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Current Strategies and Challenges for Cancer Immunotherapy

Qianyi Ma
Beijing Shuren Ribet Private School, Beijing, China.
crescent1222@sina.cn

Abstract

Cancer immunotherapy is a drastic and crucial topic in the medical field since it acts a vital role in cancer treatment. As several types of clinical and preclinical strategies have been advanced by the scientists, which are designed to respond to different kinds of cancers situations, we are still plagued by some adverse side effects brought by those existing therapeutic tactics. In the following part, we would review the so-far development of cancer immunotherapy and discuss their characteristics and potency. Furthermore, we would critically posit the barriers for today's techniques and analyze immunotherapy's future prospects.

Keywords

Cancer Immunotherapy; Strategies and Challenges.

1. Checkpoint inhibitor

1.1 Mechanism

Checkpoint inhibitors are a common tool to deal with cancer which is investigated with thoroughness. The method of checkpoint inhibitors is releasing a natural block to binding with checkpoints, allowing the T-cells to attack cancer cells. Here are two common types of checkpoint inhibitors we would specifically introduce: PD-1/PD-L1 blockade and CTLA4 inhibition which are developed profoundly in recent years. [1-3]

1.2 Different types of checkpoint inhibitor

PD-1/PD-L1 blockade: PD-1 is a key regulator (a type of checkpoint) existing in a human's immune system, which could forestall the human body from immune diseases. However, the cancer cells are able to create the receptor PD-L1 to interact with the PD-1 to the checkpoint to be protected, suppressing the T-cells from generating and harming them. Therefore, we could use the PD-1 inhibitor to combine with the PD-1or PD-L1inhibitor to combine with tumor cells' PD-L1 proteins, making the T-cells be able to attack the tumor cells. [4,5] Generally, PD-1 inhibitors and PD-L1 inhibitors demonstrate similar effects on the treatment. However, it is worth noting that the major difference is that PD-1 inhibitor would not only inhibit the PD-L1 but also the PD-L2 which is the second ligand of PD-1 while PD-L1 inhibitors would not.

CTLA4 inhibition: CTLA-4, the receptor on the activated T-cells, could bind with B7 ligands expressed by antigen-presenting cells (APCs). Besides, on the surface of the T-cells, there is also another type of receptor called CD28 competing for the combination with B7 ligands. If CD28 successfully binds with the B7, there would be a second activation signal to the T-cells, reinforcing the immune system. However, CTLA-4 has a higher affinity for B7, making CD28 less competitive to bind with it and activate the T-cells. [6,7] According to the report, the combination of CTLA-4 and B7 would actually inhibit the reproduction of IL-2 (Interleukin-2) and the activation of T-cells. Thus, exerting the inhibition to combine with CTLA-4 could let the CD28 bind with B7, enhancing the

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immune system to attack cancer cells. Little different from the PD-1/PD-L1 blockade which makes the immune system re-activate, CTLA-4 inhibition enhances the immune system.

1.3 Recent stage of Checkpoint inhibitors

It is undoubtedly that the development of checkpoint inhibitors in cancers treatments demonstrates a stable trend. Hitherto, there are seven checkpoint inhibitors that have been ratified to the market for treating a variety of cancers. There are six PD-1 or PD-L1 inhibitors and one CTLA4 inhibitor. (Table 1)

Table 1. There are six PD-1 or PD-L1 inhibitors and one CTLA4 inhibitor.

