



COMMENTARY

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# Research highlights in cancer immunotherapy from basic discovery to clinical trial

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## Abstract

Cancer research is one of the most active areas in the biomedical sciences. Recently, the tumor immune environment, crosstalk between tumor cells and immune cells, and immunotherapy remain the “hot” topic in the field of cancer research. This short review will highlight the recent interesting findings in cancer research associated with cancer immunology and immunotherapy from basic discovery, translational study to clinical trials.

**Keywords:** Immunotherapy, Prostate cancer, Colorectal cancer, PD-1, PD-L1, Interleukin-6

## 1 Background

Cancer research is one of the most active areas in the biomedical sciences. Basic discoveries are critical for developing new therapeutics to cure cancer. While translational studies help to transform basic discoveries to clinic usage, clinical trials is the last step to validate whether novel therapeutics can be safely and effectively used for treating cancer patients. Recently, the tumor immune environment, crosstalk between tumor cells and immune cells, and immunotherapy remain the “hot” topic in the field of cancer research. This short review will highlight some of the new interesting findings in cancer research associated with cancer immunology and immunotherapy from basic discovery, translational study to clinical trials.

### 1.1 Basic discoveries

Abnormal activation of Wnt/ $\beta$ -catenin signaling is associated with multiple cancer types such.

as colorectal cancer, liver cancer and head and neck squamous cell carcinoma. Adenomatous polyposis coli (APC) is a tumor suppressor gene which has been found

to be mutated in approximately 90% of human colorectal cancers. APC mutation leads to stabilization of  $\beta$ -catenin and constitutively activates  $\beta$ -catenin/TCF4-mediated transcription. Although great progress has been made in cancer targeted therapy, the specific inhibitor of  $\beta$ -catenin/TCF4-mediated transcription remains elusive. Utilizing the synthetic essentiality framework approach, Lee et al. identified Tryptophan 2,3-dioxygenase 2 (TDO2) as a druggable vulnerability for APC-deficient colorectal cancers. They showed that TDO2 is a synthetic essential effector of APC-deficient colorectal cancer. TDO2 plays a critical role in tryptophan (Trp) catabolism which converts Trp into N-formylkynurenine (Kyn). Interestingly, the expression of TDO2 depends on the  $\beta$ -catenin/TCF4-mediated transcription. Mechanistically, TDO2 promotes glycolysis by activating the Kyn–AhR pathway to promote anabolic cancer cell growth. Importantly, they found that the TDO2-Kyn-AhR signaling pathway also induced a set of chemokines including CXCL5 which helped to recruit tumor-associated macrophages (TAM) into the tumor microenvironment. TAMs are known to play a critical role in tumor development immunosuppression and angiogenesis. The inhibition of TDO2 by genetic and pharmacological approaches potently suppresses colorectal cancer cell proliferation in vitro and tumor growth in mice. They

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also showed that the inhibition of TDO2 reduced macrophages and increased CD8 T lymphocytes in the tumor microenvironment, indicating that targeting TDO2 also enhances antitumor immune profiles. These findings indicate that targeting TDO2 might provide an alternative strategy for treating APC-deficient colorectal cancer while Wnt/ $\beta$ -catenin inhibitors are not available [1].

Increasing the infiltration of TAM plays an important role in tumor development and tumor immune evasion. Using ZipSeq, a spatial transcriptomics approach, elegant studies by Kersten et al. map gene expression patterns in single cells based on their localization in the tumor microenvironment and found that there is a spatial coordination of TAM and exhausted T cells in mouse and human tumor tissues. Mechanistically, the self-enforced positive feedback loop was found to mediate the spatial coordination. The secretion of growth factors and chemokines by TAM induced and promoted CD8<sup>+</sup> Tex differentiation. CD8<sup>+</sup> Tex could express myeloid-related factors to recruit myeloid cells and to promote their differentiation into TMA in the tumor microenvironment. These findings suggest that the co-evolution of immunosuppressive cell types in the TME play a critical role in tumor immune evasion. Interfering with the positive feedback loop between TAM and Tex might provide a novel strategy for improving cancer immunotherapy [2].

