Cleaning House as We Age

Cellular Senescence, Senolytics & a Fascinating New Approach to Healthy Aging

WHY DO WE AGE?

Aging is not ONE process.

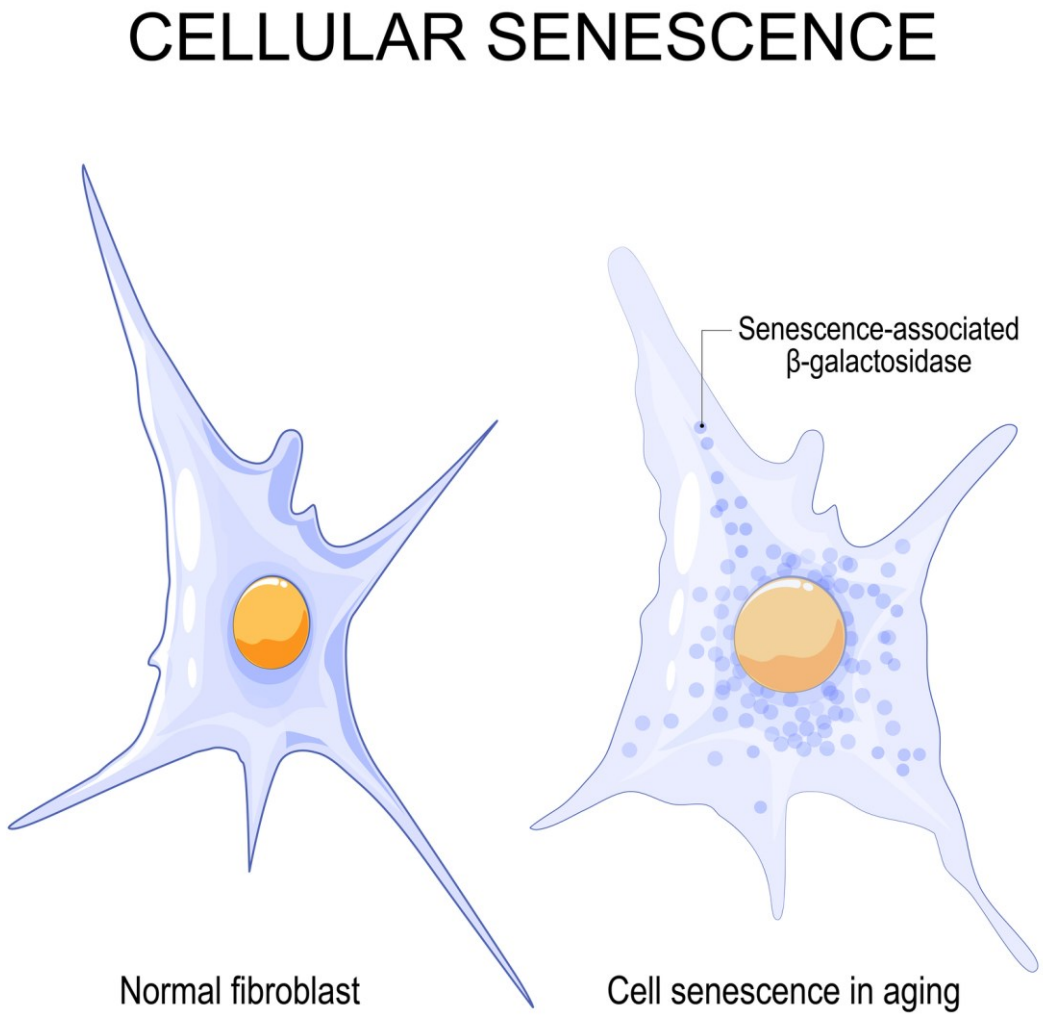
- Mitochondrial energy production declines
- Oxidative damage accumulates
- DNA damage accumulates
- Protein quality control declines
- Autophagy becomes less efficient
- Hormonal signaling changes
- Chronic inflammation increases
- Regenerative capacity declines
- Senescent cells accumulate

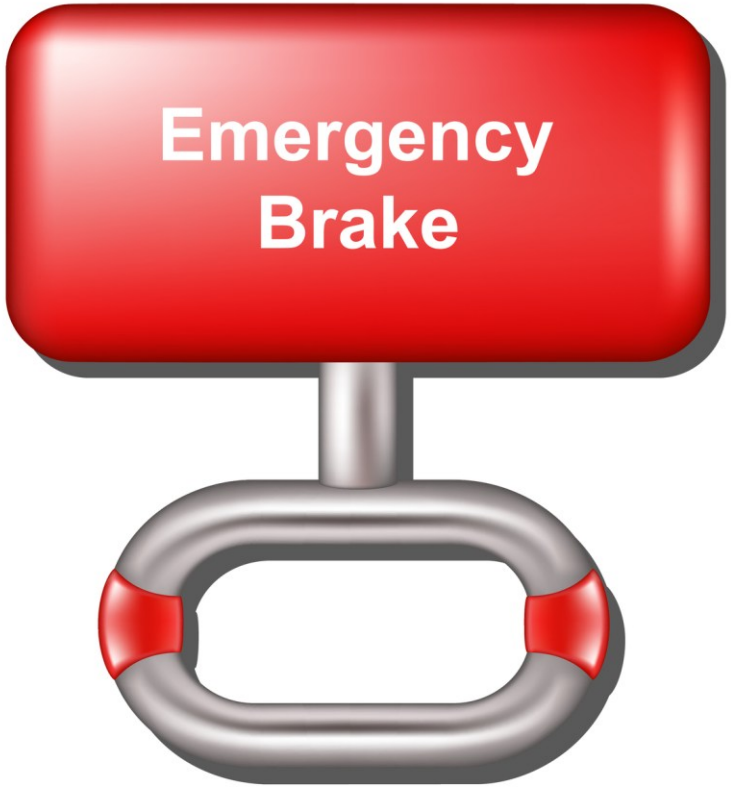
MEET THE SENESCENT CELL

A senescent cell is:

- Still alive
- Still metabolically active
- No longer dividing normally
- Resistant to ordinary cell death
- Often biologically very active
- Capable of influencing surrounding cells

It hasn't died — but it isn't functioning like a healthy cell anymore.





WHY WOULD OUR BODIES DO THIS?

Cellular senescence is **NOT** inherently bad.

It is an important protective mechanism.

When a cell becomes seriously damaged:

- **Repair it → Destroy it → OR Stop it from reproducing**

Senescence is essentially a cellular **emergency brake**.

CELLULAR SENESCENCE CAN PROTECT US

Temporary, appropriately controlled senescence participates in:

