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Review

Current status and future directions of cancer immunotherapy

Hongming Zhang, Jibei Chen✉

Department of Respiratory Medicine, Yancheng Third People's Hospital, the Affiliated Yancheng Hospital of Southeast University Medical College, Yancheng, Jiangsu, China.

✉ Corresponding author: Jibei Chen, MD., Chair, Director of Department of Respiratory Medicine, Yancheng Third People's Hospital, Jiangsu Province, P.R. China. E-mail: hmzhang149252@163.com

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Abstract

In the past decades, our knowledge about the relationship between cancer and the immune system has increased considerably. Recent years' success of cancer immunotherapy including monoclonal antibodies (mAbs), cancer vaccines, adoptive cancer therapy and the immune checkpoint therapy has revolutionized traditional cancer treatment. However, challenges still exist in this field. Personalized combination therapies via new techniques will be the next promising strategies for the future cancer treatment direction.

Key words: cancer, immune system, cancer immunotherapy, challenges, future directions

Background

For decades, the conventional anticancer treatment strategies have been surgery, chemotherapy, and radiotherapy [1, 2]. While many of these therapies have offered substantial benefit for eradication of primary tumors, the incidence of disease relapse is still a commonly encountered problem that results from residual malignant cells and/or tumor metastases [3, 4]. Therefore, alternative treatment approaches to eliminate the resistant tumor cells are warranted [5].

Cancer immunotherapy is becoming an appealing and attractive strategy among different therapeutic options over the past years and has showed its power against malignancies (**Figure 1**) [3, 6-9]. It utilizes the body's immune system to induce anti-tumor response and thus cancer can be defeated [3, 6-9]. Most recently, cancer immunotherapy field is growing tremendously, such as utilization of cancer vaccinations, chimeric antigen receptor (CAR) T-cell therapy and immune checkpoint blockade therapy [10, 11]. Several clinical trials have investigated their potentials in cancer patients lifesavings [12-16], and after witnessing the amazing effect of cancer immunotherapy it was selected as "2013's Breakthrough of the Year" by *Science* magazine [17].

Our goal in this article is to concisely summarize the molecular bases of immune system and its relationship with cancer as well as recent developments in cancer immunology. Cancer immunotherapeutic drugs and their clinical applications will also be discussed in details. Finally, challenges and future directions of cancer immunotherapy will be provided based on the previous clinical studies. We hope that this review will be of interests to both basic cancer immunologists and also clinical oncologists.

Cancer and the immune system

The relationship between immune system and cancer has been extensively investigated in numerous preclinical and clinical studies [18-22]. The basic role of our immune system is to protect human beings against foreign pathogens and also infections. The immune responses consist of two types: humoral immunity and cellular immunity, which are mediated by B and T lymphocytes as well as their products [23]. Humoral immunity can neutralize and eradicate outside microbes and toxins via antibodies produced

