Biological implications of decoding the extracellular matrix of vulva cancer

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Abstract. The present review aimed to elucidate the roles of extracellular matrix (ECM) components in the progression of vulvar squamous cell carcinoma (VSCC) and explore potential therapeutic avenues for this type of malignancy. This exploration holds promise for identifying precise molecular targets within the ECM milieu, thus facilitating the development of innovative therapeutic modalities tailored to disrupt these interactions and ultimately improve patient outcomes in VSCC. The dysregulated ECM serves as a potent driver of SCC tumor progression, orchestrating key processes such as angiogenesis, inflammation and stromal cell behavior. Yet, the exploration of ECM role in VSCC is still in its early stages. Recent research highlights the critical role of ECM organization and expression within the tumor microenvironment (TME) in influencing key aspects of VSCC, including tumor staging, grading, metastasis, invasion and patient survival. Cancer-associated fibroblasts play a pivotal role in this dynamic by engaging in reciprocal interactions with VSCC cells, leading to significant ECM alterations and creating an immune-suppressive TME. This hinders antitumor immunity and fosters therapeutic resistance in VSCC treatment. The dysregulated ECM in VSCC drives tumor progression, metastasis and affects patient survival. Targeting ECM, along with emerging therapies such as immune checkpoint blockade, offers promise for improved VSCC treatment outcomes.

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1. Introduction

Vulvar cancer is the fourth most prevalent gynecological cancer globally, representing 5% of lower genital tract tumors and ranking below uterine corpus, ovarian and cervical cancer (1-3). Key contributors to vulvar cancer development include age, human papillomavirus (HPV) infection, smoking, inflammatory vulvar conditions, prior pelvic radiation, immunodeficiency and anogenital warts (4-6). Among the different histological types of vulvar cancer, vulvar squamous cell carcinoma (VSCC) is the most common type (95%), followed by melanoma, sarcoma and basal cell carcinoma (2,3). VSCC has traditionally been regarded as a disease of postmenopausal women, although the mean age of incidence has fallen in recent years worldwide owing to the increase in HPV infections (1). Nonetheless, the age-specific incidence ranges from 0.4 per

100,000 in younger women to 20 per 100,000 in women >70 years old (7).

VSCC manifests in two types with different pathways: The basaloid and/or warty type often associated with HPV (HPV subtypes 16, 18, 31 and 33) which is predisposed from usual vulvar intraepithelial neoplasia (uVIN), and the second type linked to chronic vulvar dermatoses and differentiated vulvar intraepithelial neoplasia (dVIN) (8). Common *TP53* mutations are observed in the second type and are mostly independent of HPV (8). Although there are survival differences in these two types of VSCC, treatment is predominantly surgery with or without radio-chemotherapy. Immunotherapy has reformed the therapeutic paradigms of multiple malignancies, but its impact is limited in VSCC (1). In addition, treatment of unresectable/metastatic disease often leads to frequent comorbidities, particularly in elderly and frail women, highlighting the need for innovative and more effective treatment approaches.

Carcinomas comprise both malignant and non-malignant cells, including fibroblasts, immune cells, vascular cells and neuronal cells (9). Non-malignant cells actively shape the tumor microenvironment (TME) by secreting cytokines, chemokines, growth factors and extracellular matrix (ECM) proteins (9). Under normal physiological conditions, resident cells maintain tissue balance through ECM deposition, degradation and remodeling (10). However, carcinogenesis disrupts ECM remodeling, creating a dysfunctional ECM conducive to a supportive TME that promotes cancer growth, invasion and metastasis (11). While specific research on ECM proteins in VSCC is limited, studies are starting to explore the role of ECM remodeling in VSCC invasion and metastasis.

The present review aims to provide an overview on the role of ECM during VSCC metastasis and the current understanding of the role of ECM in regulating VSCC dissemination. The present study also explored the therapeutic potential of targeting ECM in other types of squamous-epithelial cancers, and the potential prognostic and predictive biomarkers, discussing their impact on developing more efficacious antitumor therapies.

2. Overview of ECM components

The ECM is commonly defined as the non-malignant, non-cellular component of tissue that provides essential biochemical and structural support to its cellular constituents (12,13). Emerging research suggests that the ECM is not merely an intercellular filler but a physiologically active component of living tissue, playing crucial roles in cell-cell communication, adhesion and proliferation (14,15). Resident fibroblasts are responsible for creating and arranging ECM components according to the specific needs of the tissue (14,16). Major components of the ECM, including collagen, laminin, elastin and proteoglycans, exhibit distinct physical and biochemical properties. A detailed overview of ECM components is shown in Table I.

3. ECM remodeling in tumorigenesis

Dysregulation of the ECM is a critical factor in cancer development and progression, influencing various key mechanisms. One such mechanism is cellular signaling, where abnormalities in the ECM contribute to uncontrolled cell growth, survival and proliferation, all fundamental cancer hallmarks (14). Moreover, the ECM plays a critical role in cell adhesion and migration, facilitated by proteins such as integrins and cadherins. Disruption of these processes promotes the invasion of cancer cells into surrounding tissues (Fig. 1A) (10). The ECM also affects the immune response within TME, contributing to immune evasion by cancer cells (14). It has been shown that ECM components impede and educate immune cell types such as natural killer cells, macrophages and tumor-infiltrating lymphocytes, specifically $CD8^+$ T cells, within the TME and evade the antitumor immune response (14,17,18). Components such as cross-linked collagen, fibronectin, laminin, periostin, osteopontin, integrins and matrix metalloproteinases (MMPs) can erect physical barriers, hindering immune cell movement and impairing the ability of immune cells such as cytotoxic $CD8^+$ T-cells to target and eliminate cancer cells (Fig. 1B) (19,20).

Understanding the intricate interplay between tumorigenesis and the ECM is essential for developing targeted therapeutic approaches. Fig. 1C illustrates the significant involvement of ECM components in various cancer hallmarks. Over time, intensive research has been dedicated to exploring interventions targeting ECM components or disrupting ECM-associated signaling pathways in tumors originating from squamous epithelia. These endeavors have yielded valuable scientific insights, which are outlined in Table II, and offer promising directions for advancing SCCs treatment (21-102).

4. Navigating the matrix: Understanding ECM dynamics in vulvar cancer

The ECM in VSCC is a dynamic and influential factor in tumor development (11). This intricate network of proteins, including collagens, laminin, osteopontin, dystroglycan, integrin, CD44 and MMPs, significantly contributes to the progression of VSCC (11). Fig. 1D provides a concise summary of the roles of specific ECM proteins in VSCC and their effects on the hallmarks of cancer. These hallmarks include invasion and metastasis, resistance to cell death, promotion of inflammation, facilitation of replicative immortality and evasion of immune destruction. Thus, understanding the ECM landscape in VSCC can provide valuable insights into the molecular mechanisms underlying this type of cancer.

