CANCER IMMUNOTHERAPY: A REVIEW

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SUMMARY

The Nobel Prize in Physiology or Medicine signifies that cancer immunotherapy is becoming the most promising direction in cancer research. In this paper, we review the different mechanisms of the human immune system in inhibiting cancer grow and the possible loopholes allowing the cancer cell to evade the immune system response. Understanding these mechanisms allows designing many different strategies to treat cancer using the patient's immune system as the major 'fighting force'. We would also review the most recent clinical trials in cancer immunotherapy and briefly explain the remaining challenges on applying cancer immunotherapy in larger scale.

** Key words: Cancer immunotherapy.*

INTRODUCTION

The idea of cancer immunotherapy started at the beginning of the 20th century; however, cancer immunotherapy has been a research interest for only 20 years. This is due to the rapid development of molecular biology, genetics, and the decreasing cost of sequencing. Molecular biology helps discovering many mechanisms of immune respond and the signaling pathways triggering these responses. Genetics allows finding different variation of genes participating in these signaling pathways and identifying which type of variation may help the tumor progression. Certainly, these fields could not progress without lowering the cost of sequencing, which allows studying the cancer patients' genome in larger scale.

The most significant benefit of cancer immunotherapy is that this strategy uses the patient's natural capability of immune respond as the major "fighting force" against cancer. Therefore, it is expected to cause the least side-effects or damage on the patient, as showed in [1]. However, it could be among the "hardest" treatments to design. At this point, we may expect that more than 60% of the cancer patients do not respond well with cancer immunotherapy. One example for this issue is described in [2], which is partially belong to the contribution leading to the Nobel Prize in Physiology or Medicine in 2018.

Therefore, in this paper, we review the different mechanisms of the human immune system in inhibiting cancer grow and the possible loopholes allowing the cancer cell to evade the immune system response.

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Understanding these mechanisms allows designing many different strategies to treat cancer using the patient's immune system as the major "fighting force". In addition, we review the most recent clinical trials in cancer immunotherapy and briefly explain the remaining challenges on applying cancer immunotherapy in larger scale. We would also describe the latest effort in cancer immunotherapy research at the University of Alabama at Birmingham and the prospect of Bioinformatics to actively serve in this field.

THE IMPACTS OF THE IMMUNE SYSTEM ON THE DEVELOPMENT OF CANCER

The human immune system could restrict the grow of cancer; but it could also create favorable condition for the cancer cell to grow [3]. At some extend, understanding this ambiguity is similar to knowing the fact that the human immune system, especially the T-cells, is capable to kill most of the cells, including the normal cells, in the human body. The reason why our normal cells "safely grow" is largely because of not triggering the T-cell killer mechanism. Similarly, there exist mechanism allowing the T-cell to "recognize" the cancer cell and trigger the killing response. However, the cancer cells also have the capability to evade or inhibit this response.

A well-known mechanism of how the T-cell activates the response mechanism could be seen in figure 1 [2]. Here, we can see two scenarios reducing the survivability of the T-cell. First, on the membrane of the T-cell, the two proteins CD28 and CTLA-4 competes with each other by binding to the antigens from other (including cancer) cells. CD28 sends the positive signal inside the T-cell, which helps maintaining the T-cell; meanwhile, CTLA-4 sends the negative signal, which helps triggering the T-cell apoptosis. Therefore, the T-cell may not be able to activate the killing process on cancer cell when CTLA-4 becomes abundant, or CD28 is lacking. Second, the cancer cell surface has MHC proteins, which is among one way for the T-cell to recognize the foreign substance and trigger the killing process. However, as the T-cell is activating the killing process, it produces cytokine. The cancer cell use cytokine to increase the functionality of PD-L1 protein. This protein binds to PD-1 protein on the T-cell membrane, which trigger the signal telling the T-cell to reduce cytokine and perform apoptosis.