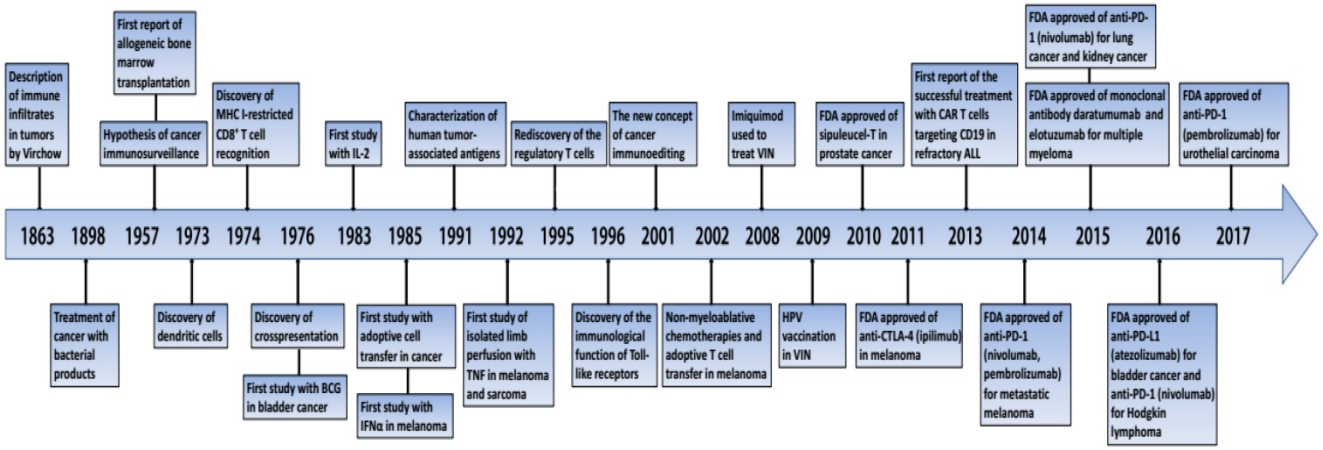

Figure 1. Important events in the history of cancer immunotherapy. BCG, bacilli Calmette-Guérin; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; FDA, Food and Drug Administration; IFNα, interferon-α; IL-2, interleukin-2; MHC, major histocompatibilty complex; PD-1, programmed death 1; TNF, tumor necrosis factor; VIN, vulvar intraepithelial neoplasia

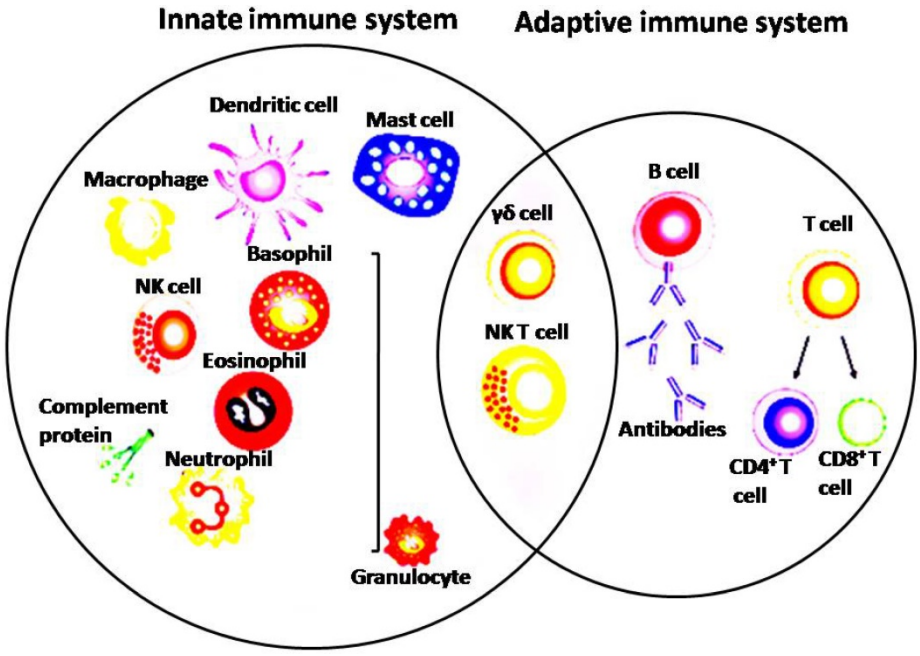

Figure 2. Depicture of cells in the innate and adaptive immune system

by B cells [24-26], whereas cellular immunity responds more quickly to eradicate intracellular microbes through recognition of antigens, activation of antigen presenting cells (APCs), activation and proliferation of T cells. [23, 27, 28].

