

Research on the differences between cytokine storms caused by cancer and COVID-19

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ABSTRACT: *This is a report about the differences between cytokine storms caused by cancer and the new epidemic COVID-19, as well as some methods and technologies that could be used to treat this reaction. Various kinds of solution will be introduced in this passage, such as old methods like radiation therapy and drugs, as well as new technologies, including gene-editing and CRISPR.*

KEY WORDS: *cytokine storm, cancer, COVID-19, gene-editing technology, CRISPR*

Introduction

The first important thing I would like to discuss at the very beginning is: what is cytokine storm?

Cytokine storm is often used to describe the rapid production of cytokines like TNF- α 、IL-1,IL-6,IL-12,IFN- α ,IFN- β ,IFN- γ , MCP-1 and IL-8 as a result of the body infection by microbes. The cytokine storm is the main reason for multiple organ failure as well as ARDS, which stands for acute respiratory distress syndrome. In a word, the cytokine storm is the overreaction of the immune system towards the invade of virus or bacteria.

The immune cells connect with each other with the help of cytokines, which are small molecules released by cells into the blood, and they lead the immune cells to their destination, where the infection occurs. So the cytokine storm is a signal to release all the potentials of the immune system to attack the causative virus or

bacteria. As a result of this, inflammation happens, and a large amount of Nitric Oxide(NO). The NO molecules have the ability to dilute blood and gradually damage blood vessel all over the patient's body. Finally, all these factors lower the blood pressure to such a low level that could cause septicshock. We can see that quite a number of patients with serious COVID do not die from the loose of blood, but the septicshock caused by cytokine storm.

The CRISPR

The very important technology in my idea to prevent the happening of cytokine storm and to reduce its damage is the CRISPR. Now I will briefly introduce it. In the CRISPR technology, the CRISPR is contained within an AAV virus. The AAV virus is abbreviation for adeno-associated virus. Since it is harmless toward human body, it is a perfect vector for CRISPR. The carrying process can be divided into five steps.

the virus get the modified DNA piece and was taken up the cell via endocytosis

the AAV enters the cell as an endosome and the cytoplasmic lysosome breaks down the vital capsid to release the AAV

the AAV will bind to cell nucleus and release its contents, which will be DNA fragments that corrects the IL-6 producing gene to stop the production of the out-numbered cytokines

the DNA CRISPR platform within the AAV once carried combines with the original DNA and forms a circular episome

Finally, the transcription occurs and a right protein got expressed to shut down the production of cytokine in immune cells

There is an underlying problem for the CRISPR technology, and it is waiting to get solved, or this new technology could not get applied in the clinics. The problem is the possibility that the wrong pieces of target DNA are very likely to be cut off during the process. For example, if a gene piece that is responsible for producing proteins that building up muscles is cut off, the corresponding protein will never get produced and the patient's muscles would weaken quickly. Another problem waiting to be solved is the response of the immune system toward the AAV

virus. Even though the AAV will not cause any disease, the immune system might recognize it and take actions to destroy it by producing neutralizing antibodies, in this way, the gene can not get transported to the right location. So new kind of virus must be used to prevent this situation, like the virus that has a special protein layer that can help it cheat against the detection of the immune system and avoid causing disease as well.

Cytokine storm in COVID-19

The cytokine storm is different from one patient to another, mainly depend on the disease they have. The newly found epidemic, COVID-19, causes serious cytokine storm in a number of people affected, which is quite similar to the cytokine storm caused by other virus such as SARS, H1N1, H5N1. According to the clinical observation, patients who have cytokine storm are recorded with a increase in cytokines like IL-6, TNF-a, and IFN-y. So in the process of curing COVID-19, doctors should also pay some attention to the patients' immune system, in case of the happening of cytokine storm. If a cytokine storm occurs in the patient's body, there are several ways to stop it or reduce the damage it could cause in the body. One common way is to use vasoactive drugs like the nitroglycerin to protect the main organs from destructive affects brought by cytokine storm and maintain their function in order to keep the patient alive. Then, various kinds of hormone like the Adrenal glucocorticoid are often applied to suppress the over production of immune cells and cytokines. In the end, large amount of Vitamin C and E are used to directly delete the over-produced cytokines. The vitamin C and E could break down the molecule structure of the cytokines and thus delete them. On the other hand, Carl H. June, who published a report on the Science, mentioned the great role of IL-6 in the appearance and curing process of the cytokine storm caused by COVID-19. Here is his main point. After large amount of IL-6 are produced by the immune system, which caused the cytokine storm and the inflammation, a IL-6 inhibitor like the Corylifol A could be injected to prohibit it from raising to a level high enough to cause the cytokine storm. However, this treatment has not tested on animals or humans so far, and there is no clear answer toward the question if the suppress on IL-6 will lead to a more serious result in fighting against COVID-19. Another critical point of the cytokine storm caused by COVID-19 is the cytokine

