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Aging and the extracellular matrix: A tumor-permissive microenvironment driving cancer progression

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Aging is a significant cancer risk factor, yet its impact on the extracellular matrix (ECM) in tumor initiation and progression has been traditionally overlooked. While significant amounts of research focus on cellular and genetic links between aging and cancer, recent studies highlight how age-induced ECM changes create a tumor-permissive environment. Here we review this emerging research area, where age-related ECM alterations, such as age-induced increases in matrix stiffness, biochemical changes, and resultant dysregulated mechanosensitive pathways, are explored for their influence in cancer initiation and progression. Additionally, recent studies have showed how aged cells contribute to ECM alterations, further reinforcing tumor-permissive changes. This review examines both aspects of ECM aging, i.e. material-driven and cell-driven, and highlights current understandings of how ECM aging influences interactions within the tumor microenvironment in multiple cancer types, with a focus on biomechanical aspects. We also discuss emerging age-mimetic in vitro models facilitating studies of age-dependent cancer progression and therapeutic responses. Finally, we review therapeutic strategies that target aging-associated components or ECM changes to improve treatment efficacy.

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Introduction

Aging is one of the most significant risk factors for a variety of diseases, especially cancer, and its impact will only increase as it is predicted that by 2030 more than one in six people will be over the age of 60, with this demographic only continuing to increase [1–4]. A critical factor in this aging-related disease incidence increase is the aging extracellular matrix (ECM). The ECM is a dynamic network that provides structural support, regulates cellular behavior and assists in cellular signaling, and plays an important role in tissue function, dysfunction, and disease response. During aging, the ECM undergoes biological and chemical remodeling, which contributes to immune system dysregulation, structural changes, and changes in cellular communication [5–7]. These changes can especially be pertinent to the onset of cancers, where the ECM regulates tumorigenesis, metastasis, and therapeutic efficacy [6,8].

In recent years, with the increased appreciation of the critical role of the ECM in disease progression, the effects of aged ECM on cancer predisposition, onset, and progression have started to gain attention [5,9]. While aging has become a well-established risk factor for cancer and is known to induce ECM changes, the specific link between the aging ECM and tumorigenesis is yet to be fully understood [10]. Historically, aging research has primarily focused on genetic and cellular-level changes, examining genomic instability, telomere attrition, epigenetic modifications, and cellular senescence, many of which overlap with the hallmarks of cancer [11]. This gene-centric perspective has provided key insights into how aging influences cancer initiation and progression, leading to breakthroughs in areas such as oncogene activation, tumor suppressor loss, and DNA repair deficiencies in aged tissues [11,12]. More recently, emerging studies have begun to highlight how the aging-induced ECM alterations actively shape cancer progression [7,13]. In addition to structural and mechanical changes, aged cells actively contribute to ECM remodeling through secreted factors such as the senescence-associated secretory phenotype (SASP) [14] and extracellular vesicles, which further reinforce tumor-promoting changes [15].

Herein, we review the current understanding of aging-associated ECM alterations, such as collagen cross-linking and mechanotransduction pathway alterations, and how they impact tumorigenesis, the importance of senescent cells and their secretory profiles on ECM biomechanics, and the consequences of aging on

