Abstract: Oral squamous cell carcinoma is a disfiguring, highly invasive and metastatic cancer. Despite advances in detection and therapy, many patients will continue to face a poor prognosis. It is well established that the predominate factor determining overall survival in patients with oral squamous cell carcinoma is lymph node involvement. Tumor growth and progression to invasive cancer requires tumor cell interactions with the extracellular matrix. An understanding of how the extracellular matrix influences tumor development and invasion is fundamental in the development of new prognostic indicators and treatment strategies for oral squamous cell carcinoma. In this review, we summarize how changes in the extracellular matrix contribute to oral cancer development.

Cancers of the head and neck constitute the sixth most common cancer worldwide and are associated with low survival and high morbidity.¹ Cancers of the oral cavity account for 40% of head and neck cancers and include squamous cell carcinomas of the tongue, floor of the mouth, palate, lips, and oropharynx.²,³ Despite therapeutic and diagnostic advances, the 5-year survival rate for oral squamous cell carcinoma (OSCC) remains at approximately 50%.²,⁴ Although oral cancers metastasize distantly, the major site of oral cancer metastasis is locoregional neck lymph nodes, and lymph node metastasis is universally accepted as the most important factor influencing survival in patients with OSCC.⁵

The spread to regional lymph nodes is made possible by the highly invasive nature of OSCC and the lymphatic drainage from the oral cavity. By degrading basement membranes and the extracellular matrix (ECM), matrix metalloproteases (MMPs) are instrumental in OSCC tumor invasion. Once the ECM is cleaved, the invading tumor cells move into the adjacent spaces. Cell motility, a requirement for tumor invasion, is a coordinated balance between the cell adhesion receptors, predominately integrins, and the ECM. In this review, we highlight how the ECM contributes to or retards OSCC tumor development and progression.

Keywords: extracellular matrix; laminin; collagen; head and neck cancer; squamous cell carcinoma; invasion; metastasis

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glycosaminoglycans derived from keratinocytes and stromal cells or from the cooperative interactions between these two cell populations. Once viewed only as an architectural support for epithelial cells, the ECM is now recognized as a major component in regulating cell activity. As ligands for integrins, ECM molecules have been shown to be important in proper tissue development, adult tissue maintenance, wound healing, and oncogenesis. Changes in composition of the ECM by altered expression, secretion, or processing contributes greatly to oncogenic development, hyperplastic growth, and tumor development. The major ECM molecules reported to be involved in OSCC development and progression include collagens, laminin, and fibronectin (Figure 1; Table 1). Changes in the ECM components and the resultant changes in their ECM receptors, integrins, are essential for conversion of premalignant squamous epithelium to malignant lesions.

Integrins are a family of cell surface receptors that mediate adhesive interactions with ECM macromolecules, linking the cytoskeleton to the extracellular environment. Each integrin is composed of a noncovalently associated α and β subunit. Integrin-mediated signaling pathways control cell growth, differentiation, apoptosis, cytoskeletal changes, cell migration, and invasion. It is well established that cell migration and invasion depend not only on integrin expression levels but also on ligand binding affinity. The major integrin receptors found in OSCC include α2β1, α3β1, α5β1, and α6β4. Thus, changes in ECM composition and integrin profiles can have profound effects on OSCC development and progression.

**COLLAGEN**

Several collagenous components are found in connection with oral epithelium. Collagen type I and type III primarily make up the dermis, whereas collagen type IV is found in the dermo-epidermal interface (Figure 1; Table 1). Several other collagen isoforms, including collagen VII and XVII, also make up the dermo-epidermal junction. Expression of most of these isoforms has been reported in OSCC. Increased collagen type I expression has been reported in malignant transformation of keratinocytes and is associated with well-differentiated OSCC. Results reported for collagen IV are less clear. Loss of collagen IV has been associated with decreasing tumor cell differentiation, whereas increased collagen IV expression is detected in laryngeal carcinoma nodal disease. We have also detected increased expression of collagen IV in OSCC using microarray expression profiling. Additional microarray studies have demonstrated that expression of minor collagen isoforms, including collagen type V and IX, are altered in OSCC (our unpublished observations). As with other ECM components, it is assumed that these changes in collagen expression promote adhesion, migration, and differentiation. To date, no thorough study has documented how changes in collagen expression affect these biologic processes in OSCC. However, from experimental evidence it is becoming increasingly clear that collagens VII and XVII seem to play a role in OSCC development and progression.

