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REVIEW

Regulation of Endogenous Stem Cells, Regenerative Capacity and Organ Aging by Lifestyle and Environmental Factors

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Abstract

Adult tissue-specific stem cells maintain organ homeostasis and support tissue repair. With age, however, their abundance, lineage output, functional competence, and niche support can change. In each organ, the trajectories of tissue stem cells develop characteristic shapes, including myeloid-biased and clonally drifting hematopoietic stem cells (HSCs), muscle satellite cells (MuSCs) that lose autophagic activity as they transition from quiescence into senescence, neural stem cells (NSCs) that become increasingly resistant to activation from quiescence, intestinal stem cells (ISCs) that lose canonical Wnt signalling, alveolar type 2 (AT2) cells associated with $p16^+$ "sentinel" fibroblasts, and cardiac stem cells in which $p16^+$ cells accumulate. Physical activity and energy intake levels, sleep and circadian disruption, psychological stress, and environmental exposures may further modify these trajectories. The main mediators and pathways within tissues include metabolic sensing, autophagy, mitochondrial and redox control, DNA damage responses, circadian regulation, and remodelling of the extracellular niche. This review integrates evidence from hematopoietic, muscle, neural, intestinal, lung, liver, skin, cardiac, adipose, and mesenchymal stem cell compartments. We propose an evidence-calibrated framework that distinguishes (i) cell-autonomous effects from niche-mediated effects, (ii) stem cell abundance from regenerative competence and oncogenic potential, and (iii) human evidence from animal, organoid, *ex vivo*, and *in vitro* findings. Lifestyle and environmental factors appear to be important, modifiable, and context-dependent determinants of regenerative reserve and organ aging. We also outline regulatory pathways, candidate biomarkers, clinical trial designs, and safety measures for evaluating regenerative interventions intended to extend healthspan.

Keywords

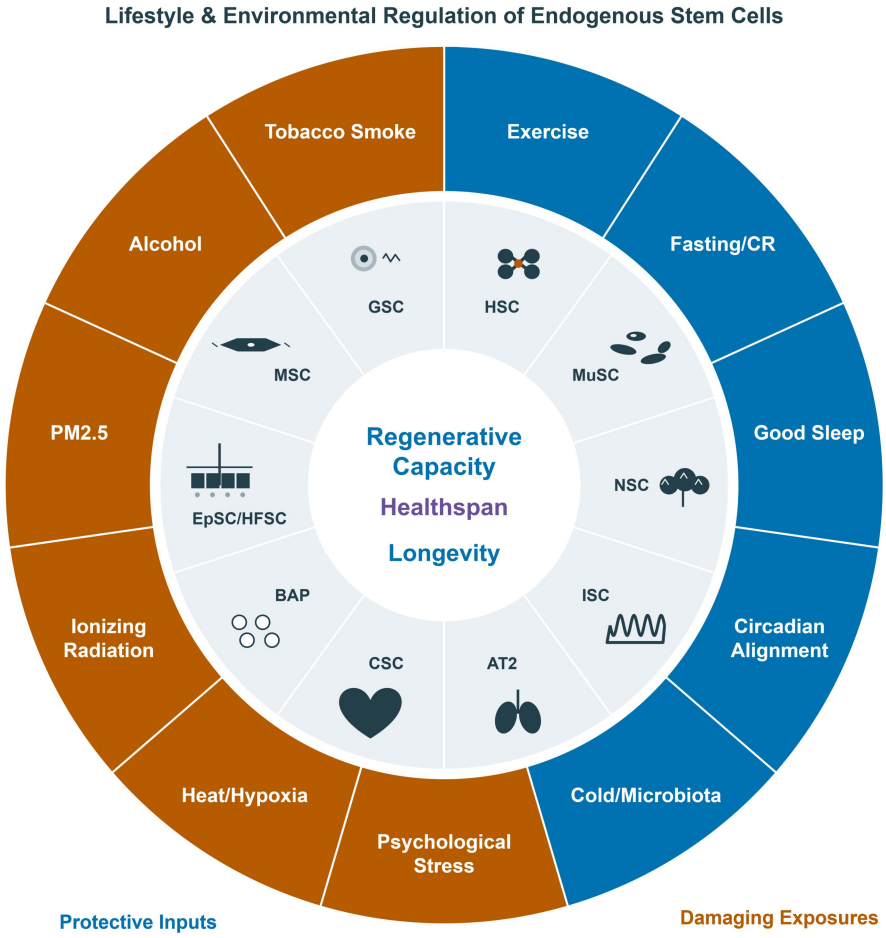
Lifestyle; Environmental factors; Stem cells; Senescence; Longevity; Endogenous regenerative capacity

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Graphical Abstract



NOTE: MSC: mesenchymal stem cell; GSC: Germline stem cell; HSC: hematopoietic stem cell; MuSC: muscle satellite cell; NSC: neural stem cell; ISC: intestinal stem cell; AT2: alveolar type 2; CSC: cardiac stem cells; BAP: brown adipose progenitors; EpSC: epithelial stem cell; HFSC: hair follicle stem cell; CR: calorie restriction.

Highlights

- Lifestyle and environmental factors play a central role in healthspan and longevity.
- Endogenous stem cells and their niches determine their regenerative capacity and are linked to tissue and organ aging and functionality.
- Lifestyle and environmental factors modulate stem cell function through tissue-dependent and context-dependent mechanisms.
- Stem cell abundance, functional competence, regenerative output, and oncogenic potential are distinct outcomes.
- Lifestyle and environmental factors impact major signalling molecules and pathways involved in the regulation of stem cells and organ aging.

1. Introduction

Stem cell pools that reside within tissue become progressively dysfunctional with age. This may include altered lineage output, impaired activation, senescence, clonal expansion, or loss of niche support, which all contribute to the age-related loss of tissue resilience. However, the strength and type of dysfunction vary among organs. In some compartments, mechanistic studies identify specific stem cell or niche pathways. In others, the evidence is indirect, correlative, or limited to animal models. This review therefore does not present stem cell dysfunction as the single immediate cause of all age-related disease. Nor does it assume that changes in stem cell abundance are associated with improved regenerative capacity. Stem cell abundance, functional competence, regenerative output, and oncogenic potential are treated as distinct outcomes[1,2].

