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THE SARS-COV-2 VACCINE IS SAFE: IT IS NEITHER HARMFUL TO HUMAN CELLS NOR IT WILL INFECT HUMAN OR CAUSE DISEASE

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ABSTRACT

The main objective of the vaccine is to stop transmission of SARS-CoV-2. The current vaccines (Moderna, Pfizer, Astra Zeneca, Sinoform, Sputnik-V, CanSino, Novavax etc.) have strands of genetic material called mRNA or DNA virus (viral vector) of spikes, inside a lipid Nanoparticles or adenovirus vectors. These nanoparticles coating will protect the mRNA from enzymes in the body that would otherwise break it down. It also helps the mRNA enter the dendritic cells and macrophages in the lymph node near the vaccination site and then activate the naive cells and remaining immune mechanism to develop humoral and cellular Immunity and their relevant memory cells. All the vaccines produce spike protein and not a whole virus. The mRNA vaccine induced SARS-CoV-2 immunity in all participants, and no trial-limiting safety concerns were been reported so far. It is hoped that these findings will help control the current pandemic. This is a review article based on the literature. It is to summarize the mechanism and safety of current mRNA vaccines. The authors do not have any conflict of interest.

KEYWORDS: COVID-19, mRNA vaccine, Human Cell, Spike Proteins, ACE-2 Receptors, SARS-CoV-2.

Vaccines have historically saved millions of lives from different infectious diseases in epidemics, endemics and pandemics. The use of mRNA vaccine is not new. These are being used for many years to targets animal models of rabies virus, influenza virus, Zika virus, and others. In recent years, its use became even more popular because of lipid-encapsulated or naked forms of sequence-optimized mRNA use e.g. COVID-19 vaccine. The mRNA vaccines are better than the conventional vaccine (live attenuated, inactivated pathogens or subunit vaccines) due to their safety profile, better potency and cost effectiveness (Figure 1).[1]

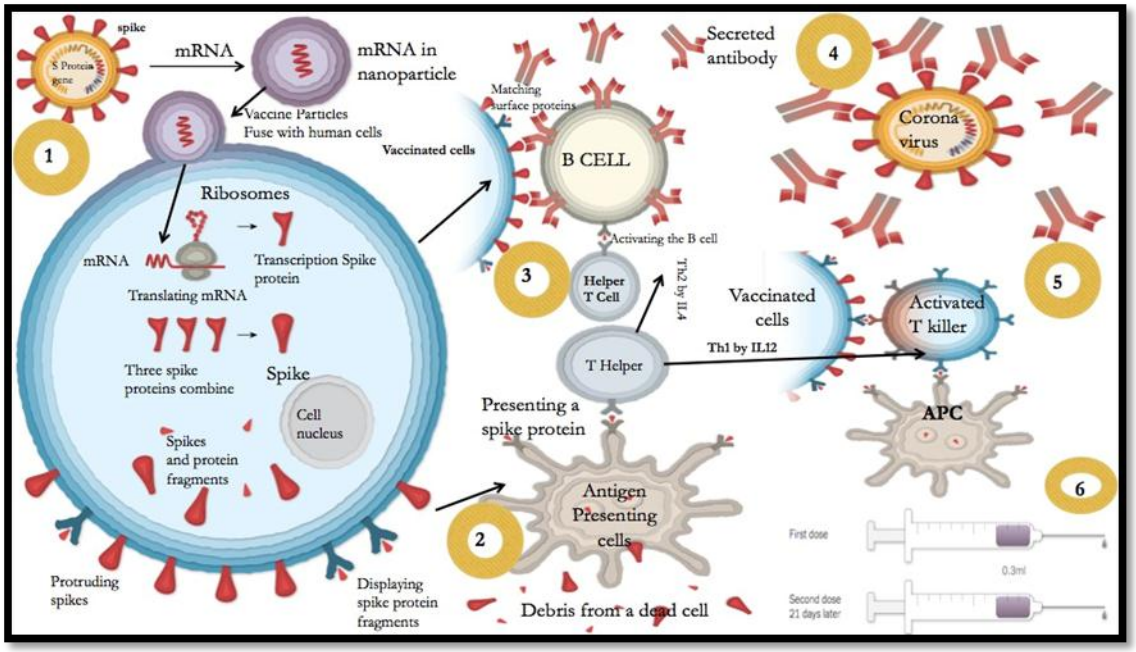

Figure 1: The mechanism of action of mRNA Vaccine, Section1; the virus similar mRNA is prepared and saved in nanoparticle, injected in deltoid muscle cells, mRNA enters the cells, translated by ribosomes, Spike proteins are expressed in the cells and taken by the APC, . In section 2; presented to T helper cells, through Th1, by IL4 B cells are activated, 3, Neutralizing antibodies (NAB) are made by B cells converting to Plasma cells through IL4. IL5, 4, NAB identify the SARS-CoV-2 and binds to the virus to help immune system to destroy it rapidly, and kill it, on the other hand 5; through IL12, cytotoxic immunity through CD-8cells, and 6; dosage of Vaccine.