Collagen type VII attaches the dermis to the basement membrane (Figure 1). Mutations in collagen type VII cause dystrophic epidermolysis bullosa, which is often accompanied by epidermal SCC. Recent evidence suggests that loss of collagen type VII is not required for tumorigenicity.
Instead, it seems that the retention of the aminoterminal noncollagenous NCI domain of collagen type VII is responsible for tumor formation. It is believed that the extracellular interaction between laminin-5 and collagen type VII NCI domain is important for tumor development and tumor invasion. This work illustrates how ECM dynamics can directly influence tumor development and progression. Recent work has also highlighted the importance of collagen type XVII in transformation of oral epithelium.

Collagen XVII is a hemidesmosomal transmembrane protein that has been hypothesized to participate in OSCC adhesion and motility. By immunohistochemical analysis, collagen XVII seems to be downregulated in mild dysplasia, with increased expression detected in moderate and severe dysplasias. It is believed that loss of collagen type XVII in the early lesions may reflect disturbances in keratinocyte adhesion to the ECM and may represent an initial step in OSCC tumor formation. In contrast, collagen type XVII is overexpressed at the invasive edge of OSCC tumors. Thus, expression of collagen XVII is suspected of playing a role in OSCC development and tumor invasion.

In contrast, keratinocytes deficient in collagen XVII expression from patients with epidermolysis bullosa were more migratory than normal keratinocytes. Interestingly, deposition of laminin-5 by these collagen XVII-deficient keratinocytes was scattered and poorly organized. This finding led to the discovery that an adhesive ECM requires interaction between laminin-5 and collagen XVII, whereas loss of collagen XVII results in a matrix that induces motility. Thus, it seems that collagens play an important role in OSCC development and progression, although the mechanisms remain unknown. However, it is too early to say whether loss or overexpression of collagen isoforms is a common prerequisite for OSCC tumor invasion.

### FIBRONECTIN

Fibronectin is a large alternatively spliced protein whose expression can directly influence the establishment and maintenance of the transformed state (Figure 1; Table 1). Microarray and immunohistochemical analyses of OSCC tumor samples have revealed that fibronectin is overexpressed in OSCC tissue, particularly at the invasive tumor site and in the tumor stroma. Oncofetal fibronectin has also been reported to be upregulated in OSCC, where it has been hypothesized to play a role in OSCC tumor progression. In more recent work, extra domain B (ED-B) fibronectin has been determined to be expressed in OSCC, and tumors expressing ED-B fibronectin were associated with lower overall patient survival. Investigative studies into the role of fibronectin in OSCC development and progression are few. Recent studies using OSCC cell lines have suggested that fibronectin is capable of promoting the metastatic phenotype. However, further studies are required to determine the role of fibronectin in OSCC.

### LAMININS

Laminins are large heterotrimeric extracellular glycoproteins composed of α, β, and γ subunit. To date, 12 different laminin isoforms have been described (Figure 1; Table 1). It is well established that all the ECM molecules, lamin-
Lamins play fundamental and various roles in OSCC development and progression. Several laminin isoforms have been reported as being involved in OSCC, including laminins 5, 6, 7, 10, and 11 (Ln-5, Ln-6, Ln-7, Ln-10/11).

Of all the laminins found in the oral epithelium, the least known are Ln-6 and Ln-7. Ln-6 and Ln-7 can bind covalently to Ln-5.23 It is believed that Ln-6 and Ln-7 become embedded in the ECM through these bonds to Ln-5 as well as bonds to nidogen.23 The contribution of these two laminin isoforms to the development and progression of OSCC has yet to be reported.

