Functional Tuning of CARs Reveals Signaling Threshold above Which CD8+ CTL Antitumor Potency Is Attenuated due to Cell Fas–FasL-Dependent AICD


Synopsis: Kunkele and colleagues demonstrate in a solid tumor model that CARs with the highest in vitro activity exhibit attenuated antitumor potency in vivo as CTLs expressing hyperactive CARs are susceptible to activation-induced cell death; CARs tuned for moderate signaling outputs mediate effective tumor eradication.

Genetic Evidence That Intratumoral T-cell Proliferation and Activation Are Associated with Recurrence and Survival in Patients with Resected Colorectal Liver Metastases

Ajay V. Maker, Hiromichi Ito, Qianxing Mo, Elliot Weisenberg, Li-Xuan Qin, Simon Turcotte, Shishir Matihel, Jinru Shia, Leslie Blumgart, Yuman Fong, William R. Jamagin, Ronald P. DeMatteo, and Michael I. D’Angelica

Synopsis: Maker and colleagues analyzed liver tumor specimens and outcomes from 96 patients with colorectal cancer liver metastases and report that genetic evidence of T-cell activation/proliferation in liver tumors, specifically the increased expression of TNFSF14/LIGHT, is associated with longer overall and disease-free survival.

Three Steps to Breaking Immune Tolerance to Lymphoma: A Microparticle Approach

Amani Makkouk, Vijaya B. Joshi, Caitlin D. Lemke, Amaraporn Wongrakpanich, Alicia K. Olivier, Sue E. Blackwell, Aliasger K. Salem, and George J. Weiner

Synopsis: Makkouk and colleagues show that intratumoral delivery of doxorubicin in polylactide-co-glycolide microparticles combined with antibodies against OX40 and CTLA-4 induced T cell-dependent systemic responses that enhanced T-cell infiltration into and eradication of distant tumors and improved survival in mouse models of lymphoma.

Induction of T-cell Immunity Overcomes Complete Resistance to PD-1 and CTLA-4 Blockade and Improves Survival in Pancreatic Carcinoma

Rafael Winograd, Katelyn T. Byrne, Rebecca A. Evans, Pamela M. Odorizzi, Anders R.I. Meyer, David L. Bajor, Cynthia Glendenin, Ben Z. Stanger, Emma E. Forth, E. John Wherry, and Robert H. Vonderheide

Synopsis: Winograd and colleagues used an engineered KPC mouse model of pancreatic ductal adenocarcinoma (PDA) reflecting that of human PDA to show that baseline refractoriness to checkpoint inhibitors can be rescued by priming a T-cell response with αCD40 plus chemotherapy with gemcitabine and nab-paclitaxel.

Galectin-3 Shapes Antitumor Immune Responses by Suppressing CD8+ T Cells via LAG-3 and Inhibiting Expansion of Plasmacytoid Dendritic Cells

Theodore Kouo, Lanqing Huang, Alexandra B. Puscek, Minwei Cao, Sara Solt, Todd Armstrong, and Elizabeth Jaffe

Synopsis: Kouo and colleagues report the development of neutralizing Abs to galectin-3 in PDA patients who showed improved survival in response to a GM-CSF–secreting allogeneic tumor vaccine, and they propose that carbohydrate signaling be considered as “signal 4” of immune-cell programming and differentiation.

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ABOUT THE MASTER

Ellis L. Reinherz, MD, is a professor of medicine at Harvard Medical School (HMS) and chief of the Laboratory of Immunobiology and codirector of the Cancer Vaccine Center at the Dana-Farber Cancer Institute (DFCI). Dr. Reinherz is known for his basic research that has revealed key functional and structural discoveries about TCRs, including their CD3 signaling subunit components, and how the TCRs, along with the CD4 and CD8 coreceptor molecules that he identified, bind to the pMHC. More recently he and his colleagues have defined the TCR as an anisotropic mechanosensor, offering a physical solution to the longstanding question of how T cells can achieve rapid and specific sensing of a single peptide bound to an MHC molecule among a sea of unrelated peptides arrayed on the surface of an antigen-presenting cell with exquisite specificity and dynamic range. His findings on the molecular basis of adaptive immunity have implications for rational vaccine design and human immunotherapy efforts in the clinic. He has authored more than 400 research publications in human and murine immunology, spanning areas in basic and translational research. The development of OKT3, the first FDA-approved monoclonal antibody (mAb) in humans, resulted from his studies demonstrating the ability of the mAb to inhibit antigen-specific T-cell responses.

Dr. Reinherz was born in Malden, MA, and is a distinguished alumnus of the Middlesex School in Concord, MA. He entered Harvard College in 1968 and graduated summa cum laude in 1971 with an AB degree. He received his medical degree from HMS in 1975. After completing his internship and residency at the Massachusetts General Hospital and a hematology fellowship at the Brigham and Women’s Hospital, Dr. Reinherz pursued research training as a postdoctoral fellow in the laboratory of Stuart Schlossman. Subsequently he was recruited to join the faculty of DFCI and HMS as an assistant professor of medicine, and he has held the rank of HMS professor of medicine since 1994. Dr. Reinherz is a member of the editorial boards of several basic and clinical immunology journals; he is the coeditor of the T-cell biology section of *Frontiers in Immunology*. Currently he chairs the steering committee of the NIH Human Immunology Project Consortium. Dr. Reinherz is a member of the American Federation for Clinical Research, the American Society of Hematology, the American Society of Clinical Investigation, and the American Association of Immunologists (AAI). He is the recipient of the 2011 AAI Human Immunology Award.