Unlike broad reviews of stem cell aging and rejuvenation, this review focuses on the interface among endogenous stem cell compartments, their local niches, and modifiable lifestyle or environmental factors. For each compartment, we describe the intrinsic aging phenotype and the best-supported exposure-mechanism relationships (**Figure 1**). We also distinguish between direct and niche-mediated effects and define the limits of inference from human studies. Human intervention and observational findings are considered separately from animal, organoid, *ex vivo*, and *in vitro* data. Mixed or indirect evidence is identified explicitly. **Figure 1** summarizes the direction of reported effects and major evidence gaps.

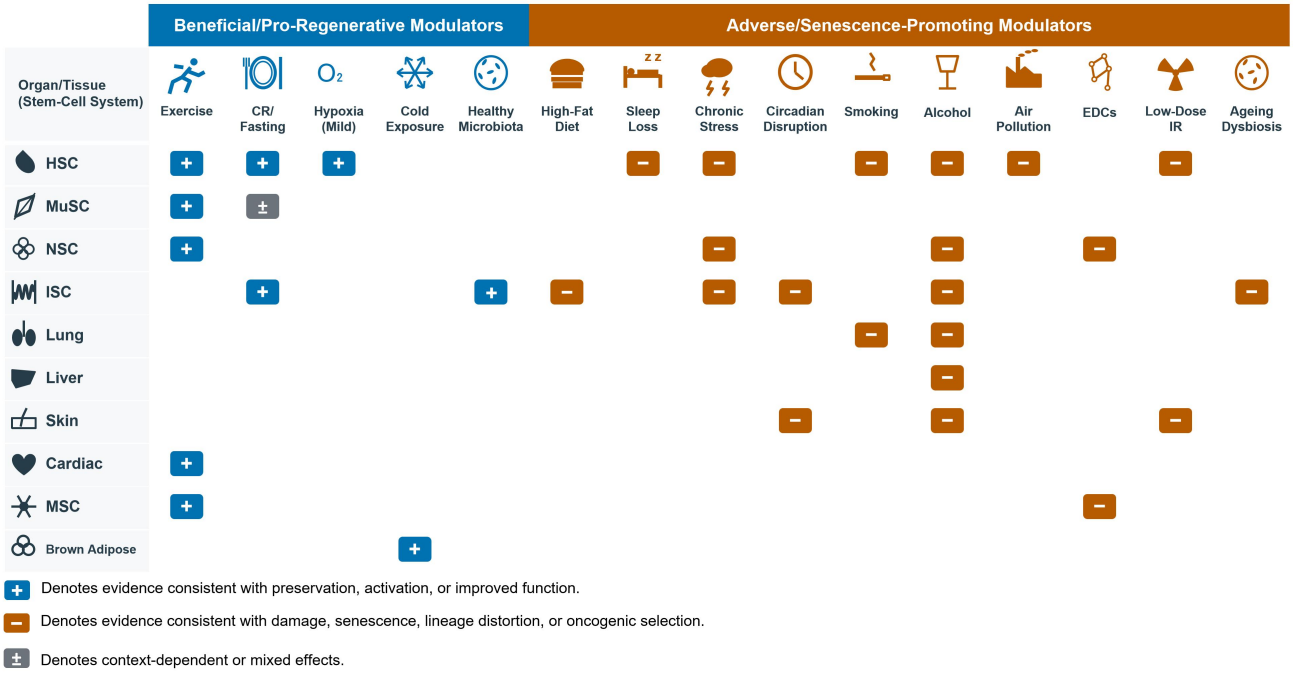


Figure 1. Lifestyle and environmental modulators of endogenous stem cell activity across organs and tissues. Rows represent stem cell compartments, and columns represent lifestyle or environmental factors. Empty cells indicate that direct evidence has not been established. **NOTE:** HSC: hematopoietic stem cell; MuSC: muscle satellite cell; NSC: neural stem cell; ISC: intestinal stem cell; Lung: alveolar type 2 (AT2)/BASC; Liver: progenitors; Skin: epidermal stem cells; Cardiac: stem cells; Brown adipose: progenitors; MSC: mesenchymal stem cell; CR: calorie restriction; EDCs: endocrine-disrupting chemicals; IR: ionizing radiation. Research findings from human, animal, organoid, *ex vivo*, and *in vitro* studies are collectively presented in this figure. Copyright: The figure was created using Microsoft PowerPoint and AI assistance (ChatGPT 5.0).

To establish a framework of evidence and interpret effect modifiers, we use four evidence categories: human (intervention, observational, or tissue-based studies), animal (*in vivo*), organoid/*ex vivo*, and *in vitro* (Table 1). Mechanistic plausibility alone does not establish anti-aging effects in humans. When possible, each exposure should be interpreted according to dose and duration, life stage, sex, genetic background, tissue or niche state, and injury repair demand. These modifiers also show context-dependent effects: transient activation may support tissue repair, whereas chronic activation may deplete the stem cell pool or select for oncogenic clones.

Table 1. Evidence frameworks set in this review

Evidence Category	What It Can Support	Key Limitation
Human	Association, feasibility, safety, or clinical response in the studied population	Often indirect for endogenous stem cell mechanisms
Animal	Causal pathway and tissue-specific regenerative mechanisms	Species, dose, and injury-model dependence
Organoid/*Ex vivo*	Cell-niche interactions and target engagement	Loss of systemic physiology
In vitro	Molecular mechanism and candidate cargo/pathways	Limited tissue and exposure complexity

2. Hematopoietic Stem Cells

2.1 Intrinsic Aging Biology

Hematopoietic aging combines an increase in cell number with a decline in cell quality. Immunosenescence, chronic inflammation, and anaemia reflect age-related changes in both hematopoietic stem cells (HSCs) and their bone marrow niches[3,4]. Aged HSCs are often more numerous, yet they show myeloid bias, reduced hematopoietic stem cell (HSC) lymphoid output, and delayed cell cycle entry. In older human bone marrow, a higher frequency of both lineage-negative cells and HSCs coexist with fewer multi-lymphoid progenitors. Elevated cell division cycle 42 (Cdc42) activity is associated with loss of polarity. In experimental models, the Cdc42 activity-specific inhibitor (CASIN) repolarizes aged HSCs and partly restores xenograft reconstitution[5].

