



# Virüsler ve Otoimmün Hastalıklar



## I. VİRAL İNFEKSİYONLAR VE BAĞIŞIKLAMA SİMPOZYUMU

19-21 EYLÜL 2024

ALİ EMİRİ EFENDİ KÜLTÜR MERKEZİ / İSTANBUL



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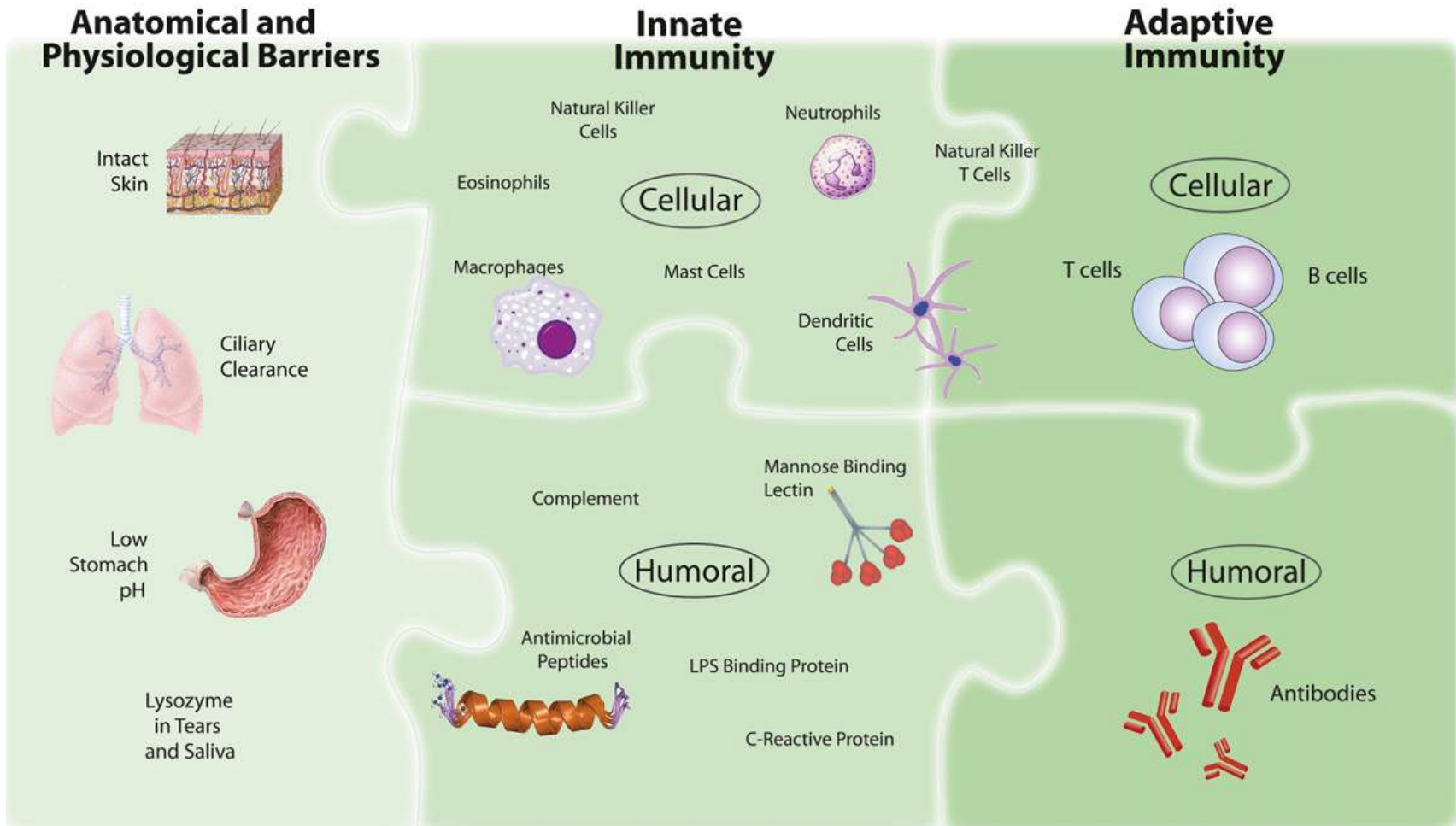


# Sunum Planı

- İmmün Yanıtlar
- Kısaca Virüsler
- İmmün Tolerans Nedir?
- Otoimmünite
- Virüsler ve Otoimmün Hastalıklar
- Çevresel Değişimler ve Tolerans

