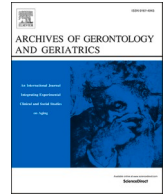




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Review

The metabolic-inflammatory axis in aging: A multi-organ framework anchored in Sarcopenia — A review

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HIGHLIGHTS

- This review focuses on the metabolic-inflammatory axis and its link to inflammaging, insulin resistance and sarcopenia in aging.
- Three core molecular modules mediating metabolic-inflammatory coupling are systematically summarized and clarified.
- The gut-liver-adipose-muscle (GLAM) axis is highlighted as the key tissue network in age-related metabolic inflammation.
- Evidence-based interventions and future research directions for aging-related sarcopenia are proposed.

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ABSTRACT

Inflammaging refers to chronic low-grade inflammation that develops with age and promotes multiple age-related diseases. It arises from the close crosstalk between metabolic disturbance and inflammation, yet how this coupling acts across tissues remains poorly understood. As a hallmark of aging, sarcopenia often coincides with metabolic-inflammatory dysfunction in the gut, liver, and adipose tissue, all tied together by insulin resistance (IR). In this review, we systematically examine the pathophysiological basis of the "metabolic-inflammatory axis" during aging, clarifying its conceptual boundaries with related terms such as "inflammaging," "immunometabolism," and "metabolic inflammation." We delineate the roles of three core molecular modules—nutrient sensing pathways (AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR)), mitochondrial stress (mitochondrial reactive oxygen species (mtROS)-p53), and epigenetic regulation (acetyl-Coenzyme A (AcCoA)-histone acetyltransferase (HAT))—in mediating metabolic-inflammatory coupling. Using sarcopenia as a clinical anchor, we construct a tissue-specific atlas of the metabolic-inflammatory axis and elucidate the principles of organ crosstalk—and its mediators—within the gut-liver-adipose-muscle (GLAM) core axis. We then summarize current intervention strategies stratified by evidence level and identify knowledge gaps and future research directions. This review establishes a mechanistic link between molecular pathways and age-related multi-organ dysfunction, supporting a paradigm shift from single-disease management to multi-system health-span interventions in aging.

1. Introduction

1.1. The multimorbidity network of aging, metabolic dysregulation, and inflammaging

First described over 20 years ago, the concept of inflammaging has

evolved from a descriptive observation of age-related inflammation to a central mechanistic framework linking metabolism, immunity, and chronic disease (Franceschi et al., 2000; Franceschi et al., 2018). Concurrently, multimorbidity has become commonplace in older adults, with >65% of this population living with two or more chronic conditions (Salive, 2013). This pattern indicates that aging is not simply a

Abbreviations: AcCoA, acetyl-coenzyme A; AMPK, AMP-activated protein kinase; ASMI, appendicular skeletal muscle mass index; AUC, area under the curve; CCFs, cytoplasmic chromatin fragments; cGAS, cyclic GMP-AMP synthase; DXA, dual-energy X-ray absorptiometry; FFA, free fatty acid; GDF15, growth differentiation factor 15; GRADE, grading of recommendations assessment, development and evaluation; HAT, histone acetyltransferase; IR, insulin resistance / insulin receptor; LPS, lipopolysaccharide; mTORC1, mTOR complex 1; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; PS, phosphatidylserine; SASP, senescence-associated secretory phenotype; SIRT1, sirtuin 1; STING, stimulator of interferon genes; TMAO, trimethylamine N-oxide.

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collection of unrelated diseases, but instead arises from shared underlying biological mechanisms.

Geroscience posits that aging per se represents the major risk factor for chronic diseases, and interventions aimed at the core mechanisms underlying aging could simultaneously defer the development of numerous age-associated pathologies (Kennedy et al., 2014; Sierra, 2016). In their analysis of the twelve signs of aging, López-Otín et al. argued that nutritional perception dysregulation and inflammatory aging are the core key elements linking upstream molecular damage to downstream organ function decline (López-Otín et al., 2023).

Nutrient perception disorder refers to the imbalance of cellular energy metabolism accompanied by declines in AMP-activated protein kinase (AMPK) activity, abnormal activation of mechanistic target of rapamycin complex 1 (mTORC1) and decreased sirtuin 1 (SIRT1) function during aging (Johnson & Rabinovitch, 2013). Inflammaging describes the chronic, low-grade inflammatory state that emerges with advancing age, characterized by modest elevations in circulating interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP), and is closely associated with adverse outcomes including frailty, sarcopenia, and cardiovascular disease (Franceschi et al., 2018; Ferrucci & Fabbri, 2018).

Research over the past three decades has revealed deep bidirectional coupling between metabolism and inflammation (Hotamisligil, 2017). Key milestones include Hotamisligil's 1993 discovery that TNF- α mediates insulin receptor inhibition, establishing the molecular foundation of metabolic inflammation (Hotamisligil et al., 1993); Medzhitov's 2008 proposal of "physiological inflammation" as an adaptive response for maintaining metabolic homeostasis (Medzhitov, 2008); Hotamisligil's 2017 articulation of "metabolic inflammation" as nutrient overload-driven inflammation (Hotamisligil, 2017); and Franceschi's 2018 reframing of inflammaging as an immune-metabolic network imbalance (Franceschi et al., 2018). Together, these conceptual advances provide the foundation for the "metabolic-inflammatory axis" framework developed in this review (see Box 1).

The "metabolic-inflammatory axis" discussed in this paper, refers to a functional coupling network that links cellular nutrient/energy status to inflammatory response pathways. This network comprises key molecular nodes (AMPK, mTOR, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), etc.) and organelle homeostasis systems (mitochondria, endoplasmic reticulum, nucleus). Dysregulation of this axis represents a core mechanism driving age-related multimorbidity.

1.2. Sarcopenia as a clinical anchor for the metabolic-inflammatory axis

Sarcopenia, characterized by loss of muscle mass and decline in

muscle function, is an independent predictor of disability, falls, hospitalization, and all-cause mortality in older adults (Cruz-Jentoft et al., 2019). Sarcopenia frequently co-occurs with gut barrier dysfunction, hepatic steatosis, and adipose tissue hypertrophy, forming a highly comorbid network in which insulin resistance serves as the central connecting thread (Kalinkovich & Livshits, 2017).

Sarcopenia serves as an ideal clinical anchor for the metabolic-inflammatory axis based on the following evidence: skeletal muscle highly expresses the IR-B/AMPK α 2 isoforms, rendering it more sensitive to metabolic-inflammatory signals than other organs (Hardie et al., 2012); muscle mass and function can be precisely quantified using dual-energy X-ray absorptiometry (DXA), handgrip dynamometry, and gait speed assessment (Cruz-Jentoft et al., 2019); the well-established prognostic significance of sarcopenia provides direct clinical interpretability for the metabolic-inflammatory axis; and skeletal muscle, as the largest endocrine organ, secretes myokines and senescence-associated secretory phenotype (SASP) factors that can feedback to amplify metabolic-inflammatory disturbances in the gut, liver, and adipose tissue (Pedersen & Febbraio, 2012).

In summary, the metabolic-inflammatory axis represents an integrative theoretical framework that unifies the phenomenological description of inflammaging, the cell-type specificity of immunometabolism, and the triggering factors of metabolic inflammation into a multi-level, multi-organ network model. This framework seeks to explain how aging-related endogenous metabolic stresses, acting through molecular checkpoints in parenchymal cells, drive local and systemic chronic inflammation, ultimately leading to multi-organ dysfunction and multimorbidity. Although the metabolic-inflammatory axis contributes to a wide range of age-related pathologies, sarcopenia offers distinct strengths as a quantifiable, bidirectional clinical readout—ideal for evaluating the predictions of our proposed framework.

