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Vaccine

Volume 41, Issue 35, 7 August 2023, Pages 5182-5194

COVID-19 mRNA vaccines as hypothetical epigenetic players: Results from an *in silico* analysis, considerations and perspectives

Rossella Talotta

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https://doi.org/10.1016/j.vaccine.2023.07.007

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Abstract

Objectives

To investigate in silico the occurrence of epigenetic crosstalk by nucleotide sequence complementarity between the BNT162b2 mRNA vaccine and whole human genome, including coding and noncoding (nc)RNA genes. To correlate these results with those obtained with the original spike (*S*) gene of Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2).

Methods

The publicly available FASTA sequence of the BNT162b2 mRNA vaccine and the SARS-CoV-2 isolate Wuhan-Hu-1 *S* gene (NC_045512.2) were used separately as key input to the Ensembl.org library to evaluate base pair match to human GRCh38 genome. Human coding and noncoding genes harboring hits were assessed for functional activity and health effects using bioinformatics tools and GWAS databases.

Results

The BLAT analysis against the human GRCh38 genome revealed a total of 37 hits for BNT162b2 mRNA and no hits for the SARS-CoV-2 *S* gene. More specifically, BNT162b2 mRNA matched 19 human genes whose protein products are variously involved in enzyme reactions, nucleotide or cation binding, signaling, and carrier functions.

In BLASTN analysis of ncRNA genes, BNT162b2 mRNA and SARS-CoV-2 *S* gene matched 17 and 24 different human genomic regions, respectively. Overall, characterization of the matched noncoding sequences revealed stronger interference with epigenetic pathways for BNT162b2 mRNA compared with the original *S* gene.

Conclusion

This pivotal *in silico* analysis shows that SARS-CoV-2 *S* gene and the BNT162b2 mRNA vaccine exhibit Watson-Crick nucleotide complementarity with human coding or noncoding genes. Although they do not share the same complementarity pattern, both may disrupt epigenetic mechanisms in target cells, potentially leading to long-term complications.

Introduction

Since December 2020, the launch of a massive vaccination campaign is giving much hope in containing the global COronaVIrus Disease-19 (COVID-19) pandemic. To shorten the time, two mRNA vaccines formulated with a new technology have been made rapidly available and widely administered in the population [1], [2]. Both the BNT162b2 mRNA vaccine and the mRNA-1273 vaccine, produced by Pfizer/BioNTech and Moderna, respectively, encode the spike (S) protein of Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), but the original nucleotide sequence has been modified to improve pharmacological properties [3]. Modifications include two amino acid substitutions at sites 986 and 987 to keep the protein in the prefusion state and replacement of uridine with N1-methylpseudouridine to prevent degradation of the mRNA molecules by endoribonucleases [3]. The two mRNA formulations are injected into the deltoid muscle at repeated intervals. Recently, the administration of additional doses after the first cycle of two injections was found to be necessary because of a time-dependent decrease in efficacy [4]. The mechanism of action of this revolutionary technology is to provide cells with S mRNA, which is used as a template for the synthesis of S proteins and subsequent immunization. This idea assumes that S-producing cells pass antigens to dendritic cells or behave themselves as antigen-presenting cells (APCs), which digest the S protein, couple epitopes to major histocompatibility complex (MHC) in the endoplasmic reticulum, and finally present them to lymphocytes. However, mRNA vaccines are administered in liposomes that are not tissue- or cell type-specific in vivo. Thus, they may fuse with the plasma membrane of muscle fibers rather than being transported to professional APCs [5]. When transported into skeletal muscle fibers, it is likely that mRNA vaccines can epigenetically interfere with essential cellular processes. Indeed, cytosolic nucleic acids can trigger a cascade of events in host cells, ranging from stress response to autophagy and cell death [6].

Some recent reports have indicated the possibility of skeletal muscle damage after COVID-19 vaccination [7], [8], [9]. Conversely, administration of an inactivated viral vaccine against SARS-CoV-2 had no adverse effects in patients with previously diagnosed autoimmune inflammatory myopathies, but such findings may be related to concurrent iatrogenic immunosuppression, at least in terms of prevention of the pro-inflammatory pathways triggered [10].

Moreover, foreign mRNAs in the cytosol can complement with host cell noncoding (nc)RNAs and orchestrate a complex crosstalk that may ultimately lead to disease. In a previous computational analysis, we showed that each of the RNA genes of SARS-CoV-2 has sequence homology to more than 100 human ncRNA transcripts [11], [12].

The clinical significance of such complementation is unclear, but related signaling pathways have been reported to play critical roles in the development of several diseases, including neurological and cardiovascular disorders, cancer, and autoimmunity. Given this similarity, it may be plausible that mRNA vaccines encoding the SARS-CoV-2 S protein engage in epigenetic crosstalk with human genes and transcripts with potential health implications.

Using *in silico* analysis, the aim of this work was therefore to investigate the existence of nucleotide sequence complementarity between the BNT162b2 mRNA vaccine and the whole human genome, including coding and ncRNA genes, and to correlate these results with those obtained with the original SARS-CoV-2 *S* gene sequence.

Section snippets

Identification of human coding and ncRNA genes complementary to BNT162b2 mRNA vaccine and SARS-CoV-2 *S* gene

Only the Pfizer/BioNTech's BNT162b2 mRNA vaccine, whose FASTA sequence is publicly available at https://web.archive.org/web/20210105162941/https://mednet-communities.net/inn/db/media/docs/11889.doc, was used for analysis. For analytic purposes, the nucleotide 1-methylpseudouridine was replaced with uridine throughout the sequence.

The FASTA sequence (NC_045512.2) of the SARS-CoV-2 isolate Wuhan-Hu-1 *S* gene was instead retrieved from the website https://www.ncbi.nlm.nih.gov/gene/?term=NC_045512....

Hits in human GRCh38 (genomic sequence) to BNT162b2 mRNA vaccine

BLAT analysis revealed a total of 37 hits between the BNT162b2 mRNA sequence and the human genome, Supplementary Table 1. More specifically, BNT162b2 mRNA matched 19 human genes whose protein products are variously involved in nucleotide-binding, cation-binding, enzyme reactions, signaling, and carrier functions, Table 1. In particular, BNT162b2 mRNA harbors 100 & identity extending for 139 nucleotides to the mitochondrial genomic region MT:759-897, which overlaps with the MT-RNR1 gene. This…

Discussion

The results of this study suggest that COVID-19 BNT162b2 mRNA vaccine may establish epigenetic crosstalk within human recipient cells by base pairing with nucleotide sequences of coding and noncoding genes. Surprisingly, the patterns of sequence complementarity to the human genome of BNT162b2 mRNA encoding the trimeric form of the S protein of SARS-CoV-2 differed from those of the original SARS-CoV-2 *S* gene. Indeed, BLAT analysis against the human GRCh38 genome sequence yielded a total of 37…

Conclusions

This pivotal *in silico* analysis demonstrates that both the *S* RNA gene of SARS-CoV-2 and the BNT162b2 mRNA vaccine encoding the S protein share Watson-Crick nucleotide complementarity with human coding and noncoding genes that, while not sharing the same complementarity pattern, may hypothetically cause epigenetic imbalance of target genes and the ultimate development of long-term complications. Further research is needed to better elucidate the epigenetic effects of BNT162b2 vaccine and, more…

CRediT authorship contribution statement

Rossella Talotta: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing.…

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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