Current progress of immunotherapy in cancer treatment

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Abstract. Currently, cancer is the second cause of death in the world. According to the Centers for Disease Control and Prevention, for every 100,000 people, 403 new cancer cases were reported and 144 people died of cancer in 2021. Nowadays, besides chemotherapy, radiation therapy, and genetic therapy which have been common treatments for cancer in clinic, scientists have kept developing other strategies to fight against cancer. One innovative and critical approach is immunotherapy. Tumor immunotherapy is a treatment method that induces the body to produce tumor-specific immune responses in an active or passive way, and exerts its function of inhibiting and killing tumor cells. Among them, immunotherapy designed to elicit or enhance the immune response is called activation immunotherapies, while reducing or suppressing the immune response is suppression immunotherapies. Immunotherapy, disparate with other therapies, depends on patients' immune systems, improving the anti-tumor ability of patients' immune cells. Nowadays, there are five main types of immunotherapy: molecularly targeted therapy; immune checkpoint blockers or inhibitors; cytokine therapy, and cancer vaccines. Despite the significant progress immunotherapy achieved in cancer treatment, still, it faces a huge challenge in application. This review introduces the pathogenesis of cancer and the function mechanism of immunotherapy, as well as introduces several different available immunotherapies, and the improved strategies of immunotherapy and other therapies.

Keywords: Cancer; Immune system; immunotherapies.

1. Introduction

Cancer is a result of disturbed cell function. Accumulating cells with genetic and epigenetic changes that lead to chromosomal or molecular mutation, cancer has its characteristic of genetic instability. Exogenous and endogenous factors, the environment, and genetic inheritance all contribute to cancer development. One critical inducement is carcinogens, involved in the environmental aspect, that cause about 80-90% of cancer with malignant tumors [1]. Tumorigenesis is a multi-step process. From the normal cells, cell damage results in the first mutation meanwhile some normal cells keep replicating normal cells. Then, cells with the first mutation replicate themselves meanwhile producing the second mutation cells via cell damage. After that, the second mutation cells duplicate themselves and contemporarily produce the third mutation cell. Such processes keep happening in the tumor site, causing the tumor to become a mix of various mutation-level cells. Because of this trait of the tumor, it is challenging to completely cure the cancer via one treatment that eliminates specific types of cancer cells. In other words, this attribute of tumor—being a mixture composed of different mutation-level cells—causes the cancer to easily recurrent after a period when the mutation level of a cell deepens enough to be seen as a cancer. Available therapeutic strategies for cancer patients are HMA (DNA hypomethylating agents), chemotherapy, metabolic targeted therapy, targeted therapy, and immunotherapy.

Immunotherapy is an innovative therapy that was invented and developed for cancer. Its working principle stems from understanding the roles immune cells play in the human immune system and improving their ability to work and fight against malignant and abnormal cells such as cancer cells. After one of their patients was infected by the Erysipelas, German physicians, Fehleisen and Busch, noticed a significant regression of the patient's tumor, which can be seen as the first time that scientists modulated patients' immune systems to cure cancer [2]. Then, the Father of Immunotherapy—William Bradley Coleyuncovered the T cell's existence and demonstrated the T cell's role in the immune response in 1967 [2]. Nevertheless, what critical work does T cells do was

not well known until Jacques Miller's description in "Nature" publication [1]. Besides, in 1945, Ruth and John Graham discovered the interferon, which led to the success of the invention of the first cancer vaccine [2]. James Allison's work on immune checkpoint molecules led to the discovery of drugs such as immune checkpoint inhibitors and immunotherapy such as CAR T-cells, making the prospect of efficiency and feasibility of immunotherapy promising. Immunotherapy, as an innovative treatment field, ultimately claimed to emerge after the invention of the first vaccine with the surface antigen of a single cell was put in the use of hepatitis B vaccine [2].

Compared to other traditional therapies, immunotherapy produces results significantly faster and it has been optimized to higher efficiency [3]. In addition, some side effects caused by traditional treatment often lead to the death risk of patients, but immunotherapy has the lowest probability of side effects and is relatively safer. Furthermore, the scope of immunotherapy is much broader due to immune cells will automatically find cancer disease to destroy, which means immunotherapy theoretically can have a therapeutic effect on all cancers.

