

The aging extracellular matrix as a missing link in senescent cell accumulation and persistence

Natalia Hernández-Bellido, Aida Perramon-Güell & Carlos Anerillas



Emerging evidence suggests that extracellular matrix (ECM) states can shape both senescence entry and persistence by tuning integrin signaling and mechanosensing. We propose a self-reinforcing circuit that contributes to age-related senescent cell accumulation, in which age-associated ECM remodeling favors senescence and senescent cells further remodel the ECM to amplify dysfunctional tissue niches.

Cellular senescence is a well-established hallmark of aging and a major contributor to age-associated tissue dysfunction and disease. During aging, senescent cells accumulate progressively in multiple organs and persist long after the initial stresses that triggered their formation. These cells are characterized by stable cell-cycle arrest, extensive metabolic and transcriptional rewiring, and the secretion of bioactive factors that influence neighboring cells, immune surveillance and tissue architecture¹.

Over the past decade, major advances have been made in identifying senescent cell markers, defining senescence-associated secretory phenotypes (SASPs) and demonstrating the causal contribution of senescent cells to aging and age-related pathologies¹. Despite these advances, many fundamental questions remain unresolved. One of the most central unknowns is why aging tissues become increasingly permissive to the accumulation and persistence of senescent cells.

Classical conceptual frameworks of senescence largely focus on cell-intrinsic stressors – including DNA damage, telomere attrition, oncogene activation and mitochondrial dysfunction – as the causes for senescence induction. Complementary models highlight non-cell-autonomous cues (including chronic inflammation, immune dysfunction and fibrotic remodeling) that reinforce senescent phenotypes after their emergence. Although these paradigms initially explain how senescent cells can arise and persist later on, they still lack a complete explanation for why senescence becomes an increasingly frequent fate and a persistent state in aging tissues.

An emerging body of evidence suggests that the tissue microenvironment – and specifically the ECM – has a decisive but underappreciated role in shaping these outcomes. The ECM is not a passive scaffold, but is instead a dynamic signaling platform that integrates biochemical composition, mechanical properties and cell adhesion cues. Importantly, the ECM undergoes profound remodeling during aging, which affects its composition, stiffness, ligand availability and architecture across organs and species^{2,3}. These age-associated changes

are increasingly recognized as biologically meaningful contributors to aging phenotypes and disease susceptibility¹.

Current models typically treat ECM alterations as downstream consequences of senescence or tissue pathology². By contrast, the framework proposed here places the ECM upstream of senescence dynamics as well. By shaping adhesion signaling, mechanotransduction, and downstream stress level interpretation, the aging ECM may bias how cells respond to damage before senescence is fully established. The influence of the ECM on aging is an emerging concept in the field that we extend here to cellular senescence by integrating evidence that mechanosensing nodes substantially affect both senescent-cell entry and persistence. Importantly, the specific ECM features that would influence these processes remain largely undefined. Identifying how specific ECM alterations (for example, composition, stiffness, ligand presentation, architecture and crosslinking) map onto these two phases is a key conceptual gap that motivates this conceptual effort.

In sum, we synthesize here recent mechanistic evidence to propose that the aging ECM actively shapes both the initiation and the persistence of senescent cells through mechanosensing pathways. We argue that ECM–integrin signaling influences whether damaged cells undergo senescence rather than cell death, that sustained mechanotransduction supports the long-term survival of senescent cells, and that senescent cells themselves remodel the ECM, which generates a self-reinforcing niche that amplifies aging-associated decline.

ECM–integrin signaling gates senescence entry

Accumulating evidence indicates that senescence is not a passive default response to cellular damage, but is rather a regulated fate decision. Following genotoxic, oxidative or metabolic stress, cells may undergo apoptosis (or die through other mechanisms), transient cell-cycle arrest followed by repair, or senescence, depending on the level of damage suffered. Importantly, the magnitude of damage alone is often not enough to explain which fate is adopted, as some contextual signals have a critical role in shaping stress responses.

We have recently identified adhesion-mediated signaling – reliant on integrins (major cellular sensors of the surrounding ECM) – as a crucial determinant of this decision⁴. In fibroblasts exposed to sublethal damage, intact integrin signaling activates SRC kinase early after stress, which promotes downstream signaling events that bias cells towards senescence rather than apoptosis. Pharmacological or genetic disruption of SRC activity, or interference with integrin engagement, shifted this balance towards apoptotic elimination of damaged cells. Conversely, ectopic activation of this signaling axis promoted senescence over apoptosis even under otherwise lethal levels of damage, which demonstrates that adhesion-dependent signaling can actively bias damage responses in either direction. This is a key observation, as it reveals that this signaling axis can modulate the induction of senescence or cell death regardless of the damage received by the cell to a great extent. Together, these findings identify integrin-dependent

signaling as an early checkpoint that integrates intracellular damage signals with extracellular context to critically determine cell fate.

