SMARCD3 co-suppresses ERα signaling pathway mediates tumor progression and its role in anti-estrogen resistance in breast cancer

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Abstract

Estrogen receptor α (ERα) is the principal oncogenic driver in ER-positive breast cancer. This study identifies SMARCD3, a constituent of the SWI/SNF chromatin remodeling complex, as a novel transcriptional co-repressor of ERα. SMARCD3 is significantly downregulated in ER+ tumors, and its low expression correlates with adverse clinical outcomes. Functionally, SMARCD3 acts as a tumor suppressor, impeding cancer cell proliferation and sensitizing cells to endocrine therapy. Mechanistically, SMARCD3 serves as a scaffold, recruiting HDAC1, HDAC2, and the E3 ubiquitin ligase TRIM21 to form a multi-protein inhibitory complex. This complex coordinately attenuates ERα-driven transcription and facilitates TRIM21-mediated ubiquitination and degradation of ERα, a process dependent on the SWIB domain of SMARCD3.
Thus, we delineate a dual-transcriptional and post-translational mechanism through which SMARCD3 constrains ERα oncogenic activity, revealing a promising therapeutic target for overcoming endocrine resistance.

Introduction

Breast cancer is the second most common female malignancy globally, with approximately 70% cases being ERα-positive. While endocrine therapy targeting ERα significantly improves survival, acquired resistance remains a major clinical obstacle. Understanding the molecular mechanisms underlying ERα signaling dysregulation is crucial for developing improved treatment strategies.
ERα functions as a master transcriptional regulator of proliferation genes in breast cancer. Its activity is precisely controlled through coordinated interactions with coregulator complexes. Identifying novel ERα coregulators represents a promising approach to overcome therapy resistance and improve patient outcomes.
SMARCD3 is an essential subunit of the SWI/SNF chromatin remodeling complex with established roles in metabolic regulation. However, its function in ERα-positive breast cancer progression remains largely unexplored. Investigating SMARCD3-ERα crosstalk may reveal new insights into hormone-dependent tumorigenesis.
We identify SMARCD3 as a previously unrecognized ERα corepressor in breast cancer. Mechanistically, SMARCD3 recruits HDAC1/2 and TRIM21 to suppress ERα transcriptional activity and promote its ubiquitin-mediated degradation through the SWIB domain. These findings establish SMARCD3 as a key negative regulator of ERα signaling and propose new therapeutic avenues for overcoming endocrine resistance.

Methods and Materials

Clinical Samples & Data
Human breast cancer samples were obtained from the First Affiliated Hospital of China Medical University and Liaoning Cancer Hospital, with Ethics Committee approval and patient consent. RNA-seq data from 907 ERα+ breast cancers and 154 normal tissues were analyzed using TCGA via cBioPortal. Survival analysis was performed with Kaplan-Meier Plotter.
Mouse Xenograft Experiments
All procedures were approved by the Animal Ethics Committee of China Medical University. 4–6-week-old mice received subcutaneous injections of stable MCF-7 cells (1×10^7 cells in 100 μL PBS/Matrigel mixture) into bilateral axillary regions. Tumor dimensions were measured weekly, and volume was calculated as 0.5 × Length × Width². After one month, tumors were excised and weighed.
Chromatin Immunoprecipitation (ChIP)
Following transfection and estrogen stimulation, cells were fixed with 1% formaldehyde and the reaction was quenched with 2.5 M glycine. Chromatin was fragmented by sonication and immunoprecipitated overnight with indicated antibodies. After extensive washes with low-salt, high-salt, LiCl wash buffers, and TE buffer, the protein-DNA complexes were eluted, reverse cross-linked, and purified for subsequent analysis.
Statistical analyses
Data analysis was performed using GraphPad Prism 8.0 and SPSS 22.0, with results expressed as mean ± SD. Group comparisons were conducted using unpaired Student's t-test or one-way ANOVA, as appropriate. Survival curves were analyzed by Kaplan-Meier method with log-rank test. A p-value < 0.05 was considered statistically significant.

