Immunotherapy

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1. Introduction

Cancer is still a kind of terrible disease, which leads patients to death. As we know, cancer cells increase by themselves, continue infiltration and metastasis, and spread all over the body rapidly. To fight against them, Cancer research has been done for a long time, but there has not been such a cancer therapy as can cure any patients perfectly. Originally, there are mainly three types of cancer cures. They are chemotherapy, radiation therapy, and surgical operation.

These days, new cancer therapy, immunotherapy — which makes use of patients' own immune system to cure cancer — is drawing attention as the forth cancer cure.

It uses patients' own immune system, so their physical burden is smaller than the others. However, it has not been put into practical use very much yet. Its cost and side effects prevent it from being used. Also, at the present stage, it is very difficult for doctors to identify the patients that may or may not respond to it. There are many researchers that research on it.

It's important to explore how we can make immunotherapy better. If immunotherapy is improved and usually used to treat cancer, it will definitely save patients regarding its cost, fewer side effects, and patients' mental state.

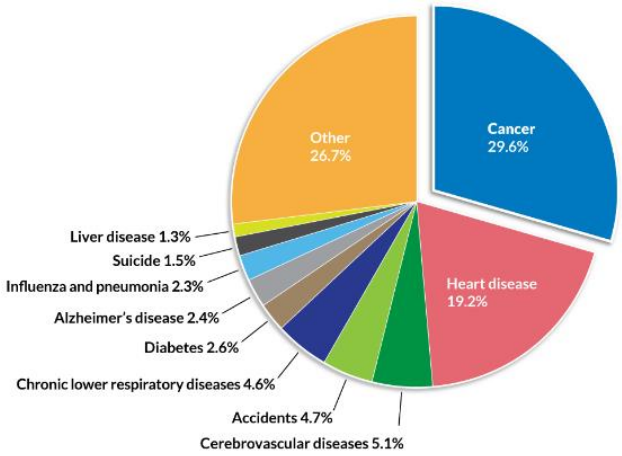

Fig.1 Proportion of Due to Cancer and Other Causes,Canada 2016
https://www.cancer.ca/en/cancer-information/cancer-101/cancer-statistics-at-a-glance/?region=on

2. Fundamentals

Cancer cell

Cancer cells have immunosuppressive factor and immune cells become weaker, Liquid immunosuppressive factor, cellur immunosuppressive factor, and immune checkpoint molecure are good examples. They suppress immune system.

In particular, immune checkpoint molecure is very hard to handle. Originally, it protects us against auto immunity. It betrays us when cancer cells grow big.

Immunotherapy

There are many ways to cure cancer by using immune system, and typical examples are the methods that use immune checkpoint inhibitor or CAR-T cell.

1）Immune checkpoint inhibitor

I would like to pick up PD-1/PD-L1 as an example and explain an immune checkpoint. Cytotoxic T Lymphocyte（CTL）usually attacks cancer cell. It is a kind of T-cell. It has PD-1（Programmed cell Death-1）and cancer cell has PD-L1,the ligand molecure of PD-1. They are a pair of molecure.

When they react to each other, CTL is suppressed. Without CTL, your immune system against cancer will be weak. Thus, cancer cells escape from an immune system.

Now, the method that prevents them from reacting to each other by letting anti PD-1, one of the immune checkpoint inhibitors, into patients' bodies, was created. The mechanism of that is the following thing. Anti PD-a clings to PD-1 and keeps it from reacting to PD-L1. (Reference:Fig2)

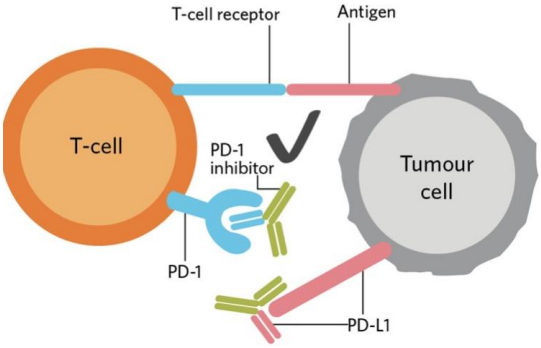

Fig.2 example of immune checkpoint

http://theconversation.com/could-your-gut-microbes-hinder-your-cancer-treatment-a-new-first-in-human-trial-investigates-99728

