Effect of Salinomycin on EMT and Stemness Pathways in 5-FU-Resistant Breast Cancer

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Received 17 August 2021; **Accepted** 24 August 2021; **Published** 31 August 2021

Perspective

Breast cancer is the second biggest cause of death in women worldwide. Every year, around 1.4 million women are diagnosed with this illness cancer in the United States alone, and 41,760 fatalities were recorded in 2019, accounting for nearly 15.2% of all cancer kinds in the United States. Every year, 0.15 million cases of breast cancer are reported in India, with a death rate of about 50%. Though targeted therapy with medications such as trastuzumab, lapatinib, and tamoxifen has improved the chances of survival in patients with specific subtypes of breast cancer, only a small fraction of people benefit. A huge number of breast cancer patients, particularly those with the triple-negative subtype, have a high risk of death and relapse. Recurrence of metastatic breast cancer has claimed many lives around the world, and with recent advances in oncology research, there is potential to increase the efficacy of traditional therapy. One of the key reasons for this failure has been the post-treatment survival of cancer stem cells (CSCs). The CSC subpopulation exists in the hypoxic niche of the tumour and is resistant to conventional therapies due to its quiescence, self-renewal, and differentiation ability.

Current anti-cancer medications are significantly more effective in removing proliferating terminally differentiated cancer cells, hence increasing CSCs in the population. CSCs have some distinct characteristics and deregulated pathways, such as stem ness qualities such as clonogenicity, tolerance to oxidative stress, and expression of epithelial-to-mesenchyme-transition (EMT) proteins such as snail, slug, and zeb. Overexpression of ATP binding cassette (ABC) transporter proteins including ABCG2, which promote drug efflux, has also been identified in these cells. They also have increased telomerase activity and an upregulated DNA repair mechanism. CSCs can be distinguished from normal cancer cells or healthy stem cells by their mix of characteristic surface markers. The extensive differentiation and migration associated with distinct cluster of differentiation (CD) markers such as CD133 and CD44 demonstrate the specific properties of CSCs of varied origins. CD44 has been extensively researched in solid tumours, and this receptor binds to hyaluronic acid, assisting in the regulation of cell adhesion and migration. Furthermore, CD44 overexpression was linked to poor survival and activation of the EMT pathway.

Similarly, CD133 is associated with cell proliferation and has been found in a variety of CSCs. In the case of breast cancer stem cells (BCSCs), Hedgehog and Wnt-Notch signalling pathways play a significant role in cancer stem cell maintenance, differentiation, and regulation. In transgenic mice, Went overexpression and related -catenin nuclear localization aid in cancer stem cell maintenance, resulting in breast tumour development. EMT is characterised by the loss of the e-cadherin protein and the growth of the n-cadherin protein, and overexpression of this pathway results in highly invasive CSCs. Sulfasalazine and Wnt/-catenin inhibitors like ICG-001 and vismodegib, which target these molecular pathways, have showed promise in treating several solid tumours and haematological malignancies. Similar discoveries in breast cancer, on the other hand, are rare. A large number of chemicals were screened utilising high throughput screening in a recent study to identify medications that particularly target CSCs. Salinomycin was shown to be the most effective at inhibiting tumour growth. This antibiotic is a coccidiostat in poultry and has been demonstrated to be effective against Streptomyces tuberculosis in humans. Salinomycin lowered the amounts of stem ness proteins such nanog in chemoresistant nasopharyngeal cancer cells. In glioblastoma CSCs, it also reduced the expression of stemness proteins Musashi-1, Sox2, and Nestin.

Salinomycin has been shown to diminish CD44 cells in melanoma and increase doxorubicin sensitivity in soft tissue sarcomas. Few researches have been published to investigate the mechanistic influence of this medication on critical molecular pathways that lead to drug resistance. 5-fluorouracil (5-FU), the most often used chemo-agent, is used to treat various solid tumours, primarily colorectal and breast cancer. However, this treatment frequently results in the development of resistance and an increased mortality rate due to metastasis. Cases of 5-FU resistance have been documented all around the world, and the molecular mechanisms at work are being investigated.

Cite this article: Bandelow S. Effect of Salinomycin on EMT and Stemness Pathways in 5-FU-Resistant Breast Cancer. Oncol Cancer Case Rep. 2021, 07 (8), 001-001.