REVIEW ARTICLE

Cancer Cell-derived Secretory Factors in Breast Cancer-associated Lung Metastasis: Their Mechanism and Future Prospects

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Abstract: In Breast cancer, Lung is the second most common site of metastasis after the bone. Various factors are responsible for Lung metastasis occurring secondary to Breast cancer. Cancer cell-derived secretory factors are commonly known as 'Cancer Secretomes'. They exhibit a prompt role in the mechanism of Breast cancer lung metastasis. They are also major constituents of host-associated tumor microenvironment. Through cross-talk between cancer cells and the extracellular matrix components, cancer cell-derived extracellular matrix components (CCECs) such as hyaluronan, collagens, laminin and fibronectin cause ECM remodeling at the primary site (breast) of cancer. However, at the secondary site (lung), tenascin C, periostin and lysyl oxidase, along with pro-metastatic molecules Coco and GALNT14, contribute to the formation of pre-metastatic niche (PMN) by promoting ECM remodeling and lung metastatic cells colonization. Cancer cell-derived secretory factors by inducing cancer cell proliferation at the primary site, their invasion through the tissues and vessels and early colonization of metastatic cells in the PMN, potentiate the mechanism of Lung metastasis in Breast cancer.

On the basis of biochemical structure, these secretory factors are broadly classified into proteins and non-proteins. This is the first review that has highlighted the role of cancer cell-derived secretory factors in Breast cancer Lung metastasis (BCLM). It also enumerates various researches that have been conducted to date in breast cancer cell lines and animal models that depict the prompt role of various types of cancer cell-derived secretory factors involved in the process of Breast cancer lung metastasis. In the future, by therapeutically targeting these cancer driven molecules, this specific type of organ-tropic metastasis in breast cancer can be successfully treated.

Keywords: Breast cancer lung metastasis, secretory factors, pre-metastatic niche, tumor micro-environment, cell lines and animal models.

1. INTRODUCTION

Among females, the most commonly occurring cancers are breast, lung and colorectal [1]. Breast cancer is one of the most common malignant tumors in women. It is considered the second leading cause of deaths worldwide, with an estimated approximately 40,450 deaths in the year 2016 [2]. Cancer has the highest capability to metastasize to distant body organs. The most common target organs for breast cancer metastasis are lung, liver, bone and brain [3, 4]. Recent advances in breast cancer treatment have estimated that among females with breast cancer, 20-30% have the tendency to develop metastatic disease [5].

1.1. Bone *versus* Lung Metastasis

The most frequent sites of breast cancer metastasis are the bones and lungs [6]. The reasons due to which metastases to these specific sites differ are their evolution, treatment, morbidity and mortality. The other major reason is the special requirement of the specific organ for disseminated cancer cells for the development of metastasis [7]. Bones (51%) followed by lungs (17%) are the two most common target organs of breast cancer distant metastasis. In fact, nearly 60% of breast cancer patients during the metastasis stage suffer from lung or bone metastasis in their life [8]. In relation to the tendency of breast cancer subtypes for metastasis, luminal subtype breast cancer develops bone metastasis at a higher rate (80.5%) than basal-like (41.7%) and HER2-like tumors (55.6%) [9]. On the contrary, basal-like, luminal B subtype and triple-negative p53 negative subtype are most frequently associated with lung metastasis in invasive ductal breast carcinoma [10, 11].

The clinical presentations of breast cancer patients secondary to metastatic complications are extremely painful. In bone metastasis, the most common complication encountered is osteolytic type metastatic lesions secondary to osteoclast-mediated hyperactive bone resorption. As a consequence, certain growth factors are released from the bone matrix during the resorption process that ultimately leads to initiate a

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"vicious cycle" of bone destruction culminating in many skeletal-related events [12, 13]. However, in lung metastasis, the clinical presentations and consequences are also extremely serious. The most frequent clinical signs and symptoms which significantly affect a patient's quality of life and survival are chest pain, cough, hemoptysis, pleural effusion, and pulmonary dysfunction [14].

Minn *et al.* were the first who identified a set of genes such as epidermal growth factor receptor ligand epiregulin, COX2, MMP-1 and MMP-2 found to be associated with lung metastases in breast cancer. Increased expression of these genes promotes lung metastasis by facilitating tumor angiogenesis, cancer progression, invasion through the tissues and early colonization of DTCs in metastatic niches (lungs) [15]. The said mechanism also involved CSCs (Cancer stem Cells) functions, metabolic alterations and immune response [16, 17]. However, in bone metastasis, integrin complexes play an important role. A study showed that integrin αvβ3 overexpression in tumor cells promotes metastasis to the bone by mediating tumor cell adhesion and signal transmission required for tumor progression [18]. Cytokines, chemokines and other growth factors also promote bone metastasis formation [19]. A 15-gene expression signatures set was analyzed by Van de Vijver group that was specifically associated with the development of bone metastases in breast cancer. The bone metastatic gene signatures (APOPEC3B, ATL2, PH-4, PGD5, SFT2D2 and STEAP3) mostly encode for protein binding membrane-bound molecules [20, 21].

The overall median survival time for bone and lung metastasis is 12 months. However, even after treatment, the overall life expectancy still remains low, with a median survival of only 22 months for lung metastasis [22].

1.2. Rationale for Lung Metastasis

In this article, we have discussed in detail the intracellular and extracellular secretory factors from cancer cells released in the tumor microenvironment, which promotes lung metastasis secondary to Breast cancer. Lungs are the second common reported site of distant metastasis in breast cancer after bone [7]. They are also twice as a commonly reported secondary site of cancer in young females (≤ 50years) [23]. Once metastasized to the organ, a very short median survival time of 12 months duration and 22 months after treatment has been reported [22]. Also, poor survival rate and disease prognosis have been reported by clinical data, referring to the patients diagnosed with primary tumors with LMSs (Lung Metastasis Signatures) expressing genes. In line with these numerous genetic studies based on microarray data, *in-vivo* experiments in xenograft models and *in-vitro* analysis in breast cancer cell lines have also been conducted to check the gene and protein expression of cancer cell-derived secretory factors that are associated with Lung metastasis in breast cancer [24, 25]. Till date, no blood biomarker has been reported that could determine breast cancer progression in terms of Lung metastasis. Only a few reports provided updates on the outcome of isolated lung metastases secondary to breast cancer [26]. This compelled us to write a detailed review on this specific subject. Hopefully, the article will help researchers in their related research work, as this review provides an extensive literature on the subject in order to evaluate the secretory factors that are involved in the phenomenon of metastatic organotropism specifically to the lungs in breast cancer.

