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The Roles of Extracellular Matrix in Breast Carcinoma: A Narrative Literature Review

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ABSTRACT

The extracellular matrix is a complex and highly dynamic molecular network and serves to provide biochemical signals in the process of development, invasion, and metastasis of breast cancer. There are several proteins that contribute to the structure and function of the extracellular matrix, including collagen, laminin, glycosaminoglycans, and proteoglycans. Alterations of the extracellular matrix in breast cancer are not only limited to the composition of the extracellular matrix but also remodeling enzymes such as matrix metalloproteinase (MMP), cathepsin, urokinase plasminogen activator (uPA), lysyl oxidase (LOX) and heparanase. The extracellular matrix can increase breast cancer progressivity and resistance to treatment, so it is important to know its role because it can be a targeted therapy in the future.

1. Introduction

Breast cancer is the most frequent malignancy for women in the world and is the fifth leading cause of death from cancer for women in the world. Based on data from the Global Burden of Cancer Study (GLOBOCAN) in 2020, the incidence of breast cancer for women is 11.7% of all cancer cases and is more common in developed countries compared to developing countries (55.9 and 29.7 per 100,000 individuals). As many as 1 in 6 breast cancer patients died from the disease. Breast cancer mortality rates in women are higher in developing countries compared to developed countries (15.0 and 12.8 per 100,000 individuals).[1,2]

The extracellular matrix is a complex and highly dynamic molecular network and serves to provide biochemical signals in the process of development, invasion, and metastasis of breast cancer. There are several proteins that contribute to the structure and function of the extracellular matrix, including collagen, laminin, glycosaminoglycans, and proteoglycans. Alteration of the extracellular matrix in breast cancer is not only limited to the composition of the extracellular matrix but also remodeling enzymes.[3,4]

The science of the biological properties of breast cancer is still unknown. However, a large number of studies mentioned that the extracellular matrix could

increase cancer progressivity and resistance to treatment, so it can be a therapeutic target in the future. The understanding of the mechanisms regarding the extracellular matrix in improving breast cancer progressivity is still not widely known, so this journal will discuss that matter.[3,5,6]

Components of extracellular matrix in breast cancer

The extracellular matrix can be classified into two groups, namely the interstitial matrix and the basal membrane. The basal membrane is a thin layer of the extracellular matrix that forms a supporting structure under the epithelium and endothelial cells. The basal membrane has a composition containing collagen type IV, laminin, and proteoglycans. The interstitial matrix is rich in collagen type I, III, V, VI, VII, and XII, as well as proteoglycans and some glycoproteins such as tenascin-C and fibronectin (Figure 1).[7]

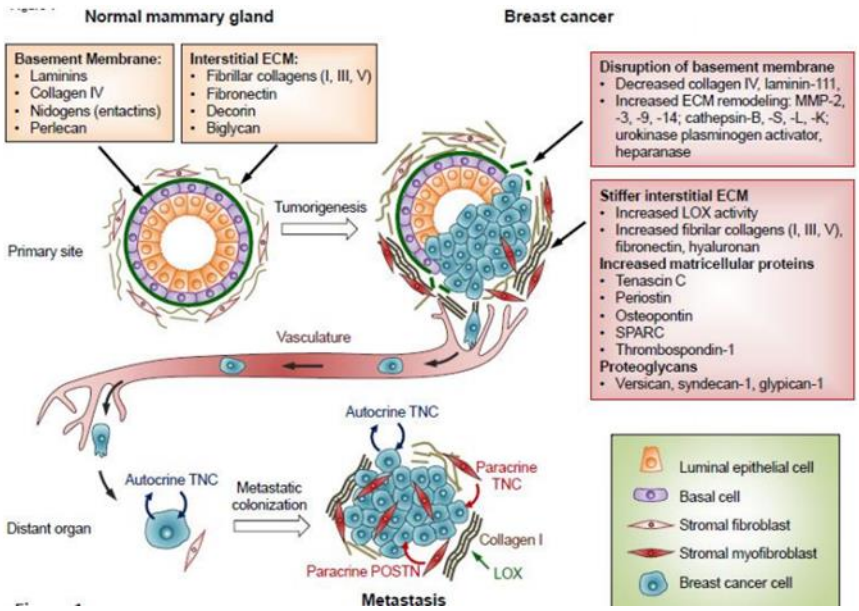

Figure 1. Extracellular matrix in breast cancer. In breast cancer, there are significant changes that occur in the composition of the extracellular matrix.[3]