In addition, the immune system could lose the capacity to inhibit the cancer cell due to other factors. First, there are evidences that chronic inflammation may lead to genetic instability and the degradation of the T-cell, which are the factors favoring the tumor cell growth [4]. It is hypothesized that due to long-time fighting the inflammation, the number of T-cells capable of inhibiting cancer cell would reduce; meanwhile the number of T-cells helping cancer may increase. Second, the cancer cell, similar to the other normal cells, is able to produce that transforming growth factor (TGF)-β. TGF-β triggers the mechanism to convert the 'killer' T-cell to regulatory T-cell, which basically does not perform the killing functionalities [5]. This mechanism is well-

known in preventing autoimmune disease. Third, the cancer cell surviving from the initial T-cell elimination is able to down-regulate the production of MHC, which is the key antigen allowing the T-cell to recognize the cancer cell as “foreigner”.

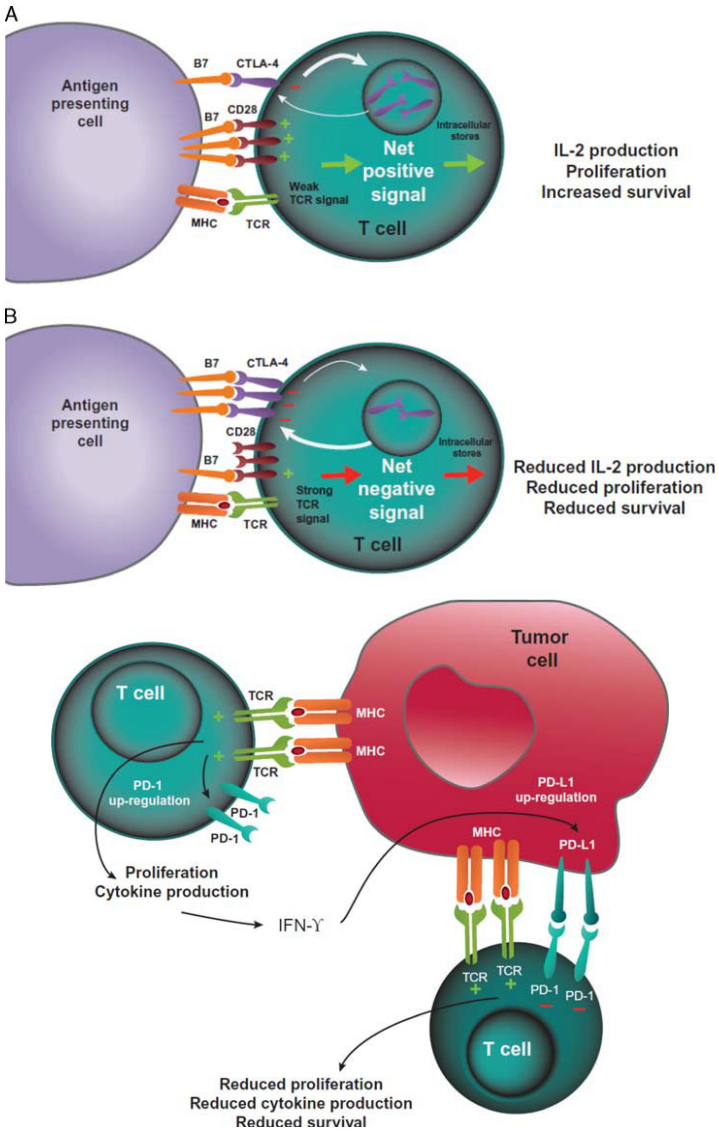

Figure 1 (recited from [2]): Two break-points reducing the survivability of T-cell.

STRATEGIES OF CANCER IMMUNOTHERAPY

From what we have been understanding about how the immune system reacts to cancer, there have been many strategies of cancer immunotherapy. From the mechanism point of view, we can categorize these strategies as follow. For each strategy, there is a certain extend to apply the Informatics techniques to enhance the discovery of new and more effective treatment.