HSC aging reflects interacting intrinsic and extrinsic processes, including genomic instability, epigenetic remodelling, metabolic dysregulation, and altered niche support. These processes can reduce self-renewal, distort differentiation, impair regenerative output, expand dysfunctional clones, and increase susceptibility to hematologic disease[3,6]. Following genotoxic stress, differentiated hematopoietic cells frequently undergo apoptosis, whereas quiescent HSCs may enter persistent senescence with reduced proliferative capacity. Oxidative DNA damage is also one proposed contributor[7]. Aged HSCs rely on autophagy to buffer inflammation-associated metabolic stress[8].

2.2 Lifestyle Modulators

2.2.1 Exercise

Sedentary behaviour drives chronic leucocytosis, which in turn fuels atherosclerosis. In mice, voluntary running reduces

steady-state hematopoietic activity without compromising emergency responses. The effect appears largely niche-mediated. Exercise lowers adipose-derived leptin, increases quiescence-supporting factors in leptin-receptor-positive bone marrow stromal cells, and produces transcriptomic and epigenomic changes in hematopoietic stem/progenitor cells (HSPCs) that can persist after exercise cessation[8,9]. A single-cell atlas of young and aged mice further shows that aerobic exercise remodels hematopoietic stem cells (HSCs) (and subsets of muscle and neural stem cells (NSCs)) and attenuates inflammatory signalling in immune compartments[10]. Acute exercise can also mobilize HSPCs into peripheral blood and alter the mesenchymal stromal cell secretome[9].

2.2.2 Caloric Restriction and Fasting

In mice, repeated cycles of prolonged fasting reduce circulating insulin-like growth factor 1 (IGF-1) and cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) activity in long-term HSCs and niche cells. These changes promote stress resistance, self-renewal, and more balanced regeneration[11]. Repeated fasting cycles also reduce chemotherapy-associated immunosuppression and may lessen age-related myeloid bias. Midlife dietary restriction improves mitochondrial pathways, increases quiescence, and reduces DNA-damage signalling in HSCs in mice aged 15−18 months. It also improves marrow reconstitution after transplantation[12]. In humans, one study reported that a three-day fast increased red blood cell count and enhanced function, especially in people with baseline cytopenia. The proposed mechanism involved autophagy-mediated suppression of membrane spanning 4-domains A3 (MS4A3) in megakaryocyte-erythroid progenitors[13]. These findings have not proved that fasting rejuvenates the entire human HSC pool.

2.2.3 Sleep and Psychological Stress

Sleep regulates HSPC behaviour through niche signalling and chromatin-associated mechanisms. In mice, sleep fragmentation increases inflammatory Ly-6Chi monocytes and accelerates atherosclerosis through reduced hypothalamic hypocretin signalling. Hypocretin normally constrains colony-stimulating factor 1 (CSF1) production by pre-neutrophils in the bone marrow[14]. Sleep disruption also produces durable changes in HSC function and clonal diversity in experimental systems[15]. These studies therefore link sleep behaviour and clonal diversity to clonal haematopoiesis risk. The brain-bone marrow axis can reinforce myelopoiesis and neuroinflammation during chronic stress, linking depressive states to durable hematopoietic remodelling[16].

2.3 Environmental Modulators

2.3.1 Tobacco Smoke and Alcohol

Multiple studies link smoking to the expansion of premalignant HSPC clones. In mouse models of clonal haematopoiesis, cigarette smoke and e-cigarette aerosols promote the expansion of Tet2-deficient and other mutant clones[17]. Human genetic analyses also support an association between smoking and clonal haematopoiesis[18,19]. These findings are most consistent with the selection and expansion of pre-existing mutant clones rather than simple depletion of the HSPC pool.

Chronic alcohol exposure has been reported to promote age-dependent myeloid bias, inflammatory signalling, epigenetic disruption, and transposon upregulation in HSPCs[20]. Acetaldehyde-mediated DNA damage is a plausible mutagenic mechanism[21]. These observations support an inflammaging and genome-instability model, although the relative contribution of direct HSPC injury and niche-mediated effects remains unresolved.

2.3.2 Air Pollution and Hypoxia

In mice, one month of intranasal PM2.5 exposure reduces bone marrow stem cell proliferation through reactive oxygen species (ROS)-associated AKT inhibition, whereas antioxidant treatment partly rescues this phenotype[22]. Early-life exposure may have long latency effects because newborn mice exposed to particulate matter develop progressive HSC senescence and impaired hematopoietic function[23].

The bone marrow HSC niche is physiologically hypoxic. In mice, sustained exposure to 10% oxygen increased HSC engraftment, expanded HSPC pools, reduced oxidative stress, and increased GATA-binding protein 1 (Gata1, also known as erythroid transcription factor) and cellular myeloproliferative leukaemia (c-Mpl) virus oncogene expression[24]. Whether comparable exposure windows are beneficial or safe in humans remains unknown.

2.3.3 Low-Dose Ionizing Radiation

Low-dose ionizing radiation (IR) can leave persistent functional deficits in HSCs through ROS-associated stress responses. In experimental systems, increased ROS activates antioxidant pathways but also reduces self-renewal and promotes senescence[25,26]. The net effect depends on radiation dose, exposure time, and the state of the recipient niche. In human cord blood HSPCs, a single 20 mGy dose, roughly the equivalent of several childhood brain CT scans, impairs their self-renewal via ROS and mitogen-activated protein kinase 14 (p38/MAPK14) signalling, independently of canonical ataxia-telangiectasia mutated-tumour protein p53 (ATM/p53) DNA damage response activation[26].

