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The molecular mechanisms of breast cancer metastasis

Rasa Ugenskienė[1]*,

Elona Juozaitytė[2]

[1] Oncology Research Laboratory, Oncology Institute of Lithuanian University of Health Sciences, A. Mickevičiaus str. 9, LT-44307 Kaunas, Lithuania

[2] Oncology Institute of Lithuanian University of Health Sciences, A. Mickevičiaus str. 9, LT-44307 Kaunas, Lithuania

The aim of the paper is to highlight some of the newest research data and to present a summary of tissue-specific mechanisms involved in breast cancer metastasis. Breast cancer spreads to different distant organs, preferentially to bones, lung, liver and brain. Tumor cell migration and colonization requires a successful cascade of molecular events where different gene mutations and altered expression play an important role. The molecular basis of breast cancer metastatic process, especially the mechanism of organ-specific metastasis, is poorly understood and is presently extensively studied. Recent research data suggest that primary tumor gene signatures predict tumor metastatic potential and organ-specific tropism. The advanced knowledge and better understanding of metastatic process should help to tailor treatment directed towards preventing or delaying metastasis formation.

Key words: metastatic breast cancer, survival, molecular mechanisms, organ-specific metastasis

INTRODUCTION

Cancer related morbidity and mortality are mainly associated with its metastatic potential. Breast cancer (BC) metastasizes to many distant organs. The most common is metastasis to bone, lung, liver and brain. The metastases significantly, from 89% to 23%, reduce 5-year relative survival (Howlader et al., 2011). Untreated BC brain metastasis considerably (till 1 month) decreases patient life expectancy (Wadasadawale et al., 2007).

Breast cancer is known as a highly heterogeneous disease. The intratumor heterogeneity is due to genetic instability, increased mutation rate, epigenetic alterations and selective pressure. During primary tumor formation cells with advanced features such as increased proliferation capacity, motility and invasiveness are favored. They form a subpopulation of cells, which are genetically programmed to enter circulation and form distant metastasis. Today it is not entirely clear whether

* Corresponding author. E-mail: rasaugenskiene@gmail.com

metastasizing cells are cancer stem cells or any tumor cell with acquired invasive features.

A process of metastasis formation is a multistep cascade of molecular events where different gene mutations and altered expressions take place. Theoretically, it could be divided into cell migration and colonization. Metastatic cell migration includes local invasion, intravasation, dissemination and extravasation. A number of genetic mechanisms have been reported to be implicated at different stages of metastasis formation (Chiang et al., 2008; Weber et al., 2008). They are all aimed at increasing cell adaptation to constantly changing environment what results in aggressive cell phenotype.

The molecular basis of breast cancer metastatic process, especially the mechanism of organ-specific metastasis, is poorly understood and presently is extensively studied. It is obvious that new knowledge could help in the development of target therapeutics, directed towards preventing or delaying metastasis formation. The aim of the paper is to highlight some of the newest research data and to present a summary of tissue-specific mechanisms involved in breast cancer metastasis.

The molecular basis of BC metastasis formation. Local invasion and intravasation

At the very beginning of local invasion cancer cells interact tightly with their microenvironment. This crosstalk results in stroma activation and cytokine release. Epidermal growth factor (EGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor β (TGFß), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF) have been reported to be the key molecules at this stage of local invasion (Yang et al., 2008). They are known as epithelial-mesenchymal transition (EMT) inducing factors which are released from cancer-associated fibroblasts (CAFs). Cancer-associated fibroblasts together with stromal pericytes support tumor proliferation (Spaeth EL, 2009). In response to EMT inducing factors, cancer cells release EMT activating transcription factors (EMT-TFs) and undergo EMT (Thiery et al., 2009). During EMT epithelial cancer cells lose epithelial and gain mesenchymal markers. They protect tumor cells during metastasis formation and enable further transformation. The process of EMT is reversible as cancer cells redifferentiate back to epithelial cells after having set into distant organs.

Once mesenchymal markers are gained, cancer cells get attracted to the chemoattractants from the circulation. That is an important signal, which triggers cell migration towards vasculature. Before cancer cells get launched into the circulation, they have to break down intraepithelial junctions and invade the surrounding stroma. E-cadherin-catenin complex is the most important for intraepithelial connections. It forms an adherence junction in normal and cancerous cells. Mutations in E-cadherin, α- and β- catenins or epigenetic silencing of E-cadherin results in the destruction of this protein complex and increased cell motility (Sarrio et al., 2003). The down regulation of E-cadherin by EGFR, FGFR, IGFR and HGFR was also reported (Thiery, 2002). Furthermore, EMT induces epithelial E-cadherin switch to mesenchymal N-cadherin. That is followed by increased cancer cell affinity to the cells of mesenchymal origin (Hulit et al., 2007).

