

CANCER IMMUNOLOGY RESEARCH

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Stefano Ugel and Vincenzo Bronte

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- 489 **Reversing Imatinib's Immunosuppressive Effects by Modulating Type I IFN Signaling**

David A. Largaespada

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REVIEW

- 490 **Imaging of T-cell Responses in the Context of Cancer Immunotherapy**

Zebin Xiao and Ellen Puré

RESEARCH ARTICLES

- 503 **Myeloma-Secreted Galectin-1 Potently Interacts with CD304 on Monocytic Myeloid-Derived Suppressor Cells**

Ji-Young Lim, Tae-Woo Kim, Da-Bin Ryu, Sung-Soo Park, Sung-Eun Lee, Byung-Soo Kim, and Chang-Ki Min

Multiple myeloma cell-derived galectin-1 is shown to interact with CD304 on monocytic myeloid-derived suppressor cells, inducing their migration and inhibiting the cytotoxic activity of melphalan, suggesting the interaction as a potential therapeutic target for multiple myeloma.

See related Spotlight, p. 488

- 514 **IDO1 Signaling through GCN2 in a Subpopulation of Gr-1⁺ Cells Shifts the IFN γ /IL6 Balance to Promote Neovascularization**

Souvik Dey, Arpita Mondal, James B. DuHadaway, Erika Sutanto-Ward, Lisa D. Laury-Kleintop, Sunil Thomas, George C. Prendergast, Laura Mandik-Nayak, and Alexander J. Muller

Neovascularization contributes to cancer pathology. Here, a subset of immune cells is identified that, through induction of IDO1 and signaling through the integrated stress response, shifts the inflammatory cytokine balance to promote neovascularization.

- 529 **Longitudinal Immune Profiling Reveals Unique Myeloid and T-cell Phenotypes Associated with Spontaneous Immunoediting in a Prostate Tumor Model**

Casey R. Ager, Aleksandar Z. Obradovic, Juan M. Arriaga, Matthew G. Chaimowitz, Andrea Califano, Cory Abate-Shen, and Charles G. Drake

A new murine model for studying cancer immunoediting is presented. Longitudinal spectral flow cytometry, dimensionality reduction analyses, and *in vivo* depletion experiments are used to detail specific T-cell and myeloid phenotypes involved in each immunoediting phase.

- 542 **Oncogenic KIT Modulates Type I IFN-Mediated Antitumor Immunity in GIST**

Mengyuan Liu, Mark S. Etherington, Andrew Hanna, Benjamin D. Medina, Gerardo A. Vitiello, Timothy G. Bowler, Nesteene J. Param, Lillian Levin, Ferdinand Rossi, and Ronald P. DeMatteo

Inhibition of oncogenic KIT in gastrointestinal stromal tumors decreases type I IFN signaling, impairing antigen presentation and diminishing CD8⁺ T-cell antitumor responses. The data suggest enhancing type I IFN signaling may counter the negative immune effects of imatinib.

See related Spotlight, p. 489

- 554 **Targeted Therapy Given after Anti-PD-1 Leads to Prolonged Responses in Mouse Melanoma Models through Sustained Antitumor Immunity**

Manali S. Phadke, Zhihua Chen, Jiannong Li, Eslam Mohamed, Michael A. Davies, Inna Smalley, Derek R. Duckett, Vinayak Palve, Brian J. Czerniecki, Peter A. Forsyth, David Noyes, Dennis O. Adeegbe, Zeynep Eroglu, Kimberly T. Nguyen, Kenneth Y. Tsai, Uwe Rix, Christin E. Burd, Yian A. Chen, Paulo C. Rodriguez, and Keiran S.M. Smalley

Anti-PD-1 immunotherapy followed by targeted therapy is associated with increased tumor-immune recognition, decreased immunosuppressive signaling signatures, and prolonged antitumor responses in mouse models of BRAF-mutant and NRAS-mutant melanoma.

