Background Tumor relapse due to antigen escape is an essential problem in adoptive T cell therapy (ACT) with limited antigen targets, such as CAR T cells. This is especially true for solid tumors since they are more heterogeneous than hematological malignancies. Moreover, systemically delivered T cells infiltrate poorly into the solid tumors and are susceptible to the immune suppressive tumor microenvironment (TME) ("cold tumor"). On the other hand, oncolytic viruses, such as oncolytic adenovirus Delta-24-RGDOX developed by our group, can turn "cold tumor" into immune active "hot tumor" and induce immune response against a variety of tumor-associated antigens (TAAs). Thus, we hypothesize that Delta-24-RGDOX potentiates the effect of ACT through activating TME and antigen spread.

Methods We used B16-OVA-C57BL/6 subcutaneous (s.c.)/s.c. melanoma model to assess systemic therapeutic effect in disseminated tumors. gp100-TCR CD8+ T cells were injected into the first tumor, followed by three injections of Delta-24-RGDOX into the same tumor. Leukocytes from the tumors were profiled for surface markers with flow cytometry. Activity of splenocytes against specific TAAs and tumor cells was measured with ELISA.

Results Delta-24-RGDOX injections following gp100-TCR CTLs in the first tumor increased total CD8+ leukocyte presence within both tumors. Further analysis revealed that treatments with either agents or combination dramatically downregulated CD62L whose expression kept at low levels in adopted gp100-TCR and endogenous OVA-specific CTLs. Moreover, although Delta-24-RGDOX significantly upregulated PD-1, TIM3 and LAGs in CD8+ leukocytes, its effect on these immune inhibitors was different in gp100-TCR or OVA-specific CTLs. The overall levels of these inhibitors in OVA-specific CTLs were remarkably higher than in gp100-TCR CTLs or CD8+ leukocytes. The virus slightly increased the inhibitors in the gp100-TCR CTLs from the treated tumor and decreased the inhibitors in the gp100-TCR CTLs from the untreated tumor. Importantly, PD-1 levels in OVA-specific CTLs were significantly downregulated in OVA-specific CTLs from both treated and untreated tumors although the other two inhibitors kept at a steady lower level. As a result, Delta-24-RGDOX drastically increased the density of OVA-specific CTLs in both tumors and the combination synergistically enhanced the effect. Consistently, the splenocytes from the combination group showed significant stronger response against other TAAs (OVA and TRP2) than gp100, leading to higher activity against tumor cells.

Conclusions Our data demonstrate that localized treatment with intratumoral ACT followed by Delta-24-RGDOX enhances global immune activation and antigen spread to expand antitumor T cell repertoire, leading to efficacious systemic anti-tumor immunity.

REFERENCE