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Review Article

PAI-1 is a common driver of aging and diverse diseases

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ABSTRACT

Plasminogen activator inhibitor-1 (PAI-1) is a key driver of aging and contributes to diverse pathologies. This review examines PAI-1's multifaceted contributions to aging. At the cellular level, PAI-1 amplifies senescence, exhausts stem cell niches, and disrupts metabolism. These cellular alterations translate into physiological decline: PAI-1 drives cardiovascular aging by promoting vascular senescence and arterial stiffening, contributes to cognitive decline by impairing amyloid-beta clearance, fuels cancer progression through angiogenesis and immune suppression, and exacerbates muscle atrophy by hindering regeneration. A rare loss-of-function *SERPINE1* mutation extends lifespan, illustrating how lifelong PAI-1 reduction can positively impact the human healthspan. Looking forward, targeting PAI-1 with inhibitors could mitigate senescence, restore stem cell function, improve metabolic profile, enhance physiological health, and promise a longer healthspan.

1. Introduction

Plasminogen activator inhibitor-1 (PAI-1), encoded by the *SERPINE1* gene, is a serine protease inhibitor primarily recognized for its role in regulating fibrinolysis by inhibiting tissue-type (tPA) and urokinase-type (uPA) plasminogen activators [1]. Active tPA and uPA facilitate the conversion of plasminogen into plasmin. Subsequently, active plasmin breaks down fibrin, which is an integral meshwork of blood clots. Hence, PAI-1 effectively slows down or prevents clot breakdown. Beyond this hemostatic function, PAI-1 has emerged as a culprit in contributing to aging and age-related diseases [2–4]. A significant body of literature outlines PAI-1's involvement in cellular senescence [5,6], inflammation [7], and tissue remodeling [8,9]. Elevated PAI-1 levels are consistently observed in conditions such as cardiovascular disease [10], metabolic syndrome [11,12], cancer [13], and neurodegeneration [14], suggesting it plays an active role in the aging process.

The association between PAI-1 and aging strengthens over time. Studies across species, including humans [15] and mice [16], demonstrate that circulating PAI-1 level increases progressively with chronological age, paralleling the accumulation of senescent cells and the onset of age-related pathologies [17]. For instance, longitudinal analyses in human cohorts reveal a steep rise in plasma PAI-1 levels after middle age, correlating with increased cardiovascular risk and frailty [3]. This temporal correlation implies PAI-1 may be an active participant in aging, and not merely a passive marker.

Epigenetic aging provides further evidence of PAI-1's involvement. The GrimAge clock, a DNA methylation-based predictor of lifespan and healthspan [18], incorporates *SERPINE1* as the strongest predictor of lifespan with a p-value of 5.4E-28 [19]. Elevated PAI-1 expression is linked to accelerated epigenetic aging, reflecting a feedback loop where cellular stress drives methylation alterations that, in turn, amplify PAI-1 production. This epigenetic signature associates PAI-1 with reduced longevity and heightened disease susceptibility, positioning it as a molecular bridge between genetic regulation and aging phenotypes. Another striking illustration of PAI-1's impact comes from klotho hypomorphic (*kl/kl*) mice, a model of accelerated aging characterized by a roughly 90 % shortened lifespan [20]. These mice exhibit elevated PAI-1 levels in plasma and tissues [21]. Remarkably, genetic deletion or pharmacological inhibition of PAI-1 restores the shortened lifespan of *kl/kl* mice [21]. This rescue highlights PAI-1's potential as a therapeutic target and prompts a deeper investigation into its mechanisms.

This review outlines the cellular and molecular changes such as senescence, stem cell niche disruption, and metabolic dysregulation that underpin physiological alterations across cardiovascular health, cognition, cancer risk, and muscle integrity. Although previous reviews have extensively covered PAI-1 in the context of cardiovascular disease [22], cancer [23], and metabolic dysfunction [11], this review integrates recent evidence with seminal articles in the literature to provide evidence for the model that PAI-1 is not only involved in age-related conditions but is a central driver of the aging process itself. We lastly,

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present limitations that the field still needs to address. As the global population over 60 is projected to double from 1 billion in 2020 to 2.1 billion by 2050 [24], it may be possible to utilize PAI-1 inhibitors as a unified strategy to target multiple age-related pathological processes through a single target.

