre grubu (CXCR5)

- Antikor üretiminde

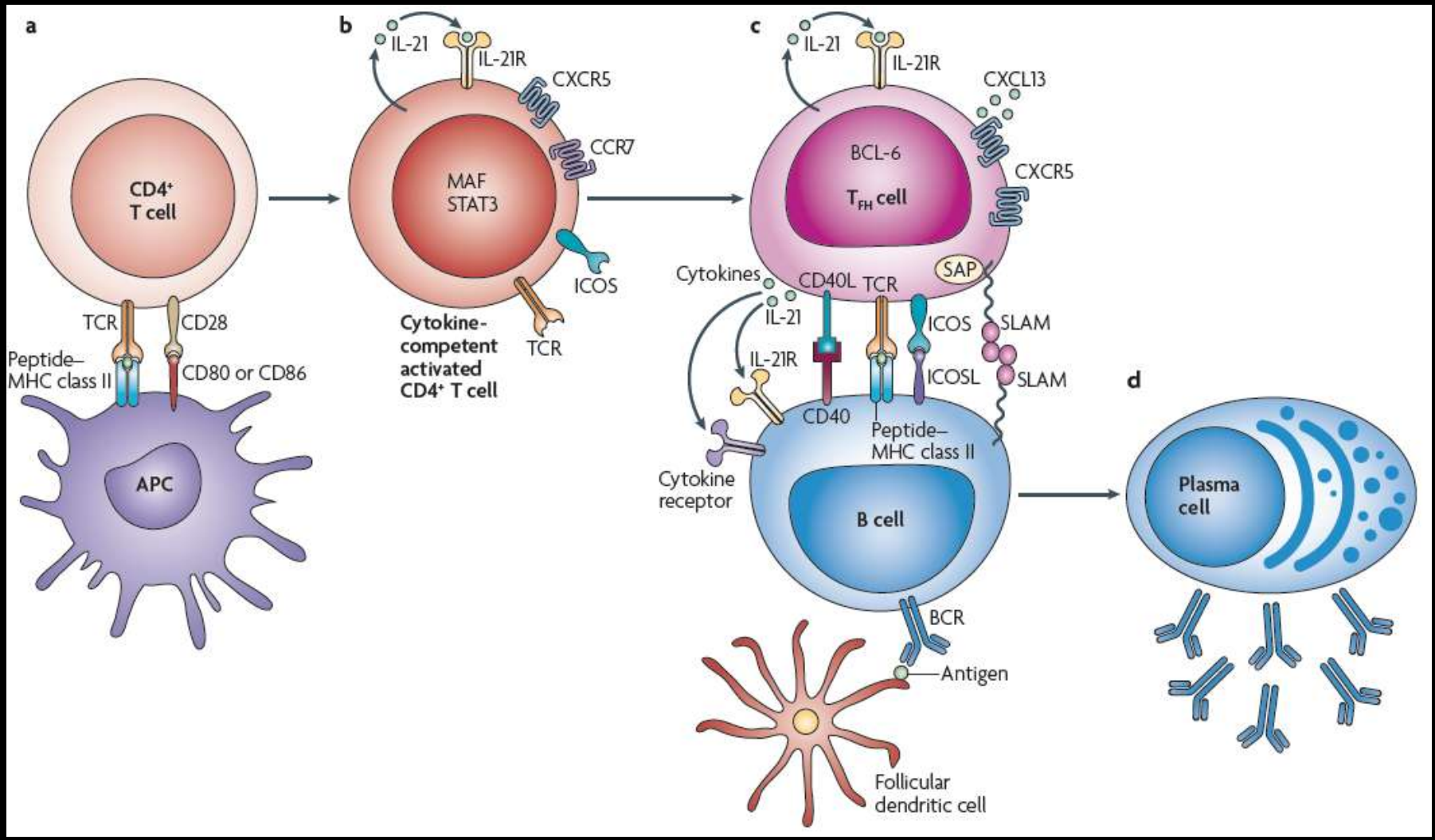
- İzotip dönüşümü



King C, Nat. Rev. Immunol. 2009: 9, 757-66.

