Aging and Disease
www.aginganddisease.org
Early access date: June 26, 2026
http://dx.doi.org/10.14336/AD.2026.0371

Perspective

Vitamin C, ACSL4, and Ferro-Aging: Mechanistic Insights and Translational Perspectives from Primate Studies

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[Received March 30, 2026; Revised June 17, 2026; Accepted June 23, 2026]

ABSTRACT: The concept of ferro-aging has been proposed as an evolutionarily conserved, iron-driven aging trajectory orchestrated by acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4), which links lipid peroxidation, cellular senescence, and systemic organ decline in primates. Emerging evidence from non-human primate studies suggests that vitamin C (VC), traditionally viewed as a broad-spectrum antioxidant, has been proposed to interact with and inhibit ACSL4 activity at supraphysiological concentrations, potentially reversing multi-omic markers of biological age and preserving neural architecture, functional connectivity, and metabolic homeostasis in aged individuals. However, the precise molecular mechanism of VC-mediated ACSL4 inhibition remains unconfirmed, and the geroprotective efficacy of VC in humans is yet to be validated. This Perspectives critically critically discusses the mechanistic underpinnings of the VC–ACSL4–ferro-aging axis, examines key limitations of current evidence, and highlights the translational potential and unresolved challenges of targeting ferro-aging for promoting healthy aging.

Keywords: ACSL4, ferro-aging, iron; primate, senescence, vitamin C.

For decades, aging research has prioritized identifying druggable, evolutionarily conserved molecular pathways capable of slowing or reversing systemic physiological decline. While iron overload, unchecked lipid peroxidation, and chronic oxidative stress have long been associated with advancing age, a unified, causal mechanism linking these processes to progressive organ dysfunction remained poorly defined. The emerging paradigm of ferro-aging addresses this critical gap, defining a chronic, acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4)-regulated biological program in which iron-dependent lipid peroxidation drives cellular senescence, tissue damage, and multi-organ functional decline across primate species.

A landmark longitudinal study published in *Cell Metabolism* (Liu et al., 2026) offers provocative and potentially transformative insights into ferro-aging regulation: vitamin C (VC), historically regarded as a nonspecific, broad-spectrum antioxidant, has been proposed to interact with and inhibit the activity of

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ACSL4 at supraphysiological concentrations, thereby attenuating ferro-aging signatures and improving healthspan in aged non-human primates [1]. Against this backdrop, this Perspectives critically evaluates the conceptual implications of the ferro-aging framework, dissects key mechanistic uncertainties surrounding the putative VC–ACSL4 interaction, and discusses the substantial translational challenges that must be overcome before these findings can be extended to human aging research and clinical practice.

Ferro-Aging: An Emerging ACSL4-Driven Aging Program

Ferro-aging is driven by progressive, age-dependent tissue iron accumulation, a conserved process that fuels iron-dependent lipid peroxidation through the key effector enzyme ACSL4 [2,3]. With advancing age, labile ferrous iron (Fe^{2+}) gradually accumulates in metabolically active organs, including the liver, brain, skeletal muscle, heart, and adipose tissue. Excess Fe^{2+} catalyzes Fenton reactions, generating reactive oxygen species (ROS) that exacerbate oxidative stress and damage cellular macromolecules. As a critical metabolic regulator, ACSL4 preferentially channels long-chain polyunsaturated fatty acids (PUFAs) into the synthesis of peroxidation-susceptible phospholipids, rendering cellular and organellar membranes highly vulnerable to iron-mediated oxidative damage. In aged humans and non-human primates, pathological iron overload, elevated ACSL4 expression, increased lipid peroxidation and associated cytotoxic by-products [such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)], and canonical cellular senescence markers exhibit consistent spatial co-localization across multiple organs [1], indicating that ferro-aging operates as a systemic, coordinated program rather than an isolated tissue-specific event.

While direct genetic evidence linking specific ACSL4 polymorphisms to the rate of biological aging is still emerging, accumulating data highlight its role in various age-related pathologies, analogous to the well-established APOE ε4 variant in Alzheimer's disease and brain aging [4]. The *ACSL4* gene is located on human chromosome Xq23.1, and its dysregulation has been implicated in a spectrum of conditions associated with advanced age, including neurodegenerative disorders, cardiovascular disease, and certain cancers [5]. For instance, a common single-nucleotide polymorphism (SNP) in the first intron of the *ACSL4* gene has been associated with altered fatty acid composition in plasma phosphatidylcholines of patients with metabolic syndrome, a condition closely linked to accelerated aging [6].

