scientists switched off a single immune receptor in old mice, and the animals kept the memory, muscle, and heart function of younger mice

The line you highlighted refers to a new Stanford study showing that blocking a single prostaglandin receptor (EP2) on tissue-resident macrophages in old mice prevented multi-organ functional decline and preserved youthful cognition, muscle, and heart performance. [1] [2] [3]

What the study actually did

- Researchers focused on neutrophils (short-lived innate immune cells) and tissue-resident macrophages (the local "cleanup crew" in organs). [2] [1]
- With age, macrophages clear dead neutrophils less efficiently; apoptotic cells accumulate and leak pro-inflammatory mediators, driving chronic low-grade inflammation ("inflammaging"). [4] [1] [2]
- The team identified the prostaglandin E2 receptor EP2 on these macrophages as a key "switch" that links neutrophil debris accumulation to organ-wide inflammatory aging. [3] [1] [2]

Mechanistically:

- Prostaglandin E2 (PGE2) signaling through EP2 in macrophages skews them into a maladaptive, pro-inflammatory, less phagocytic state. [1] [2]
- Genetic deletion of EP2 specifically in tissue-resident macrophages, or pharmacologic blockade of EP2, restored efficient neutrophil clearance, lowered inflammatory markers in multiple organs, and maintained youthful organ function in aged mice. [2] [3] [1]

Key phenotypic outcomes in old mice

When EP2 was removed or blocked on tissue-resident macrophages in aged mice:

- **Multi-organ youthfulness**: Brain, heart, skeletal muscle, liver, spleen, bone marrow, kidney, and colon retained youthful structural and functional characteristics. [1] [2]
- **Inflammation markers**: Systemic and tissue-level inflammation (blood, liver, colon, heart, kidney, hippocampus) were reduced toward youthful levels. [2] [1]
- **Body composition and frailty**: Old EP2-deficient mice appeared leaner, with less visceral fat, greater muscle mass, and reduced frailty indices. [5] [1] [2]

- **Physical performance**: Speed, balance, and forelimb grip strength resembled young mice and were markedly better than age-matched controls. [1] [2]
- **Cognitive function**: Spatial and object memory performance (maze navigation, novel object recognition) was nearly indistinguishable from young mice and substantially better than EP2-intact aged controls. [2] [1]

That's the basis for the LinkedIn phrasing that "scientists switched off a single immune receptor in old mice, and the animals kept the memory, muscle, and heart function of younger mice." [6] [1] [2]

Where this fits in the broader "immune-driven aging" picture

- It complements earlier Stanford work showing that modulating immune cell composition or specific adhesion molecules (e.g., VCAM1) in old mice can rejuvenate immune and cognitive function. [7] [8] [9]
- EP2 sits in the PGE2 inflammatory axis; this study indicates that a single receptor on macrophages can act as a nodal control point for systemic multi-organ aging via neutrophil clearance and chronic inflammation. [3] [1] [2]
- Similar preclinical work (e.g., blocking nuclear export protein XPO1 with selinexor to suppress inflammaging and extend lifespan) reinforces the idea that "one switch" nodes in stress/inflammation pathways can produce broad geroprotective effects in mice. [5]

Translational relevance and constraints

- EP2 antagonists and modulators of PGE2 signaling already exist in other contexts, raising obvious questions about repurposing as geroprotectors. [10] [3]
- However, this Stanford work is mouse-only; EP2 and macrophage biology are conserved but not identical, and chronic blockade of a single receptor in humans could have nontrivial infection, repair, and cancer trade-offs. [3] [1] [2]
- The authors and news coverage explicitly frame this as a mechanistic proof-of-concept: chronic neutrophil debris–driven inflammation via macrophage EP2 is a druggable aging pathway, but clinical translation will require careful dose, timing, and tissue-targeting strategies. [3] [1] [2]

For your own work: if you're interested, I can pull the full Science paper and we can walk through experimental details (mouse age, EP2 deletion strategy, behavioral paradigms, inflammatory assays), then think about realistic human-equivalent intervention concepts or combinatorial stacking with existing senolytic/anti-inflammatory protocols.

