

DNA/mRNA-Based Vaccines Present an Additional Risk of Human Genome Modification in HIV Epidemic Era

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Abstract

Active HIV and other retroviral infections are a substantial portion of the world's population. DNA/mRNA-based preventive vaccine might present a potential risk of reversed genetic information flow and change the genetic background of host cells, resulting in new medical challenges years after. Carefully selecting the suitable population for different vaccine regimens according to each one's biological characteristics cannot be overemphasized when a vast general population needs to be protected.

Keywords: DNA Vaccine; mRNA Vaccine, Reverse Transcription; COVID-19 Vaccine; HIV; Retrotransposon

Rapid worldwide spread of COVID-19 presents an urgent call for vaccines due to it being extremely contagiousness, disease severity and high mortality in elders. With viral antigen challenging, a protective humoral immune reaction would block viral entry to susceptible cells and prematurely arrest the viral replication cycle. Classical vaccine development strategies use physically/chemically inactivated whole viruses or recombinant antigenic fragment of the viral proteins to trigger specific immune reactions. This process requires many years for vaccine development and polishing. The full picture of vaccine benefits and side effects needs decades or several generations to be fully documented and evaluated. Persistent public pressure for the recovery of social life and the national economy initiated the endeavors of using newer technology to develop vaccines. One of the vaccine strategies uses genetically modified DNA or mRNA molecule inoculations to transiently generate desired viral specific antigenic proteins inside of a human body [1-3]. These DNA/mRNA molecules are enclosed in biologically suitable nanovehicles for non-specifically delivery of the macromolecules to cells which have vigorous intracellular protein transcription/translation activities. Although in vitro synthesized genetic materials are clean and free of protein contamination during preparation, it is truly an artificial intermediate in the symbiotic system.

Unlike proteins, locates in the end of the living machinery chain, non-host DNA fragments and mRNAs are a bidirectional intracellular intermediate within the transition hub. While the main driving force for living cells is from DNA->RNA-> proteins, evolution has also involved in a reversed countercurrent for genetic complexities and diversities. It has been defined by genetic analysis, more than half of human genetic sequences are consists of different sizes of retrotransposons [4]. These spacers are randomly distributed within the genes and might provide many unknown symbiotic advantages for biological evolution and species conservation. Some of them, however, are responsible for complex human diseases which are exhausting tremendous medical resources today. Multiple retrotransposon accumulations were derived from several explosive retroviral invasion events during

evolution through repeated “copy and paste” of foreign genetic materials. The external genetic sequences might encode different molecules with alternate reverse transcription or integration activities for the storage of genetic information in the host; and thus enlarged, and separate host individual genes. These earlier events have resulted in permanent changes of the genetic blueprint for different species, especially mammalian, avian, and amphibian. The random expression and recombination of accumulated retrotransposon might also be responsible for the production of existing or new viruses as a by-product in these species and cause new infectious disease in their hosts and further crossing the barrier to human. The real mechanisms for reversed genetic information flow is difficult to elucidate once it became a stable part of the host genome.

Human immunodeficiency virus (HIV) infection is a recently emerged human retroviral life-time infection, with more than 40 million people were actively infected. Without an effective eradication strategy, it is estimated the accumulated infected patients will slowly reach 1% of the population. As a potential retrovirally mediated genomic modification, it represents a new event in development history if it is not controlled and subsequently eliminated. Since HIV encode viral specific reverse transcriptase (RT) and integrase, they can reversely transcribe and insert the viral genetic materials into host genome. Once the virus becomes a part of host genome, there is no feasible way to kick out the viral copies from the hosts except for killing infected cells [5]. Whereas HIV mainly infects viral receptor positive human immune system cells, the latest evidence has demonstrated spermatozoon infection of the germ line cells through close contact with infected immune system cells [6]. It is raising a major concern about a new wave of hereditary additions in the human genome. Unlike in females where the number of oocytes is predetermined before birth, spermatocytes are continuously generated in a rapid rate through virile life. Other documented evidence of male germ line viral infection includes the Zika virus (positive strand RNA) and Ebola virus (negative strand RNA).

Intensive studies in retrovirology have given us a feasible approach to elucidate and understand the mechanism of the reverse flow of genetic information. In HIV, the virus uses host tRNA, in particular tRNA^{Lys3}, as a primer for the initiation of reverse transcription process [7,8]. The recognition codon of the tRNA is short (3–5 nucleotides) and the similar sequences might frequently appear within a random foreign RNA sequence. The reverse transcription is so effective that non-specific reverse transcription of RNA molecules with commercial RT and primers has become a universally used molecular biological tool. In addition to utilizing a primer, some internal reverse transcriptase could directly nick the genomic DNA sequence and use host DNA as a primer for the initiation of reverse transcription. Many RNA molecules without long terminal repeat sequences could be transcribed as such and integrated into host genome.

With explosive increases of knowledge in molecular biology, unlimited possibilities are created in conquering human diseases. Many therapeutic strategies focus on these intermediates in genetic information flow chain, especially by using modified DNA/mRNA-based macromolecules as therapeutic drugs. While permanently manipulating/changing human genetic sequences are generally unethical, using DNA/mRNA-based therapy for human diseases are well acceptable by modern society. Thousands of different DNA/mRNA molecules have been synthesized yearly and used in medical research and clinical patients; and their uses posed little dispute because they are only used against well-defined, incurable diseases with limited patient populations. It has presented no worry to otherwise healthy populations. However, when civilized society decides to use DNA/mRNA-based vaccine strategy to protect entire populations for more severe, rapidly spread contagious diseases, the pros vs cons of such a vaccine must be weighed carefully.

For example, mRNA-based vaccines for COVID-19 or other pandemic-level infectious pathogens might present some major concerns. 1) Potentially billions of healthy people need to be inoculated before reaching an effective control of the disease. It means introducing a piece of bidirectional genetic material into an unrestrained population without predetermined clear conclusions. This presents possibilities that the vaccine molecules may go in unexpected directions in some specific situations, similar to putting one cell into a huge nutrition-rich bioreactor – mutations are rare but not impossible. This sequence with defined non-self codons can get into any cells in different proliferation/metabolic stages and its final destiny may not be forced by our present knowledge and technology. 2) Active HIV infection and other retroviral infections in current population are quite high and many are under diagnosed. These patients may provide a susceptible population for a reversed genetic information flow and generate new diseases or disease variants once it is reversely transcribed and incorporated (or as an extra-chromosomal circular DNA body). 3) Expression of mRNA vaccine inside a cell may be out of control and accumulated antigen protein may do more harm than good to the cells and

body. Murphy's law cannot be ignored. The future costs for unexpected outcomes and treatments may be enormous. There are still many other concerns about DNA/mRNA-base molecules as a vaccine strategy to be used in the general population and need to be fully considered. Cautiously breaking a fast-moving car in a two-way road will always avoid a more serious accident.

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