1.3. Scope and structure of this review

This review aims to systematically synthesize the pathophysiological basis of the metabolic-inflammatory axis during aging, using sarcopenia as a clinical anchor to integrate multi-organ evidence and provide a theoretical framework for clinical translation. Chapter 2 delineates the molecular foundations of the metabolic-inflammatory axis. Chapter 3 presents a tissue-specific atlas and principles of organ crosstalk. Chapter 4 summarizes intervention strategies stratified by evidence level. Chapter 5 integrates knowledge gaps and outlines future research directions.

Box 1

Conceptual boundaries of the metabolic-inflammatory axis vs. related terms

Concept core focus distinction from metabolic-inflammatory Axis

Inflammaging: Chronic low-grade inflammation linked to aging, focused on inflammation itself and its connections to frailty, sarcopenia and cardiovascular disease (Johnson & Rabinovitch, 2013; Ferrucci & Fabbri, 2018). Distinction: Inflammaging describes a phenomenon; the metabolic-inflammatory axis provides its mechanistic explanation—addressing "how inflammaging arises, how it is sustained, and how it propagates across organs".

Immunometabolism: How metabolic reprogramming in immune cells (macrophages, T cells, etc.) shapes their differentiation, function, and fate (Hotamisligil, 2017). Distinction: Immunometabolism focuses on immune cells; the metabolic-inflammatory axis focuses on metabolic-inflammatory coupling in parenchymal cells (myocytes, hepatocytes, adipocytes) and their interactions within a multi-organ network.

Metabolic inflammation: Chronic low-grade inflammation driven by nutrient overload (e.g., obesity, high-fat diet), triggered by metabolic surplus (Hotamisligil, 2017). Distinction: Metabolic inflammation emphasizes exogenous nutrient overload as a trigger; the metabolic-inflammatory axis encompasses inflammation driven by endogenous aging-related stresses (mitochondrial dysfunction, autophagy decline, chromatin leakage, DNA damage).

2. Molecular foundations of the metabolic-inflammatory axis in aging

We acknowledge that additional pathways—including autophagy and the unfolded protein response—also contribute to metabolic-inflammatory crosstalk. Nevertheless, the three modules we selected represent the most upstream and well-characterized regulatory nodes, providing a foundational framework for integrating other mechanisms.

The molecular basis of the metabolic-inflammatory axis can be conceptualized as three core modules: the nutrient-sensing module (AMPK/mTOR/SIRT1), the mitochondrial stress module (mtROS-p53), and the epigenetic regulation module (AcCoA-HAT). Through complex crosstalk, these three modules collectively determine the coupling between cellular metabolic state and inflammatory output.

2.1. Nutrient-sensing module

2.1.1. The AMPK pathway

AMPK serves as the central cellular energy sensor, and its activity universally declines with aging (Salminen & Kaarniranta, 2012; Bobela et al., 2017). The AMPK α 2 isoform is highly expressed in skeletal muscle, rendering it particularly sensitive to energy stress. Age-related declines in NAD⁺ levels and mitochondrial function impair the ability of rising AMP/ATP ratios to effectively activate AMPK (Hardie et al., 2012).

Reduced AMPK activity directly relieves inhibition of downstream pro-inflammatory pathways: AMPK can directly phosphorylate the NF- κ B p65 subunit (Ser536), inhibiting its nuclear translocation (Salminen et al., 2011); AMPK activates PGC-1 α , promoting mitochondrial biogenesis and indirectly suppressing mtROS generation (Jäger et al., 2007); and AMPK phosphorylates ULK1 to activate autophagy, clearing damaged mitochondria and senescent cellular components (Egan et al., 2011).

2.1.2. The mTORC1 pathway

Aging cells exhibit aberrant mTORC1 hyperactivation (Chrienova et al., 2021). Mechanisms include feedback relief of mTORC1 inhibition due to diminished insulin/IGF-1 sensitivity, sustained mTORC1 activation by accumulated branched-chain amino acids (BCAAs), and loss of AMPK-mediated inhibitory phosphorylation of mTORC1. mTORC1 overactivation promotes inflammation through multiple mechanisms: phosphorylation and activation of sterol regulatory element-binding protein 1 (SREBP1) drives lipid synthesis, leading to ectopic lipid deposition (Liu & Sabatini, 2020); suppression of autophagic flux results in accumulation of damaged mitochondria and p62/SQSTM1, activating the NLR family pyrin domain containing 3 (NLRP3) inflammasome (Kim et al., 2016); and enhanced translation and synthesis of SASP factors (Labege et al., 2015).

2.1.3. The SIRT1 pathway

SIRT1 is an NAD⁺-dependent deacetylase. Aging is accompanied by a substantial decline in NAD⁺ levels, leading to reduced SIRT1 activity (Imai & Guarente, 2014). SIRT1 suppresses inflammation by deacetylating the NF- κ B p65 subunit (Lys310), inhibiting its transcriptional activity (Yeung et al., 2004); activating PGC-1 α and FOXO transcription factors to enhance antioxidant defenses (Brunet et al., 2004); and maintaining endothelial function to suppress vascular inflammation (Mattagajasingh et al., 2007).

2.2. Mitochondrial stress module

Mitochondrial dysfunction is a core feature of aging (Sierra, 2016). Age-related declines in electron transport chain efficiency increase electron leakage, resulting in sustained elevation of mtROS generation (Bratic & Larsson, 2013).

2.2.1. The dual role of mtROS

Low levels of mtROS participate in physiological signal transduction. However, sustained age-related mtROS elevation can initiate multiple inflammatory pathways: mtROS can trigger context-dependent inflammatory pathways by directly oxidizing and activating IKK kinase, thereby driving NF- κ B activation (Kamata et al., 2005); promote NLRP3 inflammasome assembly for IL-1 β /IL-18 maturation and secretion (Zhou et al., 2011); and oxidize mtDNA, causing its leakage into the cytoplasm and activation of the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway (West et al., 2015).

2.2.2. The pro-aging role of p53

mtROS stabilize p53 protein and enhance its transcriptional activity through phosphorylation at Ser15 (Vigneron & Vousden, 2010). Activated p53 induces p21CIP1 expression, promoting cell cycle arrest, and upregulates BAX/PUMA, increasing mitochondrial outer membrane permeability. This creates a positive feedback loop: mtROS \rightarrow p53 \rightarrow mitochondrial damage \rightarrow mtROS \uparrow . Concurrently, p53 transcriptionally represses PGC-1 α , impairing mitochondrial biogenesis (Sahin et al., 2011).

2.2.3. The cGAS-STING pathway

mtDNA released from damaged mitochondria is recognized by cytosolic cGAS, which catalyzes cGAMP production and activates STING. STING then drives transcription of type I interferons and pro-inflammatory cytokines via TBK1-IRF3 and NF- κ B signaling (Chen et al., 2016). This pathway serves as a critical bridge connecting mitochondrial dysfunction to inflammaging. While the cGAS-STING pathway has been most extensively investigated in cancer and preclinical murine aging models, emerging human proteomic datasets offer indirect validation of its relevance to human aging. Focused mechanistic studies in humans are thus urgently warranted (Oh et al., 2023).

2.3. Epigenetic regulation module

Metabolism and gene expression engage in bidirectional crosstalk. Rather than merely sustaining cellular bioenergetics, metabolic intermediates dynamically modulate the epigenetic landscape. Metabolite concentrations, particularly those of acetyl-CoA, can fluctuate in response to nutritional status and, in doing so, influence chromatin structure and inflammatory gene expression. The concept of "metabolism-epigenetics-inflammatory axis" is a high-level summary of the above complex physiological processes (Kaelin & McKnight, 2013).

