Aging-related alterations in the extracellular matrix modulate the microenvironment and influence tumor progression

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Abstract

Age is the greatest risk factor for the development of epithelial cancers. In this minireview, we will examine key extracellular matrix and matricellular components, their changes with aging, and discuss how these alterations might influence the subsequent progression of cancer in the aged host. Because of the tight correlation between advanced age and the prevalence of prostate cancer, we will use prostate cancer as the model throughout this minireview.

Keywords
prostate cancer; microenvironment; senescence; extracellular matrix; matricellular proteins

Introduction

Most tissues undergo significant modification with age. For the purposes of this review, the term aged refers to hosts that have reached greater than 75% of their species life expectancy and that generally have a larger percentage of cells (relative to young hosts) defined as senescent in many of their tissues.1-4 Senescent cells, which have ceased replicating but remain metabolically active, as well as normal aged cells influence the microenvironment of tissues. The relative contribution of senescent cells versus normal aged cells in remodeling the microenvironment is speculative, especially in regard to the effect of specific cell types (e.g. endothelial, epithelial, fibroblasts). In this review, we will explore the possible effects of senescent cells as just one of many factors that can alter the microenvironment in an aged host, thereby influencing tumor progression.

Whereas cells have been the focus of most research in tissue aging, it is increasingly appreciated that pervasive changes also occur in the components of the extracellular space.5-8 Modifications in the local environment, in turn, impact cellular functions. As an example, loss of tissue architecture is a defining characteristic of epithelial cancer initiation and progression. Thus an extracellular environment that provides the correct cues can serve as a powerful tumor suppressor—placing cells containing preneoplastic as well as oncogenic mutations into a normal tissue architecture reverts those cells back to a normal phenotype (e.g. polarization of epithelial cancer cells) despite the continued presence of oncogenic mutations. Conversely an environment that is rich in growth promoting mediators can spur on cells containing mutations to develop into cancer.6-8 These processes continually alter
the composition of the microenvironment and subsequently influence tumor progression in the aged host.

Within this extracellular environment, the influence of various growth factors has been at the core of cancer research. However, there is increasing interest in the roles of other components during tumor progression. The term “microenvironment” now includes the extracellular matrix (e.g. collagens, laminins), matricellular components, soluble factors (hormones, cytokines, growth factors, enzymes) that are released by resident and circulating cells or transmitted by other organs, and a myriad of cell types (e.g. various immune cell populations, endothelial cells, fibroblasts, epithelial cells). Cells use membrane receptors, such as integrins and syndecans, to physically attach to components of the extracellular matrix, including collagens and laminins. These types of receptors, in turn, are connected to the intracellular cytoskeleton network via protein signaling scaffolds. Alterations in the cytoskeleton, due to signaling through cell-matrix receptors, modify gene expression through links to the nuclear matrix and chromatin. Gene expression changes subsequently lead to modifications in the chemical and protein composition of the microenvironment.

Metastasis of the primary tumor, likewise, is affected by aging. Kaplan, et al elegantly demonstrated that when they replaced young marrow with aged marrow in young irradiated mice, tumor metastases decreased. Conversely when they replaced old marrow with young marrow in irradiated older mice, they observed an increase in metastases suggesting that tumor metastases are determined by preparation of a bone-marrow derived “metastatic niche” prior to the arrival of cancer cells and that older marrow is poorer at preparing this niche than younger marrow. There are a multitude of factors involved in metastases, including an angiogenic component and differential signaling by the tumor cells themselves. Thus the interactions of tumor cells with the host homeostatic mechanisms are highly variable and complex. The reasons behind an apparent decrease in metastases in the aged host versus young host are myriad and likely to vary with the type of cancer. In this minireview, we will use prostate cancer as the model and focus on the potential roles of extracellular matrix components during primary tumor progression in the aged host.

