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Journal

Molecular Carcinogenesis, 62(1)

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Publication Date

2023

DOI

10.1002/mc.23417

Peer reviewed

Published in final edited form as:

Mol Carcinog. 2023 January ; 62(1): 5–23. doi:10.1002/mc.23417.

Revisiting Laminin and Extracellular Matrix Remodeling in Metastatic Squamous Cell Carcinoma: What have we learned after more than four decades of research?

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Abstract

Patients with squamous cell carcinoma (SCC) have significantly lower survival upon the development of distant metastases. The extracellular matrix (ECM) is a consistent yet dynamic influence on the metastatic capacity of SCCs. The ECM encompasses a milieu of structural proteins, signaling molecules, and enzymes. Just over 40 years ago, the fibrous ECM glycoprotein laminin was identified. Roughly four decades of research have revealed a pivotal role of laminins in metastasis. However, trends in ECM alterations in some cancers have been applied broadly to all metastatic diseases, despite evidence that these characteristics vary by tumor type. We will summarize how laminins influence the SCC metastatic process exclusively. Enhanced laminin protein deposition occurs at the invasive edge of SCC tumors, which correlates with elevated levels of laminin-binding β1 integrins on SCC cells, increased MMP-3 presence, worse prognosis, and lymphatic dissemination. Although these findings are significant, gaps in knowledge of the formation of a pre-metastatic niche, the processes of intra- and extravasation, and the contributions of the ECM to SCC metastatic cell dormancy persist. Bridging these gaps requires novel *in vitro* systems and animal models that reproduce tumor-stromal interactions and spontaneous metastasis seen in the clinic. These advances will allow accurate assessment of laminins to predict responders to TGFβ inhibitors and immunotherapy, as well as potential combinatorial therapies with the standard of care. Such clinical interventions may drastically improve quality of life and patient survival by explicitly targeting SCC metastasis.

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7.2 Conflict of Interests

The authors declare that there are no conflict of interests.

1- Introduction

1.1 - Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) malignancies that arise from the stratified epithelium have a high global incidence, with metastasis frequently occurring in SCC of the skin, head, and neck[1–6]. As with other solid tumors, a primary SCC tumor can be successfully eradicated with the standard of care, including surgical resection, chemotherapy, and irradiation; however, metastases drastically lower overall survival of patients[7–10]. Despite early screening efforts, there is still a high risk of metastatic recurrence, at times detected as late as 8 years following diagnosis[11]. For this reason, there is an urgent need to discover therapeutics capable of targeting SCC metastases.

1.2 – The Steps of Metastasis

Metastasis is frequently described as a cascade of sequential events resulting in spread to distant tissue. Initially summarized by Paget[12, 13], the steps of epithelial cell metastasis are as follows: First, cells must undergo an epithelial-to-mesenchymal transition (EMT), where tumor cells lose epithelial, stationary characteristics and obtain a migratory mesenchymal phenotype with reduced binding to adjacent cells and the extracellular matrix (ECM)[14]. These cells must also resist anchorage-independent signaling that activates p53-dependent cell death, or anoikis. Second, tumor cells must breach the basement membrane to invade into surrounding regions. Once free of the basement membrane, cancer cells must remain motile and traverse an ECM that is radically different than that surrounding the primary tumor. Cancer cells must break through an additional basement membrane encircling the vasculature and subsequently extravasate to enter a vessel. Though traditional models presume extravasation must involve blood vessels, more recent discoveries suggest the lymphatic system is a preferential route of metastasis for some malignancies[15], a concept which we will address later. Once in the vasculature, cancer cells must survive sheer force while circulating. Upon arriving at a distant site, often the lungs or liver, cancer cells must adhere to the vessel wall and extravasate from the vessel. This process of extravasation includes movement through patches of ECM and more basement membrane. Finally, surviving tumor cells can begin to colonize the new site and develop secondary tumors. Throughout this process, cancer cells must avoid immune-mediated destruction, establish crosstalk with other cell populations, and maneuver through ECM of varied composition. Although this general cascade of events is accepted for the metastasis of solid tumors such as SCCs, crucial nuanced questions persist. While preferential sites for metastasis are known for individual cancers, factors that influence preference are subject to debate. Furthermore, the conditions for cells to successfully extravasate from the vasculature are still being defined. Additionally, the proclivity for lymph versus blood vessels as routes for dissemination is an ever-growing realm of investigation. Filling these gaps in knowledge may reveal novel therapeutic opportunities to prevent metastatic outgrowth.

1.3 – The Extracellular Matrix

Metastatic potential is influenced, in part, by ECM composition[16–18]. The ECM is a collection of structural fibers, signaling factors, deposited extracellular vesicles (EVs), and enzymes[19–21]. It serves as a physical barrier to macromolecules and cells, an adhesion

point for cell movement, a partition of tissues, and it influences cell differentiation and metabolism through contact between cell receptors and ECM components. Outside of normal ECM remodeling during tissue development and maintenance, wound repair, angiogenesis, puberty, and pregnancy, ECM restructuring is a major contributor to the development of disease, including cancer[22–24]. The ECM is a crucial component of the tumor microenvironment (TME), and comprises the bulk of solid tumor mass in some cases[21]. The most recent iteration of the Hallmarks of Cancer has identified ECM remodeling as a microenvironmental mechanism of epigenetic reprogramming to promote hallmark cancer characteristics, namely invasiveness[25]. Indeed, ECM composition and expression of ECM binding receptors have major mechanistic consequences throughout the metastatic journey of tumor cells[26, 27].

A diverse range of roughly 300 macromolecules comprise the core matrisome; hundreds of these are involved in ECM remodeling[19, 28]. The heterogeneity of ECM components can be appreciated in Figure 1. Fibronectin is a glycoprotein comprised of two subunits linked by disulfide bonds and may be found as cellular, plasma or fetal forms[29]. As a structural protein in the ECM, fibronectin supports collagen fibers to provide shape and rigidity. The diverse contributions of fibronectin to cancer and metastasis have been reviewed elsewhere[30, 31] and will not be discussed further. Of the ECM fibers that largely contribute to the matrix structure, the most robustly investigated is collagen. Collagen was first identified in the 1930s, its trimeric structure defined 20 years later, and a family of 28 collagens are currently recognized[32, 33]. Given that collagen comprises a significantly greater proportion of the ECM relative to other proteins and is more widely distributed in the body, collagen, particularly type I collagen, is used synonymously with ECM. However, the ECM composition, including collagen type, varies by anatomical location[34]. This is the case with the basement membrane component type IV collagen, which is rarely present outside of this zone[35].

An additional component of the ECM is the fibrous trimer, laminin. First identified in 1979, laminin has been investigated as a contributor to cancer progression and metastasis since its discovery[36]. This glycoprotein is particularly important in the process of vessel maturation and wound healing[37, 38], cell adhesion, chemotaxis, and differentiation[39, 40]. Laminin is also a necessary scaffolding ECM protein for collagen deposition, particularly collagen IV, and is essential for basement membrane stability[36, 38, 41]. Though often referred to as a singular protein, this matrix fiber is comprised of three chains, with 11 genes coding for individual chains and various compositions of the three chains in each laminin trimer (a α-chain, a β-chain, and a γ-chain)[42]. These trimers are assembled intracellularly, with disulfide binding of the β and γ subunits occurring initially. In the cytoplasm, this βγ-dimer then incorporates the α-chain, which drives the release of the mature, heterotrimeric laminin into the extracellular environment[43]. Laminins are identified by the composition of individual subunits[40]. For example, laminin-332, composed of α3, β3, and γ2 chains, is one of the most robustly investigated laminin subtypes in cancer. Like type IV collagen, laminins are generally associated with the basement membrane, but, as we will discuss, laminin distribution is heavily increased outside of this zone during metastatic progression.

