

The multifaceted role of GLP-1 in metabolic disorders, chronic inflammation, and aging: Mechanisms and therapeutic potential[☆]

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ABSTRACT

Glucagon-like peptide-1 (GLP-1), an incretin secreted by intestinal L-cells in response to nutrients, regulates glucose homeostasis by enhancing insulin secretion, suppressing glucagon release, delaying gastric emptying, and reducing appetite via hypothalamic signaling. Beyond these canonical actions, emerging evidence reveals GLP-1's pleiotropic functions across multiple systems, with relevance to metabolic disorders, chronic inflammation, and aging-related pathologies. This review summarizes molecular mechanisms underlying GLP-1's protective roles, highlighting its contributions to metabolic balance, inhibition of NF-κB-mediated inflammation, and attenuation of cellular aging through mitochondrial enhancement and autophagy promotion. GLP-1 also influences immune cell function and alleviates hallmarks of senescence, thereby offering therapeutic potential beyond diabetes. We further critically assess the translational potential of GLP-1 receptor agonists (GLP-1RAs), pharmacological agents with superior pharmacokinetics versus native GLP-1, in treating conditions linked to dysregulated metabolism, persistent inflammation, and accelerated aging. Despite demonstrated efficacy in preclinical models and clinical studies, important challenges persist, including inter-individual variability, off-target risks, and uncertainties regarding long-term safety. We conclude by emphasizing the necessity of integrated strategies to target the metabolic–inflammatory–aging axis and by advocating optimization of GLP-1RA formulations, identification of predictive biomarkers, and expansion of their utility for age-associated diseases.

1. Introduction

Aging is associated with persistent low-grade activation of the immune system, manifested by elevated levels of inflammatory markers in circulation and the activation of immune cells in both the circulatory system and tissues [1]. The hallmarks of aging represent not merely isolated pathways but rather distinct pathophysiological entry points that collectively shape the biology of senescence and enable targeted interventions in biological senescence [2]. Current research has delineated 14 interconnected hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled autophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, extracellular matrix changes, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, and psychosocial isolation [3]. Like aging itself, chronic inflammation is

linked to an increased risk of numerous age-related diseases, disability, physical frailty, and mortality [4].

The remarkable clinical success of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in treating type 2 diabetes mellitus (T2DM) and obesity has catalyzed intense investigation into their pleiotropic, extraglycemic benefits [5]. Prominent among these is their profound anti-inflammatory capacity [6], which may provide a mechanistic bridge between metabolic correction and multi-organ protection. These effects extend to robust cardioprotective [7], hepatoprotective [8], and neuroprotective effects [9], with emerging evidence suggesting therapeutic potential in pulmonary [10] and musculoskeletal disease prevention [11].

In this review, we provide a comprehensive synthesis of the expanding roles of GLP-1 in metabolic dysregulation, chronic low-grade inflammation, and aging, emphasizing its potential as a therapeutic

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target for complex, multifactorial diseases. We first summarize key features of GLP-1 biology and the pharmacological properties of GLP-1RAs, then examine the mechanistic basis of chronic inflammation, with a particular focus on nuclear factor kappa B (NF- κ B) signaling and its crosstalk with oxidative stress and inflammasome pathways. We then discuss age-associated alterations in immune function, highlighting immunosenescence and the senescence-associated secretory phenotype (SASP) as critical modulators of responses to acute stressors. Finally, we consider the influence of the gastrointestinal microbiome, age-related dysbiosis, and integrated proteomic stress responses in shaping the inflammatory reaction to cumulative cellular and tissue damage, and we integrate organ-system evidence to define translational opportunities and remaining mechanistic gaps.

1.1. Mechanisms of chronic inflammation to aging

1.1.1. Inflammation and aging

The process of senescence is a complex phenomenon driven by intertwined molecular, cellular, and systemic alterations that cumulatively impair organismal function and predispose individuals to age-related pathologies [12]. At the molecular level, this cascade is often initiated by genomic instability, leading to the progressive accumulation of DNA damage lesions [13,14]. This is compounded by mitochondrial dysfunction, which compromises cellular integrity through both diminished bioenergetic capacity and elevated production of reactive oxygen species (ROS) [15]. Together, these insults can accelerate telomere attrition and trigger widespread epigenetic alterations that dysregulate transcription [16]. Crucially, these cumulative cellular stressors converge to trigger the SASP, converting intrinsic damage into a persistent, low-grade pro-inflammatory state known as “inflammaging.” Characterized by upregulated cytokine signaling, heightened oxidative stress, and disrupted immune homeostasis, inflammaging is a core driver of biological senescence and the subsequent decline in somatic function observed in older adults [17].

1.1.2. Inflammation and immunosenescence

Sterile inflammation is a fundamental immune response initiated by cellular damage, which leads to the release of endogenous molecules known as damage-associated molecular patterns (DAMPs). These signals are recognized by a diverse array of pattern recognition receptors (PRRs)—including membrane-bound Toll-like receptors (TLRs) and cytoplasmic NOD-like receptors (NLRs)—as well as other sensors like the receptor for advanced glycation end-products (RAGE) [18]. While PRRs are classically expressed on immune sentinel cells such as macrophages and dendritic cells, many tissue-resident non-immune cells are also equipped to initiate sterile inflammation. Engagement of these receptors triggers a rapid release of pro-inflammatory mediators, including cytokines (e.g., TNF- α , IL-1), vasoactive amines, and metabolites of arachidonic acid. This response is amplified by liquid-phase inflammatory pathways and by platelets, which express TLRs that recognize DAMPs, enabling them to propagate inflammatory cascades by secreting cytokines and chemokines [18]. When dysregulated, these pathways can drive the pathogenesis of numerous conditions, from autoimmune disorders and transplant rejection to cardiovascular disease and metabolic syndromes [19].

When these inflammatory cascades fail to resolve, they can establish the chronic, low-grade pro-inflammatory state that defines “inflammaging.” This condition is characterized by a sustained elevation of pro-inflammatory cytokines, such as IL-6, TNF- α , and MCP-1 [20,21]. Importantly, age-related immune remodeling (immunosenescence) can impair the containment and resolution of sterile inflammatory responses, thereby reinforcing chronic cytokine elevation and tissue dysfunction.

Central to the transcriptional regulation of inflammaging is the NF- κ B family of transcription factors, which acts as a pivotal signaling hub. Two major pathways govern NF- κ B activation: the canonical pathway,

which is rapidly induced by pro-inflammatory cytokines (e.g., TNF- α , IL-1) and pathogen-associated molecular patterns (PAMPs) via receptors like TLR4 [22]; and the non-canonical pathway, which provides a more sustained response and is triggered by specific members of the TNFR superfamily, such as CD40 and RANK [23]. PANoptosis is a unique inflammatory cell death pattern involving the interplay of pyroptosis, apoptosis and necroptosis, which can be mediated by a multiprotein PANoptosome complex that integrates components of other cell death modalities [24]. By modulating the TLR4/NF- κ B signaling pathway, the expression of the proinflammatory cytokine TNF- α is reduced, which further inhibits the assembly of the PANoptosome complex. This subsequently attenuates the explosive release of DAMPs, fundamentally alleviates chronic low-grade inflammation, and ultimately delays the onset of senescence [25,26]. Together, these pathways enable both rapid inflammatory induction and longer-lived transcriptional programs, helping explain how repeated DAMP/PRR inputs can be “memorized” as persistent inflammatory signaling during aging. Thus, the NF- κ B pathway is a critical orchestrator of the immune responses that underpin inflammaging.

