Gas6/TAM Axis Involvement in COVID-19 Patients

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Gas6 (growth arrest-specific gene 6) is a widely expressed vitamin K-dependent protein that is involved in many biological processes such as homeostatic regulation, inflammation and repair/fibrotic processes. It is known that it is the main ligand of TAMs, a tyrosine kinase receptor family of three members, namely MerTK, Tyro-3 and Axl, for which it displays the highest affinity. Gas6/TAM axis activation is known to be involved in modulating inflammatory responses as well as fibrotic evolution in many different pathological conditions. The Axl is a SARS-CoV-2 infection driver, the use of existing Axl inhibitors is beneficial for COVID-19 management.

Gas6 TAM receptors inflammation fibrosis COVID-19

1. Gas6/TAM Axis in COVID-19

Due to its immunomodulatory role, as well as its involvement in the modulation of inflammation and subsequent fibrotic evolution, the Gas6/TAM axis is emerging as an interesting research item in the context of the ongoing COVID-19 pandemic, caused by SARS-CoV-2. This new viral agent is a positive, enveloped, single-stranded RNA virus, with high genetic similarity with both SARS-CoV and MERS-CoV, two epidemic coronaviruses responsible for two other severe pneumonia outbreaks in 2002 and 2012, respectively [1][2][3].

SARS-CoV-2-positive patients show different clinical manifestations, ranging from asymptomatic forms or mild flu-like presentation to severe interstitial pneumonia, acute respiratory distress syndrome (ARDS) and severe multiorgan failure, leading, in the most severe cases, to death [1][4][5][6][7][8]. A distinctive hallmark of severe COVID-19 manifestations is the aberrant immune response following pathogen recognition, leading to uncontrolled production and release of proinflammatory mediators, accounting for the so-called "cytokine storm", which appears to have peculiar characteristics in COVID-19 compared to what is observed in other non-COVID-19-related manifestations [9][10]. Such hyperinflammatory response correlates with disease severity and is characterized by an increase in proinflammatory cytokines, both in the bloodstream and in the bronco–alveolar lavage fluids [4][8][9][10][11][12].

Many studies have reported that a great percentage of patients surviving COVID-19 infection still display respiratory impairment even after discharge, resulting in a reduction in some key physiological parameters such as total lung capacity, forced vital capacity and forced expiratory volume as well as gas transfer ability, finally resulting in a long-term progressive and irreversible deterioration of lung function [4][5][13][14][15][16][17][18].

Consistently, recent studies showed that a large proportion of severe COVID-19 survivors develop fibrotic changes in the lung persisting for months after discharge, especially in elderly, male and mechanically ventilated patients, displaying high levels of inflammation markers (i.e., C-reactive protein (CRP), IL-6, lactate dehydrogenase (LDH), D-dimer). Furthermore, it has been observed that the degree of inflammation and the extent of lung tissue damage correlate with the degree of lung fibrosis, supporting the observed high prevalence of such complication in the most critical patients compared to those experiencing only a mild or moderate form of COVID-19 [13][15][18][19].

Considering its effect in modulating host immune responses, the Gas6/TAM axis has also gained attention in the context of COVID-19 studies, showing a direct correlation between plasma Gas6 levels and disease severity [20][21][22][23]. **Table 1** and **Table 2** summarize the most relevant papers investigating Gas6 and TAM receptor involvement in SARS-CoV-2 infection and subsequent disease.

Table 1. Summary of the most relevant literature (in vitro and clinical studies, clinical trials, and case reports) regarding Gas6 and TAM receptors involvement in SARS-CoV-2 infection and COVID-19 progression and management.

Article Type	Main Findings	Reference
Clinical study	In a cohort of moderate/severe COVID-19 patients admitted to the high-dependency/subintensive ward during the third wave of the pandemic, plasma Gas6 levels at admission predicted an adverse disease outcome.	[20]
Clinical study	In a cohort of COVID-19 patients admitted to the general wards or the intensive care unit during the first wave of the pandemic, plasma Gas6 levels correlated with negative disease evolution.	[21]
Clinical study	In a cohort of severe COVID-19 patients admitted to the intensive care unit during the first wave of the pandemic, plasma Gas6 levels discriminated survivors from nonsurvivors.	[22]
Clinical study	In a cohort of COVID-19 patients admitted to the emergency department during the first wave of the pandemic plasma Gas6 and Axl levels reflect COVID-19 severity and could predict disease evolution.	[23]
Clinical study	In a cohort of COVID-19 patients admitted to the pediatric emergency department, plasma Gas6 and MerTK levels were lower when compared to healthy controls.	[24]
In vitro study	Identification of Axl as a candidate receptor involved in SARS-CoV-2 infection and as a potential pharmacological target for clinical interventions. SARS-CoV-2 spike protein has been described as able to bind the Axl receptor and to use it as an alternative entry route, as confirmed by the lower viral load observed after Axl knockout or blocking with the soluble recombinant protein. Based on such observations, the authors suggest the use of soluble recombinant human-grade Axl as a potential therapeutic intervention in COVID-19 patients.	[25]
In vitro study	Overview of Axl's role in SARS-CoV-2 infection and role of its inhibitor bemcentinib as an antiviral agent.	[26]