In this perspective, we will summarize the roles of ECM remodelers in promoting matrix degradation and laminin deposition for metastatic progression in SCC. We will evaluate how these players impact key steps of the metastatic cascade. We will also outline the current gaps in our understanding that must be filled for the field to progress. Finally, emerging therapeutic interventions to target laminin and other ECM components in metastatic SCC will be presented.

2 – Mediators of ECM Remodeling

2.1 - Fibroblasts

While all cells have the ability to regulate ECM makeup and architecture, the major cell population to do so, besides tumor cells, is the fibroblast[44]. Fibroblasts are recognized as the chief contributor to ECM editing and the main depositors of laminins in non-malignant contexts. Fibroblasts were first identified in 1858 by Rudolf Virchow as cells that are activated for production and deposition of collagen and returned to a quiescent state following tissue development[45]. Since their identification, the profile of this population has expanded to include roles in the regulation of immune response, tissue development and repair, maintenance of homeostasis, and mediation of cell-to-cell cross talk[44, 46]. Dormant fibroblasts maintain a spindle-like formation until stimulated by cytokines, such as transforming growth factor beta (TGF-β)[47, 48]. These activated fibroblasts, termed myofibroblasts, when proximal to the tumor are generally known as cancer associated fibroblasts (CAF)[47, 49, 50]. Because of their involvement in hallmark cancer processes, CAFs have been investigated substantially and have been reviewed in prior articles[51–56].

CAFs mechanically facilitate dissemination of cancer cells by physically organizing matrix proteins. Myofibroblasts traditionally contract under the force of alpha smooth muscle actin (αSMA) that induces cellular stress fiber restructuring[57]. This activity permits tissue-infiltrating immune cells to navigate the ECM. As with many processes for homeostasis, tumor cells and CAFs likewise manipulate the normal contractile activity of myofibroblasts for cancer progression. Multi-photon laser scanning microscopy and Second Harmonic Generation microscopy demonstrated that CAFs expressing αSMA elongated collagen fibers, correlating with local and distant metastases in head and neck SCC (HNSCC)[58]. Mechanistically, ROCK and JAK1 signaling in CAFs have been confirmed to induce contraction of matrix fibers and produce tracts for invasive SCC cells[59]. In cutaneous SCC (cSCC), CAFs isolated from the primary tumor contracted collagen matrices and enhanced release of pro-collagen I when cultured *in vitro* on collagen matrices[60]. This was noted in tandem with the increased invasion of SCC cells when cultured with CAFs in a model that mimics human skin. These findings are in line with CAFs playing a role in the construction of routes through the ECM by organizing fibers for the traction of cancer cells.

In SCC, CAFs also release signaling factors that produce a more motile phenotype. In SCC of the oral cavity (OSCC), tumor cells co-cultured with CAFs had elevated signaling through the AKT/GSK-3β/β-catenin/Snail pathway. This translated to enhanced metastatic potential when both OSCC cells and CAFs were co-transplanted into mice, relative to OSCC cells injected with donor-matched normal fibroblasts [61]. CAFs may also initiate OSCC invasion by secretion of the hepatocyte growth factor/scatter factor to initiate formation of

focal adhesions[62] which are essential for all cell populations to navigate through the ECM. Our own work has shown that SCC cells co-transplanted with CAFs promoted metastasis and cancer stem cells seeding to the lungs in a TGF-β dependent manner[63]. CAF release of TGF-β has also been shown to promote laminin-332 production in cSCC cells[64]. H-Ras mutated cSCC cells in a 3D co-culture with CAFs enhanced the invasive capacity of tumor cells. Laminin-332 was shown to be elevated at the invasive edge of tumors as well. Though CAFs can secrete laminins[65], it has not been confirmed in the context of SCC. To follow the "seed and soil" hypothesis[12, 13], removing CAFs, the tillers of the soil, may be the key to limiting metastasis from the primary tumor and outgrowth of SCC at metastatic sites.

2.2 – Matrix Degrading Enzymes

Matrix degradation is a normal part of human development and is crucial for wound healing and tissue remodeling. ECM degradation is achieved by a class of enzymes called matrix metalloproteinases (MMPs)[66, 67]. These proteins are a sub-group of endopeptidases with 23 known MMPs in humans. MMPs are secreted as pro-MMPs by a range of cells, though the most common culprits in the context of SCC include macrophages, fibroblasts, and the tumor cells themselves. Once released, pro-MMPs must have their pro-domains cleaved for function. Of the MMP family, 10 are currently known to target laminins. Collectively, these enzymes can degrade any component of the ECM and are necessary for the activation of numerous signaling factors and other MMPs (see Table 1). Such degradation of matrix fibers is necessary for replacement of normal ECM architecture with proteins that promote tumor growth and metastasis, such as laminins.

The two most investigated MMPs are MMP-2 and MMP-9; both are commonly elevated in metastatic SCC[68, 69]. Indeed, MMP-2 and MMP-9 were shown to have prognostic value in predicting metastasis in SCC of the skin, head, and neck, and are known to degrade type IV collagen for invasion[70–75]. MMP-2 and MMP-9 are capable of degrading elastin and a number of collagens, but they are often associated with type IV collagen degradation in the basement membrane. In OSCC, elevated MMP-2 and MMP-9 levels were observed in the metastatic regions of tissues, and MMP-2 and MMP-9 expression correlated with collagen IV degradation and poor patient prognosis[76, 77]. Vessels are surrounded by basement membrane that has to be degraded for extravasation of tumor cells. In oseophageal SCC, MMP-9 was necessary to degrade the basement membrane of the lymphatic vasculature for metastasis to the lymph nodes[78]. Collectively, these studies suggest a role of MMPs to clear the way for trailing tumor cells. In degrading the current structure of the ECM, MMPs allow the formation of new tracts that SCC cells adhere to with greater affinity. As we will summarize, these new tracts are commonly laminins replacing previous deposits of collagens.

Other frequently overexpressed MMPs in metastatic SCC include MMP-3 and MMP-7. Although these MMPs may degrade laminins, they have primarily been shown to degrade collagens in SCC. A crucial consideration in studies of MMPs is the spatial distribution of these proteins. Investigation of MMP-7 in esopharyngeal SCC revealed heightened protein staining at the invasive front of the tumor[79]. The elevated presence of MMPs in invading tumor cells has also been noted in OSCC. MMP-3 proteins were strongly stained

at the peripheral borders of invasive tumor islands in the stroma, indicating high levels of expression[80]. As altered collagen distribution, shown by trichrome staining, was noted in combination with MMP-3, it is likely that ECM remodeling by MMP-3 mediated collagen degradation for the invasion of SCC cells[81, 82]. Interestingly, protein levels of MMP-3 were shown to correlate with lymph node metastasis in esophageal SCC (ESCC)[83] and required for lymphatic dissemination[84]. These findings suggest further assessment of MMP activity may predict preference for hematopoietic or lymphatic routes of metastasis.