Pancreatic ductal adenocarcinoma (PDA) is one of the most malignant human cancers. Understanding the molecular and immunological mechanisms which control PDA development is critical to develop a cure for PDA. Cancer-associated fibroblasts (CAF) have been found to play an important role in tumor development and progression. Recently, antigen-presenting CAFs (apCAF), which express the major histocompatibility complex class II molecules, have been identified in human solid tumors. Huang et al. convincingly showed that apCAF in PDA were differentiated from mesothelial cells by the combination approaches of integrating multiple single-cell RNA-sequencing and in vivo lineage-tracing assays. They found that interleukin-1 and transforming growth factor  $\beta$  stimulated the differentiation of mesothelial cell into apCAF. Interestingly, because anti-presenting apCAFs were deficient in the expression of costimulatory molecules such as CD40, CD80, and CD86, they were unable to fully activate CD4<sup>+</sup> T cell clone expansion following T cell receptor ligation. In contrast, apCAFs effectively ligate and stimulate naïve CD4<sup>+</sup> T cell differentiation into regulatory T cells (Tregs) in PDA in an antigen-dependent fashion. Importantly, anti-mesothelin antibody treatment potentially blocked the mesothelial cell differentiation into apCAF and subsequently prevented Treg formation in PDA, resulting in the inhibition of tumor growth. These studies suggest that apCAF

derived from the mesothelial cells might play a pivotal role in immune evasion of PDA by inducing Treg formation. Targeting mesothelial cell-apCAF transition might provide a new strategy to improve immune therapy for PDA [3].

Distant metastasis of solid tumors represents a big therapeutic challenge, and is the primary cause of death in cancer patients. Solid tumors frequently metastasize to draining lymph nodes (LN) through lymphatic vessels at the beginning. However, whether and how LN metastasis plays an active role in distant metastasis is not fully understood. Studies by Reticker-Flynn showed that LN metastases highly expressed interferon-stimulated genes due to the epigenetic and transcriptional changes. Although it is not clear how these changes are induced during the process of LN metastasis. Especially, two key genes associated with immune suppression, the interferon-inducible genes for programmed death ligand 1 (PD-L1) and the major histocompatibility class I (MHC-I) subunit beta-2 microglobulin (B2m), that are significantly elevated in LN metastases. The elevated PD-L1 and B2m potentially promote metastatic tumor cell survival and colonization in LN by escaping NK cell killing and T cell-mediated cytotoxicity. Subsequently, LN colonization induces extensive changes in the local immune repertoire by reducing T to B cell ratios and increasing antigen-specific regulatory T cell (Treg). Treg cells potentially induce tumor-specific immune tolerance and promote distant metastasis. The authors have utilized multiple human and mouse cancer models to validate their results, suggesting that there is a conserved mechanism which mediates distant metastasis. Currently, there are two models regarding the role of LN metastasis in distant metastasis. One is that tumor cells first metastasize to draining LNs where they evolve and obtain additional metastatic potentials and subsequently spread to distant organs. Another model is that LN and distant organ metastasis are not related, and LN metastases doesn't play an active role in the development of distant metastasis. New studies by Reticker-Flynn et al. reconcile these two contradicting models. They clearly show that the LN colonization of tumor cells plays a pivotal role in distant metastasis. LN metastasis mainly promotes immune evasion and tumor-specific immune tolerance, and is not necessary to provide cellular sources for distant metastasis [4].

## 1.2 Translational studies

Although anti-PD-1-based immunotherapy has been approved for treating a variety of solid tumors, the majority of tumors remain unresponsive to the treatment. Therefore, there are intensive studies investigating the underlying molecular mechanisms which control tumor immune responses. Hepatocellular carcinoma (HCC) is

a common cancer in China with low objective response rates to anti-PD-1 therapy. Hu et al. explored the combination treatment of anti-PD-1 and Interferon- $\alpha$  (INF $\alpha$ ) for HCC, and found that INF $\alpha$  therapy significantly enhanced the efficacy of anti-PD-1 by enriching cytotoxic CD27+CD8+ T cells. Based on their clinical findings, they further dissected the immunological and molecular mechanisms which are responsible for the synergy and INF $\alpha$  and anti-PD-1. They found that INF $\alpha$  significantly inhibits the HIF $\alpha$  signaling pathway by reducing the FosB expression in HCC cells. This inhibition led to a high-glucose tumor microenvironment by reducing the glucose consumption capacity which promoted the expression of the T-cell costimulatory molecule Cd27 in the infiltrating CD8+ T cells, thereby increasing the numbers of cytotoxic CD27+CD8 T cells to kill HCC tumor cells. These interesting findings have important translational values for HCC treatment and suggest that the combination treatment of INF $\alpha$  and anti-PD-1 might offer a new therapeutic strategy for combating HCC. In the near future, it will be interesting to know whether this combination could be applied to other solid tumors such as head and neck squamous cell carcinoma [5].

