WHAT WE’RE READING
853  A Sampling of Highlights from the Literature

IN THE SPOTLIGHT
854  Arid5a: A Missing Link between EMT and Tumoral Immune Resistance
Benoit J. Van den Eynde
See related article, p. 862
855  Noncanonical Functions of C1s Complement Its Canonical Functions in Renal Cancer
Elena Magrini and Cecilia Garlanda
See related article, p. 891

CANCER IMMUNOLOGY AT THE CROSSROADS
856  Mitochondria as Playmakers of CAR T-cell Fate and Longevity
Hosein Rostamian, Mohammad Khapoor-Kooheh, Keyvan Fallah-Mehrjardi, Hamid R. Mirzaei, and Christine E. Brown

RESEARCH ARTICLES
862  Arid5a Promotes Immune Evasion by Augmenting Tryptophan Metabolism and Chemokine Expression
Arid5a is a key molecule in inflammatory and autoimmune diseases, yet its role in cancer progression is unknown. Arid5a expression is shown to increase in mesenchymal tumors and augment immune evasion by promoting tryptophan catabolism and chemokine expression.
See related Spotlight, p. 854
877  Site-Dependent Immune Escape Due to Impaired Dendritic Cell Cross-Priming
Mark S. Diamond, Jeffrey H. Lin, and Robert H. Vonderheide
Data show that tumor antigenicity is necessary, but not sufficient, for effective cancer immune surveillance. Neot antigen-expressing tumors can escape in certain host tissue microenvironments in the absence of immunoeediting despite displaying high tumor immunogenicity at other sites.
891  Complement C1s and C4d as Prognostic Biomarkers in Renal Cancer: Emergence of Noncanonical Functions of C1s
Marie V. Daugan, Margot Revel, Jules Russick, Marie-Agnès Dragon-Durey, Christine Gaboriaud, Tania Robe-Rykine, Victoria Poillerat, Anne Grunenwald, Guillaume Lacroix, Antoine Bougouin, Maxime Meylan, Virginie Verkarre, Stephane M. Oudard, Arnaud Mejean, Yann A. Vano, Geraldine Perkins, Pierre Valdivie, Xavier Cathelineau, Rafael Sanchez-Salas, Diane Damotte, Veronique Fremeaux-Bacchi, Isabelle Cremer, Catherine Sauvès-Fridman, Wolf H. Fridman, and Lubka T. Roumenina
C1s is shown to drive renal cell carcinoma progression by local complement activation and complement cascade–unrelated, intracellular, noncanonical functions. This modulates the tumor microenvironment by impacting tumor cell proliferation, survival, and interaction with T cells.
See related Spotlight, p. 855
909  Intracellular Factor H Drives Tumor Progression Independently of the Complement Cascade
Marie V. Daugan, Margot Revel, Romane Thounon, Marie-Agnès Dragon-Durey, Tania Robe-Rykine, Carine Torset, Nicolas S. Merle, Rémi Noé, Virginie Verkarre, Stephane Marie Oudard, Arnaud Mejean, Pierre Valdivie, Xavier Cathelineau, Rafael Sanchez-Salas, Mathew C. Pickering, Isabelle Cremer, Audrey Mansuet-Lupo, Marco Alfano, Catherine Sautès-Fridman, Diane Damotte, Wolf H. Fridman, and Lubka T. Roumenina
The complement regulator factor H (FHR) is shown to exert protumoral actions through an intracellular, noncanonical mechanism that alters proliferation, cell cycle, morphology, and migration in clear cell renal cell carcinoma and lung adenocarcinoma.
**TABLE OF CONTENTS**

926 Metabolic Screening of Cytotoxic T-cell Effector Function Reveals the Role of CRAC Channels in Regulating Lethal Hit Delivery

A microscopy-based, automated 3D interface coculture model was developed that allows for screening modulators of antitumor responses. Among the metabolic and signaling conditions compromising CTL responses, deregulation of CRAC channels caused particularly strong impairment of lethal hit delivery.

939 Single-Cell Analysis of the Pan-Cancer Immune Microenvironment and scTIME Portal
Fang Hong, Qianqian Meng, Weiyu Zhang, Ruiqin Zheng, Xiaoyun Li, Tao Cheng, Deqing Huo, and Xin Gao

Single-cell, pan-cancer analysis of multiple tumor immune microenvironments (TIME) reveals the relationships of immune subsets within specific tumor types and is used to develop the scTIME Web portal, a user-friendly tool available to the community for TIME analysis.

952 ST8Sia6 Promotes Tumor Growth in Mice by Inhibiting Immune Responses
David J. Friedman, Sydney B. Crotts, Matthew Rajcula, Shaylene McCue, Xin Liu, Khashayarha Khazaei, Haidong Dong, and Virginia Smith Shapiro

Expression of sialyltransferase ST8Sia6 by tumor cells generates ligands that bind to Siglec-E on macrophages, resulting in their repolarization to an M2-like phenotype. The data highlight the potential targeting of ST8Sia6 to enhance antitumor responses.

967 Integrin β7 Inhibits Colorectal Cancer Pathogenesis via Maintaining Antitumor Immunity
Youhua Zhang, Ruting Xie, Hailong Zhang, Yajuan Zheng, Changdong Lin, Lei Yang, Mengwen Huang, Man Li, Feifei Song, Ling Lu, Muqing Yang, Ying Liu, Qing Wei, Jiyu Li, and Jianfeng Chen

ITGB7 (integrin β7) inhibits tumorigenesis and progression of colorectal cancer (CRC) by maintaining sufficient tumor infiltration of various immune cell subsets essential for cancer cell recognition and killing. The data highlight an immune-supportive role of ITGB7 in CRC.

981 Viral Molecular Mimicry Influences the Antitumor Immune Response in Murine and Human Melanoma

Molecular mimicry can induce autoimmunity. By developing and using a bioinformatic tool to analyze molecular mimicry between tumor and viral antigens, the authors show this phenomenon can also play a role in antitumor immune responses.

ABOUT THE COVER

Immunoediting is a mechanism by which tumors evade antitumor responses, but how tissue site of origin plays into the process is not yet clear. By testing different routes of tumor-cell administration, Diamond et al. show that tumors can undergo selective immune escape in some tissues, whereas tumors are eliminated in others. This process is independent of immunoediting and can occur even if tumors are highly immunogenic. Mechanistically, conventional dendritic cells (cDC1) in the tumour-permissive tissues have reduced CD8+ T-cell priming ability, thus, leading to insufficient induction of antitumor immunity, and can be rescued by enhancing cross-presentation via a CD40 agonist. The data highlight that although antigenicity is key for inducing antitumor responses, it alone is not sufficient, and tissue of origin needs to be considered. Read more in this issue on page 877. Original image from Supplementary Fig. S1E. Artwork by Lewis Long.