Ln-10/11 is composed of α5, β1/β2 and γ1. Ln-10/11 expression in OSCC tumor cell lines has been reported and is hypothesized to play a significant role in OSCC tumor progression.22 Unfortunately, little is known about the involvement of Ln-10/11 in OSCC, except that OSCC cells upregulate this isoform and express integrin receptors for this ligand.24

**Laminin-5: The Major Oral Squamous Cell Carcinoma Laminin Isoform.** Ln-5 is the best known of the laminins found in oral epithelium and is the major laminin isoform expressed by keratinocytes of the epidermis (Figure 1).25,26 Ln-5 is a basement membrane glycoprotein composed of three subunits, α3, β3, and γ2. This heterotrimer is secreted as a 460-kDa precursor that undergoes specific proteolytic processing after secretion.27 Ln-5 extracted from tissue is composed of α3 (165 or 145 kDa), β3 (145 kDa), and γ2 (105 kDa) chains. Cultured keratinocytes synthesize a precursor form of α3 (190 kDa) and γ2 (155 kDa), which are processed to the tissue forms extracellularly (Figure 2).27,28 Ln-5 is considered fully processed when the heterotrimer contains a 145-kDa α3 chain, a 145-kDa β3 chain, and a 105-kDa γ2 chain. The function of Ln-5 is controversial. There is evidence that Ln-5 can promote adhesion and migration. Many believe proteolytic processing determines whether Ln-5 is an adhesive factor or a migratory factor.26,29–32 Increasing evidence, although somewhat contradictory, has implicated Ln-5 in OSCC development and progression.

**Loss of Laminin-5 in Oral Squamous Cell Carcinoma.** Loss of Ln-5 expression in OSCC has been reported.33 In agreement, our recent work has shown that a loss of Ln-5 expression results in increased tumor take and larger tumors compared with Ln-5–expressing OSCC.34 How might loss of Ln-5 contribute to increased tumor growth? Loss of Ln-5 may allow interactions of other ligands such as collagen or fibronectin that may be more conducive to tumor growth. Furthermore, the unoccupied Ln-5 receptors may be able to bind laminin isoforms that stimulate tumor growth. In support of this notion, Ln-10/11, which binds the same integrin receptors as Ln-5, has been shown to stimulate keratinocyte and SCC prolifera-
Although loss of Ln-5 has been reported in OSCC, several studies have indicated that Ln-5 is also overexpressed in OSCC.

**Overexpression of Laminin-5 in Oral Squamous Cell Carcinoma.** Ln-5 overexpression has been demonstrated in many human carcinomas, including OSCC. It is generally assumed that the Ln-5 heterotrimer is overexpressed in OSCC and contributes to tumor development and progression. Specifically, Ln-5 expression has been detected along the invasive edge of OSCC tumors, and Ln-5 has been shown to correlate with OSCC tumor formation and a poor prognosis in patients with OSCC. However, in many of these previous immunohistochemical studies, expression of the Ln-5 γ2 chain was the only Ln-5 chain assayed and reported. In addition, recent work has established that the Ln-5 γ2 chain is overexpressed in invading carcinoma cells without any evidence of coexpression of the α3 and β3 chains. This brings into question whether it was the Ln-5 heterotrimer or only the γ2 chain that was overexpressed in these earlier studies. Nevertheless, the expression of Ln-5 or the γ2 chain at the invasive front may simply represent an attempt by the tumor cell to provide a substrate in a region lacking a stabilizing ECM. Thus, Ln-5 expression at the invasive front of OSCC may not play a causal role in tumor invasion. Moreover, Ln-5 may be expressed as a means to retard tumor invasion. Finally, as described later and reported elsewhere, Ln-5 can act as an adhesive factor or a migratory factor, depending on whether the Ln-5 α3 and γ2 precursor chains are proteolytically processed. Whether or not the Ln-5 at the invasive front of OSCC is processed has yet to be reported.

**Adhesion Support by Processed Laminin-5.** Processed, or mature, Ln-5 is the major component of anchoring filaments in skin and supports cell adhesion by means of α3β1 and α6β4 integrins. Several studies have provided evidence that processed Ln-5 functions in hemidesmosome assembly and acts as an adhesive factor that retards cell motility. In keratinocytes in vivo, typically greater than 50% of the Ln-5 present is fully processed. Recent work has demonstrated that only when γ2 is completely processed is Ln-5 incorporated into the ECM, resulting in cells that are more resistant to enzymatic detachment (Figure 2). These results suggest that complete processing of Ln-5 is required for ECM development and the formation of stable adhesions through hemidesmosomes. In contrast, it has been suggested that cell motility requires processing of the γ2 chain to the 105-kDa form. This is somewhat surprising, because the 105-kDa form is found in epidermal–dermal basement membranes where cells are nonmotile. In addition, in our unpublished work, we have discovered the opposite: the 155-kDa form is pro-migratory, whereas the 105-kDa form is associated with stable adhesion (our unpublished observations). However, recent evidence indicates that when the γ2 chain is processed, chemotactic migration ensues as opposed to haptotactic cell migration when unprocessed chain is present (Figure 2). Thus, it seems that the function of Ln-5 may depend on whether or not it is fully processed.

