Background
Immunotherapy has shown impressive clinical responses, but many patients do not respond to single modality immunotherapy due to a number of non-redundant resistance mechanisms. Our lab and others have proposed that tumor cells compromise T cell function by generating a metabolically inhospitable microenvironment, suggesting that immune or tumor metabolism can be differentially modified to improve T cell responses and thus immunotherapy.
Methods
We identified the adipokine leptin as a means to remodel the metabolic state of tumor infiltrating T cells. To assess the effects of leptin in the tumor microenvironment, we generated an aggressive PTEN/BRAF melanoma line overexpressing leptin, as well as an oncolytic strain of Vaccinia virus engineered to induce tumor-specific secretion of leptin.
Results
Treatment of T cells with leptin in vitro resulted in dramatic metabolic reprogramming. In vivo, intratumoral administration of leptin resulted in enhanced T cell metabolic and effector function. We then engineered melanoma cell lines to locally secrete leptin. While there was no proliferation difference between wild-type and leptin- expressing tumor cells in vitro, these cells are controlled in vivo in a CD8+ T cell specific manner. Leptin overexpressing tumors have increased T cell infiltration compared to control tumors, and these TIL are metabolically and functionally superior. In order to translate out findings to a therapeutic setting we utilized an oncolytic virus model. Oncolytic viruses are an attractive therapeutic modality promoting tumor specific killing as well as inducing an anti-tumor immune response. While wild-type oncolytic Vaccinia resulted in some tumor regression, leptin-engineered Vaccinia had superior therapeutic efficacy inducing complete regressions in 30% of mice. TIL from these tumors have improved T cell infiltration and function. We profiled immune infiltrates by single cell RNAseq and TCR sequencing. Data revealed the influx of new T cells by vaccinia which was characterized by a polyclonal repertoire. On the other hand, T cells from tumors treated with leptin-expressing virus showed a reduced polyclonal phenotype indicative of specific clonal expansion. This clonal expansion is associated with a more memory like state, and indeed leptin-engineered VV induced a greater percentage of CD127hi memory precursors than the oncolytic VV alone.
Conclusions
Taken together, these data suggest metabolic modulators like leptin can be therapeutically exploited to bolster intratumoral T cell function using the oncolytic virus platform. Our goal is to further design novel therapeutic strategies using oncolytic viruses.

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A cell-based platform to protect and enhance oncolytic virus therapies

Antonio Santidrian, Dobrin Draganov, PhD, Duong Nguyen, PhD, Okyay Kilinc, Ivelina Minev, MSc, Boris Minev, MD, Aladar Szalay, PhD
Calidi Biotherapeutics
Correspondence: Antonio Santidrian (asantidrian@calidibio.com)
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Background
Different types of viruses, including vaccinia virus (VACV), can selectively replicate in cancer cells and trigger antitumor immunity. Oncolytic virotherapies, as a monotherapy or in combination with other immunotherapeutics, have shown safety and exciting proof-of-concept results in pre-clinical studies as well as in different clinical trials. The therapeutic potential of oncolytic viruses, however, can be severely restricted by multiple innate and adaptive immune barriers that can be overcome using cell-based delivery approaches. Mesenchymal stem cells are particularly attractive carriers of oncolytic viruses due to their unique immunosuppressive properties allowing protection of the virus from complement/antibodies-mediated neutralization and to overcome antiviral cellular immunity in both autologous and allogeneic settings
Methods
As carriers of oncolytic VACV, we used cells a) freshly isolated from adipose tissue stromal vascular fraction (SVF), and b) SVF-derived cultured Adipose-Derived Mesenchymal Stromal/stem Cells (AD-MSC). We analyzed the ability of those carrier cells to take up, protect, amplify the virus as well as to overcome innate and adaptive immune barriers by flow cytometry, microscopy and virus plaque assays of ex vivo co-cultures of cells infected with VACV in the presence of human serum or peripheral blood mononuclear cells from healthy donors. Comparative analyses were performed to establish statistically significant correlations.
Results
We have demonstrated that autologous SVF cells did protect VACV against serum-inactivation. Cell sorting demonstrated that supra adventitial-adipose stromal cells (SA-ASC; CD235a-/CD45-/CD34+/CD146-/CD31-), and pericytes (CD235a-/CD45-/CD34-/CD146+/CD31-) were the two cell populations of SVF cells that were efficient facilitating the delivering of VACV to the tumor cells, validating their clinical use as a tool to potentiate oncolytic virus therapies in autologous settings. We further analyzed the potential of using cultured AD-MSC (derived from CD34+ SA-ASC) as a delivery vehicle in allogeneic settings. AD-MSCs demonstrated ability to protect against serum-inactivation as well as to amplify the virus in the presence of human PBMCs in both autologous and allogeneic settings. This activity can be linked to their intrinsic immunosuppressive properties and the evasion of allogeneic rejection. Moreover, these cells demonstrated ability to provide transient immunosuppression by inhibiting antiviral responses originating from both innate (NK)- and adaptive (T)-immune cells, thus augmenting viral oncolysis and the generation of anti-tumor immunity.
Conclusions
Overall, our findings indicate the feasibility to significantly potentiate oncolytic virotherapy by using either a simple autologous or a more scalable off-the-shelf allogeneic cell-based delivery technology allowing rational design of virus-based therapies that are not dramatically eliminated by immune barriers.
Ethics Approval
The study was approved by International Cell Surgical Society Ethics Board; IRB# ICSS-2016-024

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Selective delivery of exosome-mediated STING agonist to antigen presenting cells results in significantly improved potency and reduced toxicity

Su Chul Jang, PhD[1], Raymond Moniz[1], Christine Sia[1], Joyoti Dey, PhD, MPH[2], Rane Harrison[1], NIKKI ROSS, PhD[1], Ke Xu[1], Kevin Dooley[1], Nuruddeen Lewis[1], Christine McCoy[1], Agata Villiger-Oberbek[1], Scott Estes[1], Jorge Sanchez-Salazar[1], Kyriakos Economides[1], Sriram Sathyanarayanan[1]
[1]Codiak Biosciences, Cambridge, MA, USA; [2]Presage Biosciences, Seattle, WA, USA; [3]Codiak, Cambridge, MA, USA
Correspondence: Sriram Sathyanarayanan (sriram.sathy@codiakbio.com)
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Background
Emerging research has established the role of exosomes as an efficient natural messenger system to deliver macromolecules between cells. We have leveraged this capacity to develop a novel, engineered exosome therapeutic, to selectively deliver agonists of the Stimulator of Interferon Gene (STING) pathway to tumor resident antigen presenting cells (APC).
Methods
ExoSTING is composed of exosomes, which are molecularly engineered to over-express an exosomal membrane glycoprotein, and which are loaded ex vivo with a STING agonist (SA).
Results
In vitro assays with human PBMCs showed ExoSTING enhanced the potency of dendritic cell and monocyte activation and IFN_beta