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Research Progress on E-cadherin in Breast Cancer Metastasis

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ABSTRACT
Breast cancer, a malignant tumor, poses a significant threat to women's health globally, with metastasis being the primary cause of its high mortality rate. E-cadherin, a crucial cell-cell adhesion molecule, plays a pivotal role in the metastasis of breast cancer. This article aims to examine the molecular mechanisms underlying E-cadherin's involvement in breast cancer metastasis and its potential as a therapeutic target. The inactivation mechanism of E-cadherin in breast cancer is diverse, including gene mutation and loss of heterozygosity, DNA methylation modification, transcriptional level regulation, protein glycosylation modification, and the influence of inflammation and related signaling pathways. These alterations result in the dysfunction of E-cadherin and promote cancer metastasis. The targeted therapy research for E-cadherin has made continuous progress, including strategies such as restoring its expression, stabilizing its structure, utilizing synthetic lethal effects, and intervening in related abnormal pathways.

KEYWORDS
Metastasis; Breast cancer; E-cadherin; Inactivation mechanism; Targeted therapy

1 Introduction

Breast cancer is one of the most widespread and common malignant tumors affecting women around the world, with its high incidence and mortality rates presenting significant challenges to global public health. The metastasis of breast cancer is a major factor contributing to its elevated mortality, as the dissemination of tumor cells from the primary tumor to other organs at a distance is often linked to disease progression and a notable reduction in the effectiveness of treatment.

E-cadherin, a critical intercellular adhesion molecule, is the major factor in maintaining tight connections between cells, which helps to prevent the migration and the spread of tumor cells. However, in several cancers, the levels of E-cadherin expression is frequently downregulated or its function is lost, thereby facilitating tumor cell metastasis and invasion.

This study seeks to explore the molecular mechanisms by which E-cadherin contributes to the metastasis of breast cancer and to assess its potential as a target for therapy. By thoroughly analyzing the role of E-cadherin in metastasis and its associated regulatory network, we aim to provide a theoretical foundation for early diagnosis, prognosis assessment and personalized treatment of breast cancer. As targeted therapies focusing on E-cadherin or its related pathways are still under investigation, this research will concentrate on understanding the mechanism of E-cadherin in breast cancer metastasis and review the latest advancements in its targeted therapeutic approaches.

2 Overview of Breast Cancer

As the leading malignant tumor among women worldwide, breast cancer represents a major risk to their health and well-being. Its occurrence is affected by a combination of factors such as genetics, environmental exposure, and lifestyle habits. From a pathological perspective, adenocarcinoma accounts for the highest proportion and mainly originates from the mammary ducts (85%) or lobular epithelium (15%) [1].

Breast cancer can be classified into several subtypes based on its molecular features, including hormone receptor-positive (estrogen receptor ER+ or progesterone receptor PR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC). Each subtype has significant differences in treatment strategies and prognosis [2].

With the deepening of research on breast cancer, targeted therapy for breast cancer metastasis mechanism has become a research hotspot. At present, targeted treatment strategies for EMT related pathways have emerged gradually, bringing new hope for breast Cancer therapy. For example, some drugs inhibit the EMT process of cancer cells by suppressing key EMT regulatory signals such as the TGF - β signaling pathway and Wnt/β - catenin signaling pathway, thereby inhibiting tumor metastasis [3].

However, the heterogeneity and chemoresistance seen in breast cancer continue to pose significant challenges in treatment. Therefore, investigating the molecular mechanisms of EMT is crucial. This research is vital for developing more effective targeted therapies, which could enhance the prognosis and survival rates of breast cancer patients.

3 The inactivation mechanism of E-cadherin protein in tumor metastasis

E-cadherin, a transmembrane glycoprotein synthesized by the CDH1 gene, is a calcium-dependent protein situated on the cell surface. It plays a crucial role in promoting adhesion between epithelial cells, through establishing and preserving epithelial cell polarization and differentiation by forming intercellular adhesion complexes. Under normal conditions, E-cadherin acts as a metastasis suppressor, therefore its dysregulation is related to the infiltration and metastasis ability of tumors.

Based on the research results of multiple studies, the inactivation mechanism of E-cadherin mainly includes: gene mutation and genetic heterozygosity loss, DNA methylation modification, transcriptional regulation, protein glycosylation modification, and the impact of inflammation and related signaling pathways.

