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Review

Non-collagenous ECM proteins in blood vessel morphogenesis and cancer☆

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ABSTRACT

Background: The extracellular matrix (ECM) is constituted by diverse composite structures, which determine the specific to each organ, histological architecture and provides cells with biological information, mechanical support and a scaffold for adhesion and migration. The pleiotropic effects of the ECM stem from the dynamic changes in its molecular composition and the ability to remodel in order to effectively regulate biological outcomes. Besides collagens, fibronectin and laminin are two major fiber-forming constituents of various ECM structures.
Scope of review: This review will focus on the properties and the biological functions of non-collagenous extracellular matrix especially on laminin and fibronectin that are currently emerging as important regulators of blood vessel formation and function in health and disease.
Major conclusions: The ECM is a fundamental component of the microenvironment of blood vessels, with activities extending beyond providing a vascular scaffold; extremely versatile it directly or indirectly modulates all essential cellular functions crucial for angiogenesis, including cell adhesion, migration, proliferation, differentiation and lumen formation. Specifically, fibronectin and laminins play decisive roles in blood vessel morphogenesis both during embryonic development and in pathological conditions, such as cancer.
General significance: Emerging evidence demonstrates the importance of ECM function during embryonic development, organ formation and tissue homeostasis. A wealth of data also illustrates the crucial role of the ECM in several human pathophysiological processes, including fibrosis, skeletal diseases, vascular pathologies and cancer. Notably, several ECM components have been identified as potential therapeutic targets for various diseases, including cancer. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

1. Introduction

Cells are usually embedded in an intricate extracellular matrix (ECM) that not only provides them with mechanical support, but also influences their survival, differentiation, shape, polarity and mobility. The ECM exists either in the form of interstitial stroma or as specialized basement membranes assembled at the basolateral surface of epithelial tissues, blood vessels, surrounding muscles, adipocytes, nerves and supporting cells [1]. The molecular architecture of the ECM is strikingly heterogeneous and varies not only between different organs (e.g. skin versus blood vessels) and tissue compartments (e.g. endocrine and exocrine pancreas) but also within the same tissue depending on the developmental (embryonic versus adult) and the physiological states (e.g. normal versus fibrotic).

Typically, the ECM contains protein fibers interwoven in a hydrated gel composed of glycosaminoglycans (GAGs) and proteoglycans. The main members of the ECM are laminins, collagens, fibronectin and elastins [2]. In addition, the ECM contains a large number of other proteins with essential roles in development and disease, including other non-fibrous glycoproteins (e.g. tenascin, thrombospondins), members of the CCN family and hemostatic system (e.g. von Willebrand factor, vitronectin and fibrinogen), neuronal guidance molecules (e.g. netrins, reelin) and specific-growth factor associated proteins (e.g. latent TGF-β binding proteins, insulin-like growth factor binding proteins). Several studies have linked human pathologies and disease syndromes with dysfunctional ECM proteins [3]. For example, mutations in the Fras family of the ECM are linked to Fraser syndrome that causes skin blistering in both mice and humans [4,5]. Modifications in ECM composition and organization are extensively identified in several pathological situations including fibrosis and cancer [6,7].

The biological outcome of extracellular matrix signaling is determined at multiple levels. The molecular composition of the ECM exerts pleiotropic effects in cells, as different ECM proteins could act in concert or compete with each other to elicit cellular responses [8]. The ECM can also control cellular behavior by binding and sequestering a large number of growth factors and cytokines (e.g. FGFs, TFG-β, VEGF, Wnts). In this way, the ECM acts as a "reservoir" regulating the availability and activity of important signaling molecules [9]. Additionally, the biophysical properties of the ECM (stiffness, deformability) are

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emerging as crucial regulators of important cellular functions, including cell differentiation and migration [10].

Due to space limitation, this review will concentrate on two important and well-studied components of the ECM, laminins and fibronectin, and discuss their biological properties specifically focusing on their emerging essential role in the morphogenesis of blood vessels during development and in pathological processes, such as cancer.

2. Laminins

2.1. Molecular structure and self-assembly

Laminins are cross- or T-shaped heterotrimeric glycoproteins consisting of one α, one β and one γ-chain held together by disulfide bonds (Fig. 1). Laminins are secreted as heterotrimers and further proteolytic processing is necessary to generate their final form [11]. In vertebrates, five α, three β and three γ chains have been identified that represent distinct gene products (*Lamα*1–5, *Lamb*1–3, *Lamc*1–3), whose expression varies between cell types and during development. Different combinations of α, β and γ chains could produce 45 putative laminin trimers but until now only 18 have been identified, including splice-variants. According to the current nomenclature, laminins are named by their composition of α, β and γ chains. For example, a laminin that is composed of α4, β1 and γ1 chains is named laminin 411 and corresponds to laminin 8 (Table 1).

All laminin chains share a common structure with a number of globular and rod-like domains (Fig. 1). The N-terminal portions of the laminin subunits form short arms, consisting of a globular LN (laminin N-terminal domain), at the end followed by a rod-like region of multiple LE (laminin epidermal growth factor-domains). The LN domain is essential for the self-assembly of the laminin network and its incorporation into basement membranes. Specifically, the LN domains form stable intermolecular interactions such that, at each interacting locus there are one α, one β and one γ LN domains contributed by different laminin trimers [12]. For laminin chains that do not possess LN domains, namely α3A and α4 chains, interactions with other ECM molecules including perlecan and nidogen could mediate their incorporation into the laminin network [13]. Two additional globular domains, laminin 4 (L4) and laminin four (LF), are found in the rod domain. The more distal sequences of the three subunits are intertwined forming an extended coiled-coil domain that joins the subunits together. The α subunit

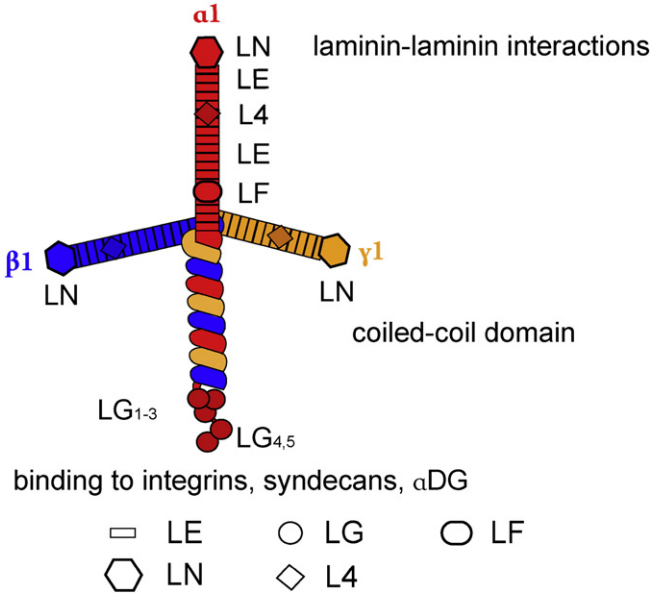

Fig. 1. The structure of the laminin trimer, consisting of one α, one β and one γ-chain depicted in different colours. Laminins domains are also indicated.

