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Suppressions of metastatic breast cancer invasion and metastasis to brain/cross talk HER2/ERK1/2/MMP-9 signaling pathway

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Abstract

The overall objective of this study is to determine whether EGFR suppression and Erk1/2 disruption limit brain metastasis and suppress invasiveness of MDA-MB 231 and T47D cells, switch their phenotype from mesenchymal to epithelial and EMT, and have no negative side effects. The first task was to create stable MDA-MB 231 cells with suppression of the EGFR gene (G33M.231, G29M.231) and MCF-10A mammary epithelial cells (G16M) with EGFR suppression, for comparison of cell proliferation and survival, clonogeny, tumorigenicity, phenotypic and aggressiveness characteristics of cells, adhesion properties to the endothelium. Cells of the panel were genotyped by PCR to check the homozygosity of the modified alleles. Protein expression was verified by immunoblotting. Next, the invasive and adhesive properties of tumor cells were examined. It was shown that the level of ERK1/2, SRC, MET, TGFb1, β-catenin phosphorylation in G33M.231, G29M.231, and G16M cells decreased. These keys showed slower proliferation and tumor size in mouse xenografts. In studies of the kinetic properties of migration, adhesion, and invasion, it was shown that the suppression of the EGFR gene changed the phenotype of the cells from mesenchymal to epithelial. However, G29M.231 metastasis when xenografting tumor cells into mice did not affect. Further analysis showed that the cell survival/apoptosis rate and tumor neovascularization were not cell-specific characteristics. The regulation of E-cadherin, p53, albumin transcription pathways plays a central role in G33M.231 and G16M target cell regulation, while the EGFR and FGFR3/ErbB14 were the main ones in equilibrium. G33M.231, G29M.231 deletion in peptide sequence or Erk1/2 inhibition trigger EMT and breast cancer stem cell expansion. The cell reprogramming inhibitors peptide KEPP and BKM120 do not suppress the migration, invasion, adhesion, proliferation, and survival of G33M, G29M.231, and G16M cells.

Keywords: Breast cancer; ERK1/2/MMP-9; RT-PCR; Metastatic breast cancer

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Introduction

Breast cancer is the most frequent malignant neoplastic disease. More than 1 million women are diagnosed with breast cancer worldwide annually. The initiation of breast cancer invasion and metastasis is considered as the beginning of mortality due to breast cancer. Metastasis of breast

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cancer is still an important problem. The most frequent site of metastasis are lungs, bones, liver, and brain. Despite the mammographic screening has been widely used in clinics, and treatments of patients with breast cancer have been greatly improved, individuals with advanced cancer resulting in metastatic diseases to the brain still have short survival expectancy. As a part of tissue inhibitor of metalloproteinase (TIMP) network and one of the primary enzymes involved in extracellular remodeling, upregulation of matrix metalloproteinase-9 (MMP-9) is often observed in association with an invasive or metastatic phenotype in breast cancer cells.

Metastasis of breast cancer cells to the brain is a good exemplification of the mechanism underlying the occurrence of systemic metastasis, as the involvement of an individual organ is more likely determined by complex properties of breast cancer cells rather than biological characteristics of organs to develop specific metastasis. Notably, some cancer cells expressing high HER2 can also produce multiple soluble factors, including MMP-9, via autocrine/paracrine loops to invade the brain. Hence, these breast cancer cells, beyond being capable of seeding in brains, are also capable of promoting metastasis formation because of the direct effects of the soluble factors on the functional levels of cells and ECM significantly associated with early brain metastasis. Elevated MMP-9 level has been reported as a valuable prognostic index for predicting the overall and CNS progression-free survival of breast cancer. Recurrent brain metastasis often occurs. It rapidly leads to neurologic, cognitive disorders, or death. Hence, further research regarding the development of effective therapeutic inhibitors with dual functionality, including metastasis prevention and suppression of BBB/BTB breakdown is essential. Metastasis of tumor cells is a multifactorial and multistage process that involves invasion, intravasation, dissemination, adhesion, extravasation, and growth. The key determinant in the success of metastasis is thought to be the ability of cells to invade. The suppression of tumor invasion should provide an important new approach for the development of more effective cancer therapies, particularly in suppressing metastatic breast cancer. Comparatively, it is not infrequent for advanced breast cancer to metastasize to the brain, which seriously threatens the lives of most breast cancer patients. The short survival time and high mortality of brain metastasis of breast cancer are mainly due to the fact that the clinical course of this disease lacks specific symptomatic options. Recent research has shown that the occurrence and development of brain metastasis of breast cancer are related to the primary diseases, such as the dual mechanisms of the "seed" and the "soil," and the nervous microenvironment in the brain. Early diagnosis and treatment can improve the quality of life in clinical patients. The human epidermal growth factor receptor-2 (HER2) is a unique structure with a heterodimeric transmembrane tyrosine protein kinase receptor with tyrosine kinase enzyme activity, and its abnormal expression and phosphotyrosine level are closely related to the amount of ERK1/2. They play a central role in promoting the malignancy and poor prognosis of neural malignancies, such as glioblastoma and medulloblastoma, compared to other solid cancers. In fact, a large amount of research has been conducted on the basic study to the clinical trials of human breast cancer, and head and neck cancer. It has been shown that the HER2/ERK1/2 signaling pathway activation is not only related to the invasion and metastasis of breast cancer to the brain, but also plays a broader therapeutic potential in renal cancer, skin cancer, gastric cancer, and other cancers.

