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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 HCoV, 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 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.coli 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, administering 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
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 activating 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.

References

[1] Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MU, Khan K. Pneumonia of unknown etiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med 2020;27(2):taaa008.
[2] Hui DS, Azhar IE, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264–6.
[3] Organization WH SCDBBN. Coronavirus (nCoV): Interim Guidance v1 J, World Health; Organization; 2020.
[4] Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen K-Y. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 2015;28(2):465–522.
[5] Elfiky AA, Mahdy SM, Elshemey WM. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. J Med Virol 2017;89(6):1040–7.
[6] Middle East WHO. Respiratory Syndrome Coronavirus (MERS-CoV). WHO; 2016.
[7] Elfiky AA. Zika viral polymerase inhibition using anti-HCV drugs both in market and under clinical trials. J Med Virol 2016;88(12):2044–51.
[8] Ganesan A, Barakat K. Applications of computer-aided approaches in the development of hepatitis C antiviral agents. Expert Opin Drug Discov 2017;12(4):407–25.
[9] Doublet S, Ellenberger T. The mechanism of action of T7 DNA polymerase. Curr Opin Struct Biol 1998;8(6):704–12.
[10] Elfiky AA, Izmail AM. Molecular docking revealed the binding of nucleoside/side inhibitors to Zika viral polymerase solved structures. SAR QSAR Environ Res 2018;29(5):409–18.
[11] Konnikat S. Dynamic Remodeling Events Drive the Removal of the IFS2 Spacer Sequence During Assembly of 60S Ribosomal Subunits in S. cerevisiae: Carnegie Mellon University; 2016.
[12] de la Cruz J, Kargin A, Woolford Jr JL. Functions of ribosomal proteins in assembly of eukaryotic ribosomes in vivo. Annu Rev Biochem 2015;84:93–129.
[13] Rodnina MV, Wintermeyer W. The ribosome as a molecular machine: the mechanism of tRNA-mRNA movement in translocation. Portland Press Ltd.; 2011.
[14] Vorgias CE, Kingswell AJ, Dauter Z, Wilson KS. Cloning, overexpression, purification and crystallization of ribosomal protein L9 from Bacillus stearothermophilus. FEBS Lett 1991;286(1–2):204–8.

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).
[15] Maki Y, Tanaka A, Wada A. Stoichiometric analysis of barley plastid ribosomal proteins. Plant Cell Physiol 2000;41(3):289–99.

[16] Ban N, Beckmann R, Cate JH, Dinman JD, Dragon F, Ellis SR, et al. A new system for naming ribosomal proteins. Curr Opin Struct Biol 2014;24:165–9.

[17] Rodnina MV, Wirtzmann W. Recent mechanistic insights into eukaryotic ribosomes. Curr Opin Struct Biol 2009;21(3):435–43.

[18] Tschochner H, Hurt E. Pre-ribosomes on the road from the nucleus to the cytoplasm. Trends Cell Biol 2003;13(5):255–63.

[19] Wild T, Horvath P, Wyler E, Widmann B, Badertscher L, Zemp I, et al. A protein inventory of human ribosome biogenesis reveals an essential function of eIF5 in 60S subunit export. PLoS Biol 2010;8(10):e1000522.

[20] Wan F, Anderson DE, Barnitz RA, Snow A, Bidere N, Zheng L, et al. Ribosomal protein S3: a KH domain subunit in NF-κB complexes that mediates selective gene regulation. Cell 2007;131(5):927–39.

[21] Warner JR, McIntosh KB. How common are extraribosomal functions of ribosomal proteins? Mol Cell 2009;34(1):3–11.

[22] Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). BioSci Trends 2020;14(1):69–71.

[23] Shannon A, Le NT, Selisko B, Eydoux C, Alvarez K, Guillemot JC, et al. Remdesivir and SARS-CoV-2: Structural requirements at both nsp12 RdRp and nsp14 Exonuclease active-sites. Antivir Res 2020;182:104793.

[24] Cui C, Zhang M, Yao X, Tu S, Hou Z, En VSJ, et al. Dose selection of chloroquine phosphate for treatment of COVID-19 based on a physiologically based pharmacokinetic model. Acta Pharm Sin B 2020.

[25] Li Y, Dong W, Shi Y, Deng F, Chen X, Wan C, et al. Rabies virus phosphoprotein interacts with ribosomal protein L9 and affects rabies virus replication. Virology 2016;488:216–24.

[26] Abbas W, Dichamp I, Herbein G. The HIV-1 Nef protein interacts with two components of the 40S small ribosomal subunit, the RPS5 protein and the 18S rRNA. Virol J 2012;9(1):103.

[27] Lu H, Dong W, Qian G, Wang J, Li X, Cao Z, et al. u510, a novel Npro-interacting protein, inhibits classical swine fever virus replication. J Gen Virol 2017;98(7):1679–92.

[28] Mazumder B, Poddar D, Basu A, Kour R, Verbovetskaya V, Barik S. Extraribosomal L13a is a specific innate immune factor for antiviral defense. J Virol 2014;88(16):9100–10.

[29] Carvalho CM, Santos AA, Pires SR, Rocha CS, Saraiva DL, Machado JPB, et al. Regulated nuclear trafficking of rpl10A mediated by NIK1 represents a defense strategy of plant cells against virus. PLoS Pathog 2008;4(12):e1000247.

[30] Rocha CS, Santos AA, Machado JPB, Fontes EP. The ribosomal protein L10/QM-like protein is a component of the NIK-mediated antiviral signaling. Virology 2008;380(2):165–9.

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