2. Materials and methods

This review is grounded in a comprehensive survey of the literature examining the relationships among GLP-1, chronic inflammation, and aging. We conducted a systematic search of PubMed, Web of Science, and Google Scholar for peer-reviewed articles using the keywords ‘GLP-1’, ‘inflammation’, ‘NF- κ B’, and ‘aging’. Our synthesis prioritized original studies and review articles published in English since 2004, a timeframe that captures the rapid expansion of research in this area. In total, we identified 155 original research articles (including clinical trials and preclinical studies) and 1103 review articles. We excluded non-English publications and studies that were not directly relevant to GLP-1 or inflammatory mechanisms. For each included original study, we extracted key information including the title, publication year, first and corresponding authors, study subjects (human or animal), number of cohorts/experiments, total sample size, aging-related indicators, and available measures of heterogeneity. We then performed a narrative, critical synthesis, giving greater weight to high-quality evidence from rigorous study designs and higher-impact sources.

3. Molecular mechanisms of GLP-1

GLP-1 is a gut-derived incretin hormone that functions as a key regulator of metabolic homeostasis. Its canonical action is to enhance glucose-dependent insulin secretion while concurrently suppressing glucagon release [27]. These effects are mediated by the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor whose broad tissue distribution—high in the pancreas and central nervous system (CNS) and lower in the heart, lungs, kidneys, and skeletal muscle—helps explain the pleiotropic biology of GLP-1 and its analogues [28]. Upon ligand binding, GLP-1R activates adenylyl cyclase, elevating intracellular cAMP and engaging downstream cAMP-sensitive effectors that coordinate metabolic and cellular responses [29].

Beyond this canonical pathway, GLP-1 biology appears to include receptor-independent signaling. Its primary metabolite, GLP-1(9–36), has been reported to exert GLP-1R-independent effects, including activation of the phosphatidylinositol 3-kinase (PI3K)–protein kinase B (PKB/Akt) signaling cascade [30]. Together, signaling initiated by GLP-1 and its analogues translates into a broad spectrum of systemic benefits, extending from improvements in insulin resistance and hyperglycemia to clinically relevant effects on weight reduction, blood pressure lowering, attenuation of ROS generation, and modulation of inflammatory responses [31].

Table 1
Characteristics of included clinical studies on GLP-1 and inflammatory markers.

Study	Country	No	Study arm, experimental	Inflammatory markers
Liping et al., 2023 [52]	China	39	Liraglutide	IL-6, IL-1 β , TNF- α , Adiponectin, CRP
Ying et al., 2023 [53]	China	30	Liraglutide	IL-6, Adiponectin, CRP
Xie et al., 2022 [54]	China	60	Dulaglutide	IL-6, TNF- α
Ahmad et al., 2021 [55]	UK	61	Liraglutide	IL-6, TNF- α
Kang et al., 2021 [56]	China	159	Exenatide	IL-6, TNF- α
Li et al., 2021 [57]	China	112	Liraglutide	IL-1 β , TNF- α
Jiang et al., 2020 [58]	China	116	Liraglutide	Adiponectin
Sun et al., 2020 [59]	China	108	Liraglutide	TNF- α
Yao et al., 2020 [60]	China	60	Liraglutide	IL-6, Leptin
Zhao et al., 2020 [61]	China	60	Liraglutide	CRP, Leptin
Wang et al., 2020 [62]	China	60	Liraglutide	CRP
Anholm et al., 2019 [63]	Denmark	39	Liraglutide	TNF- α , CRP
Ahmadi, 2019 [64]	Sweden	122	Liraglutide	Adiponectin
Li et al., 2019 [65]	China	23	Dulaglutide	IL-6, TNF- α
Pavithra et al., 2019 [66]	India	80	Liraglutide	CRP
Wagner et al., 2019 [67]	Spain	24	Liraglutide	CRP
Wang et al., 2019 [68]	China	25	Dulaglutide	IL-6, TNF- α
Yan et al., 2019 [69]	China	99	Liraglutide	IL-6
Jian et al., 2018 [70]	China	116	Liraglutide	TNF- α
Li et al., 2018 [71]	China	86	Liraglutide	Adiponectin
Said et al., 2018 [72]	Ukraine	100	Liraglutide	IL-6, TNF- α , CRP
Tian et al., 2018 [74]	China	127	Liraglutide	Adiponectin
Bouchi et al., 2017 [75]	Japan	17	Liraglutide	CRP
Pastel et al., 2017 [76]	UK	22	Liraglutide	CRP
Quan et al., 2017 [77]	China	200	Exenatide	CRP, TNF- α
Shi et al., 2017 [78]	China	31	Exenatide	IL-6, TNF- α
von Scholten et al., 2017 [79]	Denmark	27	Liraglutide	TNF- α
Liu et al., 2017 [73]	China	60	Liraglutide	CRP
Savvidou et al., 2016 [35]	Greece	110	Exenatide	CRP, Adiponectin
Dutour et al., 2016 [36]	France	44	Exenatide	Adiponectin, Leptin
Farr et al., 2016 [37]	Israel	20	Liraglutide	Adiponectin, Leptin
Monnier et al., 2016 [38]	USA	102	Exenatide	IL-6
Lin et al., 2015 [39]	China Taiwan	51	Exenatide	CRP
Simo et al., 2015 [40]	Multi	1019	Exenatide	CRP
Takeshita et al., 2015 [41]	Japan	112	Liraglutide	TNF- α
Bi et al., 2014 [42]	China	44	Exenatide	Adiponectin

Table 1 (continued)

Study	Country	No	Study arm, experimental	Inflammatory markers
Gurkan et al., 2014 [43]	Turkey	34	Exenatide	MCP-1, IL-6, IL-1 β , TNF- α , Adiponectin, CRP
Suzuki et al., 2014 [44]	Japan	40	Liraglutide	CRP
Fan et al., 2013 [45]	China	117	Exenatide	TNF- α , Adiponectin
Liang et al., 2013 [46]	China	70	Exenatide	CRP, Adiponectin, Leptin, TNF- α
Derosa et al., 2012 [47]	Italy	171	Exenatide	CRP
Forst et al., 2012 [48]	Germany	40	Liraglutide	MCP-1, CRP
Wu et al., 2011 [49]	China	23	Exenatide	CRP
Bunck et al., 2010 [50]	Multi	69	Exenatide	IL-6, CRP, MCP-1, Adiponectin
Derosa et al., 2010 [51]	Italy	128	Exenatide	CRP
Courrèges et al., 2008 [34]	Denmark	163	Liraglutide	IL-6, Adiponectin, TNF- α

Abbreviations: GLP, glucagon-like peptide; No, number of subjects; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein.

