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Immune checkpoint modulators in cancer immunotherapy: Recent advances and combination rationales

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ABSTRACT

As a new hallmark of cancer, immune surveillance evading plays a critical role in carcinogenesis. Through modulating the immune checkpoints, immune cells in tumor microenvironment can be harnessed to battle cancer cells. In recent years, the administration of anti-CTLA or/and anti-PD-1/L1 antibody has exhibited unexpected antitumor effect in multiple types of cancer, motivating the researchers to find more potential immune checkpoints as clinical targets. A wealth of clinical trials have been done to evaluate the safety and efficacy of monotherapy or combination therapy with immune checkpoint modulators. However, there still exist problems such as low response rate and adverse events in the clinical, which in turn leads us to the basic study. The better understanding of the crosstalk between the immune cells and the cancer cells within the microenvironment may inspire us new ideas for cancer treatment. In this review, we mainly summarize the recent advances in application of immune checkpoint modulators and the combination rationales, and discuss the problems existing in the precision therapy with immune checkpoint modulators.

1. Introduction

Recent years have witnessed the skyrocketed progression of immunotherapy in the clinical of cancer treatment. Among kinds of cancer immunotherapy applications, the immune checkpoint blockade therapy is the most remarkable, represented by anti-CTLA-4 and anti-PD therapy. Given the great contributions in the early basic research and promotion of the immune checkpoint based immunotherapy, its early pioneers James Allison and Tasuku Honjo were together awarded with the Nobel Laureate 2018 [1–6]. From our perspective, it can be regarded as a milestone and a new beginning, since there still exist many problems to be solved in this area, mainly in the incomplete details of the "immune checkpoints" and the failure of the immune checkpoint blockade therapy in quite a part of clinical cases.

Currently single checkpoint modulator (e.g. anti-CTLA-4 or anti-oPD-1 antibody) has been used in a broad range of cancer types. To improve the therapeutic response rate, combination therapy that combines multiple checkpoint modulators has been investigated [7]. It was reported that there are globally over 1000 ongoing clinical trials that combine with anti-PD-1/L1 antibodies, and the preliminary benefits from the combinations have been spotted [7]. Nevertheless, the best choice of therapeutic regimen still requires evaluation depending on further comparison of different combination strategies in the future.

The bench work of the cancer immunology in the past has taught much to the clinical application of cancer immunotherapy, but nowadays the clinical work raises more questions and calls for answers from the bench. Here, we mainly review the recent clinical advances of immune checkpoint modulators and the combination rationales. We will also discuss the main problems existing in precision therapy with immune checkpoint modulators.

1.1. Immune checkpoints: the beginning of the story

The concept "immune checkpoints", referred to the important immune switches that regulate the "stimulatory" or "inhibitory" state of immune cells primarily T cells, originated from the first proposal of anti-CTLA-4 as cancer immunotherapy in the late 1990s [1,8]. The immune checkpoints can be divided into two types: the stimulatory checkpoints ("accelerator") and the inhibitory checkpoints ("brake") [9].

1.1.1. Stimulatory immune checkpoints

The activation of T cells requires two signals: the first one from the TCR and the second one provided by the stimulatory checkpoints [10]. The CD28 was the first recognized stimulatory checkpoint [3,11]. Upon interaction with B7-1 and B7-2 ligands, CD28 on the T cells can mediate

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Abbreviations

APC	Antigen presenting cell
TCR	T cell receptor
CTLA-4	Cytotoxic T lymphocyte antigen 4
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein 1 ligand 1
ICOS	Inducible T cell costimulator
GITR	glucocorticoid-induced tumor necrosis factor receptor
TNFRSF	TNF receptor superfamily member
HVEM	Herpesvirus entry mediator
TIM	T cell immunoglobulin- and mucin domain-containing molecule
LAG-3	Lymphocyte-activation gene 3
TIGIT	T-cell immunoglobulin and ITIM domain
FGL1	Fibrinogen-like protein 1
OS	Overall survival
PFS	Progression-free survival
ORR	Objective response rate
irAEs	immune-related adverse events
NSCLC	Non-small cell lung cancer

the co-stimulatory signals and induce high level of IL-2 production [11,12]. Besides CD28, following studies identified series of stimulatory checkpoints including ICOS [13,14], OX-40 (TNFRSF4) [15], 4-1BB (TNFRSF9, reviewed in Refs. [16,17]), GITR (TNFRSF18, reviewed in Ref. [18]), CD27 (reviewed in Ref. [19]), HVEM (reviewed in Ref. [20]), CD40L [21], etc. Among those, ICOS belongs to CD28 subfamily, while the OX40, 4-1BB, GITR, CD27 and HVEM belong to TNF receptor (TNFR) family. As the common feature, these stimulatory checkpoints on T cells could be ligated by their specific ligands from the antigen presenting cells (APCs) to deliver positive signals [22].