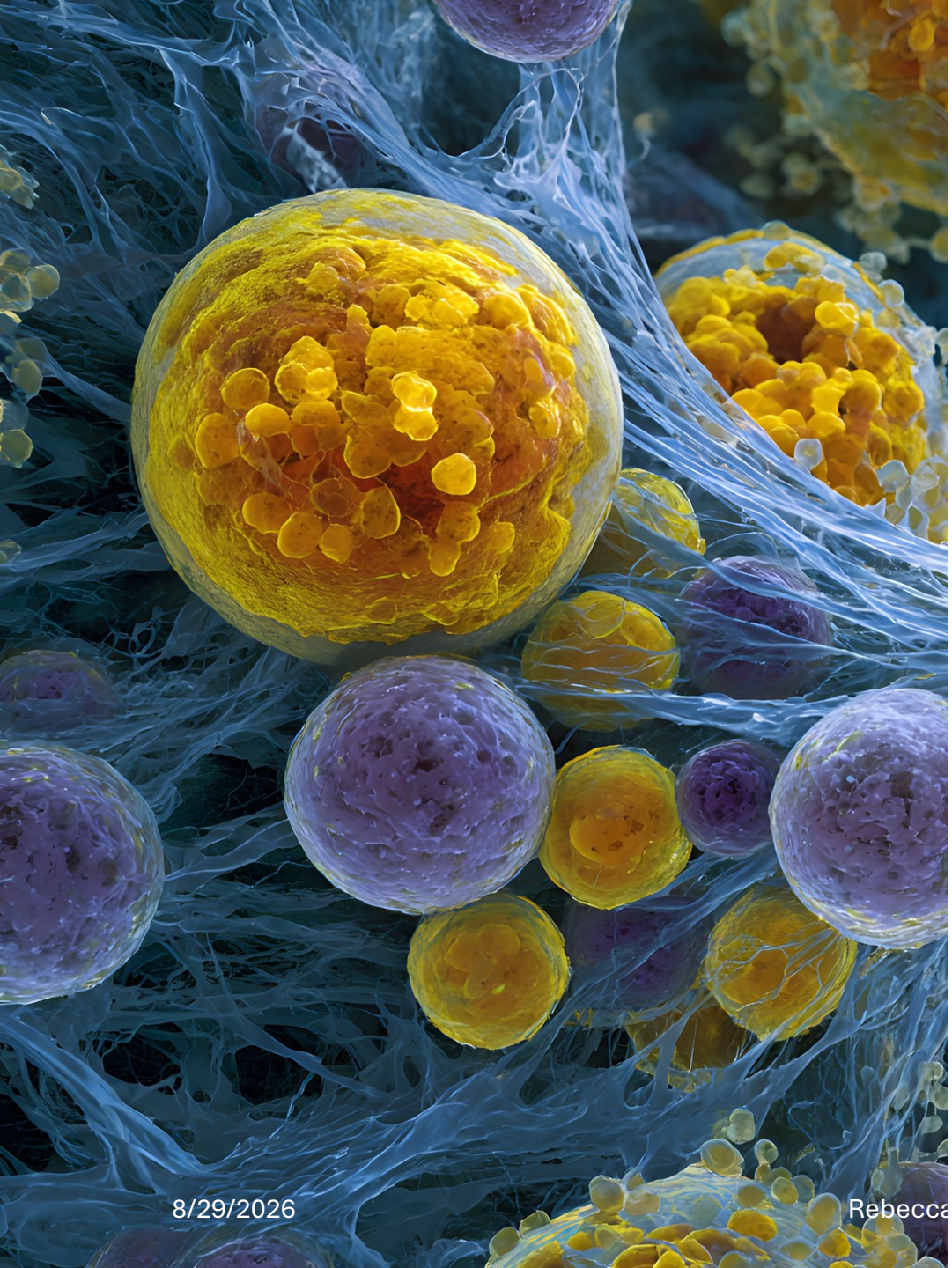
- Tumor suppression
- Prevention of damaged-cell replication
- Wound healing
- Tissue remodeling
- Embryonic development

We need cellular senescence.

The problem is not simply making senescent cells.

The problem is **failing to remove them afterward.**

Rebecca Montrone, BS - Wondrous Roots, Inc.



WHEN WE'RE YOUNG...

Damaged/stressed cell

↓

Cellular senescence

↓

Immune recognition

↓

Senescent cell clearance

↓

Problem resolved

AS WE GET OLDER…

More cellular stress and damage

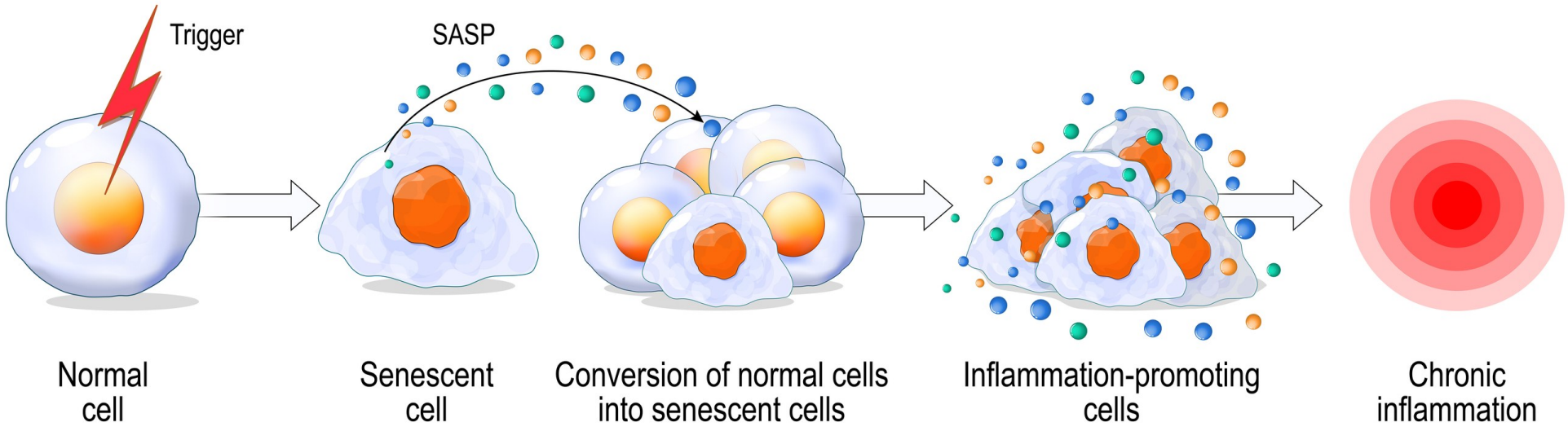
More cells entering senescence

Declining immune surveillance and clearance

↓

Senescent cells begin accumulating

CELLULAR SENESCENCE



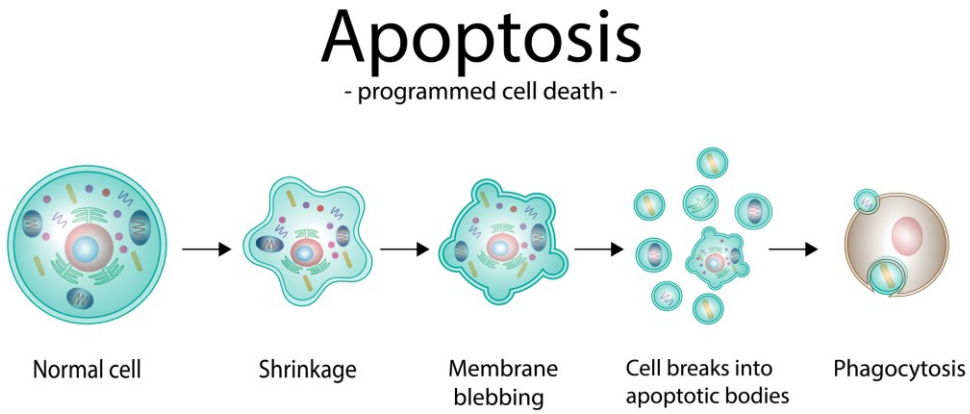
WHY DON'T THEY JUST DIE?

Senescent cells can activate powerful survival pathways.

They become unusually resistant to:

APOPTOSIS — programmed cell death

The very cells we'd rather eliminate can become remarkably good at staying alive.



