KDM5 Family as a Therapeutic Target in Breast Cancer: Mechanisms and Clinical Potential

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Keywords: KDM5 Family; Breast Cancer; Epigenetic Regulation; Targeted Therapy

Abstract: The KDM5 family is an epigenetic regulator with histone demethylase activity, consisting of four members, KDM5A-D. Through the JmjC domain, it removes H3K4me2/me3 modifications to regulate gene expression. It is abnormally expressed in breast cancer (especially KDM5A/B in TNBC and HER2-positive subtypes), and by silencing tumor suppressor genes and activating oncogenes, it regulates the cell cycle, promotes EMT, and disrupts the tumor microenvironment, thereby driving breast cancer proliferation, invasion, and drug resistance. Preclinical studies have shown that KDM5 inhibitors can suppress breast cancer cell growth, enhance the efficacy when combined with chemotherapy and targeted drugs, and that subtype-targeted therapies based on KDM5 expression and biomarker-guided personalized strategies have translational potential. However, current challenges include insufficient inhibitor specificity and difficulties in target selection due to breast cancer heterogeneity. In the future, it is necessary to develop highly specific inhibitors and optimize combination strategies to promote their integration into precision therapy systems for breast cancer.

1. Introduction

1.1. Epidemiology and Therapeutic Challenges of Breast Cancer

Breast cancer is the most common malignant tumor among women worldwide. According to statistics from the International Agency for Research on Cancer of the World Health Organization, there were more than 2.3 million new breast cancer cases globally in 2022, accounting for 24% of newly diagnosed malignant tumors in women, with nearly 700,000 deaths, and the incidence in some regions continues to rise year by year [1]. At present, clinical treatment is mainly based on surgical resection, combined with chemotherapy, endocrine therapy, and HER2-targeted therapy, but many problems are still there: patients with hormone receptor–positive breast cancer are prone to drug resistance after long-term endocrine therapy; triple-negative breast cancer lacks obvious therapeutic targets, resulting in limited treatment options; and most advanced patients develop recurrence and distant metastasis, leading to a significant decline in 5-year survival rates. Existing treatment regimens also have problems such as large individual differences in response and significant toxic side effects, showing the pressing necessity to explore new specific therapeutic targets to improve patient prognosis.

1.2. Biological Background of the KDM5 Family

The KDM5 family is a group of epigenetic regulatory proteins with histone demethylase activity, also known as the JARID1 family, including four members: KDM5A (JARID1A), KDM5B (JARID1B), KDM5C (JARID1C), and KDM5D (JARID1D) [2]. Its core function is to specifically remove dimethylation (H3K4me2) and trimethylation (H3K4me3) modifications of lysine 4 on histone H3 through the conserved JmjC catalytic domain. These two modifications are usually associated with transcriptional activation at gene promoter regions; therefore, the KDM5 family can influence downstream gene expression by regulating chromatin states. In normal physiological processes, the KDM5 family is involved in the regulation of embryonic development, cell differentiation, and proliferation. Under pathological conditions, studies have found that members

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of this family are abnormally overexpressed in breast cancer and other malignant tumors, and their expression levels are closely related to tumor aggressiveness and poor patient prognosis which provided a potential epigenetic target for breast cancer therapy.

2. Mechanisms of the KDM5 Family in Breast Cancer

2.1. Structural and Functional Basis of the KDM5 Family

2.1.1. Histone Demethylase Activity of the JmjC Catalytic Domain

The core function of the KDM5 family depends on the JmjC catalytic domain, which requires cofactors such as α-ketoglutarate and Fe2+ to specifically remove H3K4me2/me3 modifications [3]. This process reduces transcriptional activation signals at gene promoter regions, thereby regulating downstream gene expression, and represents a key step in KDM5-mediated epigenetic regulation.

2.1.2. Regulatory Mechanisms of Auxiliary Domains (PHD, BTB, etc.) in Chromatin Binding

The PHD domain can recognize and combine specific histone or DNA modification sites, helping KDM5 accurately localize to target chromatin regions [4]; the BTB domain mainly participates in protein–protein interactions, promoting the formation of complexes between KDM5 and other epigenetic regulators. These domains work together to enhance the binding efficiency of KDM5 to chromatin and ensure precise execution of its demethylase function.

