Review Article

Matrisomics: Beyond the extracellular matrix for unveiling tumor microenvironment

Jiwon Hong [a,b,1], Hyo Joon Jin [a,1], Mi Ran Choi [a,1], Darren Wan-Teck Lim [c], Jong-Eun Park [d], You-Sun Kim [a,b], Su Bin Lim [a,b,*]

[a] *Department of Biochemistry & Molecular Biology, Ajou University School of Medicine, Suwon 16499, Republic of Korea*
[b] *Department of Biomedical Sciences, Graduate School of Ajou University, Suwon 16499, Republic of Korea*
[c] *Division of Medical Oncology, National Cancer Centre, Singapore 168583, Singapore*
[d] *Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, 291 Daehak-Ro, Yuseong-Gu, Daejeon 34141, Republic of Korea*

ARTICLE INFO

ABSTRACT

The matrisome, a group of proteins constituting or interacting with the extracellular matrix (ECM), has garnered attention as a potent regulator of cancer progression. An increasing number of studies have focused on cancer matrisome utilizing diverse -omics approaches. Here, we present diverse patterns of matrisomal populations within cancer tissues, exploring recent -omics studies spanning different '-omics' levels (epigenomics, genomics, transcriptomics, and proteomics), as well as newly developed sequencing techniques such as single-cell RNA sequencing and spatial transcriptomics. Some matrisome genes showed uniform patterns of upregulated or downregulated expression across various cancers, while others displayed different expression patterns according to the cancer types. This matrisomal dysregulation in cancer was further examined according to their originating cell type and spatial location in the tumor tissue. Experimental studies were also collected to demonstrate the identified roles of matrisome genes during cancer progression. Interestingly, many studies on cancer matrisome have suggested matrisome genes as effective biomarkers in cancer research. Although the specific mechanisms and clinical applications of cancer matrisome have not yet been fully elucidated, recent techniques and analyses on cancer matrisomics have emphasized their biological importance in cancer progression and their clinical implications in deciding the efficacy of cancer treatment.

1. Introduction

The extracellular matrix (ECM) is a complex meshwork comprising collagens, glycoproteins, proteoglycans, and numerous bioactive molecules [1]. It not only provides architectural support and anchorage for cell adhesion but also serves as a reservoir for diverse molecules, including growth factors, cytokines, and ECM-remodeling enzymes. Additionally, interactions between the ECM and surrounding cells can induce various signaling pathways, controlling cell proliferation,

survival, and migration [2,3]. Therefore, the ECM provides important biophysical and biochemical cues that regulate cell behavior.

The ECM constitutes one of the principal components of the tumor microenvironment (TME), and its dysregulation is a hallmark of tumor progression [3]. Mounting evidence suggests that not only stromal cells but also cancer cells can serve as significant sources of the ECM within the TME [3]. Throughout cancer development, tumor cells actively remodel their surrounding ECM through various mechanisms, including the secretion of ECM-degrading enzymes and the synthesis of ECM

proteins [1]. Generally, excessive collagen deposition is observed in various cancers, contributing to heightened matrix stiffness [4]. This increased matrix stiffness can fuel diverse pathways in tumor progression, such as tumor growth, migration, metastasis, and resistance to anticancer therapies [1]. Moreover, gradual ECM breakdown by dysregulated ECM-remodeling enzymes may decrease matrix density, facilitating detachment and migration of cancer cells [4]. Achieving a comprehensive understanding of the TME's role in promoting or inhibiting cancer progression necessitates characterizing the aberrant deposition and degradation of ECM components in cancers.

For a better definition of ECM components, overcoming the complexity of ECM characterization in vivo, Naba and colleagues screened core ECM components through bioinformatic approaches and further characterized the proteins that are related to the ECM but are not included in the core ECM components [2]. To comprehensively understand the global ECM composition across diverse physiological contexts, they further developed the concept of the "matrisome", which encompasses ECM proteins and associated factors identified through proteomic analyses [2]. They classified matrisome genes into core matrisome genes encoding structural ECM components and matrisome-associated genes that interact with or remodel the ECM. Core matrisome genes consist of ECM glycoproteins, collagens, and proteoglycans, while matrisome-associated genes comprise ECM-affiliated proteins, ECM regulators, and secreted factors [5].

Due to its influence on all cellular processes involved in cancer initiation, progression, and dissemination, the ECM emerges as a novel source of potential biomarkers and therapeutic targets in cancer research [6,7]. The identification of cancer matrisome across diverse cancer contexts has led to the discovery of novel ECM proteins that contribute to cancer progression and dissemination [8]. Further, the growing body of matrisome studies has facilitated the identification of cancer biomarkers for diagnosis, prognosis, and prediction of drug responses [8]. Advances in next-generation sequencing techniques have accelerated comprehensive genome-wide characterization of cancer-specific matrisome genes across diverse -omics levels [9,10]. Specifically, matrisomal heterogeneity within the TME has been revealed through single-cell RNA-sequencing (scRNA-seq) and spatial transcriptomics (ST) [11]. However, to date, no systemic review encompassing diverse -omics data on cancer matrisome studies has been reported.

In this review, we have compiled matrisome studies from the past five years to comprehensively characterize the dysregulated matrisome landscape across multiple cancer types. We have incorporated a wide array of -omics approaches, including genomics, epigenomics, transcriptomics, and proteomics, and summarized the aberrantly regulated matrisome genes in diverse cancers. Additionally, we have addressed recent studies on matrisomal heterogeneity using scRNA-seq and ST analyses to provide new insights into the cancer matrisome. We further highlight several matrisome genes supported by experimental validation for their implications in tumor progression. Lastly, we demonstrate that cancer-specific matrisome genes have exhibited significant efficacy in cancer diagnosis, prognosis, and predicting drug responses in many studies, as well as in developing cancer vaccines.

2. Matrisomics in cancer

Matrisome dysregulation in various cancers has been widely identified through recent 5-year -omics studies at different levels of gene regulation, including epigenomics, genomics, transcriptomics, and proteomics (Fig. 1). Genomic analysis has unveiled mutations and copy number variations in matrisome genes, while epigenomic analysis has centered on the methylation status of matrisome genes in cancers. Transcriptomic and proteomic analyses have revealed dysregulated gene expression in bulk tissues.

2.1. Collagens

Excessive collagen deposition is frequently observed in tumor tissues and is responsible for ECM stiffness [3]. Throughout recent studies on cancer matrisomics, most types of collagens have exhibited dysregulation in various cancers (Fig. 1). Genomic alterations in collagen genes have been reported in various cancer types. Holstein and colleagues investigated mutations in post-translational modifications (PTM) of matrisome genes using the TCGA Pan-Cancer cohort and found that COL3A1 and COL14A1 were mutated in multiple tumor types [12]. Another study on mutations using the TCGA breast cancer dataset revealed that COL6A3, COL12A1, and COL14A1 exhibited high frequencies of mutation in patients with breast cancer [13], while COL6A2, COL7A1, COL11A1, and COL12A1 were frequently mutated in TCGA stomach cancer datasets [14].

Pan-cancer transcriptome analyses of the COL4 and COL6 families exhibited different gene regulation depending on cancer types, with an overall upregulation of these genes observed in most cancers [15,16]. Additional pan-cancer analysis studies revealed that COL10A1 and COL11A1 are upregulated in various tumor tissues [17,18]. Yuzhalin and colleagues established a 9-gene signature including 3 collagens (COL1A1, COL10A1, and COL11A1), which was significantly upregulated across diverse cancer types [19].

Furthermore, transcriptomic analysis of human and murine ovarian cancer showed enhanced expression of diverse collagens compared to normal tissues (COL1A1, COL1A2, COL3A1, COL5A2, COL7A1, COL10A1, COL11A1, and COL24A1) [20–22]. In addition, through multi-omics profiling, COL1A1 and COL11A1 expression was shown to be correlated with disease score in ovarian cancer metastases [23]. In breast cancer, COL1A1, COL5A1, COL5A2, COL6A1, COL11A1, and COL14A1 are highly enriched at the transcriptome level, whereas COL6A6 is downregulated [24,25]. Transcriptomic analysis of stomach cancer showed COL5A2 and COL12A1 upregulation in cancers [26,27], while proteomic analysis revealed COL10A1 as the only tumor-specific protein [28].

Proteomic analyses of pancreatic ductal adenocarcinoma (PDAC) showed a wide range of dysregulation in collagen composition in tumor tissues, with most collagens upregulated in tumors except for the downregulation of COL4A2 [29,30]. Proteomic analysis of liver cancers showed overexpression of COL3A1 and COL12A1 and decreased expression of COL4A1 and COL4A2 in tumor tissues [31,32]. Additionally, proteomic analysis of breast cancer indicated progressive upregulation of COL12A1 as the disease progresses [33,34].

2.2. ECM glycoproteins

Glycoproteins represent one of the most dysregulated groups within the cancer matrisome (Fig. 1). Some glycoproteins are commonly upregulated or downregulated across various types of cancers compared to normal tissues of their primary sites, implying their involvement in cancer progression mechanism regardless of cancer types. For example, CTHRC1, a protein regulating collagen ECM deposition [35], not only exhibits enhanced gene expression and protein abundance compared to normal tissue but also displays highly amplified copy numbers in most of the 30 cancer types [10]. On the other hand, DPT, LAMB2, LGI4, MMRN1, PCOLCE2, RELN, SRPX, and TNXB are consistently downregulated in more than 10 cancer types [17,34].

A significant body of research has indicated a notable relationship between different -omics analyses, particularly a positive correlation between the level of copy number amplification, transcript expression, and protein abundance. CILP2 shows high mRNA expression along with increased copy number and decreased methylation in most cancers [36]. Otherwise, in low-grade glioma, where CILP2 displays lower mRNA expression than corresponding normal tissue, genetic analysis revealed a significant decrease in copy number [36]. However, copy number variation does not always correlate with gene expression profile.

Classification	Matrisome	Epigenomics	Genomics	Transcriptomics	Proteomics	Adrenal gland	Biliary tract	Bladder	Blood	Brain/CNS	Breast	Colon/Rectum	Esophagus	Head and neck	Kidney	Liver	Lung	Ovary	Pancreas	Prostate	Sarcoma	Skin	Stomach	Thymus	Thyroid	Uterus/Cervix
Collagen	COL1A1			+	+																					
	COL3A1		M	+	+								*				*	*				*			*	*
	COL4A1			+/-	-																					
	COL4A2			+/-	-																					
	COL5A2			+	+																					
	COL6A1			+/-	+																					
	COL6A2		M	+/-	+																				*	
	COL10A1			+	+																					
	COL11A1		M	+	+																		*			
	COL12A1		M	+	+						*												*			
	COL14A1		M	+	+						*	*			*							*				
Glycoprotein	AGRN			+	+																					
	CILP2	Me-	M/+	+/-		*	*	*	*	*	*	*	*	*		*		*			*	*	*	*	*	*
	COMP			+	+																					
	CTHRC1		M/+/-	+	+	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*
	DPT			-																						
	FBN1	Me+	M/+/-	+/-	+	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*			*	*
	FN1			+	+																					
	HMCN1		M							*	*	*					*		*				*			*
	LAMB2				-																					
	LGI4			-																						
	MFAP2		-	+	+						*															
	MMRN1			-																						
	MXRA5			+/-	+																					
	PCOLCE2			-																						
	POSTN			+	+																					
	PXDN			+/-	+																					
	RELN		M	-						*	*	*				*	*	*	*							*
	SPARC			+	+																					
	SPP1			+	+																					
	SRPX			-																						
	TGFBI		M/+/-	+/-	+	*	*	*	*	*	*	*	*	*		*	*		*	*	*			*	
	THBS1			+/-	+																					
	TNXB			-	-																					
Proteoglycan	BGN			+/-	+																					
	OGN			-	-																					
	PODNL1	Me+/-	M/+/-	+/-		*		*	*	*	*					*	*	*			*				*	*
	VCAN	Me+	M	+/-	+	*					*															
ECM regulator	ADAM33			-																						
	BMP1			+/-																						
	CST1			+																						
	LOX			+/-	+																					
	MASP1			-																						
	MMP1	Me+		+/-									*													
	MMP7	Me-		+									*													
	MMP9	Me-		+									*													
	MMP11	Me-		+									*													
	MMP12	Me+		+									*													
ECM-affiliated protein	ANXA1			+/-	+																					
	ANXA10			+/-																						
	ANXA2			+/-	+																					
	ANXA5			+/-	+																					
	ANXA6			-	+																					
	MUC16		M			*		*		*	*	*	*	*	*	*	*	*	*			*	*	*	*	*
	MUC5B		M							*	*	*					*					*	*			*
Secreted factor	FLG		M					*			*	*	*	*			*	*	*	*		*	*			*
	INHBA		M/+	+	+																		*			
	S100A2			+/-																						
	S100A4			+/-	+																					
	S100A6			+/-	+																					
	S100A8			+/-	+																					
	S100A9			+/-	+																					

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Fig. 1. Matrisomics results across diverse cancer types. The collected results for cancer matrisomics in recent five years were summarized with studied -omics types and cancer types. Matrisome genes involved in more than four cancer types have been displayed. Me$^+$ in epigenomics indicates hypermethylation; Me$^-$ indicates hypomethylation of the gene. Genomic alterations include mutations (M), copy number amplification (+), and deep deletions (−). In transcriptomic and proteomic analyses, upregulated expression (+) and downregulated expression (−) were marked, respectively. Organ names represent the primary sites of cancers. Light, medium, and dark red (or blue) represent transcriptomic upregulation (or downregulation), proteomic upregulation (or downregulation), and both upregulation (or downregulation) in specified cancer types, respectively. The cancers reporting conflicting results were marked with both red and blue colors. Gray color indicates no significant transcriptomic changes of the gene in specified cancer types. Asterisk represents the presence of epigenomic or genomic changes of the gene in the cancers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

MFAP2, despite showing upregulated gene expression [19], presents high copy number loss frequencies in breast cancer [13].

Unlike THBS2–4, which are uniformly upregulated in various cancers [20,37,38], gene expression of members in the laminin and tenascin family shows different patterns from each other. In ovarian cancer, LAMA1/2/4 and LAMB1/2 are downregulated, while LAMA5, LAMB3, and LAMC2 are upregulated [39]. However, most laminin genes are significantly overexpressed in pancreatic cancer [40]. Similarly, while TNC is abundant in breast [34], lung [38] and pancreas cancers [29], TNXB, another member of the tenascin family, shows decreased protein abundance in those cancers [17].

The same gene can exhibit different deregulation patterns according to the cancer types. PXDN is overexpressed in esophageal, kidney, and prostate cancers, but underexpressed in bladder, colorectal, and liver cancers [41]. Similarly, decreased abundance of LAMA5 is detected in liver metastasis of colorectal cancer and intrahepatic cholangiocarcinoma (iCCA) compared to intact tissue [31,42], whereas its gene expression is upregulated in human ovarian cancer [20]. Furthermore, gene expression patterns can differ between cancer types sharing the same primary organ and even between subtypes in the same cancer. For example, ELN, forming elastic fiber that gives resilience and elasticity to various organs [43], is upregulated in invasive lobular carcinoma compared to invasive ductal carcinoma (IDC) [24]. Similarly, non-small cell lung cancer (NSCLC) consists of two histologic subtypes, adenocarcinoma and squamous cell carcinoma, which can be distinguished by the expression pattern of collagen fibrillogenesis regulator AEBP1, basement membrane NTN5, and VWA5B2 [44]. This suggests that matrisome expression patterns might play a significant role in subdividing cancers that are not yet subtyped.

Recent studies have also focused on the relation between genetic expression and disease progression. Such research revealed that transcript expression and protein abundance of AEBP1, COMP, FBLN2, FN1, MFAP2, and MXRA5 in the tumor tissue have a positive correlation with disease progression, while ABI3BP, LAMA4, LAMC1, and TNXB show a negative correlation [23,29]. Moreover, dysregulation of each gene is not consistently regulated, but exhibits various patterns during tumor progression, indicating their participation in specific steps or functions of tumorigenesis and the metastatic cascade. For instance, FGA, FGB, FGG, FN1, SPARC, SPP1, THBS1/2, and TNC show increased protein abundance in the early phase of murine pancreatic cancer but are significantly decreased in the late phase [29].