In summary, animal studies support niche-mediated effects of exercise, dietary restriction, sleep disruption, toxicant levels, and radiation on haematopoiesis. Human evidence is strongest for associations involving sleep, smoking, clonal haematopoiesis, and selected fasting-related hematologic outcomes. In humans, direct and niche-mediated effects remain difficult to separate. Increased HSC or HSPC abundance or mobilization does not necessarily indicate restored lineage balance or lower clonal risk. So far, key gaps include dose-response relationships, sex-specific effects, and whether modifying these exposures improves clinically meaningful immune aging.

3. Skeletal Muscle Satellite Cells

3.1 Intrinsic Aging Biology

Skeletal muscle aging provides a well-studied example of how stem cell dysfunction can limit tissue repair. In aged muscle, satellite cells may remain in prolonged quiescence, enter senescence-like states, and show reduced regenerative capacity. However, satellite cell number and functional competence do not always decline in parallel, and changes in the muscle niche can be equally important[27].

Three mechanisms have received particular attention. First, impaired autophagy compromises long-term quiescence and contributes to satellite cell senescence. Genetic or pharmacologic restoration of autophagy can improve homeostasis and regenerative function in experimental models[28]. Second, altered fibroblast growth factor receptor 1-alpha and beta isoforms of p38 mitogen-activated protein kinase (p38α/β MAPK) (*FGFR1*-p38α/β). Signalling contributes to cell-autonomous loss of self-renewal, with pathway modulation partly rescuing this defect[29]. Third, mitochondrial dynamics and mitophagy are required to sustain regenerative competence throughout adult life[30].

The niche also contributes to satellite cell aging. Aged satellite cell subpopulations exhibit transcriptional, chromatin accessibility, and DNA methylation changes. In experimental settings, exposure of aged cells to a younger niche can partially restore regenerative responses, supporting the view that both cell-intrinsic and microenvironmental mechanisms are relevant[31].

3.2 Lifestyle and Environmental Modulators

3.2.1 Exercise

In aged rats, 13 weeks of moderate treadmill running increased satellite cell density, the proportion of myogenic clones derived from old muscles, as well as favourable changes in body composition and locomotor activity[32]. In aged mice, aerobic exercise suppresses cellular communication network factor 2 (CCN2) secretion by senescent muscle stem cells and improves regeneration[33]. These findings support a pro-regenerative effect in rodents. However, direct evidence for endogenous muscle stem cell (MuSC) rejuvenation in humans remains limited.

3.2.2 Caloric Restriction and Fasting

Short-term caloric restriction enhances MuSC availability and activity in young and old mice, with increased mitochondrial abundance and improved donor cell engraftment in regenerating muscle[34]. By contrast, fasting can slow acute repair by inducing a deep, ketone-associated quiescent state[35]. Thus, metabolic interventions may preserve long-term resilience while transiently reducing repair speed, depending on timing and injury context.

In conclusion, accumulating evidence indicates that exercise and dietary interventions preserve or modify MuSC programs in rodents. Exercise probably acts through both systemic and niche-mediated pathways, whereas the effects of fasting and energy restriction depend strongly on duration. Regenerative benefits need to be distinguished from transient quiescence or slower repair. So far, key gaps include standardized human MuSC sampling, studies in defined injury settings, and evaluation of repeated dietary cycles over the long term.

4. Neural Stem Cells

4.1 Intrinsic Aging Biology

With advancing age, adult neural stem cells (NSCs) in the dentate gyrus and subventricular zone become less readily activated from quiescence. Inflammation, altered Wingless-related integration site (Wnt) signalling, vascular changes, and other niche abnormalities all contribute to this phenotype[36]. Chronic glucocorticoid exposure may further alter neural stem cell (NSC) survival and differentiation, although the relative importance of direct and niche-mediated mechanisms varies across models[37].

4.2 Lifestyle and Environmental Modulators

4.2.1 Exercise and Psychological Stress

In rodents, voluntary running is a robust physiological stimulus for adult neurogenesis. It promotes NSC activation, progenitor proliferation, as well as survival and maturation of newborn neurons and their integration into hippocampal circuits[38,39]. The magnitude and persistence of these effects depend on age, running paradigm, and baseline niche state.

Chronic stress can suppress adult hippocampal neurogenesis through autophagic death of NSCs rather than through apoptosis. In mice, corticosterone-driven serum/glucocorticoid-regulated kinase 3 (SGK3) signalling contributes to this process and is associated with cognitive deficits[40,41].

4.2.2 Environmental Factors

It was reported that urban air-pollution nanoparticles can induce hippocampal NSC quiescence by suppressing neurotrophin signalling in mice[42]. Epidemiologic evidence links particulate exposure to cognitive decline and dementia, but it does not establish that altered NSC activity mediates these associations in humans.

5. Intestinal Stem Cells and the Modulators

Aging intestinal epithelium shows reduced regenerative reserve that has been linked to diminished canonical Wnt signalling in leucine-rich repeat-containing G-protein coupled receptor 5-positive ($Lgr5^+$) intestinal stem cells (ISCs). Declining intestinal stem cell (ISC) function contributes to impaired repair, but whether this reflects a primary cell-autonomous defect or age-related changes in Paneth cells, immune cells, and other niche components remains incompletely resolved.

5.1 Dietary and Other Modulators

Caloric restriction enhances $Lgr5^+$ ISC function through a niche-mediated mechanism. In mice, reduced mechanistic target of rapamycin complex 1 (mTORC1) activity in Paneth cells increases Bst1-dependent cyclic ADP-ribose signalling and improves ISC self-renewal and organoid-forming capacity[43,44]. A 24 hour fast enhanced ISC function in both young and aged mice by inducing a fatty acid oxidation program[45]. Acute carnitine palmitoyltransferase 1A (Cpt1A) disruption abolished this effect, implicating fatty acid oxidation as a metabolic mediator[46]. High-fat diets increase the number and activity of $Lgr5^+$ ISCs and induce a peroxisome proliferator-activated receptor (PPAR)-δ-associated metabolic program. These changes increase organoid-forming capacity, but they can also increase susceptibility to tumours[47,48]. Greater stemness therefore does not necessarily mean better regenerative health.