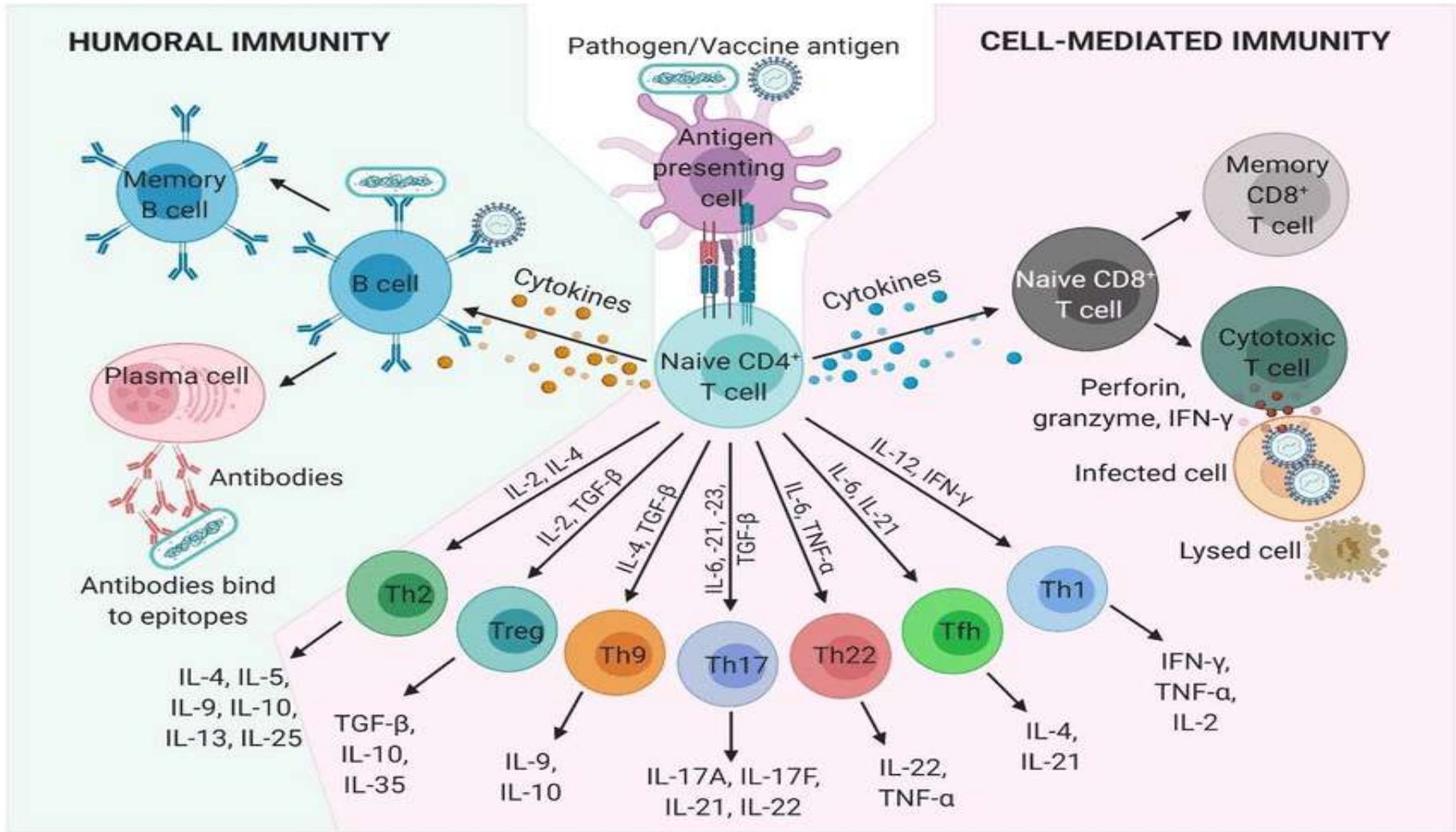


# Immün System

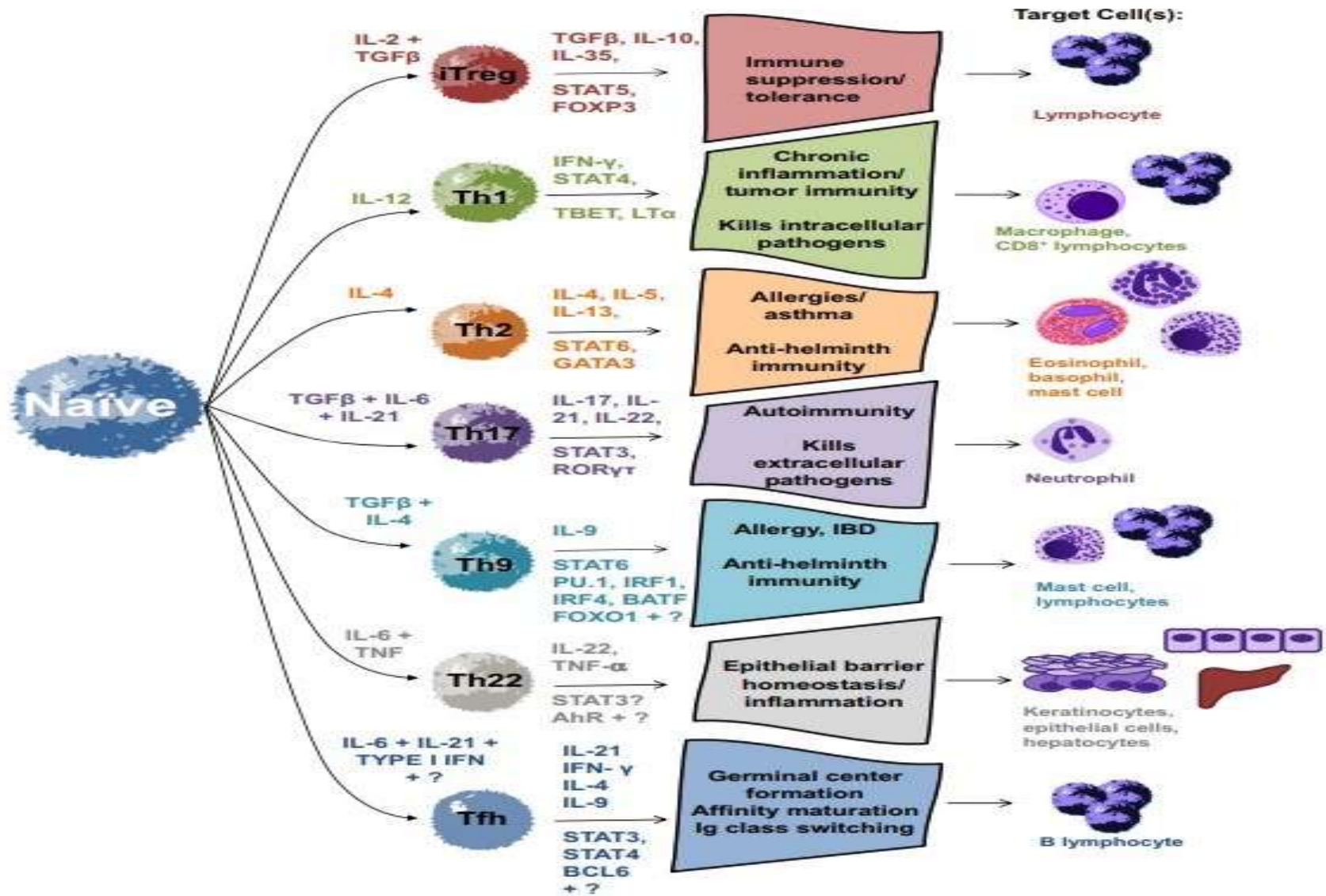




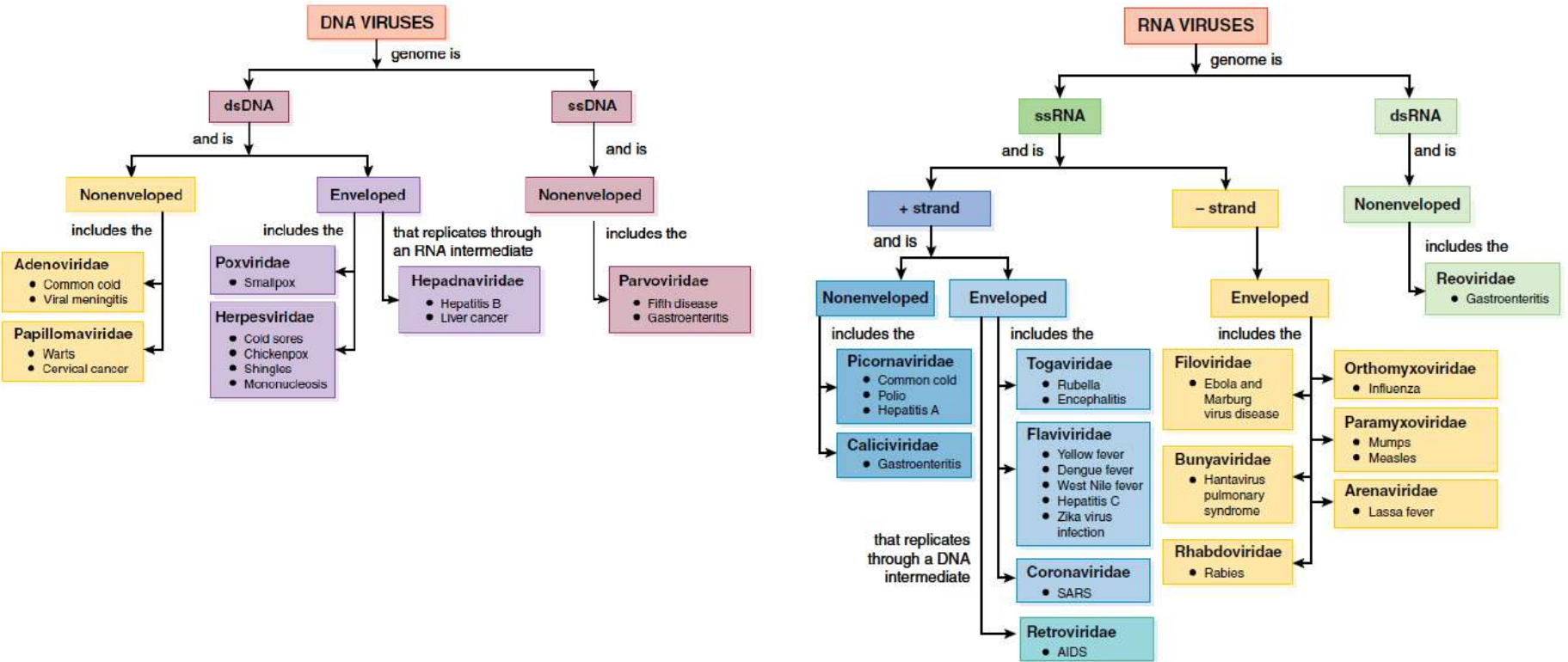
# Adaptif Immünite



# Adaptif Immünite



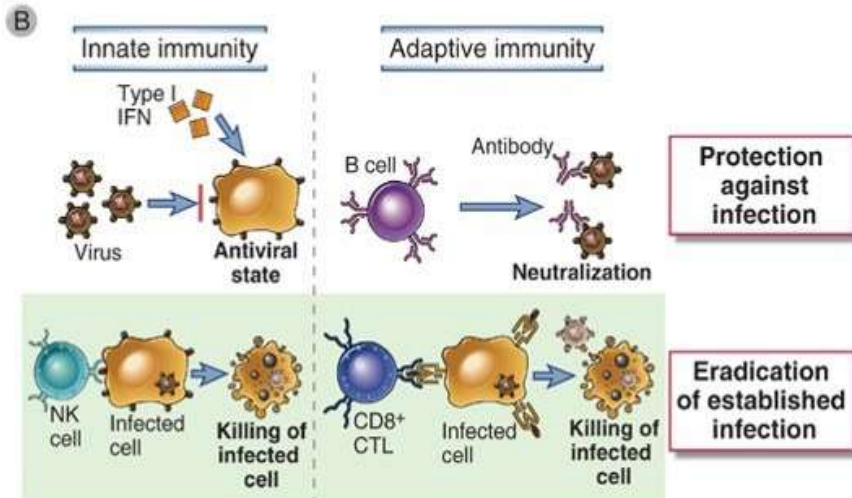
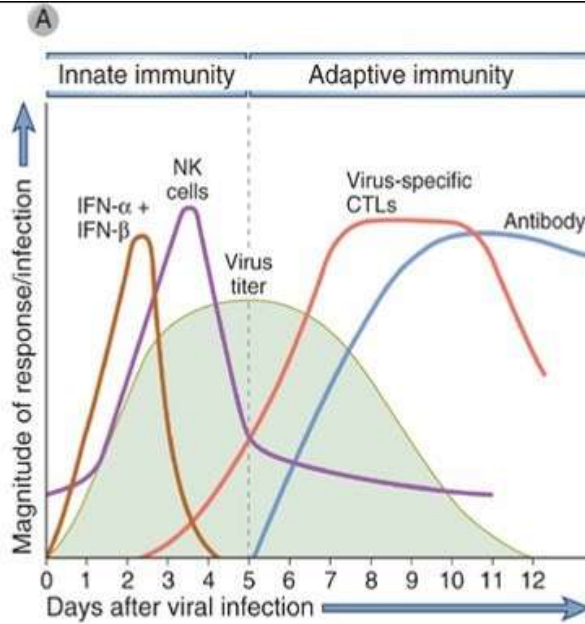
# Virüsler



- Replikasyon için hücrenin nükleik asit ve protein sentez mekanizmalarını kullanan zorunlu hücre içi patojenler
- Reseptör aracılı endositoz ile çeşitli hücre tiplerini enfekte ederler
- Doku hasarı ve çeşitli hastalıklara neden olabilirler
  - Viral replikasyon hücrenin normal protein sentezi ve fonksiyonlarını bozar
  - Hücre hasarı ve hücre ölümü (sitopatik ve litik etki)
  - İnflamasyon
  - Anti-viral immün yanıtlara bağlı doku hasarı



# Virüslere Karşı İmmün Yanıtlar



## DOĞAL İMMÜNİTE

- Tip1 IFN üretimi
  - TLR'ler ile viral DNA/RNA tanınması
  - RIG benzeri rsp (RNA) STING yolağı(RNA)
  - Viral replikasyon baskılanır
- NK Hücreleri
  - MHC-I betimlemeyen hücrelerin apoptozu

## KAZANILMIŞ İMMÜNİTE

- Antikorlar
  - Sadece hc. dışındaki virüslere karşı
  - Bağlanma-opsonizasyon-kompleman
- CD8<sup>+</sup> Sitotoksik T Lenfositleri
  - MHC-I üzerinden tanıma
  - Enfekte hücrelerin apoptozu
  - Doku hasarı??





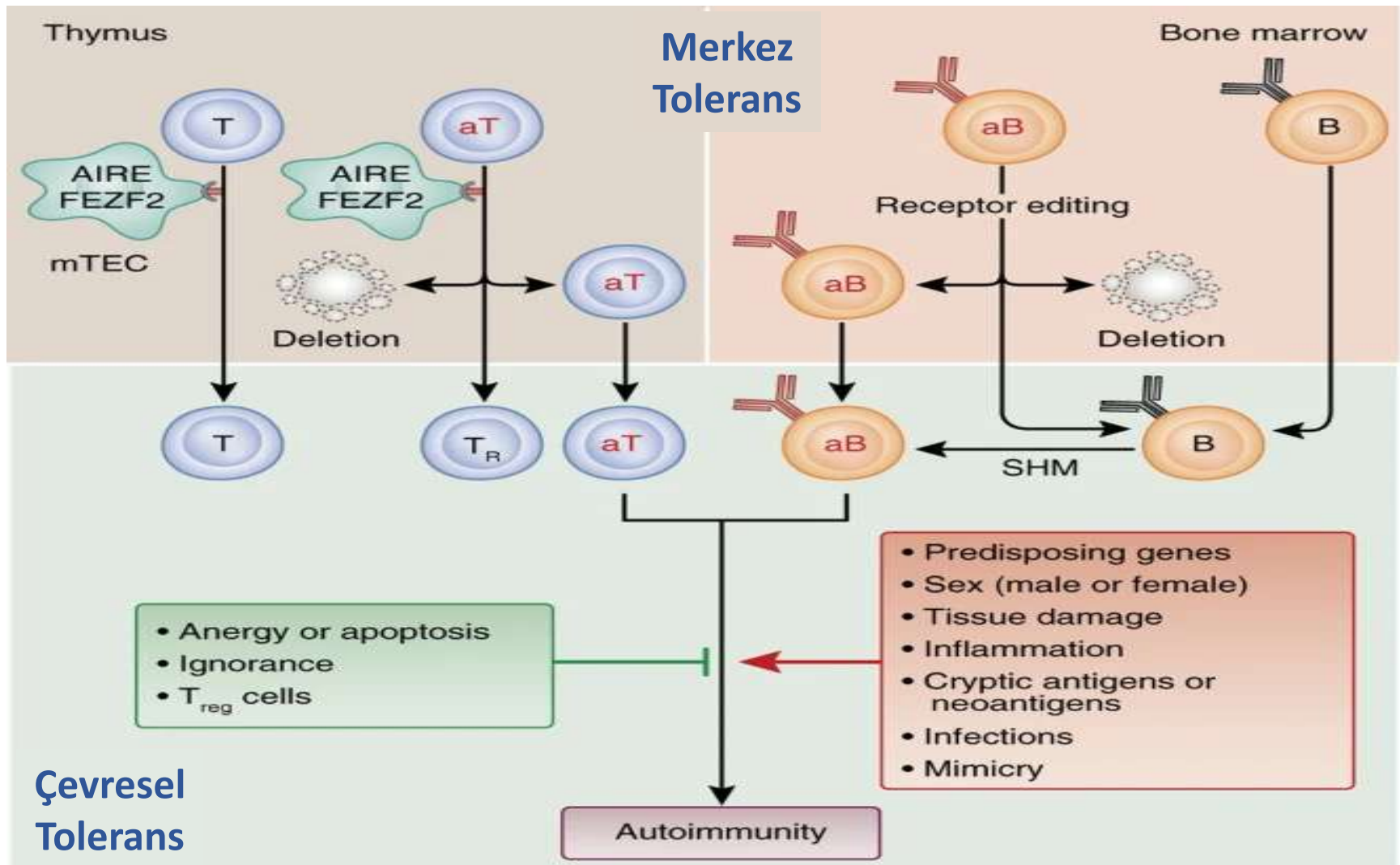
# İMMÜN TOLERANS NEDİR?

- Çeşitli yabancı antijenler (alerjen, normal flora bakterileri) ve self-antijenlere yanıtızsızlık
- Belirli bir antijene özgül reseptör taşıyan lenfosit antijenle karşılaşırsa
  - Lenfosit aktivasyonu-proliferasyon-fonksiyonel farklılaşma; **İMMÜN YANIT** (İMMÜNOJENİK ANTİJENLER; MİKROPLAR)
  - Lenfositlerin fonksiyonel inaktivasyonu-apoptozu; **TOLERANS** (TOLEROJENİK ANTİJENLER; ÖZ ANTİJENLER)
  - Bazen lenfositler antijen varlığını reddeder; **İMMÜNOLOJİK İGNORANS**
  - **Aktivasyon / Tolerans oluşumunun belirleyicisi:**
    - Antijenin doğası
    - Antijenin immün sisteme sunulduğu anda ortamda bulunan ilave sinyaller

# İMMÜN TOLERANS MEKANİZMALARI

- T ve B lenfosit olgunlaşması sırasında otoreaktif hücrelerin eliminasyonu
- Perifere çıkabilmiş otoreaktif hücrelerin non-reaktif halde tutulmaları
- Periferde regülatör hücre gruplarının otoreaktif hücreleri susturması ve homeostasi sağlamaları
- İmmün ayrıcalıklı bölgeler (beyinde kan beyin bariyeri sayesinde) immün hücre girişinin sınırlandırılması ve yoğun baskılayıcı sitokin ortamı