Vitamin E is a fat-soluble vitamin which is required for many biological functions in our bodies and is commonly used in dietary supplements. From the retrospective analysis of the clinical outcomes of patients which received anti-PD-1/PD-L1 and dietary supplements, Dr. Dihua Yu's lab found that patients with melanoma who took Vitamin E during immunotherapy had significantly improved patient survival rates compared with the patients who did not take vitamins. Dendritic cells (DCs) play a critical role in tumor antigen presentation and are required for T cell activation in tumor immunotherapy. Mechanistically, they showed that vitamin E directly binds to the protein tyrosine phosphatase SHP1, a DC-intrinsic checkpoint, and inhibit its activities, thereby restoring tumor-associated DC functions and priming T-cell antitumor immunity. These interesting findings implicate that vitamin E could be utilized for improving the efficacy of immunotherapy. However, vitamin E is also known as a potent anti-oxidant agent. It is unknown whether its anti-oxidant function plays a role in enhancing immunotherapy [6].

The inflamed or "hot" tumor have been found to be responsive to immunotherapy. However, inflammation also is pro-tumorigenic in many cases. Interleukin-6 (IL-6) is a pleiotropic cytokine associated with inflammation and immune response. An interesting study by Hailemichael et al. found that IL-6 blockade potently reduces immunotherapy toxicity and enhances anti-tumor immunotherapy by studying immunotherapy-related adverse event (irAE). Since immune-related enterocolitis (irEC) is

the most common complication of immunotherapy, they profiled the immune gene expression in irEC tissues, and found that the IL-6–Th17 signaling pathway was activated in irEC tissues from cancer patients upon immunotherapy. Using mouse models, they showed that IL-6 blockade significantly reduces Th17 cells and increases CD4+/CD8+ T cells, macrophages and myeloid cells, enhancing immunotherapy-mediated inhibition of tumor growth. These findings clearly support the combination trials of IL-6 blockade and immunotherapy for enhancing antitumor immunity while inhibiting autoimmunity [7].

Metastatic castration-resistant prostate cancer (mCRPC) which represents a big challenge in clinics is very resistant to anti-PD-1-based immunotherapy despite its great success in some solid tumors such as lung cancer and melanoma. However, it is unknown why mCRPC is resistant to anti-PD-1 therapy. Guan et al. found that androgen receptor (AR) directly repressed the expression of *IFNG* and *GZMB* associated with CD8 antitumoral functions by binding to their promoters. AR blockade collaborated with anti-PD-1 to significantly inhibit tumor growth by enhancing cytotoxic CD8 T cell functions. AR blockade potently prevented T cell exhaustion and restored *IFNG* expression, thereby overcoming mCRPC resistance to anti-PD-1 immunotherapy. The findings from these studies suggest that targeting AR could help to improve the efficacy of immunotherapy in advanced prostate cancers [8].

Growing evidence suggest that gut microbiota play an important role in tumor immunosurveillance and modulation of immunotherapy. Fecal microbiota transplantation has been found to promote immune cell infiltrates in immunotherapy-refractory melanoma patients [9]. Interestingly, Spencer et al. analyzed the effect of dietary habits and probiotics on the immune checkpoint inhibitor (ICI) response and the gut microbiome of melanoma patients. Interestingly, they found that the melanoma patients treated with immune checkpoint blockade, who took higher dietary fiber and had not probiotic use, had significantly improved progression-free survival. In contrast, the patients who took probiotics use had reduced objective response rates and progression-free survival. Interestingly, they found that the stool microbiome of the patients with high fiber intake had a more diverse microbiota. The fiber-fermenting and butyrate-producing *Faecalibacterium* and *Ruminococcaceae* were overrepresented in the patient's stool. Using a mouse model, they also showed that a low-fiber and probiotics also impaired anti-PD-1-mediated immunotherapy by reducing the infiltration of interferon- $\gamma$ -positive cytotoxic T cells in tumor tissues [10]. Although the gut microbiome has been found to modulate immunotherapy responses, it is unknown whether there are unique

microbiome characteristics which is associated with the clinical benefits of immunotherapy. Lee et al. performed shotgun metagenomic sequencing of stool samples from melanoma patients with ICI. Using a machine learning analysis, they confirmed there was the link between the microbiome and overall response rates in ICI-treated patients. However, they could not identify that single species could be used as a biomarker for ICI response. Clearly, more rigorous studies in a large scale need to be conducted for understanding of the role of gut microbiome in immunotherapy [11].