Loosened cells are ready to start extracellular matrix (ECM) invasion. They communicate with activated stroma cells, macrophages, which release a wide variety of matrix metalloproteinases (MMP). MMP is a group of proteolytic enzymes, involved in connective tissue remodeling. They destroy extracellular matrix components such as fibronectin, type I collagen and laminin. During metastatic process the enhanced expression of MMP leads to extracellular stroma disruption forming an artificial path for cancer cell invasion towards the vasculature. MMP are also known to support vascular remodeling (Gupta et al., 2007). The increased MMP expression correlates with tumor invasiveness and poor prognosis (Turpeenniemi-Hujanen, 2005).

A number of different molecules facilitating tumor cell invasion were reported (Wang, Zhang, 2005). For example, cathepsins were demonstrated to be involved in ECM degradation and other crucial steps of carcinogenesis (Gocheva et al., 2006). The overexpression of cathepsins D in primary tumors is known as a poor prognosis marker (Foekens et al., 2009). Additionally, urokinase-type plasminogen activator (uPA) system was reported to be involved in ECM destruction. It is responsible for degradation of fibrin, fibronectin and laminin. The data suggest that increased uPA

levels correlate with decreased relapse-free survival and overall survival (Look et al., 2002).

Invadopodia, invasive feet, is a three-dimensional structure similar to podosome (two-dimensional structure), which enables cancer cell motility. Actin filaments are the basic structural elements of invadopodia. Cell membrane remodeling and increased local actin synthesis forms a protuberance – invadopodia. It is a dynamic structure with stability lasting for a few minutes. Formation of invadopodia is initiated by the release of colony stimulating factor-1 (SCF-1) and phoshatidylinositol-glycan biosynthesis class F protein (PIGF) from activated tumor cells. SCF-1 and PIGF attract and activate tumor associated macrophages (TAM). They secrete a huge variety of factors, responsible for invadopodia formation (Wyckoff et al., 2004). Additionally, activated CAF release epidermal growth factor (EGF), HGF and TGFß. They could also contribute to invadopodia composition (Oxmann et al., 2008). Recently a few actin regulators such as cortactin and N-WASP (neuronal Wiskott–Aldrich Syndrome protein) have been reported. They act together with adaptor proteins, Tks4 and Tks5, and proteases (for example, MMP2, MMP1 and MT1-MMP). All those molecules are crucial not only for invadopodia formation but also for local (at the very top of invadopodia) proteolytic MMP activity (Murphy, Courtneidge, 2011). Summarizing, cytoskeleton remodeling and locally increased MMP expression participate in cancer cell motions towards the circulation.

Additionally, Sidani et al. demonstrated that tumor cells have the ability to use extracellular matrix components to speed up their migration. The researchers documented cancer cells to perform inch worm-like movements along ECM fibers in primary breast tumors. This type of high velocity migration appeared to be important for cancer cell translocation during local invasion. The ECM fibers are sometimes referred to as cancer cell highways (Sidani et al., 2006).

Once cells arrive to the capillary wall, the process known as intravasation starts. Cells have to get through the basal membrane and inner layer of endothelial cells. The earlier acquired mechanisms of cytoskeleton remodeling and increased MMP activity play a major role in passing this barrier. It has been reported that intravasating cells act as macrophages. They form pseudopodia, which helps them to penetrate (Gonda et al., 2010).

Dissemination and extravasation

During the process of metastasis formation specific genetic alterations enable cancer cells to pass beyond their limits. For example, epithelial mesenchymal transition enhances cell motility and affinity to mesenchymal signals. Furthermore, EMT increases the chances of circulating tumor cell (CTC) survival in the vasculature. It has been reported that during dissemination cancer cells express unknown cell surface markers which attract platelets. Surrounded by platelets, CTCs seem to be protected (Jin et al., 2006). Moreover, cancer cells have been reported to mimic macrophages. Cancer cells express CD11b, CD45, CD68, CXCR, F4/80 and Iba1 molecules that are known as macrophage markers (Huysentruyt et al., 2008). Both molecular mechanisms protect CTCs from the host immune system on their way to distant organs. Furthermore, most tumor cells have a reduced or abolished expression of metastasis suppressor CD82. Normally, the interaction between CD82 and endothelial cell DARC (Duffy antigen chemokine receptor) results in cancer cell anchorage to capillary wall. The loss of CD82 was reported to facilitate cell migration (Bandyopadhyay et al., 2006).

