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Editorial overview: Many shades of grey: how immune response is regulated by tumors

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During last year the field of tumor immunology continues progress at lightning speed. More clinical evidence of the effect of cancer immunotherapy was published. Old concepts were developed further and new concepts have emerged. In the April 2017 Tumor Immunology issue of the journal, the guest editors, Drs. Robert Ferris and Dmitry Gabrilovich tried to assemble and present topics that were not directly discussed in several previous issues of this rapidly evolving field. We believe that the papers included here provide readers with more comprehensive view of recent advances in the field. These days tumor immunology has become a highly complex field, that cannot be covered by small numbers of reviews. We tried to focus the discussion on some mechanisms tumors use to limit the development of immune responses and therapeutic approaches to their regulation beyond classical checkpoint inhibitors. Therapeutic targeting of these receptors, and recent FDA approvals in several cancer types, have led to re-evaluation and new understanding of the biology of immunotherapeutic targeting, reviving investigations into several lymphocyte subsets and immune receptor interactions, in order to understand responses, as well as to overcome therapeutic resistance in patients.

Several reviews are focused on the discussion of the mechanisms of induction of potent immune responses in cancer from different perspectives.

[Dr. Celis and co-authors](#) discuss recent progress in synthetic peptide vaccines. This is one of the oldest methods of generating immune responses in cancer, aiming to elicit and expand tumor-specific T cells capable of controlling or eradicating tumors. Despite the high expectations based on preclinical studies, the results of clinical trials using peptide vaccines have been disappointing. Thus, many researchers in the field have considered peptide vaccines as outdated and no longer viable for cancer therapy. The authors discuss new data that suggest a change in our evaluation of peptide vaccines. Our understanding of the critical roles of immune adjuvants, modes of vaccine administration and T cell dynamics has re-energized the field and provided evidence supporting reconsideration of potential role of the peptide vaccine in cancer treatment.

[Dr. Melero reviews](#) the important role of natural killer (NK) cells in promoting antitumor immunity. NK cells are cytotoxic lymphocytes specialized in early defense against virus-infected and transformed cells. NK cell function is regulated by activating and inhibitory surface receptors, recognizing their ligands on transformed cells. Modulation of NK numbers and/or function by a variety of agents such as cytokines and monoclonal antibodies may result in enhanced antitumor activity. Recombinant cytokines (i.e. IL-15 and IL-2), antibodies blocking inhibitory receptors (i.e. KIR, NKG2A and TIGIT) and agonists delivering signals via CD137, NKG2D and CD16 stand out as the most suitable opportunities. These authors review how therapeutic agents can be used to potentiate NK cell mediated antibody-dependent cellular cytotoxicity (ADCC) against antibody-coated tumor cells, offering potential for multiple combinatorial immunotherapy strategies against cancer.

[Dr. Fu and colleagues](#) discussed recent progress in understanding signaling mechanisms activated by DNA, and harnessing DNA sensing-mediated immune responses in cancer therapy. In addition to Toll like receptor pathways, there is now emerging evidence that cytosolic enzyme cyclic GMP-AMP synthase (cGAS) is critical for the recognition of not only pathogen-derived DNA but also tumor DNA for innate sensing. The strategies through activating DNA sensing pathways toward enhancing antitumor immunity have shown promise and are further tested in clinical studies.

Immune cell infiltration is common to many tumors and has been recognized by pathologists for more than 100 years. The application of digital imaging and objective assessment software allowed a concise determination of the type and quantity of immune cells and their location relative to the tumor and, in the case of colon cancer, characterized overall survival better than AJCC TNM staging. [Dr. Fox and co-authors](#) discuss evidence supporting clinical prognostic values of immune cells in different types of cancer. They suggest that soon, automated staining methods will improve reproducibility of multiplex staining and multiplex staining can be used to make clinical decisions. Ultimately, machine-learning algorithms will help interpret data from tissue images and lead to improved delivery of precision medicine.

The other group of reviews are focused on specific mechanisms negatively regulating immune response in cancer and therapeutic approaches to their targeting.

In reviewing the role of classical immune checkpoint receptors, [Dr. Chen Dong and co-authors](#) describe why multiple ICR may be co-expressed on progressively dysfunction ('exhausted') tumor infiltrating lymphocytes. Co-inhibitory receptors expressed on activated immune cells function to regulate T cell tolerance to self-antigens, also serving by tumor cells to escape from eradication by the host immune system. Therefore, blockade of immune checkpoint receptors (ICR) has become a promising immunotherapeutic strategy for treatment of a wide variety of cancers. However, blockade of one of the immune checkpoint receptors alone is often not sufficiently effective; co-blockade shows synergic effects in reversing immunosuppression. Authors summarize the expression patterns, mechanisms of action of different ICRs as well as the stages and sites they function in, and discuss how they execute non-redundant suppressive effects in anti-tumor immunity.

