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The extracellular matrix: A dynamic niche in cancer progression

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The local microenvironment, or niche, of a cancer cell plays important roles in cancer development. A major component of the niche is the extracellular matrix (ECM), a complex network of macromolecules with distinctive physical, biochemical, and biomechanical properties. Although tightly controlled during embryonic development and organ homeostasis, the ECM is commonly deregulated and becomes disorganized in diseases such as cancer. Abnormal ECM affects cancer progression by directly promoting cellular transformation and metastasis. Importantly, however, ECM anomalies also deregulate behavior of stromal cells, facilitate tumor-associated angiogenesis and inflammation, and thus lead to generation of a tumorigenic microenvironment. Understanding how ECM composition and topography are maintained and how their deregulation influences cancer progression may help develop new therapeutic interventions by targeting the tumor niche.

Introduction

The past 20 years have seen cancer biology and development biology converge, and both fields have greatly benefited from each other's research progress (Xie and Abbruzzese, 2003; Radtke and Clevers, 2005; Blanpain et al., 2007). Retrospectively, such a convergence is inevitable, as many of the same cell behaviors and processes essential for embryonic development are also indispensable for cancer progression (Egeblad et al., 2010a). The concept that local microenvironments, or niches, play an important role in regulating cell behavior, which is one of the central themes in classical embryology, has become increasingly accepted in cancer biology (Bissell and Radisky, 2001; Wiseman and Werb, 2002; Bissell and Labarge, 2005).

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Abbreviations used in this paper: CAF, cancer-associated fibroblast; LAIR, leukocyte-associated Ig-like receptor; LOX, lysyl oxidase; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell.

Much effort has been devoted to determining how cellular components of the niche initiate and promote cancer development (Bhowmick et al., 2004). However, recent progress has also highlighted the importance of noncellular components of the niche, especially the ECM, during cancer progression (Sternlicht et al., 1999; Paszek et al., 2005; Erler et al., 2006, 2009; Levental et al., 2009). Although long viewed as a stable structure that plays a mainly supportive role in maintaining tissue morphology, the ECM is an essential part of the milieu of a cell that is surprisingly dynamic and versatile and influences fundamental aspects of cell biology (Hynes, 2009). Through direct or indirect means, the ECM regulates almost all cellular behavior and is indispensable for major developmental processes (Wiseman et al., 2003; Stickens et al., 2004; Rebutini et al., 2009; Lu et al., 2011).

Consistent with ECM's many important roles, multiple regulatory mechanisms exist to ensure that ECM dynamics, collectively measured by its production, degradation, and remodeling, are normal during organ development and function (Page-McCaw et al., 2007). Disruption to such control mechanisms deregulates and disorganizes the ECM, leading to abnormal behaviors of cells residing in the niche and ultimately failure of organ homeostasis and function. Indeed, abnormal ECM dynamics are one of the most ostensible clinical outcomes in diseases such as tissue fibrosis and cancer (Cox and Erler, 2011).

A major challenge in ECM biology is to understand the roles of the ECM in normal development and how disruption of ECM dynamics may contribute to diseases such as cancer. Here, we examine the diverse properties of the ECM that are essential for its versatile roles in cancer. We focus on how abnormal ECM deregulates the behavior of various epithelial and stromal cell components at different stages of cancer development.

Properties and features of the ECM

The ECM is composed of a large collection of biochemically distinct components including proteins, glycoproteins, proteoglycans, and polysaccharides with different physical and biochemical properties (Whittaker et al., 2006; Ozbek et al., 2010).

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Structurally, these components make up both basement membrane, which is produced jointly by epithelial, endothelial, and stromal cells to separate epithelium or endothelium from stroma, and interstitial matrix, which is primarily made by stromal cells. Basement membrane is a specialized ECM, which is more compact and less porous than interstitial matrix. It has a distinctive composition containing type IV collagen, laminins, fibronectin, and linker proteins such as nidogen and entactin, which connect collagens with other protein components. In contrast, interstitial matrix is rich in fibrillar collagens, proteoglycans, and various glycoproteins such as tenascin C and fibronectin and is thus highly charged, hydrated, and contributes greatly to the tensile strength of tissues (Egeblad et al., 2010b).

When put together in an orderly manner, the ECM components, with their remarkable structural and biochemical diversity and functional versatility, confer upon the matrices unique physical, biochemical, and biomechanical properties that are essential for regulating cell behavior. For example, the physical properties of the ECM refer to its rigidity, porosity, insolubility, spatial arrangement and orientation (or topography), and other physical features that together determine its role in scaffolding to support tissue architecture and integrity. Additionally, by functioning as a barrier, anchorage site, or movement track, the ECM's physical properties play both negative and positive roles in cell migration (Fig. 1, stages 1–3).

In contrast, the biochemical properties of the ECM pertain to its indirect and direct signaling capabilities that allow cells to sense and interact with their environments using various signal transduction cascades emanating from the cell surface to the nucleus, resulting in gene expression or other changes of cell behavior. For example, as a highly charged protein network rich in polysaccharide modifications, the ECM can bind to a myriad of growth factors, including bone morphogenetic proteins, FGFs, hedgehogs, and WNTs (Hynes, 2009). In so doing, the ECM limits the diffusive range, accessibility, and signaling direction of ligands to their cognate receptors (Fig. 1, stages 4–6; Norton et al., 2005). Additionally, the ECM can also directly initiate signaling events, particularly by functioning as a precursor of biologically active signaling fragments (Fig. 1, stage 7; Hynes, 2009; Lu et al., 2011).