2.1.3. Subcellular Localization and Substrate Specificity of KDM5 Family Members

Most KDM5 family members are localized in the nucleus, where they directly bind chromatin to exert their functions, with only rare transient appearances in the cytoplasm. In terms of substrates, all four members primarily target H3K4me2/me3, but subtle differences exist. For example, the substrate range of KDM5D is more restricted, acting on specific H3K4 modification sites only in certain cell types, providing the basis for functional division of labor among family members.

2.2. Expression Regulation and Functional Abnormalities of the KDM5 Family in Breast Cancer

2.2.1. Expression Patterns of the KDM5 Family in Breast Cancer Tissues

Expression of KDM5 family members varies by subtype: KDM5A and KDM5B are generally highly expressed in triple-negative breast cancer (TNBC) and HER2-positive breast cancer, while KDM5C and KDM5D show lower expression, with slight elevation only in some hormone receptor–positive breast cancers [5]. Clinical sample testing shows that high expression of KDM5A/B is often associated with higher tumor grade and lymph node metastasis, as well as shortened disease-free survival, making them potential indicators of poor prognosis.

2.2.2. Regulation of KDM5 by Oncogenic Signaling Pathways

Key oncogenic pathways in breast cancer can directly regulate KDM5 expression: the ER pathway promotes transcription of KDM5B through estrogen binding to its promoter region; the PI3K/Akt pathway enhances the protein stability and nuclear localization of KDM5A through phosphorylation; MYC can bind to the promoters of KDM5A/B to activate their expression. Dysregulation of these pathways further amplifies the oncogenic effects of KDM5.

2.2.3. Association between Aberrant KDM5 Expression and Malignant Phenotypes of Breast Cancer

Aberrant KDM5 expression drives malignant progression of breast cancer: high expression of KDM5A accelerates G1/S phase transition, promoting tumor proliferation; KDM5B enhances the expression of epithelial–mesenchymal transition (EMT)-related genes, increasing tumor invasiveness and metastatic potential; aberrant KDM5C expression reduces breast cancer cell sensitivity to endocrine therapy, aggravating drug-resistant phenotypes and directly impairing treatment outcomes [6].

2.3. Molecular Mechanisms by Which the KDM5 Family Regulates Breast Cancer

2.3.1. Epigenetic Regulation: Chromatin Remodeling and Gene Transcription Activation/ Repression

The KDM5 family remodels chromatin by regulating histone modifications: removal of H3K4me2/me3 by the JmjC domain results in chromatin condensation, leading to silencing of tumor suppressor genes such as BRCA1 and PTEN. Inactivation of these genes weakens DNA damage repair and growth inhibitory functions [7]. KDM5 can also interact with other epigenetic regulators (e.g., HDAC) to form complexes that activate transcription of oncogenes such as MYC and ERα. Through the dual actions of repressing tumor suppressors and activating oncogenes, KDM5 promotes abnormal proliferation of breast cancer cells.

2.3.2. Regulation of the Cell Cycle and Apoptosis

In the cell cycle, the KDM5 family interferes with normal processes by targeting cell cycle regulatory genes: KDM5A suppresses expression of p21 (a cyclin-dependent kinase inhibitor), releasing inhibition of CDK2 (cyclin-dependent kinase 2), thereby accelerating G1-to-S phase transition and shortening the proliferation cycle [8]. In apoptosis regulation, KDM5B silences the pro-apoptotic gene Bax while upregulating the anti-apoptotic gene Bcl-2, reducing activation of the caspase apoptosis pathway. This enables breast cancer cells to evade apoptotic surveillance and achieve malignant proliferation.

2.3.3. Tumor Microenvironment and Metastasis-Related Pathways

The KDM5 family regulates key pathways affecting the tumor microenvironment and metastasis: KDM5B activates EMT-related transcription factors Snail and Twist, promoting the loss of epithelial characteristics and acquisition of mesenchymal phenotypes in breast cancer cells, thereby enhancing invasiveness. KDM5A upregulates VEGF (vascular endothelial growth factor) expression, inducing tumor angiogenesis and providing nutrient channels for metastasis. KDM5 can also regulate secretion of cytokines such as IL-6 by cancer-associated fibroblasts (CAFs), creating a pro-metastatic microenvironment and accelerating distant colonization of cancer cells.

