Metastatic disease remains the most significant life-threatening event for cancer patients. Oncolytic virus-mediated therapies in clinical trials hold great promise to treat metastases by stimulating endogenous immune reactions against metastatic tumor cells. However, these therapies have limited success due to the difficulty of delivering the oncolytic viruses specifically to the tumor sites. We have developed a new delivery platform in which hTERT-immortalized mesenchymal stem cells (MSCs) are genetically engineered and then enucleated to form nucleus-free cytoplasts. These cytoplasts have the ability to deliver different cargos such as small molecule drugs, proteins, and RNAs to diseased tissues in pre-clinical animal models. To test if cytoplasts can also deliver oncolytic viruses, we screened a group of oncolytic viruses currently used in clinical trials, including measles virus (oMV), herpes simplex virus (oHSV) and vesicular stomatitis virus (oVSV). We found oVSV can efficiently infect, propagate, package and be released from cytoplasts. Cytoplast-released oVSV can also infect tumor cells in vitro and cause virus-induced tumor cell lysis. We have established a pre-clinical metastatic tumor model using the triple-negative breast cancer (ER-, PR-, HER2/neu-) murine breast cancer cell line E0771. In vitro experiments suggest engineered cytoplasts can transduce primary mammary glands in the female to express both E0771 cells and oHSV, and that tumor cells can be killed by cytoplasts. Furthermore, the oHSV-infected cytoplasts maintain their migratory capacity. Presently, we are testing if engineered cytoplasms in a syngeneic animal model can deliver oVSV to metastatic E0771 cells and trigger the immune responses against the tumor cells. Our novel delivery strategy has the potential to greatly enhance the efficacy of current oncolytic virus therapies for treating deadly metastatic disease.

Background

> Triple Negative Breast Cancers (TNBC: ER-, PR, HER2/neu) are often highly metastatic with poor prognosis under current therapy[1].

> Oncolytic viruses (OV) such as oMV (Measles Virus), oHSV (Herpes simplex virus), and oVSV (Vesicular stomatitis virus) hold great promise as anti-cancer treatments, including metastatic TNBC[2,3].

> Systematic administration of OVs into patients is highly inefficient because the immune system rapidly clears unprotected viruses[4].

> Therefore, there is a major need to develop biocompatible vectors that improve systemic delivery of oncolytic viruses and target them to primary and metastatic tumors in a safer manner[5,6].

> To study the in vivo tumor-delivery of OVs, a syngeneic TNBC model in immuno-competent mice is ideal.

> Our platform technology enucleates hTERT-immortalized MSCs to generate nucleus-free cytoplasts, which can be extensively engineered with improved homing abilities to safely deliver oncolytic viruses to tumors.

Abstract

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References


Acknowledgements: This work was supported by NIH CA138943 and CA215601 to E.L., and NH T32 DT00148-13 to J.A.

C.N.A. We would like to thank Dr. Wenhai Zhou and Dr. Alice Segall for use of references and guidance.