2.3 – Transforming Growth Factor Beta (TGF-β)

TGF-β serves to regulate immune response, transcription of ECM components, and tumor-stromal cell crosstalk. The roles of TGF-β in tumor immunology and cancer progression have been summarized in previous reviews[85–89]. TGF-β drives metastasis in SCC, despite its inhibitory role in the early development of the cancer. TGF-β recruits pro-tumor M2-like macrophages to the tumor and activates CAFs for ECM remodeling to produce an immunosuppressive and favorable TME for SCC. This is partially because many target genes of TGF-β-Smad signaling include matrisome components such as laminins and ECM-degrading MMPs. Indeed, upregulated Smad activity is directly linked to myofibroblast activation in aberrant wound healing of the skin, a phenomenon that is associated with cancer development[90–92].

The Wang Laboratory has demonstrated the role of TGF-β-Smad in tumor progression and metastasis. As loss of Smad 4 in HNSCC cells and surrounding tissue is common in patients, our laboratory produced an appropriate model to study this phenomenon *in vivo*[93]. We reported that Smad 4 deletion results in genomic instability that parallels the effects of p53 loss, as well as significantly elevated expression of TGF-β and phosphorylation of Smad3. Together, these events produced spontaneous, metastatic HNSCC as seen in the clinic. Additional publications reveal that loss of TGF-β type II receptor (TGFβRII) results in accelerated tumor progression and metastasis[94, 95]. In these studies, an activating K-ras mutation in combination with TGFβRII deletion in epithelia of the head and neck or airway of mice produced tumors with high metastatic potential. In another HNSCC model, transforming growth factor beta 2 (TGFβ2) and TGFβ receptor type three (TGFβRIII) signaling through p38α/β regulated metastasizing tumor cell dormancy, defining restrictive TME such as the bone marrow, and permissive TME like the lungs[96]. This reinforces a bidirectional relationship between the TME and tumor cell whereby both the seed and soil modulate each other's activity. The production of such syngeneic models not only reinforce the importance of TGFβ-Smad signaling in metastatic SCC, but are instrumental for investigation of TME influences, such as the ECM and laminins that promote SCC metastasis.

2.4 - Responding to change: Integrins

The integrin family of cell surface receptors was first recognized by Hynes in 1987[97]. Integrins have an array of roles including development, immune response, cell adhesion, and reacting to mechanical stress. These heterodimeric transmembrane proteins are composed of α and β subunits and are categorized as Collagen, Laminin, Arg-Gly-Asp (RGD), and Leukocyte-specific receptors[98]. Integrin binding to laminins occurs at the C-terminal trio of

laminin globular domains. Though these domains are part of the α-chain of laminin, it is the γ-chain that is thought to maintain integrin-binding activity [42, 99].For this reason, individual laminin chains are often evaluated in studies assessing integrin-ECM interactions. For their extensive role in cancer progression [26, 100, 101] and metastasis [101–103], integrins have been reviewed in depth previously.

The ability of invading cells to grip ECM components is a crucial function for metastatic SCC cells to achieve motility. In laminin-332 matrices, integrin α2β1 expression on cancer cells is known to enhance the motility of SCC by binding to the globular domain of laminin[104]. Interruption of such binding significantly restricted motility of SCC cells and suggested the potential for therapeutic intervention by targeting integrin α2β1-ECM interactions.

Beyond serving as an anchorage point for SCC cells to navigate the ECM, ECM binding by integrins initiates intracellular signaling as well. This “outside-in” signaling is noted to induce oncogenic pathway activity in SCC. A major consequence of integrin β1 stimulation is the activation of focal adhesion kinase (FAK), leading to formation of focal adhesions for cell motility in SCC[105]. The activation of FAK is also shown to promote immune evasion in SCC[106], and targeting integrin β1 reduced stem-like characteristics conferred by FAK and Notch1 signaling in HNSCC[107]. Inversely, “inside-out” signaling directed by tumor cells may also facilitate metastasis. “Inside-out” phosphatidylinositol 3-kinase (PI3K) activity activated α4β1 integrin-adhesion for lymph node metastasis[108]. In this study, VEGF-C signaling stimulated PI3K and downstream effectors. For “inside out” signaling, PI3K pathway members FAK and Src promote cytoplasmic binding to the intracellular tail of integrin receptors producing conformational changes in integrins for cellular adhesion[109–111]. This includes adhesion to laminins commonly found in the lymph nodes. This was also documented by Shinohara and colleagues; they noted that laminin binding integrins α3 and α6 were elevated in metastatic and invasive cases of OSCC[112], particularly at the invasive edge. The authors hypothesized that these laminin-associated integrins were likely upregulated to bind to ECM components and potentially nearby invading cells, to disseminate to lymph nodes. In this way, SCC cells may interact with ECM components to disseminate to distant sites.

Additionally, the laminin integrin α7 has been proposed as a putative biomarker for OSCC cancer stem cells. Cancer stem cells are known not only for their resistance to therapy and stem-like characteristics, but also for their elevated ability to metastasize and colonize distant regions[113]. In OSCC patient tumors, the α7 integrin subunit correlates with tumor grade, stage, and lower overall survival in oesophageal SCC[114] and tongue SCC[115]. However, these studies did not explicitly assess the metastatic capability of α7 integrin positive OSCC CSCs. As FAK was shown to be activated downstream of integrin α7[114], it is likely that “outside-in” ECM signaling by laminin-integrin binding initiated FAK activity for stem-like characteristics. Given the role of FAK in metastasis, assessment of integrin α7+ OSCC cells would likely reveal enhanced metastatic potential as well.

Spatial distribution of these integrins on cells is particularly important in promoting invasion and metastasis. Quantification of immunofluorescence staining in ESCC patient samples for

laminin binding integrins α6β4 and α6β1 revealed heightened levels at the invasion front of tumors. Polarized integrin expression towards the invasive front of the tumor also served to predict ESCC aggressiveness[116]. Thus, not only is the presence of integrins necessary for cell motility, but the space these integrins occupy is crucial as well. Interestingly, it has been reported in OSCC that the loss of integrin β4 associated with nodal metastases at the time of diagnosis[117], and loss or reduced expression of β1 integrins and integrin α6β4 correlated with loss of basement membrane proteins[118]. One explanation for these conflicting reports is that integrins become down regulated once they are no longer needed by SCC cells to transverse the ECM following matrix degredation[119]. This supports a third consideration for assessment of integrin levels, which is temporal regulation of these proteins. Thus, integrin presence alone is not sufficient to serve as a biomarker but must be evaluated in the context of early metastasizing cells at the invasive front of tumors. This parallels our earlier summary of MMPs and their distribution in the ECM.

3 – The ECM Mediates Metastasis

3.1 – Leaving Home: The Primary Tumor

To pave a path from the primary tumor, obstacles including the existing ECM must be removed, a new trail of favorable matrix proteins deposited, and effective adhesions to the new ECM maintained. While degradation of laminins in the basement membrane defines invasion of SCC[120, 121], laminins also serve as key anchorage points and stimulants to activate internal SCC oncogenic pathways in this process. As reviewed by Marinkovich, laminin-332 has been identified as driving both tumorigenesis and metastasis in SCC[122]. In esophageal SCC, laminin-332 correlates with worse patient prognosis when assessing 126 patient samples[123]. *In vitro* evaluation suggested this may be due to an autocrine positive-feedback loop where laminin-332 secretion activates PI3K for invasion and additional secretion of laminin-332. Adhesion of SCC cells to laminins is known to activate internal signaling pathways necessary for migration, including FAK, PI3K, Ras/Raf, and Cdc/Rac[101]. Notably, these pathways lead to cytoskeletal remodeling and formation of complexes that adhere to the laminins and other ECM fibers for cell motility.

