Possibility to Interfere with Coronavirus RNA Replication Analyzed by Resonant Recognition Model

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Abstract: To be able to design vaccine or even a cure for COVID-19, it is particularly important to understand how SARS-CoV-2, as a single stranded RNA virus, is multiplied within host cells and which factors are controlling this multiplication. Here, we have analyzed the process of coronavirus RNA replication within host cell with the aim to find out the characteristics of this process. For that purpose, we have utilized the Resonant Recognition Model (RRM), which is biophysical model capable of identifying parameters (frequencies) related to specific macromolecular (protein, DNA, RNA) functions and/or interactions. The RRM model is unique with its capability to directly analyze interactions between amino acid macromolecules (proteins) and nucleotide macromolecules (DNA, RNA). Using the RRM model, we have identified parameters that characterize two steps in coronavirus RNA replication i.e., initiation of replication and replication by itself. These parameters can be used in our future research to design peptides, that will be able to interfere with either or both of those processes.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Coronavirus RNA Replication, Resonant Recognition Model

Introduction

Current COVID-19 pandemic is caused by SARS-CoV-2 virus, which belongs to group of single-stranded RNA viruses, more specifically coronaviruses. Coronaviruses are widely spread in nature, mostly infecting animals, but some can infect humans as well, usually with mild or non-existent symptoms [1]. However, there have been so far three instances where coronaviruses had infected humans causing severe symptoms, including SARS (Severe Acute Respiratory Syndrome, 2003), MERS (Middle East Respiratory Syndrome, 2012) and COVID-19 (2019-nCoV or SARS-CoV-2, 2019). While SARS and MERS outbreaks were within relatively limited areas of population in China and Middle East respectively, SARS-CoV-2 caused worldwide pandemic. In addition, SARS and MERS have been less infectious, but with higher mortality rate, while coronavirus SARS-CoV-2 is more infectious, but with lower mortality rate [2].

With the worldwide COVID-19 pandemic there is question if it is possible to design coronavirus vaccine or even cure. Firstly, it is particularly important to understand how SARS-CoV-2, as single-stranded RNA virus, is multiplied within host cells and which factors are controlling this multiplication. Infection begins when the viral spike protein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, this cleavage and activation process allows the virus to enter the host cell [3].

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm [4]. The coronavirus RNA genome has a 5' methylated cap and a 3' polyadenylated tail, which allows viral RNA to attach to the host cell's ribosome for translation [4]. The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a long polypeptide. The polypeptide has its own proteases, which cleave the polypeptide into multiple non-structural proteins [4]. Thus, there are two points to attack the virus, either to prevent its entry into the host cell, or to prevent its replication within the host cell. Here, we will concentrate to prevent replication within the host cell. Once, when the virus has entered the host cell, the most appropriate chance to prevent and find cure for the further infection is to prevent viral RNA translation. It is well known for initiation of RNA replication 5’ and 3’ noncoding parts of RNA could be critical in controlling RNA replication, as pointed out in ref [5]: “the nucleotide sequence of the 5’ non-coding region of messenger RNAs is particularly interesting because it may contain the signals for processing and modification of mRNA, such as its cleavage from precursor and ‘capping’ (the addition of the 5’ terminal m7Gppp) and possible recognition and binding sites for ribosomes and initiation factors”. Thus, we propose that interfering with RNA replication regulation through 5’ noncoding segment could be possible way of preventing RNA virus replication.

