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The branched-chain amino acid transaminase 1 sustains growth of antiestrogen-resistant and ERα-negative breast cancer.

Thewes V[1], Simon R[2], Hlevnjak M[1], Schlotter M[1], Schroeter P[1], Schmidt K[3], Wu Y[1], Anzeneder T[4], Wang W[1], Windisch P[1], Kirchgäßner M[1], Melling N[2], Kneisel N[1], Büttner R[5], Deuschle U[6], Sinn HP[7], Schneeweiss A[8], Heck S[1], Kaulfuss S[9], Hess-Stumpp H[9], Okun JG[3], Sauter G[2], Lykkesfeldt AE[10], Zapatka M[1], Radlwimmer B[1], Lichter P[1], Tönjes M[1].

Author information

Abstract

Antiestrogen-resistant and triple-negative breast tumors pose a serious clinical challenge because of limited treatment options. We assessed global gene expression changes in antiestrogen-sensitive compared with antiestrogen-resistant (two tamoxifen resistant and two fulvestrant resistant) MCF-7 breast cancer cell lines. The branched-chain amino acid transaminase 1 (BCAT1), which catalyzes the first step in the breakdown of branched-chain amino acids, was among the most upregulated transcripts in antiestrogen-resistant cells. Elevated BCAT1 expression was confirmed in relapsed tamoxifen-resistant breast tumor specimens. High intratumoral BCAT1 levels were associated with a reduced relapse-free survival in adjuvant tamoxifen-treated patients and overall survival in unselected patients. On a tissue microarray (n=1421), BCAT1 expression was detectable in 58% of unselected primary breast carcinomas and linked to a higher Ki-67 proliferation index, as well as histological grade. Interestingly, BCAT1 was predominantly expressed in estrogen receptor-α-negative/human epidermal growth factor receptor-2-positive (ERα-negative/HER-2-positive) and triple-negative breast cancers in independent patient cohorts. The inverse relationship between BCAT1 and ERα was corroborated in various breast cancer cell lines and pharmacological long-term depletion of ERα induced BCAT1 expression in vitro. Mechanistically, BCAT1 indirectly controlled expression of the cell cycle inhibitor $p27^{Kip1}$ thereby affecting pRB. Correspondingly, phenotypic analyses using a lentiviral-mediated BCAT1 short hairpin RNA knockdown revealed that BCAT1 sustains proliferation in addition to migration and invasion and that its overexpression enhanced the capacity of antiestrogen-sensitive cells to grow in the presence of antiestrogens.

Importantly, silencing of BCAT1 in an orthotopic triple-negative xenograft model resulted in a massive reduction of tumor volume in vivo, supporting our findings that BCAT1 is necessary for the growth of hormone-independent breast tumors.Oncogene advance online publication, 20 March 2017; doi:10.1038/onc.2017.32.

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