3. Clinical Potential of the KDM5 Family as a Therapeutic Target in Breast Cancer

3.1. Preclinical Evidence: From Cell Models to Animal Models

3.1.1. Design and Screening of KDM5 Inhibitors

Current KDM5 inhibitor design is mainly centered on the JmjC catalytic domain: by analyzing the binding pattern of this domain with its substrates, high-throughput screening technology is used to identify small molecules from compound libraries that competitively bind to the α-ketoglutarate/Fe2+ binding site. Subsequent structural optimization improves specificity (such as reducing inhibition of other JmjC family enzymes). Several candidate molecules have been developed, including the small-molecule inhibitor CPI-455 targeting KDM5A and peptide inhibitors targeting KDM5B. Some have already entered cell-based activity validation stages, laying the foundation for further research.

3.1.2. In Vitro Experiments: Effects of KDM5 Inhibition on Proliferation and Apoptosis of Breast Cancer Cells

In vitro experiments show that KDM5 inhibitors significantly suppress breast cancer cell proliferation: in TNBC cell lines (such as MDA-MB-231), treatment with CPI-455 reduced the proportion of EdU-positive cells by more than 40%, with cell cycle arrest at the G1 phase. Inhibitors restored expression of tumor suppressor genes p21 and Bax, activated caspase-3/7 apoptotic pathways, and increased the apoptosis rate by 2–3 times. In hormone receptor–positive cell lines (such as MCF-7), KDM5B inhibitors also enhanced sensitivity to tamoxifen, reducing the proportion of resistant cells.

3.1.3. In Vivo Experiments: Antitumor Effects of KDM5 Inhibitors in Xenograft Models

Xenograft models in nude mice confirmed the in vivo activity of KDM5 inhibitors: after inoculation with MDA-MB-231 cells, weekly injection of a KDM5A inhibitor reduced tumor volume by 50%–60% and tumor weight by around 45% after 4 weeks compared to controls. Immunohistochemistry revealed increased H3K4me3 levels, decreased Ki-67 positivity (a proliferation marker), and elevated Cleaved-caspase-3 (an apoptosis marker) [9]. No significant effects were observed on body weight or liver/kidney function, providing preliminary evidence of safety.

3.1.4. Combination Therapy Strategies: Synergy of KDM5 Inhibitors with Chemotherapy/ Targeted Drugs

Preclinical studies confirmed that KDM5 inhibitors can enhance the efficacy of chemotherapy and targeted therapies: combined with paclitaxel, KDM5 inhibitors prevented silencing of DNA repair genes (e.g., BRCA1), increasing sensitivity of breast cancer cells to paclitaxel-induced DNA toxicity and boosting killing efficiency by 30%. When used in combination with trastuzumab, it can reverse the drug-resistant phenotype of HER2-positive cells and reduce the formation of drug-resistant clones.When used in combination with trastuzumab, it can reverse the drug-resistant phenotype of HER2-positive cells and reduce the formation of drug-resistant clones. When used in combination with HDAC inhibitors, it further amplifies the inhibito ry effect on tumor cells by synergistically remodeling the chromatin, providing experimental evidence for combined treatment.When used in combination with HDAC inhibitors, it further amplifies the inhibitory effect on tumor cells by synergistically remodeling the chromatin, providing experimental evidence for combined treatment.

3.2. Potential Therapeutic Strategies and Clinical Translation Directions

3.2.1. Monotherapy: Targeting Breast Cancer Subtypes with High KDM5 Expression

Monotherapy can focus on breast cancer subtypes with high KDM5A/B expression, such as TNBC and HER2-positive breast cancer. In these subtypes, abnormal KDM5 expression directly drives tumor proliferation. Using KDM5 inhibitors alone can precisely block its epigenetic regulatory functions, restore tumor suppressor gene expression, and induce cell cycle arrest. In clinical translation, stratification should be based on tumor tissue KDM5 expression levels, prioritizing high-expression patients. This avoids ineffective treatment in low-expression cases and reduces unnecessary drug toxicity, providing a new monotherapy option for TNBC, which currently lacks defined therapeutic targets.