Therapy/ Name of the drug	Types	Year of the first approval	Cancer types
Ipilimumab (Yervoy)	CTLA4 mAb	2011	Melanoma
Pembrolizumab (Keytruda):	PD-1/PD-L1 blockade: PD-1 mAb	2014	Melanoma Non-small-cell lung cancer Head and neck squamous cell carcinoma Hodgkin lymphoma Urothelial bladder cancer Advanced gastric cancer Microsatellite instability-high cancer
Nivolumab (Opdivo)	PD-1/PD-L1 blockade: PD-1 mAb	2014	Melanoma Bladder cancer Hodgkin lymphoma, Hepatocellular cancer Non-small-cell lung cancer Squamous cell carcinoma of the head Neck and urothelial cancer
Atezolizumab (Tecentriq)	PD-1/PD-L1 blockade: PD-L1 mAb	2016	Urothelial cancer Non-small-cell lung cancer
Avelumab (Bavencio)	PD-1/PD-L1 blockade: PD-L1 mAb	2017	Merkel cell carcinoma Urothelial cancer
Durvalumab (Imfinzi)	PD-1/PD-L1 blockade: PD-L1 mAb	2017	Urothelial cancer Non-small-cell lung cancer
Cemiplimab (Libtayo)	PD-1/PD-L1 blockade: PD-1 mAb	2018	Cutaneous squamous cell carcinoma

1.4 Challenges

There are some barriers to the implementation of checkpoint inhibitors. Some patience would not respond to this treatment, which is mainly because there is cold tumors. Namely, there are few tumor-infiltrating T-cells. Take a more vivid example, if we compare the process that T-cells confront the tumors as a proceeding car, the checkpoint inhibitor (such as PD-1 blockade) could make the brake no longer work in order to make sure the car could never stop. However, if the car's engine breaks down, even though the brake is no longer works, the car still could not proceed. Since most of the tumors are cold tumors, the reason for the low responding rate of checkpoint inhibitors could probably be explained. Therefore, the therapy of checkpoint inhibitor is limited by the condition of the tumors, which could only be more effective when combining with other treatments. [38-40]

2. Engineered T-cells

2.1 Mechanism

Engineered T-cells are undoubtedly an emergent tactic for cancer therapy, which is a kind of adoptive immunotherapy. The first step is Leukapheresis, removing an amount of leukocyte from blood. Subsequently, the next step is using the technique of genetic editing to improve the ability of T-cells.

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Next, scientists have to replicate the enhanced T-cells to a large amount. The following step is preparation, requiring patience to do the chemotherapy to diminish the number of leukocytes in their body in order to create sufficient space for the Engineered T cells which will be implanted in their bodies.

2.2 Different types of engineered T-cells.

TCR-t (***T-cell receptor***): Compared to the CAR-t therapy, engineered TCR-t seems to be more conservative. During the engineering part, the improvement made for TCR-t is to be capable of recognizing the antigen on MHC-I by utilizing heterodimers consisting of alpha and beta-peptide chains, activating the potency of the T-cells [9]. Therefore, the editing makes the TCR-t has a higher affinity to the antigen of the tumors [10].

CAR-T (***chimeric antigen receptor T cells):***

CAR-T cells, which are installed with CAR (specific antibodies), are endowed with the superb capability to identify the Cancerous cells' antigens, which is extremely effective. Generally, the target CAR-t is CD19, CD20, and CEA, etc, which are presented in B cells widely. CAR-T has an obvious advantage that the CAR-T therapy could last long. According to the experiment, the T-cells could remain for approximately 10 years after the first injection [11-15].

TAC (**T-cells Antigen Coupler**):

2019, Triumvia Immunologics, a Canadian pharmaceutical company came out a new technique -- TAC. A tumor antigen recognition receptor is expressed on the surface of T cells. After recognizing the antigen, the receptor "drags" TCR to activate T cells through TCR but independent of MHC molecules.

2.3 Recent stage of Engineered T-cells technique

In retrospect, the engineered T-cells win a success that they become one of the most prevailing treatments in recent years. Since the engineered T cells could target the CD19 on the B cells, CAR-t is a really promising treatment for hematological malignancies [16]. Possessing stimulate molecules, CAR-t could directly identify the antigen on the tumor cells without any dependence on MHC. Therefore, it would recognize wider tumor cells [17-19].