In order to decipher key ECM proteins involved in VSCC progression, a thorough literature search was performed in the present study. The following MeSH terms were used in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/home.uri) and Web of Science (https://mjl.clarivate.com/home) to select literature describing ECM and VSCC tumor progression and development: ('genital neoplasms, female'[MeSH Terms] OR 'female genital neoplasm*'[All Fields] OR 'Gynaecologic neoplasm*'[All Fields] OR 'Vulvar Neoplasms'[MeSH Terms] OR 'vulvar neoplasm*'[All Fields] OR 'vulva neoplasm*'[All Fields] OR 'cancer of vagina*'[All Fields] OR 'cancer of vulva*'[All Fields] OR 'vulva squamous cell carcinoma*'[All Fields] OR 'vaginal neoplasm*'[All Fields] OR 'vagina cancer*'[All Fields]) AND ('Extracellular Matrix'[MeSH Terms] OR 'extracellular matrix*'[All Fields] OR 'extracellular matrix protein*'[All Fields]) AND 1980/01/01:2023/12/31 [date-publication]. In the following

Table I. An overview of extracellular matrix components.

Category	Major forms	Components
Types of collagens	Fibril-forming	I, II, III, V, XI, XXIV, XXVII
	Fibril-associated	IX, XII, XIV, XVI, XIX, XX, XXI, XXII
	Network-forming	IV, VIII, X
	Membrane-anchored	XIII, XVII, XXIII, XXV
	Multiplexin	XV, XVIII
Types of microfibrillar proteins		Elastin, Fibrillin, Fibulin, Microfibril-associated glycoproteins, Elastin microfibril interfacer 1
Types of matricellular glycoproteins		Fibulin, Thrombospondin, Osteopontin, Tenascin, Periostin, Cartilage Oligometric Matrix Protein,
Types of glycoproteins		Fibrinogen, Fibronectin, Laminin, Vitronectin, Nidogen
Types of proteoglycans	Intracellular secretory granules	Serglycin
	Transmembrane	Syndecan, Phosphacan, Neuronglia antigen-2, Betaglycan
	Pericellular	Perlecan, Argin, Collagens-XV, XVIII
	Extracellular (hyaluronan and nectin-binding proteoglycan)	Aggrecan, Neurocan, Brevican, Versican
	Extracellular (Small leucine-rich proteoglycan):	Biglycan, Lumican, Keratocan, Osteoglycin, Chondroadherin, Podocan
Types of secreted MMPs	Collagenase	MMP1, MMP8, MMP13
	Gelatinase	MMP2, MMP9
	Stromelysin	MMP3, MMP10
	Matrilysin	MMP7, MMP26
	Other MMPs	MMP11, MMP28, MMP12, MMP19, MMP20
Types of membrane-anchored MMPs	Type I transmembrane-type MMP	MMP14, MMP15, MMP16, MMP24
	Glycosylphosphatidylinositol-linked MMP	MMP17, MMP25
	Type I transmembrane-type MMP	MMP23

MMPs, matrix metalloproteinases.

section, each of the ECM proteins implicated in VSCC progression are described in detail. Table III (103-115) summarizes the key findings regarding ECM proteins in VSCC. This table provides a concise overview of the significant associations, functional implications and clinical relevance of ECM proteins identified in VSCC.

Collagens. Collagens, which are the predominant component of the ECM, are widely distributed across various types of tissue. With 28 different types, the collagen superfamily forms fibers, networks and filaments within the ECM, interacting with mesenchymal-origin cells through various receptor families to regulate their proliferation, migration and differentiation (116). While studies have extensively investigated the role of collagens in driving cancer invasion and metastasis, their specific involvement in VSCC remains understudied. Recent research utilizing Second Harmonic Generation imaging has analyzed collagen parameters (quantity, uniformity and organization) in VSCC, revealing associations with lymph node metastasis (103). Additionally, based on collagen organization, two morphologic variants have been identified in VSCC: An indolent type growing as 'sheets of cells' with a pushing border in lymphoplasmacytic stroma, and an aggressive variant growing as 'single tumor cells' with a finger-like border in fibromyxoid stroma (104). Proteomic analyses have further demonstrated that the aggressive variants are associated with higher rates of lymph node metastasis and tumor recurrences. Consistent with these findings, previous studies have shown a significant correlation between the 'sheet of cells' morphology, HPV infection and improved survival rate (8). Collectively, these findings suggest that morphological variants of collagen fibers in the TME may serve as prognostic indicators for aggressive