3.1 Gene mutations and loss of heterozygosity

Research has demonstrated that mutations leading to inactivation of the CDH1 gene are frequently observed in breast cancer, particularly in invasive lobular carcinoma (ILC). Berx et al. carried out a thorough analysis of numerous ILC cases and found that up to 56% (23/41) of cases exhibited somatic mutations in the E-cadherin gene [4]. Further research has found that these mutations often occur simultaneously with loss of heterozygosity (LOH) at the E-cadherin chromosomal site. Under normal circumstances, the E-cadherin gene maintains stable adhesion between cells through its encoded protein, inhibiting the spread and infiltration of tumor cells. When gene mutations occur, the structure and function of the protein encoded by the gene are affected, thereby affecting its localization and function on the cell surface. The emergence of LOH causes normal alleles to lose their function, further exacerbating E-cadherin impairment. In this case, the adhesion between cancer cells is weakened, and disturbance in cell polarity facilitates the detachment of cancer cells from the primary site and subsequently metastasize. These research results provide important clues for in-depth understanding of the pathogenesis of breast cancer and offer potential targets for future targeted therapies.

3.2 DNA methylation modification

DNA methylation has a key impact on the inactivation of E-cadherin. In many cancers, including breast cancer, hypermethylation of CDH1 promoter has been shown to suppress E-cadherin expression levels. Shargh et al. selected 50 instances of ductal carcinoma and their matched healthy breast tissue samples for detailed research, and found that 94% of ductal breast cancer exhibited methylation of the CDH1 promoter region [4]. When the CDH1 promoter region undergoes high methylation, it prevents transcription factors from binding to the promoter. This disruption inhibits the transcription of the E-cadherin gene, leading to a substantial decrease in E-cadherin expression levels [5]. However, some studies have pointed out that some early studies on the role of CDH1 gene methylation in breast cancer may overestimate due to methodological problems [5]. For example, some non quantitative methods used in early studies, such as methylation specific PCR (MSP), have many limitations. MSP is susceptible to factors such as primer design and PCR reaction conditions, leading to over interpretation of weak PCR products and mistaking them for biologically and clinically relevant DNA hypermethylation. In addition, MSP cannot effectively control the integrity of bisulfite treatment and is prone to false positive results. These findings suggest that DNA methylation may make a substantial contribution to the growth and dissemination of breast cancer, and also emphasize the importance of accurate detection of DNA methylation level.

3.3 Transcriptional level regulation

At the transcriptional level, multiple transcription factors bind to the E-boxes region in the CDH1 promoter, thereby suppressing E-cadherin transcription. This process activates mesenchymal genes and facilitates the induction of EMT. Among them, transcription factors like SNAIL, ZEB and TWIST play an important role in breast cancer. SNAIL can directly bind to the E-boxes region of the CDH1 promoter, hindering the formation of transcription initiation complexes, inhibiting the transcription of E-cadherin [5]. It can also promote DNA methylation by recruiting chromatin modifying enzymes, further inhibiting E-cadherin expression [6]. The ZEB family (ZEB1 and ZEB2) downregulates the presence of certain components like E-cadherin, tight junctions, and gap junctions, upregulates stromal marker proteins such as vimentin, fibronectin, N-cadherin, and matrix metalloproteinases (MMPs), leading to the loss of epithelial cell polarity and adhesion, inducing EMT and cancer cell invasion [7]. In addition, Zeb1/miR-200 can regulate the Notch signaling pathway through different mechanisms [8]. TWIST, as an element of the transcription factor class of bHLH structure, acts as a transcriptional repressor of E-cadherin, while inducing the expression of N-cadherin and fibronectin. TWIST shows high expression in breast cancer, and its expression correlates with the malignant characteristics of tumors. It is vital to cell invasion, metastasis, and the mechanisms of the resistance against medications [9].

3.4 Protein glycosylation

Abnormal glycosylation modifications make a substantial contribution on the function of E-cadherin, and are one of the important mechanisms for its inactivation. These modifications mainly include O-glycosylation and N-glycosylation. O-glycosylation modification occurs in the cytoplasmic region of E-cadherin, and this abnormal modification can hinder its exocytosis to the cell surface. Research has shown that O-glycosylation modification can attenuate the cell membrane expression of E-cadherin, weakening intercellular adhesion. This weakened adhesion aids in the release of cancer cells from the primary tumor, permitting them to enter the bloodstream or lymphatic circulation, which can contribute to metastasis [10]. N-glycosylation modification occurs at the extracellular site of E-cadherin, which is responsible for interacting with E-cadherin molecules in adjacent cells. Removing polysaccharides at specific locations will reduce protein stability, alter the composition of adhesive connections, and affect intercellular interaction [11]. The study also found that GCNT2 gene, a gene encoding glucosamine (N-acetyl) transferase 2, which functions as an I-branch enzyme, is related to the metastasis phenotype of breast cancer, and its overexpression will cause a reduction in E-cadherin levels and promote the spread of breast cancer [12].