A burgeoning area in ECM biology is how its biomechanical properties, including the elasticity of the ECM (that ranges from soft and compliant to stiff and rigid), contribute to development and disease (McBeath et al., 2004; Reilly and Engler, 2010). As it turns out, ECM elasticity helps determine how a cell senses and perceives external forces (Paszek et al., 2005; Lopez et al., 2008; Gehler et al., 2009) and thus provides a major environmental cue that determines cell behavior (Kölsch et al., 2007; Montell, 2008; Fernandez-Gonzalez et al., 2009; Pouille et al., 2009; Solon et al., 2009; DuFort et al., 2011). Indeed, the focal adhesion complex, which consists of integrins and a multicomplex of adaptors and signaling proteins, can be viewed as a mechanosensor linking the actomyosin cytoskeleton with the ECM. Many of the focal adhesion components, including talin and p130Cas, undergo conformational changes that impart functional consequences in response to applied force (Sawada et al., 2006; del Rio et al., 2009; Wang et al., 2011). Together with the cytoskeleton and nuclear

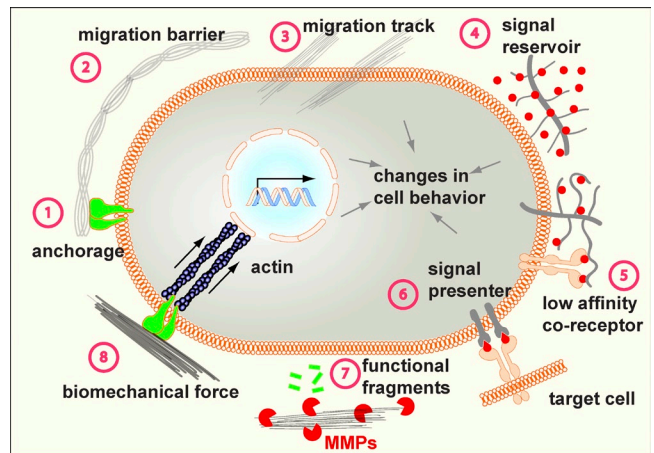


Figure 1. Mechanisms of ECM function. The versatile functions of the ECM depend on its diverse physical, biochemical, and biomechanical properties. Anchorage to the basement membrane is essential for various biological processes, including asymmetric cell division in stem cell biology and maintenance of tissue polarity (stage 1). Depending on contexts, the ECM may serve to block or facilitate cell migration (stages 2 and 3). In addition, by binding to growth factor signaling molecules and preventing their otherwise free diffusion, the ECM acts as a sink for these signals and helps shape a concentration gradient (stage 4). Certain ECM components, including heparan sulfate proteoglycans and the hyaluronic acid receptor CD44, can selectively bind to different growth factors and function as a signal coreceptor (stage 5) or a presenter (stage 6) and help determine the direction of cell–cell communication (Lu et al., 2011). The ECM also direct signals to the cell by using its endogenous growth factor domains (not depicted) or functional fragment derivatives after being processed by proteases such as MMPs (stage 7). Finally, cells directly sense the biomechanical properties of the ECM, including its stiffness, and change a wide variety of behaviors accordingly (stage 8).

matrices, nuclear envelope, and chromatin, they constitute a sophisticated mechanosensing machinery that determines how cells react to forces from the ECM (DuFort et al., 2011). Interestingly, however, changes in mechanical force can be converted into differences in TGF- β signaling activities in the mouse tendon (Maeda et al., 2011), suggesting that conventional signaling pathways can be used to interpret the biomechanical properties of the ECM. As a result, ECM's biomechanical properties regulate various essential cell behaviors, including cell fate determination, differentiation, and tissue function (Fig. 1, stage 8; Engler et al., 2006; Lutolf et al., 2009; Gilbert et al., 2010).

Importantly, several outstanding characteristics of the properties of the ECM contribute to its importance in development and disease. First, the different properties of the ECM are not independent; rather, they are intertwined. Therefore, when the ECM stiffens, as, for example, under pathological conditions, its biomechanical properties change, and cells respond by exerting markedly different kinds of force (Yu et al., 2011). In addition, matrix stiffening also changes other ECM physical properties and, as a consequence, directly impacts how migrating cells interact with the ECM. Thus, linearized cross-linked collagen bundles, which are quite stiff, potentiate cell migration, whereas a dense network of stiff cross-linked matrix fibers impedes migration, unless matrix metalloproteinases (MMPs) are simultaneously activated (Egeblad et al., 2010b).

Second, the ECM is highly dynamic, constantly being remodeled in different tissues at various embryonic and postnatal

stages. ECM dynamics may result from changes of the absolute amount or composition of the ECM, for example as a result of altered synthesis or degradation of one or more ECM components. Alternatively, ECM dynamics may show no compositional changes of its components but instead involve only how individual ECM components are laid down, cross-linked, and spatially arranged together via covalent and non-covalent modifications.

Finally, one of the most prominent features of cell–ECM interactions is that they are reciprocal. On the one hand, cells are constantly creating, breaking down, or otherwise rearranging and realigning ECM components to change one or more properties of the ECM. On the other hand, because the ECM regulates diverse cell behavior, any changes in the ECM as a result of cellular activities will in turn influence adjacent cells and modify their behaviors (Butcher et al., 2009). This feedback regulatory mechanism between cells and the ECM allows cells and tissues to swiftly adapt to their environment (Samuel et al., 2011).

Deregulated ECM dynamics are a hallmark of cancer

ECM remodeling is tightly regulated during development and primarily accomplished by controlling the expression or activities of ECM enzymes at multiple levels. Take for example ECM degrading enzymes, which include MMPs, a disintegrin and metalloproteinase with thrombospondin motifs, and the serine protease plasmin: left unchecked, the potent activities of these enzymes can have devastating destructive consequences on tissues and cause demise of the whole organism. As a result, ECM remodeling enzymes are not only regulated at the transcriptional and translational levels but also posttranslationally with the use of their functionally inhibitive prodomains and selective proteinase inhibitors (Page-McCaw et al., 2007; Aitken and Bägli, 2009).

Despite having multiple control mechanisms, activities of ECM remodeling enzymes may be deregulated with age or under disease conditions. Consequently, ECM dynamics may become abnormal as the amount, composition, or topography of the ECM turn aberrant, leading to disorganization and changes in the essential properties of the ECM. The main contributors of altered activities of ECM remodeling enzymes and thus abnormal ECM metabolism are stromal cells, including cancer-associated fibroblasts (CAFs) and immune cells (Bhowmick et al., 2004; Orimo et al., 2005). However, other cell types, including epithelial cells and mesenchymal stem cells (MSCs), may also be involved at late stages of cancer development (Quante et al., 2011; Singer and Caplan, 2011).