The phenomenon of Metastatic organotropism (MO) is defined as a selective process of distant metastases to some specific organs. It is regulated by certain factors, including molecular subtypes of breast cancer, cancer cells derived secretory factors (cancer secretomes), immune mechanism of the host, cross-talk between the cells in the tumor microenvironment, genetic alterations and the role of cancer stem cells (CSCs), which are considered as the most prominent ones [24, 27]. The metastasis process is also influenced by tumor size, nodal stage, receptor status and histologic grade. Based on biological markers, breast cancer is classified into five molecular subtypes: Luminal A, luminal B, luminal-HER2, HER2-enriched, basal-like and triple-negative (TN) breast cancer [28]. A research-based study has inferred that among the molecular subtypes, triple-negative and basal-like subtypes have the highest tendency to metastasize to the lungs, brain and distal lymph nodes [29]. Also, basal-type breast cancers more commonly tend to metastasize to lungs (52%), as compared to the other visceras [30]. However, histologically, intra-ductal carcinoma (IDC) has three times more potential to metastasize to lungs, CNS and distal lymph nodes [31]. Various studies have been implicated to date, to determine the role of causative factors that are associated with the metastatic organotropism that occur in the lungs [32].
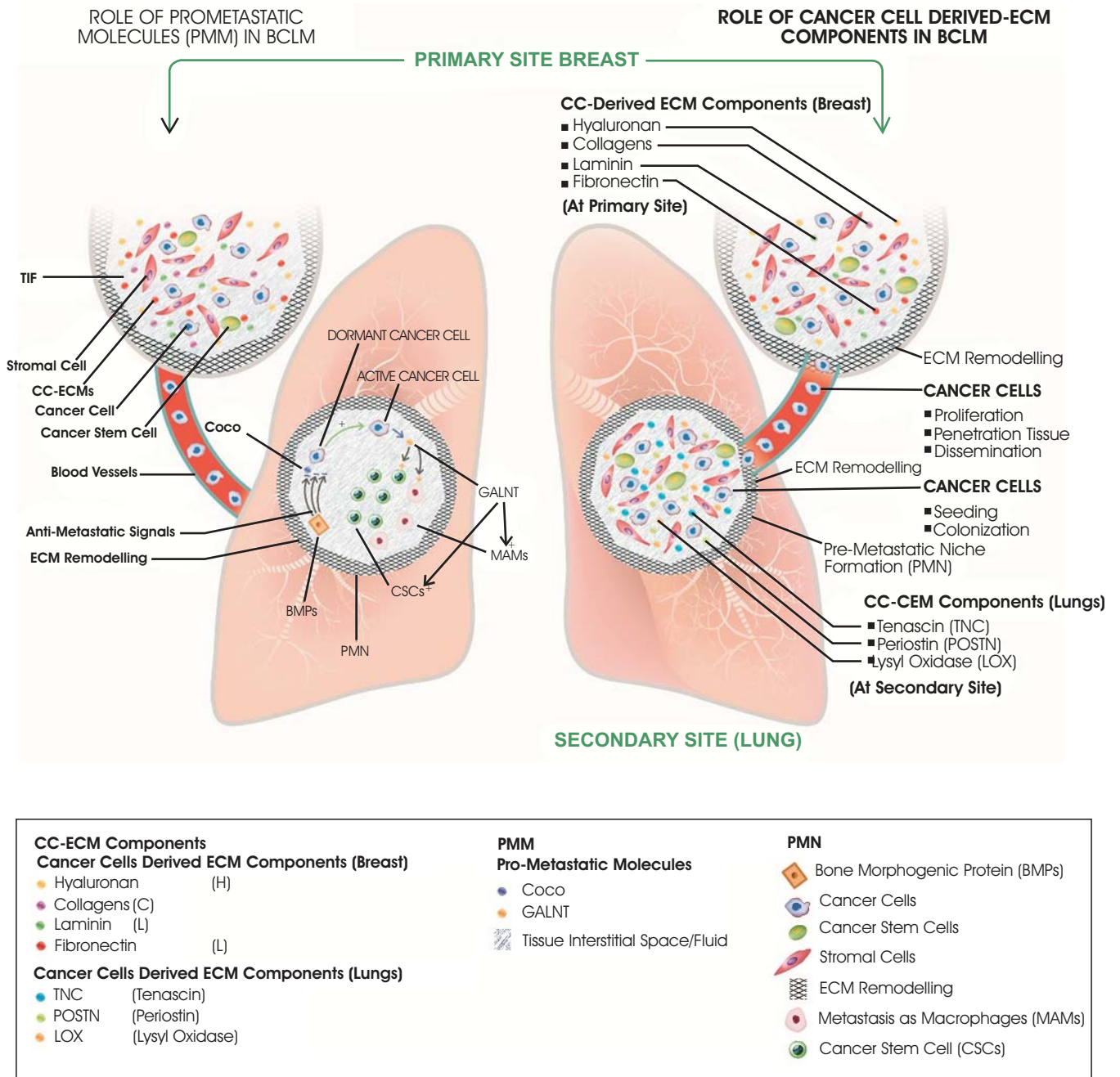
2. MECHANISM OF BREAST CANCER LUNG METASTASIS

Lung metastasis, occurring secondary to breast cancer, involves an intricate mechanism. It is mediated by the contribution of various factors, such as increased expression of specific genes, an active role of cancer stem cells (CSCs), a major contribution of cancer cell-derived secretory factors, enhancement of certain specific signaling pathways, as well as the active implication of the host-derived immune mechanism [14]. Two factors, including the function of cancer cells derived extracellular matrix (ECM) components and the active role of pro-metastatic molecules in the pre-metastatic niche (lungs), provide the basis for the mechanism of Breast cancer lung metastasis [24].

As shown in Fig. (**1**), at the primary site (breast), the cancer cell-derived ECM components such as hyaluronan, collagens, laminin and fibronectin, by inducing the phenomenon of ECM remodeling in the tumor microenvironment promote cancer cells proliferation, their penetration across the tissues and vessels, followed by their dissemination to the lungs. At the secondary site (lungs), the cancer cell-derived secretory factors such as tenascin C (TNC), periostin (POSTN) and lysyl oxidase (LOX), by modulating the mechanism of ECM remodeling and cancer cells seeding in the pre-metastatic niche, promote efficient early colonization of the disseminated tumor cells (DTCs) in the lungs [33]. The secretory factors which are released from the cancer cells in the TM also recruit bone-marrow derived cells (BMDC) in the lungs. This process in-turn further promotes the mechanism of Breast cancer lung metastasis [34].

Fig. (1). At the primary site (breast), the Cancer Cells Derived ECM Components (CCECs), hyaluronan, collagens, laminin and fibronectin induces the phenomenon of ECM remodeling in the tumor microenvironment. This promotes cancer cell proliferation, their penetration across the tissues, followed by their dissemination to the Lungs. At the secondary site (lungs), cancer cell-derived secretory factors such as tenascin C (TNC), periostin (POSTN) and lysyl oxidase (LOX) promote ECM remodeling and efficient colonization of the breast cancer metastatic cells. This contributes to pre-metastatic niche formation in the lungs. Also, at the pre-metastatic niche (PMN), the cancer cell-derived Coco, reactivates the dormant cancer cells by inhibiting the anti-metastatic signals from the lung-derived bone morphogenetic proteins (BMPs). GALNT 14 enhances the infiltration of metastasis-associated macrophages (MAMs) and also potentiates the self-activating property of cancer stem cells (CSCs) in the lungs.

New insights into the underlying molecular mechanisms of breast cancer lung metastasis have also identified the significant role of two pro-metastatic molecules, Coco and GALNT14. The cancer cell-derived Coco (a secretory antagonist of TGF-β ligand) has the characteristic to reactivate the dormant cancer cells present in the lungs by inhibiting anti-metastatic signals that are generated from the lung-derived bone morphogenetic proteins (BMPs) [35]. The second pro-metastatic molecule is N-acetyl-galactosaminyl-transferase 14 (GALNT 14). This cancer cell-derived polypeptide enzyme serves to enhance the infiltration of metastasis-associated macrophages (MAMs) in the lungs and also potentiates the self-activating property of cancer stem cells (CSCs) in the pre-metastatic niche (lungs). The above stated three mechanisms induced by these two pro-metastatic molecules thus provide the basis for the mechanism of Breast cancer-derived lung metastasis [36].