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568 Neutral Sphingomyelinase 2 Heightens Anti-Melanoma Immune Responses and Anti-PD-1 Therapy Efficacy

Anne Montfort, Florie Bertrand, Julia Rochotte, Julia Gilhodes, Thomas Filleron, Jean Milhès, Carine Dufau, Caroline Imbert, Joëlle Riond, Marie Tosolini, Christopher J. Clarke, Florent Dufour, Andrei A. Constantinescu, Nilton De França Junior, Virginie Garcia, Michel Record, Pierre Cordelier, Pierre Brousset, Philippe Rochaix, Sandrine Silvente-Poirot, Nicole Therville, Nathalie Andrieu-Abadie, Thierry Levade, Yusuf A. Hannun, Hervé Benoist, Nicolas Meyer, Olivier Micheau, Céline Colacios, and Bruno Ségui

In this study, downregulation of neutral sphingomyelinase 2 (nSMase2) contributes to immune escape and is associated with poor prognosis in human melanoma. Reconstituting nSMase2 in melanoma augments tumor infiltration by IFN γ ⁺ CD8⁺ T cells and anti-PD-1 efficacy in mice.

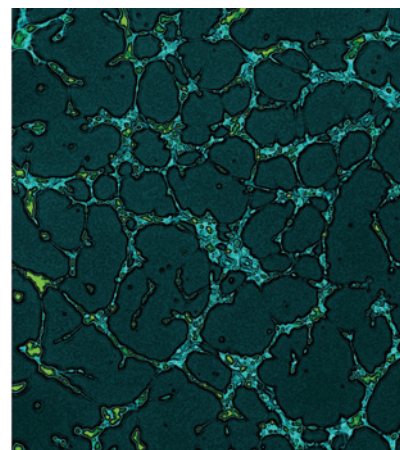
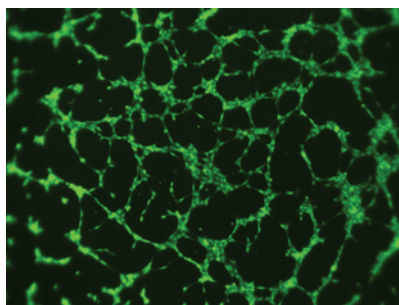
583 Differential Expression of CD49a and CD49b Determines Localization and Function of Tumor-Infiltrating CD8⁺ T Cells

Marit M. Melssen, Robin S. Lindsay, Katarzyna Stasiak, Anthony B. Rodriguez, Amanda M. Briegel, Salvador Cyranowski, Melanie R. Rutkowski, Mark R. Conaway, Cornelis J.M. Melief, Sjoerd H. van der Burg, Ukpong Eyo, Craig L. Slingluff Jr, and Victor H. Engelhard

A mechanism of CD8⁺ T-cell dysfunction is revealed. Collagen-binding CD49a and CD49b drive this dysfunction via modulation of CD8⁺ T-cell localization and motility, highlighting a new view on regulation of CD8⁺ T cells in the tumor microenvironment.

ABOUT THE COVER

Targeted therapies and immune checkpoint inhibitors (ICI) are effective treatments for melanoma, but efforts to combine these therapeutic modalities have been unsuccessful. Using mouse models of BRAF- and NRAS-mutant melanoma, Phadke et al. show that administration of an anti-PD-1 ICI before targeted therapy results in sustained antitumor immunity that leads to durable tumor responses. Single-cell RNA sequencing analysis shows that the sequential treatment alters the tumor immune microenvironment, promoting tumor infiltration by T cells, monocytes, dendritic cells, and natural killer cells, and simultaneously decreasing infiltration by tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells. The melanoma cells also have signatures characteristic of enhanced immunogenicity and no signatures associated with resistance to the targeted therapies. The study has implications for future development of combinations of targeted therapies and ICIs. Read more in this issue on page 554. Original image from work by Phadke et al. that is related to the article but not included in the final publication. Artwork by Lewis Long.



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