2. Immune cells and immunotherapies

One of the characteristics of cancer allows cancer cells to evade immunological destruction by immune cells. Innate immune cells trigger inflammation, aiming to fight infections, but instead, they result in unintentional support of several cancer hallmarks under cancer circumstances, demonstrating tumor-promoting consequences of inflammatory responses.

According to a series of studies, immune cells; including T cells, B cells, NK cells, Macrophages, Dendritic cells, and so on; in the human body contribute to cancer development or anticancer therapy disparately. The immune system is divided into two: Innate immunity, which means having a rapid response, and Adaptive immunity which means having a slow response.

In short, activating immune cells include CD8 T cells, NK cells, and Dendritic cells; Immunosuppressive cells, those bad for cancer treatment, involve Regulatory T cells, Macrophages (MDSCs), and Neutrophils. Immunotherapies develop from the fundamentals of the human immune system and different functions of disparate immune cells, becoming a huge progress in cancer treatment.

2.1. T cells

T cells are a type of leucocyte, white blood cell, that is also called T lymphocytes. T cells can be categorized into the adaptive immune system, and act as the immune system's effector and regulator. According to Speiser et al., T cells can differentiate into either inflammatory or anti-inflammatory based on the immunological environment [4]. T cells generally could differentiate into cells that are cytotoxic and function to kill cells (CD8+ T cells) and cells that can help activate or weaken the immune response, having many types (CD4+ T cells).

Recognizing the pathogen peptide that an antigen-presenting cell(APC) expressed, the T cell receptor on a CD4+ T lymphocyte initiates a series of reactions. Such reactions trigger the further production of various types of helper T cells (TH) depending on the types of pathogens that are recognized. For example, heterodimeric cytokine IL-12 makes the T cells differentiate from TH0 cells to TH1 cells, which helps activate macrophages and cytotoxic T cells. The prototypic immunoregulatory cytokine IL-4 makes the T cells differentiate from TH0 cells to TH2 cells, which helps activate B cells. The multifunctional cytokine IL-6 makes the T cells differentiate from TH0 cells to TH17 cells, which helps recruit neutrophils and macrophages.

If enough immunogenic antigens are produced during the early stages of tumor initiation, naive T lymphocytes will be primed. They, then, activate and migrate into the Tumor microenvironment (TME), an environment that tumors depend on for survival. Those T lymphocytes yield the immune response by killing cancer cells that are immunogenic.

After activating by the APCs, the CD8+ T cells apply an efficient anti-tumoral attack, resulting in the direct damage of target cells through the exocytosis of perforin- and granzyme-containing

granules [5]. Besides, The TH1 cells, the CD4+ T helper cell mentioned before, mediate anti-tumoral response by secreting proinflammatory cytokines such as IL-2, TNF-α, and IFN-γ, promoting the priming and activation of T lymphocytes, the cytotoxicity of cytotoxic T lymphocytes. The immune response of NK cells and macrophages is also activated. Besides, tumor antigens are presenting in increasing numbers as a result [6-8]. Based on such function, CD4+ T cells—especially TH1 cells—help lead to higher priming, expansion, maturation, and memory of CD8+ T cells [4].

However, whether the cell-killing ability of T cells is effective depends on whether the tumor antigen is capable of inducing an immune response and on the existence of inhibitory signals that can weaken the function of killing tumor cells. Through immune checkpoints on CTLs, normal cells and tissues are protected from inflammatory damage. Some tumors have antigens that involve immune checkpoint molecules, deactivating T cells. CTLA-4, a type of immune checkpoint molecule, acts as the replacement for the type 1 membrane glycoprotein CD40. CD40 should activate the CD4 T cell's function if attached to the T cell ligand, CD40L. In contrast, under the case of the CD40L attaching to CTLA-4, CD4 T cells will not be activated and thus won't kill that cancer cell. Similarly, PD-1 attached to its receptor PDL-1—which is expressed by other immune cells, normal tissue cells, and cancer cells—will decrease the activity of T cells. In detail, this reaction between PD-1 and PD-L1 can not only inhibit the migration of T cells, but also inhibit T cells' proliferation. Besides, the cell-killing ability of T cells is weaken [9].