Collagen

The general feature of fibrosis and breast cancer is an increase in collagen production. Collagen is a major component of the extracellular matrix, about 30% of the total protein mass in the body. There are 28 different types of collagen in fibrillar and non-fibrillar forms. The most frequent collagen in mammals is fibrillar collagen type I, which is the main component of the interstitial matrix. Collagen type I, II, III, and V are fibrillar collagen, which can aggregate to form large fibrils visible on light or electron microscopes. Type IV collagen is a non-fibrillar collagen and is an important element of the basal membrane, an extracellular component of the matrix located in the basal epithelium and endothelial, which is necessary for maintaining the polarity of tissues. Important changes in collagen composition are seen in breast cancer, where there is an increase in the accumulation of fibrillar collagen I, III, and V, as well as type IV collagen, which is decreasing.[3,8]

Collagen acts as a structural. In cancer, it can facilitate the migration of invading cancer cells. Increased collagen deposition and fibril formation are

associated with major changes in the biomechanical components of tissues. This can be influenced by another extracellular matrix protein, namely fibronectins, which form fibrils in the matrix and have been considered in the formation of collagen fibrils, and the stroma becomes denser. Stromal density has an important effect on the biochemical signaling and cell properties of breast cells. Normal breast epithelial cells form a polarized acini structure in the low-density collagen matrix. However, as these cells grow under conditions of high-density collagen, they disorganize and form a highly proliferative group of cells, which will become invasive when responding to hepatocyte growth factor (HGF). Increasing the density of stroma in the epithelial cells of the breast will also trigger activation of the MAPK pathway and promote proliferation. The dense matrix will also trigger gene expression in cancer cells that are associated with poor clinical outcomes in breast cancer patients.[3] HER2+ and TNBC breast cancer subtypes have abundant collagen deposition compared to the luminal subtype, indicating that the tissue density is associated with tumor aggressiveness.[9]

Fibronectin

Fibronectin is a glycoprotein that forms fibrils such as collagen and increases during a fibrotic response of desmoplasia. Some studies show that fibronectin is necessary for combining collagen into an extracellular matrix. Fibronectin in cancer cases is usually expressed by cancer-associated fibroblasts (CAF) and cancer cells. Fibronectin expression in breast cancer is associated with a poor prognosis. Some studies show that fibronectin is associated with an increased risk of metastases and a decrease in survivability in patients with breast cancer. Fibronectin expression is detected in circulating tumor cells in breast cancer patients. These tumor cells usually exhibit signs of epithelial-mesenchymal transition (EMT) by which the cells lose polarity and adhesion of cells to cells, which can be seen in the epithelium and obtaining a mesenchymal phenotype with high motility. Fibronectin is a mesenchymal marker, which can increase the expression of TGF-β that will activate the EMT. Fibronectin can also activate the STAT3 and MAPK signaling pathways which will increase the invasion and metastasis of breast cancer cells. Some studies have also shown that fibronectin facilitates the spread of breast cancer cells through the expression of integrins, especially in breast cancers with triple-negative molecular subtypes.[3,10]

Laminin

Laminin forms a large heterotrimeric glycoprotein group and represents the main non-collagenous protein of the basal membrane. 12 different forms of laminin have been recognized and have specific tissue and cell expression. Laminin-111 (LM-111) is an important component of the basal membrane, which is secreted by normal breast myofibroblasts to maintain epithelial polarity. In breast tumors, the expression of LM-111 is often lost and is associated with changes in cell polarity. Other laminin forms, including LM-332, LM-511, and laminin that contains alpha subunits 4, also can increase tumor progression. LM-332 is associated with an aggressive subtype of breast cancer, increasing migration and invasion of breast cancer cells through alpha 3 integrins. Expression of LM-332 in breast cancer is seen in tumor tissue, which is associated with high EMT activity. Some studies show that LM-511 can increase adhesion, migration, invasion, and metastasis of tumor cells through integrin interactions.[3]

Hyaluronan (HA)

