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Short communication

p38 MAPK inhibition: A promising therapeutic approach for COVID-19

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ABSTRACT

COVID-19, caused by the SARS-CoV-2 virus, is a major source of morbidity and mortality due to its inflammatory effects in the lungs and heart. The p38 MAPK pathway plays a crucial role in the release of pro-inflammatory cytokines such as IL-6 and has been implicated in acute lung injury and myocardial dysfunction. The overwhelming inflammatory response in COVID-19 infection may be caused by disproportionately upregulated p38 activity, explained by two mechanisms. First, angiotensin-converting enzyme 2 (ACE2) activity is lost during SARS-CoV-2 viral entry. ACE2 is highly expressed in the lungs and heart and converts Angiotensin II into Angiotensin 1–7. Angiotensin II signals proinflammatory, pro-vasoconstrictive, pro-thrombotic activity through p38 MAPK activation, which is countered by Angiotensin 1–7 downregulation of p38 activity. Loss of ACE2 upon viral entry may tip the balance towards destructive p38 signaling through Angiotensin II. Second, SARS-CoV was previously shown to directly upregulate p38 activity via a viral protein, similar to other RNA respiratory viruses that may hijack p38 activity to promote replication. Given the homology between SARS-CoV and SARS-CoV-2, the latter may employ a similar mechanism. Thus, SARS-CoV-2 may induce overwhelming inflammation by directly activating p38 and downregulating a key inhibitory pathway, while simultaneously taking advantage of p38 activity to replicate. Therapeutic inhibition of p38 could therefore attenuate COVID-19 infection. Interestingly, a prior preclinical study showed protective effects of p38 inhibition in a SARS-CoV mouse model. A number of p38 inhibitors are in the clinical stage and should be considered for clinical trials in serious COVID-19 infection.

1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, has resulted in substantial ICU admissions and excess mortality worldwide. Similar to the SARS-CoV virus implicated in the 2003 SARS outbreak, SARS-CoV-2 facilitates cell entry by attaching to angiotensin converting enzyme 2 (ACE2) located on the cell surface [1]. ACE2 is present in multiple tissues and is highly expressed in the lungs and heart [2]. Given this distribution, it is unsurprising that Acute Respiratory Distress Syndrome (ARDS) and myocarditis are the primary causes of death in COVID-19 patients [3]. The cause of overwhelming inflammation induced by SARS-CoV-2 is unclear, however. One particular pathway that has been previously implicated in animal models of acute lung injury and myocardial injury is the p38 MAPK system [4,5]. Upregulation of the p38 MAPK pathway activates pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β [6]. Herein, we argue that the inflammatory injury provoked by SARS-CoV-2 may be due to a disproportionate upregulation of p38 MAPK activity. This inflammation may be attenuated by p38 small molecule inhibitors, many of which have been safely studied in clinical trials for other indications.

2. p38 activation in SARS-CoV-2: The perfect storm

Like SARS-CoV, SARS-CoV-2 binds and downregulates ACE2 upon cell entry [7]. ACE2 converts Angiotensin II (Ang II) into Angiotensin 1–7 (Ang 1–7), which then binds to the Mas receptor to counterbalance the vasoconstrictive and pro-inflammatory effects of Ang II [8,9]. Ang II mediates its effects through p38 MAPK activation [10]. Ang 1–7 stimulation of the Mas receptor decreases p38 MAPK activation to attenuate inflammation [11]. The loss of ACE2 activity upon viral entry may therefore allow Ang II mediated activation of p38 to predominate in the lungs and heart as Ang 1–7 is downregulated. This allows unchecked inflammation and produces a positive feedback loop as p38 activation also upregulates ADAM17, a protease known to cleave the ACE2 ectodomain to further reduce local ACE2 protective activity [12]. It is worth noting that while the role of the renin-angiotensin system (RAS) is still being fully elucidated in the pathogenesis of SARS-CoV-2, a recent study found that inhibition of RAS via angiotensin-converting

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enzyme inhibitors or angiotensin receptor blockers may reduce all-cause mortality in COVID-19 patients [13]. In another study of COVID-19 patients, Ang II levels were linearly associated with degree of lung injury and viral load, further implicating RAS imbalance in the COVID-19 pathogenesis [14].

