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Lamotrigine Inhibits Breast Cancer Progression Through FoxO3a/TXNIP axis

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INTRODUCTION & AIM

Endocrine resistance remains a major challenge in the treatment of estrogen receptor α positive (ERα+) breast cancer (BC), highlighting the need for novel strategies to overcome hormonal therapy resistance (1). The antiepileptic drug Lamotrigine (LTG), previously shown to induce the tumor suppressor FoxO3a in Tamoxifen-sensitive and resistant ER+ BC (2), may serve as a potential adjuvant. Since Thioredoxin-Interacting Protein (TXNIP) is a downstream target of FoxO3a, this study investigated whether LTG exerts its antitumor anctivity by modulating the FoxO3a/TXNIP axis.

METHODS

ER+ MCF-7 cells, their tamoxifen-resistant cells (MCF-7/TR), and patient-derived metastatic BC cells were used as experimental models. Gene and protein expression were evaluated by RT-qPCR, Western Blotting, ChIP assay, while ChIP-seq analyses were used to assess FoxO3a chromatin occupancy. foxO3a and TXNIP functional effect were evaluated by Tripan Blue exclusion assay, Boyden chamber migration assay, siRNA-mediated silencing, 3D spheroids.

RESULTS

ChIP-seq analysis reveals FoxO3a genomic binding landscape in WT and TamR cells, identifying TXNIP is a common enriched target

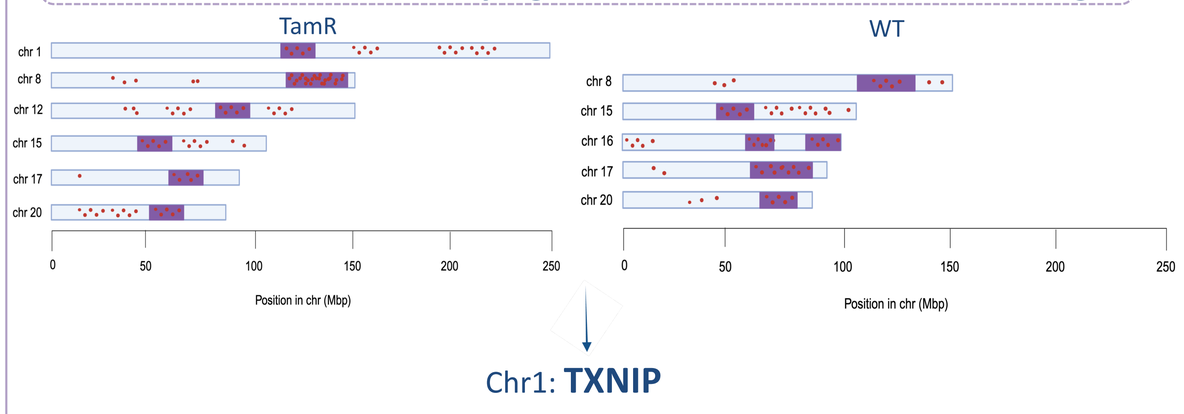

Figure 1. Genomic region enrichment analysis revealed 9 significantly regions in TamR cells (top panel) and 11 enriched regions in WT cells (bottom panel), identifying TXNIP is a common enriched target. Enriched regions are highlighted in purple and associated genes in red

