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

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ABSTRACT

Various interferon (IFN)-inducible transmembrane (IFITM) proteins are known to be expressed in human tissues though only IFITM 1–3 are inducible by IFN. Numerous studies have shown that activation of IFITM3 could suppress infection by influenza and coronaviruses such as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). In view of the potential application of IFITM proteins' induction to target SARS-CoV-2 infection that causes COVID-19, this article layout insights into the known antiviral mechanisms and therapeutic agents related to IFITM. Blocking viral entry through various mechanisms and the potential application of the FDA approved immunosuppressant agent, mycophenolic acid, as inducer of IFITM3 are among those discussed.

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]. Phylogenic 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].

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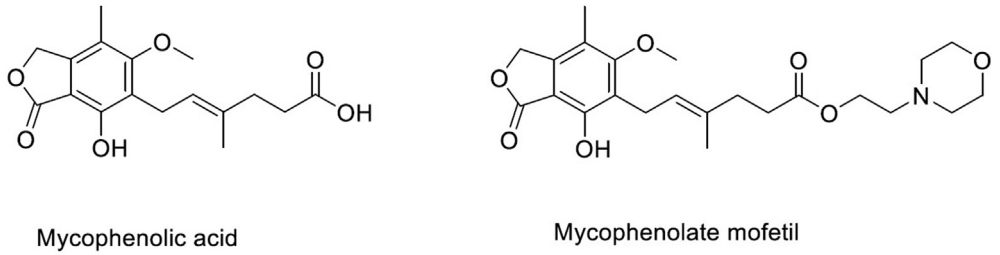

Fig. 1. Structures of mycophenolic acid and mycophenolate mofetil.

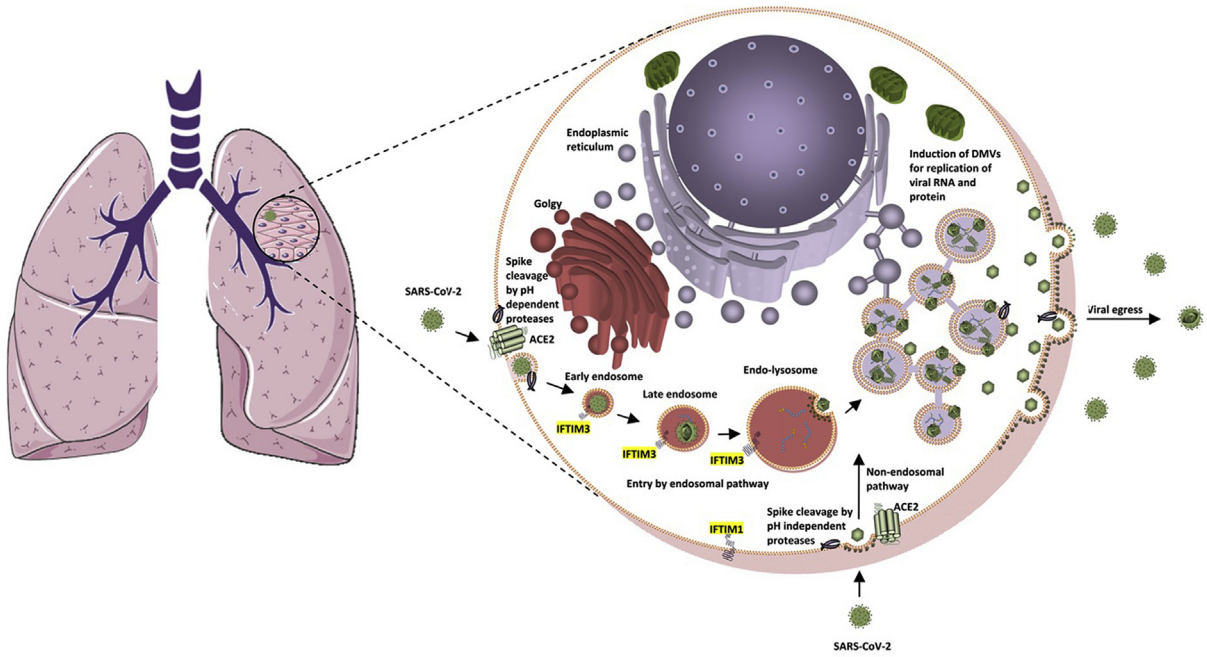

Fig. 2. Schematic representation of the potential implications of IFITM proteins in inhibiting SARS-CoV-2 entry at distinct stages of host cell trafficking. SARS-CoV-2 exploits host cells by entry through an endosomal or a non-endosomal pathway as seen in most enveloped viruses, and replicating in newly induced double membrane vesicles (DMVs) shielded from host immune responses, as a characteristic of the coronavirus family. After binding to the ACE2 receptor, an activation of the S protein by pH dependent or pH independent proteases (serine and cysteine-like) is required for an efficient fusion. IFITM1 is expressed mainly at the plasma membrane level, while IFITM3 is mainly intracellular being integrated in the membranes of the endosomal compartments. IFTIM genes overexpression and proteins can act as cellular inhibitors of the early phases of the viral infectious cycle such as the entry and the fusion steps. (Adapted after Smith et al. [18]).

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 IFTIM 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 hemostasis 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 transplantations. 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

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