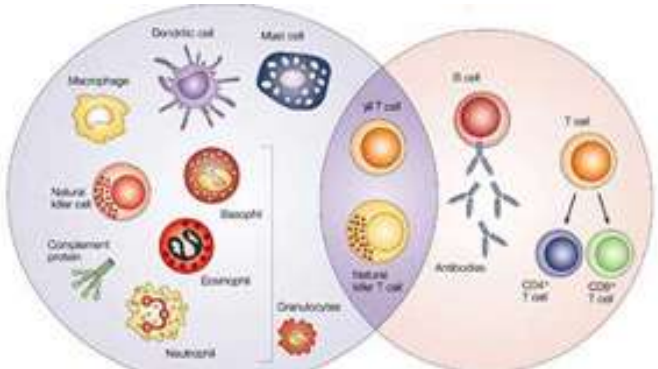
BAŞKENT ÜNİVERSİTESİ

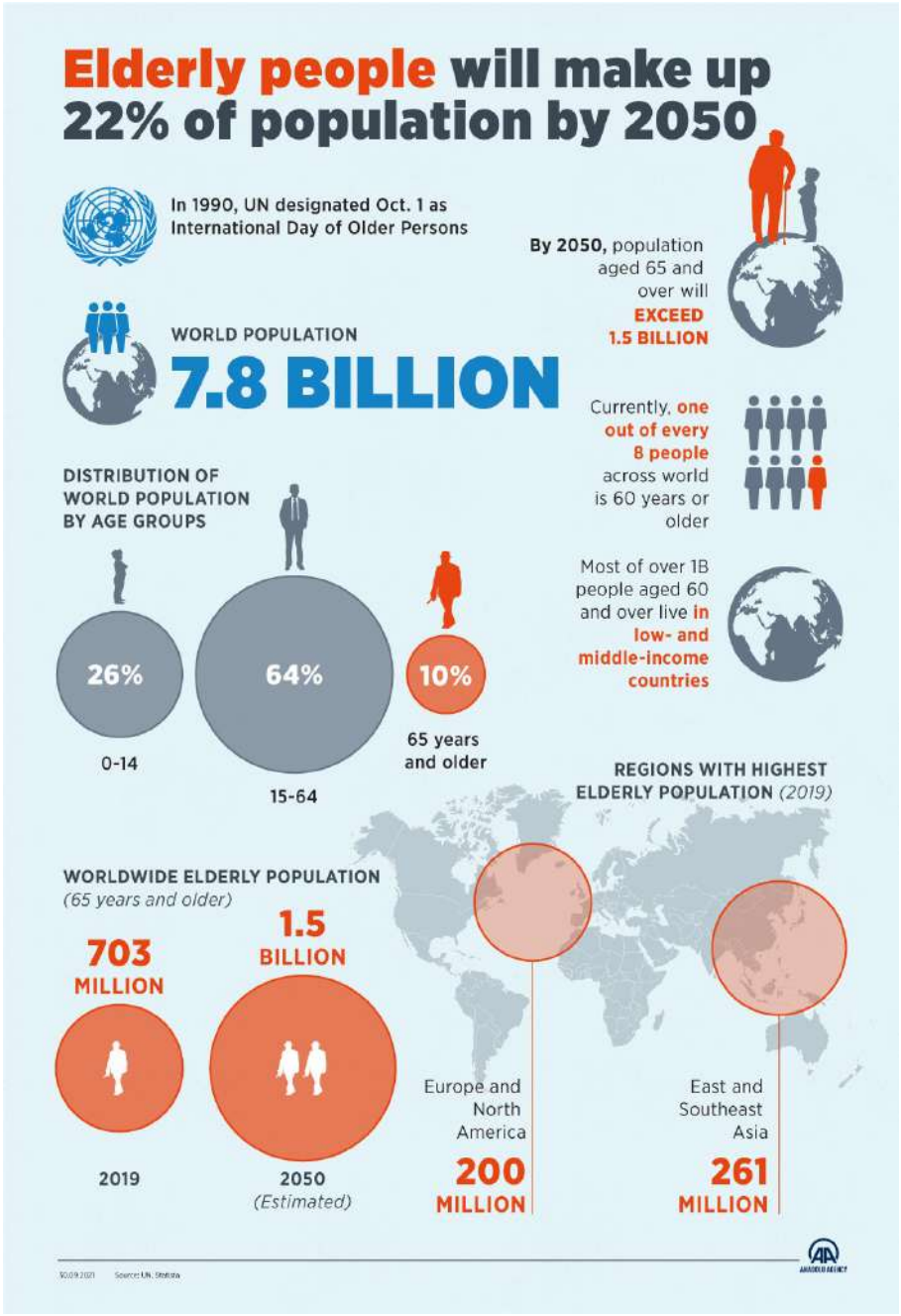
Yaşlılıkta İmmünitede Değişiklikler: Edinsel İmmünite

Doç.Dr.Çiğdem EROL

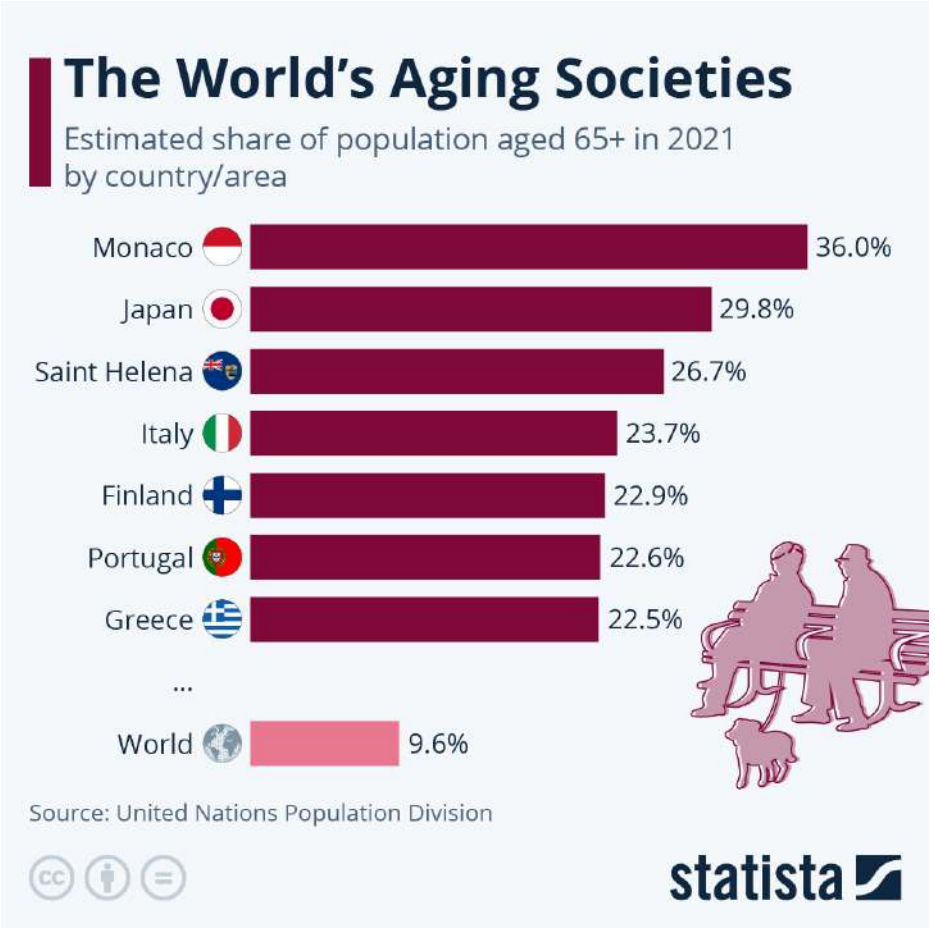
Başkent Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD



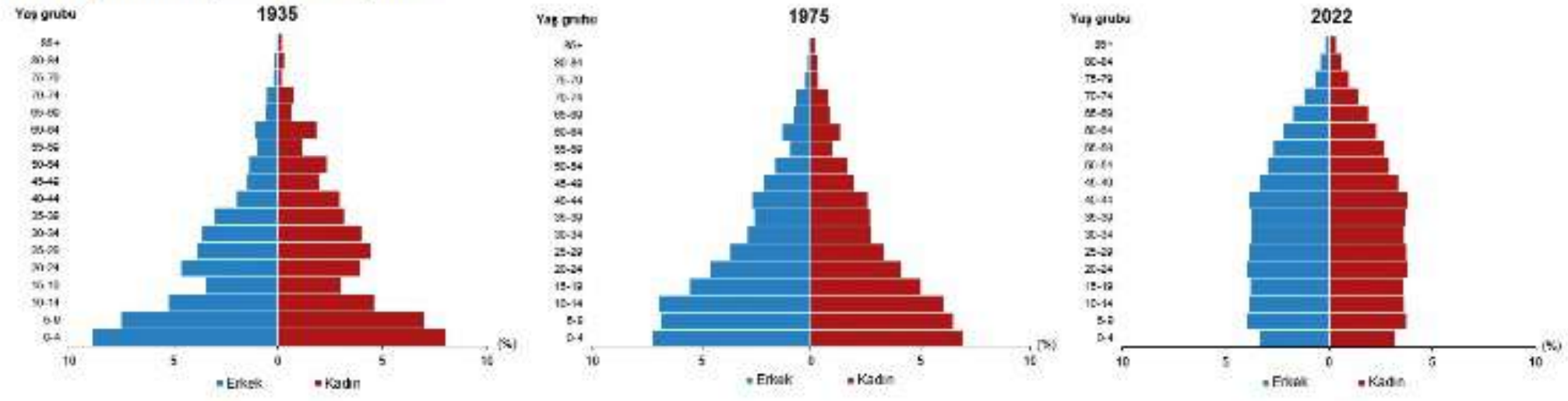


- **2050**…65 yaş ve üzeri nüfus beklentisi ***1.5 milyar (%22)



Türkiye Nüfus Dağılımı

Nüfus piramidi, 1935, 1975, 2022



Kaynak: TÜİK, Genel Nüfus Sayımları,1935, 1975
TÜİK, Adrese Dayalı Nüfus Kayıt Sistemi, 2022

Türkiye 65 Yaş Üzeri Nüfus Dağılımı

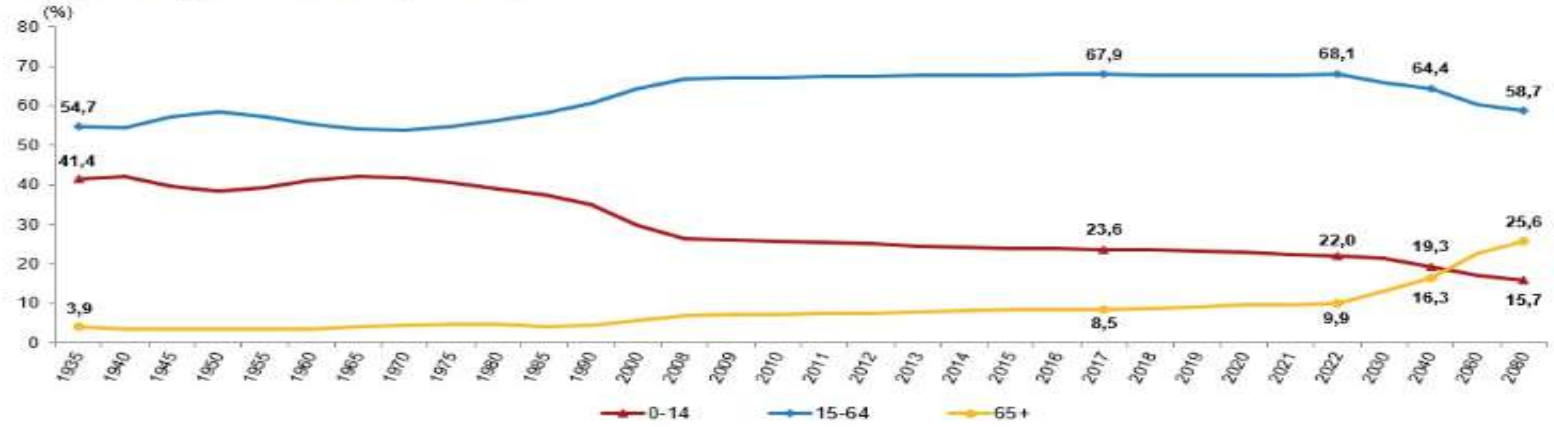
İstatistiklerle Yaşlılar, 2022

Yaşlı nüfus 8 milyon 451 bin 669 kişi oldu

Yaşlı nüfus olarak kabul edilen 65 ve daha yukarı yaştaki nüfus, 2017 yılında 6 milyon 895 bin 385 kişi iken son beş yılda %22,6 artarak 2022 yılında 8 milyon 451 bin 669 kişi oldu. Yaşlı nüfusun toplam nüfus içindeki oranı ise 2017 yılında %8,5 iken, 2022 yılında %9,9'a yükseldi. Yaşlı nüfusun 2022 yılında %44,4'ünü erkek nüfus, %55,6'sını kadın nüfus oluşturdu.

Nüfus projeksiyonlarına göre yaşlı nüfus oranının 2030 yılında %12,9, 2040 yılında %16,3, 2060 yılında %22,6 ve 2080 yılında %25,6 olacağı öngörüldü.