Activation of 5’ and 3’ noncoding control segments of RNA is done by binding with specific RNA related
proteins. One possible approach to understand this interaction process is to investigate function of argonaute proteins which are key players in small-RNA-guided gene regulation. Argonaute proteins are highly specialized small-RNA-binding proteins that coordinate downstream gene-silencing events and thus are considered to be the key components of RNA silencing pathways [6]. Recent work has made progress in understanding of argonaute-mediated gene-silencing principles, such as the effects on mRNA translation and decay, but has also implicated the argonaute proteins in several other cellular processes, such as transcriptional regulation and splicing [7]. In summary, argonaute proteins which consist of groups: AGO1, AGO2, AGO3 and AGO4, are highly specialized small-RNA-binding proteins driven by small RNAs to complementary target mRNAs, where they act together with protein binding partners to interfere with translation of target mRNAs. During virus infection individual functions of the mammalian antiviral RNA interference (RNAi) and micro-RNA (miRNA) effector proteins like argonautes (AGO1–AGO4) have been investigated showing that AGO4 has uniquely antiviral function in mammalian cells and has evolved to obtain antiviral RNAi [8].

In addition, there are number of RNA-dependent RNA polymerases that use RNA as their template for synthesis of a new strand of RNA. For instance, number of RNA viruses (such as poliovirus) use this type of enzyme to replicate their genetic material [9]. Also, RNA-dependent RNA polymerase is part of the RNA interference pathway in many organisms [10]. Of particular interest is viral replicase as well, which is enzyme that coordinates and mediates process of RNA synthesis [11].

On the other hand, there is number of 294 antibodies against SARS-CoV-2 mostly neutralizing SARS-CoV-2 by blocking its binding to ACE2 receptor, where the most prevalent of those antibodies is IGHF3-53 [12]. Besides the fact that IGHF3-53 antibody can prevent viral spike protein interaction with ACE2 receptor, we will investigate here its possible interaction with RNA regulatory 5’ segment and its possible role in preventing viral replication.

Baring all this in mind, we propose that interfering with RNA replication regulation through RNA directed transcriptase and viral replicase or through 5’ signal sequences within non-coding region of mRNA could be possible way of preventing RNA virus replication. Here, we have utilized our own biophysical Resonant Recognition Model (RRM) [13-20], which is capable of directly analyzing interaction between proteins and RNA [21-22], to analyze interaction between argonaute proteins, antibody IGHF3-53 and related RNA regulatory 5’ signal sequences within non-coding region of mRNA with the aim to find out characteristic frequencies for initiation of viral replication. In addition, we have analyzed RNA replication through RNA directed transcriptase and viral replicase to identify characteristics of RNA viral replication by itself. Once when these RRM characteristics are identified, it is possible to further utilize the RRM model to design peptides, which would be able to interfere with initiation of viral replication and/or directly interfere with viral replication to possibly prevent virus multiplication within the host cell.

**Methods**

**Resonant Recognition Model**

The Resonant Recognition Model (RRM) is biophysical, theoretical model that can analyze interactions between proteins and their targets, which could be other proteins, DNA, RNA, or small molecules. The RRM has been previously published in detail within number of publications [13-20]. The RRM model is based on the findings that certain periodicities (frequencies) within the distribution of energy of delocalized electrons along protein backbone are critical for protein biological function and/or interaction with their targets. The distribution of delocalized electrons energies is calculated by assigning each amino acid specific physical parameter representing the energy of delocalized electrons of each amino acid. Consequently, the spectral characteristics of such energy distribution (signal) are calculated using Fourier Transform. This means that the linear numerical signal representing the distribution of energies along the protein is transformed into the frequency domain and is characterized by number of different frequencies containing all information from the original signal. Comparing such spectra using cross-spectral function for proteins, which are sharing the same biological function/interaction, it has been shown that they share the same frequency within the spectrum of free energy distribution along the macromolecule [13-20]. Peak frequencies in such multiple cross-spectral function present common frequency components for all macromolecular sequences compared. The comprehensive analysis done so far confirms that all macromolecular sequences, with the common biological function and/or interaction, have common frequency component, which is specific feature for the observed biological function/interaction [13-20]. Thus, each specific macromolecular biological function/interaction within macromolecule is characterized by specific RRM frequency.

