REVIEW

The extracellular matrix in tumor progression and metastasis

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Abstract

The extracellular matrix (ECM) constitutes the scaffold of tissues and organs. It is a complex network of extracellular proteins, proteoglycans and glycoproteins, which form supramolecular aggregates, such as fibrils and sheet-like networks. In addition to its biochemical composition, including the covalent intermolecular cross-linkages, the ECM is also characterized by its biophysical parameters, such as topography, molecular density, stiffness/rigidity and tension. Taking these biochemical and biophysical parameters into consideration, the ECM is very versatile and undergoes constant remodeling. This review focusses on this remodeling of the ECM under the influence of a primary solid tumor mass. Within this tumor stroma, not only the cancer cells but also the resident fibroblasts, which differentiate into cancer-associated fibroblasts (CAFs), modify the ECM. Growth factors and chemokines, which are tethered to and released from the ECM, as well as metabolic changes of the cells within the tumor bulk, add to the tumor-supporting tumor microenvironment. Metastasizing cancer cells from a primary tumor mass infiltrate into the ECM, which variably may facilitate cancer cell migration or act as barrier, which has to be proteolytically breached by the infiltrating tumor cell. The biochemical and biophysical properties therefore determine the rates and routes of metastatic dissemination. Moreover, primed by soluble factors of the primary tumor, the ECM of distant organs may be remodeled in a way to facilitate the engraftment of metastasizing cancer cells. Such premetastatic niches are responsible for the organotropic preference of certain cancer entities to colonize at certain sites in distant organs and to establish a metastasis. Translational application of our knowledge about the cancer-primed ECM is sparse with respect to therapeutic approaches, whereas tumor-induced ECM alterations such as increased tissue stiffness and desmoplasia, as well as breaching the basement membrane are hallmark of malignancy and diagnostically and histologically harnessed.

Abbreviations

ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
CAF	Cancer-associated fibroblast
CCN	CTGF, Cyr61, and NOV
CTGF	Connective tissue growth
CXCL12 = SDF.1	C-X-X chemokine 12 = stroma cell-derived factor-1
Cyr61	Cysteine-rich angiogenic protein 61
DDR	Discoidin domain receptor
ECM	Extracellular matrix
ED-A, -B	Extra domain-A, -B
EGF-L	Epidermal growth factor-like
EGFR	Epidermal growth factor receptor
Ela-2	Neutrophil elastase
ERC	Elastin receptor complex
Endo180	Endocytic receptor 180 = C-type mannose receptor 2
FNFr	Fibronectin fragment
GAG	Glycosaminoglycan
GPVI	Glycoprotein VI
HGF	Hepatocyte growth factor
IGF-1R	Insulin-like growth factor 1 receptor
IL	Interleukin
KRAS	Kirsten rat sarcoma oncogene
LAIR-1	Leukocyte-associated immunoglobulin-like receptor 1
LG3, 4	Laminin globular domain 3, 4
LOX/LOXL	Lysyl oxidase/lysyl oxidase-like

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LRP6	Low-density lipoprotein receptor-related protein 6
LY75	Lymphocyte antigen 75 (CD205, DEC-205)
MET	Mesenchymal-epithelial transition factor proto-oncogene, hepatocyte growth factor receptor, HGFR
MMP	Matrix metalloproteinase
MR	Mannose receptor
MuSK	Muscle-specific kinase
NC1	Non-collagenous domain 1
NCAM-L1	Neural cell adhesion molecule L1
NOV	Nephroblastoma overexpressed gene
NrCAM	Neuron-glial related cell adhesion molecule
PAR	Protease-activated receptor
PD-1/PD-L1	Programmed death-1/programmed death ligand-1
PDGF	Platelet-derived growth factor
PLA$_2$R	Phospholipase-A2-receptor
Sema3F	Semaphorin 3F
SIBLING	Small integrin-binding ligand-N-linked glycoprotein
SLRP	Small leucine-rich proteoglycan
SPARC	Secreted protein, acid and rich in cysteine
TAM	Tumor-associated macrophage
TF	Tissue factor
TLR-2, -4	Toll-like receptor-2, -4
TME	Tumor microenvironment
TGF-β	Transforming growth factor-β
Treg	Regulatory T cell
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
VM	Vasculogenic mimicry

Introduction

Metastasis is the prominent cause of death in cancer. Uncontrolled growth of cells within a tissue, neoplasia, leads to solid tumors at the site of origin. Unless the neoplastic growth does not demand too much space and unless it obstructs a vessel or a nerve thereby indirectly causing ischemia, analgesia and paralysis, the tumor is considered benign and, in most cases, removable by surgery. In contrast, metastasis occurs when tumor cells invasively infiltrate normal tissues neighboring the primary tumor mass. Moreover, they spread throughout the body in a malignant way, a hallmark of cancer [1, 2]. This spreading requires the motility of malignant cells [3]. They move through the connective tissue with its meshwork of ECM proteins [4]. Moreover,

metastatic cancer cells have to penetrate layers of tightly connected epithelial and endothelial cells and have to breach barriers of several ECM structures, such as the sheet-like basement membrane (BM) [5]. In addition, cancer cells must stay alive even in suspension during lymphatic and hematogenous dissemination. Attachment and detachment as well as movement require contacts of cancer cells with different ECM proteins and distinct supramolecular arrangements of the ECM. Moreover, the ECM also determines where cancer cells settle and establish a metastasis [6]. Recent years have highlighted that even in the primary tumor mass the ECM is qualitatively and quantitatively altered in a tumor-permissive way, thereby promoting tumor progression and influencing cancer cell invasion [7].

This review pinpoints the key role of ECM in the tumor environment and its interplay with tumor cells. It is of prime medical interest to decipher how the ECM is modulated by tumor cells and how the ECM affects metastasis in diverse aspects, acting as a mechanical support for migration and metastatic engraftment or as a barrier for cancer infiltration.

ECM, more than an intercellular filling material

The highly ordered meshwork of ECM-molecules

The distinction between an organ-specific parenchyma, such as the secreting epithelial cells of a gland, and the stromal compartment of the organ, which fills the space between the parenchyma and allows access of blood vessels and nerves, was a histologic description of an organ. This gave rise to the name 'connective tissue' for the stromal compartment. However, the stroma is not just an intercellular filling but an active element in the development, homeostasis, and functionality of the entire organ [4, 8]. This is based on the complex interplays between the cells of different lineages, such as epithelial cells and mesenchymal fibroblasts, and between the cells and the ECM.

The ECM, typically found in the large intercellular spaces of the connective tissue, consists of a meshwork of fibrous proteins, proteoglycans with their properties-determining carbohydrate conjugates, amorphous materials, minerals, and water [4, 9, 10]. The ECM also contains growth factors and other cytokines at orders of magnitude lower concentrations that orchestrate developmental processes in morphogenesis, regeneration and maintenance [8].

The molecular architecture of connective tissue underlines one function of the ECM, i.e., to shape and maintain the form of tissues and organs as a three-dimensional scaffold [4, 8–10]. In addition, the ECM also forms as a thin sheet-like BM that delimits the stroma from other tissues, such as the epithelial and endothelial cell layers, neurons and

muscle cells and fibers, or adipocytes. This BM serves as mechanical substratum for cell adhesion [5, 11–15]. Forming a structural scaffold, fibrous ECM proteins can bear mechanical tensile forces generated by cells and transferred to bone and cartilage to move the body. Also, the tissue pressure caused by the swelling capacity of charged polysaccharides of proteoglycans sets the fibrillar network under tension [14, 16–18].