2.3.1. Sources of acetyl-CoA

Histone acetylation occurs and requires acetyl-CoA as a donor. There is a large accumulation of AcCoA in senescent cells, from sources such as glucose oxidation, fatty acid β oxidation, and the conversion of branched-chain amino acid acetylated derivatives from autophagy to AcCoA through mitochondrial acyl-CoA synthetase short-chain family member 2 (ACSS2) (Moussaieff et al., 2015).

2.3.2. HAT hyperactivation

When IR-Akt is inactivated, physiological inhibition of histone acetyltransferase is lifted. At this time, AcCoA accumulated in senescent cells happened to provide sufficient substrate for HAT, resulting in a significant increase in the level of H3K27 acetylation in the inflammatory gene promoter region (Ghizzoni et al., 2011). In addition, HAT directly acetylates the NF- κ B p65 subunit Lys310, enhancing its transcriptional activity (Chen et al., 2002), and acetylating STAT3 Lys685 promotes its protein-protein interaction with p65 (Lee et al., 2009).

2.3.3. Metabolic memory through epigenetic modifications

Sustained activation of the AcCoA-HAT axis locks inflammatory genes into a poised chromatin state. Even after metabolic signals normalize, cells remain hyper-responsive to secondary stimuli, shifting

from reversible adaptation to persistent pathology (Johnson & Rabino-vitch, 2013). This phenomenon, known as metabolic memory and well defined in diabetic complications, is supported by evidence of sustained inflammatory gene acetylation in senescent cells, although its role in aging skeletal muscle remains hypothetical (Ghizzoni et al., 2011; Yahagi et al., 2004).

2.4. Crosstalk among the three core modules

To think of the nutrient-sensing, mitochondrial stress, and epigenetic modules as operating in isolation would be a mistake. In reality, they are enmeshed in a complex network of mutual regulation, with each node influencing the others through multiple molecular connections. For example, in the AMPK-mTOR axis, AMPK phosphorylates TSC2 to inhibit mTORC1, and AMPK inactivation leads to mTORC1 hyperactivation (Hardie et al., 2012) (therapeutic targets: metformin activates AMPK; rapamycin analogs inhibit mTORC1). In the mtROS-NLRP3 axis, mitochondrial dysfunction is regulated, and mtROS directly promotes NLRP3 assembly (Zhou et al., 2011) (therapeutic target: MitoQ scavenges mtROS). In the p53-SREBP1 axis, p53 normally suppresses the expression of SREBP1c, which is the main regulator of lipogenesis. This negative feedback loop, however, becomes uncoupled with aging, with consequences for lipid metabolism and, potentially, for the metabolic-inflammatory axis more broadly (Yahagi et al., 2004). In the NF- κ B-NLRP3 axis, NF- κ B, for its part, does not merely respond to inflammation; it also amplifies this effect. By binding to the promoter of the NLRP3 gene, NF- κ B drives its transcription, creating a feed-forward loop that sustains inflammasome activity (Ghizzoni et al., 2011). The most closely related to this paper is the epigenetic- nutrient perception axis, where HAT-mediated insulin receptor substrate 1 (IRS1) and IRS2 acetylation impairs insulin signaling, and apparent modifications exacerbate insulin resistance (He, 2021) (therapeutic target: curcumin derivatives inhibit HAT). Acetylation of specific lysine sites (K1017/1080/1131) in IRS1 and specific lysine sites (K1173/1264) in IRS2 has been shown to disrupt insulin action (He, 2021). Amino acid metabolic reprogramming in the ACS2-AcCoA axis replenishes the AcCoA pool, establishing a connection between autophagy decline and epigenetic inflammation (Moussaieff et al., 2015).

2.5. From molecular modules to organ phenotypes

The imbalance of the above three major molecular modules is not an isolated event, but forms a networked regulation via intricate crosstalk. This network exhibits significant heterogeneity across different tissues, and its specific manifestations are determined by organ-specific AMPK/IR isoform expression profiles, cellular composition and the local microenvironment (see Chapter 3). Understanding this molecular-level heterogeneity represents the logical starting point for dissecting how multi-organ cascades evolve from local disturbances into systemic imbalance (see Chapter 4).

3. Tissue specificity and multi-organ integration of the metabolic-inflammatory axis

During aging, activation of the metabolic-inflammatory axis exhibits pronounced tissue specificity, rooted in differential expression of AMPK and IR isoforms. Tissues communicate through the gut-liver-adipose-muscle core axis, enabling trans-organ cascade amplification, and are subject to coordinated modulation by the central nervous, cardiovascular, and immune systems.

3.1. Tissue-specific atlas

To systematically compare organ-specific differences in the metabolic-inflammatory axis, key changes and their links to sarcopenia are summarized in Table 1. Each organ displays a distinct pattern,

Table 1

Tissue-specific alterations of the metabolic-inflammatory axis and mechanistic links to sarcopenia.

Tissue/System	Core Molecular Changes	Key Quantitative Indicators	Mechanistic Link to Sarcopenia
Skeletal muscle	IR-B/AMPK α 2 axis dysfunction; mTORC1-NLRP3 activation; MyoD pathway inhibition	ASMI: <7.0 kg/m ² (men), <5.4 kg/m ² (women) (Cruz-Jentoft et al., 2019); Grip strength: <26 kg (men), <16 kg (women) (Cruz-Jentoft et al., 2019); p16 ⁺ cell frequency \uparrow with age (Suryadevara et al., 2024)	Direct target organ: Inhibits satellite cell proliferation/differentiation; promotes muscle protein degradation
Adipose tissue	Adiponectin signaling impairment; PPAR γ -TLR4-MyD88; mTORC1-mediated M1 polarization	Adiponectin \downarrow (Gianopoulos et al., 2025; Kadowaki et al., 2006); UCP1 expression \downarrow (Palmer & Kirkland, 2016); CD11c ⁺ macrophage proportion \uparrow (Lumeng et al., 2007)	Indirect driver: FFA induce intramyocellular lipid deposition; SASP exacerbates muscle IR and inflammation
Liver	IR-AMPK α 1 pathway dysfunction; mtROS-p53; cGAS-STING	Intrahepatic TG content \uparrow (Browning et al., 2004); Serum IGF-1 \downarrow (Clemmons, 2009)	Indirect regulator: IGF-1 deficiency impairs muscle synthesis; hepatokines amplify muscle inflammation
Gut	Microbiota metabolite-mTOR; TLR4-LPS; SIRT1-occludin impairment	Tight junction protein expression \downarrow (Thevaranjan et al., 2017); Serum LPS, TMAO \uparrow (Wang et al., 2011)	Upstream initiator: Microbial metabolites enter circulation, activate hepatic cGAS-STING and mTORC1
Pancreas	β -cell senescence (p16 ⁺); islet macrophage infiltration; IL-1 β -mediated local inflammation HOMA- β \downarrow (Aguayo-Mazzucato et al., 2017);	Circulating insulin levels altered	Upstream driver: Relative insulin deficiency exacerbates systemic IR, impairing muscle anabolism
CNS	IR-mtROS-IKK β /NF- κ B; SIRT1-FOXO3 impairment	Microglial activation markers \uparrow (Norden & Godbout, 2013); Hypothalamic inflammatory cytokines \uparrow (Cai, 2013)	Central amplifier: Neuroinflammation disrupts energy regulation, reduces motor output
Cardiovascular	IR-AMPK α 1 dysfunction; TLR4-NLRP3 endothelial activation	Endothelial function \downarrow (Celermajer et al., 1994); Endothelin-1 \uparrow (Donato et al., 2015)	Perfusion limitation: Ischemia-hypoxia induces myofiber apoptosis, impairs regeneration

Note: Quantitative indicators were based on clinical diagnostic criteria and published literature. Specific cutoff values are population-dependent.