Chronic alcohol exposure reduces Lgr5 and Bmi1 expression and disrupts β-catenin signalling *in vivo*. In *ex vivo* organoids, 0.20% alcohol reduces growth and budding[49]. These findings provide a plausible stem cell-level explanation for persistent barrier dysfunction.

The intestinal clock regulates regeneration. Brain and muscle ARNT-like protein 1 (BMAL1) in epithelium imposes a 24 hour rhythm on proliferation after injury, and BMAL1 loss disrupts both circadian organization and the regenerative response to gastrointestinal radiation injury[50]. Chronic stress elevates corticosterone, reduces ISC abundance and proliferation, and exacerbates experimental colitis. In mice, corticosterone acts through nuclear receptor subfamily 3 group C member 1 (NR3C1), FK506-binding protein 5 (FKBP5), reduced AKT protein kinase B (PKB), also called AKT serine/threonine kinase) phosphorylation, and nuclear Forkhead box O (FOXO) signalling[51].

Age-related changes in the gut microbiome affect the regenerative capacity of ISCs. It was recently discovered that aging shifts the composition of the intestinal microbiota, which suppresses canonical Wnt signalling through the transcription factor Ascl2 in ISCs. Notably, elevated levels of the bacterium *Akkermansia muciniphila* in the aged gut were shown to drive downregulation of Ascl2-mediated Wnt signalling and impair stem cell regeneration. Ultimately, transferring microbiota from young mice restored ISC function in aged mice, highlighting gut microbiome modulation as a potential therapeutic strategy to

combat age-related intestinal decline[52]. In particular, microbial metabolites can influence ISC-mediated repair. In a mouse colitis model, Blautia coccoides-derived indole-3-lactic acid was converted by commensals to indole-3-propionic acid, which activated homeodomain-only protein homeobox (HOPX)+ ISCs and accelerated epithelial repair[53].

In summary, dietary energy state and high-fat feeding alter ISC function and tumour susceptibility in mice, often through Paneth cell or metabolic niche mechanisms, although the relevance of these findings in humans remains plausible but indirect. Increased stemness or crypt expansion is not inherently beneficial because a high-fat diet can increase tumorigenic potential. Key gaps are dose/timing studies in humans and validated mucosal regenerative-reserve endpoints.

6. Lung Stem Cells, Lifestyle, and Environmental Modulators

The distal lung is maintained by alveolar type 2 (AT2) cells and bronchioalveolar stem cells (BASCs). Lung-niche senescence is unusual because p16-positive basement membrane fibroblasts can act as reparative sentinels rather than uniform pathogenic cells[54]. This finding cautions against interpreting all p16-positive cells as targets for indiscriminate senolysis.

Cigarette smoke not only destroys alveolar epithelium; it can also reprogram AT2 cells. In mice exposed to smoke for three months, AT2 cells increased in number, showed greater organoid-forming capacity and apoptosis resistance, and acquired inflammatory and circadian-rhythm transcriptional programs[55]. Such expansion may represent maladaptive selection rather than improved regeneration.

Particulate exposures can also promote oncogenic expansion of lung progenitors. Fine particulate matter has been reported to promote lung tumorigenesis by reprogramming mutant progenitor cells[56]. Similar to smoking-associated clonal haematopoiesis, the relevant mechanism may be selective expansion rather than simple cellular damage.

7. Liver Progenitor Cells and Ethanol

Most evidence comes from alcohol-related *in vitro* and animal studies. Direct evidence that lifestyle change restores endogenous progenitor competence in humans is limited. In primary human liver stem/progenitor cells, ethanol suppresses BrdU incorporation and cyclin D1 expression while inducing a myofibroblast-like phenotype characterized by loss of E-cadherin and increased collagen I, α-smooth muscle actin (α-SMA), and Snail expression[57]. Chronic ethanol exposure can also induce oxidative stress, special AT-rich sequence-binding protein 2 (SATB2), and stem-like hepatocyte programs[58]. These processes may contribute to fibrosis and hepatocarcinogenesis rather than productive regeneration. Key gaps include longitudinal human tissue studies and measures of regenerative reserve that are independent of fibrosis severity.

8. Skin Stem Cells and Environmental Modulators

Skin is well suited to studies of circadian stem cell regulation because it is exposed to daily variation in ultraviolet radiation, temperature, and microbial exposure. In human epidermal stem cells, core clock genes show phased expression across the 24 hour cycle, creating temporal windows for proliferation and differentiation[59,60].

Age-related niche stiffening can impair epidermal stem cell function. Reduced dermal vascular support increases tissue stiffness and activates Piezo-type mechanosensitive ion channel component 1 (PIEZO1) in interfollicular epidermal stem cells, providing a mechanotransductive link between vascular aging and epidermal decline[61].

Low-dose ionizing radiation causes skin cancer in mice and has distinct effects on epidermal stem cell populations[2]. Airborne ultrafine particles impair human keratinocyte stem cell function and may contribute to skin aging phenotypes beyond ultraviolet-driven photoaging[62].

9. Cardiac Stem Cells

Cardiac aging illustrates how expansion of a stem/progenitor compartment can coexist with impaired competence. In Fischer 344 rats aged 4−28 months, the number of cardiac stem cells per niche increased; however, the proportion expressing inhibitor of cyclin-dependent kinase 4A (p16INK4a) also increased, consistent with impaired clearance and senescent cell accumulation[63].

Direct lifestyle evidence for the cardiac compartment remains limited. Exercise can reduce inflammatory hematopoietic output that contributes to myocardial inflammation[64], whereas particulate exposure is associated with cardiovascular injury. However, the senescence biology of endogenous cardiac stem cells has not been established as a major mediator of these effects in humans.

10. Mesenchymal Stem Cells, Adipose Progenitors, and the Niche

10.1 Mesenchymal Stem Cells

Aged bone marrow mesenchymal stem cells (MSCs) show reduced osteogenic potential and increased adipogenic bias. In mice, physical activity increases bone-marrow (BM)-MSC abundance, enhances osteogenic differentiation, and reduces adipogenic differentiation[65]. Endurance exercise can also mobilize developmentally early stem cell populations into peripheral blood and increase their representation in bone marrow[66]. These observations should not be generalized across all MSC sources or to clinical cell therapy products.

