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LETTER TO THE EDITOR

Hippo-YAP signaling and SARS-CoV-2 infection: a new mechanistic pathway

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Coronavirus disease 2019 (COVID-19) is the current pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) (Babalghith et al. 2022). SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) for entry to the affected cells leading to circuitous cytopathic effect and release of pro-inflammatory cytokines (PICs) (Al-Kuraishy et al. 2022a; Batiha et al. 2021). Recently, surface heat shock protein A5 (HSPA5) has been reported to be a potential receptor of some viruses, including the novel SARS-CoV-2 (Dores-Silva et al. 2020). Notoriously, SARS-CoV-2 infection may associate with exaggerated immune response and activation of different inflammatory signaling pathways (Al-Kuraishy et al. 2020; Batiha et al. 2022). One of these is the Hippo signaling pathway which is also known as Salvador-Warts-Hippo (SWH) signaling pathway (Qadir et al. 2022).

The Hippo signaling pathway is highly conserved from *Drosophila melanogaster* to mammals and plays a crucial role in organ size control, tissue regeneration, and tumor suppression. The Yes-associated protein (YAP) is an important transcriptional co-activator that is negatively regulated by the Hippo signaling pathway. The Hippo signaling pathway is also regulated by various upstream regulators, such as cell polarity, adhesion proteins, and other signaling pathways (the Wnt/β-catenin, Notch, and mitogen-activated protein kinase (MAPK) pathways) (Yang et al. 2020). YAP is negatively regulated by upstream components of the Hippo pathway (known collectively as the Hippo kinases), including neurofibromatosis 2 (NF2), large tumor suppressor homolog 1 (LATS1), LATS2, and mammalian sterile 20-like kinase 1 (MST1). Usually, the activation of the Hippo pathway leads to tumor suppression and Hippo kinase sequesters and degrades YAP in the cytoplasm (Yang et al. 2020). Hippo pathway is inhibited by YAP and TAZ. YAP-TAZ is known as the WW domain-containing transcription regulator protein 1 (WWTR1) which acts as a co-activator down-streaming Hippo signaling pathway (Qadir et al. 2022). Hippo-YAP signaling pathway comprises a series of transcription factors and protein kinases that regulate cell proliferation, tissue homeostasis, vascular inflammation, and endothelial function. The dysregulation of Hippo-YAP signaling pathway is associated with tumorigenesis and metastasis (Qadir et al. 2022). It has been reported that Hippo-YAP signaling pathway inhibits innate immune response and the production of interferon (INF). However, the core kinases of this pathway positively regulate the host antiviral immune response (Qadir et al. 2022). Besides, the activation of innate immune response induces degradation of YAP pathway during viral infections causing an unopposed Hippo pathway. The activation of toll-like receptor 4 (TLR4) during viral infections including SARS-CoV-2 triggers stimulation of Hippo-YAP signaling pathway. These observations suggest a reciprocal stimulation of innate immune response and Hippo-YAP signaling pathway (Fig. 1).

In this sense, Hippo-YAP signaling pathway positively regulates the release of PICs with the development of cytokine storm in severe SARS-CoV-2 infection (Garcia Jr et al. 2022). In severe SARS-CoV-2 infection, TLR4 and other signaling pathways are exaggerated causing the

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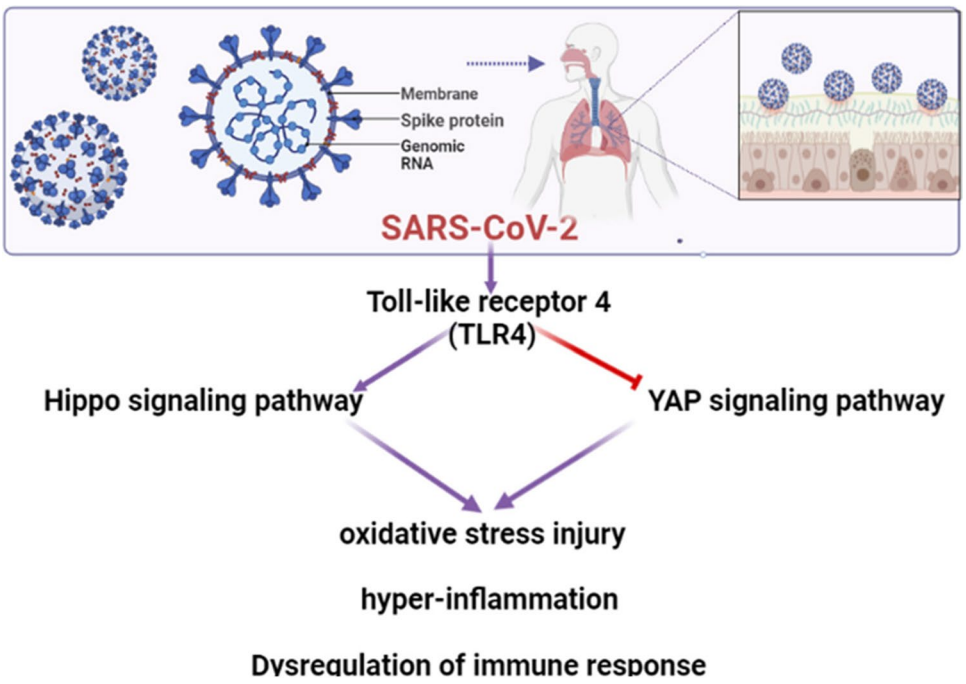