Yaş grubuna göre nüfus oranı, 1935-2080



Kaynak: TÜİK, Genel Nüfus Sayımları, 1935-2000
TÜİK, Adrese Dayalı Nüfus Kayıt Sistemi, 2008-2022
TÜİK, 2018 Nüfus Projeksiyonları, 2030-2080

65 yaş üzeri kişi sayısı:

2017: 6.895.385
.....%22,6 ARTIŞ ile
2022: 8.451.669

65 yaş üzeri kişi oranı:

2017: %8,5
2022: %9,9

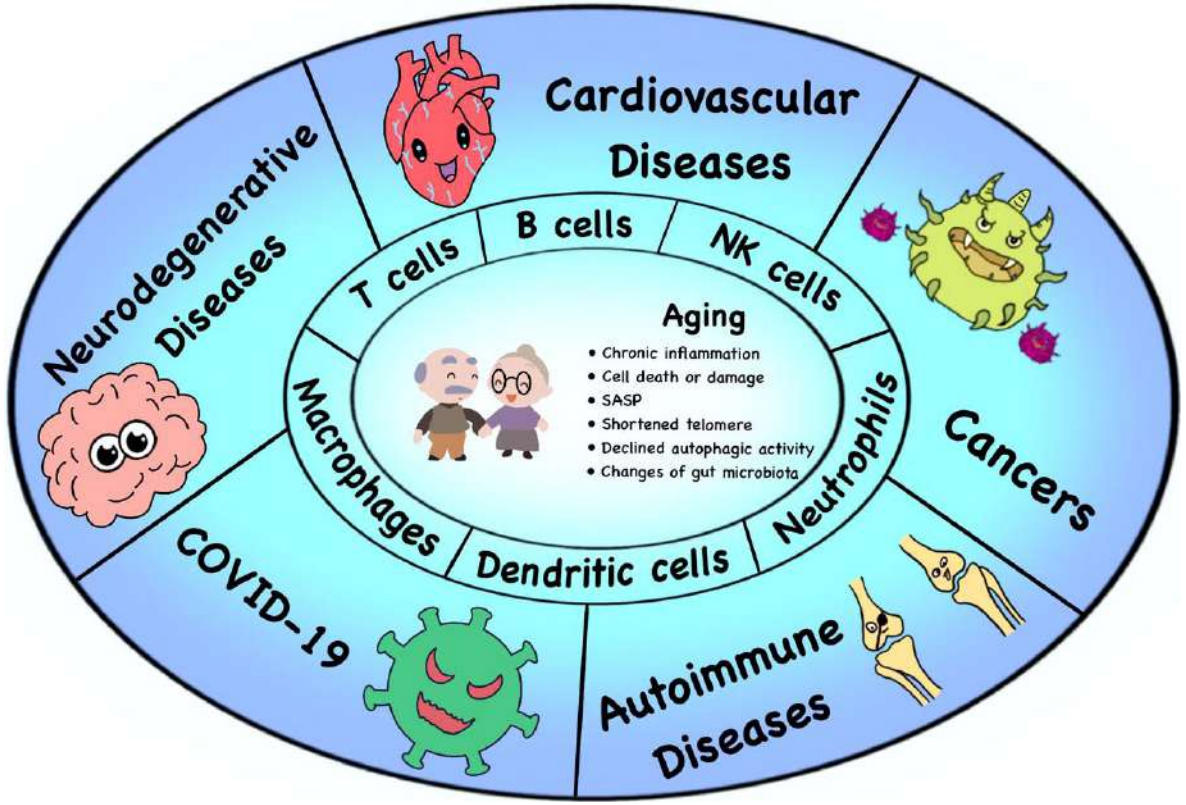
Nüfus projeksiyonu ile

2030: %12,9
2040: %16,3
2060: %22,6
2080: %25,6

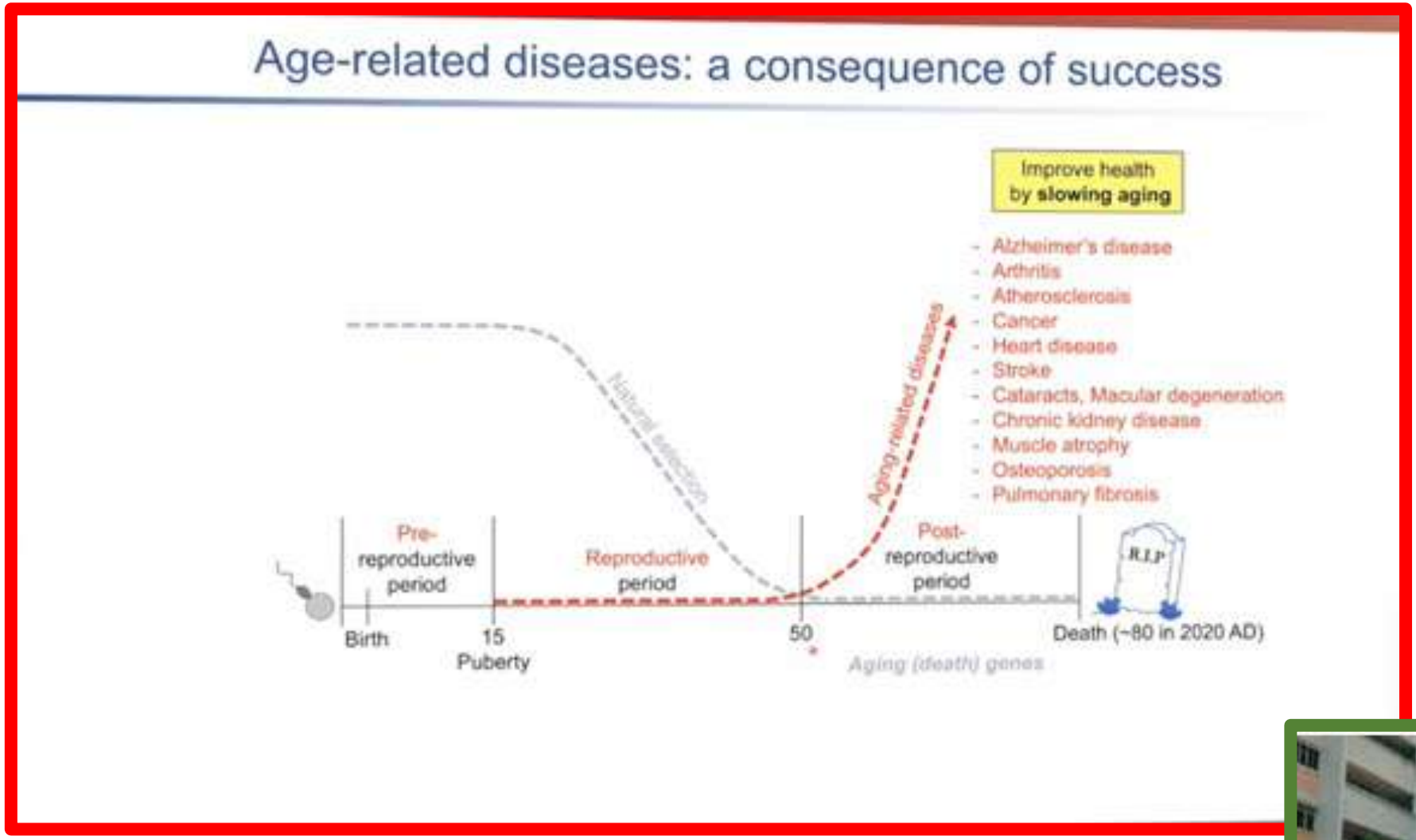
- Yaşam süresindeki bu dikkat çekici artış ile sağlık süresi (kronik hastalıklardan ve sakatlıklardan arınmış yaşam süresi) orantılı değil

- Aslında yaşlanma, yaşlanmanın ana risk faktörü olduğu 'yaşlanmanın kronik hastalıkları' olarak adlandırılan bir dizi kronik durumun artan prevalansı ile ilişkili

  - ateroskleroz (inme ve miyokard enfarktüsüne yol açan),
  - nörodejeneratif hastalıklar (Parkinson ve Alzheimer),
  - tip 2 diyabet,
  - osteoartrit,
  - makula dejenerasyonu ve glokom,
  - işitme kaybı ve
  - Bir çok kanser türü.



Asıl sorun…..İMMÜN YAŞLANMA = **IMMUNOSENESCENCE**



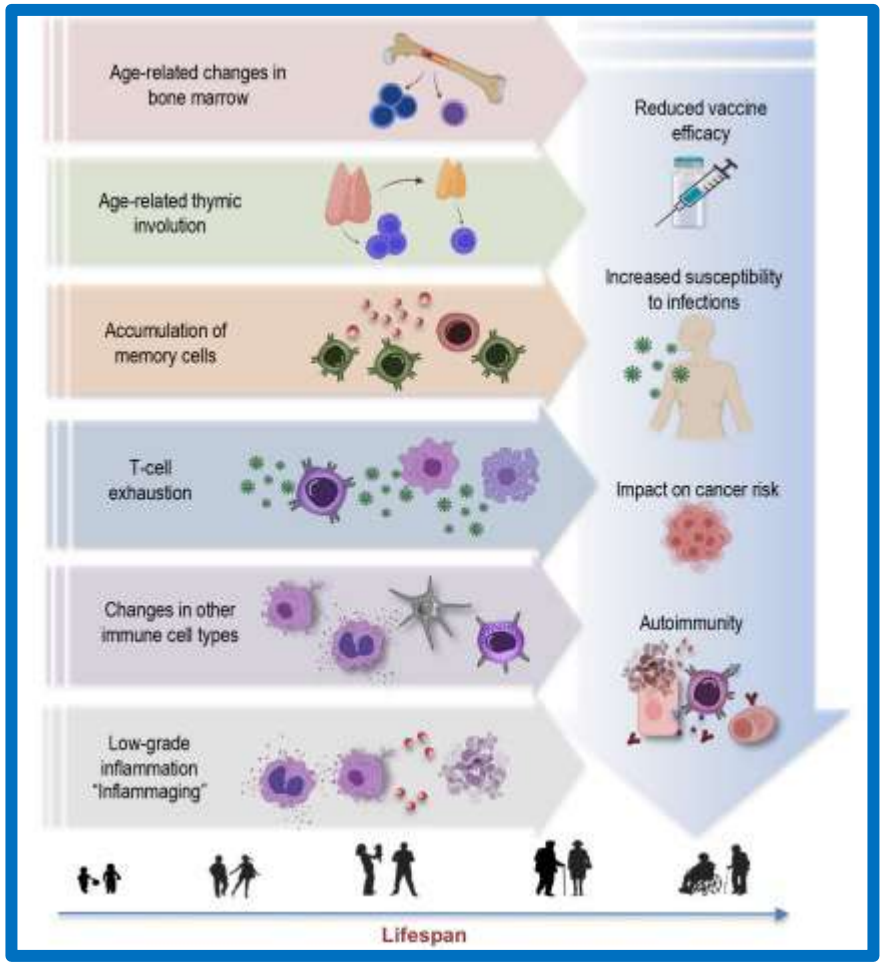
Yaşlanmayı yavaşlatarak

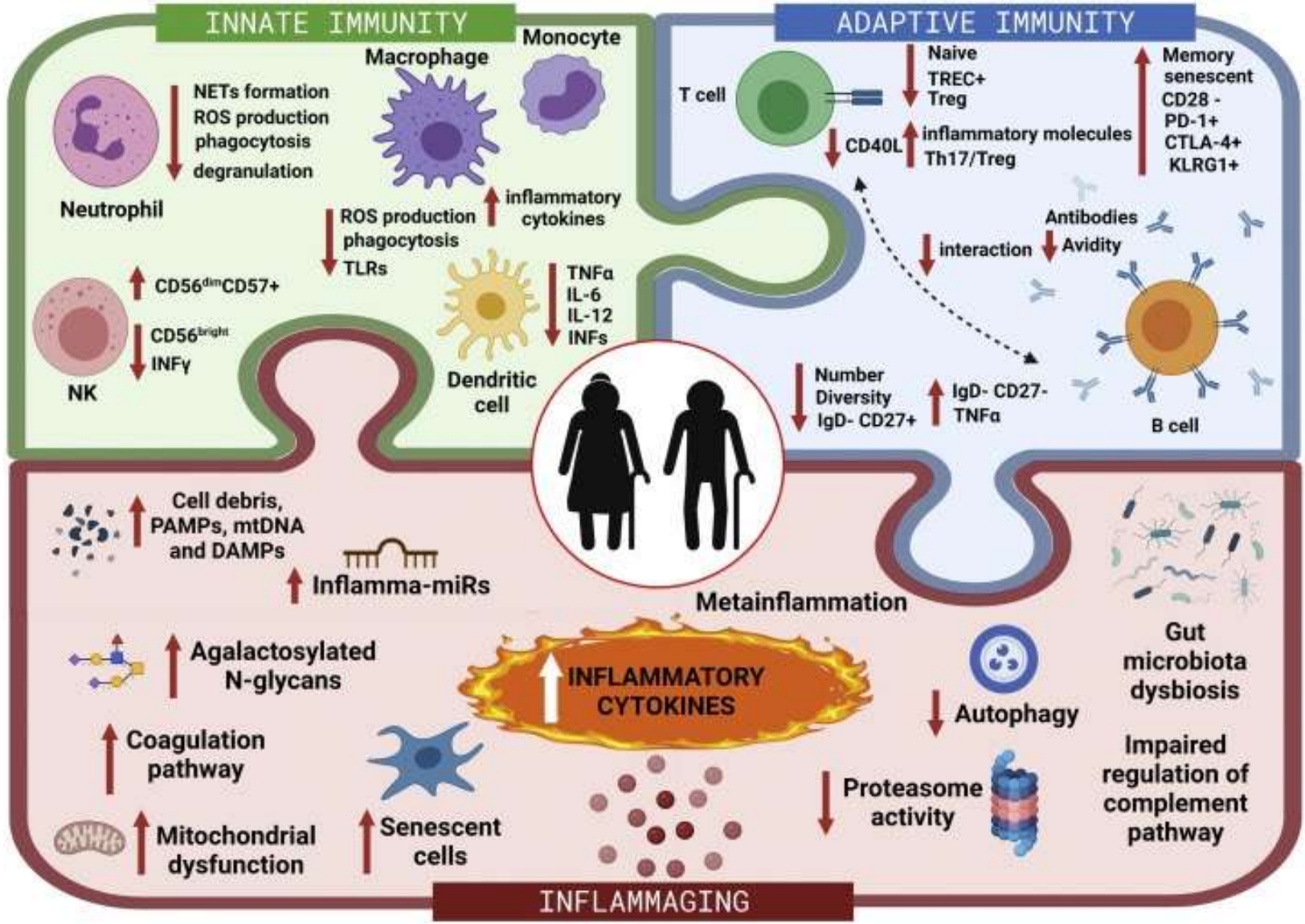
↓

Sağlık durumunu iyileştirmek

- 1960’lı yılların başında
- Yaşlanma sırasında parankimal dokular ile fagositler arasında bir mücadelenin olduğunu;
- Birincisinin canlılığının çoğunlukla azalırken, ikincisinin tam tersine artan bir aktivite gösterdiğini;
- Patolojik yaşlanma sürecinde fagositlerin saldırgan aktivitelerinin zayıflatılması gerektiğini ……vurgulamıştır.

