EDITORIAL

From Viral Vaccines to Messenger RNA Vaccines

Saeeda Baig[1], Zoha Asghar[2]
[1]Department of Biochemistry, Ziauddin University, [2]Student, Ziauddin University, Karachi, Pakistan.
doi.org/10.36283/PJMD9-2/001

Today, the swiftness of epidemics of infectious disease is alarming. To date vaccines have been an enormous success for not only preventing but completely eradicating a number of malicious infectious disease like small pox, rubella, mumps, measles and polio as well as decreasing the burden of diseases like tetanus, measles and diphtheria etc. Vaccination has been the hallmark of disease control for hundreds of years since it was first tested by English physician Edward Jenner in 1796 and further validated by Louis Pasteur through their work on smallpox vaccine.

Vaccines function by imitating an infectious agent, and by doing so, train our bodies to respond more rapidly and effectively against them. They are either a toxin or surface protein that is identical to the offending microorganism and are made from a killed or inactivated part of the pathogen. By injecting this agent our body achieves a crash course in recognizing the agent as a threat, enabling the immune system to combat the pathogen, destroy them, and lastly, protect our bodies from a future encounter.

Currently, however, the world isfacing a pandemic of the Coronavirus Disease 2019 (COVID-19) and this call for a speedy effective way of controlling the threat of infectious diseases. Anew class of vaccines that are "Ribonucleic acid (RNA) based vaccines" can prove to be more efficacious. Compared to conventional vaccines, this is more vigorous, multi-purpose, yet, equally effective having many advantages such as rapid development (no growth facilities or eggs or insects required), being part of biological sequence of our own blue print Deoxyribonucleic acid (DNA). That is no rejection problem and has multiple utility; it can be antibody or tumor antigen or an enzyme with a capability to replace an enzyme of inborn error. RNA imitates viral infections in several aspects and induces significantly strong immune responses. RNA sensors, in addition, can be triggered to meet the requirements of the individual vaccines by designing RNA-based adjuvants. Above all RNA can be easily produced *invitro* in a cell-free system.

Technological development of successful RNA

Vaccine, with stability and excellent translational ability and all above attributes which are crucial for a vaccine make RNA as a potential adjuvant alternative[1]. Hence, the main goal of groundbreaking research in RNA vaccine technology is pertaining to Messenger Ribonucleic acid (mRNA) stabilization, RNA modification to reveal the process of mRNA vaccine recognition by theimmune cells and to engineer the correct mRNA vaccine in order to ensure a balanced immune response.

How mRNA vaccines will work?

Studies[2] were earlier conducted to develop particles that could effectively deliver mRNAs to required cells and tissues. Some researchers demonstrated Lipid nanoparticles (LNPs) as valuable tools for delivering mRNA. mRNA vaccines when injected against infectious diseases, the body's immune cells will use this RNA sequence of the antigen to synthesize proteins. In essence, mRNA will serve as the software for our body to make the right proteins to trigger an immune responsewith potent T-cell and humoral immune responses. Following this step, the mechanism is identical to the events that occur in the administration of a classical vaccine i.e. the antigen is presented on the cell surface and triggers the activation of specific cells responsible for an immune response.

Sensors called receptors control our body cells. These sensors are of two types, endosomal toll-like receptors (TLRs) and the retinoic acid-inducible gene-I (RIG-I) like receptor family. Toll like receptor are of four types; TLR-3, TLR7, TLR8, and TLR9, localized in the monocytes, dendritic Cells and macrophages. TLR3 qualifies to recognize viral replication intermediates such as double stranded RNAs (dsRNAs) and single strand RNA (ssRNA). Whereas, TLR7 and TLR8 bind the same intermediates but only sense RNAs rich with polyuridine, guanosine or uridine for activation. When TLR7 is activated, itpromotes the secretion of cytokines stimulate B cell response through increasing antigen presentation[3].