SCC cells that better adhere to high concentrations of laminin in the ECM are hypothesized to migrate better[104, 124]. EGF and TGF-β1 together induced EMT of OSCC cells, which accompanied an elevated expression of laminin γ2 chain[125]. This suggested a potential intermediate phenotype of OSCC cells undergoing EMT where laminin-332 is upregulated. This is in line with higher laminin γ2 protein expression in the cytoplasm of SCC cells at the invasive front of OSCC tumors[126, 127]. Again, cells at the invasive front likely undergo EMT and prepare to release laminin-332 by assembling the sub-chains in the cytoplasm of these cells for enhanced invasive capacity. In line with this evidence, assessment of laminin in OSCC patient samples revealed that OSCC cells with high laminin concentration in the cytoplasm denoted poorly differentiated tumor cells[128]. Interestingly, those OSCC cells with high laminin staining in the surrounding basement membrane were well differentiated tumor cells. Thus, laminin in the proximity of SCC cells is not sufficient to promote motility and invasion, but the source and distribution must also be considered. This is reinforced by documentation of OSCC patients with high cytoplasmic expression of laminins correlating

with lymph nodes metastasis[129]. While the laminin comprising the basement membrane may be an initial obstacle to SCC metastasis, laminins become a crucial ally for a tumor cell traversing the ECM during invasion.

Increased laminin production is aligned with observations of elevated deposition of fibrillary proteins at the primary tumor. In metastatic breast cancer, it is dogma that a stiff ECM allows tumor cells to invade into surrounding tissue and promotes metastasis[130]. Generally, stiffness is a result of increased deposition and crosslinking of type I collagen[130]. Though these trends have been observed in some cancers, such as breast and hepatocellular carcinomas, they have been applied broadly to the field. This is not necessarily the case with metastatic SCC. Contrary to results indicating that a stiff matrix promotes stem-like characteristics in hepatocellular carcinoma, human laryngeal SCC (LSCC) cultured on a soft matrix environment showed enhanced stem cell marker expression[131, 132]. This included SOX2, which is known to promote migration and invasion[133]. In OSCC, mesenchymal cells with a low ratio of E-cadherin to N-cadherin had elevated motility on stiff collagen matrices due to decreased adhesion strength[134]. Less invasive OSCC cells with high ratios of E-cadherin to N-cadherin developed a more mesenchymal phenotype following prolonged culture on stiffened matrices, suggesting epithelial cancer cells are sensitive to, and maintain a degree of plasticity in response to matrix stiffness. Such conflicting findings highlight the need for mechanistic investigations *in vitro* and robust assessment of matrix crosslinking and fiber deposition trends *in vivo* for metastatic SCC. High collagen deposition is often considered the culprit for a stiffened ECM, however, tumor rigidity may also be a result of fluidic pressure from heightened vasculature, uncontrolled tumor growth, and an increase in the quantity of other fibrous proteins deposited[135]. Accordingly, studies that address the overarching question of whether stiffness promotes metastasis in SCC, and identification of the specific attributes that result in such stiffness, are necessary.

3.2 Finding a New Home: Intravasation, Circulation and Extravasation

To enter and exit the vasculature, metastasizing cells must navigate the ECM that provides structure for vessels and anchorage points for endothelial cells in angiogenesis[136, 137]. Perhaps the most perilous step of metastasis is circulation[13, 138–141]. Using a parallel plate flow chamber, polystyrene dishes coated with ECM solutions, including fibronectin, collagens -I, -III, and -IV, and laminins −511, −211, −111, −411, and −332 were seeded with HNSCC cells. Upon exposure to flow rates that mimicked the shear stress of the lymphatic system, β1 integrins bound to laminin-511 and laminin-211 enabled HNSCC cells to survive better than other ECM compounds[142]. As laminin-511 and laminin-211 are commonly found in lymph nodes, it is likely that HNSCC cells with elevated expression of β1 integrins may prefer lymphatic dissemination over blood circulation. However, it remains to be seen if these β1 integrins are dynamic in their levels throughout metastasis or consistent from the initial malignant transformation. Further research may reveal if targeting β1 integrins will limit lymphatic metastasis of HNSCC.

Interestingly, integrins αvβ3 and α5β1 binding with fibronectin was noted in conjunction with angiogenesis in HNSCC tissue samples[143]. Not only did HNSCC cells have significantly higher staining of integrins compared to non-malignant tissue, but these cells

were observed invading into a fibronectin rich stroma. This is notable as the tumor itself had relatively light fibronectin staining. More peculiar was the positive fibronectin staining in nearby vasculature. Fibronectin may be released to facilitate blood clotting and platelet interactions[144], but notable expression may also suggest leaky vasculature in the TME. Should the latter be the case, it would be worth investigating if ECM components, such as fibronectin or laminin, provide scaffolding to reach vessels for extraversion or if small ECM components in circulation may aid CTCs in their metastatic journey.

It is evident that while ECM remodeling at the SCC primary tumor continues to be well studied, there is a discrepancy between this body of knowledge and subsequent steps in the metastatic cascade. Additional studies that will contribute to the battle against SCC metastasis include the following:

- How do integrins contribute to the cell-cell adhesions necessary to intravasate and extravasate?
- Which ECM components predict the route of CTC metastasis?
- How do ECM components contribute to formation of tumor-cell clusters or micro-emboli? CTCs do not necessarily metastasize individually, and formation of a micro-emboli provides protection from immune detection and mechanical stress[145]. Whether ECM fibers or integrins contribute to the stability of these groupings or provide resistance to anoikis is curious to postulate.
- How to detect and expand CTC populations. Perhaps the greatest challenge to the study of CTCs is obtaining a sufficient number of cells to analyze. Until technical obstacles to studying CTCs is overcome, this discrepancy will persist[141, 146]

Notable strides have been achieved in tissue bioengineering to address some of the gaps needed to investigate intravasation, circulation, and extravasation. Microfluidic systems may be customized with ECM extract to not only reflect the shear forces present during circulation, but the processes of intra- and extravasation[147]. The coating of matrix substrates allows replication of penetrating the basement membrane and integrin-laminin interactions. The development of 3D printing also holds great promise[148, 149]. This process involves layering “bioink” consisting of live cells, biomolecules, matrix components or hydrogels[150] to generate whole tissues[151] to investigate metastasis[152]. A bioprinted system has been used to study invasion, intravasation, and angiogenesis to enhance drug screening in the context of metastatic disease[153]. This system replicated stromal-cell signaling with CAF-co culture and dissemination of these cells was tracked with immunofluorescence imaging. Utilizing mass spectrometry-based proteomics, 3D bioprinting has been shown to alter the matrisome of SCC-associated fibroblasts, confirming the ability to reproduce an ECM which alters tumor and stromal cell activity[154]. Although these techniques allow researchers greater control over matrix composition to recapitulate the tissue of interest, varying matrix composition, density, and rigidity of systems increases the challenge of reproducibility. With continued expansion of these model systems, investigation of the later steps in the metastatic cascade will be possible.

