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Multi-Alignment Comparison of Coronavirus Non-Structural Proteins Nsp13-Nsp16 with Ribosomal Proteins and other DNA/RNA Modifying Enzymes Suggested their Roles in the Regulation of Host Protein Synthesis

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Abstract

Recently we proposed that Coronavirus Nsp2 protein is a RNA topoisomerase and Nsp16 is a 2'-O-Ribose Uridine Methyltransferase. BLAST search found that Nsp13 non-structural protein was a 2'-O-Ribose Guanosine Capping Methyltransferase although it has been implicated as RNA helicase. Search with 200 RNA/DNA binding-modifying proteins confirmed Nsp13 protein homology to ribosomal L6 and L9 proteins and Nsp2 protein to L1 protein and Nsp15 protein to S1 and S22 ribosomal proteins. Further, Nsp13 has some homology with Cfr 23S rRNA methyltransferase and RNaseT whereas Nsp15 had close relation to RecA recombinase and Dcm DNA methyltransferase. Similarly, Nsp14 had homology with Cfr 23S rRNA methyltransferase and Nsp16 2'-O-Ribose MTase had some similarity to UvrC exinuclease and RNase. These suggested that Nsp2, Nsp13, Nsp14, Nsp15 and nsp16 non-structural proteins may be recruited easily to mitoribosome making chimera ribosome to methylate the rRNA or change its topology favouring viral protein synthesis and inhibiting host protein synthesis. Such change in host protein synthesis in the mitochondria may cause an inhibition in oxidative phosphorylation and ATP synthesis causing low pressure, blood clotting, coma and heart failure as seen in many Corona-infected patients. Thus, targeting those viral proteins with drugs, antisense, ribozyme and CRISPR-Cas6 may cure Corona-infected patients.

Keywords: ***Multiple corona virus methyltransferases; Capping MTases; Viral mRNA recognition; Ribosomal protein***

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Introduction

Recently, we published Coronavirus Nsp16 protein is a RlmE 2'-O-Ribose Uridine Methyl transferase implicated in 21S rRNA methylation of mitoribosome inhibiting host protein synthesis which might cause the inhibition of oxidation

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phosphorylation in patient leading to sudden death [1]. We also communicated that Coronavirus Nsp2 protein was a novel RNA Topoisomerase [2]. Coronavirus is threat to world community and now everyday claiming 500-1000 lives per day worldwide with about 280000 deaths. The discovery of molecular target for drug discovery is now urgent need as proclaimed by WHO, CDC and G-20 world leaders [3]. Coronaviruses are (+) stranded RNA virus and isolated in all forms of higher life with 40-70% sequence similarities to pandemic COVID-19 [4,5]. Molecular biology of SARS and MERS viruses have well studied and bat-Coronavirus is best dissident [6]. The main feature of RNA viruses was the presence of polyprotein which was degraded by proteases to different regulatory peptides enhancing viral synthesis, capturing the host replication, transcription and translation machineries. Thus, methyltransferases and ribonucleases discovered as Nsp13, Nsp14, Nsp15 and Nsp16 proteins of ORF1ab have pivotal roles in mRNA synthesis and viral structural protein accumulation in bronchial cells [7]. Roles of DIssE RNA gene rearrangement to make viral regulatory proteins of infectious RNA viruses seems complex but important molecular target. We will discuss the structural features of those enzymes and their interrelationship accelerating viral life cycle but at same time causing acute pathogenesis due to lysis of lung cells [1,8]. It claimed within 3 months 280000 lives worldwide and >3 million peoples suffered high fever, cough, low pressure and intensive care life for one month. Lock down crippled the world life and 100 million peoples dragged into poverty line as they have lost job and capital or both. Thus, our bioinformatics work on coronavirus non-structural proteins must have some direct values understanding its molecular biology leading to rapid drug and vaccine development.

The function of Nsp13 protein was determined as 2'-O-ribose capping Guanosine methyltransferase by bioinformatics approach comparing 200 DNA, and RNA MTases, Ligases, RNases, DNases, as well as some RNA virus associated non-structural proteins [9,10]. Dcm Methyltransferase (EC: 2.1.1.137) causes DNA methylation at the C5 or N4 positions of cytosine. *E. coli* Dam methyltransferase has GATC sequence specificity and methylates at the adenine residue at N6 regulating many genes [11]. The rRNA MTases methylate at least nine 23S rRNA nucleotides (G748, A1067, C1920, A2058, G2445, G2470, U2479, A2503, T2504 and G2535) on the large ribosomal subunit [12]. There are more than ten 16S rRNA modifying MTases (ArmA, RmtA to RmtH and NpmA) have characterized where as ArmA and RmtH are abundant. Ribosome decoding centre (nucleotides 1400–1500 of 16S rRNA) is the binding sites for aminoglycosides and endogenous methyltransferases RsmI and RsmH methylate C1402 whereas RsmE methylates U1498, and RsmF methylates C1407 [13]. Different Rlm methyltransferases methylate at various positions of bacterial 23S rRNA conferring multi-resistant to macrolides and ketolides like erythromycin, telithromycin, and solithromycin. As for example, RlmAII MTase has preference to N1 of G748 of 23S rRNA [14], RlmB MTase (protein id. BAI33654) modifies G2251 [15,16] while RlmC modifies m5U747 and RlmD is specific for m5U1939. RlmE (protein id. TJL68081) and RlmF (protein id. TZE44659) methylate 23S rRNA 2'-O-U2552 while RlmG (protein id. CRY88590) methylates at N2 of G1835 and N3 pseudo-Uridine for RlmH (protein id. QBF38433) and RlmN (protein id. QBF37927) methylates C2 at A2503 [17]. RlmM (YgdE; EC: 2.1.1.186) enzyme catalyzes the SAM-dependent 2' O-ribose methylation of C2498 in 23S rRNA of *Escherichia coli* [18].