4. GLP-1 in modulation of chronic inflammation

Consistent evidence from in vitro studies and preclinical models indicates that GLP-1 RAs exert potent anti-inflammatory and immunomodulatory effects, mediated through partially distinct pathways across tissues [32]. One important mechanism involves direct effects on adaptive immunity. For example, GLP-1R expression can be induced on activated human CD4⁺ T cells, with enrichment on induced regulatory T cells (iTregs), enabling GLP-1R agonists to act on these populations and enhance their immunosuppressive function, thereby contributing to systemic anti-inflammatory activity [33].

These mechanistic observations are supported by a substantial body of randomized controlled trials showing that GLP-1-based therapies are associated with improved indices of chronic low-grade inflammation and immune homeostasis in humans (Table 1) [34–79]. At the molecular level, the anti-inflammatory effects of GLP-1 signaling appear to be multifactorial, encompassing modulation of central inflammatory programs such as NF- κ B, engagement of metabolic stress-response pathways including AMPK/sirtuin 1 (SIRT1), attenuation of reactive oxygen species (ROS) generation, and reinforcement of cellular maintenance processes such as autophagy and mitochondrial quality control [75,76]. Building on this framework, the following sections examine how these anti-inflammatory mechanisms translate into organ-specific effects across major physiological systems.

4.1. Nervous system

Aging-associated neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease, are underpinned by a convergence of pathogenic mechanisms [80–82]. These include chronic oxidative stress, the accumulation of misfolded proteins, persistent DNA damage, and the dysregulation of crucial cellular processes such as autophagy, mitochondrial function, and apoptosis [83–86]. Within this shared mechanistic landscape, neuroinflammation has emerged not merely as a correlate but as a key amplifier of neuronal injury and disease progression.

Specifically, pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) play pivotal roles. TNF- α activates its cognate receptors (TNFR1 and TNFR2), while IL-1 β engages the IL-1 receptor (IL-1R), both initiating signaling cascades that promote neuroinflammation, excitotoxicity, and ultimately, neurodegeneration [87].

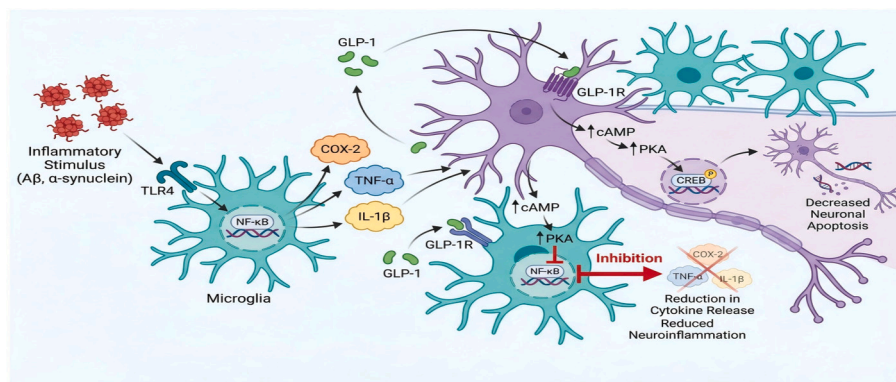


Fig. 1. GLP-1-mediated inhibition of microglial neuroinflammation and neuronal protection in rodent models. (A) Microglial activation: Inflammatory stimuli (e.g., A β , α -synuclein) bind to microglial TLR4, activating NF- κ B and driving secretion of pro-inflammatory factors (COX-2, TNF- α , IL-1 β). (B) GLP-1R signaling in microglia: GLP-1 binds to microglial GLP-1R, activating cAMP/PKA pathways to inhibit NF- κ B, thereby reducing pro-inflammatory cytokine release. (C) Neuronal protection: GLP-1 binds to neuronal GLP-1R, activating cAMP/PKA/CREB signaling to reduce neuronal apoptosis; this also synergizes with reduced microglial inflammation to alleviate neuroinflammation.

Accordingly, elevated TNF- α and IL-1 β constitute a shared pathological signature that bridges classical neurodegeneration (e.g., AD and PD) with broader neuropsychiatric phenotypes, including schizophrenia and bipolar disorder [6].

The production of inflammatory and neurotoxic mediators is linked to intracellular dysregulations, including impaired protein degradation, mitochondrial dysfunction, defective axonal transport, and apoptotic signaling, driving neurodegenerative pathology progression [88]. Emerging evidence indicates that neuroinflammation is closely associated with activation of I κ B kinase (IKK)-NF- κ B and MAPK signaling. Notably, even in the absence of neuropathological changes, physiological aging can induce astrocytes to exhibit morphological hypertrophy and functional reprogramming. These changes are related to increased levels of enzymes involved in neuroinflammatory and neurodegenerative processes, as well as adhesion molecules and chemokines essential for the inflammatory response [89]. These observations support a model in which aging primes glial cells toward a pro-inflammatory state, lowering the threshold for sustained neuroinflammation in response to subsequent insults.

GLP-1 has neuroprotective and anti-inflammatory properties, with its receptor expressed in neurons, microglia, and astrocytes in key brain regions [90]. Specifically, activation of GLP-1R in the brain enhances cAMP levels, activating PKA and stimulating the mitogen-activated PK/extracellular signal-regulated kinase (MAPK/ERK) anti-inflammatory signaling axis. This cascade promotes activation of cAMP response element-binding protein (CREB), orchestrating cellular responses to oxidative stress and DNA damage, coupled with downregulation of pro-apoptotic factors and upregulation of anti-apoptotic regulators [91]. Through these integrated signaling programs, GLP-1R activation plausibly couples neurometabolic regulation to suppression of inflammatory transcriptional outputs in the CNS.

Through these mechanisms, GLP-1 modulates neurometabolic processes within the CNS via multifaceted anti-inflammatory pathways (Fig. 1) [92]. The therapeutic potential of GLP-1 in AD and PD has been verified in primary murine mixed neuronal cultures stimulated with amyloid- β (an AD mimic) or α -synuclein (a PD mimic). In rodent models, GLP-1 agonists reverse inflammation-induced synaptic deficits in the hippocampus, alleviate amyloid- β (A β) deposition, reduce inflammatory glial activation, and decrease the expression of pro-inflammatory mediators including cyclooxygenase-2 (COX-2), TNF- α , IL-1 β , and TLR4. They also inhibit NF- κ B/TLR4 signaling activity, thereby attenuating perineuronal inflammation [29,91,93].

Real-world data studies have demonstrated that GLP-1 RAs exhibit significant potential in ameliorating clinical symptoms and delaying disease progression in AD, likely mediated through neuroprotective

mechanisms involving anti-inflammatory effects, attenuation of amyloid- β deposition, and enhancement of neuronal insulin signaling pathways [94]. However, the research lacks direct evidence to prove that GLP-1 inhibits inflammation by suppressing the NF- κ B pathway.

4.2. Cardiovascular system

The aging process exerts profound effects on the cardiovascular system through complex interplay between molecular and cellular mechanisms, leading to structural and functional alterations that compromise cardiac and vascular integrity [95]. Beyond traditional risk factors like hypertension and dyslipidemia, atherosclerosis is increasingly recognized as a chronic vascular inflammatory process driven by non-traditional contributors, including cellular senescence, oxidative stress, and epigenetic modifications [96–98].