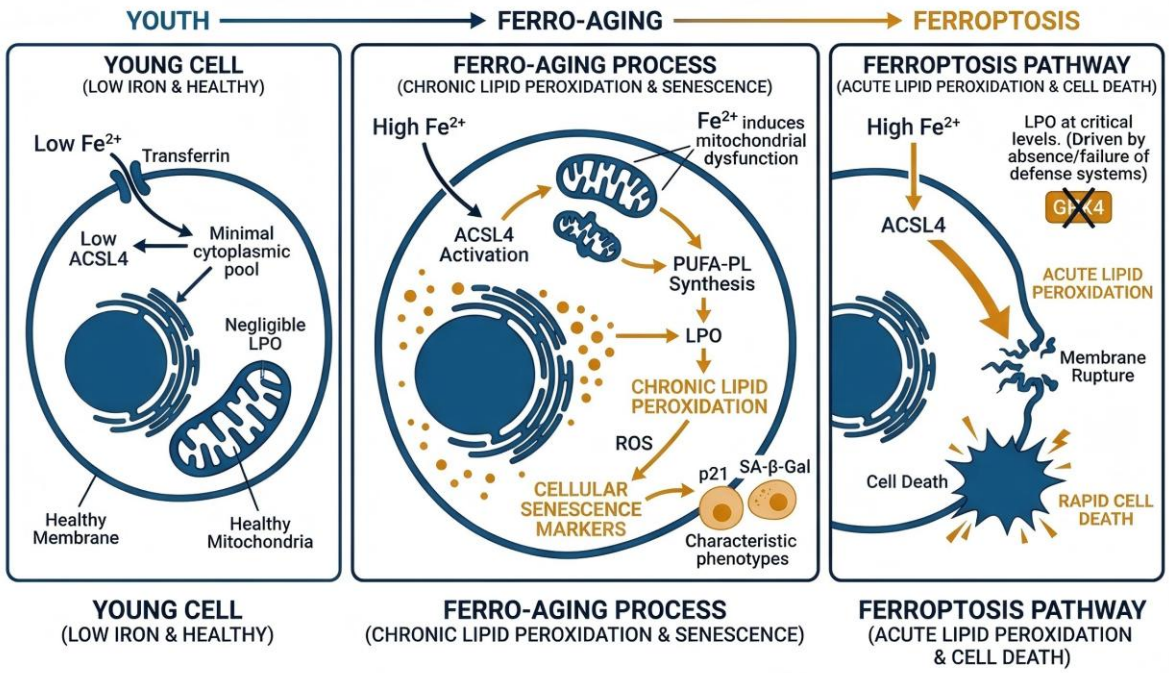

Figure 1. Ferro-aging molecular cascade. A molecular architecture delineating ferro-aging clarifies the mechanistic sequence in which iron overload initiates acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4)-mediated lipid peroxidation, thereby propelling cellular senescence and ultimately fostering systemic aging. Notably, this schematic distinguishes ferro-aging—characterized as a chronic pro-senescent condition—from ferroptosis, which represents an acute mode of regulated cell death.

Furthermore, ACSL4 expression is particularly abundant in the brain and liver, organs highly susceptible to age-related decline, suggesting that genetic variations affecting its activity could modulate the vulnerability of these organs to ferro-aging processes. Future genome-wide association studies (GWAS) and Mendelian randomization analyses are needed to systematically explore the impact of *ACSL4* genetic variants on aging trajectories and lifespan.

