


Review

The Functional Role of Extracellular Matrix Proteins in Cancer

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Simple Summary: Extracellular matrix is a three-dimensional network of macromolecules that provide structural and biochemical support to surrounding cells. Extracellular matrix plays a critical role in the development and progression of cancer. The extracellular matrix of the tumor is very different from the matrix of the normal tissue. Mainly fibroblasts produce and regulate matrix remodeling, but in cancer, the tumor matrix also originates from cancer cells. We describe the mechanisms of how the protein composition and structure of the extracellular matrix changes during cancer progression and how abnormal matrix deregulates the behavior of stromal cells and influences cancer progression.

Abstract: The extracellular matrix (ECM) is highly dynamic as it is constantly deposited, remodeled and degraded to maintain tissue homeostasis. ECM is a major structural component of the tumor microenvironment, and cancer development and progression require its extensive reorganization. Cancerized ECM is biochemically different in its composition and is stiffer compared to normal ECM. The abnormal ECM affects cancer progression by directly promoting cell proliferation, survival, migration and differentiation. The restructured extracellular matrix and its degradation fragments (matrikines) also modulate the signaling cascades mediated by the interaction with cell-surface receptors, deregulate the stromal cell behavior and lead to emergence of an oncogenic microenvironment. Here, we summarize the current state of understanding how the composition and structure of ECM changes during cancer progression. We also describe the functional role of key proteins, especially tenascin C and fibronectin, and signaling molecules involved in the formation of the tumor microenvironment, as well as the signaling pathways that they activate in cancer cells.

Keywords: extracellular matrix; tumor microenvironment; tumor progression; matrix metalloproteinases; matrikines; tenascin; fibronectin; collagen



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1. Introduction

The tumor microenvironment is a highly heterogeneous environment around a tumor, that includes cellular components (fibroblasts, endothelial cells, adipocytes, immune and inflammatory cells) and a non-cellular component termed the extracellular matrix (ECM). During cancer progression, carcinoma cells recruit host stromal cells, which change their properties and metabolism, and together they create a unique microenvironment to cooperatively remodel the surrounding matrix and promote tumor invasion [1]. Remodeling of the ECM, driven by proteolytic enzymes (such as matrix metalloproteinases) [2], by enzymes that control the modification and cross-linking of extracellular matrix proteins (such as lysyloxidases (LOX)) [3], results in increased stiffness and altered ECM composition. Tumor cells also secrete extracellular vesicles with nucleic acids, lipids and proteins, which can participate in tumor progression and behavior, including tumor environment remodeling, fibroblast activation, angiogenesis, immunomodulation or the establishment of pre-metastatic niches [4,5].

Degradation of ECM is not a passive event as it is accompanied by the release of matrix-bound growth factors as well as matrikines that interact with multiple surface receptors and trigger signal transduction, thus regulating tumor growth and cell migration [6,7].

This review aims to present the functional role of ECM components in tumor development, with particular emphasis on the involvement of fibronectin and tenascin in this process. We also describe the relationships between cancer cells and cancer-associated fibroblasts, and the mechanisms by which cancerized ECM can modulate tumor progression and aggressiveness.

2. Structural Organization and Properties of Extracellular Matrix

The extracellular matrix is a major structural component of the tumor microenvironment and is comprised of a three-dimensional network consisting of collagens, laminins, elastin and elastic fibers, glycoproteins and proteoglycans [8]. In normal tissue, ECM provides structural support for the cells and also plays a regulatory role in many cellular processes including growth, migration, differentiation, survival, homeostasis and morphogenesis [9]. Every tissue (e.g., connective tissue, cartilage or bone) has a unique ECM composition, and the components of the ECM are produced and arranged by resident cells in accordance with the needs of the tissue (reviewed in [9]).

Based on biochemical and structural characteristics, the animal extracellular matrix can be classified into interstitial matrix and basement membrane. The interstitial matrix surrounds cells, whereas the basement membrane, a thin sheet-like extracellular matrix, delimits the stroma from cells of various origins (epithelial and endothelial cells, neurons and muscle cells, or adipocytes) and surrounds muscle fibers, adipose tissue, Schwann cells as part of myelin nerve fibers [10,11]. The major components of the basement membrane are type IV collagen, laminins, nidogen 1 and 2, and proteoglycans perlecan and agrin (Figure 1) [12].

Collagens are the major proteins of the ECM. Collagens are typically homo- or heterotrimers made of one, two or three different polypeptide chains (α -chains) [13]. For example, there are six different genes designated *COL4A1-COL4A6* encoding type IV collagen chains $\alpha 1(IV)$ – $\alpha 6(IV)$ [14]. Laminins are large heterotrimeric glycoproteins, consisting of α , β and γ chains that assemble to form a Y-shaped molecule. Mammalian genomes encode five α ($\alpha 1$ – $\alpha 5$), four β ($\beta 1$ – $\beta 4$) and three γ ($\gamma 1$ – $\gamma 3$) chains [15] and the laminin isoforms are named according to the three chain composition: i.e., laminin 332 is composed of $\alpha 3$, $\beta 3$ and $\gamma 2$ chains [16].