Abnormal ECM dynamics are well documented in clinical studies of many diseases and are a hallmark of cancer. For example, excess ECM production or reduced ECM turnover are prominent in tissue fibrosis of many organs (Frantz et al., 2010). Various collagens, including collagen I, II, III, V, and IX, show increased deposition during tumor formation (Zhu et al., 1995; Kauppila et al., 1998; Huijbers et al., 2010). As we age, there is a reduction of collagen deposition and increased MMP activity (Norton et al., 2005; Butcher et al., 2009). Moreover, many

other ECM components and their receptors such as heparan sulfate proteoglycans and CD44 that facilitate growth factor signaling are frequently overproduced in cancer (Kainz et al., 1995; Stauder et al., 1995; Nasser, 2008). Thus, abnormal changes in the amount and composition of the ECM can greatly alter ECM biochemical properties, potentiate the oncogenic effects of various growth factor signaling pathways, and deregulate cell behaviors during malignant transformation.

In addition to changes in its biochemical properties, the architecture and other physical properties of tumor-associated ECM are fundamentally different from that of the normal tissue stroma; rather than relaxed nonoriented fibrils, the collagen I in breast tumors is often highly linearized and either oriented adjacent to the epithelium or projecting perpendicularly into the tissue (Provenzano et al., 2006; Levental et al., 2009). Consistent with these changes, expression of many ECM remodeling enzymes is often deregulated in human cancers. Heparanases, 6-O-sulfatases, cysteine cathepsins, urokinase, and, most notably, many MMPs are frequently overexpressed in different cancers (Ilan et al., 2006; Kessenbrock et al., 2010).

Furthermore, ECM's biomechanical properties also change under disease conditions. For example, tumor stroma is typically stiffer than normal stroma; in the case of breast cancer, diseased tissue can be 10 times stiffer than normal breast (Levental et al., 2009; Lopez et al., 2011). Part of the increase in tissue stiffness can be attributed to excess activities of lysyl oxidase (LOX), which cross-links collagen fibers and other ECM components. Indeed, up-regulation of LOX expression has been observed in various cancers, including breast cancer and head and neck cancer, and is a poor prognostic marker (Le et al., 2009; Barker et al., 2011). Importantly, a study using mouse genetics has shown that overexpression of LOX increases ECM stiffness and promotes tumor cell invasion and progression (Levental et al., 2009). In contrast, inhibition of LOX reduces tissue fibrosis and tumor incidence in the *Neu* breast cancer model (Levental et al., 2009). Together, these data demonstrate that deregulation of collagen cross-linking and ECM stiffness is more than just a secondary outcome but instead plays a causative role in cancer pathogenesis. Interestingly, however, overexpression of LOX alone is insufficient to cause tumors to form (Levental et al., 2009), suggesting that deregulation of ECM remodeling is a coconspirator rather than a primary inducer of tumorigenesis in the breast.

Abnormal ECM dynamics during cancer progression

Multicellular organisms have evolved many redundant mechanisms to prevent a cell that is intimately integrated with other cells in a functional tissue from becoming cancerous and leading to organ failure and demise of the organism. To overcome these protective measures and become cancerous, a cell must accumulate multiple oncogenic properties that ultimately result in malignant transformation. These include the acquisition by cancer cells of the ability to survive, grow, and invade (Hanahan and Weinberg, 2000, 2011). Along the way, cancer cells often lose their differentiation state and polarity, disrupt tissue integrity, and corrupt stromal cells to promote their own growth at both primary tumor and distant sites (Feigin and Muthuswamy, 2009; Luo et al., 2009).

Abnormal ECM can promote many of the aforementioned steps. An increase in collagen deposition or ECM stiffness, alone or in combination, up-regulates integrin signaling and can thus promote cell survival and proliferation (Wozniak et al., 2003; Paszek et al., 2005). Increased collagen cross-linking and ECM stiffness as a result of LOX overproduction promote focal adhesion assembly and ERK and PI3 kinase signaling and facilitate Neu-mediated oncogenic transformation (Levental et al., 2009). Moreover, various ECM components or their functional fragment derivatives have pro- or antiapoptotic effects (Mott and Werb, 2004). Therefore, deregulation of ECM remodeling can lead to apoptotic evasion by mutant cells. Among the numerous roles of abnormal ECM, we focus in the next section on how it may convert a normal stem cell niche into a cancer stem cell niche and how it may disrupt tissue polarity and integrity to promote tissue invasion, both of which are essential steps during cancer progression.

The ECM is an essential component of the stem cell niche and the cancer stem cell niche

Mounting evidence suggests that the ECM is an essential non-cellular component of the adult stem cell niche. For example, various ECM receptors have been used as markers to enrich adult stem cells in many in vitro and in vivo systems (Shen et al., 2008; Raymond et al., 2009), suggesting that contact with the ECM is necessary for cells to acquire or maintain stem cell properties. In contrast, loss of ECM contact by either functional ablation (Yamashita et al., 2005; Tanentzapf et al., 2007; O'Reilly et al., 2008) or reduction (Frye et al., 2003) of the ECM receptor integrins or reduction of ECM components, including the glycoproteins osteopontin (Kollet et al., 2006; Lymperi et al., 2010), tenascin C (Garcion et al., 2004), or biglycan (Bi et al., 2007), reduces the number of stem cells in different vertebrate and invertebrate systems.

Studies now show that the ECM plays multiple roles in the stem cell niche. For example, ECM receptors allow stem cells to anchor to the special local niche environment where stem cell properties can be maintained. Such an anchorage physically constrains stem cells to make direct contact with niche cells, which produce paracrine signaling molecules that are essential for maintaining stem cell properties (Fig. 2 A, stage 1; Li and Xie, 2005). Moreover, anchorage allows stem cells to maintain cell polarity, orient their mitotic spindles, and undergo asymmetric cell division (Fig. 2 A, stage 2), a fundamental mechanism whereby stem cell self-renewal and differentiation are thought to be determined (Lambert and Nagy, 2002; Fuchs et al., 2004; Lechler and Fuchs, 2005; Yamashita and Fuller, 2008).