Each biological function is driven by proteins that selectively interact with other proteins, DNA/RNA regulatory segments or small molecules. Through extensive use of RRM model, it has been shown that proteins and their targets share the same matching
RRM characteristic frequency [13-24]. The matching of periodicities within the distribution of energies of free electrons along the interacting proteins can be regarded as the resonant recognition and as such is highly selective. Thus, the RRM frequencies characterize not only protein function, but also recognition and interaction between protein and its targets: proteins (receptors, binding proteins, and inhibitors), DNA/RNA regulatory segments or small molecules. In addition, it has been also shown that interacting macromolecules have opposite phases at their characteristic RRM recognition frequency [13-20]. Every frequency can be presented by one sinusoid characterized with its three parameters: frequency, amplitude, and phase. The phase is presented in radians and can be between $-\pi$ and $+\pi$ ($\pi$ and $+\pi$). The phase difference of or about $\pi$ is considered to be opposite phase. The phase value can be presented in the phase circle where it is visually easier to observe phase differences.

The RRM model is unique approach, where it is possible to analyze interactions directly computationally between amino acid sequences (proteins) and nucleotide sequences (DNA and RNA), based only on matching frequencies within free electron energy distribution along these macromolecules. However, for the comparison of characteristic frequencies between proteins and DNA/RNA macromolecules, it is required to adjust for the difference in distances between amino acids (3.8Å) and nucleotides (3.4Å) along the macromolecular backbone. These adjustments are made on nucleotide sequences spectrum, so the result could be compared with frequency calculations made for the proteins. These calculations enable the RRM to be the unique model capable of analyzing and directly comparing activities and interactions of proteins, DNA and RNA by identifying their characteristic frequencies, as tested, and described in number of previous publications [13-16,21-22].

Once the characteristic frequency for biological function and/or interaction of the macromolecule is identified, it is possible to design new peptides/proteins with the desired RRM frequency components and consequently with desired biological functions and/or interactions [13-16,25-30]. This design approach has already been successfully applied and experimentally tested in the design of FGF analogue [25], HIV envelope protein analogue [26-28] and peptide to mimic myxoma virus oncolytic function [29-30].

As viruses are mutating their proteins, DNA and/or RNA very quickly, it is extremely hard to design general cure or vaccine. This explains why current approaches based on macromolecular homology are not successful enough for different viral strains. However, even when viruses are mutating so often and so quickly, they will still keep their specific functionality. It is important to understand that the RRM model is particularly efficient when it is applied to viruses, because the RRM model identifies the common characteristic parameter(s) for all mutated viruses, related to specific common virus protein’s biological function. Thus, the RRM analysis of viruses does not depend on virus mutations, as long as they keep their functionality. This RRM approach has been experimentally tested on the example of HIV virus, which is continuously mutating, but all isolates keep the same functionality, as well as common RRM characteristic frequency [26-28].

**Results**

Here, we have focused on analysis of coronavirus RNA virus replication after virus enters the host cell. At that moment protease of the host cell cleaves and activates spike protein and the complete viral RNA becomes uncoated with its RNA genome entering the cell cytoplasm [4]. This is the critical point for further viral multiplication within the host cell. If it is possible to interfere at this critical point to disable viral multiplication it would prevent the development of related disease. The viral multiplication can be prevented by either interfering with initiation of viral RNA replication or directly by interfering viral RNA replication by itself.

Signal sequence within 5’ non-coding region of mRNA is particularly interesting for initiation of viral RNA replication [5]. When we have analyzed 5’ signal sequences within non-coding region of viral mRNA from different SARS coronavirus isolates, from UniProt database (MN938384.1, MN975262.1, MN985325, MN988668.1, MN988713, MN994467, MN994468, MN997409, MT072688.1, NC_045512.2), using the RRM, the most prominent common RRM frequency has been found at f1=0.0234±0.0043, as presented in Figure 1.
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Figure 1. RRM cross-spectrum of 5’ signal sequences within non-coding region of viral mRNA different SARS coronavirus isolates with common characteristic frequency at f1=0.0234±0.0043.