A fundamental and clinically relevant distinction exists between ferro-aging and ferroptosis: ferroptosis is an acute, iron-dependent form of regulated cell death driven by catastrophic lipid peroxidation, with evidence supporting its propagation between cells via lipid peroxidation-dependent signaling [7]; in contrast, ferro-aging represents a chronic, sub-lethal, pro-senescent, and systemic aging program characterized by persistent low-grade lipid peroxidation, progressive cellular dysfunction, and cumulative organ damage (Fig. 1). Beyond ACSL4, other members of the ACSL family exert divergent functions in lipid metabolism and ferroptosis/ferro-aging. ACSL3 mediates mono-unsaturated fatty acid (MUFA) metabolism and counteracts ferroptosis [8]. Consistently, ACSL3 also plays a protective role in ferro-aging by mitigating chronic PUFA peroxidation. ACSL1 mainly regulates general fatty acid metabolism and has no prominent regulatory effect on iron-driven lipid peroxidation or ferro-aging progression. This key dichotomy positions ACSL4 as a potentially actionable therapeutic target for modulating aging and age-related diseases, though important caveats must be acknowledged. ACSL4 is not merely a driver of ferro-aging; it also mediates essential physiological functions, particularly in innate immunity, where it supports lipid remodeling in macrophages and microglia, promotes the synthesis of eicosanoid inflammatory mediators, and shapes the tumor immune microenvironment [5,9,10]. While genetic ablation of ACSL4 in preclinical murine models ameliorates age-related degenerative phenotypes without overt developmental abnormalities [11], the long-term consequences of systemic ACSL4 suppression on immune homeostasis, host defense, and tissue repair remain underexplored and require rigorous investigation.

Vitamin C: Proposed ACSL4 Inhibition and Dual Redox Effects

The provocative proposal that VC directly inhibits ACSL4 has reshaped conventional views of its biological role beyond a generic antioxidant; however, the underlying mechanistic evidence remains incomplete, preliminary, and not yet definitive. It should be emphasized that VC is not a specific inhibitor of ACSL4. Biochemical pulldown experiments, in silico molecular docking simulations, and in vitro enzymatic inhibition studies collectively suggest thatliquid chromatography-tandem mass spectrometry, molecular docking models, and in vitro enzymatic assays confirms that supraphysiological concentrations of VC may interact with the catalytic cleft of ACSL4, putatively engaging key conserved residues (Thr278, Ser279, and Thr469) to suppress enzymatic activity in a dose-dependent manner [1]. Of note, the reported half-maximal inhibitory concentration (IC50) for this effect is approximately 280 μM, which is several-fold higher than typical physiological VC levels in human plasma (50–100 μM) and substantially exceeds the Michaelis constant (Km) of ACSL4 for ATP (~10 μM), raising questions about the physiological relevance of this interaction under normal homeostatic conditions [12]. Furthermore, site-directed mutagenesis of the proposed VC-interacting residues results in severe loss of basal ACSL4 catalytic activity, confounding the interpretation of whether these residues mediate specific ligand binding or are simply essential for enzyme structure and function. To date, critical biochemical validation—including direct measurement of binding affinity (Kd), formal assessment of ATP-competitive inhibition kinetics, and structural confirmation of the VC–ACSL4 complex—remains absent, leaving the direct inhibitory mechanism unproven.

Beyond its putative direct interaction with ACSL4, VC exerts a well-characterized spectrum of indirect antioxidant and redox-regulatory effects that independently mitigate oxidative stress and cellular senescence. As a primary water-soluble antioxidant, VC directly scavenges ROS, including superoxide anion, hydroxyl radicals, and singlet oxygen, thereby neutralizing oxidative damage to lipids, proteins, and DNA. Additionally, VC modulates cellular iron redox cycling by reducing ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which can paradoxically limit iron overload-driven Fenton reactions under certain contexts [13]. A key downstream effect of VC is the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant response pathway, which transcriptionally upregulates a battery of cytoprotective genes involved in ROS detoxification, glutathione synthesis, and redox homeostasis. Notably, genetic expression of a constitutively active Nrf2 mutant recapitulates the anti-aging and anti-ferro-aging phenotypes induced by VC supplementation, with no additional benefit observed upon combined VC treatment—indicating that VC and Nrf2 converge on a unified cytoprotective program [14]. Collectively, these dual (putative direct and confirmed indirect) mechanisms provide a plausible explanation for why traditional broad-spectrum antioxidants have consistently underperformed in aging research: they lack molecularly targeted actions against core aging drivers

like ACSL4, whereas VC uniquely combines putative targeted modulation of the ferro-aging effector ACSL4 with broad, systemic redox-protective effects. The conceptual framework of ferro-aging and the proposed mechanism of VC action are illustrated in Figure 2.

