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Cell Biology Techniques in COVID-19 Vaccine Developments

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Abstract. With the outbreak of the COVID-19 pandemic, the SARS-CoV-2 virus began to spread rapidly, posing an unprecedented challenge to global public health. In the battle against the virus, the rapid development of vaccines and cell biology techniques has played a key role. They have enabled researchers to identify potential vaccine targets based on the cellular characteristics of the virus, thereby accelerating the vaccine development process. Currently, mRNA vaccines and viral vector vaccines have been put into use around the world, but they still face some technical challenges, especially long-term efficacy and immune escape. This paper analyzes the application of cell biology techniques in the development of COVID-19 vaccines and discusses the latest research progress from traditional cell culture techniques to mRNA and viral vector technologies. The research not only provides valuable references for future vaccine development but also reveals the shortcomings of current technologies in long-term immunity and production efficiency. Future research can further optimize these technologies, especially in the areas of vaccine scalability and immune responses.

Keywords: COVID-19 vaccines, Cell biology techniques, mRNA vaccines.

1. Introduction

Since late 2019, the COVID-19 outbreak, which was brought on by the coronavirus SARS-CoV-2, has posed an unprecedented risk to public health worldwide. As the virus quickly spread globally, there was an urgent demand for a rapid and effective vaccine to reduce the infection rate. During the process of inventing new vaccines, cell biology, the core of understanding cellular function, interaction, and response to infectious agents, has played a critical role. Getting an insight into the virus at the cellular level has helped researchers identify potential therapeutic targets and facilitated the quick development of vaccines.

At the beginning of the pandemic, scientists promptly sequenced the virus genome and analyzed the structure of SARS-CoV-2 to determine how it enters human cells. The coronavirus contains four principal structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) [1]. The S protein is crucial for viral entry as it attaches to the host cell receptor Angiotensin-converting enzyme 2 (ACE2), enabling the virus to penetrate the cell. Viral entry is a critical process that has been studied in cellular biology. According to a study on process of SARS-CoV-2 into cells, it stated that the binding of the spike protein to ACE2 triggers its activation by host-derived proteases like TMPRSS2, which facilitates the fusion with the host cell membrane [2]. Once inside the cell,

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SARS-CoV-2 unloads its RNA genome, which takes control of the cell's molecular machinery to generate viral proteins and construct new virus particles. The virus forms replication-transcription complexes within specialized compartments derived from the endoplasmic reticulum, enabling efficient replication [3]. Not only does this allow replication to proceed efficiently, but it also allows the virus to evade immune detection, further showing how deeply virus behavior is linked to the internal structure and function of host cells.

Building on this knowledge, cell biology techniques were applied in practical ways to develop vaccines. This included using cell lines, like HEK293 or Vero cells, to produce viral proteins, making in vitro measurements of immune response, and developing mRNA and viral vector delivery systems that operate in human cells. The successful application of these methods demonstrated the essential role of cellular models and tools, not just for understanding the nature of a virus, but also for combating it.

This paper will first explore the structural and cellular biological characteristics of the coronavirus, followed by practical examples of how cell biology technologies were used in COVID-19 vaccine development, such as traditional technique, vector vaccine and mRNA technique. These aspects show how cell biology not only supported basic research but also accelerated real-world medical breakthroughs.

2. The structure and cellular biological characteristics of the coronavirus

2.1. Basic structural components of the coronavirus

SARS-CoV-2 is a large, enveloped, positive-sense single-stranded RNA virus with a genome approximately 30 kilobases long [1]. The virus is consist of four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N), as shown in figure 1.

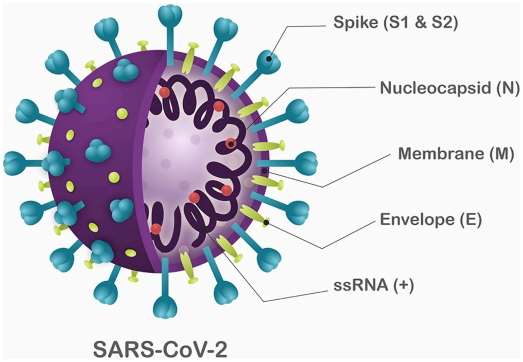

Figure 1. SARS-CoV-2 structure diagram [4]

The S protein is a large trimeric glycoprotein that protrudes from the viral surface and mediates host cell entry by binding to the ACE2 receptor. It is composed of two segments: S1, which includes the receptor-interacting domain (RBD), and S2, which enables membrane merging [1].

The M protein, the most prevalent element of the virion, plays a central role in maintaining the virion's shape and coordinating viral assembly by interacting with other structural proteins like N protein and S protein. The E protein, though present in small quantities, is essential for virion assembly and release. It is thought to function as a viroporin, which contributes to membrane curvature and viral budding [1].

The N protein attaches to the viral RNA to create a spiral-shaped ribonucleoprotein complex, which is encapsulated within the lipid membrane. This protein also participates in genome

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packaging and modulates host cellular responses [1].