3.3 – Making a New Home: The Pre-Metastatic Niche, Dormancy, and Colonization

The preferential sites of metastatic SCC colonization include the lungs, liver, bone, skin, and, to a lesser extent, the brain[155]. An intriguing avenue of research is the pre-metastatic niche, whereby the distant tissue develops a favorable immune microenvironment and ECM composition prior to CTC arrival [156, 157]. In OSCC, tumors that released EVs containing laminin-332 had enhanced ability for lymphangiogenesis, and detection of laminin-332-containing EVs in OSCC patient plasma correlated with lymph node metastasis[158]. Specifically, the laminin γ2 chain was shown to mediate dissemination as it is necessary for laminin-integrin binding. Accordingly, laminin γ2 may serve to predict lymphatic metastasis in OSCC. These finding also lend credence to the hypothesis that OSCC tumor cells release EVs for ECM remodeling at distant organs[159, 160]. It must be confirmed if ECM-containing EVs make it to distant sites, such as the lungs, or if their function is limited to escape from the primary tumor.

EVs are not the only components that may shape the pre-metastatic niche. In HNSCC, lysyl oxidase (LOX), an enzyme that chiefly crosslinks fibers in the ECM, was elevated at both the mRNA and protein levels in higher grade tumors[161]. It has been suggested that secretion of LOX by primary tumors leads to fibronectin and collagen IV interactions that prime a premetastatic niche at a distant organ[162]. Similarly, higher fibronectin composition in the ECM and a hypoxic microenvironment are shown to be characteristics of the premetastatic niche formation in several cancers, particularly breast cancer[30, 163–165]. It is thought that fibronectin patches along the endothelium of vessels direct CTCs where to extravasate at the pre-metastatic niche[102]. These findings are consistent across several cancers, however, LOX activity and fibronectin structures at the pre-metastatic niche both remain unexplored in SCC.

It is evident that the metastatic niche has only begun to be explored and can be considered a ‘new frontier’ in metastasis research. Emerging areas of research relating to the metastatic niche include:

- ECM remodeling that occurs as metastatic cells cycle between periods of dormancy and growth. Targeting cells that remain dormant has proven a challenge to fully eradicating SCC in patients[166, 167]. Understanding changes in the ECM that occur during dormancy may support diagnostic tools and open novel therapeutic windows to eradicate SCC tumor cells that have disseminated throughout the body.
- The activation of CAFs at the premetastatic niche before and during metastatic colonization. Cancer cells are known to release exosomes that can induce pro-tumor activity of fibroblasts, endothelial cells, and immune cells at distant sites[168]. Identifying when this activity occurs early in SCC tumor progression, and if stromal cell activity can be disrupted would be helpful for clinicians.

4 – Considering the ECM in the Treatment of Metastatic SCC

As the impact of laminins and other ECM components on cancer progression is not limited to SCC, the potential therapeutics targeting these proteins have been broadly addressed

in prior literature reviews[169–171]. Though integrin-targeting strategies alone have been unsuccessful in the clinic, more recent investigations suggest potential for their use in combination with the standard care and precision medicine. The therapeutic potential of integrins, particularly the laminin-binding β1 subunit, has been reviewed previously[26, 172]. Utilizing neutralizing antibodies or small interfering RNA to inhibit β1 integrin was shown to sensitize HNSCC cells to radiation therapy (RT) [173]. This was further enhanced by dual β1 integrin and EGFR inhibition [174]. As metastatic cells often have elevated expression of the β1 integrin, this treatment may prove effective in targeting distant metastases.

Unfortunately, targeting integrins and ECM components on their own has broadly failed in the realm of cancer treatment. Instead, the most promising avenue for hindering the pro-tumorigenic and metastatic influences impact of ECM fibers and associated integrins may lie upstream of their transcription by limiting TGF-β signaling. Despite the current obstacles[87, 88], hope persists that targeting this cytokine in combination with other therapeutics may be efficacious[86]. The TGF-β receptor 1 inhibitor, galunisertnib, showed potential to sensitize HNSCC cells to RT[175]. Galunisertib was shown to reduce motility of cells and move cells out of the G1 phase for adjuvant RT. *In vivo* studies will be necessary to confirm the beneficial application of this combination therapy, and there may be further benefit of maintaining ECM architecture in the presence of RT.

There is also great potential to target TGF-β signaling in the context of immunotherapy. Despite concerns of predicting responders to immune checkpoint inhibitors (ICIs), the investigation of anti-PD1/PD-L1 ICIs is being explored for SCC[176–178]. We have previously summarized the potential of dual of TGF-β and PD-L1 targeting clinically[88]. Inhibition PD-1/PD-L1 interaction and TGF-β limits immune evasion with decreased risk of T cell exhaustion. Dual target inhibition with one drug may have decreased risk for off-target toxicity and supports investigation of these treatments. The Wang Laboratory has stressed the importance of identifying responders to bintrafusp alfa, a bi-functional fusion protein that targets PD-L1 and TGF-β[179]. ECM alterations may guide when administration of TGF-β inhibitors and ICIs are most suitable for clinical use. Expression of laminin γ2 induced by TGF-β1 derived from CAFs attenuated T cell infiltration and limited anti-PD-1 therapy[180]. Furthermore, the laminin γ2 chain was shown to be overexpressed in HNSCC, with notably elevated protein staining in tumor islands at the invasive front[181]. Accordingly, laminin γ2 expression may serve not only as a prognostic biomarker, but as a biomarker to predict responders to anti-PD-1 immunotherapy and when best to block transcription by TGF-β inhibitors.

Although excessive deposition of laminins may predict response for targeted therapy, the issue of larger compounds breaching the surrounding matrix to reach tumor cells persists[21]. Hence, it would be best to administer small molecule inhibitors prior to larger antibody-based immunotherapies. In addition to targeting TGF-β, the microRNA-218 inhibits laminin-332 expression, thus limiting migration and invasion[182, 183]. As the field of microRNA continues to expand, new means to limit laminin-332 transcription may be revealed. Accomplishing efficacious application of TGF-β inhibition in the clinic will require novel methodology to identify responders and synergistic therapeutics.

As we have noted, an interesting overlap exists between the increased presence of laminin-binding integrins, collagen-degrading MMPs, and lymphatic dissemination of SCC cells. In this regard, assessment of laminin composition at the primary tumor may be valuable in predicting the route of metastasis and if anti-lymphangiogenic therapy may be leveraged. For example, type VIII collagen is elevated in SCC of the lung, as detected by the C-terminus of type VIII collagen in ELISA screening of patient serum samples[184]. Patients positive for the C-terminus of type VIII collagen were found to be potential candidates for anti-angiogenesis therapy, a treatment that has yet to be successfully implemented[185, 186]. It is conceivable that ECM correlations predicting the metastatic route of SCC cells could provide new life for a struggling therapeutic.