called GM-CSF, which stands for Granulocyte macrophage colony stimulating factor. The main function of GM-CSF is to further activate LSP recipient, a Leukocyte differentiation antigen, and Low affinity Iggfc receptor, as well as inflammatory monocytes, to produce more IL-6 and other cytokines. In this way, the two cytokines promote the production of each other and cause an even more serious result. In my opinion, there is one method using gene engineering to prevent the happening of cytokine storm during the treatment of COVID-19. Another approach is to treat with anti-inflammatory drugs.

Here is what I suppose to do with the immune system. As far as I have learned, the technology called CRISPR is designed to transfer special fragments of genes into a patient's body to replace or correct a mistake part. In this therapy, a virus encoded with the right part of gene takes into cell via endosome, then the endosome breaks down and the virus binds to the cell nucleus to release its contents, which is gene pieces that contain the information to stop the produce of cytokines like IL-6 in this therapy. At last, new protein will be expressed and the overproduction of cytokine could be stop. However, there could be two main problems for the method I proposed. Firstly, the time of modification is very hard to be determined, since the information about the COVID-19 we have at this point is very limited, and a wrong point of injection could cause more serious result than a cytokine storm. For example, if the stop production gene is input too early into the cell's DNA, there will be not enough IL-6 cytokine in order to let the immune cells communicate with each other, which could lead to a immune system break down, which causes the patient could not get cured and may die from the COVID-19 virus itself instead of a cytokine storm. On the other hand, if the time of modifying is too late, the modification will be totally useless since the cytokine will have already been overproduced. There is a second alternative to avoid the appearance of cytokine storm, which is to completely change the therapy we use. This new method also stems from the CRISPR therapy and is a great application of it. In this therapy, we could use the AVV capsid to carry the right antibody gene piece that produces a neutralizing antibody. In this way, the IL-6 cytokine will not be a essential part for curing COVID-19 and the problem of over-produced cytokine and cytokine storm could thus be solved.

Cytokine storm in cancer

The cytokine storm caused by cancer is different from the one caused by virus like COVID-19 or SARS. Firstly, the cancer cell itself normally do not have the ability to cause cytokine storm in the patient's body, but on the other hand, the very commonly-used therapies, monoclonal antibody drugs and the CAR-T cell therapy both have the chance to induce a cytokine storm in the patient's body. The CAR-T therapy need as many as 500 million T cells to be injected into the patient's body, as a large percentage of these T cells may die from the defense of the immune system and could not take effect. The cytokine storm led by the CAR-T therapy is a simple progress. After the injection of the CAR-T cells, which are used to identify the cancer cells, T cells quickly reproduce, and that causes the rapid production of another type of cytokine, thus induce the deadly cytokine storm. The whole process is generally divided into three steps. Firstly, the cancer cells generate enough amounts of GSDME(gasdermins E), a kind of protein that can make holes on the membrane efficiently, then the liquid outside the membrane will influx into the broken cell, making all the cancer cells that the CAR-T cells attack dead. Finally, the breaking process is different from normal death in that almost all the contents of the dead cell are released and cause serious inflammation as a result, and then it activates the macrophage, leading to cytokine storm, threatening the patient's life. The GSDME level also have a close connection with the new virus COVID-19 in that the higher the GSDME level is, the more likely a people will be caught in a inflammation caused by the COVID-19 virus. After realizing this side-effect of the CAR-T therapy, the researchers begin to test the GSDME level of their patients before Introducing the gene-modified T cells into them. After the clinical experiment, the researchers found that the strength of cytokine storm caused by CAR-T therapy is very likely to have a close connection with the GSDME level.