3. RATIONALE FOR SECRETORY FACTORS

The macromolecules secreted by the cells are collectively termed as secretomes. They are the major source of cell-cell communication in eukaryotes [37]. Cancer cell-derived secretomes exhibit altered composition as compared to the normal tissue. These altered secretions thus provide the basis for the characteristic hallmarks of cancer [38]. The reason for focusing on secretory factors is that the cancer cell derived-secretory factors are released in the tumor microenvironment, which ultimately ends up in one of the body fluids in a measurable concentration. Hence, they have an edge over the cellular proteome. In the current era, where cancer research is on hype, the discovery of cancer biomarkers, which will be utilized as blood-based diagnostics is currently focused. In this regard, secretome analysis serves as a promising approach to be applied for prognostic and diagnostic biomarkers as well as future therapeutic targets [39]. The second advantage of secretome analysis is that it offers reduced sample complexity co-aided with a dynamic range of detection. In addition, secretome-based researches also provide an in-depth understanding of the biology of tumor micro-environment, cancer cell progression, mechanisms of invasion and the process of metastasis [40]. The current literature search also provides evidence that cancer cell-derived secretory factors derived from cancer stem cells, non-stem cells and the surrounding stroma play a deterministic role in cancer progression, and in the future, they would be of great help in the field of cancer biomarker discovery [41].

4. ROLE OF SECRETORY FACTORS IN BREAST CANCER LUNG METASTASIS

Under normal circumstances, the secretory products that are released by the cells of the extracellular matrix serve to provide structural as well as the functional support to the tissues. However, the same secretory factors when released from the cancer cells have an ultimate aim to propagate these cells to distant sites, a mechanism known as metastasis. Interestingly, most of these studies related to cancer secretomes are conducted in breast cancer cell lines and animal models [42]. The three main factors responsible for altering these secretions in cancer are genetic mutations, the role of microRNAs and the contributing factors from the host-associated tumor microenvironment [43].

As shown in Fig. (**2**), cancer cell-derived secretory factors (CCSFs) perform the function of cancer cell propagation by mediating the crosstalk between the cancer cells and the extracellular matrix (ECM) components in the tumor microenvironment. This cross-talk by inducing angiogenesis, inflammatory cell recruitment and the phenomenon of ECM remodeling, ultimately favors the oncogenic process [44, 45]. As these secretory factors lie in close vicinity to the cancer cells, they may constitute some important proteins that correlate with the disease state hence, they can also serve as novel biomarkers [46, 47]. Currently, the secretory factors are the active source of research in the field of biomarker discovery and are also considered as the prime targets for future therapeutic strategies against breast cancer [48]. The methods, on the basis of which these secretory factors have been studied, are largely categorized into two groups; **i)** Genome-based computational prediction and **ii)** Proteomic approaches [38, 49].

Among these secretory factors, the known proteins which were analyzed are the cell surface receptors, cytokines, chemokines, cell motility factors, proteases and growth factors [25]. There are two modes of secretions that are employed by cancer cell-derived secretory factors. The first, is the ER- Golgi pathway or 'classical' pathway. The second is the Golgi-independent or 'non-classical' pathway [43].

The first method is traditionally considered as the one which is mostly employed for the secretion of proteins. Majority of the cytokines, cell surface receptors and ECM derived components opt for this method of secretion [50]. The Golgi-independent pathway is characterized by secretion in the form of micro-vesicles such as exosomes. This form of secretion besides proteins (transmembrane receptors and cytosolic proteins), also consists of lipids and nucleic acids (such as micro-RNAs, messenger-RNAs and DNA) [51, 52]. Therefore, on the basis of the biochemical structure, the cancer cells derived secretory factors are broadly classified as proteins and non-proteins. The following are the studies on various types of cancer cell-derived secretory factors that promote lung metastasis in breast cancer.

4.1. Proteins

Several different studies have been conducted on various types of secretory proteins, which have an important role in mediating Breast cancer lung metastasis. These proteins are classified in terms of structural and functional aspects and are also summarized in Table **1**.

4.1.1. Glycoproteins

This refers to the fibrous proteins that along with proteoglycans and glycosaminoglycans (GAGs), form the most essential, non-cellular component of the extracellular matrix. These macromolecules do not only provide physical support to the tissues, but also transduce various biochemical reactions, which serve to mediate cellular functions at a molecular level [53].

Nidogen 1 (NID-1), a glycoprotein and a normal constituent of the basement membrane, is also responsible for its integrity. As a Lung metastatic secretome signature (LMSS), NID1 promotes the mechanism of lung metastasis in Breast cancer *via* its five pro-metastatic functions. *In vitro* functional
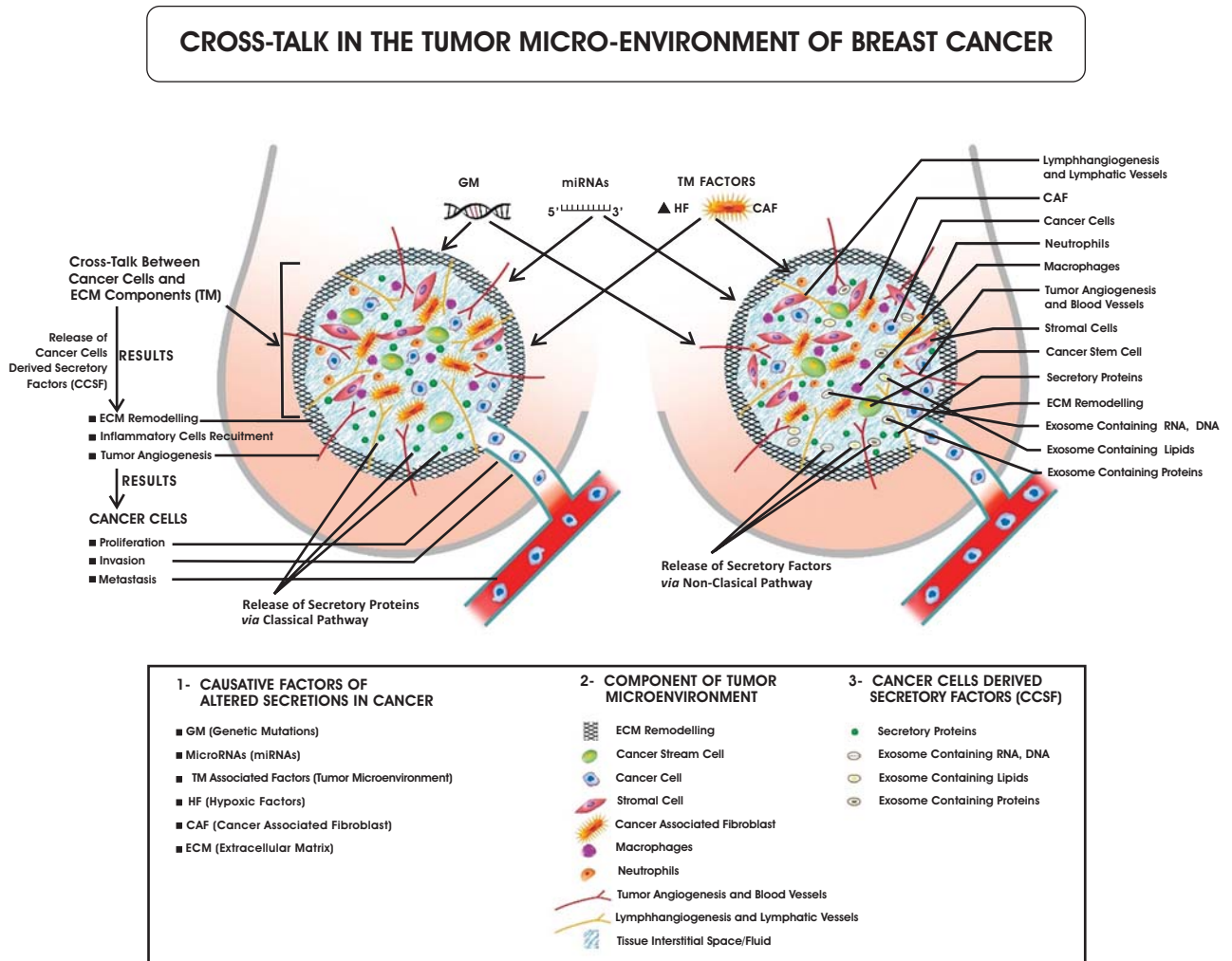
Fig. (2). Genetic mutations, microRNAs and tumor microenvironment associated factors (hypoxia, cancer-associated fibroblast), altered the secretions in cancer. Secondary to the crosstalk between the cancer cells and extracellular matrix components in the TM, cancer cell-derived secretory factors (CCSFs) are released, which cause angiogenesis, lymphangiogenesis, inflammatory cell recruitment and ECM remodeling. This mechanism ultimately favors the oncogenic process. Cancer cell-derived secretory factors (CCSFs) are released *via* the classical pathway (mostly secretory proteins) and non-classical pathway (*via* exosomes).

analysis has revealed that increased expression of this glycoprotein (NID-1) is associated with poor clinical outcome in Breast cancer. Therefore, the protein in the future may serve as a new predictive biomarker, in-order to determine the risk of lung metastasis in breast cancer [54].