Epithelial Cancers and Cellular Senescence

Age-associated epithelial cancers, such as prostate cancer, contribute significantly to morbidity and mortality in the elderly. One possible mechanism by which the body defends itself against epithelial cancers is to halt replication of damaged cells by senescence. Although senescence might initially assist in preventing the formation of epithelial tumors, the accrual of senescent cells may ultimately provide a permissive environment that promotes tumor progression. In this scenario, once a cell has entered senescence, its transcriptome is altered such that genes associated with inflammation, angiogenesis, and immune cell recruitment/activation are secreted locally. These cells acquire a unique secretome, which Campisi and colleagues term the “Senescent Associated Secretory Phenotype” (SASP). Senescent cells also alter the extracellular matrix directly through changes in structural proteins (e.g. collagens, laminins) as well as the enzymes that regulate their turnover (e.g. MMPs, TIMPs). As an example, senescent cells can overexpress specific collagen and laminin chains (e.g. Col I α2, Col IV α3, LM α4, LM β1). At the same time, these cells tend to have greater matrix metalloproteinase activity, suggesting linked biosynthetic and degradative processes. Cumulative changes in expression patterns affect not only the senescent cell, but also influence surrounding cells. This viewpoint is supported by studies demonstrating that accumulation of mutations alone is not sufficient to cause cancer; instead cells harboring mutations require a permissive microenvironment in which to progress towards tumorigenicity.
Studies on the role of senescent cells in tumor initiation and progression can appear contradictory depending on which cell type is being examined (fibroblast, epithelial, endothelial, etc) and their subsequent location. For instance, when senescent fibroblasts were co-cultured with pre-malignant epithelial cells, increased proliferation and tumorigenicity of those epithelial cells resulted, both in vitro and in vivo. Further Liu and Hornsby reported that when breast cancer cell lines were mixed with senescent fibroblasts and placed in a subcutaneous xenograft model, greater tumorigenicity occurred compared to when breast cancer cells were implanted alone or with non-senescent fibroblasts. Intriguingly, when using the kidney-capsule model, the same group found that the presence of senescent fibroblasts did not further enhance angiogenesis or tumor growth relative to the effect of control fibroblasts. In our studies using dermal fibroblasts from aged human donors, we observed that cells exhibiting features of senescence (decreased proliferation, slowed migration, positive beta-gal staining) produced growth-promoting chemokines to a greater extent than non-senescent cells from aged human donors. More work is needed on how the source of the senescent fibroblasts, as well as the subsequent location of the tumor grafts, influences the resulting growth. Such studies would provide us with a better understanding of the role of senescent fibroblasts in tumor initiation and progression.

Because fibroblasts are the primary cell type in most studies of senescence, the effect of other types (e.g. endothelial, epithelial, and cancer cells) in cancer initiation and progression remains poorly studied. The few studies published, however, often support a role for these other senescent cells in inhibition of tumor initiation and/or progression. Like fibroblasts, these cells also have a senescence-associated secretory phenotype (SASP) and are capable of altering the tumor microenvironment. Coppe, et al laser-captured prostate epithelial tumor cells from tissue samples collected during the time of radical prostatectomy and examined them for regulation of mRNA expression of SASP factors: men treated with chemotherapy prior to surgery had increased levels of SASP factors compared to men who did not receive chemotherapy. Whether an increase in SASP factors at the time of prostatectomy correlated with a significant difference in time to recurrence or with differences in survival rates was not examined. Moreover, how different senescent cell types modify the microenvironment of the aged host has not been specifically examined. Further studies investigating the role of senescent cells in the tissues of aged cancer patients are warranted and are of potential clinical importance in regard to monitoring patient response to various therapies.