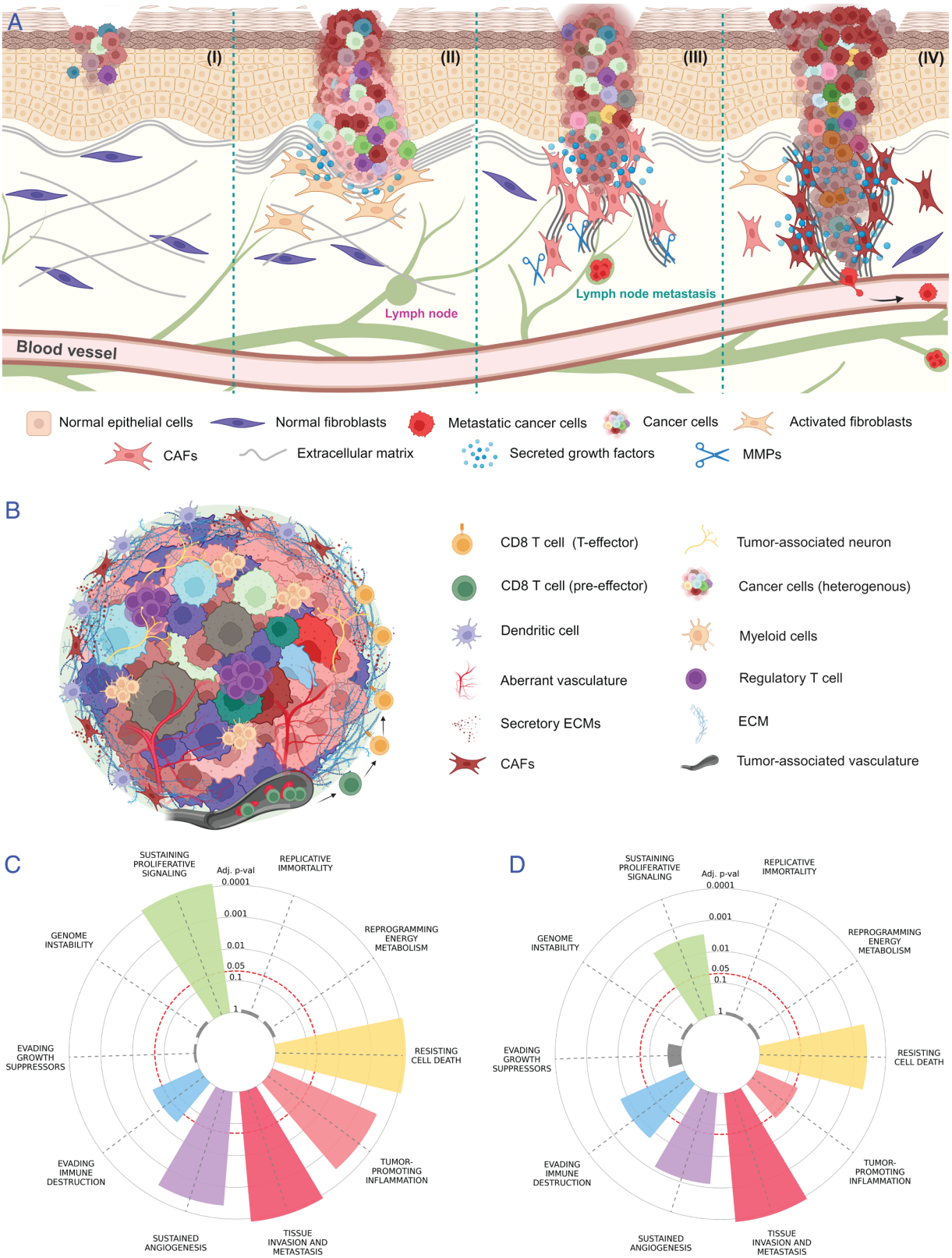

Figure 1. (A) Role of ECM components in tumorigenesis: (I) Neoplastic cells in the epithelium proliferate rapidly leading to mechanical strain on the basement membrane. (II) This leads to an increase in number of fibroblasts (now called activated fibroblasts) in the stroma. (III) Activated fibroblasts increase the deposition of collagen leading to a stiff matrix. This in turn activates various mitogenic pathways in cancer cells making them more motile and proliferative. (IV) Neoplastic epithelial cells breach the basement membrane and migrate along the aligned collagen. The neoplastic cells gain access to nearby draining lymph nodes or blood vessels leading to metastasis. (B) ECM components hindering tumor-infiltrating lymphocyte infiltration in TME: ECM constituents such as collagen, fibronectin, laminin, periostin, osteopontin, integrins and MMPs can create physical barriers, impeding immune cell movement and compromising the ability of cytotoxic $CD8^+$ T-cells to target and eliminate cancer cells. (C) ECM components and cancer hallmarks in SCCs: ECM components present across SCCs are implicated in various cancer hallmarks. The size of circles denotes significant P-values. (D) ECM components and cancer hallmarks in VSCC. ECM components specific to VSCC are associated with cancer hallmarks. The size of the circles indicates significant P-values. (Figure was created using Bio-Render; https://www.biorender.com/). ECM, extracellular matrix; TME, tumor microenvironment; MMPs, matrix metalloproteinases; SCC; VSCC, vulvar squamous cell carcinoma.

Table II. Involvement of ECM proteins in tumors of squamous epithelial origin.

Tumors	ECMs	Clinical significances	(Refs.)
HNSCC	MMP1	Promotes tumor progression and associates with poor survival outcome	(21)
	MMP3	Regulates cancer stem cells during tumor initiation and metastasis	(28)
	MMP7	Promotes invasion, proliferation, motility and metastasis	(31)
	MMP9	Plays a role in tumorigenesis	(46)
	MMP10	Promotes invasion and metastasis	(35)
	MMP11	Involves lymph node metastasis and survival	(39)
	MMP12	Correlates with extracapsular spread and nodal metastasis	(41)
	MMP13	Promotes invasion-related factors and is involved in tumor angiogenesis	(43)
	MMP14	Promotes the formation of functional invadopodia during cancer progression	(46)
	ITGA5	Promotes the progression of OSCC via activating the PI3K/AKT signaling pathway	(50)
	ITGB1	Contributes to perineural invasion and maintaining radio-resistance	(51)
	ITGB6	Increases carcinoma cell motility and growth; negatively affects fibronectin matrix assembly	(52)
	ITGA5, ITGB8	Promotes cancer cell migration and invasion on type I collagen	(53)
	ITGB1, ITGA6, ITGB4	Reduced expression relating to the loss of basement membrane proteins leading to the invasion of cancer cells	(54,58)
	COL1A1	Induces proliferation and metastasis	(61)
	COL1A2	High recurrence and less disease-free survival	(61)
	COL3A1	Promotes the differentiation of tumor cells, low survival outcome, induces tumor growth, negatively influences immune cell infiltration	(63)
	COL4A1	Promotes cancer cell proliferation and migration	(64)
	COL11A1	Advanced clinical stage (proliferation, migration, invasion) and poor overall survival, immune evasion	(65,66)
	COLXVII	Promotes growth, invasion	(67)
	LAMB3	Associates with lymph node metastasis, invasion and a poor prognosis	(68)
	LAMC2	High expression associated with high-intensity tumor budding and invasion	(69)
	CD44	High expression related to a worse tumor prognosis	(70-72)
	Periostin	Promotes invasion and anchorage-independent growth in the metastatic process	(73)
	Osteopontin	Promotes chemotherapeutic resistance and is associated with worse overall survival	(7)
ESCC	MMP1	Promotes tumor growth and metastasis	(22)
	MMP2	Promotes invasion and metastasis	(25)
	MMP3	Promotes invasion and metastasis	(27)
	MMP9	Promotes tumor progression and a poor prognosis	(25,33,34)
	MMP10	Associated with poorer disease-specific survival	(36)
	MMP11	Promotes tumor invasion and metastasis	(38)
	MMP12	Correlates with tumor grade and stage, nodal metastasis and poor survival	(42)
	MMP13	Associated with tumor staging, grading and lymph node metastasis	(44)
	MMP14	Promotes cell migration, invasion and proliferation	(48)
	ITGA6	Promotes metastasis via binding to integrin α6	(55)
	ITGB1	Promotes cancer cell proliferation, invasion and chemoresistance	(56)
	ITGA5	Promotes lymph node metastasis, tumor size and poor survival of the patient	(57)
	COL1A2	Induces proliferation and metastasis, promotes EMT	(62)
	COL6A5	Low expression associated with poor survival	(75)
	COL18A1	Associated with poor survival	(75)
	COL3A1	Down-regulation involved with growth suppression in subcutaneous xenograft mouse models and inhibited lung metastasis mouse models	(76)
	COL11A1	Advanced clinical stage and lymph node metastasis	(77)
	LAMA1	High expression associated with cell proliferation and migration	(78)
	LAMC2	Promotes invasion and metastasis	(79,80)
	LAMC1	High expression associated with cell proliferation and migration	(81)

Table II. Continued.