**Use of Unprocessed Laminin-5 for Migration.** From our recent studies and work by others, it seems that unprocessed Ln-5 is important in initiating keratinocyte migration, whereas processed Ln-5 inhibits migration and is used for anchoring (our unpublished observations). In the tumor-producing rare skin disease cylindroma, both the Ln-5 α3 and γ2 chains are not processed. It is tempting to speculate that unprocessed and processed Ln-5 bind the Ln-5 integrin receptors differently and, in this way, regulate the signaling pathways required for migration or stability. In support of this hypothesis, we recently analyzed the expression and processing of Ln-5 in a bank of OSCC cells (our unpublished observations). We found that lack of Ln-5 processing correlated with increased motility and tumor invasion. In addition, the OSCC cells used in our recent work fully processed Ln-5 and were inhibited by Ln-5 in migration assays. When Ln-5 expression was suppressed using siRNA, the OSCC tumor cells became motile. Furthermore, in OSCC cell lines, the α3 chain is secreted as the 190-KDa precursor. Processing to the mature form resulted in hemidesmosome formation, stable adhesion, and inhibition of motility. Thus, in OSCC, processed Ln-5 seems to be used for adherence while unprocessed for cell motility (Figure 2). Finally, in hypoxic conditions, similar to those exhibited by OSCC tumors, human keratinocytes displayed increased cell motility. Ln-5 is not processed under hypoxic conditions, suggesting that increased keratinocyte motility under hypoxic conditions is due to changes in Ln-5 processing. Whether Ln-5 is unprocessed in hypoxic OSCC tumor regions has not been described.
Regulation of Adhesion and Motility by Laminin-5 Adhesion Receptors. The processes of tumor cell migration and invasion are dependent on many factors, including the interaction of cells with the ECM. These interactions are principally mediated by means of integrins that, when bound, induce a cascade of cellular events related to cell migration.\(^7\) The major laminin-binding integrins expressed by OSCC cells include \(\alpha_3\beta_1\), \(\alpha_3\beta_1\), and \(\alpha_6\beta_4\). In addition to Ln-5 binding, \(\alpha_2\beta_1\) and \(\alpha_3\beta_1\) can also bind collagen. Although \(\alpha_6\beta_4\) is known to interact with Ln-5 and play a crucial role in hemidesmosome formation and stability in epithelial cells,\(^63\) its role in OSCC tumor progression is unclear. Several studies have shown that expression of \(\alpha_6\beta_4\) increases, and the normal basal polarity of \(\alpha_6\beta_4\) is lost in aggressive OSCC, recurrent tumors, and metastatic tumor cell lines.\(^64\) We and others have determined that some OSCC tumor cells fail to migrate. It has been hypothesized that these OSCC cells fail to move because \(\alpha_6\beta_4\) was inhibiting their movement. Function-blocking antibodies to \(\alpha_6\beta_4\) indicated that this integrin does not contribute significantly to OSCC tumor cell migration. Thus, it is unclear what role, if any, \(\alpha_6\beta_4\) is playing in OSCC cell migration. In contrast, \(\alpha_3\beta_1\) has been shown to have a clear role in Ln-5 motility.\(^50,61,65\)

\(\alpha_3\beta_1\) has been referred to as the principal receptor for Ln-5 and has been shown to play both positive and negative roles in Ln-5 migration.\(^26,50,53,58,66,67\) We recently determined that function-blocking antibodies to \(\alpha_3\beta_1\) or the \(\alpha_3\beta_1\) binding site on Ln-5 dramatically enhanced collagen migration of OSCC tumor cell lines. These results suggested that Ln-5 interactions with \(\alpha_3\beta_1\) can stably anchor cells and inhibit cell movement. Work with primary keratinocytes has shown a similar increase in cell motility on both fibronectin and collagen IV when the same blocking antibodies to \(\alpha_3\beta_1\) or its Ln-5 binding site were present.\(^50\) In addition, recent studies using mouse keratinocytes have indicated that Ln-5 inhibits cell movement in an \(\alpha_3\beta_1\)-dependent manner on collagen.\(^65\) Furthermore, mouse keratinocytes null for \(\alpha_3\beta_1\) expression are motile on both Ln-5 and collagen.\(^50\) Thus, the binding of Ln-5 by \(\alpha_3\beta_1\)-expressing OSCC cells can have a negative influence on cell motility, whereas loss of Ln-5 expression or blocking/absence of the \(\alpha_3\beta_1\) Ln-5 receptor can lead to hypermotility.