“the father” of gerontology


Age-related changes in bone marrow
Age-related thymic involution
Accumulation of memory cells
T-cell exhaustion
Changes in other immune cell types
Low-grade inflammation "Inflammaging"
Reduced vaccine efficacy
Increased susceptibility to infections
Impact on cancer risk
Autoimmunity
Lifespan


INNATE IMMUNITY
ADAPTIVE IMMUNITY
Monocyte
Macrophage
Neutrophil
NETs formation
ROS production
phagocytosis
degranulation
ROS production
phagocytosis
TLRs
inflammatory cytokines
NK
CD56dimCD57+
CD56bright
INFγ
Dendritic cell
TNFα
IL-6
IL-12
INFs
T cell
Naive
TREC+
Treg
CD40L
inflammatory molecules
Th17/Treg
Memory senescent
CD28 -
PD-1+
CTLA-4+
KLRG1+
interaction
Antibodies
Avidity
B cell
Number
Diversity
IgD- CD27+
IgD- CD27-
TNFα
Cell debris, PAMPs, mtDNA and DAMPs
Inflamma-miRs
Metainflammation
Agalactosylated N-glycans
INFLAMMATORY CYTOKINES
Autophagy
Gut microbiota dysbiosis
Coagulation pathway
Proteasome activity
Impaired regulation of complement pathway
Mitochondrial dysfunction
Senescent cells
INFLAMMAGING

- Claudio Franceschi…… “inflamm-aging”
- Yaşlanmayla birlikte ortaya çıkan…. KRONİK STERİL İNFLAMASYON
- İnnate immün sistemin hiperaktivasyonu…..Yaşam süresinde kısalma

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 02 August 2022
DOI 10.3389/fimmu.2022.942796

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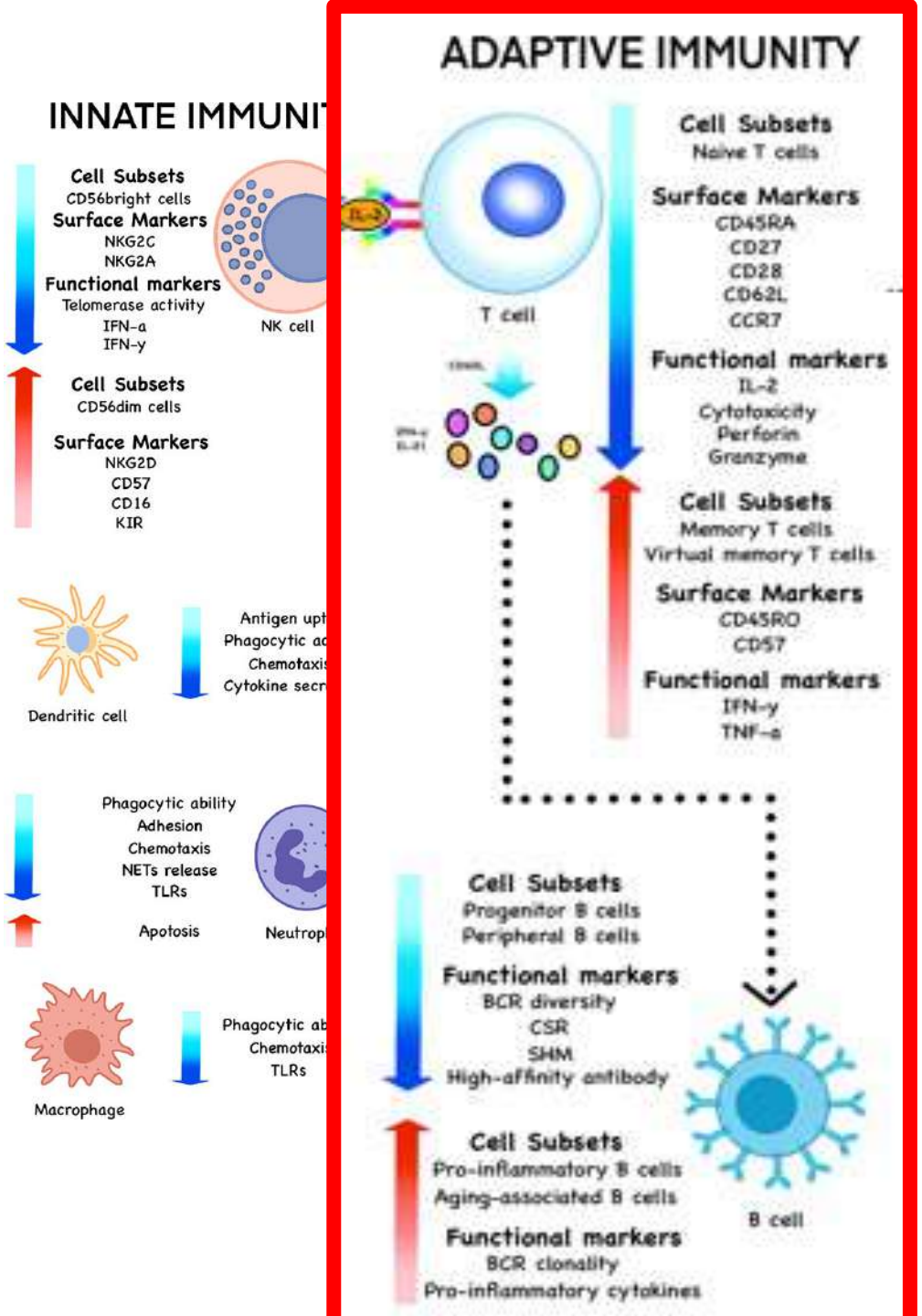
Immunosenescence, aging and successful aging

Yunan Wang[1†], Chen Dong[2†], Yudian Han[3], Zhifeng Gu[2*] and Chi Sun[4*]

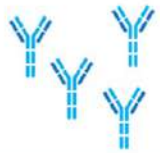
[1]Department of Rheumatology, Affiliated Hospital of Nantong University, Medical School of Nantong University, Nantong, China, [2]Department of Rheumatology, Affiliated Hospital of Nantong University, Nantong, China, [3]Information Center, The First People's Hospital of Nantong City, Nantong, China, [4]Department of Geriatrics, Affiliated Hospital of Nantong University, Nantong, China

Başarılı yaşlanma ????



Immunosenescence…İmmün yaşlanma***

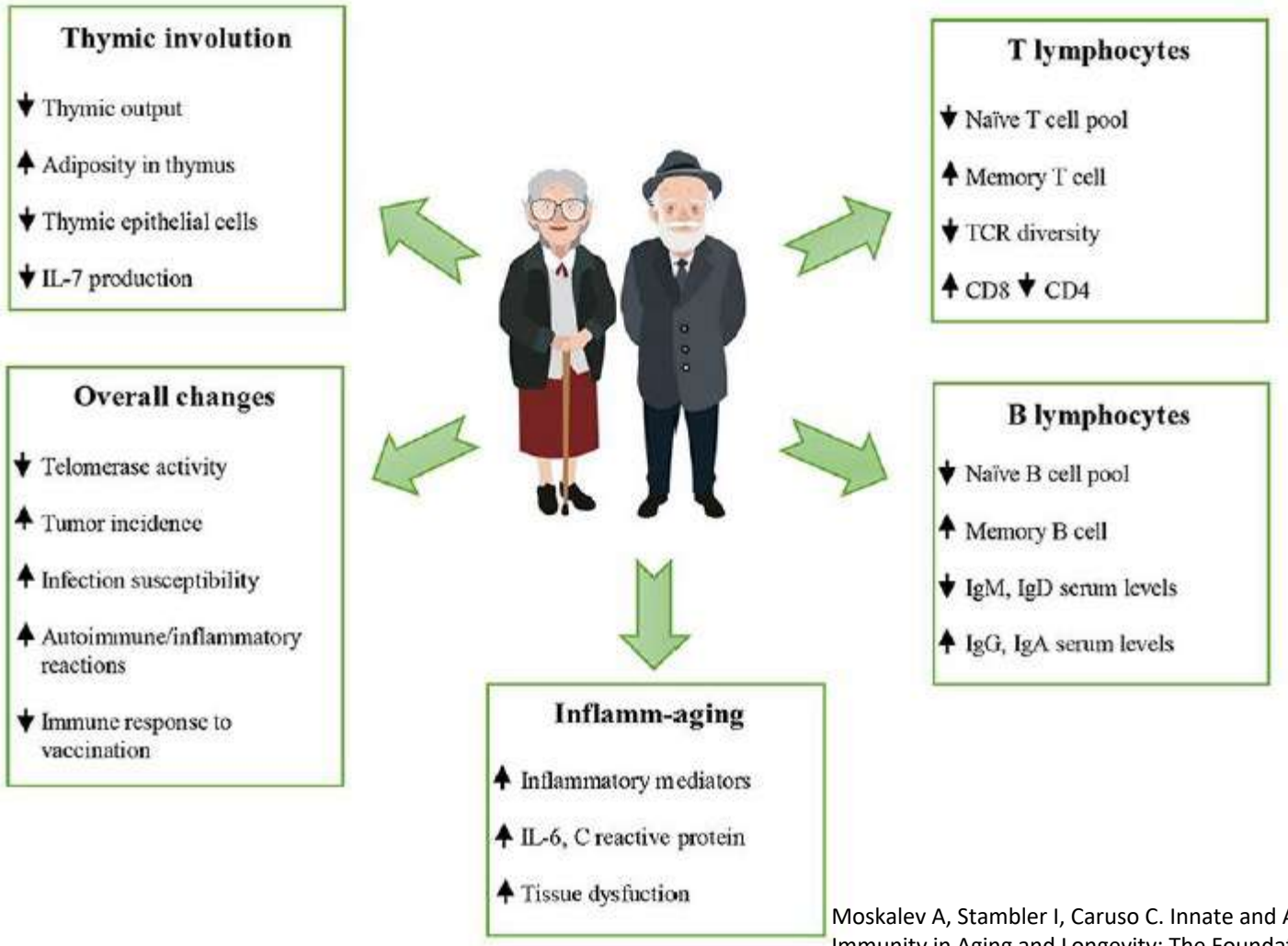
	CELL TYPE	CHARACTERISTICS
Innate Immunity	Neutrophils 	↓ Phagocytic chemotaxis capability ↓ Superoxide anion production ↓ Ability to respond to soluble factors (GM-CSF) and bacteria (LPS, fMLP)
	Dendritic cells 	
	Macrophages 	
	NK cells 	
Adaptive Immunity — Cellular Response	Thymus 	Involution from age of 9 months, thymic remnant after 50 years
	T Cells 	Variable number (↓ proliferation to PHA, varying age and health status) - HLA B8/DR3 associated with high proliferative responses ↑ Proportion of memory cells ($CD45RO^-$), especially $CD8^+$ ↓ Proportion of naïve cells ($CD45RA^+$) ↓ Proliferative capacity ↓ Synthesis of IL-2 receptor and IL-2 in memory cells ↓ $CD28^+$ ↑ $CD28^-$T cells mainly $CD8^+$ $CD28^-$ (characterized by oligoclonal expansion, shortening of telomeres, potential decreased proliferation, resistance to apoptosis, and increased production of TNF-α and IL-6) ↓ CD4 T lymphocytes Change from Th1 response to Th2 response with ↓cell-mediated responses directed against intracellular bacteria (Th1 function) and relative preservation of humoral (Th2 function) ↓ Treg population ($CD4^+$ $CD25^+$) that plays a role in the manifestations of autoimmunity Impaired immunological synapse formation and signaling pathways (calcium response, phosphorylations) ↓ CD4/CD8 rate

		CELL TYPE	CHARACTERISTICS
Adaptive Immunity	Humoral Response	B Cells 	↓ pre-B lymphocytes with peripheral B lymphocyte count unchanged ↑ $CD5^+$ B cells ($CD19^+$ $CD5^+$ clones B) that produce low affinity antibodies without cooperation of T cell ↓ naive B cells Accumulation of memory B cells with ↓ diversity and affinity of antibodies Reach primary humoral response (dependent T cell cooperation). Conserved secondary humoral response
		Immunoglobulins 	↑ serum levels of IgA and IgG (IgG1, IgG2 and IgG4). Monoclonal immunoglobulin production by $CD19^+$ $CD5^+$ clones Secretion self-Ab non organ-specific (rheumatoid factor, antinuclear antibodies, antiphospholipid antithyroglobulines and parietal cells)
		Interleukins 	↓ IL-2 production because ↓ cooperation of T cells with antibody producer B cells ↑ Production of IL-4, IL-6, IL-8, IL-10 and TNF-α ↓ Production of IL-1 and IFN-γ