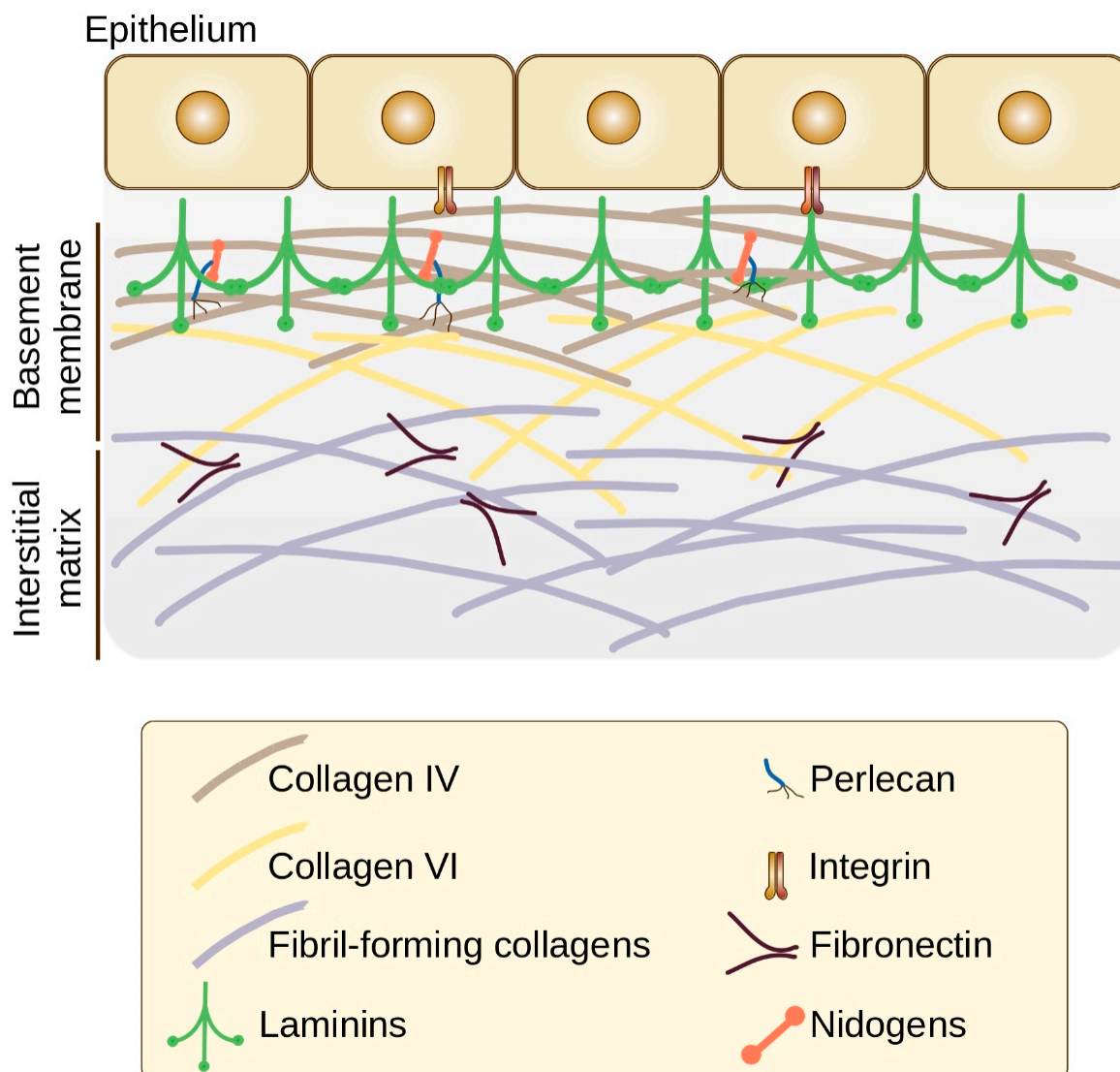


Figure 1. Schematic view of ECM organization (based on [12,17,18]). The major components of the basement membrane are the network-forming collagens (type IV collagen) and laminins. Nidogens and perlecan serve as binding bridges between the two networks: nidogens bridge laminin and collagen IV networks, and perlecan connects nidogen to collagen IV. Collagen VI interact with collagen IV, providing a link between the basement membrane and fibrillar components of the interstitial matrix.

Type IV collagen and laminin individually self-assemble into two independent but interconnected networks that serve as the foundation for basement membrane [18–20]. Globular domain of laminins at the end of the α chain binds to cellular receptors, including integrins, α -dystroglycan, heparan sulfates and sulfated glycolipids [17,21]. Nidogens and proteoglycans perlecan and agrin bridge the laminin and type IV collagen networks, increase their stability and influence the structural integrity of basement membrane [22]. Basement membrane also contains matricellular proteins such as thrombospondins, secreted protein acidic and rich in cysteine (SPARC), cartilage oligomeric matrix protein (COMP), tenascins and osteopontin (Figure 2) that interact with other matrix components and growth factors as well as with cell surface receptors contributing to tissue-specific functions [23,24].

Collagens			
<i>Fibril-forming collagens</i> I II III V XI XXIV XXVII	<i>Fibril-associated collagens with interrupted triple helices (FACITs)</i> IX XII XIV XVI XIX XX XXI XXII	<i>Network-forming collagens</i> IV VIII X <i>Beaded filaments and anchoring fibrils</i> VI VII XXVI XXVIII	<i>Membrane-anchored collagens (MACITs)</i> XIII XVII XXIII XXV <i>Multiplexin collagens</i> XV XVIII
Elastin and microfibrillar proteins – Elastin – Fibrillins – Microfibril-associated glycoproteins (MAGPs) – Fibulins – Elastin microfibril interface protein 1 (EMILIN-1)	Glycoproteins – Fibrinogen – Fibronectin – Laminins – Vitronectin – Nidogens	Matricellular (glyco)proteins are a group of nonstructural proteins that function by binding to matrix proteins and to cell surface receptors – Cartilage oligomeric matrix protein (COMP) – Fibulins – Osteopontin – Periostin – R-spondins – Secreted protein acidic and rich in cysteine (SPARC) – Thrombospondins – Tenascins	
Proteoglycans are genetically unrelated proteins that have covalently attached glycosaminoglycan (GAG) chains			
Intracellular <i>Secretory granules</i> – Serglycin	Extracellular <i>Hyaluronan- and lectin-binding proteoglycans (hyalectans)</i> – Aggrecan – Neurocan – Brevican – Versican		
Cell surface <i>Transmembrane</i> – Syndecans – NG2 – Betaglycan – Phosphacan <i>GPI-anchored</i> – Glypicans	<i>Small leucine-rich proteoglycans (SLRPs)</i> <u>Canonical</u> Class I – Biglycan – Decorin – Asporin – ECM2 – ECMX Class II – Fibromodulin – Lumican – PRELP – Keratocan – Osteoadherin Class III – Epiphycan – Opticin – Osteoglycin		
Pericellular <i>Basement membrane zone</i> – Perlecan – Agrin – Collagen XV – Collagen XVIII	<u>Non-canonical</u> Class IV – Chondroadherin – Nyctalopin – Tsukushi Class V – Podocan – Podocan-like 1 <u>SPOCK</u> – Testicans		

Figure 2. Structural-functional classification of matrix proteins (based on [13,18,24–26]).