**Extracellular Matrix Components**

Clinical observations suggest that while aging confers the greatest risk of developing cancer, once initiated, histologically similar tumors often behave less aggressively in the aged. This premise was further supported by animal studies in which young and aged mice received identical inocula of tumor cells and were subsequently monitored for tumor growth and aggressiveness. Proposed mechanisms for differences in cancer behavior have focused on age-related changes in immune mediated responses, increases in apoptosis, and decreases in pathological angiogenesis, all of which result in a less permissive milieu for tumor growth in an aged relative to a young host. In this context, it is important to note that in studies of prostate cancer, cell-specific characteristics can obviate age-related influences on tumor progression.

In this mini-review studies of age-related alterations of the matrix in normal tissues, and changes in tumor matrix in non-aged hosts, will provide a basis for discussion of several key extracellular components as additional variables in disease progression. As is common in gerontology, it is important to note that for any given matrix component, specific disease
states that are more common in the aged might confer changes in a given organ that obviate alterations due to age itself. This mini-review discusses the traditional extracellular matrix proteins, Collagen I and laminin, as well as matricellular components such as thrombospondin 1 (TSP1), SPARC (osteonectin), and the non-sulfated glycosaminoglycan, hyaluronic acid (HA).

**Collagen I**

Collagen I is a heterotrimeric, fibrillar protein (2 chains of the alpha 1(I) and 1 chain of the alpha 2(I) monomer) that is the major structural extracellular component of most tissues. Of the more than 25 collagens, Collagen I has been the most extensively examined in aged humans and the consensus is that aging confers a progressive decrease in Collagen I synthesis concurrent with an increase in Collagen I degradation. Studies examining mechanisms of decreased collagen I content in aged human tissues have noted that lower levels of fibrogenic growth factors, such as transforming growth factor-beta (TGF-β), contribute to less Collagen I synthesis. At the same time, elevated matrix metalloproteinase activity mediates increased Collagen I degradation. Whether the latter results from an increase in collagenase and other matrix metalloproteinases (MMPs) or a decrease in tissues inhibitors of MMPs (TIMPs) is still a matter of debate. There are important exceptions to this premise, such as the increased Collagen I deposition that is often noted in aged hearts as a response to hypertension. Although not due to aging per se, the observations with respect to cardiac Collagen I underscore the need to use the term “deregulation” to describe many of the changes in the matrix in aged organs.

Whether total Collagen I expression is increased or decreased in any given organ, there is consensus that Collagen I is more loose, disorganized, and fragmented in most aged tissues, especially skin (Figure 1). These alterations result in less potential for cellular attachment, which has implications for the support, as well as the function, of resident cells. As an example, age-related losses in integrin (primarily α1β1 and α2β1)-collagen binding result in less robust cell adhesion and migration. Others have proposed that age-related deficits in the collagen-integrin cascade initiate prostate tumorigenesis. Collagen density and stiffness is another parameter that influences tumor cell behavior. Weaver and colleagues have noted that enhanced collagen cross-linking, mediated by lysyl oxidase, promotes growth and invasion by normally pre-malignant human mammary epithelial cells. This same group noted that interactions between adhesion molecules such as filamin A and β1 integrin can alter the cells’ response to collagen tension, thereby permitting morphogenesis in high density gels. Taken together these data underscore the ability of the cell, in particular epithelial cells, to adapt to the stiffness of their microenvironment. Whether endothelial cells have this same capacity is unclear—although a less dense collagen matrix could facilitate vascular invasion, studies of angiogenesis in most organs have demonstrated decreased capillary density with age. Moreover, the implications of age related changes in collagen organization to epithelial tumor growth in general is still a matter of conjecture. As previously noted, in prostate tumors it is cell and tissue specific characteristics that determine progression, irrespective of host age.