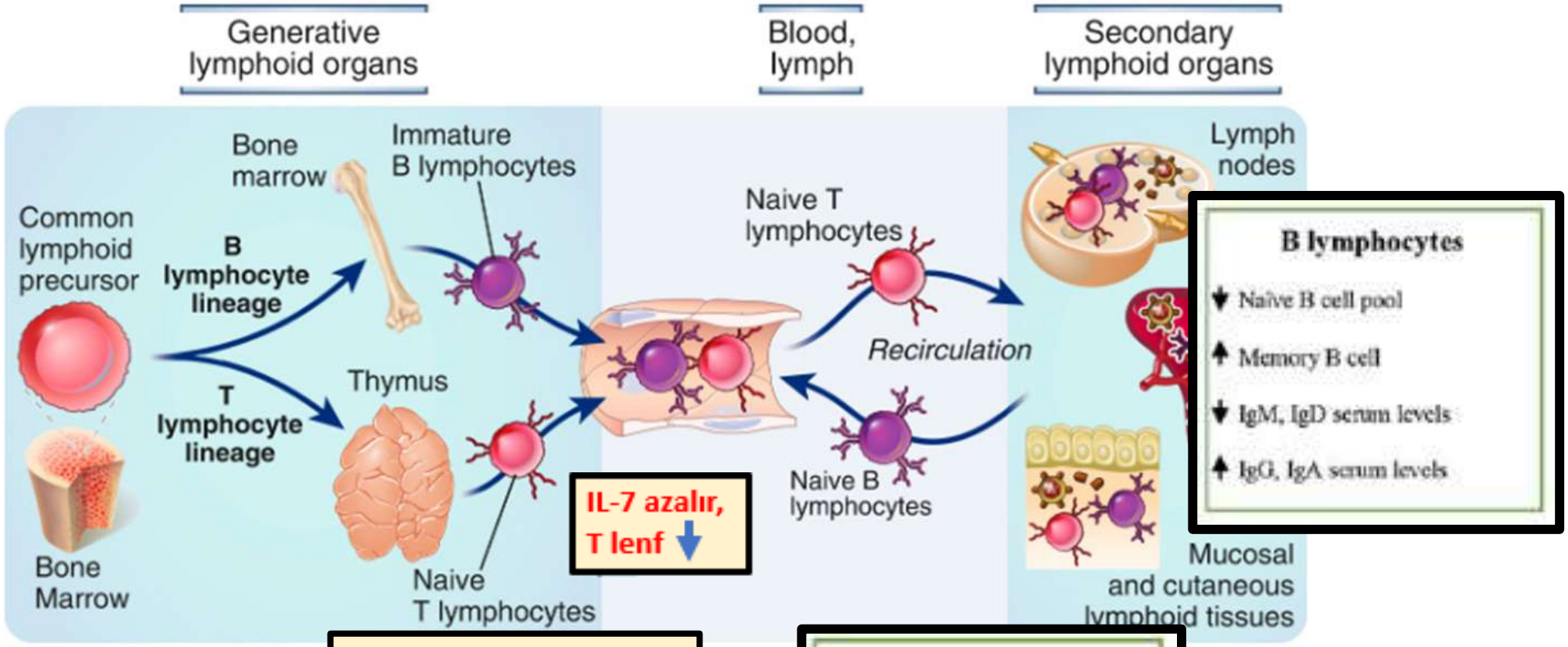
Edinsel immünitede değişiklikler

İmmün sistemin ana bölümleri:

- Fizyolojik bariyerler,
- İnnate immünite
- Adaptif immunite



Moskalev A, Stambler I, Caruso C. Innate and Adaptive Immunity in Aging and Longevity: The Foundation of Resilience. Aging Dis. 2020 Dec 1;11(6):1363-1373.



Kemik iliği değişiklikleri

- ??????

Timus:

- Yağlanma artar
- Timik epitel h. Azalır
- IL-7 üretimi azalır

HHS Public Access
Author manuscript
Curr Stem Cell Rep. Author manuscript; available in PMC 2019 August 26.

Published in final edited form as:
Curr Stem Cell Rep. 2018 June ; 4(2): 166–181. doi:10.1007/s40778-018-0128-6.

Signaling Pathways Regulating Hematopoietic Stem Cell and Progenitor Aging

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[1]Division of Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center

[2]Hoxworth Blood Center, University of Cincinnati College of Medicine

[3]Cancer & Cell Biology Program, University of Cincinnati College of Medicine

- Kemik iliği kök hücresi yaşlanması;
  - niş ve intrinsik faktörlerden,
  - hücre dışı matris dayanıklılığından,
  - sistemik inflamasyondan
  - diğer sistemik faktörlerden etkilenir.
- Yaşla birlikte,
  - HSC'ler hedef bulma ve rejeneratif kapasiteyi azaltır
  - Proinflamatuar miyeloid yönlü farklılaşmayı artırır

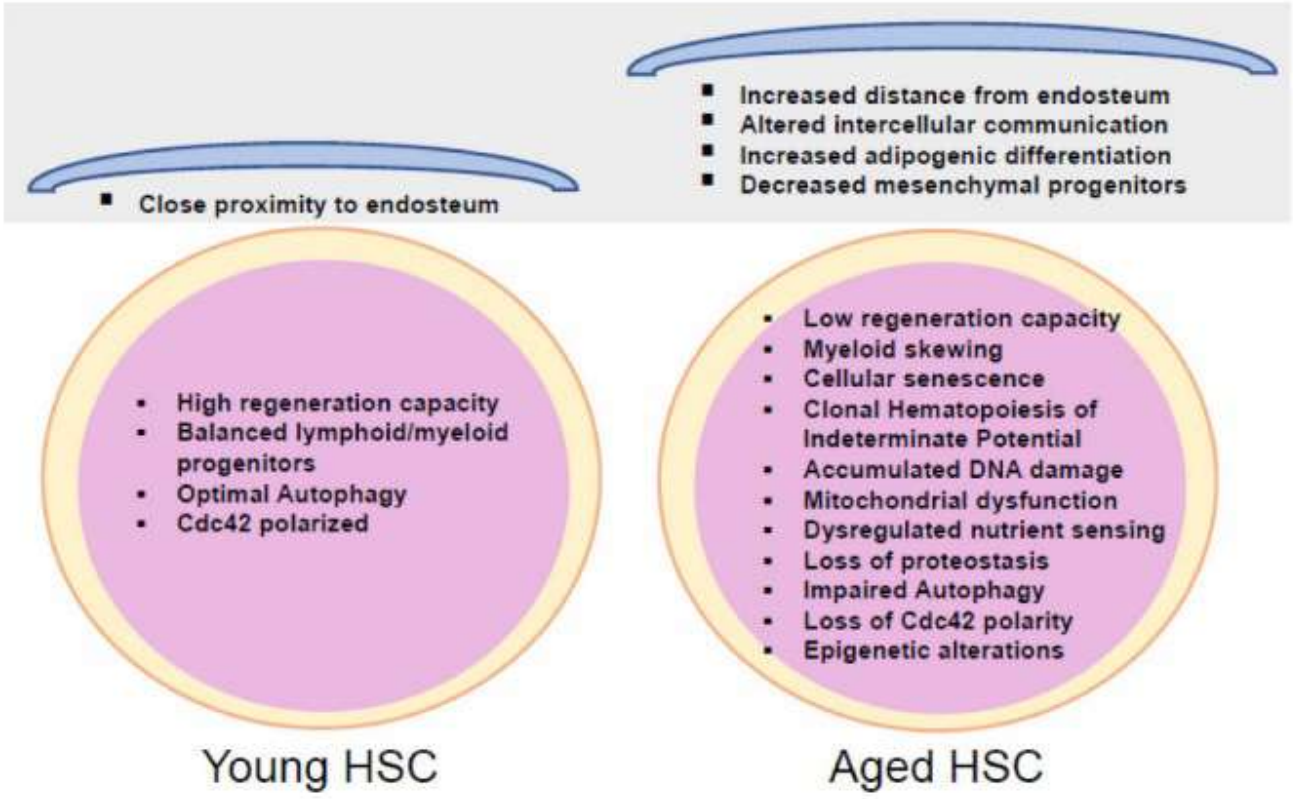


Figure 1. Phenotypic and functional changes associated with aging of hematopoietic stem cells (HSC)

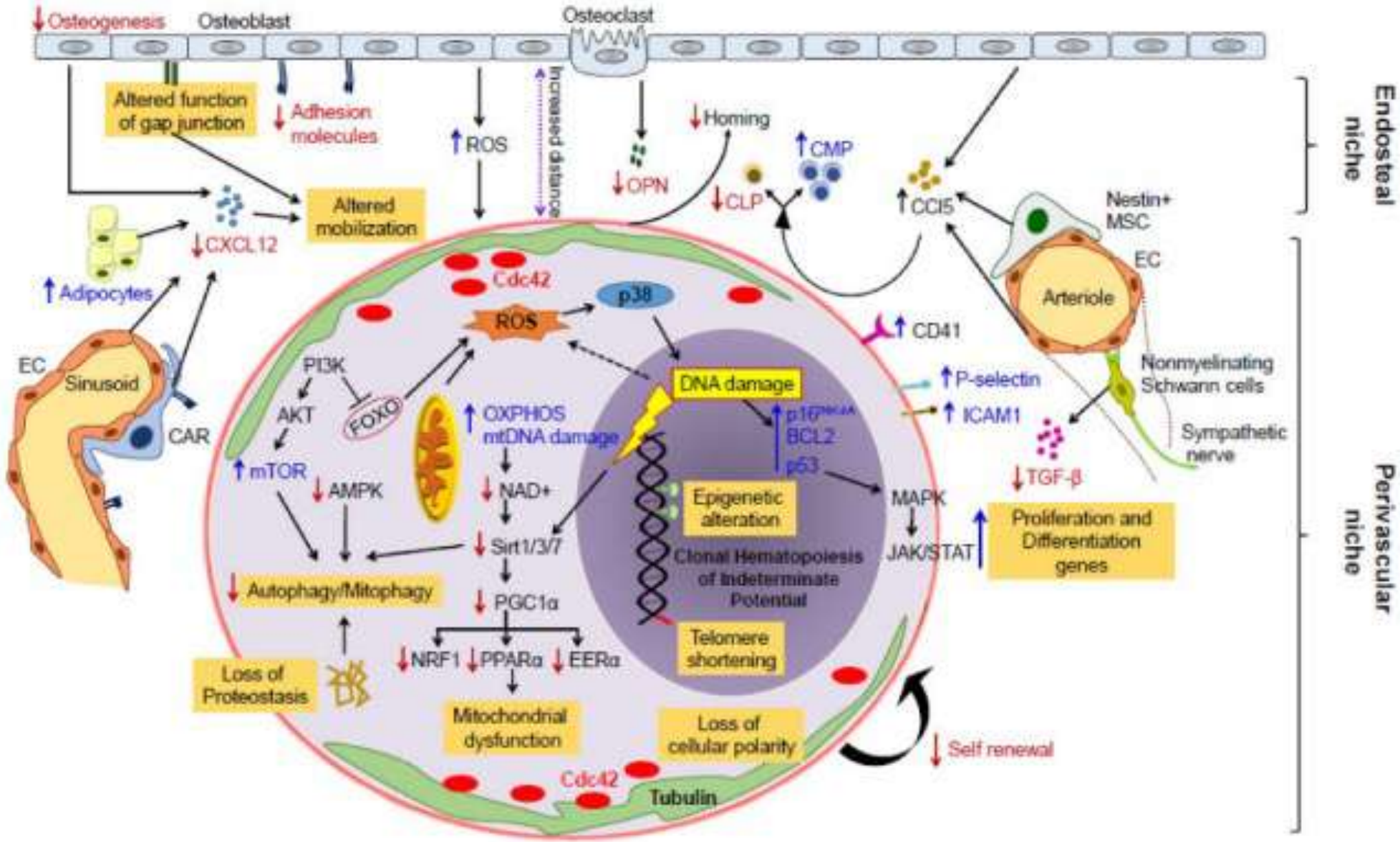


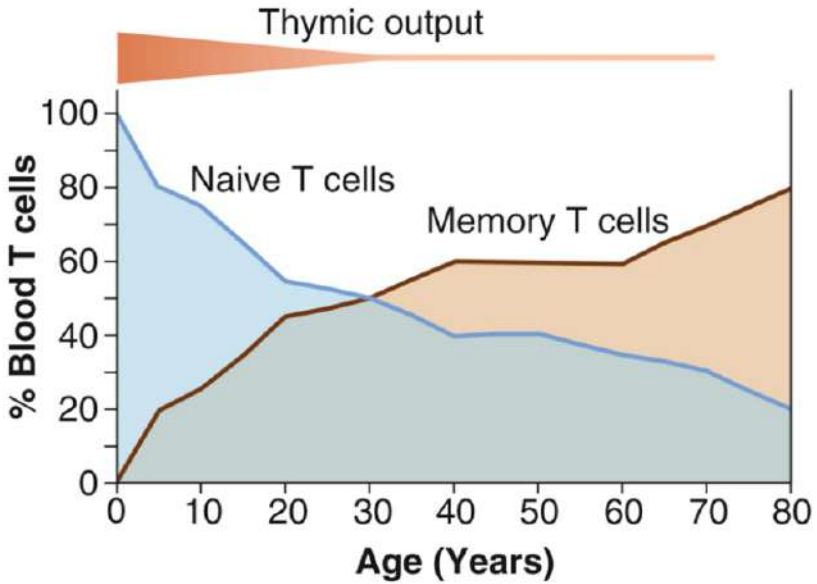
Figure 2. Cell intrinsic and extrinsic mechanisms regulating hematopoietic stem cells aging

Hücresel Adaptif İmmünite:

T hücre yaşlanması

- Hücre kontrollü immünolojik fonksiyonlarda genel düşüş
- T hücre repertuarında azalmış yanıt (CD8+ T hücre çeşitliliği)
- Yeni T hücre oluşumunda azalma
- Naive T hücreler azalırken hafıza ve aktive T hücre miktarında artış
- Bozulmuş self-tolerans !!!
- $CD28^-$ hücre birikimi****
- Apoptoziste sorunlar oluşması nedeniyle **senessent T hücre birikimi (Telomer kısalması!!)**

Adaptive Immunity	Cellular Response	Thymus 	Involution from age of 9 months, thymic remnant after 50 years
		T Cells 	Variable number (↓ proliferation to PHA, varying age and health status) - HLA B8/DR3 associated with high proliferative responses ↑ Proportion of memory cells ($CD45RO^+$), especially $CD8^+$ ↓ Proportion of naive cells ($CD45RA^+$) ↓ Proliferative capacity ↓ Synthesis of IL-2 receptor and IL-2 in memory cells ↓ $CD28^+$ ↑ $CD28^-$ T cells mainly $CD8^+$ $CD28^-$ (characterized by oligoclonal expansion, shortening of telomeres, potential decreased proliferation, resistance to apoptosis, and increased production of TNF-α and IL-6) ↓ CD4 T lymphocytes Change from Th1 response to Th2 response with ↓cell-mediated responses directed against intracellular bacteria (Th1 function) and relative preservation of humoral (Th2 function) ↓ Treg population ($CD4^+$ $CD25^+$) that plays a role in the manifestations of autoimmunity Impaired immunological synapse formation and signaling pathways (calcium response, phosphorylations) ↓ CD4/CD8 rate



Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1	IFN-γ	Macrophages	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17	IL-17 IL-22	Neutrophils	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh	IL-21 (and IFN-γ or IL-4)	B cells	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

Adaptive Immunity	Cellular Response	Thymus	Involution from age of 9 months, thymic remnant after 50 years
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- **<u>Memory T h.</u>** Artışı (öz.$CD8^+$)

- **<u>CD28</u>** azalması

-Antijenlere T h.yanıtında ve T-bağımlı B h. yanıtında gerekli

- IL-2 res. ve hafıza h.lerinde IL-2 azalır

- **<u>$CD8^+$ $CD28^-$ hücre birikimi:</u>**

- oligoklonal artış
- Telomer kısalması
- apopitoza dirençli hücreler**
- Artmış TNF-α ve IL-6 üretimi

- CD4 T lenf. azalır

- Th1'den Th2'ye
- hücre-aracılı yanıtlar azalır- İNTRASELÜLER BAKTERİ İNF:****; hümoral yanıtlar nispeten korunur

- Treg azalır

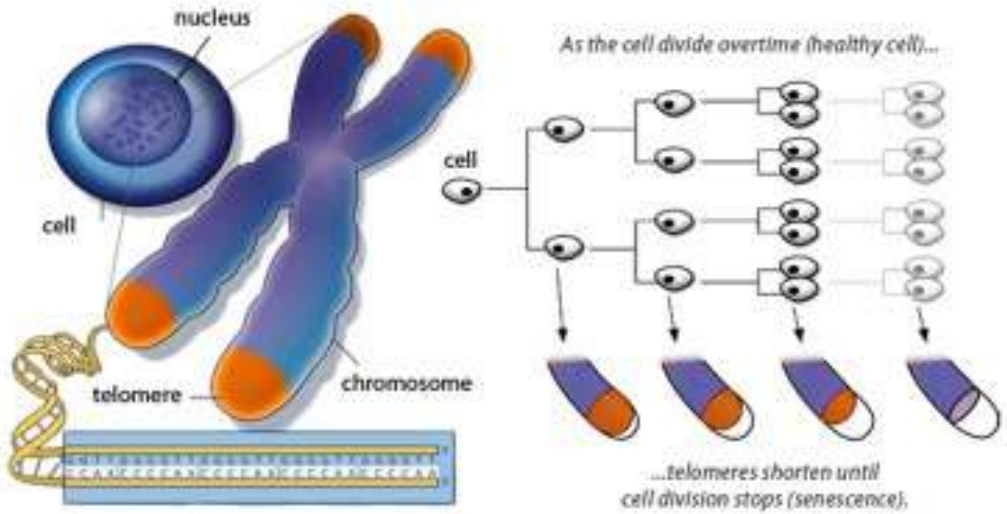
-otoimmünite

- CD4/ CD8 azalır

Replikatif yaşlanma/hücresel senesense yol açan etkenler

- **Telomer- Telomeraz Aktivitesi**

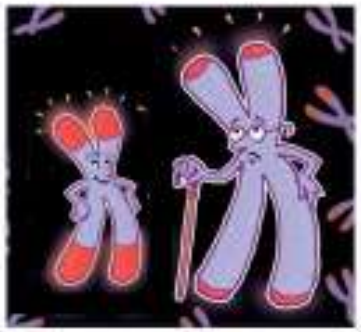
Senesensin ortaya çıkışında telomerik ve non-telomerik yolaklar vardır.



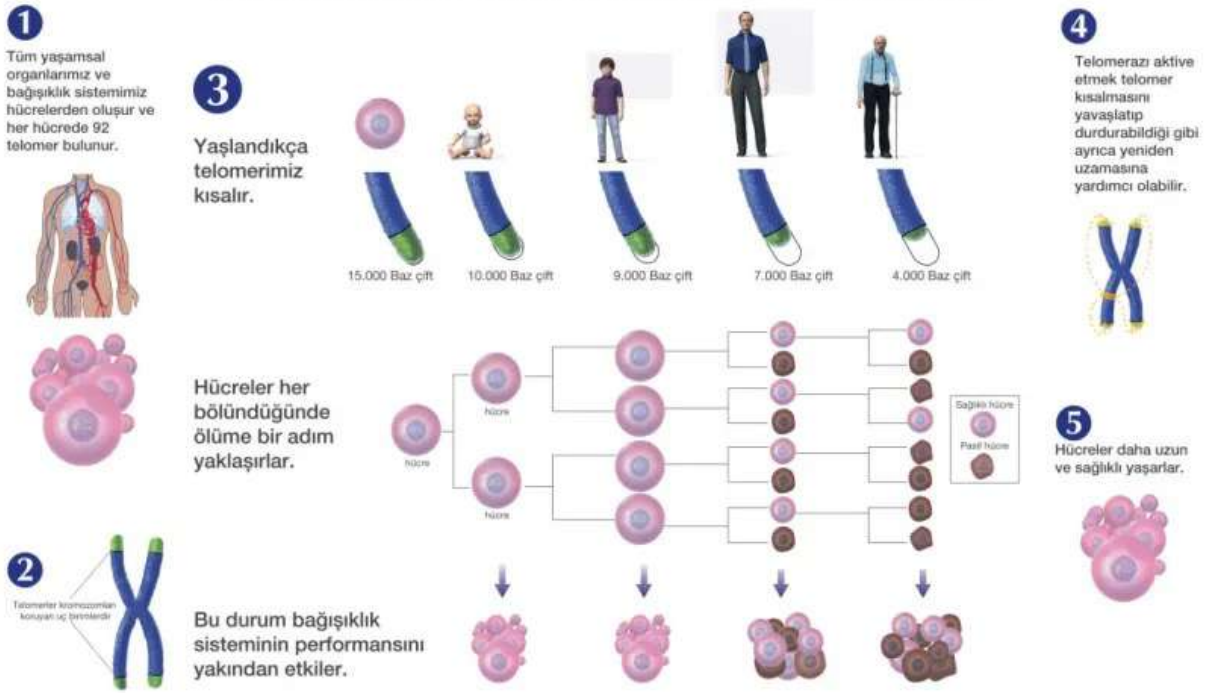
Telomerler, kromozom stabilitesi için gereklidir. Kromozomları degredasyondan, nükleaz etkisinden korur.

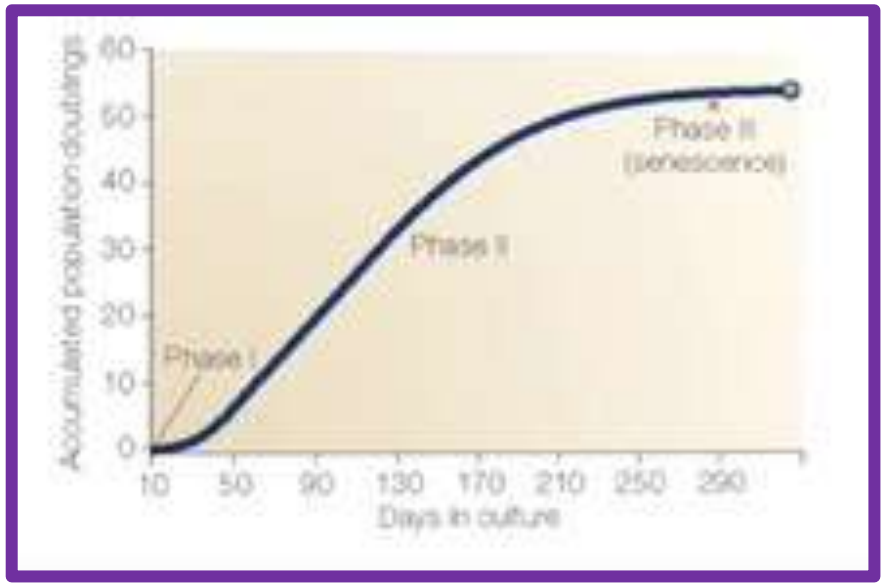
Tekrarlayan sekanslardan oluşur: TTAGGG

Telomerik yolak: telomer kısalmasıyla DNA hasarı cevabı tetiklenir ve p53 yolağı devreye girer, hücre proliferasyonu durur.



Hayflick limit***





Cellular senescence theory

Senescent cells accumulate with aging,
driving age-related tissue & organ degeneration

T follicular helper (TFH)

- Lenfoid dokular ve periferik kanda
- B lenfositlerin antikor yapımını destekler!

- Yaşlanmayla fonksiyon kaybı/ bozulması;
  - Kanser gelişimi
  - Otoimmün hastalıklar
  - Kardiyovasküler hastalıklar

Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1	IFN-γ	Macrophages	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
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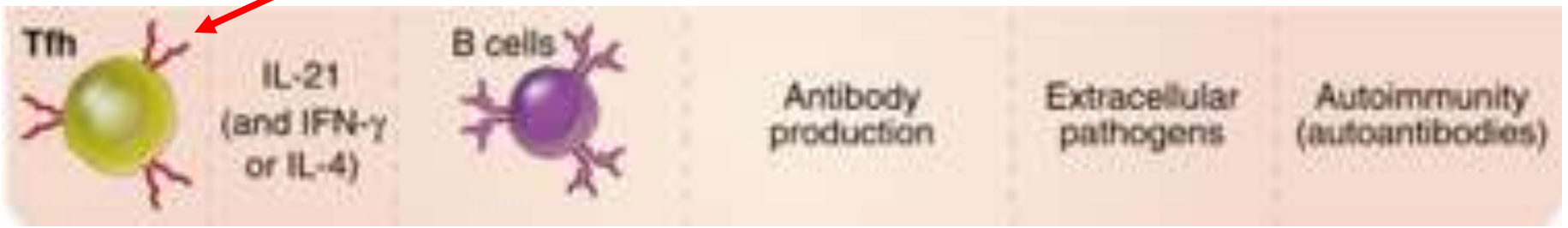
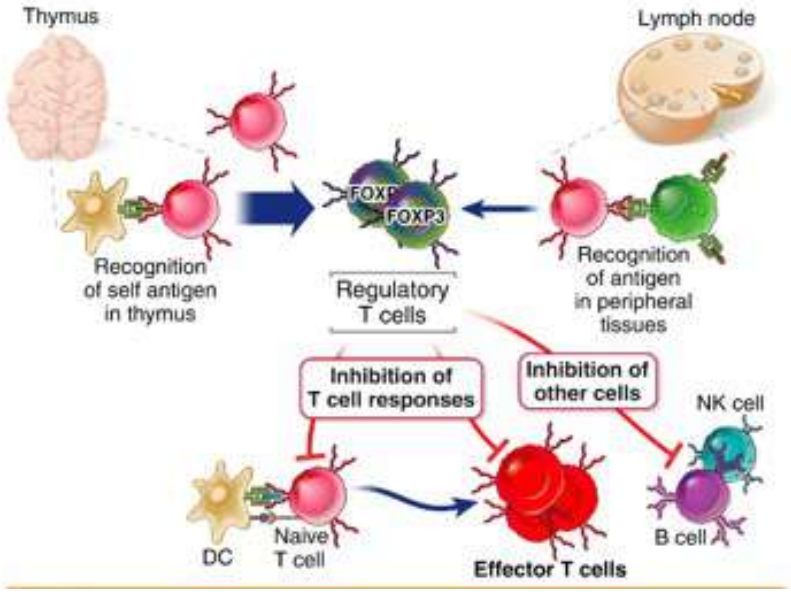
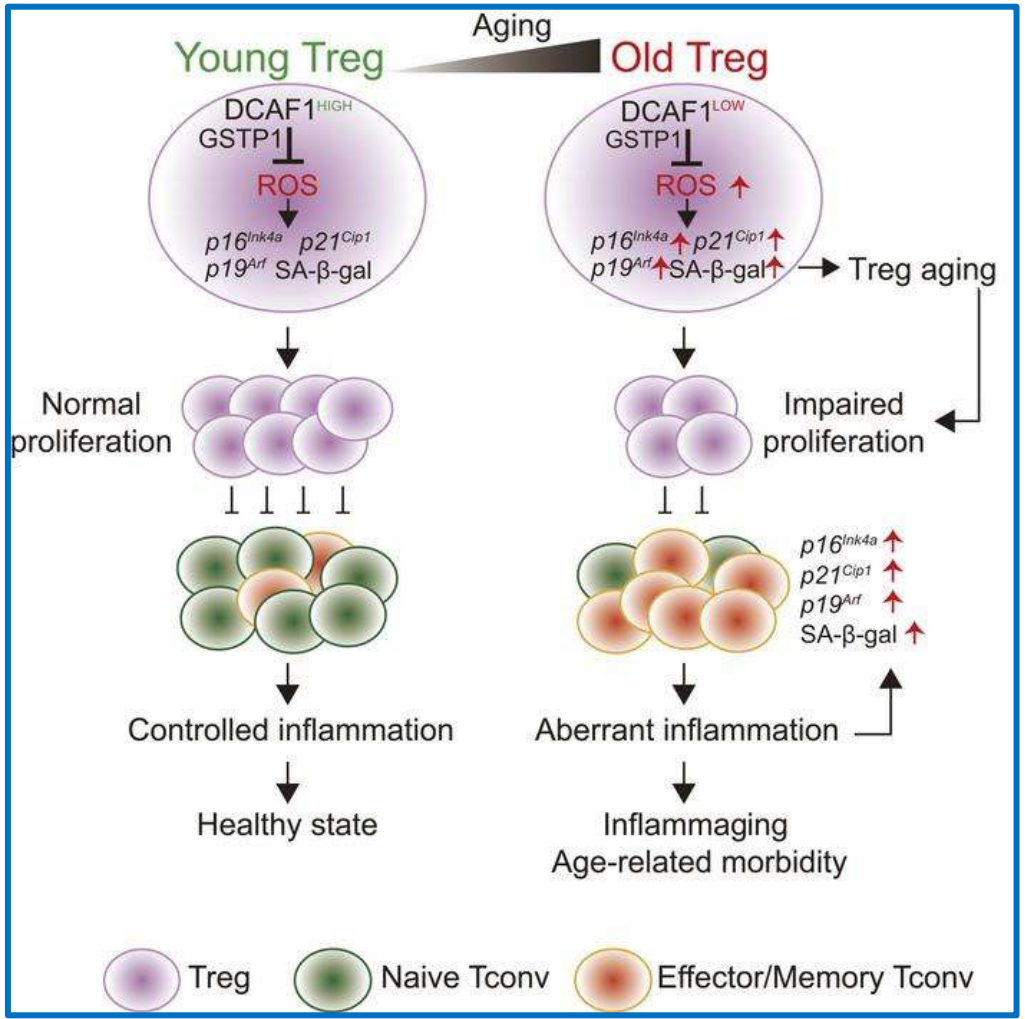




