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The mechanism and efficiency of mRNA based dendritic cell immunotherapy

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Abstract. In the recent years, the mentions of immunotherapy has become more and more frequent. What emerged along with it are the various types of immunotherapies. This essay includes an introduction to cancer and tumor with the definition, epidemiology, etiology, statistics such as curability regarding types, gender, and race and typical treatments of cancer along with how the immune system functions when targeting tumor cells and how they could potentially disfunction when deceived by tumor cells for example through immune editing. Then, leading on to the main topic to this recent and innovative treatment— immunotherapy. This essay emphasizes on two different types of immunotherapy which are dendritic cell therapy, and messenger RNA vaccine discussing their mechanism as separate treatments. Afterwards, I'll proceed to discuss the combination of the two which is known as dendritic cell based mRNA vaccine which is a form of mRNA vaccine and it's own mechanism, advantages, efficiency and current limitations in the conclusion.

Keywords: Cancer, immunotherapy, dendritic cells, mRNA vaccine

1. Introduction

For centuries, cancer was known as an incurable disease due to multiple reasons such as the vast distinctiveness of each type or sub-types of cancer since cancer arises from the cells in our own body after continuous uncontrolled growth and division of mutated cells. While tumor, a word that seemed to come right after cancer is a lump formed upon tissues due to abnormal cellular growth or division. A tumor doesn't necessarily equal cancer. It can be classified into a benign tumor or a malignant tumor in which only the malignant tumor with a vascular system and the ability to proliferate results in cancer.

Starting off with the epidemiology of cancer which relates to the factors causing cancer and the distribution of cancer. The causes of cancer could be broken down into two main perspectives, genetic, and environmental. Genetically, a mutation in the DNA results in an abnormal protein which increases the frequency of mitosis or cell division and therefore results in the formation of a tumor as over-produced cells accumulated. With the presence of a genetic risk factor poses a higher risk of getting cancer if there's a member in your family who has gotten cancer. Environmentally many risk factors could indirectly cause cancer such as over-exposure to UV light, asbestos in construction sites, or radiation along with bad habits such as smoking and excessive drinking. There're also unmodifiable risk factors such as race, gender, and age. Taking breast cancer as an example, according to medicine net women are 100 times more prone to getting breast cancer while breast cancer in men occurs in less than 1 percent of the population. Approximately 440 men die of breast cancer each year however 40,000

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women die of breast cancer each year. [1] Lastly, the median age of the diagnosis of female breast cancer patients is 63 years old suggesting age makes breast cancer more prevalent.

Non hispanic white women's incidence rate for cancer is 37.8% higher than Hispanic women [2]. If displaying typical cancer symptoms such as nausea, random bruises, swollen glands and etc. Investigations such as MRI or CT scans take place that could show parts of shadows that indicate a possible tumor. A complete blood count (CBC) could also be ordered to investigate for cancer such as Leukemia. An abnormally high white blood cell level or an abnormally low red blood cell or platelets level could indicate leukemia in which it would be followed by a bone marrow biopsy to identify the type of leukemia.

2. The Reasons We Need Immunotherapy

Moving on to the treatments. Typical cancer treatments are chemotherapy and radiation therapy. Chemotherapy for example circulates the body and kills all fast growing cells including healthy cells thus bringing about severe side effects such as hair loss, nausea, and fatigue. Furthermore, the tumor could mutate and become resistant to chemo. For radiation therapy, it harnesses radiation beams to target a specific part of the body where the tumor is present. Nevertheless, just like chemo, it has side effects such as hair loss, loss of appetite, and body burns. It is worth mentioning that although with the same treatment, each type of cancer has a different curability rate such as thyroid cancer and testicular cancer tend to have a higher curability compared to mesothelioma and pancreatic cancer, according to live science, as they have a 5 year relative survival rate of 12% and 11.5% respectively. [3].

The certain ineffectiveness of the typical therapies have brought immunotherapy into our visions. Immunotherapy is a type of therapy which targets the immune system directly instead of targeting the tumor. It improves the mechanism by which the immune system responds to the tumor cells. As for "improve", it is due to the flaws of the immune system as it can be deceived by tumor cells in mainly two ways. One way is known as immunoediting in which the tumor cells disguise as healthy cells. This is achieved through mutations in the tumor while the immune system still only targets the un-mutated cells allowing the mutated ones to become prevalent eventually disabling the immune system from targeting the tumor at all.

Another common form is called immune checkpoint in which the immune system is being "turned off". This is when a protein known as PD-L1 deactivates the T-cell receptor disabling future processes down the immune response system.

3. The Mechanism of The Immune System While Tackling a Pathogen

The entire immune response is generated from the dendritic cell engulfing the pathogen cell then expressing the same antigen as the pathogen on itself. This triggers a type of T cell known as the T helper cell with a T cell receptor that is unique to this type of antigen and binds to the antigen. Then, after cytokines were released the T cells were able to duplicate themselves and could travel around the body for their TCR to bind to any other infected cell with the same type of antigen. Another function of the T helper cell triggers the following immune response. They activate the cytotoxic killer T cells that derive from a T cell after a change in phenotype. They, along with the natural killer cells kill pathogens by puncturing the infected cell with chemicals such as perforins and granzymes. The T helper cell also activates the B cells which carry out two main functions. One group becomes plasma cells that produce antigen after activation or they become memory B cells who enables the immune system to identify foreign pathogens and kill them more quickly and efficiently for the next attack. (See figure 2 for graphic demonstration)

4. Explanation of Two Types of Immunotherapies and Their Combinations

Starting off with dendritic cell therapy. The dendritic cell could be compared to the first domino card in the domino effect initiating the entire immune response. The dendritic cell engulfs the pathogen as a phagocyte which is present in both the innate and adaptive immune system attributing to its name "nature's adjuvant". Once the dendritic cell engulfs the pathogen it releases hydrolase which then