Possible outcomes of mRNA or spike Proteins after vaccines inoculation

1. Some mRNA may remain in the tissue as naked material
2. Some mRNA taken up by muscle cells
3. Some mRNA taken up by the macrophages
4. Some Spike Proteins (SP) may attach to the ACE-2 receptors.

When a mRNA vaccine is inoculated in muscle (IM), it is exposed to variety of cells at the injection site, like muscle cells, nerve cells, fibroblasts, dendritic cells (DC) and Macrophages (MP) along with T cells and B cells. Dendritic cells are also immigrants of bone marrow which were once monocyte and after migration, they reach skin tissue and stay there in form of dendritic cells. The DC, MP and B cells are classic antigen presenting cells (APC). It is their job to pick up the antigen and present to our immune system. The MP also act as effector cells which help to clear the antigens. When vaccine is given in deltoid muscle, it is taken by these cells.[1-3]

Possibility 1. Some mRNA may remain in the tissue as naked material

When a mRNA vaccine is inoculated intramuscularly, some of the mRNA vaccines nanoparticles remain out of the cells i.e. in interstitial areas, where they are attacked by and quickly digested by tissue ***RNAses*** (enzymes) and are not internalized efficiently. These naked mRNA are not useful for immunity because these would be destroyed by our enzymes. Therefore 2nd dose (booster) is required to maximize our immune response. Some vaccines contain adjuvants in order to overcome this issue, while other vaccines have reported potent response in the absence of known adjuvants.[2]

These naked mRNA are destroyed by RNAses but spike proteins (SP) are taken up by DC, the antigen presenting cells. These SP taken up by macrophages or neutrophils are destroyed through their lysosomal enzymes, and then presented to MCH-II proteins and then to naïve CD4 cells.

Any spikes, if spilled by the action of the T cells, will be picked up by the local dendritic cells and macrophages. These cells will present this antigen on MHC class II complexes to naive T cells. This presentation in turn will start the process of B cell and cytotoxic T cell activation. These Naive cells, through IL4, activate the Th-2 cells, which will activate B cells and under the effect of IL-5 convert these into Plasma cells and memory cells. These cells produce IgG or humoral immunity against SARS-CoV-2 infection. The naive cell activate CD8+ cells and NK cells, through IL2, to activate cellular immunity against SARS-CoV-2 infection.[4-7]

Possibility 2. Some mRNA is not taken up by cells

The mRNA vaccines are instable and their efficiency depend on the intracellular delivery of mRNA, that is why these are wrapped in lipid nanoparticle. Efficient mRNA delivery in human cells is important to obtain the therapeutic success of any vaccine. It is mandatory for this recombinant mRNA to enter in the cells cytoplasm

to translate and make any proteins. The lipid layer in the cell membrane is a barrier. The cell uptake mechanisms depends upon the cell type, and the physicochemical properties of the mRNA used in any vaccine.[4-7]

When these mRNA reach in the cell cytoplasm, these are translated in cell protein manufacturing factories called Ribosomes. Ribosomes will make proteins which are encoded in these mRNA, which are Spike Proteins in case of COVID-19 vaccine. When these spike protein are formed, these do not come out from the cells or reach the nuclear DNA. These are immediately taken up by our proteasome (The primary function of the proteasome is to degrade proteins) which will degrade these Spike proteins into pieces. The newly synthetics Spike proteins can neither reach the nuclear machinery of the human cells nor it can change/control their function.