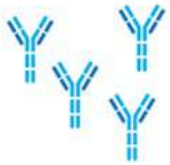
Regülatuar T (Treg) hücreler:

- Treg…Self-antijen tanıma
- FOXP3 ekspresyonunda azalma ve baskılama fonk.azalma

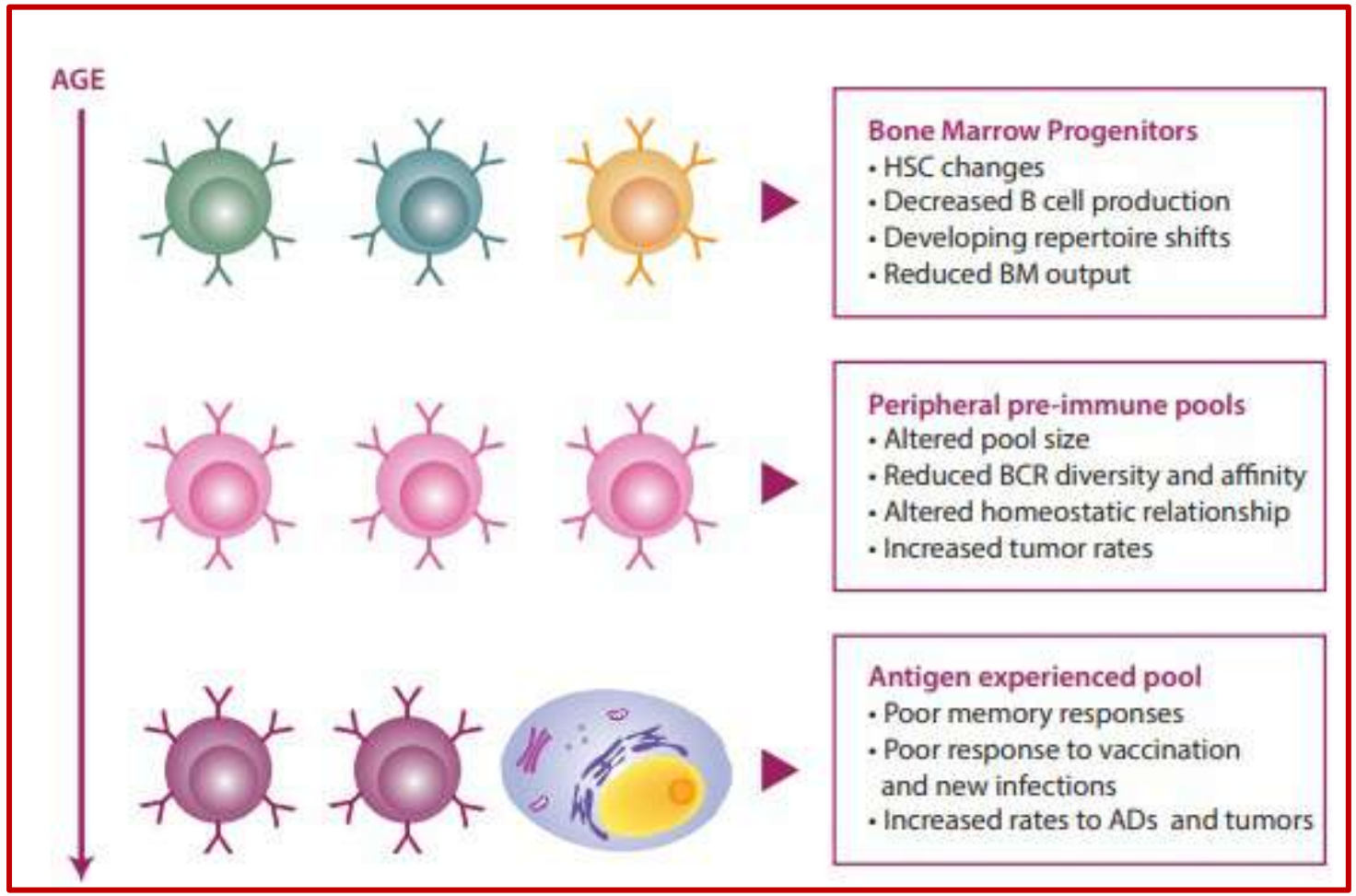
- SONUÇ: Otoreaktif hücreler*** otoimmünite***



Humoral Adaptif İmmünite

		CELL TYPE	CHARACTERISTICS
Adaptive Immunity	Humoral Response	B Cells 	↓ pre-B lymphocytes with peripheral B lymphocyte count unchanged ↑ $CD5^+$ B cells ($CD19^+$ $CD5^+$ clones B) that produce low affinity antibodies without cooperation of T cell ↓ naïve B cells Accumulation of memory B cells with ↓ diversity and affinity of antibodies Reach primary humoral response (dependent T cell cooperation). Conserved secondary humoral response
		Immunoglobulins 	↑ serum levels of IgA and IgG (IgG1, IgG2 and IgG4). Monoclonal immunoglobulin production by $CD19^+$ $CD5^+$ clones Secretion self-Ab non organ-specific (rheumatoid factor, antinuclear antibodies, antiphospholipid antithyroglobulines and parietal cells)
		Interleukins 	↓ IL-2 production because ↓ cooperation of T cells with antibody producer B cells ↑ Production of IL-4, IL-6, IL-8, IL-10 and TNF-α ↓ Production of IL-1 and IFN-γ

- Periferal B-lenfosit sayısı sabit kalırken pre-B lenfosit azalması,
- CD5+ B lenfosit artışı (düşük afiniteli ab sentezleyen)
- Naif B lenfosit azalması
- Çeşitliliği düşük-düşük afiniteli hafıza B lenfosit artışı
- IgA ve IgG (G1, G2 ve G4) artışı
- Monoklonal antikor sentez artışı***
- Otoantikor sentez artışı
- IL-2 azalması
- IL-4, 6,8, 10 ve TNF alfa artışı
- IL-1 ve IFN-gamma azalması


AGE
Bone Marrow Progenitors
• HSC changes
• Decreased B cell production
• Developing repertoire shifts
• Reduced BM output
Peripheral pre-immune pools
• Altered pool size
• Reduced BCR diversity and affinity
• Altered homeostatic relationship
• Increased tumor rates
Antigen experienced pool
• Poor memory responses
• Poor response to vaccination and new infections
• Increased rates to ADs and tumors

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Blood. 2011 Aug 4; 118(5): 1305–1315.
Prepublished online 2011 May 4. doi: 10.1182/blood-2011-01-331462
PMCID: PMC3152497
PMID: 21543762

Toll-like receptor 7 (TLR7)–driven accumulation of a novel CD11c^{+} B-cell population is important for the development of autoimmunity

Anatoly V. Rubtsov,[✉1] Kira Rubtsova,[1] Aryeh Fischer,[2,3] Richard T. Meehan,[2,3] Joann Z. Gillis,[2,3] John W. Kappler,[1,3,4] and Philippa Marrack[✉1,3,5]

- Yaşlanmayla ilişkili B hücresi (Aging-associated B cell/ ABC) alt grubu (CD19+ CD11b+ CD11c+)
- In vitro olarak, yalnızca innate immun sistem tarafından uyarılır
- Otoantikor ve sitokinlerin salınımı** ↑
- Th17 polarizasyonu (otoimmünite)
- Self/ Non-self ayırımı bozulur ***

- Dalağın fonksiyonun yaşlanma ile azaldığı,
- Memory B hücrelerin bir belirleyicisi olan CD27+ B hücrelerin arttığı,
- naive B hücrelerinin belirleyicisi olan CD27- B hücrelerin azaldığı
- IgD ve IgM cevabında azalma olduğu ileri sürülmüştür

Aging and Disease
www.aginganddisease.org
Volume 11, Number 6; 1363-1373, December 2020
http://dx.doi.org/10.14336/AD.2020.0603

Opinion

Innate and Adaptive Immunity in Aging and Longevity: The Foundation of Resilience

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[Received May 4, 2020; Revised June 1, 2020; Accepted June 3, 2020]

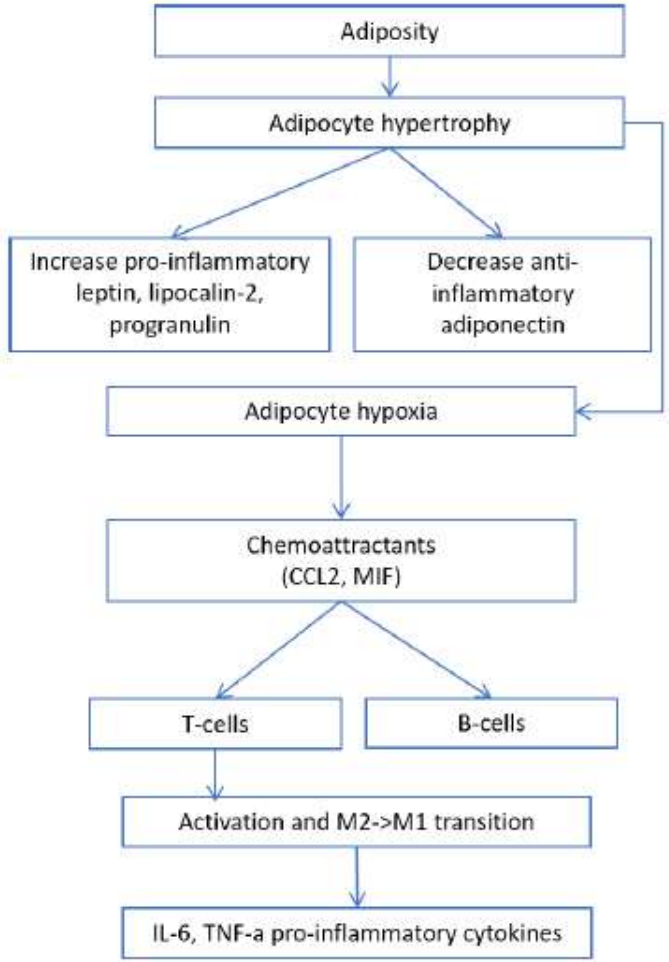

Figure 4. The role of adiposity in inflammation.