In addition to maintaining stem cell properties, the ECM, via its diverse and potent signaling abilities, can directly regulate stem cell differentiation, although the molecular details of how this is achieved have only just started to emerge. Many of the signaling pathways that play an important role in stem cell biology in numerous model systems are subject to ECM modulation. For example, tenascin C can modulate FGF2 and BMP4 signaling, both of which are essential for neural stem cell biology (Garcion et al., 2004), whereas the ECM regulates

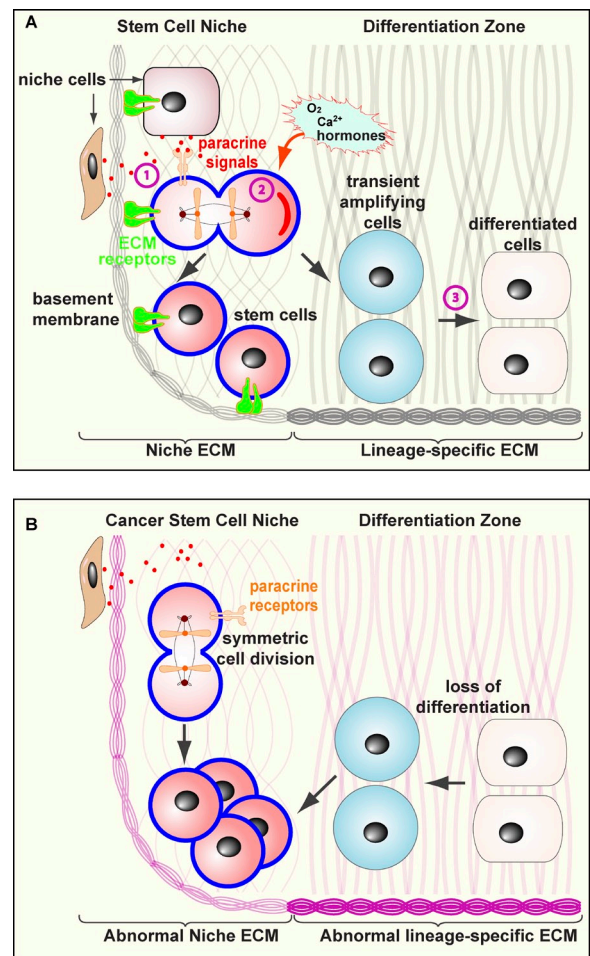


Figure 2. ECM is an essential component of normal and cancer stem cell niche. The ECM plays multiple roles in maintaining stem cell properties. (A) ECM anchorage restricts stem cells in the niche and thus allows them to be exposed to paracrine (stage 1) and cell–cell contact signals (not depicted) that are essential for maintaining stem cell properties. Anchorage is also important for orienting the mitotic spindle and makes it possible for stem cells to undergo asymmetric cell division (stage 2), which is essential for stem cell self-renewal and generation of daughter cells that are destined to undergo cell differentiation. The exact mechanism whereby ECM anchorage controls asymmetric cell division remains unclear, although one possibility is to allow cytoplasmic cell fate determinants to be differentially distributed between the daughter cells. The ECM also maintains stem cell properties via its many other features including its biomechanical properties such as ECM stiffness that affects cell fate determination (stage 3). (B) In the presence of abnormal ECM (pink) or loss of ECM contact, stem cell properties fail to be maintained and undergo symmetric cell division instead, leading to an overexpansion of the (cancer) stem cell pool. Abnormal changes of the ECM can also disrupt the cellular differentiation process, resulting in loss of differentiation and an increase of stem/progenitor cells.

ligand accessibility of the Janus kinase–signal transducer and activator of transcription signaling pathway in the fly testis (Yamashita et al., 2005).

The biomechanical properties of the ECM also play an important role in regulating stem cell biology. MSCs grown on polymer gels with similar elasticity to the brain express neuronal markers and morphology, whereas those grown on gels that are semicompliant like smooth and skeletal muscle tissues or rigid like the bone express muscle or bone proteins, respectively (McBeath et al., 2004; Engler et al., 2006). Likewise, muscle

stem cells grown on soft hydrogels with elasticity mimicking that of real muscle differentiate into functional muscle (Gilbert et al., 2010), highlighting the great promise that tissue engineering may hold in regenerative medicine. Together, it is conceivable that by modulating various aspects of ECM properties, a lineage-specific ECM may be created to facilitate cell differentiation processes during lineage specification and organ development (Fig. 2 A, stage 3).

The decision between stem cell expansion and differentiation is a delicate one and must be tightly controlled during normal organ homeostasis and function. An imbalance of these two events can lead to the generation of tumor-initiating cells, which have been called cancer stem cells by either overexpanding the stem cell pool or a failure in stem cell differentiation. Indeed, loss of cell polarity as a result of ablation of Numb or Lgl protein, essential components of the cell polarity machinery, disrupts asymmetric cell division and leads to overexpansion of neural stem cells and tumor formation in the brain (Li et al., 2003; Klezovitch et al., 2004). Therefore, the essential roles that the ECM plays in the stem cell niche make it a likely candidate to be targeted to create a cancer stem cell niche during cellular transformation. It is possible, at least theoretically, that deregulated ECM dynamics may cause formation of abnormal lineage-specific ECM and lead to cancer stem cell overexpansion and loss of differentiation (Fig. 2 B). However, whether a cancer stem cell niche may result from such an event of ECM dynamics deregulation remains to be rigorously tested.

The ECM maintains tissue polarity and architecture and prevents cancer cell invasion

An important feature of epithelial organs, which is often lost in cancer, is that cells in them have distinct polarity and architecture that are indispensable for organ formation and function (Ghajar and Bissell, 2008). Studies have shown that ECM is essential for the establishment and maintenance of tissue polarity and architecture. For example, β 1-integrin maintains tissue polarity in solid organs including the mammary gland (Akhtar et al., 2009), whereas various ECM components are important for planar cell polarity during epithelial morphogenesis (Davidson et al., 2006; Latimer and Jessen, 2010; Skoglund and Keller, 2010). Abnormal ECM dynamics can compromise basement membrane as a physical barrier and promote epithelial–mesenchymal transition, which together can facilitate tissue invasion by cancer cells (Song et al., 2000; Duong and Erickson, 2004; Radisky and Radisky, 2010).

