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Medical Hypotheses 143 (2020) 109904

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Ribosomal proteins as a possible tool for blocking SARS-COV 2 virus replication for a potential prospective treatment

ARTICLE INFO

Keywords:
SARS-COV 2
Antiviral
Coronavirus
Ribosomal proteins
Viral translation

ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-COV2 and has resulted in more than four million cases globally and the death cases exceeded 300,000. Normally, a range of surviving and propagating host factors must be employed for the completion of the infectious process including RPs. Viral protein biosynthesis involves the interaction of numerous RPs with viral mRNA, proteins which are necessary for viruses replication regulation and infection inside the host cells. Most of these interactions are crucial for virus activation and accumulation. However, only small percentage of these proteins is specifically responsible for host cells protection by triggering the immune pathway against virus. This research proposes RPs extracted from *bacillus* sp. and yeast as new forum for the advancement of antiviral therapy. Hitherto, antiviral therapy with RPs-involving viral infection has not been widely investigated as critical targets. Also, exploring antiviral strategy based on RPs could be a promising guide for more potential therapeutics.

Introduction

COVID-19 is an extremely contagious and emerging virus, which appeared in Wuhan, China in December 2019 [1,2]. Every traveler to Wuhan, Hubei Province in China, two weeks before the onset of the symptoms, is believed to be a SARS-COV 2-suspect, according to the World Health Organization (WHO) surveillance report of January 2020 [3]. In addition, the WHO provided interim guidance to laboratories performing the tests for the new outbreak and safety guidelines. COVID-19 viral pneumonia applies to the demand in seafood where an unknown species is responsible for the outbreak [2]. It is a member of Betacoronaviruses family [2,6] which includes Severe Acute Respiratory Syndrome Human coronavirus (SARS HCoV) and Middle-East Respiratory Syndrome Human coronavirus (MERS HCoV) [4,5], COVID-19 HCoVs, MERS, OC43, SARS and HKU1. While 229E and NL63 HCoV strains belong to Alphacoronaviruses [2,5].

HCoVs are positive sense virus with very long single-RNA (30,000 bp) strands. HCoVs are distinguished by two protein classes; structural proteins, such as Envelope (E), Matrix (M), Nucleocapsid (N), Spike (S), and non-proteins, such as RNA-polymerase (RdRp)[5]. RdRp is a necessary enzyme in the RNA virus life cycle including coronaviruses. It is expressed in various RNA viruses, including Coronavirus (CoV), Zika (ZIKV) and Hepatitis C (HCV) [7,8]. Its active site is strongly conserved, representing two successive aspartate protrusions. These protrusions originate from a beta-turn structure which makes them accessible to the surface *via* passing-through the nucleotide channel [9,10].

A ribosomal protein (RP) is one of the proteins that form the ribosomal subunits together with rRNA and involved in cellular translation cycle. Most of the information about these organic molecules was extracted from the research on *E. coli* ribosomes [11,12]. Numerous numbers of antibodies were produced and all the ribosomal proteins were extracted. The cooperation between these studies and electronic microscopy revealed the topography of these Ribosomal proteins. Consequently, Archaea, *E. coli* and other bacteria were found to have a 50S large subunit and a 30S small subunit. Whereas, yeasts and human have a 60S large subunit and a 40S small subunit [13]. RPs were previously isolated from several prokaryotes and eukaryotes such as bacteria (*E.coil* and *Bacillus stearothermophilus*) [14], archaea (*Haloarcula marismortui*) and yeasts (*Saccharomyces cerevisiae*) [15,16].

RNA polymerase II contributes mainly to the synthesis of ribosomal proteins in the cytoplasm, and then transported into the nucleus forming small and large ribosome subunits [17,18]. The small subunit of the ribosome contains one 18S rRNA and about 32 ribosomal proteins while, the large 60S subunit consists of 47 ribosomal proteins and one rRNA of 5S, 5.8S, and 28S. Exportin-1 and exportin-5 then export the 40S and 60S subunits [19] into the cytoplasm, forming the 80S ribosome after assembling with mRNA. Ribosomes are these organelles that catalyze protein synthesis, and ribosomal proteins are thought to promote folding and preserving the optimal configuration of rRNAs, promoting biogenesis of ribosomes, and likely accelerate and accuracy to protein synthesis. Ribosomal protein's roles have been involved in cell proliferation, differentiation, apoptosis, cancer, and gene expression regulated by NF-κB [20,21].

Current treatments and antiviral function of ribosomal proteins

Currently, attenuation of virus infection is only achieved by broad-spectrum antiviral drugs like nucleoside analogues and also HIV-protease inhibitors till the specific and effective antiviral becomes available. At present, administrating 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir orally and 0.25 g ganciclovir intravenously for 3–14 days are the available treatment doses and protocols [22]. While other study revealed that a high efficacy in controlling COVID-19

https://doi.org/10.1016/j.mehy.2020.109904
Received 16 April 2020; Received in revised form 17 May 2020; Accepted 28 May 2020