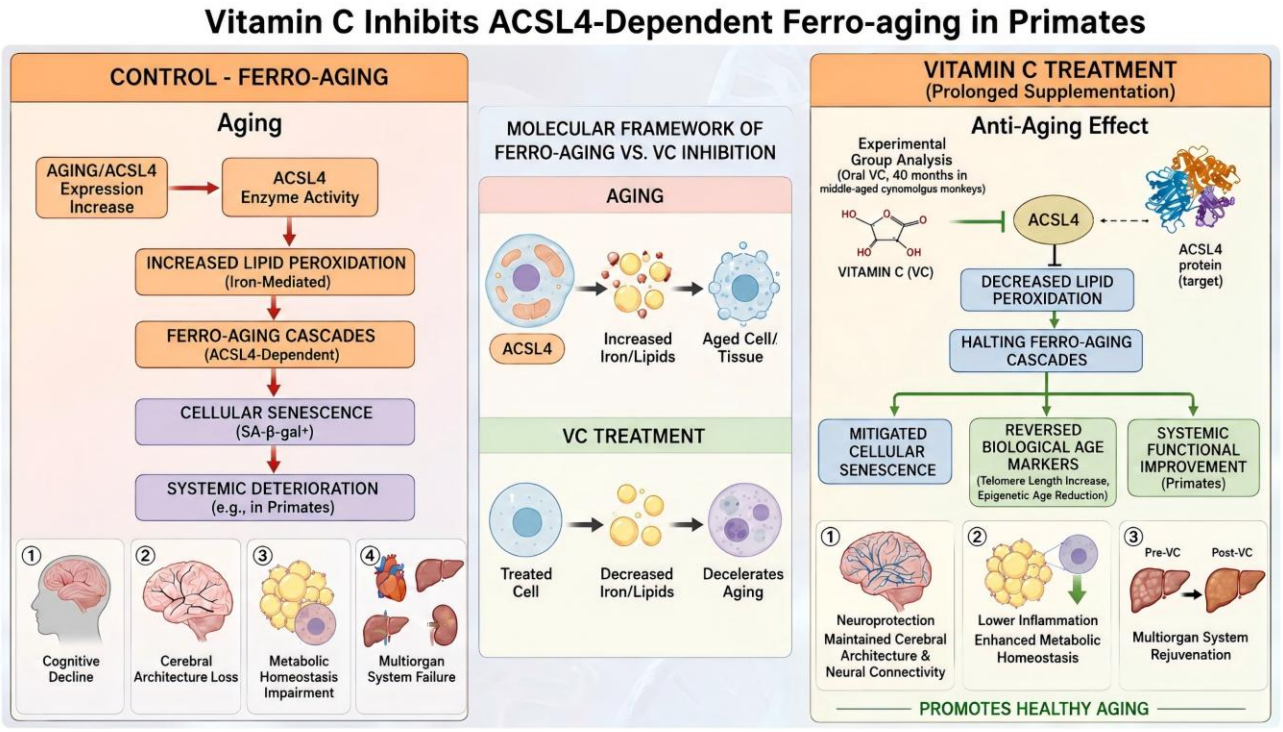

Figure 2. Evolutionarily conserved metabolic cascades underpin the aging process, with iron-dependent lipid peroxidation identified as a pivotal and therapeutically targetable mechanism. Recently conceptualized as "ferro-aging", this chronic, iron-initiated, and acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4)-mediated trajectory precipitates cellular senescence and systemic functional deterioration in primates, distinguishing it fundamentally from acute ferroptosis. Landmark study establishes vitamin C (VC) as a direct and specific inhibitor of ACSL4, effectively halting ferro-aging in human cellular models and reversing biological aging markers in non-human primates following long-term supplementation. VC treatment diminishes ferro-aging signatures, maintains cerebral architecture and connectivity, enhances metabolic homeostasis, and mitigates multi-organ senescence. This Perspective elucidates the molecular framework of ferro-aging, the dual-mode action of VC, its systemic geroprotective impacts in primates, translational prospects for human health, policy ramifications, and critical future research avenues. We posit that the VC–ACSL4–ferro-aging axis constitutes a novel paradigm for developing accessible, safe, and scalable interventions to promote healthy aging.