1.1.2. Inhibitory immune checkpoints

On the opposite, there also exist negative regulators such as CTLA-4, PD-1, TIM-3, LAG-3 (CD233), TIGIT and CD96 on the T cells to control the excessive response to infection. These inhibitory checkpoints act as a brake to maintain the homeostasis in cells. Similar to the action of the stimulatory checkpoints, the function of the inhibitory checkpoints also depend on the interaction between the receptors themselves and the relative ligands. It is now clear that as a CD28 superfamily member, CTLA-4 functions through outcompeting CD28 receptor for binding B7 ligands, resulting in the inhibition of CD28 downstream signaling [2]. In contrast, PD-1 functions in a distinct way. When ligated by PD-L1 (B7−H1) or PD-L2, PD-1 can recruit tyrosine phosphatases (SHP2) to inhibit the TCR signal [23]. The presentation of the ligand (Galectin-9) from the APCs can promote the auto-phosphorylation on Tyr256 and Tyr263 of TIM-3 and the release of Bat3 from the TIM-3 cytoplasmic tail, resulting in the inhibitory response of IFN-γ-producing T cells, FoxP3+ Treg cells and innate immune cells (macrophages and dendritic cells) [24]. LAG-3 TIGIT and CD96 are another known inhibitory checkpoints. It was recently found that fibrinogen-like protein 1 (FGL1) produced by cancer cells is the major inhibitory ligand of LAG-3 [25]. TIGIT and CD96 compete with the co-stimulatory receptor CD226 that is analogous to the CD28/CTLA-4 pathway, resulting in the inhibitory effect on T cell activation [26].

1.1.3. Harness immune cells to attack cancer cells through modulating immune checkpoints

The balance between the signals from the stimulatory and the inhibitory checkpoints determines the immune homeostasis (Fig. 1). The engagement of the stimulatory checkpoints profoundly influences the interaction between T and B cells, which is associated with the development of autoimmune diseases [27]. On the other hand, both mouse knock out model and the clinical experiments implicate that the inhibitory checkpoints play an important role in the supervision of autoimmune response [28–33]. But the immune cells in the tumor tissues are under an inhibitory state through inhibition of CTLA-4, PD-1/PD-L1, LAG-3/FGL1 and other inhibitory immune checkpoints [1,6,25,34]. And this provides the rationale of harnessing the immune cells to attack cancer cells through suppressing the inhibitory immune checkpoints and enhancing the stimulatory immune checkpoints.

1.2. CTLA-4 and PD-1/PD-L1 blockade

Among the myriad of immune checkpoints, the blockade of CTLA-4 or PD-1/PD-L1 has shown the optimal therapeutic effect. Great success has been achieved in the treatment of melanoma and other cancer types by administration of anti-CTLA-4 or anti-PD-1/PD-L1 antibody [35–39].

1.2.1. CTLA-4 blockade

As a homolog of CD28, CTLA-4 suppress the T cell activity through both intrinsic and extrinsic mechanisms [40]. Theoretically, blocking the CTLA-4 with the specific antibody may result in the inhibition of CTLA-4 mediated downregulation of T cell activation, and then CD28 may recombine with B7 ligands to activate the cytotoxicity of T cells and enhance the anti-tumor effect [1].

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a human monoclonal antibody (IgG1) that targets CTLA-4. In 2010, a landmark phase III clinical trial indicated that the application of Ipilimumab significantly prolonged the overall survival (OS) of the patients with metastatic melanoma compared with the patients receiving glycoprotein 100 (gp100) peptide vaccine alone (10.1 months vs. 6.4 month, hazard ratio = 0.66, P = 0.003) [35]. In 2011, Ipilimumab was approved by US FDA for the treatment of late-stage or metastasized melanoma. And recently, it was approved for the treatment of advanced renal cell carcinoma (in combination with Nivolumab), and the microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (in combination with Nivolumab). The cancer types of the ongoing clinical trials include non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC), bladder cancer and