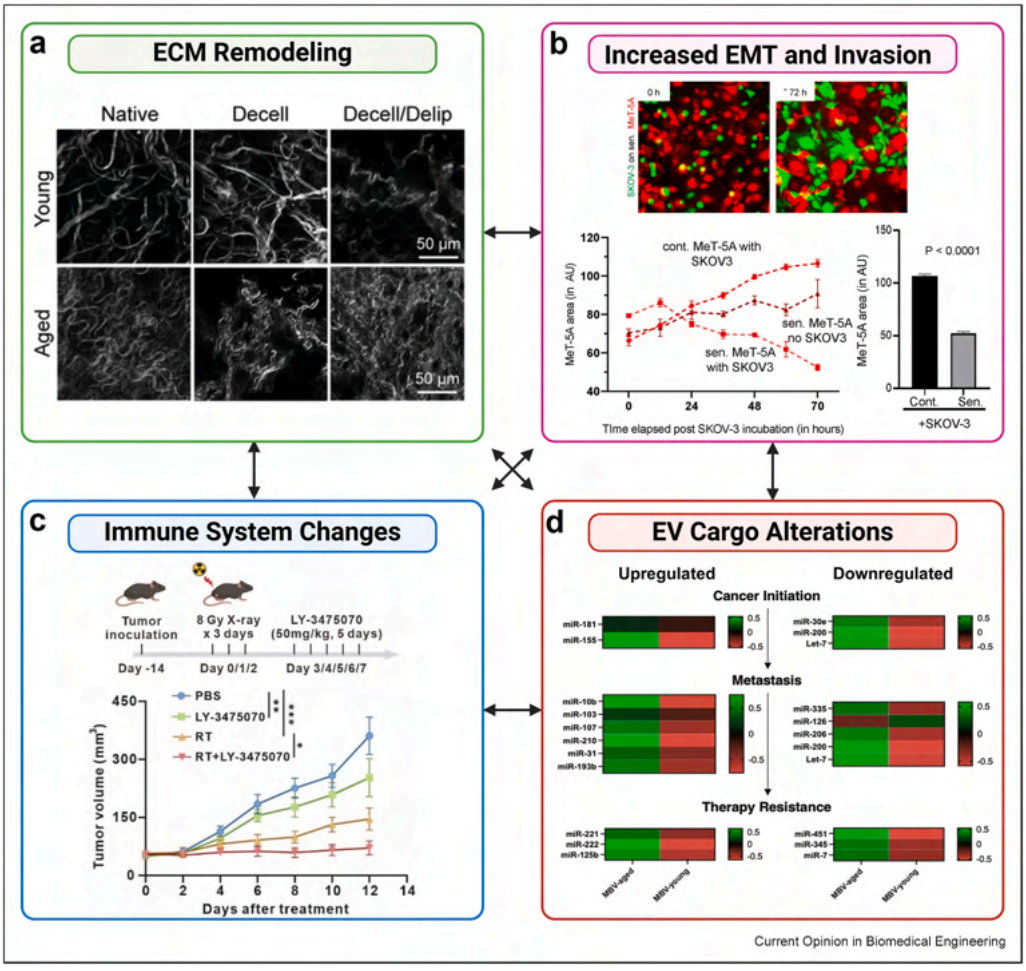
immune-cell involvement in ECM remodeling. We also discuss emerging therapeutics that target the aged ECM to counteract the effects of aging-related changes, as well as advances in biomimetic models that can facilitate a greater understanding of the interplay between aging-related diseases and changes in the local microenvironment. By examining the interaction of age-related ECM remodeling, cellular behavior, and therapeutic challenges, we aim to provide an up-to-date overview highlighting the emerging insights and strategies that pertain to the aging ECM and cancer.