5 – Summary and Future Perspectives

Decades of research have revealed the importance of the wide range of proteins that make up the ECM and their contributions to metastasis. Since the first identification of laminin in 1979, investigation of its role in cancer has revealed that the family of laminins, notably laminin-332, promotes metastatic progression. Given that metastatic disease is the leading cause of cancer-related mortality both in SCC and solid tumors broadly[187], new mechanisms to limit tumor cell dissemination are desperately needed. To expand upon our understanding of laminins and ECM components in facilitating metastasis, the development of model systems that recapitulate metastasis is necessary. This includes syngeneic mouse lines that allow study of spontaneous metastasis and influence of the TME. It is also critical that the gaps in our understanding of the later steps of the metastatic cascade and the pre-metastatic niche are filled. Turning to bioengineering and establishing standard methodology is the most hopeful avenue for this goal. Another priority is to confirm promising trends in other metastatic cancers, such as breast, pancreatic and liver cancers, in SCC. Replicating and testing such work is critical for evaluation of therapeutics that seek to limit metastatic progression. As we have summarized, lamininin-332 provides an opportunity for inhibiting metastatic spread in SCC. Even though this may not be achieved by targeting laminin interactions alone, we have outlined therapeutic opportunities to enhance current treatments. Most notably, inhibition of binding by β1 integrins and TGF-β signaling may make valuable contributions to improve RT and ICIs. Additionally, laminin-332 expression may serve to predict responders to immunotherapy and the route of metastasis. In the next four decades of research, therapies that target laminin interactions in metastatic progression may find a home in the growing arsenal of treatments for SCC.

Acknowledgements

The original work from the Wang lab by John Aleman was supported by the NIH predoctoral training grant T32CA174648. Xiao-Jing Wang is supported by NIH R01s DE024371, DE027329, and DE028420, NIH SPORE grant P50CA261605, and VA merit award I01 BX003232 and Research Career Scientist Award 1IK6BX006039. Dr. Sana Karam is funded by the National Institute of Dental and Craniofacial Research (to SDK, 1R01DE028282-01, 1R01DE028529-01) and 1P50CA261605-01. She also receives research grants from Genentech, AstraZeneca, Roche, and Ionis for work unrelated to this manuscript. We thank Pamela Garl for proofreading this review.

7.1 Funding information:

U.S. Department of Veterans Affairs; National Institutes of Health; NIH, Grant/Award Numbers: T32CA174648, R01s DE024371, DE027329, DE028420, P50CA261605

Data Availability Statement

Data sharing is not applicable to this article. No new data were created or analyzed in the current study.

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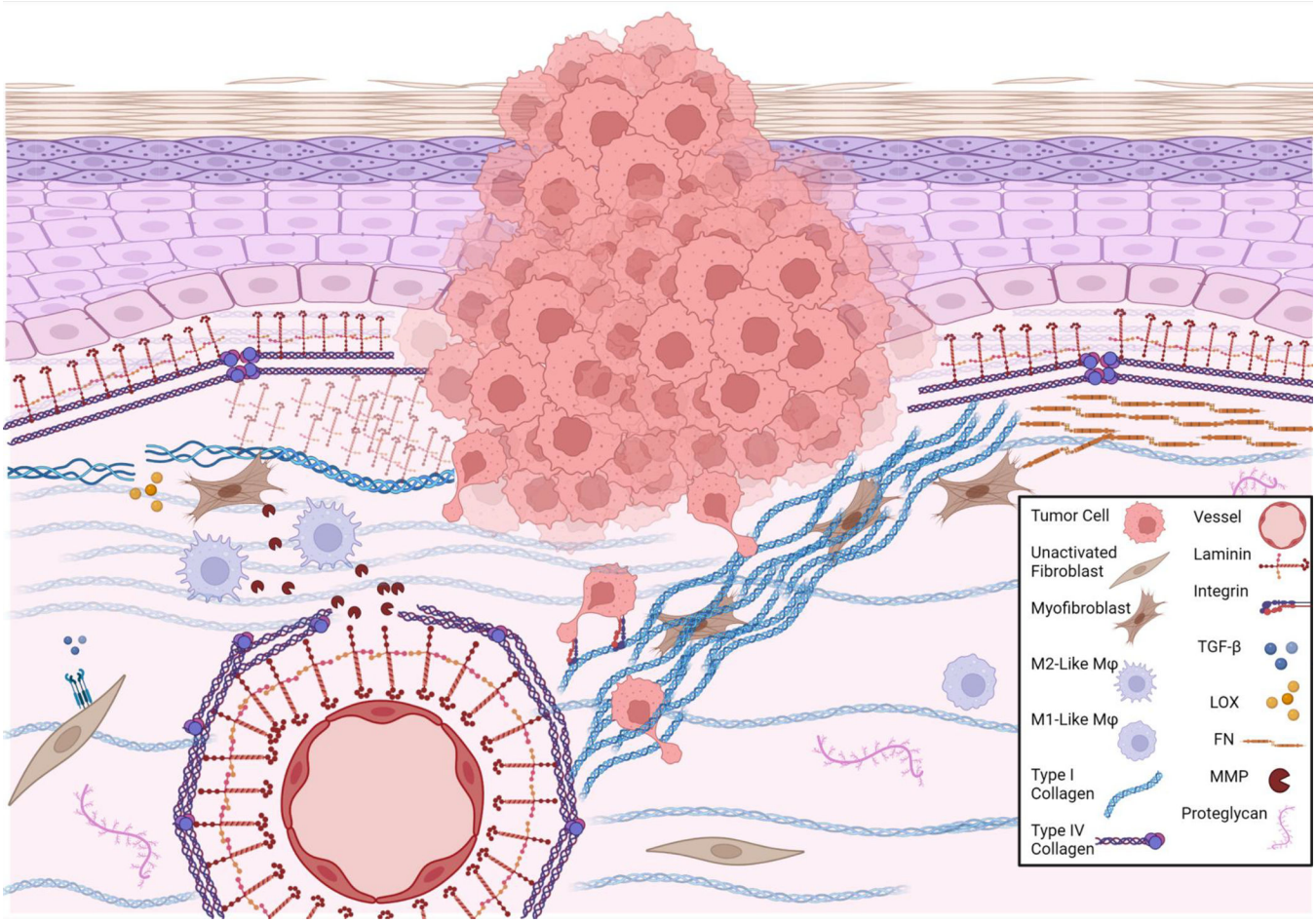

Figure 1: ECM Complexity in Invasive SCC.

Illustrated schematic of ECM components commonly found in a tumorigenic SCC ECM. Fibroblasts, macrophages and MMPs remodel the ECM to facilitate dissemination of SCC cells past a degraded basement membrane into the surrounding tissue in search of a nearby vessel (blood or lymphatic). Crosslinking of collagen fibers by LOX and myofibroblast activity produces tracts for tumor cell invasion. Integrins provide means for SCC cells to interact with ECM components, such as structural fibers. Active TGF-β is stimulates quiescent fibroblasts into myofibroblasts. Both stromal cells and SCC contribute to excessive deposition of collagens, laminins and fibronectin. Figure created with BioRender.com.