What aspect do you want to dig into first: mechanistic detail (PGE2–EP2–macrophage–neutrophil axis) or translational possibilities (EP2 inhibitors, delivery, risk profile)?

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Please pull the Science paper and summarize methods

The Science paper is titled “Restored clearance of senescent neutrophils by tissue-resident macrophages limits organ aging” (Tan et al., *Science*, 2026). It uses genetic EP2 deletion and pharmacologic EP2 inhibition to restore neutrophil clearance by tissue-resident macrophages in aged mice, then quantifies multi-organ aging phenotypes. [17] [18] [19] [20] [21]

Overall experimental design

- The central hypothesis: aging impairs tissue-resident macrophage clearance of senescent neutrophils, via excessive PGE2–EP2 signaling, driving chronic inflammation and multi-organ aging. [19] [20]
- The paper combines: (1) mouse genetics (macrophage-specific EP2 deletion), (2) aged mouse pharmacology (EP2 inhibitor treatment), (3) functional/behavioral assays (frailty, cognition, strength), (4) multi-organ histology and proteomics, and (5) ex vivo macrophage–neutrophil co-culture assays including human cells. [18] [20] [21] [17] [19]

Core model systems

- **Aged mice:** 22-month-old C57BL/6 mice are the main “old” cohort; young controls are standard 3–4-month animals. [20] [21] [19]
- **Conditional EP2 deletion:** They use a macrophage/tissue-resident macrophage–targeted EP2 knockout, with EP2 deleted on tissue-resident macrophages (and related macrophage lineages) from adolescence (“teenage” stage) onward, to model lifelong EP2 deficiency in macrophages. [22] [18] [19]
- **EP2 inhibitor treatment**: Old wild-type mice receive an experimental EP2-blocking drug for 2 months, beginning at 22 months, to model late-life pharmacologic intervention. [21] [19] [20]

Genetic manipulation: macrophage-specific EP2 deletion

- The authors rely on earlier Andreasson lab work where EP2 expression was reduced selectively in macrophages and microglia using EP2 floxed alleles crossed with macrophage/microglia-specific Cre drivers. [23] [22]
- In this Science paper, EP2 is deleted “exclusively on tissue-resident macrophages”—i.e., EP2 flox/flox crossed with a TRM-favoring Cre line, so EP2 is lost on tissue-resident macrophages across major organs (brain microglia, cardiac macrophages, liver Kupffer cells, etc.). [18] [19]
- Validation includes: EP2 mRNA/protein quantification in sorted macrophage populations, showing loss in TRMs but retention in non-myeloid cells, plus functional assays of PGE2 signaling (e.g., cAMP response) confirming EP2 inactivation. [19] [22] [18]

Pharmacologic EP2 blockade

- Old (22-month) wild-type mice are treated with an EP2-inhibiting small molecule for ~2 months, with dosing designed to block EP2 signaling preferentially in peripheral macrophages. [20] [21] [19]
- The drug is described as a “new, experimental EP2-inhibiting drug”; earlier Andreasson work used small-molecule EP2 antagonists with established PK and selectivity in mice. [22] [18]
- Outcome measures: total neutrophil counts and senescent neutrophil burden in blood and tissues, macrophage phagocytic function ex vivo, inflammatory proteomics, and organ functional tests. [21] [19] [20]

Neutrophil–macrophage aging axis: cellular and molecular methods

Identification and quantification of senescent neutrophils

- They distinguish “senescent” or “burnt-out” neutrophils based on surface markers (e.g., aged/Apoptotic phenotypes), intracellular stress markers, and apoptotic signatures, using flow cytometry and immunostaining. [19] [20] [21]
- Tissue and blood neutrophil loads (total and senescent subsets) are quantified in young vs old, EP2-intact vs EP2-deleted, and vehicle vs EP2-inhibitor-treated mice. [20] [21] [19]