Regulatory T cells mediate their suppressive effects by producing inhibitory cytokines, disrupting metabolic and modulating dendritic-cell maturation or function, thus contributing to cancer just like tumor antigens and inhibitory signals [10].

2.2. B cells

B cells, or B lymphocytes, are a type of white blood cell of the lymphocyte subtype. Secreting antibodies (such as CD40, CD80, CD52, and so on), B cells play a critical role in the humoral immunity component of the adaptive immune system. They either differentiate into short-lived plasma cells in lymphoid tissues or become antibody-secreting plasma cells and Memory B cells as the long-lived plasma cells in bone marrow or gut lamina propria. The process in lymphoid organs to differentiate B cells is the activation in the germinal centers [11].

B cell activation can be divided into two types: T cell-independent activation and T cell-dependent activation. The former requires antigens with repeating epitopes, which activate B cells after attaching to the receptor on the B cell surface. For example, one pathogenic bacteria cell expresses polysaccharide antigen with repeating epitopes that could bind to the B cell receptor, activate the B cell, and trigger the activated B cell to secrete pentameric lgM. On the other hand, T cell-dependent activation goes through the pathway that the B cells first recognize and internalize an antigen, then present that antigen to a TH cell. Such antigen reacts with the TH cell, leading to a further response that activates the T cell, stimulating T cells to release cytokines. The cytokine then activates the B cell. The activation of B cells during clonal selection and clonal expansion leads to proliferation and differentiation into B cells and plasma cells.

However, despite its help in the regular immune response, B cells are proven that they can support tumor growth, or even promote their deterioration. By secreting molecules to suppress immune responses, B cells directly associate with tumor cell proliferation. For example, in Lloyd Bod's study, a type of B cells is identified to expand in the draining lymph node in mice that bear tumors, expressing multiple co-inhibitory molecules such as PD-1 that mentioned before could suppress the immune response [12]. The types of B cells that play a suppressive role in the immune response are named regulatory B cells because of their suppressive function and their contribution to tumor development like Regulatory T cells.

2.3. NK cells

Natural Killer (NK) Cells are the lymphocytes best known for killing virally infected cells and detecting and controlling early signs of cancer, NK cells powerfully contribute to anti-tumor reactions.

NK cells are named "natural killers" for the reason that they are capable of killing tumor cells without priming and activating by antigen-presenting cells.

A balance of signals from activating receptors and inhibitory receptors on the NK cell surface decide whether the NK cell will or won't kill that cell attached to the target cell during patrol. Respectively, activating receptors recognize molecules that are expressed on the surface of cancer cells and infected cells, switching the killing function on of NK cells; inhibitory receptors identify major histocompatibility complex type 1(MHC I) which mark cells as 'self' that are expressed by most normal healthy cells, preventing NK cells from killing. Releasing cytotoxic granules containing perforin and granzymes that lead to lysis of the target cell, NK cells manage to kill an identified "bad" cell.

The killer immunoglobulin-like receptors (KIR2DL and KIR3DL) and C-type lectin receptors (CD94/NKG2A/B) are two types of inhibitory receptors that are capable of identifying the MHC in humans—human leukocyte antigen class I (HLA-I). Inhibition to activate NK cells is caused by the recognition of HLA-I, which is almost expressed on all nucleated cells, and the receipt of inhibitory signals that are transmitted when immune checkpoints bind to their ligands. Immune checkpoints are used to protect normal cells from over-attack or accidental attack of the immune system as the original goal, but some cancers stimulate immune checkpoint targets, protecting themselves from the attack of NK cells. They express normal levels of HLA I but meanwhile over-express stress-induced ligands. When the activation signal is transduced activating receptors that bind to such stress-induced ligands overcome the inhibitory signals, NK cells can be activated and start killing tumor cells.

One important stimulatory cell surface receptor named NKG2D is vindicated to be able to recognize various ligands present on the abnormal or tumor cells' surface, activating the killing function of NK cells. Overall, NK cells' function is highlighted in controlling cancer progression by clinical studies [13].