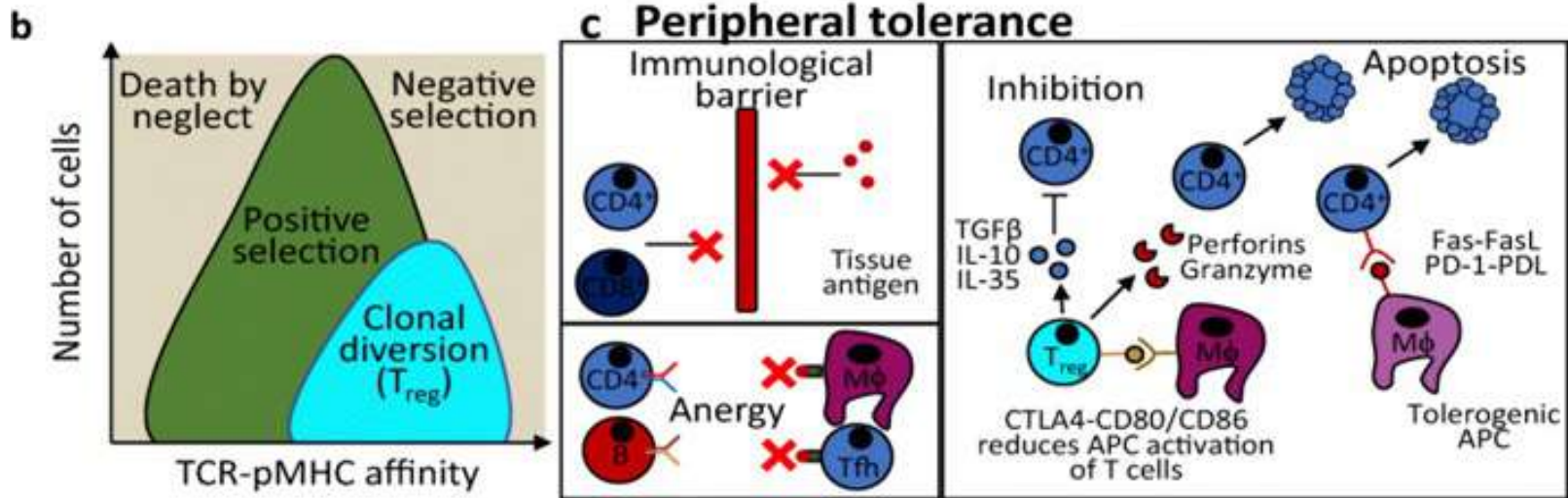
# TOLERANS MEKANİZMALARI



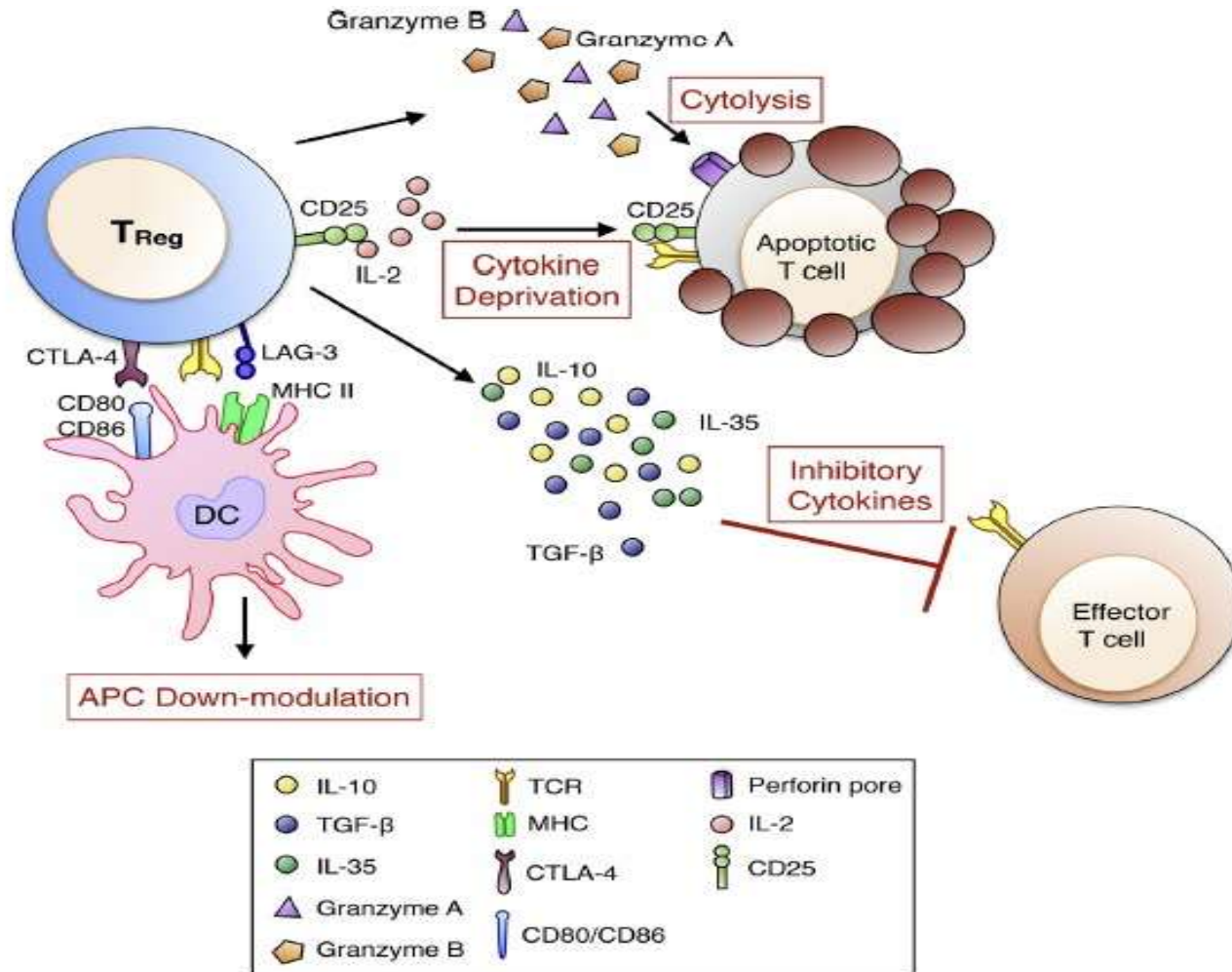
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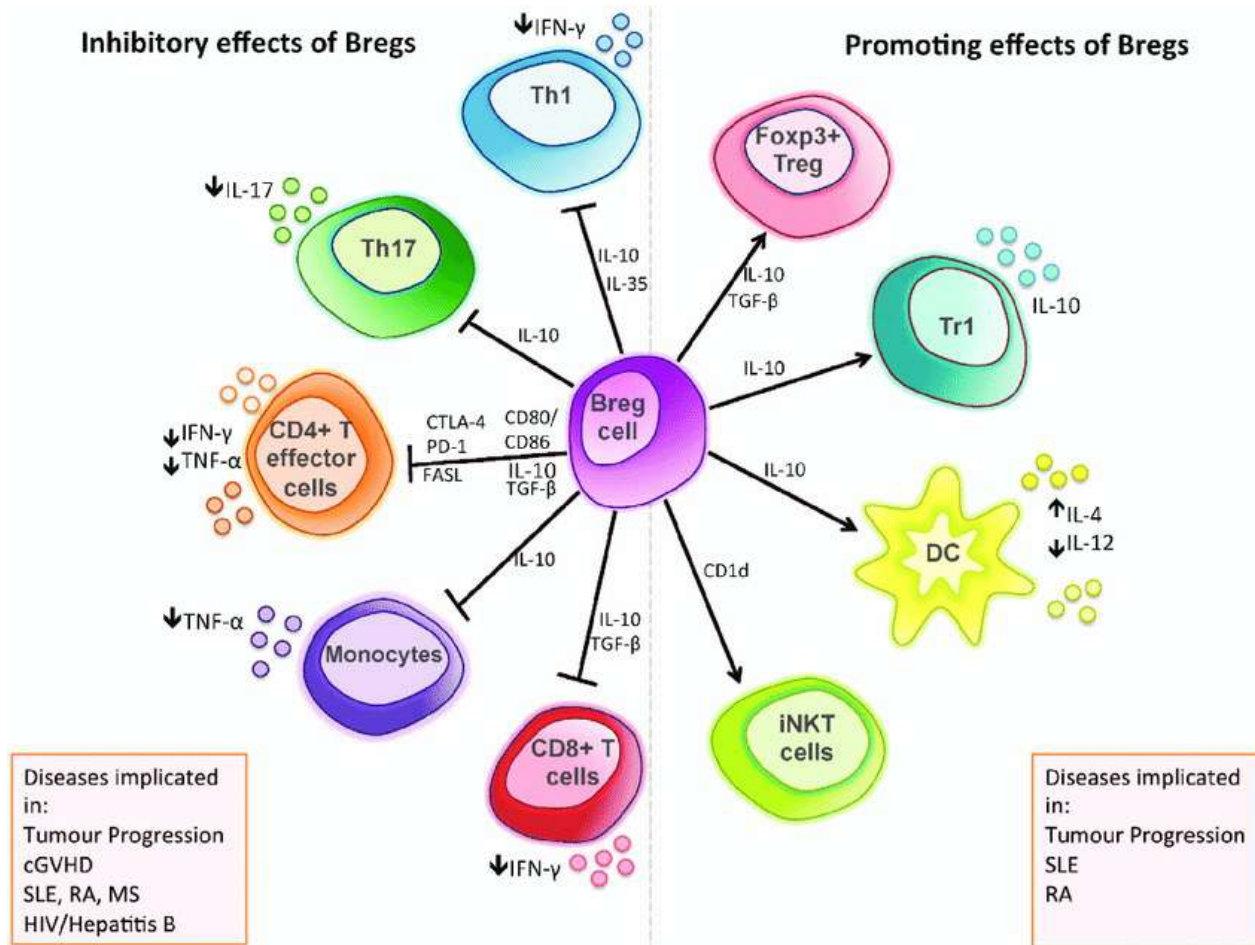
# İMMÜN TOLERANS MEKANİZMALARI



# Treg ETKİ MEKANİZMALARI



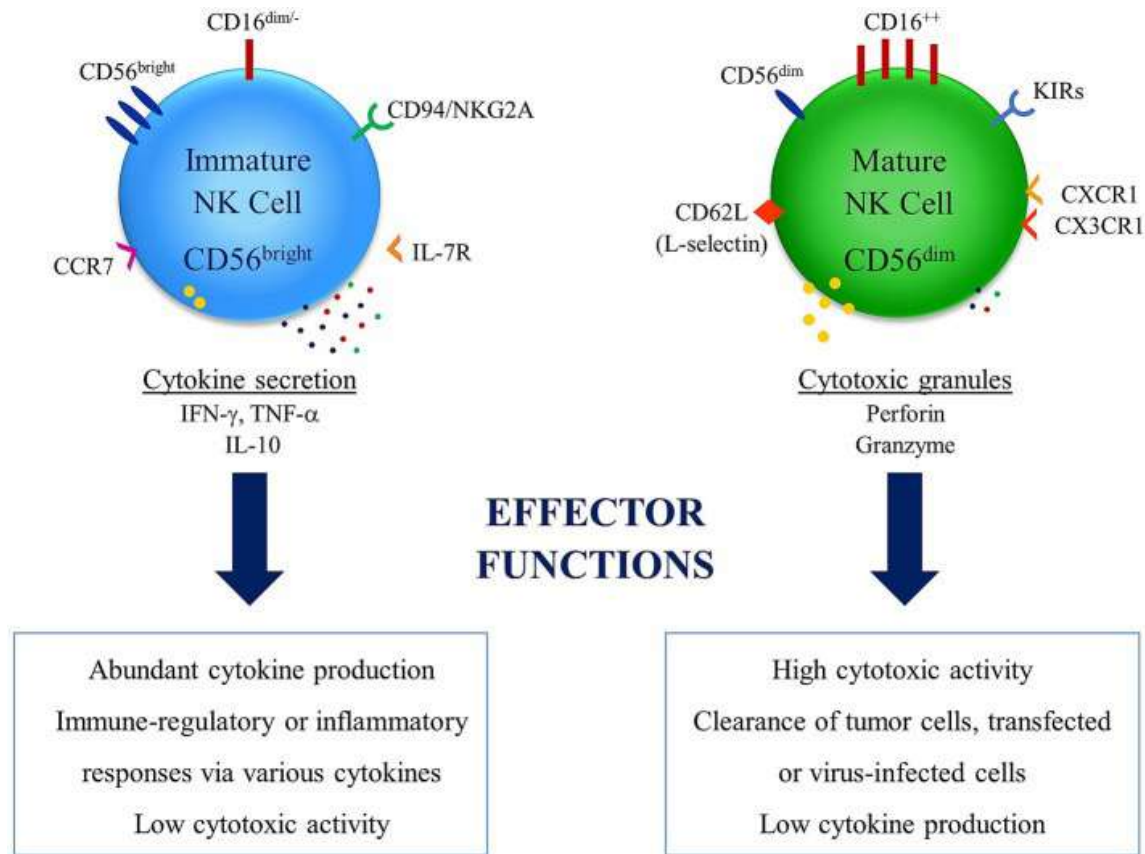
# Breg HÜCRELERİ



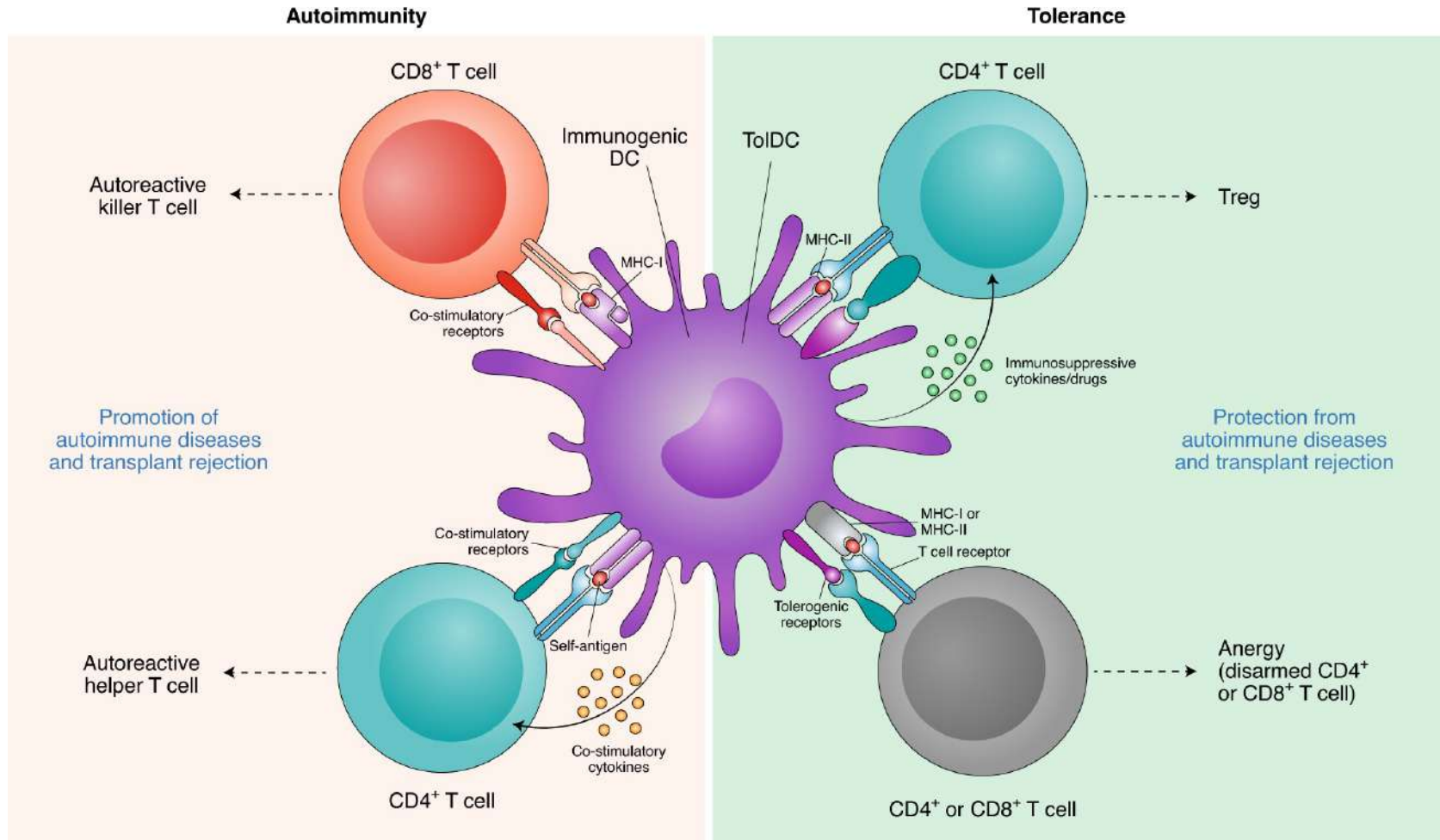
Sarvaria, A., Madrigal, J. & Saudemont, A. B cell regulation in cancer and anti-tumor immunity. *Cell Mol Immunol* 14, 662–674 (2017)



