Extracellular matrix components in breast cancer progression and metastasis

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Abstract

The extracellular matrix (ECM) is composed of highly variable and dynamic components that regulate cell behavior. The protein composition and physical properties of the ECM govern cell fate through biochemical and biomechanical mechanisms. This requires a carefully orchestrated and thorough regulation considering that a disturbed ECM can have serious consequences and lead to pathological conditions like cancer. In breast cancer, many ECM proteins are significantly deregulated and specific matrix components promote tumor progression and metastatic spread. Intriguingly, several ECM proteins that are associated with breast cancer development, overlap substantially with a group of ECM proteins induced during the state of tissue remodeling such as mammary gland involution. Fibrillar collagens, fibronectin, hyaluronan and matricellular proteins are matrix components that are common to both involution and cancer. Moreover, some of these proteins have in recent years been identified as important constituents of metastatic niches in breast cancer. In addition, specific ECM molecules, their receptors or enzymatic modifiers are significantly involved in resistance to therapeutic intervention. Further analysis of these ECM proteins and the downstream ECM mediated signaling pathways may provide a range of possibilities to identify druggable targets against advanced breast cancer.

Introduction

The extracellular matrix (ECM) is an essential component of tissues that constitute multicellular organisms. Proteins of the ECM include collagens, laminins, fibronectin, glycoproteins and proteoglycans that serve as a structural scaffold and provide the support necessary to maintain tissue integrity and sustainability. This is important for embryonic development and the generation of new tissue structures as well as the maintenance of architecture and homeostasis of adult tissues. However, the ECM is tremendously pleiotropic and is much more than simply a structural framework as it can affect cellular fate via multiple mechanisms. For example, the matrix binds growth factors and cytokines and depending on the context, it can regulate stability and bioavailability of these factors [1]. The balance between ECM mediated confinement of growth factors and their concentration to cellular surface receptors, may significantly determine the availability of signaling molecules presented to cells. Furthermore, the ECM provides adhesive surface to cells inducing survival signaling via integrins and activation of focal adhesion kinase (FAK) [2]. ECM proteins are moreover the key molecules that mediate mechanical forces within tissues and this tension can dictate how the cells respond to growth factors and cytokines [3]. Importantly, certain ECM proteins bind directly to surface receptors promoting cellular signaling that determines cell fate [4]. The combination of these effects exerted by the ECM provides an important context of cell regulation in health and disease.

ECM dynamics of the mammary gland

In a resting adult mammary gland, the basement membrane (BM) encapsulates the gland and is the principal ECM that interacts with both the luminal epithelium and the myoepithelium. The composition of the BM is primarily made up of collagen type IV, laminin (LM)-111 and LM-332, epiligrin, entactin and proteoglycans. The BM is essential to maintain the polarity of epithelial cells and LM-111 produced by myoepithelial cells has been shown to be a key BM component for this function [5]. Moreover, a combination of lactogenic hormones and ECM is required for full differentiation of mammary epithelial cells [6,7].

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A well-studied example of ECM regulating cell differentiation is the response of mammary epithelial cells to the lactogenic hormone prolactin. Prolactin induces maturation of mammary epithelial cells via signal transducer and activator of transcription 5 (STAT5) pathway leading to terminal differentiation and production of milk [2]. The control of mammary epithelial differentiation in response to prolactin is inhibited when the epithelial cells are placed on the interstitial matrix that is rich in fibrillar collagen (type I and III), proteoglycans, hyaluronan and various glycoproteins [7]. However, the epithelial cells regain prolactin response, in a STAT5 dependent manner, when placed in the presence of LM-111 [8,9]. In vivo studies also support this link, where mammary glands deficient in β1 integrin, an essential binding receptor of laminin, fail to differentiate and produce milk. Epithelial cells detach from the basement membrane and show reduced STAT5 activation [10]. These findings demonstrate the importance of the specific context that the ECM provides and show that this molecular context can dictate the response to growth factors and hormones.