3. Immunotherapies in cancer

Cancer immunotherapies are therapies that mobilize the patient's own immune system instead of targeting tumors. It can conceivably be effective against any type of cancer. Several available immunotherapies could be used today and have promising outcomes.

3.1. Immune Checkpoint Inhibitors

Immune checkpoints can be stimulatory or inhibitory. When the immune checkpoints are inhibitory, they provide a negative feedback mechanism. Immune checkpoints initiate working when proteins on the surface of immune cells bind to and identify the partner proteins, immune checkpoint proteins, on the surface of other cells. Some tumor cells present ligands on their surface, sending inhibitory signals to NK cells or T cells when they bind to them. To solve this problem that hinders immune cells from recognizing tumor cells, immunotherapy drugs called immune checkpoint inhibitors are created [14]. Immune checkpoint inhibitors are mainly antibodies against these checkpoints, blocking the checkpoint proteins from binding with their partner proteins that keep T cells in check. The effects are proven to be enduring and long-term, allowing the body to respond rapidly.

For example, since CTLA-4 and PD-1 (two checkpoint molecules) regulates T-cell activity negatively, associating with immune evasion, CTLA-4 inhibitor and PDL-1 inhibitor are developed as two efficient drugs to keep them from binding to immunosuppressed molecules, contributing to activating T cells to initiate an immune response [15]. CTLA4, also known as CD152, is a protein receptor of the B7/CD28 family that negatively regulates immune responses. Binding to CD80 or CD86 on the surface of antigen-presenting cells, CTLA4 sent an inhibitory signal to T cells, inactivating them [16]. CTLA4 inhibitors including anti-CTLA4 and anti-B7-1 or anti-B7-2, bind to CTLA4 and B7-1/B7-2 respectively, blocking CTLA4 from attaching to B7/CD28 protein. Similarly, immunotherapy drugs anti-PD-1 and anti-PD-L1 bind to PD1 and PD-L1, blocking the attachment of

PD1 and PD-L1, thus reducing the possibility of inactivation of T cells. Combine anti-PD1 therapy with anti-CTLA4 immunotherapy, cancers such as Deficient Metastatic Colorectal Cancer, Hepatocellular Carcinoma, and Lung Cancer can be treated.

Take the application of PD1 immune checkpoint inhibitors in Non-Small Cell Lung Cancer (NSCLC) as an example. About thirty-five to ninety-five percent of NSCLC patients express PD-L1 [16]. One drug the researchers used in the trial of NSCLC is called nivolumab, which is the IgG4 monoclonal antibody that targets PD-1 and is suitable for use in all human bodies [16]. Nivolumab is assigned to patients with non-squamous non-small cell lung cancer, showing significantly longer overall survival (OS) compared with docetaxel. Another study, according to Shengjie Tang, also certified that regardless of how much the expression of PD-1 level is, nivolumab provides patients with longer OS and a higher safety level [16]. Specifically, the death risk of using nivolumab is lower by about 41% than using docetaxel, and the OS is higher for 3.2 months. As numerous data proven, nivolumab is effective, safe, and well-tolerated in patients with NSCLC. Another drug, Pembrolizumab, reversibly, binds to the PD-1 receptor. In detail, 25% of cases of patients with 50% or more PD-L1 tumors show the OS of 5 years after applying Pembrolizumab, which verified its efficiency and safety of good tolerance for treatment [16]. It is proven that mono-immunotherapy benefit the patients who express high concentration of PD-L1, but it still has limitations due to the small proportion of patients with high PD-L1 level expression in the NSCLC patients group [16]. Immune checkpoint inhibitors are also used in genitourinary malignancies and advanced hepatocellular carcinoma [17, 18]. In trials of genitourinary malignancies, drugs including Atezolizumab, Avelumab, and Durvalumab that target PD-L1; Nivolumab and Pembrolizumab that target PD-1; and Ipilimumab and Tremelimumab that target CTLA-4 are used [17]. Patients with metastatic renal cell carcinoma (mRCC) after applying nivolumab have an OS of 25 months, which is longer for about 5.4 months compared with those applying everolimus [17]. One mature combination strategy of immune checkpoint inhibitor therapy and other therapies is the combination of ipilimumab–nivolumab [17]. Ipilimumab–nivolumab combination provides higher OS compared with sunitinib, but it also shows notable toxicity—250 patients experienced 3 or 4 toxicity (46%) [17]. 8 trial-associated death cases were reported [17]. Before radical cystectomy, three cycles of pembrolizumab are given to MI Bladder Cancer patients, yielding a pathologic complete response rate of 42% [17]. Compared with neoadjuvant chemotherapy, pembrolizumab as adjuvant treatment shows benefits [17]. Nivolumab and pembrolizumab are proven to be efficient for Hepatocellular carcinoma [18]. Atezolizumab combined with bevacizumab is proven to lower the death risk by 56% [18]. Compared to sorafenib, tt also decreases the deterioration of cancer by 40% [18].

