Development of immunotherapy strategies for brain tumors

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Abstract

The central nervous system (CNS) is often considered an "immune-privileged" site. However, as observed in autoimmune conditions, T-cells can traverse the blood-brain barrier (BBB) via chemokine axes and multistep adhesion processes. We have made long-standing contributions by reporting the critical role of an integrin very late antigen 4 (VLA4) and a chemokine receptor CXCR3 for T-cell homing in CNS tumors. The development of safe and effective chimeric antigen receptor (CAR)T therapy for GBM must overcome multiple challenges, including on-target off-tumor toxicity, heterogeneity of antigen expression, and exhaustion of CART cells. To this end, we adopted a novel synthetic Notch (synNotch) receptor system and developed innovative T cell circuits that recognize tumor cells based on the "prime-and-kill" strategy. In this system, the first antigen, which is expressed exclusively on GBM cells (e.g., EGFRvIII), primes the T cells to induce expression of a CAR that recognizes IL-13Rα2 and EphA2, thereby eradicating glioblastoma (GBM) cells expressing either EphA2 or IL-13Rα2. We reported that EGFRvIII-synNotch-primed EphA2/IL-13Rα2 CAR (E-SYNC) are effectively but restrictedly activated by EGFRvIII as the GBM-specific signal, thereby leading to complete eradication of orthotopic patient-derived xenografts with heterogeneous EGFRvIII expression, without attacking EphA2/IL-13Rα2-positive cells outside of the CNS. Furthermore, these synNotch-CART cells were more efficacious than conventional EphA2/IL-13Rα2 CART cells, associated with excellent persistence, and more juvenile in phenotype than conventional CART cells. We recently opened the phase I study evaluating the E-SYNC T-cells in patients with GBM (NCT06186401).

Furthermore, we address other crucial issues. We recently discovered novel mechanisms in which GBM-stimulated neuronal activities can suppress anti-GBM immune response via expression of thrombospondin-1. The use of FDA-approved anti-epileptic drugs can reverse this program and restore the immune response. We also reported a novel class of antigens derived from tumor-specific alternative splicing. I will present overviews of our current laboratory activities.

Biography

Dr. Okada is a Professor of Neurosurgery at the University of California, San Francisco, and a member of Parker Institute for Cancer Immunotherapy. Trained as a physician-scientist, Dr. Okada has been dedicated to understanding the immune mechanisms in brain tumors and developing novel immunotherapy strategies for brain tumor patients for over 25 years. Dr. Okada has translated his laboratory discoveries and developed a total of 8 investigational new drug (IND) applications that the FDA approved for early-phase clinical trials, including genetically engineered glioma vaccines and T cell receptor (TCR)- or chimeric antigen receptor (CAR)-transduced T cell therapy in both adult and pediatric patients. Recently, Dr. Okada developed a novel synNotch-primed CAR system with Dr. Wendell Lim to overcome the antigen heterogeneity, off-tumor toxicity, and T-cell exhaustion issues. Dr. Okada is opening the first-in-human study of this approach. Dr. Okada's team has also pioneered discoveries of novel immunoregulatory mechanisms in gliomas, such as one mediated by myeloid-derived suppressor cells (MDSC) and mutations of the isocitrate dehydrogenase (IDH)1 and IDH2. Dr. Okada is an elected member of the American Society for Clinical Investigation (2010-present), an honored society for physicians who promote laboratory science to the clinic.