We investigated the homology profiles of many recombinases and transposases using CLUSTAL-Omega software. Some of the IS-elements of E. coli sequenced are: IS-1, IS-2, IS-3, IS-4, IS-5, IS-10, IS-26, IS-30 and others [19,20]. Several thousand IS elements were sequenced but could be classified into ~20 families on the basis of the sequences of their transposases and terminal inverted repeats as well as associated antibiotic resistant, drug efflux and metal resistant genes as found in integrons and transposons. Tn5 transposase (accession no. U00004) is 454aa with different domains for DNA binding (15aa - 72aa), DDE catalytic domain (128aa - 365aa) and dimmerization domain (379aa - 454aa) but it has only 23% - 37% similarity with

T3 transposase. Tn10 is 4329bp (accession no. J01830) carries tetracycline resistant gene (tetA; protein id. AAB59094). Transposases like Tn1721, Tn3, Tn21 and derivatives like TN1696, Tn5060 are related and located in many MDR plasmids (protein ids. QBB00018; BAE54333). Int1I, IS30-int and Rci are different integraes and significantly integrate into DNA of host in a sequence specific manner [21-23]. *Escherichia coli* RecA enzyme (protein id. AWJ98296) is a bacterial ATP-dependent recombinase enzyme which has roles in homologous recombination, DNA repair, and the induction of the SOS response [24]. RecBCD also important recombinases that have been well characterized [25]. Bacterial and mammalian RNases are also RNA modifying enzymes and viral exonucleases may also have specificity to regulate host 16kb circular mitochondrial DNA [22,26-28]. We have compared amino acid sequences of those 100 enzymes with Nsp13 and other Nsp non-structural proteins related to polyprotein ORF1ab of coronavirus. BLAST search and Multi-alignment analysis are important tools to find the function of unknown viral protein like Nsp13 of Coronavirus. Previously, Nsp13 was predicted as RNA helicase but we suggested that it was a capping Guanine 2'-O-Ribose methyltransferase.

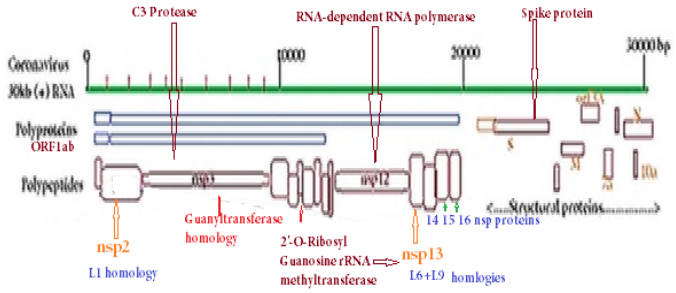
Material and Method

The BLAST search was done using web portal www.ncbi.nlm.nih.gov/blast and retrieve of covid-19 and other Coronaviruses cDNA sequences were done using web portal www.ncbi.nlm.nih.gov/nucleotide or protein. NCBI Primer Design Software was used for primer selection and oligoanalyzer 3.2 software was used to analyze primer dimmer and hairpin structure. Multalin Software and CLUSTAL Omega Software were used to multiple align of protein sequences and NCBI BLAST seq-2 analysis portal was used to analyze homology between two sequences. NCBI PubMed portal (www.ncbi.nlm.nih.gov/pubmed) used to retrieve references and papers. CLUSTAL Omega Phylogenetic tool used to determine the closer structural similarities among the proteins and Seq-2 BLAST was used to confirm percentage of sequence homology between two related proteins [1].

Results

Multi-alignment of nsp13, nsp14, nsp15 and nsp16 amino acid sequences produced no clear homology suggesting no close homology among those coronavirus non-structural proteins derived from polyprotein ORF1ab. Seq-2 BLAST analysis and best fit regions homology with mouse 2'-O-Ribose capping methyltransferase (protein id. NP_083067, 837 aa) were shown (Figure 1). In truth, it appeared that all four Nsp13/14/15/16 proteins have some similarity to mouse capping methyltransferase and such result have implicated a multi-functional methyltransferase oligomeric complex in Coronavirus performing methylation, capping and PolyA addition of its mRNA, making more assessable to host ribosome for viral specific protein synthesis. Maximum homology position alignment suggested Nsp16 match at the NH2 terminus, Nsp15 match at the middle and Nsp13 and Nsp14 mapped same position at the 2/3 sequence position of the mouse ribose 2'-O-Ribose-Guanisine capping methyltransferase (Figure 2 & Figure 3). However, major interpretation of this data is that Nsp13 is a 2'-O-Ribose Guanine capping methyltransferase, not Nsp16 protein as reported earlier [29]. The Nsp13 protein was previously assigned as RNA helicase in many literature but we suggested as 2'-O-Ribose Guanosine capping methyltransferase with helicase domain. It had no homology to the different Escherichia coli and viral RNA helicases. As for example, multiple-alignment did not produce any similarity among Escherichia coli RNA helicases like DbpA (protein id. KAF1280921), DEAD (protein id. TJL67765), REP (protein id. QEP09783), SrmB (protein id. PWE05992) and Vibrio sp RNA helicase (protein id. ORT52469) as well as bacteriophage type enzyme (protein id. SYX53793). Such analysis clearly confirmed that Nsp13 is not a classical RNA helicase but capping methyltransferase with helicase domain or dual enzyme activities (Figure 4).