The fluctuation of glycoproteins also correlates with the tumorigenic transformation of other matrisomal group members or the TME. Remarkably, THBS2 and TNC are highly upregulated in IDC and co-localize with straight collagen fibers, a histologic feature of IDC, suggesting their involvement in collagen fiber reorganization [34]. In addition, a high frequency of citrullination of glycoproteins, such as FGA, FN1, and POSTN, in colorectal, breast, and ovarian cancers, appears to be related to the infiltration of inflammatory cells into cancer tissue [45].

It seems clear that turbulence in the matrisomal population occurs during cancer progression, but this does not always indicate that dysregulated matrisome members play a critical tumor-promoting role. For example, SPARC, which regulates cell-matrix interactions, growth factor efficacy, and expression of matrix metalloproteinases (MMPs) through binding to other proteins in the ECM [46], showed homogenously high transcriptomic expression among all colorectal cancer patients studied,

but its silencing did not affect colorectal cancer cell growth in vitro [47]. Therefore, dysregulated matrisome genes suspected of playing a critical role in cancer should be verified through experiments to confirm their functional significance.

2.3. Proteoglycans

Among proteoglycans, BGN, PODNL1, and VCAN are the most mentioned for showing upregulated gene expression and/or significantly higher protein abundance in various types of cancer tissues compared to their healthy control (Fig. 1). These genes also show increasing gene expression and/or protein abundance as the disease progresses [23]. Of the two small leucine-rich proteoglycans, BGN is shown as the strongest contributor to discriminating murine pancreatic cancer samples by tumor progression [29], and PODNL1 shows increased expression among various cancers as well as increased tumor-promoting TGF-β signaling pathway [9]. Conversely, OGN displays significant downregulation in gene expression and/or protein abundance in various types of cancers [17,18,34].

While various matrisome genes exhibit consistent patterns of dysregulation across species and cancer types, some genes display different regulation profiles depending on the species and cancer type. For example, DCN appears to be increased and plays an important role in distinguishing steps of cancer progression in murine PDAC [29]. However, its gene expression significantly decreases in liver cancer [37] and colorectal cancer [48]. Moreover, proteoglycans display a range of epigenetic and genetic changes. Interestingly, among various cancers, VCAN emerges as one of the most common loci for disruptive PTM mutations, potentially impairing the protein's function within the TME [12]. Additionally, FMOD demonstrates hypermethylation in prostate cancer [49], alongside increased protein abundance in breast [34] and colorectal cancer [50].

2.4. ECM regulators

ECM regulators frequently undergo alterations in gene regulation in diverse cancers (Fig. 1), thus changing the ECM composition and consequently affecting cancer progression [4]. The lysyl oxidase (LOX) family genes have been observed to be upregulated in several cancers. Sflomos and colleagues showed LOXL1 upregulation and LOXL2 downregulation in breast cancer at the transcriptome level [24]. Notably, LOXL1 was highly upregulated in cancers with a three-fold difference, and its silencing prevented tumor progression, revealing its cancer-promoting role. Furthermore, proteomic analysis showed LOX and LOXL1 upregulation in breast cancer [34].

The expression of LOX family genes (LOX and LOXL1–4) is elevated in low-grade gliomas [51]. Among them, LOXL2 exhibits a progressive increase from low-grade gliomas to glioblastoma. Interestingly, other ECM regulators (CTSB, SERPINE1, and PLOD2) show a strong correlation with LOX genes. The transcriptional levels of LOXL2 expression are also elevated in pancreatic tumor tissues [52]. In stomach cancer, LOX upregulation has been observed in cancers by TCGA transcriptomic analysis [28]. Moreover, a comprehensive analysis of LOX expression in various cancers emphasizes remarkable upregulation of LOX in renal clear cell carcinoma, with a significant correlation with COL5A1 and COL1A2 [53].

For MMPs, numerous studies have highlighted their importance in

multiple cancer progression. Pan-cancer transcriptomic analyses have indicated that MMP1, MMP7, MMP9, MMP11, and MMP12 transcripts are upregulated in various cancer types, with the exception of MMP1 downregulation in kidney cancer [17,18]. Moreover, in colon cancer, multiple MMP transcripts are dysregulated, including upregulated MMPs (MMP1, MMP3, MMP7, and MMP9–14) and downregulated MMPs (MMP15, MMP17, MMP25, and MMP27–28) [54]. Interestingly, epigenomic analysis has revealed that most upregulated MMPs exhibit lower promoter methylation, whereas most downregulated MMPs show higher promoter methylation in colon cancer [54]. Notably, MMP13 is positively correlated with CTHRC1, identified as a major pan-cancer ECM regulator, indicating its role in regulating ECM across multiple cancers [10]. Additionally, transcriptomic analysis of human and murine ovarian cancer has shown enhanced expression of MMPs (MMP3, MMP7, MMP9–11, and MMP13) and other ECM regulators (LOXL1, ADAM8, ADAM10, ADAM17, and ADAMTS14) in cancer [20].

Other ECM regulators have also shown significant alterations in cancers. Pan-cancer transcriptome analysis has revealed that ADAM33 and MASP1 are downregulated in most cancer types studied, whereas CST1 shows upregulation in those cancers [17]. BMP1 transcripts are overexpressed in multiple cancers, particularly reflecting a poor prognosis in kidney and stomach cancers [55,56]. Titmarsh and colleagues identified matrisome protein signatures in NSCLC [38]. Diverse ECM regulators, such as MMPs (MMP2, MMP12, and MMP14), cathepsins (CTSB and CTSS), and ADAMTS16, have been found to be upregulated in tumor tissues in this study. CTSB transcripts are also upregulated in human ovarian cancers [22]. In addition, multi-omics profiling revealed that CTSB and CTSD expression is correlated with disease score in ovarian cancer metastases [23]. Proteomic analysis of PDAC has shown increased expression of diverse ECM regulators (F13A1, LOX, PLOD2, and TGM2) in cancers [29]. TGM2 is also upregulated in liver cancer [31], as opposed to its low expression in breast cancer [34] at the proteome level.

2.5. ECM-affiliated proteins

Various genes encoding ECM-affiliated proteins have been studied for their altered regulation in tumors at different -omics levels (Fig. 1). Pan-cancer analysis of the annexin family revealed different expression profiles of annexin genes across cancers, implying that annexins are closely related to tumor progression in a tissue-dependent manner [57]. In addition, proteomic analyses of several cancer types have found that annexins and galectins are generally upregulated in tumors. In PDAC, multiple galectins (LGALS1–4 and LGALS9) show increased expression in cancers [29]. LGALS8 is increased in hepatocellular carcinoma (HCC) [32]. In colon cancer liver metastases, several galectins (LGALS3 and LGALS7) and annexins (ANXA1–2) exhibit upregulation in tumors [42]. In addition, various genes encoding ECM-affiliated proteins are positively correlated with disease score in ovarian cancer metastases, including galectins (LGALS1 and LGALS3), annexins (ANXA1 and ANXA4–7), and other genes (SDC1, CLEC18B, and MUC1) [23], suggesting their implications in cancer progression.

Other ECM-affiliated proteins are also dysregulated in diverse cancers. Proteomic analysis of PDAC has shown that C1QA, C1QC, and GREM1 are overrepresented in cancers [42]. Transcriptomic analysis of colon cancer found SDC4 upregulation in colon cancer cells isolated from resected tissues [47], whereas SDC1 is upregulated in breast cancer and enriched in ECM-receptor interaction [25]. Genomic alterations have also been reported involving ECM-affiliated proteins in cancers. Pan-cancer genomic analysis has shown that MUC16 and MUC5B are mutated in multiple cancers [58]. Interestingly, another pan-cancer genomic analysis regarding PTM-disruptive mutations reported that MUC16 is among the most frequent targets of PTM mutations, suggesting its significant impact on the structure and function of ECM [12].

2.6. Secreted factors

As important components of matrisome, secreted factors have been subjected to genomic alterations in cancers (Fig. 1). Pan-cancer genomic analysis revealed that FLG is mutated in 14 tumor types [58]. In addition, PTM-disruptive mutations were most frequently observed in FLG and HRNR in pan-cancer analysis [12]. Notably, INHBA show copy number amplification and upregulated gene expression in most cancers [59]. Particularly, INHBA is upregulated at both transcriptomic and proteomic levels in stomach cancers, highlighting its potential as a stomach cancer biomarker [59].

Transcriptomic analysis of colon cancer exhibited significant upregulation of diverse secreted factors (GDF11, GDF15, HHIP, TGFA, IL18, SFRP1, and WNT11) in primary colon cancer cells [47]. Among them, GDF11 was further validated to be associated with tumor progression. In addition, multiple secreted factors were found to be upregulated in mouse and human ovarian cancer, including the S100 family (S100A1 and S100A16), Wnt family (WNT6, WNT7B, and WNT10A), TNFSF family (TNFSF4 and TNFSF11), and others (CCL25, EGF, GDF11, BTC, CXCL5, IL1RN, FGF18, NRG1, MEGF10, and PDGFC) [20].

Proteomic analysis of PDAC showed a wide range of alterations in secreted factors, with LEFTY1, WNT2B, CXCL13, TGFB1, and BMP overrepresented in cancers [30]. Pan-cancer analyses have shown that S100 family genes exhibit distinguishable fluctuation in transcript expression levels depending on the different cancer types [18,60]. Notably, S100 family proteins (S100A4, S100A6, and S100A8–11) are the most abundant and overrepresented secreted factors in pancreatic cancers [30]. S100 family proteins (S100A4, S100A6, and S100A11) are also upregulated in colon cancer liver metastases [42]. Several secreted factors, such as WIF1, CXCL2, IL6, and HHIP, were shown to be downregulated in various tumors by pan-cancer transcriptomic analysis [18]. They were incorporated into the tumor matrisome index (TMI), which holds diagnostic and prognostic value across multiple cancers [18].

3. Matrisomal heterogeneity

In cancer research, advances in single-cell RNA-sequencing (scRNA-seq) have enabled the identification of altered gene regulation at the cell type level. Furthermore, spatial transcriptomics (ST) have allowed us to investigate cancer-associated genes in different tumor regions. These techniques have been applied to identify cancer matrisome genes in diverse tumor tissues, advancing our understanding of specific cell types that express them and their implications in different tumor regions (Table 1).

Stromal cells constituting the ECM are the canonical sources of ECM molecules. Specifically, a wide range of ECM molecules in the TME could be attributed to the diverse fibroblast subtypes residing in tumor tissues, including cancer-associated fibroblasts (CAFs). Zhang and colleagues identified COL11A1+ fibroblasts which abundantly express diverse types of collagens and other matrisome genes (FN1, LOX, MMPs, POSTN, TIMPs, and TNC) in multiple cancers [61]. Notably, they confirmed the cancer-specific existence of COL11A1+ fibroblasts, promoting tumor progression. PODNL1, suggested as a potential pan-cancer biomarker, was shown to be highly produced by CAFs in bladder and head and neck cancers [9]. Another study on head and neck carcinomas showed that fibroblasts in tumor tissues highly express EGFL6, MASP1, and P4HA1 compared to other cell types [62].

Fibroblasts and CAFs highly expressing diverse matrisome genes are also observed in individual studies of breast, kidney, and lung cancers [33,44,63]. In ovary and stomach cancers, POSTN[high] CAFs are observed in tumor tissues [64,65]. Notably, ST analysis of ovary cancers revealed that POSTN[high] CAFs are more enriched in the tumor edge, highlighting their relevance to patient survival [64]. Another ST study on multiple cancer types has shown that ECM-CAFs, featured by high matrisome expression, are also highly enriched in the tumor boundary [66]. Highly expressed matrisome genes in ECM-CAFs are involved in interacting

Table 1
Matrisomal heterogeneity in the tumor microenvironment attributed by various sources.

Cell type	Subtype	Cancer type	Cell type enrichment	Highly expressing matrisome genes	Gene expression comparison	Spatial enrichment	Ref.
Stromal cells	CAFs	Bladder, head and neck		PODNL1	vs. other cell types		[9]
		Breast		COL12A1	vs. other cell types		[33]
		Kidney		COL4A1, COL6A1, COL6A2, COL6A3, COL12A1, FBN1, FN1, HSPG2, LAMA4, LAMB2, LUM	vs. other cell types		[63]
		Lung		CILP2, COL7A1, COL10A1, COL11A1, CTHRC1, SPP1	Tumor vs. adjacent non-tumor		[44]
		Ovary		POSTN	vs. other cell types	Tumor edge	[64]
		Stomach	In tumor	POSTN	vs. other cell types		[65]
	ECM-CAFs	Breast, colon, kidney, liver, pancreas	In tumor vs. adjacent normal tissue	FN1, GREM1, LAMA2, LAMB1, NID1, PLAU, SLIT2, TGFB1	vs. other CAFs	Tumor edge	[66]
	Fibroblasts	Head and neck		EGFL6, MASP1, P4HA1	vs. other cell types		[62]
		Stomach	In tumor vs. normal	COL5A2	Tumor vs. normal	Deep layer	[26]
				IGFBP7	Tumor vs. normal		[67]
	COL11A1+ fibroblasts	Breast, colon, liver, lung, ovary, pancreas, prostate	In tumor vs. adjacent normal tissue	COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, COL8A1, COL8A2, COL10A1, COL11A1, COL12A1, COL15A1, COL16A1, FN1, LOX, LOXL2, MMP2, MMP11, MMP14, POSTN, TIMP2, TIMP3, TNC	vs. other fibroblasts		[61]
	Myofibroblasts	Lung	In tumor vs. normal	COL11A1, SULF1	Tumor vs. normal		[68]
	CST1+ myofibroblasts	Esophagus	In tumor vs. adjacent nonmalignant	CST1	Tumor vs. adjacent nonmalignant		[69]
				COL1A1, COL3A1, CST1, MMP11, POSTN	vs. other fibroblasts		
Non-stromal cells	Cancer cells	Bladder, brain, head and neck, kidney, ovary		PODNL1	vs. other cell types		[9]
		Brain		BGN, COL9A1, COL9A2, COL11A1, COL11A2, FMOD, VCAN	vs. other cell types		[70]
		Head and neck		EGFL6, MASP1, P4HA1, SPP1	vs. other cell types		[62]
		Lung		CILP2, COL7A1, COL10A1, COL11A1, CTHRC1, SPP1	Tumor vs. adjacent non-tumor		[44]
	NT5E+ cancer cells	Sarcoma		BGN, COL1A1, COL1A2, COL4A2, COL5A1, COL5A2, COL6A2, COL11A1, ECM1, EFEMP2, FBN1, FMOD, FN1, FSTL1, IGFBP2, IGFBP4, LGALS1, LOX, LOXL1, MGP, MMP1, SERPINE1, SPARC, TIMP1, TNC	vs. NT5E- cancer cells	Tumor edge / invasive area	[71]
	CDKN2A+ cancer cells	Colon		LAMC2, MMP7	vs. CDKN2A- cancer cells	Invasive area	[72]
	CTCs	Lung		CXCL13, GREM1, MMP1, MMP12	Metastatic cancer vs. nonmetastatic cancer		[73]
		Lung (brain metastases)		CTSH, GDF15, LGALS3, MDK, MMP7, MUC1, S100A13, SFTA2, SFTPB, SLPI	Tumor vs. normal		[74]
	Endothelial cells	Breast		MMP7, POSTN	Tumor vs. adjacent normal		[75]
		Liver		ADAM15, ADAMTS5, COL15A1, ESM1, LAMA4, VWA1	Tumor vs. non-tumor		[76]
	PGF+ endothelial tip cells	Breast, kidney, liver, pancreas	In tumor vs. adjacent normal tissue	ANGPT2, ESM1, NID2, PDGFB, PGF	vs. other stromal cells	Tumor edge	[66]
	Oligodendrocytes	Brain		COL9A2, COL11A2	vs. other cell types		[70]
	Macrophages	Head and neck		P4HA1, SPP1	vs. other cell types		[62]
	Microglia and monocyte-derived macrophages	Brain		VCAN	vs. other cell types		[70]
	Cathepsin-secreting macrophages	Esophagus		CSTA, CSTD	Tumor vs. adjacent nonmalignant		[69]
	CD11c+/LYZ+ macrophages	Lymphoma	In tumor	CCL22, COL1A1, CSTB, MMP9, MMP12, SPP1, TIMP1	vs. other cell types		[77]
ND	ND	Brain		BGN, COL2A1, COL9A1, COL9A2, COL11A1, COL11A2, FMOD, VCAN		Malignant region	[68]
		Thyroid		POSTN		Invasive area	[78]

*Abbreviations: CAF, cancer-associated fibroblast; CTC, circulating tumor cell; ECM, extracellular matrix; ND, not determined.

with malignant cancer cells, promoting tumor progression. In addition, COL5A2[high] fibroblasts are more enriched in tumor tissues than normal tissues in stomach cancers [26]. Interestingly, they reside abundantly in the deep layer of tumors, suggesting their association with cancer invasion. Fibroblasts in stomach cancers also highly express IGFBP7 [67].