Abbreviations: ASMI, appendicular skeletal muscle mass index; FFA, free fatty acid; IGF-1, insulin-like growth factor 1; LPS, lipopolysaccharide; TMAO, trimethylamine N-oxide; SASP, senescence-associated secretory phenotype; CNS, central nervous system; IR, insulin resistance; TG, triglyceride; UCP1, uncoupling protein 1; PPAR γ , peroxisome proliferator-activated receptor gamma; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88.

supporting the need for tissue-specific approaches.

3.2. Metabolic-inflammatory profiles of key organs and their associations with sarcopenia

3.2.1. Gut: the upstream initiator organ

Aging-associated gut microbiota dysbiosis induces the inactivation of intestinal epithelial IR-AMPK α 1 and downregulates the expression of tight junction proteins including occludin and claudin-1, thereby impairing intestinal barrier integrity (Thevaranjan et al., 2017). The gut thus acts as an upstream initiator of multi-organ dysfunction cascades, with microbial metabolites such as LPS, TMAO and BCAAs serving as key early signals that drive the metabolic-inflammatory axis in distal organs (Wang et al., 2011).

3.2.2. Pancreas: the upstream driver organ

With advancing age, pancreatic β -cells adopt a canonical senescent profile, characterized by elevated proportions of p16⁺ cells and markedly impaired insulin secretory function (Aguayo-Mazzucato et al., 2017). Senescent β -cells secrete SASP factors such as IL-1 β and CCL2, which recruit macrophages into islets and create a local proinflammatory microenvironment (Ying et al., 2019). IL-1 β worsens β -cell function, forming a self-reinforcing cycle: β -cell senescence \rightarrow local inflammation \rightarrow worsening β -cell failure. This chain leads to insufficient insulin secretion, which combines with peripheral insulin resistance to form the classic “dual defect” in metabolic control. Together with impaired gut barrier function, this defect initiates a multi-organ sequence that provides the metabolic and inflammatory signals for further proinflammatory expansion in the liver and adipose tissue, disrupting systemic metabolism and inhibiting muscle protein synthesis (Halban et al., 2014).

3.2.3. Liver and adipose: midstream amplifiers

The liver is the main metabolic organ in the body. Overactive metabolic-inflammatory signaling in the liver drives lipid buildup in hepatocytes and promotes nonalcoholic fatty liver disease (NAFLD). Kupffer cells secrete abundant proinflammatory mediators including IL-6, TNF- α and CRP, thus raising the systemic inflammatory burden. Concurrently, insulin resistance inhibits insulin-like growth factor 1 (IGF-1) production and blunts its anabolic support to skeletal muscle (Clemmons, 2009).

Adipose tissue acts as both a major energy reservoir and an endocrine organ. Elevated metabolic-inflammatory axis activity in this tissue manifests as white adipose hypertrophy, compromised thermogenesis in brown adipose tissue (uncoupling protein 1 (UCP1)), and greater infiltration of M1 macrophages. These alterations drive excess free fatty acid (FFA) release and lower adiponectin secretion. Elevated FFAs promote ectopic lipid deposition, whereas the loss of adiponectin abolishes its protective actions toward skeletal muscle and liver (Kadowaki et al., 2006; Lumeng et al., 2007).

The liver and adipose form a bidirectional amplification loop through circulating FFAs and inflammatory cytokines: hepatokines promote adipose M1 polarization, while adipocyte-derived FFAs exacerbate hepatic lipid accumulation. The combined actions of these organs underpin the midstream amplification of the cascade.

3.2.4. Skeletal muscle: the downstream effector organ

Skeletal muscle is the downstream effector of this cascade, and directly integrates metabolic-inflammatory signals from upstream and

midstream organs. Circulating FFAs, LPS, and SASP activate the skeletal muscle IR-B/AMPK α 2 axis via multiple mechanisms: (1) FFAs induce intramyocellular lipid deposition, activating the mTORC1-NLRP3 inflammatory pathway; (2) LPS upregulates MuRF1/MAFbx, accelerating muscle protein degradation; (3) IL-6/TNF- α suppress MyoD expression, impairing satellite cell proliferation and differentiation (Glass, 2005). These changes push skeletal muscle into a pathologically activated state, marked by lower muscle mass (reduced appendicular skeletal muscle mass index (ASMI)) and weaker muscle strength (declined grip strength), which defines the onset of sarcopenia.

3.2.5. Retrograde reinforcement: myogenic signal feedback

Skeletal muscle is not just a passive target of this cascade—it actively amplifies upstream metabolic-inflammatory disturbances through myokine release, turning sarcopenia from an endpoint into a driver of the entire cascade:

- Intestine: IL-6 and myostatin further lower tight junction protein expression, worsening gut barrier dysfunction (Pedersen & Febbraio, 2012).
- Liver: Muscle-derived cytoplasmic chromatin fragments (CCFs⁺) exosomes accumulate in the liver, activating hepatocyte cGAS-STING and stellate cell transforming growth factor beta 1 (TGF- β 1), promoting hepatic fibrosis (Dou et al., 2017); concurrently, IL-6 further elevates intrahepatic TG (Pedersen & Febbraio, 2012).
- Adipose tissue: IL-6 promotes M1 macrophage infiltration in adipose tissue, worsening local inflammation (Pedersen & Febbraio, 2012).
- CNS: growth differentiation factor 15 (GDF15) crosses the blood–brain barrier and activates microglia, which dampens motor function and appetite, forming a vicious cycle of physical inactivity and metabolic dysregulation (Tsai et al., 2016).

4. Multi-organ crosstalk: from local disturbances to systemic dysregulation

Chapter 3 provided a systematic dissection of the intrinsic metabolic-inflammatory phenotypes and regulatory profiles of individual core organs. In the aging organism, however, these organs do not work in isolation; instead, they interact through complex communication networks to create self-sustaining multi-organ cascades. This chapter addresses the molecular mediators governing inter-organ communication and the kinetic rules governing signal transmission. We further dissect the mechanisms underlying cascade amplification and propagation along the core gut–liver–adipose–muscle axis, and finally propose precision intervention windows stratified by temporal hierarchy.

4.1. Molecular mediators of inter-organ communication

The establishment, maintenance, and propagation of inter-organ pathological cascade circuits rely on soluble signaling molecules and particulate transporters as two core classes of mediating agents.

4.1.1. Soluble mediators

Soluble mediators represent the major class of circulating factors governing inter-organ communication, the key members of which are summarized in Table 2.

4.1.2. Particulate carriers

Circulating CCFs do not exist as naked nucleic acid fragments, but are selectively packaged within CD63⁺/TSG101⁺ exosomes and large microvesicles. Compared with young controls, the abundance of CCFs⁺ exosomes in serum is markedly elevated in aged mice (Jeppesen et al., 2019).

The level of phosphatidylserine (PS) exposure on the exosomal surface acts as a key regulator of their uptake efficiency by recipient cells:

Table 2
Core soluble mediators involved in multi-organ crosstalk.

Mediator	Primary Source	Primary Target Organ/Tissue	Activated Pathway	Pathological Effect
LPS	Gut microbiota	Hepatic Kupffer cells	cGAS-STING	Type I interferon response; systemic inflammation (Thevaranjan et al., 2017)
TMAO	Gut microbiota	Hepatocytes	mTORC1	Lipid synthesis and inflammation (Wang et al., 2011)
FFA	Adipose tissue, liver	Muscle, liver	TLR4-NLRP3	Ectopic lipid deposition, insulin resistance (Kadowaki et al., 2006)
GDF15	Skeletal muscle (stress)	CNS	GFRAL-RET	Suppressed motor output and appetite (Tsai et al., 2016)

Abbreviations: LPS, lipopolysaccharide; TMAO, trimethylamine N-oxide; FFA, free fatty acid; GDF15, growth differentiation factor 15; CNS, central nervous system; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; mTORC1, mechanistic target of rapamycin complex 1; TLR4-NLRP3, Toll-like receptor 4-NLR family pyrin domain containing 3; GFRAL-RET, GDNF family receptor alpha-like-RET proto-oncogene.