Aging-associated extracellular matrix changes in cancer onset and progression

As tissues age, the ECM undergoes structural and compositional alterations, including excessive collagen crosslinking, altered deposition and degradation of ECM elements, as well as changes in the fiber organization, leading to increased ECM rigidity and loss of structural integrity, which alters tissue and cell behavior [5,7,16,17]. These biomechanical and biochemical changes provide cancer cells with a more permissive environment, enabling malignant transformation and disease progression. Moreover, current literature suggests that these aging-related changes to the microenvironment drive epithelial-to-mesenchymal transition (EMT), as seen in breast and colorectal cancer, where aging significantly influences cellular behavior along with cancer initiation and metastasis (Figure 1a) [7,18]. For instance, in vitro breast cancer studies utilizing decellularized mouse mammary glands as scaffolds have shown that the aged breast ECM alone was sufficient to facilitate both normal and cancerous cells seeded atop it to attain a more invasive phenotype. These changes also caused the loss of E-cadherin (E-cad), which led to increased cellular motility and invasion in normal human mammary epithelial cells. This loss of E-cad was reversed upon knockdown of intracellular lysyl oxidase (LOX) enzymes, which drive collagen crosslinking and ECM stiffening, which also allowed for the restoration of cellular behavior to a noncancerous phenotype on both young and aged matrices [7,19]. These aging-associated ECM modifications similarly influence metastatic potential within other cancers. In ovarian cancer, in vivo models using young and aged mice have shown that the aged ECM established a premetastatic niche, contributing to enhanced metastasis through significant remodeling of collagen fiber structure and tissue organization [20]. Another study on ovarian cancer using a human-murine hybrid ex vivo system showed that the aged coelom-lining mesothelia ECM had higher levels of invasion, where the cancer cells adhered more efficiently, metastasized better, and moved more aggressively. Inhibition of RGD (Arginylglycylaspartic acid) cyclopeptides suggested this effect was primarily attributed to both fibronectin and laminin, suggesting that the senescence-associated matrisomal phenotype of the peritoneal barrier enhances the colonization of invading ovarian cells (Figure 1b) [21]. These changes are also accompanied by dysregulation of known cancer and mechanosensitive associated pathways such as the NF-κB, yesassociated protein (YAP), and transforming growth factor beta (TGF-β), which regulate proliferation, migration, and fibrosis [22–24]. In breast cancer, both with 3D organoid culture systems and in vivo mouse models, aging-related matrix stiffening was found to activate YAP, increasing collagen deposition, and further stiffening the matrix, which promotes the secretion of periostin (POSTN), a matricellular protein involved in maintaining ECM structure and regulating cell-ECM interactions, further facilitating collagen crosslinking [25,26]. POSTN was found to increase with age and is required for age-related mammary gland stiffening, correlating with higher levels of collagen in breast tumors. This promotion of matrix rigidity also contributes to the 3D collective invasion of breast tumor cells [26]. In addition to breast cancer, ECM stiffening tends to result in a poorer prognosis for older patients with melanoma when compared to younger patients. Using young and aged mice, it was found that hyaluronan and proteoglycan link protein (HAPLN1) was decreased with age, and that this decrease in expression of HAPLN1 simulated the development of new blood vessels, triggering vascular erosion and ECM remodeling. Additionally, this tends to lead to a stiffer aged skin with differing ECM fiber alignment, facilitating melanoma cell invasion and metastasis. It was further found that reconstitution of HAPLN1 led to fibronectin, VE (Cadherin-5 (vascular endothelial cadherin))-cadherin, and ICAM1 expression similar to that of the young matrix [27] In addition to both in vitro and in vivo studies, ECM stiffening has been identified as a clinical marker in breast tissue. Through magnetic resonance imaging, it was identified that individuals at high risk for breast cancer had stiffer breast tissue when compared to those at average risk, and this trend was seen similarly between dense and nondense breasts.

Another factor contributing to age-related ECM alterations and their role in cancer initiation and progression is the accumulation of advanced glycation end products (AGEs). AGEs naturally increase with age and are formed by nonenzymatic glycation that stimulates the receptor for AGEs (RAGE) [28]. This mechanism induces substantial mechanical changes within the ECM and has been implicated in the alteration of collagen crosslinking and tumorigenesis, protein dysfunction, aberrant cell signaling, and altered collagen properties, furthering a positive feedback loop for the tumorigenic aged ECM [29]. In vitro studies of endometrial cancer showed that in both Ishikawa and HEC-1-B cancerous cells, when treated with varying concentrations of AGEs, exposure to higher AGE concentrations led to increased colony formation; furthermore, transwell studies showed