Hyaluronan (HA) is a glycosaminoglycan that is not bound to the nuclear protein and plays various biological roles, both through physiological and pathophysiological processes. They are also important for embryogenesis, morphogenesis, wound healing, tissue repair, and inflammation. They can be

involved in cancer progression and are greatly increased in breast cancer compared to normal breast tissue, as well as being able to modulate intracellular signals through direct interaction with receptors cell surfaces, like receptors for hyaluronic acid-mediated motility (RHAMM) and CD44, which can increase breast cancer cell migration and invasion. They can form complexes with ERK in invasive breast cancer cells, which increases cell motility. In addition, RHAMM and CD44 can also activate the transcription factors and release inflammatory cytokines such as TGF-β and IL-10, which increases tissue remodeling, including the expression of MMP.[3,11] The signaling pathways of cancer cells can be influenced by HA through their own receptors (e.g., CD44) or by modulating the receptor response of tyrosine kinase activity (e.g., HER2). HA levels were found to be very high in patients with HER2 positive.[12]

Hyaluronan (HA) is produced by hyaluronan synthases (HAS), which are found on the surface of the plasma membrane. The function of HAS plays an important role in the progression of breast cancer, where high levels of HAS in primary tumors of the breast predict a poor clinical prognosis. Stimulation of TGF-β from normal breast epithelial cells increases the expression of HAS, which activates the EMT, an important process in the remodeling of mammary glands. An increase in serum HA with low molecular weight in breast cancer patients is associated with a poor prognosis.[3]

Decorin

Decorin belongs to the group of small leucine-rich proteoglycans (SLPs). These proteins can bind to collagen and are involved in the preparation of fibrils, as well as signal regulation of cells. Decorin is known as a breast tumor suppressor and acts as an inhibitor of several tyrosine kinase receptors. In breast cancer, decorin inhibits ErBB family cell receptors such as EGFR and ErbB2, which are important promoters of breast cancer progression. Overexpression of decorin in breast cancer cells and inactivation of ErbB2 cause tumor growth suppression through the induction of p21 cell cycle regulators. Decorin may also inhibit TGF-β signals. Expression of decorin proteins is usually increased in ER-positive molecular subtype and is associated with a favorable prognosis.[3,5]

Syndecan and glypicans

Syndecan and glypicans are proteoglycans of heparan sulfate, which were found attached to the cell membrane. Syndecans is a type I transmembrane protein that combines five glycosaminoglycans. Glypicans are attached to the cell membrane with a glycosylphosphatidyl-inositol (GPI) anchor. Syndecan-1 (SDC-1) expression is consistently seen in the stroma of breast tumors and is produced by fibroblasts. High expression of SDC-1 in breast tumor intrastromal predicts a poor prognosis and is associated with poor survivability in the pathological response to some adjuvant chemotherapy. Fibroblasts produce SDC-1 and contribute to the formation of parallel fiber architectures of extracellular matrix. This structural formation improves cell migration, invasion, direct movement, and attachment. Excessive expression of SDC-1 in cancer cells can cause a poorly cohesive and invasive colony of cells or seeding, indicating that SDC-1 increases invasiveness at an early stage of tumorigenesis.[3]

Expression of glypican-1 (GPC1) increased in breast tumor cases compared to normal breast tissue. A decrease of GPC1 in cancer cells leads to a decrease in the mitogenic response to the heparin growth factor, indicating that GPC1 is associated with disease progression. GPC1 modulates signal pathways in cancer progression. In contrast, glypican-3 (GPC3) is a tumor suppressor. GPC3 expression is reduced in cases of breast cancer, which is caused by hypermethylation of the GPC3 promoter. Overexpression of GPC3 in breast cancer cells can inhibit cell growth, reduction of motility, and spread of cancer cells by inhibiting the PI3K/Akt

pathway, which causes apoptosis. GPC3 can increase the rate of survivability in patients with breast cancer.[3,13–15]

Matricellular proteins

Matricellular proteins are a group of extracellular matrix glycoproteins and have many types, including osteopontin, tenascin, periostin, thrombospondin, and others. The expression of the matricellular protein is strongly associated with tissue remodelings such as wound healing, inflammation, and cancer. Most matricellular proteins bind to fibronectin or collagen fibers and increase cell interactions with the matrix. Although matricellular proteins bind to the structural components of the extracellular matrix, they do not contribute significantly. Matricellular proteins can act as cell regulators and modulators of signal lines. High expression of matricellular proteins is often associated with the spread of metastases and poor prognosis in cancer patients by increasing cell motility.[3]

