# Mechanisms and rejuvenation strategies for aged hematopoietic stem cells(2020)

JOURNAL OF HEMATOLOGY & ONCOLOGY

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**Supervisor : Dr.Farsinezhad**

**Presented by : Mahsa Mottaghizadeh**

# Background

**1.A key step in hematopoietic stem cell (HSC) aging in 1996:**

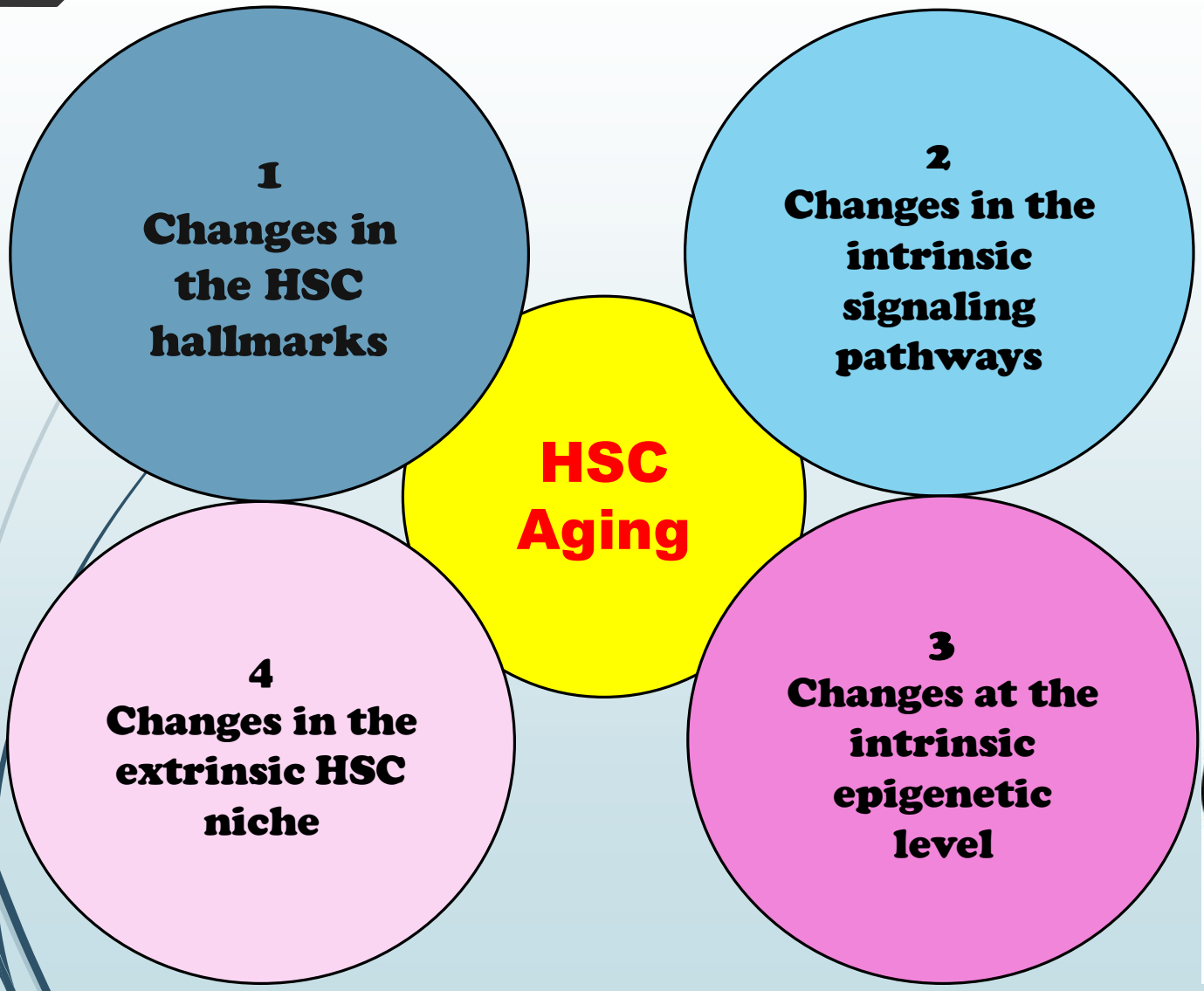
HSCs from old mice **were only one-quarter** as efficient as those from young mice at homing to and engrafting the bone marrow (BM) of irradiated recipients.

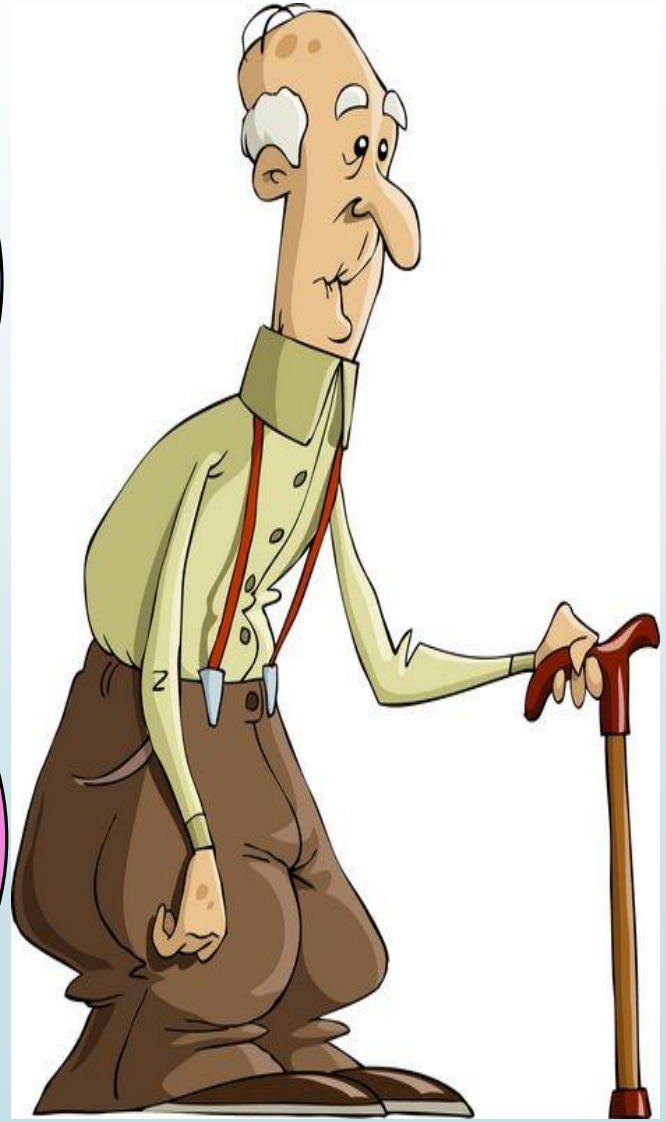
**2. in the clinic:**

donor age is carefully considered in HSC transplantation, and **young donors result in better survival** after HSC transplantation.