The molecular and supramolecular structures of its components enable the ECM to fulfil the scaffolding and mechanical force-bearing functions (Table 1). The most abundant ECM proteins are the collagens, of which 28 types have been described so far [4, 10, 19–21]. Their characteristic feature is the collagenous triple helix and its propensity to assemble into higher-order supramolecular structures, such as fibrils and networks [4, 10, 19]. The triple helix consists of three collagenous peptide strands with a typical Gly-X–Y motif, with X and Y predominantly being proline and 4-hydroxyproline. In a parallel direction, they wind around each other in a staggered manner, as their glycine residues line up along the helix axis [22, 23]. Unless the triple helix is unwound by high temperatures, it is robust against proteolytic cleavage. Several triple helical collagen molecules align laterally and in a staggered manner to form fibrils [22, 24]. From the core to the perimeter of collagenous fibrils, the different collagen types, I, V, and XI, vary in their relative abundance to contribute best to the overall function of the fibril in tissue [25]. In network-forming collagens, additional intermolecular contacts such as head-to-head and tail-to-tail interactions, including some more recently discovered redox-based methionine-derived crosslinks, stabilize the chicken wire-like sheets of type IV collagen. Together with type XV and XVIII collagens, it is the shape-determining components of BMs [12, 26–29]. Additional collagen types, such as fibrillar collagens with interrupted triple helix (FACITs) or type VII collagen [30, 31], interlink the collagenous fibrils and networks to the surrounding ECM proteins. Once assembled in the extracellular space, the collagen molecules within the scaffold can be covalently crosslinked by extracellular enzymes, family members of lysyl oxidase (LOX and lysyl oxidase-like, LOXL) and transglutaminase [32–34]. These enzymes also covalently crosslink proteins of the elastin network, comprising elastin, fibrillins, and other associating ECM proteins [35, 36].

Another ubiquitously found ECM protein is fibronectin, which consists of two disulfide-linked chains. 20 different isoforms due to alternative splicing are known (Table 1) [37–39]. Fibronectin molecules not only bind to the collagen scaffold, but also align into filaments which can aggregate into networks with the help of cellular contacts via the fibronectin receptor, integrin α5β1 [40]. As a multidomain and multifunctional protein, fibronectin also binds several growth factors and proteoglycans [41].

The tensile forces that collagen and other fibrillar networks absorb counteract the tissue pressure created by the swelling power of the highly charged glycosaminoglycan (GAG) chains of proteoglycans [16, 17, 42]. This large family of ECM proteins comprises the large size hyaluronic acid-binding hyalectans (Table 1), viz. aggrecan, neurocan, brevican and versican, and the 18 different small leucine-rich proteoglycans (SLRPs), such as decorin and biglycan [17, 18, 43]. Among the long list of potential functions, two features of proteoglycans are noteworthy in this context. With their GAG chain(s) they tether growth factors and cytokines, thereby enabling the ECM to serve as storage and present growth factors in a temporal and spatial order needed for tissue development and regeneration [13]. Moreover, by interacting with other ECM proteins, proteoglycans may regulate their assembly, such as the collagenous fibrils, and their function, such as perlecan, which is characteristically found in BMs and contributes to its negative charge and its filtration properties [13, 44, 45].

Laminins are other typical components of BMs (Table 1) [10, 12, 46]. All 16 different laminins consists of 3 chains, α, β, and γ, which characteristically are wound around each other in an α-helical coiled-coil domain [24]. This forms the long arm of these cruciform molecules, the three short arms are shaped by the N-terminal domains of the three individual chains. The C-terminal end of the long arm is flanked by a large globular G-domain, which is divided into five homologous LG domains [47]. The first three assemble into a clover leaf-like structure, while the last two LG4-LG5 domains, which bind heparan sulfate GAG chains of proteoglycans, might be proteolytically cleaved off from some laminin isoforms in a physiologically regulated manner [48]. The supramolecular assembly of laminins is essential for BMs [49].

Being abundant around cells, matricellular proteins (Table 1) affect cell contacts to the ECM [50–52]. They have characteristic domains with which they interact with ECM scaffold proteins, such as the multifunctional SLRPs, decorin and versican [18, 50, 53]. Other matricellular proteins (reviewed in [50]) from various protein families are CCN proteins, tenascins [54–56], SIBLINGs [57], galectins [58], SPARC [59], thrombospondins [60], and periostin [61] (Table 1). They undergo characteristic changes during tumor progression [62]. Moreover, matricellular proteins, such as thrombospondins, can alter redox signaling in cancer cells, thereby affecting the hypoxia-influenced redox status within a tumor mass [60, 63].

Cellular contacts with the ECM

Cells are mechanically anchored in the ECM perceiving information about the environment. Epithelial and endothelial cells are aligned along the BM, which provides the substratum and cues for cell survival, and proliferation,

Table 1 Non-exhaustive overview of matrix proteins relevant for tumor progression and metastasis

Matrix proteins	BM component	Relevant proteases	Relevant peptides released	Relevant cellular receptors	Potential use in diagnostics
Collagens [4, 10, 19]					
Fibrillar collagens [25]:					
Collagen I Collagen II Collagen III Collagen V Collagen XI		Collagenases: MMPs-1, -8, -14 Gelatinases: MMPs-2, -9 [194, 196, 203]		Integrins α1β1, α2β1, α10β1, α11β1, DDR1, DDR2, GPVI, LAIR-1, MR PLA2R, LY75, Endo180 ([351] and references therein)	
Network-forming collagens and multi-plexins (*e.g.*, in the basement membrane) [12, 26, 29]:					
Collagen IV Collagen XV Collagen XVIII	Yes	MMP-9 [194, 196, 203]	α1(IV): arresten α2(IV): canstatin α3(IV): tumstatin α4(IV): tetrastatin α5(IV): pentastatin α6(IV): hexastatin α1(XV): restin α1 (XVIII): endostatin [229, 233, 234]	Integrins α1β1, α2β1 Integrin αVβ3 binds arresten, canstatin, tumstatin, and endostatin [229, 352]	
FACITs (fibril-associated collagens with interrupted triple helix) [30]:					
Collagen XIX [353]			α1(XIX): NC-1 [232]		
Collagen of anchoring *fibrils* [31]:					
Collagen VII	Yes	MMP-1 [354]			
Elastic fibrils [9, 355]					
Elastin		Ela-2, cathepsin G, proteinase-2, cathepsins L, S, K, V, MMPs-1, -2, -7, -9, -12 [241, 356],	Elastin-derived matrikine [230, 239, 242, 356]	Elastin receptor complex (ERC) [241]	
Fibrillin		ADAMTS -10, -6 [357]		Integrins αVβ3, αVβ6, α5β1 [358, 359]	

Table 1 (continued)

Matrix proteins	BM component	Relevant proteases	Relevant peptides released	Relevant cellular receptors	Potential use in diagnostics
Fibronectins [37–39, 101, 102]					
Fibronectin ED-A [38] Fibronectin ED-B [38]	Yes	MMPs-2, -3, -7,-10, -11 [354]	Fibronectin fragments (FNFr) [360]	Integrins α5β1 [100], α9β1, α4β1, αv-integrins [101, 103, 104] growth factors and syndecans [41] ED-A: integrins α9β1, α4β1, α5β1, αv-integrins [37, 38, 361], ED-B: integrins α9β1, α4β1, α5β1, αv-integrins [37, 38, 361]	ED-A: marks tumor stroma [37–39, 102, 103, 361–364] ED-B: marks tumor stroma [37–39, 102, 103, 361–364]
Proteoglycans [17, 18, 140] **Hyalectans (lecticans) [224]:**					
Aggrecan Neurocan Brevican Versican		Aggrecan: aggrecanases; MMPs-1, -2, -3, 7, -8, -9, -13, -14, ([365] and references therein); ADAMTSs [224, 365] Brevican: ADAMTSs [366] Versican: ADAMTSs -4, -5 [367]	Versican: versican-derived matrikine [236]	Neurocan: NCAM-L1, indirectly N-cadherin [368] and NrCAM/ Sema3F [369] Versican: β1 integrins [370]	
SLRPs [17, 18, 43]: Decorin [41, 51, 368–370, 372] Biglycan [371]		Decorin: MMPs-2, -3 [371]		Decorin: EGFR [372], IGF–1R ([373] and references therein), MET [374], VEGFR2 [375], 51 kD receptor [376] Biglycan: TLR-2, TLR-4, LRP6, MuSK ([377] and references therein), 51 kD receptor [376]	
Perlecan [13, 44, 238]	Yes	MMPs-3, -7 [371, 378]	Endorepellin [237, 238]	VEGFR2/integrin α2β1 [44, 238]	Blood levels of domain IV fragments elevated in prostate carcinoma [378]
Laminins [24, 46, 49] Laminin α chain β chain γ chain	Yes	MMPs-2, -3, -7, -10 [354, 371]		Heparan sulfate proteoglycans [143], syndecans [40, 74, 75]	Marks BMs
Laminin-332	Yes	MMPs-2, -9 [230, 354, 371]	LG3, LG4 [48, 112, 118, 119], EGF-L repeats ([230] and references therein]	Integrin α3β1 [379], EGFR ([230] and references therein]	Marks tumor stroma [111–113] β3 marks tumor stroma, poor prognosis [114, 116] γ² marks tumor stroma, poor prognosis, γ² in blood samples [114, 117]