Tenascin C (TNC), another extracellular matrix glycoprotein, classified as an adhesion modulating protein, has a prompt role in the mechanism of cellular signaling as well [55]. Increased expression of this glycoprotein in the metastatic niches has been found to be directly proportional to the magnitude of lung metastasis. The glycoprotein, in the lung microenvironment, by potentiating the NOTCH and WNT signaling pathways, increases the colonization of Lung metastatic cells that are derived from Breast cancer. Therefore, by therapeutically targeting this glycoprotein and indirectly by inhibiting the specific signaling pathways that are involved in Breast cancer Lung metastasis, disease progression can come to a halt [56].

4.1.2. Proteoglycans

They are specialized glycoproteins that are bound to glycosaminoglycans. Besides performing the function of space-filling and serving as lubricants within the extracellular matrix, they also contribute to mediate the molecular movements within the matrix [57, 58].

Serglycin is a proteoglycan, which is constitutively secreted by the breast cancer cells. It stimulates the secretion of a cytokine, tumor necrosis factor α (TNF α) from the metastasis-associated macrophages (MAMs). This cytokine (TNFα), in-turn, by enhancing the Snail expression (an EMT program modulator) in the cancer cells, potentiates their motility as well as their invasive phenomenon. A proven animal study has suggested that genetic deletion of serglycin, as a future therapeutic strategy, will yield a fruitful outcome in the context of breast cancer lung metastasis [59, 60].

Table 1.   Secretory proteins associated with breast cancer lung metastasis.

Proteins	Protein Classification	Major Findings	Study Type	References
Nidogen-1 (NID-1)	Glycoprotein	It promotes the mechanism of lung metastasis in breast cancer *via* its five pro-metastatic functions. Increase expression of NID-1 is associated with poor clinical outcome in BC	Cell lines, breast cancer animal model	[33]
Tenascin C (TNC)	Glycoprotein (GP)	The GP in the pre-metastatic niche (lung) by potentiating the NOTCH and WNT signaling pathways, increases the colonization of lung metastatic cells that are derived from BC	Cell lines, breast cancer animal model	[35]
Serglycin	Proteoglycan (PG)	The PG by stimulating the secretion of a cytokine (TNF-α) from the metastasis-associated macrophages (MAMs), potentiates lung metastasis in BC	Breast cancer animal model	[38, 39]
Matrix Metalloproteinases (MMPs)	Proteolytic enzymes	Increased expression of these enzymes (MMP2 and MMP9), by causing ECM remodeling at the pre-metastatic niche (lung) promotes lung metastasis in BC	Cancer cell lines, breast cancer animal model	[42, 43]
Transforming growth factor-Beta (TGF –β)	Cytokine	By inducing the expression of another cytokine, angiopoietin-like 4 (ANGPTL4) in cancer cells through Smad signaling pathway, TGF –β also promotes the permeability of cancer cells through lungs in BC	Cell lines, breast cancer animal model	[47]
Epidermal growth factor receptor (EGFR)	Cell surface receptor	By suppressing the tumor-suppressing microRNA and by activating an onco-protein, the receptor promotes the metastatic potential of the breast cancer cells to the lungs	Cell lines, breast cancer animal model	[52]
L1 cell adhesion molecule (L1-CAM1)	Cell adhesion molecules (CAMs)	This specific CAM, by mediating the cancer cells adhesion to the lung endothelial cells *via* the cell surface receptor promotes metastasis. Integrin-αvb3 also promotes BC cells extravasation into the lungs	Cell lines, breast cancer animal models	[56, 57]
Rho-associated kinase protein (ROCK-1)	Cytoskeletal associated protein	Increased expression of ROCK-1 is associated with tumor growth and metastasis in BC. Melatonin, by inhibiting the ROCK-1 expression, prevents BCLM.	Cell lines, breast cancer animal models	[66]
Lysyl oxidase-like protein (LOXL2)	ECM crosslinking enzyme	Increased expression of LOXL2 in the TM, by transducing the EMT phenomenon and by contributing to the formation of PMN (lungs), promotes lung metastasis in BC	Cell lines, breast cancer animal models	[60]
SNAIL 1	Transcription factor	Transient overexpression of SNAIL1 that can be achieved by the stimulation of transforming growth factor-β (TGF-β), also increases the potential of lung metastasis in BC.	Cell lines, breast cancer animal models	[70]
HIF-1	Hypoxia-induced factor (HIF)	The protein (HIF-1) stimulates the transcription of PLOD gene that encodes for procollagen lysyl hydroxylase (LOX). Increased LOX in the TM promotes the mechanism of lung metastasis in BC	Cell lines, breast cancer animal models	[74]

4.1.3. Proteolytic Enzymes

Matrix Metalloproteinases (MMPs), also known as matrixins, are a group of proteolytic enzymes that are associated with the family of zinc-dependent endopeptidases. The enzymes on the basis of the targeted substrate, are categorized into six major classes. Collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other non-classified MMPs: being widely expressed in the body tissues, they are largely responsible for ECM protein remodeling, a mechanism that is required during various physiological processes such as organogenesis, morphogenesis and tissue repair.

Increased expression of these enzymes is associated with numerous pathological mechanisms such as maintenance of the tumor microenvironment, formation of pre-metastatic niche (PMN) at distant sites and cancer cell dissemination [61, 62]. A study based on breast cancer cell lines and animal models came up with the result that there is a significant decrease in the Breast cancer volume as well as its associated Lung metastasis, after treatment with the herbal medicine, Plantamajoside (PMS). The herb (PMS) serves as an antitumor agent by reducing the activity of two specific MMPs, MMP2 & MMP9 (gelatinases). The enzymes (MMP2 and MMP9), by causing ECM remodeling at the site of pre-metastatic niche (lung) in breast cancer, contribute to metastatic cell colonization. The herb, by inhibiting the role of these specific MMPs, indirectly reduces cancer cell growth as well as their ability to invade and metastasize in the Lungs. In the future, based on these results, the herb (PMS) can therefore be used as a potent anticancer agent, along with the other chemotherapeutic drugs, in-order to combat breast cancer lung metastasis [63, 64].

4.1.4. Cytokines

This refers to the biomolecules (peptides) that are secreted by the cells of the immune system. Their main function is to mediate intercellular communication at the molecular level. The proteins are required for the various body functions such as growth, maturation and immune response. Chemokines, interleukins, tumor necrosis factor α (TNF α) and transforming growth factor β (TGF-β) are some of the important protein families that lie under the umbrella of cytokines [65, 66].