**3. Aged HSCs and incomplete reconstitution potential.**

# How aged HSC dysfunction occurs?



# 1
# Changes in the HSC hallmarks

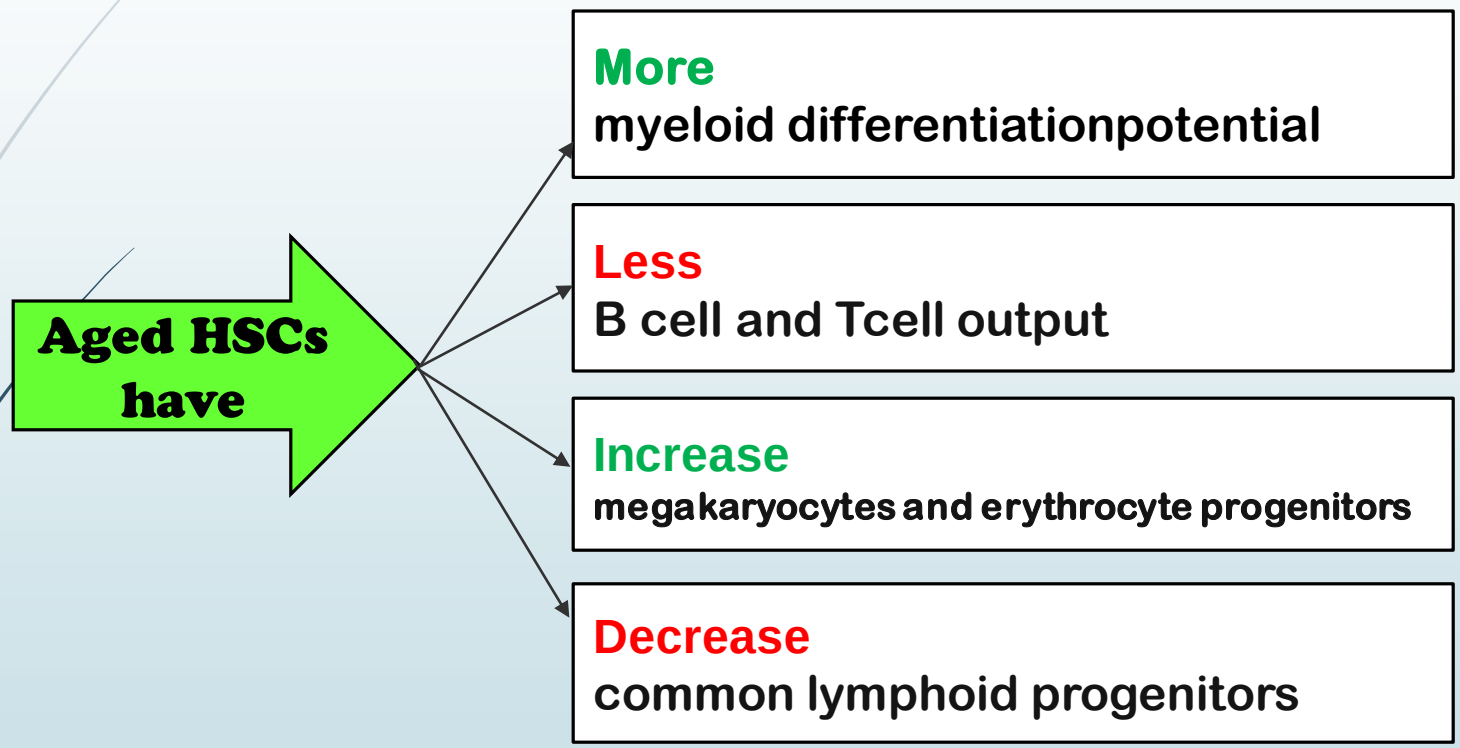
# 1.Self-renewality:

- HSCs are characterized by their capacity for long-term self-renewal and the ability to generate all functional blood cells.

- Old HSCs showed less self-renewal activity and generated smaller daughter clones.

changes in gene expression programs ⟶ **Sox17**

# 2. Differentiation bias



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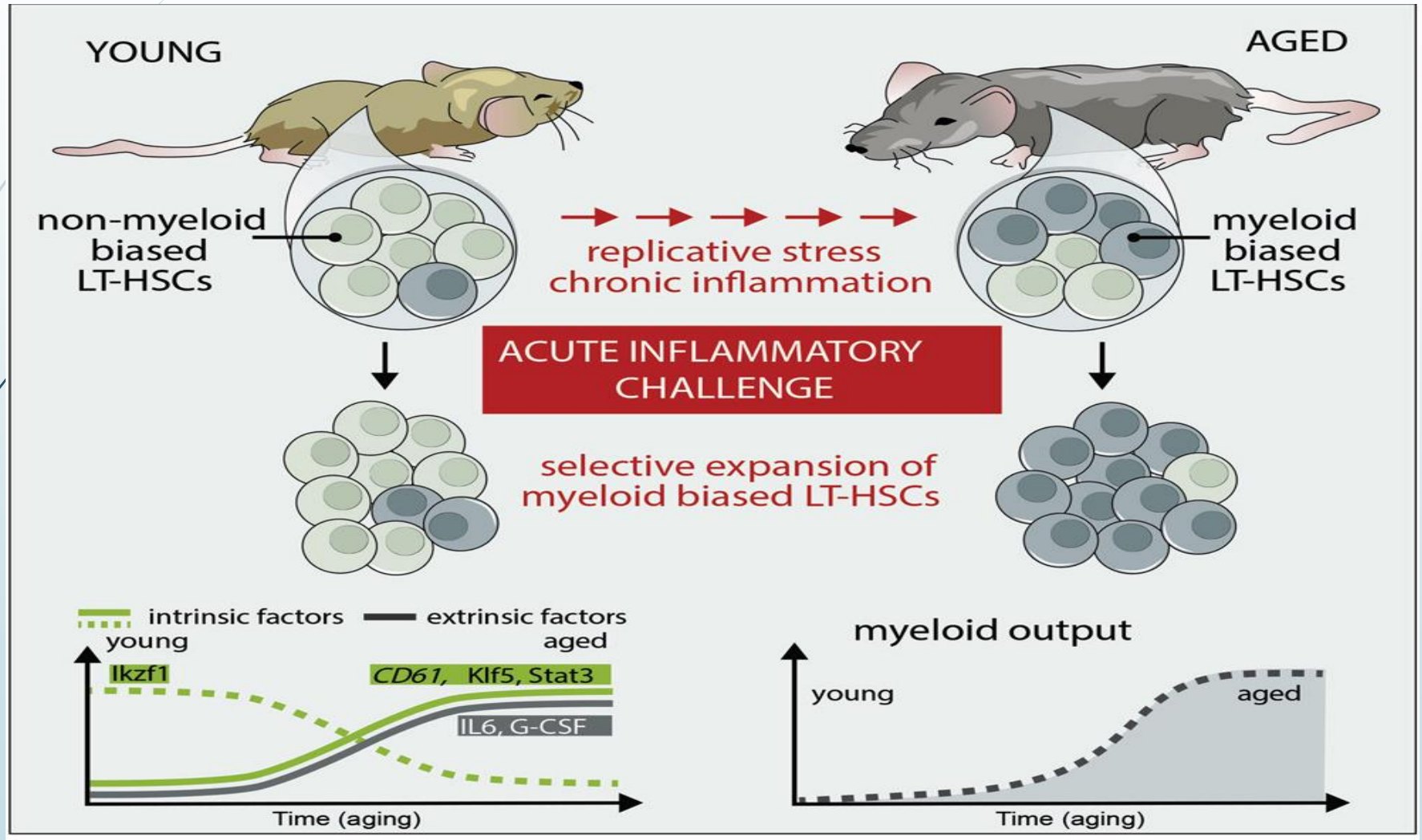


# 3. Homing and engraftment

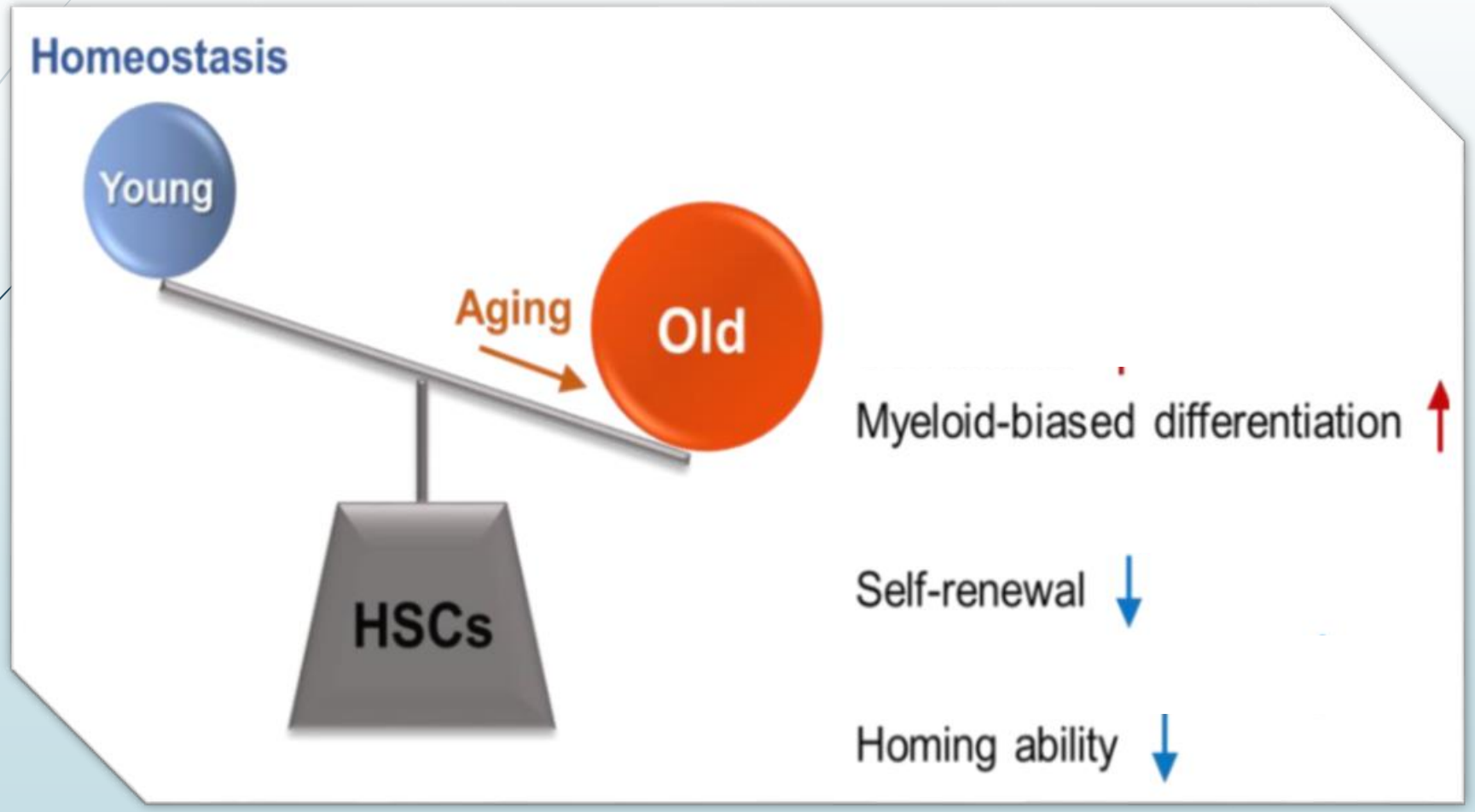
- injected young or old BM cells into congenic mice