Aging also increases the number of advanced glycation end products (AGE) present on matrix components, such as collagen. Bartling et al examined collagen from aged rats and found that various lung cancer cell lines had decreased adhesion to and migration through collagen type I and III from old rats compared to young rats. The collagen from old (24 month) rats had a significantly higher AGE load than collagen from young (2 months) and adult (12 months) rats. Collagen from young rats that was modified to have increased AGE load also led to decreased adhesion and migration of the cancer cell lines. In addition, the authors found decreased MT3-MMP proteolysis of collagen from old hosts and the AGE-modified collagen compared to the unmodified collagen from young animals.
also noted that Collagen I extracted from aged mice tail tendons differs significantly from that obtained from young mice.\textsuperscript{56} Moreover, in aged mouse prostates, Collagen I is the most significantly altered extracellular matrix protein at the mRNA, protein, and ultrastructural levels, in a manner similar to aged human skin.\textsuperscript{57} Normal dermal fibroblasts were able to contract the looser, less organized polymerized form of 3D Collagen I obtained from aged mice better than the Collagen I from young mice. Gene expression profiles of the same resident fibroblasts were significantly altered following exposure to the old Collagen I and reflected the changes in cell-matrix contacts induced by the aged Collagen I relative to young Collagen I.\textsuperscript{56} Taken together, these studies illustrate the potential utility of using aged mouse models, as well as matrices extracted from aged murine hosts, to examine changes in cell behavior that might be relevant to cell-matrix interactions that occur during tumor growth in vivo.

Laminins

Laminins (LM) are large matrix glycoproteins composed of highly homologous \( \alpha \), \( \beta \), and \( \gamma \) chains and are the main constituents of basal membranes (a special matrix that separates different cell types from one another, such as endothelial or epithelial cells from the surrounding stroma).\textsuperscript{58} Laminins are crucial components of the tissue architecture, but are also modulators of cell behavior.\textsuperscript{58} Examination of laminins, however, has been restricted to alterations during development and tumor progression.\textsuperscript{58} In part this is because laminins are thought of as developmentally regulated with stable expression in healthy adults. For instance, in fetal prostate LM111 (\( \alpha_1 \beta_1 \gamma_1 \), formerly known as Laminin 1) is the predominate laminin, but it is replaced by LM332 (\( \alpha_3 \beta_3 \gamma_2 \), formerly known as Laminin 5) as the predominate laminin in adult epithelial basement membranes.\textsuperscript{59, 60} However, a clue to the importance of laminins in the aged microenvironment may be inferred by examining alterations that occur in the basement membrane in the aged prostate. As men age, the presence of abnormal lesions within the prostate increases.\textsuperscript{61} Immunohistochemical staining of prostate tissues demonstrates that decreased expression of LM332 occurs as early as prostatic intraepithelial neoplasia (PIN).\textsuperscript{59, 60, 62} Not all PIN lesions become cancerous, but the reasons why are poorly understood. Perhaps the effect of altered laminin expression on the surrounding microenvironment could provide one clue. During progression from PIN to carcinoma, expression of LM332 is lost and remains absent in prostate metastases.\textsuperscript{59, 63, 64} LM332 is crucial for correct polarization of the epithelial cells, thus an absence of this laminin leads to disorganized epithelial cells. However, Calaluce, \textit{et al} also demonstrated that alterations in LM332 expression affect expression of a variety of genes, suggesting that the changes in laminin expression in aged prostates may influence the prostate microenvironment not only by altering ECM/cell interactions, but also by directly modifying gene expression and therefore could potentially lead to a microenvironment that is more permissive for tumor growth.\textsuperscript{65}