THE PROBLEM WITH THESE “OLD” CELLS

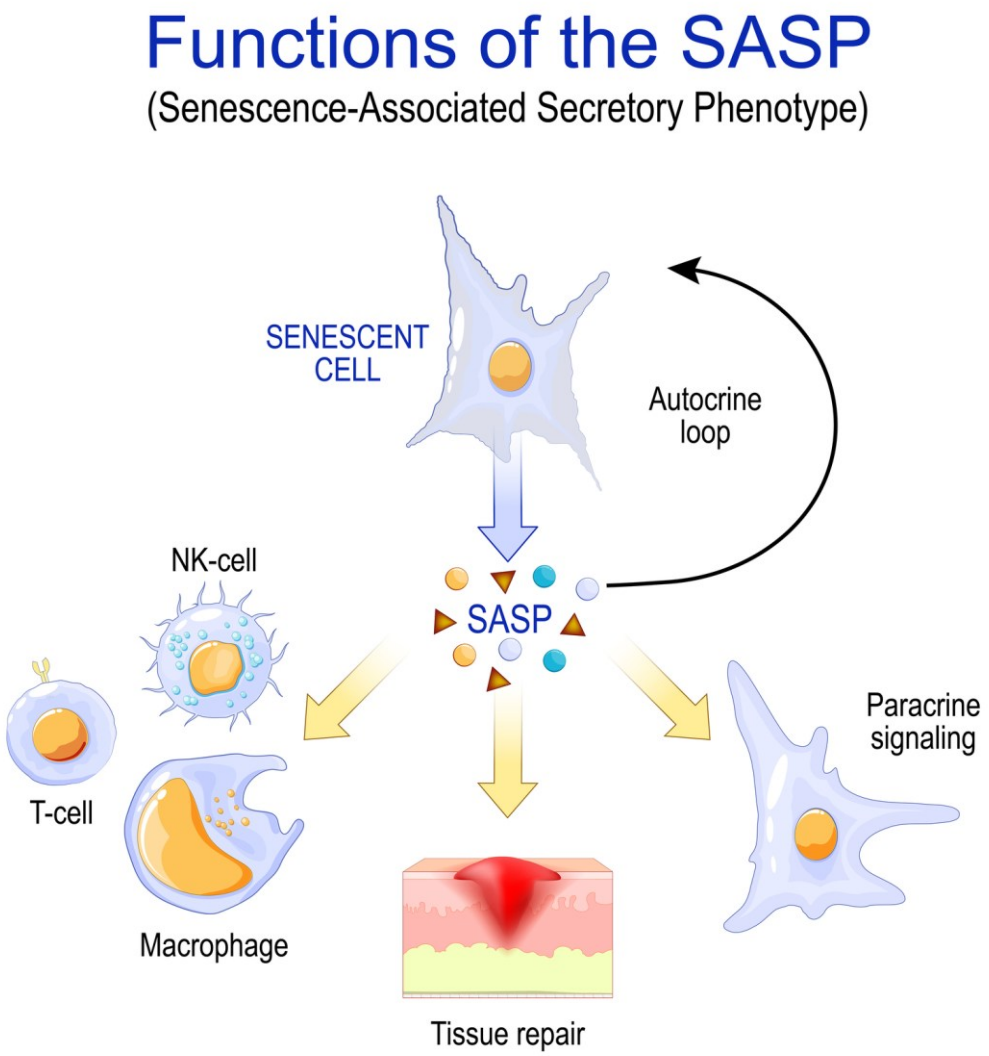
Senescent cells don't necessarily sit quietly.

Many develop:

SASP:

Senescence-Associated Secretory Phenotype

They begin releasing biologically active substances into their surroundings.



WHEN GOOD SASP GOES BAD

Acute / Transient SASP
→ Immune recruitment
→ Senescent-cell clearance
→ Tissue repair
→ Resolution

versus

Chronic / Persistent SASP
→ Chronic inflammation
→ Tissue dysfunction
→ Matrix degradation
→ Impaired regeneration
→ Neighboring-cell senescence

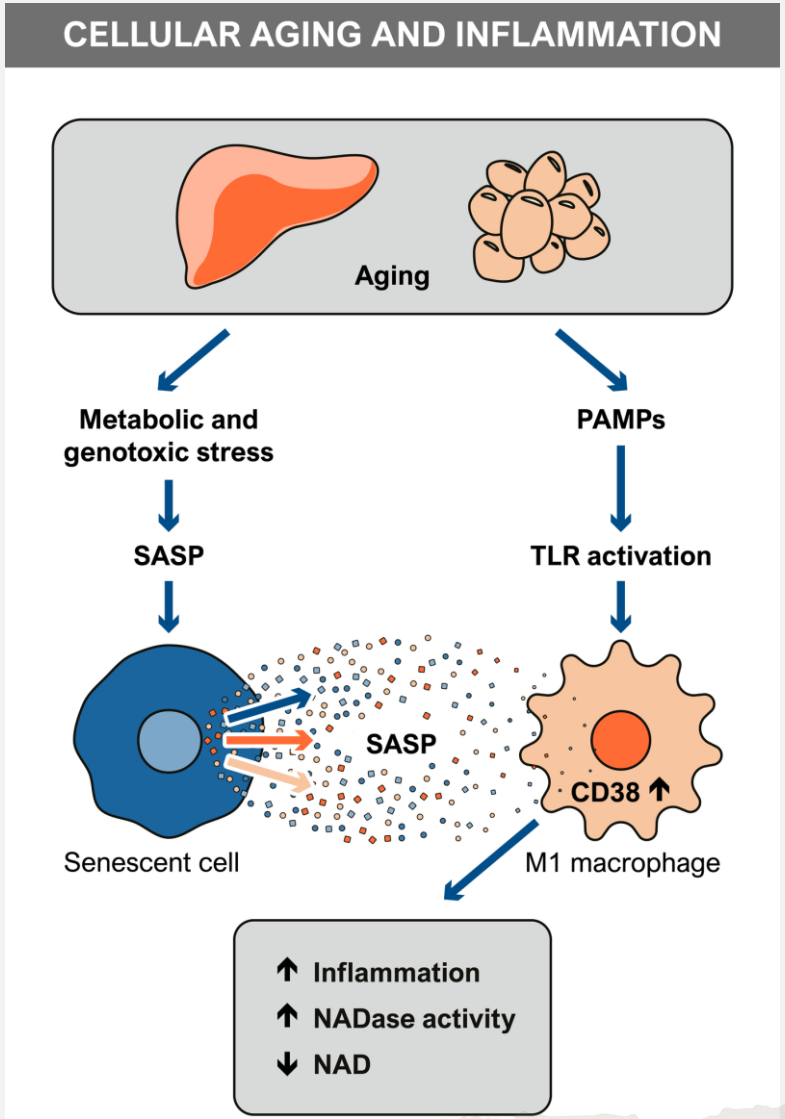
WHAT DOES SASP RELEASE?

Depending upon the cell and circumstances:

- Pro-inflammatory cytokines
- Chemokines
- Growth factors
- Proteases
- Matrix-remodeling enzymes
- Other signaling molecules

The result?

One dysfunctional cell can influence many perfectly good neighboring cells.



THE “BAD NEIGHBOR” EFFECT

Think of a neglected house in an otherwise healthy neighborhood.

It doesn't merely deteriorate itself.

Eventually it begins affecting:

- The property next door
- The surrounding environment
- Neighborhood safety
- The entire community

Senescent cells can alter the tissue environment around them.