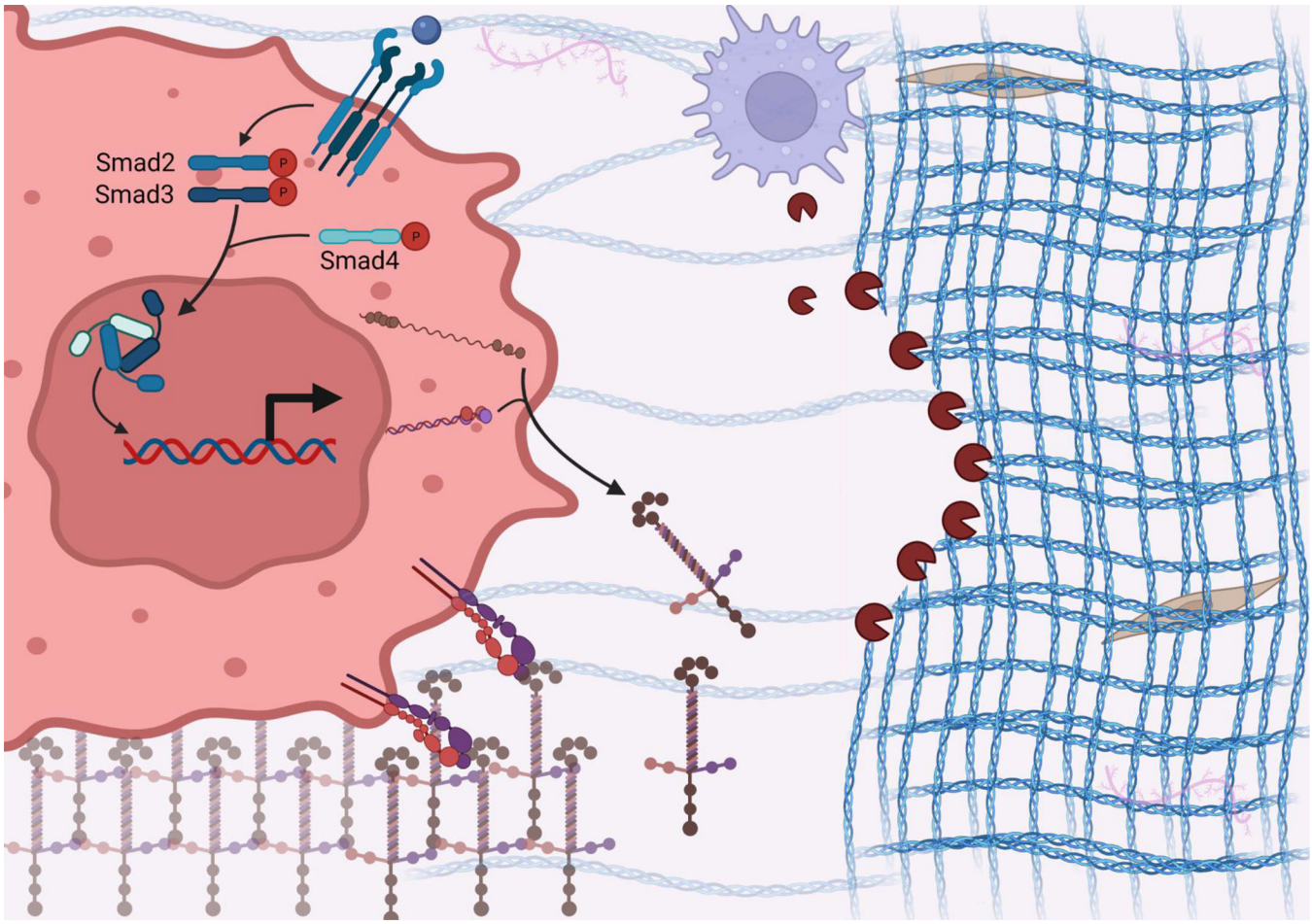

Figure 2: Schematic of laminin mediated invasion of SCC.

Transcription of genes coding for laminins (here, facilitated by TGF-β-Smad activity) results in translation of α, β, and γ laminin chains. Upon trimerization with the α chain, mature laminin is released into the ECM. Laminins binding with integrins, such as α7β1, mediate cell motility. Laminin deposition replaces the matrix proteins that previously blocked SCC cell invasion. MMPs degrade these blockading fibers, including collagens. Created with BioRender.com

Table 1:

Matrix Metalloproteases in humans and their documented aliases, substrates, and noted trends in squamous cell carcinoma.

MMP	Classification	Substrate(s)	SCC Clinical Relevance
MMP-1 (Collagenase-1; Interstitial collagenase; Fibroblast collagenase)	Collagenase	Collagens I, II, III, VII, VIII, X, and XI, gelatins, entactin, aggrecan, tenascin, fibronectin, vitronectin, myelin basic protein, ovostatin, casein, pro-MMP-1, pro-MMP-2, and pro-MMP-9	In oseophageal SCCs ESCC, and OSCC upregulated and associated with local invasion and lymph node and distant metastasis[188–190]
MMP-2 (Gelatinase A)	Gelatinase	Collagens I, III, IV, V, VII, X, and XI, gelatins, elastin, fibronectin, laminins, aggrecan, tenascin-C, myelin basic protein, and vitronection	In skin and HNSCC upregulated and associated with lymph node and distant metastasis[70–75, 188]
MMP-3 (Stromelysin 1)	Stromelysin	Collagens I, II III, IV, V, IX, and X, tenascin-C, vitronectin, gelatins, aggrecan, laminins, elastin, decorin, casein, myelin basic protein osteonectin, FIBRONECTIN, ovostatin, entactin, proteoglycans, pro-MMP-1, and pro-MMP-13.	In ESCC lymphatic dissemination mediated by expression of MMP-3[84]. In HNSCC, correlates with favorable prognosis[191]. In OSCC, salivary detection correlates with worse prognosis[192].
MMP-7 (Matrilysin)	Matrilysin	Collagen I and IV, gelatins, fibronectin, laminins, elastin, casein, tenascin, aggrecan, myelin, entactin, vitronectin, syndecan-1, E-cadherin, proteoglycans, and pro-TNF-α	In esopharangeal SCC, ESCC and OSCC upregulated and associated with invasive front and lymph node and distant metastasis[79, 188, 193–196]
MMP-8 (Collagenase 2; Neutrophil collagenase; Gelatinase B elastinase; 92-kDa Gelatinase)	Collagenase	Collagens I, II, and III, V, VII, VIII, X, FIBRONECTIN, gelatin, aggrecan and ovostatin.	In OSCC downregulated to correlate with increased invasion and worse patient survival [197].
MMP-9 (Gelatinase B)	Gelatinase	Collagens IV, V, and XI, elastin, aggrecan, vitronectin, decorin, enactin, myelin basic protein, casein, IL-8, IL-1β	In skin, oseophageal, and HNSCC elevated and predicts lymph node and distant metastasis [70–75, 78, 198]
MMP-10 (Stromelysin 2)	Stromelysin	Collagen III, IV, V, IX, and X, gelatin, casein, elastin, fibronectin, laminins, aggrecan, casein, fibrilin-10, proteoglycans, pro-MMP-1, pro-MMP-13, and pro-MMP-18.	In HNSCC elevated in higher grade tumors[199].
MMP-11 (Stromelysin 3)	Stromelysin	Collagen IV, gelatins, lamininss, aggrecan, and fibronection	In NSCLC upregulated[200].
MMP-12 (Metalloelastase)	Other	Collagen I, IV, and V, elastin, gelatin, casein, fibronectin, vitronectin, laminins, entactin, fibrinogen, osteonectin, aggrecan, myelin, proteoglycans, and α1-antitripsin	In ESCC and OSCC upregulated and associated with invasion and lymph node metastasis[83, 194, 195]
MMP-13 (Collagenase-3)	Collagenase	Collagens I, II, III, IV, IX, X, gelatin, tenascin C, plasminogen, casein, fibrillin-1, aggrecan, laminins, fibrnoectin, osteonectin, pro-MMP-2, and pro-MMP-9	In HNSCC elevated in locally invasive tumors[199].
MMP-14 (MT1-MMP)	Membrane-type	Collagen I, II, and III, gelatins, fibronectin, laminins, vitronectin, entactin, fibrilin-1, tenascin, aggrecan, α2-macroglobulin, proteoglycans, and pro-MMP2, MMP-8, and pro-MMP-13.	In NSCLC downregulated in the blood but elevated in invasive tissue[201].
MMP-15 (MT2-MMP)	Membrane-type	FIBRONECTIN, LAMININ, aggrecan, gelatin, vibronectin, entactin, tenascin, pro-MMP2, and pro-MMP-13	In ESCC upregulated and correlates with angiogenesis, but no association with metastasis[202] In NSCLC downregulated in the blood but elevated in invasive tissue[201].
MMP-16 (MT3-MMP)	Membrane-type	Collagen III, gelatins, casein, fibronectin, laminins, pro-MMP2, and pro-MMP-9	In ESCC downregulated [203].
MMP-17 (MT4-MMP)	Membrane-type	Gelatin, fibrinogen, fibrin, and pro-MMP2	In HNSCC correlates with favorable prognosis[191]