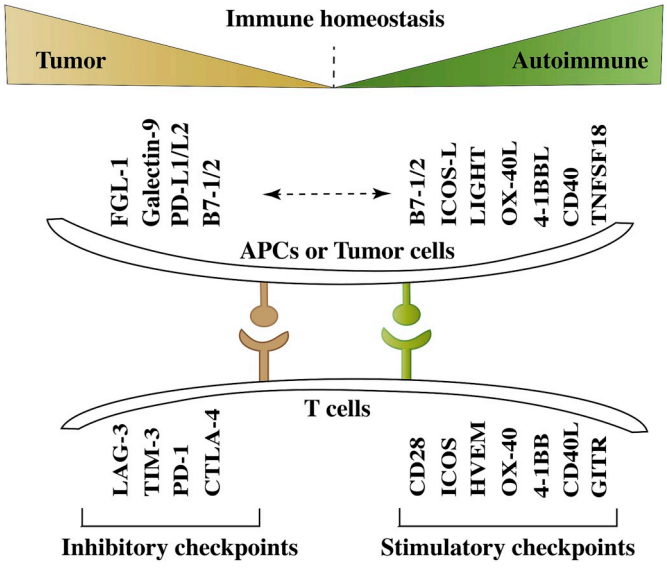

Fig. 1. The mode pattern of immune homeostasis.

metastatic castration-resistant prostate cancer (mCRPC) [refferred to ClinicalTrials.gov].

Tremelimumab is another human CTLA-4 antibody (IgG2) developed by AstraZeneca. In the phase II clinical trials of refractory/relapsed melanoma, 15 mg/kg Tremelimumab every 90 days exhibited durable response (≥170 days, 6.6% objective response rate) [41]. But Tremelimumab didn't demonstrate a significant survival benefit compared with standard-of-care chemotherapy in first-line treatment of patients with metastatic melanoma in a phase III trial [42]. Tremelimumab was also granted for the clinical trials in the treatment of unresectable malignant mesothelioma, NSCLC and metastatic urothelial carcinoma. However, the phase 2b trial demonstrated that Tremelimumab did not significantly prolong OS compared with placebo in patients with previously treated malignant mesothelioma [43]. In the phase III trial of Durvalumab (anti-PDL1) with or without Tremelimumab for the first-line treatment of advanced NSCLC, Tremelimumab failed to meet its primary endpoint of progression-free survival (PFS), and now other trials in second or third-line NSCLC with the combination of Duvalumab and Tremelimumab is ongoing [referred to AstraZeneca.com and ClinicalTrials.gov].

1.2.2. PD-1/PD-L1 blockade

There are some tumor cells that can escape from immune surveillance by upregulating the expression of PD-L1 (B7−H1) and promoting T cell apoptosis [44]. The disruption of PD-1/PD-L1 interaction by blocking antibody was shown to enhance the efficacy of T cell immunotherapy in mouse model [6,45]. Accordingly, the human PD-1 and PD-L1 antibodies were developed for clinical trials.

Nivolumab (Opdivo, Bristol-Myers Squibb) is the first human PD-1 monoclonal antibody (IgG4) evaluated in the clinical trial [39]. In the early phase I trial, Nivolumab administration produced rather good objective response rates (ORR) in NSCLC (18%), melanoma (28%), and renal cell cancer (27%) [39]. To date, Nivolumab has already been approved by US FDA for the treatment of melanoma, squamous cell lung cancer, renal cell carcinoma and Hodgkin's lymphoma. Another PD-1 antibody, Pembrolizumab (Keytruda, Merck), also shows strong promising in clinical activity. It has been approved for the treatment of advanced melanoma, metastatic NSCLC, metastatic head and neck squamous cell carcinoma (HNSCC), and advanced cervical cancer and any solid tumor with DNA mismatch repair deficiencies or a microsatellite instability-high state [referred to fda.gov]. Other PD-1 inhibitors such as AMP-224 and CT-011 are under clinical evaluation [46,47].

Unlike PD-1 antibodies, PD-L1 antibodies may not only block the PD-1/PD-L1 interaction between T cells and tumor cells, but also interfere the PD-L1/CD80 interaction between T cells and APCs, which may influence the induction and maintenance of peripheral T cell tolerance [48], implying that it may present differential effect by blockade PD-1 and PD-L1, but the detail clinical effect requires further evaluation. Atezolizumab (Tecentriq, Genentech) is a human PD-L1 monoclonal antibody (IgG1). In the phase II clinical trial, Atezolizumab showed unexpected and durable responses on the metastatic urothelial cancer patients (ORR 15%) and acquired prolonged clinical benefit [49,50], leading to the accelerated approval by US FDA. Another phase III clinical trial showed that Atezolizumab treatment resulted in a clinically relevant improvement of OS versus docetaxel [51]. Durvalumab (Imfinzi, Medimmune/AstraZeneca) is another PD-L1 antibody under clinical efficacy evaluation [52–54], and recently it was approved by US FDA for the treatment of metastatic urothelial carcinoma and the unresectable NSCLC that has not progressed after chemoradiation. Avelumab (Bavencio, Merck KGaA/Pfizer/Eli Lilly), another PD-L1 antibody, was also approved for Merkel-cell carcinoma in 2017 by US FDA [55].