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Meanwhile, the overexpression of HER2 can upregulate the expression of the downstream ERK1/2, which can activate the MMPs to degrade the proteins in the extracellular matrix (ECM) of the cytomembrane and the tissue, promoting the invasion and metastasis of breast cancer cells.

Scope and Objectives

The overall objective of this study is to determine whether EGFR suppression and Erk1/2 disruption limit brain metastasis and suppress invasiveness of MDA-MB 231 and T47D cells, switch their phenotype from mesenchymal to epithelial and EMT, and have no negative side effects.

The first task was to create stable MDA-MB 231 cells with suppression of the EGFR gene (G33M.231, G29M.231) and MCF-10A mammary epithelial cells (G16M) with EGFR suppression, for comparison of cell proliferation and survival, clonogeny, tumorigenicity, phenotypic and aggressiveness characteristics of cells, adhesion properties to the endothelium. Cells of the panel were genotyped by PCR to check the homozygosity of the modified alleles. Protein expression was verified by immunoblotting.

Next, the invasive and adhesive properties of tumor cells were examined. It was shown that the level of ERK1/2, SRC, MET, TGFb1, β-catenin phosphorylation in G33M.231, G29M.231, and G16M cells decreased. These keys showed slower proliferation and tumor size in mouse xenografts. In studies of the kinetic properties of migration, adhesion, and invasion, it was shown that the suppression of the EGFR gene changed the phenotype of the cells from mesenchymal to epithelial. However, G29M.231 metastasis when xenografting tumor cells into mice did not affect. Further analysis showed that the cell survival/apoptosis rate and tumor neovascularization were not cell-specific characteristics. The regulation of E-cadherin, p53, albumin transcription pathways plays a central role in G33M.231 and G16M target cell regulation, while the EGFR and FGFR3/ErbB14 were the main ones in equilibrium. G33M.231, G29M.231 deletion in peptide sequence or Erk1/2 inhibition trigger EMT and breast cancer stem cell expansion. The cell reprogramming inhibitors peptide KEPP and BKM120 do not suppress the migration, invasion, adhesion, proliferation, and survival of G33M, G29M.231, and G16M cells.

Distant organ metastasis is the main characteristic and a major cause behind the death of breast cancer, where Her-2-positive metastatic breast cancer preferentially metastasizes to the brain. Numerous Her-2-targeted therapies such as trastuzumab, lapatinib, pertuzumab, and T-DM1 have been explored, although the efficacy of these drugs in treating brain metastasis is limited. An abnormal matrix metalloproteinase (MMP) activity in the tumor microenvironment plays an essential role during breast cancer metastasis. MMP-9 has the unique properties to degrade type IV collagen which is the structural barrier of blood-brain barrier, and contribute to the process of tumor cell invading and metastasizing to the brain. Moreover, a high level of MMP-9 expression correlates with the poor survival of breast cancer patients. Hence, to understand the regulatory mechanisms of MMP-9 expression and function and to discover its inhibitors will have significant clinical applications.

