

CANCER IMMUNOLOGY RESEARCH

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RESEARCH ARTICLES

- 265** **The IKZF1-IRF4/IRF5 Axis Controls Polarization of Myeloma-Associated Macrophages**
 Dimitrios Mouggiakakos, Christian Bach, Martin Böttcher, Fabian Beier, Linda Röhrner, Andrej Stoll, Michael Rehli, Claudia Gebhard, Christopher Lischer, Martin Eberhardt, Julio Vera, Maike Büttner-Herold, Katrin Bitterer, Heidi Balzer, Magdalena Leffler, Simon Jitschin, Michael Hundemer, Mohamed H.S. Awwad, Martin Busch, Steffen Stenger, Simon Völkl, Christian Schütz, Jan Krönke, Andreas Mackensen, and Heiko Bruns
 Lenalidomide treatment for multiple myeloma skews M2-like macrophages to an M1 phenotype because lenalidomide triggers IKZF1 degradation, increasing IRF5 expression and decreasing IRF4. Modulating IKZF1 levels might provide a way to control macrophage polarization for cancer treatment.
 See related Spotlight, p. 254

279 **Antitumor Effects of CAR T Cells Redirected to the EDB Splice Variant of Fibronectin**

Jessica Wagner, Elizabeth Wickman, Timothy I. Shaw, Alejandro Allo Anido, Deanna Langfitt, Jinghui Zhang, Shaina N. Porter, Shondra M. Pruett-Miller, Heather Tillman, Giedre Krenciute, and Stephen Gottschalk
 CAR T cells targeting the EDB splice variant of fibronectin, a pan-cancer solid tumor target, have potent antitumor activity in preclinical solid tumor models. They can target not only tumor cells but also the tumor vasculature.

291 **ONCR-177, an Oncolytic HSV-1 Designed to Potently Activate Systemic Antitumor Immunity**

Brian B. Haines, Agnieszka Denslow, Peter Grzesik, Jennifer S. Lee, Terry Farkaly, Jacqueline Hewett, Daniel Wambua, Lingxin Kong, Prajna Behera, Judith Jacques, Caitlin Goshert, Michael Ball, Allison Colthart, Mitchel H. Finer, Melissa W. Hayes, Sonia Feau, Edward M. Kennedy, Lorena Lerner, and Christophe Quéva
 ONCR-177 is a next-generation oncolytic virus being tested in the clinic. Preclinical efficacy and safety are reported and highlight the treatment's use as a single-agent, as well as in combination with immune checkpoint blockade.

309 **IL1 β Promotes Immune Suppression in the Tumor Microenvironment Independent of the Inflammasome and Gasdermin D**

Máté Kiss, Lieselotte Vande Walle, Pedro H.V. Saavedra, Els Lebegge, Helena Van Damme, Aleksandar Murgaski, Junbin Qian, Manuel Ehling, Samantha Pretto, Evangelia Bolli, Jiri Keirsse, Pauline M.R. Bardet, Sana M. Arnouk, Yvon Elkrim, Maryse Schmoetten, Jan Brughmans, Ayla Debraekeleer, Amelie Fossoul, Louis Boon, Geert Raes, Geert van Loo, Diether Lambrechts, Massimiliano Mazzone, Alain Beschin, Andy Wullaert, Mohamed Lamkanfi, Jo A. Van Genderachter, and Dama Laoui
 IL1 β is implicated in cancer progression. The authors show that IL1 β promotes neutrophil accumulation in tumors and suppresses antitumor immunity independently of the inflammasome, suggesting that therapeutic inflammasome inhibition will not limit IL1 β production in certain cancer types.

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324 The Tumor Microenvironment Impairs Th1 IFN γ Secretion through Alternative Splicing Modifications of *Irf1* Pre-mRNA

Antoine Bernard, Christophe Hibos, Corentin Richard, Etienne Viltard, Sandy Chevrier, Sophie Lemoine, Joséphine Melin, Etienne Humblin, Romain Mary, Théo Accogli, Fanny Chalmin, Mélanie Bruchard, Paul Peixoto, Eric Hervouet, Lionel Apetoh, François Ghiringhelli, Frédérique Végran, and Romain Boidot

TGF β in the tumor microenvironment induces alternative splicing of the transcription factor IRF1, giving rise to a shortened isoform (IRF1 Δ 7) specifically in CD4⁺ Th1 cells. IRF1 Δ 7 inhibits Th1 IFN γ production, highlighting a potential target to boost antitumor responses.

337 A Machine Learning Approach Yields a Multiparameter Prognostic Marker in Liver Cancer

Xiaoli Liu, Jilin Lu, Guanxiong Zhang, Junyan Han, Wei Zhou, Huan Chen, Henghui Zhang, and Zhiyun Yang
Using a machine learning-based strategy, a multiparametric prognostic model was developed. The constructed 20-feature gradient-boosting survival classifier reproducibly identifies patients with hepatocellular carcinoma (HCC) that are at the greatest risk of HCC-related death.

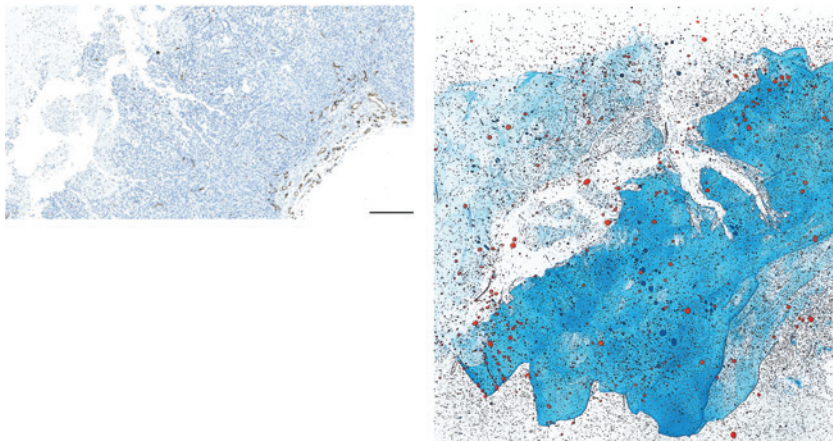
348 Notch-Regulated Dendritic Cells Restrain Inflammation-Associated Colorectal Carcinogenesis

Lei Wang, Shuiliang Yu, Ernest R. Chan, Kai-Yuan Chen, Cui Liu, Danian Che, Amad Awadallah, Jay Myers, David Askew, Alex Y. Huang, Ivan Maillard, Dan Huang, Wei Xin, and Lan Zhou

Conventional dendritic cells (DC) play a key role in the anti-tumor immune response. The data show that Notch2 deletion in all cells or in only DCs promotes inflammation-associated colorectal carcinogenesis; targeting Notch2-controlled DCs could restrain colon cancer.

ABOUT THE COVER

Chimeric antigen receptor (CAR) T cells have limited efficacy against solid tumors. Wagner and colleagues address this problem and show that CAR T cells targeting the EDB (extra domain B) splice variant of fibronectin, a pan-cancer solid tumor target, have potent antitumor activity in preclinical solid tumor models. EDB-targeting CAR T cells kill tumor targets *in vitro* and *in vivo*, while also inducing bystander killing and remodeling of the tumor vasculature. EDB-CAR T cells also persist long-term after treatment and protect animals against subsequent tumor challenges. The data highlight a cancer-specific splice variant that can safely be targeted. Read more in this issue on page 279. Original image from Supplementary Fig. S14. Artwork by Lewis Long.



Cancer Immunology Research

9 (3)

Cancer Immunol Res 2021;9:253-361.

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