If any protein belong to these Nsp13, Nsp14, Nsp15 and Nsp16 is a recombinase or transposase, we did search with many bacterial RNA/DNA modifying/binding enzymes as shown in (Figure 5). Rotavirus VP3 guanylyltransferase has similarity stretches at different positions of ORF1ab polyproteins suggesting Nsp3, Nsp6 and Nsp15 have domain similarities to capping guanylyltransferase but need further validation (Figure 6). We communicated Nsp16 protein as RlmE 2'-O-ribose Uridine methyltransferase and question arises if such enzyme also possess guanylyltransferase activity alone or in association with Nsp3 and Nsp6 [8]. We found Rotavirus VP3 guanylyltransferase has similarity to Coronavirus Nsp3, Nsp6 and Nsp15 non-structural proteins (Figure 6) [30]. Seq-2 BLAST also confirmed such finding and we were in process of further analysis (Figure 7). Phylogenetic relation of Coronavirus Nsp13/14/15/16 peptides also compared with Dcm, Dam, cfr, erm DNA/RNA Methyltransferases (Figure 8). It was found that Nsp15 has some homology to Dcm DNA methyltransferase and Nsp14 and to lesser extent Nsp13 have homology with Cfr 23S rRNA methyltransferase. Dam DNA methyltransferase has closet similarity to mouse 2'-O-Ribose guanosine methyltransferase but all Erm 23S rRNA methyltransferase have no homology with Corona virus Nsp13-Nsp16 peptides (Figure 8A). Phylogenetic relation of Rmt rRNA methyltransferases with Nsp13/14/15/16 non-structural proteins of Corona virus were also performed (Figure 8B) and with Rlm methyltransferase (Figure 8C) and Rsm methyltransferase (Figure 8D) were also compared.



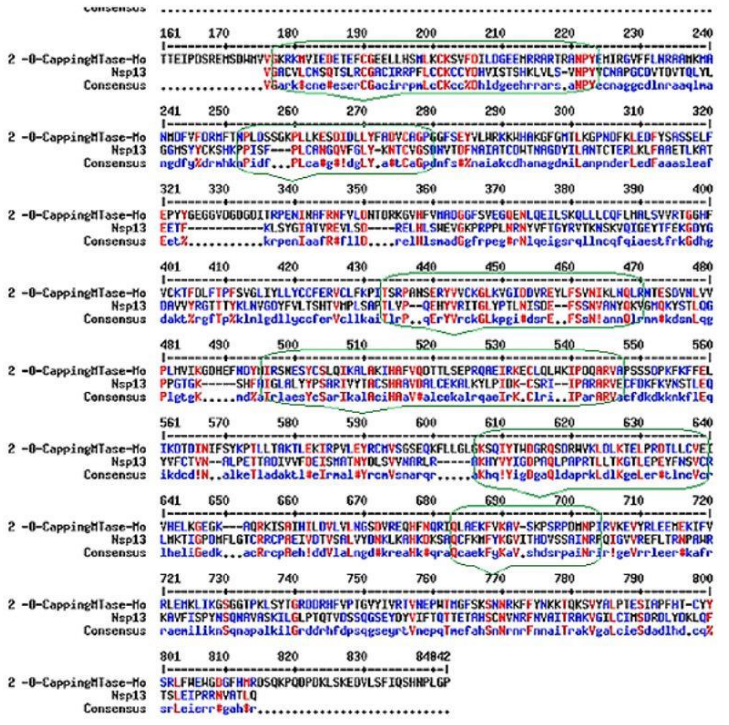


Figure 1: Genome structure of corona virus and localization of its proteins (A). Homology between Nsp13 helicase and mose 2'-O-Ribose capping Methyltransferase (B). This suggested that Nsp13 is a capping 2'-Ribose GuanidineMethyltransferase not Nsp16 as suggested by many workers. The good homology stretches were marked by green boxes.