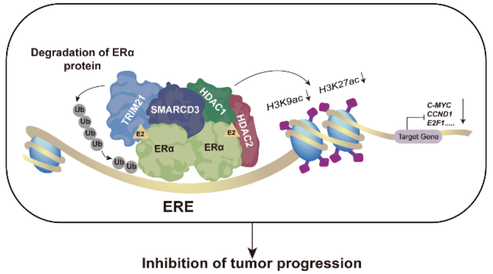


Figure 1 Mechanism of SMARCD3 action in the ERα signaling pathway.

Results

Expression, Prognostic Value and Biological Function of SMARCD3 in ER-positive Breast Cancer
SMARCD3 is significantly downregulated in ERα-positive breast cancer and its low expression correlates with poor patient survival and elevated ERα levels. Functionally, SMARCD3 acts as a tumor suppressor by inhibiting cancer cell proliferation in vitro and tumor growth in vivo, demonstrating its critical role in restraining ERα-positive breast cancer progression.

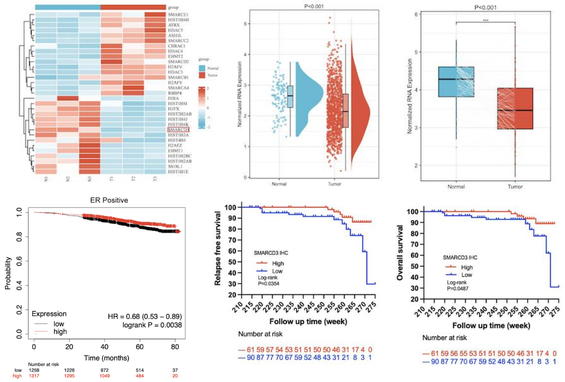
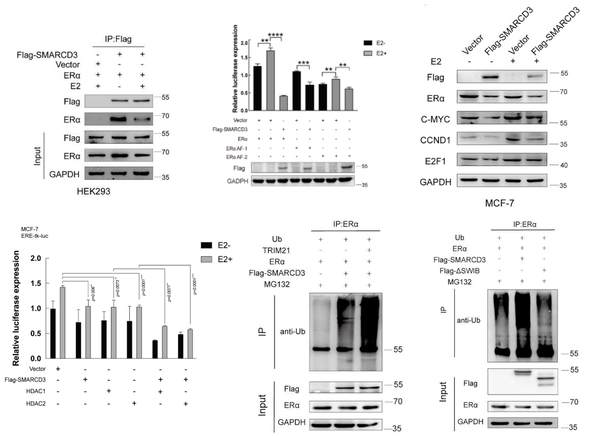


Figure 2. SMARCD3 downregulation is associated with poor prognosis in ER positive breast cancer

How SMARCD3 Modulates Breast Cancer Progression Through ERα Interaction.
SMARCD3 physically interacts with ERα and suppresses its transcriptional activity mediated by both AF1 and AF2 domains. This repressive function remains unaffected by deletion of the SWIB/MDM2 domain, indicating distinct regulatory mechanisms for transcriptional repression and protein degradation. Concurrently, SMARCD3 scaffolds the E3 ubiquitin ligase TRIM21 to promote ERα ubiquitination and degradation, a process potentially mediated by its SWIB/MDM2 domain.

Figure 3. SMARCD3 Mediates Coordinated Transcriptional and Post-translational Suppression of ERα



SMARCD3 mediates endocrine therapy resistance in breast cancer as a novel ERα coregulator.

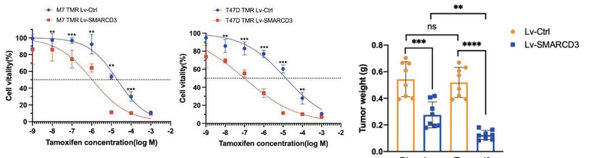


Figure 4. SMARCD3 Enhances Endocrine Therapy Response in ERα-Positive Breast Cancer

Discussion & Conclusions

This study identifies SMARCD3 as a novel tumor suppressor and ERα corepressor in ER-positive breast cancer. SMARCD3 executes its function through dual mechanisms: it recruits HDAC1/2 to suppress ERα transcriptional activity via histone deacetylation, while simultaneously scaffolding TRIM21 to promote ERα ubiquitination and degradation through its SWIB domain. Functionally, SMARCD3 overexpression inhibits tumor growth and restores endocrine therapy sensitivity. Our findings thus establish SMARCD3 as a key regulator of ERα signaling and propose a promising therapeutic strategy for overcoming endocrine resistance..

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