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RNA Vaccine Paradigm in 21st Century Cancer Treatment

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Abstract

The principle behind RNA vaccine is to use natural mRNA as a data carrier which can give instructions to the human body for the production of its proteins to fight against various diseases. RNA based vaccines provide good safety when it comes to their delivery in the cytoplasm. RNA vaccines comprise as mRNA vaccine which can offer robust safety profile with minimal genetic construction to express the desired antigen. To overcome the problems in present cancer treatment, it is important to develop next-generation treatment applying the fundamentals of genomics. With the help of the genetic profile of each individual, the particular nature of the disease condition can be targeted to advance treatment as personalized medicine. RNA vaccines which usually comprise of mRNA synthesized *in-vitro* and modified to express properly into the cytoplasm having code for the proper antigen known as tumor associated antigen (TAA) to express into the cell which can teach patients to own immune cells to fight against tumor cells more effectively. There are many advantages of RNA vaccines over other existing vaccines or therapy. Existing therapy includes chemotherapy; radiation therapy and surgery have many drawbacks with a high cost for the application. These can be overcome by the application of next-generation RNA vaccine by using genomics and apply as personalized medicine, different from every cancer patients according to the type of tumor present in every patient. For the development of RNA vaccine, an antigen can be predicted by sequencing the whole genome of the patient and finding the difference between cancer cells and normal cell genetics, basically mutation in genes of cancer cells. This mutated sequence can be analyzed and *in-vitro* converted into functional mRNA by modifying its 5'and 3' ends. This functional mRNA can produce the antigen present on the tumor and then after expressing into patients cells, it will make patient's immune cells more active to fight against the particular tumor antigen by providing them with a precise recognition. This review encapsulates the concept of recent mRNA vaccine development for the treatment of cancer including its mechanism of action with applications in personalized immunotherapy and next-generation vaccinology, which is a new era of medical science for treatment of diseases.

Keywords: Applications, Genomics, Immunotherapy, Lipid Nanoparticles, Mechanism of Action, Next

Generation Vaccines, Nucleic Acid Delivery, Personalized Medicine, RNA Vaccine.

1. Introduction

An attractive approach to vaccination is presented by nucleic acid vaccines [6, 15]. These vaccines based on DNA or RNA encoded with specific antigen and generally regarded as safe, effective which can mimic live infection with the low rise of reversion to virulence [31, 43]. RNA vaccines generally elicit humoral as well as a cellular immune response [20, 38]. Personalized medicine is the new paradigm of medical science for targeting specific characteristics of each individual by using their genetic profile to identify particular nature of the medical condition and design a unique treatment for each patient [32, 37]. Cancer immunotherapy stimulates a host antitumor immune response which can able to lead tumor shrinkage for the improvement of clinical outcomes in cancer patients [25]. Eradication of the large tumor by active immunotherapy is the biggest challenge, to overcome this challenge combination therapy of mRNA vaccine with radiation can be effective [28]. mRNA as a vaccine has many advantages including large scale production under GMP conditions is comparatively easy and robust, that's why inexpensive in contrast to the other biopharmaceuticals [29, 44]. The tumor antigens are recognizing by the immune system and this is the basis for cancer immunotherapy development [35, 36]. Vaccination is the way to instruct the immune system to recognize and attack tumor cells. RNA has many interesting features for effective vaccination that is after transfection RNA not integrate into the genome but the translated tumor proteins enter the intrinsic antigen processing pathway and enable presentation by MHC-I molecules. This activates cytotoxic $CD8^+$ T cells which can attack and kill tumor cells [1].

2. Designing of Cancer Vaccine

There are a few things which are important for designing cancer vaccines:

2.1: The Right Antigen

Antigens which can be used to design cancer vaccines should preferably be the molecules that are altered among the normal cells and tumor cells to ensure that the immune response generation by vaccination will be able to target for destruction of tumor cells expressing the particular antigen dissimilar between normal cells and cancer cells [9].

2.2: The Right Adjuvant

Adjuvants are the diverse molecules which can activate antigen-presenting cells for the stimulation of strong and vigorous cellular immune response [9].

2.3: The Right Immune Response

An operative vaccine must be able to produce and tolerate a powerful immune response which can safeguard eradication and prevent recurrence of existing tumors [9].

3. mRNA Vaccine: An Inexpensive Biopharmaceutical

mRNA vaccines are generally safe, inexpensive with maximum flexibility having self-adjuvanting property including MHC haplotype restriction, direct entry only in the cytoplasm for expression without integration into the genome [17]. For the transcription of the functional mRNA as a vaccine, cytoplasmic stability is important which can achieve by cap and poly-A tail modification [17]. Because eukaryotic mRNA is composed of the coding region which is flanked by 5' and 3' untranslated region (UTR), 5' 7-methylguanosine triphosphate cap and 3' poly-A tail [8, 14]. Vaccination by using mRNA molecules which encode specific target antigen can induce an immune response after the presentation by antigen-presenting cells [39, 40]. Because of the use of the enzymatic process for the production of mRNA vaccine,

tight control over the immunogenic profile, pharmacokinetics and dose of vaccine can be maintained. Also, optimization can be improved by codon usage, stability and the properties of antigen [10]. Care must be taken at the time of production of RNA based biopharmaceuticals because these agents are delicate to degradation [10].