Tumors	ECMs	Clinical significances	(Refs.)
	CD44	Promotes lymph node metastasis, vascular invasion and disease recurrence	(82)
	Periostin	Associated with poor postoperative outcomes	(83)
	Osteopontin	Promotes cancer cell proliferation, invasion and chemoresistance	(84,85)
LSCC	MMP2	Associated with metastasis and patient poor prognosis	(24)
	MMP7	Associated with tumor proliferation and a poor prognosis	(30)
	MMP12	Correlates with the pathological stage and lymph node metastasis	(40)
	MMP14	Higher expression predicts a poor prognosis	(45,47)
	COL1A1	Promotes immunosuppressive tumor microenvironment	(60)
	COL6A5	Low expression correlates with worse overall survival	(86)
	COL3A1	Promotes growth and cisplatin resistance, poor survival	(87)
	COL6A1	Promotes immunosuppressive tumor microenvironment	(88)
	COL11A1	Promotes cancer cell proliferation, migration, invasion and drug resistance	(89)
	LAMC2	Negatively correlated with patient survival	(90)
	LAMA3, LAMA5	Promotes cancer cell invasion	(91)
	LAMB3	Leads to apoptosis protection, cell proliferation and increased tumor invasion	(92)
	CD44	Correlates with advanced lymph node metastasis	(93)
	Periostin	No significant association of periostin and worse outcomes or survival	(94)
	Osteopontin	Presence in biofluids might be useful for diagnosis	(95)
CSCC	MMP1	Promotes angiogenesis	(23)
	MMP2	Associated with poor survival outcome	(26)
	MMP3	Promotes cancer cell proliferation	(29)
	MMP7	Associated with increased lymph metastasis, pathological grade and clinical stage	(32)
	MMP9	Associated with a favourable cervical cancer prognosis	(32)
	MMP10	Promotes cell migration and invasion, endothelial cell tube formation, and resistance to apoptosis	(37)
	MMP14	Associates with angiogenesis, invasion, metastasis and poor prognosis	(49)
	COL1A1	Induces apoptosis and inhibits cell growth	(59)
	COL6A1	Associated with poor overall and recurrent-free survival	(96)
	COL11A1	Associated with poor overall survival	(89)
	LAMC3	Promotes invasion and metastasis	(97)
	LAMC2	Promotes invasion and microinvasion	(98)
	CD44	Associated with poorer prognosis in stage III cancer patients	(99)
	Periostin	Promotes lymph node metastasis and lymph angiogenesis	(100,101)
	Osteopontin	Associated with immune suppression, high glycolytic metabolism, apoptosis, angiogenesis and EMT	(102)

HNSCC, head and neck squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; LSCC, lung squamous cell carcinoma; CSCC, cervical squamous cell carcinoma.

VSCC. This highlights the potential significance of collagen parameters in understanding VSCC aggressiveness and may offer insights into therapeutic strategies targeting the tumor microenvironment.

Laminins. The laminin family, comprising of ~20 glycoproteins, forms a cross-linked web intertwined with the type IV collagen network in basement membranes. Laminins are heterotrimers composed of three polypeptide chains (α, β, γ) and play crucial roles in early embryonic development, organogenesis and various cell type-specific functions such as adhesion, differentiation, migration, phenotype maintenance and resistance to apoptosis (15). However, in tumors of the lower female genital tract, laminin expression becomes dysregulated (117). Prior research has emphasized that elevated expression of the γ2 chain of laminin-5 (LAMC2) is linked to patient survival in VSCC. Notably, intracytoplasmic expression of the γ2 chain along the invasive tumor front correlates with short-term survival. Larger tumors tend to exhibit increased γ2 chain expression, although no significant correlation has been observed with tumor staging. These findings suggest that heightened expression of the γ2 chain may be involved in the

Table III. Involvement of extracellular matrix in VSCC.

Target protein	Study techniques	Results	Authors	(Refs.)
Collagens (I, III, VI, XVI)	Microscopy, proteomics	Induces lymph node metastasis in VSCC models. Collagens are implicated in the formation of a more aggressive tumor variant with lymph node metastasis	Castor *et al* Holthoff *et al*	(103,104)
Osteopontin	ISH	Elevated expression levels of osteopontin in VSCC samples, particularly in those with higher pathological grades	Wu *et al*	(105)
Dystroglycan	IHC	Reduced expression promotes VSCC progression	Sgambato *et al*	(106)
Integrin β1	IFC	Strong positive correlation between high integrin β1 expression and increased invasiveness of VSCC	Brockbank *et al*	(107)
CD44v3, CD44v6	ICC	Higher expression of CD44v3 and CD44v6 isoforms in VSCC samples, which correlated with poor patient survival rates and increased lymph node metastasis	Hefler *et al*	(108)
MMP13	IHC, Transcriptomics	High expression levels of MMP13, which were associated with the malignant transformation of vulvar epithelial cells in VSCC	Johansson *et al*	(109)
MMP2	ICC	Elevated MMP2 expression levels in VSCC tissues, indicating a potential role in promoting tumor invasiveness	Bovo *et al*	(110)
MMP12	ISH, Transcriptomics	Positive correlation between MMP12 expression and the histological grade of VSCC tumors, suggesting a role in tumor progression	Kerkelä *et al*	(112)
Tenascin	IFC	Promotes malignant transformation in VSCC cells, predominantly expressed in VIS, inflammatory preinvasive and invasive vulvar lesions	Goepel *et al*	(113)
Integrin α5β1	IHC	Promotes malignant transformation of VSCC cells	Surico *et al*	(114)
Laminin-5 γ2	ICC	Laminin-5 γ2 revealed a significant correlation with poor patient survival rates among VSCC cases	Hellman *et al*	(115)

VIS, vulvar intraepithelial neoplasia; ICC, immunocytochemistry; ISH, *In-situ* hybridization; WB, Western blotting; IHC, immunohistochemistry; IFC, immunofluorescence; VSCC, vulvar squamous cell carcinoma.

initiation of VSCC tumorigenesis rather than progression (115). However, further investigations are warranted to elucidate the dynamics of LAMC2 in VSCC tumorigenesis.

Osteopontin. Matricellular proteins form a diverse family of non-structural matrix glycoproteins, including thrombospondins, secreted acidic protein and rich in cysteine, tenascins, fibulins, osteopontin, cartilage oligomeric matrix protein and CNN family proteins such as periostin and R-spondins (116). Among these, osteopontin (OPN), initially identified as a bone matrix protein, is now recognized as a cytokine produced by activated T cells and transformed cells. It is highly inducible as it is expressed and secreted by both tumor cells and cells in the stroma (105). In VSCC, OPN expression was investigated across various stages of vulvar lesions, including VSCC, VIN, vulvar lichen sclerosus (VLS) and normal vulvar tissue samples. Proteomic analysis revealed a gradual increase in OPN expression from VIN to VLS, with the highest expression observed in VSCC tumor tissue samples. Additionally, OPN expression was found to be associated with the pathological stage, suggesting its potential role in VSCC tumor progression through neoplastic transformation (105). Collectively, this observation suggested that OPN could be a predictive biomarker for the early detection of VSCC, and further studies are required to understand VSCC pathogenesis through OPN.