Interactions of cells with the ECM are mediated by their surface receptors, such as integrins, syndecans and discoidin domain receptors (DDR) [8]. The family of integrins that are the main cell adhesion receptors for components of ECM includes at least 24 transmembrane heterodimers generated from a combination of non-covalently paired α - and β -subunits. Based on ligand substrate, integrins can be classified into receptors recognizing Arg-Gly-Asp (RGD) peptide motifs, collagen, laminin or leukocyte-specific integrins [27,28]. Integrins are bi-directional signaling receptors involved in outside-in and inside-out signaling. The inside-out signaling mainly acts to bring the integrin into the active conformation [29]. Upon ligand binding, integrins undergo conformation changes leading to outside-in signaling. Ligand-bound integrins engage the actin network via talin and additional cytoskeletal linker proteins, leading to integrin clustering and the following activation of focal adhesion kinase (FAK), Src-family protein tyrosine kinases

and integrin-linked kinase (ILK) [28,30]. Integrin adhesion also activates the Ras-ERK, PI3K/AKT and YAP/TAZ pathways [31,32].

Basement membranes are tightly associated with the interstitial matrix (lamina propria) through collagen fibrils, including collagens VI and VII. Collagen VI binds to laminin and collagen IV, as well as to collagen I fibrils in the interstitial matrix [33–35]. The protein composition of the interstitial matrix mainly includes collagens (I, III, V, VI), fibronectin and elastin [18].

3. Fibroblasts and Cancer-Associated Fibroblasts

ECM is a highly dynamic structure that is constantly remodeled, and fibroblasts are the major producers of ECM in normal physiology and in tissue repair [36]. After injury, tissue healing begins by activation of platelets to form a clot consisting of fibrin and fibronectin [37,38]. Platelets recruit immune cells to the injury site by releasing abundant soluble mediators and also produce adhesive glycoproteins resulting in the deposition of a fibrin clot that serves as a provisional matrix [39]. Platelets, endothelial cells and macrophages secrete signaling molecules including transforming growth factor (TGF- β) and platelet-derived growth factor (PDGF) that recruit resident and immigrating fibroblasts. These signals direct fibroblasts to either obtain pro-fibrotic phenotype, switching to ECM protein synthesis, or differentiate into myofibroblasts which participate in wound contraction [40]. Fibroblasts degrade the provisional matrix [41] by producing matrix metalloproteinases (MMPs) and replace it with immature collagens, elastin, fibronectin and proteoglycans, and forming mature collagen fibrils later in repair [39]. As the wound closes and evolves into a scar, myofibroblasts become apoptotic and finally disappear [42].

TGF- β , among other inflammatory cytokines, is a key regulator of fibroblast to myofibroblast differentiation during wound healing and cancer-associated fibroblasts (CAFs) transition in various cancers [43], including prostate, breast, pancreatic, bladder and colorectal cancer [44–50]. Active TGF- β can be released from ECM as a result of its degradation (reviewed in [51]) or can be secreted in exosomes by cancer cells [47]. CAFs in turn can also derive not only from resident fibroblasts and myofibroblast-like cells [52] but also from adipocytes [53], bone marrow-derived mesenchymal cells [54,55], hematopoietic stem cells [56,57] or endothelial cells [58], which explains, at least in part, the heterogeneity of CAFs in the tumor microenvironment [59,60].

Since CAFs produce a number of proteins that are specific to the origin of the cells and there is no specific protein to CAFs, a combination of proteins is used as markers to identify CAFs. Several intracellular and plasma membrane-associated proteins such as alpha-smooth muscle actin (α -SMA), fibroblast-activating protein (FAP), S100A4 protein/fibroblast specific protein-1 (FSP1) and vimentin have been used as CAF markers [60–64]. CAFs are characterized by increased proliferative capacity, elevated production of growth factors and ECM proteins, and increased metabolic activity [65–67]. Cancer-associated fibroblasts have been found to produce highly aligned fibronectin matrix, which promotes directional migration of cancer cells in CAF-derived matrices [68,69].

4. ECM Remodeling and Modification in Cancer

ECM deposition is considered a hallmark of cancer [70]. Mainly CAFs are responsible for ECM synthesis and remodeling. CAFs, driven by cancer cells, not only synthesize, produce and deposit substantial amounts of ECM components [71] but also contract the tissue, thus altering the ECM of the tumor stroma qualitatively and quantitatively [72]. Some tumor cells themselves can also synthesize components of the ECM such as collagen [73,74] and other ECM- and ECM-associated proteins [75,76], including secreted factors and modulators of the matrix [77]. Compared to stromal cells, cancer cells produce less amount of ECM proteins (<10% in pancreatic cancer [78]) but it was found that a number of cancer-cell-derived proteins can promote tumorigenesis and metastasis and correlate with poor patient survival [78,79].

4.1. Collagen Reorganization

Increased deposition of collagen is the most common alteration of ECM in cancer. In healthy tissues, interstitial collagen fibers are wavy, whereas the collagen fibers in tumors are often straightened [80–82] as well as quantitatively and qualitatively reorganized [83,84].

Three different orientations and deposition of collagen fibers, named tumor-associated collagen signatures (TACS), were revealed in human breast cancer to characterize tumors: TACS-1, the increased collagen fiber accumulation at a region surrounding the small tumors; TACS-2, the presence of straightened collagen fibers stretched around the tumor in non-invasive tumors and lastly TACS-3, the presence of collagen fibers aligned perpendicular to the tumor boundary [82]. Similar structural collagen signatures were found in other cancers such as ovarian cancer [85,86], basal cell carcinoma [87,88], prostate cancer [88], glioblastoma [89], renal cell carcinoma [80] and pancreatic ductal adenocarcinoma [90,91]. TACS have been shown to promote focal invasion and metastasis [82], influence disease state and tumor invasion [92,93] and correlate with significantly worse patient survival in multiple tumor types [81,84,90,94,95].

Linearly aligned collagen fibers are thought to generate migration highways that allow cancer cell invasion and dissemination [96]. It was demonstrated that ECM deposited by CAFs was remarkably aligned in a parallel pattern, and CAFs promoted the dissemination of malignant cells in vivo [97]. Increased collagen density and enzymatic cross-linking of collagen during tumor progression can lead to matrix stiffening, and stiffened cross-linked fibrillar collagen promoted enhanced PI3 kinase (PI3K) activity, and induced the invasion of an oncogene-initiated epithelium [98].