- the homing efficiency of old mouse was approximately **three-fold lower** than that of young mouse.

**p16Ink4a, a cyclin-dependent kinase inhibitor**

**CD44 , is critical in the maintenance and migration of HSCs**

# 3.Homing and engraftment



**2**
**Changes in the intrinsic signaling pathways**

# 1. DNA damaging pathways


## What We Lose With Age

As we grow older, telomeres at the end of our chromosomes shrink. New research suggests major depression also is linked to shorter telomeres, a sign of 'accelerated aging.'

Chromosome

Telomere, a protective covering

Cell

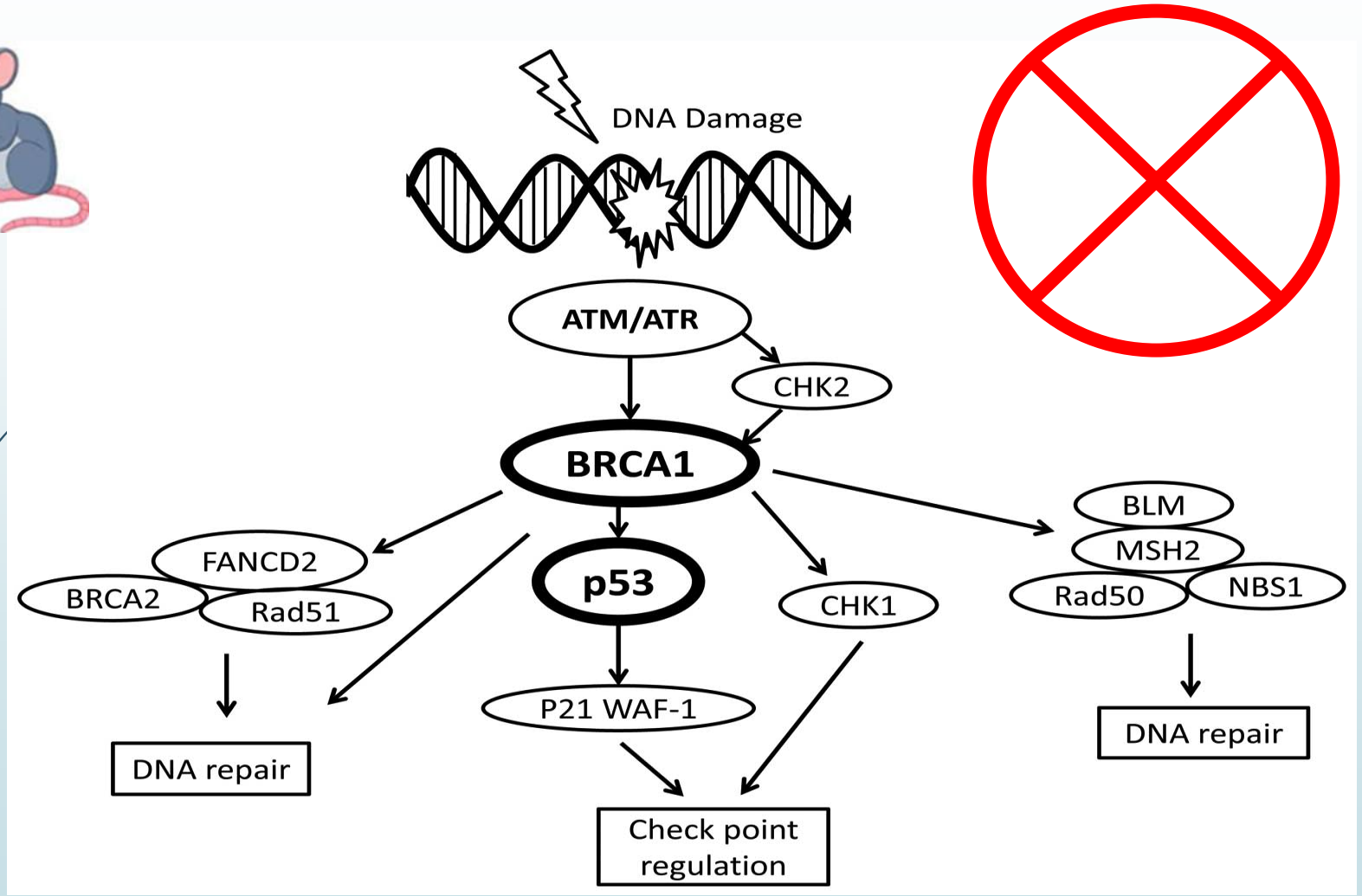
As cells divide over time...

...telomeres shorten, and eventually cell division stops.