Specifically discussing, there are actually several generations of the evolution of the CAR-t technique. In the first generation, the antigen-binding domain directly fused with the intracellular part of TCR constant chain CD3 ζ, providing the signals for destroying the tumor cells [20-22]. Nevertheless, the activation of the first generation CAR-t is limited, inducing the limitation of T cells in vivo. Therefore, the second generation of CAR-t was introduced, with an additional signal, impetus in the increment of cytokines and proliferation of T cells [23]. Generally, the molecule that would be installed would be CD28/4-1BB [24]. In the next generation, the scientists add the second costims to the T cell to enhance the potency. In the following generation, the fourth generation of CAR-t expresses more cytokines or ligands, such as IL-15 or suicide genes. [25]

2.4 Challenges

Even though engineered-T cells are an emergent plan which is effective, some of its drawbacks could be fatal. To begin with, as a really complex technique, requiring an outrageously high expense.

Moreover, CRS and neurotoxins are common phenomena in CAR-t and TCR-t therapy. As strengthened T cells owning higher activation, CAR-t is likely to secrete excessive cytokines, attacking the normal cells. CRS might breed long-term fever or some other negative reaction, even might jeopardize the life. Theodoros giavridis et al. Found that CRS occurred in mice models after 2-3 days of cart cell infusion, and the severity of CRS was not mediated by cytokines produced by cart cells but was closely related to IL-6, IL-1, and NO produced by macrophages.

Besides, neurotoxicity is probably also concomitant (or might occur alone) [26,27]. The possibility of occurrence of neurotoxicity is 4%, including the symptoms of declining consciousness, trance and brain edema, etc [28]. In addition to the side-effect of immune disease, the limitation of exertion in

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solid tumors. Having a striking efficiency on the Hematological tumor, the application of engineered T cells in solid tumors does not really demonstrate a really obvious effect.

To solve the challenges, combining the engineered-T cells with other types of therapy is indispensable. Using inhibition to inhibit the immune disease is appropriate. Tocilizumab is widely used in confronting the CRS while it still could not work for the neurotoxicity of CRS [29]. For reducing the toxicity of engineered T-cells technique, scientists could either adopt the "precautionary" tactic or "remedy: tactic [28].

3. Oncolytic virus

3.1 Mechanism

Using the organism such as bacteria to treat the cancer was practical several years ago which pyogenes and Serratia marcescans were used. Progressively, the oncolytic virus is regarded as a better substitution. It is a really novel idea to utilize the virus which are toxic to infect the tumor cells [30-32]. However, in order to lower the attack to the normal cells in the human body, the oncolytic virus is always engineered. Typically, the scientists would edit the virus to become a specific-targeted oncolytic, selectively eliminate the tumor cells [33].

3.2 Recent stage of Oncolytic virus technique

Nowadays, there are several types of viruses practiced in this project. Some of them possess the natural ability to identify the tumors while others do not. HSV I has already been practiced to treat melanoma. Meanwhile, Adenovirus, Vaccina and Reovirus, etc, are all in the experiment stage.

3.3 Challenges

The most challenging part of the oncolytic virus is the delivery. For intravenous delivery, the macrophages in the immune system of the human bodies would rapidly dispose of the virus which is the natural reaction. However, for the systematic injection, it only has low bioavailability. [34-37] Besides, acquired drug resistance or tumor adaptation to oncolytic virus or related tumor immune stress is also a possibility.

4. Conclusion

Although immunotherapy is accepted by a large number of people, there are still considerable challenges existing even though there is a big triumph in melanoma and some blood tumors. Not only are the delivery methods difficult to decide, the response rate but also a difficulty. In the following development of immunotherapy, the combining application of other therapy is extremely necessary which could reduce some negative reactions and increase the efficiency. In the future, immunotherapy would be more specific with less harm to humans' bodies. All the current techniques would keep developing, providing us with a promising prospect of healing the tumors.

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