Both innate and adaptive immune systems play important roles in anticancer immune response **(Figure 2)** [29, 30]. The innate immune cells can release signals which are essential to stimulate responses from both T cells and B cells [31]. Adaptive immune system is mainly consists of B cells, $CD8^+$ cytotoxic T cells as well as $CD4^+$ helper T cells [32]. APCs is performing as a bridge between the innate and the adaptive immune system by recognizing foreign antigens and presenting to the naive T cells [33]. In addition, after activation of toll-like receptors on dendritic cells (DCs), factors on the DC surface that is essential to antigen presentation could be increased and cytokines that facilitate the adaptive immune response would be promoted [33]. It has now been widely accepted that by the cooperativity of innate and adaptive immune system can lead to complete success of conquering cancer [34]. $CD8^+$ cytotoxic T lymphocytes (CTLs) are considered as the corner stone of immune response fighting cancer [7]. Tumor-infiltrating lymphocytes (TILs) contain an abundant level of CTLs capable of invading malignant cells [35]. Tumor antigen recognition is a necessary prerequisite for the effective antitumor immune response [3]. Tumor antigen presentation is mediated by direct presentation which cancer cells drain in the lymph node or via cross-presentation by

pAPC [36]. Cross priming of naïve $CD8^+$ T cells by pAPC invokes a program leading to tumor specific CTLs proliferating and trafficking to the tumor sites where they will finally attack cancer cells [37]. CTLs can attack tumor cells via perforin, granzymes and also ligands of the tumor necrosis factor (TNF) superfamily [38]. The anti-tumor effect can also be achieved by secreting Interferon gamma (IFN-ɣ) and TNF-α from activated $CD8^+$ T cells [39]. Naive $CD4^+$ T cells could be activated and differentiated into distinct T cell subsets such as Th1, Th2, Tregs, Th9, Th17, Th22 and also follicular helper T cells once they encounter antigens and also adequate co-stimulation signals [40]. Th1 subset of $CD4^+$ T cells play crucial antitumor roles by coordinating cell mediated immunity against cancer. Th1 cells can produce IFN-ɣ and chemokines and thus enhancing $CD8^+$ T cells expansion, priming and infiltration into the tumor site by [41]. Th1 cells can also activate inflammatory cells, such as macrophages, NK cells, granulocytes and eosinophils in around the tumor [41]. Th1 cells can kill MHC-II^+ tumor cells by releasing perforin and granzyme, and also by TNF-related apoptosis inducing ligand (TRAIL) receptor and Fas/Fas ligand pathways [41]. NK cells can destroy cancer cells directly via mechanisms as follows: secretion of TNF-α, perforin, cytoplasmic granules and granzymes, expression of death receptor-mediated apoptosis, and expression of CD16 which leads to antibody dependent cellular cytotoxicity (ADCC) [42]. NK cells have been able to have antitumor activity as well indirectly by chemokines, cytokines and growth factors production. The role of macrophages in eliminating apoptotic tumor cells also can't be ignored [42, 43]. Macrophages are an essential component of tumor stroma and tumor-associated immune dysfunction, which can be characterized as pro-inflammatory M1 or anti-inflammatory M2 macrophages [44-46]. M1 macrophages secrete pro-inflammatory cytokines boost antitumor immunity, whereas M2 macrophages produce anti-inflammatory cytokines which would promote tumorigenesis [45]. Myeloid-derived suppressor cells (MDSCs) are both immature and immunosuppressive cells increasing in inflammatory diseases, particularly tumors. They can produce inhibitory factors such as IL-10 and arginase to inhibit T cells and promote Tregs and detrimental M2 macrophages, and thus suppressing anti-tumor immunity [47, 48].

According to the concept of cancer immunosurveillance proposed by Burnet, Thomas and Medawar[49-57], it is now well established that the immune system's capability for spontaneously recognizing cancer cells that had undergone genetic aberrations and mounting a cytotoxic response through the generation of specific $CD8^+$ T lymphocytes. However, this specific $CD8^+$ T lymphocytes response ultimately fails due to cancer invasion [58-60]. Cancer immunoediting has been considered for relying on three phases: an early elimination phase with the activation of an innate and adoptive immune response, an equilibrium phase where the sporadic tumor cells may survive immune attacks, and an immune escape phase that the cancer cell variants survive in the immunosuppressive microenvironment by altering geno- or antigenic phenotype or under the control of immunoregulatory phenomena [61]. In this process, the immune system plays contradicting roles for both protecting body from tumor development however also promoting tumor progression [61].