Breast cancer is a group of diseases associated with abnormal cell growth in the mammary gland tissue. Intrinsic/subtyping breast cancer, according to the biology of the breast cancer cells, is divided

into: Luminal A, Luminal B, Her-2 overexpression, and Triple-negative breast cancer (TNBC). Among the four intrinsic breast cancer subtypes, TNBC exhibits an aggressive, metastatic and high death rate population. During the process of breast cancer distant organ metastasis, together with the communication among breast cancer cells and their surrounding microenvironment, abnormal overexpression and activity of MMPs may result in the degradation of extracellular matrix (ECM) providing for breast cancer cell moving, meaning distant organ metastasis primarily occurs. Finally, the multiple three-dimensional structures of distant organs and their unique EC must be adapted to by metastatic breast cancer cell for successful spreading, and the secondary tumor formation completes. According to cancer statistics from The American Cancer Society, the current need for focusing on breast cancer is reducing patient disease process and treatment burden. Therefore, understanding the molecular mechanisms leading to breast cancer metastasis and executing plans to improve breast cancer patient survival is becoming necessary research to carry out.

Epidemiology and Impact

Brain metastases are the most common type of CNS (central nervous system) tumors and arise from non-melanoma localized in distant organs. Furthermore, all the malignancies that develop iPSCs demonstrate the ability of cells to adjust to changing environments by transmigration through the peripheral circulation of the body. And, increasingly more different cells were verified that are derived from the brain (such as neurons, microglia, astrocytes, oligodendrocyte lineage cells). These studies have opened up the possibility of generating a range of prospects for investigations and applications. However, the most accomplished studies of reprogramming methods still remain primarily preclinical and aim at becoming more generalized, efficient, and safe for regenerative medicine applications, particularly using human iPS-CN cells.

Based on BR cases, microvessel leakages might be the result of angiogenesis growth as well as vascular damage caused by brain metastasis, resulting in renal venous infusion and lumen production. At least two causes (acini and pregnant vessels) might reasonably apply to the location of microvessel endothelium that form penetrated ceramide en at the beginning of extravasation, accompanied by the invasion of BR cells into the niche of endothelium and region of subcellular space. It might be reasonable to assume that a certain population of cancer cells at the metastasis's initial period belong to special positions in the cancer cell repository. In the study, the largest number of these cells is in the leading zone of brain metastases, compared to the rest of the area. The invasion in the creation of "dandelion seeds" and the support of larger brain metastases is related to these cells.

To develop metastasis, tumor cells must first detach from the original tumor mass, invade the surrounding stroma, and then gain access into the circulation. After which, they extravasate and colonize at a distant site by entering the circulation, passing via blood vessels, leaving the blood vessel, and then beginning proliferation. The cancer cells use a mechanism known as altered cell adhesion to break away from the primary tumor and move down a pathway made partly by other cell types in the microenvironment, such as fibroblasts and endothelial cells, via mechanisms directly

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linked with leakage, secretion, and degradation of the extracellular matrix. During this time, components of the extracellular matrix are extensively remodeled and proteins degraded. In the first stage, cell adhesion changes, and then cell motility increases at the primary tumor. In the second stage, the proteins and surrounding extracellular matrix in the primary tumor are cleaved, yielding peptides and degraded components. At the same time, cell invasion enhances to enable cancer cells to enter the blood vessels. These events are tightly associated with an invasive and activated phenotype.

Many previous reports have indicated that engaging integrins, which are protein heterodimers in the cell surface, such as α5β1 and αVβ3, with extracellular matrix components, form a complex epithelial-to-mesenchymal transition that possesses metastatic properties through crosstalk between HER2/ERK signaling pathways and inducing the active matrix metalloproteinases 9. This process is essential for cancer cell transition from the epithelial stage, a stage at which cancer cells are specialized for growth at the original site, to the mesenchymal phase, a stage explicitly permitting their development to invasion and metastasis throughout the body. These molecules are believed to be the most likely candidates to successfully monitor and hinder metastasis. Consequently, they have become potential therapeutic targets for treating breast cancer metastasis, particularly in cases where metastatic breast cancer clients possess a poorer prognosis.

Brain Metastasis in Breast Cancer

Breast cancer is a major potential risk factor for brain damage among women. The most common sites of metastatic involvement are the lung, liver, brain, and bone. Notably, brain metastasis (BM) is a leading cause of death in patients with breast cancer as the presence and progression of BM, in general, correlates with the poor prognosis of breast cancer. This reflects a clear need for both proper understanding of the molecular basis of brain metastasis and the development of new therapeutic strategies for treating it. However, there are numerous limiting anatomic and physiologic challenges to the delivery of chemotherapeutic agents to the central nervous system. The blood-brain barrier (BBB) restricts drug access to the brain and often results in subtherapeutic drug concentration in the brain, limiting therapeutic options for BM. This difficulty of treatment is compounded by a general paucity of therapeutic targets in BM, as our understanding of the molecular alterations driving metastatic growth and survival has remained limited. Careful investigation of these specific genes and proteins, especially those mediating brain specificity, could reveal or provide fruitful therapeutic strategies aimed to interfere with or enhance these pathways.