Myofibroblasts are another subtype observed in tumor tissues with abundant expression of matrisome genes. In lung cancers, myofibroblasts with enhanced COL11A1 and SULF1 expression are more enriched in tumors compared to normal tissues [68]. In esophagus cancers, CST1+ myofibroblasts express high levels of COL1A1, COL3A1, CST1, MMP11, and POSTN, with higher cell enrichment in tumors compared to adjacent nonmalignant tissues [69].

Notably, non-stromal cells, such as cancer cells and immune cells, have emerged as important contributors to the cancer matrisome. Across diverse tumor types, PODNL1 is highly expressed in cancer cells as revealed by pan-cancer analysis [9]. Moreover, in glioblastoma, scRNA-seq analysis highlighted that brain cancer cells play a predominant role in expressing multiple matrisome genes such as collagens, BGN, FMOD, and VCAN, surpassing other cell types [70]. In NSCLC, cancer cells are found to be concurrent contributors to the cancer matrisome alongside CAFs [44]. Similarly, in head and neck cancers, cancer cells demonstrate elevated expression of SPP1 along with EGFL6, MASP1, and P4HA1, which are typically produced by fibroblasts in those cancers [62]. Specifically, NT5E+ cancer cells identified in Ewing sarcoma exhibit a wide range of matrisome gene expression, concentrated along tumor borders and invasive foci, showcasing mesenchymal properties [71]. Additionally, Park and colleagues revealed that infiltrative colon cancer cells undergo spatial evolution as they move from the center to the invasive front, acquiring senescent phenotypes featured by CDKN2A expression [72]. Particularly, MMP7^{high} senescent tumor cells (STCs) are prominently observed in invasive front of colorectal cancer tissues, showing higher metastatic potential than STCs not expressing MMP7 or non-STCs [72].

Circulating tumor cells (CTCs) present in cancer patients are important in cancer metastasis. Notably, CTCs have exhibited their capacity to remodel the cancer matrisome through the expression of specific matrisome molecules. In our previous study, we reported that matrisome gene signatures in CTCs could predict metastatic cancers in patients with NSCLC [73]. Specifically, MMP1 and MMP12 were shown to be more abundant in metastatic and recurrence-prone cancers in our investigation. Another scRNA-seq analysis on CTCs found in lung cancer brain metastases by Ruan and colleagues revealed that CTCs in the cerebrospinal fluid of cancer patients express higher levels of multiple matrisome genes, including MMP7, MDK, SFTPB, SLPI, and GDF15, compared to cerebrospinal fluid cells of normal controls [74].

Endothelial cells contribute to matrisome production as well. In breast cancer, endothelial cells within tumor tissues have displayed upregulated expression of MMP7 and POSTN compared to adjacent normal tissues [75]. Similarly, endothelial cells in liver cancers have shown a broader range of matrisome upregulation in tumor tissues, accompanied by increased expression of ADAM15, ESM1, LAMA4, VWA1, etc. [76]. Specifically, PGF+ endothelial tip cells, which highly express ANGPT2, ESM1, NID2, PDGFB, and PGF, are more abundantly present in multiple tumor tissues compared to adjacent normal tissues [66]. Further ST analysis in the study has shown a high enrichment of this cell type in tumor edge regions.

Macrophages present in the TME also play a role in ECM remodeling through the secretion of various matrisome molecules. In head and neck cancer, macrophages are the primary producers of P4HA1 and SPP1 compared to other cell types [62]. Mirzaei and colleagues identified microglia and monocyte-derived macrophages with high expression of VCAN through scRNA-seq analysis of glioblastoma tissues [70]. In this study, oligodendrocytes in tumor tissues exhibited enhanced collagen production. In addition, Dinh and colleagues identified cathepsin-secreting macrophages with upregulated expression of CSTA and CSTD in esophagus tumor tissues [69]. Lastly, Feng and colleagues

identified diverse macrophage subtypes in lymphoma and reported that CD11c+/LYZ+ macrophages are enriched in tumors, expressing diverse matrisome genes such as COL1A1, CSTB, MMPs, SPP1, and TIMP1 [77].

Apart from spatially identifying several cell types expressing matrisome genes, ST analyses revealed the spatial enrichment of various matrisome genes without cell type identification. In brain cancer, a plethora of collagens, along with BGN, FMOD, and VCAN, are notably abundant in malignant tumor regions where highly proliferative cancer cells reside [70]. In thyroid cancer, POSTN was shown to be upregulated in invasive areas [78].

The results from scRNA-seq and ST studies suggest that diverse matrisome genes may undergo dysregulation, particularly at tumor edges, potentially contributing to ECM remodeling and the formation of invasion-prone environment for cancers. In addition, these alterations could be attributed to a wide range of cell types in the TME, including cell types not traditionally recognized as producers of matrisome components (Fig. 2).

4. The roles of matrisome during tumor progression

The process of cancer progression, spanning from primary tumor growth to distant organ metastasis, involves multiple stages known as the metastatic cascade. These stages include primary tumor formation and expansion, angiogenesis, local invasion, intravasation, survival in circulation, extravasation, and metastatic outgrowth [79,80]. Recent research indicates that numerous matrisome components contribute to each step of the metastatic cascade. Here, we highlight several notable matrisome genes whose roles in cancer progression have been experimentally demonstrated (Table 2).

4.1. Collagens

Within the collagen family, COL1A1, COL3A1, and COL12A1 play significant roles in cancer progression. Silencing COL1A1 was shown to decrease migration in colorectal cancer, likely through the WNT/PCP signaling pathway [81]. COL3A1 promotes proliferation and migration of iCCA cancer cells [31]. In addition, COL3A1 is strongly associated with the straightened and aligned architecture of collagen fibers in cancer cells, indicating a more aggressive phenotype in iCCA. Collagen XII (proteins encoded by COL12A1), derived from CAFs within breast tumors, regulates the organization of collagen I and the biomechanics of the matrix. This regulation ultimately promotes cancer cell invasion and facilitates the development of a TME favorable for metastatic dissemination [33].

4.2. Glycoproteins

In thyroid carcinoma, FN1 may activate proliferation, migration, and invasion through the NF-kB pathway [82]. The tumor-promoting roles of FN1 were also demonstrated in melanoma and head and neck squamous cell carcinoma (HNSCC), as silencing FN1 displayed an inhibitory effect on these cancers [83,84]. Particularly, silencing FN1 in melanoma led to cell cycle inhibition with apoptosis and reduced expression of epithelial-mesenchymal transition (EMT)-related proteins [83].

IGFBP7 and AGRN contribute to cancer progression. Specifically, increased expression and secretion of IGFBP7 through the SMAD2/3 signaling pathway in CAFs, stimulated by TGF-β1 from infiltrative-type gastric cancer cells, promote tumor growth, migration, invasion, and the EMT of cancer cells [67]. Additionally, AGRN promotes the EMT of PDAC cells and increases metastasis [85]. Moreover, knockdown of FBN1 and LAMC1 reduced resistance to chemotherapeutics and invasiveness of gastric cancer cells [86].

Meanwhile, suppressing NELL1 and PXDN led to inhibition of proliferation, invasion, and metastasis in osteosarcoma [87] and proliferation and migration in glioblastoma [88], respectively. EFEMP1 also contributes to cancer metastasis. Secretomes from murine osteosarcoma
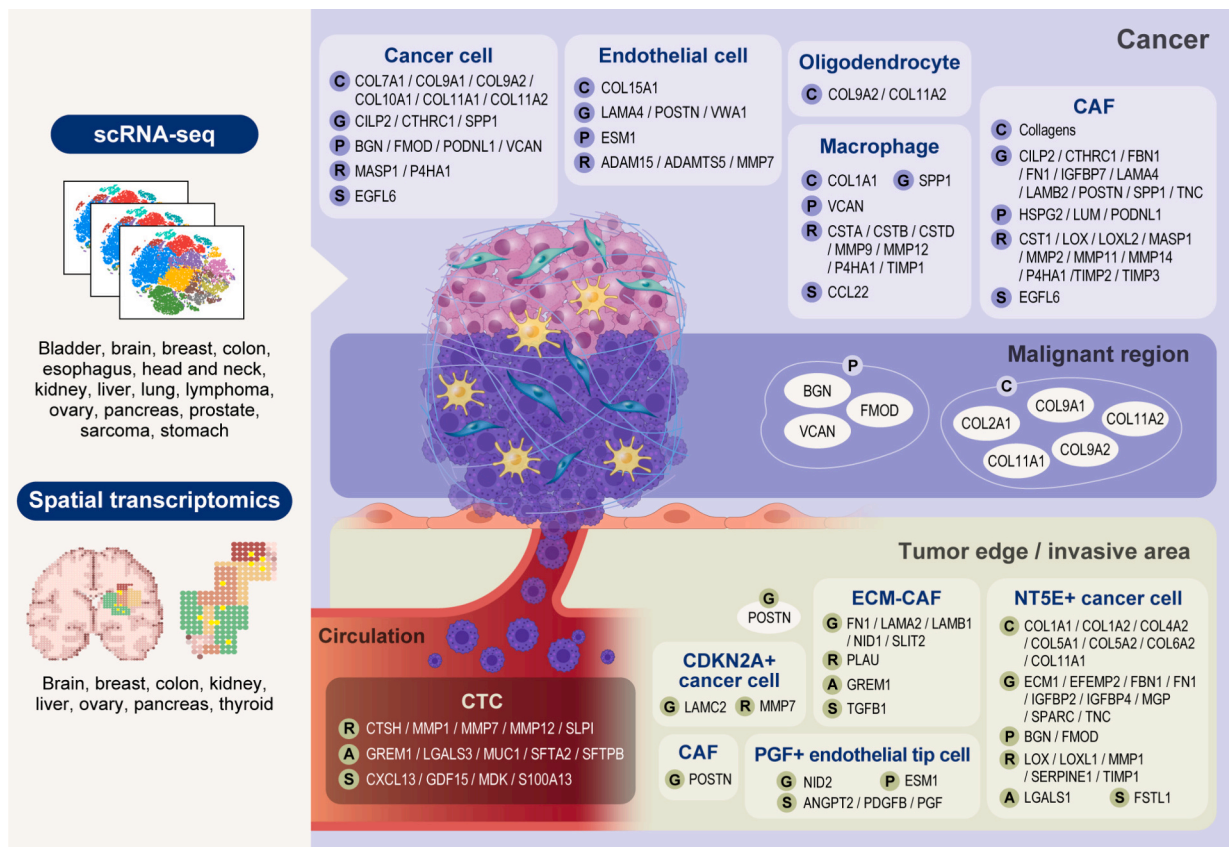
Fig. 2. Matrisome genes involved in different cell types and tumor regions. The analyses of scRNA-seq and ST in cancer matrisome were collected to explore the distribution of cell types producing matrisome genes and their spatial enrichment within cancer tissues. Cell types observed in studied tumor tissues are displayed with highly expressed matrisome genes in each cell type. Malignant region characterized by the presence of more proliferative and malignant cancer cells as well as tumor edge and invasive area are described with specific cell types inside each region. NT5E+ cancer cells in tumor edge and invasive area are observed in Ewing sarcoma tissues. CDKN2A+ cancer cells are found in the invasive area of colon cancer tissues. PGF+ endothelial tip cells are present in tumor edge region in multiple tumor tissues. (CAF, cancer-associated fibroblast; CTC, circulating tumor cell; ECM, extracellular matrix; C, collagens; G, ECM glycoproteins; P, proteoglycans; R, ECM regulators; A, ECM-affiliated proteins; S, secreted factors.)

cells induce alterations in pulmonary structure and the TME, fostering lung PMN formation [89]. In the study, silencing EFEMP1 prevented lung metastasis.

In colorectal cancer cells at primary sites and hepatic metastases, LAMA5 appears to play a crucial role in branching angiogenesis through TNFα/NFκB pathway signaling and by inhibiting endothelial Notch signaling, which is another regulator of branching angiogenesis [90]. LTBP3 is also involved in angiogenesis as well as in the intravasation of cancer cells [91]. Interestingly, the introduction of exogenous LTBP3 restored the angiogenesis-inducing potential of LTBP3-deficient head and neck epidermoid carcinoma cells [91].

Induced by TGFβ from CAFs, activated macrophages secrete TGFBI [92]. Inhibition of TGFBI reduced peritoneal tumor burden but had no effect on tumor weight in the mesentery, while increasing monocyte and unconventional T cell infiltration in tumor. This suggests that TGFBI may promote the growth of ovarian peritoneal metastases by creating an immunosuppressive environment [92].

Conversely, several matrisome genes have been proven to suppress tumor progression. TINAGL1 inhibits primary tumor growth and lung metastasis of triple-negative breast cancer (TNBC) by acting as an inhibitor of EGF-induced EGFR activation and integrin/FAK signaling pathway in cancer cells [93]. In addition, silencing LAMB4 promoted the proliferation and migration of laryngeal and oral squamous cell carcinoma, indicating its inhibitory roles in tumor progression [94].

THBS1 is known to inhibit angiogenesis [95,96]. Overexpression of THBS1 in osteosarcoma cells inhibited tumor angiogenesis in vitro and in xenograft models [97]. Apart from its anti-angiogenic effects,

overexpression of THBS1 repressed migration and invasion in vitro, as well as proliferation and pulmonary metastasis in xenograft models [97].

4.3. Proteoglycans

Recent studies have elucidated the roles of BGN and VCAN during tumor progression. BGN binds to its receptor, known as low-density lipoprotein receptor-related protein 6, on the surface of brain tumor-initiating cells. This interaction activates the downstream Wnt/β-catenin signaling pathway, thereby promoting tumor growth [70]. Overexpression or silencing of VCAN has been shown to respectively promote or hinder proliferation, migration, and invasion in vitro in gastric cancer [98].

In colorectal and ovarian cancers, elevated levels of ESM1 have been associated with tumor growth, angiogenesis both in vitro and in vivo, migration, and invasion. This heightened expression correlates with increased levels of PI3K/Akt/mTOR proteins, cell cycle-related proteins (Cyclin D1 and Cyclin A2), angiogenesis-related proteins (VEGF, COX2, and HIF-1α), and invasion-associated proteins (MMP-2 and MMP-9) [99,100]. However, the overexpression effect of ESM1 was found to be suppressed by an Akt inhibitor [100], suggesting that the PI3K/Akt/mTOR pathway may be a potential mechanism [99,100].

The involvement of FMOD in tumor angiogenesis is well-documented [101,102]. Sengupta and colleagues proposed a mechanism involving FMOD-induced angiogenesis in differentiated glioma, suggesting activation of the integrin/FAK/Src-dependent Notch pathway in endothelial

Table 2
Tumor-promoting or suppressing roles of matrisome genes.