Independent studies support this concept through complementary mechanisms. The matricellular protein CCN1 induces fibroblast senescence through engagement of integrin $\alpha6\beta1$ and heparan sulfate proteoglycans, which triggers reactive oxygen species production, DNA damage responses and stable cell-cycle arrest⁵. In pathological contexts such as diabetic kidney disease, activation of a uPAR- $\beta1$ integrin axis promotes tubular epithelial cell senescence, whereas disruption of this pathway reduces senescent burden and improves tissue function⁶. More broadly, integrin signaling has been implicated as a modulator of senescence induction across experimental systems^{7,8}.

A unifying feature of these pathways is their dependence on ECM engagement. Integrin clustering, focal adhesion maturation and downstream kinase activation are directly influenced by ECM ligand density, composition and mechanical properties⁸. Therefore, the changes in the ECM that accompany aging^{2,3} – including increased stiffness, altered collagen organization and enhanced crosslinking – may plausibly affect adhesion-dependent signaling in the cellular compartment (Fig. 1a). In this context, even relatively high levels of damage may be interpreted as insufficient to trigger cell death programs when certain integrin-dependent signaling nodes are robustly engaged, and redirect damage responses towards senescence. This does not imply that ECM cues override all damage thresholds, but rather that they can substantially shift the boundary at which damage is interpreted as lethal versus senescence-inducing. Rather than invoking heightened intrinsic damage alone, this framework suggests that aging can alter the cell-intrinsic interpretation of damage through changes in the surrounding matrix.

Mechanosensing sustains senescent cell survival

Although mechanical context can influence early commitment to senescence, recent genetic and pharmacological evidence indicates that established senescent cells also acquire mechanosensing dependencies that support their long-term survival.

Recently, in a study in which a whole-genome CRISPR screen revealed genes that are essential for viability in senescent cells, we identified the Hippo pathway and its effector complex YAP-TEAD as an essential survival module in senescent cells⁹. YAP-TEAD activity is a canonical integrator of cytoskeletal tension and ECM-derived mechanical cues, although it can also be regulated by non-mechanical inputs. However, the upstream signals that sustain YAP-TEAD activity in senescent cells – mechanical and/or non-mechanical – remain to be defined. In senescent cells, YAP-TEAD activity mitigates the endoplasmic reticulum (ER) stress that a heightened secretory phenotype causes in the cell (Fig. 1b). Disrupting YAP-TEAD selectively destabilizes senescent cells, which triggers unbearable ER stress and subsequent cell death.

Supporting this view, inhibition of focal adhesion kinase (FAK; a key mediator of integrin signaling and cytoskeletal tension) reduces senescent cell accumulation *in vivo*⁸. Indeed, dasatinib (which is part of the widely used senolytic combination dasatinib plus quercetin) exerts its senolytic function by, at least partially, tackling integrin-related signaling in senescent cells⁴. Together, these studies position mechanosensing and its related pathways not merely as a pro-senescence signals during initial damage response stages, but as essential dependencies for senescent cell persistence.

Mechanistically, senescent cells may become uniquely dependent on mechanotransduction because of their elevated secretory and proteostatic burden. Sustaining the SASP requires robust ER function