Table 1
Laminin isoforms. Current nomeclature and chain composition.

Laminin isoform	Previous name	Laminin trimer
LN 111	Laminin-1	α1β1γ1
LN 211	Laminin-2	α2β1γ1
LN 121	Laminin-3	α1β2γ1
LN 221	Laminin-4	α2β2γ1
LN 3A32	Laminin-5	α3Aβ3γ2
LN 3B32	Laminin-5B	α3Bβ3γ2
LN 311	Laminin-6	α3β1γ1
LN 321	Laminin-7	α3β2γ1
LN 411	Laminin-8	α4β1γ1
LN 421	Laminin-9	α4β2γ1
LN 511	Laminin-10	α5β1γ1
LN 521	Laminin-11	α5β2γ1
LN 213	Laminin-12	α2β1γ3
LN 423	Laminin-14	α4β2γ3
LN 523	Laminin-15	α5β2γ3
LN 212/222		α2β1γ2/α2β2γ2
LN 522		α5β2γ2
LN 3A33		α3Aβ3γ3

projects beyond the end of the common coiled-coil domain in a series of five globular (LG1–5) domains with a hinge-like region between LG3 and LG4 [14]. The LG domains of α chains mediate mainly the interactions with a variety of cell surface receptors, including integrins, dystroglycans and syndecans. In addition to triggering signaling events, these interactions also facilitate the polymerization of the laminin network [15]. Other domains in short arms of laminins may also bind to cell surface receptors, including integrins [11].

2.2. Laminin function in different tissues

Several lines of evidence show that the laminin network is absolutely required for the initial assembly of basement membranes. It has been shown that laminins are able to assemble sheet-like ECM structures on cell surface in the absence of other components [12]. Genetic mutations that eliminate laminin expression in specific tissues suggest that laminins function as scaffolds for the assembly of basement membranes. Specifically, laminins' short arms interact with various matrix proteins including nidogens, perlecan, fibulin-1 and -2, heparin and sulfatides to form a compliant sheet structure [13]. In contrast, knockout of other ECM components, including type IV collagen subunits, nidogens and proteoglycans (e.g. perlecan and agrin) affects the formation of basement membranes much later in development, suggesting a role in maintaining basement membrane stability [3].

Laminins exhibit tissue-specific distribution and developmental-specific expression patterns, mainly determined by the expression of α chains. For example, the α1 chain is expressed in the embryonic basement membrane during early embryonic development, by epithelial cells during organogenesis and by a few epithelial basement membranes in the adult [11]. Laminin α1 chain deficient mice die approximately at embryonic day 7, presumably because of defects in Reichert's membrane [16]. In general, laminin-111 and laminin-511 have been identified as the main laminins required during embryonic development, while other laminins have been referred to as important for organ maturation and specific tissue functions. The α2 chain is mainly expressed in the neuromuscular system, while the α3 chain is predominantly found in the epidermis. Mutations in α2 and α3 cause muscular dystrophy and skin blistering disease, respectively [17,18]. The α4 chain is expressed in endothelium, muscles, fat cells, Schwann cells, neuromuscular junction and bone marrow. Consistent with the expression pattern, laminin α4 chain deficient mice exhibit defects in vessels [19], neuromuscular junctions [20], peripheral nervous system [21] and in the heart [22]. The laminin α5 chain is predominantly found in embryonic basement membranes, in epithelial tissues, endothelium, smooth muscles and the neuromuscular junction. Deletion of laminin α5 chain in mice results in embryonic lethality

with multiple defects [23]. Laminin β1 and γ1 chain compose the majority of laminin trimers (Table 1). Thus, it is not surprising that elimination of these chains in mice causes early embryonic lethality due to absence of basement membranes [16,24]. Interestingly, the only mouse laminin mutant without an apparent phenotype is the laminin γ3 chain knockout mouse [25]. Considering all the findings from in vivo studies, it becomes apparent that laminin regulates critical biological activities and is a fundamental component of the ECM.

3. Fibronectin

3.1. Molecular structure and fibrillogenesis

Fibronectin is a large protein that exists in different isoforms of 240–270 kDa and different conformations, i.e. compact or extended. In vivo, fibronectin can be found in two forms, plasma fibronectin, which is a soluble molecule produced by hepatocytes that circulates in the blood at high concentrations and cellular fibronectin, which is produced in tissues where it is incorporated in a fibrillar extracellular matrix [26]. Fibronectin forms an antiparallel dimer composed of two similar monomers joined together by a pair of disulfide bonds near the C terminus. Each monomer is organized into type I, type II and type III repeats (Fig. 2). Disulfide bonds in type I and II repeats stabilize a folded protein structure. Type III modules are seven-stranded β-barrel structures that lack disulfides and provide flexibility. The different fibronectin isoforms are generated by alternative splicing, specifically in EIIIA, EIIIB and V regions [27]. The functionality of these different isoforms is not fully understood. For instance, in mice lacking both EIIIA and EIIIB domains, the mutant fibronectin isoform was incorporated in the extracellular matrix, indicating that these domains do not affect ECM assembly. However, deletion of both of these domains resulted in embryonic lethality, suggesting that this form of fibronectin is not fully functional [28]. In contrast, functional analysis showed that the N-terminal 70-kDa fragment composed mainly from type I and II repeats is important for matrix assembly [29].