Figure 1



Reciprocal interactions between the aging ECM and cancer cellular behavior (a) Aging-related remodeling of murine mammary ECM results in thinner, more curved collagen fibers, as visualized by second harmonic generation (SHG). These structural changes likely facilitate a more cancerous phenotype in both normal (KTB21) and cancerous (MDA-MB-231) epithelial cells [7]. **(b)** Ovarian cancer cells preferentially invade a more aged mesothelial environment compared to a younger control, due to enhanced mesothelial clearance [21]. **(c)** Aged immune cells from mice exhibit altered function, contributing to increased tumor cell invasion and impaired. ABT263-senescence-removal treatment in mice reduced tumor size [39]. **(d)** Matrix bound vesicles (MBVs), isolated from aged mouse mammary tissue, facilitated increased motility and invasion following pretreatment of both KTB21 and MDA-MB-231. Nanostring analysis of MBV mircoRNA (miRNA) cargo revealed distinct miRNAs that facilitate cancer initiation, metastasis, and therapeutic resistance[15]. **(a)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [7]. Copyright 2021 The Authors. Advanced Functional Materials published by Wiley-VCH GmbH. **(b)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [21]. Copyright 2023 The Authors. Cellular and Molecular Life Sciences published by Springer Nature Link. **(c)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [51]. Copyright 2024 The Authors. Theranostics published by Ivyspring. **(d)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [39]. Copyright 2024 The Authors. Biomaterials published by Elsevier. ECM, extracellular matrix.

a significant increase in the number of invasive and migratory tumor cells. These cellular changes were found to be mediated by the AGE-RAGE upregulation of CHKA (Chlorine Kinase Alpha), which activates the PI3K/AKT pathway [30]. Additionally, it has been shown in breast cancer that the accumulation of AGEs also resulted in increased matrix stiffness and increased cancer cell contractility and migration [31]. The accumulation of AGE and its relationship with the RAGE pathway has been increasingly explored not only in preclinical studies, but also within clinical studies. The presence of AGEs and their relationship to cancer risk and progression has been studied in several cancers such as lung, breast, colorectal, hepatocarcinoma, pancreatic,

and several others [32]. These findings highlight how aging-induced ECM remodeling promotes tumor progression by increasing stiffness, disrupting ECM organization, and altering mechanotransduction.

Cellular and immune response to aging extracellular matrix in cancer

Beyond ECM structure and composition changes, aging leads to altered cellular behavior through cellular senescence, secretion profiles, and immune dysfunction, driving aging-relating ECM alterations, furthering tumorigenesis, and metastasis [33,34]. Stromal cells, such as cancer-associated fibroblasts (CAFs), play an integral role in ECM remodeling, particularly in aged tissues [35,36]. CAFs are a heterogeneous population of activated fibroblasts that influence cancer initiation and progression by remodeling the ECM, activating mechanosensitive pathways, and promoting a tumor-permissive environment [36]. In the aged tumor microenvironment, senescent CAFs exhibit distinct molecular characteristics and an altered secretome, furthering their ability to enhance tumor growth, promote resistance, and influence immune checkpoint efficacy [35,37]. Their role in shaping tumor resistance has been shown in low-grade gliomas, where CAFs have been identified as prognostic markers, underscoring their broader relevance in cancer progression.[35] The aging process not only impacts stromal cell behavior but also immune modulation, by creating a physical barrier that hinders immune cell infiltration and alters immune checkpoints, thereby improving tumor evasion and survival from the immune response [6,38]. Additionally, the aged immune system regulates ECM biomechanics and cancer behavior within the aged microenvironment (Figure 1c) [39]. Aging-related immune dysfunction in cancer is largely mediated through macrophages. Macrophages are typically classified into classically activated (M1) and alternatively activated (M2) phenotypes. While M1 macrophages are traditionally proinflammatory, M2 macrophages induce tissue remodeling and ECM deposition [40,41]. Tumor-associated macrophages (TAMs), phenotypically and functionally similar to M2 macrophages, are essential for malignant metastasis and therapeutic resistance in addition to ECM remodeling. Recent studies, both in vitro and in vivo, also reveal that macrophage infiltration increases with aging in colorectal cancer tissues, where TAMs promote cancer growth and altered expression signatures by inducing aberrant NF-κB signaling, amplifying protumorigenic activity within the aged microenvironment [42].