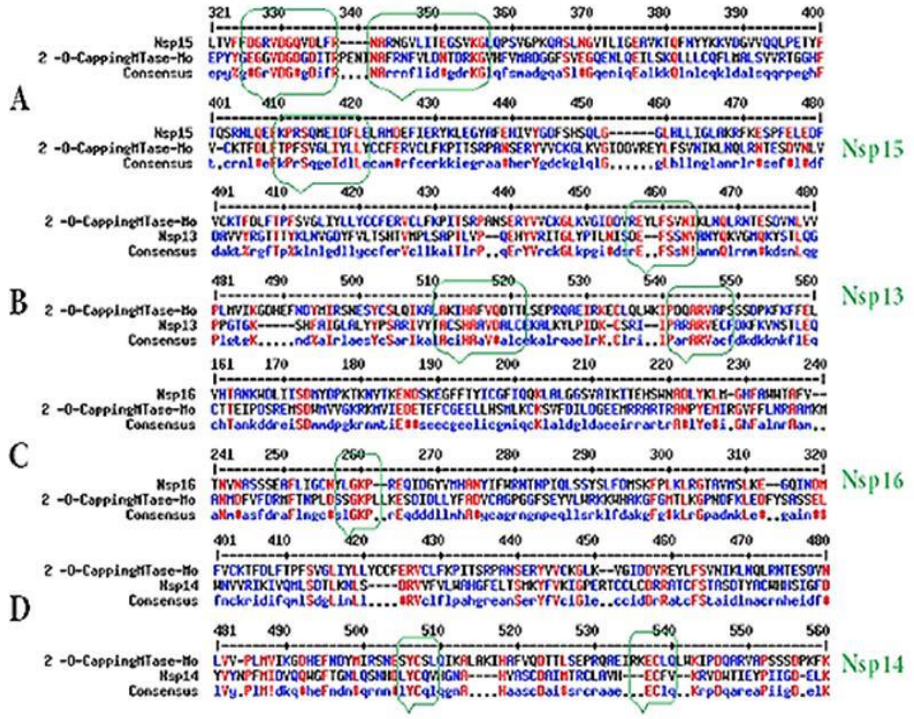


Figure 2: Multi-alignment of Nsp13, Nsp14, Nsp15 and Nsp16 peptides of coronavirus large polyprotein ORF1ab. Multi-alignment data shown no homology among the four proteins (data not shown). Instead alignment between mouse 2'-O-Ribose capping MTase (protein id. NP_083067, 837aa) and any one of Nsp protein showed some homology but best fit was found Nsp15 (A), Nsp13 (B), Nsp16(C) and Nsp14 (D). We hypothesized that all four Nsp13/14/15/16 proteins may form a multi-functional methyltransferase oligomeric complex performing methylation, capping and PolyA addition of corona mRNA, making more assessable to host ribosome for viral specific protein synthesis.

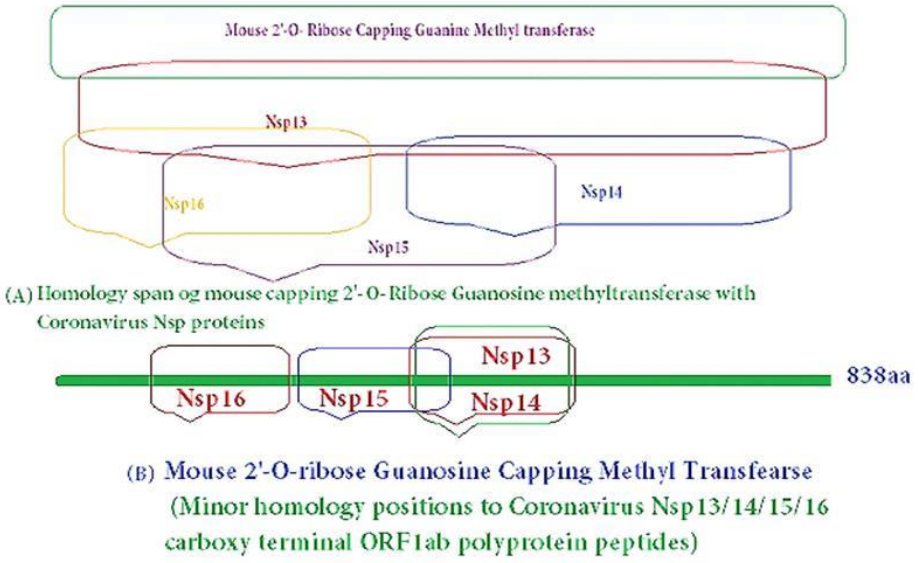


Figure 3: Homology extended pattern of different methyltransferases of ORD1ab polyprotein of coronavirus. Maximum homology position alignment suggested Nsp16 match at the NH2 terminus, Nsp15 match at the middle and Nsp13 and Nsp14 mapped same position at the 2/3 sequence position of the mouse ribose 2'-O-Ribose-Guanosine capping methyltransferase.

This suggested Nsp13 and Nsp14 were similar RNA binding proteins and Nsp16 and Nsp15 also might perform similar methylation and or capping utilities of viral mRNAs.

