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COMMENT

Eye disease drug as a potential cure for COVID-19: one foot-in-the-door

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Every virus relies on cellular host components and pathways to replicate successfully. Because they are genetically more stable than viral targets and may be shared by similar viruses, these proviral host factors are appealing targets for antiviral treatment [1].

The crowning accomplishment by Garcia and team through their research showed that this eye disease treating drug has the potential to target one of the pro-viral host factor and reduce the SARS-CoV-2 infection [2].

Verteporfin is a small molecule derivative of porphyrin, is a YAP-TEAD inhibitor. It has been approved by USFDA for treatment of subfoveal choroidal neovascularization (CNV) caused by age-related macular degeneration (AMD) [3, 4].

Recently, verteporfin has been receiving a significant amount of attention and interestingly researchers have repurposed it and discovered several novel therapeutic uses and the rising publications which demonstrates its potential use in hepatocellular carcinoma [5], triple-negative breast cancer [6] *Staphylococcus aureus* infection [7] etc, clearly justifies it. Considering that YAP/TAZ is a proviral factor, pharmacological inhibition may open up more therapeutic possibilities for COVID-19 therapies, Recently, Gu et. al had demonstrated antiviral activity of verteporfin [8]. They studied the antiviral activity of protoporphyrin IX and verteporfin and found that verteporfin can effectively inhibit SARS-CoV-2 infection at 0.31 μmol/L. This encouraging results from existing literature provided the base for the researchers to dwell more into understanding connecting the dots between SARS-CoV, hippo pathway and this miraculous drug. Hippo-YAP pathway was originally identified in *Drosophila* and highly conserves in mammals.

Several studies suggest that the key components of Hippo-YAP cascade govern the innate immune response extensively, and that the activation of the innate immune signalling pathway, on the other hand, significantly modifies the Hippo-YAP pathway. According to several clinical reports, the absence of Hippo signalling was linked to a range of immunodeficiency symptoms, such as recurrent bacterial and viral infections, suggesting that this signalling is crucial for immunological regulation [9, 10]. Hippo pathway, specifically, is involved in infection by a variety of virus such as Influenza virus, zika virus, hepatitis B virus, hepatitis C virus, Ebolla virus, human papilloma virus, etc [11, 12].

Under normal conditions, when this pathway is activated, the MST1/2 (mammalian Ste20-like kinases 1/2) and its adaptor, Sav; phosphorylate and activate the downstream kinase LATS1/2 (large tumour suppressor 1/2. Then, in the next step, LATS1/2 and its adaptor protein MOB1A/B (Mps one binder 1 A and B) phosphorylate the transcriptional co-activator YAP (Yes-associated protein, Yorkie ortholog) and TAZ (transcriptional co-activator with PDZ binding motif), which causes their cytoplasmic retention through interaction with 14-3-3 or poly-ubiquitination and degradation in the proteasome. (Fig. 1G) When the signalling is off, inactivated MST1/2 and LATS1/2 release YAP and TAZ from inhibitory phosphorylation, which results in their accumulation in the nucleus. YAP and TAZ then bind with transcription factors TEAD1-4 (TEA domain, Scalloped orthologs) to induce gene transcription that leads to cell proliferation and survival [2, 10].

In this breakthrough study by Garcia and co-workers, they investigated SARS-CoV-2 viral replication and the Hippo signalling pathway in two types of cell lines: primary human proximal airway cell culture model, which consisted of mucociliary epithelial cells grown at an air–liquid interface (ALI): Human lung airway basal stem cells (ABSC). They reported that both the parental and Delta variant strains of SARS-CoV-2 increased phospho-YAP (Ser127) level in the infected Calu-3 cell cultures. Hippo signalling pathway is activated in COVID-19 infected lungs and SARS-CoV-2 infected in vitro lung culture systems. Upon infection, the antiviral STAT1 Type I interferon (IFN) pathway is activated in hPSC-CM; indicating that Hippo signalling cascade is also active during SARS-CoV-2 infection of cardiomyocyte systems. Immunohistochemical analysis revealed that the shRNA-mediated partial knockdown of YAP1 gene in hPSC-CM cells resulted in significantly reduced SARS-CoV-2 infection, whereas LATS1 knockdown, increased SARS-CoV-2 infection. It is evident from this that the YAP/TAZ is a pro-viral factor, whereas LATS1 has antiviral function (Fig. 1A–E).

They also observed that pretreated verteporfin Calcu-3 cells not only showed reduction of YAP/TAZ protein level compared to vehicle-treated cells, but also there was significant decrease in SARS-CoV-2 replication. In addition, there was significant reduction in viral production. Correlating and understanding this with mechanism, YAP, generally, inhibits the antiviral defence mechanisms by antagonizing the function of proinnate immune factors TBK1 and IRF3. But verteporfin inhibited the suppression of TBK1 and IRF3 by YAP and this results in antiviral response by stimulating the production of type I and III interferons which can decrease viral load and protect host against SARS-CoV-2 infection. The clinical implication of this research clearly indicates that antiviral effect of Hippo signalling pathway plays a major role in SARS-CoV-2 infection. In addition, it can be seen that YAP/TAZ can be COVID virus's Achilles' hill, and vertporfin can be used as a potential weapon against it to reduce the infection of SARS-CoV-2