While cells and the ECM can naturally age, therapies such as radiation, and chemotherapy can exacerbate ECM remodeling and create a biologically aged phenotype through therapy-induced damage. Radiation therapies can induce fibrosis by activating fibroblasts and increasing collagen deposition, leading to a stiffer ECM that can negatively affect tissue function [43]. Additionally, chemotherapies have been linked to the accumulation of SASP, promoting ECM remodeling and chronic inflammation. It was shown that young cancer survivors experience accelerated biological aging, aging approximately 5% faster per year, with biological ages averaging 0.6−6.44 years older than controls and 5−16 years older than age-matched individuals in the general population. This effect is particularly pronounced in those who have undergone hematopoietic cell transplants or vinca alkaloid chemotherapy, which were associated with the most rapid trajectories of biological aging. Survivors who exhibit greater biological age acceleration also face an increased risk of frailty, increased ECM stiffness, elevated DNA methylation levels, and a greater susceptibility to secondary cancers [44].

Therapy induced aging has been essential for a better understanding of the aging process and how senescent cells and their downstream effects impact the ECM, other cells, and cellular secretions. In breast cancer, mesenchymal stem cells (MSCs) have been implicated as drivers of ECM remodeling that promote an invasive cancer phenotype [14]. Additionally, senescence induced myofibroblastic CAFs (senCAFs) have been used to understand their key role in pancreatic ductal carcinoma (PDAC), an aggressive cancer characterized by desmoplasia [45] These senCAFs are a phenotypically distinct subset of myofibroblastic CAFs that localize near tumor ducts, stiffening the ECM and suppressing the immune response. In both genetic and pharmacologic models, senCAF depletion relieved macrophage-mediated immune suppression, delayed tumor progression, and improved chemotherapeutic response [46]. Furthermore, either as cells age or by chemotherapeutic induction, their protein and secretion profiles change, leading to the production and buildup of SASP, soluble and insoluble factors that alter the ECM and facilitate cancer onset and progression. One major SASP factor is interleukin-1β (IL-1β), which is a key factor for a tumor-permissive environment that helps tumor cells evade immune attacks by inducing programmed death ligand-1 (PDL-1) [47]. High levels of IL-1β have been shown to be highly expressed in both hepatocellular carcinoma and in PDAC [48,49]. In mice, it was found that when mice are injected with pancreatic grafts lacking IL-1β, there were differences in ECM both from an immune and fibrosis standpoint. This study implicated IL-1β as a key player in creating a tumor permissive microenvironment by creating one that is both immunosuppressant and promotes fibrosis through increased collagen deposition [48].

Other SASP factors include those released by extracellular vesicles (EVs), which are membrane-bound particles released by cells into the ECM. Senescent

fibroblasts in lung cancer have been shown to drive tumor progression via exosome-mediated signaling, a type of EV. These exosomes upregulate senescence markers, promoted EMT and invasion, and significantly increase exosomal MMP1, a collagen degrader whose upregulation is attributed to ECM remodeling and cancer progression, activating the PI3K-AKT-mTOR pathway, a key driver of cancer proliferation [50]. Additionally, it was found that both in vitro and in vivo mouse studies showed therapy-induced senescent tumor cell-derived EVs independently promote colorectal cancer through SERPINE1-mediated NF-κB p65 nuclear translocation [51]. In breast cancer studies, EVs released from senescent MSCs, were found to accumulate in primary tumor sites, leading to increased fibrosis, exhibit a unique miRNA profile that transfers profibrotic signaling cargo to neighboring cells, regulating the TGF-β pathway, and stiffening the surrounding matrix. This local ECM remodeling was found to also lead to a more aggressive breast cancer cellular behavior, and while these senescent cells make up a smaller fraction of the cellular composition in vivo, their ability to communicate with other cells and their downstream fibrotic effect via EVs can be transferred to other cells [52]. Furthermore, matrix-bound vesicles (MBVs) isolated from aged mouse mammary tissues also exhibit a unique molecular profile than those isolated from young mouse mammary tissue. Nanostring analysis revealed an age-respective microRNA (miRNA) cargo, where aged MBVs are enriched with miRNAs pertaining to cancer initiation, metastasis, and therapeutic resistance. Additionally, when both normal and cancerous cells were pretreated with these MBVs, the aged MBVs shifted the cells toward an invasive phenotype (Figure 1d) [15].