It is crucial to acknowledge the potential non-specificity of VC as an ACSL4 inhibitor. While in vitro studies suggest direct interaction, VC is a known antioxidant with pleiotropic effects on cellular redox status. Its ability to reduce Fe^{3+} to Fe^{2+} could, paradoxically, enhance Fenton chemistry under certain conditions, and its activation of the Nrf2 pathway provides broad cytoprotection independent of ACSL4. Therefore, the observed anti-ferro-aging effects in primates may result from a combination of these indirect effects rather than specific ACSL4 inhibition alone.

Moreover, the use of supraphysiological doses of VC raises significant safety concerns. High-dose VC supplementation increases urinary excretion of oxalate, a metabolite of VC, which can lead to the formation of calcium oxalate kidney stones in susceptible individuals [15]. Several clinical cases have reported nephrotoxicity, including acute kidney injury and end-stage renal disease, associated with megadoses of intravenous VC, particularly in patients with pre-existing renal impairment or those receiving renal replacement therapy. A daily oral dose exceeding 1000 mg has been associated with an increased risk of kidney stone formation in men [16,17]. These potential adverse effects necessitate careful consideration of the risk-benefit profile before advocating for high-dose VC as a geroprotective strategy in humans.

Primate Evidence: Safety and Systemic Geroprotective Effects

To rigorously evaluate the geroprotective potential of VC in a biologically relevant model, a 40-month, placebo-controlled longitudinal trial was conducted in middle-aged cynomolgus monkeys (*Macaca*

fascicularis), a non-human primate species that closely recapitulates key features of human aging, iron metabolism, and age-related organ decline. The study employed chronic oral VC supplementation at 30 mg/kg/day, a dose selected to achieve sustained supraphysiological circulating levels without inducing acute toxicity. Over the entire trial period, the VC regimen was excellently tolerated, with no detectable adverse events, abnormal clinical signs, or significant perturbations across 70 monitored physiological and biochemical parameters, including hematology, serum biochemistry, organ function, and body weight [1].

Table 1. Systemic geroprotective effects of long-term vitamin C supplementation in aged non-human primates.

Category	Assay / Index	Effect of Vitamin C	Biological significance
Safety & Tolerability	70 longitudinal physiological and biochemical parameters	Safe, well-tolerated, no adverse events	Suitable for long-term clinical translation
Ferro-aging inhibition	Serum Fe^{2+}	↓	Reduced systemic iron overload
	Tissue ACSL4 expression	↓	Blocked core ferro-aging executor
	Lipid peroxidation (MDA, 4-HNE)	↓	Attenuated oxidative membrane damage
	Hepatic hepcidin	↓	Restored systemic iron homeostasis
Biological age reversal	DNA methylation age	↓ (max –5.91 years)	Epigenetic rejuvenation
	Transcriptomic age	↓ (max –5.67 years)	Transcriptional rejuvenation
	Cell-type-specific aging clock	↓ (microglia –7.39 years)	Cell-type-resolved rejuvenation
Brain structure & function	Frontal cortical surface area	↑	Prevented age-related brain atrophy
	Brain structural connectivity	↑	Restored neural network integrity
	Microgliosis / astrogliosis	↓	Reduced neuroinflammation
	Aβ aggregation	↓	Alleviated proteinopathy
Metabolic health	Plasma insulin	↓	Improved insulin sensitivity
	Glucose tolerance	↑	Better glycemic control
	Triglycerides	↓	Improved lipid profile
	HDL-C	↑	Enhanced cardioprotection
	Visceral fat mass	↓	Reduced metabolic aging
	Liver function (albumin, bile acids)	Improved	Attenuated hepatic aging
Multi-organ senescence	Cardiac p21/S100A8	↓	Reduced cardiac senescence
	Lung p21 / IL-6 / H3K9me3	↓ / ↓ / ↑	Alleviated lung aging & inflammation
	Renal p21 / H3K9me3	↓ / ↑	Improved kidney homeostasis
	Pancreatic p21	↓	Preserved islet function

Note: ↑ = significantly increased; ↓ = significantly decreased. All effects were observed in middle-aged cynomolgus monkeys (*Macaca fascicularis*) treated with 30 mg/kg/day oral vitamin C for 40 months. The link between observed effects and the proposed ferro-aging program remains subject to further mechanistic validation.