Pregnancy leads to dramatic changes in the mammary gland architecture. This is particularly evident during post-lactational mammary gland involution, that is associated with a prominent wound healing response and extensive remodeling of the ECM [11]. Involution leads to a significant upregulation of fibrillar collagens, fibrillin and increased proteolysis. Moreover, several matricellular glycoproteins are induced during mammary gland involution [11,12]. Laminin as well as entactins and collagen type IV are however degraded. The dynamic potential of the ECM is vividly exhibited during responses to stress and tissue remodeling as is seen during involution. Importantly, the process of ECM remodeling in response to stress must be carefully controlled, otherwise it can lead to pathological conditions like fibrosis and cancer [2].

**ECM components in breast cancer progression**

*Link to tissue remodeling*

Several different changes in ECM are associated with breast cancer and promote the progression of the disease. Interestingly, the involuting mammary gland has been suggested to contain components that promote cancer. ECM isolated from involuting mammary gland harbors tumorigenic matrix fragments that facilitate growth of breast cancer cells in culture and enhance metastasis in animal models [13–15]. This has been suggested to be an explanation for increased risk of breast cancer associated with pregnancy [16]. The ECM can have a profound effect on epithelial cells during tissue remodeling and cancer. However, in addition to directly affecting cancer cells, the ECM can also promote significant changes in stroma. For example, the matrix from involuting mammary gland is chemotactic for macrophages. Fibrillar collagen and proteolysis is increased during the remodeling and denatured collagen type I is a chemo-attractant for macrophages which are also a prominent cell type of cancer stroma [17,18].

Intriguingly, when analyzing specific components of the ECM, a significant overlap is seen between ECM composition of involuting mammary gland and cancer (Fig. 1). In breast cancer, an increase is observed in the deposition of fibrotic stromal matrix. These are molecules such as collagen type I, III and V, elastin, vitronectin, matricellular proteins and oncofetal fibronectin [19]. Moreover, the glycosaminoglycans like hyaluronan and chondroitin sulfate are also upregulated while collagen type IV and LM-111 are reduced [5,20].

The involuting mammary gland exhibits an immense proteolytic activity with the ECM fragmentation primarily induced by matrix metalloproteinases (MMPs) [16]. The fragmentation of the matrix has several consequences. It provides room and migration paths for cancer cells and it can free ECM bound growth factors. Moreover, proteolytic activity can reveal unexposed ECM domains and make them accessible to surface receptors. The MMP-2 can be considered exemplary of this, since MMP-2 exposes the cryptic site on LM-332 during mammary gland involution. The LM-332 cryptic site has EGF like properties and binds the EGF receptor [21].

Lamins play a significant role during cancer development. In breast cancer, research efforts have focused on LM-111 and LM-332. Importantly, LM-111 which is a major unit of the basement membrane, is broken down in cancer progression [5]. Invasive breast cancer induces LM-332 production in myofibroblasts to promote survival through the phosphatidylinositol 3-kinase (PI3K) – AKT pathway [22]. LM-332 moreover induces migration and invasion in breast carcinoma cells via α3 integrin and is strongly associated with cancer progression and metastasis.

**Fig. 1.** Common extracellular matrix (ECM) proteins induced during mammary gland involution and cancer. A. Structure and cellular context of the virgin adult mammary gland (cross-section). B. The common ECM components increased in involuting mammary gland and cancer [11,12,16]. TNC, tenascin C; SPP1 osteopontin; POSTN, peristin; SPARC, secreted protein, acidic and rich in cysteine; THBS1, thrombospondin-1; MMP, matrix metalloproteinase; uPA, urokinase plasminogen activator.
with triple negative breast cancer [23,24]. Although less attention has been focused on LM-511, this laminin isoform has surfaced as a significant player in breast cancer. LM-511 regulates migration, tumor invasion and metastasis in breast cancer, correlates with breast tumor grade and is linked to metastatic potential in experimental models [25,26]. In the light of the significant number of possible laminin subunit compositions identified it is important to dissect their individual roles, particularly in the context of lethal disease like metastatic breast cancer.