One way the physical barrier of basement membrane can be removed, at least partially, is by overexpressing MMPs. Consistent with this notion, mice overexpressing MMP3, MMP7, or MMP14 form mammary tumors (Sternlicht et al., 1999). It is reasonable to predict that cancer cells or their accompanying stromal and immune cells bearing MMPs have selective advantage over those that are not because, presumably, they can readily enter and exit the endothelial basement membrane and metastasize to distant sites. Additionally, changes in ECM topography may also facilitate cancer cell migration. Thickening and linearization of collagen fibers are common in cancers, and

they are often found in areas where active tissue invasion and tumor vasculature are observed (Condeelis and Segall, 2003; Provenzano et al., 2006; Levental et al., 2009), suggesting that they play an active role in facilitating cancer cell invasion. Indeed, studies using live imaging have shown that cancer cells migrate rapidly on collagen fibers in areas enriched in collagen (Wang et al., 2002; Condeelis and Segall, 2003; Wyckoff et al., 2007).

Together, deregulation of ECM dynamics can facilitate cellular dedifferentiation and cancer stem cell expansion. Additionally, they disrupt tissue polarity and promote tissue invasion. As a result, epithelial cells are directly affected by deregulated ECM dynamics, leading to cellular transformation and metastasis.

Abnormal ECM promotes formation of a tumor microenvironment

Abnormal ECM also indirectly affects cancer cells by influencing the behavior of stromal cells, including endothelial cells, immune cells, and fibroblasts, which are the main initial culprits that cause abnormal ECM production (Bhowmick et al., 2004; Orimo et al., 2005; Quante et al., 2011). As a result, abnormal ECM further perpetuates the local niche and promotes the formation of a tumorigenic microenvironment.

Role of the ECM in tumor angiogenesis and lymphangiogenesis

As a disorganized organ, tumor develops by using many of the same cellular and developmental processes essential for organogenesis (Ruoslahti, 2002; Egeblad et al., 2010a). For a tumor to increase in size, for example, tumor cells face the same increasing demand for nutrient, oxygen, and waste exchange as normal cells do in a growing organ during development. As in normal development, such a demand is met by angiogenesis, the process whereby new blood vessels sprout from the existing vasculature (Davis and Senger, 2005). Furthermore, tumor vasculature, together with the lymphatic system, is the main route through which cancer cells metastasize and immune cells infiltrate. Consequently, tumor-associated angiogenesis and lymphangiogenesis, the process whereby lymphatic vessels are generated, are important aspects of cancer progression (Fig. 3; Avraamides et al., 2008).

The role of abnormal ECM in tumor angiogenesis is a result of the various functions that ECM components play in blood vessel formation during normal development. For example, many ECM fragments, including endostatin, tumstatin, canstatin, arretsen, and hexastatin, all of which are derived from collagens type IV and XVIII, have potent stimulatory or inhibitory effects on angiogenesis (Mott and Werb, 2004). They are likely to collaborate with other pro- or antiangiogenic factors, including VEGF, to determine where to initiate vascular branching and the final branch pattern (Fig. 3 A, stage 1). To initiate vascular branching, vessel basement membrane ECM needs to be removed most likely by MMPs expressed by invading endothelial cells (Fig. 3 A, stage 2). MMPs, for example MMP14 (MT1-MMP), are also required for the invading tip cell, which is at the leading edge of an endothelial branch, to wade through the interstitial matrix toward target cells (Fig. 3 A, stage 3; Genís et al., 2007; van Hinsbergh and Koolwijk, 2008). In addition,

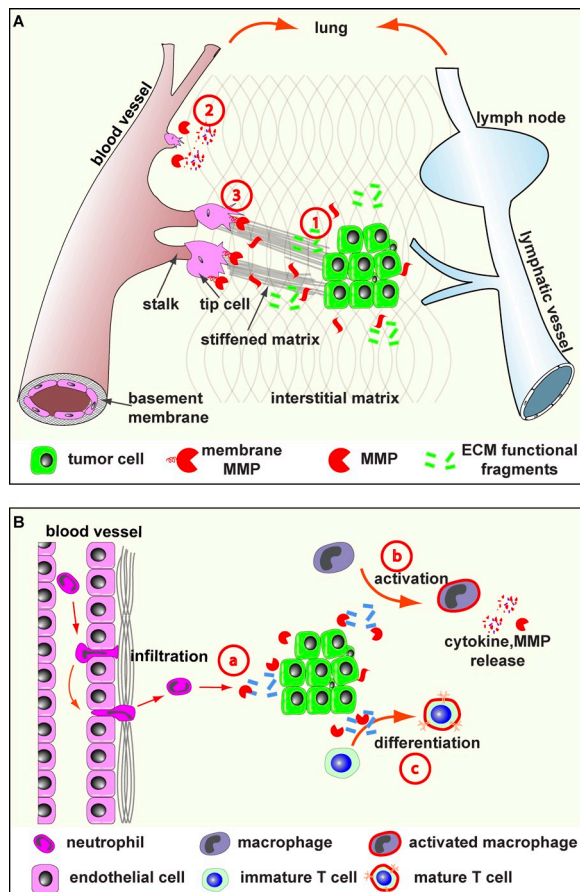


Figure 3. ECM role in tumor angiogenesis, lymphangiogenesis, and inflammation. (A) Angiogenesis and lymphangiogenesis depend on the ECM. Tumor cells produce various components, including VEGF and angiogenic and antiangiogenic ECM fragments, to regulate blood vessel formation (stage 1). During branch initiation, endothelial cells secrete proteases to break down the basement membrane to grow out (stage 2). The outgrowth process of endothelial branching is propelled by at least two groups of cells: tip cells, which lead the migration toward the angiogenic chemoattractant source, and stalk cells, which depend on the ECM and its derivatives to survive and proliferate to provide building blocks for vessel formation (stage 3). Additionally, ECM components participate in cell migration and other aspects of tubulogenesis of blood vessels. Although details remain unclear, lymphangiogenesis depends on the ECM and, together with angiogenesis, provides routes for cancer cell metastasis and immune cell infiltration. (B) The ECM plays multiple roles in tumor inflammation. In addition to promoting survival and proliferation (not depicted), ECM components function as a chemoattractant to immune cells (stage a). The exact details of how immune cells including neutrophil transigrate endothelial basement membrane are not clear, though it seems the ECM plays both positive and negative roles in the process. Macrophage activation depends on the ECM to release its potent cytokine signals and protease content (stage b). Further, immune cell differentiation, including maturation of T helper cells, requires participation of ECM components (stage c).