Osteopontin

Osteopontin, or secreted phosphoprotein 1 (SPP1), is a highly modified matricellular glycoprotein that has been associated with breast cancer progression. In normal breast glands, SPP1 expression is greatly increased, especially during lactation. The expression of SPP1 increases the proliferation and inhibits the differentiation of epithelial cells. Breast cancer cells which have the ability to metastasize, usually show a high expression of SPP1. In addition, SPP1 increases EMT while metastasizing. SPP1 can also be used as a useful biomarker for breast cancer progression, which is associated with poor survivability and relapse.[3,16]

Tenascin C

Tenascin C (TNC) is a large hexameric matricellular glycoprotein that can interact with cell surface receptors and other extracellular matrix proteins. The polymerization state of actin is interpreted by cells through two transcription factors, including megakaryoblastic leukemia 1 (MKL1) and yes activating protein (YAP). In a poorly cohesive state, the cells fail to polymerize actin and cannot form actin fibers. TNC expression can damage MKL1 and YAP activity on tumor cells, thereby inhibiting the polymerization of actin. When cells are attached to fibronectin that occurs through integrin α5β1/syndecan-4, the cells will form an actin stress fiber. MKL1 and YAP are the two sensors. When there is actin stress fiber, these two molecules are then translocated to the cell nucleus, where they act as transcription factors to polymerize actin. TNC inhibits the formation of actin stress fiber by inhibiting the integrin α5β1/syndecan-4 signal.[3,17]

Thrombospondin

Thrombospondin consists of glycoproteins that bind calcium and play a role in tissue healing and inhibiting angiogenesis. Thrombospondin is an inhibitor of angiogenesis, binding to CD36 receptors on endothelial cells and triggering apoptosis. In breast cancer, thrombospondin can inhibit tumor growth. However, the effect of thrombospondin on cancer cells and tumor stroma can increase cancer progression and metastases. Thrombospondin enhances the invasion of cancer cells through the activation of the TGF-β and the plasminogen activator urokinase system.[3]

Extracellular matrix remodeling enzymes

Alterations in the extracellular matrix during tissue regeneration and cancer are not limited only to the composition of the extracellular matrix but also to remodeling enzymes. Extracellular matrix modifying enzymes such as matrix metalloproteinase (MMP), heparanase, cathepsins, urokinase plasminogen activator, and cross-linking enzymes of the lysyl oxidase family are often elevated in cases of breast tumors, and contribute to the progression of breast cancer and metastases. These enzymes can modify the extracellular matrix in several ways and

facilitate cancer cell invasion as well as migration. They can directly affect the biological properties and functions of extracellular matrix components by releasing growth factors or proteins solvent of the extracellular matrix. Remodeling enzymes can change the physical shape of the extracellular matrix by cross-linking reaction. Extracellular matrix remodeling enzymes are crucial for breast cancer progression and metastases (Figure 2).[3]