Table 1 (continued)

Matrix proteins	BM component	Relevant proteases	Relevant peptides released	Relevant cellular receptors	Potential use in diagnostics
Matricellular proteins					
CCNs [50]:					
CCN1 (CYR61)				CCN1: integrins αvβ3, αvβ5, α6β1, syndecan-4 [381–383]	
CCN2 (CTGF)			CCN2-fragments [380]	CCN2: integrin α6β1, αvβ3 [384, 385]	CCN2: marks VM [156–159]
Tenascins [56, 107]:					
Tenascin C [54]		MMP-1, -8, -13 [371]	Tenascin C: EGF-L repeat [230]	Tenascin C: integrin α9β1 [386]; EGFR (EGF-L) ([230] and references therein]	Tenascin W: marks tumor stroma [55, 108, 110, 387]
Tenascin W [108]					
Thrombospondins [9]				CD36, αV and β1 integrins, syndecan, CD47	
Periostin [61]				Integrins αVβ3, αVβ5 [388]	Marks tumor stroma [7, 51, 61, 98, 109, 114, 270, 315, 316, 389]
SPARC [59]					Abundant in healthy vessels and tumors of good prognosis [59]
Galectins [58]					Promote tumor angiogenesis [390]; Affect tumor immunology [391]
SIBLINGs [57, 207]		MMPs-3, -7, MMP-9, thrombin [392, 393]	Osteopontin N-terminal fragment binds integrins αvβ3, αvβ5, α9β1, α4β1 [394, 395] Osteopontin C-terminal frament binds to CD44 [396]	Integrins αvβ3, αvβ5, αvβ1, α4β1, α8β1 and α9β1, (through both RGD and non-RGD motifs), CD44, MMPs, complement factor H [57]	Osteopontin and to a lesser extent bone sialoprotein mark tumor progression [397]
Osteopontin					
Bone sialoprotein					
Dentin matrix protein 1					
Sialophosphoprotein					
Matrix extracellular glycoprotein					

The ECM is very diverse and contains a wide variety of matrix proteins. Many of these ECM proteins release bioactive peptides by enzymatic cleavage. This may be of considerable interest for diagnosis. For better understanding of matrix regulation and cancer metastasis, ECM proteins are listed with their relevant proteases, and the respective peptides released by them, as well as specific receptors. More details can be found in the text

and other biochemical and physiological functions of the cells [11, 14]. Entirely embedded within the ECM, fibroblasts also intimately interact with the ECM by producing and assisting assembly of ECM molecules and by exerting mechanical forces onto the fibrillar network within the ECM, thereby contributing to ECM tension, an important biophysical parameter for the embedded cells [64, 65].

At the molecular level, interactions of cells with the ECM are mediated by various adhesion receptors, among which integrins and about 13 transmembrane proteoglycans take a principal role (Table 1) [17, 66, 67]. 18 members constitute the family of integrins, all of which consist of two subunits, α and β [66, 67]. The N-terminal domains of both subunits jointly form the head domain, which harbors the ECM ligand binding site. From the head, the two chains individually form two stalks, which can take different conformations representing different activation states. Via short membrane-spanning α-helices, both subunits possess short cytoplasmic domains, except for the large cytoplasmic domain of the integrin β4 chain [67]. Integrins lack, unlike growth factor receptors, any signaling domains. By recruiting adaptor molecules and signal transducing molecules, such as focal adhesion kinase (FAK) and members of the Src family, they serve as intracellular docking sites for the cytoskeleton and relay signals between the ECM and the cell interior [68]. This supramolecular protein array, which is recruited to the ligand-bound and clustered integrins, can be considered as an adhesion-dependent cell organelle, which was termed adhesome [69–72]. Depending on its stage of formation or on its function to support stable adhesion or cell migration, different types of adhesomes, such as focal contacts and focal adhesions, can be distinguished [72, 73]. However, due to experimental accessibility, most studies on these adhesion complexes have been carried out with cells adhering to and migrating on ECM-coated surfaces. These adhesome structures differ from the ones formed by cells in the three-dimensional system of the ECM. Nevertheless, integrins as transmembrane connectors between the ECM and the cytoskeleton allow transmission of forces, which the cells generate with their actomyosin system, onto the ECM [70, 72].

The four syndecan isoforms belong to the transmembrane glycoprotein, which also mediate cellular interaction with the ECM [4, 17]. Moreover, via their heparan and chondroitin sulfate GAG chains, syndecans and other cell surface proteoglycans are able to regulate integrin-ligand interactions, such as between fibronectin and laminins and their corresponding receptors (Table 1) [40, 74, 75]. Thus, they may assist integrins in recruiting signaling molecules to the adhesomes [40, 75–77].

## Tumor-induced ECM remodeling

After injury, tissue healing begins by forming the fibrin network of a hemostatic blood thrombus. Platelets, enclosed into the thrombotic plug, release growth factors and attract fibroblasts, which replace the provisional fibrin matrix for a collagenous matrix. The immigrating and resident fibroblasts differentiate into myofibroblasts [78, 79]. Marker proteins for myofibroblast differentiation are α-smooth muscle actin (αSMA), indicative of a strengthened actomyosin activity, and a bunch of secreted and deposited ECM-proteins, such as fibrillar collagens and fibronectin. The strengthened actomyosin machinery results in increased force exertion, which brings the newly deposited ECM under tension and causes wound contraction. Resembling chronic wounds, neoplastic tumors have been compared to a 'wound that never heals' [80, 81]. In fact, resident fibroblasts within a solid tumor mass differentiate into myofibroblast-like, cancer-associated fibroblasts (CAFs) under the influence of neighboring cancer cells [7, 79, 82, 83]. Transforming growth factor-β (TGF-β) is a key regulator in myofibroblast differentiation during wound healing and in CAF differentiation during tumor progression [7, 84]. Within the ECM meshwork, TGF-β is complexed by latent TGFβ-binding protein (LTBP) and the latency-associated protein (LAP) and tethered to the fibronectin network, which is connected to the fibrillar meshwork of the ECM [38]. Notably, partial proteolysis of LAP and mechanical tension along the ECM fibrils cause the release of TGF-β from its LTBP-cage and hence its activation. This promotes the differentiation of fibroblasts into more contractile CAFs, which further increase tension and release of TGF-β in a self-perpetuating circle [38, 79, 82, 85]. In addition, CAFs express a repertoire of diverse growth factors, such as vascular endothelial growth factor-A (VEGF-A), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and several chemokines, thereby attracting other cells, such as endothelial and immune cells to the tumor mass, and orchestrating them to join the tumor-supportive environment [7, 86].