### 1.3 Clinical trials

Recently, anti-PD-1-based immunotherapy continues to make some exciting advancements. For locally advanced rectal cancer, the combination of neoadjuvant therapy and surgery is a standard approach. Unfortunately, rectal cancers that are deficient in DNA mismatch-repair are resistant to neoadjuvant therapy, thereby making rectal preservation very challenging. Cercek et al. reported a very impressive outcome of small clinical trials on rectal cancers with DNA mismatch-repair deficiency upon the treatment with dostarlimab (anti-PD-1 antibodies). Based on magnetic resonance imaging, endoscopic evaluation, and digital rectal examination, all 12 patients had clinical complete response at least 6 months of follow-up with a range of 6 to 25 months. There were no cases that needed to receive neoadjuvant therapy or surgery because of tumor progression and recurrence. However, it is unknown whether the results could be applied and generalized to a larger population of patients with rectal cancer. If the results are confirmed in a larger population, the treatment could be the paradigm shift for patients with rectal cancers [12].

Esophageal squamous cell carcinoma (ESCC) is one of the most common cancers in Asia. Unfortunately, patients with ESCC are frequently diagnosed at the advanced stage with a poor prognosis. Cisplatin-based therapy is the standard first-line treatment for advanced or metastatic ESCC. Wang et al. conducted a multi-center phase 3 clinical trial in which patients with advanced ESCC received toripalimab (anti-PD-1 antibodies) in combination with paclitaxel plus cisplatin (TP) or standard paclitaxel plus cisplatin. They found that toripalimab in combination with paclitaxel plus cisplatin significantly improved the progression-free survival and overall survival of patients with advanced ESCC. Intriguingly, the efficacy of toripalimab in combination with paclitaxel plus cisplatin is independent of PD-L1 expression with a manageable safety profile. The trial convincingly showed that toripalimab plus chemotherapy can be used as the first-line treatment for ESCC [13].

Neoadjuvant chemotherapy is often used for patients with resectable non-small-cell lung cancer (NSCLC) before surgery. However, neoadjuvant chemotherapy only provides a mild benefit compared with surgery alone for NSCLC. Forde et al. conducted the first stage 3 randomized nivolumab (anti-PD-1 antibodies) plus platinum-based chemotherapy in resectable NSCLC compared with platinum-based chemotherapy regardless of PD-L1 expression. They found that that nivolumab plus platinum-based chemotherapy significantly improved event-free survival and pathological complete response than chemotherapy alone. The results from this trial have changed our routine practice for resectable NSCLC. However, it should be pointed out that long-time follow-up might be needed because it is important to know whether nivolumab plus platinum-based chemotherapy could improve patients' overall survival [14].

### Abbreviations

APC: Adenomatous polyposis coli; apCAF: antigen-presenting CAFs; AR: Androgen receptor; B2m: beta-2 microglobulin; CAF: Cancer-associated fibroblasts; DCs: Dendritic cells; ESCC: Esophageal squamous cell carcinoma; HCC: Hepatocellular carcinoma; INF $\alpha$ : Interferon- $\alpha$ ; IL-6: Interleukin-6; irEC: immune-related enterocolitis; Kyn: N-formylkynurenine; LN: lymph nodes; mCRPC: Metastatic castration-resistant prostate cancer; NSCLC: non-small-cell lung cancer; PDA: Pancreatic ductal adenocarcinoma; PD-L1: Programmed death ligand 1; TAM: Tumor-associated macrophages; TCF4: T cell factor-4; TDO2: Tryptophan 2,3-dioxygenase 2; Tregs: Regulatory T cells; Trp: Tryptophan.

### Acknowledgments

No

### Author's contributions

CYW did literature searching and writing the manuscript. The author(s) read and approved the final manuscript.

### Funding

No

### Availability of data and materials

All data from public domains.

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The author C.Y.W. is an Associate Editor-in-Chief for *Holistic Integrative Oncology*. The paper was handled by the other Editor and has undergone rigorous peer review process. C.Y.W. was not involved in the journal's review of, or decisions related to, this manuscript. C.Y.W. is a scientific board member of Curigin Co. and Acroimmune Inc. and receives the research support from RNAimmune Co.

Received: 18 July 2022 Accepted: 23 September 2022

Published online: 12 October 2022

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