Some studies suggest that expression of other laminin chains also are altered with increased age of the host. Luo \textit{et al} and Bavik \textit{et al} demonstrated that senescent prostate epithelial cells found in regions of benign prostatic hyperplasia (BPH) as well as senescent prostate fibroblasts have increased expression of the laminin \( \alpha_4 \) and \( \beta_1 \) chains.\textsuperscript{16, 66} The laminin \( \alpha_4 \) chain is normally present in laminins that are important to vessel architecture; most endothelial cells throughout the body express the laminin \( \alpha_4 \) chain.\textsuperscript{58} Normal blood vessel maturation and loss of malignant characteristics are associated with conversion to LM421 (\( \alpha_4 \beta_2 \gamma_1 \), formerly known as laminin 9), whereas sprouting and tumor blood vessels express LM411 (\( \alpha_4 \beta_1 \gamma_1 \), formerly known as laminin-8).\textsuperscript{67} In a cell model of senescent prostate cancer cells, we have found increased expression of both the laminin \( \alpha_4 \) and \( \beta_2 \) chains.\textsuperscript{20} Overexpressing both chains in prostate cancer cell lines decreased tumor growth in vivo, while overexpressing either chain alone resulted in increased tumor growth. In addition,
overexpression of the laminin α4 chain alone resulted in increased levels of collagen deposition and increased microvessel density in the tumors suggesting that alterations in laminins influence reorganization of the matrix as well as infiltration of other cell types, including endothelial cells. Wu et al demonstrated that the ability of immune cells to infiltrate tissue sites might also be influenced by laminin composition. In a mouse model of brain inflammation, disease-associated CD4+ T cells had markedly lower infiltration through endothelial basement membranes containing only LM511 rather than the usual LM411. However, the infiltration of other immune cells, such as macrophages and CD8+ T cells, was not affected by the presence of LM511. By extrapolation, increased levels of the laminin α4 chain without an increase in the laminin β2 chain in aged prostates may enhance the infiltration of regulatory CD4+ T cells, thereby altering the microenvironment into one that more favorably supports tumor growth. Thus, in the aged host, accumulation of senescent cells could have a dichotomous function on tumor initiation and progression depending on which laminins are expressed.

Matricellular Components

The term “matricellular” refers to components of the extracellular space that primarily regulate cell function without providing significant structural support. The “matricellular” designation implies a protein has a tremendous range of effects, many of which are contextual (i.e., dependent upon the local milieu). Although few have been investigated with respect to tumors in the aged host, the proteins Thrombospondin 1 (TSP1) and SPARC (osteonectin) have been examined separately in aging and cancer biology. For the purposes of this review and its focus on prostate cancer, we will also include the non-sulfated glycosaminoglycan, hyaluronan (HA).

Thrombospondin 1

Thrombospondin 1 (TSP1) is one of several members of a family of large trimeric glycoproteins that are classically matricellular in character. TSP1 is of greatest interest due to its ability to inhibit endothelial cell functions and angiogenesis. TSP1 expression is increased in most aged cells and is thought to contribute to decreased angiogenesis in aged tissues, such as the kidney, in their basal state. Moreover, the increase in TSP1 in aged organs is presumed to play a role in deficient blood vessel formation during tissue repair in older hosts.

Higher levels of TSP1 have been postulated to decrease tumor angiogenesis, thereby slowing tumor growth. TSP1 inhibits blood vessel formation by blocking pro-angiogenic mediators (such as the potent vasodilator nitric oxide, which is already deficient in aged tissues), growth factor mediated functions (such as proliferation and migration), and enhancing apoptosis of activated endothelial cells. TSP1 has additional influences on other cells in the microenvironment by modulating the balance of matrix metalloproteinases and their inhibitors, the TIMPs. The negative effects of TSP1 on endothelial cell functions have resulted in great interest in the role of this glycoprotein during tumor progression. In many cancers, TSP1’s presence is associated with a non-angiogenic phenotype and tumor regression; conversely, the absence of TSP1 expression is correlated with an angiogenic switch and metastases.

Expression of TSP1 is highly regulated by cellular and extracellular mediators as well as unexpected compounds including certain cholesterol lowering agents. In prostate cancer cell lines, the tumor suppressive β1C integrin increases TSP1 expression; while at the same time androgens repress TSP1 transcription. The influence of androgens on TSP1 expression and subsequent tumor vascularity and growth depends on the duration of TSP1 exposure. Androgen withdrawal initially leads to increases in TSP1 and vessel regression;
however, with continued exposure prostate cancer angiogenesis and growth continue despite persistently high levels of TSP1. Similar results have been reported in other cancers: persistently high levels of TSP1 in the breast tumor stroma ultimately result in disease progression, an effect that may result from increased expression of VEGF. These multiple effects have dampened enthusiasm for the use of TSP1 in clinical intervention studies.