Role	Classification	Matrisome	Involved steps in tumor progression	Studied species	Cancer type	Ref.
Tumor-promoting	ECM glycoprotein	AGRN	Metastasis	Orthotopic xenograft (NSG mice, BxPC3 G1.1 cells)	Pancreas	[85]
		EFEMP1	Metastasis	Xenograft (Athymic Swiss nude mice, 143B cells)	Sarcoma	[89]
		FBN1	Invasion	Hs746T and AGS cells	Stomach	[86]
		FN1	Primary tumor proliferation, migration, invasion	MDM-T85 and MDM-T41 cells	Thyroid	[82]
				A375 and B16F10 cells	Skin	[83]
				PCI-37B cells	Head and neck	[84]
		IGFBP7	Primary tumor proliferation, migration, invasion	XGC-1 and MGC-803 cells	Stomach	[67]
		LAMA5	Angiogenesis, metastatic tumor proliferation	HCT-116 and HT29 cells	Colon	[90]
		LAMC1	Invasion	Hs746T and AGS cells	Stomach	[86]
		LTBP3	Angiogenesis, intravasation	Xenograft (chick embryo and NOD-SCID mice, Hep-3, PC-3, and HT-1080 cells)	Head and neck, prostate, sarcoma	[91]
		NELL1	Primary tumor formation, invasion, metastasis	Orthotopic xenograft (NOD-SCID mice, 143B cells)	Sarcoma	[87]
		PXDN	Primary tumor proliferation, migration	U87 and A172 cells	Brain	[88]
		TGFBI	Metastatic tumor proliferation	Orthotopic mouse model (C57BL/6NCrl mice, HGS2 cells)	Ovary	[92]
	Collagen	COL1A1	Migration	SW480 and SW620 cells	Colon	[81]
		COL3A1	Primary tumor proliferation, migration	Intrahepatic cholangiocarcinoma primary cells	Liver	[31]
		COL12A1	Invasion, metastasis	Orthotopic xenograft (FBV/n mice, co-implantation of PyMT cancer cells and CAFs)	Breast	[33]
	Proteoglycan	BGN	Primary tumor proliferation	Human brain tumor initiating cells; syngeneic mouse model (C57BL/6 mice, mBT0309 cells)	Brain	[70]
		ESM1	Primary tumor proliferation, angiogenesis, migration, invasion	SW480 and SW620 cells; xenograft (athymic BALB/c nude mice, SW480 cells)	Colon	[99]
				A2780, SKOV3, and CAOV3 cells; xenograft (BALB/c nude mice, A2780 cells); zebrafish model (zebrafish embryos, A2780, SKOV3, and CAOV3 cells)	Ovary	[100]
		FMOD	Angiogenesis	Xenograft (C57BL/6 mice, primary human glioma cells, AGR53 and DBT-Luc cells)	Brain	[103]
			Primary tumor proliferation, migration, invasion	CAL-27 and SCC-15 cells; xenograft (BALB/c nude mice, CAL-27 cells)	Head and neck	[104]
				5637 cells	Bladder	[105]
		PODNL1	Primary tumor proliferation, migration	U87 and U251 cells; xenograft (BALB/c nude mice, U87 cells)	Brain	[106]
		VCAN	Primary tumor proliferation, invasion, migration	MGC803 and SGC-7901 cells	Stomach	[98]
	ECM regulator	CTSB	Extravasation, metastasis	Orthotopic xenograft (NSG mice, BxPC3 G1.1 cells)	Pancreas	[85]
		LOXL1	Primary tumor proliferation, invasion, metastasis	Orthotopic xenograft (NOD-SCID mice, SUM44 and MM134 cells)	Breast	[24]
		LOXL2	Primary tumor proliferation, intravasation, premetastatic niche formation, metastasis	Patient-derived xenograft (NU-Foxn1nu nude mice, primary pancreatic cancer cells); genetically-engineered mouse model	Pancreas	[52]
		LOXL3	Collective invasion	PyMT MDO cells	Breast	[111]
		MMP12	Migration, invasion	Patient-derived head and neck cancer cells	Head and neck	[112]
		SERPINB5	Extravasation, metastasis	Orthotopic xenograft (NSG mice, BxPC3 G1.1 cells)	Pancreas	[85]
	ECM-affiliated protein	ANXA2	Invasion, migration, metastasis	MDM-MB-231 and AsPC-1 cells; xenograft (Female RAG or NOD-SCID mice, MDM-MB-231 cells); zebrafish model (yolk sac of zebrafish larvae, MDM-MB-231 and AsPC-1 cells)	Breast, pancreas	[121]
		ANXA3	Primary tumor proliferation, invasion	SGC-7901, MKN-45, BGC-823, and AGS cells	Stomach	[122]
			Invasion, metastasis	MDM-MB-231, MDM-MB-468, and 4 T1 cells; xenograft (nude mice, MDA-MB-231 cells)	Breast	[123]
		ANXA5	Primary tumor proliferation, migration	SGC-7901 cells	Stomach	[124]
		ANXA9	Primary tumor proliferation, migration, invasion	MCF7 and T-47D cells; xenograft (BALB/c nude mice, MCF7 cells)	Breast	[125]
				HCT116 and HT29 cells	Colon	[126]
	Secreted factors	GDF11	Primary tumor proliferation	Orthotopic mouse model (nude mice, CACO-2, RKO, and LoVo cells)	Colon	[47]
		OSM	Metastasis	Patient-derived xenograft (NU-Foxn1nu nude mice, primary pancreatic cancer cells)	Pancreas	[52]
		S100A4	Migration, invasion, metastasis	MHCC97-L cells; orthotopic xenograft (BALB/c nude mice, MHCC97-L cells)	Liver	[132]
		S100A6	Primary tumor proliferation, migration, invasion	FTC-133, TPC-1, and BCPAP cells	Thyroid	[133]
				HeLa, SiHa, and CaSki cells	Cervix	[134]
		S100A7	Primary tumor proliferation, angiogenesis, migration, invasion, metastasis	KYSE-30 and KYSE-150 cells; xenograft (NOD-SCID mice, KYSE-30 and KYSE-150 cells)	Esophagus	[135]
Tumor-suppressing	ECM glycoprotein	LAMB4	Primary tumor proliferation, migration	AMC-HN-8 and JHU011 cells	Head and neck	[94]
		THBS1	Angiogenesis, metastasis	MG-63 cells; xenograft (BALB/c nude mice, MG-63 cells)	Sarcoma	[97]
		TINAGL1	Primary tumor proliferation, metastasis	LM2, M1a, and MDA-MB-231 cells; Tinagl1-KO and MMTV-PyMT mice	Breast	[93]
	Proteoglycan	DCN	Primary tumor proliferation, migration, invasion, metastasis	SUM149 and BCX010 cells; orthotopic xenograft (SCID-Beige mice, MDA-IBC3 and SUM149 cells)	Breast	[108]
		PODN	Primary tumor proliferation, migration, invasion	143B and MG-63 cells; xenograft (BALB/c nude mice, MG-63 cells)	Sarcoma	[109]
	ECM regulator	BMP1	Primary tumor proliferation, metastasis	Orthotopic xenograft (NOD-SCID mice, BxPC3 cells)	Pancreas	[110]
	ECM-affiliated protein	ANXA6	Primary tumor proliferation	Orthotopic xenograft (Nu/J nude mice, BT-549 and HCC1806 cells)	Breast	[126]
		FCN3	Primary tumor proliferation	A549 and H23 cells; xenograft (BALB/c nude mice, A549 cells)	Lung	[129]

cells [103]. Conversely, in oral squamous cell carcinoma, knockdown of FMOD resulted in reduced proliferation, migration, and invasion through the EGFR/AKT or EGFR/ERK signaling pathways [104].

PODNL1 may promote proliferation, migration, and EMT in bladder cancer and glioma [105,106]. In glioma, PODNL1 may contribute to tumor progression through activation of the Akt/mTOR pathway [105]. Knockdown of PODNL1 inhibited the phosphorylation of Akt/mTOR, and the effects of overexpression or silencing can be reversed by Akt inhibitor or activator [105].

DCN has been reported to suppress tumor progression [107]. In inflammatory breast cancer, DCN was found to repress migration, invasion, proliferation, incidence of metastasis, and metastatic burden. Hu and colleagues suggested that DCN degrades E-cadherin via autophagy, leading to reduced E-cadherin/EGFR/Erk pathway activation, thereby suppressing colony formation, migration, and invasion [108]. Han and colleagues proposed that PODN plays a suppressing role through the inactivation of the TGF-β/Smad2/3 pathway [109]. PODN overexpression inhibited proliferation, migration, invasion, and the expression of TGF-β/Smad2/3, but this suppression was reversed by TGF-β [109].

4.4. ECM regulators

ECM regulators also play crucial roles in various steps of the metastatic cascade. SERPINB5 and CTSB are essential for the extravasation of PDAC cells through invadopodia formation and regulation of MMP activity, leading to increased metastasis [85]. The LOX family genes also contribute significantly to tumor progression. Silencing and inhibiting LOXL1 have been shown to decrease tumor growth, invasion, and metastasis in invasive lobular carcinoma [24]. Moreover, OSM, derived from tumor-associated macrophages, activates LOXL2 expression in PDAC cells, promoting primary and metastatic tumor growth and intravasation [52]. LOXL2 activation also favors the formation of metastatic features, including alterations in collagen fiber organization and mechanical characteristics in multiple organs, contributing to premetastatic niche formation [52].

Conversely, with the assistance of PCOLCE, BMP1 cleaves the C-prodomain of procollagen, resulting in increased collagen 1 fiber, which suppresses PDAC growth and lung and liver metastasis selectively in conditions of high collagen 1 deposition [110]. In invasive lobular breast cancer, cancer cell invasiveness depends on the structural characteristics of collagens, such as collagen stiffness, bundling, and alignment [111]. Particularly, local collagen stiffness, which can be enhanced by LOXL3 at the invasive front, promotes collective invasion of cancer cells [111]. Additionally, our previous study on HNSCC revealed that MMP12 was particularly overexpressed in HNSCC and silencing MMP12 reduced migration and invasion potential [112].

Interestingly, mounting evidence has shown that Hippo signaling pathways can influence the TME by activating CAF and thus modulating matrisome expression. YAP regulates CAF transformation [113–115], contributing to proliferation and invasion abilities of colorectal and prostate cancer cells [114,115]. Cancer progression could be attributed to increased ECM remodeling by enhanced YAP/TAZ activity in CAFs [116]. In melanoma, β-catenin/YAP signaling axis stimulates melanoma-associated fibroblasts to promote ECM remodeling and tumor progression [117]. In this study, YAP inhibition impaired ECM remodeling by suppressing the expression of ECM regulators (ADAMTS1, MMP10/13, and TIMP2/3), as well as collagens and glycoproteins (COL1A1, COL6A1, and TNC). In addition, stiffened ECM promotes YAP-TEAD activation, thereby upregulating MMP24 and MMP7 expression [118]. Notably, MMP24 expression induced by YAP-TEAD impeded tumor progression [118]. Moreover, cancer cells exploit YAP signaling pathways to facilitate cancer progression through ECM deposition, producing fibronectin and collagens [119]. Particularly, ECM stiffness modulates metabolic crosstalk between tumor cells and CAFs through YAP/TAZ-dependent mechanotransduction cascade

[120]. In this study, LOX inhibition hampered tumor cell proliferation by decreasing glutamine metabolism and ECM stiffness.

4.5. ECM-affiliated proteins

The dysregulated expression of ANXA2 and ANXA3 has been experimentally shown to commonly influence invasion and metastasis [121–123]. Knockdown of ANXA2 in breast and pancreas cancers, or knockdown of ANXA3 in breast cancer, inhibited invasion in vitro and metastasis in vivo [121,123]. Silencing ANXA5 inhibited proliferation and migration in gastric cancer cells [124]. Similarly, silencing ANXA9 inhibited proliferation, migration, and invasion in breast cancer [125] and colorectal cancer via the Wnt signaling pathway [126]. The functional role of ANXA6 is controversial, acting as either a promotor or a suppressor depending on the cancer types [127]. Particularly, ANXA6 overexpression inhibited the growth of xenograft tumors of TNBC [128]. In addition, FCN3 expression in lung adenocarcinoma inhibited tumor growth through G1 and G2/M arrest and apoptosis [129].

4.6. Secreted factors

A soluble matrisome component, GDF11, which is secreted by colorectal tumor-associated lymphatic endothelial cells, contributes to colorectal cancer growth [47]. As mentioned earlier, OSM, secreted by tumor-associated macrophages, influences pancreatic cancer metastasis by acting as an inducer of LOXL2 activation [52].

S100 family genes also play a role in cancer progression. S100A4, also known as metastasin or Mts1, is frequently implicated in promoting metastasis and is involved in initiating metastatic steps such as migration, invasion, and metastasis [130]. In TNBC, proteolysis of S100A4 inhibits metastasis [131]. Exosomes rich in S100A4 increase migration, invasion, and metastatic abilities in HCC [132]. S100A6 promotes proliferation, invasion, and migration in thyroid and cervical cancers through the PI3K/AKT signaling pathway [133,134]. S100A7 is involved in proliferation, angiogenesis, migration, invasion, and metastasis in esophageal squamous carcinoma [135]. The angiogenic function of S100A7 may be attributed to endothelial cell proliferation via RAGE [135,136].

To summarize, matrisome genes validated for their roles in each pathway of tumor progression in recent studies over the past 5 years are visualized in Fig. 3. Particularly, matrisome genes involved in the circulation process have not been experimentally validated yet. Several genes in ECM regulators, ECM-affiliated proteins, and secreted factors identified in -omics studies have great potential for further investigation regarding their significance in circulation during tumor progression.

5. Matrisome biomarkers

The clinical relevance of cancer matrisome lies in its potential as effective biomarkers for cancer diagnosis, prognosis, predicting drug responses, and developing cancer vaccines. Numerous genes identified in cancer matrisomics have been investigated for their clinical significance in cancer patients, emphasizing the significance of matrisome genes in cancer research (Table 3).

5.1. Diagnostic biomarkers

Early detection of cancer is crucial for effective treatment. Accurate diagnostic biomarkers play a vital role in distinguishing tumor tissues from normal tissues. In this review, various matrisome genes with dysregulated expression in cancers have been discussed. Among them, certain genes have shown promising diagnostic potential for differentiating tumor tissues.