By secreting ECM components and ECM-modifying enzymes, cancer cells modify their environment [87]. But even more, CAFs, driven by cancer cells, produce and deposit substantial amounts of ECM components, thus altering the ECM of the tumor stroma qualitatively and quantitatively [88, 89]. Therefore, the ECM at the primary site of the tumor dramatically changes in its composition and relative abundance, respectively. In addition, the ECM components are more frequently crosslinked by members of the LOX and transglutaminase family, especially LOX-1, LOXL-2 and transglutaminase-2, which are upregulated in neoplastic tumor tissue [32, 33, 90, 91]. Other posttranslational modifications of the ECM scaffold may also occur, as the nonenzymatic glycation of ECM proteins during hyperglycemia

may explain the increased risk to develop certain tumors in diabetes patients [92]. Caused by these biochemical alterations, the ECM also changes in its biophysical parameters, such as topography, stiffness/rigidity, and tension (Fig. 1) [65, 93, 94], as increased deposition of fibrillar collagen and cross-linkage *inter alia* stiffens the tissue and causes desmoplasia, the tumor-typical fibrotic deposition of ECM. Fibrillar collagens abundantly expressed in desmoplastic tumor tissue and other ectopically expressed ECM proteins can serve as diagnostic tumor stroma markers (Table 1) [89, 95]. Among these tumor stroma-typical ECM proteins are tenascin-W, laminin-332 [96–99], and the splice variant of fibronectin expressing the extra domains A and B (ED-A and -B).

Fibronectin is strongly expressed in the tumor stroma, in particular its splice variants ED-A and ED-B [37, 38, 100–105]. The two extra domains are partially redundant, as either of them can compensate for the loss of the other in the corresponding knockout mice. Nevertheless, the two

extra domains contain additional binding sites for integrins, α9β1 and α4β1, in addition to the fibronectin-binding αv subunit-containing integrins and the classical fibronectin receptor, α5β1 integrin [101, 103, 104]. Presumably due to its enhanced ability to contact cells via integrins, the ED-A-containing FN variant releases TGF-β1 from its LTBP-LAP complex especially in a mechanical force-dependent manner, without any need of partial proteolysis [38, 84]. Thus, mechanical tension, based on integrin-transmitted forces, promotes CAF differentiation [85, 103]. Moreover, the fibronectin meshwork also tethers other growth factors and may deliver them to proliferating tumor cells [41]. With respect to the increased deposition of cell-adhesive ECM proteins in the tumor stroma, it is intriguing that the tenascin isoforms, tenascin-W and -C, are highly upregulated among the tenascin family in a TGF-β1 dependent manner [106, 107]. They interact with fibronectin and attenuate cell adhesion [50, 54, 56]. Tenascin-W may even serve as specific molecular marker for the tumor stroma (Table 1) [108–110].
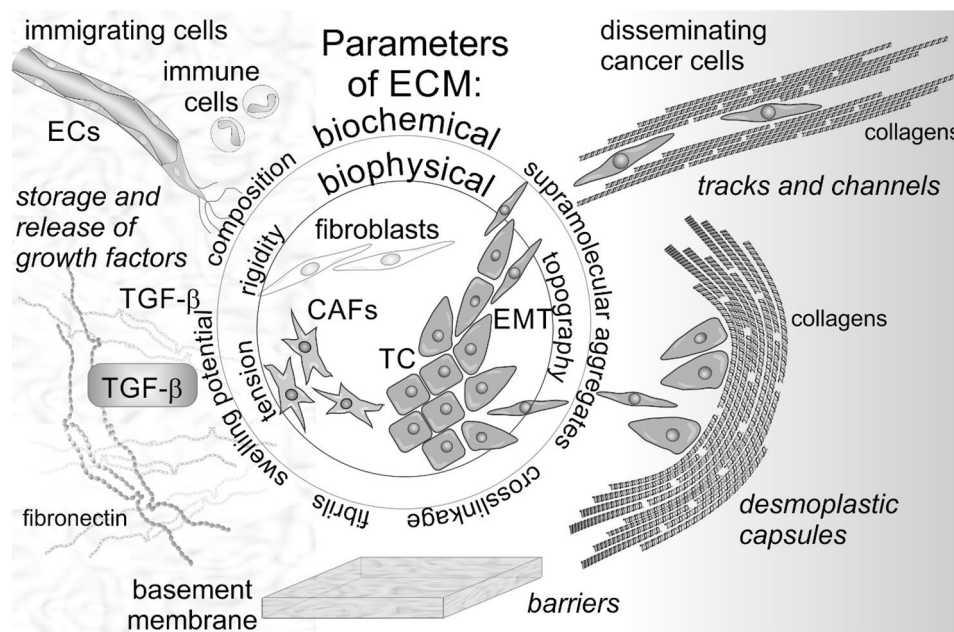
Fig. 1 Potential roles of the ECM in tumor progression and metastasis. The ECM embeds tumor cells (TC), resident fibroblasts and their derivatives, the cancer-associated fibroblasts (CAFs). Tumor-induced CAF differentiation is a hallmark of tumor progression, as CAFs contribute to the tumor-permissive and supportive tumor microenvironment (TME), as CAFs remodel the ECM by synthesis, modification, and cross-linkage of ECM components, especially under the influence of transforming growth factor-β (TGF-β). ECM composition, supramolecular aggregates, such as collagenous fibrils, and the swelling potential of proteoglycans are biochemical parameters of the tumor stroma ECM. In addition, TGF-β and other growth factors are stored within the ECM and released in a tension-dependent manner. The increased ECM deposition and desmoplasia, and the biochemical cross-linkage increases the stiffness/rigidity. In addition, the topography of the ECM components and the tension on the ECM are bio-physical parameters, which reinforce CAF differentiation and tumor progression. Both the swelling potential of proteoglycans and the high contractility of CAFs, the latter in a self-perpetuating manner, are responsible for the mechanical tension within the tumor stroma ECM. The biochemical and biophysical parameters of the tumor stroma ECM, together with the metabolic changes within the TME, attract endothelial and specific subsets of immune cells, which consequently contribute to tumor progression. Disseminating from the tumor mass, cancer cells undergo epithelial mesenchymal transition (EMT) and migrate either along tracks and channels within the ECM scaffold or are impaired by dense ECM obstacles, such as desmoplastic capsules of fibrillar collagen of the basement membrane. In the latter case, ECM-degrading enzymes clear a pathway and release ECM fragments, which as matrikines can stimulate cancer cell proliferation and invasion

In normal tissue, laminins are characteristically found in BMs. The ectopic expression of laminin-332 within the tumor stroma, especially at the invading front of tumor cells, is striking as other BM proteins are scarcely, if at all, expressed in this compartment (Table 1) [111–113]. However, some tumor entities apparently do not express laminin-332. For others, the expression of single laminin-332 chains, especially the laminin γ2 and β3 chains are reported. They correlate with poor prognosis for the patient (Table 1) [114–117]. Laminin-332 is also exceptional in terms of its diversity of partial proteolytic processing and the resulting altered cell migration [48]. Cleavage within the linker sequence between LG3 and LG4 of the laminin α3 chain may affect interaction sites for several integrins and the heparan sulfate chain of syndecan-4 and thus cell motility [48, 112, 118, 119]. Different proteases, also expressed by cancer cells, are involved in the proteolytic cleavage within the laminin chains, β3 and γ2, with different effects on tumor progression and cancer cell migration [48, 120, 121]. The ectopically expressed laminin-332 in tumor stroma promotes CAF differentiation and sustains the differentiated phenotype of CAFs [122].

