Targeted Delivery of Fusogenic Peptide for Breast Cancer Treatment

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Breast cancer is the second most common form of cancer diagnosed in women only following behind skin cancer. Approximately 1 in 8 women will develop breast cancer in their lifetime, and this year an estimated 43,600 women will die from this disease in the United States[4]. There is no definitive known cause for breast cancer although there are risk factors that have been associated with breast cancer development such as drinking, smoking, radiation exposure, and genetic inheritance of the BRCA1 and BRCA2 genes[4]. There are currently five treatment options for breast cancer: chemotherapy, surgery, hormone therapy, radiation therapy, and targeted drug delivery. Targeted drug delivery focuses on the site-specific delivery of antibodies or RNAi to repress oncogenic proteins or silence oncogenes. A common form of RNAi is short interfering RNA or siRNA. These molecules have been discovered to attach to a target mRNA sequence and cleave the molecule so that transcription of the selected gene is prevented[2]. A carrier particle is needed to deliver these siRNAs into a cell's nucleus to prevent the siRNA from being degraded. One common form of carrier is a peptide-based nanoparticle. This form of carrier is beneficial because it can accomplish cell specific delivery, pH-based membrane disruption, efficient packaging, and efficient membrane transport[2].

My project will focus on the targeted delivery of siRNA via a fusogenic peptide derived nanoparticle delivery system by attaching a targeting peptide for HER2 receptor protein found on HER2 positive breast cancer cells. The amplification of HER2 occurs in approximately 25% of breast cancers and is termed HER2 positive breast cancer. This form of cancer has an increased incidence of metastasis and a higher mortality rate[3]. For these reasons, we will be focusing our research on this type of breast cancer. Once internalized into the cancer cells, the siRNA will target and silence the CD44 oncogene which is known to be directly involved in carcinogenesis and tumor progression[1]. The fusogenic peptide that we will be using is DIV3W which was previously developed in the Nanobiotechnology Lab. DIV3W has demonstrated the ability to form nanoparticles with siRNA and protect siRNA from degradation. My first aim for this project is to discover a targeting peptide and linker that can be attached to the DIV3W-siRNA nanoparticle to target HER2 positive breast cancer cells. My second aim is to evaluate the effectiveness of the targeted nanoparticle of reducing metastatic properties in different cell lines. I will be testing three different HER2 positive BRC cells: SKBR3, HCC1954, and BT474. I will also be using MCF10A-normal human breast epithelial cells.

References:

1. Chen C, Zhao S, Karnad A, Freeman JW. The biology and role of CD44 in cancer progression: therapeutic implications. *J Hematol Oncol*. 2018;11(1):64. Published 2018 May 10. doi:10.1186/s13045-018-0605-5
2. Dana, H., Chalbatani, G. M., Mahmoodzadeh, H., Karimloo, R., Rezaiean, O., Moradzadeh, A., Mehmandoost, N., Moazzen, F., Mazraeh, A., Marmari, V., Ebrahimi, M., Rashno, M. M., Abadi, S. J., & Gharagouzlo, E. (2017). Molecular Mechanisms and Biological Functions of siRNA. *International journal of biomedical science: IJBS*, *13*(2), 48–57.
3. Geng L, Wang Z, Jia X, et al. HER2 Targeting Peptides Screening and Applications in Tumor Imaging and Drug Delivery. *Theranostics*. 2016;6(8):1261-1273. Published 2016 May 28. doi:10.7150/thno.14302
4. National Breast Cancer Foundation, Inc. https://www.nationalbreastcancer.org/breast-cancer-facts