Comprehensive multi-omic, histological, and imaging analyses revealed profound, systemic geroprotective effects of VC supplementation, summarized as follows: (i) Attenuated ferro-aging signatures: Transcriptomic profiling across multiple tissues demonstrated significant downregulation of ferro-aging-associated gene networks, alongside reduced expression of canonical molecular markers of iron overload, lipid peroxidation, and cellular senescence. (ii) Improved iron homeostasis and reduced oxidative damage: Chronic VC supplementation significantly lowered circulating Fe^{2+} levels, suppressed tissue-specific ACSL4 expression in vulnerable organs, and markedly reduced systemic accumulation of lipid peroxidation by-products (MDA and 4-HNE), mitigating oxidative membrane damage. (iii) Preserved brain structure and neural connectivity: Quantitative neuroimaging analyses confirmed maintained frontal cortical surface area and restored structural connectivity within key brain networks, counteracting age-related atrophy and disconnection. (iv) Enhanced metabolic health: VC supplementation improved glucose tolerance and insulin sensitivity, normalized dysregulated lipid metabolism (reduced triglycerides, elevated HDL-cholesterol), and preserved hepatic function, alleviating age-related metabolic decline. (v) Reversed biological age: Multi-tissue aging clock analyses—including epigenetic (DNA methylation), transcriptomic, and metabolomic clocks—consistently demonstrated significant reversal of biological age, independent of chronological age.

Notable rejuvenation effects were most pronounced in the brain, liver, pancreas, and adipose tissue—organs particularly vulnerable to iron-mediated ferro-aging due to high metabolic activity and iron accumulation.

Advanced neuroimaging further validated preserved cortical volume and parietal network connectivity, supporting the maintenance of cognitive integrity and motor function in aged monkeys. Collectively, this landmark study provides preliminary but rigorous long-term evidence in non-human primates that a safe, orally bioavailable, and widely accessible nutrient can mitigate multi-dimensional biological aging and preserve organ function in late life. The systemic geroprotective effects of long-term VC supplementation are summarized in Table 1.

Translational Implications and Limitations

These findings offer three key translational perspectives for aging research and geroprotection, each accompanied by critical caveats that temper overinterpretation and premature clinical extrapolation: (i) Ferro-aging as a modifiable, integrated aging pathway. The ferro-aging framework unifies dysregulated iron homeostasis, perturbed lipid metabolism, chronic redox imbalance, and cellular senescence into a single, interconnected molecular axis that drives age-related cerebral decline and metabolic dysfunction [18,19]. At the core of this axis, ACSL4 functions as a key metabolic node that links lipid remodeling to aging trajectories, operating in parallel with well-established aging hallmarks—including mitochondrial dysfunction, chronic inflammation, loss of proteostasis, telomere attrition, and epigenetic dysregulation. Unlike many aging pathways that are tissue-specific or context-dependent, ferro-aging appears to act systemically across multiple organs, making it a broadly relevant target for intervention. (ii) VC as a promising but unproven geroprotective candidate. VC stands out as an attractive candidate for anti-aging interventions due to its low cost, oral bioavailability, widespread dietary accessibility, and excellent safety profile in non-human primates. However, its translational potential is constrained by conflicting human epidemiological data: large-scale clinical cohorts and observational studies in developed populations have consistently reported neutral or inconsistent effects of VC supplementation on mortality, cardiovascular disease, cancer, and other chronic age-related conditions [20,21]. Importantly, the beneficial effects observed in middle-aged cynomolgus monkeys are preliminary, primate-specific, and not yet validated in humans. Direct extrapolation to human populations is therefore unwarranted, and rigorous clinical trials are essential to confirm efficacy, define optimal dosing, and assess long-term safety. (iii) Combination therapy potential with mechanistic compatibility constraints. VC's multi-modal mechanism of action—putative ACSL4 inhibition plus broad antioxidant and Nrf2-activating effects—suggests potential synergies with other anti-aging strategies that target complementary aging pathways. Rational combinations may include agents that clear senescent cells (senolytics), restore proteostasis, reduce chronic inflammation, or enhance antioxidant defenses (e.g., spermidine, Nrf2 activators, sirtuin modulators) [22]. However, mechanistic compatibility is critical to avoid antagonistic interactions. For example, metformin, which has been linked to pro-ferroptotic effects in certain contexts, would conflict with VC's anti-ferro-aging actions and requires rigorous preclinical safety and efficacy testing before any combinatorial use can be considered [23]. Future research should prioritize designing mechanism-aligned combination regimens that amplify geroprotection without counterproductive cross-talk. It is also critical to note the limitations of current lipid oxidation markers. MDA and 4-HNE are general lipid peroxidation products and cannot specifically reflect PUFA peroxidation associated with ferro-aging or ferroptosis. To date, there remains a lack of fully validated, highly specific in vivo biomarkers for ferroptosis and ferro-aging, which hinders accurate evaluation of intervention efficacy in preclinical and clinical studies.

