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Research on the Expression and Clinical Significance of KLF4 and KLF5 in Breast Cancer

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Abstract: As members of the Kruppel-like transcription factor family, KLF4 and KLF5 play critical roles in the development and progression of breast cancer, yet their functions are complex. KLF4 exhibits a dual role: on one hand, it inhibits metastasis by suppressing epithelial-mesenchymal transition (EMT) and activating E-cadherin transcription; on the other hand, it can sustain tumor stem cell properties to promote progression. Its tumor-suppressive or tumor-promoting effects are highly dependent on the status of p21 and the cellular microenvironment. KLF5 is significantly overexpressed in basal-like breast cancer (BLBC) and triple-negative breast cancer (TNBC), promoting tumor proliferation and metastasis by regulating the cell cycle (inducing Cyclin D1 and inhibiting p27), maintaining stemness (activating Slug/Nanog), and forming a positive feedback loop with KLF5-XPO1. Clinical studies have demonstrated that overexpression of KLF4 is associated with poor prognosis in patients, while small-molecule inhibitors targeting KLF5 (such as mifepristone and CDK7/BRD4 inhibitors) can inhibit the growth of triple-negative breast cancer (TNBC). Both KLF4 and KLF5 influence breast cancer heterogeneity and treatment response by regulating key signaling pathways. Future research should further elucidate their environment-dependent mechanisms to develop precise targeting strategies.

Keywords: Breast cancer; KLF4; KLF5; Clinical significance

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1. Introduction

Cancer has become a major public health challenge facing our country at present. Its high incidence and mortality not only pose a serious threat to residents' health but also profoundly affect the sustainable development of the national economy and social stability. Effective prevention and control of cancer is not only an urgent task to comprehensively promote the construction of a healthy China, but also an important focus to achieve high-quality development and ensure people's livelihood and well-being [1]. Breast cancer is the most common malignant tumor

among women worldwide. It exhibits high heterogeneity and is classified into four molecular subtypes based on gene expression patterns: Luminal A, Luminal B, HER-2 overexpressing, and basal-like (including triple-negative breast cancer). Among them, triple-negative breast cancer (TNBC) stands out as the most aggressive subtype of breast cancer due to its lack of ER, PR, and HER2, accounting for 10%-15% of all breast cancer types [2,3]. Despite significant advancements in TNBC treatment, its high molecular heterogeneity and the absence of effective targeted therapies have left chemotherapy as the primary treatment option, resulting in a poor prognosis for TNBC patients. Exploring new drivers and therapeutic targets is crucial for improving outcomes in TNBC patients [4]. Therefore, identifying novel key genes involved in breast cancer progression and elucidating their underlying molecular mechanisms are essential for developing new advanced therapeutic strategies and enhancing the treatment efficacy of breast cancer.

The Kruppel-like factor (KLF) family includes 17 zinc finger transcription factors. Each member contains three evolutionarily conserved Cys2/His2 zinc finger domains located at the C-terminus [5]. These proteins are involved in regulating a wide array of cellular functions, including growth, differentiation, programmed cell death, and migration. Current research indicates that many tumors are associated with KLF [6]. Emerging research indicates that KLF proteins hold the reins in controlling downstream protein expression, which plays a pivotal role in tumor development [7]. Nevertheless, the connection between KLF and cancer is anything but straightforward; distinct KLF family members can wear different hats when influencing the same type of tumor, while a single KLF protein might play completely different cards across various tumor types [8,9]. KLF4 and KLF5 are two key members in current cancer research, especially in the study of breast cancer-related mechanisms. Both play a central role in breast tissue homeostasis by regulating important physiological processes such as cell cycle, differentiation program, and maintaining stem cell properties. In the process of tumorigenesis, the abnormal expression or dysfunction of KLF4 and KLF5 can respectively or synergistically drive cell proliferation runaway, differentiation disorder and metabolic reprogramming, thereby promoting the occurrence, evolution and metastasis of breast cancer.

2. The Role of KLF4

2.1. Introduction to KLF4

KLF4 is one of the key members of the KLF zinc finger transcription factor family, also known as intestinal Kruppel-like factor-rich or epidermal zinc finger protein. It is a protein composed of 470 amino acids and is mainly expressed in gastrointestinal epithelial cells. Its C-terminal contains a nuclear localization signal sequence composed of 20 amino acids, which is responsible for mediating the nuclear localization of the protein. KLF4 exhibits dual functions during development and tumorigenesis, with both transcriptional activation and transcriptional inhibition activities. Through the regulation of multiple downstream target genes, KLF4 participates in essential physiological processes, including cell proliferation, differentiation, and apoptosis. This allows it to broadly influence cell fate and plays a significant role in the initiation and progression of various human cancers. Research indicates that KLF4 functions as a tumor suppressor in several cancers, such as colon, bladder, prostate, and gastric cancer [10,11], but paradoxically acts as an oncogene in oral and cutaneous squamous cell carcinomas [12,13].