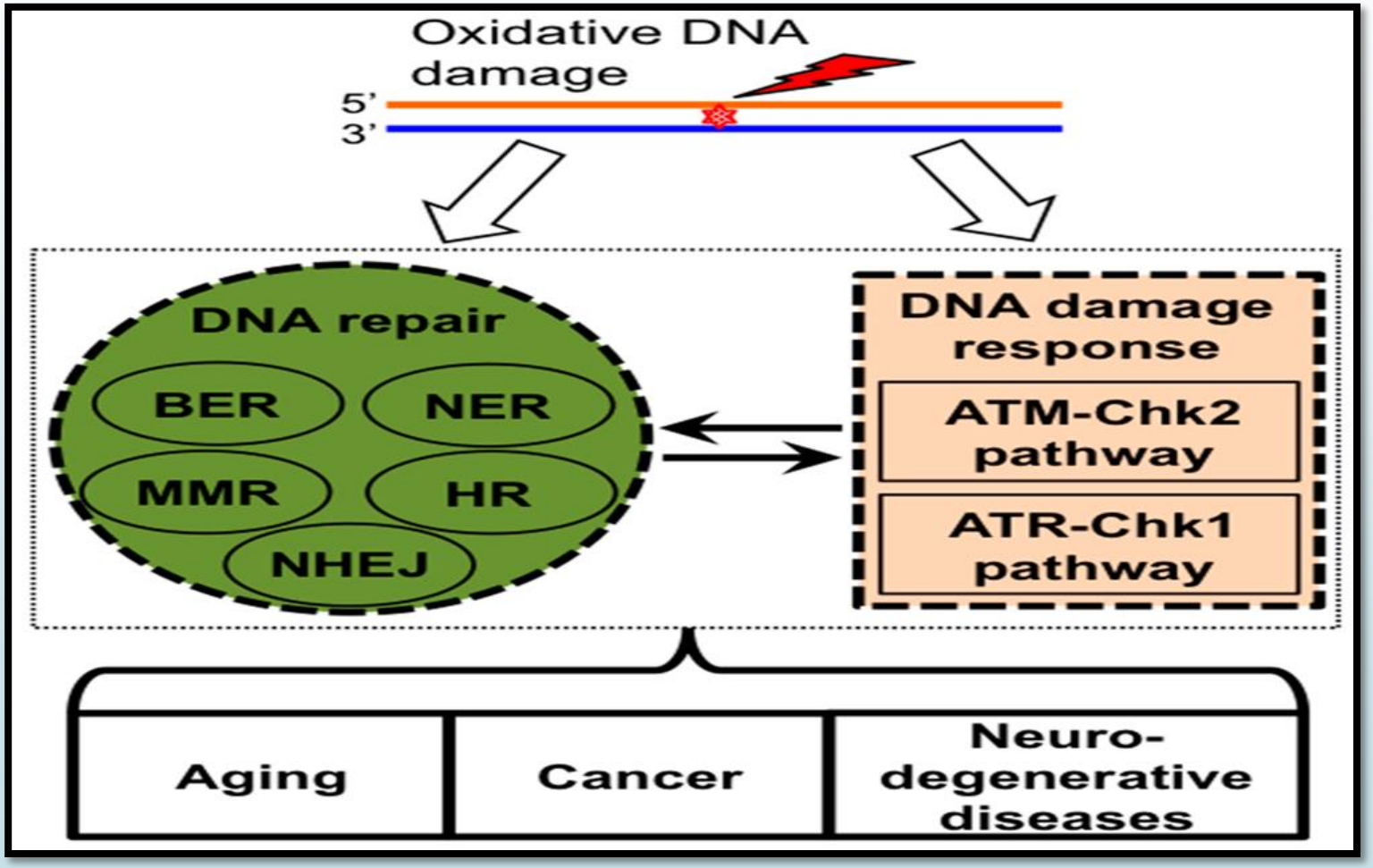
Source: WSJ research

The Wall Street Journal

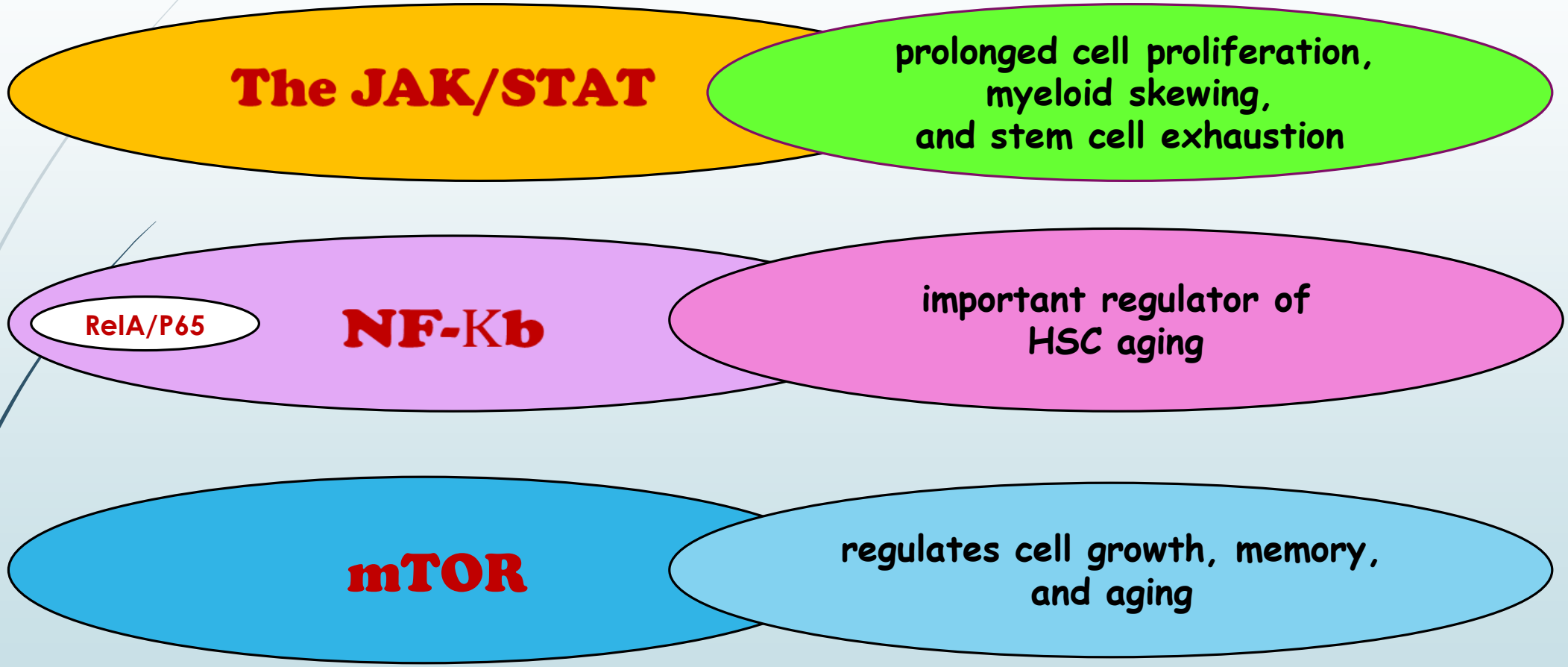
# 1. DNA damaging pathways

DNA damage leads to a cascade of cellular events known as the **DNA damage response (DDR).**