The next step of metastasis formation is extravasation. For successful completion of this process, cells must adhere to vascular endothelium and escape from the circulation. The increased expression of specific cell adhesion molecules is known to be extremely important for this process. For example, metadherin participates in CTC adhesion to lung and brain endothelium (Brown, Ruoslahti, 2004). Once the cells are stuck, different molecular mechanisms of cytoskeleton remodeling take place. They increase cell elasticity and stiffness. The former is important for crossing the vasculature and invading distant organ as it requires cell passage through extremely small intracellular spaces. On the other hand, increased cytoskeleton stiffness plays an important role in cell survival within a capillary. It is known that during extravasation cells are squeezed as a capillary diameter is at least 3 times smaller than that of a cancer cell.

Colonization

The majority of the molecular alterations are bounced to protect cancer cells on their way from primary tumor to distant organs. Despite of huge variety of "protective" mechanisms, metastasis formation is accomplished with losses. It has been reported that only a small proportion (<0.01%) of tumor cells entering circulation colonize distant organs (Fidler, 1970). Therefore distant metastases are often referred to as a successful sequence of molecular events.

The layout of circulation is the most important for most tumor metastatic tropism; however a few molecular mechanisms have been reported to be responsible for organ-specific colonization. Generally, distant organ colonization depends on the structure of the capillary. There are two types of capillaries: fenestrated and continuous. The former are found in bones and liver, while the latter in brain and lung. Cancer cell penetration through continuous capillary requires enhanced expression of cell adhesion molecules. For example, elevated expression of cyclooxygenese 2 (COX2), EGFR and heparin binding epidermal growth factor (HBEGF) facilitates BC seeding to brain (Bos et al., 2009), while COX2, EREG, MMP1 and MMP2 – to lung (Gupta et al., 2007). As far as fenestrated capillary are concerned, they allow spontaneous cell passage. It is believed that capillary structure (fenestrated) makes bones the most frequent site of distant metastasis.

The successful cell seeding might require extra molecular events. Weber et al. described a ligand, osteopontin, which facilitates CD44+ cell homing (Weber et al., 1996). Most of the distant organs (bone, liver, lung and lymph nodes) physiologically express osteopontin. That increases the probability of CD44+ cell "accommodation". Additionally, specific molecules, participating in organ-specific colonization, have been reported. For example, enhanced matrix metalloproteinase expression is usually detected in metastatic bone lesions (Smid et al., 2006). A comprehensive overview of genes and protein facilitating organ-specific colonization is presented below.

Furthermore, the process of colonization depends not only on the readiness of "seed" (metastatic cell), but also on the maturity of "soil" (distant organ). The recent research suggests that primary tumor signaling plays a major role in premetastatic niche formation. For example, breast cancer signaling through vascular endothelial growth factor A (VEGF-A), SDF-1, TNF-α, TNF-β and PIGF leads to the reorganization of bone structure. Bone marrow-derived cells are recruited to a newly formed premetastatic niche. Consequently, cells release chemoattractive factors such as lysyl oxidase (LOX), S1000-A8, S100-A9, which facilitate CTCs colonization (Peinadoa et al., 2011).

Organ-specific metastasis. BC metastasis to bone

Bones are the most frequent sites of breast cancer metastasis. A huge variety of crosstalk between primary breast tumors and bone microenvironment has been reported (Fong, Komarova, 2011). Firstly, breast cancer inhibits osteoblast differentiation. Consequently, immature osteoblasts together with hematopoietic stem cells start forming a premetastatic niche (Mendoza-Villanueva et al., 2011). Secondly, primary breast tumors are known to release parathyroid hormone related protein (PTHrP). It stimulates osteoblasts, which in response release RANKL (a receptor activator of nuclear factor kappa-B ligand). Its partner, RANK, is expressed by CTCs. As a result, RANKL / RANK interaction facilitates metastatic cell homing to bone (Yin et al., 1999).

Another important interaction involved in bone metastasis formation is between SDF-1 and C-X-C chemokine receptor type 4 (CXCR4). SDF-1 is highly expressed in bone, while CXCR4 – in breast cancer tissue. The SDF-1/CXCR4 interaction participates in breast cancer bone metastasis formation. The increased expression of CXCR4 in primary tumor correlates with poor prognosis (Dewan et al., 2006).