For instance, our previous research revealed that a TMI of 29 matrisome genes exhibits nearly perfect accuracy for diagnosing lung cancer [18] and HNSCC [112]. Both cancer types display significantly
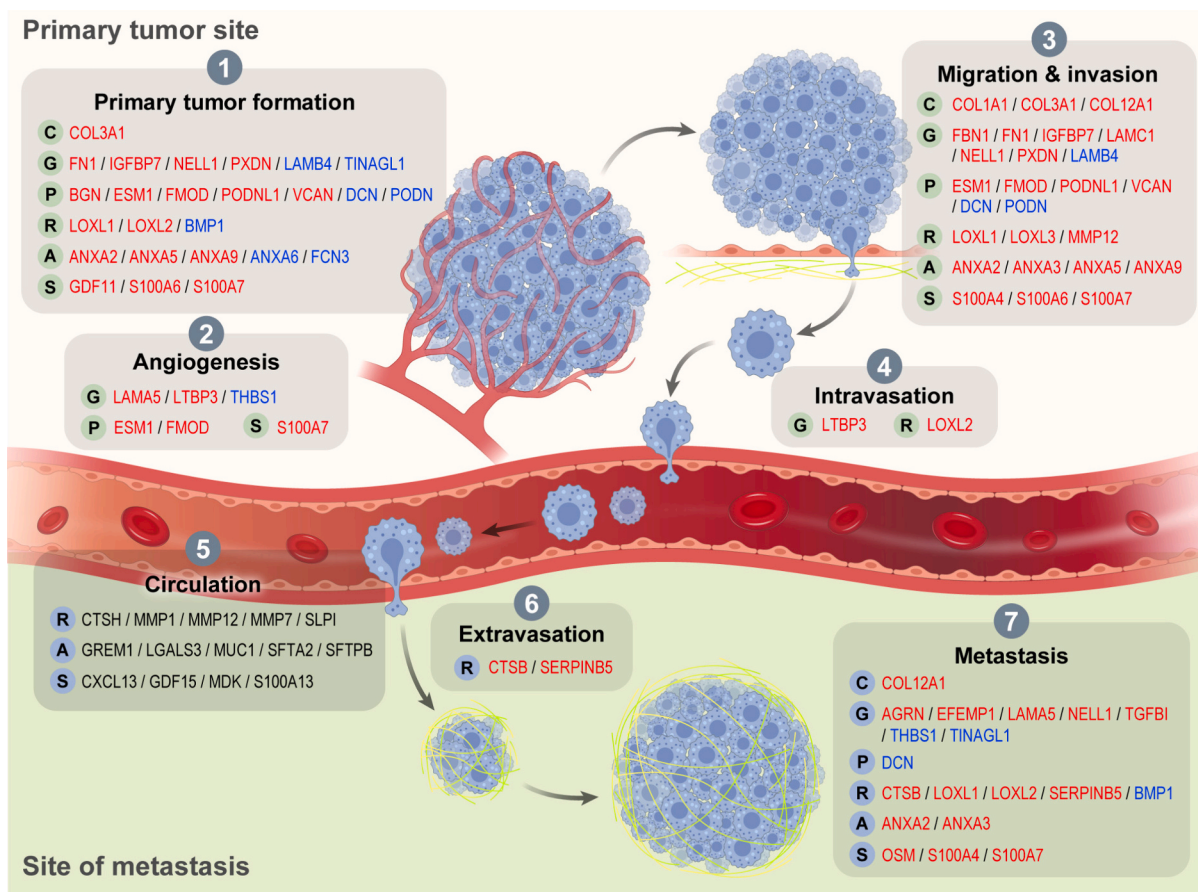
Fig. 3. Matrisome genes involved in each step of tumor progression. Matrisome genes experimentally validated to be involved in tumor progression were displayed. The steps in tumor progression were divided into seven steps from primary tumor formation to metastasis. Metastasis step includes premetastatic niche formation, colonization, and metastatic tumor proliferation. Matrisome genes with tumor-promoting roles were marked in red, whereas tumor-suppressing genes were marked in blue. Matrisome genes in black color were identified through patient-level -omics studies, with potential to be validated for the relevance to the step. (C, collagens; G, ECM glycoproteins; P, proteoglycans; R, ECM regulators; A, ECM-affiliated proteins; S, secreted factors.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

higher TMI compared to non-tumor and normal tissues, respectively. Additionally, Parker and colleagues developed a 28-gene matrisome signature that demonstrates high accuracy in distinguishing lung squamous cell carcinoma from non-tumor tissues [44].

Furthermore, specific genes have demonstrated excellent diagnostic potential in distinguishing HBV-associated HCC from non-tumor tissues [44]. In this study, 80 matrisome genes exhibited high diagnostic accuracy, each with a high AUC, including several genes depicted in Fig. 1. For example, the upregulation of COL4A1, CTHRC1, and SPP1, and the downregulation of ANXA10, BGN, DPT, MASP1, MXRA5, S100A8, and SRPX have been proven to be effective diagnostic markers for HBV-associated HCC across multiple datasets.

5.2. Prognostic biomarkers

Another significant implication of dysregulated matrisomal genes in cancers is their potential as prognostic markers, aiding in the prediction of cancer patient outcomes. Matrisome genes have shown close associations with patient survival across diverse cancer types, leveraging their altered expression patterns and mutation status in cancer cells.

Notably, elevated expression of collagens has demonstrated significant prognostic potential across multiple cancers, often correlating with poorer outcomes. For example, increased expression of COL5A2 and COL11A1 is associated with poorer overall survival (OS) in multiple cancer types [10,26,61,137]. In ovarian cancer, COL6A1 upregulation is linked to short progression-free survival (PFS) [138], while elevated

COL6A2 and COL10A1 levels are associated with decreased OS and PFS [21,138]. The adverse prognostic impact of COL10A1 has been further validated in a pan-cancer study [10]. Interestingly, COL12A1 expression is correlated with poor OS, PFS, disease-specific survival (DSS), and distant metastasis-free survival (DMFS) in breast and stomach cancers [27,33,34]. Notably, elevated levels of COL5A2, COL6A2, and COL11A1 have been predominantly observed in the invasive regions of tumor tissues (Fig. 2), implying their potential involvement in cancer invasion and subsequent poor prognosis. Moreover, the mutation status of collagens also serves as a prognostic indicator for cancer patients. Mutations in COL5A2 and COL11A1 are associated with improved OS in stomach cancers [14], whereas mutations in COL6A1 in stomach cancer and COL14A1 in colon and skin cancers are linked to poorer OS [14,58].

MMP genes also serve as reliable prognostic biomarkers in cancers. Elevated MMP9 is associated with poor OS in brain cancer [139], whereas patients with abundant MMP1 and MMP12 are correlated with better OS and disease-free survival in colon cancer [54]. Additionally, many other matrisome genes have shown their relevance to poor prognosis in diverse cancers, including several ECM glycoproteins (AGRN [85], CTHRC1 [10], PXDN [38,88], and TGFBI [94]) and proteoglycans (OGN [10] and PODNL1 [9]). In contrast, upregulation of TNXB is related to better prognosis in breast and lung cancers [140]. Additionally, mutations in mucins (MUC16 and MUC5B) have been correlated with longer OS in several cancers [58].

It is intriguing that several genes specifically upregulated in invasive tumor foci, as confirmed by ST analyses (Fig. 2), have demonstrated

Table 3

Matrisomal biomarkers in diverse cancers.

Biomarker	Matrisome	Status	Outcome	Cancer type	Refs.
Diagnosis	COL4A1, CTHRC1, SPP1	+	Tumor	Liver	[37]
	ANXA10, BGN, DPT, MASP1, MXRA5, S100A8, SRPX	−	Tumor	Liver	[37]
Prognosis	AGRN	+	- OS	Pancreas	[85]
	BGN	+	- OS	Brain	[70]
	COL5A2	+	- OS	Bladder, lung, stomach	[26], [137]
		M	+ OS	Stomach	[14]
	COL6A1	+	- PFS	Ovary	[138]
		M	- OS	Colon, skin	[58]
	COL6A2	+	- OS, PFS	Ovary	[138]
	COL10A1	+	- OS, PFS	Pan-cancer, ovary	[10], [21]
	COL11A1	+	- OS	Pan-cancer, bladder, lung	[10], [61]
		M	+ OS	Stomach	[14]
	COL12A1	+	- OS, PFS, DSS, DMFS	Breast, stomach	[28], [33], [34]
	COL14A1	M	- OS	Stomach	[14]
	CTHRC1, OGN	+	- OS	Pan-cancer	[10]
	FBN1	+	- survival	Stomach	[86]
	FN1	+	- OS	Brain, head and neck, ovary, sarcoma	[87], [94], [138], [141]
	LOX	+	- OS	Brain, stomach	[27], [51], [139]
	MMP1, MMP12	+	+ OS, DFS	Colon	[54]
	MMP9	+	- OS	Brain	[139]
	MUC16	M	+ OS	Lung, uterus	[58]
	MUC5B	M	+ OS	Skin, uterus	[58]
	PODNL1	+	- OS, PFS, DFS, DSS	Bladder, brain, kidney, ovary, pancreas, stomach	[9]
	POSTN	+	- OS	Pan-cancer, bladder, lung	[10], [61]
	PXDN	+	- OS	Brain, lung	[38], [88]
	TGFBI	+	- DMFS	Breast	[94]
	TNXB	+	+ survival	Breast, lung	[140]
Prediction of drug response	COL3A1, COL10A1, COL11A1	+	- chemotherapy	Ovary	[138]
	COL5A2	−	+ pembrolizumab	Stomach	[26]
	OGN	−	+ neoadjuvant chemotherapy	Breast	[142]
	PODNL1	+	- immunotherapy	Pan-cancer	[9]

*In status section, (+) stands for gene upregulation; (−) for gene downregulation; (M) for mutations. In outcome section, (+) stands for better survival or response to cancer therapy; (−) for worse survival or response to cancer therapy. Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; OS, overall survival; PFS, progression-free survival.

their impact on poor prognosis in diverse cancers. For example, BGN is implicated in brain cancer [70], while FBN1 is involved in stomach cancer [86]. In addition, LOX is correlated with poor prognosis in brain and stomach cancers [28,51,139]. FN1 and POSTN have exhibited prognostic significance across multiple cancers in various studies [10,61,87,94,138,141].

5.3. Predictive biomarkers for the drug response

Several matrisome genes emerged as crucial determinants of drug response in cancer patients. Yu and colleagues identified an 8-gene risk signature composed of eight immune-related matrisome genes, which shows predictive potential for anti-PD1/PDL1 immunotherapy response in glioma patients [139]. Interestingly, patients classified in the high-risk group have exhibited elevated immune infiltration scores, correlating with higher response rates to immunotherapy.

In ovarian cancer, heightened expression of COL3A1, COL10A1, and COL11A1 is associated with chemotherapy resistance [138]. Conversely, in stomach cancer, lower expression levels of COL5A2 are linked to favorable responses to pembrolizumab, suggesting COL5A2 as a potential predictor of immunotherapy response [26]. Furthermore, the proteoglycan OGN demonstrated predictive biomarker potential in breast cancer, with low OGN levels associated with more complete responses following neoadjuvant chemotherapy [142].

Lastly, pan-cancer analysis has unveiled that elevated expression of PODNL1 correlated with diminished response to immunotherapy across various immunotherapeutic cohorts [9]. These findings underscore the potential of matrisome as robust predictors of cancer therapy outcomes, highlighting the prospect of targeting these genes to augment therapeutic effectiveness in cancer treatment.

5.4. Targets for cancer vaccines

Cancer vaccines are one of the promising therapeutics in cancer immunotherapy. For the development of cancer vaccines, defining proper tumor antigens is critical for achieving enhanced treatment efficacy [143]. Interestingly, glycoproteins have emerged as valuable targets for cancer vaccination in light with aberrantly modified glycosylated structures and altered expression during tumorigenesis [144]. Moreover, overcoming the limitation of the lack of broadly expressed tumor antigens across multiple cancers and the presence of intertumoral heterogeneity, utilizing the whole tumor cells or some components of tumor cells in defining tumor antigens has been a promising alternative for developing cancer vaccines [143].

Among them, the ECM of tumor tissues has displayed its potential to be used to generate nanobodies selectively targeting tumor cells. For instance, Jailkhani and colleagues developed a nanobody, specific for an alternatively spliced EIIIB domain of fibronectin, a major glycoprotein that constitutes tumor ECM [145]. They showed that the fibronectin EIIIB-specific nanobody effectively detects primary tumors and metastases in breast and pancreatic cancer model [145]. They further identified a metastasis-associated matrisome signature by proteomic profiling of TNBC metastases and colon cancer metastases and developed a nanobody specific for TNC, which is widely overrepresented in primary and metastatic tumor ECM [146]. They confirmed that the TNC-specific nanobody can bind to small metastases in vivo [146]. Noninvasive imaging using immuno-PET/CT by both nanobodies outperforms conventional 2-fluorodeoxyglucose PET/CT imaging, with higher clarity and specificity in vivo, highlighting enhanced diagnostic performance of nanobodies targeting ECM components [145,146].

Notably, chimeric antigen receptor (CAR) T cells that target

fibronectin EIIIB splice variant were shown to hinder melanoma tumor growth and improve survival in mouse model, demonstrating the feasibility and efficacy of CAR T cells that target the tumor ECM [147]. These findings suggest that cancer vaccines against matrisome proteins that display tumor-specific abundance or structural alterations in primary tumor and metastases have the potential to be used as effective vehicles for delivery of imaging and therapeutic agents. Further exploration of their application in cancer immunotherapy would contribute to accurate cancer diagnostics and elevated treatment efficacy.

5.5. Prospects for clinical applications of matrisome biomarkers

As discussed above, the exploration of diverse -omics studies suggests that matrisome genes hold significant promise for clinical applications in cancer treatment. To summarize, their roles as cancer biomarkers and therapeutic targets enhance our understanding of the TME across diverse cancer types, thus improving cancer treatment. As previously addressed in our discussion about HCC biomarkers, several optimization processes are required for matrisome biomarkers to be practically applied to clinical settings [148]. For example, a universal cutoff to differentiate patients from non-patients should be defined with respect to sensitivity and specificity to achieve optimal diagnostic results. Also, diverse platforms for detecting gene expression should be standardized, facilitating the development of clinically applicable gene expression-based assays [148]. Similarly, if matrisome biomarkers are optimized for their cancer-specific status through the integration of a wide range of -omics studies, they could be effectively applied to clinical practice for cancer treatment.

6. Conclusions

The matrisome emerges as a pivotal contributor to cancer progression across diverse malignancies, as evidenced by recent cancer -omics studies. This review has synthesized the altered regulatory patterns of matrisome genes observed in various cancer types over the past five years. Importantly, these genes, secreted by heterogenous cell populations, exhibit distinct spatial distributions within tumor tissues, indicative of functional relevance in cancer progression. Several matrisome members have been experimentally validated for their functional roles in driving tumor progression. In addition, numerous matrisome genes hold promise as effective cancer biomarkers, serving diagnostic, prognostic, and predictive roles in therapeutic, as well as roles in developing cancer vaccines. These insights underscore the matrisome as a crucial clinical target in cancer treatment, warranting further investigation in cancer research endeavors.

Author contributions

Conceptualization: JH, HJJ, MRC, SBL. Funding acquisition: SBL. Investigation: JH, HJJ, MRC, SBL. Project administration: SBL. Supervision: SBL. Visualization: JH, HJJ, MRC. Writing – original draft: JH, HJJ, MRC, DWTL, JEP, YSK, SBL. Writing – review & editing: JH, HJJ, MRC, DWTL, JEP, YSK, SBL.

Declaration of competing interest

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

Data availability

Data will be made available on request.

References

[1] H. Raskov, S. Gaggar, A. Tajik, A. Orhan, I. Gögenur, The matrix reloaded-the role of the extracellular matrix in cancer, Cancers (Basel) 15 (7) (2023) 2057.

[2] A. Naba, K.R. Clauser, S. Hoersch, H. Liu, S.A. Carr, R.O. Hynes, The matrisome: in silico definition and in vivo characterization by proteomics of normal and tumor extracellular matrices, Mol. Cell. Proteomics 11 (4) (2012) M111.014647.

[3] J. Huang, L. Zhang, D. Wan, L. Zhou, S. Zheng, S. Lin, Y. Qiao, Extracellular matrix and its therapeutic potential for cancer treatment, Signal Transduct. Target. Ther. 6 (1) (2021) 153.

[4] A.E. Yuzhalin, S.Y. Lim, A.G. Kutikhin, A.N. Gordon-Weeks, Dynamic matrisome: ECM remodeling factors licensing cancer progression and metastasis, Biochim. Biophys. Acta Rev. Cancer 1870 (2) (2018) 207–228.

[5] A. Naba, K.R. Clauser, H. Ding, C.A. Whittaker, S.A. Carr, R.O. Hynes, The extracellular matrix: tools and insights for the "omics" era, Matrix Biol. 49 (2016) 10–24.

[6] S. Brassart-Pasco, S. Brézillon, B. Brassart, L. Ramont, J.B. Oudart, J. C. Monboisse, Tumor microenvironment: extracellular matrix alterations influence tumor progression, Front. Oncol. 10 (2020) 397.