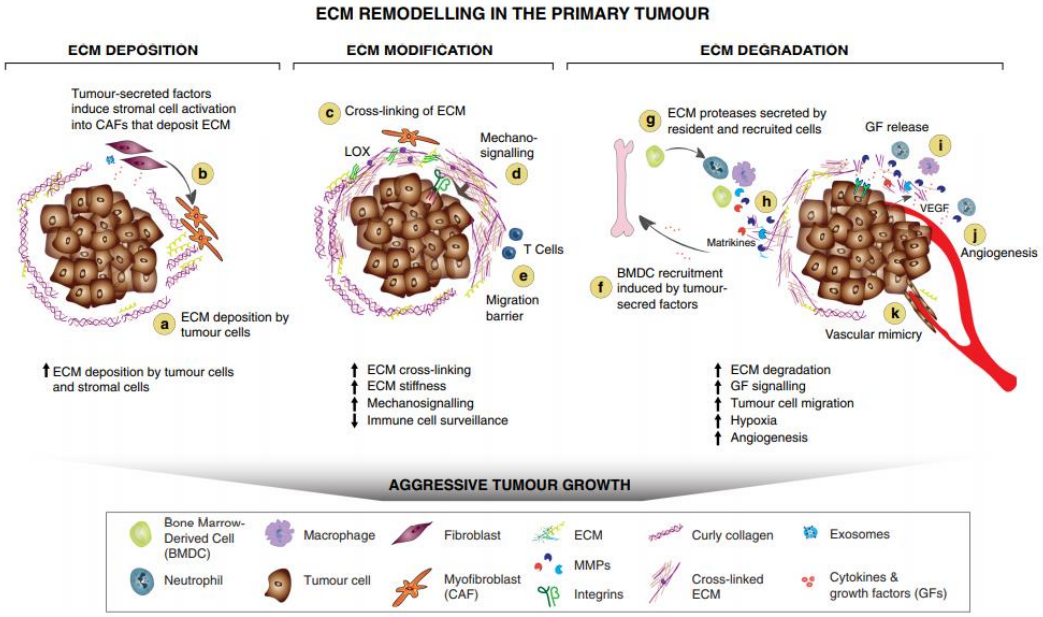

Figure 2. Remodeling of the extracellular matrix in primary tumors. A and B) In tumors, stromal cells differentiate into CAF, causing secretion and deposition of extracellular matrix components in cancer cells. C) Extracellular matrix remodeling enzymes such as LOX which are expressed by tumor cells, increased the density of the matrix around the tumor. D) An increase in matrix density cause interactions between the components of the extracellular matrix and the cell surface receptors, which activate mechanosignalling by integrins. E) Formation of physical barriers to avoiding the immune response of T cells. F) To maintain the tumor microenvironment, the tumor cells and immune cells can secrete cytokines, chemokines, and growth factors that differentiate and recruit bone marrow-derived cells (BMDCs). G) BMDCs, CAF, and tumor cells secrete proteases that degrade extracellular matrix, such as MMP-9. H) These proteolytic can produce bioactive matrikines and I) release growth factors. These factors increase tumor proliferation, migration, invasion and angiogenesis. J) These alterations in the extracellular matrix cause a hypoxic environment.[18]

Heparanase

Heparanase is an important enzyme in the remodeling of the extracellular matrix in breast cancer. Heparanase is an endo-β-D-glucuronidase that cleaved the heparan sulfate chain, forming fragments with a low molecular weight. In normal breast glands, heparanase is expressed at the edges of the invading epithelial cells and is associated with MMP-14 expression during gland formation. Heparanase can increase neovascularization and breast cancer growth through SDC-1 induction. Heparanase can also trigger the activation of EMT.[3,19]

Cathepsins

Cathepsins are a family of lysosome proteases and are associated with the extracellular matrix

remodeling and breast cancer progression through tumor proliferation, angiogenesis, invasion, metastases as well as EMT (Figure 3).[3,20]