3.2. Cancer vaccines

Vaccines are capable of training the immune system to recognize and destroy harmful substances. Cancer vaccines have two main types, prevention vaccines and treatment vaccines. Ingredients of cancer vaccines can be divided into two: antigens, distinctive markers that distinguish cancer cells from normal cells, and a chemical named adjuvant that alerts the immune system that the cancer is present. After one patient injects a cancer vaccine, the combination of antigens and adjuvants would optimize the ability to identify and cancer cell-killing ability of the human immune system [19].

Specifically, the prevention cancer vaccine creates immunity by providing a weakened form of a disease antigen, which may be dead or living, to the body. Then, the body's immune system reacts to these weak antigens by creating antibodies to attack them. After such processes, the body'e immune system antibodies will be prepared to fight whenever the particular antigen enters the body again. The cancer treatment vaccine, also known as the therapeutic vaccine, functions to prevent cancer from recurring, destroy residual cancer cells, and deteriorate of the tumor. Similar to the working mechanism of the prevention cancer vaccine, the cancer treatment vaccine provides some molecules called cancer-specific antigens that often be expressed on the surface of the cancer cells. The cancer-specific antigens provided stimulate the immune system to identify and destroy cancer cells that have these molecules on their surface.

Most cancer treatment vaccines are only available through clinical trials. Currently, intravesical BCG live, sipuleucel-T, and T-VEC are three FDA-approved therapeutic cancer vaccines. Take sipuleucel-T as an example, it is used for patients with metastatic prostate cancer [20]. Sipuleucel-T is customized for each person through a series of steps: First, remove some leukocytes from the patient's blood; Then, modify the removed leukocytes in a laboratory, enabling the leukocytes to have the ability to target cancer cells that have not developed yet; After completely modified, inject these engineered cells back to the patient; ultimately, the modified cells teach other immune cells in the immune system to target and destroy such cancer cells. Rising prostate-specific antigen levels as one recurrence evidenced decrease or decelerate after patients apply sipuleucel-T [20]. Clinical trials yield the result of prolonging the OS by 4.1 months [20]. Besides sipuleucel-T, T-VEC (Talimogene laherparepvec) is one of the Oncolytic Immunotherapies [21]. T-VEC is an engineered type I herpes simplex virus that can enhance antigen presentation [21]. According to Louie's study of eighty melanoma patients, 39% of them were anesis completely and 18% of them were anesis partially [21]. Regardless it has yet no Phase III trials, T-VEC has been proven to be useful in non-melanoma cancers such as Merkel cell carcinoma, squamous cell carcinoma of the head and neck, sarcoma, and lymphoma [21]. Besides, patients with NSCLC after applying the CV9202 cancer vaccine (a vaccine which encodes 5 antigens associated with NSCLC tumor with MUC-1) show good tolerance [21]. Among 25 patients, about 84%, 21 people were detected to have CV9202 antigen-specific immunity [21]. 1 patient demonstrated partial anesis, and 12 patients obtained stability in disease [21].

Overall, the cancer vaccine is certified to be a promising way to outsmart cancer, especially when it cooperates with other treatments such as immunotherapy drugs.