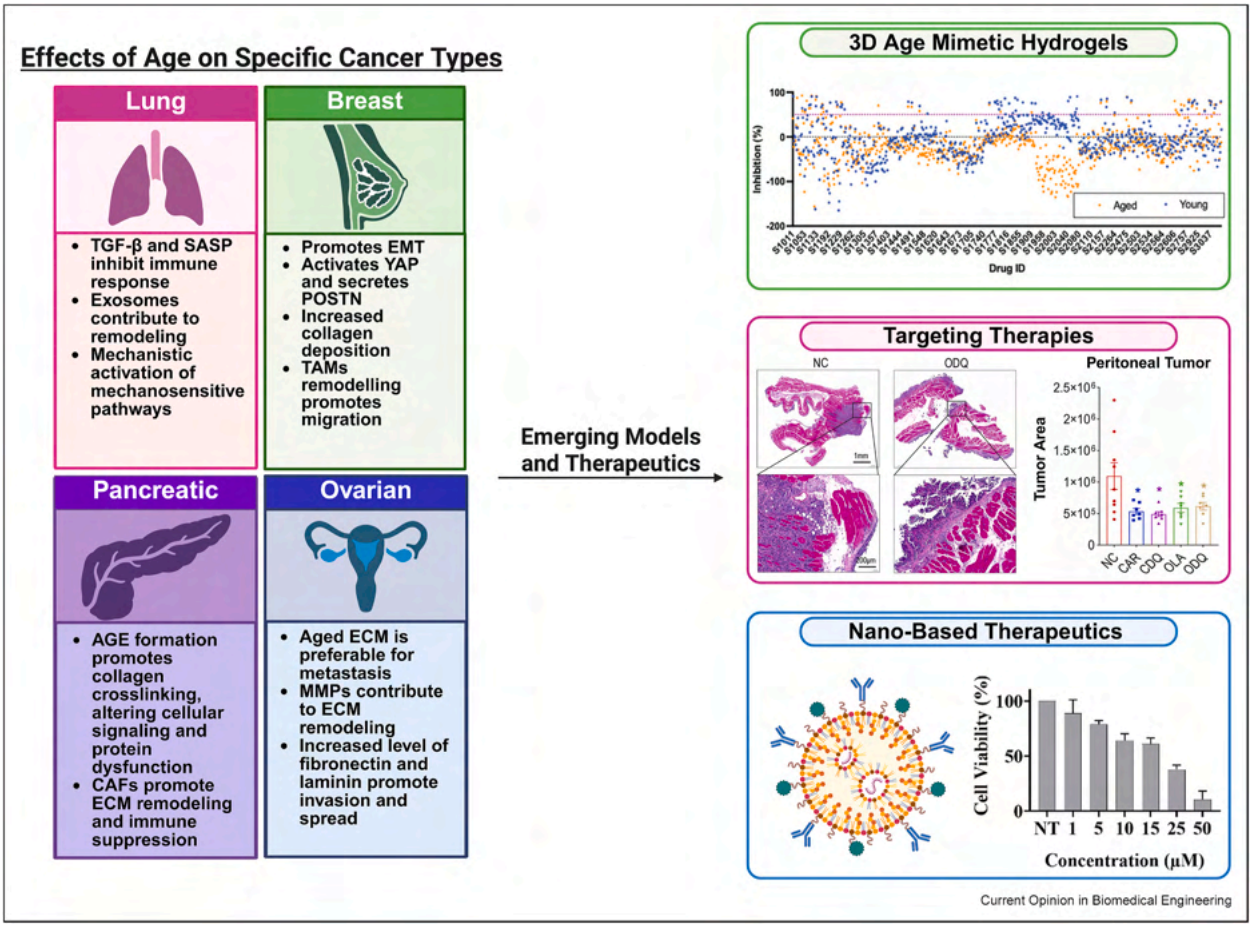
These findings highlight the relationship between the aged ECM, cellular behavior, and immune dynamics in shaping a protumorigenic environment, promoting metastasis and therapy resistance. Moreover, various existing therapies, such as radiation and chemotherapeutics, can cause the surrounding tissue areas to show signs of advanced biological aging, leading to increased levels of fibrosis, production of SASPs, and a higher chance of developing secondary cancer. This further highlights the need for models that can accurately recapitulate the aging microenvironment and for therapeutics that consider aging as a factor in improving outcomes in the population.