10.2 Brown Adipose Progenitors and Cold Exposure

Cold exposure expands brown adipose tissue by inducing the proliferation of both mature brown adipocytes and stromal-vascular progenitors through β3-adrenergic signalling. In mice, cold housing increased Ki67 + mature brown adipocytes within one day and increased Ki67 + stromal-vascular cells by day five, while β3-adrenergic blockade attenuated both responses[67].

Figure 2 provides an experimental example of an environmental input directly activating an endogenous progenitor compartment. Cold exposure increased proliferation in mature adipocytes within one day and in the stromal-vascular compartment more gradually by day five. Both effects depended on β3-adrenergic signalling.

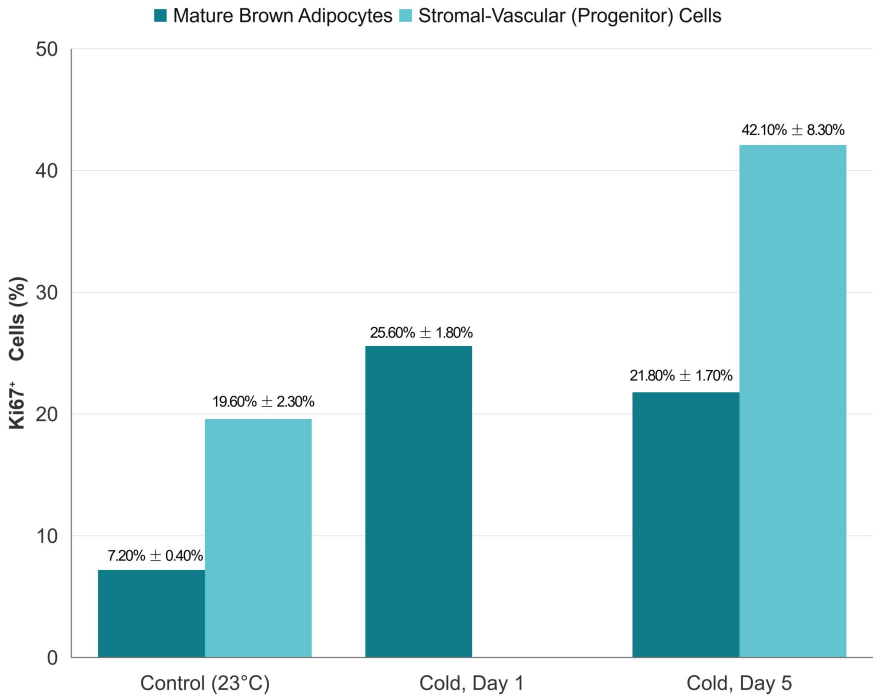


Figure 2. Cold exposure drives proliferation of brown-adipose progenitors and mature brown adipocytes in a mouse model. The graph shows the percentage of Ki67-positive cells among mature brown adipocytes and stromal-vascular cells from interscapular brown adipose tissue of C57BL/6J mice housed at 23 ℃ or 10 ℃ for 1 or 5 days. The result of stromal-vascular cells at Day 1 was not shown because it is not significantly different from that in control (23 ℃), as indicated in the refence [67]. Copyright: Redrawn from references[67,68].

11. Cross-Cutting Endocrine, Environmental and Lifestyle Modulators

Several lifestyle and environmental axes operate across compartments and merit their own framing.

11.1 Endocrine-Disrupting Chemicals and Environmental Toxicants

Endocrine-disrupting chemicals, including bisphenols, phthalates, perfluoroalkyl substances, dichlorodiphenyltrichloroethane (DDT), and dioxins, can act through hormone-responsive pathways in stem and progenitor cells. Reported mechanisms include altered endocrine signalling, DNA damage, epigenetic remodelling, oxidative stress, and changes in gene expression, with potential consequences for obesity, infertility, developmental abnormalities, and cancer[69]. A systematic review identified pesticides, tobacco smoke, radiation, and heavy metals as major toxicant classes linked to stem cell aging, often through oxidative stress and potentially persistent epigenetic effects[70].

11.2 Combined Nutrition and Exercise Interventions

Nutritional interventions, including calorie restriction and fasting-mimicking diets, may influence stem cell resilience through 5'-AMP-activated protein kinase (AMPK)-related, mechanistic target of rapamycin (mTOR)-related, and autophagy-related metabolic reprogramming. Exercise may act through mechanosensitive pathways and systemic factors. However, combined lifestyle interventions have not yet been shown to rejuvenate endogenous stem cell compartments in humans. Claims regarding polyphenol bioavailability also extend beyond the available evidence[71].

12. Regulatory Mechanisms of Senescence and Rejuvenation by Lifestyle and Environmental Factors

Stem cell aging does not reflect a uniform loss of cells. In most tissues, stem cell function declines with age even when stem cell abundance is maintained. Their functional decline reflects age-related changes in the genome, epigenome, and proteome. Some changes are cell autonomous, whereas others arise from alterations in the local niche or systemic environment. Many epigenomic and proteomic changes may be reversible through environmental or genetic interventions[72].

Cellular senescence is a stable state of cell cycle arrest accompanied by a characteristic senescence-associated secretory phenotype (SASP). It is a major mechanism underlying age-related functional decline. The Bmi1/INK4a-ARF axis is a central regulatory hub. Bmi1 represses genes that promote cellular senescence and cell death[73], and it is required to maintain adult stem cells in several tissues. Loss of Bmi1 relieves this repression, increases p16INK4a and p19 alternative reading frame (p19ARF) protein expression, and promotes irreversible cell cycle arrest and the SASP. These changes can reduce stem cell function and alter the surrounding niche. Senescence can therefore act directly on stem cells or indirectly through the niche. Senescent p16-positive niche cells may be harmful because their SASP disrupts nearby stem cells.