# 2.The JAK/STAT, NF-κB, and mTOR pathways

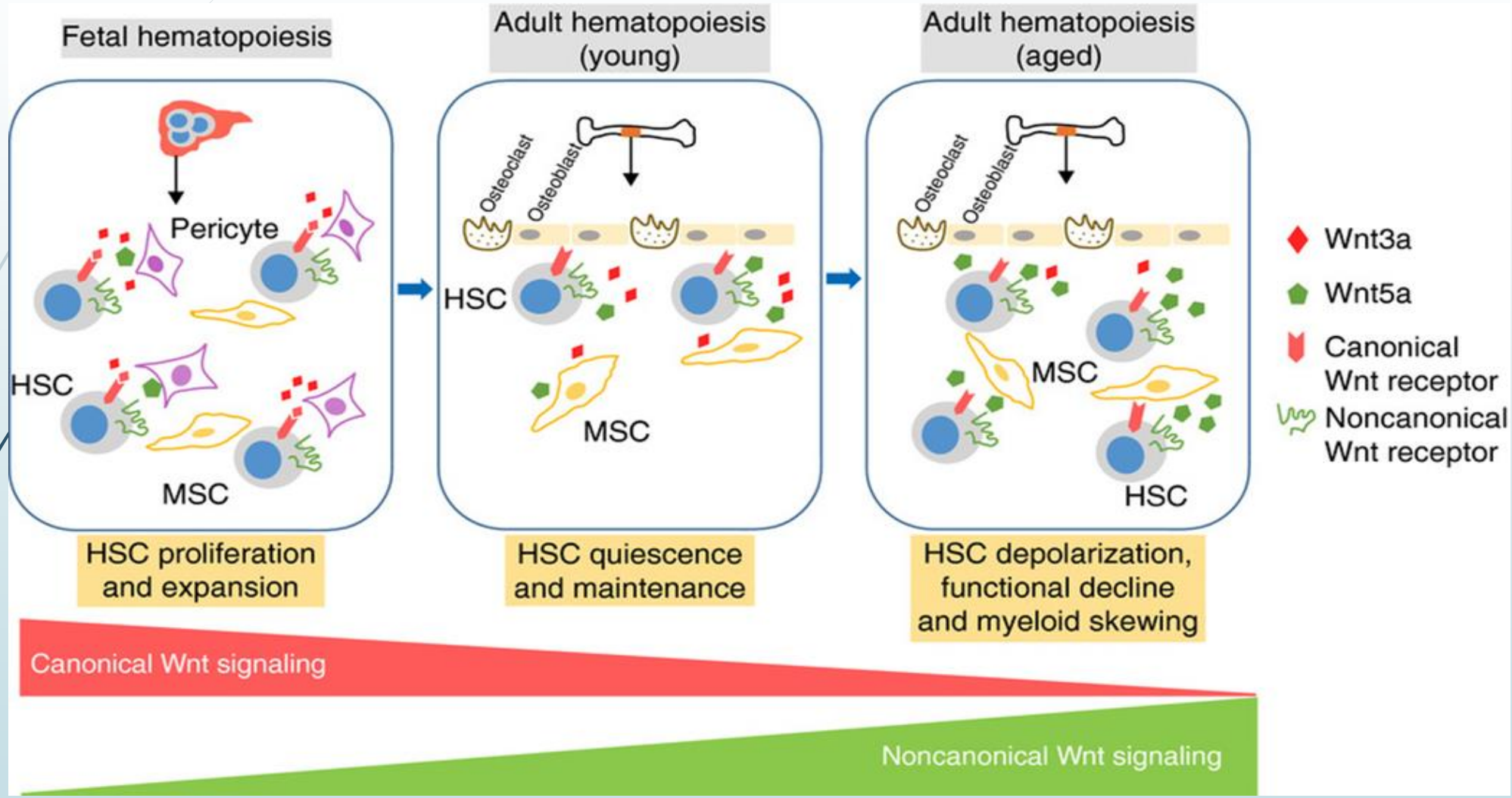


# 3.The Wnt pathway

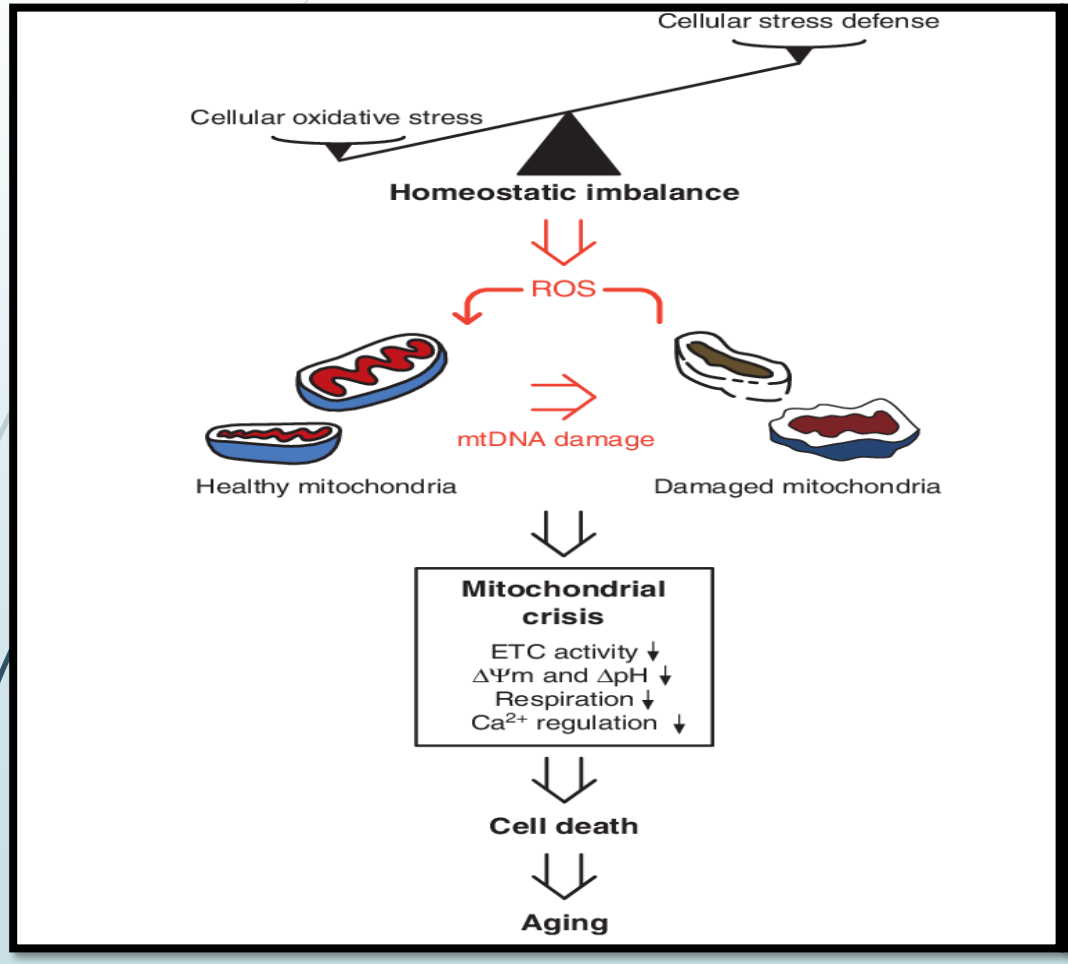
- Polarity is associated with specialized functions in HSC.

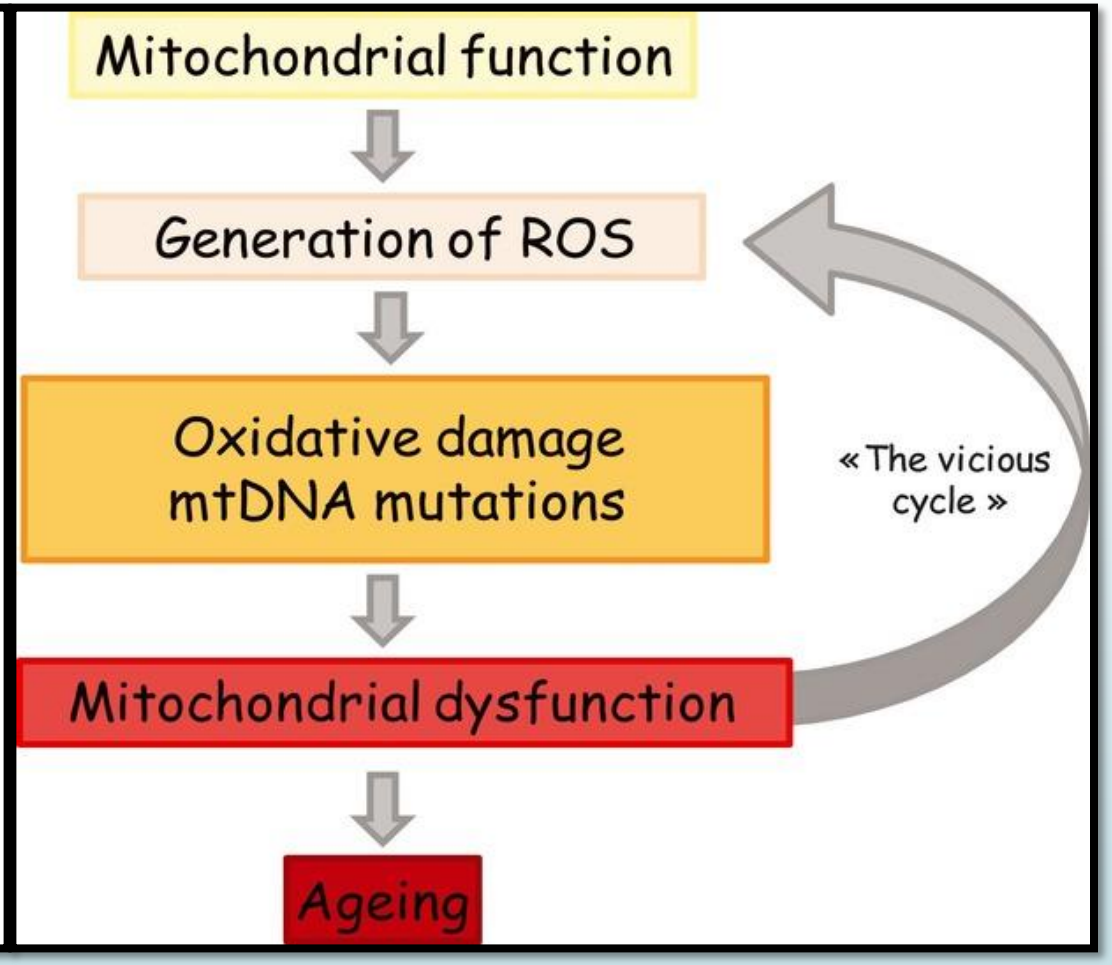
1. The small RhoGTPase **Cdc42** showed **elevated** activity in aged HSCs.
2. a shift from **canonical** to noncanonical Wnt signaling