2.2. Mechanism of viral entry into the host cells

SARS-CoV-2 enters human cells using a highly coordinated process involving both viral and host proteins. The key to this process is the viral spike glycoprotein. Before the virus encounters a host cell, the spike protein is partially activated by a host enzyme called furin, which cuts it into S1 and S2 (Figure 2).

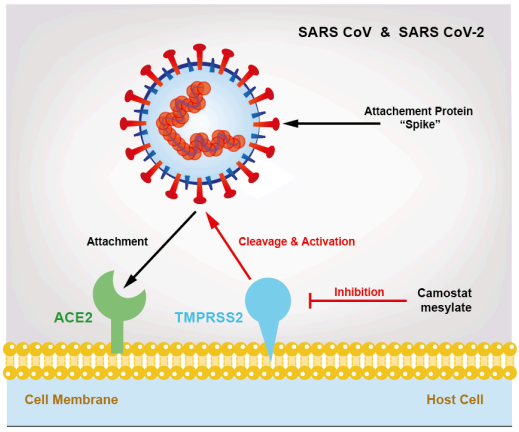

Figure 2. Process of viral entry into the host cell [5]

When the virus approaches a target cell, the S1 subunit binds to ACE2, which is especially abundant in lung and intestinal cells. This binding triggers a change in the shape of S, revealing a second critical site on S2 called S2′. This site must also be cleaved by a cell-surface enzyme called Transmembrane serine protease 2 (TMPRSS2). This second cut activates the fusion machinery in S2, allowing the virus to merge its outer membrane with the cell's membrane [2].

After that, there are two main entry pathways into the host cell. If TMPRSS2 is present, the virus fuses directly at the cell surface. If not, the virus and ACE2 receptor are brought into the cell through endocytosis, and fusion will happen inside the acidic compartments called endosomes [2]. In both routes, once fusion occurs, the virus delivers its RNA genome into the cytoplasm of the host, where infection occurs.

2.3. Replication and assembly inside the host cell

After entered and uncoating, the coronavirus releases its plus-strand RNA genome into the cytosol. It then immediately binds to host ribosomes and begins translation, resulting in the synthesis of two extensive polyproteins, pp1a and pp1ab. They undergo proteolytic processing by viral proteases, yielding approximately 16 nonstructural proteins (NSPs). They then assemble to form the replication-transcription complex (RTC), which is responsible for generating a minus-strand RNA [3]. It functions as a template for producing new copies of the plus-strand RNA genome and a set of sub genomic RNAs encoding structural proteins.

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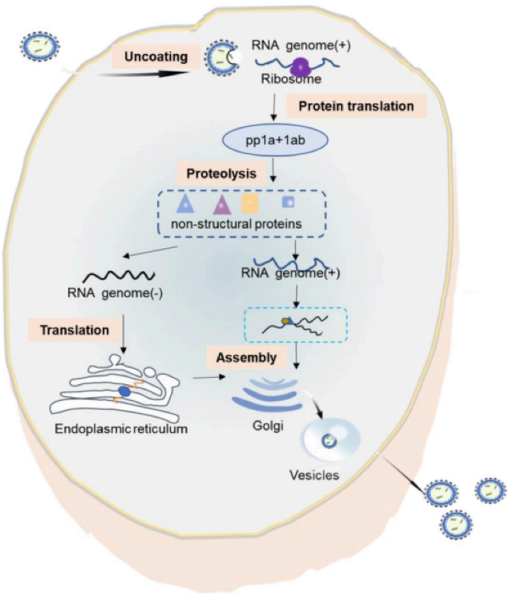

Figure 3. Replication process inside the host cell [6]

During genome replication, the structural proteins, including S, M, E, and N, are translated using host ribosomes on the rough endoplasmic reticulum (ER). According to Figure 3, these structural proteins are then transported through the Golgi apparatus. Meanwhile, the new RNA genomes associate with N proteins to form ribonucleoprotein complexes. Within the endoplasmic reticulum–Golgi intermediate compartment (ERGIC), they come together with the membrane-bound S, E, and M proteins to initiate the assembly of new viral particles.

Once assembled, the complete virions are packaged into vesicles that bud off from the Golgi and move toward the cell membrane. The virus is then released from the host cell via exocytosis, a process in which the vesicle merges with the plasma membrane, discharging fully formed virions into the surrounding extracellular environment. The new viruses are then capable of infecting neighboring cells.

The replication and assembly process is a coordinated interaction between viral and host cells. It allows the virus to efficiently reproduce while hiding parts of its life cycle within membrane-bound compartments, which help it evade immune detection.

3. Applications of cell biology in COVID-19 vaccine development

3.1. Traditional cell biology techniques in vaccine development

Traditional cell biology techniques have been fundamental in the development of vaccines. It enables researchers to study viral behavior, evaluate immune responses, and identify potential antigens for vaccine formulations. These methods have laid the groundwork for future vaccine development.