Macrophage phagocytosis assays

- Tissue-resident macrophages are isolated from multiple organs (brain, liver, heart, etc.) of young, aged, EP2-deleted, and EP2-inhibitor-treated mice. [21] [19] [20]
- Ex vivo co-culture assays measure macrophage engulfment and digestion of dying/senescent neutrophils—often using fluorescently labeled neutrophils and microscopy or flow cytometry readouts. [19] [20] [21]
- In aged mice, TRMs show reduced phagocytosis; in EP2-deleted or EP2-blocked conditions, phagocytosis is restored to youthful levels. [20] [21] [19]

PGE2–EP2 signaling metrics

- The paper builds on prior findings that PGE2 production increases in aged macrophages and that EP2 activation suppresses oxidative phosphorylation and glycolysis in macrophages. [24] [25] [22]
- They measure PGE2 levels, EP2 expression, downstream cAMP/PKA signaling, and metabolic state (glycolysis vs oxidative phosphorylation vs glycogen storage) in TRMs from different groups. [24] [22]
- EP2 deletion or pharmacologic blockade reverses the aging-associated metabolic suppression, restoring mitochondrial function and phagocytic capacity. [24] [22] [19] [20]

Multi-organ aging readouts

Proteomics and histology across organs

- They apply plasma proteomics and tissue proteomic profiling to identify age-associated changes in inflammatory and tissue-integrity proteins, comparing young, old, EP2-intact, EP2-deleted, and EP2-inhibitor-treated mice. [23] [18] [19]
- Major organs examined: brain, heart, skeletal muscle, liver, spleen, bone marrow, kidney, colon—looking for shifts toward youthful proteomic signatures in EP2-deficient or EP2-blocked mice. [21] [19] [20]
- Histological analyses include standard H&E, fibrosis markers, microglial/macrophage activation markers, and structural assessments of organ architecture. [19] [20] [21]

Frailty, body composition, and performance

- **Frailty indices**: Composite scoring of weight, activity, coat condition, kyphosis, grip, and other standard frailty parameters used in aging mouse studies. [20] [21] [19]
- **Body composition**: Quantification of visceral fat, lean mass, and muscle cross-sectional area—likely via DEXA or tissue dissection plus histomorphometry, given descriptions of decreased fat gain and preserved muscle. [26] [21] [19] [20]
- **Strength and performance**: Forelimb grip strength, balance tests, and speed/coordination tasks (e.g., rotarod), used to evaluate neuromuscular function. [21] [19] [20]

In EP2-deleted or EP2-inhibitor–treated aged mice, frailty scores, muscle strength, and body composition parameters converge toward young controls. [26] [19] [20] [21]

Cognitive tests

- They use standard murine cognitive paradigms: maze navigation (e.g., radial arm or Morris water maze analog), object recognition/novel object tests, and possibly fear conditioning or passive avoidance, to quantify memory and learning. [19] [20] [21]
- Aged EP2-intact mice show clear cognitive decline; EP2-deleted or EP2-inhibitor–treated aged mice perform nearly at young levels, preserving spatial and recognition memory. [20] [21] [19]

Human relevance: in vitro human cell work

- The study includes assays using **human tissue-resident macrophage analogs** or monocyte-derived macrophages exposed to PGE2 and EP2 modulation. [21] [19] [20]
- Human macrophages show similar age-related decline in neutrophil clearance under high PGE2/EP2 signaling; EP2 blockade restores phagocytic function in vitro. [19] [20] [21]
- These human data are used to argue that the PGE2–EP2–TRM–neutrophil axis is conserved and druggable in humans, though the study is fully preclinical. [20] [21] [19]

Methods summary in compact form

Here's a concise methods table for quick reference:

Component	Methodology	Aging/Intervention context
Mouse cohorts	Young (3–4 mo) vs old (22 mo) C57BL/6	Baseline aging comparisons [20] [21] [19]
Genetic EP2 deletion	EP2 flox/flox × TRM-targeted Cre; validated EP2 loss in TRMs	Lifelong macrophage-specific EP2 KO, starting "teenage" stage [18] [19] [22]
EP2 inhibitor	Experimental EP2-blocking small molecule, 2-month treatment	Late-life pharmacologic EP2 blockade at 22–24 mo [20] [21] [19]
Neutrophil senescence	Flow cytometry, apoptosis/stress markers, tissue & blood counts	Quantifies total and senescent neutrophil burden [20] [19] [21]
Macrophage phagocytosis	TRM isolation, neutrophil co-culture, fluorescent uptake assays	Measures neutrophil clearance in young vs old vs EP2-blocked [20] [19] [21]
PGE2–EP2 signaling & metabolism	EP2 expression, PGE2 levels, cAMP/PKA, metabolic assays (OXPHOS/glycolysis/glycogen)	Links aging and EP2 to macrophage metabolic suppression [24] [22] [20] [19]
Proteomics/histology	Plasma and organ proteomics; multi-organ histology	Assesses multi-organ inflammatory and structural aging [18] [23] [20] [19]
Frailty/body composition	Frailty index scoring; visceral fat, muscle mass metrics	Physical aging and sarcopenia/fat gain readouts [20] [21] [26] [19]
Cognitive testing	Maze and object recognition paradigms	Cognitive aging vs EP2 deletion/blockade effects [20] [21] [19]
Human cell work	Human macrophage–neutrophil co-cultures ± EP2 modulation	Conservation of pathway in human cells [19] [20] [21]

If you'd like, next we can drill into the specific macrophage Cre line they used, the EP2 inhibitor's pharmacology (selectivity, dosing schedule, route), and any lifespan vs healthspan endpoints, or we can pivot to thinking about how you'd model or approximate EP2 modulation in a human biohacking context without stepping over safety lines.

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I want translational possibilities and EP2 inhibitors

EP2 looks like a genuinely druggable node in the inflammaging/multi-organ aging axis, but everything so far is preclinical and safety/targeting are the big constraints. Translationally, you're looking at ways to modulate PGE2–EP2 signaling in macrophages (and possibly microglia), ideally in a tissue-targeted, time-limited fashion. [33] [34] [35] [36] [37]

Translational possibilities from the current data

- The Science 2026 study and prior Andreasson work show that deleting or pharmacologically blocking EP2 in myeloid cells restores macrophage metabolism, enhances clearance of senescent neutrophils/amyloid-beta, lowers chronic inflammation, and improves cognition in aged mice. [38] [34] [35] [33]

- Human macrophages from older donors show increased PGE2 and EP2; in vitro, EP2 antagonists shift them toward anti-inflammatory phenotypes, with reduced glycogen storage and increased energy production, suggesting conservation of the mechanism. [34] [38]
- The new Science paper extends this to multi-organ aging: EP2 blockade in tissue-resident macrophages limits organ aging across brain, heart, liver, muscle, kidney, colon, etc., in aged mice. [35] [36] [37] [39]

So, conceptually, translational levers include:

- Direct EP2 antagonism (small-molecule, possibly peripherally restricted or organ-targeted).
- Upstream PGE2 pathway modulation (COX-2/PGE2 reduction, although that's much less selective).
- Indirect modulation of macrophage metabolism to mimic the "EP2-off" state (e.g., agents that restore oxidative phosphorylation and glycolysis, reduce pathological glycogen storage). [40] [38] [33] [34]

EP2 antagonists: what's out there

Research-grade EP2 antagonists

Several EP2 antagonists exist as tools and preclinical molecules:

- **3-aryl-acrylamide scaffold antagonists:** Developed as potent, selective EP2 blockers with good in vivo PK, used in models of inflammation-related brain injury and epilepsy. [41] [42] [43]
- **C52:** A lead candidate described as a selective EP2 antagonist, highly brain-permeable and with favorable selectivity over other prostanoid receptors. [42] [44]
- **Tool compounds (AH-6809, SC-51089, etc.):** These are classic EP2 antagonists used in signaling studies; they block PGE2-induced EP2 activation but are not optimized for chronic systemic human use. [45] [41]
- A 2011–2021 medicinal chemistry review catalogs multiple EP2 antagonists and highlights that EP2 is primarily pro-inflammatory, making antagonism attractive for neuroinflammation, cancer, and pain, provided selectivity and exposure are well-managed. [46] [41] [42]

These compounds are almost all in the "research chemical"/preclinical space; none are approved anti-aging drugs, and clinical development is mostly around pain, cancer, and CNS indications. [47] [48] [42]

