Journal of Cancer Stem Cell Research (2018), 6:e1008
 ISSN 2329-5872
DOI: 10.14343/JCSCR.2018.6e1008
http://cancerstemcellsresearch.com

Research Article Open Access

Targeting Cancer Stem Cells in Breast Cancer through Inhibition of WAVE3/YB1 Interaction

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Abstract: Resistance to therapy is the main cause of tumor recurrence and metastasis, and cancer stem cells (CSCs) play a crucial role in this process, especially in triple-negative breast cancers (TNBCs), for which chemotherapy is the main course of treatment. Unfortunately, no FDA-approved treatment is currently available for this subtype of BC, which explains the high rate of mortality in patients with TNBC tumors. WAVE3, a member of the WASP/WAVE actin-cytoskeleton remodeling family of protein, has been established a major driver of tumor progression and metastasis of several solid tumors, including those originating in the breast. Recent studies found WAVE3 to mediate the process of chemoresistance in TNBCs. The molecular mechanisms whereby WAVE3 regulates chemoresistance in TNBC tumors remains largely unknown, as does the role of WAVE3 in CSC maintenance. Here we show that WAVE3 mediates chemoresistance by promoting CSC self-renewal and transcription of CSC-specific genes. Our data show that WAVE3 is enriched in the CSC-subpopulation of TNBC cell lines. Knockout of WAVE3 via CRISPR/Cas9 significantly depletes CSC-subpopulation and inhibits transcription of CSC transcription factors. Mechanistically, we established a link between WAVE3 and the Y-box binding protein 1 (YB1), a transcription factor and CSC-maintenance gene. Indeed, the interaction of WAVE3 with YB1 is required for the translocation of YB1 to the nucleus of cancer cells, and the subsequent activation of transcription of CSC-specific genes. Collectively, our findings identify a new WAVE3/YB1 signaling axis that regulates the CSC-mediated resistance to therapy and opens a new therapeutic window for the treatment of TNBCs.

Keywords: WAVE3, Triple Negative Brest Cancer, Cancer Stem Cells, YB1, CRISPR/Cas9, Chemoresistance.

ACKNOWLEDGMENTS

This work was supported by Cleveland Clinic Seed Funds.
Research work was presented at the Cancer Stem Cell Conference (2018), Cleveland, Ohio, USA.

Received: November 12, 2018; Revised: November 12, 2018;
Accepted: November 12, 2018