# 3.The Wnt pathway



# 4.The ROS and UPRmt pathway



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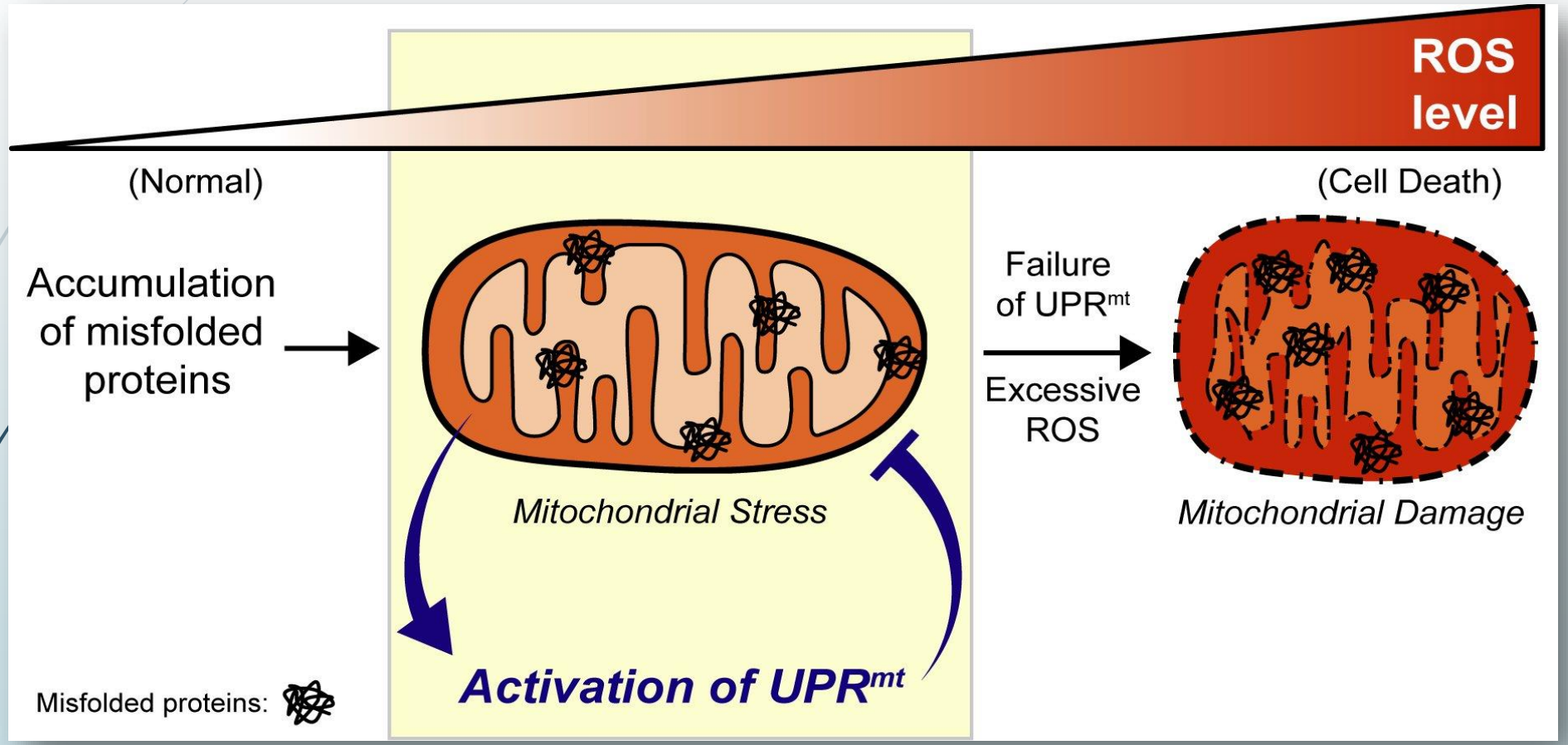
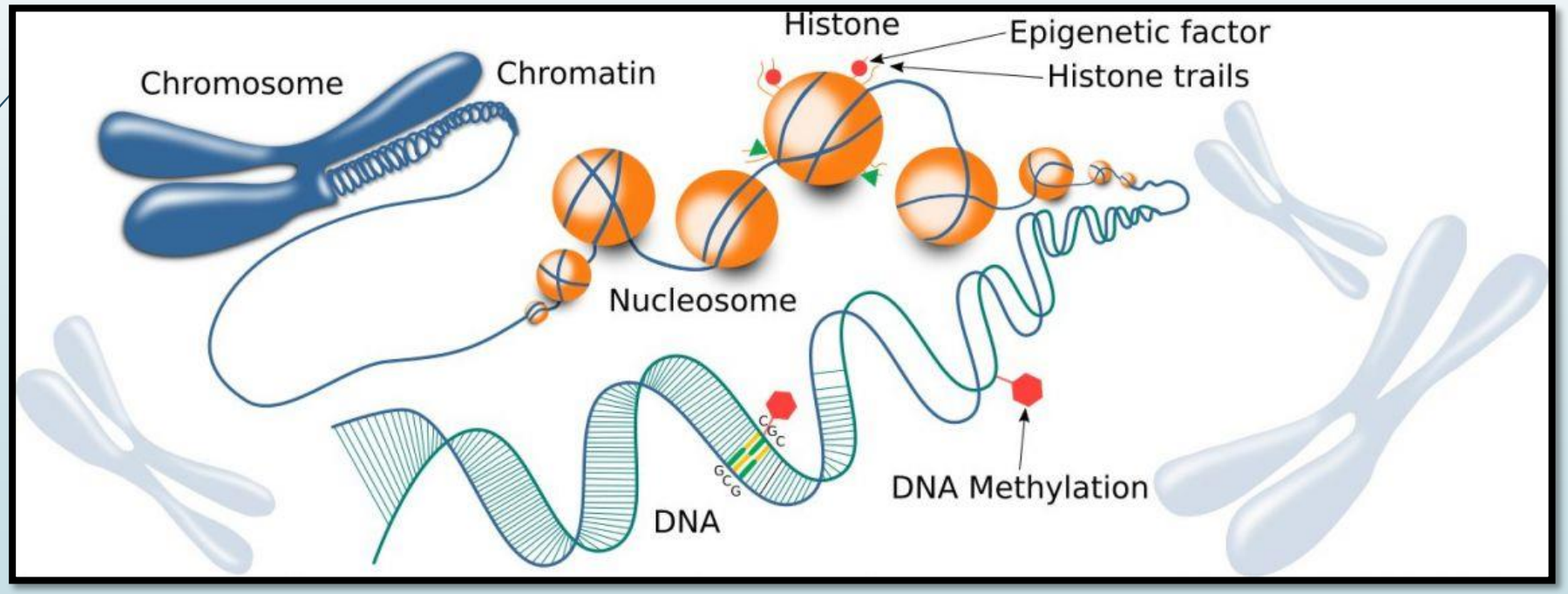


**3**
**Changes at the intrinsic epigenetic level**

- Epigenetics refers to changes in gene expression but does not involve changes in the DNA sequence of organisms.

- Loss of epigenetic regulation at the chromatin level may drive both cellular functional attenuation and other manifestations during aging.



# Changes at the intrinsic epigenetic level during HSCaging

## 1. DNA methylation

**Table 1** Differences in DNA methylation and histone modification levels between young and aged HSCs

| | Alterations with age | Functions |
|---|---|---|
| **DNA methylation** | | |
| DNMT1 | Downregulated | Myeloid skewing and self-renewal defects |
| DNMT3A | Downregulated | Lead to an increase in self-renewal with age at the expense of differentiation |
| DNMT3B | Downregulated | Lead to an even more severe arrest of HSC differentiation |
| TET1 | Downregulated | Enhance HSC self-renewal; increase B cell production; develop B cell malignancies |
| TET2 | Downregulated | Attenuate differentiation and lead to myeloid transformation and myeloid malignancies |
| 5-mC | Not studied | Hypermethylation at promoters associated with lineage potential |
| | Not studied | Hypermethylation selectively targeting PRC2 and PU.1-binding sites |
| | Not studied | Hypomethylation at the HSC fingerprint genes and rRNA genes |

# Changes at the intrinsic epigenetic level during HSCaging

## 2. Histone modifications

| Histone modification | | |
|---|---|---|
| H3K4me3 | Upregulated | Alter promoter usage and upregulate some genes (*Selp*, *Nupr1*, and *Sdpr*) |
| H3K27me3 | Upregulated | Alter promoter usage and downregulate *Flt3* expression with age |
| H4K16ac | Downregulated | Downregulate nuclear polarity with age |
| H3K27ac | Downregulated | Link to leukocyte activation and apoptotic signaling |
| H3K9me2 | Downregulated | Anchor lamina-associated domains to nuclear lamin A/C |
| H3K4me1 | Downregulated | Link to myeloid and erythroid differentiation and functions |
| H3K23ac | Upregulated | Not studied |
| H2BS14ph | Upregulated | Not studied |
| H3K9me2 | Upregulated | Not studied |

# Changes at the intrinsic epigenetic level during HSCaging

## 3. Noncoding RNAs

- expression of micro-RNA miR-125b increased with age in human HSCs
- inhibition of miR-125 improvedthe capacity of HSCs from elderly individuals to generate B cells.