2）CAR-T cell

The method that uses Chimeric Antigen Receptor（CAR）-T cell is also effective. It was invented to treat intractable tumors. By extracting the patient's own T-cell and using the technic of genetic treatment, it enables T-cells to produce CAR, the special protein. CAR is designed to be able to recognize the specific antigen that expresses on the surface of cancer cells and attack them.(Reference:Fig.3)

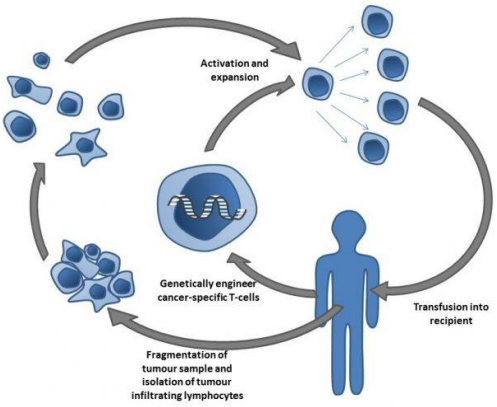

Fig.3 The Mechanism of CAR-T therapy

https://www.wakenbtech.co.jp/topics/post-7505

Both of the methods are effective, but the kind of cancer that they may cure is limited.

３． Method

To discuss my hypothesis and ask the research questions, I met with two Cambridge University researchers.

・I met with Dr.Francesco Colucci at King's College.(30 JUL 2019) (Pic.1)

His research group has been working on immune cells at the fetal-maternal interface, control of tumor growth by immunity, and cell transplantation.

・I met with Professor Klaus Okkenhaug at the department of pathology.(2 AUG 2019)(Pic.2)

He researches immunology, infection, cancer, Treg, immunodeficiency, cell signaling, P13K.

Pic.1 Dr.Francesco Colucci

Pic.2 Prof.Klaus Okkenhaug

Hypothesis :

Cure for baby

A baby who has the high possibility of carcinogenesis suffers from their patients' generic information, such as Familial Adenomatous Polyposis（FAP）can inhibit carcinogenesis by having some cure of immune system by the time he or she gets 6 months old.

Research questions :

１）Cure for immune deficiency

Is it possible that the patients, who have an immune deficiency such as the people who have little TCR, undergo immunotherapy?

２）When immunotherapy works effectively

When does immunotherapy work effectively, in an early stage of cancer or in a terminal stage of cancer?

３）The problem of immunotherapy

What is the biggest problem of immunotherapy these days?

Predictions were :

Hypothesis :

It is possible. This is because the baby who is under 6 months old has weak immune system, and the doctor can change his or her immune system easily.

Research questions :

1）It is possible. This is because even if the patients have immune deficiency, for instance, little TCR, the doctor can treat by cultivating normal cells.

2） It is more effective in an early stage of cancer. This is because by treating the patients' immune system early, it can stop cancer from growing. I have read the paper that says it is more effective in a terminal stage than in an early stage, but I don't think so.

3）Its side effects. This is because immunotherapy has effects not partly but entirely on patients' body, so if side effects are expressed, it is very dangerous.

4． Result

Hypothesis :

Cure for baby

Dr.Francesco Colucci's answer → It is difficult.

In principal, it is a good idea, but such an experiment as affects a young baby, has not been done before. In natural, immune check inhibitors work in 25 to 30 percent of patients, not all of them. So it may not be effective. Also, there's the risk of anti burst effect. Some patients develop colitis, inflammation in their large bowels. If it happens to babies, it is very dangerous.

Professor Klaus Okkenhaug's answer → It may be possible.

Althrough such a trial is limited, but it is an interesting idea. Maybe it is better to make CAR-T cells. If the doctor can take a baby's cold blood, grow CAR-T cells from that, and keep that then he or she can treat after a little time from the baby was born. The CAR-T cell is preserved by freezing.

Research questions :

1） Cure for immune deficiency

It depends on the kind of immunotherapy.

・immune checkpoint inhibitor → No. Dr,Francesco Colucci

This is because the immunotherapy relies on the host immune system to push it over drive. If an immune system has deficiency, it is highly possible that the immunotherapy doesn't work.

・CAR-T cells therapy → Yes. Dr,Francesco Colucci

This is because the immunotherapy is independent of the host immune system.

2） When immunotherapy works effectively

→It works in both stage. Dr,Francesco Colucci

・This is because most of clinical immunotherapy trials are done the terminal cancer patients. Actually, it is not the problem of immunotherapy, but chemotherapy is effective in an early stage of cancer.