3.5 Inflammation and related signaling pathways

The inflammation related signaling pathway has a key impact on the regulation of E-cadherin expression. Under inflammatory and hypoxic conditions, C/EBPδ can regulate the expression of COX-2, thereby affecting the stability of E-cadherin. Specifically, C/EBPδ, serves as a transcription factor, interacting with the promoter region of COX-2 gene under inflammation and hypoxia stimulation, promoting COX-2 transcription and expression. After the increase of the expression of COX-2, its downstream metabolite PGE2 also increases accordingly. PGE2 activates the AKT signaling pathway and inhibits the activity of GSK3β [13]. After the inhibition of GSK3β activity, the degradation of proteins such as E-cadherin, β-catenin, and p120 catenin decreases, thereby stabilizing intercellular adhesion connections. This is beneficial for tumor cells to survive in the circulatory system and form metastases. At the same time, the expression and activity of COX-2 are regulated by many factors, and its effect on E-cadherin may be different in different breast cancer subtypes.

4 E-cadherin is a potential therapeutic target

E-cadherin deficiency is relatively common in breast cancer. Although E-cad has not yet become a therapeutic target for intervention, many references have shown that it is possible to recover E-cad from its inactivated state through targeted treatment, thereby inhibiting cancer metastasis. At present, the research on targeted treatment of breast cancer targeting E-cadherin continues to advance, mainly focusing on restoring its function, stabilizing its structure, using the synthetic lethal effect, and intervening in related abnormal pathways.

4.1 Targeted therapy for restoring E-cadherin expression

Firstly, E-cadherin expression can be restored by inhibiting the binding of relevant transcription factors to the CDH1 promoter. For example, inhibitors targeting transcription factors like SNAIL, ZEB, and TWIST can be developed to block their interaction with the promoter of E-cadherin and restore its expression [14]. However, transcription factors have diverse functions, and when developing inhibitors, it is necessary to avoid adverse effects on normal cellular physiological functions. Secondly, mutations or high methylation of the CDH1 gene promoter are important reasons for the downregulation of E-cadherin transcription. In response to the above mechanism, demethylation drugs can be developed to act on the highly methylated CDH1 promoter region, restore gene transcription activity by removing methyl groups, and enable normal expression of E-cadherin [15]. At present, there are some demethylating drugs in research and clinical trials, such as azacitidine, which bring hope for the restoration of E-cadherin activation. Intervention in protein glycosylation modification is also a therapeutic strategy for restoring E-cadherin function. For example, within breast cancer cell models, inhibition of specific O-glycosyltransferase significantly increases the localization of E-cadherin at the cell surface, and significantly reduces the migration capacity of cells [10]. For N-glycosylation modification, the glycosylase related to breast cancer metastasis such as GCNT2 was intervened, and the transcription of E-cadherin was increased by suppression of GCNT2, thus inhibiting breast cancer metastasis. For example, reducing the expression of GCNT2 through gene editing or the use of small molecule inhibitors can enhance the activation of E-cadherin and suppress the metastasis of cancer cells [12].

4.2 Targeted therapy for stabilizing the structure of E-cadherin

Throughout tumor progression, E-cadherin is often cleaved into fragments, resulting in impaired function. Research

has shown that cancer cell lines with normal E-cadherin expression have significantly lower invasive ability than those with damaged E-cadherin structure, indicating that stabilizing their structure can effectively inhibit tumor metastasis [15]. Although there is currently no mature and stable treatment method for E-cadherin structure and function, the direction can be explored from its mechanism of action and influencing factors. On the one hand, drugs that can inhibit the activity of related lytic enzymes and reduce the production of E-cadherin fragments can be developed to address the mechanism by which E-cadherin is cleaved in the cytoplasm. On the other hand, by regulating intracellular signaling pathways, the affinity between E-cadherin and catenin is strengthened, stabilizing the complex and allowing it to better connect with the actin cytoskeleton, thus enabling it to function normally.