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integrates into a molecular tag equivalent to the antigen on the pathogen it has engulfed becoming an antigen presenting cell. This antigen then triggers the T cells who thus drives the immune response. The theory behind the dendritic cell therapy is that after analyzing the antigen presented on the tumor, the scientists could insert the same antigen onto the dendritic cells into the lymphoid tissues [4]. That way, instead of the dendritic cell carrying out the engulfing, the hydrolyzing, the integrating, and presenting the antigen; the dendritic cells arrive with the antigens that trigger and activate the T cells straight away speeding up the anti-tumor response's efficiency. According to Constantino et al, this method of loading antigen to dendritic cells has been proven effective on vivo trials. [4]

Then I want to focus on is called mRNA-based vaccine. This was first developed in 1996 when dendritic cells were pulsed with RNA in vitro.[5]. An RNA (short for ribonucleic acid) is the transcribed version of the DNA in short for deoxyribonucleic acid. Transcribed in this case means each nucleotide in the DNA has to match with their corresponding nucleotide who matches in shape. Adenine has to be matched to thymine while guanine is matched with cytosine. However, if thymine appears in the RNA strand it is replaced by Uracil. Now the m in mRNA stands for messenger. The messenger RNA's job instructs the ribosomes of the recipe of the nitrogen sequence for making the correct protein. So, similar to the mRNA covid vaccine, the mRNA vaccine for cancer uses a similar property. The ability to activate naive CD8+ T cells is an exclusive property of a specialized type of cells called professional antigen-presenting cells (APC). [6] They take the neo-antigens from the tumors engineer it then extract a stable form of this mRNA from the antigen. The mRNA, as messengers, once infused into the body would instruct the APCs to expose the same antigen as the tumor priming for more attacks and launching more anti-tumor response. This technique works closely with the dendritic cells as it pertains the property of an APC.

As a matter of fact, one type of mRNA-based vaccine used for cancer patients is called dendritic cell-based mRNA vaccine, a separate therapy consisting of the combination of the two therapies mentioned above, since dendritic cells are also antigen presenting cells who display the antigens and activate the immune response. The mechanism of the dendritic cell- based mRNA vaccine is similar to the mRNA cell. The mRNA retained from the tumor cell can instruct protein equivalent to the neo-antigens on the tumor to form on dendritic cells therefore inducing the entire anti-tumor immune response. According to Gilboa et al. It is recently proven that this procedure induces Cytotoxic T lymphocyte (CTL) responses who mediate immunity against tumors and enhances expansion of activated or memory CTL. Furthermore, evidences support that the main form of professional APC is the dendritic cell. [6].Through studies, we could conclude that the combination of dendritic cell therapy with the procedure of mRNA vaccine has a promising prospect according to evidences.

Some of the most prominent advantages of Dendritic cell-based vaccine include its efficiency as in how it targets the first domino-dendritic cell in the domino effect of an immune response; and that their ex-vivo stage would be simpler and has hopes to be even more simplified. At the same time examples of experiments would be mentioned to support the advantages. This DC based vaccine has a very direct way of channeling engineered antigen into the dendritic cell system. According to Gilboa et al this treatment was remarkably effective in this post-surgical metastasis model, more so than the traditional GMTV vaccine on animal vivo studies. Furthermore, according to conducted experiments and trials, it triggers a more protective tumor immunity compared to traditional methods [6] since the dendritic cell system is altered through the infusion of mRNA which enables a more effective and swift initiative for the B memory cells who are in charge of the body's future immunities towards foreign pathogens. Lastly, another great benefit of the DC based vaccine is that it is easy to prepare, or at least, easier. Unlike the GMTV vaccine for example needs an irradiated environment for ex-vivo cultivation however the radiation could adversely effect the production of cytokines. Furthermore, this vaccine is very specific targeting. Instead of using defined tumor antigens, a tumor-derived material such as the mRNA initiated immune response would be preferable as it is directed to the specific tumor in the specific patient with a higher guaranteed rate of efficiency

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5. Conclusion

From my own point of view and based on my current knowledge on immunology DC-based mRNA vaccine is the most intriguing one out of various types of immunotherapy and the one I believe it have the best and most efficient prospect. Since they are the therapies involving the dendritic cell such as this dendritic cell-based mRNA vaccine. The reason for that is that the role of dendritic cells in the immune system acted as the first card in the long domino path of the entire immune response as it holds the responsibility to trigger the immune response. (Reason for their efficiency has been discussed above.) If this crucial card can be designed to be functioned more efficiently or in other words getting a lesser burden while tackling various highly modifiable tumor cells through bioengineering, the treatment of cancer can step to a new level due to this fundamental change. Furthermore, the experiments done on vivo that are present so far mostly show that it is a well-tolerated procedure which breaks another typical issue of cancer treatment which is oppressive side effects. Furthermore, in terms of the dendritic cell-based mRNA vaccine, the covid mRNA vaccine acts as a great foundation for it being one of the few beneficial influences of this unprecedented 3 years. Hopefully the recently prevailed covid mRNA vaccine could assist dendritic cell-based mRNA vaccine to become as efficient, mature and universal.

Yet with all of the above being said, immunotherapy is still a very new and overall less commonly practiced and mature type of cancer therapy along with the even newer dendritic cell-based mRNA vaccine due to lack of time therefore lack of experiments. Certain factors are still waiting to be determined such as the method of injection. Undeniably, immunotherapy in general still has a long road ahead. However, it is hopeful that after years of sediment of time in the future, immunotherapy could enhance curing rate for cancer and bring profound changes to humankind.

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