**SPARC**

SPARC is a small, secreted glycoprotein that is highly expressed in injured and inflamed tissues. Accordingly, high levels of SPARC are found in many cell types and in most aged organs. The absence of a defined receptor and a clear understanding of its functional significance have led some to propose that SPARC is a general marker of a stress response and subsequent cellular activation. Studies in vitro indicate SPARC can delay early collagen initiation. However, the association of SPARC with collagen synthesis and processing *in vivo* has suggested it is a beneficial, but not necessary, variable in structural matrix assembly and organization. Interestingly, we have noted that young fibroblasts secrete more SPARC when placed in aged, relative to young, 3D collagen I. It is possible that the increase in SPARC reflects the cells' response to the looser, less organized aged matrix.

As a result of the tight link between SPARC expression and remodeling tissues, it is not surprising to note a differential increase in the expression of SPARC during progression of prostate cancer. In prostate metastases to bone, cathepsin K and other mediators are thought to increase the expression of SPARC, thereby further inducing boney involvement with tumor cells. Intact SPARC might inhibit the angiogenic response by impairing proper collagen alignment and blocking pro-angiogenic growth factors. At the same time it has been reported that cleaved SPARC facilitates vessel growth by enhancing endothelial cell proliferation. However, in young SPARC-null versus wild-type counterparts, increases in angiogenic invasion were found in the SPARC-null mice in a sub-dermal sponge model. In aged hosts, differences in fibrovascular migration and vessel formation exhibited by SPARC-null versus wild-type mice were no longer apparent. Hence, the role of SPARC in the angiogenic response was presumably obviated by age-related deficits in cellular functions and loss of pro-angiogenic mediators, such as VEGF.

The relative ease by which *in vivo* SPARC expression can be manipulated has resulted in examination of its specific effects in the initiation, progression, and metastases of many tumors. After decades of examination it is clear that SPARC's influence, like that of aging, is dependent on the tumor cell type and the specific microenvironment of the host. In a TRAMP model of spontaneous prostate tumors, modulation of SPARC in mice from a mixed genetic background did not effect prostate tumor initiation, progression, or metastases. In contrast, when Said et al crossed TRAMP mice with *SPARC-null* mice on a pure C57/Bl6 background, they reported that prostate cancer progression was more aggressive and resulted in a greater number of metastases in TRAMP/SPARC-/- mice compared to TRAMP/SPARC+/+ mice. Furthermore, the TRAMP/SPARC-/- mice demonstrated decreased levels of stromal collagen I and III deposition within the adenocarcinomas, enhanced MMP-2 and -9 activity in tumor lysates, increased levels of angiogenic factors, and increased microvascular density compared to TRAMP/SPARC+/+ mice. These changes are similar to those noted in pancreatic cancer and ovarian cancer cell lines placed in SPARC-null versus wild-type mice. These data suggest that in certain microenvironments, SPARC acts as a tumor suppressor and is anti-angiogenic. It is possible that much of SPARC's function is dependent on the status of Collagen I: if both are highly expressed the resulting extracellular architecture could provide greater stability against tumor progression.
Hyaluronan

Hyaluronan (HA) is a large, unbranched polymer of the disaccharide glucuronic acid/N-acetylglucosamine. A normal constituent of tissues, native HA is comprised of from 2,000–25,000 disaccharides with molecular masses of $10^6$–$10^7$. HA's size and affinity for water promotes its binding and organization of other ECM macromolecules, thereby mediating ECM assembly and homeostasis. The relationship between HA and aging is not well defined and appears to vary among, as well as within, tissues depending upon exogenous exposures, such as UV light. Moreover, many of the studies have been performed on cells aged in vitro, an important but not universally accepted model of cellular aging. Accurate measures of changes with age are also complicated by decreased extractability and impaired organization of HA with aging. Despite all of these considerations it is generally accepted that young cells synthesize more newly formed HA than their aged counterparts in response to injury as well as HYAL activity. At the same time it is thought that HA content may accumulate with age as a result of increased half-life as well as less efficient degradation.