Hyaluronan (HA) is a highly abundant oligosaccharide and forms a significant part of the ECM. HA regulates a variety of cell behaviors like adhesion, motility, growth and differentiation and acts through surface receptors such as CD44 [27]. In breast cancer, a dramatic HA increase is observed and HA levels have been suggested to predict clinical outcome [28]. The key enzyme in HA biosynthesis is hyaluronan synthase (HAS). In animal models for breast cancer, expression of HAS2 has been shown to promote mammary tumor progression and metastasis [29]. Furthermore, inhibition of HAS2 significantly reduces cancer progression in breast cancer models, suggesting its important role in this process [30,31]. HA may be an important factor in recruitment of stroma to the developing tumor. It causes increased hydration and interstitial pressure, promoting penetration of fibroblasts as well as migratory and invasive activity via CD44 [27]. Moreover, HA also induces invasive behavior in the cancer cells themselves [32].

**Enzymatic modification of the cancer matrix**

ECM modifying enzymes are intricately associated with breast cancer and metastatic progression. Matrix metalloproteinases (MMPs) mentioned previously, urokinase plasminogen activator (uPA) system, cathepsins and crosslinking enzymes of the lysyl oxidase (LOX) family are highly expressed in cancer and serve versatile roles. Essentially, these enzymes are also known to play an important role in mammary gland involution and wound healing.

MMPs are the most prominent proteases during both tissue remodeling and cancer. The main MMPs expressed during invasion are MMP-2, -3, -9 and -14 (MT1-MMP) [16]. Importantly, the same MMPs play a significant role in breast cancer progression. MMP-2 and MMP-9 are efficient in degrading collagen type IV which is the main composition of basement membrane that needs to be invaded during tumor progression. Moreover, the membrane bound MMP-14 promotes survival of breast cancer cells embedded in collagen [33]. Interestingly, experiments have shown that even in the absence of oncogenic transformation, overexpression of ECM remodeling enzymes like MMP-3 and MMP-14 alone can lead to malignancy [34,35]. This underscores how signaling mediated by the ECM remodeling can profoundly dictate cell fate and is a strong indication that ECM remodeling may indeed be a driving force in cancer progression.

The urokinase plasminogen activator (uPA) system consists of serine proteases that promote ECM degradation. High levels of uPA are a significant inducer of cancer progression and predict poor metastasis free and overall survival [36]. Cathepsins, a family of lysosomal proteases, are also significant contributors to cancer progression. Cathepsin B is the family member that is best studied in the context of breast cancer. Cathepsin B promotes collagen type I degradation, breast cancer invasion and metastasis to lung and bone [37–39]. Another family member, Cathepsin K, is highly expressed by osteoclasts promoting resorption of the bone matrix. Moreover, cathepsin K is also expressed in breast cancer cells and is required for invasion and colonization of the bone [40].

In the context of collagen rich matrix, the crosslinking enzyme lysyl oxidase (LOX) has surfaced as a major player in cancer. LOX facilitates collagen crosslinking leading to increased ECM stiffness and promotes thereby invasive behavior in breast cancer cells [41,42]. Under high stiffness the tensile forces will cluster integrins leading to FAK activation and PI3K induced invasion and tumor progression [42]. LOX is frequently expressed in breast tumors and is associated with poor clinical outcome [41].

**Matricellular proteins**

Matricellular proteins are ECM glycoproteins that are highly expressed during embryonic development but tightly regulated in the adult [4]. However, during tissue remodeling like mammary gland involution and wound healing and pathological conditions such as cancer these proteins are greatly upregulated [11]. In malignancies of the breast, matricellular proteins are frequently associated with metastatic spread and poor clinical prognosis [4]. Interestingly, these matrix proteins do not contribute significantly to the mechanical structure of the ECM but are important cell regulators and modulate signaling pathways [4].

Tenascin C (TNC) is a protein of the matricellular family that assembles into a hexameric structure. TNC forms a significant constituent of the provisional matrix of wounds and is highly upregulated during tissue regeneration [43]. Very low expression is observed in healthy mammary glands while it is highly upregulated in breast cancer especially at invasive fronts [44,45]. TNC has been shown to be one of six genes in a signature regulated by microRNA 335 in metastatic breast cancer [46]. TNC and MMPs often co-localize in areas of tissue remodeling and MMP-9 and MMP-13 are induced by TNC leading to invasive behavior in cancer cells [47,48]. Moreover, TNC promotes the fitness of metastasis initiating breast cancer cells in the lung by promoting Notch and Wnt signaling [45]. TNC positively correlates with tumor grade and size in breast cancer and its expression at the invasive front predicts both local and distant relapse [49]. Evidence suggests that TNC expression predicts poor 5-year survival in patients with breast cancer [45,50]. Interestingly, TNC expression in both stroma and cancer cells has been shown to have an exceptionally poor outcome for patients when compared to expression in stroma alone [51].