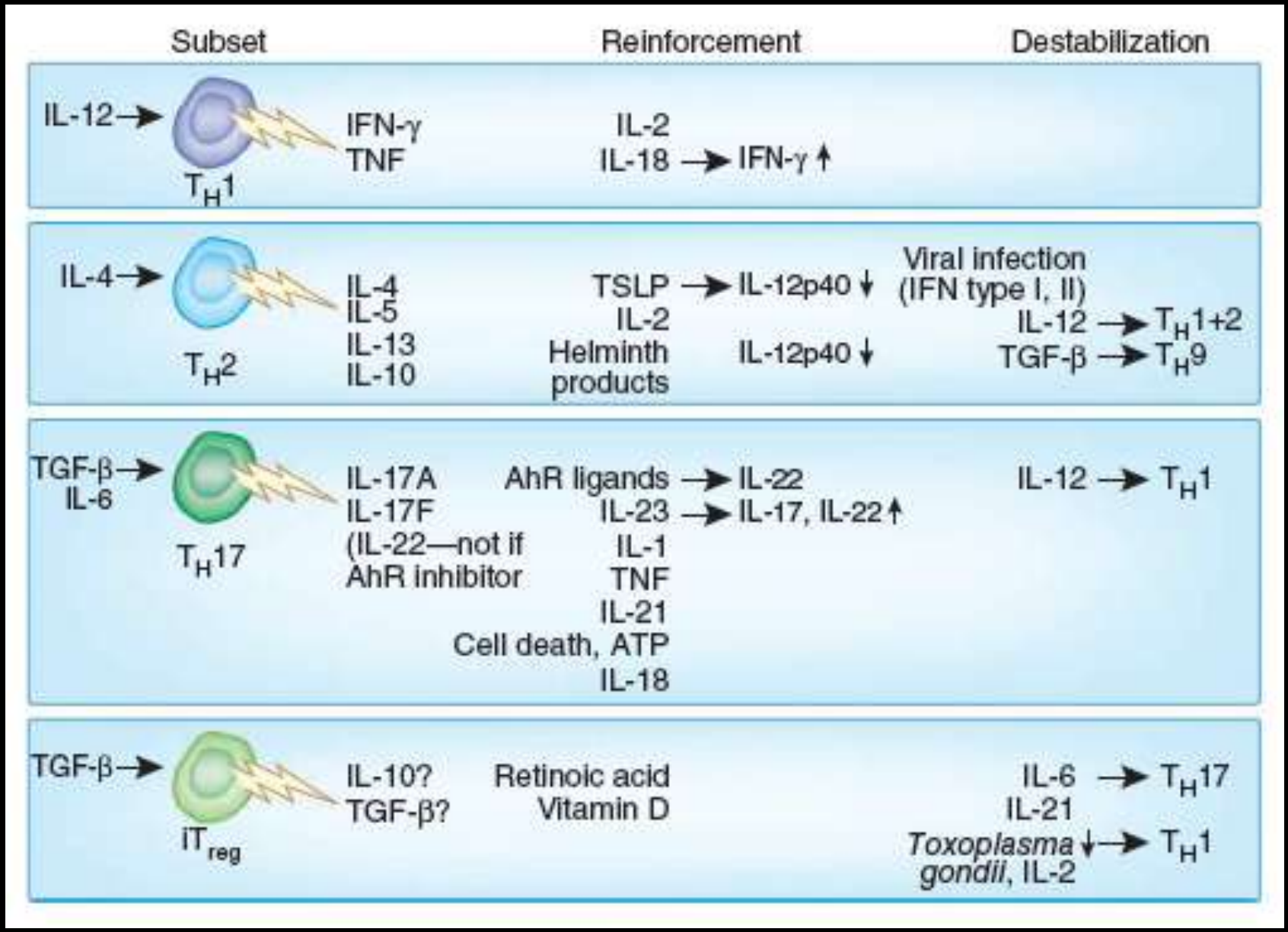


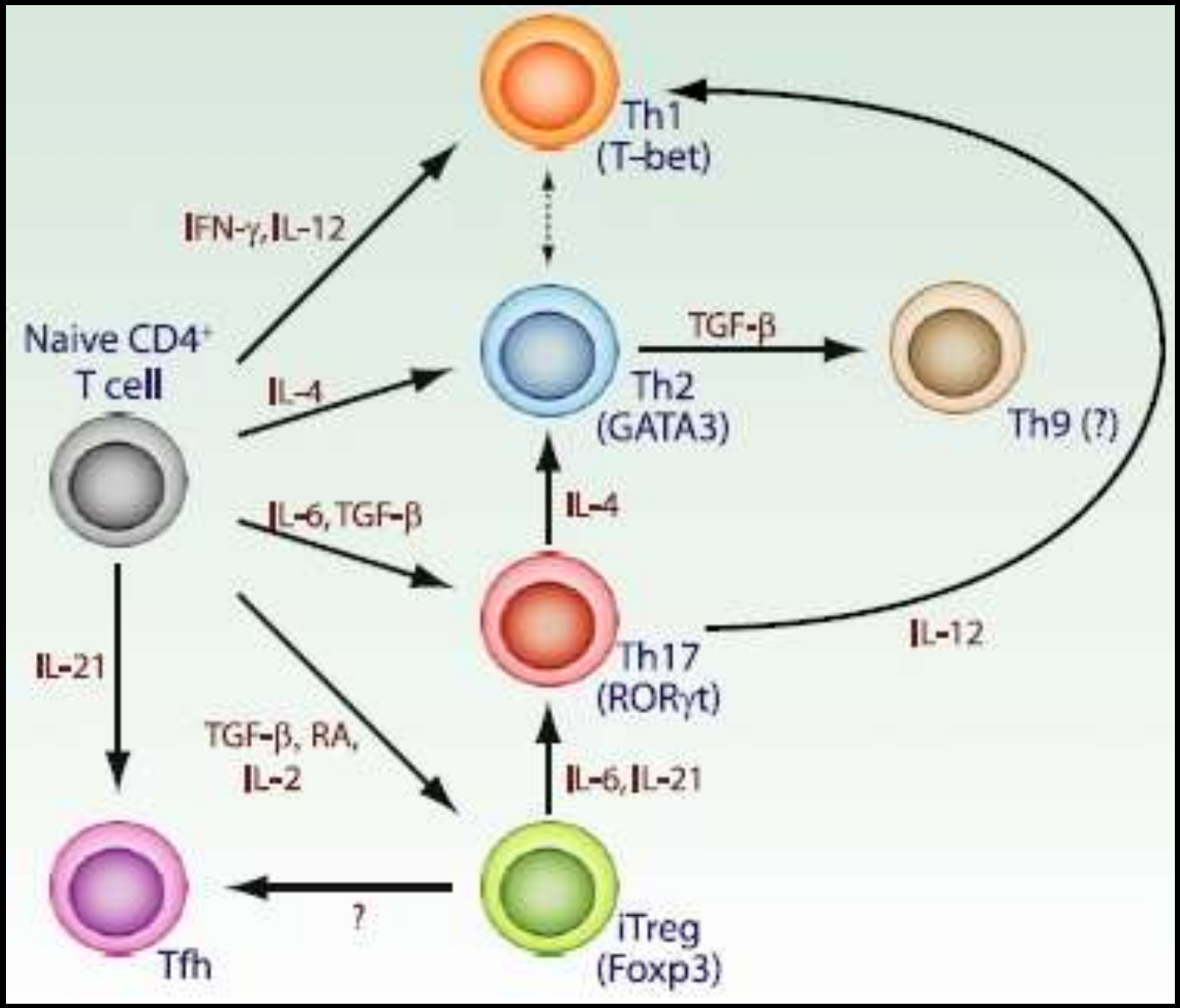
King C, Nat. Rev. Immunol. 2009: 9, 757-66.