hypoxia can lead to overproduction of LOX-like protein-2 and a subsequent increase in ECM cross-linking and stiffening, resulting in sprouting angiogenesis (Bignon et al., 2011). These data suggest that ECM biomechanical properties also play essential roles in angiogenesis.

Angiogenesis is a complex process, requiring coordination of many cellular activities. Thus, in addition to guiding endothelial cell migration and branching, ECM and its fragments may be involved in endothelial cell survival and proliferation to supply

cellular building blocks for vessel growth (Sweet et al., 2011). Furthermore, ECM components are involved in cellular morphogenesis, including vessel lumen formation (Newman et al., 2011) and other aspects of tubulogenesis during tumor angiogenesis (Davis and Senger, 2005). The biomechanical properties of the ECM appear to play an especially important role in this process. Indeed, vascular networks with markedly distinct branching patterns have been observed when endothelial cells are grown on matrix with different elasticity (Myers et al., 2011).

Finally, new ECM is deposited to form basement membrane to surround blood vessels during tumor angiogenesis. Importantly, however, the basement membrane of the tumor vasculature is more porous and leaky than normal (Hewitt et al., 1997; Hashizume et al., 2000), which facilitates tumor cell metastasis and immune cell infiltration and promotes cancer progression (Ruoslahti, 2002; Egeblad et al., 2010a). Likewise, the lymphatic system can also transport tumor and immune cells. Recent studies show that the ECM receptor integrin $\alpha 9 \beta 1$ plays an important role in the formation of lymphatic vessels (Huang et al., 2000; Avraamides et al., 2008), suggesting that the ECM is likely to play a role in tumor lymphangiogenesis as well. However, this suggestion awaits further experimental testing, as do the details of how abnormal ECM dynamics may deregulate lymphangiogenesis during cancer progression.

Role of the ECM in tumor-associated inflammation

Inflammation, characterized by massive influx of immune cells, plays a causative role in cancer development. Although their initial function is supposed to suppress tumor growth, immune cells including macrophages are often altered and recruited by tumor cells at later stages to promote cancer (Coussens and Werb, 2002). As in tumor angiogenesis, abnormal ECM affects many aspects of immune cell behaviors, including infiltration, differentiation, and functional activation.

For example, mice lacking the ECM glycoprotein SPARC (secreted protein acidic and rich in cysteine) have an increased number of macrophages in tumors, suggesting that the ECM can influence the number of immune cells. One way the ECM affects immune cells is by regulating cell proliferation (Adair-Kirk and Senior, 2008; Sorokin, 2010). ECM components also may function as chemoattractants to immune cells (Fig. 3 B, stage a). For example, elastin fragments are able to recruit monocytes, but not neutrophils, in the rat lung (Houghton et al., 2006). The acetylated tripeptide Pro-Gly-Pro derived from collagen I proteolysis by MMP8 or MMP9 can functionally mimic the chemoattractant CXCL8 on neutrophils in a lung inflammation model (Weathington et al., 2006). Alternatively, activation of collagen receptor DDR1 can also promote macrophage infiltration in atherosclerotic plaques (Franco et al., 2009).

To reach the inflamed or tumor sites, immune cells encounter two kinds of potential ECM barriers: the endothelial basement membrane and interstitial matrix. Studies using EM and, more recently, intravital imaging have shown that transmigration across the endothelial basement membrane is a rate-limiting step during T cell extravasation (Wang et al., 2006; Bartholomäus et al., 2009). Interestingly, however, inhibition of

integrin $\alpha 6 \beta 1$, which binds to laminin, results in reduced neutrophil infiltration and trapping of neutrophils between endothelium and the basement membrane (Dangerfield et al., 2002). These data suggest that, although the basement membrane is a barrier to immune cell extravasation, binding and attachment to ECM components are necessary for transmigration to occur. It remains unclear how immune cells transmigrate across the basement membrane, for example, regarding whether ECM degradation is involved and whether immune cells have preferred and presumably more porous passage sites along the vessel wall (Rowe and Weiss, 2008). Once they enter the stroma, immune cells travel through the interstitial matrix during infiltration. As in the cases of tumor and endothelial cells, ECM topography such as collagen fibril size and density can influence migration of immune cells (Fig. 3 B, stage a; Lämmermann et al., 2008).

The ECM also regulates the activation of immune cells. For example, increased ECM stiffness can promote integrin-mediated adhesion complex assembly and activate T cells (Ashkar et al., 2000; Adler et al., 2001; Hur et al., 2007; Sorokin, 2010). Although collagen type I promotes infiltration of immune cells, it inhibits the ability of macrophages to kill cancer cells by blocking polarization and, thus, activation of macrophages (Fig. 3 B, stage b; Kaplan, 1983). These results highlight the complex nature of how ECM deregulation may affect behaviors of different groups of immune cells. The inhibitory effect of collagen I on immune cells is likely mediated by its binding with the leukocyte-associated Ig-like receptors (LAIRs), which are expressed at the surface of most immune cells (Meyaard, 2008; Frantz et al., 2010). At present, it is not clear whether LAIRs and integrins cooperate; however, the activation of LAIRs is a plausible mechanism whereby high levels of tumor collagen can attenuate the otherwise tumor-suppressive function of immune cells. Additionally, the ECM plays an important role in immune cell differentiation, including the maturation process of T helper cells (Chabas et al., 2001; Hur et al., 2007). A study also shows that hyaluronan can induce regulatory T cell differentiation from effector memory T cell precursors (Bollyky et al., 2011). Therefore, one plausible mechanism whereby abnormal ECM sabotages the immune system during cancer development may be to prevent immune cells from undergoing their normal differentiation and maturation process (Fig. 3 B, stage c).