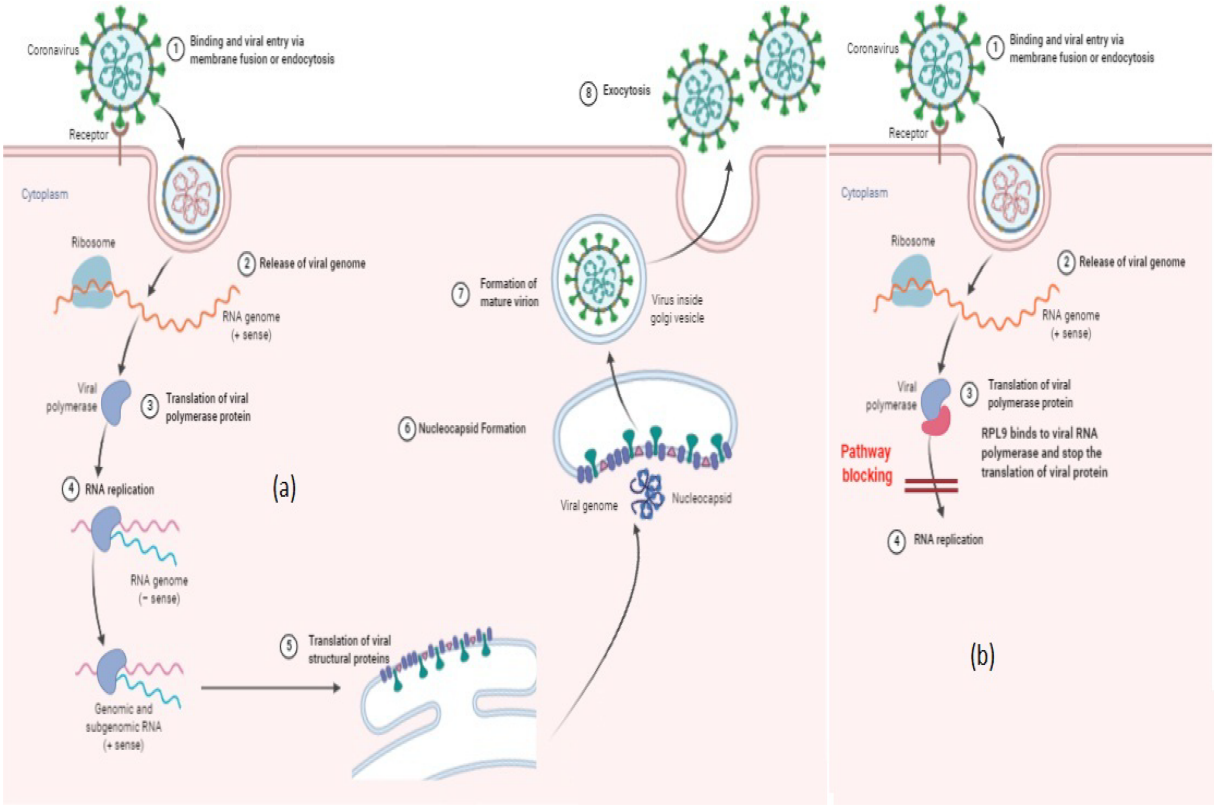

Fig. 1. Diagrammatic pathway of SARS-COV-2 in a host cell shows the normal viral replication cycle (a) and the possible blocking of the virus replication process by RPL9 binding to the virus phosphoprotein P (b).

infection *in vitro* was reached when antiviral remdesivir [23] and chloroquine [24] were used.

Compared with positive viral infection-regulating RPs, studies on antiviral activity of RPs are uncommon and recently occur. Initially, RPs have two major antiviral mechanisms which have been identified. First, the RPs directly react with viral proteins to hinder virus's transcription or translation (Fig. 1). For example, the first stage of Rabies virus (RABV) transcription is inhibited when RPL9 binds to phosphoprotein P which is a vital cofactor of viral RNA polymerase. Then, RPL9 relocates from nucleus to cytoplasm [25]. In the same context, RPS10, 18S rRNA and lesser tRNAs bind HIV-1 to Nef protein diminishing the synthesis of viral proteins [26]. Second, RPs can act as immune factors activate signaling pathways for antiviral defense. For instance, RPS20 prevents replication of CSFV (Classical Swine Fever Virus) in cells by modulating Toll-like receptor 3 (TLR3), which can activate the immune response [27]. In response to Respiratory Syncytial Virus infection, RRL13a is released from the 60S subunit and assembles an interferon-independent antiviral complex to suppress the translation of a particular viral mRNA(matrix protein M), which represents a novel antiviral innate immunity model [28]. Additionally, RRL10 serves as an immediate downstream sector of antiviral signaling in the geminivirus nuclear shuttle protein (NSP)-interacting kinase (NIK)-mediated antiviral defense pathway in plants, in which RRL10-a common partner and substratum of NIK - is phosphorylated and redirected to the nucleus to modulate viral infection [29,30].

Conclusion

Ribosomal proteins are proteins synthesized naturally by different bacterial strains and yeasts. These proteins can be used to block the viral replication by binding to the specific phosphoproteins or act as activators for the host immune factors. Thus, several ribosomal proteins such as RPL 9 and RPL 10 could be extracted, purified and tested on more animal models to evaluate its activity against Covid-19. Another application of these proteins is that they could be improved as pre-and post-exposure prophylaxis against Covid-19 such as vaccines or a potential medication.

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