Fibronectin interacts with several extracellular matrix molecules, including collagen/gelatin, fibrinogen, heparin, thrombospondin and tenascin [27]. Thus, it acts as a scaffold for the assembly of other matrix components. Through the RGD (Arg-Gly-Asp) motif, located in the type III_{10} domain, it binds to integrin cell-surface receptors [30]. Additional sites in the type $III_{9–11}$ repeats bind to integrins and the type $III_{12–14}$ repeats to syndecans at the surface of endothelial cells. These interactions have a synergetic role in transmitting signals to integrin receptors and modify cellular behavior [31]. Therefore, functions of the fibronectin depend not only on its linear sequence but also on the three-dimensional protein structure and its correct assembly into a functional fibrillar matrix.

Fibronectin fibril assembly is a cell-driven process in which integrins play a decisive role. Interestingly, soluble fibronectin does not form fibrils de novo due to its compact conformation. The initial step for fibrillogenesis is the binding of fibronectin dimers to $\alpha_5\beta_1$ integrin via the RGD motif and additional synergy sites. This step triggers conformational changes in fibronectin molecule and facilitates intermolecular fibronectin interactions via the N-terminal assembly domain. Fibrilogenesis depends on the generation of traction forces at cell-matrix adhesions driven by integrin-associated intracellular proteins and Rho-GTPase activity. Cell contractility induces additional conformational alterations in the fibronectin molecule, exposing cryptic self-assembly sites and fibrillogenesis proceeds as integrins translocate along paths of growing fibrils, leading eventually to the formation of a stable insoluble fibrillar matrix [27]. In the absence of RGD motif or $\alpha_5\beta_1$ integrin, the additional synergy sites and α_V integrins can compensate for fibril assembly but not fully for fibronectin function [32,33]. A recent study demonstrated that interactions of fibronectin with $\alpha_5\beta_1$ integrin drive nascent adhesion formation and generation of initial cell traction forces via RhoA-GTPase and myosin II driven contractility whereas binding of fibronectin to α_V integrins promotes the development of stable focal adhesions and contributes to rigidity sensing. Fibroblasts that expressed only $\alpha_5\beta_1$ integrin could not distinguish between substrates of different stiffnesses and adjust their contractility respectively. Establishment of fibronectin–integrin α_V bond was required for proper cellular responses to substrate rigidity and elevated traction forces [34]. This data suggests that fibronectin forms stronger bonds of longer lifetimes with αv integrins than $\alpha_5\beta_1$.

3.2. Fibronectin function

Several lines of evidence demonstrate the essential role of fibronectin in cell attachment and migration during both physiological and pathological conditions [35]. Furthermore, fibronectin could provide a scaffold for the assembly of several matrix proteins, including fibrillar collagens, thrombospondin-1, fibulin-1, fibrinogen, fibrilins and tenascin-C, thus, participating in the organization of basement membranes [36]. An additional function for fibronectin stems from its ability to stretch and to expose cryptic sites for additional interactions with cell-surface receptors and other ECM components. It has been suggested that in response to force, intramolecular structural changes in fibronectin could elicit signals that modulate cellular responses. Thus, fibronectin has emerged

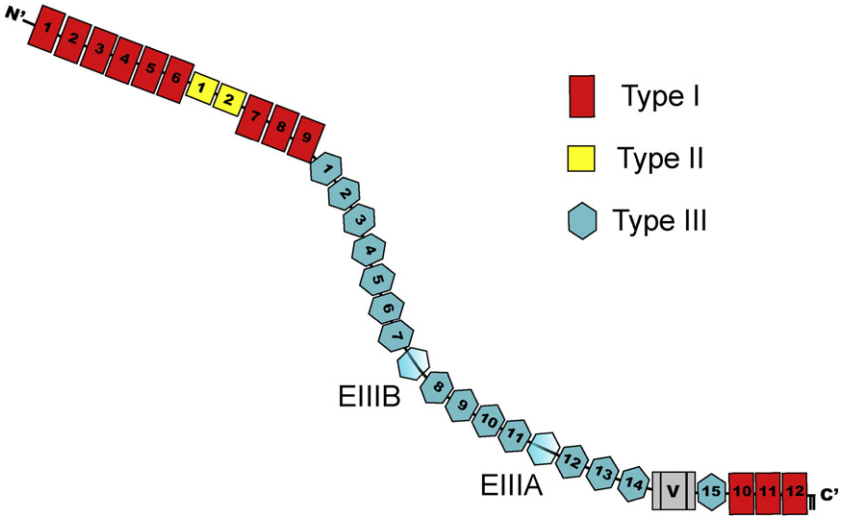

Fig. 2. The structure of the fibronectin monomer with the different domains depicted in colour. Fibronectin forms an antiparallel dimer consisted of two monomers joined by a pair of disulfide bonds near the C terminus.

as an important mechano-regulator of the tissue microenvironment [31,34].

In vivo deletion of fibronectin in mice revealed severe mesodermal, vascular and neural tube defects leading to lethality at around embryonic day (E) 8.5 [37]. Besides the crucial function of fibronectin in the vascular system (discussed below), elegant studies have revealed a role of fibronectin in epithelial branching. Fibronectin is specifically deposited in the area where the epithelium will invaginate and split to form a branch in several epithelial tissues, including the salivary gland, lung and kidney [38].

4. Properties of vascular basement membrane

The formation of the vascular system in which blood vessels develop branched networks penetrating all tissues to ensure adequate blood supply is one of the most crucial events in development and organ homeostasis. Blood vessels are composed of endothelial cells, which stably adhere to extracellular matrix, namely the vascular basement membrane (Fig. 3). The endothelial layer is surrounded by supporting cells (pericytes and smooth muscle cells) to different ranges, depending on the vessel identity and size. Endothelial functions extend beyond nutrient or oxygen transport and waste removal. Vascular endothelial cells provide inductive cues and pattern information during organ development and regeneration. For instance in the developing endocrine pancreas, the laminin-rich vascular basement membrane provides cues for β cell proliferation and insulin secretion [39]. Additionally, they regulate immune responses and facilitate communication between different tissues in the organism. It is well established that a reciprocal interaction between endothelial cells and tissue microenvironment regulates biological responses in physiological and pathological conditions [40].

