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Assessment of feasibility of mRNA vaccines for cancer treatment

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Abstract. Cancer is the group of disease that has high morbidity rate, the traditional treatment people keep using have a lot of limitations. Although the concept of mRNA vaccines has just emerged in the 20th century, it has demonstrated its good availability during the COVID-19 pandemic. From this, researchers infer that mRNA also has great application prospects in other areas, and cancer immunotherapy has become one of them. mRNA vaccine used to have low translation efficiency and strong mRNA immunogenicity but recent research about mRNA sequence optimization could overcome most of these problems. But to apply this platform vaccine to target tumour cells specifically, the target chosen is very important and still needs a lot of research about it. This article reviews the current approach to mRNA vaccine and its therapeutic usage for cancer. Based on the current clinical studies, the mRNA vaccine might be a good auxiliary tool for cancer treatment.

Keywords: mRNA, vaccines, cancer.

1. Introduction

Cancer is a large group of diseases caused by the uncontrolled abnormal/tumor cell growth [1]. The increasing and ageing population result in higher and higher morbidity rate of cancer. Based on statistics from the World Health Organization, in 2020, there were about 10 million deaths caused by cancer. According to the estimation using GLOBOCAN 2020 from the International Agency for Research on Cancer, the case of cancer burden will rise to 28.4 million in 2040 [2].

Nowadays, a variety of clinical methods are used for the therapy of cancer, including chemotherapy, radiotherapy and surgery. The advanced technology has greatly increased the rate of cancer survivors. From 2019 to 2020, the death rate declined by 1.5% overall; specifically for leukemia, melanoma and renal carcinoma, the death rate decreased by 2% annually [3]. However, the limitations of current treatments are still severe. The common drugs for chemotherapy have side effects, for example, hair loss, drug resistance, gastrointestinal lesions, bone marrow suppression, neurologic dysfunction or cardiac toxicity [4]. If the tumor grows aggressively and the formation of metastasis is rapid, like pancreatic cancer [5], a low percentage of patients have potentially treatable tumors and get operation surgery timely so palliative therapy will apply to these patients commonly. A new way to cure cancer is essential.

The idea of vaccination could be traced back to the 10th century, ancient China and India used variolation against smallpox, but that was just a local lesion only. In 1796, Edward Jenner conferred that

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cowpox is an efficient way to protect from smallpox, calling this procedure as “vaccination”. Then Louis Pasteur developed vaccines against rabies, avian cholera and anthrax based on attenuated microorganisms about two hundred years ago, this brought the great revolution of vaccines [6]. In the 21st century, vaccine has now become one of the most cost-efficient ways to intervene in public health [7]. The platform of vaccine is not live attenuated microorganisms only, delivering vaccines through inactive viruses or bacteria, virus vectors, Virus-like particles (VLP), protein subunits and nucleic acids are very common now. And the prophylactic usage of vaccines is not the only function anymore. Many researchers have concentrated on the therapeutic use of vaccination.

Cancer is a group of intractable diseases, people always looking for a new and better way to against cancer. Vaccine has been shown as an efficient technique to prevent cancer caused by virus infection. From 2012 to 2019, cervical cancer in young women under 30s has apparently declined due to the receiving of human papillomavirus vaccine [3]. The therapeutic use of the vaccine for cancer has great potential also. VLP vaccine could be used as an active immunotherapy for cancer as VLP is able to stimulate response of T cell and B cell to the tumor cells, as this show very positive results in mouse model and clinical trials [8].

RNA vaccine just came out 40 years ago, the development was relatively slow. Recently, this platform of vaccine has presented great versatility, favorable immunogenicity and safety during the COVID-19 pandemic because of the advanced technology used. This technology shows the possibility to apply to cancer treatment [9]. This article will evaluate the possibility of RNA vaccines being used in cancer treatment through the development of RNA platform vaccines and the related research progress of RNA vaccines as cancer treatments. This article will update the understanding of the prospects of RNA vaccines for cancer.