The initiation of atherosclerosis is mediated by endothelial cell (EC) activation in response to pro-atherogenic stimuli. Following exposure to oxidized low-density lipoprotein (ox-LDL), vascular ECs upregulate cytokines, chemokines, and cell adhesion molecules, thereby recruiting circulating leukocytes to the subendothelial space of the arterial intima [99]. A diverse array of pro-atherogenic factors—including pro-inflammatory cytokines (TNF- α , IL-1), microbial products, and advanced glycation end products (AGEs)—converge on activation of the NF- κ B pathway, establishing it as a central hub in vascular inflammation [100].

Oxidative stress further amplifies this cascade. Excessive ROS production in ECs induces overexpression of adhesion molecules such as MCP-1, ICAM-1, and VCAM-1, which facilitate monocyte adhesion and infiltration [101]. Mechanistically, ROS also function as second messengers activating NF- κ B in response to angiotensin II (Ang II). The Ang II-ROS-NF- κ B axis establishes a critical molecular link between hypertension and atherosclerotic risk by perpetuating vascular inflammation, triggering endothelial nitric oxide synthase (eNOS) uncoupling, and stimulating vascular smooth muscle cell (VSMC) proliferation [102].

This chronic inflammatory state within vessel walls contributes to acute thrombotic events such as myocardial infarction (MI). In MI, inflammatory platforms including the NLRP3/caspase-1 inflammasome and TLR4/MyD88/NF- κ B signaling cascade become central regulators of tissue damage and adverse cardiac remodeling, making them promising therapeutic targets [103,104].

Reflecting these insights, extensive clinical studies demonstrate that GLP-1 RAs significantly reduce MI incidence, attenuate atherosclerosis progression, and improve heart failure outcomes. These benefits are mediated through pleiotropic actions including glycemic control, direct anti-inflammatory modulation, and the restoration of endothelial

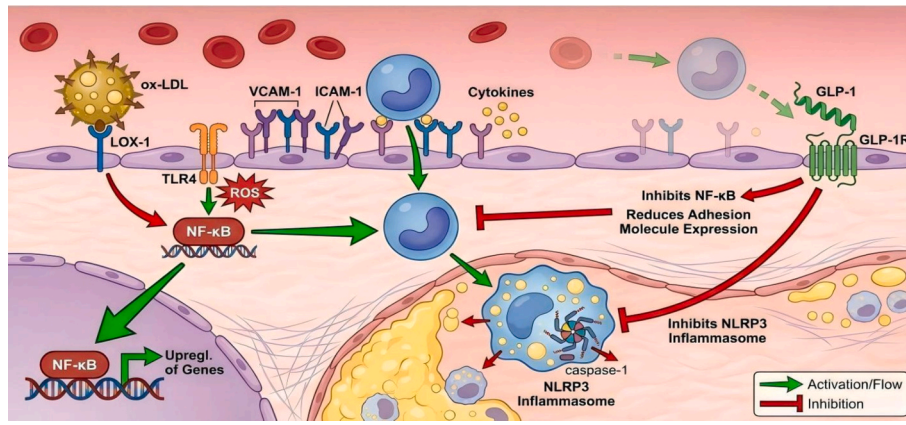


Fig. 2. GLP-1 suppresses vascular inflammation and leukocyte recruitment via dual inhibition of NF-κB and NLRP3 inflammasome. (A) Vascular inflammation initiation: ox-LDL binds to endothelial LOX-1, activating TLR4/ROS/NF-κB to upregulate adhesion molecules (VCAM-1, ICAM-1) and cytokines, promoting leukocyte adhesion/recruitment; NF-κB also drives NLRP3 inflammasome activation (caspase-1 cleavage). (B) GLP-1-mediated inhibition: GLP-1 binds to endothelial GLP-1R, suppressing NF-κB (reducing adhesion molecule expression) and NLRP3 inflammasome activation, thereby attenuating vascular inflammation and leukocyte infiltration.

function [105–108]. Preclinical data show that liraglutide alleviates myocardial inflammatory responses in murine models of ischemia-reperfusion (I/R) injury by activating the TANK-binding kinase 1 (TBK1)-NF-κB signaling pathway [109]. Clinical findings further indicate that GLP-1 analogs downregulate Raf kinase inhibitor protein expression in human cardiomyocytes and activate the TBK1–NF-κB axis, thereby suppressing pro-inflammatory cytokine production and inhibiting NLRP3 inflammasome activation [110,111].

Therefore, GLP-1 RAs exert cardioprotective effects by modulating the NF-κB signaling pathway, attenuating chronic inflammatory responses, and ultimately mitigating the development of cardiovascular diseases (Fig. 2).

4.3. Respiratory system

Accumulating evidence suggests that pulmonary aging is characterized by an increased susceptibility to diverse lung pathologies, a process fundamentally linked to dysregulation of the NF-κB inflammatory pathway. Chronic NF-κB activation promotes neutrophil inflammation, protease–antiprotease imbalance, and accelerated destruction of alveolar structures—hallmark features driving chronic obstructive pulmonary disease (COPD) and acute lung injury (ALI) [112]. Advances in immunohistochemical analysis have revealed distinctive structural characteristics of the aging lung, providing new insights into mechanisms underlying chronic respiratory diseases such as COPD and ALI

[112].

In ALI, overexpression of Toll-like receptor 4 (TLR4) activates NF-κB signaling, driving pro-inflammatory cytokine production and promoting apoptosis through caspase-3 activation [113,114]. Parallel investigations in COPD patients and murine models further reveal that non-canonical NF-κB signaling enhances inflammation, characterized by elevated levels of cytokines (IL-6, IL-8) and matrix metalloproteinases (MMPs). Notably, pharmacological inhibition this pathway significantly reduces airway neutrophil infiltration and pulmonary parenchymal destruction [115].

Given that GLP-1R is robustly expressed within lung tissues, its potential as a therapeutic target has gained significant attention. A retrospective study reported that COPD patients treated with GLP-1 RAs had milder disease severity compared with those on insulin or oral hypoglycemic agents [116]. These clinical observations are corroborated by animal studies demonstrating that GLP-1 reduces systemic inflammation, lowers mortality, and improves overall lung function in COPD models [117,118]. Preclinical work further shows that liraglutide and exenatide alleviate leukocyte infiltration and ROS accumulation in sepsis- and ALI-induced mice [119,120].