Finally, another group of stromal cells, MSCs, has emerged as an important player in the cancer niche. As multipotent stem cells, MSCs normally can give rise to various cell types, including osteoblasts, chondrocytes, adipocytes, and, at least under pathological conditions, CAFs (Quante et al., 2011), which are essential for abnormal ECM metabolism. Because the ECM plays an important role in MSC differentiation (Engler et al., 2006), it is likely that MSCs may be yet another target cell population of abnormal ECM dynamics in the formation of a cancer niche. This is an especially important point, as MSCs can exert pleiotropic effects on inflammation (Aggarwal and Pittenger, 2005; Ripoll et al., 2011; Singer and Caplan, 2011). Together, these data reinforce the possibility that, once beyond a certain threshold, deregulated ECM dynamics may cause irreversible changes to the normal niche and convert it into a cancer-promoting environment.

In summary, abnormal ECM dynamics deregulate behaviors of both cancer cells and stromal cells. On the one hand, ECM anomalies promote cancer cell transformation and tissue invasion; on the other hand, they help generate a tumorigenic niche that further facilitates cancer progression. Such a double-whammy effect is a recurring theme at later stages of cancer metastasis, as is evident from the next section.

The ECM: An essential component of premetastatic and metastatic niches

Cancer cell metastasis is a multistep process, consisting of local invasion and intravasation at the primary site, survival in the circulation, and extravasation and colonization at the distant site (Paget, 1889). Depending on cancer type and organ destination, these steps may have distinct kinetics during cancer metastasis (Nguyen et al., 2009). A successful metastasis requires not only a local niche to support cancer cell growth at the primary site but also one, the metastatic niche, to allow invading cancer cells to survive, colonize, and expand to form a macrometastasis (Psaila and Lyden, 2009).

Although still in its infancy, studies support that the ECM is, as in the primary tumor niche, an essential component of the metastatic niche. For example, although most metastatic cancer cells die, mammary carcinoma cells expressing the hyaluronan receptor CD44 survive better than cells with low levels of CD44 (Yu et al., 1997). These data imply that hyaluronan and maybe other ECM components promote survival of metastatic cancer cells. Moreover, as in the case of primary tumor niche, LOX activities are often up-regulated in metastatic cancer sites as a result of increased production from cancer cells or activated fibroblasts at the metastatic niche (Erler et al., 2009). Increase in mechanical force as a result of LOX expression and ECM stiffening presumably facilitates colonization of cancer cells and infiltration of immune cells at the metastatic site. These changes may be similar to the ones at the primary niche and together may further trigger the angiogenic switch and lead to cancer cell expansion from micrometastasis to macrometastasis (Fig. 4). However, this notion remains to be tested experimentally.

Remarkably, mounting evidence suggests that cancer cells may remotely modify, often with the involvement of other cell types including hematopoietic progenitor cells, distant sites and proactively participate in the creation of a premetastatic niche before metastasis (McAllister and Weinberg, 2010; Bateman, 2011). For example, cancer cells at the primary site produce osteopontin and other factors to recruit granulin-expressing hematopoietic progenitor cells, which can then deregulate behaviors of the distant stromal cells (Elkabets et al., 2011). Interestingly, granulin, belonging to the epithelin family of secreted growth factors, can increase the expression of a variety of ECM components and their modifying enzymes in stromal fibroblasts (Elkabets et al., 2011).

Changes of ECM composition are important for continued recruitment of hematopoietic progenitor cells to the premetastatic niche. For example, increased fibronectin expression is essential for VEGF receptor 1⁺ (VEGFR1⁺) hematopoietic progenitor cells, which also express the fibronectin receptor integrin $\alpha 4 \beta 1$, to migrate and adhere to the niche in the lung

