EDITORIAL

# Mechanistic insights into cancer immunity and immunotherapy

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While immunotherapy has had an important impact on cancer treatment, only approximately a quarter of patients respond to these treatments. Why does it work in some patients but not in other patients? How can we improve the therapeutic efficacy of current immunotherapy? Are there potential new strategies to tackle this problem? The answers to these questions may rely on our in-depth understanding of the basic mechanisms of the cancer immune response, immunotherapeutic efficacy, and resistance.

Keeping these questions in mind, in this special issue, I am pleased to introduce the review theme "Mechanistic insights into cancer immunity and immunotherapy". We will publish a series of six review articles highlighting the key immunosuppressive networks, the phenotype, and function of T cells and myeloid cells, and the abnormalities in tumor metabolism in the tumor microenvironment. In addition, the reviews will discuss the potential novel translational strategies, perspectives, and challenges we face in this new era of tumor immunology and immunotherapy.

The tumor microenvironment is the primary location in which tumor cells and the host immune system interact. Early studies have defined the phenotype, trafficking, and functional characteristics of different immune cell subsets in the tumor microenvironment and provided scientific rationales for current immunotherapy[1–6]. However, the nature of tumor immune responses and the underlying mechanisms remain to be fully understood. It is becoming increasingly apparent that metabolic programs affect immune cell fate, form, and function in the tumor microenvironment. Accordingly, there has been a surge of interest in defining the mechanisms by which aberrant immune cell metabolism impacts cancer progression and therapeutic outcomes. In this issue, Rodriguez and Peng discuss the latest research advances in cancer immunometabolism and how novel insights can be harnessed to treat cancer[7,8]. Myeloid cells contribute to the suppressive intratumoral environment and may directly promote human tumor stemness[9]. Tumor-infiltrating myeloid cells are the subject of a review by Rodriguez[7]. These heterogeneous and developmentally immature myeloid cells are responsive to dysfunctional metabolism such as poor glycolysis and enhanced lipid metabolism and the associated metabolites, such as adenosine, cAMP, IDO, lactate, succinate, PGE2, fatty acid, lipoproteins, and oxidized forms that may promote their intratumoral accumulation and suppressive effects on T cells[7,8]. In the review by Peng and colleagues, in addition to discussing the tumor-associated metabolites and myeloid cells, they emphasize that abnormal metabolism impacts the phenotype and function of naive T cells, effector T cells, and regulatory T cells. Furthermore, they examine the expression and role of Toll-like receptor (TLR) in tumor cells and suggest that manipulation of the TLR signaling pathway may normalize tumor metabolism and improve the function of macrophages, dendritic cells, and T cells[8]. Interestingly, in this context, innate TLR signaling has recently been reported to be involved in colon cancer chemoresistance[10], further stressing the significance of the TLR pattern in tumorigenesis and therapy.

PD-L1 is highly expressed in antigen-presenting cells and tumor cells and mediates immunosuppression in the human tumor microenvironment and tumor draining lymph nodes[11]. PD-L1 (B7-H1) and PD-1 signaling pathway blockade is at the central stage of current cancer immunotherapy[3,12]. Substantial academic and industrial efforts are being made to explore additional targetable checkpoints for cancer therapy. In this regard, Wang and collaborators suggest that VISTA may be a potential checkpoint for cancer immunotherapy[13]. Wang reviews the structure, expression, and multifaceted role of VISTA in different contexts, including cancer. She notes that VISTA may have a negative role in anti-tumor immune responses and that blocking VISTA with an anti-VISTA neutralizing monoclonal antibody (mAb) would be a potential approach in cancer therapy alone or in combination with PD-L1 and PD-1 blockade[13]. Wainwright and colleagues[14] focus on indoleamine 2,3-dioxygenase 1 (IDO1) in cancer. IDO1 can be expressed by many types of cells, including antigen-presenting cells and tumor cells. They highlight the immunosuppressive role of IDO1 and review its canonical association with IDO1-dependent tryptophan metabolism, as well as document evidence showing the dispensability of the enzyme activity for its immunosuppressive effects[14]. There are ongoing clinical trials

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using IDO1 inhibitors to enhance and support the efficacy of immunotherapy for patients with cancer.

The remaining two featured reviews focus on two effector T cell subsets, Th17 cells[15] and $CD8^+$ T cells[16]. Paulos and colleagues review what is known regarding the stem-like phenotype and function of Th17 cells and their different roles in carcinogenesis, tumor immunity, and autoimmunity[6,17,18]. They discuss how Th17 cells may be linked to checkpoint therapy efficacy and therapy-associated autoimmunity. In addition to PD-L1 and PD-1 checkpoint therapy, the remarkable successes of chimeric Ag receptor (CAR) T cell-based immunotherapy are appreciated in treating hematologic cancers[19]. However, it is challenging to use CAR-T cells to eliminate solid epithelial cancers due to the difficulty of identifying relevant antigen targets, the susceptibility of T cells to the immunosuppression in the cancer microenvironment, and the impediments to T cell trafficking into the solid tumors. Given the stem-like feature, plasticity, and survival advantage of Th17 cells,[6,20–22]. Paulos and colleagues[15] argue that Th17 cells and/or Tc17 cells may potentially surmount these barriers and move immunotherapy into new territories in the clinic. Guevara-Patino et al.[16] emphasize a role of natural killer group 2 member D (NKG2D) in $CD8^+$ T cells. They note that NKG2D is needed for optimal T cell function, including memory formation outside the priming phase. In terms of translation, as NKG2D is expressed in T cells and tumor cells, the authors suggest a DNA vaccination approach in which the gene encoding NKG2D ligands could be incorporated in a vaccine along with the desired antigen. Furthermore, they hope to design a NKG2D-CAR-T cell therapy that may eliminate tumors expressing ligands for NKG2D. Hopefully, manipulation of the NKG2D pathway may be meaningful in the clinical arena of cancer treatment.

Characterization of the nature of immune responses in the human cancer microenvironment holds the key to understanding protective tumor immunity and improving and empowering current cancer immunotherapy[12]. These compiled reviews are a testament to our further efforts to understand the tumor microenvironment. The engendered knowledge will provide scientific rationales for clinical applications. I hope that this special issue will add additional fuel to this exciting area and serve as a platform for cross-fertilization among basic immunologists, oncologists, and drug-developers.

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