As the result of the experiment showed, patients with a higher level of GSDME are generally more likely to be caught in a cytokine storm when treated with the same amount of T cells in the patient's body. So clearly, patients with high GSDME level are unsuitable for CAR-T treatment and should turn to other methods as an alternative. Another kind of cytokine storm caused by cancer is the result of the monoclonal drug therapy. What is monoclonal drug? It is a great number of antibodies which are cloned from a single B cell and are almost identical in every

aspect, and these antibodies are put into human body to kill the cancer cells. And the next question is how this therapy causes cytokine storm. There are two main reasons for it. The first reason is the antibodies that enter the body as well as the immune system is not part of the body, but could be a kind of invade identified by the immune system. So the immune system may take actions to stop the spread of the new antibodies from entering the blood vessels or the internal organs. By doing this, the immune cells release cytokines to respond to the order from immune system and thus cause a cytokine storm. Another potential cause is much more likely: the B cell itself is a kind of immune cell and will secret an additional amount of cytokine as soon as it recognizes the cancer cells in the body to kill it, and this becomes a problem. Using the B cells that are cloned from the patient's gene may provide help to reduce the chance of a cytokine storm, but turn to radiation therapy may be a better choice with fewer risks. To draw a conclusion, the cytokine storm can either be caused by the B cell antibodies injected or the immune system of the patient.

Conclusion

In summary, we know exactly when the cytokine storm develops in cancer and we can diminish its effects before it gets out of hand. In contrast, we don't always know exactly when the cytokine storm will develop in COVID.

Now, I would like to express some of my own opinions on how to relief or avoid the cytokine storm caused by cancer(and its therapies)and the damage it brought to the body.

In my point of view, the best way to prevent cytokine storm caused by cancer therapy is to focus on new ways to cure cancer instead of improving the original ones. However, as the gene engineering therapy for cancer is not mature enough to be put into practical use, doing some improvements is the best way now. For the cytokine storm caused by CAR-T therapy, one way is to turn to drug or radiation therapy instead, like I have mentioned before, another way is to use AVV to carry specific gene pieces and replace those on the original parts to reduce the amount of GSDME protein produced and thus reduce the possibility that too many cytokine get into the membrane to cause a cytokine storm. This is probably the most efficient and safe way, for the reduction of GSDME will not influence the effectiveness of the

therapy, nor will it put the patient's body in danger because of mistakes in time of inject, since it can just be injected at any point after the CAR-T cell starts to work. If the technology could not support the use of AVV to replace the gene, other methods to control the damage of cytokine storm caused by CAR-T therapy are ought to be considered. For example, the method to clear the already produced cytokines is a critical point. Unlike the IL-6 cytokines produced by COVID-19 therapies, the cytokines produced by either CAR-T therapy or monoclonal therapy are unnecessary for the treatment. The two treatments either uses additional T cells or Additional B cell antibodies, so the cytokines produced by the immune system will not take an active part and could thus be removed to prevent any risk. Common ways like put in Vitamin C & E could definitely be used in this situation, new methods like CRISPR will also get more room for application once the precise gene piece has been found. Nevertheless, some risks could still occur despite the fact that time does not matter so much in the cancer therapies. One main risk is the continuous existence of the Cas9 nuclease raises the risk for cutting DNA sequences at off-target sites. A solution toward this problem is already on the way: a new editor tool kit that converts GC base pairs to AT base pairs. Traditional CRISPR/Cas9 serves as molecular scissors, while the new base editors are like pencils. These will directly change the fragments instead of cutting them off, so the chance of mis-cutting will be minimized.

To draw a conclusion of the differences between the cytokine storm caused by COVID-19 and cancer (and their corresponding therapies), and also the solution now used, as well as the solutions I proposed, which may get used in future:

For the cytokine storm caused by COVID-19, the main cytokines are the IL-6 as well as the GM-CSF. The solution is to use vasoactive drugs and vitamins to stop the production and delete the over-produced molecules.

For the cytokine storm caused by cancer, they can be divided into two types, depending on the therapy used. The 1st one is led by CAR-T therapy, which could be avoided by turn to alternative therapies since it is caused by the GSDME level. While the 2nd one is a result of the monoclonal therapy, and it could be solved by using B cells (and antibodies) that are cloned from the patient's own gene. Both problems can be solved by turn to traditional therapies like the radiation therapy.

And at last, I will give a conclusion of my own thoughts, using the new CCRISPR technology may be a great help. To summarize, replacing or modifying the gene fragments with problems by means or injecting AVV that carry new gene particles could offer a fast and safe way to avoid the cytokine storm happening during the treatments. And the drawbacks are, the CRISPR technology still need more clinical tests to be put into application and its cost may be unaffordable towards many people.

References

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