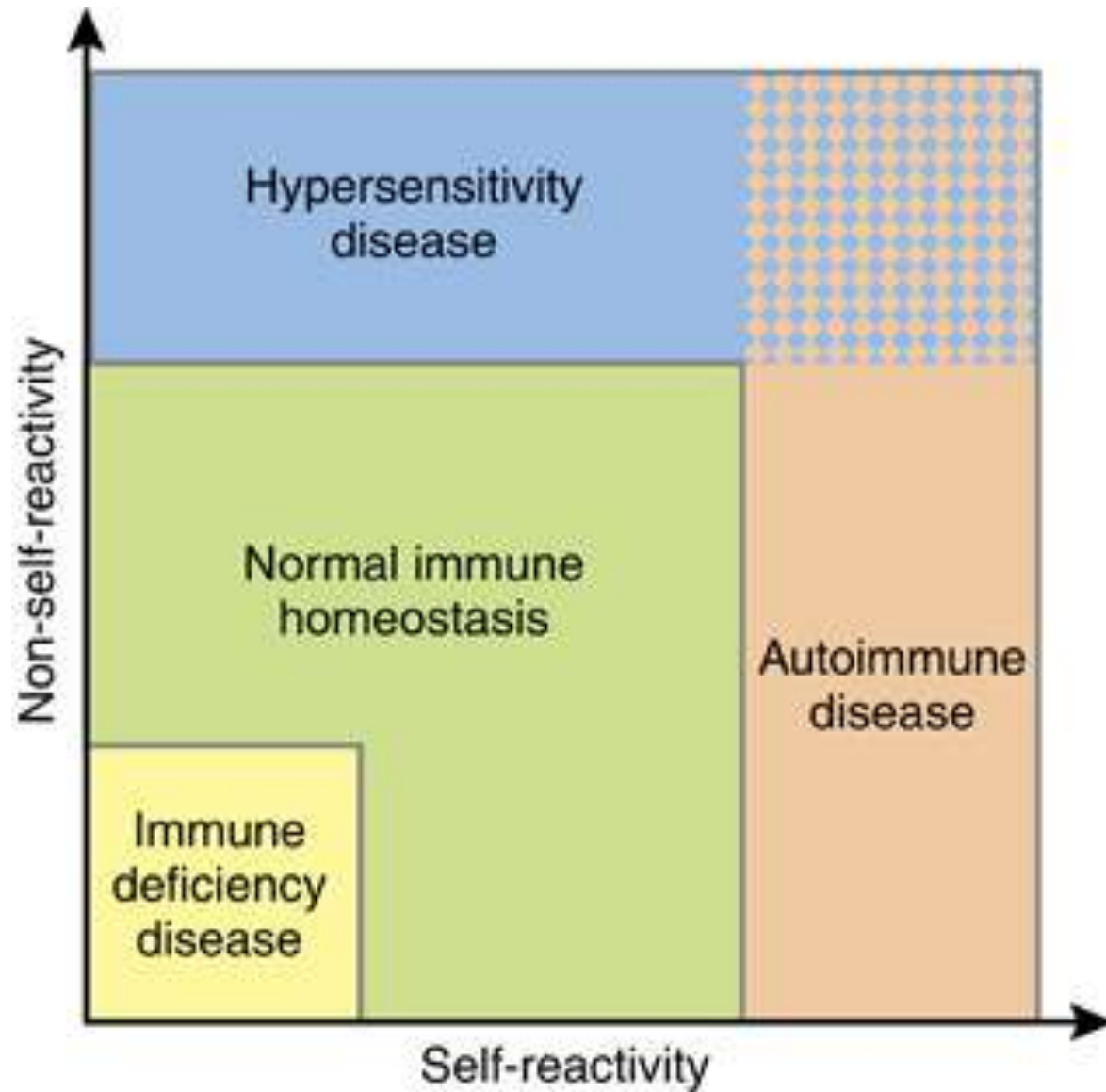
# DOĞAL ÖLDÜRÜCÜ (NK) HÜCRELERİ



# DH ve TOLERANS



# İMMÜN ARACILIKLI HASTALIKLAR

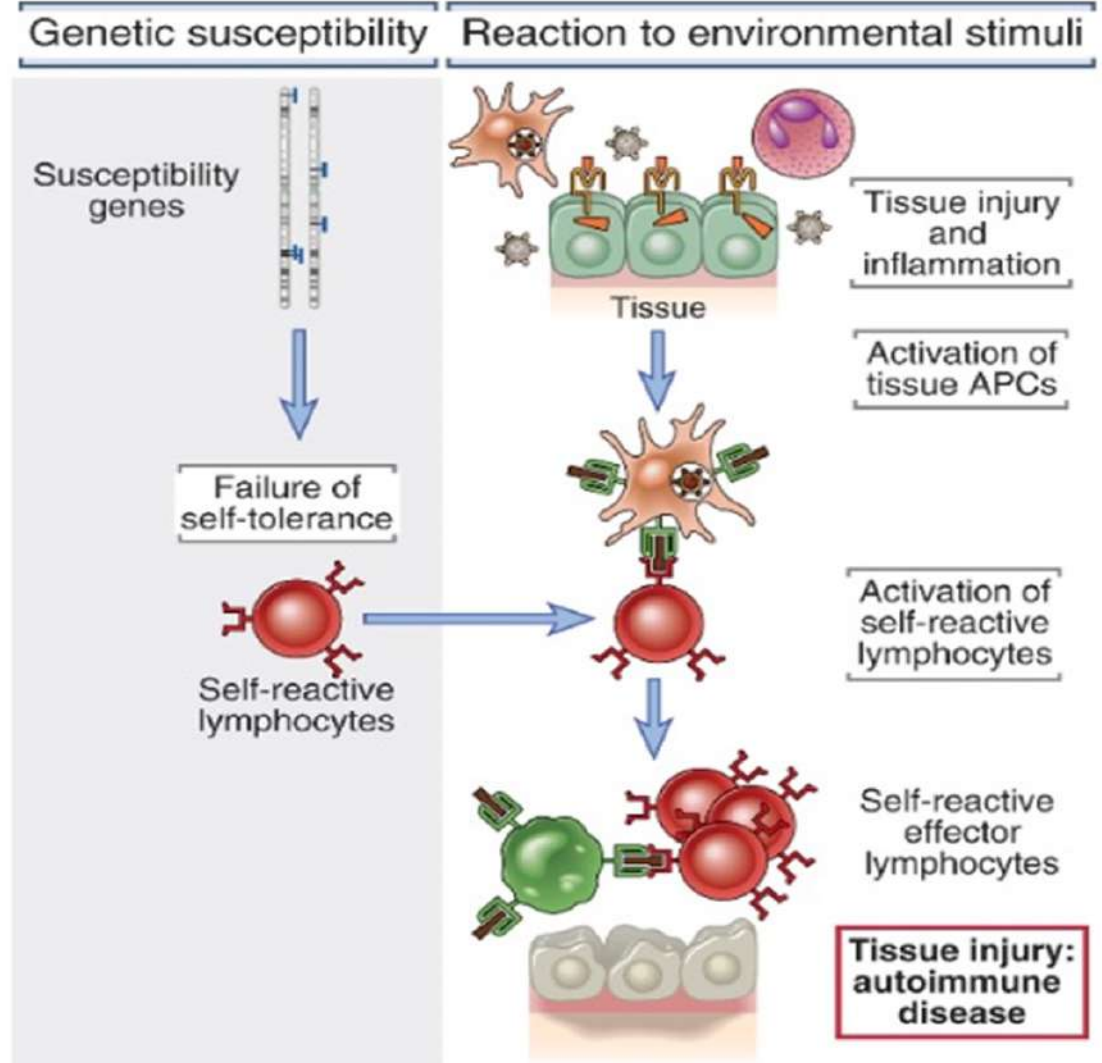




A word cloud centered around the word "AUTOIMMUNITY". The words are arranged in various orientations and sizes, with "AUTOIMMUNITY" being the largest and most prominent. Other words include "ADRENOCORTICAL", "NUCLEOPROTEINS", "SCLEROSING", "PURPURA", "ANKYLOSING", "MELLITUS", "RECEPTOR", "APOPTOSIS", "INFLAMMATORY", "SPECIFIC", "PATHOGENESIS", "ATTENUATES", "PROPOSED", "IMMUNODEFICIENCY", "DISEASE", "NEOPLASTIC", "SYSTEMIC", "ANTIBODY", "LYMPHOCYTE", "ANTIGEN", "IMMUNE", "IMMUNOLOGICAL", "ETANERCEPT", "CHRONIC", "SPONDYLITIS", "CORRELATE", "ANTIGEN", "ABERRANT", "RESPONSE", "CELL", "LUPUS", "MECHANISM", "DIABETES", "CHOLANGITIS", "LYMPHOID", "MECHANISM", "DIABETES", "EPITOPE", "RHEUMATOID", "PUTATIVE", "TOLERANCE", "ACTIVATION", "AUTOIMMUNE", "HYPOPARATHYROIDISM", "NEMIMYTHYROIDITIS", "ARTHRITIS", "GRANULOMATOUS", "ERYTHEMATOSUS", "SCLERODERMA", "SINOCULATION", "MIMICRY", "ANTIGEN", "ABERRANT", "MECHANISM", "DIABETES", "RHEUMATOID", "PUTATIVE", "ACTIVATION", "AUTOIMMUNE", "NEMIMYTHYROIDITIS", "GRANULOMATOUS", "SCLERODERMA", "HYPOPARATHYROIDISM", "ARTHRITIS", "ERYTHEMATOSUS".

# OTOİMMÜNİTE NEDİR?

- Öz antijenlere yanıtılık
- Gelişmiş ülke nüfusun %2-5'i etkilenir
- Multi-faktöryel
  - Çevresel faktörler
  - Genetik yatkınlık
  - Enfeksiyon
  - Lokal doku hasarı



# OTOİMMÜNİTEDE GENETİK YATKINLIK

HLA- and gender-associated risk for autoimmune disease			
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Type 1 diabetes	DQ2 and DQ8	~25	~1
Goodpasture's syndrome	DR2	15.9	~1
Pemphigus vulgaris	DR4	14.4	~1
Autoimmune uveitis	B27	10	<0.5
Psoriasis vulgaris	CW6	7	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Addison's disease	DR3	5	~13
Multiple sclerosis	DR2	4.8	10
Rheumatoid arthritis	DR4	4.2	3
Graves' disease	DR3	3.7	4–5
Hashimoto's thyroiditis	DR5	3.2	4–5
Myasthenia gravis	DR3	2.5	~1
Type I diabetes	DQ6	0.02	~1

**TABLE 15-3 Selected Non-HLA Genetic Polymorphisms Associated with Autoimmune Diseases**

Gene of Interest	Function	Diseases
<b>Genes Involved in Immune Regulation</b>		
<i>PTPN22</i>	Protein tyrosine phosphatase; role in T and B cell receptor signaling	RA, T1D, IBD
<i>CD2/CD58</i>	Costimulation of T cells	RA, MS
<i>IL23R</i>	Component of IL-23 receptor; role in generation and maintenance of T <sub>H</sub> 17 cells	IBD, PS, AS
<i>IL10</i>	Downregulates expression of costimulators, MHC molecules, IL-12 in dendritic cells; inhibits T <sub>H</sub> 1 responses	IBD, SLE, T1D
<i>CTLA4</i>	Inhibitory receptor of T cells, effector molecule of regulatory T cells	T1D, RA
<i>IL2/IL21</i>	Growth and differentiation factors for T cells; IL-2 is involved in maintenance of functional Tregs	IBD, CdD, RA, T1D, MS
<i>IL12B</i>	p40 subunit of IL-12 (T <sub>H</sub> 1-inducing cytokine) and IL-23 (T <sub>H</sub> 17-inducing cytokine)	IBD, PS
<i>BLK</i>	B lymphocyte tyrosine kinase, involved in B cell activation	SLE, RA
<i>IL2RA</i>	IL-2 receptor $\alpha$ chain (CD25); role in T cell activation and maintenance of regulatory T cells	MS, T1D
<b>Genes Involved in Responses to Microbes</b>		
<i>NOD2</i>	Cytoplasmic sensor of bacteria	IBD
<i>ATG16</i>	Autophagy (destruction of microbes, maintenance of epithelial cell integrity)	IBD
<i>IRF5, IFIH1</i>	Type I interferon responses to viruses	SLE