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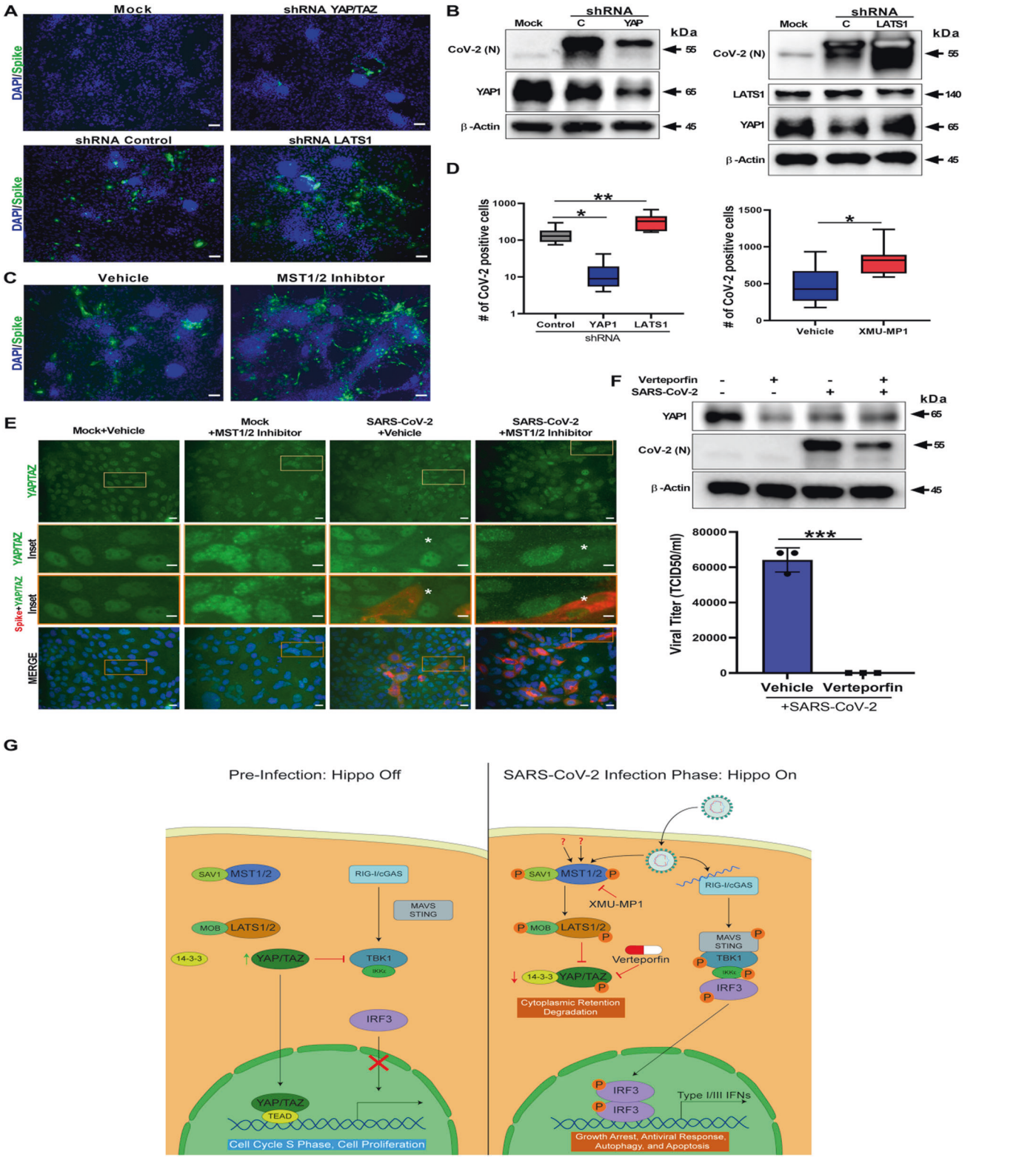

Fig. 1 Schematic representation of hypothetical model of Hippo pathway and IHC/Western blot analysis data. A Immunohistochemistry (IHC) analysis representing reduced/increased replication of SARS-CoV-2 virus (green) relative to shRNA control due to knockdown of YAP1 and LATS1- specific shRNA in hPSC-CMs. **B** Western blot analysis showing the protein expression due to knockdown of YAP1 and LATS1. **C** IHC images of the human pluripotent stem cell-derived cardiomyocyte (hPSC-CMs) cells: vehicle (left), treated with XMU-MP-1 (MST1/2 inhibitor) (right). XMU-MP-1 increased the replication of SARS-CoV-2 virus (green). **D** Graphical representation showing increase in number of CoV-2 positive cells co-relating with panels (**A**) and (**C**). **E** Images of IHC analysis showing YAP/TAZ protein (green) and SARS-CoV-2 Spike antigen (red) in Calu-3 cells. **F** Western blot analysis and viral titer graph represent that Verteporfin (1 μm) resulted in reduction in SARS-CoV-2 infection in Calu-3 cells. **G** Schematic diagram of hypothetical model of hippo signaling pathway involved in SARS-CoV-2 infection [2].

virus and help combat COVID-19 pandemic. Although it might not be sufficient enough to use this as a single-drug therapy, however, it may be co-administered or used in combination therapy with other COVID-19 drugs which could be beneficial in avoiding the development of drug resistance. Drugs with proven human safety can be repurposed to treat new diseases using repurposing approach as a fast and effective choice. It has several advantages such as cost effectiveness, reduction in animal experimentation and acceleration in the drug development process. There is still research needed to dwell more into it. Several other analogues of YAP-TEAD inhibitors with better safety and efficacy can be synthesized or repurposed and can be tested for their synergistic pharmacological action The future research needs to be focused more on studying verteporfin's effect on emerging variants such as XBB 1.5 'Kraken', B.Q.1 etc. We also need to observe its effectiveness in patients with different COVID-9 severity as the parameters such as age, sex, medical history etc are needed to be taken into consideration.

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AUTHOR CONTRIBUTIONS

PP wrote the first and all subsequent versions of this article.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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