2. Developing of mRNA vaccine

mRNA was discovered in 1961, and scientists found that mRNA can transport into mouse and human cells and induce protein expression via liposomes, a fatty membrane structure. In 1987, Robert Malone did a similar experiment, he mixed mRNA with fatty droplets, and human cells could absorb this mixture. This experiment inspired the idea of RNA drugs as treatment and led to the development of mRNA platform vaccines [10]. The superiorities of mRNA platform vaccines evidently, include safety as it will not interact with the genome, great flexibility as it is possible to encode all types of protein, and production of this vaccine platform will be relatively easier compared to the other platforms as process do not need adjustment [11]. However strong mRNA immunogenicity, low stability and efficiency limit the mRNA platform vaccines’ development.

3. SARS-CoV-2 mRNA vaccine

The first identification of betacoronavirus — Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2) in 2019 and led a huge pandemic. Almost billions of people get infected and millions of people die. An efficient and safe vaccine is urgent for need. Under this situation, although the mRNA vaccine still has many unknowns, the ability to quickly produce mRNA vaccine and result in efficient immune response made mRNA vaccine develop rapidly and become a popular platform for SARS-CoV-2 vaccines [12]. The spike (S) glycoprotein of SARS-CoV-2 has been chosen as target antigen of vaccine. The mRNA for SARS-CoV-2 S needs to be modified, uridine is replaced with N1-methyl-pseudouridine ($m1\Psi$) is very common so the translation will be 10 times more and avoid excessive inflammation or unwanted side effects. Lipid nanoparticles (LNP) can deliver mRNA in vivo efficiently and avoid mRNA degradation by nucleases. In human clinical trials, SARS-CoV-2 mRNA shows positive humoral and cellular responses [13]. However recent reports about rare cases of anaphylaxis indicate the potential risk of COVID-19 mRNA vaccine. The time length of immunity conferred by COVID-19 mRNA vaccine is unsure also.

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4. mRNA Induce Immunogenic Regulation

Dendritic cells (DC) as antigen-presenting cell are essential to initiate T-cell response. They uptake, process and present protein antigens to the lymphocytes. These antigen signals have two big classes, major histocompatibility complex (MHC) class I molecules loaded with intracellular antigens and MHC class II load extracellular antigens. MHC complexes can then be recognized by the T cell receptor of CD8+ T cells or CD4+ T cells and activate them [14]. mRNA vaccine could be exogenous genes, it will be recognized by APCs and enter the cytoplasm, combined with the ribosome and translate into antigen protein. These antigen proteins can either be degraded by the proteasome into the antigenic peptides in the cytoplasm and take part in the MHC I pathway. Or they will be released from the host cell and then be taken by DCs. mRNA in vitro transcription product can activate the pattern recognition receptors (PRRs) and produce toll-like receptor-mediated inflammation. Nonetheless, type I interferon (IFN) present in a high level may inhibit the mRNA translation and result in RNA degradation, CD8+T cell activity decreases, finally stopping the immune response [15].

5. Therapeutic Vaccination for Cancer

Since the FDA has approved the prophylactic COVID-19 mRNA vaccine and immunotherapies, people have put more attention on the therapeutic mRNA vaccine to treat cancer as it has both therapeutic and prophylactic potential. Vaccines can deliver tumor-associated or tumor-specific antigens that target antigen over-expressed malignant cells specifically, stimulate humoral or cell-mediated immune response, modify the suppressive tumor microenvironment and the immunologic memory allows the response long lasting and treatment be chronic. Compared mRNA vaccine with other vaccine platforms, it is less likely to be affected by vaccine resistance, cheaper and faster for preparation in large-scale production. Currently there are more than twenty clinical studies based on the mRNA vaccine immunotherapy [16].