3.3. Cytokine therapies

Cytokines are one of the regulators of innate and adaptive immunity, enabling immune cells to communicate over short distances [22]. Currently, engineered cytokine mutants called superkines and chimeric antibody-cytokine fusion proteins called immunokines are under investigation to solve the problem of cytokines that are often associated with severe doses- limiting toxicities [22]. Superkines have been engineered to bind to various receptor subtypes with disparate specificity and affinity. It is capable of tuning signaling pathways and cellular responses. Additionally, it enables the generation of immunokines and long-acting Superkines by fusing Superkines to antibodies or inactive protein scaffolds, providing additional functionality, targeted delivery, and improved pharmacokinetics.

According to Yutong Liu's experiment of combining Adoptive T cell transfer (ACT) with cytokine therapy, the result demonstrates that the combination increases the T cells scale that infiltrat into solid tumors, activating the immune response and promoting antigen spreading, thus improving control of solid tumors [23]. Cytokine therapy- ACT combination reaches the goal of complete regression of blood cancer without curative doses of CAR-T cells, which validated that cytokine therapy is effective in cancer treatment [23]. Besides, take the application of High-dose interleukin-2 in mRCC as an example, 7% of 255 patients showed complete anesis [22].

3.4. Adoptive Cell Therapy

Adoptive cell therapy (ACT) is a type of treatment that modifies patients' own immune cells to treat cancer. Two main approaches are used for ACT—the first one, isolate immune cells, expand them, and then reintroduce them into the cancer patient. This approach is to directly isolate the patient's immune cells and simply amplify their numbers; The second one, genetically modify immune cells to optimize the ability to kill cells and then reintroduce them into the cancer patient. This approach is to genetically engineer patient's immune cells through gene therapy to enhance their cancer-fighting capabilities. For example, TIL (Tumor-Infiltrating Lymphocyte) therapy is to remove the naturally occurring T cells that have already infiltrated a patient's tumor from a resected tumor specimen, activated and expanded in vitro. Then, reintroduce the activated T cell into the patient. The normal result should increase the scale of activated immune cells, optimizing the body's immune response to fight cancer cells. However, to receive TIL therapy, the patient is required to have pre-

existing tumor-reactive T cells that can be harvested from a tumor resection or a biopsy and expanded in vitro in enough numbers. TCR (Engineered T cell Receptor) therapy is developed to solve the issue in some cases in that a patient's T cells are unable to expand to enough scale or target a tumor. This therapy removes T cells from a cancer patient first and then modifies them by adding a new receptor, allowing them to recognize and target specific tumor antigens. One promising benefit of TCR therapy is that it has the potential to be genetically modified, so T cells can identify the neoantigen, antigens unique to each patient's tumor cells, and then attack cancer cells. Compared to TCRs, CAR (Chimeric Antigen Receptor) T cell therapy can recognize a smaller scale of potential antigen targets due to the chimeric antigen receptor, CAR. CAR's main components are a specific antibody and an intracellular T cell signaling domain, fusing together.

CAR-T cell products, such as tisagenlecleucel and axicabtagene ciloleucel, target CD19, having an overall response rate (ORR) of 81% and 82%, respectively; idecabtagene vicleucel and ciltacabtagene autoleucel that are target BCMA, have ORR of 73% and notably 97% respectively [24]. Currently, CAR-T cell therapy is proven to be capable of targeting ligands in several cancers. In specific, ligand CD138, BCMA, CD38, CS1, CD229, APRIL, and GPRC5D in Multiple myeloma; CD20, CD19, and CD22 in B cell Leukemia or Lymphoma; CD30, CD5, CD7, CD4, CD99, TRBC1, and CCR9 in T cell Leukemia; CD30 in Hodgkin lymphoma; and Siglec-6, FLT3, Cll-1, LILRB4, CD33, CD38, CD123, and CD70 in Acute Myeloid Leukemia [24]. Additionally, after applying TIL therapy, five out of eighteen cervical cancer patients show tumor responses; two out of eleven patients with other HPV cancers also show tumor responses [25].

4. Efficiency optimization in immunotherapies

Although immunotherapies have been developed so far, several problems such as insufficient treatment efficiency, drug resistance, and targeting accuracy remain, waiting for improvements. One approach this paper will focus on is the combination of immunotherapies.