3） The problem of immunotherapy

→It is very difficult for the doctors to tell whether the patients may respond or may not respond

Professor Klaus Okkenhaug

5． Discussions

Hypothesis :

Cure for baby

I had thought that a weak immune system is good for treat, but I found that it is not true. Because of immature immune system, when the side effects express, molecure that prevents auto-immune disease don't work very much and the condition of the baby will be worse. I should have taken not only whether it is easy to change the ability to attack cancer cells of immune cells, but also whether the baby's immune cells have the ability to cope with the side effects, such as colitis. Even if his or her immune system could attack cancer cells, it's meaningless that his or her condition got worse.

On that point, CAR-T cell therapy is very suitable to the babies. If the doctor gathers blood from the baby who has carcinogenesis possibility, right after birth and treat CAR-T cell therapy, it may be possible to make good effect. The doctor can preserve the baby's CAR-T cells by freezing them< so they can treat them after they have mature immune system.

Research questions :

1） Cure for immune deficiency

I had thought that not only CAR-T cell therapy, but also immune checkpoint inhibitor can treat people who have immune deficiency by using a cell cultivate or a genomic treatment, but this idea was not completely right. Professor Klaus Okkenhaug said that the more we use drug, the more side effects there will be. I had understood that a doctor should not treat too much, but I might have had too strong a preference for immunotherapy. I decided to explore immunotherapy because I wanted to consider the way that doctors can treat cancer without patients' distress. I might have not realized the essentials in my research activity when I made some predictions for this research question.

2） When immunotherapy works effectively

I thought my prediction was not entirely wrong. As a result, I found that immunotherapy can treat both patients in an early stage of cancer and patients in a terminal stage of cancer. Also I found that clinical trials have difficulty. The patients who have early stage cancer are more likely to be cured by chemotherapy than by immunotherapy. If the patients know that chemotherapy is more effective in an early stage of cancer, who wants to be subjects to have immunotherapy in an early stage of cancer? Unless some patients accept immunotherapy in an early stage of cancer, clinical trials cannot be realized. It contains some ethical problems, which we have to take into consideration with medical practice.

3） The problem of immunotherapy

There's a bigger problem than side effects, whether immunotherapy affects each patient or not is very important. I think it is difficult to identify patients who may respond or who may not respond. I keenly realized the necessity of the tools to figure out whether it is effectable.

Through the interviews, I could discuss further things related to research questions.

Related questions：

1）・Can we suppress the side effects?

→Yes, we can. By injecting steroids, monoclinic antibody, or TNF inhibitor, we can make immune system weaker. In other words, we can suppress auto-immune, but that is the only way to control side effects. If immune system is weakened, it can't attack cancer cells. If it becomes so, it is no point in treating immunotherapy. The balance between strengthening immune system and weakening immune system is important, and to keep it good condition is very difficult. Dr,Francesco Colucci

2）・Will the day immunotherapy can cure all types of cancer and people of all ages come?

→No. There are always some cancer which have very low antigen burden , and they are difficult for immunotherapy. Professor Klaus Okkenhaug

・Then, are there any common characteristics among cancer that are suitable for immunotherapy?

→Yes. For example, as for anti-PD-1, the more tumor have neo antigens(mutations), the more effectively it works. In other words, if tumor has few neo antigens, that kind of cancer shouldn't be cured by immunotherapy. As the following Fig.4 shows, melanoma, a kind of skin cancer, has a lot of neo antigens(mutations). Immune cells can attack it. That's why melanoma is often said to be suitable for immunotherapy. Professor Klaus Okkenhaug

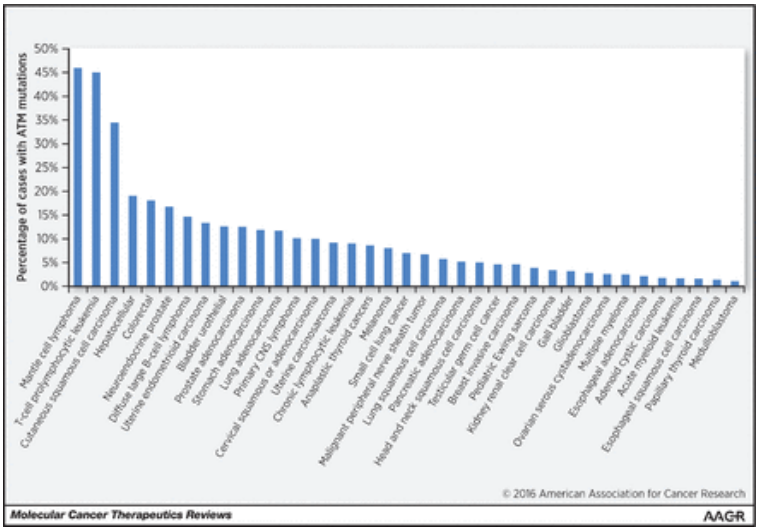

Fig.4 Percentage of cases with ATM mutations

https://mct.aacrjournals.org/content/15/8/1781.full

3）・Do chemotherapy and immunotherapy affect each other?

