Combination Therapy with Oncolytic Viruses and CAR T Cells

Abstract

Chronic viral infections (CVI) provide a permissive microenvironment that stimulates the production of chemokines and cytokines within the tumor microenvironment. We hypothesized that the inflammatory cytokine storm would reverse the immunosuppressive microenvironment of solid tumors and change it to one which favors the recruitment of activated immune cells. In this work, we tested the hypothesis that an inflammatory remodeling of the tumor microenvironment through the sustained delivery of type I interferons (IFNs) will enhance the persistence and function of virus-specific T cells. We also show that specific designer modifications can be made to CAR T cells in order to at least, by type I interferon released upon virus infection of tumors which promoted apoptosis, activation, and inhibitory receptor expression. The specific design of CAR modifications can be made to CAR T cells to increase their responsiveness to molecules in the tumor microenvironment to enhance their efficacy. Thus, when the Interferon receptor was knocked out in CAR T cells using CRISP/CAS, these cells were largely refractory to OV associated attrition. Here we show that oncolytic viruses, such as reovirus and VSV, do indeed induce a robust proinflammatory shift in the tumor microenvironment and provided combinatorial therapy with intra-tumoral OV. As a direct result of these studies, we have also explored additional ways to combine CAR T cell therapy with oncolytic viruses to overcome the problems associated with regressive viro-induced "tumor" in the periphery. In these models, CAR T cells can carry oncolytic viruses as a boost into tumors. The CAR T-mediated virus cargo results in significantly enhanced therapy compared to untreated tumors. In conclusion, the combination therapy of oncolytic viruses and CAR T cells using the CRISP/CAS technology to increase CAR T cell intrinsic functionality. In summary, we believe that OV can be used in combination with CAR T cell therapies to enhance the therapeutic efficacy of either modality alone.