Mechanistically, the protective effects of GLP-1 in the respiratory system are multimodal. GLP-1 suppresses NF-κB-mediated release of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ) while simultaneously activating the eNOS/soluble guanylate cyclase/PKG pathway. This activation enhances NO-dependent vasodilation and

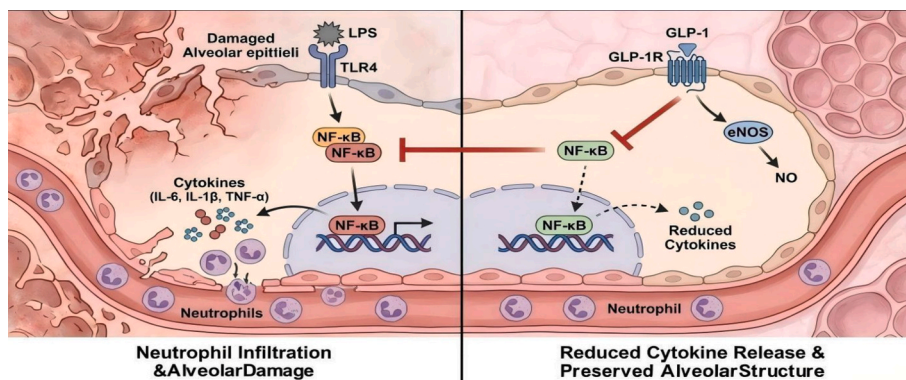


Fig. 3. GLP-1 attenuates LPS-induced alveolar inflammation and preserves lung structure via NF-κB inhibition and eNOS activation. (A) LPS-induced alveolar damage (left): LPS binds to alveolar epithelial TLR4, activating NF-κB to drive pro-inflammatory cytokine (IL-6, IL-1β, TNF-α) release, promoting neutrophil infiltration and alveolar epithelial injury. (B) GLP-1-mediated protection (right): GLP-1 binds to alveolar epithelial GLP-1R, suppressing NF-κB (reducing cytokine release) and activating eNOS (generating NO), thereby reducing neutrophil infiltration and preserving alveolar structure.

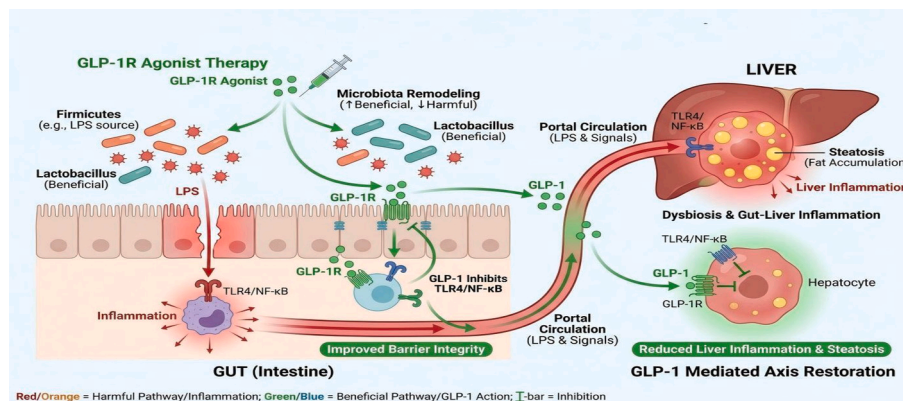


Fig. 4. GLP-1R agonist restores gut-liver axis homeostasis by remodeling microbiota and inhibiting inflammation. (A) Gut dysbiosis and gut-liver inflammation (harmful pathway): Firmicutes (LPS source) dominate gut microbiota, disrupting intestinal barrier integrity; LPS enters portal circulation, activating hepatic TLR4/NF-κB to drive liver steatosis and inflammation. (B) GLP-1R agonist action (beneficial pathway): Remodels gut microbiota (increase Lactobacillus, decrease harmful Firmicutes) and improves intestinal barrier integrity; Inhibits gut/hepatic TLR4/NF-κB signaling, reducing LPS translocation and hepatic inflammation. Directly acts on hepatocytes via GLP-1R to alleviate steatosis, restoring gut-liver axis homeostasis.

restores vascular homeostasis, which collectively mitigate alveolar–capillary barrier damage, oxidative stress, and pulmonary edema during ALI [121,122]. While these findings strongly position GLP-1RAs as pleiotropic agents for inflammatory respiratory diseases (Fig. 3), a substantial translational gap remains.

4.4. Gastrointestinal system

Aging is associated with a progressive decline in gastrointestinal integrity, characterized by epithelial barrier weakening, microbial dysbiosis, and reduced hepatic regenerative capacity. These changes contribute to heightened susceptibility to chronic inflammation, metabolic liver disease, and age-related GI malignancies, collectively termed ‘gut aging’ [123]. A hallmark of this pathological progression is the activation of the TLR4/NF-κB signaling cascade, fueled by elevated levels of circulating bile acids and lipopolysaccharides (LPS), which orchestrates the upregulation of pro-inflammatory cytokines. Conversely, modulating the gut environment—through probiotic supplementation or fecal microbiota transplantation—can stimulate farnesoid X receptor (FXR), pregnane X receptor (PXR), and efflux transporters (e.g., BSEP, MRP2). These interventions effectively attenuate liver inflammation by lowering bile acid concentrations and fortifying intestinal integrity through the suppression of TLR4/NF-κB signaling [124–126].

The oncogenic potential of gut dysbiosis further highlights the centrality of the NF-κB pathway. Pathogenic infiltration, notably *Helicobacter pylori* in gastric cancer and *Fusobacterium nucleatum* in CRC, exploits NF-κB to maintain a chronic inflammatory milieu (via TNF-α and IL-6) and trigger neoplastic transformation through the Wnt/β-catenin pathway. Furthermore, NF-κB activation drives the expression of anti-apoptotic factors such as cyclin D1 and Bcl-2, thereby facilitating genomic instability and immune evasion [127,128].

Emerging evidence suggests that GLP-1 RAs, beyond their established metabolic roles, provide robust gastrointestinal protection. Pre-clinical studies indicate that GLP-1 RAs remodel the gut microbiota by enriching beneficial taxa (e.g., *Lactobacillus reuteri*) and suppressing pathogens (e.g., *Staphylococcus*). This microbial reshaping modulates group 3 innate lymphoid cells (ILC3s) and inhibits NF-κB-driven signaling, thereby ameliorating experimental colitis [129].

Clinically, GLP-1 RAs alleviate liver injury in patients with metabolic dysfunction-associated steatohepatitis (MASH) through dual mechanisms: (i) stabilization of IκBα, thereby blocking downstream NF-κB/IκBα pro-inflammatory signaling; and (ii) inhibition of ERK1/2–NF-κB activation, reducing oxidative stress and caspase-dependent hepatocyte apoptosis [130–133]. GLP-1RAs have achieved substantive progress in the

treatment of MASH, the principal advance lies in their capacity to confer hepatic benefits through systemic metabolic modulation, a finding corroborated by real-world evidence. Nonetheless, this therapeutic domain continues to confront critical challenges, most notably the limited efficacy in reversing advanced liver fibrosis and a deficit of long-term efficacy and safety data.

By modulating gut microbiota composition and suppressing NF-κB signaling, GLP-1 exerts protective effects against intestinal inflammation, liver fibrosis, and MASH-induced injury (Fig. 4).

4.5. Endocrine system

Biological senescence profoundly reshapes the endocrine landscape, instigating physiological and biochemical shifts that compromise systemic homeostasis and metabolic integrity. Epidemiological data underscore an age-dependent escalation in the prevalence of diabetes mellitus (DM) and prediabetes, characterized by progressive pancreatic β-cell senescence and dysfunction in both Type 1 (T1DM) and Type 2 (T2DM) cohorts [134,135]. Within the diabetic milieu, accelerated cellular aging, renal impairment, and the systemic accumulation of advanced glycation end-products (AGEs) synergistically exacerbate tissue injury. Mechanistically, the LPS-TLR4-NF-κB axis, alongside the p38 mitogen-activated protein kinase (p38 MAPK) cascade, functions as a critical molecular conduit for propagating chronic inflammation and driving insulin resistance, thereby anchoring the pathophysiology of diabetic progression [136–138].