The unique ability of DC makes them a good target theoretically, Currently in clinical trials about mRNA platform cancer vaccines, the DC-based mRNA vaccine therapeutics hold the majority, and try to generate an ex-vivo population of antigen-loaded dendritic cells to induce CD8+ and CD4+ T-cell responses to treat cancer chronically. However, current research still cannot fully recapitulate the immunoprotein dendritic cell development in ex-vivo to have effective anti-tumor immune responses. Though the clinical efficiency in most trials is not ideal, but DC-based mRNA vaccine still shows great potential to extend the patient survival time as it can prevent or delay disease relapse[17]. In vitro transcription (IVT) mRNA-based immunotherapy injected intratumorally or intranodally can modify the suppressive tumor microenvironment which shows the potential as a cancer treatment. Target mRNA encoding for immunostimulants can activate the T cell responses, but these immunostimulants are considered adjuvants co-administer with cancer vaccines not vaccines. Target mRNA vaccine encoding for tumor-associated antigens has problems with antigen selection. The common choice is the TAA expression in the tumor cells, in clinical studies metastatic melanoma treatment will use mixture of mRNA vaccine encoding for all TAAs. In clinical study NCT02410733, advanced melanoma patients were injected with mRNA vaccine encoding for four types of TAA, and two of them reacted to the 2 types of TAA (NY-ESO-1 and MAGE-A3) at the same time. The efficiency of the TAA-based mRNA vaccine is limited due to the identification and variation of TAA for certain patients is complex, and TAA is also expressed in normal cells. To improve this, many researchers focus on tumor-specific antigens, antigens originate from random somatic mutations in tumor cells and are not present in normal cells, so will be recognized as non-self motifs by the immune system [16].

6. Sequence Optimization of mRNA

mRNA is single-stranded RNA essential for protein synthesis. Currently, there are mainly two classifications of mRNA studied in vaccines, self-amplifying RNA (saRNA) and non-replicating mRNA.

Non-replicating mRNA is generally composed of untranslated regions (UTR), open-reading frame(ORF) and poly(A) tail[18]. Untranslated regions can divide into 3'UTR and 5'UTR, although they non-coding parts of the mRNA, they can alert the replication and translation process via reaction

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to RNA binding proteins. 3'UTR usually enriched with unstable factors. It is important to avoid these unstable elements like AU-enriched sequences during the mRNA synthesis or insert stable elements in 3'UTR to stabilize and expand the half-life of the mRNA. The 5'UTR will directly affect the translation of ORF, an identical gene sequence with the upstream sequence of ORF may result wrong start and replacement during reading the ORF. Specific sequences like GCC-(A/G)-CCAUGG inserted into this region increase the accuracy of the start of the translation. But ribosome binding with the mRNA will be inhibited if the secondary structure of 5'UTR is too stable so 5'UTR is better to be short and loose when design. ORF is the part coding for the protein, so it is very important that it will be translated accurately. The optimized synonymous codons' frequency or codons' tRNA abundance depends on the target antigen, so different codon optimization strategies should be used to maximize the translation rate and expressed antigen quality. Poly(A) tail can slow down the degradation process of RNA exonuclease which has an effect on stability and translation efficiency. This means the optimized length of the poly(A) tail needs to be adjusted depending on situation [15].

saRNA vaccine is idea about the viral RNA replication gene from the alphavirus genome comprised with the transgene coding for antigens, so replicase enzyme can amplify the saRNA inside the cell. The immune response caused by the saRNA vaccine will be stronger and longer lasting. The saRNA could be classified into three types as the antigen expression could be obtained in different ways. First is DNA plasmid-based saRNA, using plasmid DNA as a carrier. The saRNA will be transferred into the nucleus and transcribed there, then moved to the cytosol for replication and translation. The VLP packages saRNA have a simpler process, VLP can be recognized by cell receptors and mediate endocytosis, delivering saRNA into the cytosol. Lastly, in vitro transcribed saRNA use lipid nanoparticles as vectors, delivered in form of saline or synthetic formulations[19]. There are researchers using trans-amplifying RNA(tRNA) to improve the saRNA vaccine. This is based on the TR encoding the vaccine antigen and a second molecule coding for a trans-acting alpha viral replicate, which has a longer RNA half-life and higher translation efficiency [19].