King C, Nat. Rev. Immunol. 2009: 9, 757-66.

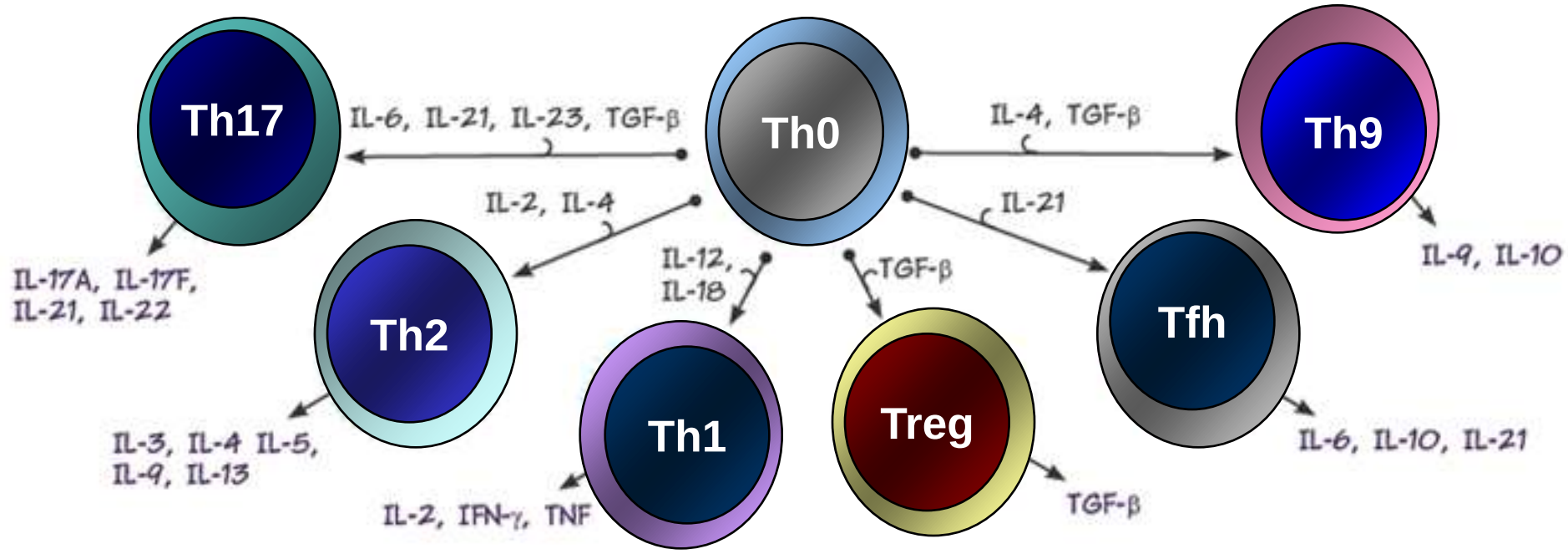
T hücre Plastisitesi



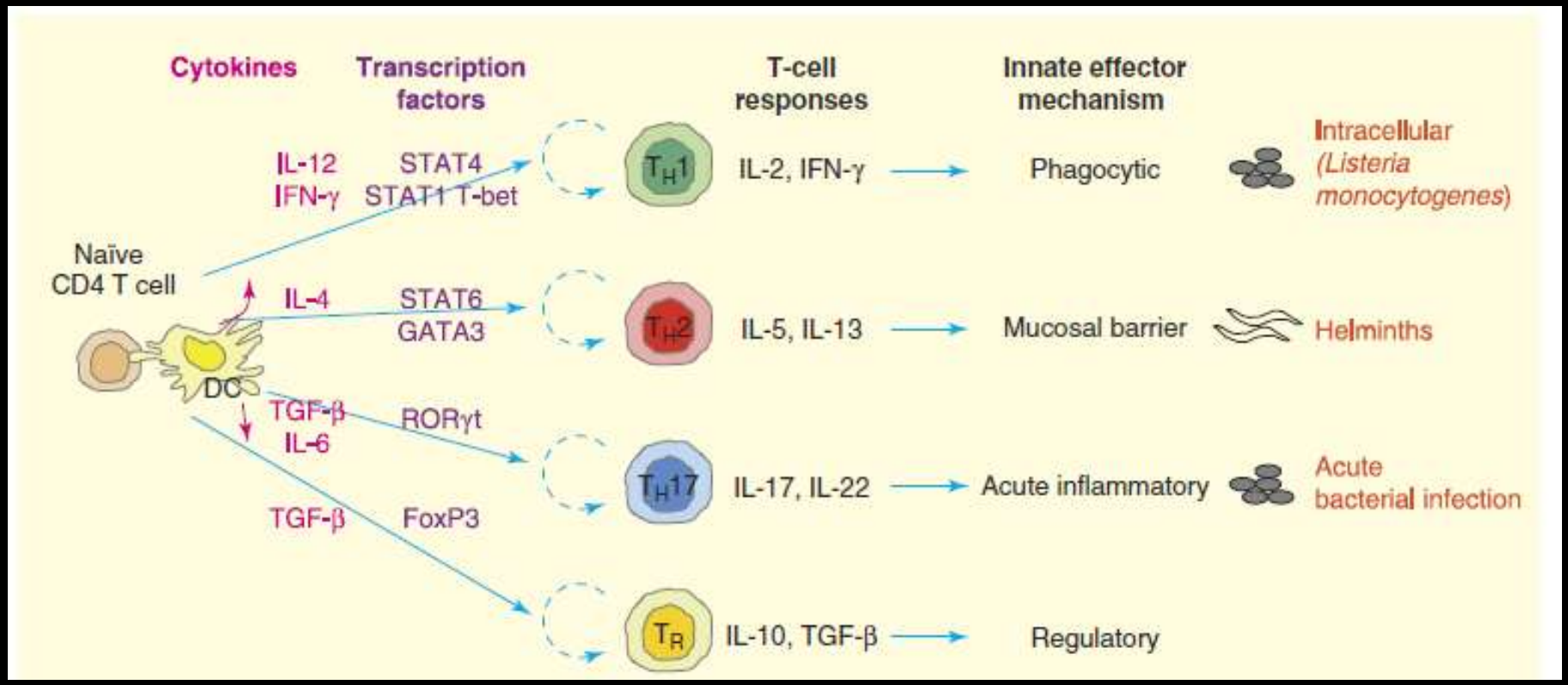


Zhou et al. Immunity 2009: 30, 646-55.

ÖZET


Th17
IL-6, IL-21, IL-23, TGF-β
Th0
IL-4, TGF-β
Th9
IL-9, IL-10
IL-17A, IL-17F,
IL-21, IL-22
IL-2, IL-4
IL-21
IL-12,
IL-18
TGF-β
Th2
Tfh
IL-3, IL-4 IL-5,
IL-9, IL-13
Th1
Treg
IL-6, IL-10, IL-21
IL-2, IFN-γ, TNF
TGF-β

ÖZET



Tfh antikor üretimi, affinite olgunlaşması, izotip dönüşümü

Th22 derinin inflamatuvar hastalıklarında

Th9 alerjik inflamasyonda ve paraziter hastalıklarda ?

İmmün sisteminiz sizi korusun

www.ulusalimmunoloji2011.org