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The Cancer Immunotherapy Revolution: Mechanistic Insights FREE

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Editorial

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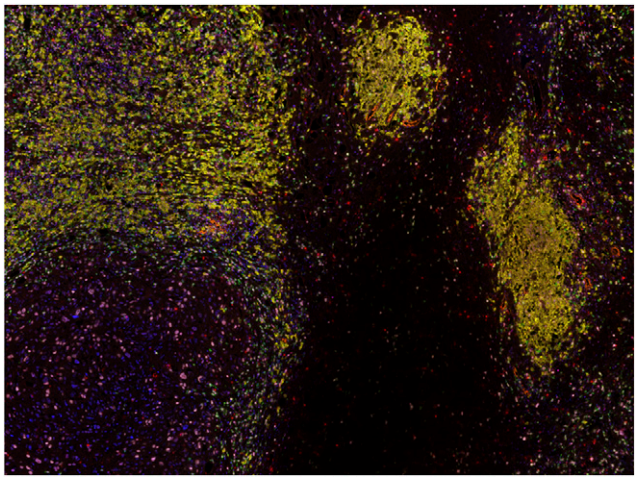
The Cancer Immunotherapy Revolution: Mechanistic Insights

With this editorial, I am pleased to introduce "The Cancer Immunotherapy Revolution: Mechanistic Insights," the second topical issue of reviews published in *The Journal of Immunology*. In acknowledgment of the growing interest in immuno-oncology and building on the success of our first topical issue of Brief Reviews, "The Macro Influence of the Microbiome," we now publish a series of 10 Brief Reviews and 1 Translating Immunology article highlighting the principles, applications, and challenges immunologists and cancer specialists face in this new era of tumor immunology and its clinical partner, cancer immunotherapy.

Finn sets the stage for this topical issue by tracing the evolution of the concept of immunosurveillance through its "in- and out-of-favor" phases and discussing how the modern techniques of immunotherapy seek to stimulate the process through which the immune system scans for damage inflicted by nascent tumors (1). Authors Zamora, Crawford, and Thomas focus on the antigenic targets of tumor-specific T cell activity and the ways by which antigenic cross-reactivity and immunodominance may modulate tumor immunity mediated by endogenous T cells (2). T cell repertoire and tumor mutation profiles aside, Sugiura and Rathmell discuss the metabolic barriers to efficacious T cell function erected by the acidic and hypoxic tumor microenvironment (TME) that is stingy on nutrients and awash with metabolic waste products (3). It is clear that promoting the elimination of solid tumors will require tools to relieve the defective metabolic reprogramming of intratumoral T cells imposed by the immunosuppressive TME. Nixon and Li emphasize that T cells are not the only tumor-infiltrating cytolytic cells. Tumor-resident innate lymphoid cells of ill-defined lineage receive signals derived from IL-15 and stress-associated ligands that promote their proliferation and cytolytic capacity (4). Harnessing the antitumor activity of these still mysterious but likely critical first responders will require continued research to better understand how their responses can be modulated. Tumors are populated not only by lymphocytes bent on tumor elimination, but also by cells with recognized immunosuppressive activity. Chao and Savage review our current understanding of tumor-associated regulatory T (Treg) cell control and function, including their conserved tumor-specific transcriptional signature and associated molecular programs, knowledge that may pave the way for specifically targeting the activity of intratumoral Treg cells (5). These authors emphasize that assessing the risks inherent in modulating tumor-infiltrating Treg cell function requires further investigation into the little-studied activities of intratumoral Treg cells that extend beyond dampening antitumor responses. Myeloid-derived suppressor cells (MDSCs) also contribute to the suppressive intratumoral environment, and are the subject of a review by Ostrand-Rosenberg and Fenselau (6). These heterogeneous and developmentally immature myeloid cells are responsive to tumor-derived growth factors, chronic inflammation, and proinflammatory mediators such as PGE_2, calcium-binding proteins, and cytokines such as IL-6 and IL-1β that promote their intratumoral accumulation and suppressive function. MDSCs mediate suppression in part by enhancing metalloprotease production, neovascularization, oxidative stress, cysteine sequestration, and arginine depletion, many of which require cell-to-cell contact within the TME. Specialized tertiary lymphoid structures within some tumors provide the platform for the cellular cross-talk that defines the set point between immunosuppressive and immunity-promoting TMEs, and are the focus of a review by Engelhard and coauthors (7). Understanding the generation and function of these heterogeneous lymph node–like structures is a prerequisite for learning to manipulate the development of intratumoral tertiary lymphoid structures to promote T cell infiltration and the generation of antitumor responses in both primary and metastatic lesions.



Multispectral immunofluorescence image depicting three tertiary lymphoid structures (TLS) in close proximity to a mouse melanoma metastasis that lacks immune infiltration. The image depicts $CD8^+$ (green), $CD20^+$ (yellow), $Foxp3^+$ (magenta), $Ki67^+$ (light pink), $PNAd^+$ (orange) and $CD83^+$ (red) cells. The large TLS directly above the tumor nest on the left side of the figure contains $PNAd^+$ high endothelial venules and B and $CD8^+$ T cells that are intermixed, and not segregated into distinct zones as they would be in lymph nodes. In contrast, the other two smaller TLS contain distinct T cell and B cell zones. $Foxp3^+$ cells and $CD83^+$ cells are found in the T cell region of the classically organized structures but are intermixed among $CD8^+$ T and B cells in the disorganized structure. Image provided by Dr. V. Engelhard, University of Virginia.