Endothelial cells are polarized cells resting on the vascular basement membrane. Typically, vascular basement membranes contain laminin-411, laminin-511, type IV collagens, perlecan, nidogens, collagen XVIII and von Willebrand factor [30]. Interestingly, the different ECM constituents can regulate the composition of vascular membrane by affecting

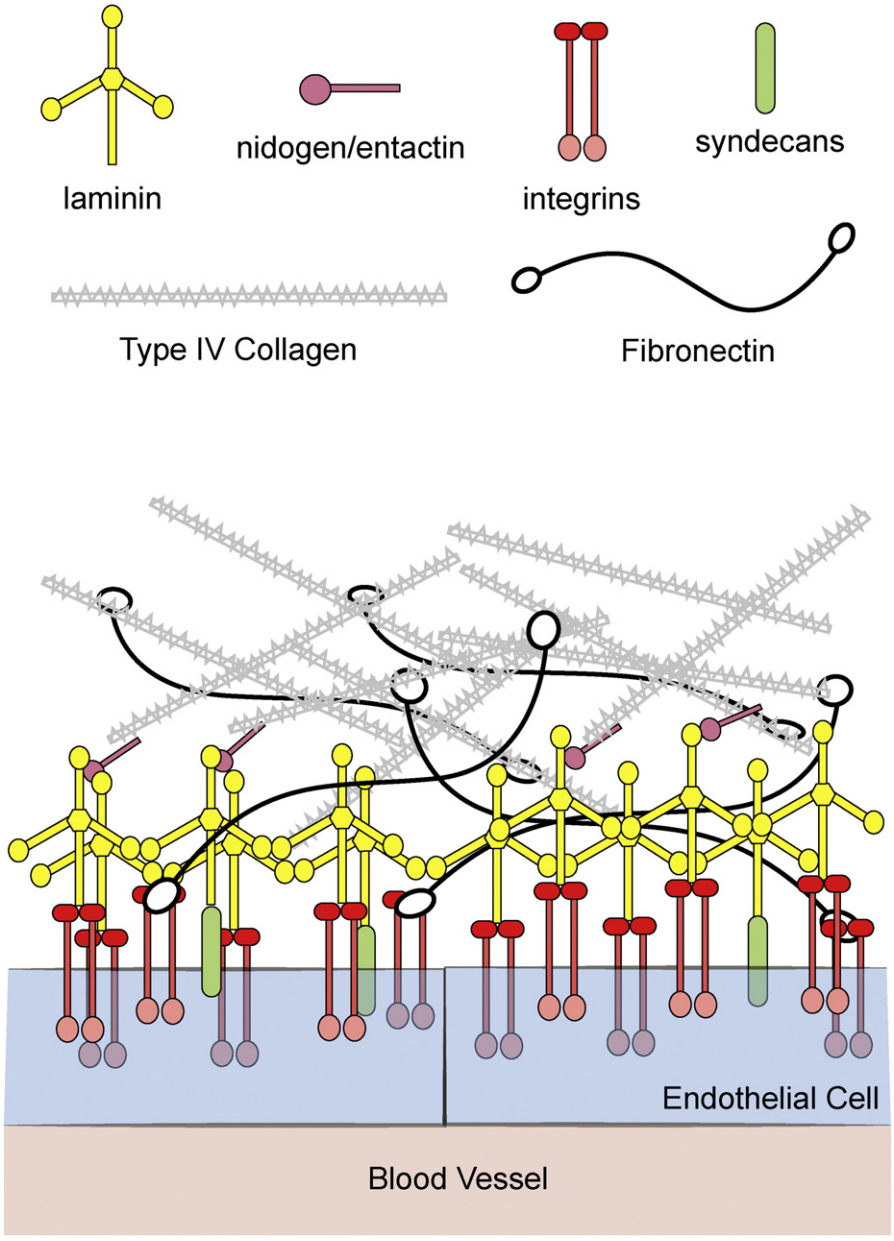

Fig. 3. A simplified model of the vascular basement membrane demonstrating the interactions between the non-collagenous and collagenous extracellular matrix with the endothelial compartment of blood vessels via their transmembrane receptors, integrins and syndecan.

the expression of other extracellular matrix molecules. For example, lack of laminin γ1 chain expression decreased collagen VI and increased fibronectin deposition in vascular basement membrane [41].

The structure of vascular basement membrane differs in various vascular beds depending on the organ-specific needs. For instance, blood vessels in endocrine organs, such as the adrenal gland, the pituitary and the pancreas are characterized by a thin basement membrane surrounding fenestrated (i.e. containing pores) endothelial cells. Presumably these structures facilitate long-range regulated processes, such as glucose responses [42]. Similarly, in liver, sinusoids have discontinued basement membrane and endothelial cells with intercellular gaps and large fenestra. Elimination of endothelial fenestrations in the liver has been associated with faulty lipid uptake [43]. Contrary to the fenestrated vasculature of high-transport organs, vascular basement membrane in neural and ocular tissues is continuous and endothelial cells form extensive tight junctions. The role of the basement membrane in these tissues is to restrict transendothelial movement and form the 'blood–brain barrier' facilitating interactions of endothelial cells with astrocytes [44]. Astrocytes secrete and deposit ECM molecules contributing to the strengthening of vascular basement membrane. Recent studies showed that disruption of astrocytic-derived laminin in mice resulted in vascular wall disassembly and hemorrhagic stroke [45], indicating the important role of extracellular matrix in maintaining blood vessel integrity.

The composition of vascular basement membrane varies not only among tissue-specific vessels but also depending on the state of the vessel, i.e. quiescent or activated. In resting vessels, endothelial cells are stably attached to the basement membrane, which they usually share with surrounding pericytes. During vascular development the quiescent endothelium becomes activated and the endothelial cells modify and breach the basement membrane in order to migrate into surrounding tissue and form a new vessel [46].

4.1. Vascular basement membrane in blood vessel formation

Generally, new blood vessels develop through the processes of vasculogenesis and angiogenesis. Vasculogenesis refers to the formation of blood vessels from endothelial progenitor cells, while angiogenesis is the expansion of the vascular network through sprouting of new vessels from pre-existing ones or splitting of vessels by collateral bridges [47]. In both processes, interactions between endothelial cells and their surrounding environment are essential for vascular development, maturation and function. The ECM of quiescent vessels contains elevated amounts of laminin and collagen providing structural support for vascular endothelium. During angiogenesis the basement membrane is extensively remodeled by proteases, such as MMPs and the secretion of new matrix, including fibronectin [48]. It is interesting that pro-angiogenic growth factors, such as the VEGF, induce endothelial cells to produce new ECM molecules that get incorporated into a "provisional" matrix [49]. This matrix scaffold provides migratory and proliferative signals to endothelial cells enabling them to re-organize their attachment sites and invade the surrounding microenvironment. During these angiogenic steps, the endothelium encounters and interacts with interstitial ECM components including vitronectin, thrombospondins, type I collagen and tenascins [30]. Such interactions induce key signaling events regulating further vessel morphogenesis.