The alterations in composition and cross-linkage of ECM, dictated by the cancer cells or mostly carried out by CAFs, result not only in biochemical properties and storage of growth factors [123], but also change biophysical parameters, such as stiffness and tension of the tumor stroma [65, 93, 124]. Although the ECM undergoes constant turnover, the life-time of these alterations limits plasticity of the tumor microenvironment, which can be considered as the 'memory' of the tissue or as a cancer-related 'ECM signature' [125–127]. This environmental niche provided by the biochemical and biophysical characteristics of the ECM is not only permissive to survival and proliferation of the cancer cells, but also it initiates and promotes oncogenic transformation and is able to influence somatic mutation rates [64, 65, 128]. This cancer growth-permissive tumor microenvironment (TME) also encompasses metabolic changes such as high concentration of lactic acid, acidosis, low support of oxygen and an altered redox status. These metabolic changes are caused by metabolic rewiring of cancer cells to use glycolysis as the primary source of energy, known as Warburg effect, their addiction to glutamine and their demand of oxygen [129, 130] [129, 130]. Other metabolic parameters of the TME are the altered metabolism of reactive oxygen species and of electrolytes, such as Ca^{2+}-ions, which have been reviewed elsewhere [63, 131, 132]. CAFs also contribute to these metabolic changes and are driven by cancer cells to support their metabolic needs [97, 133]. The desmoplastic changes of the ECM and the metabolic reprogramming of both cancer cells and CAFs influence the susceptibility of tumors to the most common therapeutic strategies, chemo- and radiotherapy [130, 134–137].

The tumor stroma ECM influences endothelial and immune cells within the tumor mass

CAFs are derived from fibroblasts and other mesenchymal cells, such as stellate cells, preadipoctyes, bone marrow-derived cells, endothelial cells and pericytes [138]. During tumor-induced angiogenesis, endothelial cells are attracted to the tumor bulk by members of the VEGF family, which are expressed by cells within the hypoxic tumor mass [139, 140]. Among the VEGF family members, VEGF-A$_{165}$ is the predominant angiogenic cytokine. In addition, CAF-produced cytokines, such as TGF-β and PDGF, stimulate angiogenic sprouting of vascular cells [7, 141]. These cytokines diffuse from the tumor mass and, by being tethered to GAG-chains of the ECM, form a stable gradient along which endothelial cells sprout into the tumor mass [142, 143]. Moreover, stiffness and other biophysical properties of the ECM influence angiogenetic sprouting, as endothelial cells form new capillaries especially at sites of high scaffold tension [144–146]. The outgrowing endothelial cells align longitudinally to form a lumenized tube that anastomoses and forms a closed circuit for blood flow [129, 147, 148]. The endothelial cell tubes are ensheathed by a newly formed BM. In contrast to vessels of normal tissue, tumor vessels are often tortuous, sometimes blunt-ended and with different calibers, which impairs blood flow through the tumor mass [147, 149]. Moreover, when reaching the tumor bulk, endothelial cells at the tip of the sprouts get in direct contact with the tumor stroma ECM and the tumor cells. Tumor cells not only coopt existing blood vessels, but also can integrate into the monolayer of endothelial cells or even replace the endothelial cells lining entirely, forming mosaic vessels or vasculogenic mimicry (VM) vessels [129, 147, 150–152]. Among other factors, ECM stiffness within the tumor mass favors the upregulation of the matricellular protein CCN1, which in turn induces N-cadherin expression in endothelial cells and thus allows direct intercellular contacts with tumor cells [153]. VM vessels are histologically recognized by their lack of the endothelial cell marker CD31 and by the presence of a sleeve of BM glycoproteins in periodic acid Schiff (PAS) staining [152, 154]. The presence of such VM vessels correlates, probably due to the direct access of tumor cells to the blood stream, with a poor prognosis [155]. Recent studies revealed that ECM proteins, their fragments and their supramolecular aggregates, foster the formation of such VM vessels. This has been reported for the matricellular protein CCN2, produced by CAFs, the proteolytically cleaved γ2 chain of laminin-332, and a dense three-dimensional collagen-network, respectively [156–159].

The new vascular tubes grown into the tumor mass provide nutrients and oxygen and remove waste products from the tumor cells, thereby supporting further tumor progression. Another advantage for the cancer cells is that ingrowing

blood vessels facilitate their spread through the blood stream [160]. For this hematogenous metastasis, tumor cells gain access to the blood stream by penetrating the endothelial cell layer and its subjacent BM. Also, lymph vessels are subverted by cancer cells to spread throughout the body. This lymphogenic metastasis explains why metastases are frequently formed in the lymph nodes into which the tumor tissue-draining lymph vessels converge [161–163].

During vessel formation, endothelial cells are assisted by diverse immune cells [164–166]. Also on their route of immunological surveillance, immune cells encounter the tumor mass [167]. However, the TME keeps most cells of the innate and adaptive immune system in an immunosuppressive state [168]. The contact of immune cells with the desmoplastic ECM deposition plays a yet not fully understood role in this immunosuppression, which further fosters tumor progression [169]. Within the tumor stroma, monocyte-derived macrophages preferentially acquire the M2 phenotype. These tumor-associated macrophages (TAMs) secrete various cytokines and interleukins (ILs), especially the immune reaction-attenuating IL-10, as well as TGF-β [168, 170]. TGF-β attracts the subclass of regulatory T-cells (T_{reg}s) and other adaptive immune cells to the tumor mass [84, 141]. Along with the myeloid suppressor cells, they suppress the attack of CD8$^+$-T-cells and of natural killer (NK) cells to cancer cells [168, 171–173]. This is mediated by direct cellular contacts via membrane-bound receptors and counterreceptors, among them the immune checkpoint receptor PD-1 and its ligand, PD-L1 [164, 174–176]. T_{reg}s also secrete TGF-β and help in activating ECM-tethered TGF-β, thereby reinforcing the tumor-supportive effects of this growth factor [173]. TGF-β was shown to cause expression of a set of ECM genes, which contribute to the immunosuppression of the TME [177]. Moreover, the selective recruitment of specific immune cells to the tumor stroma reinforces the desmoplastic process while the immune cell-secreted interleukins add an additional immunosuppressive tendency to the TME and contribute to the immunotolerance against cancer cells [168, 170, 178]. While reprogramming of T_{reg}s via immune checkpoint inhibitors is already an approved therapy to reactivate immune response against cancer cells [174–176], selective immigration of subgroups of immune cells into the tumor stroma likely depends on the ECM of the tumor stroma and might become another strategy to curb tumor progression and metastasis [179].

Cancer cells on the move: along or across the ECM

In order to metastasize, cancer cells spread throughout the body along different routes in successive steps of the metastatic cascade (Fig. 2). Cancer cells disseminate from the primary tumor site, where they separate from their neighboring cancer cells. Then, they migrate through the ECM scaffold and have to overcome barriers made by the dense ECM meshwork. Sometimes, they are transported by the blood stream or by the lymph for long distances and thus get to other organs, where they settle down and form a metastasis. Along their routes, cancer cells encounter ECM proteins, and the ECM scaffold plays an ambivalent role in cancer cell migration and metastasis. On the one hand, ECM supports cancer cell dissemination as fibrillar supramolecular structures serve as stabilizing scaffold, tracks and channels, which enable cancer cells to move at considerable rates through the stromal tissue. On the other hand, the ECM meshwork may impair cell migration by barring the way of cancer cells and forming impermeable dense ECM barriers, such as at the BM [64]. Cells sense their ECM environment by forming very thin cell protrusions, the filopodia, in which molecular ECM receptors probe the ECM environment [68, 180]. In addition, cancer cells have molecular tools and strategies to deal with supportive or impairing types of ECM.