- Exosomes with high PS exposure are efficiently sequestered by Kupffer cells via the TIM4 receptor;
- In contrast, exosomes with low PS exposure are preferentially cleared by splenic marginal zone macrophages.

Such a vesicular carrier paradigm explains the molecular basis through which even a mild increase in systemic CCF levels is capable of driving pathological alterations in distant target organs. Successful signal transmission depends not on free nucleic acid levels, but on exosomal surface “address tags” (e.g., PS exposure) and how well they bind to matching receptors on recipient cells (e.g., TIM4).

4.2. Threshold kinetics and exposure time-dependent impacts

The pathological effects of signaling mediators depend on both concentration and exposure time, not just concentration alone. For instance, chronic low-dose lipopolysaccharide (LPS) triggers hepatic insulin resistance and activates the cGAS-STING pathway in Kupffer cells. These events fuel the metabolic-inflammatory axis associated with age-related sarcopenia. By contrast, high-dose LPS causes similar pathological changes but acts much more rapidly (Johnson & Rabinovitch, 2013; Thevaranjan et al., 2017). Cumulative exposure models best capture the overall pathological effects of these mediators. These models are defined by the concentration–time integral (area under the curve, AUC) (Johnson & Rabinovitch, 2013) and highly relevant to sarcopenia, a core clinical anchor of this review.

This cumulative exposure model carries clear clinical relevance: conventional single-point clinical measurements often underestimate the full pathological impact of chronic low-grade inflammation. Such inflammation contributes directly to sarcopenia by disrupting muscle protein homeostasis and accelerating cellular senescence in skeletal muscle, gradually weakening muscle health.

Even in older adults whose serum inflammatory markers fall below standard clinical cutoffs, the cumulative burden of hepatic inflammation—and the resulting metabolic-inflammatory dysregulation—can be as damaging as a single acute high-level exposure, further promoting muscle atrophy and functional decline.

Together, these findings show that cumulative exposure indices (based on the concentration–time AUC) capture the progressive risk of chronic inflammation and sarcopenia far better than instantaneous concentrations. Such metrics thus provide a new quantitative approach

for risk stratification and early clinical assessment of age-related chronic inflammatory conditions, aligning this review’s focus on connecting molecular mechanisms with clinically actionable strategies for sarcopenia.

4.3. Core axis cascade dynamics: from signal generation to systemic dysregulation

Based on the above mediator basis and kinetic principles, activation of the gut–liver–adipose–muscle core axis follows the dynamic logic of “signal generation → sensing and amplification → effector execution → feedback reinforcement” (Fig. 1A), rather than simple sequential organ transmission.

4.3.1. Signal generation: dual upstream drivers

The cascade is triggered by two parallel upstream events: gut barrier dysfunction, which releases LPS, TMAO and other microbial metabolites (Thevaranjan et al., 2017), and pancreatic β -cell senescence, which drives relative insulin deficiency and local islet inflammation (Aguayo-Mazzucato et al., 2017; Ying et al., 2019; Halban et al., 2014). These two processes jointly drive the earliest systemic metabolic-inflammatory signals.

4.3.2. Signal sensing and amplification: the liver–adipose relay station

As the body’s frontline metabolic defense organ, the liver translates upstream signals into local hepatic inflammation and lipid accumulation—via Kupffer cells that sense LPS and hepatocytes that detect TMAO and FFAs (Browning et al., 2004; Clemmons, 2009). Circulating FFAs and inflammatory cytokines relay these signals to adipose tissue, driving macrophage M1 polarization and SASP secretion (Kadowaki et al., 2006; Lumeng et al., 2007). Reciprocal crosstalk between the liver and adipose tissue amplifies these signals, establishing a systemic inflammation state.

4.3.3. Effector execution: terminal damage to skeletal muscle

Amplified metabolic-inflammatory signals (including FFA, LPS, and SASP) act directly on skeletal muscle. Through multiple pathways, they drive excessive muscle protein breakdown and impair satellite cell regeneration, ultimately promoting the development of sarcopenia (Glass, 2005). Clinically, these disruptions present as reduced muscle mass, diminished muscle strength, and progressive sarcopenia.

4.3.4. Feedback reinforcement: from endpoint to engine

Skeletal muscle, once activated, releases myogenic factors (IL-6, myostatin, GDF15, CCFs* exosomes) that circulate and retro-act on upstream organs: IL-6 further impairs gut barrier function (Pedersen & Febbraio, 2012); CCFs* exosomes activate hepatic stellate cells (Dou et al., 2017); and GDF15 suppresses central motor output (Tsai et al., 2016). In this process, sarcopenia shifts from the terminal effector of the pathological cascade to a central driver of the cascade, thereby fueling a self-sustaining, amplifying state of multi-organ homeostatic imbalance.

4.4. Systemic amplifiers

Beyond the gut–liver–adipose–muscle axis, three additional systems function as critical cascade amplifiers that further aggravate sarcopenia driven by the metabolic-inflammatory axis.

4.4.1. CNS-mediated potentiation

Circulating CCFs and GDF15 are capable of crossing the blood–brain barrier to elicit IKK β –NF- κ B signaling activation in microglia, which in turn leads to dysregulation of hypothalamic energy homeostatic control and impaired motor output (Norden & Godbout, 2013; Tsai et al., 2016).