Osteopontin, also known as secreted phosphoprotein 1 (SPP1), is another member of the matricellular family. SPP1 is a phosphorylated glycoprotein that interacts with surface receptors including several integrins and CD44 [52]. Integrin αvβ3 is the best characterized interacting receptor of SPP1 and mediates SPP1 induced cell survival signaling [53]. The protein is detected in bone mineral produced by matrix synthesizing osteoblasts. SPP1 has a thrombin cleavage site and after cleavage both fragments are recognized by integrin receptors. Thrombin cleavage of SPP1 has been suggested to lead to an increase in its activity [52].

Overexpression of SPP1 promotes mammary tumor formation and development of metastasis in a rat model [54]. Breast cancer cells transfected with SPP1 have been shown to exhibit increased invasion as well as increased expression of the proteolytic enzyme uPA [55]. Although the majority of cases shows SPP1 expression in stromal cells (infiltrating macrophages or lymphocytes), this protein is also expressed by cancer cells directly. Interestingly, like several other proteins of the ECM, SPP1 exists both as an immobilized part of the ECM and as a soluble factor circulating in the blood. SPP1 is expressed in node negative breast cancer and its presence both in tumor tissue and in plasma may be a prognostic indicator of aggressiveness [56,57]. Indeed, high levels of SPP1 in blood plasma are associated with increased metastatic spread and poor overall survival [58,59]. Moreover, studies in mouse models suggest that SPP1 expressed by breast cancer cells injected orthotopically is required for mobilization of bone marrow-derived stromal cells,
indicating that circulating plasma SPP1 might be more than a passive biomarker [60].

Periostin (POSTN) is a matricellular protein whose most significant function in healthy tissues has been linked to bone and heart development [61]. POSTN is expressed in various cancers and has been shown to affect tissue stiffness, a phenomena that is tightly linked to cancer progression [42]. POSTN bound to BMP-1 promotes activation of LOX by which it promotes collagen cross-linking and tissue stiffness [62]. In a mouse model for breast cancer, POSTN is induced by TGFβ3 and was shown to be required for metastatic colonization of the lung [63]. Interestingly, high periostin levels in serum of breast cancer patients are associated with bone metastasis [64].

Secreted Protein, Acidic and Rich in Cysteine (SPARC) is a matricellular ECM protein that is nearly absent in normal mammary stroma while its expression is very strong in breast cancer [65]. Integrin β4 mediates SPARC upregulation and breast cancer invasion and SPARC can regulate the activation of MMP-2 in breast cancer cell lines [66]. Moreover, SPARC overexpression is able to promote metastasis to lungs in a mouse model [67]. SPARC is associated with basal, HER2+ and luminal B breast cancer subtypes while the luminal A subtype does not express the protein [68]. Interestingly, some evidence suggest an inverse correlation between estrogen receptor and SPARC [69]. The expression of SPARC in breast cancer is associated with poor metastasis free- and overall survival [70–72].

Thrombospondin (THBS) was first described as a component of platelets but is found expressed by a variety of cells like fibroblasts, macrophages, osteoblasts and cancer cells [73]. THBS1 has been shown to be anti-angiogenic and represses growth of primary tumors in experimental model systems. However, THBS1 is intriguingly an effective inducer of metastasis where it induces migration of breast cancer cells and promotes cancer invasion through activation of TGFβ3 and upregulation of the uPA system [74,75]. While inhibiting primary tumor growth by anti-angiogenic mechanisms, THBS1 promotes lung metastasis in mouse models [76]. Moreover, THBS1 is expressed in human breast cancer and associates with poor metastasis free survival [77]. This raises an intriguing question on the differences and similarities between qualities of primary tumors and metastases.