Laminin-5 and Cell–Cell Adhesion. It is becoming apparent that loss of e-cadherin–mediated cell–cell adhesion is a prerequisite for tumor invasion. In several recent studies, Ln-5 promotes and maintains e-cadherin–dependent cell–cell adhesion.\(^68,69\) In contrast, it has recently been reported that in OSCC Ln-5 can disrupt cell–cell junctions.\(^68\) Whether loss or presence of Ln-5 disrupts the e-cadherin functional complexes in OSCC requires further work. However, once e-cadherin junctions are disassociated, one of the structural proteins, \(\beta\)-catenin, transverses the nucleus and stimulates gene transcription.\(^70\) The list of genes induced by \(\beta\)-catenin is increasing and includes MMPs, MT-MMP, and CD44.\(^70\) It is possible that loss of Ln-5 expression results in disruption of cell–cell adhesion with concomitant \(\beta\)-catenin–induced synthesis of the proteinases and stimulators of cell migration like CD44 that are required for tumor invasion. In support of this scenario, expression of a dominant negative e-cadherin in an early stage transformed keratinocyte cell line abolished cell–cell adhesion and resulted in an invasive phenotype that was associated with loss of basement membrane integrity because of degradation of collagen IV and Ln-5.\(^71\) Further work is required to determine whether such a scenario is, indeed, the case in OSCC tumor cells lacking Ln-5 expression.

Release of Matikines by Proteolytic Cleavage of the Extracellular Matrix. OSCC cells produce many of the ECM proteins and also synthesize and secrete MMPs. Most, if not all, of the ECM components found in the oral epithelium ECM are proteolytically processed. As described with Ln-5, proteolytic processing can expose cryptic sites that can, for example, regulate tumor cell migration positively or negatively.\(^72\) However, in general, processing of ECM molecules results in the liberation of peptides that affect various cellular activities. These include proliferation, migration, apoptosis, and angiogenesis. The term “matikine” has been coined to designate those peptides liberated by proteolysis of ECM macromolecules (Figure 2).\(^73\) Matikines, by their effect on biologic properties, may be important in OSCC.

Several matikines are generated during proteolytic processing of the Ln-5 precursor. All three chains of the Ln-5 molecule are processed (Figure 2). For example, the 190-kDa \(\alpha_3\) chain is processed extracellularly to 165 and 145 kDa, releasing peptides of 25 kDa and 45 kDa, whereas the \(\beta_3\) chain is processed to generate an 80-kDa fragment. Recent evidence has demonstrated that both proteolytic fragments generated from the \(\alpha_3\) and \(\beta_3\) chains promote migration.\(^57,74\) Their contribution
to OSCC tumor development and progression has not been reported. Finally, processing of the α3 chain precursor by plasmin allows access to a cryptic α6β4-preferred binding site on Ln-5 that inhibits cell motility. The γ2 chain of Ln-5 is also proteolytically processed. Several enzymes have been implicated in the processing of the γ2 chain and include bone morphogenetic protein (BMP)-1/mtolloid, MT1-MMP, and MMP-2. MMP-2 and MT1-MMP liberate a peptide, DIII, which consists of several epidermal growth factor (EGF)–like repeats. The recombinant form of DIII was recently shown to bind to erb-b1, a member of the EGF receptor family, and induce chemotaxis and proliferation (Figure 2). In addition, the N-terminal γ2 chain fragments have also recently been detected in the serum of patients with pancreatic ductal cell adenocarcinoma, suggesting that Ln-5 fragments could be used for clinical diagnosis. Finally, the γ2 chain and its proteolytic fragments have been found at the invasive fronts of several tumors. As described previously, several reports have detected the γ2 chain at the invasive front of OSCC tumors. It is unknown whether the proteolytic fragments of the γ2 chain are present at the invasive front or can be used for diagnosis in OSCC.