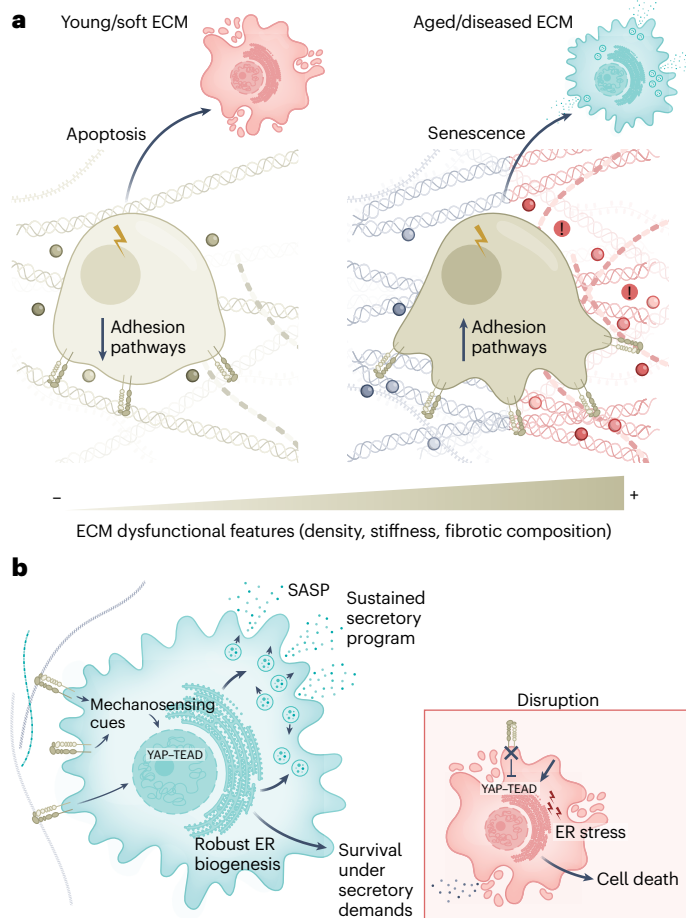


Fig. 1 | Roles for ECM features and mechanosensing in senescence entry and persistence. **a**, Age- and disease-associated ECM changes alter matrix composition, organization and mechanical properties across tissues. These shifts, including tissue-specific rebalancing of ECM constituents and changes in stiffness and architecture, can modulate integrin engagement and adhesion signaling following cellular damage. In a young or mechanically compliant ECM (left), limited integrin signaling would bias damaged cells towards apoptotic elimination, whereas in an aged or diseased ECM (right), strengthened adhesion signaling could shift fate decisions towards senescence rather than cell death. **b**, Mechanosensing-dependent survival of established senescent cells through YAP-TEAD-ER coupling. In senescent cells, mechanosensing cues that lead to YAP-TEAD activation support ER homeostasis and preserve secretory capacity, which enables sustained SASP output while limiting ER stress. Disruption of YAP-TEAD signaling (and potentially other mechanosensing-related nodes) destabilizes ER homeostasis, which leads to unresolved ER stress and selective senescent-cell death.

and stress-buffering capacity, which, for instance, YAP-TEAD signaling helps to maintain. Moreover, integrin signaling is essential for triggering an epithelial-mesenchymal transition-like transcriptional program in senescent cells⁴. Importantly, the epithelial-mesenchymal transition program is known to promote cell survival in multiple contexts, which might also be the case in senescence.

These observations suggest that the link between adhesion signaling and senescent cell viability may involve multiple pro-survival mechanisms. Those that are known so far range from comparatively

unexpected modules, such as sustaining ER biogenesis, to more canonical pro-survival transcriptional states, including pro-survival epithelial–mesenchymal transition-like programs. How these pathways are coordinated, whether they operate sequentially or in parallel, and to what extent they differ across tissues, senescence triggers and stages of aging remains largely unexplored. Dissecting these layers of mechanosensing-dependent regulation will be essential to fully understand why senescent cells are preferentially retained in aging tissues and to identify vulnerabilities that could be selectively exploited for therapeutic intervention. Moreover, it remains unclear which specific alterations of the ECM engage and sustain these programs *in vivo*.

The aging ECM as an active regulator

Another key element in this framework is the fact that the ECM undergoes extensive remodeling during aging, which affects both its molecular composition and mechanical traits. Proteomic analyses across tissues and species reveal age-dependent alterations in collagens, glycoproteins, proteoglycans and ECM-associated regulators^{2,3}. These changes are accompanied by increased crosslinking, glycation and tissue stiffening, which result in altered mechanical landscapes within aging organs. Aging is also associated with impaired ECM homeostasis and turnover, including changes in the expression of enzymes involved in physiological matrix degradation and renewal.

Importantly, these alterations seem to be coordinated rather than stochastic. Large-scale proteomic atlases demonstrate consistent matrisome aging signatures across multiple organs, which suggests that ECM remodeling is a conserved feature of aging biology³. This frequently reflects tissue-specific rebalancing of ECM constituents – some increasing, while others decline – and thereby the reshaping of overall matrix composition. Although the specific molecular components altered may differ between tissues, the functional consequences (changes in ECM features, including stiffness, ligand presentation and mechanotransduction) are remarkably convergent. Comparable ECM states also emerge in pathological contexts such as fibrosis, chronic inflammation and tissue injury^{2,10}. This convergence suggests that aging and disease can generate overlapping – yet not necessarily identical – ECM signatures, which positions the matrix as a shared structural substrate across diverse forms of tissue dysfunction (Fig. 1a). Chronological ECM aging and pathology-associated remodeling (for example, fibrosis) could therefore be viewed as related but distinct matrix states whose degree of overlap is probably tissue-dependent and context-dependent. Accordingly, the ECM–integrin and mechanosensing mechanisms proposed here may operate during physiological aging as these matrix features accrue over time, and may be further intensified in disease settings that accelerate the emergence of aging-like ECM features. Notably, senescent cells frequently accumulate following tissue injury, in which transient senescence can support repair but must be efficiently resolved. In aged or chronically diseased tissues, however, injuries occur within pre-altered ECM environments, which raises the possibility that such matrices may bias post-injury responses towards excessive or persistent senescence rather than timely resolution.