Lamotrigine, via FoxO3a, increases TXNIP expression

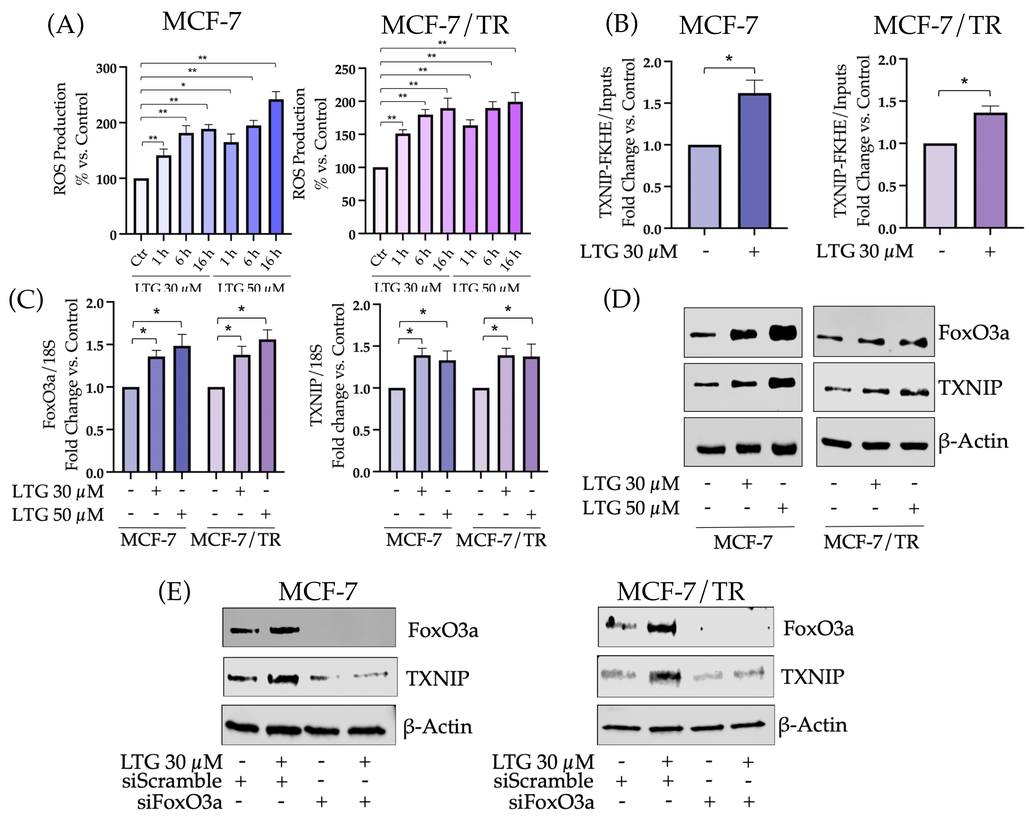

Figure 2. Lamotrigine induces ROS production in a time-dependent manner (A), promotes FoxO3a binding to consensus sequences within the TXNIP Promoter (B), and increases TXNIP expression at both mRNA (C) and protein (D) levels via FoxO3a-dependent regulation (E)

TXNIP is a mediator of Lamotrigine anticancer activity

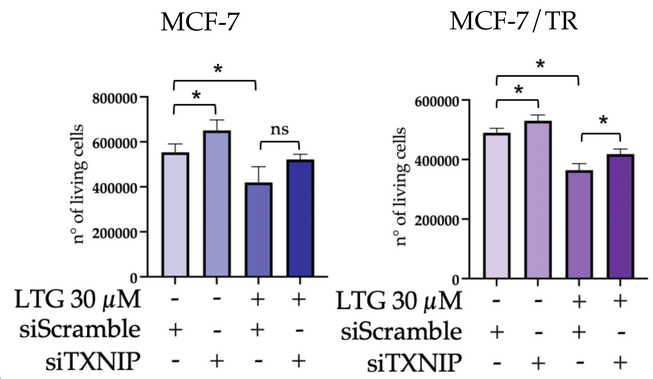

Figure 3. These results identify TXNIP as a critical mediator of Lamotrigine-induced inhibition of cancer cell proliferation

The mutual role of FoxO3a and TXNIP on cell proliferation and migration

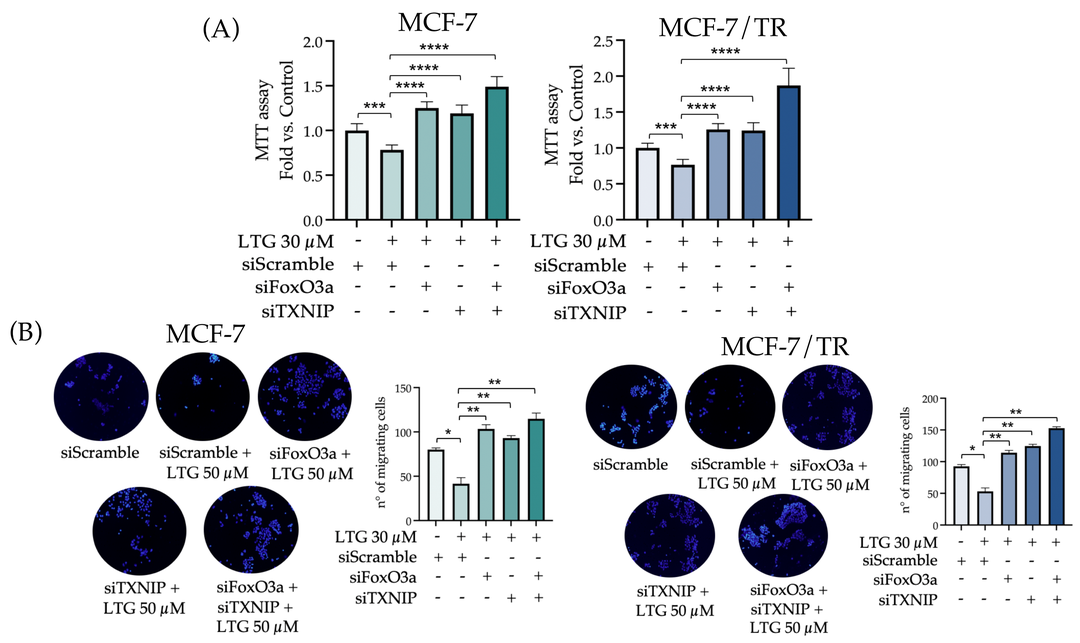

Figure 4. Silencing either gene significantly counteracted Lamotrigine inhibitory effects of proliferation (A) and migration (B), and their combined silencing resulted in an even greater effect, particularly in MCF-/TR, suggesting that both tumor suppressors play crucial roles in reducing growth and motility in ER+ BC cells