The Wnt/β - catenin signaling pathway is a major factor in preserving the stability of E-cadherin structure. Under normal physiological conditions, E-cadherin tightly binds with β - catenin to form a stable complex, which further connects to the actin cytoskeleton and plays an important role in maintaining cell polarity and intercellular adhesion. However, when the Wnt signaling pathway is abnormally activated, it can lead to a significant accumulation of β-catenin in the cytoplasm. Excessive accumulation of β-catenin will enter the nucleus, interact with relevant transcription factors, and initiate the transcription process of specific genes [16]. This series of changes causes β-catenin to detach from its binding state with E-cadherin, disrupting the stability of the E-cadherin-β-catenin complex and impairing the structural stability of E-cadherin. In addition, the activation state of the PI3K/Akt signaling pathway has a significant impact on the structural stability of E-cadherin. When the PI3K/Akt signaling pathway is activated, Akt protein is phosphorylated and activated. Activated Akt can phosphorylate β-catenin, leading to a decrease in the binding ability between β-catenin and E-cadherin. The decrease in binding force causes E-cadherin to detach from the cell membrane, thereby disrupting the structural stability of E-cadherin. Research has shown that there is a close relationship between abnormal activation of the PI3K/Akt signaling pathway and downregulation of E-cadherin activation in various tumors, including lung cancer and gastric cancer [17].

4.3 Targeted therapy utilizing E-cadherin synthesis for lethal effects

E-cadherin deficiency may lead to specific metabolic and signaling pathway changes in cancer cells, which can be utilized to design synthetic lethal strategies. For example, for certain small molecule inhibitors targeting MET, ALK, and ROS1 like Crizotinib and Entrectinib, when targeting cancer cells with E-cadherin deficiency or CDH1 gene deficiency, they inhibit specific targets to cause cancer cell death with minimal impact on normal cell. In the ROSALINE study (NCT04551495), a neoadjuvant multicenter trial, the combination of Entrectinib and Letrozole demonstrated promising preliminary therapeutic effects in treating ILC patients [18].

There are also studies on constructing CDH1 gene knockout models in cell lines such as MCF10A and NCI-N87 [19]. Through screening inhibitors targeting autophagy, endocytosis, and sphingolipid metabolism, it was found that blockers targeting sphingolipid metabolism and vesicle transport processes (such as sphingosine kinase 1 inhibitor PF-543, the autophagic inhibitor chloroquine, the endocytosis inhibitor chlorpromazine, and PP1) have synthetic lethal effects on CDH1 deficient MCF10A cells, and some inhibitor combinations have synergistic effects, enhancing the killing effect on CDH1 deficient cells.

4.4 Targeted therapy for E-cadherin related abnormal pathways

Research has identified the E-cadherin-epidermal growth factor receptor (EGFR) heterodimer is a potential target of intervention [4]. The heterodimer formed by E-cadherin and EGFR is instrumental in regulating the normal physiological processes of cells. Extracellular E-cadherin mutations can reduce its affinity for EGFR, disrupt the integrity of E-cadherin-EGFR complexs, increase the proportion of unbound EGFR, and these unbound EGFR are more easily activated by ligands, thereby activating downstream RhoA signaling pathways. The RhoA signaling pathway is crucial for regulating the cytoskeleton, and its activation leads to remodeling of the cytoskeleton, thereby enhancing cellular motility. HER2 is a receptor tyrosine kinase with a structure similar to EGFR. In the E-cad-EGFR pathway, HER2 may affect the signaling pathway by forming heterodimers with EGFR or by affecting the expression and activity of other related proteins. Currently, targeted therapy using HER2 inhibitors, such as trastuzumab, is a crucial approach in the treating breast cancer. Trastuzumab can specifically bind to HER2, block the HER2 signaling pathway, and inhibit the expansion and spread of cancer cells.

5 Summary and Prospect

At present, multiple studies have revealed the molecular mechanisms of E-cadherin protein dysfunction or abnormal expression, as well as its related intracellular signaling pathways. Moreover, research targeting E-cadherin has made some

progress. Although most targeted strategies are still in the laboratory stage, some antibodies and small molecules have been proposed as potential therapeutic strategies.

In the future, the exploration of E-cadherin's role in breast cancer metastasis will continue to be in-depth. First, the specific molecular mechanism underlying E-cadherin dysfunction and its capacity in breast cancer cell metastasis still need further exploration. Especially whether there are differences in the regulatory network of E-cadherin across different breast cancer subtypes remains an area of ongoing concern. Secondly, the clinical translation of E-cadherin targeted therapy still needs to overcome multiple obstacles, such as the effectiveness, side effects, specificity of targeting, and drug resistance issues of E-cadherin targeted therapy. In addition, tumor microenvironment may make a substantial contribution to the functional regulation of E-cadherin. Therefore, future research can combine the research of E-cadherin with tumor immunotherapy and changes in tumor microenvironment, providing a new direction for comprehensive treatment of breast cancer.

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