Dystroglycan. Dystroglycan, a transmembrane glycoprotein, serves as a crucial link between the ECM and the intracellular cytoskeleton, thereby providing structural integrity. Comprising α and β components, dystroglycan facilitates cell adhesion to the ECM and plays a pivotal role in regulating cytoskeletal organization (118,119). Dysregulation of dystroglycan is a common occurrence observed in various human epithelial cancers, suggesting its potential involvement in tumor development (118,119). Notably, previous research has revealed disrupted expression levels of α-dystroglycan in conditions such as VLS, squamous cell hyperplasia, VIN and invasive VSCC. Specifically, decreased expression of α-dystroglycan

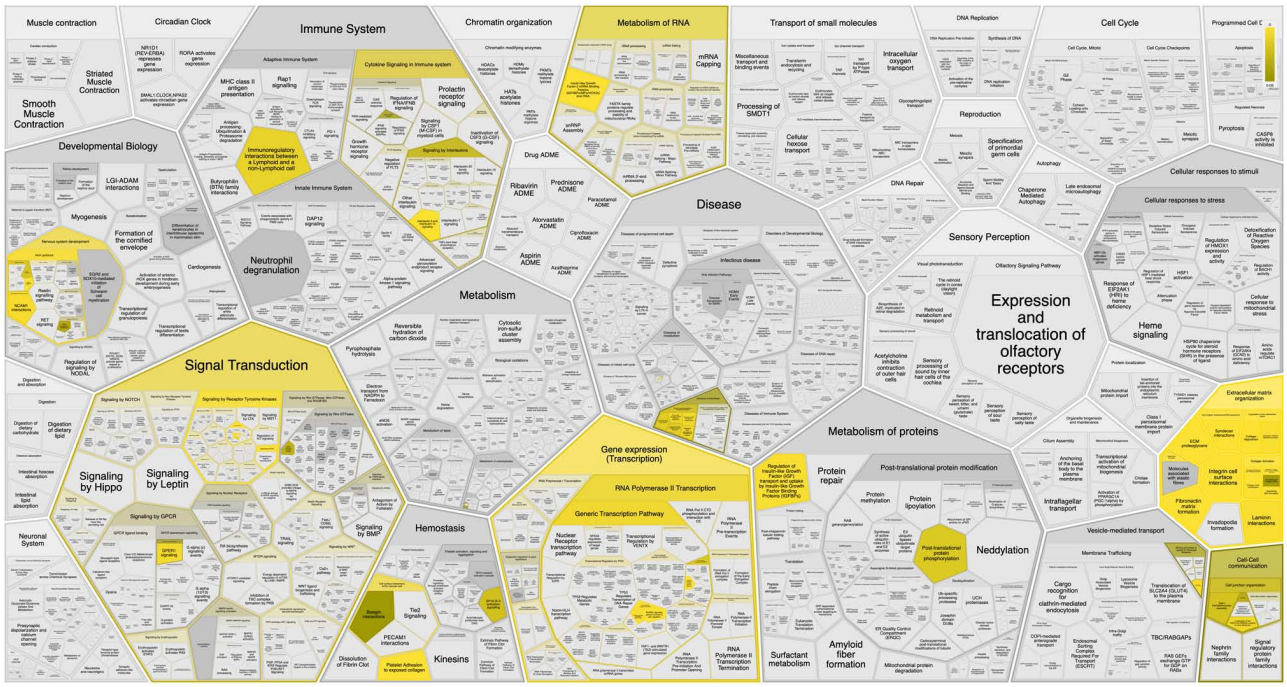

Figure 2. Potential pathways associated with ECM components in VSCC. The ECM components of VSCC are involved with several pathways modulating different signaling pathways. The dark brown color represents the pathways associated with significant P-value (P<0.05). ECM, extracellular matrix; VSCC, vulvar squamous cell carcinoma.

has been observed across preneoplastic lesions of VSCC, and this downregulation is associated with advanced stages of VSCC. These findings suggest that α-dystroglycan may play a significant role in maintaining cytoskeletal dynamics, and its reduced expression could promote VSCC progression (106).

Integrins β1. Integrins, heterodimeric receptors comprising α and β subunits, are frequently dysregulated in skin cancers (107). Serving as bridging molecules, integrins connect ECMs with the cell cytoskeleton, governing cell adhesion and motility. The intracellular tail of integrin β1 associates with proteins such as talin, α-actinin and vinculin, linking it to the actin cytoskeleton and regulating cell motility, keratinocyte wound healing and the collective movement of tumor cells (115). Increased expression of various integrin (ITG) family proteins, including α2, α3, α5, α6 and β1 has been observed in VSCC. Among these, β1 (ITGB1) plays a pivotal role in mediating cell adhesion, migration and invasion (107). Knockdown experiments targeting β1 result in significant alterations in VSCC tumor morphology compared with control tumors. Specifically, β1 knockdown leads to a more encapsulated and less invasive tumor phenotype, indicating the crucial involvement of integrin β1 in VSCC invasiveness and disease progression (107). The present study underscores the significance of β1 integrin in VSCC tumor advancement and suggests potential therapeutic avenues for intervention.

Hyaluronic acid receptor CD44. Hyaluronic acid receptor CD44 is a surface-expressed glycoprotein that facilitates interactions with a spectrum of molecules, including collagen, fibronectin, OPN, MMPs and growth factors (70,71). CD44 plays a pivotal role in cell adhesion, interactions, migration and metastasis. CD44 isoforms bolster malignant cell affinity to ECM ligands, thereby fostering tumor dissemination (70,71). A previous study has demonstrated a significant association between CD44 variants, particularly CD44v3 and CD44v6 and VSCC tumor progression, as well as adverse patient outcomes (108). Elevated CD44 expression correlates with poor tumor differentiation, positive lymph node involvement, advanced-stage VSCC and diminished survival rates, indicating its potential as a prognostic marker (108).

MMPs. MMPs are a family of calcium-dependent, zinc-containing endopeptidases that target various molecules, including matrix components, growth factors, cytokines and signaling molecules. Synthesized as zymogens, MMPs are secreted after cleavage of their propeptide form. Invasion and metastasis of malignant cells involve the degradation of the stromal matrix, mediated by specific MMPs (120).

MMP2. MMP2 plays a pivotal role in degrading crucial components of basement membranes such as type IV collagen and fibronectin, facilitating the invasion of tumor cells into stromal and vascular regions (25,110). Overexpression of MMP2 has been observed across various disease stages of VSCC, including VIN (grades-I, II, III) and VLS and this heightened expression is significantly associated with the invasiveness of VSCC (110). Morphologically, MMP2 manifests as cytoplasmic granular or diffuse staining in stromal cells. However, in cases of invasive VSCC, MMP2-positive cells are notably observed in the stroma adjacent to neoplastic islands or infiltrating groups of tumor cells (110). These highly MMP2-expressing tumor cells secrete factors that contribute to the aggressiveness of VSCC, including invasion and metastasis, suggesting potential therapeutic approaches targeting MMP2.