2. Cellular and molecular alterations

2.1. Senescence

Cellular senescence, a state of irreversible proliferative arrest induced by stressors like DNA damage, telomere shortening, or oxidative stress, is a hallmark of aging [25]. PAI-1 is intricately tied to this process [Fig. 1A)], serving as both a marker and a driver of senescence across multiple cell types, including fibroblasts, endothelial cells, and epithelial cells [6]. In healthy organisms, cellular senescence facilitates wound healing and halts the replication of aged cells as a mechanism to protect against cancer. PAI-1's expression surges in senescent cells, contributing to the senescence-associated secretory phenotype (SASP), a pro-inflammatory milieu rich in cytokines (e.g., IL-6, IL-8), chemokines (e.g., CCL2), and matrix metalloproteinases (MMPs) that perpetuate tissue dysfunction [26]. Mechanistically, PAI-1 operates downstream of p53, a regulator of senescence. Early studies by Kortlever et al. reveal that PAI-1 overexpression alone can induce senescence in fibroblasts, independent of p53, by inhibiting uPA-mediated proteolysis, which disrupts extracellular matrix (ECM) homeostasis and amplifies cellular stress signals [27]. Additionally, PAI-1 enhances TGF-β signaling, upregulating MMP-2 and MMP-9, which further enforce the senescent state by remodeling the ECM into a rigid, pro-inflammatory scaffold [28]. Although PAI-1 is generally accepted as a SASP component, the exact role of this molecule in inducing senescence remains unsolved. It is not yet clear whether PAI-1 induces senescence through direct interaction with specific membrane receptors, via intracellular signaling mechanisms, or indirectly through secondary molecular pathways. Future studies should focus on deconvolving intracellular and extracellular signaling of PAI-1 to shed light on this mechanism.

The consequences of PAI-1-driven senescence are detrimental, but its reduction offers a counterpoint. Research has shown that interventions targeting senescent cells can extend lifespan of murine models [29–31]. Specifically in *klotho* hypomorphic mice, *Serpine1* haploinsufficiency significantly lowers senescent cell burden, as evidenced by the decreased expression of $p16^{INK4a}$ and p21 in kidney and vascular tissues [21]. This reduction dampens SASP components, mitigating chronic inflammation and fibrosis. Pharmacological approaches complement this genetic finding: TM5441, a selective PAI-1 inhibitor, protects endothelial cells from doxorubicin-induced senescence by suppressing reactive oxygen species (ROS) production and downregulating SASP factors including IL-6 and TNF-α [32]. Furthermore, *in vitro* studies with human fibroblasts show that PAI-1 silencing via siRNA delays replicative senescence, preserving proliferative capacity and reducing β-gal activity, which is an indicator of senescence [33]. These findings suggest PAI-1 not only accelerates senescence but is a target whose inhibition could limit the accumulation of senescent cells, potentially slowing aging-related tissue decline.

2.2. Stem cell niches

Stem cell niches are specialized microenvironments that sustain stem cell function, enabling tissue repair and regeneration which are processes that falter with age [34]. As a serine protease inhibitor, PAI-1's inhibition of proteases shapes the ECM landscape of tissues important for stem cell migration. PAI-1's downstream targets of senescence also disrupt these niches through multiple pathways, compromising stem cell vitality and niche integrity [35]. In mesenchymal stromal cells (MSCs), PAI-1 inhibits tPA-dependent cleavage of insulin-like growth factor binding protein-3 (IGFBP-3), a regulator of IGF-1 signaling critical for MSC proliferation and differentiation [Fig. 1B] [36,37]. Ozcan et al. identified this PAI-1-IGFBP-3 axis as a key driver of stress-induced MSC senescence, marked by mitochondrial dysfunction (e.g., reduced ATP production) and upregulation of senescence markers [38]. Additionally, PAI-1 binds vitronectin and engages low-density lipoprotein receptor-related protein 1 (LRP1), altering ECM composition, impairing MSC adhesion, and hindering migration, which are essential for niche maintenance [39,40].