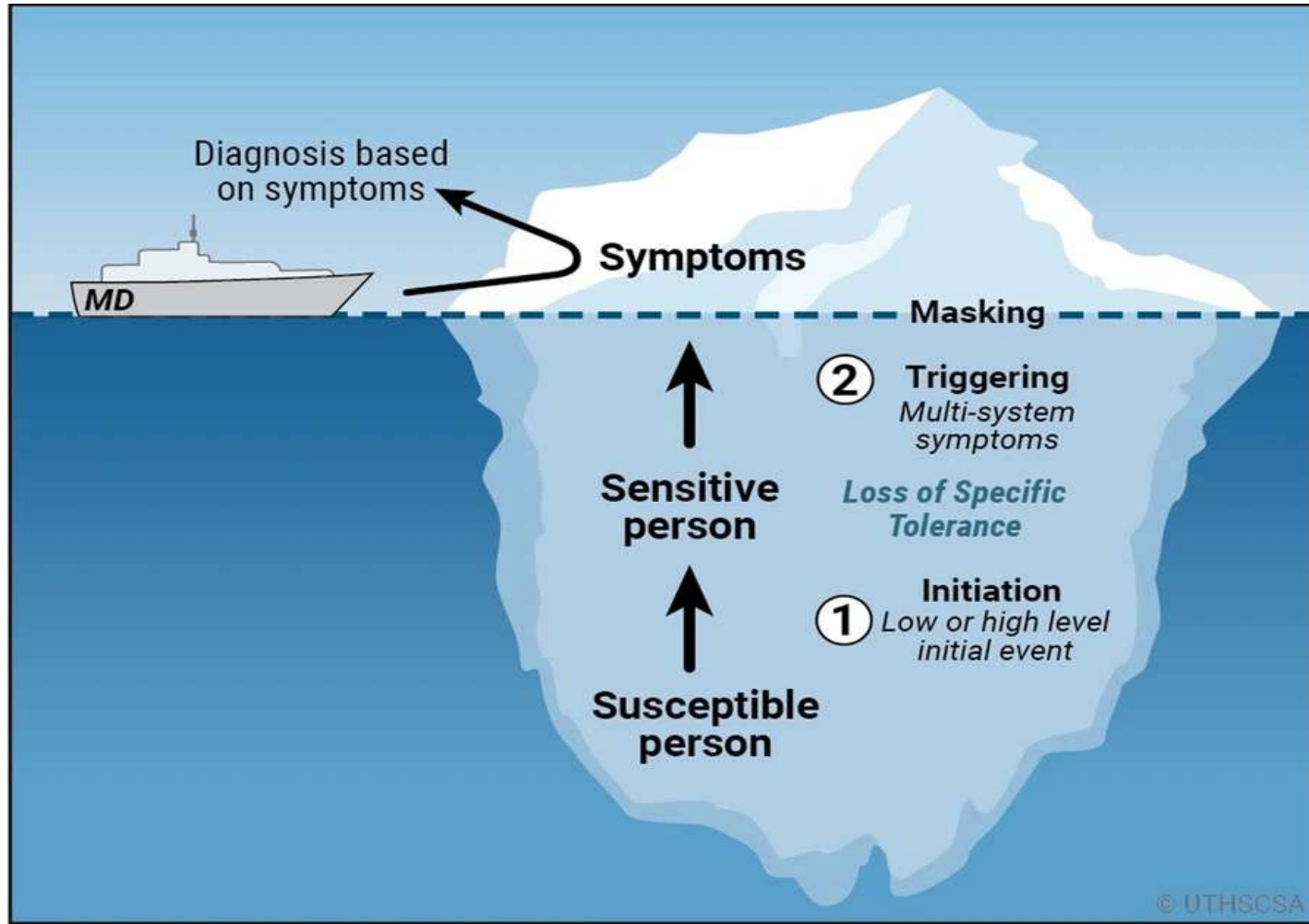
# OTOİMMÜNİTE İLİŞKİLİ GEN MUTASYONLARI

**TABLE 15-4 Examples of Single-Gene Mutations That Cause Autoimmune Diseases**

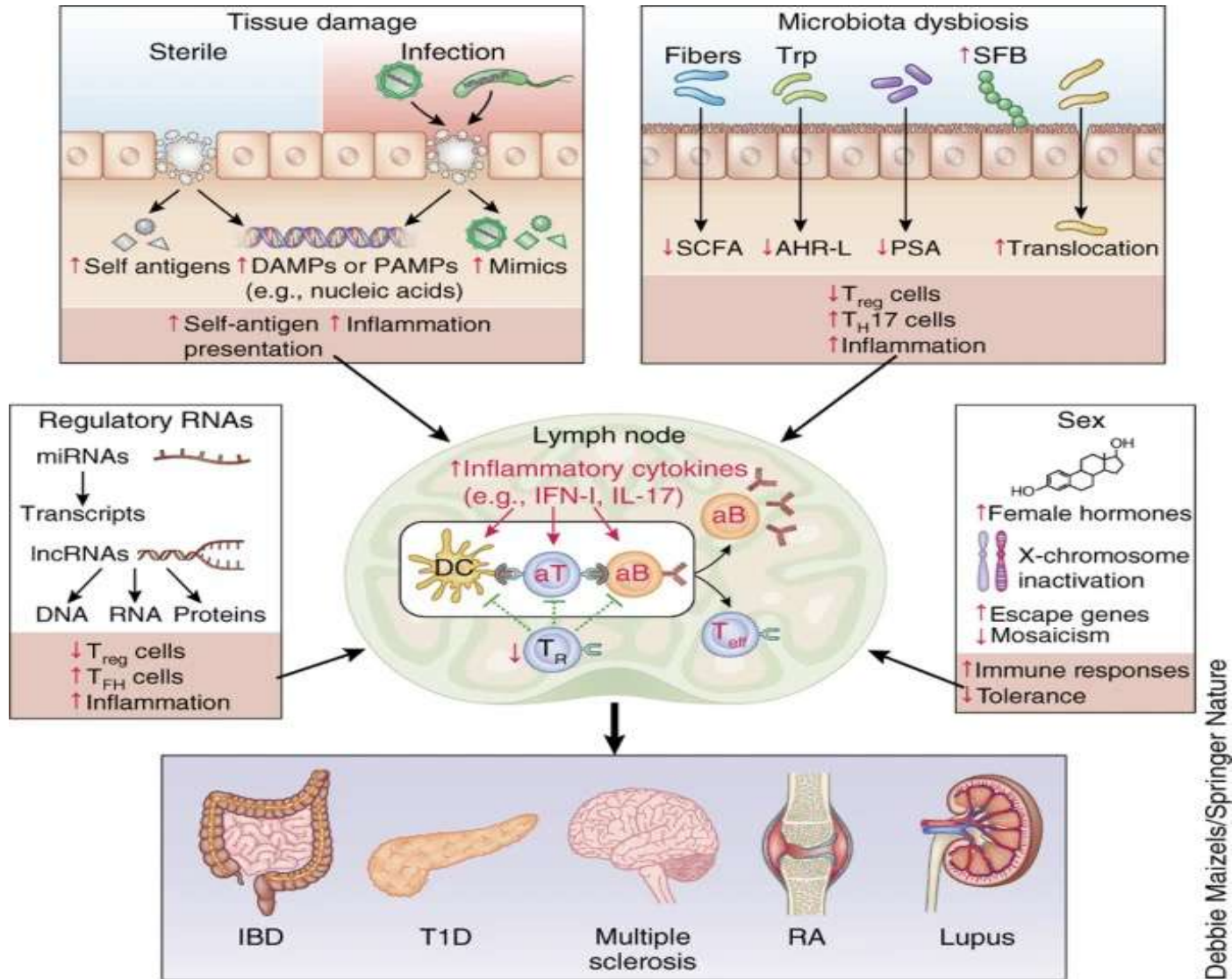
Gene	Phenotype of Mutant or Knockout Mouse	Mechanism of Failure of Tolerance	Human Disease?
<i>AIRE</i>	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
<i>C4</i>	SLE	Defective clearance of immune complexes; failure of B cell tolerance	SLE
<i>CTLA4</i>	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in CD4 <sup>+</sup> T cells; defective function of regulatory T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
<i>FAS/FASL</i>	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature CD4 <sup>+</sup> T cells	Autoimmune lymphoproliferative syndrome (ALPS)
<i>FOXP3</i>	Multiorgan lymphocytic infiltrates, wasting	Deficiency of functional regulatory T cells	IPEX
<i>IL2, IL2R<math>\alpha/\beta</math></i>	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival, or function of regulatory T cells	None known
<i>SHP1</i>	Multiple autoantibodies	Failure of negative regulation of B cells	None known



