DEVELOPMENT AND MECHANISM OF ACTION OF A NOVEL CELLULAR IMMUNOTHERAPEUTIC PLATFORM FOR THE TREATMENT OF CANCER


Background Therapeutic cancer vaccines are designed to program a patient’s immune system to recognize and eliminate tumor cells. We sought to harness gene-modified tumor cells as a vaccine platform and developed cancer vaccines composed of breast cancer cells expressing GM-CSF (SV-BR-1-GM). We have recently reported favorable clinical outcomes in patient populations that match SV-BR-1-GM at one or more HLA alleles. Mechanistically, SV-BR-1-GM cells can directly activate CD4+ T-cells in an antigen-specific HLA-restricted manner, as demonstrated by an in vitro antigen presentation assay. Building upon these observations, we hypothesized that tumor cells could function as antigen-presenting cells, and that direct CD4+ T-cell allorecognition may provide T-cell help for the generation of self-HLA restricted T-cell responses to tumor antigens.

Our rationale was to genetically modify tumor cells to express a semi-allogeneic range of HLA molecules and T-cell co-stimulatory molecules & cytokines. The goal is to develop an off-the-shelf cell-based vaccine that enhances existing tumor-specific T-cell responses and expand the T-cell repertoire by inducing new responses from naïve T-cells.

Methods SV-BR-1 (Breast cancer), PC-3 (prostate cancer), SK-MEL-24 (Melanoma), and NCI-H2228 (Lung cancer) were chosen for vaccine development based on their expression of an immune signature. To create semi-allogeneic cell lines that closely match over 99% of the population in terms of at least one HLA allele, four cell lines were generated for each parental tumor cell line. Each of these cell lines carries two HLA-A alleles and two HLA-DRB3/4/5 alleles. Subsequently, the tumor cells were genetically modified using a lentiviral-mediated expression system to express co-stimulatory molecules and immunomodulatory cytokines. To monitor the immune responses elicited by the newly generated cell lines, we established a modified mixed lymphocyte reaction assay (mMLRA). This assay involved co-culturing tumor cells with peripheral blood mononuclear cells. Additionally, we performed T-cell activation assays using transgenic Jurkat cells that expressed HLA-restricted T-cell receptors.

Results Four cell lines (for each tumor type) that secreted GM-CSF, IFNα, IL-12, IL-7 and expressed CD80, CD86, 4-1BB, and different combinations of both Class I and Class II HLA alleles were generated. By using the mMLRA and T-cell activation assays we successfully demonstrated that these novel cell lines can effectively induce and enhanced immune response involving multiple immune populations.

Conclusions Overall, this study provides evidence for the potential of genetically modified tumor cells as a promising cell-based vaccine platform for enhancing immune responses against cancer.

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