The broken pieces of SP are taken in the endoplasmic reticulum and then are uploaded with MHC I and II system, through transporter associated with antigen processing (TAP) channels on the endoplasmic reticulum (EPR). The EPR is a large, dynamic structure that serves many roles in the cell including calcium storage, protein synthesis and lipid metabolism. The diverse functions of the EPR are performed by distinct domains; consisting of tubules, sheets and the nuclear envelope (Figure 2)

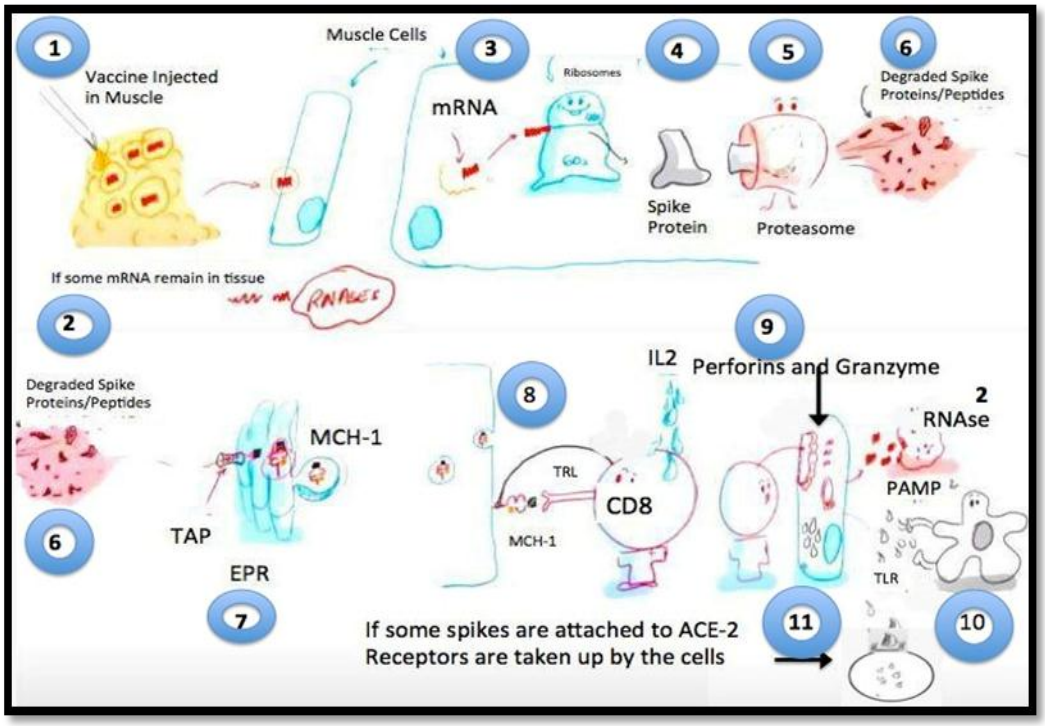

Figure 2: Photomicrograph of the all possibilities shown (1-11), When vaccine is injected (1), is taken by the muscle cells, and read by ribosomes(3), to make spike protein (4), these SP are broken in proteasomes (5) into degraded peptides (6), through TAP pathway are internalized by (7) endoplasmic reticulum (EPR), are expressed by MHC-1 to activate DC-8 cells (8), which contain granzymes and perforins to break the SP (9) into small particles which are read by APC (10). Not a small particle of mRNA or Spike protein remains unchecked, if any small amount of mRNA remains in tissue are broken by tissue RNAses (2), or if few spike proteins are attached to ACE-2 receptors, none of them has capacity to become SARS-CoV-2 because these do not have other structure proteins and a consequence degraded by the cells (11).

In human cells there is a controlled system and not a single piece of antigen is released without proper processing. Spikes are produced inside a cell. These will be presented on MHC class I, dendritic cells and cytotoxic T cells. These CD 8+ cells, with the help of IL-2, identify these antigen uploaded material. These are broken in these CD8+ cells through perforin and granzymes, which will kill these CD8+ cells by releasing few SP and mRNA. (Figure 2)

Possibility 3. The mRNA taken up by the macrophages

These EPR present these uploaded pieces of SP to the macrophages through MHC-II system. Other nucleated cells work through MHC-I system. These SP antigen are taken up by MHC proteins and are loaded with segments of SP antigen. These are then expressed on the cells walls in a controlled manner that not a single piece of SP antigen is left unchecked (Figure 3).[4]