4. Different Types of mRNA Vaccine

Two forms are available for mRNA vaccine including self-amplifying and conventional non-amplifying. Self-amplifying [18, 19, 45] vaccines have high expression of encoded gene as compared to non-amplifying [6, 47]. Non-amplifying mRNA vaccines contain five important elements which are important for expression of mRNA. 1. Methylated cap 2. 5' untranslated region 3. 3' untranslated region 4. Poly-A tail 5. Coding sequence [46, 49]. All elements are important for the stability of the mRNA, its convenience to ribosome including circularization and insertion with the translational machinery of the host cell. The advantage of the conventional mRNA vaccine comprises simplicity of the construction having a relatively small size of RNA compared to self-amplifying molecules [6]. Due to its short half-life and instability of RNA, only transient and low level of expression can be accomplished *in-vivo*. Self-amplifying mRNAs are significantly larger than non-amplifying mRNA. Also contains all the elements of an mRNA [6]. self-amplifying RNA accomplishes high levels of expression. The attractive features of self-amplifying RNA vaccines are their auto-replicative capacity which maintains high levels of expression in the host cells [6].

5. Delivery System of mRNA as Vaccine

There are few differences between tumor and healthy tissue, after that the challenge is to clarify the immune system to identify them and this can be done only by governing TAA to the body [3]. The major thing which can be remembered for making the immune system capable to fight against which must be applied and another thing is the way by which the antigen should be administered [3]. When the type of antigen is considered than many approaches can be used including peptides from the TAA or the whole protein is used also lysates of the whole tumor or treated apoptotic tumor cells will be used [3]. Also, the selection of the antigen, strategy of the antigen administration is important for the effective and safe delivery of the complete TAA encoding RNA for the proper expression [3]. In one approach of vaccination, mRNA can be extracted from tumor tissue of the patient. But the disadvantage of this approach is the amount of mRNA for use as vaccination. This disadvantage can be overcome by using *in-vitro* RNA synthesis technique to generate complete tumor cDNA libraries for obtaining the proper amount of RNA encoding multiple patients specific TAA [3]. Two methods are more preferred for the efficient delivery of mRNA as a vaccine: Viral based [23] and non-viral based delivery. mRNA vaccine delivery can be made effective by wrapping the mRNA into the nano-sized carriers [30] like lipoplexes [48] which can protect mRNA from degradation and increase uptake by dendritic cells *in-vivo* [2]. Lipid nanoparticles [1, 11, 13, 22, 27, 34, 35, 43, 18, 42, 48], gene gun [1, 25, 48], protamine condensation [25] encapsulation [25] and adjuvants based [25] are non-viral based method of mRNA delivery [5, 6]. Lipid nanoparticles are more promising for mRNA delivery among all other non-viral delivery methods because it can be synthesized very easily in a highly scalable manner, provide protection against degradation with facilitation to endosomal escape, targeted delivery can be achieved to the desired cell type by decorating surface with proper ligands and can be co-delivered with adjuvants [34].

6. Mechanism of Action

mRNA which is encoded with a tumor associated antigens also known as TAA or the total tumor RNA can be delivered to the host cells by taking care of mRNA degradation in response to elicit an immune response against the specific antigen [1-4, 12, 16]. That's why either DNA or RNA which carrying the information particularly to synthesize TAA can be directed to experimental model laboratory animals in preclinical studies or the patients who are under clinical trials having the aim to induce and synthesis of TAA [7, 21]. After the induction of the particular TAA gene, protein formation occurs [24, 26, 33]. This protein can be degraded into the cytosol of the cells and degraded by the specific macrophages as it is recognized as foreign protein by the cells of the immune system [42]. This kind of degraded molecules which are known as antigen presented by the antigen-presenting cells to the T-cells or B-cells of the immune system for further processing [22]. This whole process occurs with the help of cell to cell communication by using MHC molecules present on the surface of the cells and then the degraded part of the foreign protein can be processed by the T and B cells of the immune system to develop immunity against that specific antigen [1, 27]. Another mechanism is mRNA which is encoded with chimeric antigen receptor can be transfected into natural killer cells or T cells *in-vitro* after deriving those cells from the patient's body. These kinds of cells are now able to recognize the cancer cells more effectively to kill the tumor cells which express the mRNA coded antigen [11, 17]. RNA vaccine can be delivered naked or encapsulated to manipulate antigen-presenting cells for translation into specific protein which can trigger TH0 and stimulate TH1 and TH2 for activation of naïve B cells [41, 50]. An alternative approach for the delivery of the TAA as genetic material is to use RNA as vaccination. Because of the advantage of escaping the step of genome integration into the host genome. RNA can be administered into the cytosol of the cells and modified *in-vitro* to express into the cell to produce the desired protein, which can then be used as foreign protein to elicit the immune response [1].

7. Applications and Advantages

A clinical application of mRNA includes therapeutic and prophylactic vaccines for infectious diseases, cancer immunotherapy, genetic engineering and reprogramming of cells [13, 40]. mRNA vaccine can mimic natural infection which can lead strong immune responses, it can be easily scaled up, it is highly economic when it comes to cost, time and resources, it can be designed very easily at the rapid rate [17].

8. Conclusion

In the initial phase of pre-clinical studies, it was confirmed that mRNA vaccines are safe with low manufacturing cost and they do not require a cold chain for transportation. The activity perceived by mRNA vaccines as prophylactic and therapeutic vaccines and in immunotherapy showed great promising results in the models. mRNA based vaccines will successfully become next-generation vaccination against infectious disease and cancer personalized immunotherapy. Prescription for the treatment will be directly given to the person's body to make the medicines needed by the body either it is for prophylactic or therapeutic purposes. Patients body will make needful medicines by itself after receiving the right natural prescription. The medicines will be as unique as the patient and provide personalized medicine at a low cost having good results.

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