Dr. Ferris and co-authors discuss how oncogenic, HER-family receptors downregulate tumor antigen presentation and upregulate suppressive membrane- bound or soluble secreted inhibitory molecules that ultimately lead to impaired cellular immunity mediated by cytotoxic T lymphocyte recognition. HER family of receptors is a valuable therapeutic target. It is well known that unrestrained growth factor signals can promote carcinogenesis, as well as other hallmarks of cancer such as immune evasion. However, these receptors also mediate escape from recognition by the host immune system.

Understanding of these mechanisms may to inflammatory DCs (inf-DCs), which are a critical component of antitumor responses. This paper examines the role of inf-DCs along with other DC subsets in the regulation of immune responses in cancer, which may provide new targets for immunotherapy.

The important field of T cell costimulation has yielded clinically useful targeting strategies, and an emerging example is the CD27/CD70 interaction. Bullock and co-authors have reviewed this axis in the context of T cell activation and potential application to cancer therapy, being evaluated clinically at the present time. Indeed, stimulating CD27 may quantitatively and qualitatively shape adaptive immunity to cancer, and the combination with immune checkpoint blockade presents a promising strategy in the clinic, but one in which a detailed mechanistic understanding of signaling cross talk is necessary to understand the likelihood of success and potential autoimmune adverse sequelae which may result.

Dr. Rabinovich and colleagues review the role of galectins, as emerging regulatory checkpoints linking tumor immunity and angiogenesis. Immune checkpoints, the plethora of inhibitory pathways aimed at maintaining immune cell homeostasis, can be co-opted by cancer cells to evade immune destruction, and are important therapeutic targets. Galectins, a family of glycan-binding proteins, have emerged as novel regulatory checkpoints that promote immune evasive programs by inducing T cell exhaustion, limiting T-cell survival, favoring expansion of regulatory T cells, de-activating natural killer cells and polarizing myeloid cells toward an immunosuppressive phenotype. Concomitantly, galectins can trigger vascular signaling programs, serving as bifunctional messengers that couple tumor immunity and angiogenesis. Thus, targeting galectin glycan interactions may halt tumor progression by simultaneously augmenting antitumor immunity and suppressing aberrant angiogenesis.

Dr. Gabrilovich and his team re-visit the important role of dendritic cells (DC) in cancer models and patients. With their potent antigen presenting ability, DC have long been considered as a critical factor in antitumor immunity. Despite high potential in promoting antitumor responses, tumor-associated DCs are largely defective in their functional activity and can contribute to immune suppression in cancer. In recent years the existence of immune suppressive regulatory DCs in tumor microenvironment was described. Monocytic myeloid derived suppressor cells (M-MDSCs) can also contribute to the pool of tumor associated DCs by differentiating regulating anti-tumor cellular immunity. We hope that this issue clarifies some of the emerging and re-evaluated immune receptors and cellular interactions, in order to understand clinical responses, as well as to overcome therapeutic resistance in cancer patients.

As mentioned earlier, immunotherapeutic targeting in several cancer types have provided a validation of the importance, as well as window on the biology, of several lymphocyte subsets in the tumor microenvironment, including NK cells, DC and T cells, ultimately help to develop new therapeutic strategies to enhance tumor immunogenicity and may restore effector cell mediated immune clearance of tumors and clinical efficacy of tumor-targeted immunotherapy against HER receptor overexpression.

Biographies

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Dmitry Gabrilovich, MD, Ph.D. is Christopher M. Davis Professor in Cancer Research and Program Leader, Translational Tumor Immunology, at the Wistar Institute in Philadelphia and Wistar Professor, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania. He has demonstrated that DCs in cancer were functionally impaired and described and characterized immature myeloid cells with immune suppressive activity now called myeloid-derived suppressor cells (MDSC). His group is working on evaluation of the accumulation and function of MDSC and DCs in cancer and investigation of the mechanisms of therapeutic targeting of these cells.

Robert L Ferris

Robert L. Ferris, MD, PhD is Associate Director for Translational Research, Co-Leader of the Cancer Immunology Program, and Co-Director of the Tumor Microenvironment Center at the University of Pittsburgh Cancer Institute. His NIH-funded laboratory is focused on reversal of immune escape and immunotherapy using cellular and peptide vaccines, as well as monoclonal antibodies targeting HER family growth factor receptors and immune checkpoints, including combinations to enhance cancer therapy.