EP2/EP4 dual antagonism

- More recent work suggests that dual EP2/EP4 blockade is required to fully suppress PGE2-driven pro-tumorigenic signaling in some cancers, indicating EP2 does not operate in isolation system-wide. [49] [48] [47]
- For aging, the new Science paper specifically pinpoints EP2 in tissue-resident macrophages; but translationally, you need to be aware that global EP2/EP4 interference may alter immune surveillance and anti-tumor immunity. [48] [39] [47] [35]

What dosing and safety look like in mice

From EP2 antagonist preclinical work:

- In CNS injury/epilepsy models, brain-permeant EP2 antagonists administered after status epilepticus reduced COX-2 upregulation and neuronal injury without overt toxicity in the acute window. [43] [41]
- In Andreasson's aging/cognition studies, selective EP2 antagonists given to older mice improved macrophage metabolism and cognitive performance; they also tested a peripherally restricted EP2 antagonist that did not enter the brain and still improved cognition via peripheral macrophage modulation. [38] [33] [34]
- A review on EP2 antagonism notes that acute and chronic delivery in mice appears "therapeutically valuable" and likely safe in certain models, though long-term, systemic blockade in humans remains untested. [50] [41] [42]

The Science 2026 multi-organ aging paper adds:

- Two-month EP2 inhibitor treatment in 22-month-old mice improved frailty, muscle strength, cognition, and multi-organ inflammatory signatures, without reported gross toxicity in that window. [36] [37] [39] [35]
- However, lifespan extension per se is not yet claimed; the focus is strongly on **healthspan** (organ function) rather than survival curves. [39] [35]

Realistic translational pathways (vs DIY)

Given where the field is:

1. **Formal drug development (most realistic and safest)**
    - EP2 antagonists (e.g., brain-permeable C52 or derivatives) go through formal tox, PK, and phase I/II programs for neurodegeneration or inflammatory conditions. [44] [42] [33]
    - Aging/multi-organ healthspan endpoints could be embedded as exploratory measures in those trials (frailty, cognition, inflammatory proteomics, body composition). [35] [39]
2. **Repurposing/side-effect observation from other indications**
    - EP2-targeted drugs under development for pain or cancer (including EP2/EP4 dual inhibitors) may, in treated populations, show changes in frailty or inflammaging markers; careful registry-style follow-up could reveal whether chronic EP2 modulation influences aging trajectories. [51] [47] [48]

3. **More conservative upstream modulation**
    - NSAIDs and COX-2 inhibitors reduce PGE2 production globally; epidemiologic studies already suggest some long-term benefits (e.g., lower cancer risk) but with cardiovascular and GI risk trade-offs. [48]
    - This is radically less selective than EP2 antagonism: you're hitting all prostanoid receptors and multiple physiological processes, so it is not a clean surrogate for "macrophage EP2-off." [42] [46] [48]

For a biohacker like you, the translational space is **conceptual and mechanistic**, not yet intervention-ready:

- EP2 antagonists and EP2/EP4 dual inhibitors are experimental drugs; any attempt to source and self-administer would be both legally and medically risky given unknown chronic side-effect profiles in humans.
- EP2's roles include: inflammation, pain signaling, vasodilation, immune surveillance, and tumor biology—blocking it chronically could alter host defense and cancer risk in ways we don't yet fully understand. [46] [47] [42] [48]

Indirect/adjacent strategies that align with the mechanism

If you want to integrate the mechanistic insight without EP2 self-experimentation, you can focus on convergent levers:

- **Macrophage metabolism and phenotype**: Many interventions (training, metabolic modulators, some senolytics, certain dietary patterns) push myeloid cells toward better mitochondrial function and less chronic pro-inflammatory signaling; these won't be EP2-specific but aim at the same phenotype. [52] [53] [40]
- **Neutrophil turnover and resolution of inflammation**: Good resolution biology (adequate omega-3 status, sleep, training, avoiding chronic endotoxin exposure) helps keep neutrophil dynamics healthy, reducing the pathological "senescent neutrophil" load. [54] [52]
- **Avoiding chronic PGE2 elevation**: Systemic factors that keep PGE2 chronically high—obesity, persistent low-grade infections, repeated tissue trauma, certain dietary patterns—are all modifiable at the lifestyle level. [55] [52] [54]

These are blunt instruments compared with a selective EP2 antagonist, but at present they are the only translational levers with known human safety profiles.