2.2. Expression and mechanism of KLF4 in breast cancer

In breast cancer, KLF4 can simultaneously exhibit tumor-suppressive and oncogenic functions [14]. Therefore, the

role of KLF4 is highly dependent on the cellular and tissue context, and its specific role in breast cancer remains controversial. KLF4 can promote stem cell characteristics in breast cancer cells, which is consistent with its function as a pluripotency transcription factor [15]. According to reports, KLF4 also suppresses metastasis in breast cancer by preventing invasion, migration, and proliferation while encouraging apoptosis and cell cycle arrest [16,17]. KLF4 is also vital in regulating epithelial-mesenchymal transition (EMT), a key driver of metastasis. In breast cancer, KLF4 functions as a tumor suppressor by inhibiting metastasis. It promotes an epithelial cell state by upregulating E-cadherin and repressing mesenchymal genes [18]. Furthermore, in vivo studies confirm that KLF4 reduces both primary tumor growth and metastatic spread [19].

Some studies suggest that KLF4 may function as an oncogene in breast cancer [20,21]. For instance, knocking down KLF4 can significantly decrease the proportion of breast cancer stem cells, thereby inhibiting tumor formation and metastasis. KLF4 is highly expressed in primary ductal breast carcinomas [22] and exerts oncogenic effects in breast cancer, depending on the status of p21Cip1 [23]. Additionally, recent reports have revealed that ATXN3 promotes breast cancer metastasis by deubiquitinating KLF4 [24]. Crucially, Zou et al. established that elevated KLF4 expression correlates with poorer breast cancer patient outcomes [9]. In breast cancer, KLF4 has been proven to play an oncogene function and promote tumor progression. However, many studies in recent years have also shown that its overexpression can inhibit the growth and metastasis of breast cancer under certain conditions, reflecting a complex dual regulatory role [25]. Overexpression of KLF4 inhibits the growth, metastasis, and invasion of breast cancer cells by suppressing Snail, estrogen receptor, and epidermal growth factor receptor [26]. E-cadherin (CDH1) has been found to be a direct transcriptional target of KLF4 in earlier research [27]. In MDA-MB-231 cells, overexpression of KLF4 is sufficient to increase CDH1 expression and decrease invasion and migration. This modulation is crucial for preserving the phenotype of normal mammary epithelial cells. Moreover, KLF4 expression is adequate to stop the spread of metastases in vivo. In related research, Tiwari et al. discovered that KLF4 is a key regulator of EMT, transcriptionally inhibiting mesenchymal genes like VIM, CTNNB1, and CDH2 and transcriptionally activating epithelial genes like CDH1 and END1[28]. Therefore, the absence of KLF4 leads to the induction of the EMT program in breast cancer cells. These studies emphasize that KLF4 plays a key role in breast cancer. It co-inhibits the malignant biological behavior of invasive breast cancer by coordinating the activation and inhibition of different gene targets. Overall, this research strengthens the understanding that KLF4's function varies by biological setting. Its action as either a gene activator or repressor is shaped by the specific cell type involved, and its precise role in breast cancer continues to be unresolved.

2.3. Clinical significance of KLF4

Current research suggests that the tumor-suppressive effect of KLF4 is primarily achieved by inhibiting the process of epithelial-mesenchymal transition, while its tumor-promoting effect is related to its ability to maintain telomerase activity in both normal stem cells and cancer stem cells, thereby preserving cancer stem cell-like properties. Several recent studies have also shown that inhibiting KLF4 expression can suppress the stem cell characteristics of breast cancer cells and enhance the therapeutic effects of drugs. Therefore, small-molecule inhibitors that target the KLF4 protein in precancerous lesions, either alone or in combination with chemotherapy, could be valuable for cancer prevention and treatment. Moving forward, a comprehensive understanding of KLF4's signaling networks and molecular regulatory mechanisms across different tissues during precancerous progression will help clarify its context-dependent role, as either a "tumor suppressor" or "tumor promoter," at specific disease stages. This knowledge will also provide an important theoretical basis for designing effective

strategies to intervene in breast cancer.

3. Role of KLF5

3.1. Introduction to KLF5

KLF5 is a transcription factor belonging to the Kruppel-like factor family. KLF5 exhibits specific expression across a variety of cells and plays a pivotal role in development, metabolism, and cellular pluripotency. Additionally, KLF5 promotes the progression and metastasis of diverse tumors. From a structural standpoint, KLF5 contains a C-terminal triple zinc finger domain that enables it to bind specifically to DNA sequences such as CACC or GC boxes. This binding regulates the expression of downstream genes, including p27, cyclin D1, and Slug, that influence cancer pathways. KLF5 plays a key role in the initiation and advancement of numerous cancers by affecting processes like tumor stemness, cell proliferation, invasion, metastasis, and the tumor microenvironment. Overall, KLF5 acts as a promoter in a variety of cancer types.