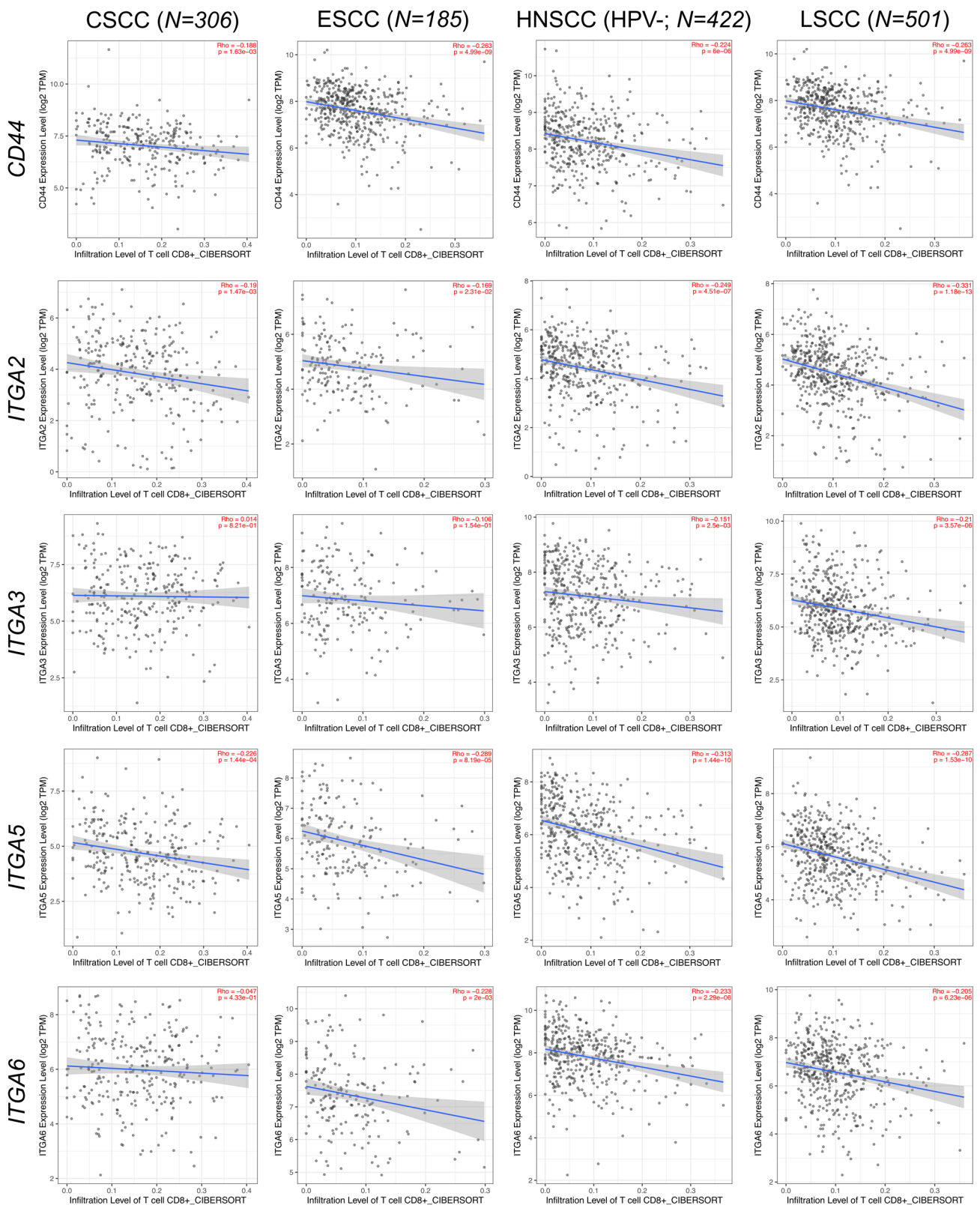

Figure 3. Expression levels of ECM-related genes (*CD44*, *ITGA2*, *ITGA3*, *ITGA5*, *ITGA6*) and $CD8^+$ T-cell infiltration correlation in epithelial-driven tumors from the TIMER2 bioinformatics platform. P<0.05 was considered statistically significant. HNSCC, head and neck squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; LSCC, lung squamous cell carcinoma; CSCC, cervical squamous cell carcinoma; CD, cluster of differentiation; ECM, extracellular matrix.

MMP12. MMP12, recognized for its ability to degrade elastin and various substrates such as type IV collagen, fibronectin and laminin, plays a multifaceted role in cancer progression, particularly in VSCC. It contributes to limiting tumor growth by converting plasminogen into angiostatin, which inhibits endothelial cell proliferation and angiogenesis, essential processes for tumor vascularization (111). While typically associated with macrophages, MMP12 is

Table IV. Summary of extracellular matrix components inhibitors across human cancers.

A, Integrin inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
Abituzumab (EMD525797)	Monoclonal Ab	Integrin αV	PC, CC	Phase II	PFS not significant	(144)
Intetumumab (CNTO 95)	Monoclonal Ab	Integrin αV	Melanoma, PC	Phase II	PFS not significant	(144)
Vitaxin (MEDI-523)	Monoclonal Ab	Integrin αVβ3	Metastatic cancers	Phase II	No tumor regression	(144)
Etaracizumab (MEDI-522, Abegrin)	Monoclonal Ab	Integrin αVβ3	Melanoma	Phase II	PFS not significant	(144)
Cilengitide (EMD 121974)	Inhibitory peptide	Integrin αVβ3, Integrin αVβ5	Multiple cancers, GB	Phase II	OS not significant	(144)
Volociximab (M200)	Monoclonal Ab	Integrin αVβ1	Pancreatic, NSCLC, OC, Peritoneal, RC	Phase II	Partial or no significant effects	(144)
Natalizumab	Monoclonal Ab	Integrin α4	MM	Phase II	No results	(144)
ATN-161	Inhibitory peptide	Integrin α5β1	GBM, RC and other solid cancers	Phase I/II	No therapeutic benefits	(144)

B, MMP inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
Batimastat (BB-94)	Zinc chelator	MMP-1, 2, 3, 7, 9, 14	Pancreatic, CC, GC, OC, Cholangiocarcinoma, Mesothelioma, NSCLC, BC, Melanoma, RC	Phase III (cancelled)	Developed toxicity	(145)
Marimastat (BB-2516)	Zinc chelator	MMP-1, 2, 3, 7, 9	BC, NSCLC, CC, Pancreatic, GC, PC, GBM	Phase III (cancelled)	Prolongation of survival in randomized Ph-II in gastric cancer	(145)
Tanomastat (BAY 12-9566)	zinc chelator	MMP-2, 3, 8, 9, 13	Pancreatic, OC, NSCLC	Phase III (cancelled)	Developed toxicity	(145)
Andecaliximab (GS-5745)	Monoclonal Ab	MMP-9	GC, BC, Pancreatic, NSCLC, ESCC, CC	Ongoing phase I, II III	Developed toxicity	(145)
AB0041, AB0046, GS-5745	Monoclonal Ab	MMP-9	CC	Preclinical	Data not available	(145)
DX-2400	Monoclonal Ab	MMP-14	BC, Melanoma, Fibrosarcoma	Preclinical	Data not available	(145)
Intetumumab (CNTO 95)	Monoclonal Ab	MMP-1,2, 3	BC	Preclinical	Data not available	(145)

C, Osteopontin inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
100D3 and 103D6	Monoclonal Ab	Osteopontin	Colon	Preclinical	Promotes antitumor immune responses	(146)

Table IV. Continued.