MMP	Classification	Substrate(s)	SCC Clinical Relevance
MMP-19 (RASI-1; Stromelysin-4)	Other	Collagen I and IV, gelatin, fibronectin, laminin, nidogen, tenascin-C, entactin, aggrecan, and pro-MMP-9	In HNSCC correlates with favorable prognosis[191]
MMP-20 (Enamelysin)	Other	Amelogenin and Aggrecan	Elevated in LSCC[204]
MMP-21 (Xenopus-MMP)	Other	No known ECM Substrates at this time.	In ESCC upregulated at the invasive front, correlates with late-stage tumors, and lymph node and distant metastasis[205, 206]
MMP-23A/B (Cysteine array-MMP)	Other	Gelatin	Limited investigation in SCC, no current prognostic value.
MMP-24 (MT5-MMP)	Membrane-type	Fibronectin, gelatin, proteoglycans, and pro-MMP2	In NSCLC downregulated in the blood[201].
MMP-25 (MT6-MMP)	Membrane-type	Collagen IV, gelatin, fibronectin, proteoglycans, and pro-MMP2	In HNSCC correlates with favorable prognosis and enhanced immune infiltration[207].
MMP-26 (Matrilysin-2; endometase)	Matrilysin	Collagen IV, fibrinogen, fibronectin, gelatin, vitronectin, α1-antipripsin, β-casein, α2-macroglobulin, IGFBP-1, and pro-MMP9.	In ESCC upregulated in early-stage tumors, correlates with invasion and metastasis[205, 208, 209].
MMP-27 (No Alternative Name)	Other	Gelatin	In HNSCC decreased[199].
MMP-28 (Epilysin)	Other	Casein	In NSCLC downregulated[200].

Substrates and aliases retrieved from the following publications[210–217]. MMP-18 is not included as there is no human ortholog.

Table 2:

Integrin subunits and their documented implications in squamous cell carcinoma metastasis.

Integrin	Alias(es)	Classification	Implications in Metastatic SCC
α1	CD49a	Collagen Receptor	No known value.
α2	CD49b, α2 subunit of very late antigen 2 (VLA-2)	Collagen Receptor	Elevated in metastatic and invasive cases of OSCC[112]. Integrin α2β1 enhances motility of SCC cells[104].
α3	CD49c, α3 subunit of VLA-3	Laminin Receptor	In HNSCC and cervical cancer unfavorable prognosis[218]. Elevated in metastatic and invasive cases of OSCC[112].
α4	CD49d, α4 subunit of VLA-4	Leukocyte Receptor	In HNSCC favorable prognosis[218]. Integrin α4β1 mediates lymph node metastasis[108].
α5	CD49e, fibronectin receptor alpha	RGD Receptor	In HNSCC, cervical and lung cancers unfavorable prognosis[218]. Elevated in metastatic and invasive cases of OSCC[112]. Plays a role in ESCC metastatic progression[219].
α6	CD49f, ITGA6B	Laminin Receptor	Unfavorable prognosis in HNSCC[218]. Elevated in metastatic and invasive cases of OSCC[112].
α7	-	Laminin Receptor	Biomarker for cancer stem cells in oesophageal SCC[114] and tongue SCC[115].
α8	-	RGD Receptor	No known value.
α9	-	Leukocyte Receptor	Integrin αvβ6 and α9β1 enhanced migration of HNSCC cells[220].
α10	-	Collagen Receptor	No known value.
α11	-	Collagen Receptor	Analysis is confounded by expression on fibroblasts[221, 222].
αV	CD51, MSK8, vitronectin receptor α (VNRα)	RGD Receptor	In OSCC patients, integrin αvβ6 elevated in invasive tumors[80]. Integrin αvβ6 enhanced migration of HNSCC cells[220]. In OSCC, integrin αvβ5 is downregulated, and integrin αvβ6 is elevated metastasis[223, 224]. In cervical SCC, integrin αvβ6 correlates with poor prognosis[225]. In ESCC and OSCC, αvβ8 associated with EMT, invasion, and metastasis[226, 227].
αL	CD11a (p180), lymphocyte function-associated antigen 1 (LFA-1) α subunit	Leukocyte Receptor	In HNSCC favorable prognosis[218].
αM	Mac-1, CD11b, complement receptor 3 (CR3) subunit	Leukocyte Receptor	Analysis is confounded by expression on myeloid-derived suppressor cells.
αX	CD11c, CR4 subunit	Leukocyte Receptor	Analysis is confounded by expression on monocytes.
αD	-	Leukocyte Receptor	No known value.
αE	CD103, human muscoal lymphocyte antigen 1α	Leukocyte Receptor	In SCC of the skin favorable prognosis[228].
αIIb	GTA, CD41, GP2B, HPA3, CD41b, GPIIb	RGD Receptor	Promotes transmigration in SCC cells[229].
β1	Fibronectin receptor β, CD29, MDF2, MSK12	Collagen, Laminin and RGD Receptor	In lung and cervical cancer unfavorable prognosis[218]. Integrin α4β1 mediates lymph node metastasis[108]. Integrin α9β1 enhanced migration of HNSCC cells[220]. Integrin α2β1 enhances the motility of SCC cells[104].
β2	Leukocyte cell adhesion molecule, CD18, CR3 subunit, CR4 subunit	Leukocyte Receptor	No known value.
β3	CD61, GP3A GPIIIa, platelet glycoprotein IIIa	RGD Receptor	No known value.

Integrin	Alias(es)	Classification	Implications in Metastatic SCC
β4	CD104	Laminin Receptor	In lung cancer unfavorable prognosis[218]. In OSCC it has been reported that the loss of the integrin β4 associated with nodal metastases at the time of diagnosis[117].
β5	-	RGD Receptor	In OSCC integrin αvβ5 is downregulated[216].
β6	-	RGD Receptor	Elevated in situ and invasive OSCC[230]. In OSCC integrin αvβ6 is elevated in invasive tumors[80]. Integrin αvβ6 enhanced migration of HNSCC cells[220]. In OSCC integrin αvβ6 expression is elevated in metastasis[223, 224]. In cervical SCC integrin αvβ6 correlates with poor prognosis[225].
β7	-	Leukocyte Receptor	No known value.
β8	-	RGD Receptor	In ESCC and OSCC αvβ8 associated with EMT, invasion, and metastasis[226, 227].

Alternative names and classifications of integrin subunits are broadly known and documented in previous reviews[26, 100–103].