[7] X. Shao, C.D. Gomez, N. Kapoor, J.M. Considine, C. Grams, Y.T. Gao, A. Naba, MatrisomeDB 2.0: 2023 updates to the ECM-protein knowledge database, Nucleic Acids Res. 51 (D1) (2023) D1519–d1530.

[8] A.M. Socovich, A. Naba, The cancer matrisome: from comprehensive characterization to biomarker discovery, Semin. Cell Dev. Biol. 89 (2019) 157–166.

[9] G. Dai, Y. Sun, R. Wei, L. Xi, Small leucine-rich proteoglycan PODNL1 identified as a potential tumor matrix-mediated biomarker for prognosis and immunotherapy in a Pan-Cancer setting, Curr. Issues Mol. Biol. 45 (7) (2023) 6116–6139.

[10] K. Harikrishnan, S.S. Prabhu, N. Balasubramanian, A pan-cancer analysis of matrisome proteins reveals CTHRC1 and a related network as major ECM regulators across cancers, PLoS ONE 17 (10) (2022) e0270063.

[11] G.C. Bingham, F. Lee, A. Naba, T.H. Barker, Spatial-omics: novel approaches to probe cell heterogeneity and extracellular matrix biology, Matrix Biol. 91-92 (2020) 152–166.

[12] E. Holstein, A. Dittmann, A. Kääriäinen, V. Pesola, J. Koivunen, T. Pihlajaniemi, A. Naba, V. Izzi, The burden of post-translational modification (PTM)-disrupting mutations in the tumor Matrisome, Cancers (Basel) 13 (5) (2021).

[13] Q. Tian, H. Gao, Y. Ma, L. Zhu, Y. Zhou, Y. Shen, B. Wang, The regulatory roles of T helper cells in distinct extracellular matrix characterization in breast cancer, Front. Immunol. 13 (2022) 871742.

[14] A.S. Brodsky, J. Khurana, K.S. Guo, E.Y. Wu, D. Yang, A.S. Siddique, I.Y. Wong, E. D. Gamsiz Uzun, M.B. Resnick, Somatic mutations in collagens are associated with a distinct tumor environment and overall survival in gastric cancer, BMC Cancer 22 (1) (2022) 139.

[15] X. Zeng, H.Y. Wang, Y.P. Wang, S.Y. Bai, K. Pu, Y. Zheng, Q.H. Guo, Q.L. Guan, R. Ji, Y.N. Zhou, COL4A family: potential prognostic biomarkers and therapeutic targets for gastric cancer, Transl. Cancer Res. 9 (9) (2020) 5218–5232.

[16] X. Li, Z. Li, S. Gu, X. Zhao, A pan-cancer analysis of collagen VI family on prognosis, tumor microenvironment, and its potential therapeutic effect, BMC Bioinformatics 23 (1) (2022) 390.

[17] T.O. Nieuwenhuis, A.Z. Rosenberg, M.N. McCall, M.K. Halushka, Tissue, age, sex, and disease patterns of matrisome expression in GTEx transcriptome data, Sci. Rep. 11 (1) (2021) 21549.

[18] S.B. Lim, M.L.K. Chua, J.P.S. Yeong, S.J. Tan, W.T. Lim, C.T. Lim, Pan-cancer analysis connects tumor matrisome to immune response, NPJ Precis. Oncol. 3 (2019) 15.

[19] A.E. Yuzhalin, T. Urbonas, M.A. Silva, R.J. Muschel, A.N. Gordon-Weeks, A core matrisome gene signature predicts cancer outcome, Br. J. Cancer 118 (3) (2018) 435–440.

[20] E. Maniati, C. Berlato, G. Gopinathan, O. Heath, P. Kotantaki, A. Lakhani, J. McDermott, C. Pegrum, R.M. Delaine-Smith, O.M.T. Pearce, H. Pirani, J.D. Joy, L. Szabova, R. Perets, O.J. Sansom, R. Drapkin, P. Bailey, F.R. Balkwill, Mouse ovarian cancer models recapitulate the human tumor microenvironment and patient response to treatment, Cell Rep. 30 (2) (2020) 525–540.e7.

[21] S. Mitra, K. Tiwari, R. Podicheti, T. Pandhiri, D.B. Rusch, A. Bonetto, C. Zhang, A. K. Mitra, Transcriptome profiling reveals Matrisome alteration as a key feature of ovarian cancer progression, Cancers (Basel) 11 (10) (2019).

[22] R.M. Delaine-Smith, E. Maniati, B. Malacrida, S. Nichols, R. Roozitalab, R. R. Jones, L.S.M. Lecker, O.M.T. Pearce, M.M. Knight, F.R. Balkwill, Modelling TGFβR and Hh pathway regulation of prognostic matrisome molecules in ovarian cancer, iScience 24 (6) (2021) 102674.

[23] O.M.T. Pearce, R.M. Delaine-Smith, E. Maniati, S. Nichols, J. Wang, S. Böhm, V. Rajeeve, D. Ullah, P. Chakravarty, R.R. Jones, A. Montfort, T. Dowe,

J. Gribben, J.L. Jones, H.M. Kocher, J.S. Serody, B.G. Vincent, J. Connelly, J. D. Brenton, C. Chelala, P.R. Cutillas, M. Lockley, C. Bessant, M.M. Knight, F. R. Balkwill, Deconstruction of a metastatic tumor microenvironment reveals a common matrix response in human cancers, Cancer Discov. 8 (3) (2018) 304–319.

[24] G. Sflomos, L. Battista, P. Aouad, F. De Martino, V. Scabia, A. Stravodimou, A. Ayyanan, A. Ifticene-Treboux, P. Bucher, M. Fiche, G. Ambrosini, C. Brisken, Intraductal xenografts show lobular carcinoma cells rely on their own extracellular matrix and LOXL1, EMBO Mol. Med. 13 (3) (2021) e13180.

[25] M.H. Yeh, Y.J. Tzeng, T.Y. Fu, J.J. You, H.T. Chang, L.P. Ger, K.W. Tsai, Extracellular matrix-receptor interaction signaling genes associated with inferior breast cancer survival, Anticancer Res. 38 (8) (2018) 4593–4605.

[26] M. Chen, X. Zhu, L. Zhang, D. Zhao, COL5A2 is a prognostic-related biomarker and correlated with immune infiltrates in gastric cancer based on transcriptomics and single-cell RNA sequencing, BMC Med. Genet. 16 (1) (2023) 220.

[27] X. Jiang, M. Wu, X. Xu, L. Zhang, Y. Huang, Z. Xu, K. He, H. Wang, H. Wang, L. Teng, COL12A1, a novel potential prognostic factor and therapeutic target in gastric cancer, Mol. Med. Rep. 20 (4) (2019) 3103–3112.

[28] A.M. Moreira, R.M. Ferreira, P. Carneiro, J. Figueiredo, H. Osório, J. Barbosa, J. Preto, P. Pinto-do-Ó, F. Carneiro, R. Seruca, Proteomic identification of a gastric tumor ECM signature associated with cancer progression, Front. Mol. Biosci. 9 (2022) 818552.

[29] A.S. Barrett, O. Maller, M.W. Pickup, V.M. Weaver, K.C. Hansen, Compartment resolved proteomics reveals a dynamic matrisome in a biomechanically driven model of pancreatic ductal adenocarcinoma, J. Immunol. Regen. Med. 1 (2018) 67–75.

[30] C. Tian, K.R. Clauser, D. Öhlund, S. Rickelt, Y. Huang, M. Gupta, D.R. Mani, S. A. Carr, D.A. Tuveson, R.O. Hynes, Proteomic analyses of ECM during pancreatic ductal adenocarcinoma progression reveal different contributions by tumor and stromal cells, Proc. Natl. Acad. Sci. USA 116 (39) (2019) 19609–19618.

[31] G. Carpino, D. Overi, F. Melandro, A. Grimaldi, V. Cardinale, S. Di Matteo, G. Mennini, M. Rossi, D. Alvaro, V. Barnaba, E. Gaudio, C. Mancone, Matrisome analysis of intrahepatic cholangiocarcinoma unveils a peculiar cancer-associated extracellular matrix structure, Clin. Proteomics 16 (2019) 37.

[32] R. Desert, W. Chen, X. Ge, R. Viel, H. Han, D. Athavale, S. Das, Z. Song, D. Lantvit, L. Cano, A. Naba, O. Musso, N. Nieto, Hepatocellular carcinomas, exhibiting intratumor fibrosis, express cancer-specific extracellular matrix remodeling and WNT/TGFB signatures, associated with poor outcome, Hepatology 78 (3) (2023) 741–757.

[33] M. Papanicolaou, A.L. Parker, M. Yam, E.C. Filipe, S.Z. Wu, J.L. Chitty, K. Wyllie, E. Tran, E. Mok, A. Nadalini, J.N. Skhinas, M.C. Lucas, D. Herrmann, M. Nobis, B. A. Pereira, A.M.K. Law, L. Castillo, K.J. Murphy, A. Zaratzian, J.F. Hastings, D. R. Croucher, E. Lim, B.G. Oliver, F.V. Mora, B.L. Parker, D. Gallego-Ortega, A. Swarbrick, S. O'Toole, P. Timpson, T.R. Cox, Temporal profiling of the breast tumour microenvironment reveals collagen XII as a driver of metastasis, Nat. Commun. 13 (1) (2022) 4587.

[34] L.A. Tomko, R.C. Hill, A. Barrett, J.M. Szulczewski, M.W. Conklin, K.W. Eliceiri, P.J. Keely, K.C. Hansen, S.M. Ponik, Targeted matrisome analysis identifies thrombospondin-2 and tenascin-C in aligned collagen stroma from invasive breast carcinoma, Sci. Rep. 8 (1) (2018) 12941.

[35] Y.J. Liu, J. Du, J. Li, X.P. Tan, Q. Zhang, CTHRC1, a novel gene with multiple functions in physiology, disease and solid tumors (review), Oncol. Lett. 25 (6) (2023) 266.

[36] D. Liu, C. He, Z. Liu, L. Xu, J. Li, Z. Zhao, X. Hu, H. Chen, B. Sun, Y. Wang, The prognostic and immune significance of CILP2 in pan-cancer and its relationship with the progression of pancreatic cancer, Cancers (Basel) 15 (24) (2023).

[37] W. Chen, R. Desert, X. Ge, H. Han, Z. Song, S. Das, D. Athavale, H. You, N. Nieto, The Matrisome genes from hepatitis B-related hepatocellular carcinoma unveiled, Hepatol, Commun. 5 (9) (2021) 1571–1585.

[38] H.F. Titmarsh, A. von Kriegsheim, J.C. Wills, R.A. O'Connor, K. Dhaliwal, M. C. Frame, S.B. Pattle, D.A. Dorward, A. Byron, A.R. Akram, Quantitative proteomics identifies tumour matrisome signatures in patients with non-small cell lung cancer, Front. Oncol. 13 (2023) 1194515.

[39] B. Diao, P. Yang, Comprehensive analysis of the expression and prognosis for laminin genes in ovarian cancer, Pathol. Oncol. Res. 27 (2021) 1609855.

[40] C. Yang, Z. Liu, X. Zeng, Q. Wu, X. Liao, X. Wang, C. Han, T. Yu, G. Zhu, W. Qin, T. Peng, Evaluation of the diagnostic ability of laminin gene family for pancreatic ductal adenocarcinoma, Aging (Albany NY) 11 (11) (2019) 3679–3703.

[41] X. Zhou, Q. Sun, C. Xu, Z. Zhou, X. Chen, X. Zhu, Z. Huang, W. Wang, Y. Shi, A systematic pan-cancer analysis of PXDN as a potential target for clinical diagnosis and treatment, Front. Oncol. 12 (2022) 952849.

[42] A.E. Yuzhalin, S.Y. Lim, A.N. Gordon-Weeks, R. Fischer, B.M. Kessler, D. Yu, R. J. Muschel, Proteomics analysis of the matrisome from MC38 experimental mouse liver metastases, Am. J. Physiol. Gastrointest. Liver Physiol. 317 (5) (2019) G625–g639.

[43] F. Ramirez, Pathophysiology of the microfibril/elastic fiber system: introduction, Matrix Biol. 19 (6) (2000) 455–456.

[44] A.L. Parker, E. Bowman, A. Zingone, B.M. Ryan, W.A. Cooper, M. Kohonen-Corish, C.C. Harris, T.R. Cox, Extracellular matrix profiles determine risk and prognosis of the squamous cell carcinoma subtype of non-small cell lung carcinoma, Genome Med. 14 (1) (2022) 126.

[45] P. Rappu, U. Suwal, E. Siljamäki, J. Heino, Inflammation-related citrullination of matrisome proteins in human cancer, Front. Oncol. 12 (2022) 1035188.

[46] R.A. Brekken, E.H. Sage, SPARC, a matricellular protein: at the crossroads of cell-matrix communication, Matrix Biol. 19 (8) (2001) 816–827.

[47] F. Ungaro, P. Colombo, L. Massimino, G.S. Ugolini, C. Correale, M. Rasponi, V. Garlatti, F. Rubbino, C. Tacconi, P. Spaggiari, A. Spinelli, M. Carvello, M. Sacchi, S. Spanò, S. Vetrano, A. Malesci, L. Peyrin-Biroulet, S. Danese, S. D'Alessio, Lymphatic endothelium contributes to colorectal cancer growth via the soluble matrisome component GDF11, Int. J. Cancer 145 (7) (2019) 1913–1920.

[48] G. Li, M. Li, X. Liang, Z. Xiao, P. Zhang, M. Shao, F. Peng, Y. Chen, Y. Li, Z. Chen, Identifying DCN and HSPD1 as potential biomarkers in Colon Cancer using 2D-LC-MS/MS combined with iTRAQ technology, J. Cancer 8 (3) (2017) 479–489.

[49] Y. Hou, J. Hu, L. Zhou, L. Liu, K. Chen, X. Yang, Integrative analysis of methylation and copy number variations of prostate adenocarcinoma based on weighted gene co-expression network analysis, Front. Oncol. 11 (2021) 647253.

[50] T. Deng, Y. Hou, G. Lin, C. Feng, K. Liu, W. Chen, W. Wei, L. Huang, X. Dai, A novel Fibromodulin antagonist peptide RP4 exerts antitumor effects on colorectal Cancer, Pharmaceutics 15 (3) (2023).

[51] T.S. Laurentino, R.D.S. Soares, S.K.N. Marie, S.M. Oba-Shinjo, Correlation of matrisome-associatted gene expressions with LOX family members in astrocytomas stratified by IDH mutation status, Int. J. Mol. Sci. 23 (17) (2022).

[52] M. Alonso-Nocelo, L. Ruiz-Cañas, P. Sancho, K. Görgülü, S. Alcalá, C. Pedrero, M. Vallespinos, J.C. López-Gil, M. Ochando, E. García-García, S.M. David Trabulo, P. Martinelli, P. Sánchez-Tomero, C. Sánchez-Palomo, P. Gonzalez-Santamaría, L. Yuste, S.M. Wörmann, D. Kabacaoğlu, J. Earl, A. Martin, F. Salvador, S. Valle, L. Martin-Hijano, A. Carrato, M. Erkan, L. García-Bermejo, P. C. Hermann, H. Algül, G. Moreno-Bueno, C. Heeschen, F. Portillo, A. Cano, B. Sainz Jr., Macrophages direct cancer cells through a LOXL2-mediated metastatic cascade in pancreatic ductal adenocarcinoma, Gut 72 (2) (2023) 345–359.

[53] S. Lin, L. Zheng, Y. Lu, Q. Xia, P. Zhou, Z. Liu, Comprehensive analysis on the expression levels and prognostic values of LOX family genes in kidney renal clear cell carcinoma, Cancer Med. 9 (22) (2020) 8624–8638.

[54] M. Buttacavoli, G. Di Cara, E. Roz, I. Pucci-Minafra, S. Feo, P. Cancemi, Integrated multi-omics investigations of metalloproteinases in colon cancer: focus on MMP2 and MMP9, Int. J. Mol. Sci. 22 (22) (2021).