A study conducted in the Breast cancer animal model has revealed the importance of transforming growth factor-Beta (TGF-β), a chief cytokine that is predominantly found in the tumor microenvironment (TM) of the breast cancer. This multifunctional cytokine under normal circumstances mediates a vast range of functions such as immune mechanism, synthesis and degradation of ECM and tissue response to injury [67]. The cytokine, by inducing the expression of another cytokine, that is angiopoietin-like 4 (ANGPTL4) in the cancer cells through the Smad signaling pathway, promotes permeability through lung capillaries in breast cancer, thus promoting lung metastasis [68]. This cell-signaling protein (TGF-β) also induces the cancer cells to undergo epithelial-to-mesenchymal transition (EMT), a phenomenon that promotes the cancer cells to adapt the property of invasion followed by extravasation. The study by highlighting the role of TGF-β- ANGPTL4 cytokine relay system, provides another opportunity to determine the therapeutic strategy, in order to fight against breast cancer lung metastasis [69].

4.1.5. Cell Surface Receptors

They are specialized transmembrane proteins, which serve to mediate cell signaling mechanism, necessary for cell-ECM communication. Once activated by ligand binding, signal transduction occurs through various mechanisms, depending upon the type of receptor. An important example is of epidermal growth factor receptor (EGFR), a transmembrane protein and a member of Erb B family of proteins. After binding to its specific ligands (EGF and TGF α), through tyrosine kinase activity, the receptor mediates various intracellular functions. Altered or increase expression of this receptor is associated with multiple cancers [70-72].

In vitro study has highlighted the role of epidermal growth factor receptor (EGFR) in Breast cancer Lung metastasis. Once dysregulated, the protein (EGFR), by suppressing the tumor-suppressing microRNA (miRNA-338-3p) and by activating an onco-protein (EYA2), promotes the metastatic potential of Breast cancer cells to the Lungs. This finding, therefore, suggests that by targeting EGFR/miR-338-3p/ EYA2 axis, a new horizon will be explored in treating Lung metastatic Breast cancer [22].

4.1.6. Cell Adhesion Molecules (CAMs)

This refers to the glycoproteins that are located at the cell surface and are enrolled for the formation of various types of complexes and junctions that are meant to form different types of connections (cell-cell, cell-ECM and cell cytoskeleton-ECM). At the molecular level, nearly all of the fundamental cellular processes (cell proliferation, cell migration and signal transduction) across the cell are mediated through these cell-ECM interactions *via* cell adhesion molecules [73]. If they get dysregulated, they ultimately result in the initiation or progression of various diseases [74].

Physical contact between the cancer cells *via* vascular cell adhesion molecule (VCAM1) and the macrophages *via* α4-integrin, also aid the lung metastatic cells from breast cancer to colonize within the leukocytes enriched lung parenchyma. This interaction triggers PI3K/Akt signaling within the cancer cells, which in turn, promotes their survival within the lung parenchyma [75]. Another cell adhesion molecule (L1-CAM), which is expressed on breast cancer cells, serves as a ligand for the cell surface receptor, integrin-αvb3. The cell adhesion molecule (L1-CAM), by mediating the cancer cells adhesion to lung endothelial cells, also promotes their extravasation into the lungs [76, 77]. The pro-metastatic effects of vascular cell adhesion molecule-1 (VCAM-1) in breast cancer when therapeutically targeted by succinobucol (SCB), a potent and a selective inhibitor of VCAM-1 expression, showed a significant reduction in lung colonization, occurring secondary to breast cancer. The results of all these recent researches have clearly pointed out that the breast cancer lung metastasis can be treated, if integrin-VCAM-1 interaction that is held between the macrophages and the cancer cells can be targeted *via* effective therapeutic means [32].

4.1.7. ECM Crosslinking Enzymes

The most abundant protein of the extracellular matrix is collagen. It has approximately 28 types and it is expressed by 44 genes. In order to transform from premature to mature state and for the purpose of crosslinking, the protein requires various enzymes among which one of them is, Lysyl oxidase-like protein (LOXL2). It is an enzyme that belongs to the family of lysyl oxidase (LOX). By serving as a catalyst, the enzymes serve to crosslink the fibrous components, mainly collagens and elastin within the extracellular matrix [78, 79]. A study conducted in the Breast cancer animal model has revealed that increased expression of LOXL2 in the tumor microenvironment, by transducing the epithelial to mesenchymal transition phenomenon and by contributing to the formation of pre-metastatic niche (lungs), promotes the mechanism of Breast cancer Lung metastasis. Therefore, on the basis of this informative pre-clinical model study, effective therapeutic strategies could therefore be designed that should be aimed to target the intra-tumor LOXL2. This could also turn a milestone in the treatment of breast cancer lung metastasis in the near future [79, 80].

4.1.8. Cytoskeletal Associated Proteins

Cytoskeletal proteins represent the cellular scaffold or a framework of protein fibers within the cell. They do not only maintain the cellular shape but also anchor the intracytoplasmic organelles. The proteins also serve to provide the key cellular functions such as cell division and growth, cell motility and contraction. The three main components attributed to the cytoskeletal proteins are the microtubules, microfilaments and intermediate filaments [81, 82].

An important cytoskeletal associated protein, Rho-associated kinase (ROCK) and its associated pathway (c-Myc), by regulating the actin rearrangement (cytoskeleton) within the cell and by mediating the intra-cellular signals,

play a central role in cellular morphology, adhesion and its motility. Increased expression of this protein is said to be associated with tumor growth and metastasis in Breast cancer [83, 84]. This metastatic effect secondary to an increase in ROCK expression can, therefore, be nullified by ROCK inhibitors [85]. An animal-based research study has recently explored the function of melatonin, serotonin derived secretory biomolecule that by inhibiting the ROCK-1 expression in the metastatic cancer cells, prevents lung metastasis, occurring secondary to breast cancer. It is thus concluded that inhibition of cytoskeletal associated proteins (ROCK-1) and its associated pathway, through an effective therapeutic strategy, could, therefore, set an advent in the field of breast cancer lung metastasis [86].

4.1.9. Transcription Factors

It refers to the family of proteins that modulates the mechanism of gene expression either by stimulating or suppressing it. The protein after binding to the short DNA sequences, regulates the process of information transfer from DNA to the messenger RNA [87]. The Snail family of proteins, important transcription factors and transcriptomic repressors to be more specific, are said to be co-related with epithelial to mesenchymal transition (EMT) in cancer cells. The protein associated gene, when deleted in mouse models of Breast cancer, reduces the lung metastatic foci in mice substantially, thus exhibiting its profound role in breast cancer lung metastasis [88].

Cancer cells secreting SNAIL 1, by influencing the infiltration of tumor-associated immune cells, potentiates the formation of tumor microenvironment [89]. An animal-based study has revealed that transient overexpression of SNAIL1 that can be achieved by the stimulation of transforming growth factor β (TGF β), also increases the potential of lung metastasis in breast cancer [90, 91]. The metastatic potential of triple-negative breast cancer (TNBC) to lungs has been found to be regulated by another transcription factor, forkhead box C1 (FOXC1). This protein, by increasing the expression of chemokine receptor-4 (CXCR4), also promotes the Lung metastatic capability of Breast cancer cells *in vivo* [92]. In conclusion, Snail 1 and forkhead box C1 that influence the immune microenvironment in Breast cancer, if targeted therapeutically, the desired results to overcome breast cancer lung metastasis in the future, can, therefore, be accomplished.

4.1.10. Hypoxia-Inducible Factors (HIF)

This refers to the secretory factors that are released by the breast cancer cells in response to hypoxia. Hypoxia-inducible factor 1 (HIF-1) is a secretory protein that is secreted by breast cancer cells [93]. The protein stimulates the transcription of PLOD gene, which encodes for an enzyme, procollagen lysyl hydroxylase (LOX). The enzyme (LOX) has a key function in the biosynthesis of collagen. High PLOD expression secondary to HIF-1 leads to increased secretion of LOX in the tumor micro-environment. LOX, in turn, contributes to the formation of pre-metastatic niche (lungs), thus promoting the mechanism of lung metastasis in Breast cancer [94].