Current cancer immunotherapy strategies

At present, new strategies aiming at blocking of immune checkpoint regulators, overcoming immune tolerance such as engineered T cell therapy, or the identification of novel tumor antigens through next-generation sequencing opened a new era of cancer immunotherapy [62-64]. Cancer immunotherapy includes passive or active immunotherapy (**Table 1**) [65, 66]. Passive immunotherapy is administration of agents such as mAbs, lymphocytes or cytokines that enhance existing anti-tumor response [34]; active immunotherapy attempts to stimulate self-immune system to attack tumor cells via vaccination, non-specific immunomodulation, or targeting specific antigen receptors [34]. Promising methods were discussed below.

Table 1. Classification of cancer immunotherapy

Passive immunotherapy		Active immunotherapy	
Immunomodulating antibodies	Adoptive immunotherapy	Specific	Non-specific
- Immune checkpoints inhibitors - Immune co-stimulatory antibodies	- Tumor-infiltrating lymphocytes - TCR gene-modified lymphocytes - Chimeric antigen receptors (CARs)	- Vaccines	- Immune adjuvants - Cytokines

Monoclonal antibodies

Antibodies are modified proteins aimed at to target a specific part of deregulated signals transduction pathways in cancer or interfere with immunological processes [57, 67]. FDA has already approved more than a dozen mAbs for the treatment of both solid and hematological malignancies, and also more new mAbs clinical trials are now being investigated [67, 68]. Monoclonal antibody and gene transfer technologies have promoted further exploitation of our fundamental knowledge on

antigen recognition, T cell activation as well as T cell co-stimulation, thus leading to the invention and also the success of checkpoint blockade and CAR T cell therapy [69]. Several types of mAbs are being used in cancer treatment now, including naked, conjugated and bipecific mAbs [70, 71]. Naked mAbs are the most common type of mAbs for treating cancer, and it can work via boosting the immune response against cancer cells and acting as a marker for the immune system's destroying them. Alemtuzumab is an example of naked mAb which can bind to the CD52 antigen on lymphocytes attacking them which is used to treat chronic lymphocytic leukemia (CLL) [72, 73]. Other naked mAbs work mainly by attaching to and blocking antigens on tumor cells helping cancer cells grow and spread, like trastuzumab, an antibody against the HER2 on breast and stomach cancer cells [74]. Conjugated mAbs are those mAbs joining to a chemotherapy agent or a radioactive particle taking one of these substances directly to the cancer cells [75]. Chemolabled antibodies are those antibodies with powerful chemotherapy attached to them, such as brentuximab vedotin an antibody that targets CD30 antigen found on lymphocytes, attaching to a chemotherapy drug and thus treating Hodgkin lymphoma and anaplastic large cell lymphoma [76-78]. Radiolabeled antibodies have radioactive particles attached to them [79]. Bispecific mAbs are made up of parts of 2 different mAbs, like blinatumomab binding to both CD3 and CD19 used to treat acute lymphocytic leukemia (ALL) [80, 81]. Possible side effects of mAbs may include fever, chills, headache, weakness, nausea, diarrhea, rashes and hypotension [82].