# OTOİMMÜNİTE vs OTOİMMÜN HASTALIK

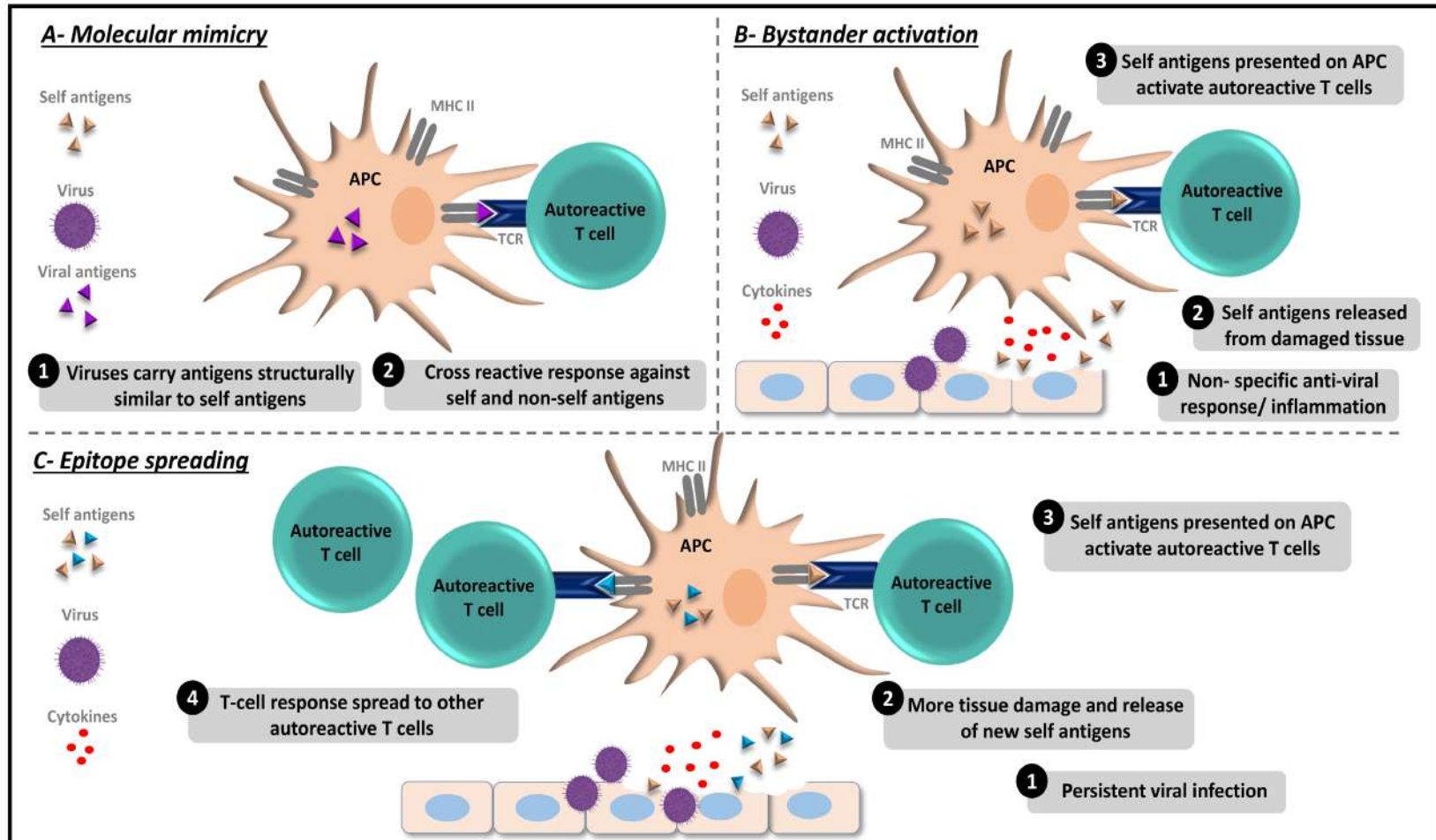


# OTOIMMÜNITE

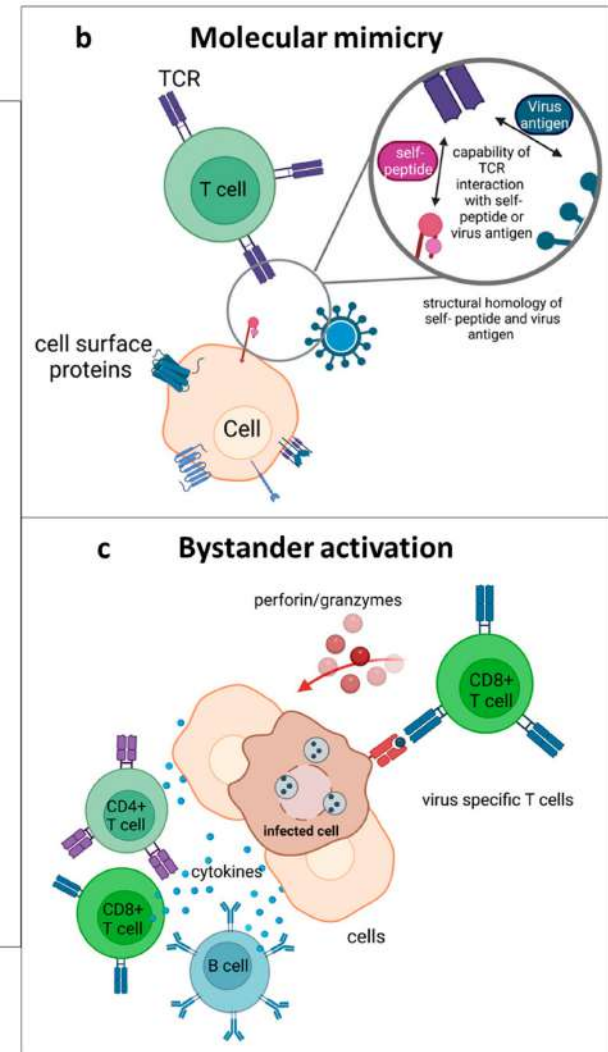
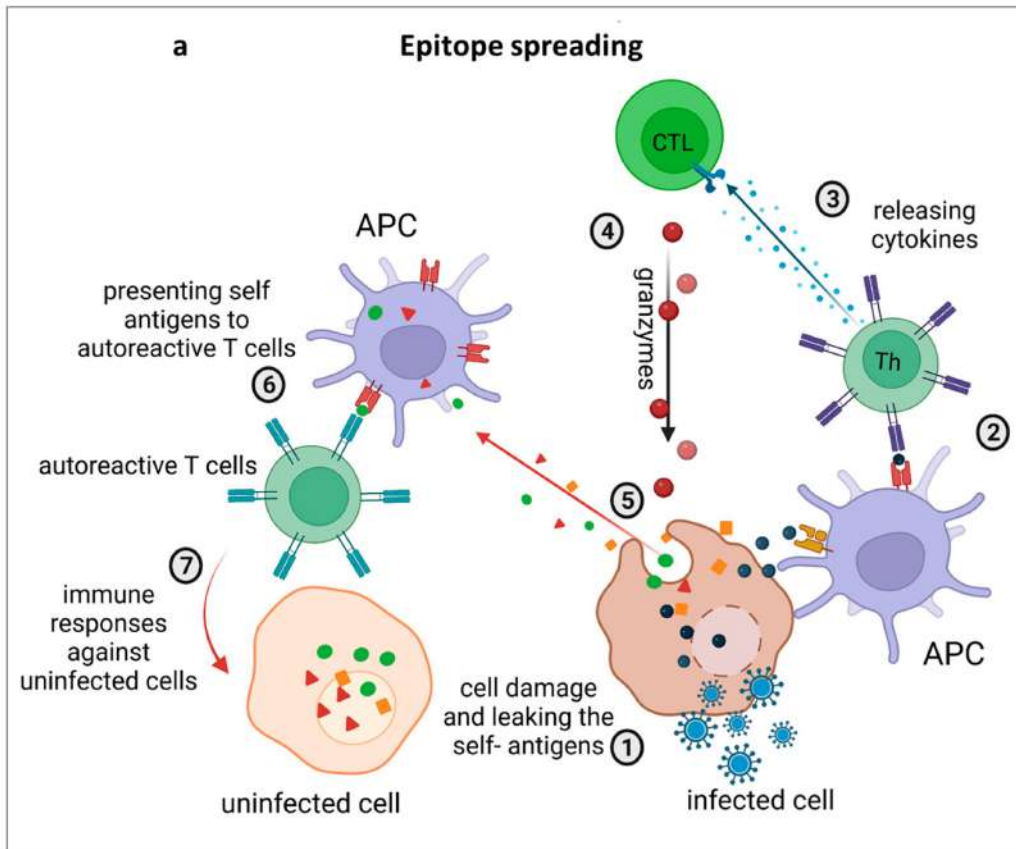


Debbie Maizels/Springer Nature

# İMMÜN TOLERANS NASIL KIRILIR?

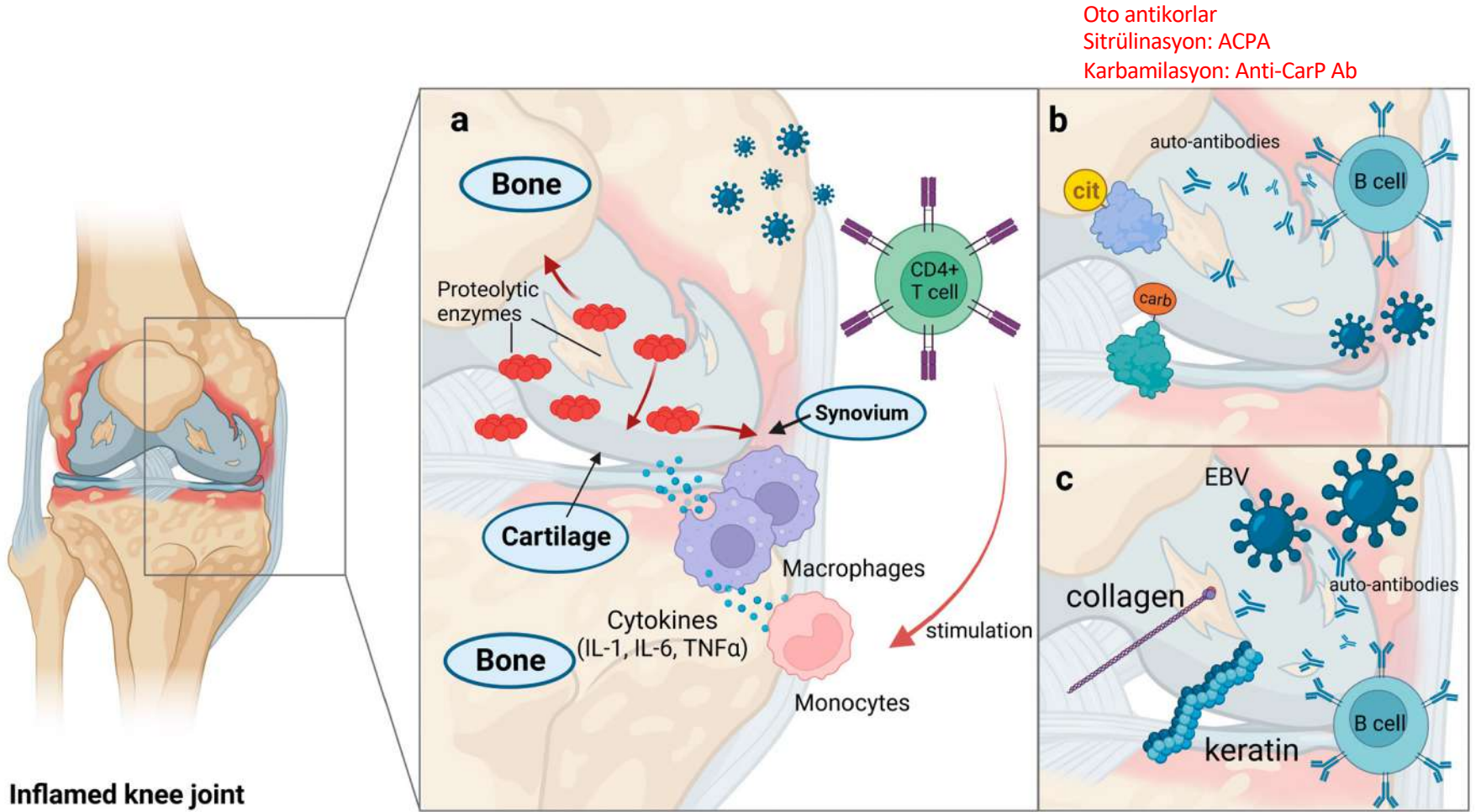


# VİRÜSLER ve OTOİMMÜNİTE





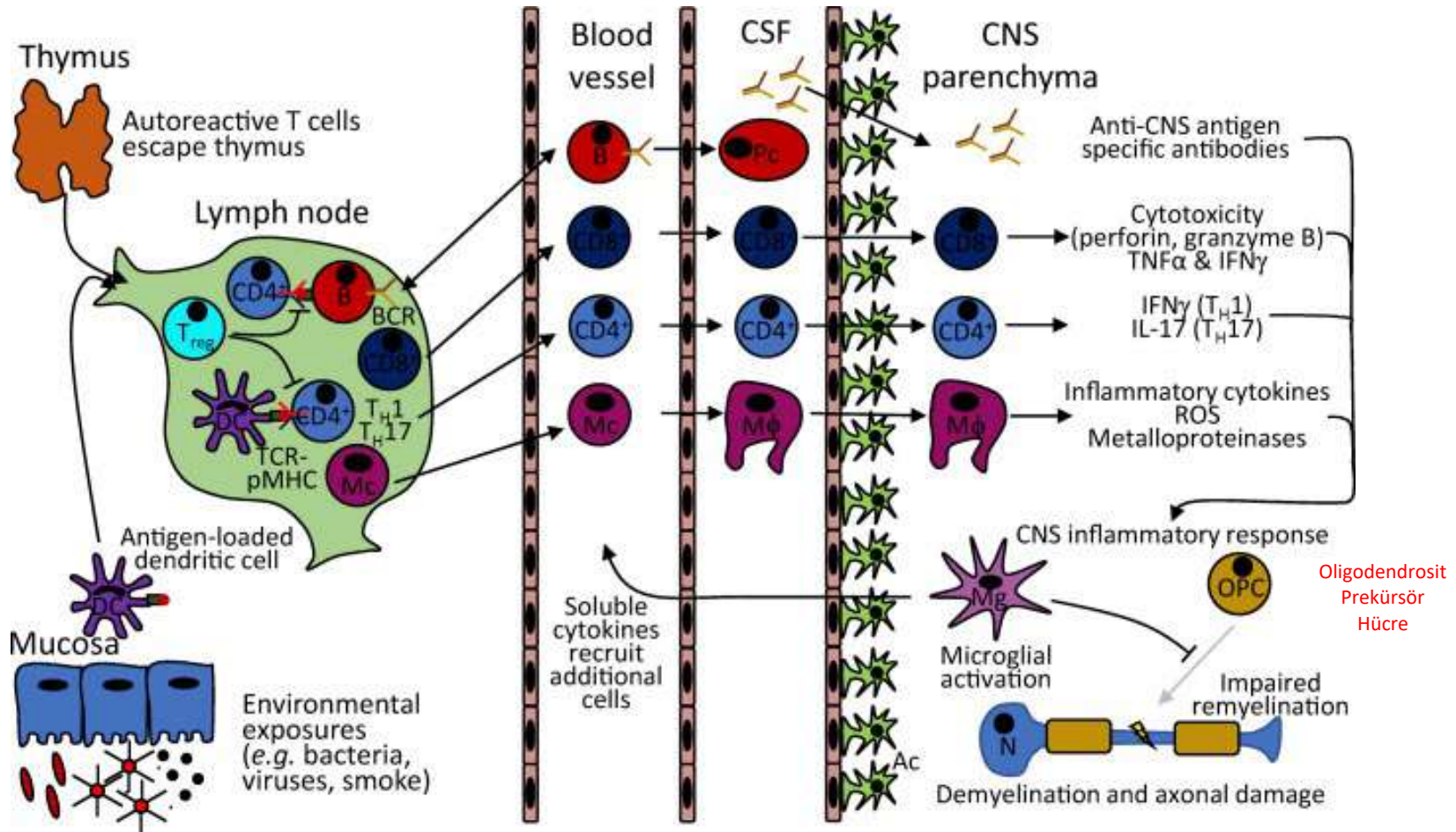
# Bir Örnek Olarak Romatoid Artrit



Oto antikorlar  
Sitrülinasyon: ACPA  
Karbamilasyon: Anti-CarP Ab

Moleküler Benzeşme: EBV tarafından kodlanan EBNA-1'in p107 epitopuna reaktif antikorlar keratin ve kollajene yönelebilir

# MSS'de İNFLAMASYON



Multiple Skleroz ile ilişkili virüsler: EBV, CMV, Varicella-Zoster

# VİRÜSLER ve OTOİMMÜNİTE

Autoimmune Disease	Virus	Target Cells or Self-Peptides	Immune Cells or Cytokines	Pathomechanism	Ref.
Rheumatoid Arthritis	HTLV	Synovial cells	IL1, IL6, TNF- $\alpha$	Autonomous proliferation of synovial cells and inflammation	[163,164,165]
	EBV	Collagen and keratin	Autoreactive T cells	Molecular mimicry	[166,167,168]
Multiple Sclerosis	Herpes simplex virus (HSV1, HSV2)	Peripheral sensory nerves, sensory ganglia in CNS	Cytotoxic T lymphocyte, IL-6	Molecular mimicry of HSV-1 glycoprotein gB epitope and a brain-specific factor	[169,170]
	Epstein–Barr Virus (EBV)	CNS, myelin basic protein (MBP), anoctamin 2, glial cell adhesion molecule (GlialCAM)	CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells	Antibodies against EBV antigens viral capsid antigen (VCA), Epstein–Barr nuclear antigen 1 (EBNA1), and early antigen (EA), Epstein–Barr latent membrane protein 1 (LMP1), molecular mimicry	[127,171,172,173,174,175,176]
	Human Herpesvirus 6 (HHV-6)	Oligodendrocyte, MBP	T cells	Molecular mimicry of virus peptide U24 with MBP	[177,178,179]
	Varicella-Zoster Virus (VZV)	Ganglia in CNS, peripheral blood mononuclear cells (PBMCs)	CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells	-	[180]
	Human Endogenous Retroviruses (HERVs)	CNS in white matter lesion, (PBMCs)	TNF- $\alpha$	Induction of free radicals, ER stress	[169,170,181,182]
Systemic Lupus Erythematosus	EBV	B- and epithelial cells; autoantibodies: SmB and Ro60	EBV-specific T cells	Molecular mimicry	[183,184,185]
Diabetes Mellitus Type 1	Coxsackie B4	GAD65 in the beta-cells of pancreas	IFN- $\gamma$ /type-1-IFN, IL-4	Molecular mimicry	[186]
	Rubella	GAD65/67 of the pancreatic islets	CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells	Molecular mimicry	[187,188]
	Rotavirus	Tyrosine phosphatase IA-2	Type I IFN	Molecular mimicry and Bystander activation	[189,190]
	Cytomegalovirus	GAD65	GAD65 specific T-cells	Molecular mimicry	[191]



