CANCER IMMUNOLOGY AT THE CROSSROADS

Revolutionizing Cancer Immunology: The Power of Next-Generation Sequencing Technologies

Meromit Singer and Ana C. Anderson

PRIORITY BRIEFS

A Synthetic DNA, Multi-Neoantigen Vaccine Drives Predominately MHC Class I CD8⁺ T-cell Responses, Impacting Tumor Challenge

Elizabeth K. Duperret, Alfredo Perales-Puchalt, Regina Stoltz, Hiranjith G.H., Nitin Mandloi, James Barlow, Amitabha Chaudhuri, Niranjan Y. Sardesai, and David B. Weiner

A multi-neoantigen DNA cancer vaccine was designed and tested against multiple tumor types. The vaccine was efficiently delivered and elicited CD8⁺ T-cell responses, highlighting how this platform could be used to target a variety of neoantigens in cancer.

An Antagonism of IAPs Enhances CAR T-cell Efficacy

Jessica Michie, Paul A. Beavis, Andrew J. Freeman, Stephin J. Vervoort, Kelly M. Ramsbottom, Vignesh Narasimhan, Emily J. Lelliott, Najoua Lalaoui, Robert G. Ramsay, Ricky W. Johnstone, John Silke, Phillip K. Darcy, Ilia Voskoboinik, Conor J. Kearney, and Jane Oliaro

Antagonizing “inhibitor of apoptosis proteins” (IAPs) with the clinical SMAC-mimetic, birinapant, enhances the antitumor activity of CAR T cells in a TNF-dependent, perforin-independent manner. The data illustrate the potential for this combination therapy to enhance antitumor efficacy.

RESEARCH ARTICLES

Intracellular Activation of Complement C3 Leads to PD-L1 Antibody Treatment Resistance by Modulating Tumor-Associated Macrophages

Haoran Zha, Xinxin Wang, Ying Zhu, Diangang Chen, Xiao Han, Fei Yang, Jianbao Gao, Chunyan Hu, Chi Shu, Yi Feng, Yulong Tan, Jinyu Zhang, Yongsheng Li, Yisong Y. Wan, Bo Guo, and Bo Zhu

Intracellular activation of complement C3 by tumor cells was found to suppress CD8⁺ T-cell responses by modulating tumor-associated macrophages. The data suggest that a combined strategy of PD-L1 blockade with C3 targeting may enhance antitumor immunity.

CD16⁺ NKG2A⁺ Natural Killer Cells Infiltrate Breast Cancer–Draining Lymph Nodes

Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, and Anne Caignard

NK cells infiltrating breast cancer–draining lymph nodes express activating NK receptors, the inhibitory NKG2A receptor, and PD-1 and are capable of degranulation and tumor cell lysis. These findings support potential therapeutic development targeting these cells.

Antagonism of IAPs Enhances CAR T-cell Efficacy

Jessica Michie, Paul A. Beavis, Andrew J. Freeman, Stephin J. Vervoort, Kelly M. Ramsbottom, Vignesh Narasimhan, Emily J. Lelliott, Najoua Lalaoui, Robert G. Ramsay, Ricky W. Johnstone, John Silke, Phillip K. Darcy, Ilia Voskoboinik, Conor J. Kearney, and Jane Oliaro

Antagonizing “inhibitor of apoptosis proteins” (IAPs) with the clinical SMAC-mimetic, birinapant, enhances the antitumor activity of CAR T cells in a TNF-dependent, perforin-independent manner. The data illustrate the potential for this combination therapy to enhance antitumor efficacy.

CD16⁺ NKG2A⁺ Natural Killer Cells Infiltrate Breast Cancer–Draining Lymph Nodes

Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, and Anne Caignard

NK cells infiltrating breast cancer–draining lymph nodes express activating NK receptors, the inhibitory NKG2A receptor, and PD-1 and are capable of degranulation and tumor cell lysis. These findings support potential therapeutic development targeting these cells.

An Antibody Designed to Improve Adoptive NK-Cell Therapy Inhibits Pancreatic Cancer Progression in a Murine Model

Jaemin Lee, Tae Heung Kang, Wonbeak Yoo, Hyunjoo Choi, Seongyea Jo, Suyong Seo, Sun-Ilk Lee, Ji-Su Kim, Duck Cho, Janghwan Kim, Jeong-Yoon Kim, Eun-Soo Kwon, and Seokho Kim

Antibody targeting of the EGFR on tumor cells is a form of immunotherapy that works by inducing NK-cell killing through antibody–NK-cell interactions. Resistance develops via the downregulation of the interaction molecules; thus, NK cells are not activated.

Mouse PVRIG Has CD8⁺ T Cell–Specific Coinhibitory Functions and Dampens Antitumor Immunity

Dalal S. Aldegahither, David J. Zahavi, Joseph C. Murray, Elana J. Fertig, Garrett T. Graham, Yong-Wei Zhang, Allison O’Connell, Junfeng Ma, Sandra A. Jablonski, and Louis M. Weiner

Expression of PVRIG, an immune checkpoint target, is upregulated on activated and tumor-infiltrating CD8⁺ T cells in mice. Disrupting the PVRIG (receptor)/PVRL2 (ligand) pathway using PVRIG-deficient mice or monoclonal antibodies inhibited tumor growth.

