HMGCS2 promotes malignant phenotype and apatinib resistance in HER2-negative breast cancer via the RAB23/β-Catenin/TCF signaling axis

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Background

- Existing studies have primarily focused on the clinical efficacy of Apatinib, a selective VEGFR2 inhibitor, leaving a significant gap in understanding the biological mechanisms underlying its resistance. In this study, we identify 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), a rate-limiting enzyme in ketogenesis, as a novel biomarker associated with Apatinib resistance in HER2-negative breast cancer . Furthermore, we investigate its biological function and molecular mechanism.

Methods

- Metabolomics analysis and immunohistochemical verification were performed on Apatinib-treated clinical samples to identify genes associated with Apatinib resistance. The biological role of these genes in HER2-negative breast cancer was validated through in vitro cell experiments and in vivo animal studies. The specific molecular mechanisms involved were elucidated using proteomics analysis , along with techniques such as co-immunoprecipitation and western blotting.

Results

- HMGCS2 was found to be overexpressed in Apatinib-refractory tumors and was associated with resistance to Apatinib. Compared to normal mammary epithelial cells, HMGCS2 expression levels were significantly elevated in breast cancer cells (Figure 1).

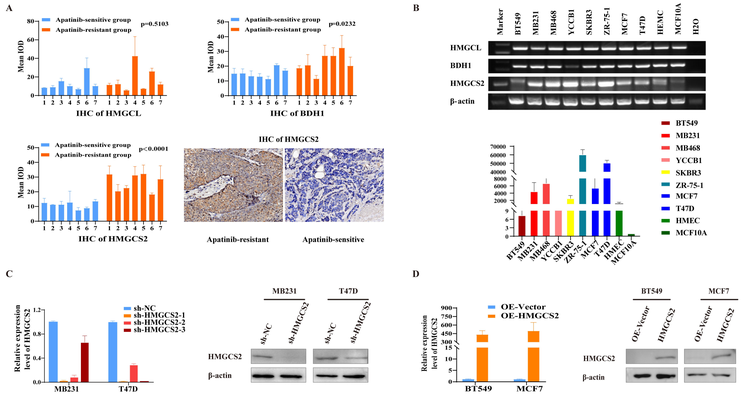


Figure 1. The expression of HMGCS2 in breast cancer cells and tissues.

- Knockdown of HMGCS2 via shRNA effectively suppressed tumor proliferation and invasion in HER2-negative breast cancer cell lines and reduced tumor burden in xenograft mouse models (Figure 2 and Figure 3).
- Conversely, overexpression of HMGCS2 markedly enhanced malignant phenotypes in vitro (Figure 4).

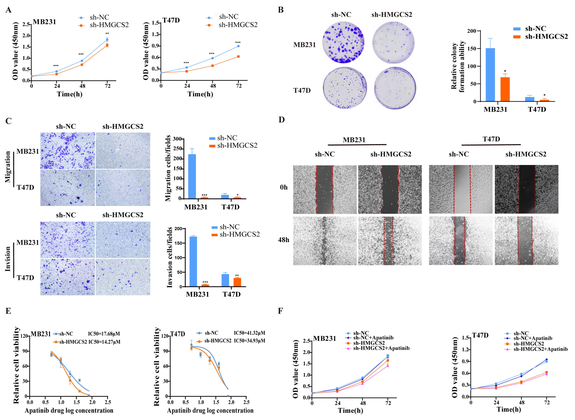


Figure 2. Sh-HMGCS2 inhibited the malignant phenotype in vitro.

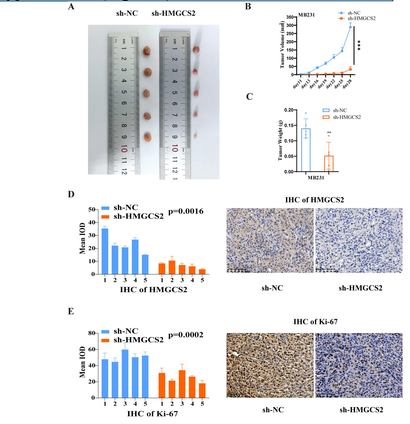


Figure 3. Sh-HMGCS2 inhibited the malignant phenotype in vivo.

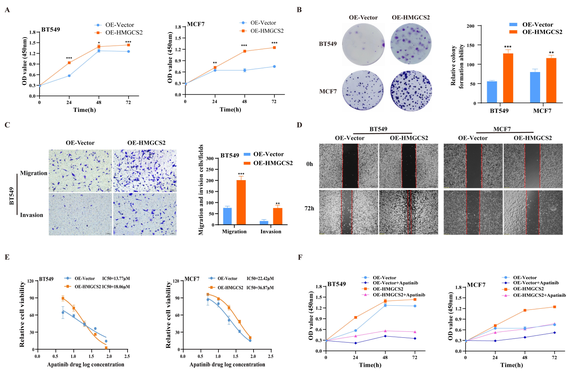


Figure 4. Overexpression of HMGCS2 enhanced the malignant phenotype.

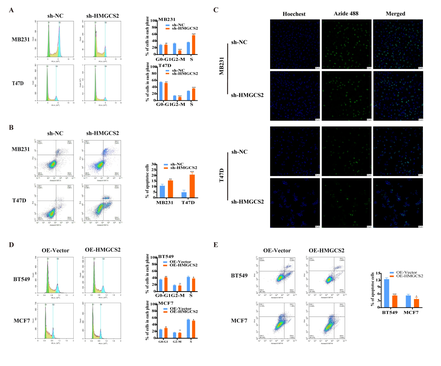


Figure 5. HMGCS2 modulated cell cycle and cell apoptosis.

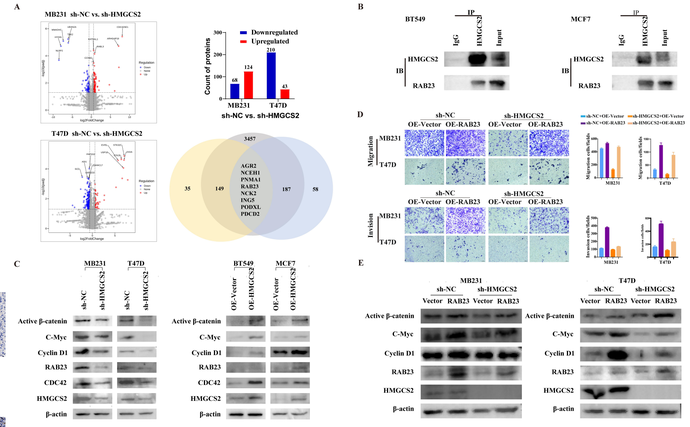


Figure 6. HMGCS2 promoted tumorigenesis via RAB23-mediated activation of the β-catenin/TCF signaling axis.

- Knockdown of HMGCS2 induced S-phase arrest and promoted apoptosis in HER2-negative breast cancer cells, whereas its overexpression led to G0/G1 phase arrest and suppressed apoptosis (Figure 5).
- Mechanistic investigations revealed that RAB23-dependent β-catenin/TCF activation served as the primary driver of carcinogenesis (Figure 6).

Conclusions

- Our study revealed a critical role of HMGCS2 in mediating Apatinib resistance in HER2-negative breast cancer. Mechanistically, HMGCS2 promoted malignant progression in HER2-negative breast cancer by activating the β-catenin/TCF transcriptional axis through RAB23-mediated signaling, highlighting HMGCS2 as a potential therapeutic target for precision oncology.

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