[55] W. Xiao, X. Wang, T. Wang, J. Xing, Overexpression of BMP1 reflects poor prognosis in clear cell renal cell carcinoma, Cancer Gene Ther. 27 (5) (2020) 330–340.

[56] J.H. Rafi, T. Jafar, M.T. Pathan, R. Reza, S. Islam, I.J. Sourna, R. Alam, A. Samad, F. Ahammad, High expression of bone morphogenetic protein 1 (BMP1) is associated with a poor survival rate in human gastric cancer, a dataset approaches, Genomics 113 (1 Pt 2) (2021) 1141–1154.

[57] C. Shen, S. Zhang, Z. Zhang, S. Yang, Y. Zhang, Y. Lin, C. Fu, Z. Li, Z. Wu, Z. Wang, Z. Li, J. Guo, P. Li, H. Hu, Pan-cancer evidence of prognosis, immune infiltration, and immunotherapy efficacy for annexin family using multi-omics data, Funct. Integr. Genomics 23 (3) (2023) 211.

[58] V. Izzi, M.N. Davis, A. Naba, Pan-cancer analysis of the genomic alterations and mutations of the matrisome, Cancers (Basel) 12 (8) (2020).

[59] F. Liu, J. Liu, X. Shi, X. Hu, L. Wei, B. Huo, L. Chang, Y. Han, G. Liu, L. Yang, Identification of INHBA as a potential biomarker for gastric cancer through a comprehensive analysis, Sci. Rep. 13 (1) (2023) 12494.

[60] M.L. Zeng, X.J. Zhu, J. Liu, P.C. Shi, Y.L. Kang, Z. Lin, Y.P. Cao, An integrated bioinformatic analysis of the S100 gene family for the prognosis of colorectal cancer, Biomed. Res. Int. 2020 (2020) 4746929.

[61] J. Zhang, S. Lu, T. Lu, D. Han, K. Zhang, L. Gan, X. Wu, Y. Li, X. Zhao, Z. Li, Y. Shen, S. Hu, F. Yang, W. Wen, W. Qin, Single-cell analysis reveals the COL11A1 (+) fibroblasts are cancer-specific fibroblasts that promote tumor progression, Front. Pharmacol. 14 (2023) 1121586.

[62] Y. Belotti, S.B. Lim, N.G. Iyer, W.T. Lim, C.T. Lim, Prognostic matrisomal gene panel and its association with immune cell infiltration in head and neck carcinomas, Cancers (Basel) 13 (22) (2021).

[63] K.H. Bond, T. Chiba, K.P.H. Wynne, C.P.H. Vary, S. Sims-Lucas, J.M. Coburn, L. Oxburgh, The extracellular matrix environment of clear cell renal cell carcinoma determines cancer associated fibroblast growth, Cancers (Basel) 13 (23) (2021).

[64] S. Ferri-Borgogno, Y. Zhu, J. Sheng, J.K. Burks, J.A. Gomez, K.K. Wong, S.T. C. Wong, S.C. Mok, Spatial transcriptomics depict ligand-receptor cross-talk heterogeneity at the tumor-stroma Interface in long-term ovarian cancer survivors, Cancer Res. 83 (9) (2023) 1503–1516.

[65] Z. Zhao, T.K. Mak, Y. Shi, K. Li, M. Huo, C. Zhang, Integrative analysis of cancer-associated fibroblast signature in gastric cancer, Heliyon 9 (9) (2023) e19217.

[66] Y. Du, J. Shi, J. Wang, Z. Xun, Z. Yu, H. Sun, R. Bao, J. Zheng, Z. Li, Y. Ye, Integration of Pan-cancer single-cell and spatial transcriptomics reveals stromal cell features and therapeutic targets in tumor microenvironment, Cancer Res. 84 (2) (2024) 192–210.

[67] Z. Hong, W. Xie, H. Zhuo, X. Wei, K. Wang, J. Cheng, L. Lin, J. Hou, X. Chen, J. Cai, Crosstalk between cancer cells and cancer-associated fibroblasts mediated by TGF-β1-IGFBP7 signaling promotes the progression of infiltrative gastric Cancer, Cancers (Basel) 15 (15) (2023).

[68] C.J. Hanley, S. Waise, M.J. Ellis, M.A. Lopez, W.Y. Pun, J. Taylor, R. Parker, L. M. Kimbley, S.J. Chee, E.C. Shaw, J. West, A. Alzetani, E. Woo, C.H. Ottensmeier, M.J.J. Rose-Zerilli, G.J. Thomas, Single-cell analysis reveals prognostic fibroblast subpopulations linked to molecular and immunological subtypes of lung cancer, Nat. Commun. 14 (1) (2023) 387.

[69] H.Q. Dinh, F. Pan, G. Wang, Q.F. Huang, C.E. Olingy, Z.Y. Wu, S.H. Wang, X. Xu, X.E. Xu, J.Z. He, Q. Yang, S. Orsulic, M. Haro, L.Y. Li, G.W. Huang, J.J. Breunig, H.P. Koeffler, C.C. Hedrick, L.Y. Xu, D.C. Lin, E.M. Li, Integrated single-cell

transcriptome analysis reveals heterogeneity of esophageal squamous cell carcinoma microenvironment, Nat. Commun. 12 (1) (2021) 7335.

[70] R. Mirzaei, C. D'Mello, M. Liu, A. Nikolic, M. Kumar, F. Visser, P. Bose, M. Gallo, V.W. Yong, Single-cell spatial analysis identifies regulators of brain tumor-initiating cells, Cancer Res. 83 (10) (2023) 1725–1741.

[71] E.D. Wrenn, A.A. Apfelbaum, E.R. Rudzinski, X. Deng, W. Jiang, S. Sud, R.A. Van Noord, E.A. Newman, N.M. Garcia, A. Miyaki, V.J. Hoglund, S.S. Bhise, S. B. Kanaan, O.G. Waltner, S.N. Furlan, E.R. Lawlor, Cancer-associated fibroblast-like tumor cells remodel the Ewing sarcoma tumor microenvironment, Clin. Cancer Res. 29 (24) (2023) 5140–5154.

[72] S.S. Park, Y.K. Lee, Y.W. Choi, S.B. Lim, S.H. Park, H.K. Kim, J.S. Shin, Y.H. Kim, D.H. Lee, J.H. Kim, T.J. Park, Cellular senescence is associated with the spatial evolution toward a higher metastatic phenotype in colorectal cancer, Cell Rep. 43 (3) (2024) 113912.

[73] S.B. Lim, T. Yeo, W.D. Lee, A.A.S. Bhagat, S.J. Tan, D.S.W. Tan, W.T. Lim, C. T. Lim, Addressing cellular heterogeneity in tumor and circulation for refined prognostication, Proc. Natl. Acad. Sci. USA 116 (36) (2019) 17957–17962.

[74] H. Ruan, Y. Zhou, J. Shen, Y. Zhai, Y. Xu, L. Pi, R. Huang, K. Chen, X. Li, W. Ma, Z. Wu, X. Deng, X. Wang, C. Zhang, M. Guan, Circulating tumor cell characterization of lung cancer brain metastases in the cerebrospinal fluid through single-cell transcriptome analysis, Clin. Transl. Med. 10 (8) (2020) e246.

[75] A. Ravichandran, J. Monkman, A.M. Mehdi, T. Blick, C. Snell, A. Kulasinghe, L. J. Bray, The in situ transcriptomic landscape of breast tumour-associated and normal adjacent endothelial cells, Biochim. Biophys. Acta Mol. basis Dis. 1870 (2) (2024) 166985.

[76] H. Massalha, K. Bahar Halpern, S. Abu-Gazala, T. Jana, E.E. Massasa, A.E. Moor, L. Buchauer, M. Rozenberg, E. Pikarsky, I. Amit, G. Zamir, S. Itzkovitz, A single cell atlas of the human liver tumor microenvironment, Mol. Syst. Biol. 16 (12) (2020) e9682.

[77] Y. Feng, S. Wang, J. Xie, B. Ding, M. Wang, P. Zhang, P. Mi, C. Wang, R. Liu, T. Zhang, X. Yu, D. Yuan, C. Zhang, Spatial transcriptomics reveals heterogeneity of macrophages in the tumor microenvironment of granulomatous slack skin, J. Pathol. 261 (1) (2023) 105–119.

[78] V. Condello, J.O. Paulsson, J. Zedenius, A. Näsman, C.C. Juhlin, Spatial transcriptomics in a case of follicular thyroid carcinoma reveals clone-specific dysregulation of genes regulating extracellular matrix in the invading front, Endocr. Pathol. 35 (2) (2024) 122–133.

[79] A.W. Lambert, D.R. Pattabiraman, R.A. Weinberg, Emerging biological principles of metastasis, Cell 168 (4) (2017) 670–691.

[80] S.Z. Eslami, L.E. Cortés-Hernández, C. Alix-Panabières, The metastatic Cascade as the basis for liquid biopsy development, Front. Oncol. 10 (2020) 1055.

[81] Z. Zhang, Y. Wang, J. Zhang, J. Zhong, R. Yang, COL1A1 promotes metastasis in colorectal cancer by regulating the WNT/PCP pathway, Mol. Med. Rep. 17 (4) (2018) 5037–5042.

[82] C. Chen, Z. Shen, FN1 promotes thyroid carcinoma cell proliferation and metastasis by activating the NF-Kb pathway, Protein Pept. Lett. 30 (1) (2023) 54–64.

[83] B. Li, W. Shen, H. Peng, Y. Li, F. Chen, L. Zheng, J. Xu, L. Jia, Fibronectin 1 promotes melanoma proliferation and metastasis by inhibiting apoptosis and regulating EMT, Onco Targets Ther 12 (2019) 3207–3221.

[84] W.H. Zhou, W.D. Du, Y.F. Li, M.A. Al-Aroomi, C. Yan, Y. Wang, Z.Y. Zhang, F. Y. Liu, C.F. Sun, The overexpression of fibronectin 1 promotes Cancer progression and associated with M2 macrophages polarization in head and neck squamous cell carcinoma patients, Int. J. Gen. Med. 15 (2022) 5027–5042.

[85] C. Tian, D. Öhlund, S. Rickelt, T. Lidström, Y. Huang, L. Hao, R.T. Zhao, O. Franklin, S.N. Bhatia, D.A. Tuveson, R.O. Hynes, Cancer cell-derived matrisome proteins promote metastasis in pancreatic ductal adenocarcinoma, Cancer Res. 80 (7) (2020) 1461–1474.

[86] Z. Yang, F. Xue, M. Li, X. Zhu, X. Lu, C. Wang, E. Xu, X. Wang, L. Zhang, H. Yu, C. Ren, H. Wang, Y. Wang, J. Chen, W. Guan, X. Xia, Extracellular matrix characterization in gastric cancer helps to predict prognosis and chemotherapy response, Front. Oncol. 11 (2021) 753330.

[87] Q. Qin, M. Gomez-Salazar, R.J. Tower, L. Chang, C.D. Morris, E.F. McCarthy, K. Ting, X. Zhang, A.W. James, NELL1 regulates the matrisome to promote osteosarcoma progression, Cancer Res. 82 (15) (2022) 2734–2747.

[88] W. Shi, W. Ding, Z. Zhao, R. Wang, F. Wang, Y. Tang, J. Zhu, C. Su, X. Zhao, L. Liu, Peroxidase is a novel potential marker in glioblastoma through bioinformatics method and experimental validation, Front. Genet. 13 (2022) 990344.

[89] S.F.F. Almeida, L. Santos, G. Sampaio-Ribeiro, H.R.S. Ferreira, N. Lima, R. Caetano, M. Abreu, M. Zuzarte, A.S. Ribeiro, A. Paiva, T. Martins-Marques, P. Teixeira, R. Almeida, J.M. Casanova, H. Girão, A.J. Abrunhosa, C.M. Gomes, Unveiling the role of osteosarcoma-derived secretome in premetastatic lung remodelling, J. Exp. Clin. Cancer Res. 42 (1) (2023) 328.

[90] A. Gordon-Weeks, S.Y. Lim, A. Yuzhalin, S. Lucotti, J.A.F. Vermeer, K. Jones, J. Chen, R.J. Muschel, Tumour-derived laminin α5 (LAMA5) promotes colorectal liver metastasis growth, branching angiogenesis and notch pathway inhibition, Cancers (Basel) 11 (5) (2019).

[91] E.I. Deryugina, E. Zajac, L. Zilberberg, T. Muramatsu, G. Joshi, B. Dabovic, D. Rifkin, J.P. Quigley, LTBP3 promotes early metastatic events during cancer cell dissemination, Oncogene 37 (14) (2018) 1815–1829.

[92] L.S.M. Lecker, C. Berlato, E. Maniati, R. Delaine-Smith, O.M.T. Pearce, O. Heath, S.J. Nichols, C. Trevisan, M. Novak, J. McDermott, J.D. Brenton, P.R. Cutillas, V. Rajeeve, A. Hennino, R. Drapkin, D. Loessner, F.R. Balkwill, TGFBI production by macrophages contributes to an immunosuppressive microenvironment in ovarian cancer, Cancer Res. 81 (22) (2021) 5706–5719.

[93] M. Shen, Y.Z. Jiang, Y. Wei, B. Ell, X. Sheng, M. Esposito, J. Kang, X. Hang, H. Zheng, M. Rowicki, L. Zhang, W.J. Shih, T. Celià-Terrassa, Y. Liu, I. Cristea, Z. M. Shao, Y. Kang, Tinagl1 suppresses triple-negative breast cancer progression and metastasis by simultaneously inhibiting integrin/FAK and EGFR signaling, Cancer Cell 35 (1) (2019) 64–80.e7.

[94] C. Huang, Y. Liang, Y. Dong, L. Huang, A. Li, R. Du, H. Huang, Novel prognostic matrisome-related gene signature of head and neck squamous cell carcinoma, Front. Cell Dev. Biol. 10 (2022) 884590.

[95] T. Huang, L. Sun, X. Yuan, H. Qiu, Thrombospondin-1 is a multifaceted player in tumor progression, Oncotarget 8 (48) (2017) 84546–84558.

[96] J.S. Isenberg, D.D. Roberts, THBS1 (thrombospondin-1), Atlas Genet. Cytogenet. Oncol. Haematol. 24 (8) (2020) 291–299.

[97] Y.K. Jian, H.Y. Zhu, X.L. Wu, B. Li, Thrombospondin 1 triggers osteosarcoma cell metastasis and tumor angiogenesis, Oncol. Res. 27 (2) (2019) 211–218.

[98] Y. Cheng, H. Sun, L. Wu, F. Wu, W. Tang, X. Wang, C. Lv, VUp-regulation of VCAN promotes the proliferation, Invasion and migration and serves as a biomarker in gastric cancer, Onco Targets Ther 13 (2020) 8665–8675.

[99] L. Yang, Z. Dong, S. Li, T. Chen, ESM1 promotes angiogenesis in colorectal cancer by activating PI3K/Akt/mTOR pathway, thus accelerating tumor progression, Aging (Albany NY) 15 (8) (2023) 2920–2936.

[100] Y.K. Li, T. Zeng, Y. Guan, J. Liu, N.C. Liao, M.J. Wang, K.X. Chen, X.Y. Luo, C. Y. Chen, F.F. Quan, J. Wang, Q.F. Zhang, J. Zou, Validation of ESM1 related to ovarian cancer and the biological function and prognostic significance, Int. J. Biol. Sci. 19 (1) (2023) 258–280.

[101] M.H. Pourhanifeh, R. Mohammadi, S. Noruzi, S.A. Hosseini, S. Fanoudi, Y. Mohamadi, M. Hashemzehi, Z. Asemi, H.R. Mirzaei, R. Salarinia, H. Mirzaei, The role of fibromodulin in cancer pathogenesis: implications for diagnosis and therapy, Cancer Cell Int. 19 (2019) 157.