A VICIOUS CYCLE CAN DEVELOP

Cellular damage

↓

Cellular senescence

↓

SASP

↓

Inflammation + tissue dysfunction

↓

Additional cellular stress

↓

MORE SENESCENCE

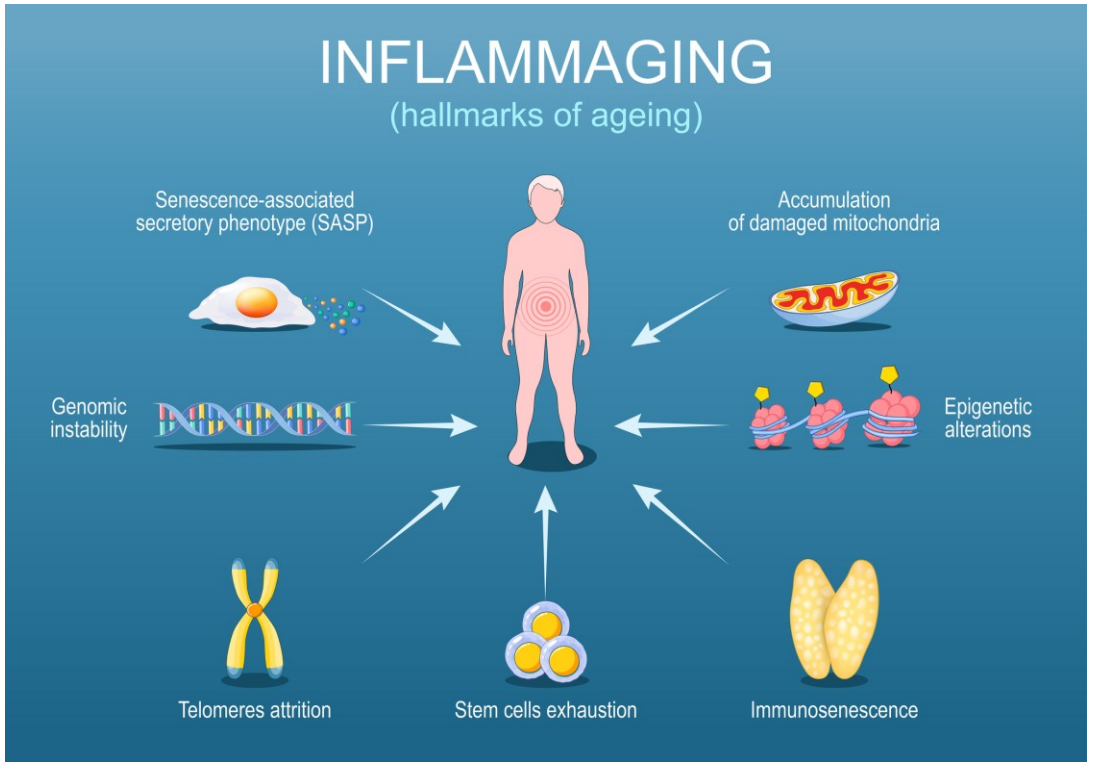
“INFLAMMAGING”

Aging is commonly accompanied by persistent, low-grade, sterile inflammation.

This phenomenon has been called:

INFLAMMAGING

Senescent cells and SASP are considered important contributors to this inflammatory aging environment.

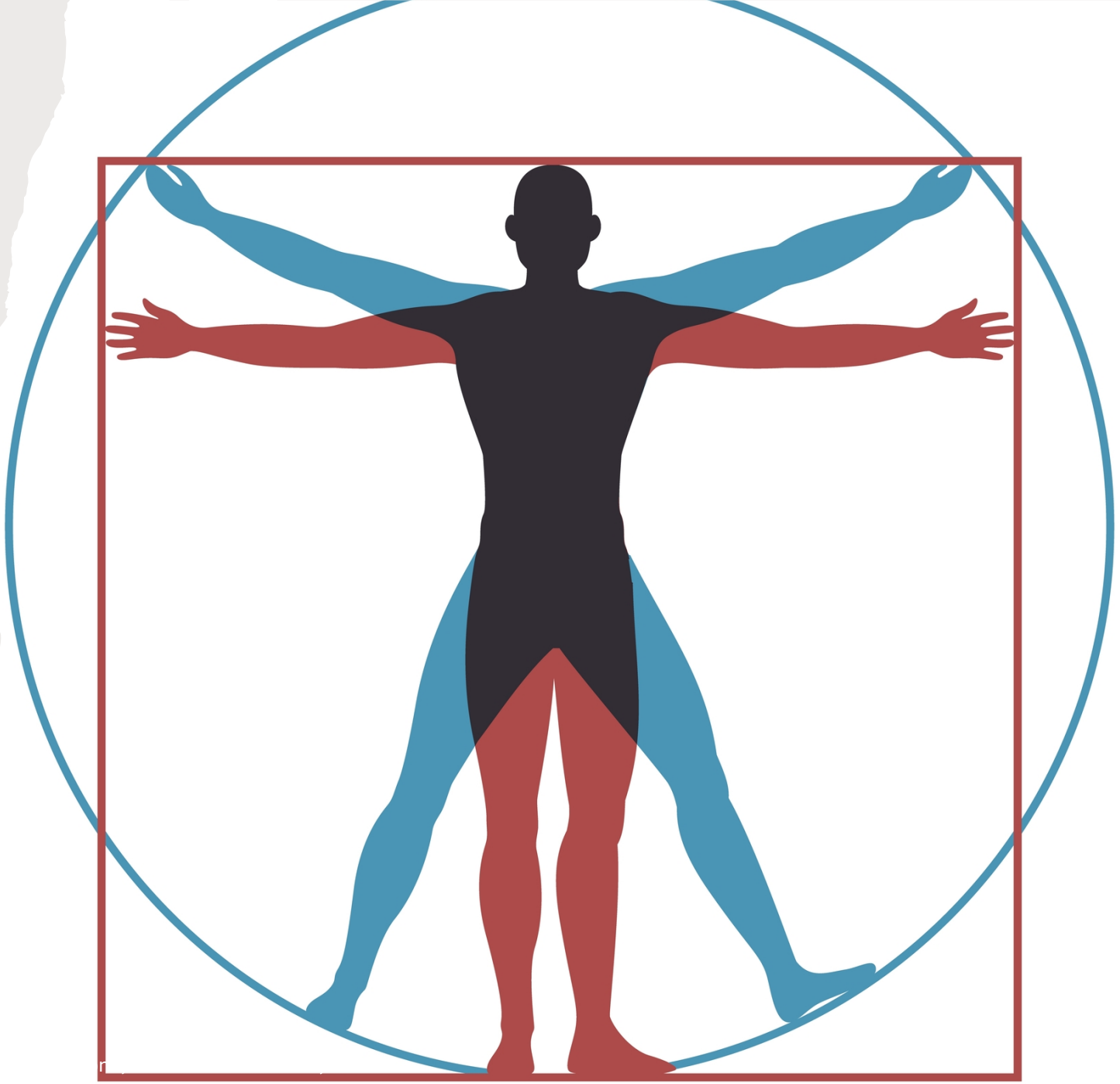


WHERE DO SENESCENT CELLS ACCUMULATE?

Potentially throughout the body:

- Blood vessels
- Adipose tissue
- Muscle
- Bone
- Cartilage
- Skin
- Liver
- Kidney
- Lung
- Immune tissues
- Nervous system

Cellular senescence is a whole-body aging phenomenon.



CELLULAR SENESCENCE & AGE-RELATED DISEASE

The contribution of senescence is being investigated in connection with:

