Conclusion: Combination therapy of oncolytic adenovirus with NK cells for the treatment of aggressive solid tumors

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Background

NK cells are a type of innate lymphocyte that specializes in killing of infectively infected solid tumors and tumor cells. Adenovirus NK therapy has been successful for the treatment of many types of solid tumors, including leukemia and lymphomas. However, due to the suppressor tumor microenvironment (TME), NK cells are not effective for targeting solid tumors. Oncolytic virus Delta24RGD has been shown to induce inflammation in the TME via cytokine release in the local injection. In addition, NK cells have been shown to be effective in eliminating adenovirus-infected cells. Therefore, this study will examine whether the combination of Delta24RGD and NK cells can be effective for treating highly aggressive solid tumors, and what the mechanisms behind the synergy is. This study will focus on investigating 1) the phenotypic changes in tumors following infection by the oncogenic virus, 2) the phenotypic and functional changes in NK cells following exposure to infected tumor cells, 3) the changes to the TME following viral infection of the tumor cells and how these changes can affect NK function and persistence. The results from this study can lay the foundation for potentially moving this treatment into the clinic. In addition, the mechanistic discoveries can be helpful for future genetic engineering of oncolytic viruses and NK and be even more effective at targeting tumors.

Materials

PDAC and glioblastoma tumor cells: For this aim, as a proof-of-concept experiment, we will be using glioblastoma (GB) and pancreatic ductal adenocarcinoma (PDAC) as tumor models for aggressive solid tumors because these are two of the most difficult tumors to target with immunotherapy so far. The GB cell lines used are U87, which is an example of a glioma precursor GB cell line and GSC 8, which is a glioma precursor GB cell line. Both cell lines are used to determine whether the combination therapy can target both the main GB tumor and the GB stromal cells. For this purpose, we will be using CAPAN1, an example of a slow-growing PDAC model and BXPC3 as an example of a fast-growing PDAC model to cover a wide variety of PDAC types.

NK cells: All the NK cells used in this aim are cord blood NK cells that are isolated from fresh cord blood, expanded with IL-2, and maintained with GMP capable 3 to 4 days by cytoselectively and continuously cytokine-replete to reflect the clinical use of cord blood NK cells.

Viruses: All Delta24RGD and Delta24RGDOX viruses are synthesized by the Gomez-Manzano lab and Fueyo lab.

Objectives

1.3 Aim 3: Determine the changes in TME in vivo under the combination therapy and its long-term effect on the activity of adoptively transferred NK cells.

We will measure the changes in immune cell infiltration and cytokine secretion in the tumor microenvironment in the primary tumor as well as the non-infected secondary tumor. In addition, we will determine the ability of the adoptively transferred NK cells to eradicate the tumor, the chronopharmacology of those NK cells, and duration of persistence after initial injection.

The experiments described in this proposed work will characterize the efficacy of combination therapy with oncolytic viruses and NK cells, and provide a mechanistic explanation of it. The findings of this study may serve as a translational tool to justify the use of oncolytic viruses with NK cells in the clinic to treat aggressive solid tumors that were previously resistant to immunotherapy.

Conclusions

After analyzing the previous graphs that encompass three different cell lines and express similar results to the same procedure, we can see that the combination between oncolytic adenoviruses and natural killer cells is more effective in eliminating adenovirus-infected cells than NK cells alone. This suggests that by combining these two therapies, we are able to conclude that oncolytic viruses, by themselves are highly ineffective against tumor cells. Lastly, NK cells are better at eliminating tumors, but their efficacy tends to be dampened by the non-oncogenic components of the microenvironment. The findings from these experiments can potentially allow for further exploration with additional models in vitro, which is currently ongoing. Additionally, these findings could be laid towards clinical to justify the use of combination therapy between oncoytic adenoviruses and NK cells in a clinical setting where it could be used to treat solid tumors previously resistant to immunotherapy.

References


TheAcknowldgements

This research presented in this poster could not have been made possible without the generous support of Candelaria Gomez, Rafet Basar, and Dr. Katy Rezvani for making this experience possible by allowing me to partake in her laboratory. Her ongoing exploration which includes but is not limited to new therapy for solid tumors and what the mechanisms behind the synergy is. This study will focus on investigating 1) the phenotypic changes in tumors following infection by the oncogenic virus, 2) the phenotypic and functional changes in NK cells following exposure to infected tumor cells, 3) the changes to the TME following viral infection of the tumor cells and how these changes can affect NK function and persistence. The results from this study can lay the foundation for potentially moving this treatment into the clinic. In addition, the mechanistic discoveries can be helpful for future genetic engineering of oncolytic viruses and NK cells to be even more effective at targeting tumors.

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Objectives

1.3 Aim 1: Investigate the phenotypic changes in tumor cells after infection

We will characterize the changes in surface ligand expression in the infected tumor cells using immunohistochemical analysis of stress induced expression and downregulation of MIC expression. In addition, we will look at our ability 2) the changes to the TME associated with this infection and how it can impact the synergic effect of the combination therapy.

1.2 Aim 2: Determine the phenotypic and functional changes in NK cells following exposure to tumor cells infected by the oncolytic virus.

We will investigate the changes in the cytotoxic capabilities and cytotoxic effector molecules of NK cells induced by the oncolytic virus in vivo. We will then confirm the results in vitro.

1.3 Aim 3: Determine the changes in TME in vivo under the combination therapy and its long-term effect on the activity of adoptively transferred NK cells.

We will measure the changes in immune cell infiltration and cytokine secretion in the tumor microenvironment in the primary tumor as well as the non-infected secondary tumor. In addition, we will determine the ability of the adoptively transferred NK cells to eradicate the tumor, the chronopharmacology of those NK cells, and duration of persistence after initial injection.

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