In hematopoietic stem cell (HSC) niches within the bone marrow, PAI-1's effects are equally pronounced [41]. Elevated PAI-1 levels in aged marrow correlate with reduced HSC self-renewal and skewed differentiation toward myeloid lineages, a phenomenon linked to increased ROS and disrupted CXCL12/CXCR4 signaling [42]. Similarly, in muscle satellite cell niches, PAI-1's antifibrinolytic activity impedes ECM degradation, preventing satellite cell activation and proliferation after injury [43]. When PAI-1 levels rise, niches degrade, and regenerative capacity erodes. Conversely, reducing PAI-1 restores niche dynamics as PAI-1 knockout mice exhibit improved HSC function and muscle repair

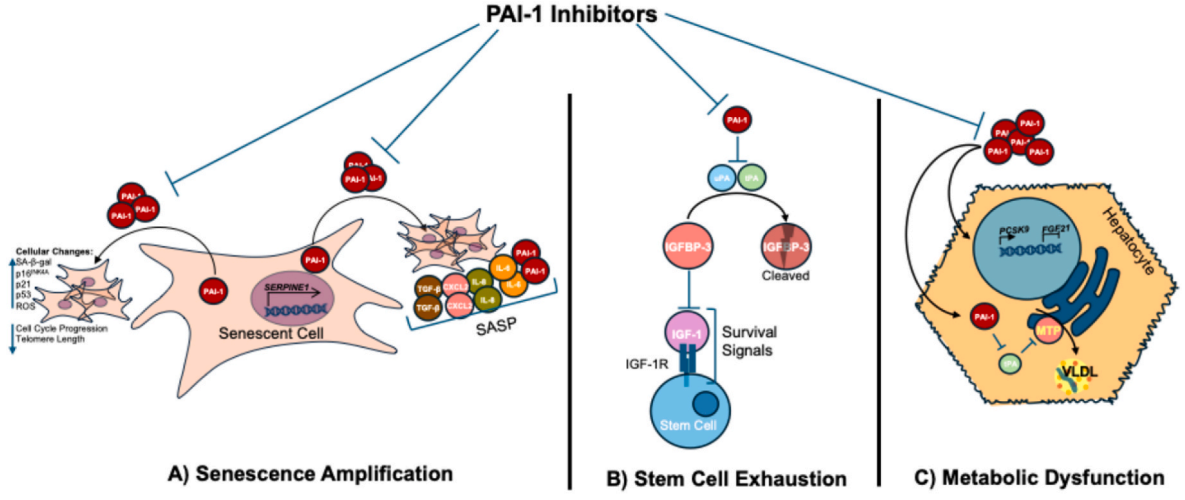


Fig. 1. PAI-1 Drives Aging Pathways via Senescence, Stem Cell Exhaustion, and Metabolic Dysfunction. (A) Senescence Amplification: PAI-1 promotes p53-driven senescence, SASP (e.g., IL-6, TGF-β), and ROS, causing cell cycle arrest and ECM remodeling. (B) Stem Cell Exhaustion: PAI-1 inhibits uPA/tPA, blocking IGFBP-3 cleavage and IGF-1 signaling, leading to stem cell senescence and niche dysfunction. (C) Metabolic Dysfunction: PAI-1 increases ROS, PCSK9, and FGF21, promoting lipid accumulation (e.g., VLDL) and mitochondrial dysfunction, exacerbating metabolic syndrome.

[44,45]. Although current data are limited to select stem cell populations, with potential relevance to other populations such as stem cells, these findings highlight PAI-1 as a regulator of stem cell aging. Modulating its activity may offer a strategy to preserve regenerative capacity and mitigate age-related decline.

2.3. Metabolism

PAI-1 also heavily influences metabolism [Fig. 1C]. Excess PAI-1 is linked to the metabolic syndrome, a cluster of conditions such as obesity, insulin resistance, and dyslipidemia that escalate with age [3]. During high fat-induced wight gain, there is experimental evidence suggesting that PAI-1 recruits inflammatory macrophages to visceral white adipose tissue, possibly to clear dead adipocytes [46]. In adipocytes, PAI-1 contributes to inflammation by upregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6), which impair insulin signaling through the PI3K-Akt pathway, reducing GLUT4 translocation to the cell membrane and diminishing glucose uptake [47]. IL-6 has independently been shown to recruit macrophages to adipose tissue and mediate the creation of foam cells [48]. However, no groups have directly demonstrated that PAI-1's role in inflammation is mediated through IL-6's ability to recruit macrophages and is a concept that prompts further investigation. This inflammatory cascade is amplified by PAI-1's inhibition of fibrinolysis, which fosters microvascular dysfunction, limiting oxygen and nutrient delivery to metabolically active tissues, and ultimately exacerbating insulin resistance [10].