4.4.2. Cardiovascular constraint

Aberrant activation of the metabolic-inflammatory axis within the

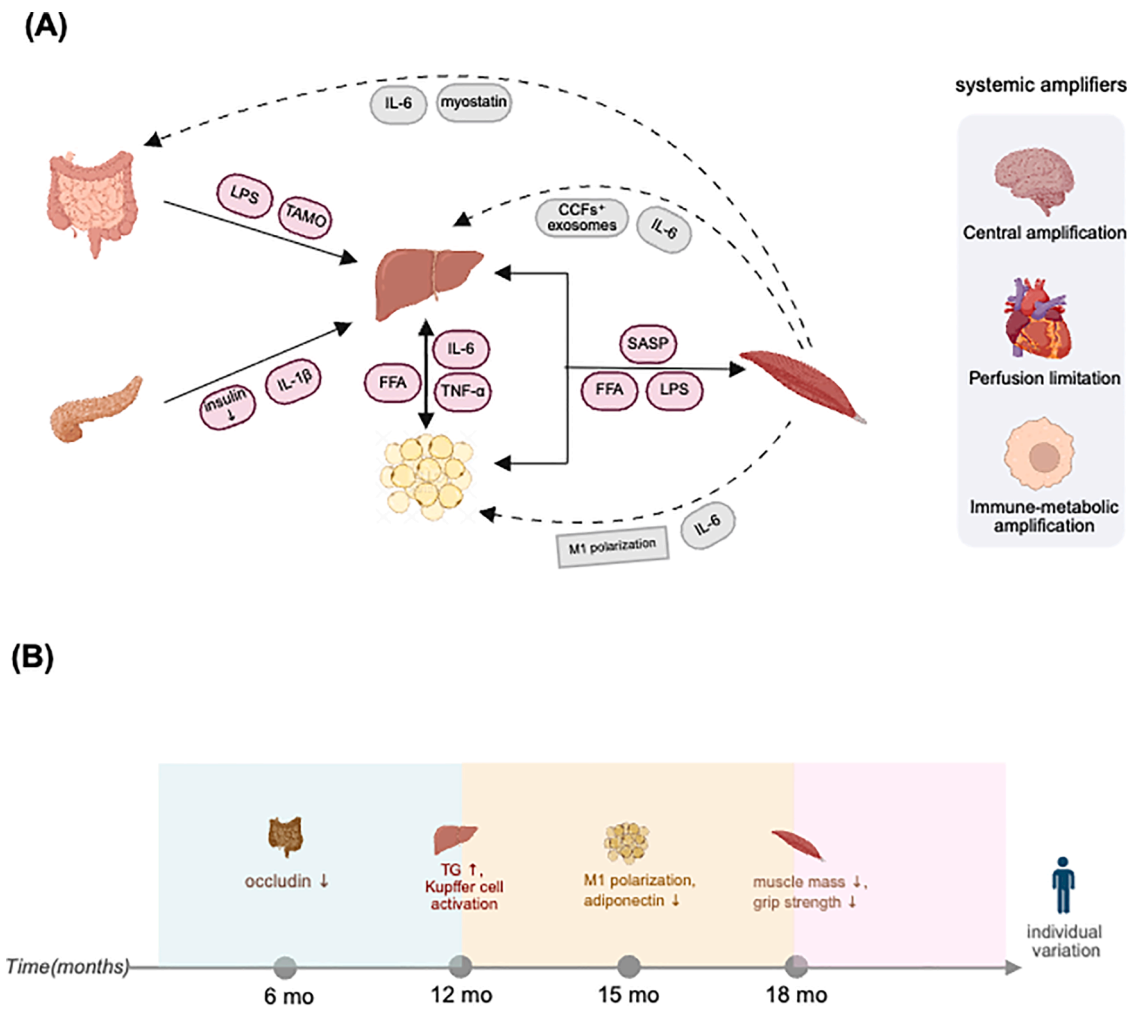


Fig. 1. Cascade dynamics of the gut-liver-adipose-muscle core axis and temporal intervention windows. (A) Multi-organ cascade dynamics following a four-stage logic based on Sections 4.3–4.4. Signal generation originates from gut (LPS/TMAO) and pancreas (insulin↓/IL-1β). These signals are sensed by liver and adipose, which form a bidirectional amplification loop. Convergent signals (FFA, LPS, SASP) then drive skeletal muscle dysfunction via multiple mechanisms, leading to sarcopenia (Glass, 2005). Feedback reinforcement occurs through muscle-derived factors (IL-6, myostatin, GDF15, CCFs⁺ exosomes) that retro-act on upstream organs (dashed arrows) (Pedersen & Febbraio, 2012; Dou et al., 2017; Tsai et al., 2016). Systemic amplifiers: CNS (brain icon) broadly exacerbates gut/liver/pancreas dysfunction via microglial activation (Norden & Godbout, 2013); cardiovascular (heart icon) restricts muscle perfusion through endothelial dysfunction (Celermajer et al., 1994; Donato et al., 2015); immune (macrophage icon) amplifies SASP burden via M1 polarization and impaired NK clearance (Ovadya et al., 2018). Detailed mechanisms of these systemic amplifiers are described in Section 4.4. (B) Temporal intervention windows based on natural aging mouse models (Schaum et al., 2020). Time points (6, 12, 15, 18 mo) mark key events: gut barrier dysfunction (occludin↓), hepatic steatosis (TG↑, Kupffer cell activation), adipose M1 polarization (adiponectin↓), and sarcopenia (muscle mass↓, grip strength↓). Color-coded windows define intervention opportunities: Early intervention window (cyan, <12 mo) targets gut barrier and liver metabolism (Rossman et al., 2018); Systemic amplification window (yellow, 12–18 mo) requires multi-organ intervention; Effector failure window (pink, >18 mo) focuses on preserving function. Individual aging rates vary, necessitating calibration with biological age markers (Johnson & Rabinovitch, 2013). Abbreviations: LPS, lipopolysaccharide; TMAO, trimethylamine N-oxide; FFA, free fatty acid; SASP, senescence-associated secretory phenotype; CCFs, cytoplasmic chromatin fragments; CNS, central nervous system; mo, months; y, years.

vascular endothelium results in reduced nitric oxide (NO) bioavailability and increased endothelin-1 (ET-1) levels, which in turn compromises perfusion in skeletal muscle. Persistent ischemic insult subsequently promotes myofiber apoptosis and attenuates the regenerative potential of skeletal muscle satellite cells (Celermajer et al., 1994; Donato et al., 2015).

4.4.3. Immune-metabolic amplification

Aging enhances M1 macrophage polarization and impairs NK cell senescence clearance capacity, leading to senescent cell accumulation and amplified SASP burden, which potentiates multi-organ metabolic-inflammatory crosstalk (Ovadya et al., 2018).

While these three systems do not form integral parts of the core axis, they propagate local perturbations within the core axis into a systemic homeostatic network imbalance by regulating energy metabolism, tissue

perfusion, and senescent cell clearance, thereby emerging as critical synergistic targets for therapeutic intervention.

4.5. Temporal hierarchy and strategic intervention windows

Systematic longitudinal tracking of natural aging mouse models showed that the activation of the metabolism-inflammation axis of multiple organs showed a clear chronological evolution pattern, in order of intestine → liver → adipose → skeletal muscle (Schaum et al., 2020) (Fig. 1B):

- 6 months: Reduced expression of the gut barrier protein occludin.
- 12 months: Hepatic triglyceride (TG) accumulation and Kupffer cell activation.

- 15 months: Increased M1 polarization in epididymal adipose tissue and decreased adiponectin.
- 18 months: Lower skeletal muscle mass and weaker grip strength.

This temporal sequence provides a foundation for defining intervention windows:

- Prior to 12 months: A key upstream window for interrupting the metabolic-inflammatory cascade; targeting the gut barrier and liver can effectively prevent the development of sarcopenia downstream.
- After 18 months: Skeletal muscle has transformed from "cascade endpoint" to "cascade engine," necessitating multi-organ synergistic intervention

Based on this temporal sequence, a preliminary framework for intervention windows can be delineated (Fig. 1B):

- Early intervention window: Target gut barrier and liver metabolism to block cascade initiation and amplification.
- Systemic amplification window: Requires simultaneous targeting of liver, adipose, and muscle through multi-organ synergistic intervention.
- Effector failure window: Focus on preserving muscle function and preventing disability, with multi-organ support as needed.

Of note, the above intervention windows are primarily derived from temporal observations in animal models. Aging trajectories exhibit marked inter-individual heterogeneity, making chronological age an imperfect surrogate for biological aging (Ferrucci & Fabri, 2018). For this reason, translating this framework into clinical practice requires individualized calibration of intervention timing using biological age markers (Horvath, 2013; Elliott et al., 2021)(e.g., the Horvath epigenetic clock) or organ-specific senescence markers (Oh et al., 2023), rather than relying solely on chronological age.

5. Targeting the metabolic-inflammatory axis: intervention strategies

5.1. Intervention logic framework

Based on the pathophysiological hierarchy of the metabolic-inflammatory axis, intervention strategies can be categorized as: upstream source intervention (Remove senescent cells), midstream node intervention (Regulate core molecular nodes), and downstream systemic intervention (repair tissue-specific disorders and multi-organ synergy).

5.2. Intervention strategies stratified by evidence level (GRADE)

To aid clinical translation, interventions targeting the metabolic-inflammatory axis are graded by evidence level and summarized in Table 3. This classification helps prioritize strategies with robust support.