**4**
**Changes in the extrinsic HSC niche**

# Changes in the extrinsic HSC niche during aging

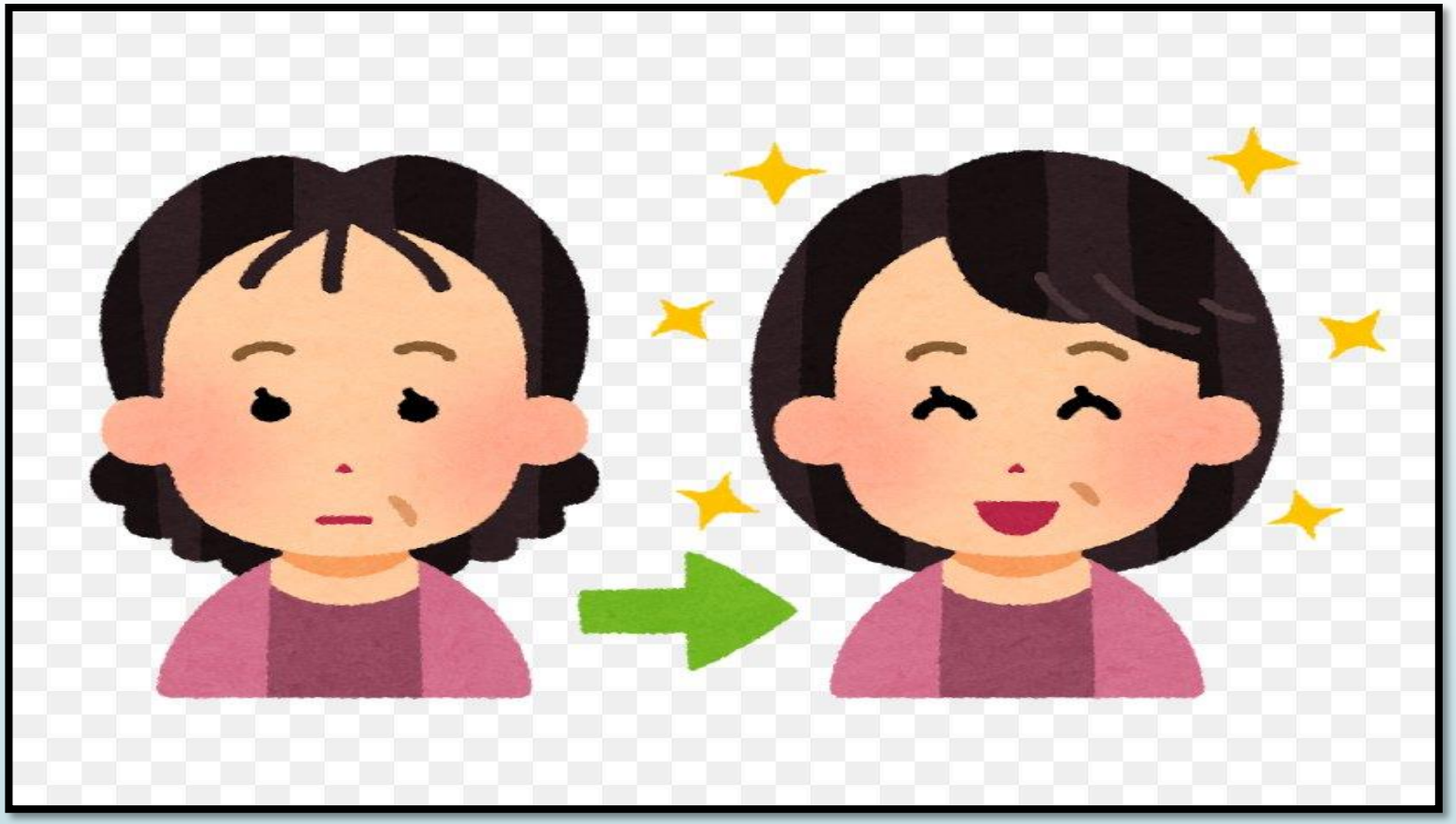
The BM microenvironment niche is a crucial factor for HSC functions

- **Megakaryocytes**
- **VCAM-1+ macrophages**
- **CD150 high BM Tregs**
- **Sympathetic nervous system (SNS)**

خوش است پیری اگر مانده بود جان جوانی
ولی ز بخت بد از من نه جسم ماند و نه جانی

شهریار

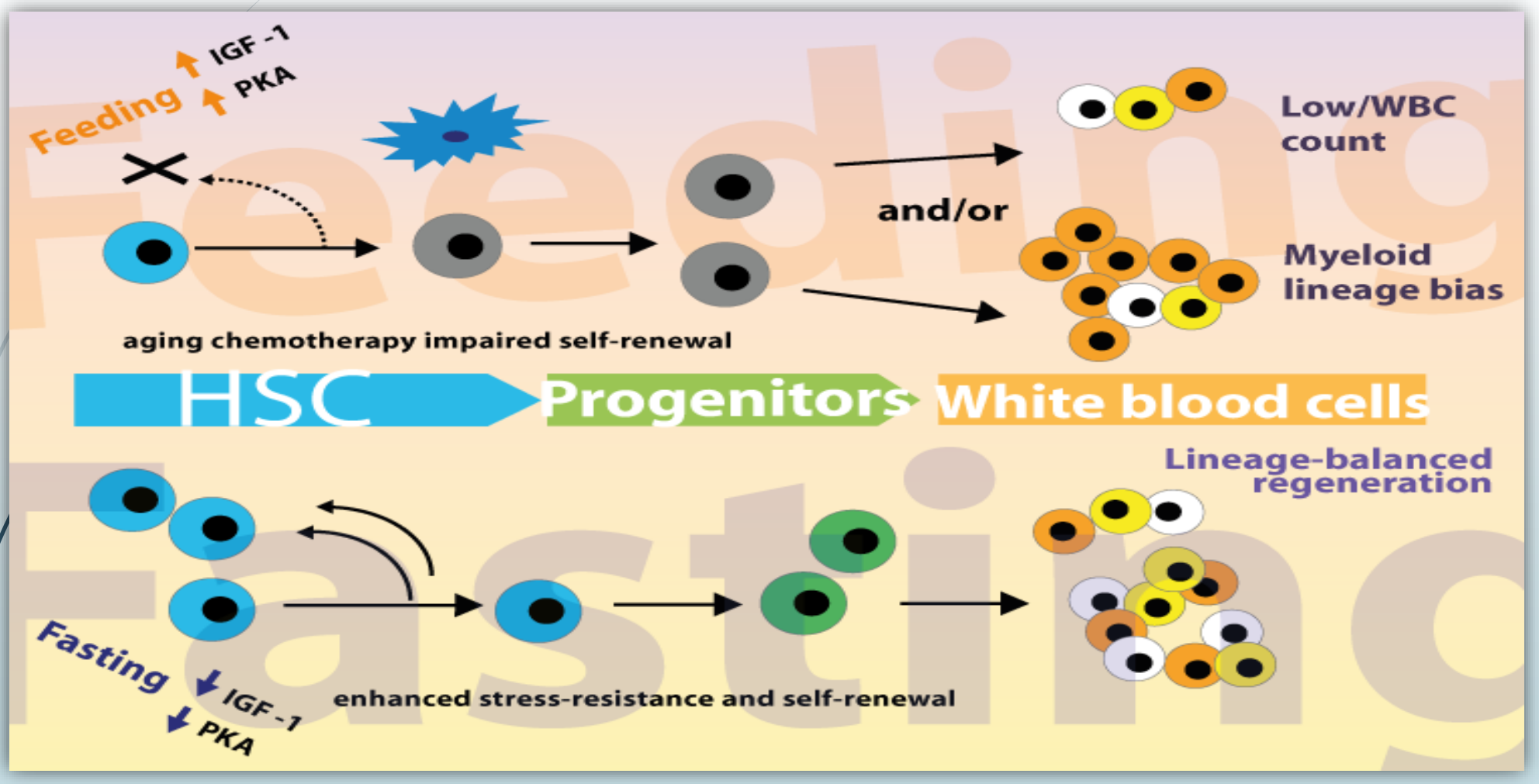
# Aged HSC rejuvenation strategies



# Aged HSC rejuvenation strategies

1. prolonged fasting
2. Genetic modulators
3. Pharmacological intervention
4. Changing the BM niche