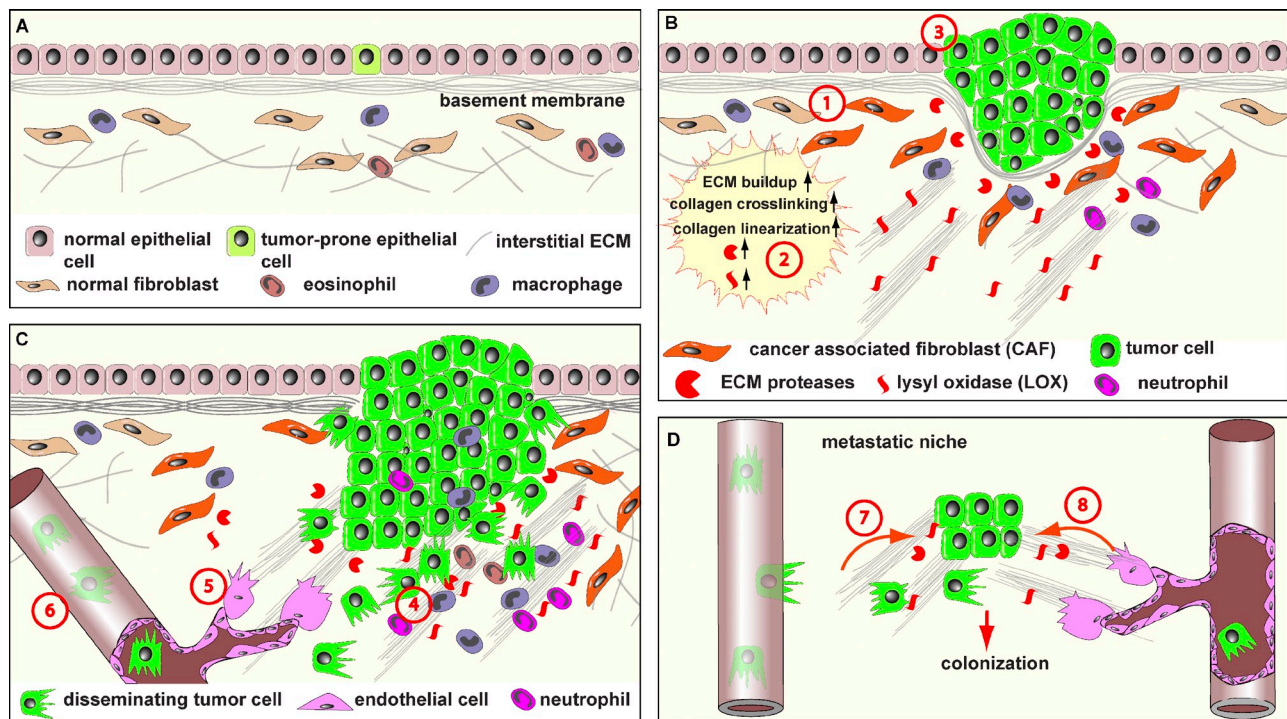


Figure 4. Abnormal ECM promotes cancer progression. (A) ECM remodeling is tightly controlled to ensure organ homeostasis and functions. Normal ECM dynamics are essential for maintaining tissue integrity and keep rare tumor-prone cells, together with resident fibroblasts, eosinophils, macrophages, and other stromal cells, in check by maintaining an overall healthy microenvironment. (B) With age or under pathological conditions, tissues can enter a series of tumorigenic events. One of the earlier events is the generation of activated fibroblasts or CAFs (stage 1), which contributes to abnormal ECM buildup and deregulated expression of ECM remodeling enzymes (stage 2). Abnormal ECM has profound impacts on surrounding cells, including epithelial, endothelial, and immune cells and other stromal cell types. Deregulated ECM promotes epithelial cellular transformation and hyperplasia (stage 3). (C) In late-stage tumors, immune cells are often recruited to the tumor site to promote cancer progression (stage 4). In addition, deregulated ECM affects various aspects of vascular biology and promotes tumor-associated angiogenesis (stage 5). Creation of a leaky tumor vasculature in turn facilitates tumor cell invasion and metastasis to distant sites (stage 6). (D) At distant sites, cancer cells leave the circulation and take hold of the local tissue. Together with local stromal cells, cancer cells express ECM remodeling enzymes and create a local metastatic niche. Abnormal niche ECM promotes extravasation, survival, and proliferation of cancer cells (stage 7). At later stages when cancer cells awake from dormancy, abnormal ECM turns on the angiogenic switch (stage 8), presumably using a mechanism similar to that used at the primary site (stage 5), and promotes the rapid growth of cancer cells and an expansion of micrometastasis to macrometastasis.

(Kaplan et al., 2005). Once there, VEGFR1⁺ hematopoietic progenitor cells secrete MMP9, which is known to play a role in lung-specific metastasis (Hiratsuka et al., 2002), and thus further modulate and deregulate the premetastatic niche. In addition to fibronectin, other ECM components may also be important for the function of the premetastatic niche. For example, hyaluronan and its receptor CD44 facilitate signaling via C-X-C chemokine receptor 4 (CXCR4) and its ligand stromal-derived growth factor 1 (SDF1/CXCL12; Netelenbos et al., 2002; Avigdor et al., 2004), which are essential for organ-specific metastasis of tumor cells to the lung or bone marrow (Jones et al., 2006). Thus, these data suggest that deregulation of ECM dynamics is an important step during the formation of a premetastatic niche.

Collectively, a picture has started to emerge with regard to ECM's roles in cancer progression: normal ECM dynamics are essential for embryonic organ development and postnatal function (Fig. 4 A); deregulated ECM dynamics disrupt tissue polarity, architecture, and integrity and promote epithelial cell transformation and invasion (Fig. 4 B). Furthermore, abnormal ECM dynamics derail stromal cell behavior, leading to tumor-promoting angiogenesis and inflammation by endothelial cells and immune cells, respectively, both at the primary

and metastatic sites. The resultant changes in the stromal components further exacerbate the tumorigenic microenvironment and facilitate the process of oncogenic transformation, tissue invasion, and metastasis during cancer initiation and progression (Fig. 4, C and D).

Concluding remarks

From the initial belief that the intrinsic properties of cancer cells determine most major aspects of cancer initiation and progression, our understanding of cancer biology has taken remarkable strides. We now regard cancer as a heterogeneous disease not only in the sense that different molecular etiologies may underlie the same clinical outcome but also that multiple cell types, in addition to cancer cells, and noncellular components need to be mobilized and coordinated to support the survival, growth, and invasion of cancer cells. As a major component of the local niche, the ECM has emerged as an essential player at various stages of the carcinogenic process. Its functional diversity and dynamic nature, which allows the ECM to be an active participant in most major cell behavior and developmental processes, also makes it a necessary target whose deregulation may be a rate-limiting step in cancer progression.

An important area of future cancer research will be to determine whether abnormal ECM could be an effective cancer therapeutic target. To achieve this goal, we must understand how ECM composition and organization are normally maintained and regulated and how they may be deregulated in cancer. A daunting task in this regard will be to determine the kind of ECM changes that have causative effects on disease progression and how these changes of the ECM, alone or in combination, may affect cancer cells and cells in the stromal compartment. Additionally, with the growing documentation of the diverse functions of the ECM in development and cancer, a major challenge will be to understand the molecular basis of these functions, whether they involve only receptor signaling, rearrangements of the cytoskeleton, changes of gene expression, or other aspects of cell behavior, and how such changes are integrated with conventional signaling cascades that are known to play a role in these processes.

Abnormal ECM stiffness, as observed in tissue fibrosis, clearly plays an important role in cancer progression. However, we have only begun to decipher how different cell types respond to changes in ECM elasticity and which receptors detect the various types of physical force. It remains to be an important area of research to determine whether ECM elasticity may be restored to normal in cancer and how such a restoration may benefit treatment prognosis. ECM anomalies, including stiffness, have been associated with delivery and resistance of conventional drugs (Egeblad et al., 2010b). Indeed, a decrease in the fibroblast pool and thus the ECM improves drug uptake in the mouse (Loeffler et al., 2006; Olive et al., 2009). Therefore, targeting abnormal ECM may provide yet another effective avenue to combat the complicated illness that is cancer.

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