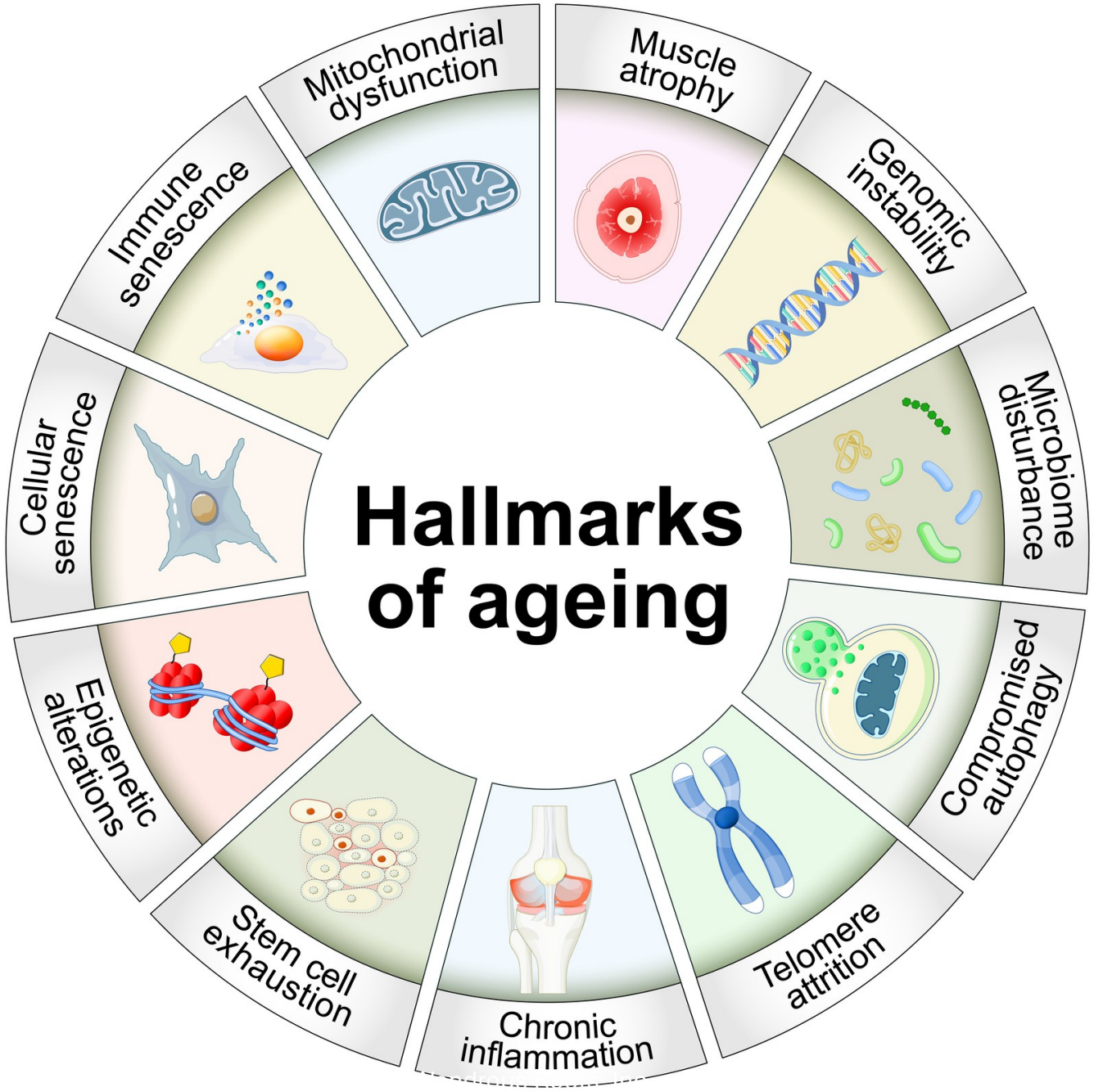
- Cardiovascular disease
- Osteoarthritis
- Osteoporosis
- Sarcopenia
- Metabolic dysfunction
- Insulin resistance
- Fibrosis
- Kidney disease
- Pulmonary disease
- Neurodegeneration
- Immune aging

CELLULAR SENESCENCE IS A HALLMARK OF AGING

Cellular senescence is recognized as one of the major interconnected biological processes of aging.

It interacts with:

- Mitochondrial dysfunction
- DNA damage
- Telomere attrition
- Loss of proteostasis
- Impaired autophagy
- Stem-cell exhaustion
- Chronic inflammation
- Altered cellular communication



AGING IS AN ACCUMULATION PROBLEM

Over time we accumulate:

Damage we haven't completely repaired

Damaged components we haven't completely recycled

Dysfunctional cells we haven't completely removed

Healthy aging, then, involves BOTH:

REDUCING NEW DAMAGE

and

IMPROVING HOUSEKEEPING

AUTOPHAGY IS NOT SENOLYSIS

Important distinction!

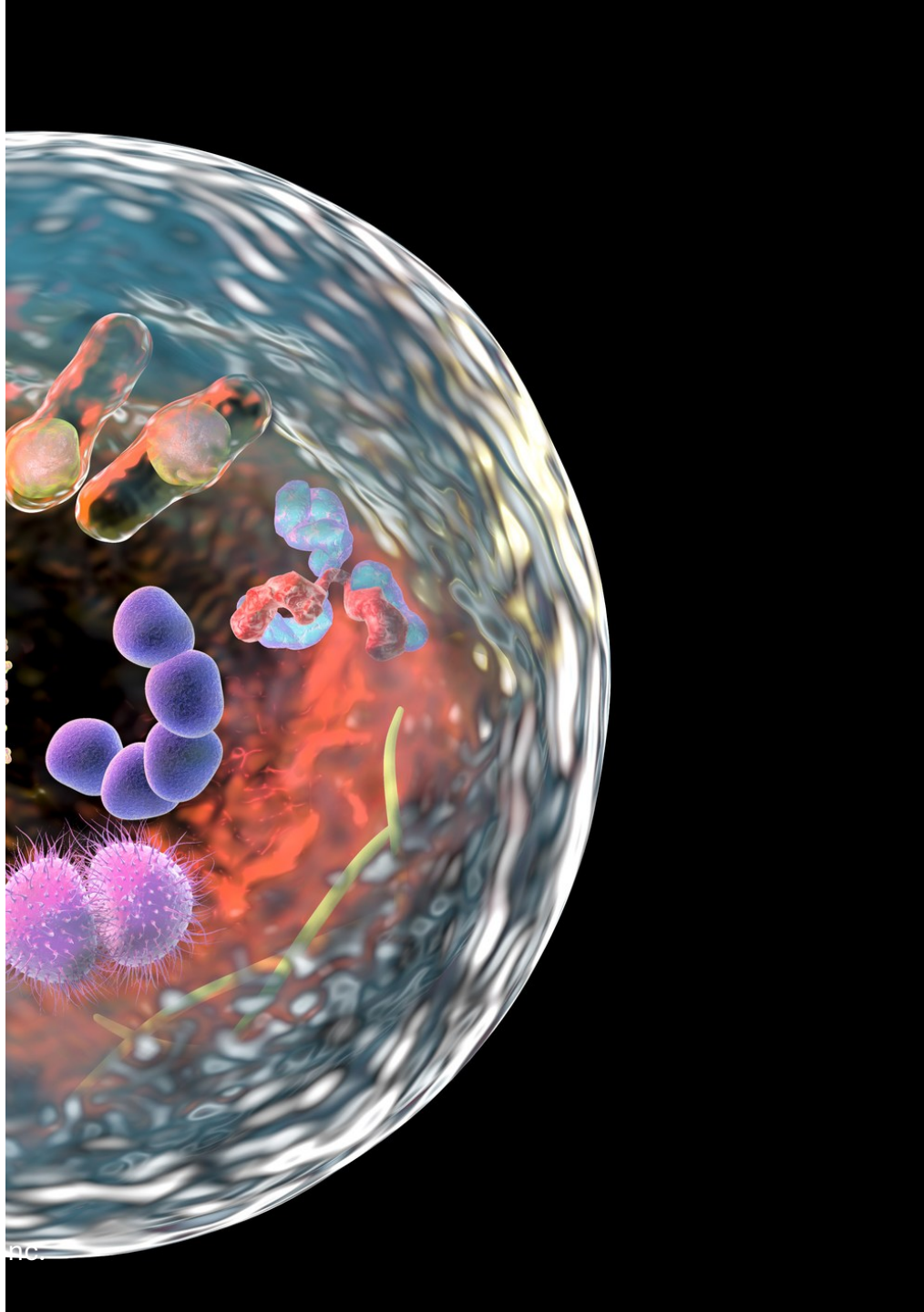
AUTOPHAGY

A cell cleans out and recycles damaged components **inside itself**.

SENOLYSIS

An entire senescent cell is **eliminated**.

Cleaning the house versus demolishing a house that is beyond repair.