5.3. Clinical interpretation of intervention strategies

Among Class I evidence interventions, metformin has been shown in multiple large RCTs to improve HOMA-IR and CRP levels in older populations (Diabetes Prevention Program Research Group, 2015). Long-term follow-up of the Diabetes Prevention Program Outcomes Study (DPPPOS) demonstrated that metformin treatment was associated with favorable body composition changes, including preservation of lean mass, compared with placebo over 15 years (Diabetes Prevention Program Research Group, 2015). Resistance training improves muscle strength by about 30% and increases appendicular skeletal muscle mass index (ASMI) by about 0.8 kg/m² in older adults (Peterson et al., 2010; Liu & Latham, 2009; Kemmler et al., 2010). Aerobic exercise reduces CRP and improves insulin sensitivity in older populations (Bouaziz et al., 2017). Omega-3 fatty acid supplementation, supported by a recent meta-analysis, improves gait speed by approximately 0.05 m/s and reduces IL-6 levels by 12% in older adults (Bird et al., 2021), these findings are supported by mechanistic insights from RCTs and mechanistic studies (Smith et al., 2015; Calder, 2015). Canakinumab targeting IL-1 β , has demonstrated cardiovascular benefits in large-scale RCTs, though its

Table 3
Intervention strategies targeting the metabolic-inflammatory axis with GRADE evidence levels.

Intervention Level	Representative Strategy	Intervention Target	Evidence Level	Representative References
Non-pharmacological	Resistance training	Increase muscle mass/strength, activate AMPK	Class I	(Peterson et al., 2010; Liu & Latham, 2009)
	Aerobic exercise	Improve IR, reduce CRP	Class I	(Bouaziz et al., 2017)
	Time-restricted feeding	Activate AMPK, inhibit mTORC1	Class II	(Sutton et al., 2018)
	Omega-3 fatty acids	Reduce IL-6, improve gait speed	Class I	(Smith et al., 2015; Calder, 2015; Bird et al., 2021)
Metabolic sensing	Dietary fiber/probiotics	Modulate microbiota, improve gut leak	Class II	(Wu et al., 2021; Liu et al., 2021)
	Metformin	Activate AMPK, improve IR	Class I	(Diabetes Prevention Program Research Group, 2015; Lee et al., 2011)
Nutrient sensing	SRT2104	Activate SIRT1, inhibit NF- κ B	Class III	(Hoffmann et al., 2013)
	Rapamycin analogs	Inhibit mTORC1	Class II	(Mannick et al., 2014)
Oxidative stress	MitoQ	Scavenge mtROS	Class III	(Rossman et al., 2018; Gioscia-Ryan et al., 2014)
Cellular senescence	Dasatinib + Quercetin	Clear senescent cells	Class III	(Justice et al., 2019; Hickson et al., 2019)
	Fisetin	Clear senescent cells	Preclinical	(Liu et al., 2022)
Inflammatory pathways	Canakinumab	Target IL-1 β	Class I	(Ridker et al., 2017; Ridker et al., 2017)
Epigenetic regulation	Curcumin derivatives	Inhibit HAT	Preclinical	(Marcu et al., 2006; Morimoto et al., 2008)
Emerging technologies	Muscle-specific AMPK agonists	Restore AMPK function	Preclinical	(Narkar et al., 2008)
	STING inhibitors	Block cGAS-STING pathway	Preclinical	(Haag et al., 2018)

Note: Evidence levels based on GRADE system: Class I = high certainty (multiple RCTs or meta-analyses); Class II = moderate certainty (small RCTs or large cohort studies); Class III = low certainty (exploratory human studies); Preclinical = cell/animal models only. The level of evidence was based on the effect of interventions on metabolic-inflammatory parameters in the aging population; The specific efficacy of sarcopenia as the primary endpoint needs to be further verified. The limitations of traditional evidence grading in aging populations should be noted (Murad et al., 2014).

Abbreviations: AMPK, AMP-activated protein kinase; IR, insulin resistance; CRP, C-reactive protein; mTORC1, mechanistic target of rapamycin complex 1; IL-6, interleukin-6; SIRT1, sirtuin 1; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; mtROS, mitochondrial reactive oxygen species; HAT, histone acetyltransferase; STING, stimulator of interferon genes; RCT, randomized controlled trial.

specific effects on sarcopenia require further investigation (Ridker et al., 2017; Ridker et al., 2017).

Among Class II interventions, time-restricted feeding elevates AMPK activity and alleviates insulin resistance, yet its efficacy in preserving muscle mass remains to be validated in larger clinical cohorts (Sutton et al., 2018). Dietary fiber and probiotics modulate the gut microbiota and strengthen gut barrier integrity, with early data supporting favorable metabolic outcomes (Wu et al., 2021; Liu et al., 2021). Rapamycin analogs show potential for improving immune function in older adults, although their role in preventing sarcopenia is still under evaluation (Mannick et al., 2014).

Class III evidence comes from exploratory human studies. SRT2104, a SIRT1 activator, displays favorable pharmacokinetics and preliminary anti-inflammatory effects in early-phase trials (Hoffmann et al., 2013). The senolytic combination dasatinib plus quercetin (D + Q) has yielded encouraging early results, reducing SASP markers and enhancing physical function in small pilot studies (Justice et al., 2019; Hickson et al., 2019). MitoQ, a mitochondria-targeted antioxidant, improves vascular endothelial function in healthy older adults (Rossman et al., 2018), with supporting mechanistic data from preclinical models (Gioscia-Ryan et al., 2014).

Preclinical research lays the foundation for emerging treatment strategies. Fisetin, as a senescent cell scavenger, has shown efficacy in removing senescent cells and improving muscle stem cell function in animal models of aging (Liu et al., 2022). Curcumin derivatives inhibit HAT activity and attenuate inflammatory responses in cellular and animal studies (Marcu et al., 2006; Morimoto et al., 2008). Emerging technologies in preclinical development include muscle-specific AMPK agonists that mimic exercise-like effects (Narkar et al., 2008) and STING inhibitors that block the cGAS-STING inflammatory pathway (Haag et al., 2018). These strategies hold promise for future clinical translation, though their efficacy and safety in humans remain to be established.

5.4. Outlook for multi-organ synergistic interventions

Based on organ crosstalk mechanisms, the following synergistic intervention regimens can be proposed: probiotics combined with glutamine and metformin targeting the gut-liver-muscle axis to repair gut barrier, improve hepatic IR, and activate muscle AMPK; metformin combined with Omega-3 and resistance training achieving metabolic-inflammatory-functional synergy; and D + Q pulse therapy combined with time-restricted feeding simultaneously targeting senescent cell clearance and metabolic improvement. These synergistic strategies currently remain primarily theoretical, with their efficacy and safety awaiting prospective clinical trial validation.

6. Knowledge gaps and future research directions

6.1. Core knowledge gaps

Despite recent progress, major challenges remain for clinical translation. Key knowledge gaps and future directions are outlined in Table 4, providing a focused roadmap for subsequent research.

6.2. Future research roadmap

Near-term priorities (2026–2028): Validation and standardization

- Test causal relationships between the IR-AMPK α 2 axis and sarcopenia using Mendelian randomization in large cohorts such as UK Biobank (Sanderson et al., 2022).
- Develop and validate standardized assays for circulating CCFs to predict sarcopenia in independent cohorts, building on foundational studies of CCF biology (Dou et al., 2017).

Table 4

Knowledge gaps and future research directions in metabolic-inflammatory axis research.