Recently the role of $\alpha_v\beta_3$ integrin has been emphasized. $\alpha_v\beta_3$ integrin is a receptor for osteopontin, fibronectin and vitronectin, which are highly expressed in bone marrow. The circulating breast cancer cells, expressing $\alpha_v\beta_3$ integrin, interact with fibronectin and finally attach to it. This interaction stimulates MMP2 secretion, and, consequently, increases cell invasiveness. To date, $\alpha_v\beta_3$ integrin is considered the most important molecule for CTC homing to bones (Takayama et al., 2006).

Despite of the above mentioned verified single protein contribution, it has become clear that multiple gene expression changes and numerous

protein interactions drive successful colonization process. Kong et al. analyzed gene expression profile in MDA-MB-231 metastatic breast cancer cell line. They determined a group of differently expressed genes – a gene signature for bone metastasis. When tested on primary tumors, metastatic bone signature (52 genes) clearly predicted bone colonization (Kang et al., 2003). In a study reported by Smid et al. 69 genes responsible for BC metastasis were identified. Gene expression profile analysis enabled a correct identification of primary breast tumors relapsing to bone (Smid et al., 2006). The recent research data provide strong evidence that primary tumor gene signatures predict its metastatic potential (Weigelt et al., 2003; Ramaswamy et al., 2003; Wang et al., 2005; van de Vijver et al., 2002).

Furthermore, gene signature appeared to comprise even more meaningful information. Kleina et al. analyzed gene expression profile in the samples excised from BC brain and bone metastasis. They identified 73 differently expressed genes while comparing brain to bone metastasis and their matched primary tumors. Gene cluster analysis identified two differently expressed gene groups. One set of genes (51 gene) was characteristic for brain, while the other (22 genes) – for bone metastasis. The authors demonstrated that primary tumor gene expression analysis predicts BC organ-specific metastatic tropism (Klein et al., 2009).

BC metastasis to lung

Lung metastasis gene-expression signature (LMS), a set of 54 differently expressed genes, was reported by Minn et al. Firstly, it was identified in the experiments with MDA MB-231 human breast cancer cell line and mouse xenograft model. Sequentially LMS was verified on primary human breast cancers. Minn et al. demonstrated that LMS clearly predicts patients who are at high risk for lung metastasis (Minn et al., 2005). Additionally, in 2007, they demonstrated that LMS affects primary tumor growth, which is accomplished by LMS^+ cell number expansion (Minn et al., 2007). A continuous aggressive cell clone selection within the primary tumor is congruent with Darwin's evolution theory.

Landemaine et al. studied gene expression profile in metastatic breast cancer. They analyzed BC tissue samples, excised from different distant metastatic sites. Landemaine et al. determined a group of genes (21 gene) whose expression significantly differed between lung and non-lung metastasis. Further functional validation of the data brought them to a 6-gene signature. It was significantly associated with an increased risk of lung metastasis (Landemaine et al., 2008).

BC metastasis to liver

The molecular mechanisms responsible for BC liver metastasis are poorly understood. In the study of Erin et al. gene expression patterns of primary BC and their matched liver metastasis were analyzed. The scientists identified a group of 4 differently expressed genes, which participate in tight- and adherence junction formation. Erin et al. demonstrated a reduced or abolished expression of claudin 4, claudin 7, γ-catenin and ZO-1 in the samples excised from liver metastasis. The authors suggest that gene expression differences were due to the interaction between tumor cells and microenvironment (Erin et al., 2009).

In the study of Sanz-Pamplona et al., a protein-protein network interaction analysis identified 15 proteins, which were functional representatives of BC liver metastasis signature. Generally, they were involved in inflammation response and wound healing. The protein network taxonomy showed that liver-specific proteins interact in signal transduction, proteolysis and hepatic glucose metabolism. However, none of the protein from liver metastasis signature was verified as liver-specific metastasis marker (Sanz-Pamplona et al., 2012).

BC metastasis to brain

Different approaches have been used to track genes involved in BC metastasis to brain. *In vitro* cell culture models revealed the importance of crosstalk between primary tumor and brain microenvironment (Carlini et al., 2011). In the study of Sierra et al. 435-Br1 breast cancer cell line showed increased growth rates when exposed to astrocyte-conditioned medium (Sierra et al., 2007). Fitzgerald et al. demonstrated that coculture of MDA-B-231 breast cancer cell line with glia cells intensify cancer cell proliferation (Fitzgerald et al., 2008).

Combined techniques of cell culture and animal models were used in the study of Mendes

et al. They demonstrated that ENU1564 rat breast cancer cell line responds to the signals from activated astrocytes by increased invasiveness and MMP2 expression. Furthermore, tissue inhibitor of MMP2 (TIMP2) significantly decreased tumor growth and prevented metastasis development *in vivo*. The authors demonstrated that extracellular signal-regulated kinases 1 and 2 (ERK1/2) control MMP2 activity. Summarizing, the authors suggest that ERK1/2 might be involved in BC brain metastasis formation through an increased MMP2 activity (Mendes et al., 2007).