Current models and emerging therapeutics of the aged extracellular matrix in disease progression

As the ECM undergoes various alterations with age, it presents significant barriers to effective cancer therapy as explained in previous sections [53]. Additionally, preclinical models and clinical studies largely overlook aging as a factor, leaving aged patients undertreated [54]. This disproportionately affects older patients, who have higher rates of cancer diagnoses and experience worse outcomes compared with younger populations, partially attributed to their differences in the microenvironment and the occurrence of comorbidities [55–57]. To better understand the mechanisms of age-related ECM remodeling, disease progression, and age-specific therapeutic response, biomaterials and preclinical models that mimic the aged ECM are necessary. In one such study, an age-representative preclinical model that utilizes 3D age-mimetic hydrogels was developed by utilizing the collagen derived from mouse tail tendons. Tail tendons were shown to mimic the morphological and biochemical age-related alterations observed in aged mammary glands, making them a good source of material for generating 3D breast cancer models capable of mimicking the aging breast microenvironment. MDA-MB-231 spheroids were embedded in the ECM models and evaluated for therapeutic and survival response to over 700 Food and Drug Administration (FDA)-approved therapeutics (Figure 2a). Interestingly, the 'age' of the model significantly affected the effectiveness of the therapy and cell response. Although this model was utilized for the evaluation of breast cancer spheroids, this model is adaptable to other soft-tissue cancers and demonstrates the necessity of evaluating aging-related microenvironment contributions in drug testing [58]. These findings highlight the impact of the aged ECM on therapeutic response, showcasing the need for more studies that assess age-related therapeutic efficacy.

In addition to models, therapies that integrate SASP-targeting drugs or targeting of proteins that cause ECM changes (such as excessive stiffening) with chemotherapeutics are being explored to enhance drug effectiveness by improving delivery and overcoming ECM-related treatment barriers. Therapies that combine senolytics, a class of drugs that selectively target and clear senescent cells, have been utilized to improve therapeutic efficiency in a variety of age-related diseases [59–61]. Dasatinib and quercetin (DQ) are common senolytics used together, where they promote apoptosis of senescent cells without affecting nonsenescent cells [61]. Recent studies have shown that these senolytics can be combined with traditional cancer therapies to counteract the protumorigenic effects of therapy-induced senescence, such as ECM remodeling and DNA methylation, reducing migration, invasion, and proliferation of cancer cells while improving patient outcomes (Figure 2b) [62,63]. Other combinatorial therapies work to actively target both the stiffer ECM and cancer cells. Due to the upregulation of LOX in several cancer types and the understanding that its upregulation leads to worse prognosis alongside ECM stiffening, LOX inhibitors paired with another