To locally degrade and to penetrate ECM barriers, cells use actin-rich protrusions termed invadosomes, which include invadopodia (in cancer cells) or podosomes (in stromal cells) [99]. It was shown that a high-density fibrillar collagen matrix can itself induce a formation of invadopodia via a specific integrin signaling pathway even in the absence of a significantly altered gene or specific protein expression [100]. Collagen I and IV have been demonstrated to promote invadopodia extension and migration of tumor cells as well as fibroblasts, endothelial cells and macrophages [101,102].

Some collagens also bind and activate receptor tyrosine kinases discoidin domain receptors (DDR1 and DDR2) that are thought to mediate metastases and cancer aggressiveness [103–106]. DDR1 activation induces Src, Notch and IKK signaling pathway, DDR2 promotes oncogenic signaling via mTORC2 and AKT pathway, and recent findings have demonstrated that DDR-collagen signaling plays an important role in cancer progression and metastasis (reviewed in [107–109]).

4.2. Collagens and Laminins

Many types of collagen are upregulated in cancer and involved in almost all steps of tumor progression including proliferation, invasion, angiogenesis and metastasis [110,111].

Fibril-forming collagens provide three-dimensional frameworks of tissues and organs, and their involvement in cancer progression has been the most studied in comparison to other types of collagens [112]. The most abundant type I collagen plays a significant role in different cancers and metastases [113–117]. Type I collagen-dense ECM can drive the metastases of estrogen receptor 1 (ER α +) breast cancers by altering hormonal signals [118]. It was also demonstrated that type I collagen can induce resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) via mTOR activation through an AKT-independent pathway [119,120]. Type XI collagen, a minor fibril-forming collagen, is a component of fibrils both in cartilage and a wide variety of non-cartilaginous tissues [121,122]. Its alpha 1 chain (COL11A1) has been found to be upregulated in a variety of cancers [123–128] and is supposed to promote proliferation, angiogenesis, invasion and drug resistance of cancer cells [129–132]. Proteolytic products of type XI collagen released into the circulation can be used as predictive markers for patients with pancreatic ductal adenocarcinoma [133]. Type V collagen, another minor fibril-forming collagen, was also

shown to be upregulated in squamous cell carcinoma, colorectal, gastric and breast cancer and associated with poor prognosis [134–137].

Collagen VI is expressed in many tissues where it interacts with different ECM proteins and cell surface molecules and functions as a bridge between the basement membrane and interstitial matrix [138,139]. Type VI collagen expression is elevated in many human cancers such as pancreatic, ovarian, lung, breast and colon cancer, favoring cell survival and tumor progression [140–145]. In recent studies, it has been demonstrated that alpha-3 chain of collagen VI and the cleaved C5 domain fragment, called endotrophin [146], are highly expressed in a variety of cancers and play a crucial role in tumorigenesis [147,148].

Laminins are also involved in cancer progression, including invasion, migration, angiogenesis, metastasis and drug resistance [149–151]. Expression of various laminin subunits is often upregulated in tumor or stromal cells of malignant tissues. Laminin-332 has attracted a lot of attention by its altered expression pattern in several human carcinomas: expression of laminin-332, or its $\gamma 2$ chain, is markedly elevated in mammary, colon, melanoma and sarcoma cancer cells and correlates with tumor invasiveness and poor patient prognosis [152]. It is proposed that laminin-332 involvement in tumor progression is mediated by binding to integrins $\alpha 6\beta 4$ or $\alpha 3\beta 1$ [153–156] and subsequent activation of focal adhesion kinase (FAK) and extracellular signal-regulated kinase (ERK) [156,157]. Increased laminin-332 $\gamma 2$ chain expression is a significant poor prognostic indicator for the patients with esophageal or colorectal carcinoma [158,159]. The fragment of laminin-332 $\gamma 2$ chain after cleavage by MT1-MMP [160,161] or MMP-2 [162] can bind to and activate EGFR and downstream MAPK signaling in cancer cells as well as MMP-2 gene expression and cell migration [163].

4.3. Fibronectin

Fibronectin is a high-molecular-weight glycoprotein that consists of two subunits, covalently linked by a pair of disulfide bonds at the C-termini [164,165]. Despite fibronectin protein being produced from a single gene, there are 20 isoforms of human fibronectin as a result of alternative splicing [166–168]. Fibronectin exists soluble as a dimer in the plasma (pFN) or as an insoluble part of the ECM (cellular FN) [169] where it interacts with many other ECM components. Fibronectins have been shown to interact with integrins, collagen, tenascin-C, fibrillin, glycosaminoglycans as well as with growth factors (reviewed in [170]).

Plasma fibronectin is synthesized and secreted without ED-A or ED-B segments (Figure 3) by hepatocytes [171]. Cellular fibronectin is synthesized by many cell types, including fibroblasts, endothelial cells, macrophages and tumor cells, and secreted with ED-A and/or ED-B extra-domains [172,173]. In cancer, CAFs have generally considered a source of fibronectin [174,175]. CAFs secrete and assemble fibronectin as parallel fibers mediating directional cancer cell migration [68,69].

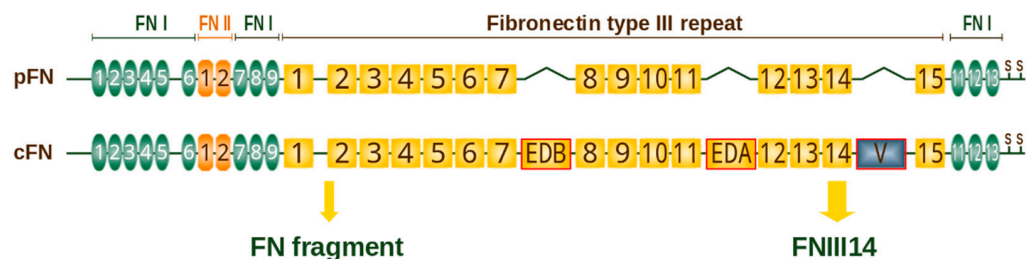


Figure 3. Domain structure of human fibronectin (based on SMART-tool [176] and review [177]). Each monomer contains three types of repeats: fibronectin type I (green ovals), type II (orange) and type III (gold rectangles). One or both of the FN type III modules (ED-A or ED-B) may be present in cellular fibronectin (cFN) but never in plasma fibronectin (pFN). A “variable” V or IIICS region is located between FNIII14 and FNIII15 and spliced out in ~50% subunits of pFN [178]. Two subunits are linked by a pair of C-terminal disulfide bonds to form a protein dimer. FNIII14 and “FN fragment” are proteolytic bioactive fragments derived from fibronectin.