Hence, TLR7 is the target for intra dermal vaccination developed by CureVac AG using RNA active vaccine

technology, currently under human trials. The TLR7 signal activation enhances the upregulation of chemokines that recruit the cells of innate immunity, dendritic cells and macrophages, to name a few, to the site of administration[4]. In addition, activation of pro-inflammatory cytokines, IL-6 and TNF-a have also been observed at the site of injection[5]. Researchers also proved that purity of mRNA produces better translation and eliminates immune reaction, which is a requirement for a vaccine[6]. In 2018 a group of researchers characterized and developed vaccine platform, showing modified mRNA encapsulated into lipid nanoparticles (mRNA-LNP vaccines). Their comparative studies demonstrated mRNA-LNP vaccines to be far better compared to other adjuvant proteins and viral vaccines[7]. Following these, a number of publications have proven mRNA-based vaccine to be a new horizon, which is effective, highly modifiable, cost-effective and can be easily developed, transported and stored. Any emerging infectious diseases endemic or pandemic can easily be dealt with effective vaccines, without any distribution or supply issues[8]. Unlike other vaccines or genetically mutated viral vectors, mRNA vaccines do not carryany risk of infection or escape into other systems causing mutagenesis. With its regulated half-life, mRNA degradation by normal cellular responses can be controlled by various modifications in RNA and its delivery systems. It does have some degree of inherent immunogenicity, which can be down regulated to further increase the safety of the vaccine. mRNA is highly translatable which makes it more efficacious. With adequate financing to enhance the production capacity to meet the demands during a pandemic, the RNA vaccine market will only be expanding.

By effectively delivering mRNA through carrier, molecules will allow quick uptake and expression in the cytoplasm. Since, mRNA is a genetic vector, there is minimal to no risk for anti-vector immunity, hence mRNA vaccines can be administered recurrently. Thus, recent developments in the technology for RNA modifications have ensured that mRNA vaccines have the potential for rapid, economical and sizeable manufacturing[9]. It is anticipated that a transition to mRNA vaccines can ensure immunization of the masses and mitigation of the global burden of infectious diseases. Main routes of administration will be direct intramuscular (IM), intradermal (ID) or subcutaneous injection. While, intraperitoneal (IP) and intravenous (IV) administration will be employed where therapeutic applications are required such as in cancers[2].

REFERENCES

1. Ziegler A, Hinz T, Kalinke U. RNA-based adjuvants: immunoenhancing effect on antiviral vaccines and regulatory considerations. Crit Rev Immunol. 2019;39(1):1-14.
2. Pardi N, Tuyishime S, Muramatsu H, Kariko K, Mui BL, Tam YK, et al. Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. Journal of Controlled Release. 2015;217:345-51.
3. Ablasser A, Poeck H, Anz D, Berger M, Schlee M, Kim S, et al. Selection of molecular structure and delivery of RNA oligonucleotides to activate TLR7 versus TLR8 and to induce high amounts of IL-12p70 in primary human monocytes. J Immunol. 2009;182(11):6824-33.
4. Kallen KJ, Heidenreich R, Schnee M, Petsch B, Schlake T, Thess A, et al. A novel, disruptive vaccination technology: self-adjuvanted RNActive® vaccines. Hum Vaccin Immunother. 2013;9(10):2263-76.
5. Lutz J, Lazzaro S, Habbeddine M, Schmidt KE, Baumhof P, Mui BL, et al. Unmodified mRNA in LNPs constitutes a competitive technology for prophylactic vaccines. NPJ Vaccin. 2017;2(1):1-9.
6. Kariko K, Muramatsu H, Ludwig J. Weissman D. Generating the optimal mRNA for therapy: HPLC purification eliminates immune activation and improves translation of nucleoside-modified, protein-encoding mRNA. Nucleic Acids Res. 2011;39(21):e142.
7. Pardi N, Hogan MJ, Naradikian MS, Parkhouse K, Cain DW, Jones L, et al. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. J Experiment I Med. 2018;215(6):1571-88.
8. Zhang C, Maruggi G, Shan H, Junwei Li. Advances in mRNA Vaccines for Infectious Diseases. Front Immunol. 2019;10:594.
9. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261.

 doi.org/10.36283/PJMD9-2/001