Several collagen-derived matrikines also have been reported. The tripeptide GHK is present in the α2 chain of type I collagen. This peptide has been shown to stimulate angiogenesis in vivo, stimulate ECM synthesis, and increase the expression of MMP-2. Another matrikine is the 185-203 peptide of the NCI, C-terminal domain, of the α3 chain of type IV collagen. Interestingly, this peptide decreases tumor cell proliferation and migration. Migration is reduced by the peptides’ ability to downregulate αvβ3 and MT1-MMP. The C-terminal domain of type XVIII collagen, also referred to as endostatin, possesses antiangiogenic properties. Finally, recent evidence has indicated that collagen type XVIII is expressed in OSCC and associated with those OSCC tumors that do not have nodal metastasis. More work is required to determine whether and how matrikines contribute to OSCC tumor development and progression.

**FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS**

The studies reviewed here illustrate that much work is needed to understand how the ECM contributes to OSCC development and progression. For example, how does the tumor microenvironment, which is composed of the tumor cells, infiltrating cells, and host stroma, regulate the production and processing of the ECM? How does the ECM produced within this environment affect tumor progression, cell motility, and tumor invasion? Unraveling these complex interactions is paramount for the development of new diagnostic, prognostic, and therapeutic approaches for OSCC. For OSCC, gene expression profiling has revealed several changes in expression of ECM molecules. Furthermore, the use of RNA interference (siRNA) has demonstrated the power of this technique to determine the functional contribution of ECM molecules to OSCC tumor development and tumor invasion. Finally, intravital imaging has highlighted the importance of laminin-5 and its integrin receptor α3β1 to vascular arrest and tumor invasion. More thorough studies, combining these three technologies, are necessary to identify which ECM genes are expressed within the tumor microenvironment and how each contributes to OSCC development and progression. However, several of the ECM studies reviewed here have identified new potential therapeutic approaches for OSCC.

As receptors for ECM molecules, integrins have been identified as potential treatment modalities for cancer. For example, several integrin receptors are upregulated in human cancers, including OSCC, where they play an important role in tumor invasion and metastasis. Furthermore, several integrin receptors are required for the process of tumor angiogenesis and are good targets for cancer therapeutics. Therefore, it has been hypothesized that antagonists against integrins may be useful in blocking tumor growth and tumor cell dissemination. Several integrins inhibitors, both antibodies and peptide inhibitors, are currently under investigation as potential therapeutic approaches for cancer. For example, humanized anti-integrin antibodies are currently in phase I/II trials, and a cyclic peptide inhibitor is in phase I/II trials for several human cancers. Whether these inhibitors will work to inhibit OSCC tumor invasion and tumor angiogenesis has not been described.

ECM molecules and ECM proteolytic fragments have potential as targets for cancer therapy. Several collagen isoforms are expressed in OSCC and are believed to be important in tumor angiogenesis. Fragments derived from type I and IV collagens have angiogenic and tumor growth–promoting activities. These fragments could be
targeted as therapeutic approaches for OSCC. The C-terminal domain of type XVII collagen, also referred to as endostatin, possesses antiangiogenic properties that may be exploited as a therapy for OSCC invasion.\textsuperscript{75} Endostatin is currently in clinical trials for therapeutic use in human cancer.\textsuperscript{80} Proteolytic cleavage of the laminin-5 molecules also releases small fragments. These fragments interact with the erb-b1 receptor providing motility-inducing and growth-promoting effects (Figure 2).\textsuperscript{57} This suggests that antibody or peptide inhibitors to this fragment or to the erb-b1 receptor may reduce or inhibit tumor invasion. Finally, inhibitors directed at the MMPs responsible for releasing these proteolytic ECM fragments are also currently being investigated as a potential therapy source for OSCC. Thus, these studies demonstrate that unraveling how the ECM contributes to OSCC development and progression will lead to new target opportunities for OSCC therapy.

**CONCLUSION**

OSCC is one of the most invasive human tumors. Unraveling how the ECM influences tumor development and invasion is fundamental in the development of new prognostic indicators and treatment strategies for OSCC. The ECM is not solely a supporting structure for epithelial tissues. The ECM is a highly complex array of interacting proteins that are constantly being synthesized, processed, and assembled while maintaining cell homeostasis and regulating cell adhesion, migration, wound repair, and tumor development and progression. More work is needed to understand how the ECM can enhance and inhibit OSCC tumorigenicity.

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