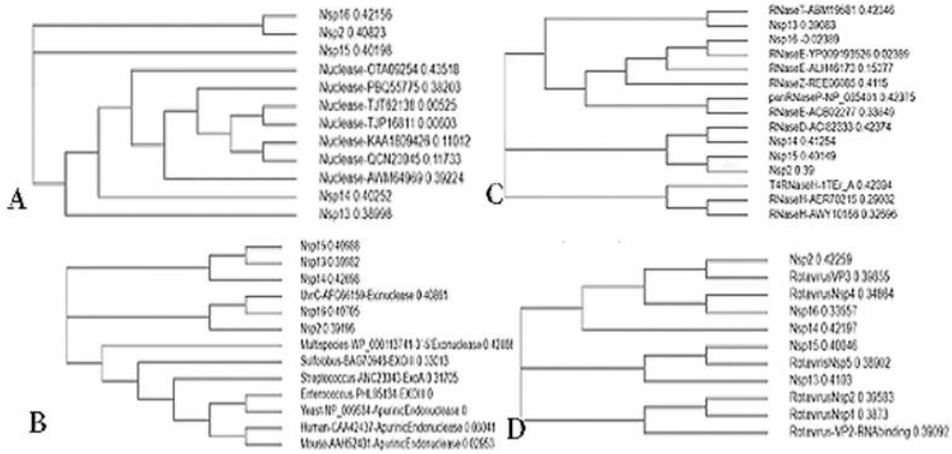


Figure 4: Phylogenetic analysis of different DNA/RNA modifying enzymes. **(A)** RNA helicases compared to prove that Nsp13 is not a RNA helicase. **(B)** Phylogenetic analysis of recombinationases in relation with Nsp13 ORF1ab-deived protein of Coronavirus showing recB homology withNsp14 and bin recombinase homology with Nsp16 and RecA recombinase homology with nsp15 whereas 2'-O-Ribose capping MTase has some relation to Int-core recombinase. **(C)** Phylogenetic relations with XerC, XerD, SpoJ, Rci recombinases with Corona proteins showing no closest relation. **(D)** Phylogenetic analysis and comparison with transposases.

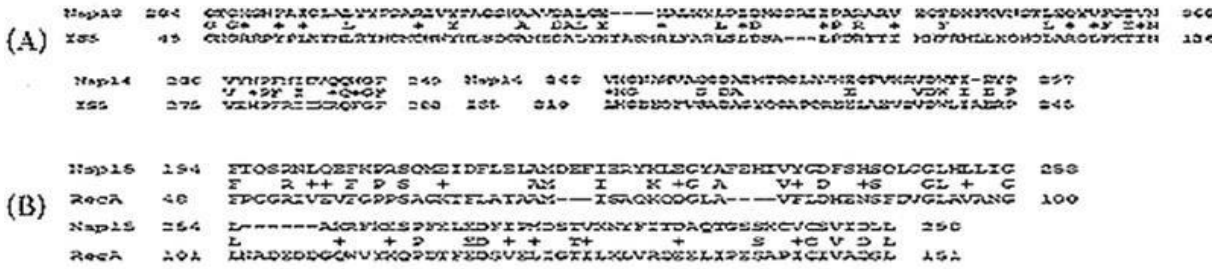


Figure 5: Seq-2 BLAST align of Nsp13 and Nsp14 ORD1ab coronavirus proteins with IS5 transposase (A). Seq-2 BLAST align between Nsp15 and RecA protein of *Escherichia coli* (B). Significant homology may suggest that Nsp15 is a RecA recombinase-like endoribonuclease. But figure 7 also suggested that Nsp15 was not a transposase whereas Nsp14 although suggested as IS5-like transposase but homology was insignificant.

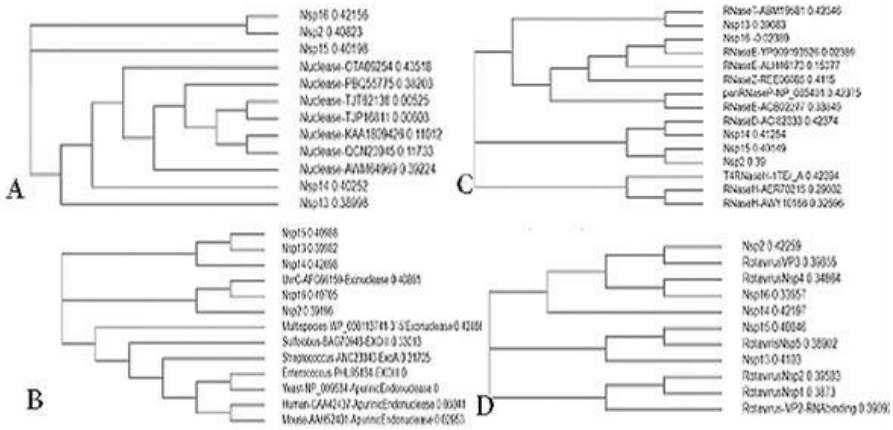


Figure 6: Homology search with Nuclease (protein id. PBQ55775) and 2'-O-capping MTase of mouse has some relation to a nuclease (protein id.OTA09254) (A). Phylogenetic tree with EXOIII and Nsp proteins. It appeared Nsp16 has close homology to UvrC exinuclease (B). Phylogenetic relation of RNases with Nsp2, Nsp13, sp14, Nsp15 and Nsp16 (C). It appeared RNaseT has distance relation to Nsp13 whereas Nsp14 has close relation to T4 RNaseH and pancreatic RNaseH has distance relation to Nsp16 (C). Rotavirus Nsp2 and VP2/VP3 homologies (D). No VP3 guanylyltransferase homology to 8096 aa ORF1ab but such enzyme should be present in coronavirus for efficient capping but it may be derived from host.