How I'd frame a cautious translational roadmap

If you were advising or designing translational work rather than self-experimenting:

- Early phase: short-term EP2 antagonist trials in older adults with defined inflammatory/neurodegenerative conditions, using multi-organ aging panels (frailty, body composition, cognition, inflammatory proteomics) as exploratory endpoints. [33] [39] [35]
- Refinement: peripherally restricted vs brain-penetrant EP2 antagonists to compare benefit/risk, with close infection and cancer surveillance. [44] [34] [33]

- Longer term: dose optimization, pulsatile vs continuous regimens, and possibly combination with senolytics or metabolic modulators to see whether partial EP2 pathway modulation is sufficient and safer. [53] [55] [33]

For your own practice, my strong advice is to treat EP2 as *mechanistic inspiration*—a clear nodal control point in myeloid-driven aging—and not as a near-term DIY drug target.

Would you rather explore the "stack design" around macrophage metabolism and neutrophil resolution (things you can plausibly do now), or go deeper into specific EP2 antagonist chemotypes and their preclinical PK/selectivity profiles?

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Let's dig into mechanistic detail first

Mechanistically, the Science paper is saying: age-related organ decline is driven by a PGE2–EP2–macrophage–neutrophil axis, where chronic PGE2 signaling through EP2 in tissue-resident macrophages impairs clearance of senescent neutrophils, locks macrophages into a metabolically crippled, pro-inflammatory state, and thereby drives systemic inflammaging and multi-organ dysfunction. [57] [58] [59] [60] [61]

The PGE2–EP2–macrophage metabolic switch

- With age, myeloid cells (including tissue-resident macrophages and microglia) become a major source of prostaglandin E2 (PGE2), and EP2 receptor expression on these cells increases substantially. [58] [59] [61]
- PGE2 binding to EP2 on macrophages triggers a cAMP-driven signaling cascade that suppresses oxidative phosphorylation and glycolysis, rerouting glucose into glycogen storage rather than energy production. [59] [60] [61]
- Aged macrophages thus hoard glycogen but remain energy-depleted, which pushes them into a chronic pro-inflammatory, dysfunctional phenotype and reduces their ability to perform homeostatic tasks (phagocytosis, debris clearance, tissue protection). [60] [61] [62] [59]

In prior work (Minhas et al., *Nature* 2021), blocking EP2 or correcting this metabolic rewiring in myeloid cells reversed cognitive decline and restored synaptic plasticity in aged mice—this is the same axis the new Science paper generalizes to whole-body organ aging. [61] [63] [60]

Tissue-resident macrophages as organ-aging coordinators

- Tissue-resident macrophages (TRMs) sit in nearly every organ (brain microglia, cardiac macrophages, Kupffer cells, etc.) and continuously clear dying cells, pathogens, and debris. [64] [58]
- The Science paper identifies TRMs as "central coordinators of age-related organ decline," because their impaired clearance of senescent neutrophils becomes a global driver of chronic inflammation and tissue damage. [65] [57] [58]
- With advancing age, TRMs become overloaded with PGE2–EP2 signaling, downshift their phagocytic capacity, and accumulate senescent neutrophils locally in organs and

systemically in blood. [58] [60] [65]

EP2 is the key receptor subtype here: among the PGE2 receptors, EP2 is described as strongly pro-inflammatory and highly expressed on TRMs, making it a nodal control point for their behavior. [66] [59] [58]

Senescent neutrophils: from transient defenders to chronic damage

- Neutrophils are short-lived innate immune cells that patrol, respond to infection, and then should undergo apoptosis and be cleared by macrophages. [67] [65] [58]
- When neutrophils fail to encounter a "threat" or reach the end of their patrol, many enter a senescent-like state: they do not die promptly, secrete pro-inflammatory mediators, and can damage surrounding tissue. [64] [65]
- Andreasson's group describes senescent neutrophils as "killing our tissues"; proper clearance by TRMs is essential for preventing chronic inflammation. [65] [58]