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The remaining four featured reviews focus on mechanisms to enhance immunosurveillance and antitumor immunity through vaccination and therapeutic interventions. Santos and Butterfield examine what is known about phenotypically and functionally defined dendritic cell subsets and their potential employment as cancer vaccines (8). As a means to promote antitumor T cell immunity, vaccination strategies have been developed in an effort to harness the ability of dendritic cells to activate T cells and to identify damaged cells by sensing the release of intracellular molecules. Much remains to be learned to predict accurately the relative efficacy of using various starting cell populations, culture conditions, Ag loading strategies, injection site preconditioning regimens, and appropriate combination therapies. Bridle and coauthors focus on the implications of using oncolytic virus–induced cancer cell death in combination with other immunotherapies to trigger immune cell–mediated tumor elimination (9). Vaccinia- and adenovirus-based oncolytic viruses that are engineered to express alkylating agents, immune checkpoint inhibitors, or key cytokines show promise as cancer vaccines in enhancing antitumor immune responses through the induction of immunogenic cell death. Srivastava and Riddell review the current state of knowledge about chimeric Ag receptor (CAR) T cell–based immunotherapy, highlighting the recent remarkable successes in treating hematologic cancers and the challenges of extending this approach to the treatment of solid tumors (10). Obstacles to using engineered T cells to eliminate solid tumors include the difficulty of identifying (often multiple) Ag targets that are neither lost by the tumor cells nor recognized on vital extratumoral tissues, the susceptibility of T cells to the suppressive influences of the TME, and impediments to T cell infiltration into the malignant tissue. These authors argue that discovery-driven experimentation using appropriate preclinical animal models is essential to provide the tools needed to surmount these barriers and move immunotherapy into new territories in the clinic. Sharpe and coauthors also emphasize this mutually beneficial interrelationship between basic research and translational applications by tracing the development of antitumor response–promoting checkpoint inhibitors from the discovery of PD-1 and the elaboration of its inhibitory signaling pathway to the exploitation of this knowledge in the clinical arena of cancer treatment (11). Enhancing the efficacy and durability of checkpoint inhibitors while reducing the accompanying adverse events will require further experimentation to discover biomarkers that predict responsive tumors more accurately and to enable the rational development of combination therapies.

These compiled reviews reveal that a solid platform built on the findings of curiosity-inspired basic research provides the essential launching point for translational studies and clinic-ready therapies. It is important to remember that the wave of exhilarating success in the realm of cancer immunotherapy was initially fueled by solid laboratory work conducted by researchers intent on simply understanding the way things work. It is our hope that, by pulling together these reviews into a single topical issue of *The Journal of Immunology*, this fertile cross-talk is placed firmly in the spotlight. This foundational partnership between basic research discoveries and revolutionary therapies that help patients is a cause for celebration, with the kudos for recent successes and future triumphs being shared by immunologists of all stripes.

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References

1. Finn, O. J. 2018. A believer's overview of cancer immunosurveillance and immunotherapy. *J. Immunol.* 200: 385–391.
2. Zamora, A. E., J. C. Crawford, and P. G. Thomas. 2018. Hitting the target: how T cells detect and eliminate tumors. *J. Immunol.* 200: 392–399.
3. Sugiura, A., and J. C. Rathmell. 2018. Metabolic barriers to T cell function in tumors. *J. Immunol.* 200: 400–407.
4. Nixon, B. G., and M. O. Li. 2018. Tissue-resident cytolytic innate lymphocytes in cancer. *J. Immunol.* 200: 408–414.
5. Chao, J. L., and P. A. Savage. 2018. Unlocking the complexities of tumor-associated regulatory T cells. *J. Immunol.* 200: 415–421.
6. Ostrand-Rosenberg, S., and C. Fenselau. 2018. Myeloid-derived suppressor cells: immune-suppressive cells that impair antitumor immunity and are sculpted by their environment. *J. Immunol.* 200: 422–431.
7. Engelhard, V. H., A. B. Rodriguez, I. S. Mauldin, A. N. Woods, J. D. Peske, and C. L. Slingluff, Jr. 2018. Immune cell infiltration and tertiary lymphoid structures as determinants of antitumor immunity. *J. Immunol.* 200: 432–442.
8. Santos, P. M., and L. H. Butterfield. 2018. Dendritic cell–based cancer vaccines. *J. Immunol.* 200: 443–449.
9. van Vloten, J. P., S. T. Workenhe, S. K. Wootton, K. L. Mossman, and B. W. Bridle. 2018. Critical interactions between immunogenic cancer cell death, oncolytic viruses, and the immune system define the rational design of combination immunotherapies. *J. Immunol.* 200: 450–458.
10. Srivastava, S., and S. R. Riddell. 2018. Chimeric antigen receptor T cell therapy: challenges to bench-to-bedside efficacy. *J. Immunol.* 200: 459–468.
11. LaFleur, M. W., Y. Muroyama, C. G. Drake, and A. Sharpe. 2018. Inhibitors of the PD-1 pathway in tumor therapy. *J. Immunol.* 200: 375–383.