For instance, in breast tumor tissues the expression of fibronectin, and specifically the ED-B isoform, was significantly higher compared to the adjacent tissues. Immunohistochemical analysis showed ED-B expression in cancer cell-associated fibroblasts, stroma and stromal fibroblasts, as well as in primary breast tumor and lymph node, lung, and brains metastases [179]. The expression of fibronectin is elevated in many solid tumors and is supposed to correlate with tumor grade/aggressiveness and can serve as a prognostic marker [174,180–184].

Although it is assumed that the role of fibronectin in oncogenesis and malignant progression is highly controversial [185] the mechanisms of fibronectin action in cancer are being actively studied (reviewed in [186–188]).

The role of fibronectin in promoting growth, survival and invasion of cancer cells has been highlighted by in vitro studies. It was shown that detachment of pancreatic cancer cells from ECM stimulated necrosis but fibronectin and laminin markedly increased the cells' survival by inhibiting both mitochondrial dysfunction and caspase activity [189]. Then this group of authors provided evidence that in pancreatic cancer cells fibronectin increased intracellular reactive oxygen species (ROS) production and NADPH oxidase activation [190]. The prosurvival effect of fibronectin on pancreatic cancer cells has been further investigated and shown to be mediated through the trans-activation of IGF-IR. The mechanism involved fibronectin-mediated complex formation between integrin $\beta 3$ and protein-tyrosine phosphatase SHP-2 that prevented SHP-2 from dephosphorylation of IGF-IR resulting in its sustained phosphorylation and the downstream activation of AKT kinase, up-regulation of anti-apoptotic Bcl-xL and inhibition of apoptosis [191].

It was also found that exogenous fibronectin stimulates lung carcinoma cell proliferation via integrin $\alpha 5\beta 1$ through activation of the AKT/mTOR/p70S6K pathway and inhibition of AMPK and LKB1 expression [192]. Exogenous fibronectin significantly enhanced proliferation and invasion in gallbladder cancer cell lines and markedly activated AKT/mTOR/4E-BP1 signaling cascade [193]. The role of fibronectin in promoting growth and migration via Src and TGF- $\beta 1$ signaling was also demonstrated in renal cell carcinoma [194]. Fibronectin can support cancer cell proliferation through Erk and Rho-kinase signaling [195]. A recent study provided evidence that collagen and fibronectin together, but not alone, facilitate proliferation and tumorigenesis of glioma cells through PI3K/AKT/SOX2 and CDC42/F-actin/YAP-1/Nupr1/Nestin signaling pathways via integrin $\alpha v\beta 3$ [196].

Fibronectin is also a cargo in extracellular vesicles (EV) from different cell types (reviewed in [197]). EV is a term used to define lipid bilayer membrane particles secreted by cells [198]. EVs can be generally divided into exosomes, microvesicles, apoptotic bodies and recently identified matrix-bound nanovesicles (MBV) [198–200]. Exosomes have been shown to play a major role in different stages of cancer progression, including cell proliferation, angiogenesis, invasion and metastasis [201–203]. MBVs, vesicles integrated within the dense fibrillar network of the ECM [200], are different from exosomes in membrane composition and luminal cargo [204]. MBVs are supposed to have a potential role in development, homeostasis, wound healing, tissue regeneration and neoplasia [205], but to date, there is no information on their involvement in cancer.

Fibronectin was found on the surface of fibroblast-derived extracellular vesicles. The EV surface-associated fibronectin induced an invasive phenotype in recipient fibroblasts, and the effect was dependent on interaction with the fibronectin receptor $\alpha 5\beta 1$ integrin, and activation of FAK and Src family kinases [206].

In a mouse model, circulating fibronectin enhanced the amount of local fibronectin in tumors through a positive feedback loop as well as enhanced tumor growth by increasing vascular endothelial growth factor (VEGF) content and VEGF-mediated signaling [207].

The production of fibronectin by cancer cells also contributes to the tumor development. In suspension cultures, squamous cell carcinoma cell aggregates, but not single cells, had high levels of fibronectin and were more resistant to anoikis through a mechanism involving fibronectin and the integrin αv receptor/FAK signaling [208]. An upregulation

of fibronectin levels due to detachment has also been demonstrated for lung and breast cancer cell aggregates, and this upregulation was suggested to be important for the development of anoikis resistance and further metastasis [209]. In a mouse model, a decrease in fibronectin production by cancer cells was shown to inhibit cancer growth due to inhibition of proliferation by decreasing ERK phosphorylation and diminishing YAP expression [210].

4.4. Tenascin

Tenascin-C, the first discovered member of the tenascin family, is a multifunctional ECM glycoprotein [211–214]. Other members of the family are tenascin-R, tenascin-W, tenascin-X and tenascin-Y [215].

The molecule of tenascin-C consists of six ~250 kDa subunits that are linked together at one end by disulfide bonds, and each subunit has four distinct domains [216–218]. Eight FNIII repeats (FNIII 1–8) are constitutively present in the tenascin-C molecule (Figure 4), but the nine FNIII repeats located between the fifth and sixth FNIII domain may be present due to alternative splicing [219]. The alternative splicing is thought to control the tenascin-C versatile functions by modulating its interaction with specific binding partners [219]. Moreover, splice isoforms demonstrate different sensitivity to proteases [220]. Tenascin-C has been shown to interact with various ligands, for instance with integrins [221], EGFR [222], fibronectin [223,224] and other ECM components (reviewed in [225]).

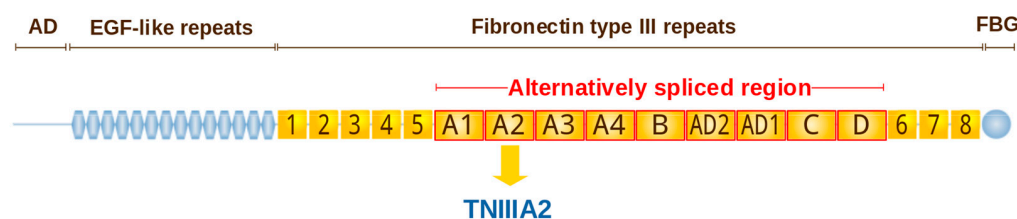


Figure 4. Domain structure of human tenascin-C (based on SMART-tool [176] and review [226]). N-terminal assembly domain (AD) links the tenascin chains and mediates the oligomerization and formation of hexamers. The assembly domain is followed by the EGF-like repeats and two types of FN-III domains: conserved (yellow rectangles) and alternatively spliced (yellow with red), and the C-terminal fibrinogen-like domain (FBG). Tenascin-C-derived 22-mer peptide TNIIIA2.