1.2.3. The distinction between CTLA-4 and PD-1/PD-L1 blockade

Large numbers of studies have demonstrated that CTLA-4 and PD-1 inhibit T cell activity through distinct mechanisms [9]. And in a recent study James Allison and colleagues further revealed that the immune responses induced by blockade of CTLA-4 and PD-1 checkpoints are driven by distinct cellular mechanisms [56]. PD-1 blockade mainly induces the expansion of specific tumor-infiltrating exhausted-like CD8 T cell subsets, while CTLA-4 blockade induces the expansion of an ICOS + Th1-like CD4 effector population in addition to engaging specific subsets of exhausted-like CD8 T cells [56].

Interestingly, two recent independent clinical trials demonstrated that the administration of PD-1 blockers (Nivolumab and Pembrolizumab) could bring better benefit than CTLA-4 blocker (Ipilimumab) for advanced melanoma patients [57,58]. It remains unclear whether this distinction of clinical efficacy is derived from the intrinsic property of the antibody or from the distinct cellular mechanisms between PD-1 and CTLA-1 blockade. Nevertheless, the non-redundant tumor microenvironment features of PD-1 and CTLA-4 blockade seem to well support the combination therapeutic approach [56].

1.3. Other immune checkpoint modulators under clinical trials

In addition to CTLA-4 and PD-1/L1 modulators, there are other checkpoint modulators that are under clinical evaluation, including inhibitory antibodies (such as LAG-3) and agonistic antibody (such as CD27, OX-40, CD40, ICOS, 4-1BB and GITR). The underlying mechanisms have been reviewed before [9]. Here we mainly pay attention to the recent progression of clinical studies:

(i) **LAG-3 inhibitors**: Several clinical trials (NCT02658981; NCT03489369; NCT02061761; NCT01968109; NCT03005782) aiming at evaluating the safety and efficacy of anti-LAG-3 antibody alone or combining PD-1 antibody in the treatment of malignances are ongoing, but the efficacy is pending.

(ii) **CD27 agonists**: It has been shown that humanized CD27 agonistic monoclonal antibody could induce T cell activation and tumor immunity in human CD27 transgenic mice [59]. A recent phase I clinical trial demonstrated that Varlilumab (CD27 agonist) was well-tolerated and clinically active in advanced solid tumors [60]. The phase II trial with the combination of Varlilumab and Nivolumab in advanced refractory solid tumors is ongoing (NCT02335918).

(iii) **OX-40 agonists**: In a phase I clinical trial, OX-40 agonistic antibody showed an acceptable toxicity profile and regression of at least one metastatic lesion in 40% advanced cancer patients (12 out of 30), validating OX-40 as a potent immune-stimulating target for cancer treatment [61]. Other clinical studies of anti-OX-40 antibody in progressive metastatic prostate cancer and head and neck cancer are ongoing (NCT01303705; NCT02274155).

(iv) **ICOS agonists**: There are two ongoing trials that evaluate the safety and efficacy of anti-ICOS agonistic antibodies (MEDI-570 and GSK3359609) alone or plus Tremelimumab in the treatment of relapsed or refractory peripheral T-cell Lymphoma follicular variant or angioimmunoblastic T-cell lymphoma and advanced solid tumors, respctively (NCT02520791; NCT03693612).

(v) **CD40 agonists**: The safety of ChiLob7/4 (CD40 agonistic antibody) was evaluated in a Cancer Research UK phase I study, but the efficacy is pending [62].

(vi) **4-1BB agonists**: The safety of PF-05082566 (4-1BB agonistic antibody) has been evaluated in a recent phase I clinical, but the detail analysis has not been published (NCT02179918). Another ongoing phase I clinical trial is about the combination of PF-05082566 with Trastumumab (HER2 antibody) for the treatment of advanced HER2-positive breast cancer (NCT03364348).

(vii) **GITR agonists**: It has been reported that the stimulation of GITR pathway with GITR agonist significantly reduces intra-tumor Treg cells and enhances the anti-tumor effect of $CD8^+$ T cells [63]. But

in a recent phase I clinical trial of GITR agonistic antibody AMG 228 in patients with advanced solid tumors, although AMG 228 showed favorable pharmacokinetic properties, there was no evidence of T-cell activation or anti-tumor activity with this monotherapy, probably due to the oligomerisation or crosslinking with AMG 228 [64].