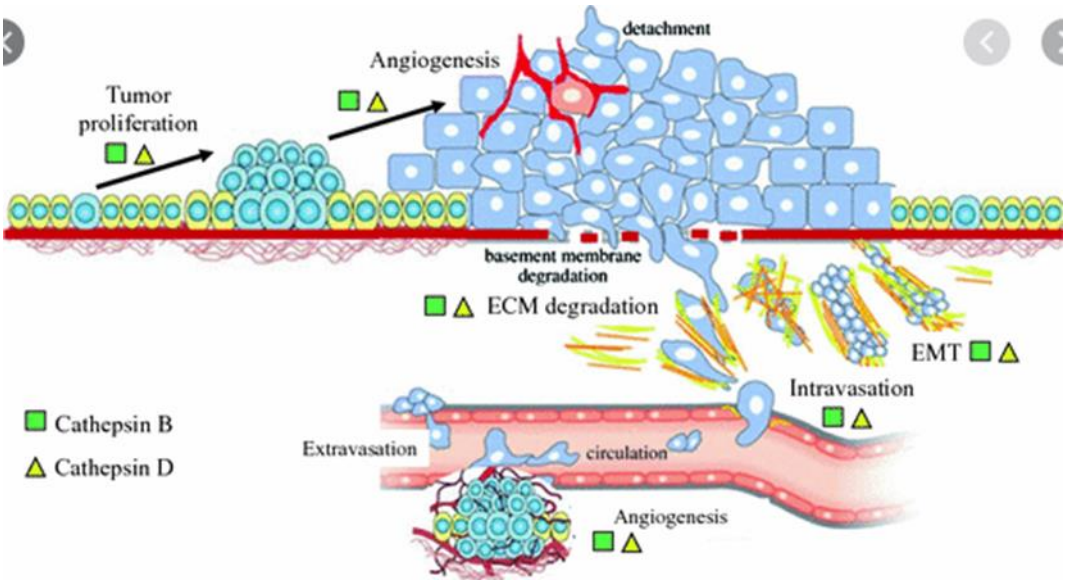

Figure 3. The role of cathepsins in breast cancer. Cathepsins are associated with extracellular matrix remodeling and breast cancer progression through tumor proliferation, angiogenesis, invasion, metastasis as well as EMT.[20]

Urokinase plasminogen activator (uPA)

Urokinase plasminogen activator (uPA) is a serine protease that cleaved the inactive plasminogen proenzymes into active plasmin, leading to extracellular matrix degradation and remodeling. There is a link between uPA activity and breast cancer progression as well as metastases, which can predict a poor prognosis in breast cancer patients. Plasmin can digest some collagen proteins such as laminin, fibronectin, and heparan sulfate proteoglycans. Plasmin also contributes to activating several MMPs, one of which is MMP-9, in degrading the extracellular matrix. The Urokinase plasminogen activator will bind to its receptor, namely uPAR, and must interact with integrin in order to activate the signal pathway that will convert plasminogen into plasmin. One of the inhibitors is plasminogen activator inhibitor-1 (PAI-1). Plasmin can activate or release pro-angiogenic factors such as FGF2 and VEGF.[3,21]

Lysyl oxidase (LOX)

The family of lysyl oxidase (LOX) consists of enzymes that can bind to each other with a component of an extracellular matrix, such as collagen. The bonds between LOX and collagen can cause an increase in the density of the extracellular matrix, which is related to tumor progressivity in breast cancer (Figure 4). LOX expression is usually increased in malignant tumors compared to the normal tissues of the breast. Increasing LOX expression correlates with poor survivability. An increase in the density of the extracellular matrix can increase the expression of the LOX protein through the activation of the integrin signal pathway in cancer cells. The LOX protein will bind to collagen and increase the density of the extracellular matrix, causing stabilization of the integrin complex and increasing the proliferation of cancer cells, as well as invasion.[3,17]

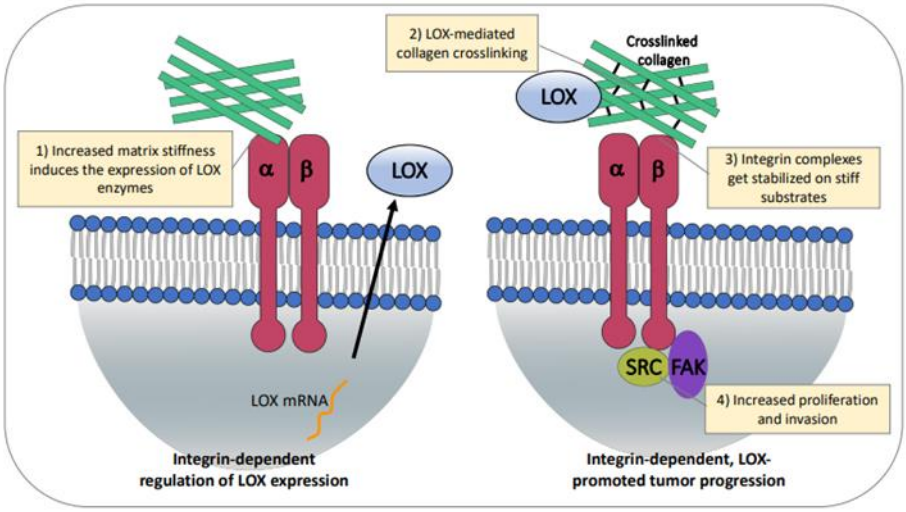

Figure 4. Matrix density increases the expression of the enzyme LOX. The interaction of integrins with type I collagen increases LOX expression in stromal cells. The density of the extracellular matrix improves the regulation of LOX through the activation of integrin signal pathways in cancer cells. The density of the extracellular matrix causes stabilization of the integrin complex and increases the proliferation of cancer cells as well as invasion.[17]

