Various interferon (IFN)-inducible transmembrane (IFITM) proteins for COVID-19, is there a role for the combination of mycophenolic acid and interferon?

Razieh Dowran a, Seyed Fazel Nabavi b,c, Solomon Habtemariam d, Maciej Banach e,f, Shiva Shahmohamadnejad g, Cosmin Andrei Cismaru h,i, Ioana Berindan-Neagoe h,k, Adeleh Sahebnasagh j, Seyed Mohammad Nabavi b,c,*

a Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
b Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
c Division of Translational Medicine, Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Tehran, Iran
d Pharmacognosy Research Laboratories & Herbal Analysis Services UK, University of Greenwich, Chatham-Maritime, ME4 4TB Kent, UK
e Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland
f Polish Mother’s Memorial Hospital Research Institute (PMMHRI), Lodz, Poland
g Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
h Research Center for Functional Genomics, Biomedicine and Translational Medicine, The “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
i Department of Functional Sciences, Immunology and Allergology, The “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
j Clinical Research Center, Department of Internal Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
k Functional Genomics and Experimental Pathology, The Oncology Institute “Prof. Dr. Ion Chiricuta”, Cluj-Napoca, Romania

1. Introduction

The novel coronavirus SARS-CoV-2 that causes COVID-19 and first identified in the Wuhan region of China [1] is an enveloped positive sense RNA virus of the family Coronaviridae and genus Betacoronavirus [2]. On the basis of 79.5% genomic homology to severe acute respiratory syndrome coronavirus (SARS-CoV), the International Committee on Taxonomy of Viruses (ICTV) renamed the virus as SARS-CoV-2 [2]. Phylogenetic analysis also demonstrated that SARS-CoV-2 have 97% nucleotide sequence similarity with a bat SARS-like (SL) CoV which was discovered in 2013 in a cave in China [3]. The receptor binding domain (RBD) of SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2) from human and other species [4].

Interferon (IFN) is produced by the innate immunity in response to the viral aggression. It induces the expression of interferon-inducible transmembrane (IFITM) proteins. The IFITM genes are highly conserved in vertebrates [5] and are found on cell membrane, early and late endosomes as well as lysosomes. The IFITM1, IFITM2, IFITM3, IFITM5, and IFITM10 are expressed in humans but only IFITM 1–3 are IFN-inducible and therefore related to the immune system [6].
2. Functional link between IFITM and antiviral activity

It is noticeable that two phenylalanine residues are critical for the antiviral activity of IFITM3. As evidence for this, mutation of F75 and F78 called (IFITM3-FF mutant) could abrogate its antiviral activity [5]. Several in vitro and in vivo studies demonstrated that IFITM3 might be efficient against influenza and other respiratory viruses including coronaviruses. For example, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) cell entry is inhibited by IFITM proteins [5,7].

When surface proteins of enveloped viruses attach to a cellular receptor, they undergo conformational changes which lead to viral entry [8]. The spike (S) protein of SARS-CoV-2 also needs proteolytic cleavage by type II membrane serine proteases (TMPRSS) and lysosomal cathepsin L for fusion. Between S1 and S2 subunits of SARS-CoV-2 is a furin cleavage site (RRAR motif), which is similar to highly pathogen influenza viruses [9]. IFITM proteins block the entry of several enveloped viruses by blocking fusion step at hemifusion stage, formation of fusion pore stage by decreasing plasma membrane fluidity or by expanding outer membrane leaflet curvature; and its function is independent of viral receptor expression [7,8].

It should be noted that Coronaviridae family viruses cell entry in 293T cells but not A549 can be inhibited by IFITM proteins [7]. The inhibition of coronavirus (e.g. MERS-CoV) into host cells by IFITM3 was also shown to be insensitive to cholesterol accumulation in endosomes [7]. While these results suggest that the antiviral effect of IFITM3 was not associated with modulation of cholesterol synthesis/transport, other reports show disruption of cholesterol homeostasis as the antiviral mechanism of IFITM [10].

3. Can we use the combination of mycophenolic acid and interferon for treatment of covid19?

Mycophenolic acid (MPA, Fig. 1) is an FDA-approved immunosuppressant which is used as prophylaxis against organ rejection [11]. It is an active metabolite of the prodrug morpholinoethyl ester derivative, mycophenolate mofetil (Fig. 1), which is hydrolyzed...
in vivo to release it. By targeting the key enzyme of purine synthesis, inosine monophosphate dehydrogenase, MPA has been shown to suppress the proliferation of both B and T lymphocytes. The selectivity of mycophenolic acid to B and T lymphocytes appears to be due to the crucial role of de novo purines synthesis in lymphocytes proliferation. Hence, it is among the clinically relevant immunosuppressive agents that are effectively used against rejection in solid-organ transplantsations. Recently, much attention has been paid to its potent antiviral effects [12,13]. Pan et al. [14] reported that treatment of HuH7 reporter cell line with MPA leads to significant upregulation of the IFN regulatory factor 1 and 9 as well as IFITM3. They also found that combination of MPA and IFN-α has synergistic antiviral effect against hepatitis C viral infection as well as the expression of the interferon-stimulated genes. Potent in vitro antiviral effects of MPA and its derivative, mycophenolate mofetil, against four coronaviruses infections (i.e HCoV-OC43, HCoV-NL63, MERS-CoV and MHV-A59) have also been reported previously [15]. Hart et al. [16] reported that combination of IFN-β and MPA can synergistically inhibit MERS-CoV infection in Vero E6 cells, while Kato et al. [17] showed anti SARS-CoV-2 activity of MPA and IMD-0354. Taken together, a therapeutic strategy based on combining exogenous IFN-β and MPA may be of benefit in high risk patients. Overall, further evidence is required to establish the mechanism of action and efficacy of IFITM3 and possible role of MPA administration against SARS-CoV-2 infection but research in this direction should be encouraged (see Fig. 2).

Declaration of competing interest

This statement is to certify that all Authors have seen and approved the manuscript being submitted, and agree to the submission to BIOCHIMIE. We warrant that the article is the Authors' original work. We warrant that the article has not received prior publication, is not under consideration for publication elsewhere, and will not be submitted for publication elsewhere, in whole or in part, while under consideration for publication in BIOCHIMIE. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. We attest to the fact that all Authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and their interpretation, and agree to its submission to BIOCHIMIE. We further attest that no other person has fulfilled the requirements for authorship as stated in the Elsevier Authorship-factsheet (2017_ETHICS_AUTH02 - attached), but is not included in the list of authors, and that no other person has contributed substantially to the writing of the manuscript but is not included either among the authors or in the acknowledgements. All authors agree that no modification to the author list can be made without the written acceptance of all authors and the formal approval of the Editor-in-Chief. All authors accept that the Editor-in-Chief's decisions over acceptance or rejection or in the event of any breach of the Principles of Ethical Publishing in BIOCHIMIE being discovered, of retraction are final.

References