WHAT WE'RE READING

881 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

882 Treg Fragility: A Prerequisite for Effective Antitumor Immunity?
Abigail E. Overacre-Delgoffe and Dario A.A. Vignali

RESEARCH ARTICLES

888 The Mutation-Associated Neoantigen Functional Expansion of Specific T Cells (MANAFEST) Assay: A Sensitive Platform for Monitoring Antitumor Immunity
The MANAFEST assay tracks the antitumor immune response in all biological compartments of patients receiving checkpoint blockade immunotherapy. It matches antigen specificity with T-cell clonotypic identity, which enables the monitoring of patients through prognostic and correlative analyses.

900 Primary T Cells from Cutaneous T-cell Lymphoma Skin Explants Display an Exhausted Immune Checkpoint Profile
Christian Querfeld, Samantha Leung, Patricia L. Myskowski, Shane A. Curran, Debra A. Goldman, Glenn Heller, Xiwei Wu, Sung Hee Kil, Sneh Sharma, Kathleen J. Finn, Steven Horwitz, Alison Moskowitz, Babak Mehrara, Steven T. Rosen, Allan C. Halpern, and James W. Young
T cells are exhausted in lesions of cutaneous T-cell lymphoma. Genome-wide mRNA expression analysis and flow cytometry indicated that such T cells overexpress immune checkpoints, suggesting avenues for more effective therapies.

910 Exosomes Shuttle TREX1-Sensitive IFN-Stimulatory dsDNA from Irradiated Cancer Cells to DCs
Julie M. Diamond, Claire Vanpouille-Box, Sheila Spada, Nils-Petter Rudqvist, Jessica R. Chapman, Beatrix M. Ueberheide, Karsten A. Pilones, Yasmeen Sarfaraz, Silvia C. Formenti, and Sandra Demaria
Irradiated tumor-derived exosomes were shown to contain dsDNA that, when transported to DCs, induced upregulation of costimulatory molecules and IFN-1 responses. In vivo, vaccination with the irradiated tumor-derived exosomes reduced tumor growth and induced potent CD8\(^+\) T-cell responses.

921 PD-L1 Binds to B7-1 Only In Cis on the Same Cell Surface
Apoorvi Chaudhri, Yanping Xiao, Alyssa N. Klee, Xiaoxu Wang, Baogong Zhu, and Gordon J. Freeman
PD-L1 and B7-1 only interact in cis on the same cell surface, but not in trans between two cells. Their coexpression is found, for example, on tumor-infiltrating myeloid cells. Cis B7-1 competes with trans PD-1 for binding to PD-L1.

930 Antitumor Activity of TLR7 Is Potentiated by CD200R Antibody Leading to Changes in the Tumor Microenvironment
Zofia Pilch, Katarzyna Tonecka, Agata Braniewska, Zuzanna Sas, Marcin Skorzymski, Louis Boon, Jakub Golab, Linde Meynard, and Tomasz P. Rygiel
Treatments that alter the immune composition of the tumor microenvironment affect antitumor activity. Stimulating TLR7 in combination with an agonistic mAb to CD200R improved the antitumor effects of TLR7 signaling. Subsequent changes affected myeloid cell composition and activation.

941 Wnt3a/β-Catenin Signaling Conditions Differentiation of Partially Exhausted T-effector Cells in Human Cancers
Valeria Schinzari, Eleonora Timperi, Giulia Pecora, Francesco Palmucci, Daniela Gallerano, Alessio Grimaldi, Daniela Angela Covino, Nicola Guglielmo, Fabio Melandro, Emi Manzi, Andrea Saguotta, Francesco Lancellotti, Luca Sacco, Piero Chirletti, Gian Luca Grazzi, Massimo Rossi, and Vincenzo Barnaba
The Wnt3a/β-catenin pathway supports a protumor environment. Secreted Wnt3α was found to be overexpressed in human colorectal and hepatocellular carcinomas, interfere with naive and effector T-cell differentiation, and affect the function of infiltrating T cells.

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Wnt3a Neutralization Enhances T-cell Responses through Indirect Mechanisms and Restrains Tumor Growth

Ilenia Pacella, Ilenia Cammarata, Chiara Focaccetti, Stefano Atacci, Alessandro Gulino, Claudio Tripodo, Micol Rava, Vincenzo Barnaba, and Silvia Piconese

The Wnt3a/β-catenin pathways modulate antitumor T-cell responses. In a mouse tumor model, administration of an anti-Wnt3a neutralizing antibody controlled tumor growth by reshaping signals in the tumor microenvironment.

Enhanced Cancer Immunotherapy with Smad3-Silenced NK-92 Cells

Qing-Ming Wang, Patrick Ming-Kuen Tang, Guang-Yu Lian, Chunjie Li, Jinhong Li, Xiao-Ru Huang, Ka-Fai To, and Hui-Yao Lan

Knockdown of Smad3 in the NK-92 cell line, currently in clinical trials, improved its anticancer effectiveness relative to the parental line in vitro and in mice bearing human tumors. This may represent a promising approach for cancer treatment.

Experimental Lung Metastases in Mice Are More Effectively Inhibited by Blockade of IL23R than IL23

Juming Yan, Stacey Allen, Dipti Vijayan, Xian-Yang Li, Heidi Harjunpää, Kazuyoshi Takeeda, Jing Liu, Daniel J. Cua, Mark J. Smyth, and Michele W.L. Teng

IL23 is an inflammatory cytokine with protumoral effects and is present in the serum of patients with some malignancies. In three different mouse tumor models, blocking IL23R was more effective at suppressing metastases than was neutralizing IL23.

ABOUT THE COVER

Cutaneous T-cell lymphoma (CTCL) develops in chronic inflammatory conditions. However, how this inflammation affects T-cell antitumor functions remains unclear. Querfeld et al. showed that in skin explants and skin biopsies from 86 patients with CTCL, mature PD-L1⁺ dendritic cells are detected and T cells are activated, but the T cells also express immune checkpoint molecules known to be markers of exhaustion. RNAseq at different disease stages demonstrated that expression of checkpoint molecules increased with progression, indicating that an exhausted T-cell phenotype is a hallmark in CTCL. Read more in this issue starting on page 900. Original image is an H&E stain of a patch/plaque lesion, from Fig. 4. Artwork by Lewis Long.