Among the first to suggest a possible role for the vascular ECM in angiogenesis were Clark and colleagues. Their studies showed that perivascular matrix changes to a 'soft gel' during the formation of capillary tubes [50]. Others also demonstrated that several factors, including fibroblast growth factor (FGF), alter the adhesiveness and the mechanical properties of the ECM during angiogenesis [51]. It is worth mentioning that quiescent vascular basement membrane is highly cross-linked and only certain domains of the various components form adhesive interactions with endothelial cells, inhibiting proliferation and supporting firm cell adhesion. However, following extensive angiogenic remodeling of the ECM, the endothelial cells are exposed to different domains of these molecules, promoting vascular morphogenesis. Therefore, it seems that different structural configurations of the same ECM constituents could trigger differential biological outcomes [46].

Strikingly, several ECM proteins or fragments generated by ECM remodeling have been implicated as negative regulators of angiogenesis. MMP-mediated degradation of the basement membrane promotes the generation of fragments with anti-angiogenic activity, such as endostatin, arrestin, canstatin and turnstatin [52]. Among the best-studied anti-angiogenic ECM components are thrombospondin-1 and -2 (TSP-1 and TSP-2). Specifically, it has been shown that fragments of TSP-1 induce apoptosis of endothelial cells in vitro, presumably acting via the cell surface receptor CD36 [53]. Consistent with this, overexpression of TSP1 decreased angiogenesis and tumor growth in squamous cell carcinoma xenografts [54] and in a mammary tumor mouse model, while TSP1 deficient mice exhibit increased tumor growth and angiogenesis [55]. In addition, TSP-2 knockout mice display connective tissue abnormalities that are associated with defective collagen assembly and increased vascular density [56]. In summary, the vascular basement membrane displays a great plasticity and is capable of providing both quiescent and angiogenic signals depending on the molecular composition and the structural architecture.

5. Laminins in vascular morphogenesis

Several in vitro and in vivo models have been employed to characterize the function of laminins in the vascular system [57]. Initial studies were performed using the matrix of the murine EHS tumor (matrigel), which is rich in laminin-111. Endothelial cells plated on matrigel, stop to proliferate, align and form capillary-like structures, indicating an angiogenic role for laminin-111 [58]. Using synthetic peptides, Kleinman and co-workers identified both pro- and anti-angiogenic sequences in laminin α1, β1 and γ1 chains [58–62]. For instance, the IKAV motif in laminin α1 chain promoted EC migration and increased angiogenesis in the chorioallantoic membrane assay (CAM) and tumor vascularization [60,61]. In contrast, the YIGRS sequence inhibited endothelial cell tube formation in matrigel and angiogenesis in the CAM assay [62]. Expression of laminin α1 and α2 has been reported in the capillaries of the central nervous system [63,64]. Other studies have shown that these chains are components of the basement membrane surrounding the astrocyte endfeet of the blood–brain barrier and not constituents of the vascular basement membrane [65,66]. Similarly, no expression of laminin α1, α2 and α3 chain was observed in the newly developed vessels during the corneal angiogenic assay [19]. The early lethality of the α1 chain knockout mice at embryonic day (E) 6.5 precludes any in vivo analysis of vascular development [16]. Although it appears that endothelial cells do not express laminin α1 chain and that laminin-111 is not a major component of vascular basement membrane, several line of evidence shows that exogenous administration of laminin-111 affects angiogenesis. Overexpression of laminin α1 chain in human colon adenocarcinoma cells increased in vivo tumor growth and angiogenesis [67]. Likewise, exogenous applied laminin-111 promoted angiogenesis in the CAM assay and enhanced the FGF-2-induced formation of vascular structures in embryoid bodies angiogenic assay [68]. Furthermore, deletion of laminin α1 chain expression from Sox2 positive cells affected the development of the vascular plexus and the regression of hyaloid vessels in the retina [69]. Taking all this data together, it is tempting to speculate that laminin-111 could influence angiogenic responses, as invading endothelial cells of the newly formed vessels become exposed to extravascular matrix.

The main laminin isoforms of the vascular basement membrane are laminin-411 and laminin-511. In particular, laminin α5 chain is widely expressed in many tissues, including epithelial, endothelial, myogenic cells and in tumors. During embryonic development laminin α5 is expressed mainly in the large vessels and is absent from embryonic

capillaries. In adult mice laminin α5 chain is also found in capillaries and is regarded as a marker of mature quiescent vessels [70]. Mice lacking the α5 laminin chain appear normal until embryonic day (E) 9 but then exhibit developmental retardation and die by E16.5, presumably because of placental defects. The majority of the embryonic vasculature had no obvious phenotype but the placental vasculature was less elaborated with reduced branching and enlarged vessel diameter. Ultrastructural analysis showed that the vascular basement membrane exhibited variations in width, splits and discontinuities [23]. It is still unclear why there are differences between placental and embryonic vasculature and more studies are needed to establish the role of laminin α5 chain in angiogenesis.

Similarly, the laminin α4 knockout mice show transient defects in endothelial cell basement membrane that cause hemorrhaging in embryos and newborns but not in adult mice [19]. Concomitant with the loss of α4 chain, reduction in the expression of laminin β1 and γ1 chain as well as collagen IV and nidogen was observed in skeletal muscle capillaries of *lαmα4* null newborns and ultrastructural analysis showed a discontinued and disrupted basement membrane. However, no phenotype was obvious in adult mice lacking laminin α4 chain and the expression of basement membrane components including collagen IV, nidogen and laminin-511 was fully rescued, generating a basement membrane that was identical to wild type mice. Notably, there was no difference in vessel density between *lαmα4* null and control mice, suggesting that developmental angiogenesis proceeds normally. In contrast, in a corneal angiogenesis assay, ablation of laminin α4 chain led to a transient increase in blood vessel diameter, neovessel sprouting, and hemorrhages in response to FGF2, that eventually converted to an apparently normal vascular network [19]. These studies demonstrate that laminin-411 is necessary for the stabilization of blood vessels and its absence could cause excessive new vessel formation upon exposure to pro-angiogenic factors. In accordance with this, loss of laminin α4 chain caused increased angiogenic sprouting in the developing retina vasculature. The excessive formation of endothelial tip cells and membrane protrusions called filopodia, phenocopied the effect of disruption of Delta/Notch signaling. Indeed, it was shown that laminin α4 chain induces Delta-like 4 (Dll4) expression in an integrin-β1 dependent manner and affects Notch signaling [71].