Figure 2



Summary of aging-related ECM changes, current models, and emerging therapeutics. Left: Summary chart compiling age-associated ECM alterations across various cancer types including changes in mechanics, composition, and immune response with their known downstream effects on cancer progression. **Right: (a)** Engineered age-mimetic collagen hydrogels embedded with MDA-MB-231 breast cancer spheroids exhibit differential drug response compared to young ECM counterparts [58]. **(b)** Treatment with Olaparib in combination with dasatinib and quercetin reduced peritoneal tumor area in an ovarian cancer model, as shown through histopathological staining and quantification following four weeks of continuous treatment [63]. **(c)** Nano-based targeting therapeutics enhance senescent cell clearing by improving cellular internalization and reducing cancer cell viability, as demonstrated by an MTT assay [69]. Left panel shows a schematic representation of a lipid-nanoparticle-based therapeutic delivery system, created using BioRender. **(a)** Reproduced under the terms of the CC by Attribution-Non Commercial-No Derivatives 4.0 International (https://creativecommons.org/licenses/by-nc-nd/4.0/) [58]. Copyright 2025 The Authors. Advanced Healthcare Materials published by Wiley. **(b)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [63]. Copyright 2024 The Authors. Biomedicine and Pharmacotherapy published by Elsevier. **(c)** Reproduced under the terms of the CC by Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [69] Copyright 2022 The Authors. International Journal of Pharmaceutics published by Elsevier. ECM, extracellular matrix

therapeutic are being studied. β-aminopropionitrile (BAPN), a LOX inhibitor, has shown promise in reducing ECM stiffness and improving therapeutic outcomes [64]. In breast cancer models, combination therapies using BAPN alongside the NAD(P)H quinone oxidoreductase 1 (NQO1)-responsive drug, NQO1-SN38, demonstrated a marked reduction in collagen deposition, improved tissue elasticity, and enhanced drug delivery efficiency [64]. Similarly, losartan, originally an angiotensin receptor blocker, has been used in tandem with other chemotherapeutics in colorectal, ovarian, and breast cancer to reduce solid stress, inhibit tumor growth, and enhance drug delivery in a variety of cancers [65–67]. While these therapeutic strategies show promise, limitations in delivery and efficacy remain, particularly with some senolytics. While they are effective at selective clearing of senescent cells, they may also disrupt beneficial senescent signaling, leading to negative downstream effects [68]. These concerns underscore the importance of new strategies aimed at the aging ECM. One such strategy has been exosomes and other nanoparticle-based therapies designed to

enhance targeting and efficacy of current therapeutics (Figure 2C) [69]. By recalibrating the general hallmarks of ECM aging, such as stiffness and senescent cell accumulation, normalization-based approaches aim to restore tissue homeostasis, reduce the risk of unintended consequences associated with ECM degradation, and offer a more physiologically relevant method for enhancing therapeutic efficacy in aged or tumor-associated microenvironments.

Conclusion and future directions

The aged ECM plays a key role in cellular behavior and therapeutic resistance in many cancers. Aging-related alterations foster a tumor-permissive microenvironment and diminish the native immune response to tumorigenesis. Despite the importance of the ECM in cancer progression, the aged ECM remains understudied in the literature, as many preclinical models are unable to evaluate aging-related contributions in a biomimetic way, and clinical models often struggle to isolate aging-related effects from comorbidities and biological variation. Recent efforts to address this have resulted in the development of models to deliberately study the complex interaction between aging, the ECM, and cancer. Based on these insights, promising novel therapeutic strategies are being developed to counteract the effects of aging in the ECM with respect to cancer. Expanding these models and therapies to more accurately recapitulate the aged microenvironment in cancer-specific models is key to enhancing our understanding of cancer onset, progression, treatment, and response. As the global population continues to age, addressing the relationship between the aged ECM and cancer is critical. By integrating this relationship, clinicians and researchers can work to develop therapies that promote healthier aging, improve patient outcomes, and enhance quality of life.

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Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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