It the study of Bos et al. three genes responsible for brain colonization were identified. Two of them, COX2 and HBEGF ligand, had been previously reported to be associated with breast cancer metastasis to lung (Minn et al., 2005). Bos et al. suggest that the mediators of extravasation play a major role in priming cells for brain and lung metastasis. α2,6-sialyltransferase (ST6GALNAC5) was the third identified gene. It appeared to be exclusively important for brain metastasis. α2,6-sialyltransferase is a molecule that is normally expressed only in brain tissue. Cancer cells, expressing ST6GALNAC5, were capable of both: adhering to brain endothelium and passing through the blood–brain barrier. In this study cell-surface glycosylation was first reported to be important for organotrophic metastasis formation (Bos et al., 2009). A number of other genes have been reported to be important for breast cancer brain metastasis (Palmieri et al., 2009; Ratmathulla et al., 2012; Saunus et al., 2011).

Potentially "druggable" targets

The identification of gene signatures responsible for BC organ-specific metastasis is a priority field of future cancer research. It is believed that gene signatures will broaden our knowledge on metastatic process and will offer an individualized treatment for every cancer patient. Generally, the final goal is to prevent the metastatic process itself by blocking the genes involved in early stage of metastasis development. For example, phase 1–2 trail molecules GC1008 and ARQ197 are the inhibitors of metastatic initiator genes *TGF*-β and *c-MET*, respectively (Smith et al., 2012; Previdi et al., 2012).

While a universal antimetastatic treatment is under development, high metastasis-risk patients could benefit from well established agents. At present, in the case of increased risk for bone metastasis, bisphosphonates are proved to be effective. They prevent or delay metastasis formation (Body et al., 2004). Bisphosphonates selectively attach to bone and trigger osteoblast apoptosis. RALK is another molecule that draws a lot of attention. The efficiency of anti-RANK antibody, denosumab, in preventing BC bone metastasis is currently under investigation in phase 3 trials (Stopeck et al., 2011).

No target therapy for other BC metastatic lesions is available. Generally, any molecule participating in BC organ-specific colonization could be a candidate for further analysis. For example, genes involved in LMS or 6-gene signature could serve as a background for future search of lung specific antimetastatic treatment. Concerning BC liver metastases, family of claudin is of interest. α2,6-sialyltransferase was first reported to be important for brain metastasis. It could possibly be a therapeutic target for patients with increased risk of brain metastasis. In the future, the identification of high metastatic-risk patients, who could benefit from tailored treatment, might be implemented into treatment protocols.

CONCLUSIONS

Technological progress enabled high throughput analysis of primary tumors and their matched metastatic lesions. The results are encouraging in both disclosing the basis of tumor biology and being translated into clinics. The organ-specific metastasis signatures were demonstrated to predict tumor metastatic potential and organ-specific tropism. The integrated model of research involving gene expression analyses, functional and protein interaction assays will help to identify the missing molecules in the complicated "cobweb" of tumor biology.

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Rasa Ugenskienė, Elona Juozaitytė

MOLEKULINIAI KRŪTIES VĖŽIO METASTAZAVIMO MECHANIZMAI

Santrauka

Straipsnyje pateikiami naujausių mokslinių tyrimų duomenys, taip pat molekulinių mechanizmų, nulemiančių krūties vėžio organinių specifinių metastazių išsivystymą, apžvalga. Žinoma, kad krūties vėžys metastazuoja į daugumą tolimųjų organų: kaulus, plaučius, kepenis ir smegenis. Navikinių lastelių migracijai ir kolonizacijai būtina sėkminga molekulinių įvykių seka, kurią lemia įvairių genų mutacijos bei jų raiškos pokyčiai. Molekuliniai krūties vėžio metastazavimo mechanizmai, ypač organinės specifinės metastazės, yra mažai žinomi ir šiuo metu intensyviai tiriami. Šiuolaikinių tyrimų rezultatai rodo, kad pirminio naviko genų parašas nusako naviko metastatinį potencialą bei organinį specifinį tropizmą. Naujos žinios ir geresnis metastazavimo proceso supratimas padės individualizuoti pacientų gydymą, kuris užkirs kelią metastazėms arba atitolins jų formavimąsi.

Raktažodžiai: metastazuojantis krūties vėžys, išgyvenamumas, molekuliniai mechanizmai, organinės specifinės metastazės