1. Monoclonal antibody.

Table 1:

Antibody	Antigen	Cancer disease
Rituximab	B-lymphocyte antigen (CD20)	Non-Hodgkin lymphoma, chronic lymphocytic leukemia
Trastuzumab	Receptor tyrosine-protein kinase (ERBB2)	Breast cancer, metastatic stomach cancer
Gemtuzumab ozogamicin	Sialic acid binding Ig-like lectin 3 (CD33)	Acute myeloid leukemia
Alemtuzumab	CAMPATH-1 antigen (CD52)	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma, T-cell lymphoma
Ibritumomab tiuxetan	B-lymphocyte antigen (CD20)	Non-Hodgkin's lymphoma
Cetuximab	Epidermal growth factor receptor (EGFR)	Metastatic colorectal cancer, metastatic non-small cell lung cancer, head and neck cancer
Bevacizumab	Vascular endothelial growth factor A (VEGFA)	Metastatic colorectal cancer, HER2-negative metastatic breast cancer.
Panitumumab	Epidermal growth factor receptor (EGFR)	Metastatic colorectal carcinoma
Ofatumumab	B-lymphocyte antigen (CD20)	Chronic lymphocytic leukemia
Ipilimumab	Cytotoxic T-lymphocyte-associated protein 4 (CTLA4)	Metastatic melanoma, cutaneous melanoma, renal cell carcinoma, metastatic colorectal cancer
Brentuximab vedotin	Tumor necrosis factor receptor superfamily member 8 (CD30)	Classical Hodgkin lymphoma, refractory Hodgkin lymphoma
Pertuzumab	Receptor tyrosine-protein kinase (ERBB2)	HER2-positive metastatic breast cancer
Trastuzumab emtansine	Receptor tyrosine-protein kinase (ERBB2)	HER2-positive metastatic breast cancer
Obinutuzumab	B-lymphocyte antigen (CD20)	Chronic lymphocytic leukemia
Ramucirumab	Kinase insert domain receptor (KDR)	Gastric or gastro-esophageal junction adenocarcinoma
Tositumomab	B-lymphocyte antigen (CD20)	Non-Hodgkin's lymphoma
Dinutuximab	Ganglioside GD2	Neuroblastoma
Daratumumab	Cyclic ADP ribose hydrolase (CD38)	Multiple myeloma
Necitumumab	Epidermal growth factor receptor (EGFR)	Metastatic squamous non-small cell lung cancer
Elotuzumab	SLAM family member 7 (SLAM7)	Multiple myeloma

This strategy, which is very popular in vaccine design, finds the antigens presented on the cancer cell surface and the "right" antibodies to attach to these antigens. The antibodies will signify the appearance of the cancer cell and draw the attention of the immune system. The US Food and Drug Administration has approved 23 treatments of cancer using monoclonal antibody. Due to the limited space, we do not present the references for table 1, which shows 19 cases. The other 4 cases would be presented in another section due to some overlapping with 'check point blockade strategy'. Information of these antibodies could be found in DrugBank (https://www.drugbank.ca/) database.

2. Checkpoint inhibitor.

The information showed in figure 1 is the fundamentals to develop this strategy. As showed in figure 1, there are two points in the chain of immune reactions critical to the survivability of the T-cell: CTLA-4 and PD-1 receptors. Since these receptors triggers the T-cell apoptosis, the checkpoint inhibitor would blockade these two receptors to increase the survivability of the T-cells. In addition, since PD-1 only binds to PD-L1, blockading PD-L1 would have the similar outcome to blockading PD-1. Methods of blockading these receptors are the same to monoclonal antibody strategy, by finding the antibodies binding to these receptors. Drugs having this mechanism include pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab and durvalumab (https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html). In addition, since PD-L1 is activated by the Interferon gamma (INF-γ) pathway (*figure 1*), another potential checkpoint is cytokine, especially around the INF-γ pathway. However, there have been no cytokine-based drugs approved to treat any cancer diseases.

3. CAR T-cell therapy.

This strategy is developed from the same theory developing the first smallpox vaccine. Here, the immune system does not respond to the cancer cell because the immune system is "unfamiliar" with the cancer cells. Therefore, one way to solve the problem is to extract the white blood cells from the patient and "modify" these white blood cells by attaching specific chimeric antigen receptor to these cells. The chimeric antigen receptor would make the cells "familiar" and "specialized" for detecting the cancer cells. Later, these modified white blood cells are injected to the patient. Since these cells are already familiar with the cancer cell, they would detect and trigger the immune response toward the cancer cells. Since this treatment uses the patient's white blood cell, one treatment can be applied to only one patient. There are two CAR T-cell therapies approved for a limited cases of cancer treatment[6]. First, Kymria is approved for young adults with refractory or relapse (R/R) B cell acute lymphoblastic leukemia. Second, Yescarta is approved for adult patients with R/R large B cell lymphoma.