Future Research Directions

Despite the promising primate findings, several critical knowledge gaps and unresolved challenges must be addressed to advance the ferro-aging concept and VC-based interventions toward clinical translation. These priorities are outlined below:

1) Age-dependent efficacy and optimal therapeutic windows. The geroprotective effects of VC may exhibit profound age-dependent variability, yet the optimal life stage for intervention remains undefined. Midlife may represent a critical window, when iron burden and ACSL4 activity begin to rise, while tissue repair capacity and cellular resilience remain relatively preserved—potentially enabling robust reversal of early ferro-aging signatures. In contrast, late-life interventions may be less effective due to accumulated irreversible damage, widespread cellular senescence, and tissue remodeling that limit functional recovery. Systematic, age-stratified preclinical studies across the lifespan are essential to define the timing, duration, and persistence of VC effects.

2) Tissue-specific ACSL4 inhibition to minimize off-target risks. Systemic ACSL4 suppression may disrupt essential physiological functions, including innate immune responses, lipid homeostasis, and inflammatory signaling. Developing potent, selective, tissue-restricted ACSL4 inhibitors—such as liver- or brain-targeted prodrugs, nanoparticle formulations, or cell-type-specific gene silencing tools—could selectively block ferro-aging

in vulnerable organs while preserving immune and metabolic homeostasis. Such precision-targeted agents may outperform VC in potency, selectivity, and safety for long-term anti-aging applications.

3) Pharmacokinetic–pharmacodynamic (PK/PD) relationships and tissue bioavailability. A major limitation of current primate data is the absence of direct measurements of VC concentrations in target tissues (e.g., brain, liver, adipose, muscle). Without these data, it is impossible to establish causal PK/PD links between local VC bioavailability, ACSL4 occupancy, lipid peroxidation suppression, and observed phenotypic improvements. Future studies must integrate tissue-specific VC quantification, ACSL4 activity assays, and target engagement biomarkers to validate mechanism and optimize dosing regimens.

4) Standardized quantitative metrics and consensus biomarkers for ferro-aging. The field currently lacks reproducible, cross-species validated biomarkers to define, grade, or stage ferro-aging severity. While iron overload, ACSL4 expression, lipid peroxidation products (MDA, 4-HNE), and senescence markers correlate with ferro-aging, these readouts are not standardized or normalized for cross-tissue or cross-study comparison. Establishing a unified ferro-aging index, integrating iron status, lipid metabolism, redox state, and cellular senescence, will be critical for trial design, intervention monitoring, and meta-analytic synthesis.

5) Upstream regulators of ACSL4 expression during aging. The transcriptional, post-transcriptional, and metabolic mechanisms driving age-related ACSL4 upregulation remain poorly understood. Elucidating upstream regulators, including transcription factors, epigenetic modifiers, microRNAs, and iron-sensing pathways, will identify novel entry points to modulate ferro-aging independently of ACSL4 itself, expanding the therapeutic toolkit for aging-related diseases.

6) Rigorous human clinical validation of VC's geroprotective potential. Translating primate findings to humans requires well-designed, long-term clinical trials to address key unknowns: defining safe and effective geroprotective VC dosing, identifying optimal initiation age, assessing long-term safety in diverse populations, and evaluating efficacy for ferro-aging-associated pathologies (e.g., neurodegeneration, metabolic syndrome, non-alcoholic fatty liver disease). These trials must also account for genetic variability, baseline iron status, and dietary habits that may modify VC's effects in humans.