In other settings, however, they may have a protective, sentinel-like role, as discussed above. In aged bone marrow, senescent mesenchymal stromal cells provide less effective support for HSCs and contribute to metabolic dysfunction in hematopoietic

progenitors[6,70]. Across tissues, recurrent drivers include (1) DNA damage and replication stress, (2) ROS and mitochondrial dysfunction, (3) impaired autophagy, (4) epigenetic drift, (5) niche stiffening and SASP-driven inflammaging, and (6) selection of premalignant clones. Lifestyle and environmental factors can influence each of these processes (**Figure 3**).

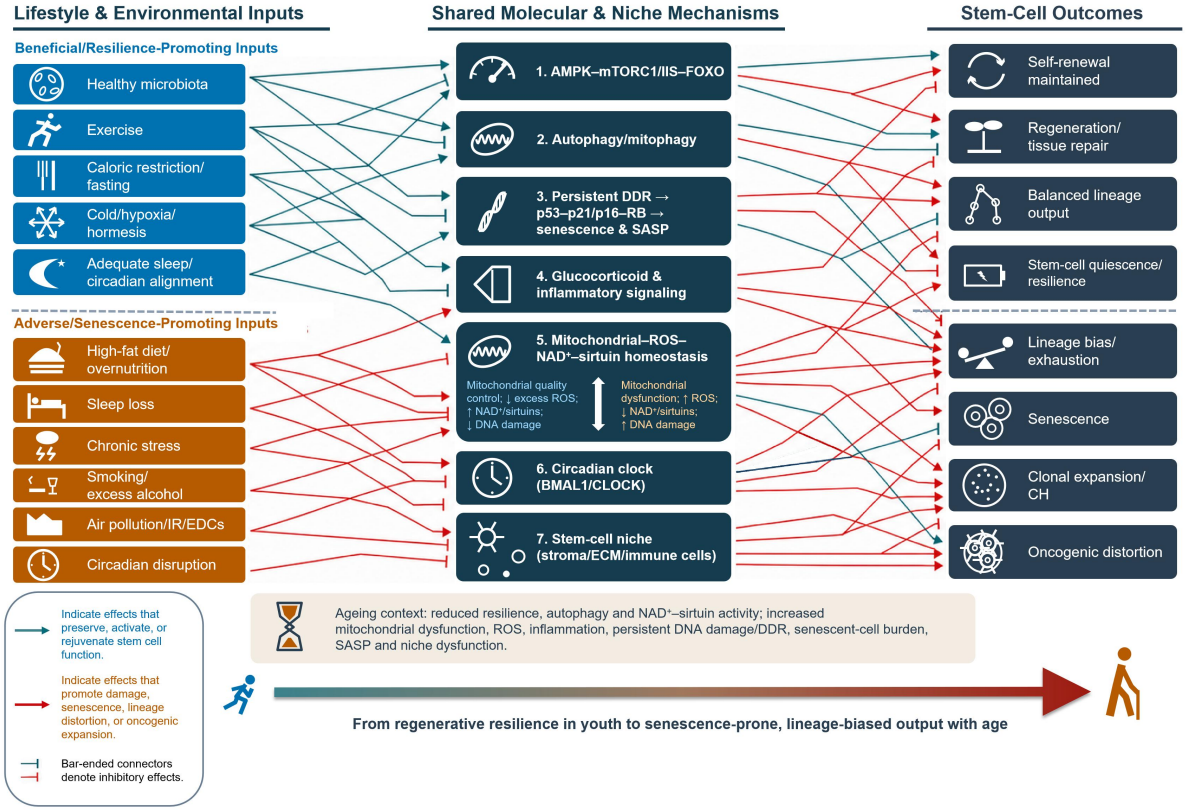


Figure 3. Shared molecular pathways through which lifestyle and environmental factors influence endogenous stem cell senescence and regenerative output. Lifestyle and environmental inputs (left) converge on a limited set of intracellular and niche-level mechanisms (centre), which then determine stem cell outcomes (right). The figure shows representative connections and additional pathways that are discussed in the text. Aging progressively shifts this integrated network from regenerative resilience toward senescence-prone and lineage-biased output. The diagram collectively synthesizes representative findings from human observational and intervention studies, animal models, organoids, *ex vivo* tissues and *in vitro* experimental systems. The figure does not imply that every depicted relationship has been independently demonstrated in humans. The full names for the abbreviations presented solely in the figure include: p16-RB for p16INK4a–retinoblastoma (pRb) pathway, clonal expansion/CH for clonal expansion and clonal hematopoiesis, DDR for DNA damage response, IIS-FOXO for insulin/insulin-like growth factor-1 signaling (IIS) pathway and its primary downstream effector, the forkhead box O (FOXO) family of transcription factors. NAD for nicotinamide adenine dinucleotide, and ECM for extracellular matrix. Copyright: The figure was created in Microsoft PowerPoint with AI assistance (ChatGPT 5.0).

A common set of mechanisms recurs across tissues and exposures. **Figure 3** shows how lifestyle and environmental inputs converge on shared molecular and niche pathways, which then shape stem cell outcomes. Caloric restriction provides a clear example. A 40% reduction in caloric intake lowers circulating insulin/IGF-1 levels and amino acid availability. This suppresses mTORC1 in intestinal Paneth cells, the niche cells located beside Lgr5-positive ISCs[43]. Reduced mTORC1 activity increases Bst1 expression. Bst1 is a cell-surface ectoenzyme that generates extracellular cyclic adenosine diphosphate ribose (ADPR)-ribose. Paneth cell-derived cyclic ADP-ribose then acts on nearby Lgr5-positive ISCs to promote self-renewal and organoid formation[43]. The overall effect is an increase in ISC abundance and improved crypt regeneration. Paneth cell-specific inhibition of mTORC1 or treatment with rapamycin produces similar effects. These findings indicate that the Paneth cell niche, rather than the ISC itself, is the primary cellular target.

This example also illustrates the broader logic of **Figure 3**. Caloric restriction does not act directly on stem cells. Instead, Paneth cells detect the dietary input and transmit it through the shared mTORC1 pathway. This niche signal then promotes stem cell self-renewal. Most connections in **Figure 3** follow the same three-step sequence: input, niche or intracellular pathway, stem cell outcome. The direction of the effect depends on the pathway involved and whether it is activated or inhibited.