PAI-1's metabolic reach extends to systemic effects. In the liver, it enhances hepatic stellate cell activation via TGF-β, promoting fibrosis and impairing lipid metabolism, which contributes to steatosis [49]. Human studies reinforce this: elevated plasma PAI-1 correlates with higher HbA1c in prediabetic patients [50]. More recently, it has been shown PAI-1's target tPA inhibits the ER-embedded Microsomal Triglyceride Transfer Protein (MTP) from synthesizing VLDLs in hepatocytes [51]. Hence, excess PAI-1 sequesters tPA from inhibiting MTP and leads to an increase in VLDL release *in vitro* and in murine models.

Reducing PAI-1 reverses these metabolic impairments. In obese mice, PAI-1 knockout enhances NAD+/NADPH ratio, improving mitochondrial function, glucose tolerance, and reducing adiposity [52]. Pharmacological inhibition of mice with TM5614 mimics this, lowering hepatic *PCSK9* expression while augmenting *FGF21* [53]. Caloric restriction, a proven anti-aging intervention, similarly suppresses PAI-1 [54], implicating a conserved pathway. These findings position PAI-1 as a metabolic switch, where its reduction could mitigate age-related metabolic decline and enhance systemic health.

3. Physiological alterations

3.1. Cardiovascular aging

Cardiovascular aging characterized by vascular senescence, arterial stiffening, and thrombosis [55] is deeply intertwined with PAI-1 and has been reviewed extensively [22,56] [Fig. 2A]. Briefly, in endothelial cells, PAI-1 contributes to dysfunction by directly binding to endothelial Nitric Oxide Synthase (eNOS), inhibiting the production of nitric oxide (NO) [57]. Since NO is required as a vasodilator maintaining vascular tone [58], the negative interaction of PAI-1 and eNOS promotes vascular stiffness. Additionally, NO is capable of reducing endothelial senescence burden [59]; therefore, PAI-1's inhibition of NO production may mediate further senescence induction. However, data supporting the model that PAI-1 directly inhibits eNOS are limited to *in vitro* systems and thus requires in vivo validation. It is also important to note that since PAI-1's role in a healthy organism is to promote blood clots, a complete loss of PAI-1 is detrimental to the cardiovascular system and causes bleeding disorders [60].

Together with PAI-1 as a component of SASP, accumulation of senescent cells along the vasculature contribute to the arterial