Furthermore, the previous SARS-CoV virus was shown to express a protein that directly upregulates p38 MAPK in vitro, a pathogenic step thought to be utilized in the lifecycle of many RNA respiratory viruses, including influenza strains associated with severe inflammatory responses such as H5N1 [15,16]. It has been suggested that, among other functions, viral p38 MAPK activation induces endocytosis of viral receptors to facilitate cell entry [17]. Interestingly, p38 MAPK activation has been implicated in the endocytosis of ACE2 [18,32,33]. Given its homology to SARS-CoV, SARS-CoV-2 could use a similar mechanism to directly upregulate p38 MAPK, and a recent study notes that SARS-CoV-2 activates p38 MAPK activity *in vitro*but does not speculate on the mechanism of increased activity [34]. Thus, SARS-CoV-2 could be propagating severe inflammation and organ damage by both directly upregulating p38 MAPK activity and downregulating a key p38 MAPK shut off mechanism by reducing ACE2 activity. Furthermore, p38 MAPK activation could simultaneously be propagating the SARS-CoV-2 viral lifecycle. Interestingly, a small preclinical study with a p38 inhibitor in SARS-CoV infected mice showed 80% survival in the treatment group ($N = 5$) and 0% in the control ($N = 5$) [19].

Importantly, overactivation of p38 MAPK activity can also explain additional clinical findings in patients with SARS-CoV-2 infection. There are reports of significant thrombotic events in severely ill COVID-19 patients, and a recent study in COVID-19 patients notes that the vascular endothelium is directly infected in target organs of SARS-CoV-2 [20–22]. Elevated p38 MAPK activity in the endothelium has been implicated in platelet aggregation, arterial thrombosis, and apoptosis of endothelial cells, a clinical finding also shown in the histology of the aforementioned study [23]. Cardiac dysfunction in COVID-19 patients could partly be due to this endothelial dysfunction, or due to overactivation of p38 MAPK in infected cardiomyocytes, which has been shown to induce apoptosis, impair contractility, and increase fibrosis [24]. Additionally, elevated p38 MAPK levels are implicated in hypoxic pulmonary vasoconstriction and vascular remodeling, which are poor predictors of outcome in acute lung injury [25,26]. These effects are not entirely unexpected as excessive Ang II signaling, which transmits through p38 MAPK, also produces similar effects. However, in this instance, both direct viral activation of p38 MAPK and overactive Ang II p38 signaling may combine to create severe clinical complications.

3. Implications for therapy

A number of direct p38 MAPK inhibitors are in clinical trials for other indications and could be repurposed for randomized, controlled trials (RCT) in patients at risk for serious COVID-19 infection. Losmapimod is the most clinically studied p38 inhibitor and has a favorable safety profile. In 12 healthy volunteers, a single IV infusion of 3 mg of losmapimod and a subsequent 15 mg oral dose were safe and well-tolerated. Headache was the only adverse event reported more than once. Also reported were nausea, fatigue, dry mouth, neuralgia and nasopharyngitis. Nausea was the only adverse event thought to be drug related [27]. In a 28-day RCT comparing 7.5 mg of losmapimod twice daily versus placebo in hypercholesterolemic patients, losmapimod was well-tolerated and safe in 27 patients, with no serious adverse events. The most commonly reported side effect was headache and there were no differences between treatment groups in other safety data—labs, vital signs, and ECG—including liver function tests [28]. In a 12-week RCT of 7.5 mg of losmapimod twice daily in 3503 patients previously hospitalized with acute myocardial infarction, 16% of the 1738 patients in the on-treatment group experienced serious adverse events compared to 14.2% in the placebo group, requiring study drug discontinuation in 4.4% of on-drug patients and 3.9% of placebo patients [29]. Dilmapimod is another p38 inhibitor previously studied in 77 patients at risk of acute lung injury following trauma in a clinical trial with no relevant safety findings [30]. Various other p38 MAPK inhibitors are currently in clinical trials for a range of indications.

4. Conclusions

The p38 MAPK pathway is a key mediator of inflammation implicated in lung and heart injury. The SARS-CoV-2 virus, like SARS-CoV and other RNA respiratory viruses, may directly upregulate p38 MAPK, perhaps for replication purposes. However, the unique viral entry mechanism of SARS-CoV-2 disables a key counterbalancing mechanism employed by the cell to dampen p38 signaling through ACE2 activity. This combination may allow unrestrained p38 MAPK activity, promoting inflammation, vasoconstriction, and thrombosis, while simultaneously benefiting the viral lifecycle. As such, p38 MAPK inhibition may be an appropriate treatment for SARS-CoV-2 infection. This is supported by a small preclinical study of SARS-CoV infection in a mouse model. Further preclinical trials should be performed to elucidate the role of p38 activation in animal models of SARS-CoV-2. More importantly, safe and well tolerated p38 MAPK inhibitors that are already in clinical development could be readily repurposed in randomized, controlled trials enrolling patients at risk for serious COVID-19 complications.

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