3.2.2. Combination Therapy: Enhancing Sensitivity to Existing Treatments

Combination therapy can specifically address resistance to existing treatments: in hormone receptor–positive breast cancer, KDM5 inhibitors combined with tamoxifen or fulvestrant can reverse KDM5-mediated endocrine resistance, increasing responsiveness to hormonal blockade. In HER2-positive breast cancer, combination with trastuzumab weakens KDM5's co-activation of the HER2 pathway, enhancing targeted therapy efficacy. In TNBC, combination with paclitaxel or other chemotherapeutics amplifies DNA damage effects and boosts cytotoxicity. Clinical translation requires subtype-specific combination regimens, using low-dose combinations to balance efficacy and toxicity, thereby improving patient tolerance.

3.2.3. Epigenetic Combination Strategies: KDM5 Inhibitors with HDAC Inhibitors

Combining KDM5 inhibitors with HDAC inhibitors (histone deacetylase inhibitors) enhances therapeutic effects via synergistic chromatin regulation: KDM5 inhibition maintains transcriptionally open regions of tumor suppressor genes, while HDAC inhibitors preserve histone acetylation. Together, they activate tumor suppressors (e.g., p21, BRCA1) and simultaneously suppress oncogenes (e.g., MYC). Clinically, this strategy is especially suitable for TNBC with pronounced epigenetic dysregulation and allows lower single-agent doses, reducing hematologic

toxicity and gastrointestinal side effects, thus improving treatment safety.

3.3. Biomarkers and Prospects for Personalized Therapy

3.3.1. Clinical Value of KDM5 Family Members as Prognostic Biomarkers

Clinical analyses show that high KDM5A/B expression is an important indicator of poor prognosis: in TNBC and HER2-positive breast cancer, patients with high KDM5A/B expression had >30% shorter 5-year disease-free survival compared to low-expression patients, and expression was significantly associated with high tumor grade and lymph node metastasis. Conversely, low KDM5C expression indicates a higher risk of endocrine therapy resistance in hormone receptor–positive breast cancer, serving as a convenient molecular marker for clinical prognosis evaluation.

3.3.2. Development of Predictive Biomarkers for Treatment Response

Current efforts focus on two classes of predictive biomarkers: (a) histone modification levels (e.g., H3K4me3), where patients with high baseline levels respond better to KDM5 inhibitors; and (b) expression of downstream target genes (e.g., p21, Bax), where low pre-treatment expression correlates with greater benefit from inhibitors. These biomarkers can help identify patients most likely to benefit, avoid ineffective treatments, and promote implementation of personalized medicine.

4. Challenges and Future Perspectives of Targeting the KDM5 Family in Breast Cancer Therapy

4.1. Challenges in Clinical Translation

4.1.1. Specificity Issues of KDM5 Inhibitors

The catalytic regions of the KDM5 family share high sequence similarity with other JmjC domain–containing histone demethylases (such as the KDM2 and KDM6 families). Current small-molecule inhibitors are prone to off-target binding, inhibiting non-target enzyme activities and causing epigenetic dysregulation in normal cells, such as affecting hematopoietic stem cell differentiation or neuronal functions, leading to side effects including anemia and neurotoxicity. Within the KDM5 family itself (A–D), structural conservation is high, making it difficult for most inhibitors to selectively target the strongly oncogenic KDM5A/B without interfering with the physiological roles of KDM5C/D in normal tissues, thereby reducing therapeutic safety.

4.1.2. Target Selection Challenges Due to Breast Cancer Heterogeneity

The high heterogeneity of breast cancer complicates KDM5 target selection. KDM5 functions differ significantly across subtypes: TNBC is primarily driven by KDM5A/B, while in Luminal subtypes, KDM5C may be associated with drug resistance [10]. Using KDM5A/B as a uniform target could render treatment ineffective in Luminal patients. Furthermore, intratumoral heterogeneity exists within the same subtype; in a single patient, different lesions may show varying KDM5 expression levels and functional states. Some lesions may not depend on KDM5 for survival, resulting in residual disease after treatment and increased recurrence risk.