Beyond traditional glycemic management and adiposity reduction, GLP-1 RAs have demonstrated substantial therapeutic efficacy against microvascular and macrovascular complications, including retinopathy, nephropathy, and neuropathy. These benefits are largely attributed to their potent anti-inflammatory and endothelial cytoprotective properties [5,139,140]. Clinical evidence, such as findings from a Korean cohort, reveals that the co-administration of liraglutide and insulin significantly reduces circulating MCP-1 levels and sequesters NF-κB activation. This molecular suppression alleviates systemic inflammation and insulin resistance, ultimately optimizing glycemic control in T2DM patients [141].

Complementing clinical observations, experimental models elucidate that GLP-1 RAs suppress the NF-κB-driven priming and activation of the NLRP3 inflammasome within perivascular adipose tissue. This targeted inhibition effectively rebalances the cytokine profile—marked by diminished IL-1β and NF-κB expression alongside elevated IL-10 levels—and restores superoxide dismutase (SOD) activity. Consequently, these agents attenuate vascular inflammation and enhance insulin sensitivity, offering a multi-layered defense against metabolic

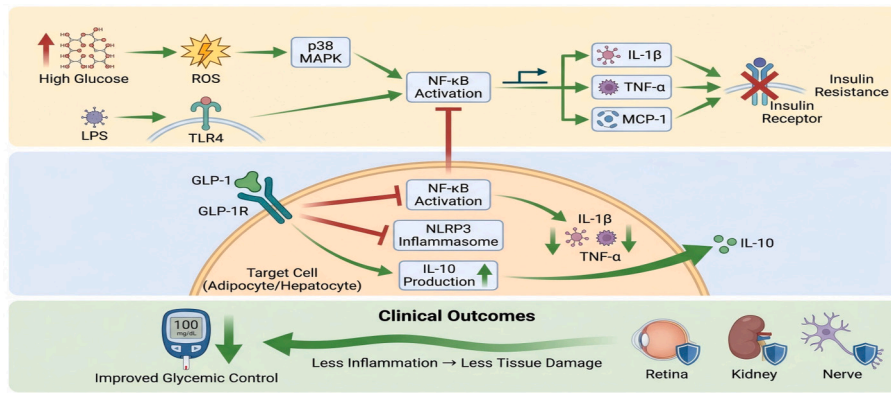


Fig. 5. GLP-1 alleviates inflammation-induced insulin resistance and tissue damage via multi-pathway regulation. (A) Inflammation and insulin resistance initiation: High glucose (via ROS/p38 MAPK) or LPS (via TLR4) activates NF-κB, driving pro-inflammatory cytokine (IL-1β, TNF-α, MCP-1) release to impair insulin receptor function. (B) GLP-1-mediated modulation: GLP-1 binds to GLP-1R on target cells (adipocytes/hepatocytes) to: Inhibit NF-κB activation and NLRP3 inflammasome; Reduce pro-inflammatory cytokines and promote anti-inflammatory IL-10 production; Attenuated inflammation improves glycemic control and reduces tissue damage in retina, kidney, and nerves.

dysregulation (Fig. 5) [142,143].

4.6. Genitourinary system

Aging exerts profound and multifaceted deleterious effects on the genitourinary system, characterized by a progressive decline in reproductive senescence and the emergence of chronic, low-grade inflammation as a pivotal pathogenic driver [144].

In the aging male, serum testosterone levels undergo a steady attrition of approximately 1% annually post-30, an effect that accelerates significantly beyond the age of 60. This hypogonadal state is inextricably linked to sarcopenia, osteopenia, and erectile dysfunction. Furthermore, by the seventh decade of life, the sperm DNA fragmentation index frequently surpasses 30%, severely compromising fertility. Concurrently, benign prostatic hyperplasia affects over 50% of men over 50, manifesting as lower urinary tract symptoms and nocturia, with refractory cases necessitated by surgical intervention [145]. In women, ovarian senescence—typically occurring around age 50—is marked by a precipitous collapse in estradiol (E2) levels (to <10% of premenopausal concentrations) and a terminal depletion of the primordial follicle reserve. This transition results in a near-total loss of natural fecundity alongside systemic perimenopausal metabolic shifts [146].

The NF-κB signaling pathway serves as a central hub for genitourinary pathologies by orchestrating inflammatory cascades, tissue fibrosis,

and cellular dysfunction. In chronic kidney disease (CKD), renal tubular injury is propagated by a novel glycolysis–lactate–histone lactylation axis that activates NF-κB, thereby inducing pro-fibrotic cytokine expression [145,147]. Within the reproductive domain, NF-κB activation in polycystic ovary syndrome (PCOS) promotes granulosa cell apoptosis and ferroptosis, while in male models, it drives testicular damage through IL-6-mediated inflammatory injury [148,149]. Beyond benign pathology, NF-κB is indispensable to oncogenesis; it fosters a tumor-permissive microenvironment in ovarian and prostate cancers via IL-6 transcription, and in bladder cancer, it upregulates adhesion molecules (ICAM1, VCAM1) and matrix metalloproteinases (e.g., MMP9) to facilitate invasion and metastasis [150].

GLP-1 RAs have emerged as multimodal protective agents across the genitourinary spectrum. Their potent renoprotective efficacy in diabetic kidney disease is well-established through landmark clinical trials [139,151]. Emerging evidence also highlights their oncological potential, where they inhibit tumor proliferation and modulate angiogenesis in prostate and endometrial malignancies [152]. Mechanistically, GLP-1 RAs mitigate diabetic testicular dysfunction through the GLP-1/kisspeptin-1/GnRH and TGF-β/Smad pathways [151].

Notably, GLP-1 RAs demonstrate significant therapeutic promise in PCOS management. Preclinical models indicate that semaglutide attenuates ovarian inflammation by modulating the AMPK/SIRT1/NF-κB axis, restoring ovarian morphology. Clinically, agents like liraglutide