Anti-sitokin antikorlar ve İnfeksiyonlara Yatkınlık

- Covid-19 pandemi öncesi dönemde yapılmış çalışmalarda, sitokin ya da reseptörlerini kodlayan genetik defektlere benzer şekilde yatkınlık;
  - IFN-γ'ya karşı aAb …….mikobakteriyel hastalıklara,
  - IL-6'ya karşı aAb ……..stafilokokkal infeksiyonlara,
  - IL 17-A/ IL 17-F'ye karşı aAb …….mukokutanöz hastalıklara,
  - GM-CSF'ye karşı aAb ……kriptokokkoz ve nokardiyoza
  - Tip I IFN'lara karşı aAb ……viral infeksiyonlara (influenza, varicella zoster gibi)

viruses

MDPI

Review

Autoantibodies to Interferons in Infectious Diseases

Eugenia Quiros-Roldan [1], Alessandra Sottini [2], Simona Giulia Signorini [2], Federico Serana [2], Giorgio Tiecco [1] and Luisa Imberti [3,*]

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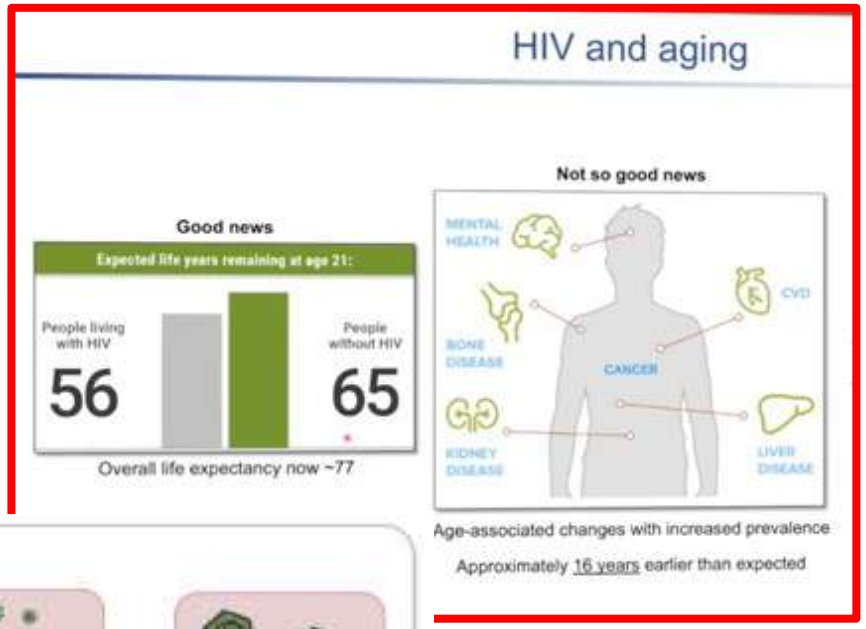
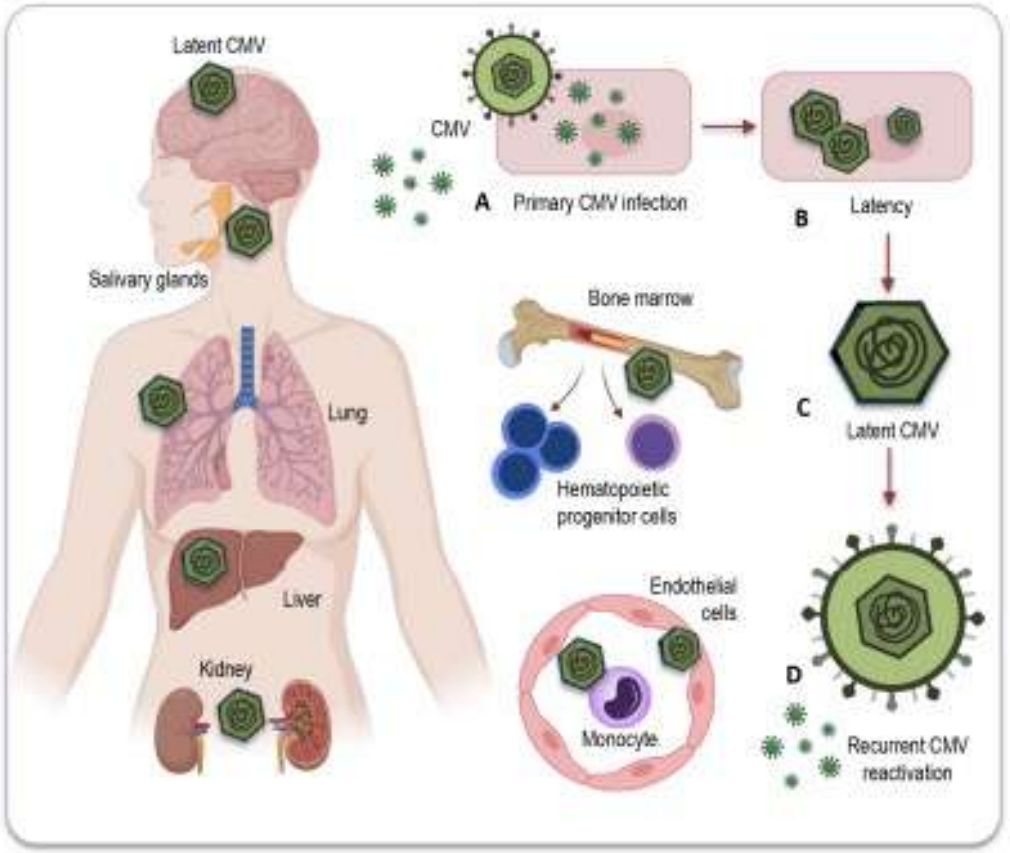
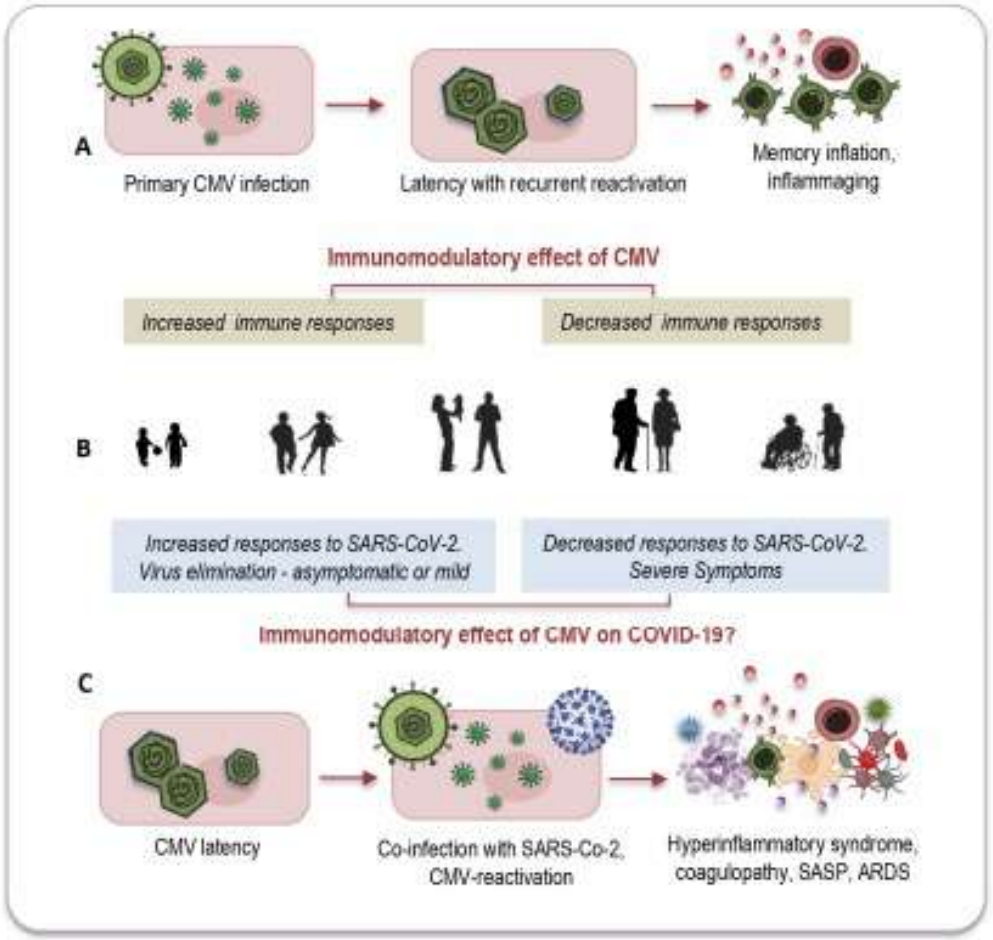
- Genetik temel;
  - İmmün sistem çeşitliliği (yaş, cinsiyet, beslenme, çevresel maruziyetler, mikrobiyom…) infeksiyonlara karşı duruşumuzu belirlerken !!!
  - Kimi zaman immünolojik temelli / otoimmün hastalıklara yatkınlığımızı oluşturuyor ***
- IFN'lar oldukça önemli (Hücre gelişimi düzenlenmesi , antiviral etki !!)
- Otoantikor varlığında …AĞIR VİRAL ENFEKSİYONLAR !!!!

Latent Viral İnfeksiyonlar ***

- İmmunosenescense- inflammaging ***
- CMV…..atherosclerosis
- HPV….kanser gelişimi
- HSV…. Alzheimer Hastalığı







- Gençlerde immün yanıtlar artarken yaşlılarda AZALIYOR
-Gençlerde hem innate hem de adaptif immün destek…sekonder patojenlerden koruyucu
-CMV ve SARS CoV-2 birlikteliği YIKICI !!!

International Journal of Molecular Sciences

MDPI

Review

Immunosenescence and Cytomegalovirus: Exploring Their Connection in the Context of Aging, Health, and Disease

Ludmila Müller * and Svetlana Di Benedetto

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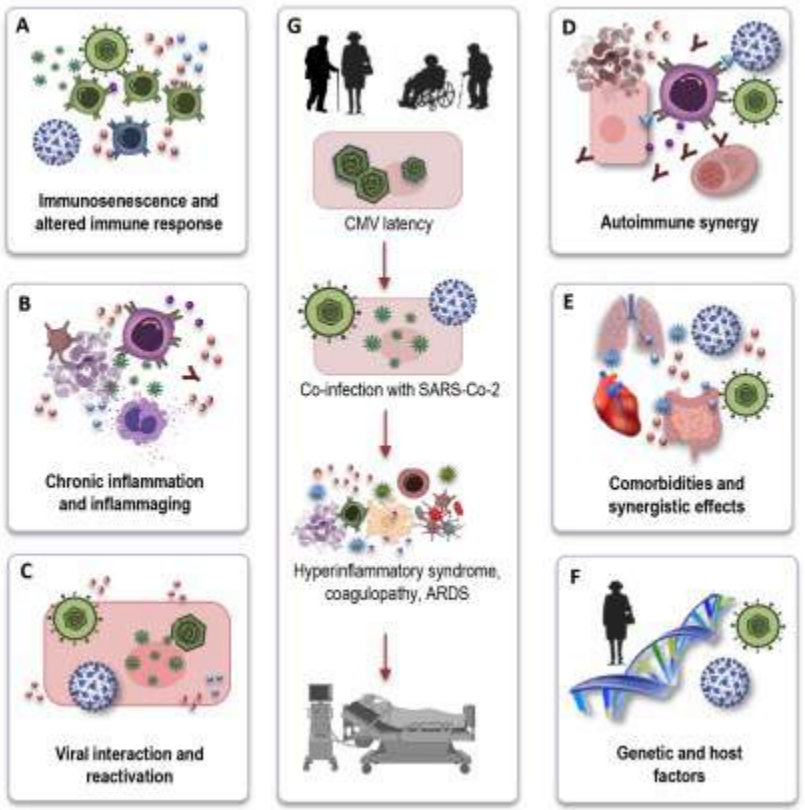
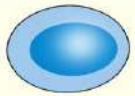
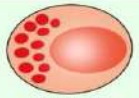
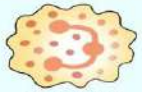


‘Centenerians’

Differences	 Elderly	 Centenarians
 CD4+ T cell	Increased subtypes from naive to exhausted, cytotoxic and regulatory T cells	Expansion of cytotoxic CD4+ T cells
 CD8+ T cell	Decrease in proliferation ability and cytotoxicity of CD8+ T cells	Highly differentiated CD8+ T cells
 B cell	Decrease in naive B cells and high-affinity antibody	Decrease in the number of B cells Increase of naive B cells and IgM
 NK cell	Decreased CD56bright immunoregulatory cells Increased CD56dim cytotoxic cells	Increased cytotoxic capacity of NK cells Increased IFN-γ production of NK T cells
 Neutrophil	Decreases in phagocytic ability, adhesion and chemotaxis	Increase of neutrophil chemotaxis and microbicidal capacity Decreases in neutrophil adherence
 Inflammatory molecules	Increased inflammatory molecules, such as IL-1β, IL-6, TNF-α, IL-8, CRP and CXCL9	Increased anti-inflammatory molecules, such as TGF-β1, IL-10 and IL-1RA
 Age-related diseases	Be susceptible to	Avoid or Delay

Mavi Bölgeler

Uzun yaşamın sırları

Loma Linda, Amerika

- Sağlıklı sosyal çevre
- Kuruyemiş tüketimi

- Tam tahıllar
- Korunmuş yerel kültür

- Yüksek soya tüketimi
- Alkol yok
- İnanç

- Aile
- Sigara yok
- Sebze ağırlıklı beslenme
- Bakliyat
- Sosyal bağlar

Sardunya
İtalya

- Bakla
- Yüksek polifenol içerikli şarap

- Güçlü kadınlar
- Güneş ışığı
- Bahçe işleri

- Yavaş yaşam
- Sevilebilirlik
- Zerdeçal

Okinava
Japonya

Terapötik seçenekler ???

AMAÇ:

1. Eski HSC'lerin gençleştirilmesi,
2. Miyeloid ve lenfatik sistemler ile T ve B hücrelerinin sayısı arasındaki dengenin yeniden sağlanması

Timusun yapısını ve işlevini eski haline getirmek mümkün mü ?!.

- IL-10, leptin, keratinosit büyüme faktörü (KGF) ve timik stromal lenfopoietin (TSLP)'nin timo-uyarıcı özelliği yaşlılarda immün yeniden yapılanmaya katkıda bulunabilir mi?

- **IL-7**, T hücresi gelişimi için çok önemli !!! (IL-7 tedavisi, periferik T hücrelerinin genişlemesini ve TCR çeşitliliği**

- **Telomeraz,** T hücresi gelişimi için önemli bir bileşen
  - Telomeraz ekspresyonunun düzenlenmesi, T hücresi yanıtını arttır ve ömrünü uzatır

- Yaşlanan hücreler, birçok kronik hastalıkla bağlantılı olan SASP'yi biriktirerek bağışıklık hücrelerinin işlev bozukluğuna neden olur, bu nedenle yaşlanan hücrelerin temizlenmesi büyük önem taşır.