4.2. Mechanisms of Drug Resistance and Counterstrategies

4.2.1. Epigenetic Mechanisms of Resistance to KDM5 Inhibitors

Breast cancer cells can develop resistance to KDM5 inhibitors via epigenetic remodeling: (a) compensatory activation of histone methyltransferases (e.g., MLL1, MLL2), which increase H3K4me3 levels and counteract the demethylation blockade, sustaining oncogene transcription; (b) alterations in chromatin remodeling complexes (e.g., SWI/SNF), which adjust chromatin accessibility, enabling oncogenic pathways to be activated independently of H3K4 modifications; (c) long-term drug exposure induces “epigenetic memory,” where DNA methylation fixes expression patterns of resistance-related genes, rendering inhibitors ineffective [11].

4.2.2. Potential Combination Strategies to Overcome Resistance

Targeted combination therapies can be designed against resistance mechanisms: co-treatment with MLL inhibitors can block compensatory H3K4me3 elevation and restore KDM5 inhibitor efficacy; combining with EZH2 inhibitors (another class of epigenetic regulators) can remodel chromatin and weaken adaptive resistance; co-administration with PI3K/Akt inhibitors can suppress resistance-related signaling pathways and reduce compensatory activation triggered by KDM5 inhibition. These strategies can disrupt resistance mechanisms at multiple levels, prolonging treatment response.

4.3. Future Research Directions and Clinical Application Prospects

Future research should prioritize overcoming current technical bottlenecks. First, the development of highly specific KDM5 inhibitors: using cryo-EM to resolve binding conformations between KDM5 subtypes and substrates, followed by structure-based drug design (SBDD) to optimize small-molecule structures, or employing PROTAC technology to achieve selective degradation of KDM5A/B, thereby reducing off-target effects. Second, combining single-cell sequencing and spatial transcriptomics to dissect functional heterogeneity of KDM5 across breast cancer subtypes, clarifying core dependency targets in each subtype and resolving target selection challenges.

At the clinical application level, efforts should be made to promote the coordinated implementation of biomarkers, drugs, and treatment plans. On one hand, companion diagnostic kits for KDM5 expression and H3K4me3 levels should be developed for patient stratification prior to treatment, ensuring drugs are precisely administered to those most likely to benefit. On the other hand, new combination approaches should be explored, such as KDM5 inhibitors with PD-1/PD-L1 inhibitors. KDM5 inhibition can remodel the tumor immune microenvironment, for example, by increasing T-cell infiltration, thereby enhancing immunotherapy efficacy—particularly promising in immunologically “cold” TNBC. Early-phase clinical trials focusing on high-KDM5-expression subtypes, such as phase II basket trials, should be launched to accumulate clinical evidence and gradually incorporate epigenetic-targeted therapy into standard breast cancer treatment, ultimately providing patients with more precise therapeutic options.

5. Conclusion

The KDM5 family, as key epigenetic regulators, plays a central role in the initiation and progression of breast cancer: through the JmjC domain, they remove H3K4me2/me3 modifications, silence tumor suppressor genes, activate oncogenes, regulate cell cycle progression, promote EMT and tumor microenvironment disruption, thereby driving breast cancer proliferation, invasion, and drug resistance. Preclinical studies have confirmed that KDM5 inhibitors can suppress breast cancer cell growth and enhance the efficacy of chemotherapy and targeted therapies. Moreover, monotherapy/combination therapies targeting high KDM5 expression subtypes, as well as biomarker-guided personalized approaches, provide a direction for clinical translation.

The off-target risks of KDM5 inhibitors, the challenges in target selection due to breast cancer heterogeneity, and the mechanisms of drug resistance still need to be overcome. Future efforts focusing on the development of highly specific inhibitors, biomarker-based stratified treatment, and multi-target combination strategies hold promise for integrating KDM5-targeted therapy into precision breast cancer treatment, offering new pathways to improve patient outcomes and address unmet clinical needs.

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