7. Conclusion

The history of mRNA vaccine development is not as long as other platforms, but it is quick. The mRNA platform remarkable advantage in economic and time cost in large-scale production compared to other platforms. The advanced technology in sequence optimization developed in recent years including modification in different regions of mRNA and 5' cap greatly increases the stability of mRNA and translation efficiency. COVID-19 mRNA vaccine brings another sharp increase of preclinical and clinical research on this vaccine platform. Though the prophylactic usage is conspicuous, the potential of it being used as a therapeutic vaccine for cancer is worthy also. DC-based mRNA vaccines and immunostimulants encoding mRNA may become good adjuvants or treatments for cancer in the early stages. Using tumor-specific antigens as mRNA encoding targets might be the best choice for cancer therapeutic mRNA vaccines, but identifying these antigens and predicting corresponding neoepitopes for individual HLA alleles remains difficult. The vaccine administration route alerts the efficiency. The best administration method might be the intravenous injection as it is direct and can stimulate strong CD8+ T-cell response. The dosage for mRNA vaccine for cancer treatment needs to be considered carefully too. Overall mRNA vaccine is a potential platform in both prophylactics and therapeutic usage, and it is in a fast-developing stage. How to eliminating mRNA immunogenicity, stabilizing mRNA vaccines, increasing vaccine efficiency should always be the aims of investigation. How to quickly identify and apply tumor-specific antigens is also an important question we should keep working on.

References

[1] National Institutes of Health (US) Biological Sciences Curriculum Study NIH Curriculum Supplement Series 2007 Understanding Cancer https://www.ncbi.nlm.nih.gov/books/NBK20362/

DOI: 10.54254/2753-8818/33/20240897

[2] Sung H Ferlay J Siegel RL Laversanne M Soerjomataram I Jemal A Bray F Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries CA Cancer J Clin 71 209-249
[3] Siegel R L Miller K D Wagle N S & Jemal A 2023 Cancer statistics 2023 CA: a cancer J clinic 73(1) 17–48
[4] Hosseini A & Ghorbani A 2015 Cancer therapy with phytochemicals: evidence from clinical studies Avicenna J phytomedicine 5(2) 84–97
[5] Robatel S Schenk M 2022 Current Limitations and Novel Perspectives in Pancreatic Cancer Treatment Cancers; 14(4):985
[6] Josefsberg JO and Buckland B 2012 Vaccine process technology Biotechnol Bioeng 109: 1443-1460
[7] World Health Organization 2009 State of the World's Vaccines and Immunization UNICEF World Bank :5–210
[8] Mohsen MO Speiser DE Knuth A Bachmann MF 2020 Virus-like particles for vaccination against cancer WIREs Nanomed Nanobiotechnol 12:e1579
[9] Huff A L Jaffee E M & Zaidi N 2022 Messenger RNA vaccines for cancer immunotherapy: progress promotes promise J clinic investing 132(6) e156211
[10] Dolgin E 2021 The tangled history of mRNA vaccines Nature 597(7876) 318–324
[11] Schlake T Thess A Fotin-Mleczek M & Kallen K J 2012 Developing mRNA-vaccine technologies RNA biology 9(11) 1319–1330
[12] Park J W Lagniton P N P Liu Y & Xu R H 2021 mRNA vaccines for COVID-19: what why and how Intern J biolog sci 17(6) 1446–1460
[13] Bettini E Locci M SARS-CoV-2 2021 mRNA Vaccines: Immunological Mechanism and Beyond Vaccines; 9(2):147
[14] Verbeke R Lentacker I De Smedt S C & Dewitte H 2019 Three decades of messenger RNA vaccine development Nano Today 28(Complete)
[15] Xu S Yang K Li R Zhang L 2020 mRNA Vaccine Era—Mechanisms Drug Platform and Clinical Prospection Internat J Mol Sci 21(18):6582
[16] Miao L Zhang Y & Huang L 2021 mRNA vaccine for cancer immunotherapy Mol Cancer 20 41
[17] Lorentzen C L Haanen J B Met Ö & Svane I M 2022 Clinical advances and ongoing trials on mRNA vaccines for cancer treatment The Lancet Oncol 23(10) e450–e458
[18] Wang Y Zhang Z Luo J et al 2021 mRNA vaccine: a potential therapeutic strategy Mol Cancer 20 33
[19] Beissert T Perkovic M Vogel Aet al 2020 A Trans-amplifying RNA Vaccine Strategy for Induction of Potent Protective Immunity Molecular therapy the journal of the American Society of Gene Therapy 28(1) 119–128