4.1. Combination of chemotherapy with immunotherapy

Studies have found that some interactions between immunotherapies and chemotherapies can lead to good outcomes. For example, Zhu S points out that mice models with undamaged immune systems have greater tumor responses to drugs called anthracyclines based on other studies [26]. Since chemotherapies can debulk tumor cells which contributes to the immunosuppressive tumor microenvironment, the use of chemotherapies could bring benefits to the immune system and further immune therapies [26]. Additionally, the reduction of tumor cells' volume can decrease the volume of cancer cells that require immune cells to be eliminated, and a series of evidence shows that cytotoxic drugs positively regulate antigen-presenting machinery, which is also a benefit the chemotherapy brings to immune therapies [26]. Recently several available combinations of immunotherapies and chemotherapies have been approved by FDAs, mainly for lung cancer. For example, in lung adenocarcinoma patients, compared with chemotherapy or immunotherapy alone, pembrolizumab with platinum-based doublet chemotherapy significantly increases the survival time [26]. In small-cell lung cancer, two immune checkpoint inhibitors—atezolizumab and durvalumab—combined with standard-of-care platinum-based chemotherapy, increasing the overall survival for two to three months [26].

4.2. Combination of radiation therapy with immunotherapy

Radiation therapy (RT) can optimize both antigenicity and adjuvanticity which are important for immune response, and RT has the additional function of alternating the local tumor microenvironment. Similar to chemotherapy, RT can enhance tumor antigen presentation and induce Immunogenic cell death (ICD). Besides, RT negatively regulates CD47 which is overexpressed on the cancer cell surface. CD47 generally sends inactivate signals to immune cells, thus the downregulation of CD47 enhances the antigen presentation of cancer cells and the activation of immune cells [26]. In addition

to the improvement of immunity, RT also contributes to immunotherapy by increasing adjuvanticity [26]. In short, the combination of RT and immunotherapy has verified that they can significantly optimize the efficiency of treatments and improve clinical outcomes.

5. Conclusion

Cancer is defined as caused by normal cells' genetic damage that dysfunctions those cells. Genetic damage could be caused by various reasons, mainly the environment with cancerogenic substances. Since cancer has the attribute of being a mixture of different mutation-level cells, it is challenging to prevent its cyclicity recur. The human immune system is one of the most powerful defenses to cancer. Immunotherapies are derived from the fundamental function of immune cells with anti-tumor immune response. Immune checkpoint inhibitors are drugs that attach to the T cells' receptor and ligand on the surface of cancer cells. Cancer vaccines and Adoptive cell therapy both aim to amplify the number of immune cells and improve their ability to identify specific antigens expressed on cell surfaces. Cytokine therapy is to engineer cytokines. Recently, the combination of cytokine therapy with other immunotherapy has been proven to lead to great results. Overall, some challenges in immunotherapy such as insufficient efficiency have been improved by the combination of other therapies such as chemotherapy and radiation therapy, bringing promising outcomes. In prospect, more combination strategies will develop, and it is conceivable that immunotherapy can complementarily solve issues that other therapies remain.

References

[1] Lewandowska AM, Rudzki M, Rudzki S, Lewandowski T, Laskowska B. Environmental risk factors for cancer - review paper. Ann Agric Environ Med. 2019 Mar 22;26(1):1-7.

[2] Dobosz, P. & Dzieciątkowski, T. The Intriguing History of Cancer Immunotherapy. Front. Immunol. 10, 2965 (2019).

[3] Tan S, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. Biomed Pharmacother. 2020 Apr;124:109821.

[4] Speiser, D., Ho, PC. & Verdeil, G. Regulatory circuits of T cell function in cancer. Nat Rev Immunol 16, 599–611 (2016).

[5] Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, Arthur CD, White JM, Chen YS, Shea LK, Hundal J, Wendl MC, Demeter R, Wylie T, Allison JP, Smyth MJ, Old LJ, Mardis ER, Schreiber RD. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012 Feb 8;482(7385):400-4.

[6] Pardoll DM, Topalian SL. The role of CD4+ T cell responses in antitumor immunity. Curr Opin Immunol. 1998 Oct;10(5):588-94.