# CEVRESEL DEĞİŞİMLER ve TOLERANS





# CEVRESEL DEĞİŞİMLER VE EPİTELYAL BARIYERLER

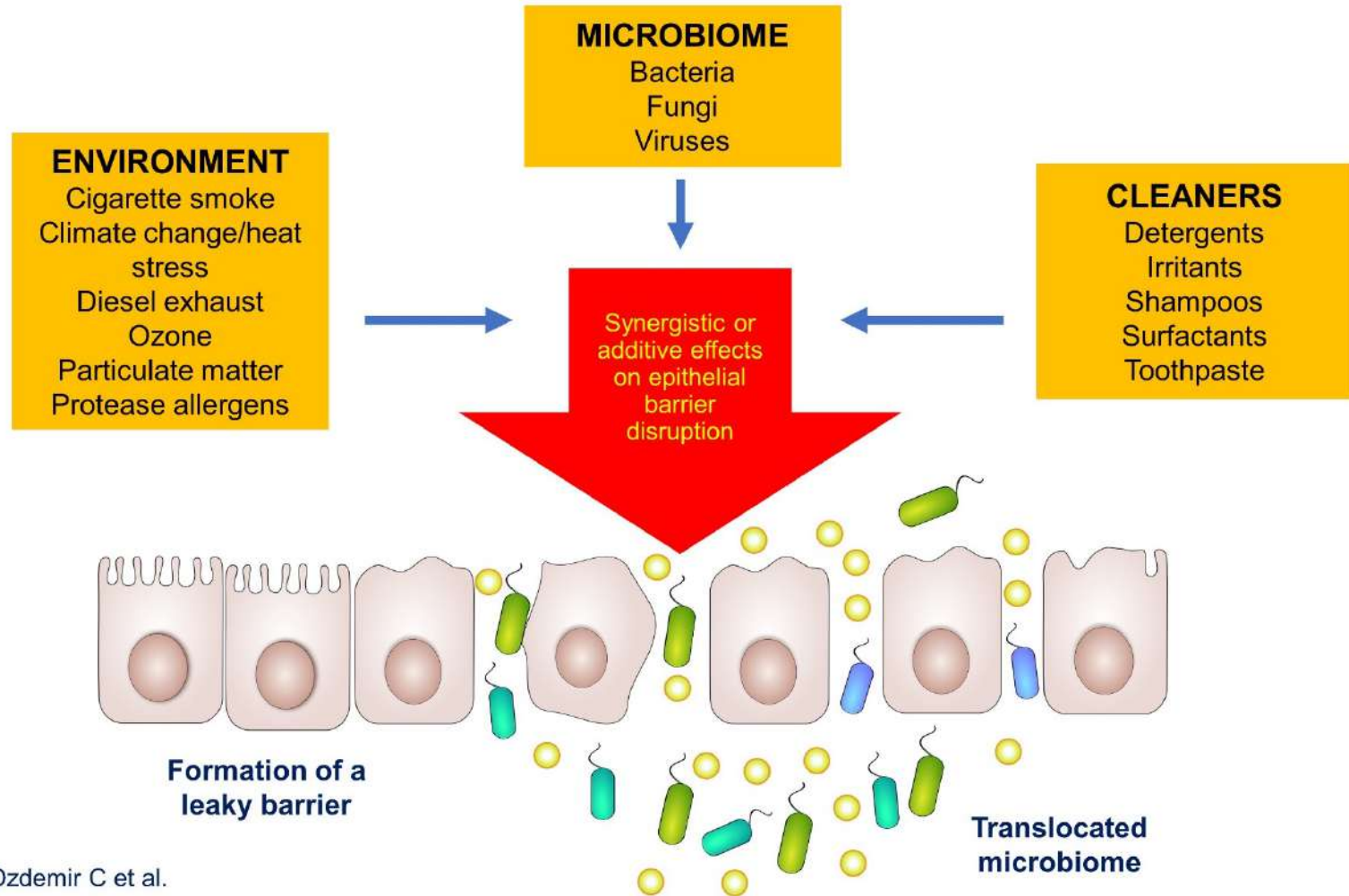


FIGURE-2 Ozdemir C et al.

# CEVRESEL DEĞİŞİMLER VE EPİTELYAL BARIYERLER

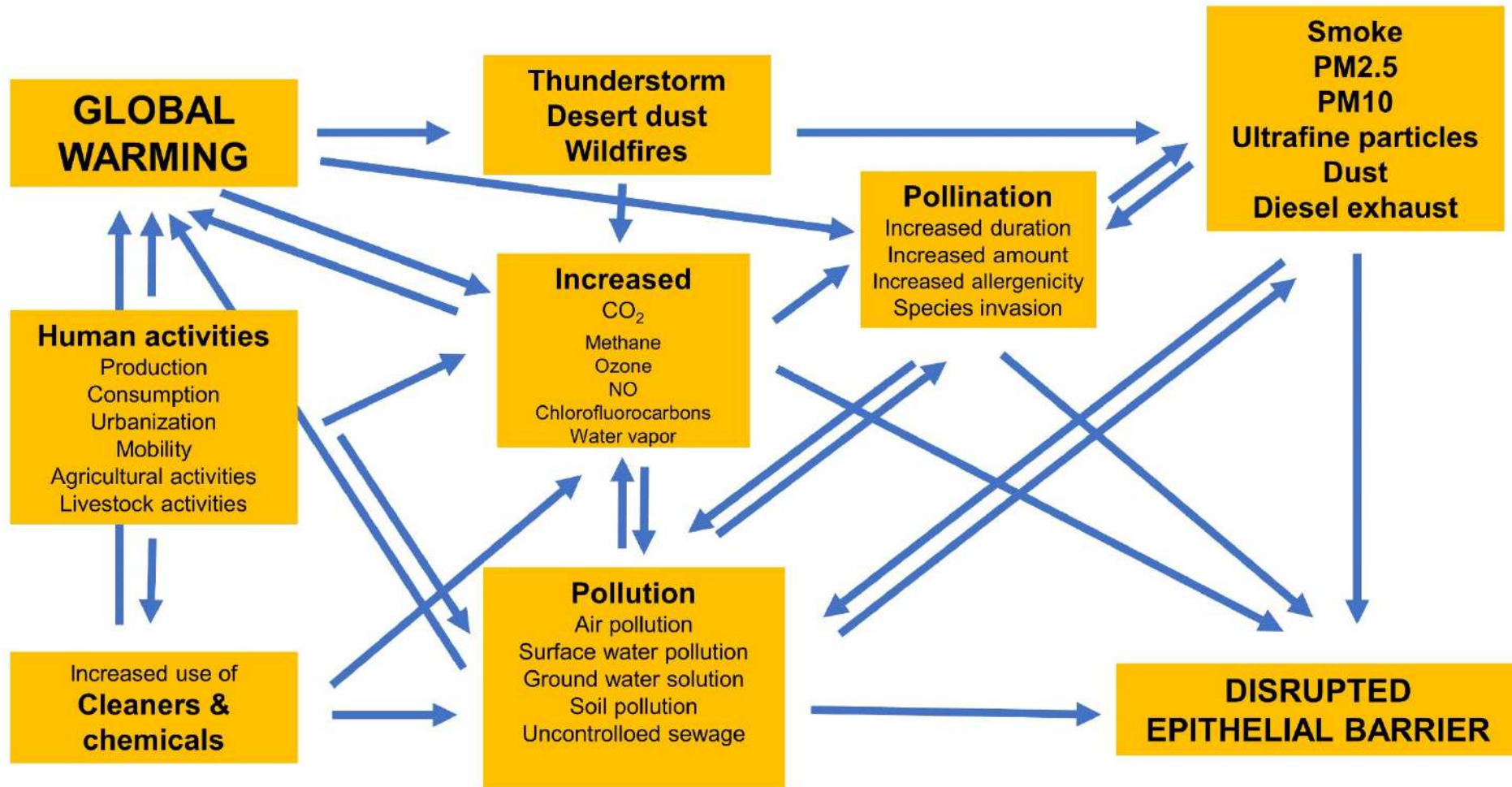
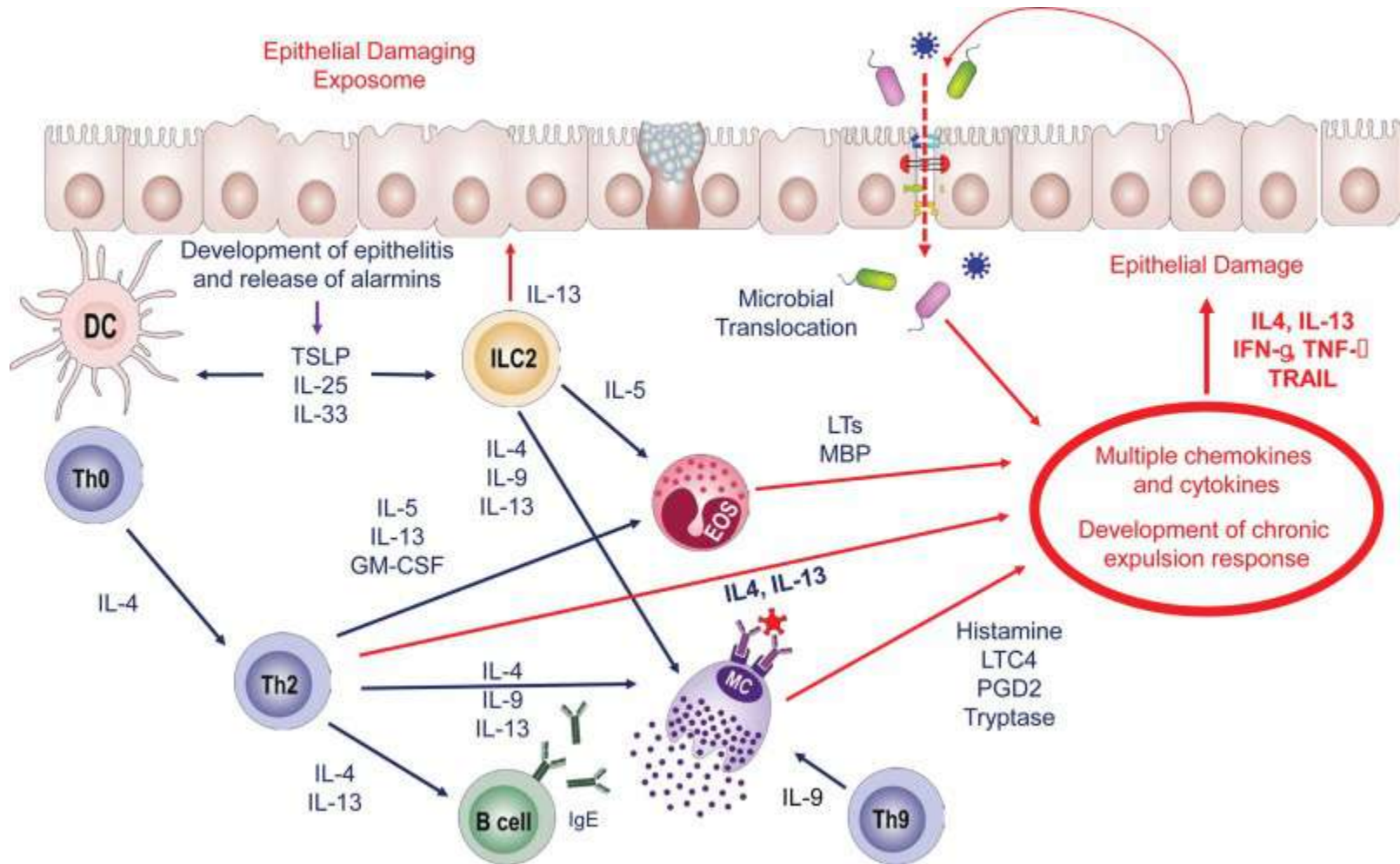


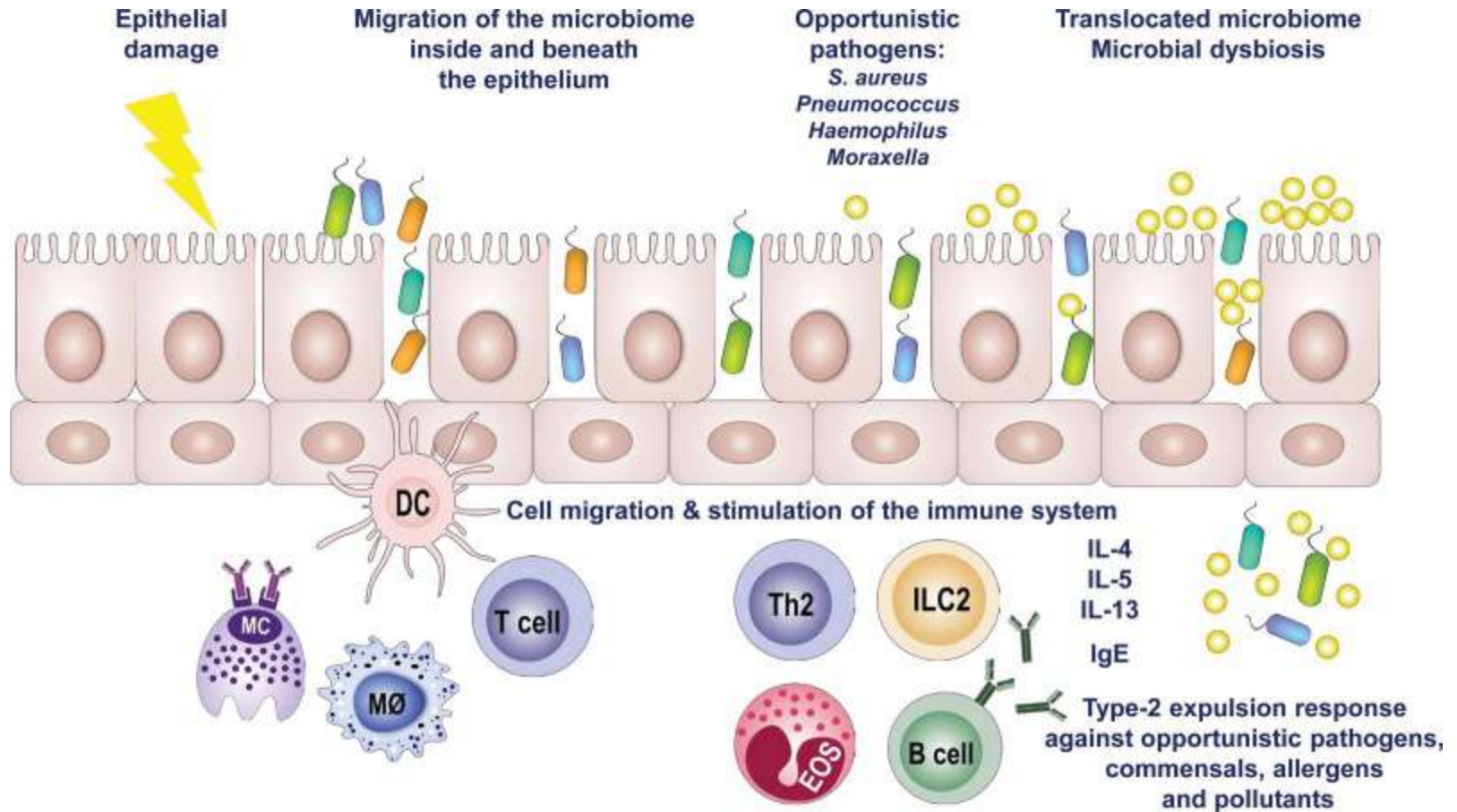
FIGURE-1 Ozdemir C et al.

