Title: Targeting Chemoresistant Breast Cancer Stem Cells with Oncolytic Adenovirus: A Promising Approach.

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The recurrence of metastatic breast cancer, particularly in luminal estrogen-receptor positive (ER+) cases, poses a significant challenge due to acquired resistance to standard endocrine and chemotherapy treatments. This recurrence is often fueled by the persistence and expansion of breast cancer stem cells (BCSCs), which are inherently resistant to conventional therapies. To address this issue, our study explores the potential of oncolytic adenoviruses (OAd) as a targeted therapeutic approach against BCSCs.

OAd viruses are engineered to replicate selectively within cancer cells, holding the promise of targeted cancer tissue destruction. In our research, we have developed an OAd construct encoding the sodium/iodide symporter (NIS), a protein crucial for cellular iodine uptake, essential for radiotherapy and imaging. Our hypothesis posits that OAd-NIS can effectively target and destroy BCSCs, thus reducing the risk of local recurrences by treating preexisting micrometastatic deposits that are clinically undetectable. Our research findings demonstrate that OAd-NIS exhibits superior binding and oncolytic activity in human breast cancer cells of all subtypes, including ER+ luminal cells. Importantly, it displays minimal oncolytic activity and NIS expression in normal human mammary epithelial cells. Deletion of the Adenovirus Death Protein (ADP) significantly enhances NIS expression in breast cancer cells, likely due to increased NIS membrane localization. To assess OAd-NIS's potential to target BCSC populations, we utilized ER+ paclitaxel-resistant (TaxR) cells and 3D models expressing stem cell markers (e.g., ALDH+ or CD44hi/CD24lo). Remarkably, OAd-NIS showed increased cytotoxicity in TaxR cells compared to control MCF-7 cells, accompanied by elevated NIS gene and protein expression. Crucially, co-treatment of TaxR cells with OAd-NIS and paclitaxel reversed chemoresistance, sensitizing TaxR cells to paclitaxel upon virus infection. In a tumorsphere assay, OAd-NIS inhibited tumorsphere formation in TaxR and MCF-7 3D cultures and effectively destroyed preformed tumorspheres upon infection.

This study underscores the potential of OAd-NIS to effectively target and eliminate BCSC populations, suggesting its role as an adjuvant therapy in combination with paclitaxel for treating ER+ breast cancer patients with recurrent metastatic disease. Future investigations will include assessing the in vivo potential of OAd-NIS for radioiodine-based imaging and therapy.