C, Osteopontin inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
Simvastatin, Cetuximab, andrographolide and parecoxistep	Inhibitors	Osteopontin	Colon, PC, BC	Preclinical	Inhibiting Osteopontin expression	(146)
Parecoxib	COX-2 inhibitor	Osteopontin	CC	Preclinical	Inhibiting Osteopontin expression	(147)

D, Laminins inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
HYD1	Inhibitory peptide	Laminin-5	PC	Preclinical	Tumor growth suppression	(148)
G45	Monoclonal Ab	Laminin-332	SCC	Preclinical	Tumor growth suppression	(149)

E, CD44 inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
VFF18	Monoclonal Ab	CD44	SCC	Preclinical	Promising targeting vehicle for radioimmunotherapy	(150)
cMAb U36	Monoclonal Ab	CD44	HNSCC	Preclinical	Biomarker of early detection	(151)

F, Collagen inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
Baicalein	Antioxidant	Col-I	LC, Osteosarcoma, Bladder, BC, PC, CSCC, HNSCC	Preclinical	Inhibiting Col-I transcription	(152)
Phenylbutyrate, sodium phenylbutyrate	Fatty acid	Col-I	LC, PC, BC, OC, Bladder	Preclinical	Decreases collagen synthesis	(152)
Ethyl 3,4-dihydroxybenzoate (EDHB), 2-(5-carboxythiazol-2-yl) pyridine-5-carboxylic acid (pythiDC)	Antioxidant	Col-I	CC, BC	Preclinical	Decreases collagen synthesis	(152)
Minoxidil	Synthetic compound	Col-I	PC, BC, OC	Preclinical	Decreases collagen synthesis	(152)
Galunisertib (LY2157299)	RTK-inhibitor	Col-XI	OC, Pancreatic, BC	Phase II	Decreases collagen synthesis	(152)
SC66	AKT-inhibitor	Col-XI	OC, Pancreatic, BC	Under trial	Decreases collagen synthesis	(152)
Clostridium Histolyticum (EN3835)	Collagenase	Col-I, III	Uterine leiomyoma, Lipoma	Phase I/II	Decreases tumor burden	(153)
TRC093	Monoclonal Ab	Collagens	Locally advanced or metastatic solid cancers	Phase I	Dose escalation study	

Table IV. Continued.

G, Periostin inhibitors in cancer

Inhibitor	Types	Targets	Cancer	Status	Results	(Refs.)
Anti-PN peptide	Inhibitory peptide	Periostin	BC	Preclinical	Improving doxorubicin sensitivity	(154)
PN21-Ab	Monoclonal Ab	Periostin	BC	Preclinical	Promotes chemosensitivity	(155)
α-periostin	Monoclonal Ab	Periostin	CC	Preclinical	Promotes chemosensitivity	(156)
MZ-1	Monoclonal Ab	Periostin	OC	Preclinical	Tumor growth suppression	(156)
PNDA3	DNA aptamers	Periostin, Integrin (αVβ3, αVβ5)	BC	Preclinical	Tumor growth suppression	(157)
PNDA3	DNA aptamers	Periostin	GC	Preclinical	Reducing metastasis and angiogenesis	(158)

PC, prostate cancer; CC, colorectal cancer; GBM, glioblastoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; RC, renal cancer; GC, gastric cancer; BC, breast cancer; LC, lung cancer; MM, multiple myeloma; ESCC, oesophageal squamous cell carcinoma; CSCC, cervical squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma; Ab, antibody; Col, collagen; PFS, progression-free survival; OS, overall survival; RTK, receptor-tyrosine kinase.

also expressed by transformed epithelial cells in VSCC, with its expression level correlating with tumor dedifferentiation and histological aggressiveness (112). In a study involving 33 VSCC samples, MMP12 mRNA was prevalent, and higher expression in cancer cells was associated with more aggressive and poorly differentiated tumors (112). Notably, macrophage-derived MMP12 was more abundant in well-differentiated grade I tumors compared with grade III tumors (112). These findings suggest MMP12 potential role in modulating VSCC histology and influencing treatment strategies. However, further research is warranted to fully understand MMP12 implications in VSCC and its therapeutic relevance.

MMP13. MMP13, recognized for its ability to cleave fibrillar collagens and various stromal matrix components, stands out as a versatile proteolytic tool crucial for tumor cell invasion (16,116,120,121). A previous study has highlighted the abundant expression of MMP13 in VSCC tumor tissues, often correlating with lymph node metastasis (109). Moreover, *in vitro* investigations have revealed a significant increase in MMP13 levels in VSCC cell lines compared with control epithelial cells (109). These findings underscore MMP13 specific expression by malignantly transformed squamous epithelial cells, including VSCC cells, suggesting its potential as a marker for their invasive potential (109).

5. Elucidating molecular synergies: Cancer-associated fibroblasts (CAFs) and ECM in VSCC progression

Fibroblasts are the main architects of the ECM, orchestrating changes that play a major role in tumor progression, inflammation, therapy resistance and immunosuppression (9,122). CAFs are perhaps the cells most proficient at remodeling the ECM as they deposit collagens and release various growth factors, chemokines, cytokines and MMPs (Fig. 1A). Significantly altered gene pathways in CAFs include regulation of substrate adhesion, tissue remodeling, cell migration, secretion, growth regulation and angiogenesis (123). Although, at present, VSCC-specific subpopulations of CAFs have not been reported, single-cell RNA sequencing data suggests that various CAF subpopulations exist in the TME of other types of SCCs (124,125).

The most commonly identified CAF subpopulations are those involved in ECM remodeling [myofibroblast CAFs (myCAFs)] and immunomodulatory cancer-associated fibroblasts] (126). MyCAFs have been reported to be involved in tissue remodeling and often express *ACTA2* gene (126). Inflammatory CAFs often exhibit increased IL-6 signaling in various tumor types (126-129). This makes them potential targets for anti-IL-6 therapies, such as siltuximab and tocilizumab (130). Moreover, research has shown that immunoregulatory CAFs can activate JAK-STAT signaling in cancer cells (129), suggesting that inhibition of this pathway may be a promising therapeutic strategy.

Mounting evidence suggests that CAFs also play a key role in therapy-resistance in SCCs, particularly in head and neck SCC (HNSCC) and esophageal SCC (131-133). It has been previously reported that chemotherapy promotes CAF survival and alters exosome biogenesis, which leads to malignant characteristics in HNSCC (134). Notably, CAFs also respond to radiotherapy by upregulating transforming growth factor β1 (TGFβ1) expression via IL-8/NF-κB signaling in HNSCC, which increases the rate of invasive growth. This signaling can be inhibited by using Tranilast, a known TGFβ1 inhibitor (135). A subset of CAFs have