Matrix metalloproteinase (MMP)

Matrix metalloproteinase (MMP) enzyme, including MMP-2, MMP-9, and MMP-14, is often overexpressed in breast cancer cases. These enzymes can degrade type IV collagen so that the cancer cells can invade the basal membrane.[3] Collagen proteolysis is an important mechanism that alters the biomechanical characteristics of the extracellular matrix, where the edge of the tumor mass can produce MMP-14 and degrade the interstitial collagen to form a path and facilitates invasion. In breast cancer cells, MMP-2 can increase aggressiveness by cleaving the gamma 2 chain of laminin-332 (LM-332), a protein component of the extracellular matrix in the basal membrane. Fragments of LM-332 can bind to EGFR, increase MAPK signals, and enable cell migration. MAPK activation can also increase MMP-2 expressions, providing a positive feedback loop. This positive feedback loop is also amplified by MMP-14, which is an important activator of MMP-2 and releases gamma chain fragment 2 of the LM-332. In addition, MMP-14 can also increase the expression of SDC-1 in breast cancer fibroblasts and increase the proliferation of breast cancer cells by recruiting fibroblast growth factor-2 (FGF2).[3]

Matrix metalloproteinase-9, also known as gelatinase B, plays an important role in the remodeling of extracellular matrix by degrading extracellular matrix, alterations of the cell-cell and cells-extracellular matrix interactions, protein cleavage on the cell surface as well as in the extracellular environment, which is associated with tumor invasion, metastasis, angiogenesis, inflammation, and proliferation (Figure 5). In humans, some cells can synthesize and secrete MMP-9, including neutrophils, macrophages, fibroblasts, and endothelial cells. Breast cancer cells can also secrete MMP-9. They are synthesized as proenzymes and secreted into the extracellular environment as inactive pro-MMP-9. MMP-9 expression in normal breast tissue is usually low and increases significantly in breast cancer cells. MMP-9 overexpression is usually increased in triple-negative and HER2-positive breast cancer.[22,23]

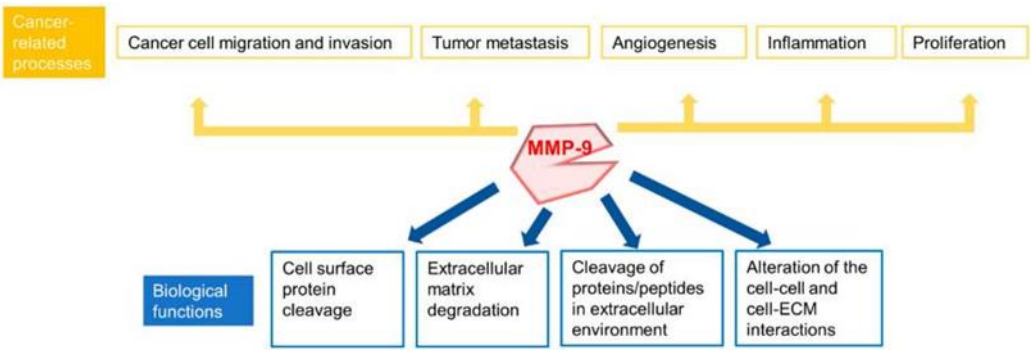

Figure 5. The biological function of MMP-9 in cancer. Matrix metalloproteinase-9, also known as gelatinase B, plays an important role in the remodeling of the extracellular matrix by degrading the extracellular matrix, alteration of cell-cell and cell-ECM interactions, as well as cleavage proteins on the cell surface and in the extracellular environment, which are associated with tumor invasion, metastases, angiogenesis, inflammation and proliferation.[23]

2. Conclusion

The extracellular matrix is a complex molecular network around tumor tissue and consists of several proteins that contribute to the structure of the extracellular matrix and its functions. The extracellular matrix plays an important role in breast cancer by changing its composition and can increase the growth, invasion, and metastasis of cancer cells. Alterations of extracellular matrix in tumors are not only limited to its composition but also the remodeling enzymes. These enzymes can change the physical shape of the structure of the extracellular matrix by way of cross-linking to collagen. The effect of extracellular matrix remodeling on clinicopathology, subtypes, and prognosis in breast cancer has not been widely studied, so further research is needed.

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