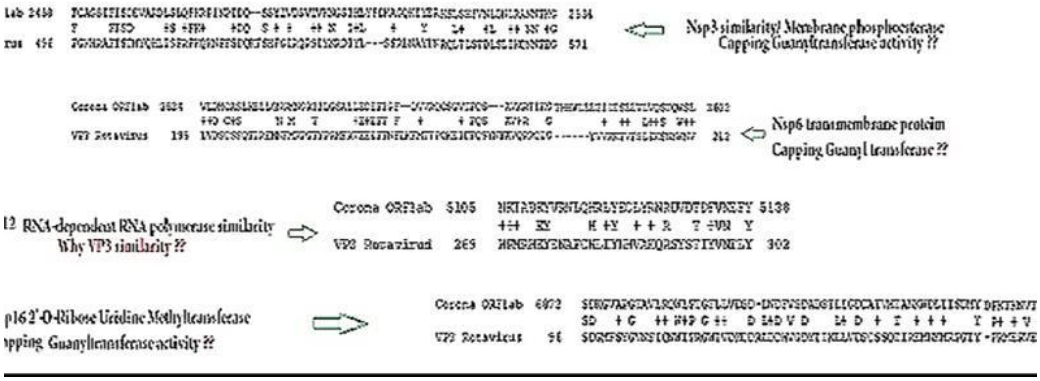


Figure 7: Rotavirus VP3 guanylyltransferase homology to the ORF1ab polyprotein of corona virus showing Nsp3, Nsp6, Nsp12 and Nsp16 have minimum similarity stretches. This further implies that Nsp16 has both guanylyltransferase and 2'O-Ribose-Uridine methyltransferase activities or Nsp3 and Nsp6 bind to Nsp16 to perform such capping specificity. Need further laboratory work.

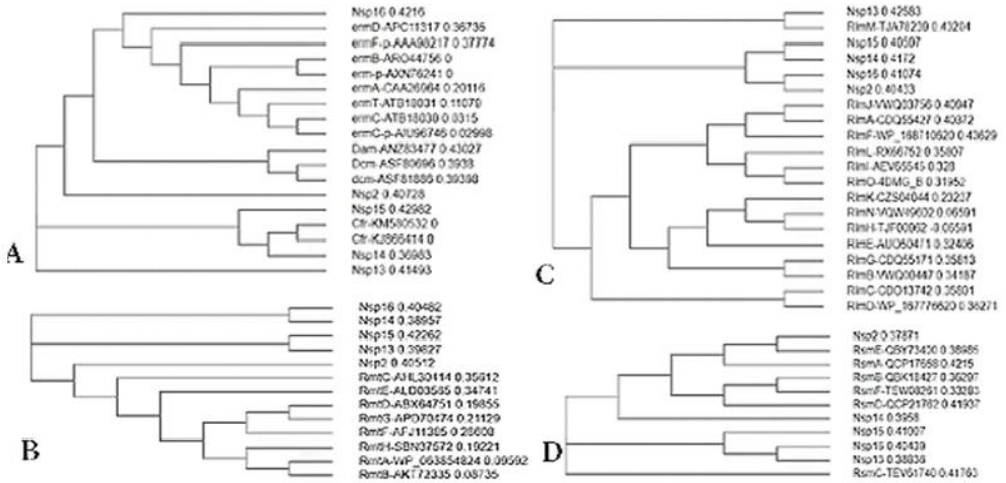


Figure 8: Phylogenetic relation of Coronavirus Nsp13/14/15/16 peptides with Dcm, Dam, cfr, erm DNA/RNA Methyltransferases (A). It was found that Nsp15 has close relation to Dcm DNA methyltransferase and Nsp14 and to lesser extent Nsp13 have homology with Cfr 23S rRNA methyltransferase. Dam DNA methyltransferase has closet similarity to mouse 2'-O-Ribose guanosine methyltransferase but all Erm 23S rRNA methyltransferase have no homology with coronavirus Nsp peptides. (B) Phylogenetic relation of RmtA-F RRNA methyltransferases with Nsp13/14/15/16 non-structural proteins of coronavirus. Phylogenetic relation of RlmA-O methyltransferase with Nsp13/14/15/16 non-structural proteins of coronavirus (C) and (D) Phylogenetic relation of RsmA-E Methyltransferases with Nsp13/14/15/16 non-structural proteins of coronavirus.