Additionally, functional studies reinforce the biological relevance of the aging ECM. Increasing levels of high-molecular-mass hyaluronan reshape ECM features towards those observed in long-lived species, improving healthspan, reducing inflammation and cancer incidence, and extending lifespan¹¹. Conversely, engineered matrices that recapitulate aged ECM stiffness and ligand composition induce dysfunctional

phenotypes in cardiac and stromal cells, which mimic aspects of tissue aging¹⁰. In line with these observations, age-dependent ECM alterations affect mechanotransduction circuits, and ultimately influence tissue homeostasis and aging trajectories¹².

Together, these findings support the view that ECM integrity is a determinant of aging outcomes rather than a passive byproduct. Given the sensitivity of integrin signaling and mechanotransduction pathways to changes in the ECM, age-associated ECM remodeling is well positioned to shape cellular behavior at the tissue level, even in the absence of overt pathology. At present, however, the specific matrix features that bias integrin signaling towards senescence implementation over apoptotic elimination – and those that may support the persistence of established senescent cells – remain largely undefined, which represents a key gap in our understanding of how the extracellular context shapes senescence dynamics.

A self-reinforcing ECM–senescence circuit

In parallel with sensing and responding to the ECM, senescent cells actively remodel their surrounding matrix. As part of their secretory programs, senescent cells upregulate structural ECM components, matrix-modifying enzymes and pro-fibrotic factors, which contributes to sustained changes in tissue architecture². Reviews and experimental studies have documented increased production of certain collagens, matricellular proteins and proteases by senescent cells, which positions senescence as a major driver of local ECM remodeling and turnover rather than a passive bystander. *In vivo*, senescent cells contribute directly to pathological ECM deposition in fibrotic lung disease, and genetic or pharmacological clearance of senescent cells reduces ECM accumulation and improves tissue function, which establishes a causal link between senescence and matrix remodeling¹³.

Recent work further indicates that senescent cells do not remodel the ECM in a uniform manner, but instead generate distinct matrix signatures depending on tissue context, senescence trigger and cell identity. During muscle regeneration, senescent cells assemble aged-like inflammatory and fibrotic niches that impair regenerative capacity across the lifespan¹⁴. In biomaterial-associated fibrosis, discrete senescent subtypes deposit ECM programs that range from strongly pro-fibrotic to pro-angiogenic, which demonstrates that senescent heterogeneity translates directly into matrix heterogeneity¹⁵.

Importantly, the ECM states generated by senescent cells often resemble those that arise during physiological aging and in chronic disease contexts, including fibrosis and persistent inflammation. In line with this, proteomic and functional analyses indicate that aging tissues and fibrotic lesions share many features such as altered matrisome composition, increased stiffness and disrupted matrix turnover^{2,10}. These shared features suggest that aging, disease and senescence converge on certain ECM architectures, which positions the matrix as a common structural substrate across diverse forms of tissue dysfunction.

In this light, aging-associated and disease-associated matrices may help to explain why senescent cells preferentially accumulate in these settings, by creating extracellular environments that favor senescence initiation and persistence. Integrating these observations, a self-reinforcing circuit emerges. Age-associated or disease-associated ECM remodeling enhances integrin engagement and mechanosensing, which biases damaged cells towards senescence rather than death and supports the long-term survival of established senescent cells^{4,9}. In turn, senescent cells further remodel the ECM towards increasingly stiff, fibrotic and inflammatory states, which

