Breast Cancer RESEARCH

VIEWPOINT

Die and let live: harnessing BikDD to combat breast cancer stem cells

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Abstract

One of the possible mechanisms contributing to the intrinsic resistance of cancer stem cells (CSCs) to conventional therapies is the inefficiency of activating the apoptotic machinery. In a recent study by Lang and colleagues, the engineered constitutively active pro-apoptotic protein BikDD, which works by inhibiting multiple Bcl-2 family members, was tested in various preclinical breast cancer models. Delivered to cells via an innovative cancer cell-specific gene-therapy approach, BikDD showed potent activity against CSCs and synergized with lapatinib and paclitaxel treatment. This novel and promising therapy warrants further translation to the clinic.

Background

Despite significant improvements in breast cancer therapy achieved in the last decades, tumor progression occurs often and is associated with high mortality. Treatment resistance and disease progression are thought to occur due to the inability of conventional therapies to eradicate all the tumor cells, especially the cancer stem cells (CSCs) [1]. These CSCs are resistant to chemotherapy and radiation, capable of self-renewal, and thus responsible for tumor progression [1,2]. No drugs are currently available in the clinic to effectively and selectively target CSCs.

One of the potential mechanisms of CSC-related treatment resistance is their unique survival property, which enables them to escape from drug-induced apoptosis [3]. It has been shown in both hematologic and solid tumors that CSCs express high levels of mRNAs encoding anti-apoptotic proteins, including Bcl-2 family members [4,5]. In addition, overexpression of Bcl-2 and its family members has been associated with resistance to various chemotherapeutic drugs as well as targeted therapies, in both preclinical and clinical settings [6-9]. Because the anti-apoptotic machinery can be regulated by several mechanisms in CSCs, this redundancy presents a challenging obstacle for the development of effective pro-apoptotic treatments [10].

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The article

In line with these premises, Lang and colleagues [11] studied the anti-tumor activity of BikDD, a constitutively active form of the pro-apoptotic protein Bik. The authors found that BikDD effectively targeted the breast CSCs by inhibiting multiple anti-apoptotic Bcl-2 family members (Bcl-2, Bcl-xL, Bcl-W, and Mcl-1), significantly reducing the percentage of $CD44^+/CD24^-$ CSCs, and impairing mammosphere formation in various pre-clinical models of breast cancer. BikDD also reduced tumor-initiating capacity of mammospheres injected into NOD/SCID mice. Importantly, while silencing of individual Bcl-2 family members by short hairpin RNA (shRNA) knock down had only a modest effect on the survival of CSCs, co-silencing by either combined shRNAs or BikDD resulted in significant CSC reduction.

Additionally, the authors integrated the BikDD gene in a vector-liposome complex named VISA-claudin4-BikDD for selective delivery to and expression in breast cancer cells. The complex inhibited tumor cell growth *in vitro* and *in vivo*, with only limited effects on normal cells and low toxicity in mice. Inadequate apoptosis can limit the efficacy of HER2-targeting drugs such as lapatinib [8,9], and BikDD gene therapy enhanced lapatinib efficacy in HER2-positive and epidermal growth factor receptor (EGFR)-positive breast cancer models *in vitro* and *in vivo*, though no complete tumor regressions were observed. Lastly, the combination of VISA-claudin4-BikDD with the chemotherapeutic drug paclitaxel prevented the CSC increase observed after paclitaxel alone and significantly reduced tumor growth *in vivo*, even after the cessation of treatment. Thus, BikDD may also target chemotherapy-resistant CSCs.

The viewpoint

Several lines of evidence emphasize the importance of targeting CSCs to improve treatment outcome in breast

cancer. Nevertheless, only a few preclinical studies in this effort have shown positive results to date [3,12]. Resistance of CSCs to drug-induced apoptosis [10] suggests that approaches to induce apoptosis in CSC populations would be promising. Furthermore, apoptosis-inducing treatments, such as tumor necrosis factor-related apoptosis inducing ligand (TRAIL) agonists and Bcl-2 antagonists, have yielded positive results in the preclinical setting and are already under clinical investigation in breast cancer and other malignancies [13,14]. However, only a limited number of studies have explored the direct role of pro-apoptotic treatments in CSCs [15].

Lang and colleagues have conducted a pioneering study of the novel and potent pro-apoptotic molecule BikDD, which was used to target breast CSCs. The innovation of their approach is two-fold. First, BikDD can inhibit all the major Bcl-2 anti-apoptotic family members, representing a 'super' pro-apoptotic molecule for breast cancer cells, including CSCs. Second, the innovative gene therapy protocol developed by the authors using VISA-claudin4-BikDD shows selective delivery of BikDD to cancer cells, with little or no effect on normal cells. Combining its potent pro-apoptotic activity with its selectivity for breast cancer cells, VISA-claudin4-BikDD enhanced the efficacy of lapatinib and killed paclitaxel-resistant CSCs. Therefore, BikDD represents a potential remedy for drug resistance. The evidence justifies the authors' intention to rapidly move this novel strategy to the clinical research setting.

Despite the comprehensive approach taken by Lang and colleagues, there are some unanswered questions, which should be considered during BikDD's translational path to the clinic. While improved efficacy of lapatinib was observed with BikDD, complete tumor eradication was still not achieved. This could be related to several factors. First, additional survival pathways beyond the key Bcl-2 family members may operate in breast CSCs. Second, VISA-claudin4-BikDD may not be able to infect and induce the expression of BikDD in all the tumor cells, including CSCs. Third, tumor cell and CSC heterogeneity may affect the overall efficacy of this therapy. In spite of these limitations, the novelty of delivering BikDD to breast cancer cells and its preclinical efficacy suggest that BikDD gene therapy may represent a new paradigm in the treatment of breast cancer patients.

Abbreviations

CSC, cancer stem cell; EGFR, epidermal growth factor.

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