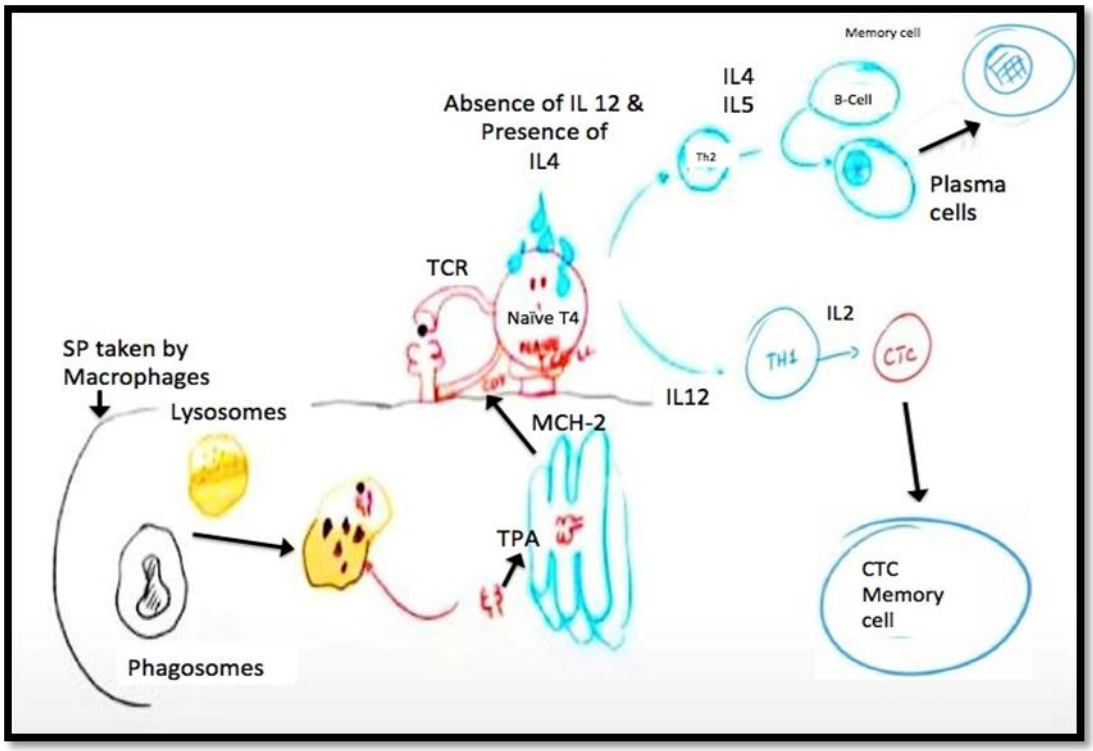

Figure 3: The diagrammatic presentation of whole process, when the spike proteins or products of SP are taken up by Macrophages to activate MCH-2 pathway.

Possibility 4. Some Spike Proteins (SP) may attach to the ACE-2 receptors (Figure 2)

Any antigen still outside cell might bind to the ACE-2 receptors. But that happen at a very low, almost negligible, level. The use of ACE Inhibitor drugs is not required as cells continue to make new enzyme, and the previous enzyme complexes are removed. The spike protein binding to these ACE-2 receptors does not cause disease or symptoms as this happen in negligible amount. Moreover, actual virus causes a disease, not just because of the spike protein but because of the viral antigens produced in cells stimulating the immune system, and by the destruction of the cells which it infects. A vaccine based spike protein cannot offer more antigens that are part of the whole virus, neither can these replicate and infect other cells.[7]

SUMMARY

The vaccines against SARS-CoV-2 are now available in the market and approved for the emergency use to control the transmission of COVID-19. Vaccines such as inactivated vaccines, nucleic acid-based vaccines, and vector vaccines, have already completed clinical trials and have been found to induce immunity against SARS-CoV-2 in all participants, and no trial-limiting safety concerns were reported and these findings will, hopefully, help in controlling the current pandemic.

Spike proteins are produced inside a cell and are presented on MHC class I, dendritic cells and cytotoxic T cells. Spike proteins, if spilled by the action of the T cells, will be picked up by the local dendritic cells and macrophages. These cells will present this antigen on MHC class II complexes to naive T cells. This presentation in turn will start the process of B cells and cytotoxic T cells activation. Any antigen still left over might bind to the ACE-2 receptors. But, that amount will be very low, almost negligible and are removed enzymatically.

Finally, actual SARS-CoV-2 virus continues to produce not only the spikes, but the whole viruses in a large number. A vaccine based spike protein cannot offer more antigens that are part of the whole virus, neither can these replicate nor infect other cells. Hence, these vaccines are safe and effective to control COVID-19 pandemic.

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