[7] Kalams, S. A. & Walker, B. D. The Critical Need for CD4 Help in Maintaining Effective Cytotoxic T Lymphocyte Responses. J. Exp. Med. 188, 2199–2204 (1998).

[8] Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. Pillars Article: IFNγ and Lymphocytes Prevent Primary Tumour Development and Shape Tumour Immunogenicity. Nature. 2001. 410: 1107-1111. J Immunol. 2018 Aug 1;201(3):827-831.

[9] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015 Apr 13;27(4):450-61.

[10] Vignali, D., Collison, L. & Workman, C. How regulatory T cells work. Nat Rev Immunol 8, 523–532 (2008).

[11] De Silva NS, Klein U. Dynamics of B cells in germinal centers. Nat Rev Immunol. 2015 Mar;15(3):137-48.

[12] Bod L, Kye YC, Shi J, Torlai Triglia E, Schnell A, Fessler J, Ostrowski SM, Von-Franque MY, Kuchroo JR, Barilla RM, Zaghouani S, Christian E, Delorey TM, Mohib K, Xiao S, Slingerland N, Giuliano CJ, Ashenberg O, Li Z, Rothstein DM, Fisher DE, Rozenblatt-Rosen O, Sharpe AH, Quintana FJ, Apetoh L,

Regev A, Kuchroo VK. B-cell-specific checkpoint molecules that regulate anti-tumour immunity. Nature. 2023 Jul;619(7969):348-356.

[13] Guerra N, Tan YX, Joncker NT, Choy A, Gallardo F, Xiong N, Knoblaugh S, Cado D, Greenberg NM, Raulet DH. NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. Immunity. 2008 Apr;28(4):571-80.

[14] Tang Q, Chen Y, Li X, Long S, Shi Y, Yu Y, Wu W, Han L, Wang S. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. Front Immunol. 2022 Sep 13;13:964442.

[15] Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med. 2018 Dec 13;50(12):1-11.

[16] Tang S, Qin C, Hu H, Liu T, He Y, Guo H, Yan H, Zhang J, Tang S, Zhou H. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. Cells. 2022 Jan 19;11(3):320.

[17] Thana M, Wood L. Immune checkpoint inhibitors in genitourinary malignancies. Curr Oncol. 2020 Apr;27(Suppl 2):S69-S77.

[18] Li Q, Han J, Yang Y, Chen Y. PD-1/PD-L1 checkpoint inhibitors in advanced hepatocellular carcinoma immunotherapy. Front Immunol. 2022 Dec 19;13:1070961.

[19] Sobhani N, Scaggiante B, Morris R, Chai D, Catalano M, Tardiel-Cyril DR, Neeli P, Roviello G, Mondani G, Li Y. Therapeutic cancer vaccines: From biological mechanisms and engineering to ongoing clinical trials. Cancer Treat Rev. 2022 Sep;109:102429.

[20] Handy CE, Antonarakis ES. Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. Future Oncol. 2018 Apr;14(10):907-917.

[21] Salloum A, Koblinski J, Bazzi N, Zeitouni NC. Talimogene Laherparepvec in Non-Melanoma Cancers. J Clin Aesthet Dermatol. 2021 Nov;14(11):18-25.

[22] Conlon KC, Miljkovic MD, Waldmann TA. Cytokines in the Treatment of Cancer. J Interferon Cytokine Res. 2019 Jan;39(1):6-21.

[23] Liu Y, Adu-Berchie K, Brockman JM, Pezone M, Zhang DKY, Zhou J, Pyrdol JW, Wang H, Wucherpfennig KW, Mooney DJ. Cytokine conjugation to enhance T cell therapy. Proc Natl Acad Sci U S A. 2023 Jan 3;120(1):e2213222120.

[24] Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. Front Immunol. 2022 Jun 10;13:927153.

[25] Norberg SM, Hinrichs CS. Advances in Adoptive Cell Therapy for Head and Neck Cancer. Otolaryngol Clin North Am. 2021 Aug;54(4):761-768.

[26] Zhu S, Zhang T, Zheng L, Liu H, Song W, Liu D, Li Z, Pan CX. Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 2021 Sep 27;14(1):156.