# EPİTEL YANITLARI





# EPİTEL YANITLARI





# EPİTEL HASARININ KISIR DÖNGÜSÜ

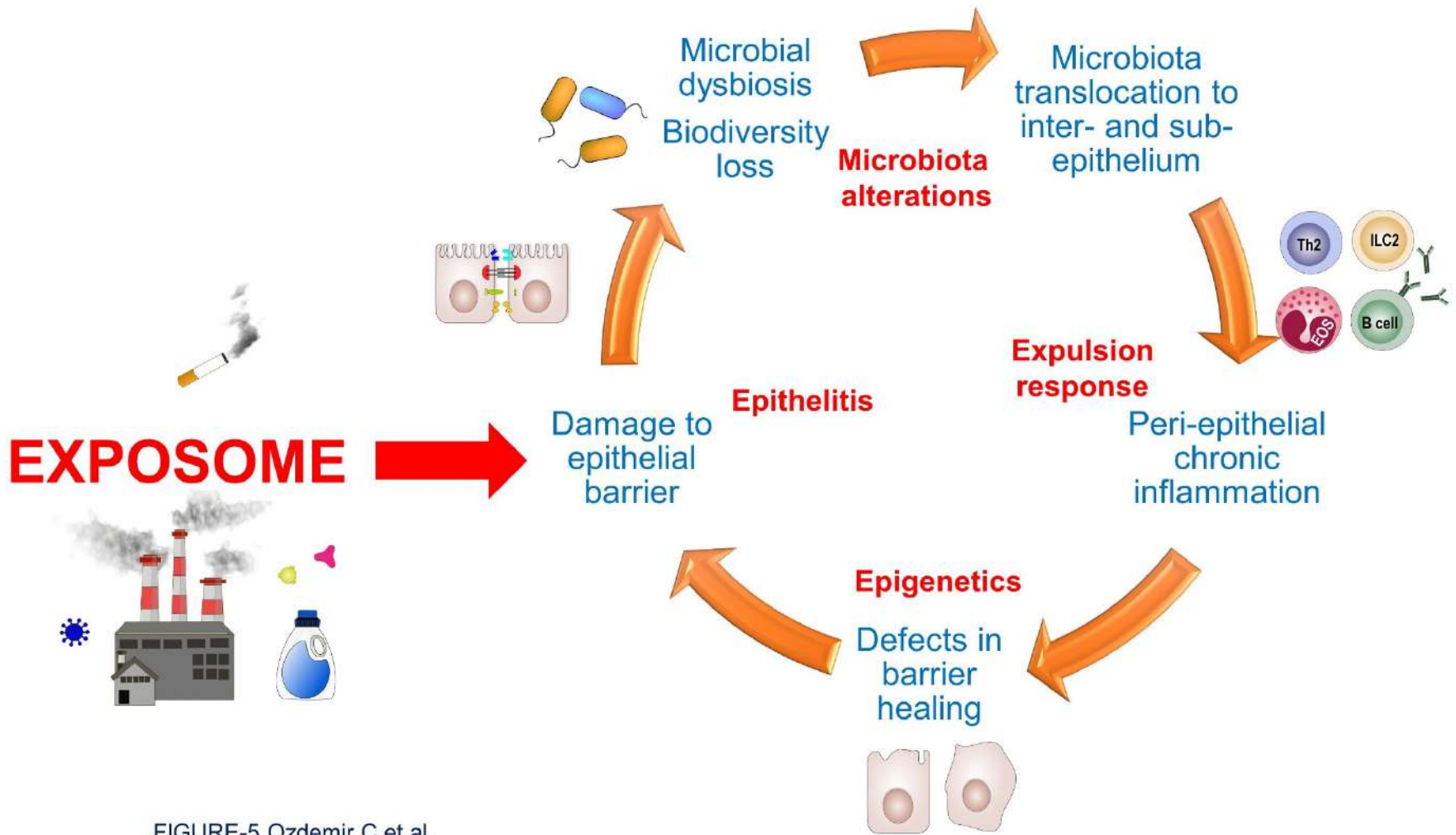


FIGURE-5 Ozdemir C et al.

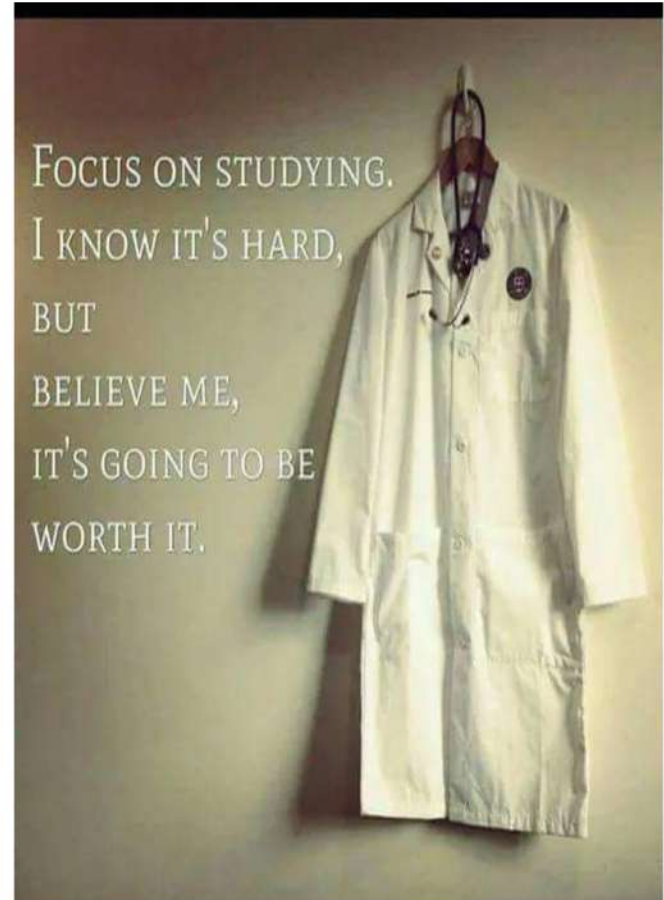
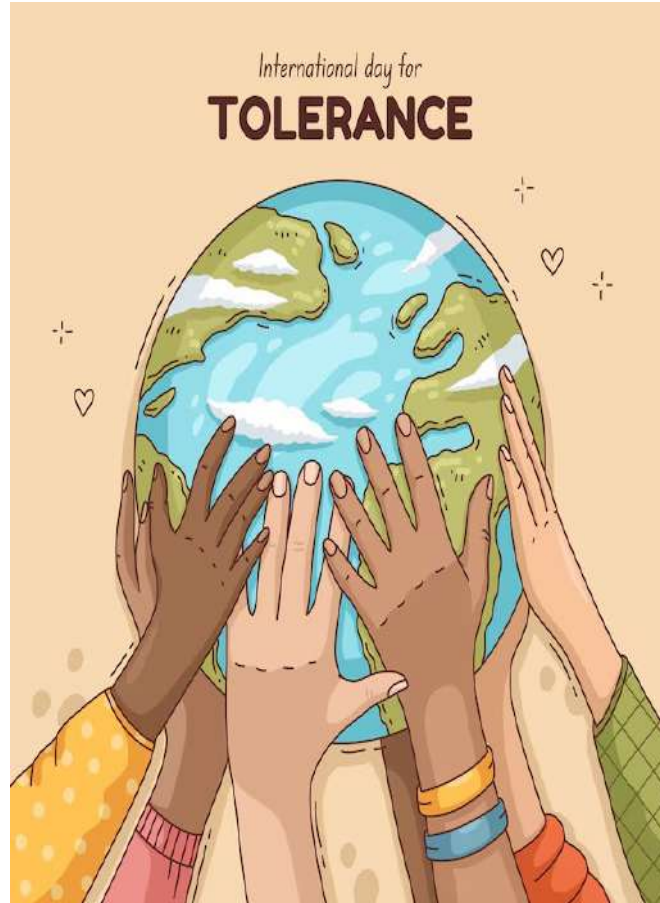
# EPİTEL İLİŞKİLİ İNFLAMATUVAR HASTALIKLAR

**Table 2.**

## **Diseases in which epithelial barrier disruption has been linked to pathogenesis**

<b>Disease related to epithelial barrier disruption</b>	<b>References</b>
Obesity	[130]
Nonalcoholic steatohepatitis	[131]
Liver cirrhosis	[87]
Multiple sclerosis	[132]
Systemic lupus erythematosus	[133]
Ankylosing spondylitis	[134]
Type 1 diabetes	[135]
Autism spectrum disorders	[136]
Parkinson disease	[137]
Alzheimer disease	[138]
Stress-related psychiatric disorders	[139]
Chronic depression	[140]

# SONUÇ OLARAK...



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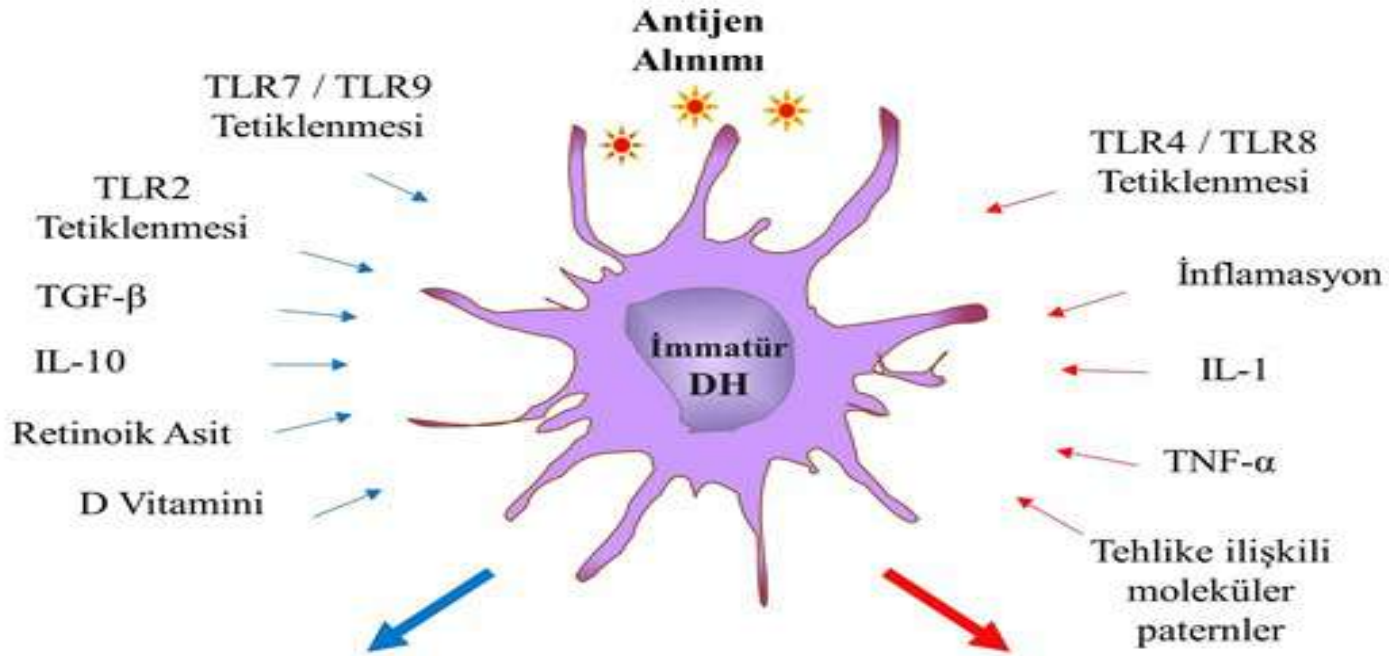




TEŞEKKÜRLER...



# TOLEROJENİK vs İNFLAMATUVAR



## TOLEROJENİK DH

- Düşük CD80/86
- Düşük MHCII
- IL-10, TGF- $\beta$  üretimi
- ILT2, ILT3, ILT4 betimlenmesi
- Treg uyarımı
- Baskılayıcı etkiler
- Patolojik yanıtları engeller

## İNFLAMATUVAR DH

- Yüksek CD80/86
- Yüksek MHCII
- IL-1, IL-12, IFN- $\gamma$  üretimi
- Artmış ASH kapasitesi
- Th1/Th2/Th17 uyarımı
- İnflamatuvar etkiler
- Patolojik potansiyel