Cell culture systems are pivotal in vaccine development, serving as platforms for virus propagation and antigen production. For instance, the Vero cell line, which originates from African green monkey kidney cells, has used for producing inactivated vaccines. A notable example includes the creation of a whole-virus H5N1 influenza vaccine using Vero cells, which demonstrated high immunogenicity and cross-neutralizing antibody production without the need for adjuvants [7]. Similarly, HEK293 cells, originating from human embryonic kidney cells, are utilized for producing

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recombinant proteins and viral vectors [8]. These cells have been instrumental in developing vaccines for diseases like rabies and Ebola, where they facilitate the expression of viral glycoproteins necessary for inducing immune responses [8].

Additionally, assessing the immune response to vaccine candidates is crucial for determining their efficacy. Traditional assays, such as neutralization tests, involve exposing cultured cells to the virus in the presence of serum from vaccinated individuals. The reduction in viral infectivity indicates the presence of neutralizing antibodies. For example, the potency of the Dengvaxia® dengue vaccine was evaluated using HEK293T cells, where sera from vaccinated subjects achieved a 50 % focus reduction neutralization titer ($FRNT_{50}$) of approximately 1:128 (range 1:64–1:256) against all four dengue serotypes, and over 80% plaque reduction at serum dilutions of 1:40, confirming robust cross neutralizing activity and validating the use of human cell lines for potency assays [9].

3.2. Cell biology techniques in viral vector vaccine development

Viral vector vaccines, specifically, the AstraZeneca and Johnson & Johnson COVID-19 vaccines, apply modified viruses to transfer genetic information encoding antigens into host cells to trigger an immune reaction. The development of these vaccines relies on advanced cell biology techniques, including genetic engineering, cellular transfection, and viral packaging.

The foundation of viral vector vaccines lies in the modification of viral genomes to carry specific genetic material. For instance, adenoviruses are engineered by deleting essential genes such as E1 and E3 to render them replication-deficient. This modification ensures safety by preventing the virus from replicating within the host cell. Subsequently, the gene encoding the SARS-CoV-2 S protein is incorporated into the adenoviral genome. This design allows the host cell to synthesize S protein that elicits an immune response without causing disease. The Oxford-AstraZeneca vaccine employs a chimpanzee adenovirus vector, while the Johnson & Johnson vaccine employs a human adenovirus type 26 vector [10].

Once the viral vector is constructed, it will be introduced into host cells to produce the vaccine. Cellular transfection involves delivering the recombinant adenoviral DNA into packaging cells, such as Human embryonic kidney cells (HEK293). These cells are chosen because they can support the replication of adenoviral vectors due to their expression of the E1 gene, which is necessary for viral replication. Once inside, the cells will produce the adenoviral particles containing the spike protein gene. After transfection, the packaging cells are cultured to allow the amplification of the recombinant adenoviral vectors. These vectors are then harvested and purified for use in vaccine formulations.

These methods not only facilitate the rapid development of vaccines in response to emerging infectious diseases but also ensure the use of safety and efficacy.

3.3. Emerging cell biology techniques in mRNA development

The development of mRNA vaccines for COVID-19, such as Pfizer-BioNTech and Moderna, has been significantly advanced by emerging cell biology techniques. These innovations have addressed challenges related to mRNA stability and immune system activation.

Lipid nanoparticles (LNPs) shield mRNA from enzymatic breakdown and assist in its entry into human cells. LNPs encapsulate mRNA and enhance its stability and cellular uptake. Upon administration, they are engulfed by cells through endocytosis, and the acidic environment within endosomes triggers the ionizable lipids to become positively charged, facilitating the release of

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mRNA into cytoplasm. This mechanism is crucial for the efficacy of mRNA vaccines, as it ensures the mRNA reaches its target site within the cell for protein synthesis [11].

Advancements in high-throughput screening and single-cell RNA sequencing have provided deeper insights into the immune responses elicited by mRNA vaccines. High-throughput screening allows for the rapid evaluation of numerous mRNA constructs and delivery systems, identifying those with the most promising efficacy profiles. The sequencing will allow researchers to examine gene expression in each cells. It reveals how different cell types respond to mRNA vaccines and identifies biomarkers associated with robust immune responses. These techniques have been essential in refining vaccine designs to enhance their effectiveness against COVID-19.

4. Conclusion

The advancement of COVID-19 vaccines demonstrated the role of cell biology in combating global health crises. Understanding the structural and cellular properties of SARS-CoV-2 was essential for developing targeted vaccines. Cell biology techniques provided insights into how the virus's mechanism cooperated with the immune system, which allow researchers to design vaccines that target the S protein.

Throughout the development of COVID-19 vaccines, traditional cell biology techniques, such as cell culture systems and immune assays, were fundamental in studying viral behavior and assessing immune responses. These methods paved the way for more advanced approaches, including the development of viral vector vaccines and mRNA technology, which further facilitated the safe and efficient production of vaccines, ensuring their large-scale availability.

However, while the success of these vaccines is a major achievement, there are still ongoing efforts to improve mRNA stability and long-term efficacy. Additionally, the use of viral vectors faces limitations due to pre-existing immunity in some individuals. As the world prepares for future health crisis, continued research into these technologies will be important for improving vaccine development and ensuring rapid, global responses to emerging infectious diseases.

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