Lamotrigine suppresses 3D cell growth

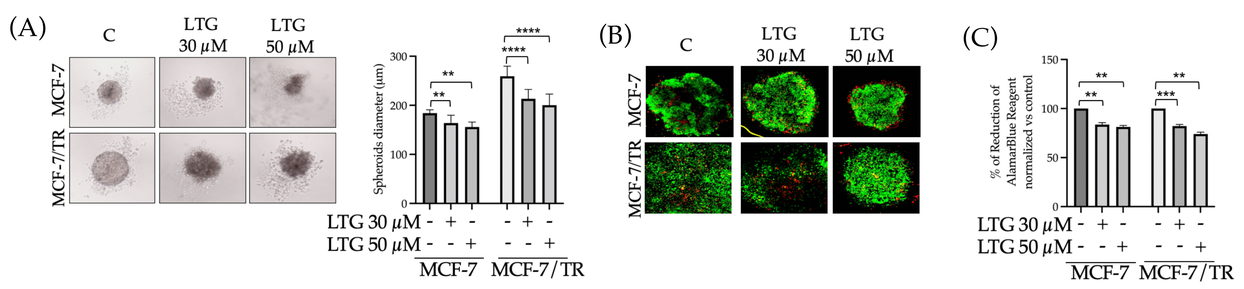

Figure 5. Lamotrigine reduced spheroid growth (A) and viability, as shown by increased PI-positive cells, decreased AO staining (B), and a dose-dependent reduction in AlamarBlue signal (C), further confirming the relevance of these effects in a more physiologically relevant context

Lamotrigine's effects in metastatic BC patients

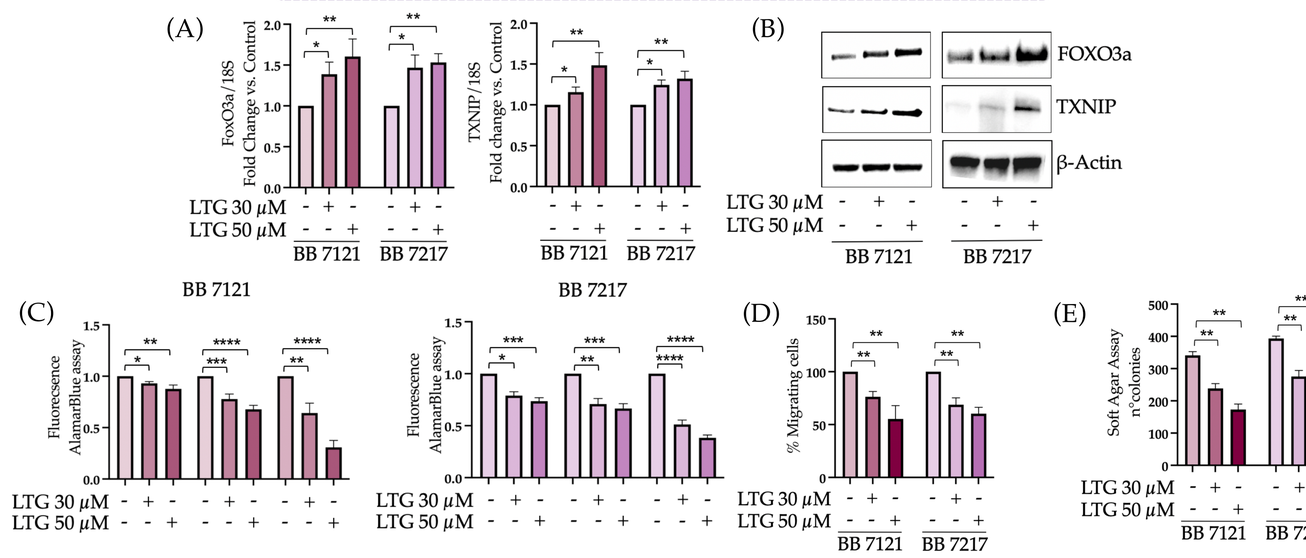

Figure 6. Lamotrigine induced a dose-dependent increase in FoxO3a and TXNIP expression at both mRNA (A) and protein (B) levels, and inhibited proliferation (C), migration (D), and colony formation (E) in metastatic breast cancer cells derived from Tamoxifen-resistant patients.

CONCLUSIONS

These data suggest that Lamotrigine, for its ability to activate the promising therapeutic targets FoxO3a and TXNIP, could represent a potential candidate for drug repurposing in breast cancer treatment, particularly for patients resistant to conventional hormonal therapies.

FUTURE WORK

Explore the role of LTG in the modulation of redox homeostasis and cellular metabolism to further clarify the mechanisms involved in its antitumor activity.

REFERENCES, ACKNOWLEDGMENT

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