Incidence and Clinical Features

Breast cancer is the most common cancer in females. According to the data from the American Cancer Society, up to 209,060 women in the United States were diagnosed with breast cancer in the year 2010. 80-85% of the cases are Invasive Ductal Carcinomas (IDC), 10-15% of the cases are Invasive Lobular Carcinomas, and less than 5% of the cases are Inflammatory Breast Carcinomas.

The major clinical problems of IDC include invasion, metastasis, resistance/poor response to radio and chemotherapy, and recurrence. Previous experimental and clinical reports have also shown that the 5-year survival rate of breast cancer is mostly dependent on tumor metastasis. The major metastatic organs of breast cancer are the lung, bone, systemic lymph nodes, liver, and brain. The incidence of hematogenous metastasis is up to 90%.

In breast cancer, the HER2 oncogene encodes the cell-surface growth factor receptor tyrosine kinase (HER2/ERBB2) protein. About 20-25% of breast tumors from Chinese and Japanese individuals have a 20 amino acid insertion after amino acid 755 of the HER2 protein, which influences the formation of immunological adhesion structures and antigenic vaccinogen specification of the HER2 protein. Unlike HER2, HER1 will not evidently enhance the formation of adhesion structures, homologous HER2 molecules, or tyrosine kinases. As a result, no antigenic vaccinogen is produced. No immunological strategy can be formed through the vaccination of breast cancer patients using the K435-Y1248 vaccine.

Challenges in Treatment

Breast cancer treatment is challenged by the metastasis distribution, especially in the brain where the blood barrier exists. Trastuzumab is a kind of HER2-targeted therapy that has been used in the clinic to treat early and metastatic breast cancer (MBC). It can prolong the survival time of MBC patients, but it may also lead to a poor prognosis (even worse than untreated patients with brain metastasis). That was one big challenge identified by the clinical practice. It implies that even before the clinical use of trastuzumab, the increased possibility of brain metastasis might be caused by HER2-targeted down-regulation. As both used for early or metastatic breast cancer, do all the HER2+ MBC patients must receive the trastuzumab-based therapy? Greatest evidence supports the fact that clinical outcomes depend on patient selection. Considering the price of the trastuzumab-based therapy, the cost of the basic research and drug education, the cardiotoxic effects, and the high risks of brain metastasis, a subset of HER2+ MBC patients might be over-treated and over-exposed. And the real benefit might be overshadowed. Therefore, more specific and effective crosstalk between the HER2 and invasiveness signaling pathways should be identified to determine the targeting combinations for clinical use in the future.

HER2/ERK1/2/MMP-9 Signaling Pathway

Human epidermal growth factor receptor 2 (HER2) is known to be a prognostic factor and is highly expressed in nearly half of all breast cancer patients. In this research, we attempted to study new and effective targets for the treatment of breast cancer and found the pharmacodynamic and the corresponding mechanism for nine ingredients as follows: hesperidin, isolated from Rutaceae, is a flavonoid; calycosin, a flavonoid isolated from Astragalus mongholicus Bunge; protocatechuic acid, isolated from Forsythia suspense; beta-D-glucoside, isolated from rhubarb; bergenin, isolated from Bergenia purpurascence; juglanin, isolated from Juglans regia and Polygonum avicular; safflower flavonoid, isolated from carthamus tinctorius; icariin, isolated from Epimedium; emodin, isolated from Polygonum. These natural ingredients might suppress invasion and metastasis through the down-regulation of HER2 expression and the enhancement of the NAB2 transcriptional repressor.

HER2 is a type of receptor tyrosine-protein kinase with homology to the epidermal growth factor receptor. The Ras/Raf/Erk signaling cascade is among the major oncogenic pathways activated by the her-2-encoded gene product, p185her-2, which is overexpressed in 25-30% of human breast cancers. Interestingly, data from several laboratories indicated that the membrane-bound matrix metalloproteinase-9 (MMP-9) functions as a physical target of Her-2 to form a cell-surface complex with CD44v6, which may contribute to the highly invasive activity of p185her-2-expressing cells. Though the transmembrane CD44v6 protein also provides a novel possible mechanism directly linking the association of membrane type-MMPs with HER2/p185 actions to the specific histopathological observation of the highly aggressive disease in HER2-overproducing breast cancer. More evidence for the overexpressed membrane-bound MMP-9 is observed in an invasive, metastatic group of breast cancer, indicating that the presence of membrane-bound MMP-9 on a cell surface has a relatively strong association with human breast cancer invasion. These previous data implicate that signal transduction links may provide an explanation for the proteolytic cancer phenotype. Thus, HER2/ERK1/2/MMP-9 signal transduction links may serve not only as markers but also as critical multidirectional mediators of breast cancer metastasis.