OUR BODIES ALREADY HAVE A SENOLYTIC SYSTEM

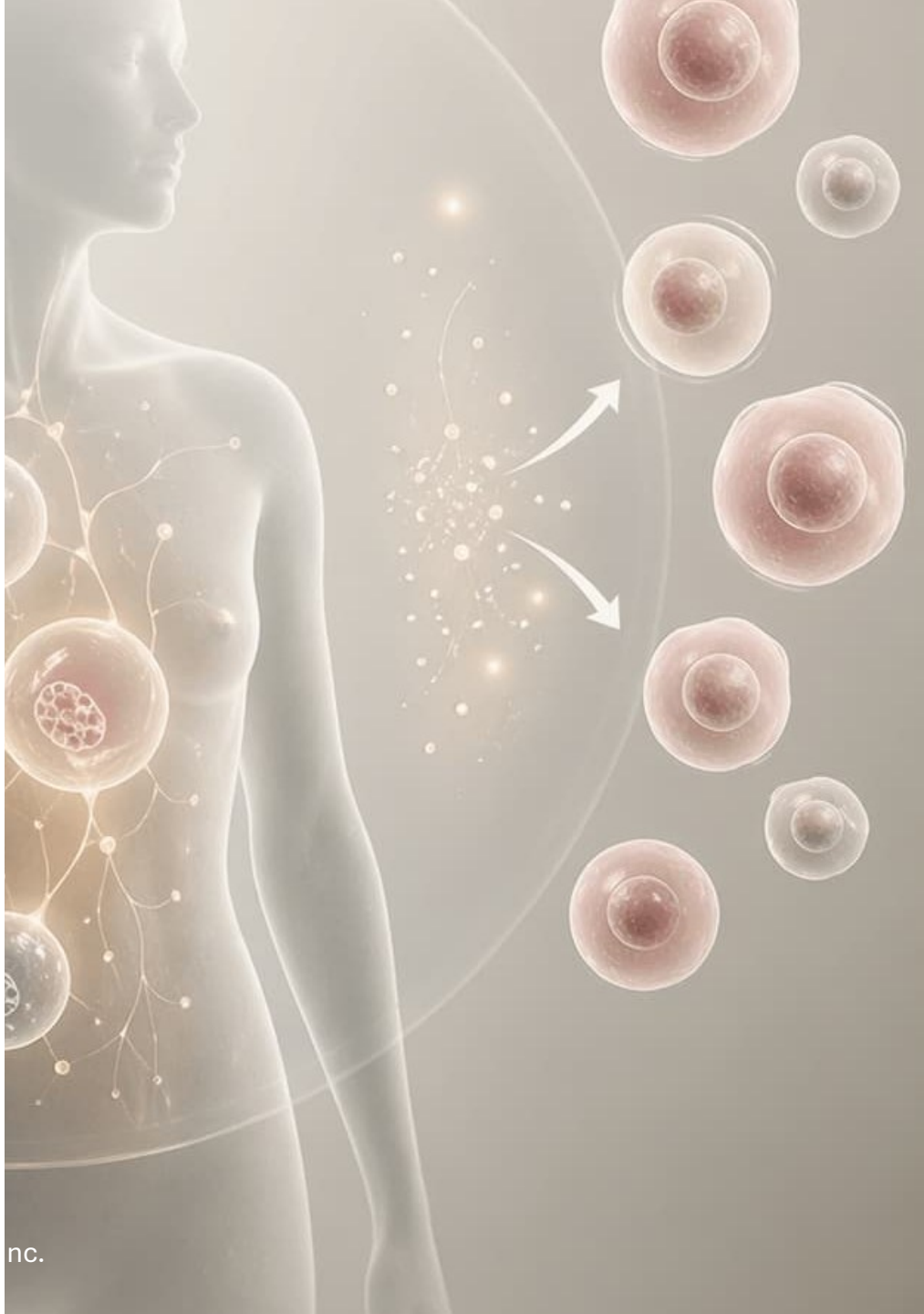
Immune surveillance helps recognize and remove senescent cells.

Important players include:

- Natural killer cells
- Macrophages
- T cells

The fundamental problem with aging may involve BOTH:

Increasing creation + decreasing clearance

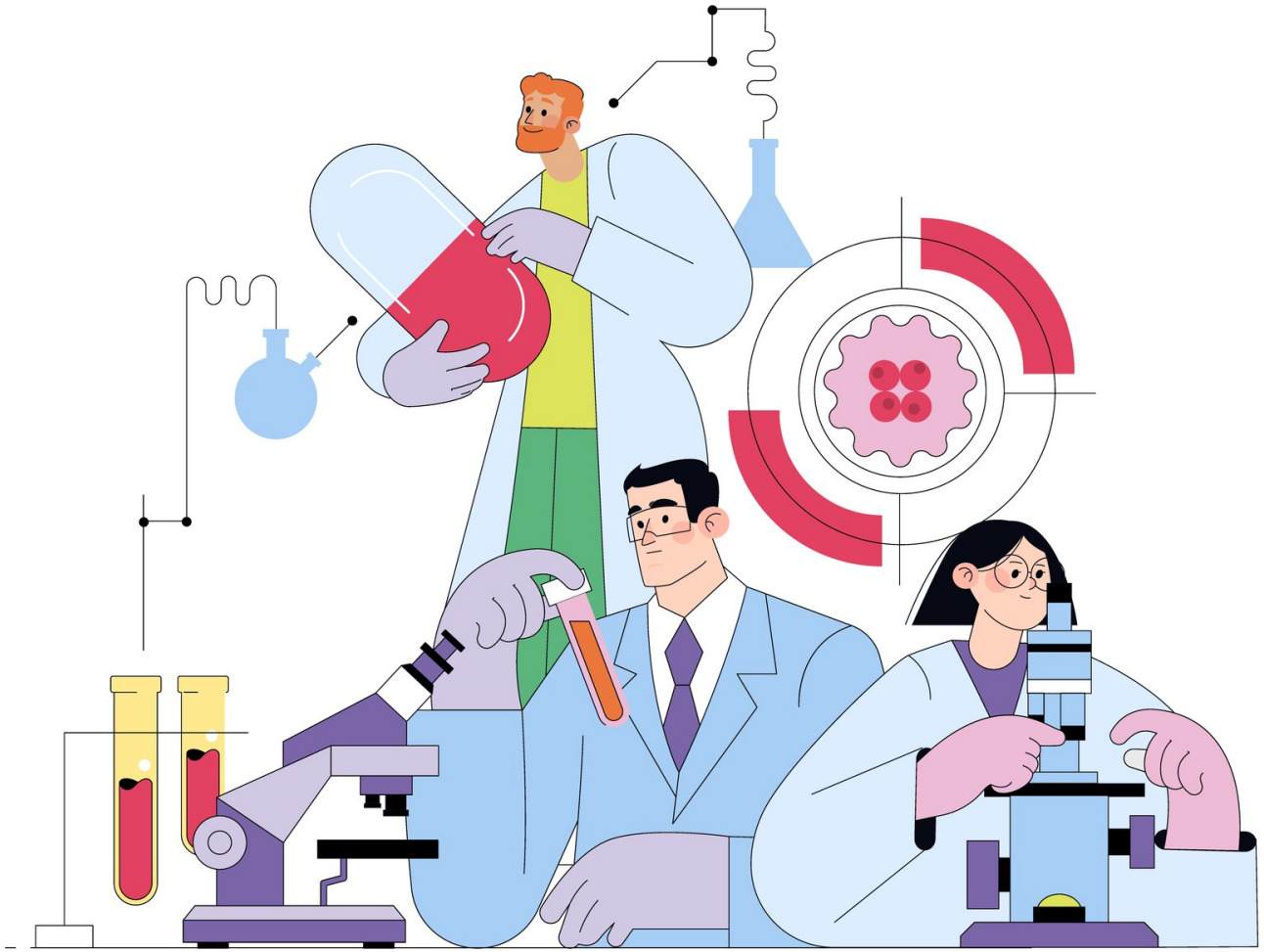


CAN WE SELECTIVELY REMOVE SENESCENT CELLS?