Another mouse-based study has concluded that when the activity of hypoxia-inducible factor (HIF-1), along with the expression of angiopoietin-like 4 (ANGPTL4) and L1-cell adhesion molecule (L1-CAM) is blocked, secondary to RNA interference, vascular metastasis by the breast cancer cells to the lungs is compromised [77]. Emerging evidence also suggests that increased expression of Lysyl oxidase (LOX) along with fibronectin, crosslinks collagen IV and also recruits the bone marrow-derived cells (BMDCs) in the lungs. This mechanism also contributes to the formation of PMN (pre-metastatic niche) in the lungs. Therefore, by therapeutically targeting these hypoxia-induced secretory factors that are released from the Lung metastatic breast cancer cells, two chief processes that are ECM remodeling and formation of pre-metastatic niche, the ultimate requirements for the process of Lung metastasis, are affected [95].

4.2. Non-Proteins

This refers to the non-protein secretory factors that are also released from the cancer cells as the constituents of exosomes, which is also shown in Table **2**. The exosomes are extremely small nano-sized vesicles (30nm-100 nm in diameter) that are released from the cancer cells in the tumor microenvironment and in addition to proteins, also consist of lipids and nucleic acids such as RNA (microRNA, mRNA), DNA and even sequences of mutated or amplified oncogenes. The presence of nucleic acids within the exosomes also represents the genetic status of the tumor. Currently, they serve as the most potent cancer biomarkers. The acquired genetic information from these micro-structures is available for the horizontal gene transfer within the tumor micro-environment [96, 97]. These also contribute greatly to the mechanism of Breast cancer Lung metastasis, as proven by various animal studies.

Exosomes are released by various types of cells such as immune, mesenchymal and cancer. They are a major source of cell-cell communication *via* cargo that has been transferred through them from the donor to recipient cells in the tumor micro-environment. However, recent researches in cancer biology have introduced their major role in the mechanism of organ- tropic metastasis by their evident contribution in the formation of pre-metastatic niche [98-100]. Recent research studies came up with the conclusion that cancer cell-derived exosomes, by mediating the crosstalk between the cells of the tumor microenvironment, by transducing the mechanism of extracellular matrix remodeling and by inducing the invasive potential within the recipient cells of the host, significantly contribute to cancer cell propagation as well as in the mechanism of distant dissemination [101, 102].

A study conducted in a murine based breast cancer model showed that exosome secretion from the breast cancer cell is Rab27a (GTPase enzyme) dependent. When exosome secretion is blocked by inhibiting Rab27a, neutrophilic infiltration in the pre-metastatic niche (PMN) is also compromised. This ultimately decreases the primary tumor growth, along with the capability of the breast cancer cells to metastasize to Lungs [103, 104]. In another animal-based study, it has been revealed that exosomes derived from fibroblasts, by inducing Wnt-PCP signaling within the breast cancer cells, stimulate their invading potential as well as their capability to metastasize to the lungs [105]. The following constituents present within the exosomes also contribute significantly to breast cancer lung metastasis.

Table 2. Secretory factors (non-proteins) associated with breast cancer lung metastasis.

Non Proteins	Classification	Major Findings	Study Type	References
Exosomes	Extracellular vesicles (EVs)	By blocking Rab27a (GTPase enzyme) dependent exosome secretion, the neutrophilic infiltration in the PMN is compromised	Cell lines, breast cancer animal models	[83, 84]
-	-	Exosomes derived from fibroblasts, by inducing Wnt-PCP signaling within the breast cancer cells, potentiate their capability to metastasize to lungs	Cell lines, breast cancer animal models	[85]
Long non-coding RNA	LacRNA	The molecule serves to inhibit lung metastatic cascade that is occurring secondary to breast cancer	Breast cancer animal models	[101]
miR-200s	microRNAs	Overexpression of miR-200s is associated with lung colonization by the murine type of breast cancer cells	Breast cancer animal models	[94]
mRNA-122	microRNAs	The nucleic acid by providing the energy reserves (glucose) to the niche cells, promotes the mechanism of lung metastasis	Breast cancer animal models	[95]
miRNA-203	microRNAs	Expression of miRNA-203, inhibits breast cancer cells invasion in lungs both *in vitro* as well as *in vivo*	Breast cancer animal models	[97]
miR-9	microRNAs	By blocking the effects of miR-9 in breast cancer animal models, lung metastasis is compromised	Breast cancer animal models	[97, 99, 100]
Circulating or cell-free DNA (cfDNA)	DNA	Circulating or cell-free DNA (cfDNA) concentration and cell-free DNA integrity (cfDI), can also serve as important diagnostic as well as prognostic biomarkers in primary and metastatic BC.	Human blood samples	[106]
Mitochondrial DNA (mtDNA)	DNA	Horizontal transfer of mitochondrial DNA (mtDNA) *via* exosomes in the TM, is required for the metabolic revival of the breast cancer cells	Xenograft models	[103]
-	-	A delayed tumor growth is observed in the cell lines that are grown from primary tumor cells of breast cancer that lacks mtDNA. Lung metastatic cells from BC, do not show any change in their growth and proliferation in the absence of mtDNA.	Breast cancer cell lines	[107]

4.2.1. RNAs

Exosomes constitute all types of RNAs however, microRNAs (miRNA) and non-coding RNAs are considered as the predominant ones [106]. The microRNAs are 21 nucleotides, endogenous, non-coding RNA molecules that serve to regulate the gene expression at a post-transcriptional level. MicroRNA-messenger RNA pairing, resulting in either mRNA translational repression or cleavage. The outcome is reduced levels of the target protein [107, 108]. Lu *et al.* in 2005, for the first time discovered the altered expression of miRNA in cancer along with its co-relation with the tumor origin as well as with its differentiation stage [109]. Abnormal expression of this type of nucleic acid is reciprocal to an altered gene expression, leading to the phenomenon of tumorigenesis [110]. Emerging as cancer biomarkers, these cancer driven molecules are specialized in mediating ECM remodeling at the distant sites, resulting in the process of cancer progression as well as metastasis [111, 112].

Various studies have proven results that show the association of miRNAs with Breast cancer Lung metastasis. A short, metastasis-free survival time is associated with high levels of specific miRNAs, miR-200s. However, overexpression of the same type of microRNAs potentiates the mechanism of Lung colonization by the murine type of breast cancer cells [113, 114]. High miR-122 levels, secreted by the breast cancer cells, are also said to be associated with Lung and Brain metastasis. This specific miRNA (miRNA-122),

by providing the energy reserves in the form of glucose to the niche cells, promotes the mechanism of metastasis [115]. The expression of miRNA-203 inhibits Breast cancer cells invasion in the lungs both *in vitro* as well as *in vivo* [116-118]. On the contrary, by blocking the effects of miR-9 in breast cancer animal models, metastasis formation in the lungs has also been found to be compromised [117, 119, 120]. Another *in vitro* animal study has also revealed the role of long non-coding RNA (LacRNA) in breast cancer lung metastasis. The study showed that increased expression of LacRNA is associated with better clinical results. The molecule serves to inhibit lung metastatic cascade that occurs secondary to Breast cancer [121]. Recent advances in the field of cancer has therefore, embarked on a new metastatic regulatory role of miRNAs. Hence, in the future, this new emerging role of miRNAs will hopefully set up a new example in the field of cancer biology.