Cancer vaccines

Cancer vaccines are the response modifiers working by stimulating or restoring the ability of immune system to fight cancer [83]. It consists of preventive vaccines and therapeutic vaccines [84]. The goal of preventive vaccine is preventing cancer from developing. They are based on antigens carried by infectious agents and easy for the immune system to recognize as foreign invaders [85]. FDA has approved hepatitis B virus (HBV) vaccines and human papilloma virus (HPV) vaccines [84, 86, 87]. It stimulates the immune system with tumor antigens, peptides, or whole cancer cells [88]. The mechanism involves activating the immune system with targeted T cells to destroy target cancer cells. Therapeutic vaccines first directly target the immune system and expand the immune system's attack on cancer cells. A broadening of the immune response may also be observed as it might attack additional tumor-specific antigens (antigen spread) [57, 89]. In this therapy, peripheral blood mononuclear cells are isolated from the patient and *ex vivo* activated with a recombinant fusion protein consisting of a prostate antigen prostatic acid phosphatase (PAP) conjugated with granulocyte-macrophage colony-stimulating factor (GM-CSF), and the cells are then re-infused into the patient to activate PAP-specific T cells [90]. T-VEC can trigger an antitumor immune response in non-injected lesions. The side effects of cancer vaccines vary from different vaccine formation and person, and the most commonly reported side effect of cancer vaccines is inflammation at the site of injection [91].

Adoptive T cell therapies and T cell engineering

Adoptive cell transfer (ACT) of tumor-associated antigen-specific T cells is a very attractive form of immunotherapy for hematologic malignancies as well as solid cancers [92]. Initial studies of ACT utilizing tumor-infiltrating lymphocytes (TILs) have promising clinical results in metastatic melanoma patients to some degree [17, 93]. But later on this approach had been limited by the difficulty in expanding viable TILs and only showing specific effector functions [94]. In order to overcome this problem, strategy of CAR- and T-cell receptor (TCR)-engineered T cells have been developed based on various approaches by genetic modifications, and inspiring efficacy in various clinical trials for particular cancers have been observed [95, 96].

Traditionally, two major sources of T cells for ACT are the tumor itself and the peripheral blood of the cancer patient [92]. Transferring of antigen-specific TCR genes into lymphocytes isolated from the patient's peripheral blood becomes an alternative approach [95, 97]. It is via T cell transductions with retroviruses or lentiviruses, thus they can express TCRs targeting specific cancer antigens and eradicate those cancer cells [97]. Although promising results have been achieved in metastatic melanoma patients, TCR technology seems less attractive because it is MHC-restricted which limited its further development [98]. CAR modified T cells are a second class of engineered T cells [99]. Compared to TCRs, CARs have antibody-like specificities which can recognize major histocompatibility complex (MHC)-non-restricted structures on the surfaces of target cells, thereby allowing for cancer cell recognition in the MHC-unrestricted manner [100]. CAR is composed of an antigen-binding single-chain variable fragment (scFv) domain, a transmembrane domain (TMD) and a signal transduction domain (STD) [101]. ScFv is designed to target a specific surface molecule on B cells [101]. By altering the changeable components of a

CAR like the epitope-recognition part, cell function could be improved [100]. CAR constructs also differ in flexibility and length of the hinge region conjoining the scFv to the transmembrane region [100]. Once modified, CAR T cells are expanded and infused back to lymphodepleted cancer patients where they can eradicate the cancer [89]. CAR-expressing T (CAR-T) cells have shown remarkable efficacy targeting CD19 on B-cell malignancies [102]. The most investigated CAR target is CD19 expressing on normal B cells and the majority of B cell leukemia's and lymphomas [103]. In refractory or relapsed ALL, patients can get 90% complete remission after reinfused with anti-CD19 CAR T cells. Promising results have also been observed in some refractory diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL) [12]. However, this therapy's widespread to solid tumors is one of the major future goals of ACT because of the difficulties to find suitable target antigens and also for the tumor immunosuppression and complex tumor microenvironment [90, 104]. In addition, ACT needs to be optimized to reduce toxicity and to enhance anti-tumor efficacy [105, 106].