Fig. 1 The role of Hippo-YAP signaling pathway in severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Oxidative stress injury and hyperinflammation are developing due to either activation of the Hippo pathway or suppression of the YAP pathway

release of PICs which in turn induce Hippo-YAP signaling pathway leading to cytokine storm (Qadir et al. 2022; Al-Kuraishy et al. 2022a).

Of interest, YAP inhibits nuclear factor kappa B (NF-κB) activation and associated immune stimulation. YAP negatively regulates the expression and release of PICs preventing the development of immune-mediated disorders (Garcia Jr et al. 2022). YAP inhibits antiviral defense mechanisms by antagonizing the function of pro-innate immune factor tank-binding kinase 1 (TBK1) which is a key signal transducer of cytosolic RNA-sensing retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) pathway. Therefore, Hippo signaling pathway plays a critical role in SARS-CoV-2 antiviral response and COVID-19 pathogenesis (Garcia Jr et al. 2022).

Thus, according to these observations, Hippo induces the release of PICs while the YAP pathway does the reverse. Herein, abnormal activation of Hippo-YAP signaling pathway in SARS-CoV-2 infection may cause dysregulation of immune response and abnormal release of PICs. Of note, oxidative stress triggers the activation of YAP pathway independent of another Hippo pathway (Garcia Jr et al. 2022; Wang et al. 2023). Therefore, in severe SARS-CoV2 infection, oxidative stress injury and hyperinflammation are developing due to either activation of the Hippo pathway or suppression of the YAP pathway (Fig. 1).

In this sense, targeting of Hippo-YAP signaling pathway could be a promised therapeutic strategy to prevent the development of hyperinflammation, oxidative stress, and abnormal immune response in COVID-19. In vitro study demonstrated that XUM-MP inhibits the activity of kinases in Hippo-YAP signaling pathway by enhancing YAP/TAZ activity. XUM-MP attenuates cardiomyocyte injury and apoptosis after oxidative stress (Garcia Jr et al. 2022). Moreover, verteporfin a selective inhibitor of Hippo-YAP signaling pathway prevents the activation of YAP which is implicated as a proviral promoter (Garcia Jr et al. 2022). Therefore, verteporfin could be the possible candidate that attenuates the replication of SARS-CoV-2. Gu et al. (2021) in vitro study revealed that both verteporfin and protoporphyrin IX inhibit the cytopathic effect of SARS-CoV-2 through the modulation of Hippo-YAP signaling pathway and expression of ACE2. In addition, the natural compound naringin in grapefruits prevents the development of endothelial dysfunction through the regulation of Hippo-YAP signaling pathway (Zhao et al. 2020). Thus, naringin may reduce the risk for the propagation of endothelial dysfunction in patients with COVID-19. The inhibition of YAP pathway in SARS-CoV-2 infection is developed due to activation of TLR4 or through exaggeration of AngII leading to oxidative stress and development of hyperinflammation (Al-Kuraishy et al. 2022b). Moreover, pirfenidone attenuates post-COVID-19 pulmonary fibrosis through modulation expression and activation of Hippo-YAP signaling pathway (Al-Kuraishy et al. 2022b). Therefore, YAP pathway inhibitors may exaggerate abnormal immune response in SARS-CoV-2 infection (Al-Kuraishy et al. 2022b). Moreover, pirfenidone attenuates post-COVID-19 pulmonary fibrosis through modulation expression and activation of Hippo-YAP signaling pathway (Al-Kuraishy et al. 2022b). Interestingly, the dysregulation of Hippo-YAP signaling pathway has been observed in infection

with SARS-CoV-2 variants including Omicron (B.529) variant. It has been revealed that melatonin reduces infection severity caused by SARS-CoV-2 and its variants by different mechanisms including the modulation of Hippo-YAP signaling pathway (Begum et al. 2022).

Taken together, targeting of Hippo-YAP signaling pathway could be a new avenue in the management of COVID-19. Experimental, preclinical, and clinical studies are warranted in this regard.

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