We found that 30S ribosomal S1 and S22 proteins have some similarities to Nsp15 as shown by homology search with all 30S ribosomal proteins of Escherichia coli (Figure 9). Nsp13 has two domains for similarities to ribosomal L6 and L9 proteins (Figure 10). Nsp13 has identity to Ribonuclease T. Nsp16 was RlmE 2'-O-Ribose Uridine Methyltransferase and closest to UvrC exonuclease but not to ExoII and XerD recombinases (Figure 9). Multi-alignment of Nsp13, Nsp14, Nsp15 and Nsp16 peptides of Coronavirus large polyprotein ORF1ab shown no homology among the four proteins (data not shown). Instead alignment between Mouse 2'-O-Ribose capping MTase (protein id. NP_083067, 837aa) and any one of Nsp13-Nsp16 protein

showed some homology but best fit was found with Nsp15 (Figure 10A), with Nsp13 (Figure 10B), Nsp16 (Figure 10C) and with Nsp14 (Figure 10D). We hypothesized that all four Nsp13/14/15/16 proteins might form a multi-functional methyltransferase oligomeric complex performing methylation, capping and PolyA addition of Corona mRNA, making more assessable to host ribosome for viral specific protein synthesis (Figure 9 - Figure 11). Such intruder assembly of ribosome favored due to homology of viral Nsp2/9/10/13/14/15/16 to the ribosomal proteins. Ribosomal proteins like L1, L6, L9, S1 and S22 have homologies to Nsp2, Msp9/10 and Nsp13-Nsp16 suggesting ribosome assembly in presence of those viral proteins was complex but surely favored viral protein synthesis and methylation of rRNAs were crucial event likely inhibiting COXI and COXII synthesis impairing ATP synthesis at the ETC (Figure 11) [31]. We also shown the chemical structures of methylated Guanosine and Uridine by non-structural proteins of Coronavirus (Figure 12) and a model for preferential methylation of rRNAs by non-structural proteins due to similarities with ribosomal proteins was presented for easy understanding (Figure 13). It was suggested that Nsp13 and other corona virus proteins easily bound ribosome to methylate and in case of Nsp2 to make torsional stress on rRNA with havoc preferential synthesis of viral proteins.

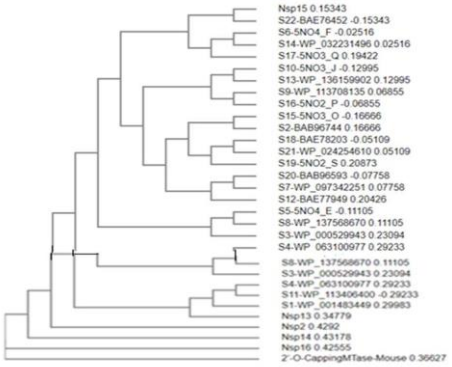


Figure 9: Phylogenetic relations of *Escherichia coli* S30 ribosomal proteins with Nsp12/14/15/16 of coronavirus. It was found that S22 has some homology to the Nsp15.

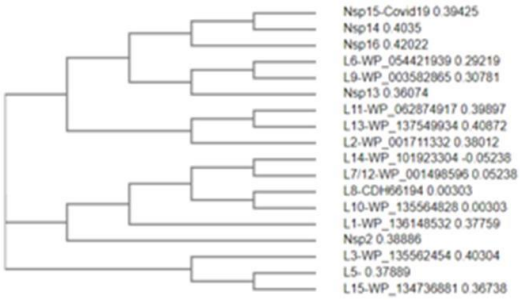


Figure 10: Phylogenetic relation among *Escherichia coli* 50S ribosomal L1-L15 proteins with Nsp2/13/14/15/16 proteins of coronavirus.

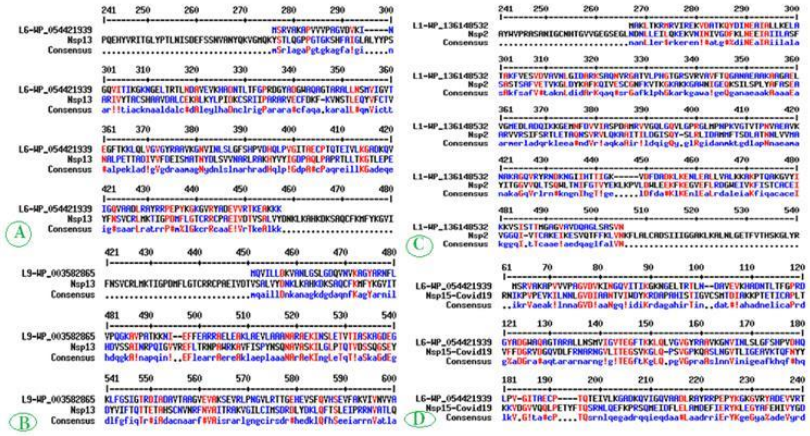


Figure 11: (A) Homology between ribosomal L6 protein and 275aa-453aa of Nsp13 protein of coronavirus. (B) Homology between ribosomal L9 protein and 457aa-5596aa of Nsp13 protein of coronavirus. (C) Homology between ribosomal L1 protein and Nsp2 protein (RNA topoisomerase) of coronavirus. (D) Homology between ribosomal L6 protein and Nsp15 protein of coronavirus.

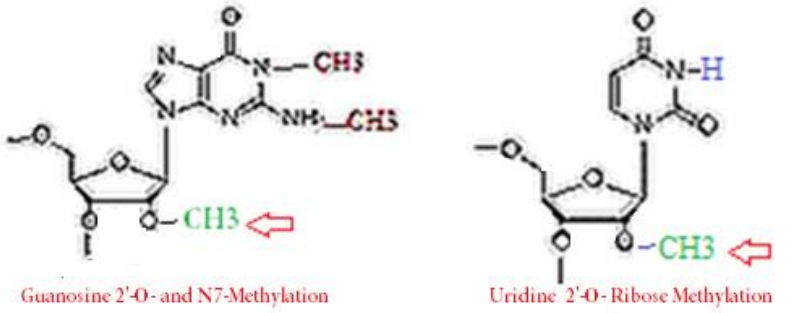


Figure 12: Methylation of rRNA guanosine and uridine by many coronavirus methyltransferases.