4.2.2. DNAs

The discovery of single-stranded DNA, followed by the double-stranded DNA took place as constituents of exosomes [96, 122]. Emerging as the representatives of the whole genome, the exosomal DNA (exoDNA) originates from both the cell nucleus (nDNA) as well as from the mitochondria (mtDNA) [122, 123]. They are present in significantly high concentrations in cancer cells derived exosomes as compared to the ones that are released from the non-

cancerous cells. Increased concentration of exoDNA actually represents genomic instability and is secondary to the increased concentration of cytosolic DNA (cytDNA) within the cancer cells. They are ultimately liberated as constituents of exosomes in the tumor microenvironment [124]. Increased mutational allelic frequency in the exoDNA pool is correlated with poor cancer prognosis and survival [125].

A study conducted on human blood samples of Breast cancer has revealed that circulating or cell-free DNA (cfDNA) concentration and cell-free DNA integrity (cfDI) can also serve as important diagnostic as well as prognostic blood biomarkers in primary breast cancer (PBC) as well as in metastatic breast cancer (MBC) [126]. Another study based on xenograft models and patients has concluded that horizontal transfer of mitochondrial DNA (mtDNA) *via* exosomes in the tumor microenvironment is required for the metabolic revival of the breast cancer cells. This also potentiates their oncogenic potential as well as their capability to metastasize to distant sites [123]. A study conducted on breast cancer cell lines came up with this view that mitochondrial DNA is an essential requirement for cancer cell growth as well as for metastasis. Delayed tumor growth is observed in the cell lines that are grown from the primary tumor cells of breast cancer that lacks mtDNA. On the contrary, the lung metastatic cells from breast cancer do not show any halt in their growth and proliferation in the absence of mtDNA [127]. By causing EMT (epithelial to mesenchymal transition) phenomenon, the cancer cells with deficient mtDNA copy number are also said to promote the mechanism of metastasis [128].

5. MECHANISMS OF FEW SECRETORY FACTORS INVOLVED IN BREAST CANCER LUNG METASTASIS

5.1. Tenascin C

Being a widely expressed extracellular matrix glycoprotein, Tenascin C (TNC) is found at two important sites in adults, a region of stem cell niches and at sites of epithelial – mesenchymal transition [129]. Expression levels of TNC are found to be elevated secondary to mechanical stress and inflammation in conditions such as wound healing and in connective tissue associated with tumors [130]. The glycoprotein (TNC) was introduced as one of the members of lung metastasis gene by Minn *et al.* Its mRNA expression levels in breast cancer are directly proportional to lung relapse as well as predictable of overall poor prognosis of the disease [15, 131].

Cancer cells expressing TNC have an edge in the lung micro-environment. When its underlying mechanism was explored, integral links were evolved between TNC and NOTCH and WNT, the known stem and progenitor cell pathways, which are associated with pro-metastatic role in stem cell niches [56]. The hexabrachion complex molecular structure of TNC normally interacts with various ECM proteins such as fibronectin, periostin, integrins, EGF receptors, syndecan-4 and other membrane-associated proteins [55]. Most of these proteins are also found to be expressed in the CN34 and MDA231 breast cancer cells, known for their high metastatic potential [132, 133]. This extensive molecular interactions of extracellular proteins also lead to affect the

growth and survival pathways within the cell. Tenascin C, by directly enhancing the expression of some of the key components of these pathways such as LGR5, and MSI1, indirectly potentiates the pro-metastatic functions of these pathways in the metastatic niches (Lungs). One of the key target genes of WNT pathway in adult stem cells is LGR5, leucine-rich repeat-containing G protein-coupled receptor 5 [134]. By potentiating the effect of this G protein-coupled receptor gene, TNC promotes the supportive function of WNT pathway for early colonization of DTCs in the pre-metastatic niche. In parallel to WNT, NOTCH pathway also contributes significantly in supporting the fitness and metastasis initiating capacity of disseminated tumor cells (DTCs) in the lungs. MSI1 (musashi homolog 1) is a positive regulator of NOTCH signaling [135, 136]. By enhancing the expression of MSI1in stem cell niches, TNC also promotes the pro-metastatic role of this pathway in Breast cancer lung metastasis. Knockdown studies of TNC in animal models, which decrease the signaling functions of WNT and NOTCH, further validate its pro-metastatic role associated with these pathways [137]. It also emphasizes Tenascin C supporting role as an ECM protein in the Lung metastatic niche [33].

5.2. MicroRNAs

MicroRNAs (miRNAs) are known for their specific role in gene expression [43]. In cancer, genomic instability leads to altered miRNAs expression with resultant biochemical changes [109]. On the contrary, recent studies have embarked a new role of miRNAs in cancer. By altering the secretome in cancer, these small, non-coding RNA molecules drive cancer cell progression. On the basis of biological functions, microRNAs are classified broadly into two groups. Tumor suppressor and oncogenic miRNAs [138].

The tumor suppressor miRNAs are themselves downregulated in cancers. They target cellular oncogenes. The classical example is of Lung cancer, targeting KRAS (oncogene) gene, whereas let-7 family is the tumor suppressor miRNAs [139]. Oncogenic miRNAs such as miR-17/92 cluster, also known as oncomir-1, control tumor suppressor genes and are found to be overexpressed in cancer [140]. MicroRNAs, by significantly contributing to mediating the crosstalk between cancer and stromal cells in the host associated-tumor micro-environment, also played a vital role in cancer cell progression and metastasis [141]. In cancer, dysregulated miRNAs execute various mechanisms that facilitate the adaptation and modulation of the primary tumor microenvironment. The following mechanisms are proposed and validated by cancer researches that have labelled the prompt role of miRNAs in the mechanism of metastasis.

i. MicroRNAs regulate the phenomenon of epithelial-mesenchymal transition, a phenomenon not only considered as a migratory strategy adopted by the cancer cells but also crucial for the maintenance of cancer cell stemness [142].

ii. They significantly contribute to ECM remodeling, a key mechanism that facilitates the process of cancer cell progression and metastasis [33].

iii. MiRNAs, as constituents of exosomes, have also acquired the capability to change the gene expression of the recipient cells in the host associated-microenvironment

Table 3.   List of factors which serves as a biomarker or therapeutic targets.

Secretory Factors	Role as Biomarker or Therapeutic Targets	Uses of Biomarker	References
Nidogen-1 (NID-1)	Biomarker and therapeutic target to prevent breast cancer lung metastasis	For breast cancer prognosis	[54]
Tenascin C (TNC)	Biomarker	Patient selection for adjuvant therapy, for cancer-associated fibroblast (CAF) and for breast cancer stroma	[164-166]
Serglycin	Therapeutic target to prevent breast cancer lung metastasis	-	[59]
Matrix Metalloproteinases (MMPs)	Biomarker and therapeutic target	For breast cancer prognosis	[167, 168]
Transforming growth factor-Beta (TGF-β)	Biomarker	For breast cancer prognosis	[169, 170]
Epidermal growth factor receptor (EGFR)	Biomarker	for selection of targeted therapy in TNB (triple negative-breast cancer)	[171]
L1 cell adhesion molecule (L1-CAM1)	Therapeutic target to prevent breast cancer lung metastasis	-	[76, 77]
Rho-associated kinase protein (ROCK-1)	Biomarker	For breast cancer prognosis	[172]
Lysyl oxidase-like protein (LOXL2)	Biomarker	For breast cancer prognosis	[173, 174]
SNAIL 1	Therapeutic target to prevent metastatic breast cancer	-	[175]
HIF-1	Therapeutic target for the prevention and treatment of breast cancer lung metastasis	-	[95, 94]
Exosomes	Biomarker and therapeutic target	For breast cancer prognosis	[176, 177]
Long non-coding RNA (LacRNA)	Biomarker and therapeutic target	For breast cancer prognosis	[178, 179]
miR-200s (microRNA)	Biomarker and therapeutic target	For breast cancer prognosis	[180, 181]
mRNA-122	Biomarker and therapeutic target	Potential and predictive biomarker for breast cancer	[115]
miRNA-203	Biomarker and therapeutic target	Potential and predictive biomarker for breast cancer	[117]
miR-9	Biomarker and therapeutic target	Potential and predictive biomarker for breast cancer	[119, 120]
Circulating or cell-free DNA (cfDNA)	Biomarker	For breast cancer prognosis	[182, 183]
Mitochondrial DNA (mtDNA)	Biomarker	Potential and predictive biomarker for breast cancer	[184]

hence directly influencing the process of metastasis by inducing tumor-stromal interactions [112].