Tenascin-C has highly specific and restricted expression patterns in the embryo [227] but is almost undetectable in most adult tissues [228]. In adults, tenascin-C expression can be upregulated by mechanical stress, upon tissue repair or in cancer (reviewed in [228,229]). By mechanical stress, tenascin-C expression was found to be regulated by dynamic (cyclic) strain [230,231] as well as by static tensile stress, for instance by stressed collagen gels [232]. Tenascin-C expression is elevated in fibroblasts in response to TGF- β [233,234] or PDGF via PI3K/AKT pathway [235] upon inflammation or wound repair (reviewed in [229]). Although the expression of tenascin-C in the adult tissue is usually low, it has been described to be elevated in many human cancers [236,237].

Tenascin-C is highly expressed by cancer-associated fibroblasts and stromal cells, as well as by some cancer cells, and has been involved in promoting proliferation, migration, angiogenesis and metastasis [237–244]. High expression of tenascin-C correlates with cancer grade and poor prognosis in various cancers [245], including esophageal squamous cell carcinoma [246], glioma [247], gastric [248], prostate [249], breast [250] and colorectal cancer [251–253].

Expression of tenascin-C in tumor stroma was found in regions called tumor matrix tracks that are composed of several matrix molecules and are enriched with stromal cells including endothelial cells, fibroblasts and immune cells [243,254,255]. It was also found that tenascin-C and thrombospondin-2 co-localize with aligned collagen fibers in patient samples with invasive ductal carcinoma [256]. Tenascin-C expression can be induced in cancer cells as well as in stromal cells by different factors, including EGF, TGF- β , b-FGF and TNF- α [219,229]. For instance, mammary tumor cells produce TGF- β 1, which induces fibroblasts to synthesize tenascin [257]. Ras-transformed epithelial cells express tenascin-C

in response to TGF- β , and elevated ERK/MAPK signaling but not PI3K signaling was required for high expression levels of tenascin-C [258].

In vitro experiments suggested that tenascin-C can induce epithelial-to-mesenchymal transition (EMT) in breast cancer cells via binding to α v β 6 and α v β 1 integrins [259], colorectal [260] and pancreatic cancer cells [261] or promote invadopodia formation in Ewing sarcoma [262]. Knockdown of tenascin-C inhibited the proliferation and invasion of gastric cancer cells and EMT process through inhibited ERK phosphorylation [248]. Tenascin-C has been found to induce and activate others signaling pathways in cancer cells such as JNK, Wnt, Notch, AKT/HIF1 α and TGF- β [241,242,244,261,263–265].

The effect of tenascin on stromal formation has also been investigated. The addition of tenascin-C to fibroblasts significantly up-regulated α -smooth muscle actin and calponin that are the specific markers of differentiation to myofibroblasts, as well as significantly up-regulated the production of tenascin itself through integrin α v β 1/TGF- β signaling axis [266]. Yeo et al. demonstrated that tenascin-C is not only produced from fibroblasts but also is essential for their activation. They have found a positive feedback loop comprising basic helix-loop-helix transcription factor Twist1, homeobox transcription factor Prrx1, and tenascin-C functions as a bistable (ON/OFF) switch to initiate fibroblast activation [267].

Like fibronectin, tenascin-C was also detected in extracellular vesicles released into the extracellular space by most cell types, including fibroblasts and tumor cells (reviewed in [197]). Moreover, tenascin-C was detected in exosomes isolated from the blood of glioblastoma patients [268]. The authors established an immunosuppressive role for tenascin-C, since it was shown that tenascin-C inhibited T-cell proliferation through interaction with integrins α 5 β 1 and α v β 6 on T lymphocytes and decrease in AKT/mTOR signaling [268]. Jachetti et al. have also demonstrated that tenascin-C produced by prostate cancer stem-like cells inhibited T-cell proliferation by interacting with α 5 β 1 integrin and blocking reorganization of the actin-based cytoskeleton [269].

Experiments in vivo showed that knockdown of tenascin-C inhibited tumor growth and peritoneal dissemination and suggested the involvement of tenascin-C in vasculogenic mimicry formation [248]. It was also shown that stromal-derived tenascin-C promotes lung metastasis by impacting blood vessels invasions (BVI) at multiple levels [244]. Tenascin-C may generate barriers for infiltrating T lymphocytes (TIL), thus contributing to the escape from anti-tumor immunity [270].

In cancer, not only increased expression of tenascin is observed, but also various splice isoforms generated through alternative splicing of exons within fibronectin type III repeats (reviewed in [219,271]). Certain splice isoforms of tenascin-C were found in particular types of cancer [236]. Some studies have shown that larger tenascin-C isoforms are expressed only in tumorous but not in healthy tissues and their expression correlate with cancer progression and poor prognosis in glioma [272], bladder [273,274], ovarian [275] breast [276,277], pancreatic [278], esophageal [246] and lung cancer [279]. However, there are also data that the higher molecular weight of the isoform may not be the most relevant to cancer progression as there are examples of cancers where the smallest tenascin-C isoform is predominantly expressed or smaller splice variants promote invasion more effectively than does the unspliced tenascin-C [280–282].

5. Degradation of the Tumourigenic Matrix

5.1. Matrix Remodeling Enzymes

To permit invasion and cell migration, the extracellular matrix must be destroyed. The ECM is cleaved and degraded by target-specific proteases such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs), a disintegrin and metalloproteinases with thrombospondin motifs (ADAMTS), cathepsins and plasminogen activation system components (reviewed in [2,283,284]). These proteases are secreted primarily by stromal cells but also by cancer cells [285]. It was found in several studies in vitro and in vivo that CAFs induce migration, invasion and metastasis of cancer cells by producing various MMPs, including MMP-1, -2, -3, -7, -9 and -14 [286–290].

Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases: 28 different MMPs were found in vertebrates, of which at least 23 MMPs are expressed in humans [291,292]. On the basis of their substrate specificity and domain organization, MMPs are classified into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs and other MMPs [292]. MMPs are initially secreted as inactive zymogens [293] due to the interaction of a cysteine residue of the pro-domain with the zinc ion of the catalytic site. Only after disruption of this interaction by proteolytic removal of the pro-domain the enzyme become proteolytically active [294–296].

Gelatinases MMP-2 and MMP-9 as well as transmembrane MMP-14 (also known as MT1-MMP) are enriched at invadopodia that are essential for the degradation of ECM components and cell invasion [297–300]. A number of signals from the tumor environment, such as growth factors, hypoxia, extracellular pH, metabolism or direct interactions with stromal cells affect invadopodia formation and function [301,302]. The number and activity of invadopodia can also be directly increased by ECM rigidity, indicating a potential mechanism for the reported correlation of tissue density with cancer aggressiveness [303,304].

MT1-MMP (MMP14) is considered to play a key role in the early stages of tumor invasion and cancer progression [305]. Cancer cells concentrate MT1-MMP at invadopodia membranes [306–309] that can degrade a number of ECM molecules including collagen types I, II, III, fibronectin, tenascin, nidogen, perlecan and aggrecan [310,311]. MT1-MMP also activates MMP-2 [312,313] and combined action of MT1-MMP and MMP-2 is thought to enhance ECM proteolysis: MT1-MMP denaturates collagen into gelatin, which is subsequently digested by MMP-2 gelatinase [314]. Elevated expression of MMP-2 and MMP-9 is indeed considered a hallmark of cancer aggressiveness, and it is suggested that their levels can be useful prognostic biomarkers [315,316]. As a result of basement membrane degradation, tumor cells gain access to the blood and lymphatic vessels. As a result of excessive collagen remodeling by matrix metalloproteinases, small protein fragments of degraded collagens are released into the circulation and can be used to measure tumor activity and invasiveness as well as to serve as a prognostic and/or predictive biomarkers in different cancers [317–319].

5.2. Matrikines

Proteases secreted into the tumor microenvironment are not only essential for ECM remodeling, but they also release bioactive ECM fragments matrikines [320,321] or expose matricryptins [322]. These fragments in turn can regulate a wide array of biological processes, including angiogenesis, cell migration, adhesion and differentiation as well as tumor growth and metastasis [323]. It was found that matrikines can originate from collagen [324,325], elastin [326,327], tenascin [328,329], fibronectin [330,331], laminins [332], decorin, thrombospondin and versican [333].

In cancer, the most well-studied matricryptins are derived from collagens (e.g., collagens I, IIB, IV, VIII, XV, XVIII and XIX) [334]. A number of well-studied collagen fragments have anti-tumorigenic properties: arresten [335], canstatin [336–338], endostatin [339–341], pentastatin [342] and vastatin [343,344]. In contrast, there are matrikines that exhibit pro-tumorigenic activity. For instance, endotrophin plays a critical role in cancer development and is considered to be a target for anti-tumor therapy [139,148,345].

Tenascin-C is also proteolytically cleaved by MMP-2 and cathepsin B [346,347], and degradation was associated with higher recurrence and a worse prognosis for the patients with lung cancer [346,348]. It was found that tenascin-C molecule contains cryptic sequence YTITIRGV within the FN type III repeat A2 (Figure 4) that is exposed by MMP-2 processing [349]. The 22-mer peptide containing YTITIRGV termed TNIIIA2 is capable to induce activation of integrin $\alpha 5\beta 1$ and to rescue non-transformed fibroblasts from serum starvation-elicited apoptosis through activation of the AKT/Bcl-2 pathway [350]. It was also found that activation of integrin $\alpha 5\beta 1$ by TNIIIA2 caused active proliferation, disseminative migration and anoikis resistance in glioblastoma cells [351,352]. In glioblastoma cells, TNIIIA2 was also able to stimulate PDGF production that resulted in upregulation of

the tenascin-C expression in these cells. Tenascin-C induced increased expression of the active form of MMP-2 in glioblastoma cells, which was supposed to contribute to continuous PDGF production suggesting a positive feedback loop of tenascin-C/TNIII A2/PDGF leading to hyper-proliferation of glioblastoma cells [353,354]. TNIII A2 also promoted colon cancer cell invasion in vitro by upregulating MMPs and boosted pulmonary metastasis of colon cancer cells in a mouse model [355].

Unlike TNIII A2, which has the ability to activate β 1-integrins and is involved in the aggressive development of cancer, FNIII14, the peptide containing the bioactive site of plasma fibronectin, demonstrated an anti-tumor effect [329]. It was found that plasma fibronectin has a cryptic functional site YTIYVIAL, termed FNIII14 within the 14th FN type III repeat (Figure 3) [356]. FNIII14 was shown to attenuate the TNIII A2-induced aggressive phenotype of glioblastoma cells through β 1-integrin inactivation as well as delayed glioblastoma growth in a mouse xenograft model [352]. Another proteolytic fragment of fibronectin (Figure 3) secreted by bone marrow-resident mesenchymal stromal cells induced chemotaxis of prostate cancer cells via classic fibronectin-binding integrins α 5 β 1 [330]. It was supposed that proteolytic fragments of fibronectin may function as matrikines in the bone marrow niche and are involved in seed-and-soil mechanisms of disease progression [330].

Elastin is highly resistant to proteolysis and shows essentially no turnover in healthy tissues [357]. However, MMPs, aspartic proteases, serine proteases and cysteine proteases can fragment elastin to elastin peptides under several pathological processes, and elastin fragments can, in turn, activate MMPs (reviewed in [358]). In melanoma, fragmentation of elastin was found to occur at the invasive front of the tumor. Elastin fragments enhanced MMP-2 and MMP-14 production by melanoma cells that allowed further melanoma cell invasion through a type I collagen matrix by upregulating MMP-2 expression and activation [359].