This common frequency f1 could be proposed to characterize functionality of 5’ signal sequence, which allows viral RNA to attach to the host cell ribosome and is critical for initiation and control of viral RNA replication [5].

In addition, as it has been pointed out in Introduction, argonaute proteins (AGO1, AGO2, AGO3, AGO4) have a role in mRNA translation, transcriptional regulation, and splicing [6-7]. In particular, AGO4 protein has uniquely antiviral function in mammalian cells [8]. Thus, we propose that argonaute (AGO4) protein function is related to activation of 5’ signal sequences within non-coding region of viral mRNA. When we compared 5’ signal sequences within non-coding region of viral mRNA from different SARS coronavirus isolates with mammalian AGO4 proteins, from UniProt database (Q9ZVD5, Q5ZMW0, Q9HCK5, Q8CJF8, Q9SDG8, Q0JF58, Q4KLV6), using the RRM, the same even more prominent common RRM frequency has been found at f1=0.0234±0.0043, as presented in Figure 2.

Figure 2. RRM cross-spectrum of 5’ signal sequences within non-coding region of viral mRNA from different SARS coronavirus isolates and mammalian AGO4 proteins with common characteristic frequency at f1=0.0234±0.0043.

It is interesting to note that there is one unique common characteristic frequency for 5’ signal sequences within non-coding region of viral mRNA and argonaute (AGO4) proteins indicating the possibility that initiation of viral RNA replication involves host AGO4 proteins and viral 5’ signal sequences within non-coding region of viral mRNA.

On the other hand, as explained in Introduction, there is large number of antibodies against SARS-CoV-2, where the most prevalent one is IGHF3-53 [12]. Besides the fact that IGHF3-53 antibody can prevent viral spike protein interaction with ACE2 receptor, we have investigated here possible interaction of IGHF3-53 antibody with viral RNA regulatory 5’ signal sequences within non-coding region of viral mRNA as possible pathway for preventing initiation of viral replication.

When we have compared IGHF3-53 antibody with...
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previously analyzed 5’ signal sequences within non-coding region of viral mRNA different SARS coronavirus isolates and mammalian AGO4 proteins, from UniProt database (P01767), using the RRM, the same RRM frequency of f1=0.0234±0.0043, became even more prominent, as presented in Figure 3.

![Figure 3. RRM cross-spectrum of IGHF3-53 antibody, 5’ signal sequences within non-coding region of viral mRNA different SARS coronavirus isolates and mammalian AGO4 proteins with common characteristic frequency at f1=0.0234±0.0043.](http://www.ijSciences.com)

This result indicates that IGHF3-53 antibody may be also able to interfere with activation of viral 5’ signal sequences within non-coding region of viral mRNA and mimic activity of host AGO4 proteins, and thus prevent initialization of viral RNA replication. This result can be significant as we can use RRM frequency f1=0.0234±0.0043 as the basis to design peptides that can prevent initialization of viral RNA replication.

Another way to interfere with viral RNA replication is to prevent RNA dependent RNA polymerase and/or RNA replicase activity, which is critical for replication of viral RNA [9-11]. When we have analyzed RNA dependent RNA polymerase and RNA replicase, from UniProt database (Q02382, P25328, Q07048 and P35928, P20126, P36304, P20127, P10358, P20128, P28477, P59595), using the RRM, the most prominent RRM frequency was identified at f2=0.0713±0.0011, as presented in Figure 4.

![Figure 4. RRM cross-spectrum of RNA dependent RNA polymerase and RNA replicase proteins with common characteristic frequency at f2=0.0713±0.0011.](http://www.ijSciences.com)

This frequency f2=0.0713±0.0011 is characterizing RNA dependent RNA polymerase and RNA replicase activity, i.e., replication of viral RNA.