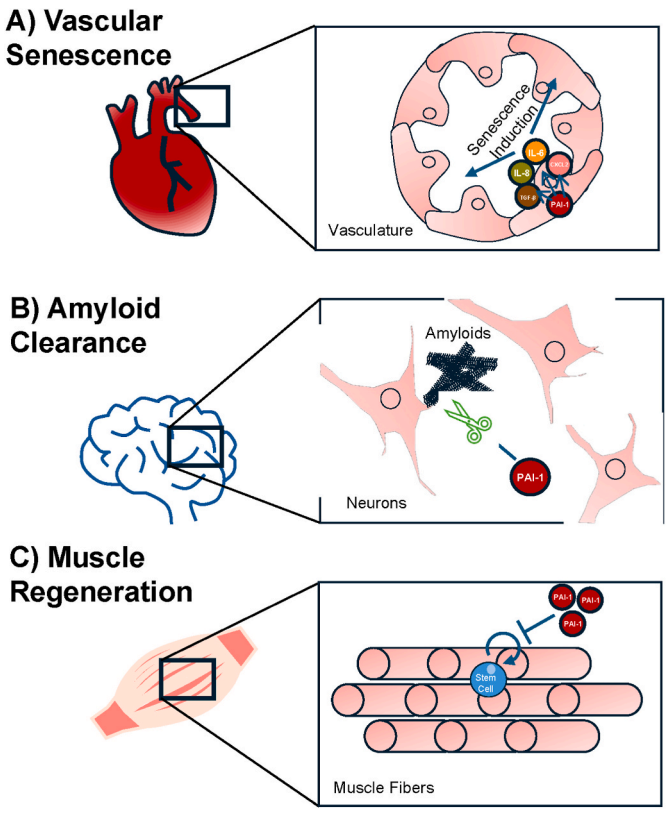


Fig. 2. PAI-1's Impact on Aging-Related Physiological Decline. (A) Vascular Senescence: PAI-1 promotes endothelial senescence and SASP (e.g., IL-6, IL-8, TNF-α) in the vasculature, driving arterial stiffness and cardiovascular aging. (B) Amyloid Clearance: PAI-1 inhibits tPA, impairing plasmin-mediated amyloid-beta (Aβ) degradation in neurons, contributing to Alzheimer's pathology. (C) Muscle Regeneration: PAI-1 blocks stem cell activation and ECM remodeling in muscle fibers, hindering fiber repair and exacerbating sarcopenia.

pathophysiology seen in advanced age [61]. In vascular smooth muscle cells (VSMCs), it has been suggested that PAI-1 promotes actin filament assembly and contributing to cellular stiffness [62]. In transgenic mice overexpressing a stabilized form of human PAI-1, animals develop age-dependent spontaneous coronary arterial thrombosis [63]. Moreover, treatment with PAI-1 inhibitor TM5441 prevents vascular senescence and perivascular fibrosis in mice treated with L-NAME which inhibits eNOS [64]. Human cohort studies link high plasma PAI-1 to increased cardiovascular disease risk, particularly in older adults [65,66]. These insights frame PAI-1 as a cardiovascular aging architect, with targeted inhibition poised to mitigate its effects.

3.2. Cognitive decline

Excess PAI-1 is increasingly implicated in cognitive decline, notably Alzheimer's disease (AD) [67]. In AD, increased PAI-1 plays a critical role in brain cell senescence, particularly in astrocytes, contributing to neurodegenerative pathology [14]. Studies suggest that senescent astrocytes, influenced by elevated PAI-1, may exacerbate neuroinflammation through the release of SASP components like IL-6, which are associated with Alzheimer's disease progression [68]. In humans, aging is the greatest risk factor for late-onset Alzheimer's disease (LOAD), and elevated PAI-1 levels are linked to this condition [69], potentially contributing to cognitive decline. Although specific associations with PAI-1 plasma levels and independence from vascular risk factors require further investigation. Moreover, the stiffening of blood vessels discussed previously is an important physiological driver of cognitive impairment [70].

At the cellular level, PAI-1 inhibits tPA, reducing plasmin generation and hindering Aβ clearance [Fig. 2B] [71,72]. This inhibition could indirectly affect neurodegenerative processes, but its specific role in amyloid-beta clearance or other AD-specific mechanisms requires further investigation. Additionally, PAI-1's contribution to cellular senescence and neuroinflammation in AD, as seen in brain cells, may exacerbate disease progression, though specific links to reactive oxygen species, microglia, or hippocampal damage are not established in the available data. Our current knowledge regarding PAI-1 and its possible role in cognitive function includes experimental studies. In a transgenic mouse with a chimeric human/mouse amyloid precursor protein (APP/PS1 mouse), PAI-1 inhibition improved memory function and reduced the amyloid burden [73]. Other experimental work has begun to suggest that excess PAI-1 is also implicated in cognitive impairments such as PTSD memory formation [74] and late-life depression [75,76]. Interestingly, these studies have also shown that PAI-1 inhibitors are capable of ameliorating these conditions. Collectively, these findings support a model in which PAI-1 acts as an effector molecule in age-related cognitive declines.

3.3. Cancer

Aging is an important risk factor for cancer and PAI-1's role in cancer is extensively documented [23,77–79]. Briefly, PAI-1 promotes tumorigenesis by enhancing angiogenesis through VEGF upregulation, protecting tumor cells from apoptosis via PI3K/Akt signaling, and facilitating metastasis by modulating ECM degradation [79]. High PAI-1 expression is a poor prognostic marker in breast [80], lung [81], bladder [82], and endometrial [83,84] cancers. PAI-1's pro-inflammatory effects in the tumor microenvironment, mediated by SASP, further fuel progression. An interesting illustration of this concept is the participation of PAI-1 in the ovarian reproductive system. Within the ovary, PAI-1 tightly regulates ECM remodeling required for folliculogenesis and ovulation [85]. There, dysregulation of PAI-1 remodels the ECM that is permissive to tumor invasion and metastasis [86].