See related article, p. 257.
PVRIG and PVRL2 Are Induced in Cancer and Inhibit CD8⁺ T-cell Function
Sarah Whelan, Eran Ophir, Maya F. Kotturi, Ofer Levy, Sudipto Ganguly, Ling Leung, Ilan Vaknin, Sandeep Kumar, Liat Dassa, Kyle Hansen, David Bernados, Benjamin Murter, Abba Soni, Janis M. Taube, Amanda Nickles Fader, Tian-Li Wang, Ie-Ming Shih, Mark White, Drew M. Pardoll, and Spencer C. Liang

PVRIG acts as an immune checkpoint in human tumors that express its ligands. A PVRIG antagonistic antibody, COM701, may be useful as monotherapy or combined with other immunotherapies. COM701 is in clinical trials for patients with solid tumors.

See related article, p. 244.

Late-Stage Tumor Regression after PD-L1 Blockade Plus a Concurrent OX40 Agonist
Fanny Polesso, Andrew D. Weinberg, and Amy E. Moran

PD-L1 blockade with concurrent OX40 agonism enhanced frequency and functionality of antigen-specific CD8⁺ T cells in mouse models of large tumors. Th1 skewing, CD8⁺ T cell metabolism, and antitumor immunity were augmented, and tumor regression was promoted.

Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function
Paul E. Clavijo, Jay Friedman, Yvette Robbins, Ellen C. Moore, Ernest Smith, Maurice Zauderer, Elizabeth E. Evans, and Clint T. Allen

Neutralization of Semaphorin4D within the tumor microenvironment inhibited recruitment and function of myeloid-derived suppressor cells, sensitizing carcinomas to CTLA-4 or PD-1 blockade. Semaphorin4D mAb may be useful as an adjuvant for immune checkpoint immunotherapies.

LncRNA-MM2P Identified as a Modulator of Macrophage M2 Polarization
Ji Cao, Cong Dong, Li Jiang, Yanling Gong, Meng Yuan, Jieqiong You, Wen Meng, Zhanlei Chen, Nian Zhang, Qinjie Weng, Hong Zhu, Qiaojun He, Meidan Ying, and Bo Yang

A long noncoding RNA (lncRNA), called lncRNA-MM2P, is specifically expressed in M2 macrophages, and its knockdown prevents polarization. This lncRNA could serve as a marker for protumoral tumor-associated macrophages and highlights the role of lncRNAs in macrophage polarization.

Autocrine TGFβ Is a Survival Factor for Monocytes and Drives Immunosuppressive Lineage Commitment
Alba González-Junca, Kyla E. Driscoll, Ilenia Pellicciotta, Shisuo Du, Chen Hao Lo, Ritu Roy, Renate Parthy, Iliana Tenvoorren, Diana M. Marquez, Matthew H. Spitzer, and Mary Helen Barcellos-Hoff

TGFβ expression in lung adenocarcinoma correlates with myeloid markers and poor prognosis in patients. TGFβ promotes immunosuppressive myeloid cell differentiation at the expense of DCs, and inhibition of TGFβ reverses this effect, promoting antigen-presenting DC maturation.

IL13-Mediated Dectin-1 and Mannose Receptor Overexpression Promotes Macrophage Antitumor Activities through Recognition of Sialylated Tumor Cells
Mohamad Alaeddine, Mélissa Prat, Vérona Poinsot, Valérie Gouazé-Andersson, Hélène Authier, Etienne Meunier, Lise Lefèvre, Camille Alric, Christophe Dardenne, José Bernad, Laurent Alich, Bruno Segui, Patricia Balard, François Coudrec, Bettina Coudrec, Bernard Pipy, and Agnès Coste

Cytotoxicity of tumor-associated macrophages may be enhanced through IL13 activation, enhanced expression of C-type lectin receptors (CLRs), and subsequent recognition of tumor cells through sialic acid. These results identify CLRs as potential therapeutic targets to improve antitumor responses.

Lactate-Mediated Acidification of Tumor Microenvironment Induces Apoptosis of Liver-Resident NK Cells in Colorectal Liver Metastasis
Cathal Harmon, Mark W. Robinson, Fiona Hand, Dalal Almuaili, Keno Mentor, Diarmaid D. Houlihan, Emir Hoti, Lydia Lynch, Justin Geoghegan, and Cliona O’Farrell

In colorectal liver metastasis, liver-resident NK cells are depleted from the tumor microenvironment. NK-cell apoptosis is induced by metabolic changes resulting from tumor-derived lactate. Targeting tumor metabolism represents a promising therapeutic avenue to restore liver NK-cell activity.
ABOUT THE COVER

Complement is known to play a role in antitumor immunity. However, specific complement molecules can be enriched in the tumor microenvironment where they can regulate the function of tumor and immune cells to promote tumor progression, and thus, interfere with immune-checkpoint blockade efficacy. Zha et al. show that expression and activation of complement C3 in murine tumor cells created an immunosuppressive milieu by facilitating the accumulation and suppressive function of tumor-associated macrophages, mediated by signaling through the C3a receptor. Deletion of C3 in the tumor cells enhanced the efficacy of checkpoint blockade, illustrating the potential of targeting tumor cell-derived complement to boost responses to immune-checkpoint blockade. Read more in this issue on page 193. Original image from Fig. 1D. Artwork by Lewis Long.