iv. By changing the expression levels of specific chemokines, miRNAs regulate the recruitment of several stromal cell types such as inflammatory, mesenchymal, endothelial and immune into the primary tumor microenvironment [143, 144].

v. Recent studies have also highlighted the role of microRNAs, in controlling the hypoxia- inducible transcription factors to regulate oxygen homeostasis within the hypoxic tumor microenvironment in cancer [145, 146].

vi. In cancer, dysregulated miRNAs also facilitate immune surveillance mechanism, greatly required by the cancer cells for their propagation as well as for the mechanism of metastasis [147, 148].

vii. They greatly influence the preparatory mechanism in the distant organs by the name of pre-metastatic niche which is required for the early colonization of the DTCs (Disseminated Tumor Cells) in cancer [149, 150].

5.3. CfDNA/ctDNA (Cell-Free/Circulating DNA)

Mandel and Metais in 1948 were the first ones to report the presence of circulating cell-free DNA (cfDNA) in human blood [151]. Till date, various researches have been established that have focused on molecular profiling and kinetic analysis of cfDNA in cancers and various other diseases [152]. However, the origin of cfDNA is still not clear and declared as controversial. The proposed two main origins of cfDNA are:

i. Secondary to the cellular breakdown process.

ii. Release/secretion of active DNA into the circulation.

However, this mechanism also includes the transport of cfDNA *via* a vesicular mechanism such as *via* exosomes. When the cause of secretion was analyzed, it was found that the release was as a result of various biological and pathological mechanisms such as phagocytosis mediated release from dead cells, autophagy, aging, exercise, inflammation, immune reaction, sepsis, oxidative stress and cancer [153]. In addition, another hypothesis has also explained that

cfDNA in cancer are derived from both necrotic and apoptotic cells whereas in healthy controls, it originates predominantly from apoptotic cells [154]. Generally, circulating DNA is described as cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA) that is released in serum or plasma of cancer patients [155]. Its levels in the blood directly correlate with tumor genetics, tumor burden, mechanism of cancer progression and drug resistance. The analysis of cfDNA in the body fluids of cancer patients will, therefore, serve as a novel, noninvasive method, which is not only an inexpensive approach but also provides an easy screening and monitoring modality in order to determine tumor progression [156].

5.4. MtDNA (Mitochondrial DNA)

Altered energy metabolism is one of the characteristic hallmarks of cancer [157]. Genetic mutations secondary to alteration of nDNA (nuclear DNA) are not the only causative factor but mutations related to mtDNA (mitochondrial DNA) along with the changes in its copy number are equally involved [158, 159]. One of the typical features that lead to cancer towards metastatic progression is the shift to aerobic glycolysis, which occurred secondary to mtDNA mutation [157, 160]. In various human pathological conditions such as diabetes, obesity, neurodegenerative disorders, aging and cancer, mtDNA mutations along with the reduction in mtDNA copy number have also been reported. In breast cancer, mtDNA mutations and low mtDNA copy number are associated with poor prognosis and increased incidence of metastasis [161]. Also evident from studies conducted in cancer cell lines and animal models that cancer cells are devoid of mtDNA, are initially dependent on mtDNA of host origin, followed by a gradual recovery of respiration as they are gradually promoted from primary to metastatic cancer cells [162]. Also postulated from other mouse exogenous tumor model study was that when mtDNA depleted cancer cells were injected in mice, a higher tumor burden (related to incidence and size) was evident as compared to the control group, which was injected with parental cells [163].

CONCLUSION AND FUTURE PROSPECTS

In this review, we have discussed in detail the role of various cancer cell-derived secretory factors that are involved in lung metastasis occurring secondary to Breast cancer. Till date, numerous genomic, proteomic and computational based studies have been conducted to get insight related to the intricate mechanism acquired by cancer cell-derived secretory factors, which are involved in the mechanism of breast cancer lung metastasis. Nearly all these studies have implicated the complex interlinked molecular mechanisms that were altered in this process. This altered mechanism involves specific genes, stromal cells, cancer cells-derived secretory factors and signaling pathways, which provide the basis for the underlying mechanism involved in the process of breast cancer lung metastasis.

An expert collaboration of all these molecular events, along with the clinical correlation, is the dire need to understand the underlying complex mechanism of lung metastasis. An implication of all these studies conducted in cell lines and animal models should also be validated in humans. Use of secretory factors as predictive, diagnostic and prognostic biomarkers as well as future therapeutic targets in the future, will hopefully prevent this type of metastatic organotropism occurring secondary to Breast cancer. Table **3** shows a few of the secretory factors that are recently identified and may be used as biomarkers or therapeutic targets. It has, therefore, become evident through all these secretome-based researches that the cancer secretomes played a crucial role in Breast cancer Lung metastasis. Effective therapeutic strategies and core understanding of the chemistry of these cancer-associated biomolecules that are involved in this mechanism will greatly help the oncologists in the future to halt the devastating cascade of lung metastasis occurring secondary to Breast cancer progression.

LIST OF ABBREVIATIONS

ANGPTL4	=	Angiopoietin-Like 4
BCLM	=	Breast Cancer Lung Metastasis
BMDC	=	Bone-Marrow Derived Cells
BMPs	=	Bone Morphogenetic Proteins
CCECs	=	Cancer Cell-derived Extracellular Matrix Components
CCSFs	=	Cancer Cell-derived Secretory Factors
cfDI	=	Cell-free DNA Integrity
cfDNA	=	Circulating or Cell-free DNA
CSCs	=	Cancer Stem Cells
CXCR4	=	Chemokine Receptor-4
cytDNA	=	Cytosolic DNA
ECM	=	Extracellular Matrix
EGFR	=	Epidermal Growth Factor Receptor
EMT	=	Epithelial-to-Mesenchymal Transition
exoDNA	=	Exosomal DNA
FOXC1	=	Forkhead box C1
GAGs	=	Glycosaminoglycans
GALNT 14	=	N-Acetyl-galactosaminyltransferase 14
HIF-1	=	Hypoxia-inducible Factor 1
IDC	=	Intra-ductal Carcinoma
LacRNA	=	Long Non-coding RNA
LOX	=	Lysyl Oxidase
LOXL2	=	Lysyl Oxidase-like Protein
MAMs	=	Metastasis Associated Macrophages
MBC	=	Metastatic Breast Cancer
miRNA	=	microRNA
MMPs	=	Matrix Metalloproteinases
MO	=	Metastatic Organotropism
mtDNA	=	Mitochondrial DNA
NID-1	=	Nidogen-1
PBC	=	Primary Breast Cancer

PMN	=	Pre-Metastatic Niche
PMS	=	Plantamajoside
POSTN	=	Periostin
ROCK	=	Rho-associated kinase
SCB	=	Succinobucol
TGF-β	=	Transforming Growth Factor-β
TM	=	Tumor Microenvironment
TNBC	=	Triple Negative Breast Cancer
TNC	=	Tenascin C
TNF-α	=	Tumor Necrosis Factor-α
VCAM1	=	Vascular Cell Adhesion Molecule

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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