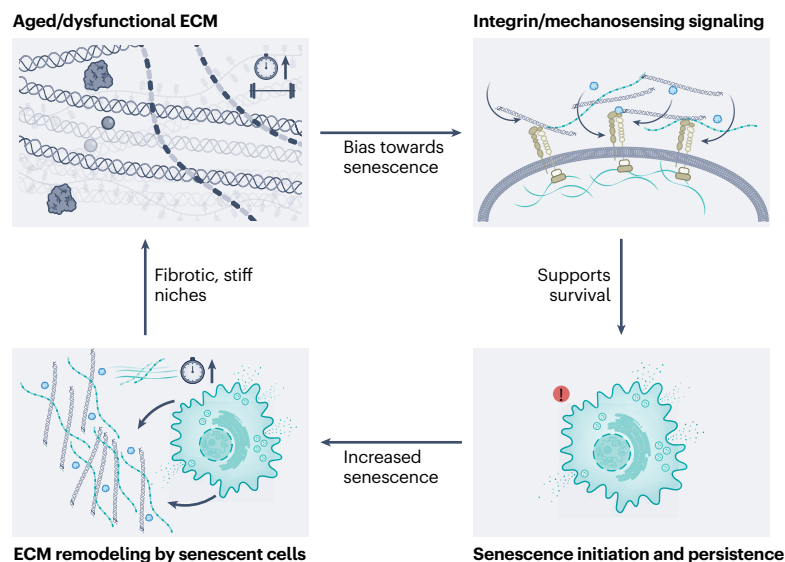


Fig. 2 | A self-reinforcing ECM–senescence circuit in aging. Conceptual model that illustrates a self-reinforcing circuit that links ECM remodeling, mechanosensing and senescent cell accumulation. Age- or disease-associated ECM remodeling leads to altered matrix composition and mechanical properties, including increased stiffness and disrupted matrix organization. These ECM changes enhance integrin engagement and mechanosensing signaling, and bias damaged cells towards senescence rather than apoptotic elimination and support the persistence of established senescent cells. Sustained mechanosensing activity promotes senescent cell survival by supporting stress-buffering and secretory programs. In parallel, senescent cells actively

remodel their surrounding ECM through the secretion of structural matrix components, matrix-modifying enzymes and pro-fibrotic factors, which generates mechanically and compositionally altered niches that are often inflammatory and fibrotic. These senescence-associated ECM states overlap with those observed during physiological aging and in chronic disease contexts, such as fibrosis and persistent inflammation. Over time, this reciprocal interaction between senescent cells and the ECM may amplify extracellular cues that favor senescence initiation and persistence, which provides a mechanistic framework for the progressive accumulation and spatial enrichment of senescent cells in aging and diseased tissues.

amplifies the very extracellular cues that promote senescence^{2,15}. This feedback loop provides a compelling mechanistic explanation for the accumulation of senescent cells during aging and for their spatial enrichment within fibrotic or mechanically altered tissue regions (Fig. 2).

By positioning the ECM as both a driver and a product of senescence, this framework moves beyond linear cause–effect models and instead emphasizes the dynamic reciprocity between cells and their extracellular environment. Such self-reinforcing ECM–senescence circuits could represent an additional non-cell intrinsic explanation for how senescence becomes a frequent and persistent cellular state in aging tissues, even in the absence of continuous or escalating intrinsic damage.

Conclusion and perspectives

The accumulation and persistence of senescent cells are defining features of aging biology, with broad implications for tissue dysfunction and disease. Here, we propose that age-associated ECM alterations probably influence this process. By shaping integrin signaling and mechanosensing pathways, the aging ECM may bias damaged cells towards senescence and support the long-term survival of senescent cells.

This perspective has important therapeutic implications. Interventions that disrupt mechanosensing dependencies, modulate ECM composition or restore youthful matrix properties may complement, or even serve as, senolytic strategies. Targeting the ECM–mechanosensing–senescence circuit offers an orthogonal avenue to

attenuate age-associated dysfunction by limiting both senescence entry and persistence, rather than eliminating senescent cells alone. Nevertheless, the senescence and aging fields need to first bridge the knowledge gap on which ECM features would promote senescence entry and/or persistence, and whether distinct ECM states substantially control these phases across tissues and damage contexts. Additional open questions include the extent to which these mechanisms are tissue-type-dependent and cell-type-dependent, the need for *in vivo* causal tests in aging and disease models, and how interactions with the immune system and inflammatory cues influence the role of the ECM in shaping senescence induction and maintenance.

In sum, considering the ECM as an active regulator of senescence underscores the importance of tissue context in aging biology. As geroscience moves towards precision approaches, integrating ECM biology into models of senescence may be essential for understanding – and ultimately modulating – the aging process.

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Author contributions

C.A. conceived the Comment and supervised the work. N.H.-B. and A.P.-G. contributed to literature curation and drafting. All authors wrote and edited the manuscript and approved the final version.

Competing interests

The authors declare no competing interests.

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