That question created an entirely new area of longevity research.

SENOLYTICS

Compounds that preferentially cause senescent cells to die while sparing healthier cells.



SENOLYTIC vs. SENOMORPHIC

SENOLYTIC

Get rid of the troublesome cell.

SENOMORPHIC

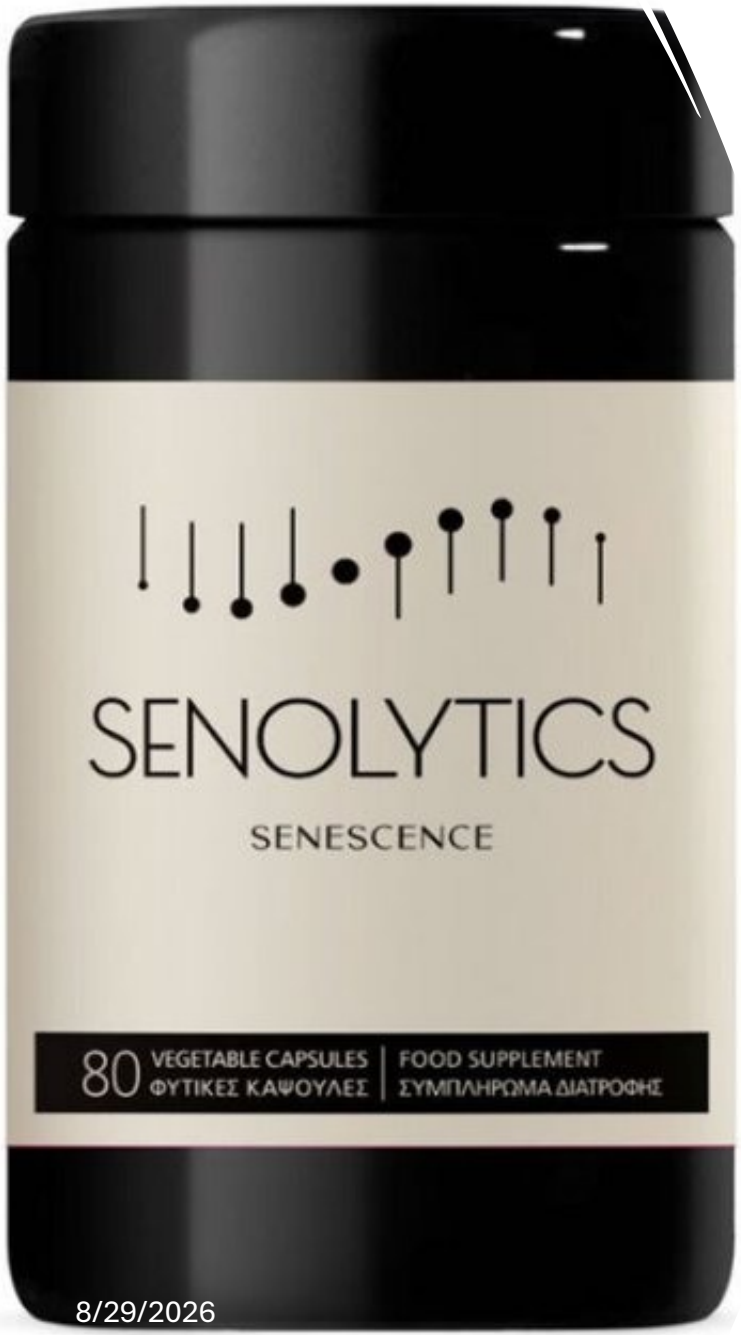
Reduce the troublesome behavior of the cell, including aspects of SASP, without necessarily killing it.

Two very different approaches to the same biological problem.

Senomorphics: Quieting the Senescent Cell

Not every strategy for dealing with senescent cells involves eliminating them. **Senomorphics, sometimes called senostatics, are compounds that help reduce the harmful behavior of senescent cells—particularly their inflammatory SASP—without necessarily killing the cells themselves.** In essence, rather than evicting the troublesome neighbor, we convince the neighbor to behave better! Examples being investigated for senomorphic activity include **rapamycin, metformin, resveratrol, curcumin, apigenin, and kaempferol**, which can influence pathways such as mTOR and NF-κB that help regulate inflammatory SASP signaling. The distinction is not always absolute, since the effects of a compound can vary with dose, cell type, and circumstances.

Nevertheless, it provides a useful framework: **senomorphics attempt to quiet senescent cells; senolytics attempt to eliminate them.**



Senolytics: Eliminating the Senescent Cell

Senolytics take a different approach: rather than simply reducing the troublesome behavior of senescent cells, they are intended to selectively eliminate them. Senescent cells develop survival mechanisms that allow them to resist apoptosis—the normal process of programmed cell death—and senolytic compounds target vulnerabilities in those survival pathways, making senescent cells more likely to undergo apoptosis while ideally sparing healthy cells.

Examples of compounds being investigated as senolytics include **fisetin, quercetin (particularly in combination with dasatinib), navitoclax, and the dasatinib-quercetin combination (D+Q)**. The effects can vary considerably by cell type and tissue, so no senolytic works equally well against every type of senescent cell. In simple terms: **senomorphics quiet the troublesome neighbor; senolytics encourage the troublesome neighbor to leave altogether.**

This ability to actually reduce senescent-cell burden is what makes senolytics such an intriguing area of healthy-aging research.

Rebecca Montrone, BS - Wondrous Roots, Inc.

THE “SPRING CLEANING” IDEA

Here's where **senolytics** become especially interesting.

If the objective is to eliminate a population of unwanted cells…

Why would we necessarily need to take the senolytic every day?

Expose senescent cells

↓

Trigger their elimination

↓

Stop treatment

↓

Allow time to pass

↓

Repeat periodically

PERIODIC HOUSECLEANING

ENTER FISETIN

Fisetin is a naturally occurring plant flavonol.

Food sources include:

- Strawberries — particularly notable source
- Apples
- Persimmons
- Grapes
- Onions
- Cucumbers

But dietary exposure is far below amounts typically explored experimentally for senolytic purposes.

FISETIN DOES MORE THAN ONE THING

Fisetin has been investigated for:

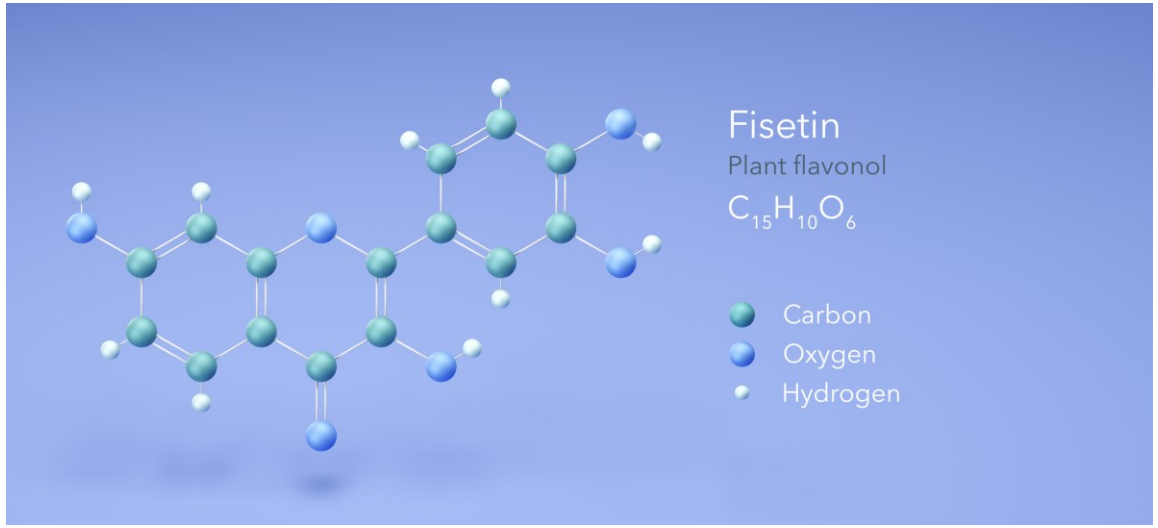
- Antioxidant activity
- Anti-inflammatory activity
- Cellular signaling effects
- Neuroprotective effects
- Metabolic effects
- **Potential senolytic activity**

Its senolytic properties are what make it particularly interesting to longevity researchers

WHY DID FISETIN GET SO MUCH ATTENTION?