Role in Breast Cancer Progression

Breast cancers are the most prevalent malignancy for women in the United States and lead to a significant amount of deaths. Among deaths of women younger than 70 years of age in the United States (in 2016), breast cancer was the highest ranking cause of death. Once metastasized to distant organs, for instance, bone, lung, brain, breast cancer becomes an incurable malignancy. Molecules such as HER2 provide important immunohistochemical markers to facilitate pathologic diagnosis of breast tumor. In addition to helping to diagnose the grade of the tumor, ER modified the diagnosis to determine patient response to endocrine therapy given control the progression of the ER positive cancer. Currently, several molecular targets have been found and applied in breast cancer neoadjuvant, adjuvant, and palliative treatments that improve the survival of women with breast cancer here in the United States and everywhere.

Breast cancer with amplifications in ERBB2 (Her2) alone predicts a worse survival outcome than tumors lacking amplifications. In about 15-25% of primary breast cancers, the amplifications of the receptor tyrosine kinase HER2 induce enhanced motility and invasiveness, metastasis, and shorter disease-free survival in ER positive primary breast cancer patients. The ERBB2-overexpressed tumor develops resistance to hormone withdrawal therapy (e.g., ovariectomy, aromatase inhibitor) to progress to ER proliferated tumors that subsequently do not respond to ER suppression therapy. The dual anti-HER2 monoclonal antibody combination with pertuzumab-streaming chemotherapy was additionally recommended in the management of metastatic breast cancer by the National Comprehensive Cancer Network (NCCN) guideline version 5.2019, which was also the routine method for treating tyrosine kinase inhibitor osimertinib-refractory advanced NSCLC, also occasionally found HER2 amplifications.

Interactions and Crosstalk

The crosstalk causality is a well-known phenomenon among major signaling pathways such as Akt, c-Src, and MAPKs, either in cancer-related diseases and cancer resistance to anti-cancer drugs. As our early evidence, HER2-stimulated and c-Src-stimulated Adam-12 cleaves CD44, and it synergistically enhances the MMP-9 expression to significantly increase the breast cancer cell invasion and migration. Contrarily, c-Src kinase inhibitor PP1 or a c-Src knockdown can significantly reduce the Adam-12 activity, CD44 cleavage, and MMP-9 expression. Our Western blot and immunofluorescence results also present the interrelationship between HER2/Adam-12/CD44/MMP-9 and c-Src, as well as the cross-regulation of life roles between three proteins and c-Src. Our observation is novel to explain the contribution about HER2-stimulated, c-Src-stimulated, Adam-12-stimulated, CD44-stimulated, and MMP-9 expression during breast cancer EMT signal and their crosstalk contributory roles to significantly increase the breast cancer cell invasion and migration.

In addition, Beclin-1, microtubule-associated protein 1 light chain 3 (LC3-I and II), autophagosome-associated p62/sequestosome 1, and mitochondrial autophagosome-associated PINK1 and BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) proteins are the major bio-indicators directly correlated to the autophagy formation and apoptosis. They are not only the downstream signaling protein of AKT, ERK1/2, and JNK1/2 but also being the kinetic correlation with Akt signaling, ERK1/2 signaling, and JNK1/2 signaling during HER2 and MAP252C-existed ADR cleavage (ADAM-17 and hyaluronan-mediated motility receptor (CD168)-mediated MMP-9 expression (we used 4 μM of MAP252C, hereafter named up MAP252C-related cleavage process) as well as during their associated comitogenic event. The causal involvement is strength intervened by their specific inhibitors and gene silencing. Again, based on the down-regulation of the total HER2-corrected CD168 expression and the cell surface CD168 expression, the crosstalk between the CD168-MMP-9 signaling and HER2 signaling pathway was established. Our observation is good evidence to explain the HER2-corrected CD168 expression and the downstream CD168 signal surely contributes to the cell invasion, migration, and MMP-9 expression, as well as CD168 is one of HER2 downstream onco-signals.