Interestingly, an increase in circulating levels of THBS1 in plasma is observed in breast cancer patients compared to healthy women and this associates particularly with tumors that are negative for estrogen receptor and progesterone receptor [78]. THBS1 in plasma may be a marker of aggressiveness since a further increase in THBS1 is seen in patients with advanced disease linked to lymph node metastasis compared to early disease [79,80].

The metastatic niche

In recent years, it has become evident that the cancer microenvironment and specific ECM components are major factors promoting metastasis initiation and outgrowth. The metastatic niche has emerged as a noticeable concept in the field as the microenvironment that can support outgrowth of cancer cells and development of metastasis in distant organs. While several aspects on the nature of the niche remain to be learned, significant progress has been made in the past few years.

In animal models, the primary tumor has been suggested to exert a systemic effect, early during breast cancer progression, leading to biological changes in distant organs termed a pre-metastatic niche [81]. This involves for example the mobilization of bone marrow-derived cells (BMDCs) and their recruitment to the lungs leading to significant changes in the ECM in the lung parenchyma. In fact, ECM remodeling is a central feature in the formation of the pre-metastatic niche. Fibronectin is upregulated at the distant site as well as the remodeling enzymes MMP-2 and MMP-9 [81]. Furthermore, LOX accumulates in the pre-metastatic niche and promotes recruitment of MMP-2 producing myeloid cells [82].

Recently, two matricellular proteins, TNC and POSTN, were shown to be important components of the metastatic niche [83]. Interestingly, the function of the two molecules shows significant overlap. Both TNC and POSTN promote lung metastasis in breast cancer models, TNC via activation of Notch signaling and induction of the Wnt target gene LGR5, and POSTN by induction of Wnt signaling by binding and presenting Wnt ligand to cancer cells [45,63]. Moreover, POSTN has been demonstrated to bind directly to TNC [84]. This may suggest a possible collaboration of the two molecules to support metastasis initiation within the niche [83].

Matrix and therapy resistance

In breast cancer, several gene expression signatures have been identified that predict clinical prognosis in patients. Interestingly ECM and ECM modifying enzymes are frequently prominent constituents of these signatures. For example, expression of certain matrix genes can classify breast cancer into subgroups with different clinical outcome [85]. Moreover, it has also become evident that the ECM may hold a significant role in mediating resistance to treatment. The ECM provides an adhesive substrate promoting survival mechanisms and specific matrix components support and induce stem cell pathways enhancing viability and fitness of metastatic cells. An intriguing study by Farmer and colleagues showed that a gene expression signature derived from stromal components in breast cancers could predict metastatic resistance to the chemotherapeutic agents 5-fluorouracil, epirubicin and cyclophosphamide [86]. Furthermore, the composition of the stromal signature that predicted chemotherapy resistance showed a prominent exhibition of ECM proteins. These are proteins like various collagens, SPARC, POSTN, Fibulin-1 and Thrombospondin-2 [86].

Several studies using cell culture systems have shown a significant role for the ECM in promoting cancer cell resistance to therapy. These specific molecules that promote resistance are various components of the matrix inducing different cell responses. The matricellular proteins SPP1 and THBS1 induce resistance to apoptosis mediated by chemotherapeutics cyclophosphamide and doxorubicin, respectively [87,88]. Furthermore, Type I collagen mediates resistance to the antimigratory effect of doxorubicin and THBS1 promotes resistance to doxorubicin mediated apoptosis [88,89]. In addition, doxorubicin induces expression of the ECM proteins fibulin-1 and LM-111 in vitro and in vivo breast cancer models [90]. Hyaluronan is another component of the ECM that promotes resistance to a variety of chemotherapeutic drugs, by activation of PI3K signaling that supports survival via AKT and also induces multidrug transporter MDR1 [91,92]. Indirect evidence linked to matrix proteases moreover suggests that the ECM may be an important player in therapy resistance. Cathepsins promote chemotherapy resistance in mammary cancer cells in vitro and in vivo where cathepsin B and S play a significant role [93].