Role of ECM in cancer cell dissemination

The vast majority of solid tumors are epithelial cell-derived carcinomas, which are characterized by their close cell–cell contacts. These intercellular connections are mediated via cadherins, a family of cell-membrane anchored immunoglobulin fold-containing proteins, which favor a homophilic, Ca^{2+}-dependent trans-interaction between cells of the same tissue [181–185]. These cadherin-mediated contacts allow the selective formation of epithelial cell layers and enable cells to withstand intercellular forces thereby clustering epithelial cells. Such intercellular bonds are loosened when individual cancer cells or a group of cancer cells leave the carcinoma in situ to disseminate (Fig. 2, step ❶ [183]. Along with the loss of cell–cell contacts, these carcinoma cells undergo additional changes, such as changing their morphology and becoming motile. This step of epithelial-mesenchymal transition (EMT) depends on several factors, such as the ECM and growth factors [186, 187]. The process is conveyed by intracellular signaling pathways, receiving signals from the ECM via integrins and from several growth factors, such as TGF-β and hepatocyte growth factor (HGF) via the corresponding growth factor receptors [141, 186, 187]. In particular, TGF-β is of key importance not only to CAF differentiation and immunosuppression but also to EMT of carcinoma cells, initiating their metastatic movement [141]. Additional CAF-derived growth factors, such as SDF1/CXCL12, reinforce this process [188].
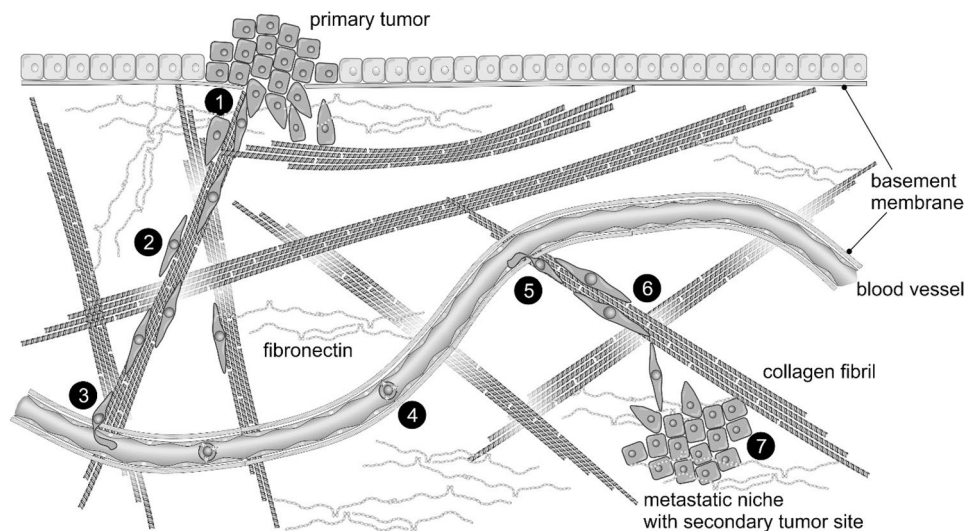
Fig. 2 The metastatic cascade. After the oncogenically transformed epithelial cells have grown into a neoplastic tumor (carcinoma in situ), they reveal their malignancy by undergoing metastasis and colonizing distant organs. The metastatic cascade encompasses the following steps, in which cancer cells encounter ECM molecules. ❶ Breaching the basement membrane (BM) and infiltrating into the underlying connective tissue requires proteolytic activity of the cancer cells and is a hallmark of malignancy. ❷ Taking advantage of collagen fibrils, cancer cells migrate through the interstitial space along these fibrillar tracks or through channels between collagen fibrils. ❸ Approaching the blood vessels, cancer cells again breach the suben- dothelial BM, intravasate and reach the blood stream. ❹ Decorated with thrombocytes in a fibrin-dependent manner, blood-borne cancer cells reach distant organs via the circulation. ❺ After attaching to the vessel wall, cancer cells extravasate by breaching the subendothelial BM and access the interstitial stroma. ❻ Again by migrating along the fibrillar components of the ECM scaffold, cancer cells migrate towards the premetastatic niche. ❼ Reaching it, cancer cells engraft within the ECM of the metastatic niche and progress to a secondary tumor mass or temporally remain in a dormant state, until tumor pro- gression resumes

Cancer cells breach ECM barriers

Epithelial neoplasias progress but remain in their original site. However, a decisive hallmark of malignancy is that they breach the BM which separates the epithelium from the neighboring connective tissue [2]. The BM is imper- meable to cells except immune cells and malignant tumor cells. To penetrate the dense ECM network of the BM, can- cer cells secrete several proteases of different types [87, 189–191]. Among these proteases, the Zn^{2+} ion-dependent matrix metalloproteinases (MMPs) play a crucial role and hence have a high prognostic value [192–195]. Among the 28 members of the MMP family, most studies in the last few years have focused on the two collagenases, MMP-1 and membrane-type 1 MMP (MT1-MMP, MMP-14), as well as on the gelatinases, MMP-9 and MMP-2 (Table 1) [194, 196–203]. Whereas gelatinases cleave only denatured col- lagen chains, collagenases are able to partially unwind and cleave the otherwise proteolytically stable triple helix of col- lagen [204–206]. After collagenolytic cleavage by MMP1 and MT1-MMP, the triple helix is destabilized, unwinds and becomes a substrate to MMP-9 and MMP-2. Moreover, acti- vation of MMP-2 also depends on the membrane-anchored MT1-MMP in a complex binding and cleaving mechanism [206–208]. Synthesis and secretion of MMPs by cancer cells depend on various factors of the TME, such as certain growth factors and the tumor-specific variants of fibronectin [209].

Invasion of cancer cells is hindered by the BM and cap- sules of fibrillar collagens surrounding desmoplastic tumors [2, 93]. Yet, invasive cancer cells can break through these dense collagen meshworks that are in their way with the aid of MT1-MMP-containing invadopodia, which take a cen- tral role in the proteolytic penetration of the ECM barrier [198, 201, 210, 211] (Fig. 3). These cellular protrusions are formed under the influence of the TME, especially TGF-β, HGF, and epidermal growth factor (EGF). Hypoxia also pro- motes invadopodia formation in cancer cells [198, 212–214]. The most appropriate stimulus is mechanical stiffness of the ECM, which is sensed via integrins in a Rho- and WASP/ WAVE-dependent manner [68, 212, 215, 216]. This results in a Rac-, PAK1- and cortactin-dependent formation of the core structure of the invadopodia [198, 212, 217, 218]. This core structure consists of F-actin bundles, which stabilize the cell protrusion and extend it into the ECM barrier at the front of an invading cell [198, 212, 219]. During maturation, various signaling molecules, such as PAK-1 and -4, which prolong the half-life of invadopodia, are recruited [220]. In addition, collagenolytic MT1-MMP is recruited to the inva- dopodium, which enables local proteolysis to facilitate the

Fig. 3 Invadopodia and adhesomes are ECM-contacting cell organelles, which are relevant in metastasis. Cancer cells can produce special membrane protrusions, termed invadopodia, which in many ways resemble adhesomes but also show differences [71, 180, 212, 349, 350]. Like adhesomes, invadopodia are equipped with integrins as ECM adhesion molecules, and similar to endothelial cell podosomes, these form an adhesion ring during invadopodium maturation [225]. In addition to the adhesive capability of adhesomes, invadopodia have ECM-degrading abilities. Therefore, invadopodia are important promoters of the metastatic cascade. Invadopodia are remarkably long-lived compared to adhesomes. Preferably using the nucleus as a mechanical abutment, they possess a stiff actin core that, together with various adapter and signaling molecules, can propel the invadopodium far into the ECM like a molecular drilling rod. Essential components of invadopodia and adhesomes are listed for comparison

	invadopodia	**adhesomes**
function	adhesion to and degradation of the ECM; drivers of the metastatic cascade	adhesion; migration
description	actin-rich core surrounded by actin-associated and signaling molecules	clusters of ECM receptors and adapter proteins that connect the ECM to the actin cytoskeleton
size	diameter 0.5-2 µm; length > 2µm	0.1 to 6 µm
location	ventral; often beneath the nucleus	cell border; leading edge
half-life	hours	minutes to hours; dependent on the rate of cell migration
components		
adhesion molecules	integrins; CD44	integrins
proteases	MMP14; MMP2; MMP9; ADAM12; ADAM15; ADAM19; uPAR; seprase	none
actin machinery	F-actin: core of unbranched filaments through the tip; branched at the cell surface; Tks5; cortactin; vinculin; zyxin; talin; ILK; IQGAP; N-WASP; WIP; Arp2/3; formins α-actinin; fascin; cofilin; coronin; myosin-X	F-actin: parallel bundles that branch at the end of the filament; kindlin; PINCH; paxillin, filamin; talin; tensin; vinculin; α-actinin; zyxin; VASP; PDLIM1; PDLIM5
microtubule machinery	required for elongation but not for formation; kinesins	inhibition promotes focal adhesions
GTPases	Rho, Cdc42, Arf6, AMAP1, dynamin	Rho; Rac
kinases	ABL; ERK; FAK; LIMK; PAK; PKC; PYK2; SRC	ILK; FAK
lipids	PIP2, PIP3, PI3P	PIP2