- Senoterapötik stratejiler:
  - senolitik (removing senescent cells selectively)
  - senomorfik (changing senescence phenotypes)

İmmünoterapi : ‘senescent’ hücrelere karşı

- ABT-263 (yeni senolitik ajan)…Bcl-2 ailesini hedefleyerek apopitozu destekler

- FOXO4 peptid…. FOXO4-p53 etfileşimi aracılığı ile apopitozu destekler

- Üzüm çekirdeği eksratktı prosiyanidin C1 (PCC1) …Doğal senolitik ajan **
- NKG2D reseptörü içeren modifiye T hücreleri- **CAR-T hücre** (chimeric antigen receptor)…NKG2D ligandı içeren ‘senescent’ hücreleri tanıma ve elimine etme özellikli
- Kemoterapötik ajanlar (doxorubicin, melphalan and bortezomib)…NK hücrelerinin ‘senescent’ hücreleri öldürme etkisini arttırır

- Hücre yaşlanmasının ana sorumlusu: **SASP- senescence-associated secretory phenotype**
- Hücre yaşlanmasını önlemenin yolu***…… GATA4, NF-κB ve BRD4 sinyalizasyon moleküllerini bloke ederek veya hedefleme ilaçları kullanarak SASP'yi kontrol etmek veya nötralize etmektir
- **Rapamycin…**mTOR inhibitörü (priferik T h.lerinde yaşlanma markerlarını ve SASR regülatörlerini inh.eder)
- **Metformin…** NF-κB sinyalizasyonunu düzenler ve yaşlanma sürecini geciktirir

- İmmün ‘check point’ inh.leri… PD-L1 ve IDO, T hücre aktivitesini sınırlayabilir (Güvenlilik ???)
- ‘Treg targeted therapy’ kanser ve otoimmün hastalık tedavisi
  - Tümör hücrelerinin immün sistemden kaçışı ve kanser riski !!
- GDF15 (Growth differentiation factor 15)..mitokondriyal disfonksiyona neden olan stres yanıt geni
  - T reg immünsupresif fonksiyonlarını potansiyelize

- **Rituximab (anti-CD20 monoklonal antikoru)**, proinflamatuar B hücrelerin inh. (ABC /Aging-associated B cell gibi)- yaşlanma ile ilişkili otoimmün hastalık önlenmesi
- Karotenoidlerden zengin meyve ve sebzeler…NK hücre sayısını ve Th fonksiyonlarını arttırır,
- Vitamin E destekleri…Makrofajlardaki PGE’ üretini azaltarak T hücre fonksiyonlarını destekler
- **EGZERSİZ**….Th17 sayısını azaltır ve IL-7 düzeyini,timik fonksiyonları ve otofajiyi arttırır
- DİYET + EGZERSİZ ….ÖNEMLİ!!!

GYNECOLOGICAL ENDOCRINOLOGY

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

Gynecol Endocrinol, 2014; 30(1): 16–22
© 2014 Informa UK Ltd. DOI: 10.3109/09513590.2013.852531

informa healthcare

IMMUNE SYSTEM

The immune system and aging: a review

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[2]*Hospital Clinic-Institut d'Investigacions Biomèdiques, August Pi i Sunyer (IDIBAPS), Barcelona, Spain*

Table 1. Immunosenescence: causes and associated factors.

- Lifelong antigenic stress
- Filling of the immunological space
- Accumulation of effector T and memory cells
- Reduction of naïve T cells
- Deterioration of clonotypical immunity
- Up-regulation of the innate IS
- Lifelong antigenic stress
- Filling of the immunological space
- Mitochondrial damage causing tissues dysfunction
- Micronutrient inadequacy accelerates aging because of
- metabolic malfunctioning
- The number of telomeres is proportional to life
- expectancy. They avoid DNA damage
- Reactivity to self-antigens – risk of triggering autoimmune diseases

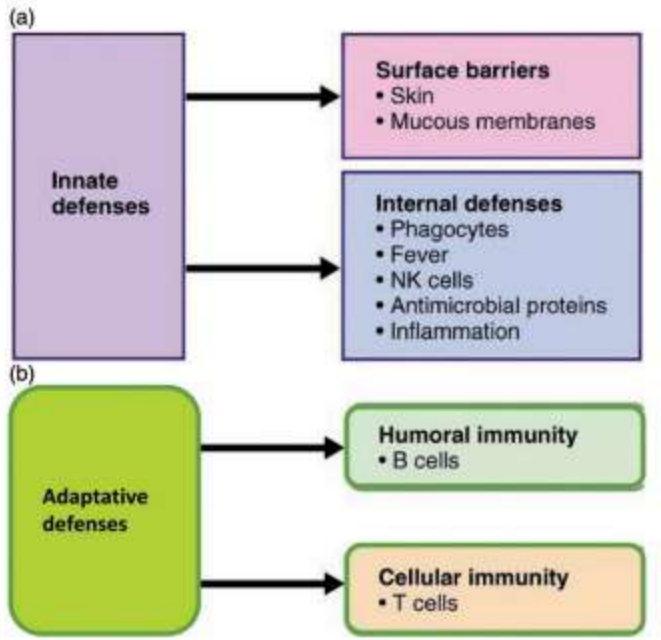

Figure 1. Biological defense mechanisms that protect the body. The immune system is a functional system rather than an organ system involving hematopoietic, vasculature and lymphatic systems. (a) Innate defenses; (b) adaptive defenses.

REVIEW ARTICLE
https://doi.org/10.1038/s41590-017-0006-x

nature immunology

Corrected: Author Correction

The twilight of immunity: emerging concepts in aging of the immune system

Janko Nikolich-Žugich

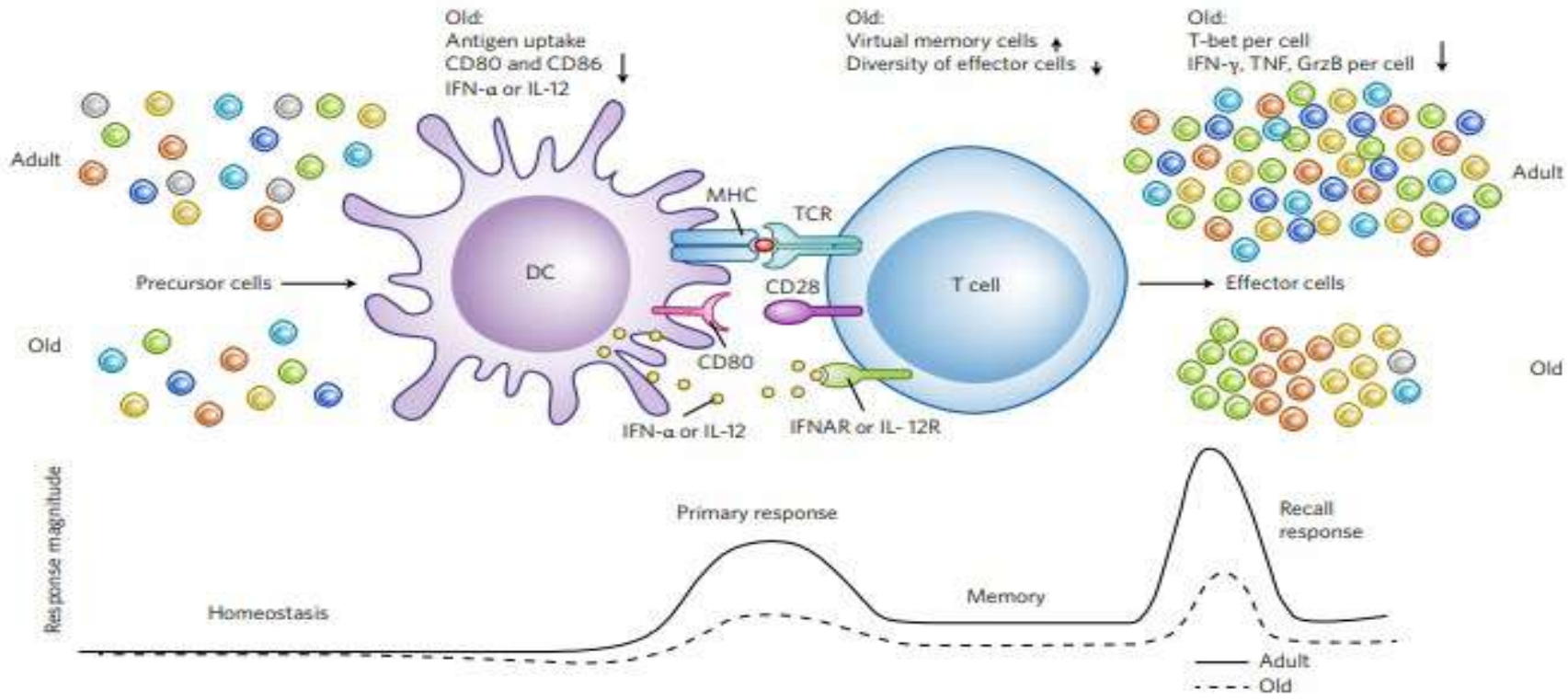

Fig. 1 | Defective activation of naive CD8⁺ T cell responses with aging. Aging results in a decrease in the number of naive CD8⁺ T cells, an increase in the number of memory-like precursor cells ('virtual memory cells') and a moderate reduction in the diversity of the TCR repertoire. During the primary response to intracellular pathogens in the aged environment, DCs exhibit impaired maturation, lower antigen uptake and reduced production of signal 3 (cytokines). Coordination of the response is also impaired (Figs. 2 and 3). The outcome is severely impaired population expansion of effector cells, diminished polyfunctionality and considerable narrowing and homogenization of the TCR repertoire elicited. Recall responses are similarly affected if the memory was formed in old age but are less affected if it was formed in youth. CD80 and CD86, co-stimulatory molecules; MHC, major histocompatibility complex; CD28, co-receptor; IFNAR, interferon-α receptor; IL-12R, IL-12 receptor; GrzB, granzyme B. Credit: Marina Corral Spence/Springer Nature.

Vaccine 38 (2020) 8264–8272

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Understanding immunosenescence and its impact on vaccination of older adults

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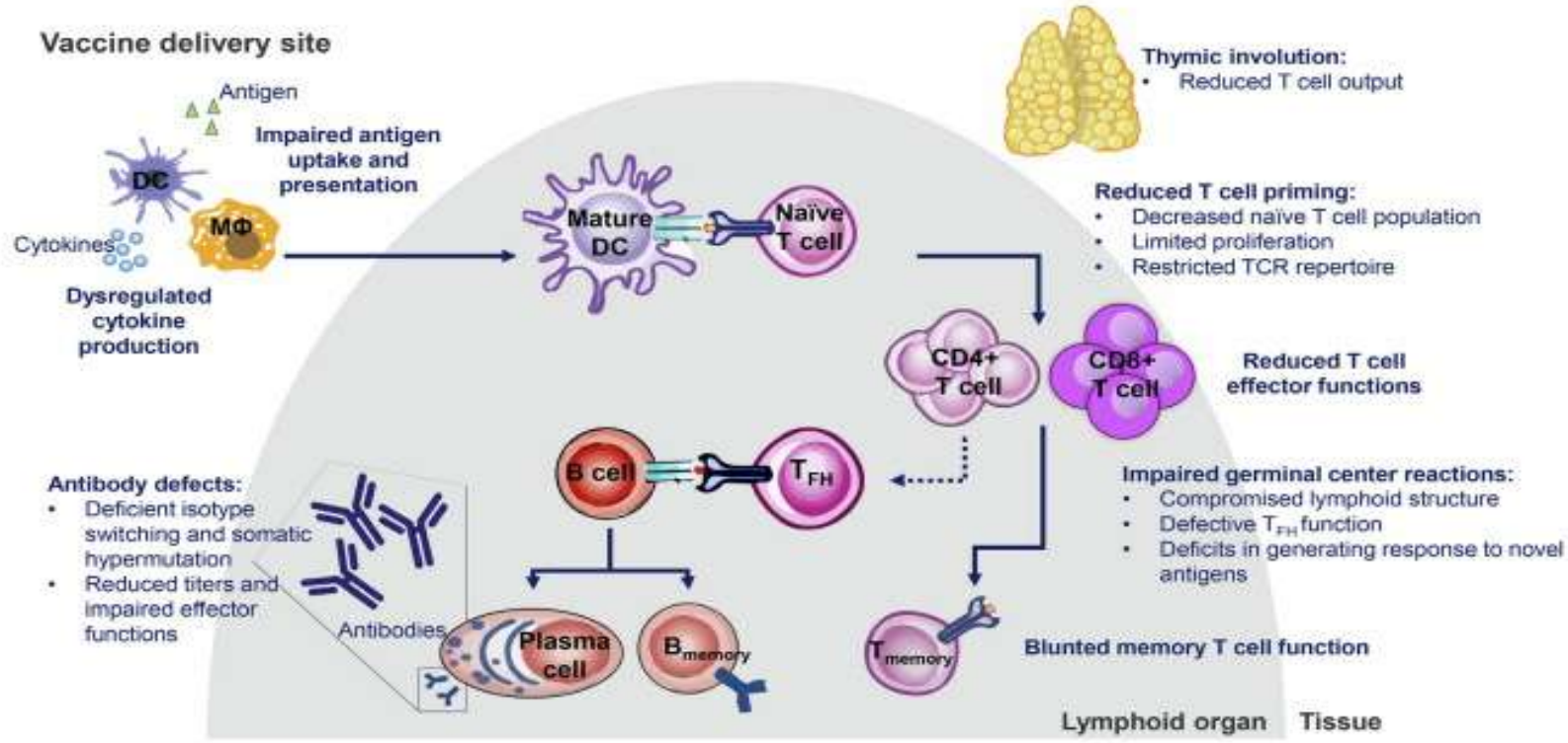

Fig. 1. Schematic diagram of immune deficits in older adults. Abbreviations: DC, dendritic cell; MΦ, macrophage; T_{FH}, T follicular helper; TCR, T cell receptor.