Immune checkpoint blockade therapy

Immune checkpoint inhibitors are a class of drugs aimed to increase immune response against cancer cells [107-109]. The immune system consists of various checkpoint pathways focusing on T-cell activation that play an important role in modulating anti-tumor immunity [110]. Molecules that play a crucial role in checkpoint regulation include the T-cell surface molecules CTLA-4, PD-1, T-cell immunoglobulin and mucin domain containing protein 3 (Tim-3), and lymphocyte activation gene-3 (LAG-3) [88]. Tumor expressions of these markers will results in hyporesponsiveness or even exhaustion of the immune system [111]. As a result, these molecules are highly attractive as targets for removing the inhibition and enable cytotoxic T cells to attack cancer cell for destruction [34, 57]. In 2011, FDA approved anti-CTLA-4 antibodies ipilimumab for the treatment of metastatic melanoma, which marked the beginning of a new era for cancer immunotherapy [89, 111]. Subsequently, antibodies against PD-1 pembrolizumab and nivolumab have been approved in 2014, also for the metastatic melanoma [112]. Nivolumab has also been approved in 2015 for previously treated advanced or metastatic squamous lung cancer, an approval later expanded also to small cell lung cancer [113]. In 2016, anti-PD-L1 atezolizumab was approved for bladder cancer [114] and nivolumab was approved for Hodgkin lymphoma [115]. At present, more than 100 clinical trials are ongoing to test the efficacy and safety of immune checkpoint blockers in several cancer types **(Table 2)** [90, 110, 116-118]. Checkpoint inhibition is also associated with a unique spectrum of side effects including gastrointestinal, dermatologic, endocrine, hepatic, and other less common inflammatory events [119, 120]. Treatment of moderate or severe side effects requires interruption of the checkpoint inhibitor and the use of corticosteroid [119, 120].

Monitoring the response of immunotherapy

To monitor the immune response, abundant of assays have been tried. Since the immune system is a very complex network, it is crucial to monitor the cell milieu, phenotype of cell subsets, cell surface molecules responsible for cell-cell interactions and intracellular signaling events of the immune system

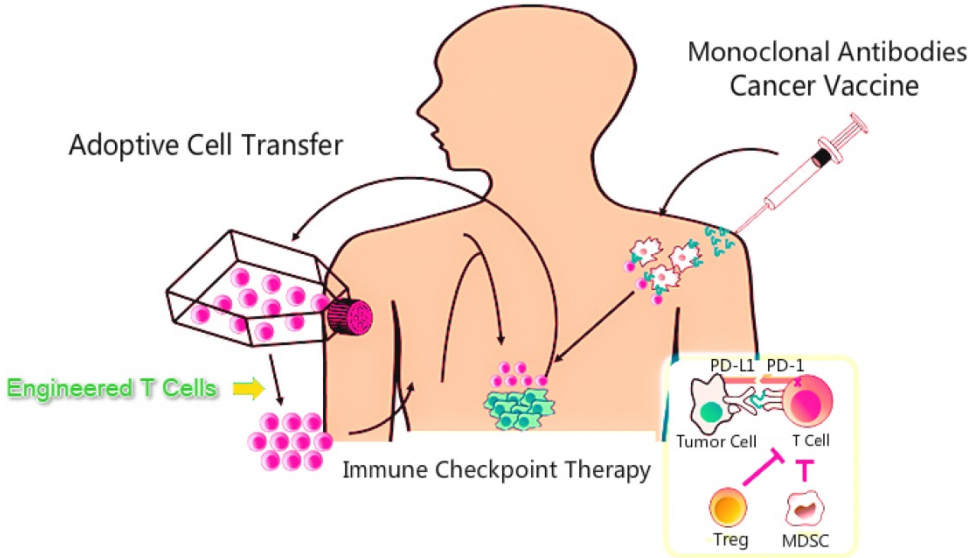

Figure 3. Methods of immunotherapy. MDSC, myeloid-derived suppressor cells; PD-1, programmed death-1; PD-L1, programmed death-ligand 1

[121-123]. Several methods such as mass cytometry, direct labeling, imaging techniques can be used [122, 124, 125]. Though there are criteria of clinical response of in cancer treatment, there are no specific criteria of monitoring the immunotherapy up to date [7]. Genetic markers, tumor size changes, new tumor lesions, adverse effect, patients' survival are important indications in the clinical trials by immunotherapy [126, 127].