1.4. Combination therapy with multiple immune checkpoint modulators

Theoretically, combination with cocurrent blockade of inhibitory immune checkpoints or increasing stimulatory immune signals with specific modulators may enhance the immune response and clinical efficacy. For instance, PD-1 and CTLA-4 combination blockade could expand infiltrating T cells and reduce regulatory T and myeloid cells, shifting the tumor microenvironment from suppressive, making it more than twice as effective as either alone in tumor rejection [65]; The dual blockade of LAG-3 and PD-1 could enhance T cell activation [66]; The combination of 4-1BB agonist and PD-1 antagonist is sufficient to elicit a robust antitumor effector/memory T-cell response in an aggressive tumor model [67].

There are currently over 1000 combination trials, most of which are based on anti-PD-1/L1 and anti-CTLA-4 combination [7]. In fact, we have already seen the benefits from this combination strategy. For example, the phase III clinical trial in untreated melanoma has demonstrated that the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone (PFS of combination = 11.2 months vs. PFS of Nivolumab alone = 5.3 months) [68]. Other combination strategies in different cancer types remain to be confirmed in the future.

1.5. Prospects for precision therapy with immune checkpoint modulators

The PD-1/L1 and CTLA-4 blockades have brought a paradigm shift in immunotherapy for cancer [69]. But to achieve precision therapy with immune checkpoint modulators, there are still many problems in front to be solved.

First, there are still a lot of cancer patients who failed to respond to the immune checkpoint blockades [69]. For example, the average ORR of anti-PD-1/L1 in melanoma is about 33% [69]. To achieve a more precise application in clinical practice, it is necessary to identify predictive biomarkers, albeit with great challenges [70]. Recently Krieg and colleagues found that the frequencies of $CD14^{+}CD16^{-}HLA\text{-}DR^{hi}$ monocytes in the peripheral blood of patients with advanced melanoma well predict their OS in response to anti-PD-1 immunotherapy [71]. But further studies are needed to confirm this signature in larger cohort of patients with melanoma as well as other cancer types, and other potential biomarkers are valuable to investigate.

Second, for those patients who achieve effective response to immune checkpoint modulators, the biggest challenge is from the adaptive and acquired resistance caused by the tumor cell intrinsic and extrinsic mechanisms [72]. The intrinsic mechanisms include the absence of antigenic proteins, the absence of antigen presentation, the genetic T cell exclusion and the insensibility to T cells, while the extrinsic mechanisms include the absence of T cells, the inhibitory immune checkpoints and the immunosuppressive cells (TAM/Tregs) [72]. Considering the complexity, there is an urgent need to test different combination strategies in the pre-clinical models before clinical trials.

Third, by unbalancing the immune system, the immune checkpoint modulators also generate dysimmune toxicities, called immune-related adverse events (irAEs) that mainly involve the gut, skin, endocrine glands, liver, and lung but can potentially affect any tissue [73]. It has been observed that the adverse events of combination therapy were more frequent than monotherapy [74]. Considering the potential linkage between immune cell populations in cancer and autoimmune diseases (e.g. rheumatoid arthritis or lupus, etc), the future investigation of the mechanisms of chronic inflammation in immune-mediated diseases may not only help to manage the irAEs, but also help to pinpoint the inflammation in tumor immunity [75].

Last, the heterogeneous tumor microenvironments may impede the effective application of immune checkpoint modulators. Recent studies revealed that the cancer-associated stromal cells (e.g. fibroblasts) play an important role in the homeostasis of infiltrating lymphocytes (e.g. T cells), which is closely associated with the response rate of treatment with immune checkpoint modulators [76,77]. Single-cell technologies (e.g. single-cell RNA sequencing) provide an opportunity to reveal the heterogeneities of tumor-associated cells (e.g. lymphocytes, macrophages or fibroblasts) in the microenvironments [78–80]. The investigation of the subtypes and the functions of tumor-associated cells will help to better understand the immune suppressive mechanisms within the tumor microenvironment and to improve the clinical efficacy of immune checkpoint modulators.

Conflicts of interest

No conflict of interest.

Authors statement

Li Fan, Yue Li, Jia-Yu Chen, Yong-Fa Zheng and Xi-Ming Xu all serve as the coauthors of this review. Dr. Xi-Ming Xu is the corresponding author, and he mainly drafted the manuscript and organized the discussion. Li Fan, Yue Li and Jia-Yu Chen contribute equally in writing and editing this review. Yong-Fa Zheng participated in the discussion and partial editing work. All the authors are affiliated to the Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China.

2. Declaration

XM-X mainly drafted the manuscript and organized the discussion. L-F, Y-L and JY-C contribute equally in writing and editing this review.

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