In addition to chemotherapy, the ECM has also been linked to resistance to endocrine and targeted therapies as well as radiotherapy. ECM gene cluster predicts patient prognosis and resistance to tamoxifen therapy where fibronectin, LOX, SPARC and TIMP3 are linked to poor prognosis and TNC expression associates with resistance to endocrine therapy [72]. Furthermore, examining targeted therapy, the treatment sensitivity of HER2 positive cancer cells is associated with laminin response. LM-332 promotes resistance to anti-HER2 therapy via αvβ5 or α3β1 integrins and tetraspanin CD151 [94]. Finally, ECM promoted resistance to cancer
therapy also extends to radiotherapy. Fibronectin and laminin increase resistance to ionizing radiation and cytotoxic drugs in human tumor cells and normal cells in vitro [95].

Besides a possible role in promoting cancer cells’ escape from therapeutic intervention, the ECM may also provide insights into the progression of the disease and be used for diagnosis and estimation of treatment efficacy. Patients with metastatic breast cancer have been shown to have increased levels of several matricellular proteins in blood circulation compared to healthy women and this associates with poor survival [58,64,79,96]. This is intriguing in the light of the possibility of using matricellular proteins as biomarkers for disease progression and response to therapy.

Today, chemotherapy, endocrine- and targeted therapies and radiotherapy are the clinical options as adjuvant treatments. The ECM is linked to resistance to all of these therapies, suggesting a major role for the matrix in maintaining viability of cancer cells under high stress. The role of reactive oxygen species (ROS) in sensitivity to cancer therapy has been increasingly recognized in recent years. The ECM attachment has interestingly been shown to significantly affect metabolism and the levels of ROS. Mammary epithelial cells that are deprived of ECM attachment were shown to display increased ROS levels and were prone to apoptosis providing another measure how ECM can promote resistance to cancer therapy [97].

Discussion and future outlook

In recent years, the microenvironment has received increased attention as an essential part of cancer development and metastasis [18]. Moreover, the last years have also given rise to studies that demonstrate a functional role for the microenvironment in resistance to cancer therapy [98,99]. The importance of the microenvironment should be taken into account when developing new therapies against breast cancer. Would it be possible to interfere with the ECM — cancer cell interaction thereby disconnecting the cancer cells from the niche and sensitizing them to therapy? Interesting examples have been generated suggesting that the ECM may hold promise as a target for cancer therapy. Evidence of direct inhibition of the matricellular protein POSTN is encouraging. Antibody mediated neutralization of POSTN has been shown to inhibit lung metastatic outgrowth in breast cancer models [100]. Moreover, drugs that inhibit the production of ECM components may provide alternative means to target breast cancer. For example, inhibition of hyaluronan synthesis in breast cancer cells by 4-Methylumbelliferone (MU) restrains metastatic growth in the bone [101]. ECM remodeling may also be an attractive target and promising results have been shown for cathepsin inhibitors. Blocking cathepsin activity sensitizes mammary tumors to chemotherapy in mouse models [93]. Furthermore, in a phase II clinical trial, a cathepsin K inhibitor has been shown to repress bone matrix resorption in women with breast cancer metastasis to bone [102]. Inhibition of ECM receptors could moreover provide important opportunities in treating cancer. In mouse models for breast cancer metastasis to bone, the inhibition of 

\[ \beta 3 \] and 

\[ \beta 5 \] integrins represses bone resorption and metastasis growth in the bone [103]. Finally, the matrix composition at invasive fronts of tumors can be used to deliver drugs or radiation specifically to active sites of cancer. This has been shown in a xenograft breast cancer model where antibody against TNC was coupled to interleukin-2 (IL-2) and this targeted treatment with IL-2 synergized with paclitaxel therapy to repress tumor growth [104]. These are promising examples of how targeting the ECM and ECM turnover may provide benefit as cancer treatment. However, the role of the ECM in tissue remodeling and malignancies must be better understood and dissected in the context of metastasis for a realistic consideration of the matrix and downstream effectors as therapeutic targets against advanced breast cancer. Expanding the pool of possible targets may provide necessary means to prevent or inhibit ECM promoted breast cancer progression.

Conflict of interest statement

The author has no conflict of interest to declare.

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