Domain	Knowledge Gap	Current Status	Future Research Directions
Mechanistic	Spatiotemporal dynamics of AMPK-mTOR-inflammation	Mostly static, single time-point studies	Develop in vivo dynamic monitoring; construct spatiotemporally controllable animal models
	p53-SREBP1 axis uncoupling in aging	Only validated in HCC models (Yahagi et al., 2004)	Muscle-specific p53 models; human muscle sample validation
Organ-level	Tissue specificity of ACS2-amino acid-AcCoA pathway	Only reported in mouse liver (Moussaieff et al., 2015)	Muscle-specific ACS2 functional studies
	Temporal kinetics of organ-specific metabolic-inflammatory axis activation	Primarily from mouse models	Multi-organ synchronous biopsy studies; develop circulating markers
	Carrier repertoire for organ communication	CCFs* exosome research nascent (Dou et al., 2017)	Systematic identification of exosome subpopulations and cargo
Intervention	Quantification Clinically applicable metabolic-inflammatory burden metrics	Existing metrics are limited	Develop composite scores; multi-center cohort validation
	Cross-platform comparability of detection methods	High inter-laboratory variability	Establish standardized detection protocols
	Predominantly single-target interventions	Network properties underappreciated	Design multi-target combination interventions; adaptive platform trials
Population	Insufficient tissue selectivity	Broad target activation/clearance	Develop tissue-targeted delivery systems
	Underrepresentation of older adults in clinical trials	Enrollment of adults >75 y < 20% (Marcu et al., 2006)	Advocate regulatory policy changes; design geriatric population trials
Translation	Metabolic-inflammatory heterogeneity in multimorbid patients	Mostly single-disease studies	Multimorbidity-based inclusion criteria
	Long bench-to-bedside timelines	Basic-clinical disconnect	Establish rapid translation pathways; develop companion diagnostics

Abbreviations: AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; HCC, hepatocellular carcinoma; ACS2, acyl-CoA synthetase short-chain family member 2; AcCoA, acetyl-Coenzyme A; CCFs, cytoplasmic chromatin fragments; IR, insulin resistance; REBP1, sterol regulatory element-binding protein 1; FFA, free fatty acid; TAME, Targeting Aging with Metformin; SPRINT, Systolic Blood Pressure Intervention Trial.

- Establish multi-center prospective cohorts to determine the predictive value of metabolic-inflammatory burden scores.
- Analyze biorepository samples from large-scale trials, including TAME and SPRINT (Wright et al., 2015), to assess how prior interventions modulate the metabolic-inflammatory axis.

Mid-term priorities (2029–2032): Mechanistic tool development and intervention innovation

- Develop spatiotemporally controllable animal models to dissect AMPK-mTOR-inflammatory dynamics [addressing the spatiotemporal dynamics gap].
- Generate muscle-specific p53 transgenic models, complemented by validation in human muscle specimens, to determine whether p53-SREBP1 uncoupling occurs in aging muscle [addressing the p53-SREBP1 gap].
- Generate conditional knockout mice targeting ACSS2 in muscle to define tissue-specific roles of the ACSS2-AcCoA pathway [addressing the ACSS2 tissue specificity gap].
- Recapitulate key phenotypes such as CCFs trans-organ transmission and FFA-induced intramyocellular lipid deposition using human iPSC-derived multi-organ-on-a-chip platforms.
- Establish a systematic atlas of organ communication mediators during aging, including comprehensive profiling of exosome subpopulations and their cargo.

Long-term priorities (2033–2036): Subtype-based precision medicine and clinical translation

- To design and implement adaptive clinical trials stratified by the dominant activating axes (oxidative, metabolic, and epigenetic), with the aim of validating the superior efficacy of subtype-stratified therapeutic interventions.
- Establish a point-of-care testing platform using dried blood spot sampling, thereby enabling rapid and reliable evaluation of metabolic-inflammatory burden.
- Develop a multidisciplinary clinical model that incorporates metabolic-inflammatory burden scores as standardized enrollment and discontinuation criteria for personalized patient management.
- Facilitate regulatory acceptance of the metabolic-inflammatory burden score as a surrogate endpoint for interventions aimed at healthspan extension.

6.3. Critical perspectives

Preclinical research lays the foundation for emerging treatment strategies. Fisetin, as a senescent cell scavenger, has shown efficacy in removing senescent cells and improving muscle stem cell function in animal models of aging.

6.3.1. Causality vs. correlation in organ crosstalk

The gut-liver-fat-muscle cascade proposed here is mainly supported by observational studies and animal models (Thevaranjan et al., 2017; Schaum et al., 2020). Solid evidence of causality in humans – e.g., enterogenic LPS directly drives muscle protein degradation without relying on liver or fat as an intermediate medium – remains lacking. Emerging research methods, such as Mendelian randomization using large biobanks (e.g., the UK Biobank), can help establish causal associations through genetic variation as instrumental variables (Sanderson et al., 2022). Future research should prioritize well-designed randomized controlled trials to examine whether interventions targeting upstream organs, such as repairing the gut barrier, provide downstream benefits (e.g., muscle mass preservation).

6.3.2. Heterogeneity across sarcopenia subtypes

Sarcopenia is not a homogeneous disease (Cruz-Jentoft et al., 2019). The relative contribution of the metabolic-inflammatory axis may vary between clinically recognized subtypes:

- In obese sarcopenia, adipose tissue dysfunction and excess FFAs may predominate, making this axis highly correlated (Kalinkovich & Livshits, 2017).
- In cachexia-related sarcopenia (e.g., in cancer or heart failure), tumor-derived factors or systemic catabolic cues often take

precedence, potentially overshadowing metabolic-inflammatory mechanisms (Argilés et al., 2023; Fearon et al., 2011).

To date, most studies have not stratified by subtype, which may dilute effect sizes and obscure subtype-specific treatment opportunities. Future studies should employ subtype-stratified analyses to determine whether the metabolic-inflammatory axis is a pervasive driver or a context-dependent contributor.

6.3.3. Temporal directionality

The time series proposed here (changes in the gut first, followed by liver, fat, and finally muscle) is derived from mouse transcriptome data (Schaum et al., 2020). Whether this order holds in humans – and whether gut dysfunction is a real initiator or merely an early amplifier of systemic inflammation – remains unclear.

There is an urgent need for longitudinal human cohort studies with repeated measures of intestinal permeability (e.g., serum zonulin, LPS-binding proteins), liver/inflammatory markers, and muscle mass/function to determine temporal directionality. Such studies may also identify key turning points where interventions are most effective.

7. Conclusions

The metabolic-inflammatory axis connects core aging mechanisms to functional decline across multiple organs. This review describes the molecular basis of this axis: age-related changes in nutrient-sensing pathways trigger the axis upstream. Mitochondrial stress creates a self-sustaining oxidative-inflammatory feedback loop, and epigenetic regulation stabilizes inflammatory states through metabolic-epigenetic crosstalk. Interactions between these three components form a spectrum from reversible adaptation to persistent disease.

Using sarcopenia as a clinical anchor, this review outlines the multi-organ cascade in the gut-liver-adipose-muscle core axis. Gut barrier dysfunction starts this cascade. The liver-adipose amplification loop shapes how strong inflammatory signals become. Skeletal muscle, the downstream target, is directly affected; it also feeds back through myokines to worsen upstream metabolic-inflammatory abnormalities. Soluble mediators and particulate carriers drive inter-organ communication, with the effectiveness of this signaling depending on the concentration gradient, exposure duration, and target organ uptake of these molecules.

For therapies, current evidence supports a multidimensional approach: focus on lifestyle modifications, with pharmacological interventions as a supplement. According to the GRADE grading system, Type I evidence interventions can be used as a core protocol in clinical practice, class II evidence interventions represent viable options for personalized implementation, and class III evidence—together with preclinical studies—points to future directions for targeted precision interventions.

The metabolic-inflammatory axis theoretical framework shifts the cognitive pattern of aging-related multimorbidity from isolated management of single-organ lesions to an integrated assessment of multi-system homeostasis. In the next ten years, it is urgent to rely on mechanism-oriented cohort research, key technical tool research and development, and adaptive clinical trials to gradually fill the existing evidence gap and promote the efficient transformation of this theoretical framework into clinical practice.

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