The main pathways are summarized below:

(i) mTORC1 and AMPK link nutritional status to stem cell self-renewal. Examples include Paneth cell mTORC1 during caloric restriction, PPAR-delta/fatty acid oxidation during a high-fat diet, and AMPK signalling in muscle stem cells and HSCs during fasting.

(ii) Autophagy can be protective or harmful, depending on the context. It protects aged HSCs from inflammation-driven glycolytic dysfunction, maintains muscle stem cell quiescence, and supports fasting-induced erythropoiesis. In contrast, it can drive neural stem cell death during chronic stress. Thus, the same machinery may protect a satellite cell from senescence but kill a hippocampal neural stem cell after corticosterone exposure.

(iii) The p16INK4a/SASP axis is harmful in bone marrow

niche cells, aged cardiac stem cells, and muscle satellite cells (MuSCs). In aged cardiac stem cells, impaired clearance allows senescent cells to accumulate. By contrast, p16-positive fibroblasts in the lung basement membrane may have a protective sentinel function. Senolytic strategies may therefore need to be tissue-specific rather than systemic.

(iv) ROS are a common mediator of low-dose radiation, PM2.5 exposure, ethanol-derived acetaldehyde, smoking, and inflammation. HSCs are especially sensitive to ROS through the p38/MAPK14 pathway.

(v) Mitochondrial dynamics, including the balance between fission and fusion and the control of mitophagy, influence muscle stem cell competence. These processes also interact with the metabolic effects of caloric restriction and fasting.

(vi) Glucocorticoids translate psychological stress into stem cell-specific senescence programs. In NSC, they promote autophagic death through SGK3. In ISC, they act through the FKBP5-AKT-FOXO pathway. In hematopoietic stem and progenitor cells, they promote myeloid bias.

(vii) The circadian clock regulates the timing of stem cell proliferation in the skin and gut. It also interacts with the effects of sleep loss and fragmentation on hematopoietic stem and progenitor cells.

(viii) The niche is as important a target of lifestyle factors as stem cells. Key niche cells include Paneth cells for ISCs, leptin-receptor-positive stromal cells and endothelial cells for hematopoietic stem and progenitor cells, basement membrane fibroblasts for AT2 cells, dermal blood vessels for epidermal stem cells, and cardiomyocytes for cardiac stem cells. Many reported rejuvenating effects of young plasma also appear to act through the niche.

A concise rejuvenation framework can therefore be proposed. Tissue-specific stem cells maintain tissue homeostasis and support repair. With age, however, changes in stem cell function contribute to declining organ function and age-related disease. Potential rejuvenation strategies include environmental interventions such as diet and exercise, heterochronic approaches, and cellular reprogramming[74].

13. Translational Implications

13.1 Measuring Regenerative Reserve in Humans

Regenerative reserve should be defined as the tissue-specific ability to maintain homeostasis and recover after a defined stressor. Stem cell abundance alone is not sufficient. Candidate measures include: (i) functional performance, such as vaccine response and blood cell recovery for haematopoiesis, strength and recovery after standardized exercise for muscle, and epithelial barrier or wound-healing dynamics where appropriate; (ii) circulating and tissue biomarkers of inflammation, clonal haematopoiesis, senescence, and matrix remodelling; (iii) imaging or histologic measures of tissue structure; and (iv) mechanism-linked molecular markers used as exploratory pharmacodynamic endpoints. No single biomarker currently provides a validated measure of whole-body regenerative reserve.

13.2 Clinical Trial Design and Safety

Early clinical studies should enrol people with a defined functional deficit or exposure-related risk. They should specify a functional primary endpoint in advance. Molecular measures of stem cells or their niches should be used to test mechanism, not as substitutes for clinical benefit. One practical approach is a randomized lifestyle or exposure-reduction intervention with baseline stratification by age, sex, tissue function, inflammatory state, and relevant genotype or clonal status. Sampling should capture both early pharmacodynamic effects and durable functional outcomes. Safety monitoring should include clonal expansion, dysplasia or malignancy signals, fibrosis, maladaptive hyperplasia, and loss of protective senescence or quiescence. An intervention should not be considered rejuvenating if it increases progenitor abundance without improving competence or if it improves repair but increases oncogenic risk.

13.3 Evidence Gaps and Research Priorities

Major gaps include lack of validated measures of human regenerative reserve, limited longitudinal tissue sampling, uncertain dose and timing windows, and poor understanding of how exposures interact with sex, genotype, comorbidity, and injury context. Evidence for the cardiac and liver compartments, and for several toxicant-related effects, remains indirect. Future work should prioritize registered human studies with prespecified evidence categories, harmonized tissue and niche endpoints, and long-term safety surveillance. Such studies are more informative than extrapolation from exposure-associated molecular signatures alone.

14. Conclusions

Lifestyle and environmental exposures modulate endogenous stem cell compartments and their niches. However, the direction, magnitude, and relevance of these effects depend on context. Recurrent candidate mechanisms include metabolic sensing, autophagy, mitochondrial and redox regulation, DNA damage responses, p16/p21-associated senescence, circadian programs, immune signalling, and niche remodelling. Evidence is strongest in animal models and mechanistic systems. Direct human evidence remains limited and uneven across tissues. Lifestyle and environment should therefore be viewed as important and potentially modifiable contributors to regenerative reserve, not as factors proven to be equivalent to intrinsic genetic and epigenetic properties. Progress will require tissue-specific human biomarkers, trials centred on functional outcomes, a clear distinction between cell abundance and competence, and long-term monitoring for clonal and oncogenic risks.

Author Contributions

Guangqian Zhou contributed to study conception and design and revised the manuscript. Ting Wang contributed with data collection, preparation of first version of the manuscript, and comments for revisions. All authors have read and agree to the published version of the manuscript.

Artificial Intelligence (AI) Statements

Authors disclose that the figures of this manuscript were polished with the assistance of ChatGPT 5.0. The authors take full responsibility for the accuracy, originality, and integrity of the manuscript and its figures.

Data Availability

This review only applied published data and information.

Conflicts of Interest

No conflict of interest.

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