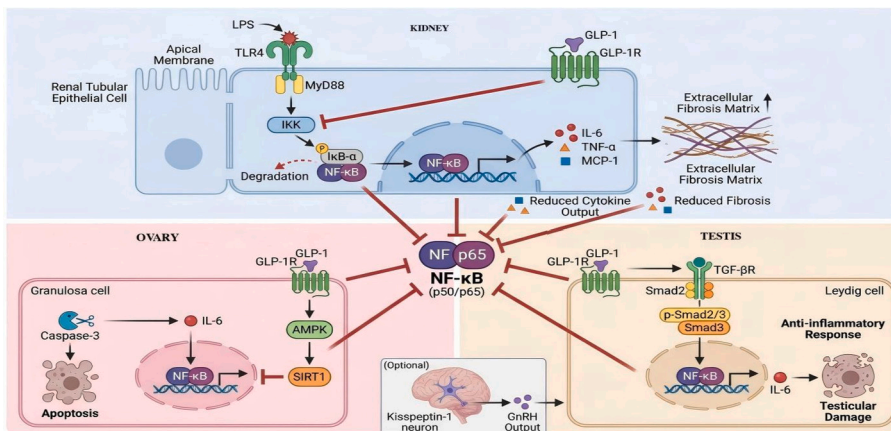


Fig. 6. GLP-1 inhibits NF-κB-mediated inflammation and tissue damage across renal, ovarian, and testicular tissues. (A) Renal tubule: LPS activates TLR4/MyD88/IKK to degrade IκB-α, releasing NF-κB to drive pro-inflammatory cytokines (IL-6, TNF-α, MCP-1) and fibrosis; GLP-1R signaling blocks IKK, reducing cytokine output and fibrosis. (B) Ovary: NF-κB promotes IL-6 release to induce granulosa cell apoptosis; GLP-1R activates AMPK/SIRT1 to inhibit NF-κB, reducing apoptosis. (C) Testis: NF-κB drives IL-6 to cause testicular damage; GLP-1R inhibits NF-κB (and modulates TGF-βR/Smad) to trigger anti-inflammatory responses.

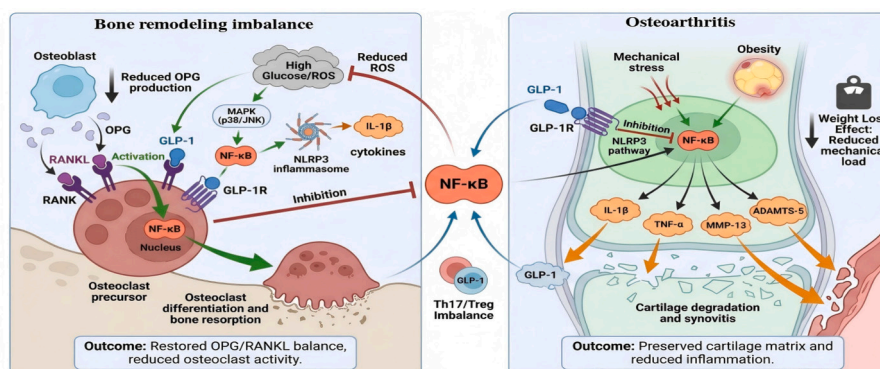


Fig. 7. GLP-1 restores bone remodeling balance and alleviates osteoarthritis via NF- κ B inhibition. (A) Bone remodeling imbalance: High glucose/ROS reduce osteoblast OPG production; RANKL activates osteoclast precursors via NF- κ B/MAPK/NLRP3, promoting osteoclast differentiation/resorption. GLP-1 (via GLP-1R) inhibits NF- κ B, restoring OPG/RANKL balance and reducing osteoclast activity. (B) Osteoarthritis: Mechanical stress/obesity activate NF- κ B/NLRP3, driving pro-inflammatory cytokines (IL-1 β , TNF- α) and matrix-degrading enzymes (MMP-13, ADAMTS-5) to induce cartilage degradation. GLP-1 (via GLP-1R) inhibits NF- κ B/NLRP3, preserves cartilage matrix, and reduces inflammation (aided by weight loss reducing mechanical load).

offer dual benefits: improving anthropometric parameters (BMI, waist circumference) and metabolic markers (insulin sensitivity) while simultaneously suppressing hyperandrogenism and optimizing adipose tissue distribution [153–155]. Collectively, these findings underscore that the systemic anti-inflammatory actions of GLP-1 RAs—specifically the suppression of NF- κ B-mediated transcription—constitute a fundamental mechanism for preserving genitourinary health (Fig. 6).

4.7. Musculoskeletal system

The physiological trajectory of skeletal senescence is marked by the decline of growth hormone and insulin-like growth factor 1 activity—a state termed somatopause. This endocrine transition is inextricably linked to chronic systemic inflammation, sarcopenia, and impaired regenerative capacity [156,157]. At the cellular level, aging-associated reductions in osteoblast numbers diminish osteoprotegerin (OPG) secretion, thereby increasing the bioavailability of RANKL to its receptor, RANK. This uncoupling of the OPG/RANKL ratio triggers the NF- κ B signaling cascade, accelerating osteoclastogenesis and disrupting bone homeostasis, which serves as a primary driver of osteopenia and osteoporosis [158].

Parallel to endocrine shifts, immune dysregulation further destabilizes the skeletal microenvironment. While regulatory T (Treg) cells typically restrain osteoclast differentiation and promote bone formation via Wnt10b induction in CD8⁺ T cells, an imbalance in the Th17/Treg axis shifts the milieu toward pro-inflammatory cytokine dominance. Th17 cells enhance the secretion of bone-resorptive mediators, fundamentally contributing to the pathogenesis of age-related bone loss [159]. Metabolic disturbances further amplify this deterioration; under hyperglycemic conditions, excessive ROS function as upstream triggers for a synergistic MAPK–NF- κ B–NLRP3 interplay. This molecular loop accelerates osteoclast activity and facilitates the progression of osteoporosis through sustained inflammasome activation [160].

Degenerative musculoskeletal disorders, such as osteoarthritis (OA) and intervertebral disc degeneration, arise from a convergence of mechanical strain and metabolic insults (e.g., obesity, insulin resistance, and dyslipidemia). These stressors synergistically activate NF- κ B, leading to the pathological release of catabolic enzymes (MMP-13, ADAMTS-5) and pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6). Such cascades drive cartilage degradation, synovial inflammation, and deleterious subchondral bone remodeling [161–163].

GLP-1 RAs offer robust therapeutic potential against these degenerative processes. Clinical meta-analyses and randomized trials demonstrate that GLP-1 RAs—such as liraglutide—protect against bone loss even during significant weight reduction. Specifically, long-acting GLP-1 RAs have been shown to maintain bone mineral density and increase

bone formation markers by approximately 16% in obese cohorts [164–166]. In the context of OA, GLP-1 RAs exert pleiotropic effects: they alleviate mechanical load through weight loss while simultaneously exerting direct anti-inflammatory actions on chondrocytes and synovial cells. These effects are mediated both by the suppression of systemic cytokine release via neuronal GLP-1R signaling and by local modulation of the joint environment [167,168].

Emerging paradigms highlight a novel metabolic–microbial crosstalk in musculoskeletal health. OA patients frequently exhibit dysregulated bile acid metabolism, characterized by depleted *Clostridium* species and reduced levels of GUDCA. Preclinical evidence suggests that exogenous GUDCA attenuates OA progression through FXR-dependent inhibition of synovial inflammation and pyroptosis. Furthermore, intra-articular administration of liraglutide suppresses the NF- κ B/NLRP3 axis, mitigating cartilage damage. Collectively, these findings point to a transformative gut microbiota–GUDCA–intestinal FXR–GLP-1–joint axis as a sophisticated therapeutic target for musculoskeletal longevity (Fig. 7) [169].