Insight into the role of laminin γ1 chain in endothelial functions comes from studies of vascular structures developed in embryoid bodies in response to angiogenic factors [41]. Deletion of β1 or γ1 laminin chains in mice results in early embryonic lethality at E5.5 before the onset of vasculogenesis [16]. In embryoid bodies with targeted deletion of laminin γ1 chain the differentiation of embryonic stem cells to endothelial cells in response to angiogenic factors was not affected. Similarly, endothelial cells could develop angiogenic sprouts and form a vascular network. However, the vascular plexus exhibited fewer branched points and flatted endothelial cell morphology. Interestingly, deposition of laminin 411 and 511 was absent from the vascular basement membrane. Consistent with the enlarged vascular lumens observed in laminin α4 and α5 chain knockout mice, expansion of vascular lumens was observed in *lamc1* knockout embryoid vascular structures [41]. Taken together, these studies suggest that laminins control lumen diameter and stabilize blood vessels.

6. Fibronectin in vascular morphogenesis

Fibronectin is an important basement membrane component, essential for vascular development. Genetic ablation of fibronectin in mice resulted in embryonic lethality with mesodermal abnormalities and major cardiovascular defects. Initial specification of endothelial precursor cells occurs but sprouting angiogenesis is completely absent in the fibronectin null embryos [72]. Depending on the genetic background, vasculogenesis and cardiac development are completely arrested or severely impaired. Specifically, on the 129/Sv genetic background, blood vessels that are formed by the assembly of endothelial progenitor cells such as dorsal aorta and yolk sac blood vessels are totally missing, indicating that vasculogenesis could not proceed in the absence of fibronectin. Similarly, heart development was blocked as cardiac progenitor cells failed to fuse and form a single heart tube [73]. On a C57/BL6J genetic background, dorsal aortae and heart tube initially formed but were not functional and appeared collapsed, indicating that although initial steps of vasculogenesis occurred, lumen formation and vessel stability were severely affected [37,72]. Likewise, the formation of vascular structures in embryoid bodies lacking fibronectin expression was severely disrupted, establishing an essential function for fibronectin in vessel development.

In accordance with this, fibronectin is strongly expressed in provisional matrix around developing blood vessels. Studies on vascular patterning in the developing retinal vasculature demonstrated that fibronectin fibrils deposited by astrocytes guide endothelial cell migration at the angiogenic front [74]. Fibronectin expression wanes off in mature vessels and is barely detectable in the normal adult blood vessels. Expression of fibronectin in the adult organism occurs during pathological angiogenesis in various diseases such as wound healing, fibrosis, vascular diseases and cancer. Consistent with a "pro-angiogenic" role for fibronectin, increased fibrillogenesis is observed in sites of active angiogenesis. Furthermore, blocking fibronectin polymerization decreased endothelial cell proliferation and tube formation in a three-dimensional cell culture model in vitro and in the CAM assay in vivo [75]. Other studies also showed that fibronectin is able to induce endothelial cell survival, indicating a critical role for fibronectin in endothelial function and vessel formation [76].

Regarding the effect of the different splice variants of fibronectin in vessel development, mice lacking either the EIIIA or the EIIIB variants showed no obvious defects in vascular development [77,78]. However, a mutant mouse strain deficient in both these segments in *cis* as well as the double EIIIA and EIIIB mutant displayed hemorrhages and severe vascular defects in the yolk sac and the embryonic head region [79]. In particular, endothelial cells failed to organize into a network of large and small vessels and instead they formed vascular sheets of irregular size and decreased numbers of intervascular spaces. It is worth noting that in the double EIIIA and EIIIB mutant mice fibronectin is expressed and deposited into the vascular basement membrane. Therefore, the presence or absence of EIIIA and EIIIB exons does not impede fibronectin expression or ECM deposition but could modify fibronectin function by affecting the mechanical properties of extracellular matrix or altering its interactions with specific integrin receptors and the responses to growth factor signaling.

Taken together, existing evidence demonstrates a critical role for fibronectin in endothelial function and vessel formation.

7. Laminins and fibronectin receptors in the vascular system

Extracellular matrix components exert their biological effects via an extended variety of interactions with cell surface receptors that link vascular basement membrane constituents to intracellular signaling pathways. Both laminins and fibronectin induce various cellular responses by interacting with integrin and non-integrin receptors, including syndecans and dystroglycans. Several studies demonstrate the role of integrins and syndecans in the blood vessel morphogenesis and function.

7.1. Integrins

Integrins are a large family of transmembrane glycoproteins composed of one α-subunit and one β-subunit that are non-covalently associated to form a heterodimer. In mammals, there are 18 different types of α-subunits and 8 types of β-subunits that can assemble into at least 24 known distinct integrin heterodimers. Ligand specificity is mainly determined by the α-subunit. Inside the cell the short cytoplasmic domains of integrins associate with a plethora of signaling and

adaptor proteins that trigger multiple signal transduction pathways [80]. The expression of different integrin receptors in various physiological and pathological situations provides cells with the required flexibility to interact with the palette of extracellular matrix molecules and coordinate cellular responses. In the vascular system, a panel of integrins exists on the surface of endothelial cells, including $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_6\beta_4$, $\alpha_5\beta_1$, $\alpha_9\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$ and their expression differs in quiescent vessels and during angiogenesis [81]. The major laminin isoforms of the vascular basement membrane, laminin-411 and laminin-511, interact mainly with integrins $\alpha_3\beta_1$ and $\alpha_6\beta_1$, while fibronectin binds to integrins $\alpha_5\beta_1$ and $\alpha_v\beta_3$. In vitro studies have shown that laminin-111 can also interact with integrins $\alpha_6\beta_1$ and $\alpha_v\beta_3$, as well as integrins $\alpha_1\beta_1$ and $\alpha_2\beta_1$ [82]. Furthermore, the laminin α5 chain in laminin-511 contains an arginine–glutamine–aspartic acid (RGD) motif, which supports binding to $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_5\beta_1$ [83]. Genetic evidence demonstrates a pivotal role for integrin α_5 in embryonic angiogenesis. Integrin $\alpha_5\beta_1$ is the major receptor for fibronectin. Genetic ablation of this integrin subunit results in embryonic lethality by E10–E11 with hemorrhages and defects in vascular architecture both in the embryo proper and in the yolk sac, similar to the vascular defects of fibronectin deletion [84,85]. Interestingly, endothelial specific deletion of α_5 integrin had no effect on developmental angiogenesis, suggesting a contribution from other α_5 integrin-expressing cell types in blood vessel formation [86]. However, the fibronectin assembly in α_5-deficient endothelial cells was impaired. Furthermore, the upregulation of both fibronectin and $\alpha_5\beta_1$ integrin upon growth factor signaling as well as antibody and peptide inhibitor studies strongly suggested a pro-angiogenic role of the fibronectin–$\alpha_5\beta_1$ pair in angiogenesis [87].