penetration of barriers and to activate the soluble gelatinase MMP-2 [198, 220]. Due to the recruitment of Tks-4 and -5, invadopodia are stabilized for more than 60 min, in contrast to cellular protrusions, called podosomes, of endothelial cells during tumor-induced angiogenesis, which are also equipped with proteolytic MT1-MMP activity [221–223]. Structurally homologous to MT1-MMP, the membrane-anchored proteinases of the ADAMTS family (a disintegrin and metalloproteinase with thrombospondin-1 motif) have been identified to cleave proteoglycans if they are obstacles to the cancer cell movement (Table 1) [224]. To allow attachment to the ECM, integrins are located in a ring-like fashion at the base of the invadopodium [225]. Either lacking or possessing ECM-cleaving proteinases, adhesomes and invadopodia, respectively, are cellular organelles, which mediate cellular contacts with the ECM in a metastasis-relevant manner (Fig. 3).

ECM barrier-penetrating proteinases also cleave protease-activated receptors (PARs) on cancer cells and CAFs, such as PAR-1 and PAR-2 [226]. These G-protein coupled receptors are cleaved canonically by thrombin and non-canonically by MMPs, such as MMP-1 and MMP-13, at their extracellular N-terminus [227, 228]. In the tumor stroma, activated monocytes/macrophages secrete thrombin. This is activated by cancer cell-derived tissue factor (TF) via an extrinsic coagulation cascade [226]. Likewise, MMPs are also activated at sites of ECM penetration. Proteolytic processing activates $G\alpha_{12/13}$ of the heterotrimeric G-protein and thereby Rho signaling. This affects the actomyosin machinery with its motor protein myosin II and thus increases cell contractility and cell movement. This further promotes invasion through the ECM barrier. Moreover, Rho activation promotes EMT of cadherin-interlinked cancer cells [227, 228].

In addition, ECM barrier-penetrating proteinases release soluble and bioactive fragments, so-called matrikines (Table 1), from insoluble matrix proteins that indirectly affect the TME [229–231]. Thus, fragments of BM collagen types IV, XV, XVIII, and XIX are released by proteolytically active infiltrating tumor cells. In addition to affecting cancer cells [232], endostatin and other such fragments are angiostatic and prevent sprouting of endothelial cells into the tumor mass [143, 229, 233, 234]. Endostatin also reverses

immunosuppression [235], and a versican-derived matrikine causes selective recruitment of a specific subset of dendritic cells to the tumor stroma [236]. Similarly, the perlecan fragment endorepellin impairs angiogenesis by interacting with integrin α2β1 on endothelial cells [237, 238]. Some fragments of matricellular proteins and of laminin-332 agonistically bind to the EGF receptor, thereby promoting cancer cell from motility [230, 239]. Likewise, matrikines can be cleaved off elastin [240–242].

ECM provides the molecular tracks for cancer cell dissemination

The molecular details of cell migration are described in other reviews [243–248]. Here, it may suffice to name the relevant molecules: (i) the force-generating actomyosin system, consisting of F-actin fibers and the interconnecting motor proteins myosin II [249–252] (ii) the actin cytoskeleton-organizing members of the Rho family, the WAVE/WASP family and Arf family [215, 216, 253–255], (iii) the motor protein-regulating kinases [256], and (iv) the adhesome proteins including integrins [251, 257] as well as adaptor proteins, such as vinculin, α-actinin, and paxillin. Vinculin and α-actinin change their conformation and thus unmask cryptic binding sites for other proteins upon force transmission [258–263]. Moreover, paxillin and vinculin are recruited after phosphorylation to the adhesome in a sustained and force-dependent manner [264, 265]. Therefore, they sense mechanical forces, including the stiffness/rigidity and the tension of the ECM, and serve as receptors for mechanotransduction. Moreover, linkage of the cytoskeleton with the nuclear membrane and force-dependent translocation of the transcription-factors, YAP and TAZ, results in a force-dependent gene expression along the Hippo pathway [266–268].

Cancer cell migration depends on the biochemical properties of the ECM, as cell adhesion receptors must interact with the appropriate strength to the scaffold protein to allow both attachment and detachment of the cell in an ordered manner [269] Collagen fibers are ideal tracks, along which tumor cells migrate (Fig. 2, steps ❷ and ❺ [270, 271]. In haptotactic migration, cells sense the density of cell attachment sites of the deposited ECM proteins [272, 273]. In addition, biophysical parameters of the ECM, such as fiber topography and geometry, stiffness/rigidity and tension determine cell migration (Fig. 1) [64, 65, 274]. Moreover, cancer cells perceive the mechanical conditions of their environment and regulate the migration rate in correlation to the ECM stiffness in durotactic migration [65].

Following the path of least resistance, infiltrating cells recognize and use open pores within the ECM. These pores must have an open cross-sectional area of at least 7 μm^2, which is necessary for the rather rigid nucleus of a eukaryotic cell to be squeezed through [3, 275, 276]. Otherwise, protease-assisted invadopodia open the pore to the necessary size. But also disruption and subsequent repair of nuclei have been observed [277]. Usually, cancer cells move through channel-like tracks of the ECM which are 3–30 μm in diameter and 100–600 μm in length [3]. Once such a migration track through the ECM scaffold is found or opened by a path-finding cancer cell, several cancer cells follow this path [127, 278, 279]. If adhesion strength to the ECM proteins in these channels is too low, cancer cells move in an amoeboid fashion, which is driven by the contractile activity of the cortical actin network. Upon integrin-mediated firm adhesion, cells migrate faster with a spindle-like fibroblastic shape. In adhesomes, integrins are connected to the actin cytoskeleton. Together with F-actin stress fibers, which stretch through the entire cell soma, myosin motor proteins generate the forces, which move the cell relative to the ECM. There are other additional types of migration between amoeboid and fibroblast-like migration, such as lobopodial migration with characteristic bleb-like membrane protrusions [3, 278–280].

Depending of the degree of intercellular contacts between the cancer cells, not only single cells but also groups of interconnected cancer cells can invade the ECM [281, 282]. Collectively migrating cancer cells are linked by cadherins and gap junctions, making them slower but also more robust to antimetastatic factors [283, 284]. In contrast, single cells or cohorts of less interconnected cancer cells migrate faster [281]. The transition from single cell migration to collective cell migration is multifactorial [127, 278, 279, 285]. Among other factors, it depends on the biochemical composition of the ECM, since, for example, fibronectin supports single cell migration [286]. Moreover, cancer cells adapt their migration mode to the biophysical properties of the ECM [286], to the status of pericellular proteolysis [287] and to metabolic conditions, including the hypoxic status, of the tissue [288, 289].

Also during cancer cell infiltration and migration, CAFs are not mere bystanders but reportedly promote cancer cell infiltration into the surrounding normal tissue by taking the lead and forming ECM tracks in which tumor cells follow [290]. Integrin α3β1 on CAFs and its ligand, laminin-332, in the tumor stroma play key roles in this context and confer migratory and invasive properties on cancer cells [122].