3.2. Expression and mechanism of KLF5 in breast cancer

KLF5 is an oncogenic transcription factor in Basal-Like Breast Cancer (BLBC). Despite this, the precise function of KLF5 and its heightened presence in BLBC remains incompletely elucidated. In TNBC, KLF5 also exhibits high expression levels. In tumor specimens from patients with TNBC, there is a positive correlation between the expression of KLF5 and LncRNA PVT1. Moreover, LncRNA PVT1 can regulate TNBC through the KLF5/beta-catenin signaling pathway, making it a potential therapeutic target for TNBC.

Increasing evidence suggests that KLF5 shares similar oncogenic mechanisms with KLF4. KLF5 maintains cellular stemness by inducing the transcription of Slug 7 and Nanog [30]. In line with these findings, KLF5 drives breast cancer progression by accelerating the G1/S phase transition of the cell cycle. It promotes tumor cell proliferation and cycle advancement through the transcriptional activation of genes such as FGF-BP1, mPGES1, TNFAIP2, and Cyclin D1. Concurrently, KLF5 suppresses the expression of the cell cycle inhibitors p21 and p27 [31]. The research team led by Researcher Chen Ceshi discovered a novel mechanism by which KLF5 promotes the proliferation of BLBC cells through inducing the transcription of the XPO1 gene. XPO1, in turn, increases KLF5 expression by enhancing the nuclear export of FOXO1 mRNA. Consequently, a positive feedback regulatory loop is established between KLF5 and XPO1 in BLBC. Meanwhile, in BLBC, KLF5 not only promotes the transcription of the CCND1 gene (encoding the Cyclin D1 protein) and the phosphorylation of RB1 but also facilitates the transcription of the XPO1 gene and the nuclear export of RB1. These two mechanisms collectively contribute to the inactivation of RB1 within BLBC cells, thereby accelerating the progression of the cell cycle [32]. Recently, researchers have demonstrated that YB-1 and KLF5, acting as co-transcriptional factors, regulate a series of oncogenes, including KRT16 and Ly6D, to promote the proliferation of BLBC cells [33].

3.3. Clinical significance of KLF5

A growing number of studies are exploring KLF5 as a therapeutic target in cancer, given its pivotal role in tumor initiation and progression. For example, mifepristone has been demonstrated to suppress KLF5 expression via the induction of miR-153, leading to the inhibition of proliferation, survival, and cancer stem cell populations in triple-negative breast cancer cells [34]. On top of conventional pharmaceutical approaches, our team has uncovered that both the CDK7 inhibitor THZ1 and the BRD4 inhibitor JQ-1 pack a punch when it comes to dialing down

KLF5 transcription and stifling the in vitro growth of TNBC cells [35]. What's more, glucocorticoids kickstart KLF5 expression via the glucocorticoid receptor (GR), which in turn makes triple-negative breast cancer cells tough as nails when it comes to docetaxel and cisplatin treatment. KLF5 shows up in abundance in basal-like breast cancer cells and goes hand in hand with grim patient outcomes and brief periods before relapse. The deubiquitinating enzyme BAP1 stabilizes KLF5, promoting the growth and metastasis of basal-like breast cancer. Therefore, targeting and inhibiting the BAP1-KLF5 axis represents an effective strategy for treating basal-like breast cancer. In summary, the transcription factor KLF5 plays a significant role in maintaining mammary stem cells and mammary gland development. Moreover, the discovery of its driving role in breast cancer occurrence provides further supporting evidence for exploring KLF5 as a clinical target for breast cancer therapy.

4. Conclusion

In summary, KLF4 and KLF5 are closely related to the initiation and progression of breast cancer, serving as regulatory factors for cell proliferation, differentiation, and transformation. Currently, numerous studies have elucidated the mechanisms of action of KLF4 and KLF5, which regulate the initiation and progression of breast cancer by intervening in gene expression processes at the transcriptional initiation level. However, this process is highly complex and influenced by multiple factors, such as the external environment, the stability of the internal microstate, and the intrinsic states of KLF4 and KLF5 themselves, all of which play distinct roles. Any change in any factor or step could potentially lead to uncontrolled gene expression and altered cell proliferation, ultimately resulting in the onset of breast cancer. To date, the mechanisms underlying the involvement of the typical zinc finger transcription factors KLF4 and KLF5 in breast cancer initiation still require further exploration and research.

Disclosure statement

The authors declare no conflict of interest.

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