Similarly, integrin β_1 is required for developmental angiogenesis. Specific deletion of integrin β_1 from endothelial cells causes abnormalities in vascular lumen formation and branching [88,89]. Genetic studies of other integrin subunits demonstrated that integrins α_6, α_3, α_v, β_3 and β_5 are dispensable for endothelial differentiation and blood vessel development during embryogenesis, but have important functions in pathological angiogenesis [90]. In particular, endothelial cell specific deletion of either α_6 or α_3 resulted in increased pathological angiogenesis, suggesting that these integrins and their interaction with laminins act as negative regulators of angiogenic responses [91,92]. The role of integrin $\alpha_v\beta_3$ in endothelial biology is more complex. Initial studies have shown that $\alpha_v\beta_3$ is upregulated in tumor blood vessels and specific integrin inhibitors blocked tumor growth and retinal angiogenesis, indicating a pro-angiogenic role for this integrin [93,94]. Surprisingly, genetic ablation of β_3 and β_5 integrin subunits in mice increased pathological angiogenesis and assessment of the dose–effect of a specific integrin β_3 inhibitor indicated a suppressive effect in tumor angiogenesis [95,96]. Recent studies also showed that acute endothelial deletion of β_3 integrin decreased angiogenesis in the initial phases of tumor growth but had no effect in established tumor vasculature [97]. Furthermore, compensatory mechanisms exist between different α subunits that determine vascular outcomes. For example, endothelial-specific deletion of both α_5 and α_v subunits in mice enhanced the vascular defects, indicating a synergistic effect in fibronectin signaling [33,86]. However, integrins containing α_v subunit such as $\alpha_v\beta_3$ cannot fully compensate and rescue the vascular phenotypes observed in the global deletion of α_5 or β_1 integrins [33,88]. Fibronectin also binds to integrin $\alpha_9\beta_1$ that is expressed in the lymphatic vessels. Deletion of α_9 integrin subunit results in perinatal lethality with severe defects in lymphatic vessel development and lymphatic valve morphogenesis [98,99].

Integrins directly link the basement membrane to cell cytoskeleton and signal transduction pathways contributing not only to mechanical support, but also to the stability of motile processes. Integrins do not possess any enzymatic activity. Therefore their action is mediated by the assembly of an intricate and dynamic protein network at their cytoplasmic tail, called adhesome [80]. The adhesome network regulates also the affinity of integrin for binding to extracellular ligands, a process called “inside-out” signaling. Adhesome proteins influence signaling cascades activated by growth factor receptors, thus providing the integrating platform to co-ordinate cellular responses. Several common intracellular signaling pathways including activation of FAK, Src, MAPKs, PI3Ks, and Rho-GTPases are triggered by ligation of integrins to extracellular matrix [100]. Recent studies demonstrated a co-operation between Notch/Delta and integrins. Specifically, ligation of laminin to $\alpha_6\beta_1$ and $\alpha_2\beta_1$ stimulated Delta-like 4 (Dll4) expression on vascular endothelial cells and activated Notch signaling, regulating vascular branching morphogenesis in vitro and angiogenic sprouting in vivo [71,101].

In addition, the composition of basement membrane could modify cellular responses by modulating integrin crosstalk. For example, it has been shown that collagen signaling via integrin $\alpha_2\beta_1$ expression in endothelial cells suppressed NFκB activation and inflammatory responses to shear stress. Shear stress stimulated fibronectin matrix assembly and activated $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins, leading to NFκB signaling. Collagen-induced activation of integrin $\alpha_2\beta_1$ suppressed the activation of $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins and fibronectin matrix assembly, dumping NFκB responses in bovine aortic endothelial cells [102].

The interactions of integrins with the vascular basement membrane regulate cellular survival and proliferation, cell attachment, motility and invasion and endothelial cell polarity and lumen formation. Taken together existing data suggest that integrins could have multifacial roles in blood vessel morphogenesis depending on the developmental stage, the presence of other integrins and the availability of extracellular matrix ligands. Additionally, integrins expressed on vascular supporting cells, pericytes and smooth muscles could also interact with the vascular basement membrane, stabilizing blood vessels and modulating vascular responses.

7.2. Syndecans

Syndecans are transmembrane proteoglycans that carry heparin sulfate modifications on their protein core. Syndecans-1, -2 and -4 have been shown to bind laminin α4 and α5 chains. Syndecan-2 interacts also with fibronectin and deletion of the syndecan-2 cytoplasmic tail in CHO cells prevented the assembly of fibronectin and other matrix proteins into the extracellular matrix [103]. Consistently, downregulation of syndecan-2 in mouse brain microvascular cells decreased the migration rates of endothelial cells on fibronectin [104]. In addition, syndecan-1 and -4 expression is upregulated in the endothelium during wound healing and syndecan-4 null mice show defects in wound angiogenesis [105,106]. However, syndecan function in developmental angiogenesis is redundant. Interestingly, syndecan-4 null mice display higher blood levels of urea nitrogen and renal tubule dilation upon stress, indicating kidney vascular dysfunction [107]. Elevated levels of syndecan-4 have been reported in fetal endothelial cells of the placental labyrinth and deletion of syndecan-4 was associated with increased thrombus formation in placenta vasculature [108].

Syndecans could both act as co-receptors modifying the activity of integrins as well as interact with heparin-binding domains in extracellular matrix molecules and growth factors, including VEGF and FGF-2. It has been shown that syndecan-4 is involved in the formation and the stabilization of integrin-mediated adhesion [109]. Furthermore, overexpression of syndecan-4 expression in endothelial cells mediated the vasodilation effects induced by FGF-2 administration through a production of nitric oxide [110]. However, further work is required in order to clarify the significance of syndecans in the biology of the vascular extracellular matrix.