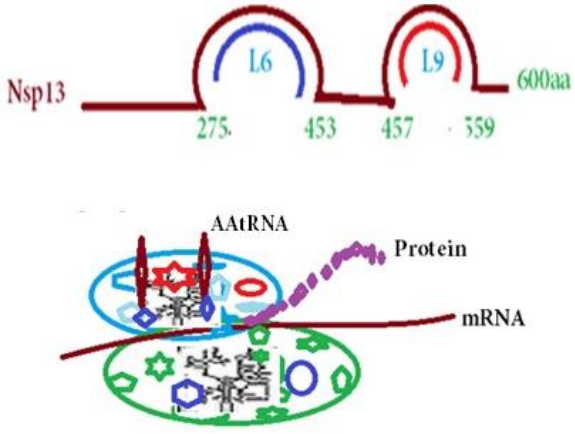


Figure 13: Model of ribosomal proteins L6/L9 similarity to Nsp13 and others ribosome intruders and host preferential synthesis of viral proteins likely in the mitochondria. (A) Similarities between host L6 and L9 ribosomal proteins with Nsp protein of coronavirus. (B) Ribosome with intruder Nsp 13, Nsp 14 corona viral proteins facilitating viral protein synthesis by methylation of rRNA.

Discussion

We searched the 200 different DNA/RNA modifying/binding enzymes from gene bank database to compare with Nsp13/14.15/16 of coronavirus OFR1ab-derived non-structural proteins and obtained very good information regarding the structure and functions of those proteins. Such analysis documented rarely and could not found in the NCBI PubMed database [1]. We also like to work on phytoantibiotics and nanocarrier-mediated toxic drug delivery and such technology may welcome

for coronavirus therapy. We see many homologies with the viral non-structural proteins with ribosomal proteins indicating ribosome structure was altered during coronaviral pathogenesis and such information was lacking in the PubMed database. So publication of the paper is extremely important because all famous laboratories may have missing such crucial information important for drug design against coronavirus. We suggested that Nsp13 was not a RNA helicase as it functions to bind ribosome PTC and methylates the rRNAs in such a way that viral mRNAs only be recruited for viral specific protein synthesis inhibiting host protein synthesis [32-34].

Although we studied by bioinformatics approach, our findings were very important to determine the functions of non-structural proteins of coronavirus and those proteins surely regulate vital mechanism of viral genes expression and pathogenesis preventing host defense mechanisms and cellular homeostasis. We concluded that Nsp13 was a 2'-O-Ribose Guanosine methyltransferase but RNA helicase as well as ATPase activity of MERS helicase was well documented [32,35,36]. We predicted that Nsp13 had profound similarity to Escherichia coli ribosomal proteins L6 and L9 and less to recA-like domains. Nidovirus helicase and Artiriviruses helicase also have studied [37,38]. Thus it seems COVID-19 RNA helicase may also have methyltransferase activities but remains to be determined by purified enzyme. Nsp2 is a RNA topoisomerase and has some homology to L1 ribosomal protein and never the less some homology with S1 and S22 30S ribosomal proteins with Nsp15 may be important. PubMed search indicated compare of 200 RNA/DNA binding and modifying enzymes with corona virus Nsp-13-16 proteins to determine the functions of its unknown proteins never been done. Subissi et al. [39] has disclosed such corona viral proteins are good targets for antiviral agents [39]. Novel types of RNA helicase like Upf1 was reported and others with similarity to coronavirus helicase [40-43]. Adedeji et al. [43] showed that nsp13 helicase unwound in a 5' to 3' direction and efficiently unwound the partially duplex RNA substrates with a long loading strand relative to those of the RNA substrates with a short or no loading strand [44]. Taken together more work necessary to prove that Nsp13 also have 2'-O-Ribose guanosine capping methyltransferase activity [10].

Conclusion

We have disclosed that Nsp13-Nsp16 have methyltransferase activities as well as RNA helicase-recombinase types activities and such enzymes acts to the ribosome due to their similarities with domains of many ribosomal proteins like L6, L9, L1 and S1 and S22 [45]. These dual enzymes likely act in complex with ribosome and are well target for antiviral drugs [46]. We compared 200 RNA/DNA modifying enzymes of bacteria and viruses to decipher the functions of Nsp2/13-Nsp16 proteins of COVID-19. Phytochemicals are good drugs but have not tested much on the replication and transcription of corona virus [47-50] and nanocarriers are good to efficient delivery of toxic drugs into target cells [51,52].

Acknowledgment

I thank WHO and CNN for updating the research on Corona virus and also thank our Prime Minister Sir Narendra Modi to inspire doctors and scientists to work on Coronavirus of any kind to save mankind.

Ethical Issues

No patient was used in the study being bioinformatics work.

Conflict of Interest

The Author has no conflict of interest.

Funding

Lock down research from Kolkata home using my own computer.

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