5. Evidence linking GLP-1 to aging processes

Aging is characterized by a progressive erosion of homeostatic resilience and physiological function, manifesting as an increased vulnerability to a spectrum of chronic pathologies, including cardiovascular diseases [170,171], respiratory disorders [172], neurodegenerative diseases [173], urogenital pathologies [174], deterioration of musculoskeletal health [175], and metabolic syndromes [176]. A primary hallmark of this senescence is “inflammaging”—a state of chronic, sterile, low-grade systemic inflammation. This process is driven by the sustained activation of the NF- κ B and NLRP3 inflammasome signaling axes, which disrupt the tissue microenvironment and promote cellular senescence [177–179]. These inflammatory cascades further aggregate systemic damage by accelerating stem cell exhaustion, compromising immune surveillance, and reinforcing telomere attrition and epigenetic remodeling, ultimately culminating in multi-organ dysfunction [180,181].

Within the biology of aging, the NF- κ B pathway occupies a quintessential role, functioning not merely as a consequence of cellular decline but as a potent molecular catalyst of the aging process itself. A self-perpetuating “vicious cycle” emerges: NF- κ B activation exacerbates systemic inflammation, which in turn provides the necessary feedback to sustain chronic NF- κ B signaling. Extensive preclinical evidence corroborates that NF- κ B-mediated inflammatory orchestration is a central mechanism underlying the synchronized aging across diverse physiological systems [182–184].

While the anti-aging potential of GLP-1 RAs has long been inferred

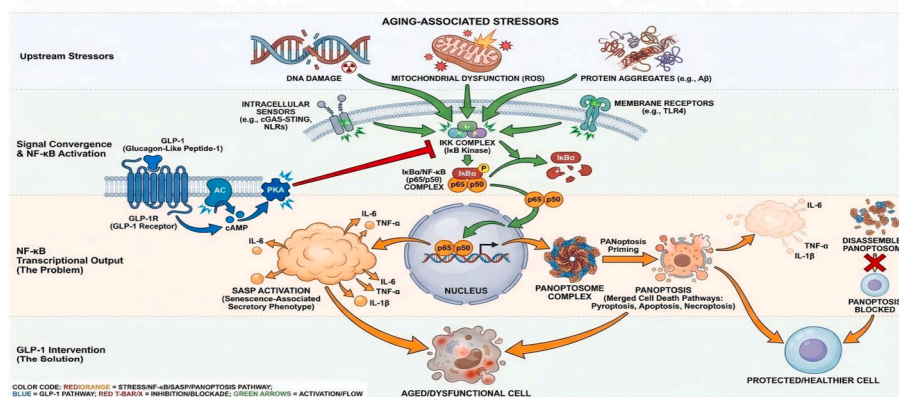


Fig. 8. GLP-1 Receptor Signaling Mitigates Aging-Associated NF-κB Activation and Restores Cellular Homeostasis. GLP-1 binding to GLP-1R activates adenylate cyclase (AC), increasing cAMP levels and activating protein kinase A (PKA). PKA inhibits the IKK complex (red blocked arrow), thereby suppressing NF-κB activation. This reduces SASP output and blocks PANoptosome assembly, ultimately protecting cells from dysfunction and promoting a healthier cellular state. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

from their secondary benefits in age-related metabolic and neurodegenerative diseases [185–187], direct evidence focusing on aging as a primary endpoint is now emerging. Recent preclinical evidence indicates that low-dose exenatide broadly counteracts aging-associated alterations at transcriptomic, methylomic, and metabolomic levels across multiple murine tissues and circulating leukocytes. Notably, these effects exhibit high similarity to those induced by rapamycin—currently the most potent pharmacological anti-aging intervention. While certain limitations remain, including the absence of lifespan extension data, exclusive use of male animals, and administration of a sub-clinical dosage, the study's integrative multi-omics design, mechanistic validation, and direct benchmarking against a gold-standard comparator collectively provide compelling preclinical support for GLP-1 receptor agonists as a promising systemic anti-aging strategy with significant translational relevance [188].

6. Limitations and future directions

Despite robust mechanistic evidence demonstrating that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) potently suppress the nuclear factor-κB/senescence-associated secretory phenotype (NF-κB/SASP) axis and panoptosis—thereby inhibiting systemic “inflammaging”—integrating these agents into geriatric therapeutic paradigms faces significant hurdles. A primary limitation is the prevalent translational gap between preclinical findings and clinical validation. While murine models and in vitro studies consistently demonstrate that GLP-1 Ras modulate aging hallmarks, direct evidence from prospective longitudinal human trials—with physiological aging as the primary endpoint—remains lacking. Consequently, the impact of these agents on the “core aging process” in disease-free or pre-symptomatic populations requires further elucidation.

The clinical translation pathway is further complicated by dual challenges in application strategy. First, preventive interventions aimed at delaying age-related decline are hindered by the lack of validated geriatric-specific biomarkers. Persistent concerns also remain regarding potential long-term chronic use spanning decades, including the risk of pancreatic β-cell exhaustion from sustained receptor overstimulation and the possibility of tachyphylaxis that may reduce clinical efficacy [189]. Second, while repurposing GLP-1 RAs as adjunctive therapy for established age-related diseases offers a more direct therapeutic avenue, a key challenge is to distinguish their specific anti-aging effects from their well-characterized metabolic and weight-loss benefits. This necessitates rigorous head-to-head trial designs to determine whether these agents genuinely modulate the rate of physiological aging per se or merely ameliorate symptoms of metabolic dysfunction.

Furthermore, real-world data indicating a weak therapeutic response in nearly 43% of certain clinical cohorts underscore substantial inter-individual variability in receptor sensitivity and downstream signaling [190]. Therefore, advancing GLP-1 RAs from efficacious, disease-specific adjuncts to cornerstone agents in aging intervention may hinge on synergistic combinations with other anti-aging targets. Validating such multi-target strategies requires interdisciplinary collaboration and innovative trial designs focusing on pre-frail populations. Only through these efforts can it be determined whether the systemic anti-inflammatory potential of GLP-1 truly extends human healthspan and enhances organismal resilience against aging.

7. Conclusion

Decades of research have mapped complex molecular pathways in aging, yet identifying actionable systemic targets remains a central challenge. Beyond its established role in metabolic regulation, GLP-1 has emerged as a key modulator of inflammatory adaptation across multiple physiological systems. GLP-1 suppresses the widely prevalent NF-κB-mediated SASP and subsequent PANoptosis—an integrated cell death process—thereby directly disrupting the pathogenic link between chronic inflammation and various age-related diseases (Fig. 8). These mechanisms provide a scientific rationale for its potential as an adjunct anti-aging therapy and, with advancing clinical translation, position GLP-1-based interventions to evolve into a cornerstone strategy for mitigating aging-associated decline.

CRediT authorship contribution statement

Mo Li: Writing – original draft, Investigation. **Shenghao Xu:** Supervision, Resources. **Hanqing Cai:** Resources, Data curation. **Jianlin Xiao:** Writing – review & editing, Investigation, Conceptualization. **Yanguo Qin:** Validation, Supervision, Funding acquisition, Conceptualization.

Role of the funder/sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Declaration of competing interest

The authors declare no conflict of interest. This research was not funded by. The authors have no financial or personal relationships with any companies or organizations that could influence the results of this study.

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