7.3. Other cell surface receptors

Other non-integrin receptors that have been shown to bind laminins are dystroglycan and Lutheran blood group glycoprotein (Lu/B-CAM) but their function in the vascular system is still obscure [11]. Dystroglycans are composed of an extracellular α chain and a

transmembrane β chain and interact with laminin-111 via the laminin α1 chain subunit. Dystroglycan has been reported to be upregulated in endothelial cells during tumor angiogenesis [111]. However, the early lethality of the dystroglycan null mice before the onset of vasculogenesis precludes studying the role of dystroglycan in blood vessel formation [112]. Lutheran blood group glycoprotein belongs to Ig superfamily and has been implicated in the adhesion of sickled red blood cells to laminin α5 chain subunit in the vascular basement membrane [113].

8. An overview of the role of non-collagenous ECM in tumorigenesis

During tumor development, the molecular composition and structure of the ECM is dynamically modified [46]. Tumor remodeling involves upregulation of ECM components not normally expressed in the tissue, including fibronectin, tenascin and different isoforms of laminin as well as extensive remodeling of existing ECM molecules, through the action of metalloproteinases and other modifying enzymes. Cancer cells both influence ECM architecture and respond to changes in their immediate microenvironment, favoring cell proliferation, de-differentiation, survival and invasion. There is evidence that a physiologic or 'normal-like' extracellular matrix can even inhibit tumor initiation and progression [114].

Furthermore, like normal tissues, tumors require sufficient blood supply for their sustainability and growth. Most tumors activate angiogenesis at an early stage of their development, causing normally quiescent vasculature to develop new vessels. It is well established that angiogenesis is a hallmark of tumor growth and metastasis [115]. Similar to physiological vasculogenesis, the vascular basement membrane influences tumor angiogenesis. Basement membranes in tumor vessels display various abnormalities, including loose associations with endothelial cells, multiple layers with irregular thickness, holes and broad extensions into the tumor stroma [116]. Matrix molecules of the basement membrane such as laminins and fibronectins play a decisive role. Vascular basement membrane in tumors is also a source of pro- and anti-angiogenic molecules. For example, heparin binding could immobilize VEGF in close proximity to the vasculature, inducing angiogenic sprouting of new vessels. On the other hand, proteolytic fragments of collagen, including endostatin and tumstatin, could suppress angiogenesis [46]. Additionally, the reciprocal interaction of tumor cells with the vascular basement membrane determines the metastatic potential of cancer. Tumor cells need to be able to breach the vascular basement membrane twice, once to enter the blood or lymphatic circulation and another to extravasate and form metastasis.

Apparently, the elucidation of the elaborate interactions between the extracellular matrix and the tumor cells will contribute to major therapeutic advances regarding the eradication of dormant cancer cells and the treatment of metastatic malignancies.

8.1. Laminins in tumorigenesis

As important components of the basement membranes, laminins constitute structural barriers that need to be remodeled or invaded by tumor cells during tumorigenesis. Usually, tumors display the same laminin isoforms found in the corresponding tissue. For example, laminin-532 is expressed in all epithelial tumors, whereas laminin-111 in only a few, including renal, prostate, breast, ovary and lung carcinomas [117]. However, their expression and structural composition is altered. For instance, both laminin γ2 chain mRNA and protein have been found to be highly expressed in budding cancer cells at the tip of invading malignant epithelium and has been identified as a marker in squamous cell carcinomas and malignant melanomas [118]. Additionally, it has been reported that expression of laminin γ2 chain could facilitate the incorporation of melanoma cells in vessel-like structures, a phenomenon called vasculogenic mimicry. In particular, a microarray gene expression chip analysis indicated significant upregulation in the expression of laminin γ2 chain and MMP-1, -2, -9 and MT-MMP-1 in highly compared to poorly aggressive melanoma cells [119]. In contrast, decreased levels of laminin β1 and γ1 chains have been reported in several carcinomas [120]. Consistently, laminin-111 induces polarity of luminal breast epithelial cells that is lost in cancer while interactions of laminin-532 with integrin α3β1 induce epithelial cell dispersion and enhance motility [121]. Emerging evidence suggests that laminin-332 plays an important role in invasion of colon, breast and skin cancer cells. Elevated expression of laminin-332 and its protease degradation products are not only found at the invading front of several tumors but also promote tumor cell migration. Therefore, laminin-332 has been identified as a potential target for the treatment of malignant tumors [122].

Exposure of masked binding sites within the intact laminin molecules, by the action of proteases, alters laminin activity to promote loss of contact inhibition, cell migration and invasion. Depending on the surrounding microenvironment, different isoforms of laminin may modulate tumor angiogenesis by similar mechanisms to developmental angiogenesis, as discussed above [57].

8.2. Fibronectin in tumorigenesis

There is abundant evidence that fibronectin, including the EIIIA and EIIIB splicing isoforms, is significantly upregulated around the tumor vasculature in both human and mouse tumors [76]. However, despite the tight regulation of EIIIA and EIIIB splice variants in tumor vasculature, deletion of either EIIIA or EIIIB did not have a significant effect on tumorigenesis in the transgenic Rip1-Tag2 model of pancreatic islet carcinogenesis [28]. Other studies have shown that EIIIA promoted the differentiation of fibroblasts to myofibroblasts and was able to transduce TGF-β signals, processes altered in several cancers [123]. Several studies implicate both fibronectin and its integrin receptor α5β1 in tumor angiogenesis but the role of the different fibronectin variants and extracellular matrix interactions in tumor development needs further investigation [124]. Recent studies showed that expression of tumor fibronectin enhances collective cell migration of glioblastoma cells and increases tumor growth and angiogenesis [125].

9. Conclusion

Several lines of evidence establish the extracellular matrix and in particular its non-collagenous components as crucial factors providing tissues much more than mechanical support. The ECM activities go beyond cell adhesion and migration, regulating crucial cellular responses and contributing to a diverse range of normal or abnormal processes. Further investigations of the functions of ECM components in the vascular system will lead to the elucidation of critical and elaborate circuits that determine human pathophysiology. Understanding in detail the regulating signaling events elicited by vascular basement membrane could identify potential therapeutic targets for several diseases including cancer.

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