# 1.prolonged fasting

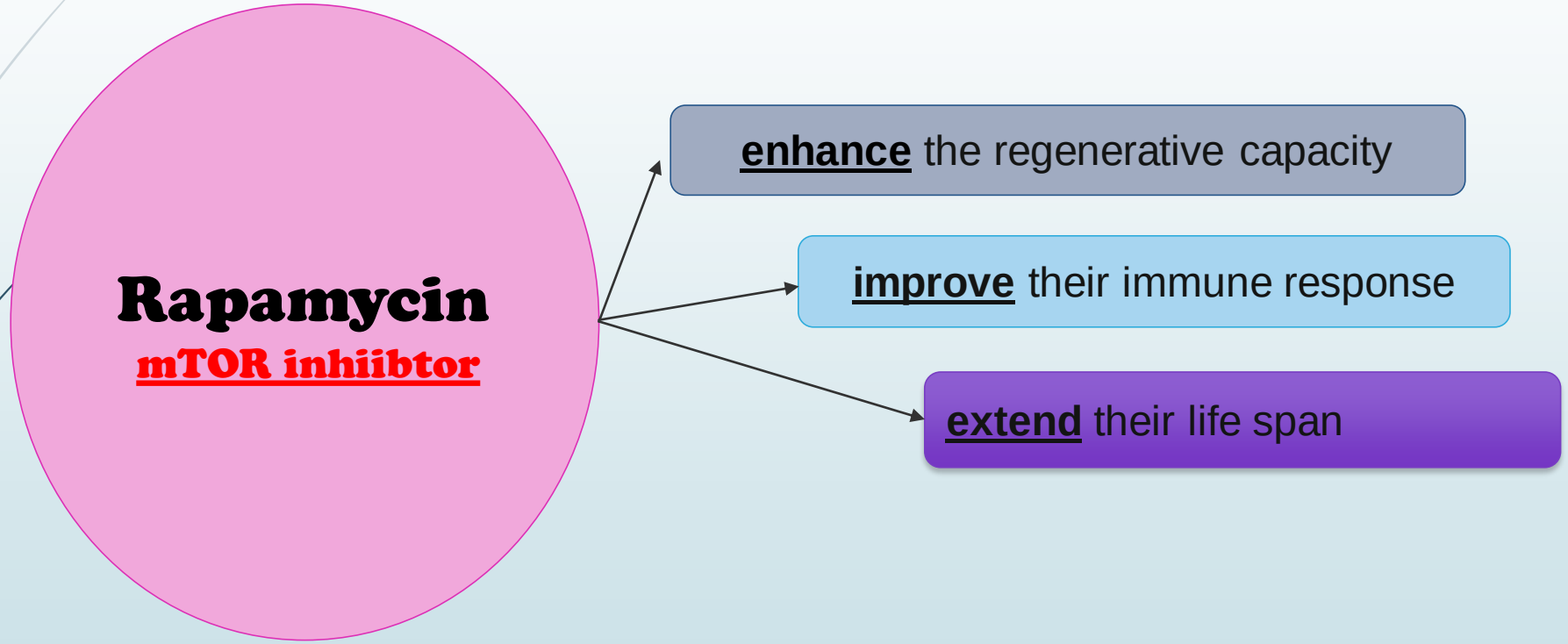


# 2.Genetic modulators

**Table 4** Aged HSC rejuvenation strategies

| Rejuvenation approach | Mechanism | Functions |
|---|---|---|
| **Prolonged fasting** | | |
| Prolonged fasting | Reduces circulating IGF-1 levels | Promote stress resistance, self-renewal, and lineage-balanced regeneration |
| **Gene expression regulation** | | |
| *Satb1* overexpression | Epigenetic modification | Restore the lymphopoietic potential of aged HSCs |
| *Sirt3* overexpression | ROS levels | Restore the long-term competitive repopulation ability |
| *Sirt7* overexpression | Mitochondrial functions | Rescue myeloid-biased differentiation |

# 3.Pharmacological intervention



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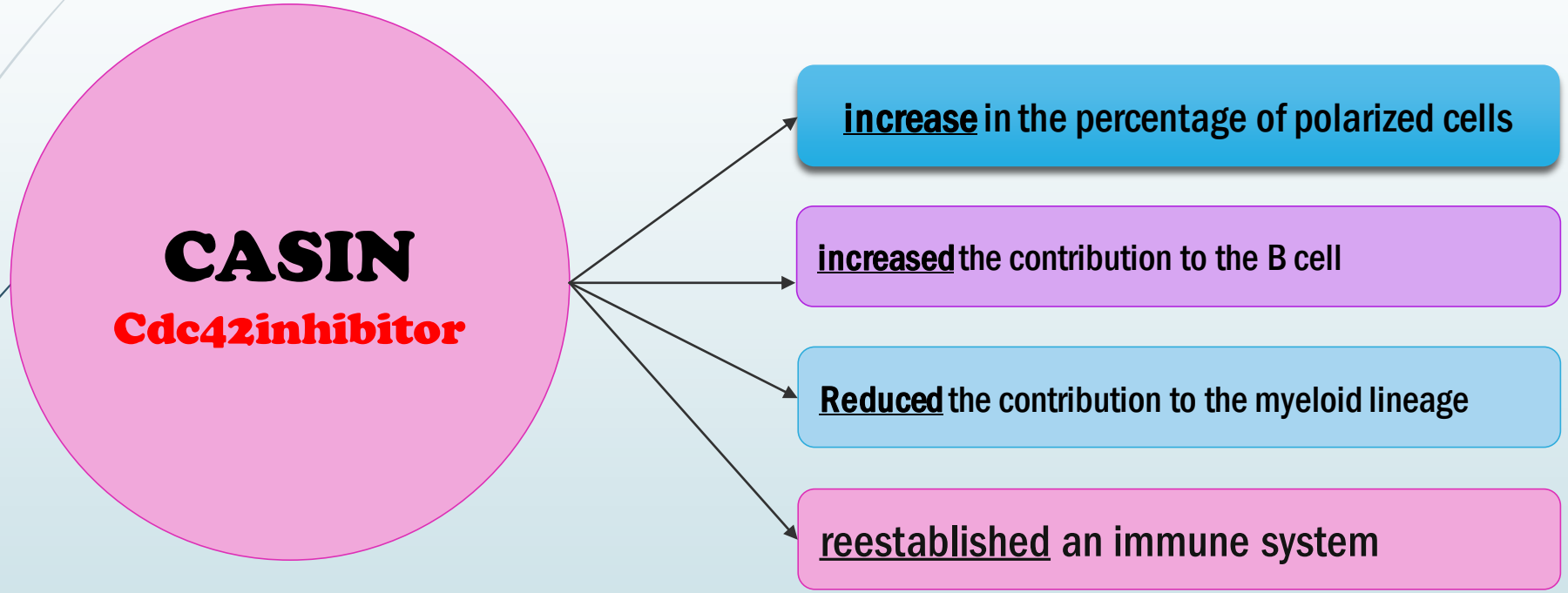

# 3.Pharmacological intervention

## Others.....

| Pharmacological intervention | | |
|---|---|---|
| Rapamycin | Inhibition of mTOR | Enhance the regenerative capacity of HSCs from aged mice |
| CASIN | Inhibition of Cdc42 | Increase the percentage of polarized cells, restore the spatial distribution of H4K16ac, increase lymphoid output, and reduce myeloid lineage output |
| TN13 | Inhibition of p38 MAPK | Decrease ROS level and increase homing ability |
| SB203580 | Inhibition of p38 MAPK | Restore the repopulating capacity and maintain quiescence of HSCs |
| ABT263 | Inhibition of BCL-2 and BCL-xL | Selectively kill senescent cells |

# Changing the BM niche


transplanted 20-month-old aged HSCs into10-week-old young mice


Collected aged HSCs engrafted in young mice


The gene expression profiles were similar to young HSCs


Whether these alterations drive HSC aging or whether these alterations are only accompanied by HSC aging remains unknown.

These problems may be effectively overcome once HSC aging mechanisms are fully revealed and rejuvenation strategies are optimized.


“thankyou for
your ATTENTION
:)”

گرچه جان عزیز است،

و مرگ نادلخواه

با این حال چیزی فراتر از مرگ و زندگی هست،

یعنی جست‌وجوی نوعی "معنا" در زندگی،

و آن این است که "شرف" آلوده نشود.

دکتر محمدعلی اسلامی‌ندوشن

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