[102] Z. Ao, S. Yu, P. Qian, W. Gao, R. Guo, X. Dong, J. Xu, R. Zhang, C. Jiang, F. Ji, G. Qian, Tumor angiogenesis of SCLC inhibited by decreased expression of FMOD via downregulating angiogenic factors of endothelial cells, Biomed. Pharmacother. 87 (2017) 539–547.

[103] S. Sengupta, M. Mondal, K.R. Prasasvi, A. Mukherjee, P. Magod, S. Urbach, D. Friedmann-Morvinski, P. Marin, K. Somasundaram, Differentiated glioma cell-derived fibromodulin activates integrin-dependent notch signaling in endothelial cells to promote tumor angiogenesis and growth, Elife 11 (2022).

[104] L. Xia, T. Zhang, J. Yao, K. Lu, Z. Hu, X. Gu, Y. Chen, S. Qin, W. Leng, Fibromodulin overexpression drives oral squamous cell carcinoma via activating downstream EGFR signaling, iScience 26 (11) (2023) 108201.

[105] Y. Geng, P. Zuo, X.O. Li, L. Zhang, PODNL1 promotes cell proliferation and migration in glioma via regulating Akt/mTOR pathway, J. Cancer 11 (21) (2020) 6234–6242.

[106] X. Liu, Y. He, Y. Tong, Q. Huang, H. Shang, Z. Chen, K. Tang, PODNL1 promotes cell migration and regulates the epithelial/mesenchymal transition process in bladder cancer, Biochem. Biophys. Res. Commun. 620 (2022) 165–172.

[107] T.A. Järvinen, S. Prince, Decorin: a growth factor antagonist for tumor growth inhibition, Biomed. Res. Int. 2015 (2015) 654765.

[108] X. Hu, E.S. Villodre, R. Larson, O.M. Rahal, X. Wang, Y. Gong, J. Song, S. Krishnamurthy, N.T. Ueno, D. Tripathy, W.A. Woodward, B.G. Debeb, Decorin-mediated suppression of tumorigenesis, invasion, and metastasis in inflammatory breast cancer, Commun. Biol. 4 (1) (2021) 72.

[109] X. Han, Y. Zhang, F. Lu, J. Feng, C. Zhang, G. Wang, Hypermethylated PODN represses the progression of osteosarcoma by inactivating the TGF-β/Smad2/3 pathway, Pathol. Res. Pract. 238 (2022) 154075.

[110] C. Tian, Y. Huang, K.R. Clauser, S. Rickelt, A.N. Lau, S.A. Carr, M.G. Vander Heiden, R.O. Hynes, Suppression of pancreatic ductal adenocarcinoma growth and metastasis by fibrillar collagens produced selectively by tumor cells, Nat. Commun. 12 (1) (2021) 2328.

[111] T. Koorman, K.A. Jansen, A. Khalil, P.D. Haughton, D. Visser, M.A.K. Rätze, W. E. Haakma, G. Sakalauskaitè, P.J. van Diest, J. de Rooij, P.W.B. Derksen, Spatial collagen stiffening promotes collective breast cancer cell invasion by reinforcing extracellular matrix alignment, Oncogene 41 (17) (2022) 2458–2469.

[112] K.Y. Goh, K.W. Lau, T.Y. Cheng, S.C. Tham, C.T. Lim, N.G. Iyer, S.B. Lim, D. W. Lim, Matrisomal genes in squamous cell carcinoma of head and neck influence tumor cell motility and response to cetuximab treatment, Cancer Commun. 42 (4) (2022) 355–359.

[113] H. Qiu, X. Zhang, J. Qi, J. Zhang, Y. Tong, L. Li, L. Fu, Y.R. Qin, X. Guan, L. Zhang, Identification and characterization of FGFR2(+) hematopoietic stem cell-derived fibrocytes as precursors of cancer-associated fibroblasts induced by esophageal squamous cell carcinoma, J. Exp. Clin. Cancer Res. 41 (1) (2022) 240.

[114] C. Naktubtim, W. Payuhakrit, T. Uttarawichien, A. Hassametto, P. Suwannalert, YAP, a novel target regulates F-actin rearrangement-associated CAFs transformation and promotes colorectal cancer cell progression, Biomed. Pharmacother. 155 (2022) 113757.

[115] T. Shen, Y. Li, S. Zhu, J. Yu, B. Zhang, X. Chen, Z. Zhang, Y. Ma, Y. Niu, Z. Shang, YAP1 plays a key role of the conversion of normal fibroblasts into cancer-associated fibroblasts that contribute to prostate cancer progression, J. Exp. Clin. Cancer Res. 39 (1) (2020) 36.

[116] N. Ferrari, R. Ranftl, I. Chicherova, N.D. Slaven, E. Moeendarbary, A.J. Farrugia, M. Lam, M. Semiannikova, M.C.W. Westergaard, J. Tchou, L. Magnani, F. Calvo, Dickkopf-3 links HSF1 and YAP/TAZ signalling to control aggressive behaviours in cancer-associated fibroblasts, Nat. Commun. 10 (1) (2019) 130.

[117] T. Liu, L. Zhou, K. Yang, K. Iwasawa, A.L. Kadekaro, T. Takebe, T. Andl, Y. Zhang, The β-catenin/YAP signaling axis is a key regulator of melanoma-associated fibroblasts, Signal Transduct. Target. Ther. 4 (2019) 63.

[118] W. Sugimoto, K. Itoh, H. Hirata, Y. Abe, T. Torii, Y. Mitsui, Y. Budirahardja, N. Tanaka, K. Kawauchi, MMP24 as a target of YAP is a potential prognostic factor in cancer patients, Bioengineering (Basel) 7 (1) (2020).

[119] M. Park, J. Jin, D.Y. An, D.H. Kim, J. Lee, J.W. Yun, I. Hwang, J.S. Park, M.K. Kim, Y.M. Lee, J.K. Byun, Y.K. Choi, K.G. Park, Targeting YAP activity and glutamine metabolism cooperatively suppresses tumor progression by preventing extracellular matrix accumulation, Cancer Res (2024) (Epub ahead of print).

[120] T. Bertero, W.M. Oldham, E.M. Grasset, I. Bourget, E. Boulter, S. Pisano, P. Hofman, F. Bellvert, G. Meneguzzi, D.V. Bulavin, S. Estrach, C.C. Feral, S. Y. Chan, A. Bozec, C. Gaggioli, Tumor-stroma mechanics coordinate amino acid availability to sustain tumor growth and malignancy, Cell Metab. 29 (1) (2019) 124–140.e10.

[121] R. Xie, J. Liu, X. Yu, C. Li, Y. Wang, W. Yang, J. Hu, P. Liu, H. Sui, P. Liang, X. Huang, L. Wang, Y. Bai, Y. Xue, J. Zhu, T. Fang, ANXA2 silencing inhibits proliferation, invasion, and migration in gastric cancer cells, J, Oncol 2019 (2019) 4035460.

[122] R. Du, B. Liu, L. Zhou, D. Wang, X. He, X. Xu, L. Zhang, C. Niu, S. Liu, Downregulation of annexin A3 inhibits tumor metastasis and decreases drug resistance in breast cancer, Cell Death Dis. 9 (2) (2018) 126.

[123] C. Gounou, L. Rouyer, G. Siegfried, E. Harté, F. Bouvet, L. d'Agata, E. Darbo, M. Lefeuvre, M.A. Derieppe, L. Bouton, M. Mélane, D. Chapeau, J. Martineau, V. Prouzet-Mauleon, S. Tan, W. Souleyreau, F. Saltel, F. Argoul, A.M. Khatib, A. R. Brisson, R. Iggo, A. Bouter, Inhibition of the membrane repair protein annexin-A2 prevents tumor invasion and metastasis, Cell. Mol. Life Sci. 81 (1) (2023) 7.

[124] Z. Hong, P. Wen, K. Wang, X. Wei, W. Xie, S. Rao, X. Chen, J. Hou, H. Zhuo, The macrophage-associated prognostic gene ANXA5 promotes immunotherapy resistance in gastric cancer through angiogenesis, BMC Cancer 24 (1) (2024) 141.

[125] C. Lu, Y. Zhan, Y. Jiang, J. Liao, Z. Qiu, Exosome-derived ANXA9 functions as an oncogene in breast cancer, J. Pathol. Clin. Res. 9 (5) (2023) 378–390.

[126] X. Lu, L. Hu, J. Mao, S. Zhang, Y. Cai, W. Chen, Annexin A9 promotes cell proliferation by regulating the Wnt signaling pathway in colorectal cancer, Hum. Cell 36 (5) (2023) 1729–1740.

[127] H. Qi, S. Liu, C. Guo, J. Wang, F.T. Greenaway, M.Z. Sun, Role of annexin A6 in cancer, Oncol. Lett. 10 (4) (2015) 1947–1952.

[128] D.S. Whalen, S.E. Widatalla, O.Y. Korolkova, G.S. Nangami, H.K. Beasley, S. D. Williams, C. Virgous, B.D. Lehmann, J. Ochieng, A.M. Sakwe, Implication of calcium activated RasGRF2 in annexin A6-mediated breast tumor cell growth and motility, Oncotarget 10 (2) (2019) 133–151.

[129] H. Jang, Y. Jun, S. Kim, E. Kim, Y. Jung, B.J. Park, J. Lee, J. Kim, S. Lee, J. Kim, FCN3 functions as a tumor suppressor of lung adenocarcinoma through induction of endoplasmic reticulum stress, Cell Death Dis. 12 (4) (2021) 407.

[130] K. Boye, G.M. Maelandsmo, S100A4 and metastasis: a small actor playing many roles, Am. J. Pathol. 176 (2) (2010) 528–535.

[131] T.M. Ismail, R.G. Crick, M. Du, U. Shivkumar, A. Carnell, R. Barraclough, G. Wang, Z. Cheng, W. Yu, A. Platt-Higgins, G. Nixon, P.S. Rudland, Targeted destruction of S100A4 inhibits metastasis of triple negative breast cancer cells, Biomolecules 13 (7) (2023).

[132] H. Sun, C. Wang, B. Hu, X. Gao, T. Zou, Q. Luo, M. Chen, Y. Fu, Y. Sheng, K. Zhang, Y. Zheng, X. Ren, S. Yan, Y. Geng, L. Yang, Q. Dong, L. Qin, Exosomal S100A4 derived from highly metastatic hepatocellular carcinoma cells promotes metastasis by activating STAT3, Signal Transduct. Target. Ther. 6 (1) (2021) 187.

[133] B. Chen, D. Zheng, C. Liu, A. Bhandari, S. Hirachan, C. Shen, S. Mainali, H. Li, W. Jiang, J. Xu, X. Zhang, K. Tang, W. Zhang, S100A6 promotes the development of thyroid cancer and inhibits apoptosis of thyroid cancer cells through the PI3K/AKT/mTOR pathway, Pathol. Res. Pract. 242 (2023) 154325.

[134] A. Li, Y. Gu, X. Li, H. Sun, H. Zha, J. Xie, J. Zhao, M. Huang, L. Chen, Q. Peng, Y. Zhang, Y. Weng, L. Zhou, S100A6 promotes the proliferation and migration of

[135] cervical cancer cells via the PI3K/Akt signaling pathway, Oncol. Lett. 15 (4) (2018) 5685–5693.

[135] Z. Lu, S. Zheng, C. Liu, X. Wang, G. Zhang, F. Wang, S. Wang, J. Huang, S. Mao, Y. Lei, Z. Wang, N. Sun, J. He, S100A7 as a potential diagnostic and prognostic biomarker of esophageal squamous cell carcinoma promotes M2 macrophage infiltration and angiogenesis, Clin. Transl. Med. 11 (7) (2021) e459.

[136] E. Shubbar, J. Vegfors, M. Carlström, S. Petersson, C. Enerbäck, Psoriasin (S100A7) increases the expression of ROS and VEGF and acts through RAGE to promote endothelial cell proliferation, Breast Cancer Res. Treat. 134 (1) (2012) 71–80.

[137] A. Giguelay, E. Turtoi, L. Khelaf, G. Tosato, I. Dadi, T. Chastel, M.A. Poul, M. Pratlong, S. Nicolescu, D. Severac, A. Adenis, O. Sgarbura, S. Carrère, P. Rouanet, F. Quenet, M. Ychou, D. Pourquier, P.E. Colombo, A. Turtoi, J. Colinge, The landscape of cancer-associated fibroblasts in colorectal cancer liver metastases, Theranostics 12 (17) (2022) 7624–7639.

[138] E.A. Pietilä, J. Gonzalez-Molina, L. Moyano-Galceran, S. Jamalzadeh, K. Zhang, L. Lehtinen, S.P. Turunen, T.A. Martins, O. Gultekin, T. Lamminen, K. Kaipio, U. Joneborg, J. Hynninen, S. Hietanen, S. Grénman, R. Lehtonen, S. Hautaniemi, O. Carpén, J.W. Carlson, K. Lehti, Co-evolution of matrisome and adaptive adhesion dynamics drives ovarian cancer chemoresistance, Nat. Commun. 12 (1) (2021) 3904.

[139] H. Yu, M. Wang, X. Wang, X. Jiang, Immune-related matrisomes are potential biomarkers to predict the prognosis and immune microenvironment of glioma patients, FEBS Open Bio 13 (2) (2023) 307–322.

[140] S. Liot, A. Aubert, V. Hervieu, N.E. Kholti, J. Schalkwijk, B. Verrier, U. Valcourt, E. Lambert, Loss of tenascin-X expression during tumor progression: a new pan-cancer marker, Matrix Biol. Plus 6-7 (2020) 100021.

[141] F. Kabir, M.N.H. Apu, Multi-omics analysis predicts fibronectin 1 as a prognostic biomarker in glioblastoma multiforme, Genomics 114 (3) (2022) 110378.

[142] J. Liu, B. Lei, X. Yu, Y. Li, Y. Deng, G. Yang, Z. Li, T. Liu, L. Ye, Combining immune-related genes for delineating the extracellular matrix and predicting hormone therapy and neoadjuvant chemotherapy benefits in breast cancer, Front. Immunol. 13 (2022) 888339.

[143] L. Diao, M. Liu, Rethinking antigen source: Cancer vaccines based on whole tumor cell/tissue lysate or whole tumor cell, Adv. Sci. 10 (22) (2023) e2300121.

[144] E. Béraud, A. Collignon, C. Franceschi, D. Olive, D. Lombardo, E. Mas, Investigation of a new tumor-associated glycosylated antigen as target for dendritic cell vaccination in pancreatic cancer, Oncoimmunology 1 (1) (2012) 56–61.

[145] N. Jailkhani, J.R. Ingram, M. Rashidian, S. Rickelt, C. Tian, H. Mak, Z. Jiang, H. L. Ploegh, R.O. Hynes, Noninvasive imaging of tumor progression, metastasis, and fibrosis using a nanobody targeting the extracellular matrix, Proc. Natl. Acad. Sci. USA 116 (28) (2019) 14181–14190.

[146] N. Jailkhani, K.R. Clauser, H.H. Mak, S. Rickelt, C. Tian, C.A. Whittaker, K. K. Tanabe, S.R. Purdy, S.A. Carr, R.O. Hynes, Proteomic profiling of extracellular matrix components from patient metastases identifies consistently elevated proteins for developing nanobodies that target primary tumors and metastases, Cancer Res. 83 (12) (2023) 2052–2065.

[147] Y.J. Xie, M. Dougan, N. Jailkhani, J. Ingram, T. Fang, L. Kummer, N. Momin, N. Pishesha, S. Rickelt, R.O. Hynes, H. Ploegh, Nanobody-based CAR T cells that target the tumor microenvironment inhibit the growth of solid tumors in immunocompetent mice, Proc. Natl. Acad. Sci. USA 116 (16) (2019) 7624–7631.

[148] S.B. Lim, H.J. Cho, Correspondence to editorial on "multiomics profiling of buffy coat and plasma unveils etiology-specific signatures in hepatocellular carcinoma", Clin. Mol. Hepatol. (2024) (Epub ahead of print).