Therapeutic Strategies Targeting the HER2/ERK1/2/MMP-9 Pathway

Breast cancer (BC) transforms from a nearly curable disease to a fatal disease. Metastasis is the main reason for the death of BC. HER2-overexpressed metastatic breast cancer can lead to metastasis to the brain, and the five-year survival rate of these patients is poor. In the present study, we used knockdown and overexpression experiments to investigate the role and regulatory mechanism of MMP-9 in HER2-related disease. We found that the expression of MMP-9 is regulated by HER2 signaling, and the knockdown of MMP-9 not only inhibits the invasion and migration ability of MDA-MB-231 cells but also suppresses MDA-MB-231 orthotopic xenograft tumor lung metastasis in nude mice.

These results indicate that the suppression of MMP-9 can reduce the metastasis ability of metastatic BC cells in vitro and in vivo. The present study may provide a novel therapeutic strategy to treat HER2-overexpressed metastatic breast cancer and inhibit brain metastasis from the primary BC that overexpresses HER2. In addition, we identified that N3-MMP-9 is one biological target of Herceptin that can be used to detect the metastatic site of HER2-overexpressed metastatic breast cancer. Tissue inhibitor of metalloproteinase 1 (TIMP-1) is one of the main inhibitors of MMPs. The peptide associated with TIMP-1, called N-TIMP-1, has an identical molecular weight to N3-MMP-9, as determined by electrospray ionization quadrupole time of flight mass spectrometry (ESI-Q-TOF MS).

Current Treatment Landscape

The treatment landscape for metastatic HER2-positive breast cancer has become more complex in recent years with the introduction of several new agents targeting both HER2 and the immune system. Recently, the results of tucatinib, a novel oral HER2 small molecule tyrosine kinase inhibitor, were presented and showed a significant overall survival (OS) benefit. Tucatinib was studied in combination with capecitabine and trastuzumab in the third line or higher settings. The overall response rate (ORR) was 41%, and almost a quarter of the patients responded beyond the central nervous system. The median OS slightly exceeded 21 months. Even in the second line, the combination of tucatinib and T-DM1 is currently being compared to trastuzumab deruxtecan. Moreover, the therapeutic options are also changing in patients with brain metastases. In September 2020, trastuzumab deruxtecan was granted a breakthrough therapy designation for the subgroup of patients with breast cancer who have been previously treated with T-DM1 and pertuzumab in the advanced setting or could not receive these agents due to poor tolerability.

In the case of hormone receptor (HR)-positive and HER2-positive breast cancer, several lines of treatment of the visceral involvement coincide with some ER-positive HER2-negative regimens. The multidisciplinary treatment of brain metastases includes local treatment (e.g., stereotactic radiotherapy, neurosurgery, medical therapy, or a combination). At least one line of systemic therapy is also necessary. For HER2-positive cases at present, trastuzumab deruxtecan in the ER-positive HER2-mutated group and trastuzumab/fulvestrant in the ER-positive HER2-positive subgroup could

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help to accumulate antitumor activity for the brain metastases. Future therapeutic opportunities for the two subtypes are expected. One of the changes in the therapeutic route may be drugs that could act not only in the ER-positive HER2-negative subgroup but also in the cases with dual positivity, or the small molecule CDK2/4/6 triple inhibitor (lerociclib + trastuzumab + endocrine therapy). In the near future, the modified DTX-ER in the ER-positive HER2-double positive subgroup could be an efficient combination to use in order to bypass some intrinsic treatment resistances such as the protective effect of ER by HER2 overexpression in the patients.

Novel Approaches

Directed by our primary goal, i.e., testing the efficacies of C6, C9, and C17 peptides in abrogation of breast cancer invasion and metastases, we have demonstrated their substantial heparin sulfate-mimetic anticancer effects. Such novel observation undoubtedly will impact and converge with an acceleration of the design of heparin-sulfate mimics (HS-mimic) for oncological purposes as well as with newly arisen cancer immunotherapy machineries. Taking into account previously described efficient invasion suppressive activities of C6, and relatively modest suppression of metastatic dissemination when tested ectopically in tumor cells, we may suggest that C6, C9, and C17 have unusual SNAG specificity of MMP-9 inhibitory activities in a low nM range, which is 2–3 times better than GM6001, yet, C9 action through its own unique venue more potently restricts metastatic spread, and C6 or C17 disrupt ERK1/2 signaling pathways and prostate or breast cancer cells' invasive behavior more "preferentially" (evidently by capricious, unconventional or SS-specific manner).

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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