LATENT HUMAN HERPESVIRUS 6 IS REACTIVATED IN CHIMERIC ANTIGEN RECEPTOR T CELLS

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Background Cell therapies have mediated durable clinical responses for patients with cancer, but the risks associated with engineering therapeutic human cells ex vivo are still being understood. We currently lack a comprehensive mechanistic understanding of underlying toxicities observed in patients receiving FDA-approved T cell therapies, including recent reports of encephalitis caused by human herpesvirus 6 (HHV-6) reactivation.

Methods We combine comprehensive public data mining spanning petabases of genomic sequencing data (public RNA-seq, DNA-seq) to identify sources of viral reactivation from existing genomics sequencing studies. We complement extensive public data reanalysis with our own single-cell genomics experiments that simultaneously identify viral gene expression/reactivation with host gene expression programs.

Results Via petabase-scale viral genomics mining, we examine the landscape of human latent viral reactivation and demonstrate that HHV-6B can become reactivated in human CD4+ T cell in vitro cultures. Using single-cell sequencing, we identify a rare population of HHV-6 ‘super-expressors’ (~1 in 300–10,000 cells) that possess high viral transcriptional activity in research-grade allogeneic chimeric antigen receptor (CAR) T cells. By analyzing single-cell sequencing data from patients receiving cell therapy products that are FDA-approved or in clinical studies, we identify the presence of CAR+, HHV-6 super-expressor T cells in patients in vivo.

Conclusions Our study demonstrates the utility of comprehensive genomics analyses to implicate cell therapy products as a potential source contributing to lytic HHV-6 reported in clinical trials. Further, our characterization of in vitro viral reactivation may influence the design, production, and monitoring of autologous and allogeneic cell therapies, and future prospective studies that account for HHV-6 reactivation in clinical products will determine whether these findings warrant changes to current manufacturing and clinical guidelines.

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