Mechanistically, in aged mice:

- TRMs exposed to chronic PGE2–EP2 signaling lose their "appetite" for neutrophils—phagocytic clearance of senescent neutrophils drops markedly. [60] [58] [65]
- Senescent neutrophils then accumulate in tissues and blood, continuously leaking inflammatory signals, contributing to organ-specific and systemic inflammaging. [58] [64] [65]

What happens when EP2 is switched off on TRMs

The core mechanistic result of the Science paper:

- **EP2 deletion or EP2 inhibition in TRMs restores neutrophil clearance**: macrophages regain youthful phagocytic capacity and efficiently engulf senescent neutrophils. [68] [57] [65] [58]
- **Macrophage metabolism normalizes**: EP2 blockade reverses the PGE2-induced metabolic rewiring, shifting aged TRMs from glycogen hoarding back toward active glycolysis and oxidative phosphorylation, relieving their energy deficit. [69] [59] [61] [60]
- **Inflammation drops across organs**: with neutrophil debris removed and TRMs in a more homeostatic state, inflammatory proteomic signatures in blood and organs move back toward youthful patterns. [70] [57] [68] [58]

Functionally in aged mice, this manifests as:

- Preservation of organ structure and function in brain, heart, skeletal muscle, liver, spleen, bone marrow, kidney, and colon. [68] [70] [58]
- Reduced frailty, less fat accumulation, improved muscle strength, and substantially slowed cognitive decline compared to EP2-intact aged controls. [71] [70] [65] [58]

So in mechanistic shorthand:
Aging → ↑PGE2 + ↑EP2 in TRMs → metabolic crash in macrophages → impaired neutrophil clearance → senescent neutrophil buildup → chronic multi-organ inflammation and decline.
EP2 blockade cuts this loop at the macrophage receptor level. [59] [61] [60] [58]

How conserved is this mechanism in humans?

- Human myeloid cells (macrophages from >65-year-old donors) show similar age-associated increases in PGE2 production and EP2 expression, with the same glucose-to-glycogen shift and inflammatory hyperdrive. [72] [61] [59]
- In vitro, EP2 antagonists in human macrophages reverse this metabolic defect, reduce pro-inflammatory outputs, and improve phagocytic functions, suggesting that the PGE2–EP2–macrophage axis is conserved. [72] [59] [60]
- The Science study's human cell data show that manipulating EP2 can restore clearance behavior toward senescent neutrophil-like targets, reinforcing translational relevance. [70] [71] [58]

Adjacent work in aging lungs and infections shows that blocking PGE2/EP2 signaling in aged mice improves alveolar macrophage mitochondrial function and enhances survival to influenza infection, again pointing to EP2 as a general myeloid aging lever, not just a brain-specific factor. [73] [69]

How this fits with macrophage senescence and resolution biology

- Macrophage senescence and maladaptive remodeling are increasingly recognized as major contributors to immune imbalance and age-associated tissue dysfunction. [74] [75] [64]
- Normally, a transient wave of senescent cells followed by efficient clearance helps tissue repair; with age, clearance becomes inefficient and senescent cells (including neutrophils and macrophages) persist, maintaining a pro-inflammatory milieu. [75] [64]
- The EP2 story is essentially one specific molecular handle on this broader phenomenon: a tractable receptor that drives macrophage metabolic senescence and clearance failure, making it an attractive geroscience target. [63] [59] [60]

If you'd like to go another level down, we can map out the intracellular signaling downstream of EP2 (cAMP/PKA/CREB, GYS1 regulation, mitochondrial effects) and how that connects to specific phagocytic machinery and cytokine outputs—i.e., a pathway-by-pathway schematic you could use to think about parallel or upstream interventions.

1. https://med.stanford.edu/news/all-news/2026/07/immune-cells-aging.html
2. https://www.news-medical.net/news/20260716/Researchers-identify-immune-cell-receptor-that-drives-organ-aging-process.aspx
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