Hematogenous metastasis also depends on the ECM

The fastest way for cancer cells to colonize distant organs is the transport by the blood stream. During intravasation and extravasation, cancer cells gain access to and exit from the blood stream by penetrating the dense ECM network of the BM (Fig. 2, steps ❸ and ❺). Blood-borne cancer cells recruit platelets (Fig. 2, step ❹). The latter support the cancer cells

with growth factors and shelter them from immune attack [291]. The formation of such tumor cell-platelet aggregates is indispensably required for hematogenous metastasis [292]. Most of the multifactorial interactions between cancer cells and platelets are mediated via direct receptor-counterreceptor contacts. Nevertheless, fibrin is also an essential bridging molecule, which is recognized by both tumor cells and platelets via the integrins, αvβ3 and αIIbβ3, respectively [291]. Tissue factor (TF) expressing tumor cells activate the extrinsic pathway of the coagulation cascade and initiate the conversion of soluble fibrinogen to insoluble fibrin [293]. Like the scaffolding proteins of the ECM, fibrin molecules form highly ordered fibrin bundles, which bridge tumor cells and platelets, and thus contribute to hematogenous metastasis [226]. Von Willebrand factor (vWF), an ECM proteins usually expressed by endothelial cells, but also by cancer cells, may serve the same tumor cell-platelet-bridging function, and assist tumor cells to attach to the endothelial cells upon extravasation, along with cell adhesion molecules on tumor cells and platelets (Fig. 2, step ❺) [294, 295].

The metastatic niche, the site of settlement and colonization of cancer cells

If cancer cells find suitable conditions in a distant organ, they settle there and form a secondary, metastatic tumor (Fig. 2, step ❼). The question, whether the tumor cells are actively targeting a particular tissue or accidentally encountering an environment suitable for further cancer progression, has not yet been fully resolved. The first option is underlined by the fact that certain cancer entities show organotropism and form metastases preferentially in certain organs [296–299]. Another option was first phrased as 'seed and soil' theory by Stephen Paget in 1889, which states that metastasizing cancer cells like seeds engraft and grow only in tumor cell-permissive tissues (soil). In reality, both options are partly realized, as a primary tumor mass is able to influence secondary sites of the organism to prepare those distant sites for tumor cell engraftment, even before cancer cells take their metastatic routes. Hence, these primed secondary tissue sites were named premetastatic niches [300, 301].

Chemokines and matrikines, as well as exosomes, 30-100 nm-sized extracellular vesicles, are systemically released from the primary tumor [298, 302–304]. On their surface, exosomes bear integrins, which adhere to the ECM of the targeted tissue after being systemically distributed via blood and lymph throughout the body [298]. At the target sites, they fuse with normal cells and release their contents, among them translatable mRNA and regulatory microRNA (miRNA), along with proteins [303, 304]. Thus, these cells may change their phenotype, alter their metabolism, and secrete ECM proteins or ECM-modifying enzymes, such

as LOXs [305]. In addition, systemically spread cytokines and growth factors are recognized by corresponding receptors in the target tissue [126, 306]. Among the latter, also TGF-β educates the designated sites of metastatic settlement by altering the ECM and resident cells in a biochemical and biophysical manner similar to the ones in the primary tumor mass [306–308]. For example, tenascin-W is a component of the (pre)metastatic niche in bones [106]. LOX family members, secreted from a primary tumor and distributed systemically via the blood circulation, can interfere with bone homeostasis by promoting osteoclastogenesis, leading to the formation of premetastatic lesions that can be colonized by circulating cancer cells [309]. LOX also promotes tissue stiffening and induces premetastatic niche and metastasis in breast cancer [310, 311]. Also, immune cells immigrate into the chemokine- and exosome-responsive tissue, further preparing the properties of the (pre)metastatic niche [312]. Upon engraftment of metastasizing cancer cells, the premetastatic niche becomes a metastatic niche, which fosters its own progression, thus closing the metastatic cycle, or its dormancy [299, 313, 314].

Translational aspects and perspectives

The knowledge about the biophysical alterations of tumor tissue has been used diagnostically for a long time. For example, palpation examination of the breast detects tissue regions of stiffer ECM and desmoplasia, which are suspicious and prompt further examination of the patient. Biochemical alteration of the tumor stroma is analyzed histologically in tissue biopsies. Fibronectin splice variants containing the domains ED-A and ED-B, laminin-332, periostin and tenascin-W are such markers typical of tumor stroma [7, 61, 98, 109, 114, 315, 316]. Microscopic and other imaging techniques have been improved to diagnostically analyze more accurately tumor-associated alterations of the ECM [97, 271]. Therapeutic approaches to use these markers as antigenic targets to direct antitumor agents to the tumor site have been only experimental so far [96, 99]. Some of these tumor stroma-typical proteins and fragments thereof are diagnostically detected in blood samples, such as the laminin γ^2 chains [117]. They may develop into more robust and easily accessible tumor markers.

Therapeutics which directly target ECM components are still awaited. Several attempts, also in clinical trials, have been made to pharmacologically target ECM-modifying enzymes such MMPs and LOXs [32, 189, 191, 202]. Inhibition of MMPs might support the endogenous ECM barrier. Therefore, such inhibitors might prevent cancer cells from breaching the BM and curb or even prevent metastasis [5, 317]. Moreover, inhibitors of MMP-activated PARs, which

enhance the metastatic invasion of cancer cells, have been used in clinical trial [227].

While the use of MMP inhibitors as anti-cancer drugs was initially difficult due to lack of specificity and side effects, several new MMP inhibitors with improved properties have been developed and are currently under investigation ([318] and references therein). Neovastat (Benefin/AE-941) inhibits MMPs-2, -9, and -12, which is well tolerated by cancer patients in phase I/II clinical trials [319, 320]. Yet, in a phase III trial, no efficacy was found in patients with non-small cell lung carcinoma [321]. The broad-spectrum MMP inhibitor BMS-275291 was well tolerated in a phase I study and showed little musculoskeletal toxicity [322], but in a phase III study, it did not improve patient survival in advanced non-small cell lung carcinoma [323]. Also, another phase III study with tanomastat (BAY 12-9566), a non-peptidomimetic MMP inhibitor directed against MMPs-2, -3, and -9, did not show any efficacy in slowing or halting cancer progression [324]. Similarly, prinomastat (AG-3340), which inhibits MMPs-2, -3, 9, -13, and -14, caused arthralgia and myalgia in a phase I study and failed in a phase III trial of efficacy in non-small cell lung cancer [325, 326]. Yet, several monoclonal antibodies against MMP-9 [327, 328] and MMP-14 [329, 330] appear promising in preclinical models. With regard to MMP-directed tumor therapy, microRNA-mediated post-transcriptional MMP regulation is also of interest [331–333].

The other group of collagen-modifying enzymes, the copper-dependent LOX family members are also tangible targets for tumor therapy [32]. In a phase II study on copper depletion using tetrathiomolybdate, triple-negative breast cancer patients showed a marked decrease in the LOX activity involved in the formation of a premetastatic niche [334]. In other phase II trials, however, the LOXL2 function-blocking antibody simtuzumab did not improve clinical outcomes in patients with KRAS mutant colorectal or pancreatic adenocarcinoma [335, 336], although it is well tolerated in patients with solid tumors and inhibits the desmoplastic reaction in vitro [337, 338].

When inhibitors of ECM-modifying enzymes are used, in addition to limited specificity, undesirable side effects pose a considerable problem. For example, the broad-spectrum MMP inhibitor marimastat, although better bioavailable than its analog batimastat [339], proved inappropriate in phase III trials because it caused musculoskeletal pain and inflammation [340]. Similarly, the development of the low molecular weight inhibitor CGS 27023A/MMI270 directed against MMPs-2, -8 and -9 was discontinued because of poorly tolerated joint and muscular pains in phase II studies in early stage non-small cell lung carcinoma patients [341].

The potential to harness ECM molecules as antimetastatic therapeutics or to deliver anticancer compounds to the tumor have recently been evaluated in detail in a series of excellent reviews [16, 20, 39, 42, 43, 52, 237, 318, 342, 343]. Also, the ECM-receptors might be relevant pharmacological targets in blocking cancer cell progression and migration [243, 344, 345]. However, attempts to "normalize" the tumor stroma and its ECM into a non-tumor supporting environment [346] or to prevent the tumor-induced formation of premetastatic niches [347, 348] are desirable goals for the future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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