4. Cancer vaccine.

This strategy is similar to the CAR T-cell therapy, except that in vaccine, the white blood cell is experienced with the cancer causes instead of being modified by

antigens. The cancer vaccine is applied in two cases. First, it is used in the cancer caused by chronic inflammation, such as the vaccine for human papilloma virus could help preventing cervical, anal, throat, and some other cancers, and vaccine for hepatitis B virus could help preventing some types of liver cancer [7]. Second, some cancer vaccines approved for early-phases of cancer, such as oncophage, are the patients' white blood cells that are trained with heat shock protein gp96 [8]. This protein is extracted from kidney cancer patients.

CHALLENGES IN CANCER IMMUNOTHERAPY

Despite the long-time researched and prospect of lower side-effect, immunotherapy has not been widely applied in cancer treatment, when compared to other types of cancer therapy due to many pharmaceutical reasons. First, immunotherapy is usually the last resort when all other types of therapy have failed. Patients entering trials or treatments of immunotherapy after many rounds of chemotherapy and radiation therapy. At that point, the patients' immune system would severely weaken due to the side effects of these therapies, which makes immunotherapy much less successful. Second, immunotherapy usually successes in a narrow number of cases, especially in CAR T-cell and cancer vaccine strategies. This is largely because the treatment needs the personalized patients' white blood cell. Third, for the less personalized strategy such as checkpoint inhibitor, targeting the checkpoint proteins may bring affects other anti-cancer mechanisms via intra-cellular signaling pathways. For example, in [2], the experimental results showed that after blockading both CTLA-4 and PD-1, many genes contributing to tumor suppressor lose the copy numbers among the non-responding patients. This result suggested that blockading these checkpoints may inhibit other anti-tumor mechanism, which cancel out the anti-tumor effects of immunotherapy and the pro-tumor effects of other mechanisms. Forth, at this point we have not been able to detect many antigens which are distinct for cancer cells [9]. Most of the antigens showed in table 1 strongly express in cancer cells. However, these antigens also appeared on the normal cells. Therefore, the monoclonal antibody strategy, which is currently the most widely applied strategy in cancer immunotherapy, could have the similar side effects to the side effects of chemotherapy, where the normal cells also take damage from the therapy.

In addition to the pharmaceutical issues, several social economic factors make cancer immunotherapy less popular. First, cancer immunotherapy is an expensive strategy. In the United States, the blockading checkpoint treatment costs between $30,000 and $145,000 per patient per year [9]. Costs for the new CAR T-cell therapy and cancer vaccine are even more, which is greater than $400,000 per dose, and a patient usually takes 3 doses. Second, the CAR T-cell therapy and cancer vaccine face several ethical issues since the human cells are the component to produce the treatment.

Informatics, which includes health informatics and bioinformatics, could help solving several challenges in cancer immunotherapy. Using various techniques in modeling and prediction, informatics would increase the personalized capability, such as identifying the important antigens and other significantly expressed tumor suppressors in individuals. The higher personalized capability is, the better we can to predict whether the patient would respond to cancer immunotherapy, thus decrease the cost of treatment and clinical trials. Informatics is also capable of gene prioritization, which would help selecting more candidate antigens among the list of many possible human antigens as the targets for designing new immunotherapy strategies. Furthermore, the informatics tool computing the binding affinity is able to point out the antibodies likely to bind to these antigens above. These are the main research directions at the University of Alabama at Birmingham, in which the Informatics Institute would actively participate.

CONCLUSIONS

Discoveries at the molecular biology level of the immune system has opened many possibilities to unleash the capability of the patients' immune system to treat cancer. Among these possibilities, the monoclonal antibody is the most suitable direction for immunotherapy research in the developing countries due to its relatively lower cost and the utilization of computational tools. This direction is still fairly underexplored, but yet exciting.

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