Baring all above in mind, we propose that by interfering with frequency f1, we can prevent initiation of viral RNA replication or by interfering with frequency f2, we can prevent viral RNA replication by itself. Using either or both of those ways, we propose that it would be possible to develop cure for coronaviruses. One possibility is to design peptides, using RRM model, that will be able to interfere with either or both of those activities.

To achieve this, we have firstly identified two RRM characteristic frequencies: f1=0.0234±0.0043 characterizing initiation of viral RNA replication and f2=0.0713±0.0011 characterizing viral RNA replication by itself. As described in RRM methodology, it is possible to design peptides having only the characteristic frequency and phase related to targeted protein. Thus, we have identified phases for all participants involved in initiation of RNA replication, as presented in Figure 5, within phase.
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...mRNA replication. One possible approach would be to design peptides, using the RRM model, that will be able to interfere with either or both of these processes. This design will be a matter of our future research.

Discussion and Conclusion

Here, we have analyzed the process of coronavirus RNA replication within host cell with the aim to find out the characteristics of this process. These characteristics can be used further in design of peptides possibly capable to interfere with this process and prevent viral RNA replication within host cell. For that purpose, we have utilized the Resonant Recognition Model (RRM), which is biophysical model capable of identifying parameters (frequencies) related to specific macromolecular (protein, DNA, RNA) function and/or interaction. The RRM model is unique with its capability to directly analyze interactions between amino acid macromolecules (proteins) and nucleotide macromolecules (DNA, RNA).

Using the RRM model, we have identified parameters that characterize two steps in RNA replication i.e., initiation of replication and replication by itself. Within the first step, we have identified RRM frequency f1=0.0234±0.0043, which is common for all 5' signal sequences within non-coding region of viral mRNA different SARS coronavirus isolates. As these 5' signal sequences are critical for initiation of viral RNA replication, we propose that this frequency f1 is characterizing initiation of viral RNA replication. In addition, we have found that the same frequency f1 is common with host’s argonaute AGO4 proteins, which are key components of RNA silencing pathways [6] and thus we propose the possibility that negative control of initiation of viral RNA replication involves host’s AGO4 proteins. We have also found that IGHF3-53 antibody shares the same common frequency f1 with 5' signal sequences within non-coding region of viral mRNA different SARS coronavirus isolates and mammalian AGO4 proteins and thus we propose that IGHF3-53 antibody also have a role in negative control of initiation of viral RNA replication. As both AGO4 and IGHF3-53 antibody are proteins involved in negative control of initiation of viral RNA replication, sharing the same RRM characteristic frequency f1 with 5' non-coding signal sequence, but with opposite phase, is confirming that frequency f1 is critical for negative control of initiation of viral RNA replication within host cell.

Within the second step of our analysis, we have identified RRM frequency f2=0.0713±0.0011, which is common to RNA dependent RNA polymerase and RNA replicase, and thus is proposed to characterize the process of viral RNA replication by itself.

Having identified the characteristic frequency f1=0.0234±0.0043 for initiation of RNA replication and frequency f2=0.0713±0.0011 characterizing viral RNA replication, we propose that by interfering with frequency f1, we can prevent initiation of viral RNA replication and by interfering with frequency f2, we can prevent viral RNA replication. One possible approach would be to design peptides, using the RRM model, that will be able to interfere with either or both of these processes. This design will be a matter of our future research.
Contributions
Conceptualization, I.C.; Methodology, I.C. and D.C.; Software, D.C.; Resources I.L.; Writing—Original Draft Preparation—Review and Editing, I.C., D.C. and I.L.

Competing Interests
Authors declare they have no competing interests.

Human/Animal Involvement
Authors declare that there were no human participants nor any animal involvement in this study.

Funding
This research received no external funding.

Acknowledgement
The authors would like to thank Miss Amy Cosic for proofreading this manuscript.

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