Researchers compared naturally occurring compounds for senolytic activity.

Fisetin emerged as a particularly promising candidate.



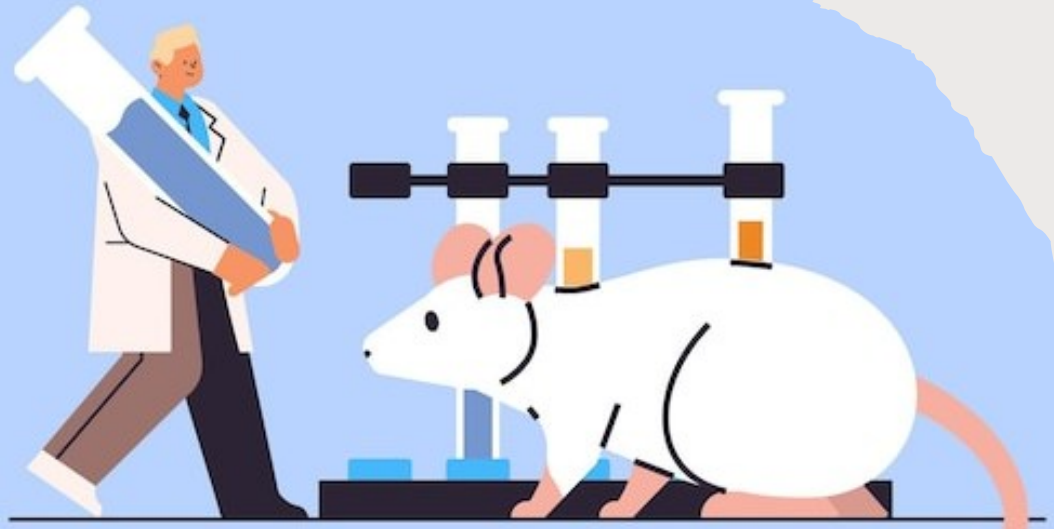
Experimental research suggested that it could:

Reduce senescent-cell burden

and potentially improve measures of:

Healthspan and tissue function

THE ANIMAL RESEARCH GETS REALLY INTERESTING



Animal research has reported effects involving:

- Reduced markers of cellular senescence
- Improved tissue homeostasis
- Reduced age-associated pathology
- Improved physical function
- Increased median and maximum lifespan in an important mouse study

Perhaps most intriguing:

BENEFIT WAS OBSERVED EVEN WHEN TREATMENT BEGAN LATE IN LIFE.

WHAT ABOUT HUMANS?

The evidence for fisetin as a senolytic is strongest in cell and animal research, with emerging human evidence.

We don't yet know whether the remarkable healthspan and lifespan findings seen experimentally will translate to humans.

However, fisetin is a naturally occurring flavonoid with human exposure and some clinical safety data, making it an especially interesting candidate for those who choose to act on promising evidence before definitive longevity trials exist.

SO WHY ARE PEOPLE USING IT?

Because the proposition is intriguing:

Established biology of cellular senescence

Strong experimental rationale for senolysis

Promising preclinical fisetin research

A naturally occurring compound already available to humans

=

A VERY INTERESTING LONGEVITY STRATEGY TO WATCH

Rebecca Montrone, BS - Wondrous Roots, Inc.

WHY INTERMITTENT FISETIN?

For ordinary nutritional/phytochemical effects:

Daily supplementation may make sense.

For a specifically SENOLYTIC objective,

Intermittent higher exposure may make more theoretical sense.

The goal isn't necessarily maintaining fisetin in the bloodstream.

The proposed target is the senescent cell itself.

Why Fisetin Dosing Is Different for Senolytic Use

At lower doses taken regularly, fisetin behaves much like other beneficial dietary flavonoids such as quercetin, with antioxidant, anti-inflammatory, neuroprotective, and cell-signaling effects that may support health over time. **Senolytic use is a different objective.**

Here, substantially higher doses are used for a very short period in an effort to reach concentrations capable of preferentially triggering apoptosis in accumulated senescent cells, followed by a period with no treatment. The goal is not—and should not be—to eliminate every senescent cell.

Cellular senescence has important beneficial roles in tumor suppression, wound healing, tissue remodeling, and normal biological signaling. The proposed purpose of intermittent senolytic treatment is therefore not to abolish senescence, but to periodically reduce the excessive burden of persistent senescent cells that tends to accumulate with aging.

AGAIN, THE MONTHLY “HOUSECLEANING” CONCEPT

Instead of:

Fisetin every day forever

A longevity-oriented approach sometimes proposed is:

Periodic senolytic exposure

↓

Recovery interval

↓

Repeat periodically

Monthly commercial protocols are one practical interpretation of this concept.

Monthly dosing itself has NOT been established as an optimal anti-aging regimen in humans, but…

WHY MONTHLY?

Senolytics are designed as “hit-and-run” therapies. A brief high-dose exposure is intended to eliminate accumulated senescent cells; once those cells are gone, there is no reason to maintain continuous exposure. Because senescent cells generally take weeks to develop and accumulate again, **researchers have successfully used intermittent schedules ranging from every few weeks to monthly**.

The treatment-free interval may also preserve the beneficial functions of normal cellular senescence and minimize unnecessary off-target effects.

FISETIN SUPPLEMENTS

Products range from:

- Plain fisetin
- Higher-dose fisetin
- Enhanced-bioavailability formulations
- Combination senolytic formulas

Qualia Senolytic is one commercial example of an intermittent senolytic formulation.

It is certainly not the only way fisetin is available.

BIOAVAILABILITY MATTERS

One complication:

Fisetin has relatively poor oral bioavailability.

That raises important questions about:

- Dose
- Absorption
- Formulation
- Blood concentrations
- Tissue concentrations

This is one reason two products containing “fisetin” may not necessarily be equivalent.

CAN LIFESTYLE AFFECT CELLULAR SENESCENCE?

Senolytics aren't the whole story.

Strategies associated with healthier aging biology include:

- Exercise
- Metabolic health
- Healthy body composition
- Nutrient-dense diet
- Adequate sleep
- Circadian health
- Avoiding smoking
- Limiting excessive UV exposure
- Supporting immune function
- Maintaining mitochondrial health

Another Piece of the Healthy-Aging Puzzle

I view senolytics as an exciting addition to the growing toolbox of strategies aimed at promoting healthier aging. We already know that aging is multifactorial, which is why a truly comprehensive approach might address **mitochondrial energy production, oxidative stress, chronic inflammation, metabolic health, hormonal balance, autophagy and cellular repair, immune function, and the preservation of muscle, bone, and brain health.** Cellular senescence adds another important piece to that puzzle: not simply protecting our cells from future damage, but potentially helping the body periodically remove some of the dysfunctional cells that have already accumulated. For me, that makes senolytic support—alongside all of these other healthy-aging strategies—an especially intriguing avenue for maintaining function, resilience, and healthspan as the years go by.