→Yes. When the doctor treat the cancer patient with both of chemotherapy and immunotherapy, at first, chemotherapy stresses cancer cells. Then, cancer cells send the signal to immune system, and immune cells will be able to detect cancer cells. This mechanism is very effective. Dr.Francesco Colucci

→Yes. In a condition chemotherapy can generate inflammatory environment in the tumor and a lot of immune system. Tumor grows big while immune cells can't detect it, and it can suppress immune system. To prevent this, chemotherapy kills cancer cells, and the immune system will be released by combining both of chemotherapy and immunotherapy. Professor Klaus

Okkenhaug

・Should chemotherapy be used in early stage of cancer? How about immunotherapy?

→Many people who were found tumor in their bodies, at first, are treated by chemotherapy. Then, if the treatment is invalid, the patients are treated by immunotherapy. This is because this order of the treatment spent more money than the treatment whose order is immunotherapy first. Professor Klaus Okkenhaug

But, Professor Klaus Okkenhaug said **"**I think immunotherapy should be done first.**"** Why he thinks so is that immunotherapy won't work on some types of cancer and should be the primary treatment.

・What is the best point of immunotherapy, compared to chemotherapy?

→Immunotherapy can cure perfectly of some kinds of cancer. In contrast, chemotherapy can rarely cure perfectly. Generally, it prolongs the lives of cancer patients. Professor Klaus Okkenhaug

4）・What is the most important thing to identify the patients who may respond or may not respond?

→Whether the immunotherapy cures patients or not depends on the patients' genetic information that makes up for immune system and genetic mutation in cancer cells. So, it is important to combine patients' genetics and immunology, and get data from them. Dr,Francesco Colucci

6. Conclusions

I have learned the following things through my research.

・A baby who has the high possibility of carcinogenesis by nature may be able to be cured with CAR-T cells therapy.

・The patients who have immune deficiency may also be able to be cured with CAR-T cells therapy.

・Immunotherapy works well both in an early stage of cancer and in a terminal stage of cancer.

・Combining genetics and immunotherapy is very important to ascertain whether the patient is suitable for cancer treatment.

・Strengthening an immune system and weakening an immune system should be kept "well-balanced" for a good immunotherapy.

・The more tumor has neo antigens(mutations), the more effectively immunotherapy works.

・Chemotherapy and immunotherapy interact with each other and when they are combined, immunotherapy becomes more effective.

The best thing of immunotherapy is, after all, is that the possibility of side effects can lower. Even if it can cure specific types of cancer now, it is the new cure with tremendous potential. For example, CAR-T cells therapy may be able to cure a baby who has the high possibility of carcinogenesis by nature and the patients who have immune deficiency. To make it possible, more and more research is needed, such as the combination of the other kind of cure. By interacting with other treatments, a "well-balanced" immune system may be created and the day will come when more and more people overcome cancer through continuous research for immunotherapy and other cures.

7． Acknowledgements

For this research, Dr.Francesco Colucci and Professor Klaus Okkenhaug met me and discuss my research question. I would like to thank them. Also, Ms.Keiko Kurokawa, Ms.Misaki Nakamura, and Mr.Masato Suzuki helped me. I would like to thank them.

8．Reference

Books)　がんのプレジション免疫学
いまこそ知りたい！がん治療薬オプジーボ
新生ペプチドとがん免疫新薬の力
免疫が挑むがんと難病

Site)　https://www.path.cam.ac.uk/directory/klaus-okkenhaug
https://www.immunology.cam.ac.uk/Networkdirectory/fc287　medschl.cam.ac.uk
https://mct.aacrjournals.org/content/15/8/1781.full
https://www.cancer.ca/en/cancer-information/cancer-101/cancer-statistics-at-a-glance/?region=on
https://www.wakenbtech.co.jp/topics/post-7505