Two categories of elastin-derived peptides have been described: Val-Gly-Val-Ala-Pro-Gly (VGVAPG, VG-6) with a xGxxPG consensus and Ala-Gly-Val-Pro-Gly-Leu-Gly-Val-Gly (AGVPGLGVG, AG-9) with the xGxPGxGxG consensus sequence [360,361]. Elastin peptide VGVAPG has been shown to stimulate fibrosarcoma cell invasion through the activation of MMP-2 and uPA [362,363], upregulate MMP-14 and stimulate the angiogenic phenotype of endothelial cells [364] and increase the invasiveness of lung cancer cells by post-transcriptional regulation of MMP-2 and uPA [365]. VGVAPG increased the migration of melanoma cells and the generation of elastin-derived peptides, enhancing the expression of elastin-degrading MMP-2 and MMP-3 through binding to galectin-3 and EBP receptors. VGVAPG also increased cells attachment and the expression of major adhesion molecules CD44, ICAM-1 and NCAM on melanoma cells through galectin-3 and integrin α v β 3 receptors [366]. The other peptide, AG-9, has been also shown to induce tumor growth, MMP-2 and uPA secretion, cell migration and cell adhesion [361]. The pro-invasive effects of AG-9 in squamous carcinoma cells were mediated through the ribosomal protein SA (RPSA) receptor [367].

6. Future Perspectives and Approaches in ECM Research

As outlined above, there are numerous publications implicating ECM proteins in cancer progression. We would like to outline here the main directions and methodological approaches for studying the role of ECM proteins in cancer.

6.1. Animal Models

In future experiments, experimental mouse models have to be established to further prove the functional role of ECM proteins in the process of tumor metastasis. There have been already several knockdown experiments of ECM proteins performed and analyzed in xenotransplantation mouse models. Recently, knockdown of tenascin-C in a human gastric cancer cell line has been shown to be implicated in the process of epithelial-mesenchymal transition and inhibited subcutaneous tumor growth and peritoneal metastasis in a xenotransplantation mouse model in vivo [248]. In further experiments, tissue-specific knock-

outs by using e.g., the Cre/LoxP system have to be made in order to analyze the tissue-specific function of ECM proteins during the process of metastasis in distinct organs [368]. Alternatively, by using the same Cre/LoxP system, tissue-specific overexpression of ECM proteins can be induced in order to analyze their functional role in metastasis.

An additional aspect is the functional role of the tumor microenvironment in mediating the functional role of ECM proteins. As outlined above, distinct signaling processes have been implicated in the functional role of ECM proteins in mediating the metastatic process. Therefore, distinct conditional and/or organ-specific knockout mice with deletions in the proposed signaling molecules like EGF receptors, WNT signaling, RAS-RAF-MAPK and PI3K-AKT-mTOR signal transduction have to be used to further pin down these signaling events in the tumor-infiltrating stroma cells after metastasis in distinct organs.

As we have already mentioned, there is a close interplay between tumor cells and the surrounding microenvironment. Tumors, arising from a single cell, gradually develop into heterogeneous cancer cell populations. Thus, mouse models can also be used to study tumor heterogeneity [369]. By using red, green, blue (RGB) marking as a lentiviral multi-color clonal cell tracking technology, the clonal development of subpopulations within tumors and metastases can be analyzed after transplantation of the RGB marked cells in mice [370]. The combination of RGB marking with immunohistochemical staining of distinct ECM proteins with fluorescently labeled antibodies will give additional information of the functional role of ECM proteins during the process of clonal development in tumorigenesis and/or metastasis.

6.2. Proteomic Approach

By analyzing the structure and functions of ECM, the proteomics-based and bioinformatic methods are undoubtedly needed to be mentioned. Proteomic characterization of matrisomes (“a list of all the proteins in any given matrix”) [371] or integrin adhesomes can be performed using mass spectrometry methods [76,372,373].

6.3. Imaging Technologies

ECM, and especially cancerized ECM, can be characterized not only by the protein composition and spatial organization but also by such a parameter as stiffness. As it was mentioned in the review, ECM remodeling, driven by proteolytic enzymes and cross-linking enzymes results in increased stiffness of ECM surrounding the tumor [374]. Sometimes conventional cell and molecular biology methods are not enough to characterize complex physico-chemical properties of ECM in cancer.

High-resolution microscopy techniques, for instance, second harmonic generation (SHG) or coherent anti-Stokes Raman scattering (CARS), are successfully used to quantify tissue structural changes during cancer progression [375,376]. It was also reported about the combined use of SHG microscopy and mass spectrometry [377].

6.4. 3D Cell Models and Tissue Engineering

Engineering approaches can be used to examine the effects of tumor-associated alterations in the ECM or ECM composition [378]. To explore the molecular mechanisms of tumor progression and metastasis, 3D cancer models can be used for the imitation of key steps of cancer dissemination (invasion, intravasation and angiogenesis) [379,380]. The decellularized matrix allows a comprehensive study of the ECM role in the regulation of cancer cell behavior [381,382].

7. Conclusions

In this review we have presented a picture of the versatile role of ECM proteins in cancer progression. Researchers focus now not only on the intrinsic properties of cancer cells and consider cancer not only as a disease of uncontrolled cell proliferation, but as a complex interplay of cancer and stromal cells in the dysregulated microenvironment.

To understand the mechanisms of ECM deregulation in cancer, it is crucial to elucidate the molecular basis of the cancer-dependent ECM remodeling, changes in gene expression and ECM composition, and the involvement of certain signaling pathways. Understanding the molecular mechanisms underlying survival, proliferation and invasion will help in the development of new therapeutic agents targeting tumor development and metastasis.

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Abbreviations

ADAM	disintegrin and metalloproteinases
ADAMTS	a disintegrin and metalloproteinases with thrombospondin motifs
AMPK	AMP-activated protein kinase
b-FGF	basic fibroblast growth factor
Bcl-xL	B-cell lymphoma-extra large
CAF	cancer-associated fibroblast
DDR	discoidin domain receptor
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR-TKI	epidermal growth factor receptor tyrosine kinase inhibitors
EMT	epithelial-to-mesenchymal transition
ERK	extracellular signal-regulated kinases
EV	extracellular vesicles
FAK	focal adhesion kinase
LOX	lysyl oxidases
MBV	matrix-bound nanovesicles
MMP	metalloproteinase
PDGF	platelet-derived growth factor
ROS	reactive oxygen species
TACS	tumor-associated collagen signatures
TGF- β	transforming growth factor
TNF- α	tumor necrosis factor alpha
uPA	urokinase-type plasminogen activator
VEGF	vascular endothelial growth factor

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