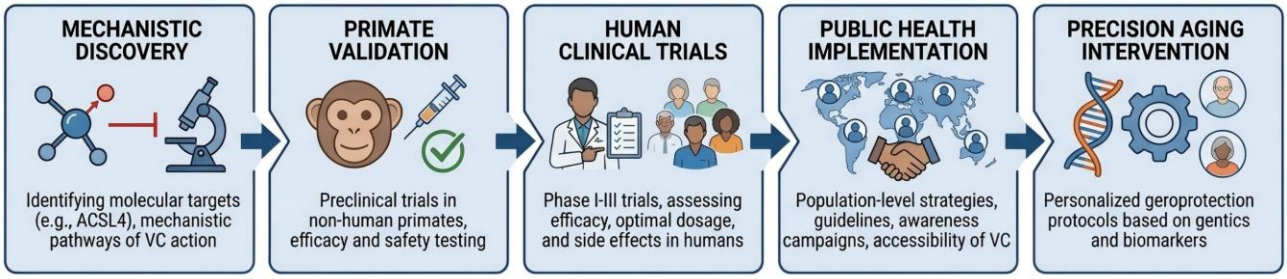

Figure 3. A translational framework maps the comprehensive translational arc from basic mechanistic discovery to targeted anti-aging therapeutics. The proposed pipeline incorporates essential validation phases, spanning non-human primate models and rigorous human clinical trials, before final integration into public health initiatives.

Concluding remarks

Ferro-aging has emerged as an evolutionarily conserved, iron- and lipid-driven metabolic program that orchestrates progressive systemic senescence across primate species, with ACSL4 serving as a critical, non-universal enzymatic mediator of this process. Historically regarded as a ubiquitous, broad-spectrum antioxidant with nonspecific redox effects, VC has been proposed to interact with and inhibit ACSL4 at supraphysiological concentrations, alongside well-documented indirect antioxidant and Nrf2-mediated cytoprotective actions. Collectively, these dual mechanisms converge to mitigate ferro-aging signatures, preserve organ integrity, and attenuate biological aging in aged non-human primates. These landmark findings integrate iron homeostasis, lipid metabolism, redox biology, and cellular senescence into a cohesive, mechanistic framework for understanding systemic aging, offering a provocative but unvalidated strategy to promote healthy aging and delay age-related disease. Importantly, the ferro-aging paradigm remains an emerging hypothesis, and the VC–ACSL4 interaction is mechanistically unproven, with all geroprotective effects observed exclusively in non-human primates.

For aging researchers, the ferro-aging concept expands our understanding of systemic senescence beyond traditional hallmarks, highlighting iron-lipid dysregulation as a modifiable, conserved driver of primate aging. For clinicians and public health specialists, VC represents a low-cost, accessible candidate intervention—

but one that requires rigorous, long-term human clinical trials to confirm efficacy, define optimal dosing and timing, and establish safety before any clinical or public health recommendations can be considered. The translational blueprint for VC-mediated geroprotection is presented in Figure 3.

The field of mechanism-driven aging research has advanced significantly with the identification of ferro-aging and the preliminary validation of VC's geroprotective potential in primates. Nevertheless, translating these promising preclinical insights into actionable human interventions demands extreme caution, scientific rigor, and critical evaluation of all evidence. Future research must prioritize mechanistic validation, targeted therapeutic development, and human clinical testing to determine whether ferro-aging modulation can fulfill its promise as a safe and effective strategy for promoting healthy human aging.

Authorship contribution

Chenxi Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Funding acquisition, Conceptualization. Zhong-cheng Gong: Writing – original draft, Writing – review & editing, Supervision, Methodology, Conceptualization. Jishi Ye and Yuchen Ni: Writing – original draft, Writing – review & editing, Validation. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Xinjiang Talent Development Fund (grant number: XJRC-2025-KJ-PY-KJLJ-118); Natural Science Foundation of Xinjiang Uygur Autonomous Region (grant number: 2025D01C175); Xinjiang Science and Technology Support Project (grant number: 2026E02065); Jiangsu Province Engineering Research Center of Stomatological Translational Medicine (grant number: GCZX2026-07); Open Fund of Guangdong Provincial Key Laboratory of Oral Diseases (grant number: KF2025120102).

Acknowledgements

Authors appreciate all financial support that granted, and are also grateful to Shiyang Deng, MSc, PhD (Faculty of Life Sciences, Division of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Chuo-ku, Kumamoto 860-8556, Japan), Dishu Huang, MD, PhD (Department of Neurology, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatrics. Chongqing 400014, China) and Shanshan Peng, MD, PhD (Department of Geriatrics, Huashan Hospital, Fudan University. Shanghai 200040, China) for participating in the discussion of this paper with the first author.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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