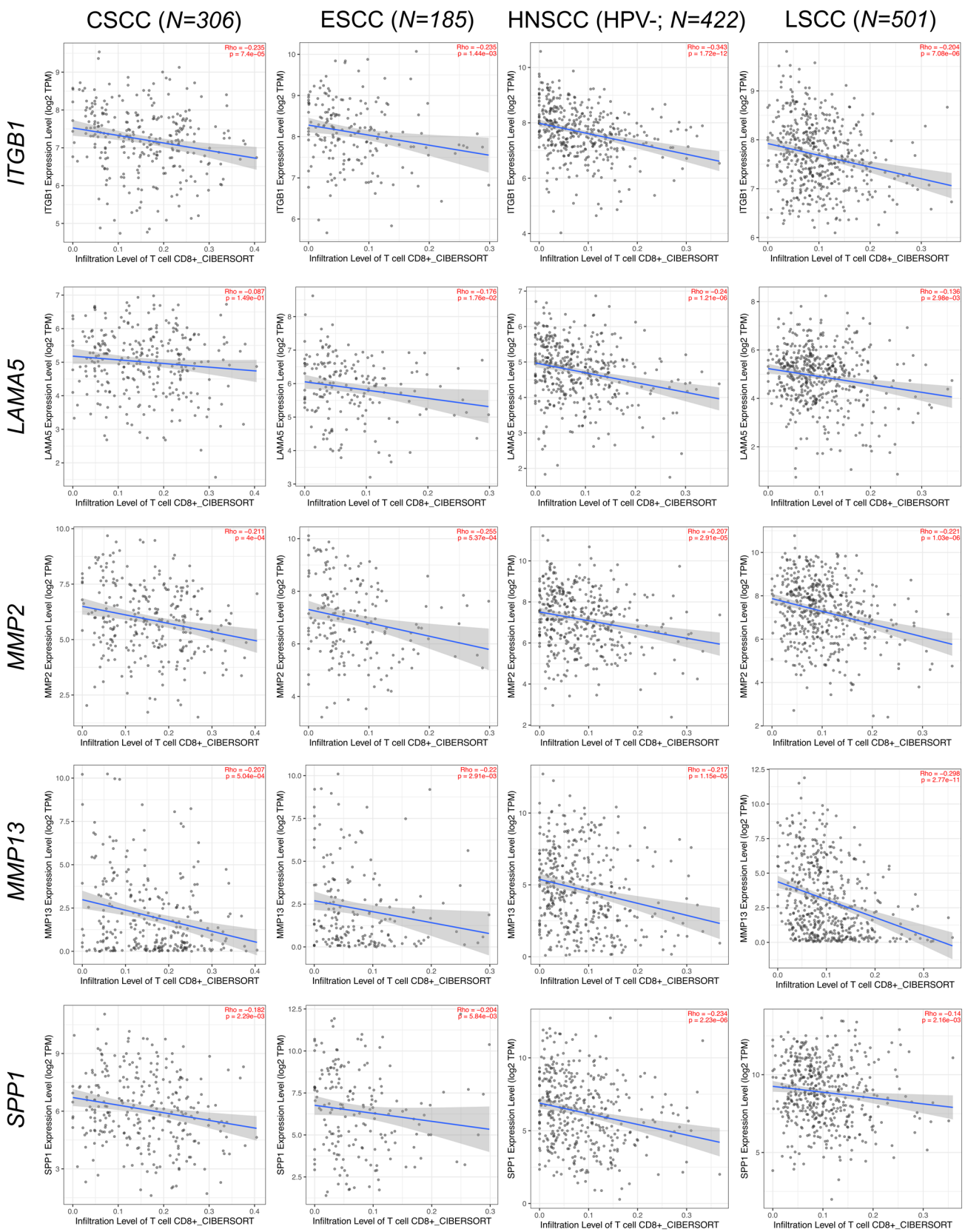

Figure 4. Expression of ECM-related genes (*ITGB1*, *LAMA5*, *MMP2*, *MMP13*, *SPP1*) and $CD8^+$ T-cell infiltration correlation in epithelial tumors from TIMER2 bioinformatics platform. P<0.05 was considered statistically significant. ECM, extracellular matrix; ITGB1, integrin β1; MMP, matrix metalloproteinases; SPP1, secreted phosphoprotein 1.

also been reported to be involved in TGFβ1 dependent $PD\text{-}1^+/TIM\text{-}3^+$ exhaustion of CD8 T cells in HNSCC, leading to exclusion of T cells, thereby negatively impacting immunotherapy response (124,136). Previously, we have shown that CAFs play a decisive role in VSCC invasion and that VSCC cells exhibit a fibroblast-dependent tumorigenic

potential (137). However, there exists a significant heterogeneity with CAFs showing both tumor-promoting and tumor-inhibiting CAFs (9,122). Gaining a more profound insight into the molecular and phenotypic variations among CAF populations in VSCC may contribute to overcoming challenges related to therapy resistance and the targeting of cancer cells.

6. Decoding therapeutic prospects: ECM proteins in VSCC

The therapeutic potential of ECM proteins in treating VSCC holds promise for pioneering treatment strategies. Identifying specific ECM proteins involved in VSCC tumorigenesis will unveil potential therapeutic targets. While the pathways linked with ECM proteins in VSCC are not fully understood, emerging bioinformatic platforms (138) provide opportunities to pinpoint key pathways and potential targeted therapies for this relatively underexplored cancer. Notably, these proteins, irrespective of ECM organization, are implicated in modulating immune systems, as depicted in Fig. 2.

Despite the absence of reports on ECM proteins regulating immune compartments in VSCC, insights from other epithelial-origin tumors in The Cancer Genome Atlas suggests that investigating ECM in VSCC may be beneficial. Bioinformatics platforms such as TIMER2 (http://timer.cistrome.org/) (139) confirm that higher expression levels of ECM-related genes are associated with reduced $CD8^+$ T cell infiltration within the TME, fostering immune evasion and tumor progression across various epithelial cancers (140-143) (Figs. 3 and 4). Consequently, over the last few decades, several ECM inhibitors have been developed and successfully employed across different SCCs (Table IV) (144-158). Therefore, understanding the intricate relationship between ECM components in the context of VSCC is essential for devising innovative therapeutic strategies tailored to this patient population. Such endeavors hold the potential to pave the way for the emergence of novel therapeutics.

7. Exploring future avenues: Research directions in VSCC and ECM interactions

The present study thoroughly investigated the intricate landscape of the ECM in VSCC, examining the roles of various components such as collagens, laminin, osteopontin, dystroglycan, integrin, CD44 and MMPs in VSCC progression. Furthermore, the present study highlights the evolving understanding of ECM, going beyond its structural role to actively influence adhesion, proliferation and cell communication. Attention is provided to collagen types, emphasizing their structural significance and their correlation with changes in collagen levels and lymph node metastasis in VSCC.

8. Conclusion

The present study acknowledges the rising incidence of vulvar cancer and the limitations of current treatment approaches, particularly in incurable or metastatic cases. It advocates for the exploration of novel therapeutic pathways and targets based on the detailed analysis of ECM components in VSCC. Recognizing the complex interactions within the TME underscores the necessity for innovative and targeted therapeutic approaches to enhance outcomes for individuals affected by VSCC. Further research and clinical exploration of these ECM targets could pave the way for more effective therapeutic strategies in the management of VSCC.

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Authors' contributions

EI and KCD conducted the literature review and drafted the manuscript. RM, KO, SI and HND contributed to the writing of the manuscript and made corrections. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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