Table 2. Checkpoint Blockade Targets in Clinical Development

Target	Drug name	Cancer types	Current Status
CTLA-4	Ipilimumab	Melanoma	FDA approved
		Multiple cancers	Phase I-III
	Tremelimumab	Multiple cancers	Phase I-III
PD-1	Nivolumab	Melanoma, lung	FDA approved
		Multiple cancers	Phase I-III
	Pembrolizumab	Melanoma	FDA approved
		Multiple cancers	Phase I-III
	MED10680	Multiple cancers	Phase I
	AMP-224	Multiple cancers	Phase I
	Pidilizumab	Multiple cancers	Phase I-II
PD-L1	Atezolizumab	Multiple cancers	Phase I-III
	MED14736	Multiple cancers	Phase III
	Avelumab	Multiple cancers	Phase I-III
	BMS-936559	Multiple cancers	Phase I
LAG-3	IMP321	Multiple cancers	Phase I
	BMS-986016	Multiple cancers	Phase I
B7-H3	Enoblituzumab	Melanoma, prostate	Phase I

CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG-3, lymphocyte activation gene-3; PD-1, programmed death-1; PD-L1, programmed death-ligand 1

Challenges and future directions

Numbers of challenges of cancer immunotherapy still exist for translating these promising approaches to clinically feasible therapies that treat a larger range of cancer types though recent years' success.

Implementation of next-generation sequencing technologies

Caner is genomically unstable [128]. Altered ploidy, heterogeneity and normal contamination are the features characterizing the cancer sequencing data that prompt the need for new bioinformatics approaches [128]. Next-generation sequencing (NGS) can provide novel and insights into the molecular machinery inside the cancer cells [129]. Besides expression profiling of transcripts and genes as well as detecting alternative splicing, it has enabled the discovery of single nucleotide variants (SNV), insertions, deletions, amplifications and inter-chromosomal rearrangements in the whole genome and transcriptome [130]. The advent of NGS and improvements in bioinformatic algorithms that predict immunogenicity of the mutated genes wound certainly lead to the development of more safe, efficient and effective personalized cancer therapy [3, 90, 131].

Biomarker-driven clinical trials

In the process of cancer progression, tumors will acquire somatic mutations, and those cells that acquire certain mutations have survival advantages and will dominate localized tumor areas by displacing those lacking these genomic alterations [132, 133]. Driver mutations dominate in all metastatic sites of cancer and the heterogeneity will certainly affects subclonal mutations [134]. Tumor heterogeneity (both inter- and intra-tumor heterogeneity), together with the clonal mutations are the main challenges of personalized cancer treatment [135]. Therefore, repeated biopsies at progression and biomarker-driven personalized therapies are needed to determine resistant mechanisms and their potential targeted inhibition [136]. Next-generation clinical trials taking into account the premise of tumor heterogeneity using genomic analysis of circulating cancer cells and circulating-free DNA are being developed [132, 137].

Combinational immunotherapy

The combination of different immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 have demonstrated enhanced efficacy; however, how to treat with the most suitable dosing and how to identify the most efficacious combinations are the main challenges. In addition, combining immunotherapy with other types of treatment such as chemotherapy, radiation therapy and targeted therapies can also be explored [138-140]. Preliminary evidences indicated that there will be promising synergistic effects when combining other types of therapies with immunotherapy [138, 141].

Conclusions

In summary, with the advent of cancer immunotherapy and recent advances of it, curing cancer seems to be a real possibility for cancer patients. The development of cancer vaccines, CAR-T cell and checkpoint inhibitors has revolutionized the cancer treatment. Combination therapy might be a promising therapeutic strategy to treat cancer in the future. Recognition and management of toxicities of cancer immunotherapy will also be a key factor for treatment success. Personalized combination therapies that specifically drive each patient' cancer biology via new techniques will be the most promising strategies for cancer treatment.

Competing Interests

The authors have declared that no competing interest exists.

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