Reducing PAI-1 bolsters anti-tumor immunity. PAI-1 increases PD-L1 expression on cancer cells, allowing for immune evasion and hindering cytotoxic T-cell activity [87]. Interestingly, senescent cells also upregulate PD-L1 to evade immune surveillance [88,89]. This immune evasion mechanism employed by both tumor and senescent cells implies that targeting PAI-1 can address both tumor and dysfunctional senescent cells. It is intriguing to speculate how PAI-1 inhibitors could target multiple aging-related diseases simultaneously. Clinical trials targeting PAI-1 specifically for caner have gained traction, with current trials including chronic myelogenous leukemia [90], metastatic melanoma [91], and non-small cell lung cancer [92], angiosarcoma [93].

3.4. Muscle atrophy

Emerging evidence implicates PAI-1 in age-related muscle atrophy known as sarcopenia [Fig. 2C] [94]. Through its canonical role, PAI-1 blocks plasminogen activation and ECM degradation which are important processes essential for muscle repair and regeneration [95]. Indeed, aged muscles are correlated with higher expression of mRNA encoding for PAI-1 [96,97]. Experimental work in murine models have suggested that by promoting plasmin degradation, PAI-1 inhibits the plasmin-mediated activation of Pax7-positive satellite cell proliferation and muscle fiber repair [43]. Perhaps most clinically relevant, pharmacological treatment of old mice with PAI-1 inhibitors demonstrated the ability to prevent muscle atrophy [98]. Although more work is needed to elucidate how PAI-1 hinders muscle growth, current studies highlight PAI-1's role as a sarcopenia mediator and a potential therapeutic target.

4. Limitations

Despite substantial progress, critical knowledge gaps remain regarding PAI-1's precise mechanisms of action. Unresolved questions include how excess PAI-1 changes the proteoform landscape of key tissues. As a serine protease inhibitor, PAI-1 can potentially inhibit numerous proteases, and an excess of PAI-1 can create a proteoform landscape that exerts pathological effects. Future studies should include unbiased proteomics and identify downstream targets. Additionally, while PAI-1 inhibitors such as TM5614 demonstrate therapeutic promise in preclinical models, rigorous clinical trials are essential to validate their anti-aging potential as therapeutic agents in humans. Specific guidelines for optimal dosing, treatment duration, and patient selection remain undefined and warrant careful investigation to translate findings into clinical applications. Moreover, it is intriguing to speculate if a combination of PAI-1 inhibitors with other lifestyle changes, such as caloric restriction, can yield synergistic effects.

5. Conclusion/outlook

PAI-1 intersects multiple pathways central to aging, including senescence, stem cell exhaustion, metabolic dysfunction, and muscle degradation. Its consistent involvement across these systems highlights it as a key regulator rather than a secondary marker. Remarkably, the field has insight into a natural experiment where we can observe changes associated with a lifelong PAI-1 reduction. A rare loss-of-function *SERPINE1* mutation lowering PAI-1 levels in an Amish population correlates with longer telomeres, enhanced metabolic function, and a 10 % extension of lifespan [99]. With increasing support from genetic, pharmacologic, and preclinical studies, targeting PAI-1 is a realistic therapeutic strategy to decelerate the pace of aging. Inhibitors such as TM5614 have shown potential, and future approaches may include gene editing or epigenetic modulation. These strategies could delay multiple aging-related diseases at once, offering a more unified approach to improving healthspan. By targeting senescence, stem cell function, metabolism, and physiological systems, such strategies could delay cardiovascular, cognitive, oncogenic, and muscular decline. As research advances, PAI-1 emerges not just as an aging culprit but as a gateway to healthier, longer lives.

Authors' contributions

All authors contributed substantially to literature review and writing the manuscript.

Availability of data and materials

Not applicable.

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