HA is produced by prostate tumor cells as well as the stroma that surround tumors. It is generally accepted that HA accumulation is a poor prognostic indicator in prostate cancer and predicts unfavorable outcomes including metastases. HA content is regulated by at least 3 HA synthases (HAS-1, -2, -3), which differ in tissue distribution, rate of HA synthesis, and size of HA produced. Tumor cell lines that overexpress HAS-2 and -3 show increased tumorigenesis; cell lines with HAS-2 and -3 suppressed by antisense oligos or siRNA exhibited reduced tumorigenicity.

HA facilitates tumor progression by multiple mechanisms. HA influences ECM porosity by binding to collagen I as well as versican and fibrin, thereby increasing tumor cell motility in vitro. HA also enhances cell migration via CD44-dependent mechanisms, including those that increase MMP activity. Accordingly, modification of CD44 expression is gaining increasing interest as a target in prostate cancer therapy. The presence of HA also induces signaling complexes that contain activated ErbB2, a transmembrane protein that promotes tumor malignancy and drug resistance.

HA may also promote tumor growth by enhancing tumor vascularization. High molecular weight (MW) HA is anti-angiogenic, however, low MW oligosaccharides of HA stimulate angiogenesis in vitro and in vivo. Correspondingly degradation of high MW HA by hyaluronidase (HYAL) enhances angiogenesis in tumors and correlates with cancer invasiveness. Tumor extracts contain pro-angiogenic HA oligomers that may arise via digestion of HA by tumor-associated HYALs. Of particular note is HYAL-1, which is implicated in prostate cancer progression and recurrence.

The effect of age on HA metabolism into high and low MW forms is as poorly understood as age-related changes in total HA content and organization. Middle-aged rat skin appears to express HA of higher MW, but the influence of age on the ratio of high MW to low MW HA has not been examined in detail. It is probable that each organ has its own regulation of HA expression with respect to both amount and size distribution. Consequently, additional determination of age related effects on HA turnover and size are likely of greater significance in highlighting factors associated with cancer progression, than measures of total HA expression in the tumor microenvironment.

Conclusion

Body-wide levels of factors associated with tumor progression might decrease with aging, but their level of expression can increase locally. The prostate provides a unique model for this paradigm. For example, senescent cells in the prostate are more prevalent with host age...
and display a transcriptome and secretome that appears to encourage cellular proliferation, inflammation, and angiogenesis. Matricellular components (eg. TSP1, SPARC, and HA) as well as extracellular matrix proteins (eg. collagens, laminins, and their associated integrins) are modulated by aged cells, but in a locally specific manner. These components can interact with resident cells to further alter the microenvironment to one that promotes epithelial tumor growth (Table 1). Consequently, while tumor growth, angiogenesis, and metastases are often impaired in the aged host, the local microenvironment of primary epithelial tumors such as the prostate may be as supportive of tumor progression as that found in the young host.

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**References**


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Figure 1. Differences in organization of Collagen I extracted from aged and young mice
Shown are sections of polymerized Collagen I from aged and young mice tail tendons
stained with Picosirius Red and viewed with a polarized lens. Note Collagen I from aged
hosts display looser and less organized polymerization of fibrils (arrow, left panel), while
Collagen I from young mice has the expected organized and dense striated pattern (arrow,
right panel). Magnification=40×
Table 1
Age-related changes in ECM components and potential effects on tumor progression

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