Article Type	Main Findings	Reference
	SARS-CoV-2 spike protein has been described as able to directly bind Axl, which can then act as an alternative receptor for virus entry, and the pharmacological inhibition of the Axl pathway by bemcentinib strongly reduced viral load.	
In vitro study	Identification of gilteritinib as an antiviral agent against SARS-CoV-2. Gilteritinib's antiviral effect is supposed to rely on its ability to activate innate immunity by blocking Axl, which acts as an inhibitor of innate immune responses.	[27]
Preclinical study	Identification of gilteritinib as an in vitro antiviral agent and confirmation of its protective effect in vivo (Syrian hamster model). Gilteritinib's antiviral effect has been supposed to rely on its ability to interfere with Axl-mediated viral entry.	[28]
In vitro study	Identification of bemcentinib as an antiviral agent against SARS-CoV-2 in different cellular lines. The authors suppose that the observed pharmacological effect relies on Axl involvement in viral entry, as previously observed for other viral agents.	[29]
In vitro study	Identification of gilteritinib as a potent antiviral agent against SARS-CoV-2. Gilteritinib inhibits Axl and consequently downregulates the p38/MAPK pathway, which is involved in proinflammatory cytokine production.	[30]
In vitro study	Identification of bemcentinib as an antiviral agent against SARS-CoV-2. Bemcentinib inhibits Axl, which has been observed to be upregulated in COVID-19-infected lung cells. As Axl-mediated signaling is known to downregulate interferon-related host immune responses, its pharmacological inhibition could help in reducing viral infection.	[31]
Clinical trial	Overview of an ongoing clinical trial aimed to evaluate different drugs, including bemcentinib, as candidate agents for COVID-19 treatment.	[32]
Case report	Case report showing the successful use of gilteritinib in a patient with FLT3-mutated acute myeloid leukemia and severe COVID-19.	[33]
In vitro study	Identification of Axl as a candidate pharmacological target to revert SARS-CoV-2-induced epithelial-to-mesenchymal transition (EMT). Axl is a tyrosine kinase receptor typical of a mesenchymal phenotype, the expression of which is induced by SARS-CoV-2 infection and drives the EMT responsible for ARDS. The authors hypothesize that Axl inhibition by gilteritinib and bemcentinib, two drugs with proven antiviral activity, will not only reduce viral infection load but also will improve patients' conditions by reverting EMT.	[34]

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Article Type	Main Findings	Reference
Review	Description of the possible Gas6/TAM axis involvement in SARS-CoV-2 infection and COVID-19 complications. Overview of the first studies focused on TAM-targeted inhibition for COVID-19 management. TAM (in particular Axl) signaling is supposed to be involved at different stages of COVID-19 evolution. In particular, it has been supposed that the TAM pathway supports viral entry but also the development of immunothrombosis, which has been described to be associated with respiratory failure. According to Axl's supposed role in the viral	[35]

Article Type	Main Findings	Reference
	infection process, the already clinically available Axl inhibitors are being tested in clinical trials as anti-COVID-19 drugs.	
Review	Overview of Axl involvement in SARS-CoV-2 infection. Axl has been described as an alternative receptor for SARS-CoV-2 viral entry. Interestingly, the interaction involves the spike protein N-terminal domain instead of the receptor binding domain that is recognized by ACE-2. Axl's role as an entry receptor appears of particular interest in those cells and tissues where it is not co-expressed with ACE-2.	[36]
Review	Overview of Axl inhibitors as potential pharmacological treatments for COVID-19. Axl receptor acts as an alternative receptor for SARS-CoV-2 entry and its pharmacological inhibitors are currently being tested as potential anti-COVID-19 drugs.	[37]
Review	Overview of Axl inhibitors (gilteritinib and bemcentinib) as antiviral agents against COVID-19. Gilteritinib and bemcentinib antiviral action mainly rely on their ability to inhibit Axl signaling and consequently the downstream p38/MAPK pathway.	[38]

saus and colleagues, who suggested the TAM pathway involvement at different stages of SARS-CoV-2 infection, mainly focusing on viral mimicry and immunothrombosis, which is often observed as a complication in severe patients experiencing ARDS [35]. Since the publication of that work, many research groups focused their attention on this signaling pathway activation in COVID-19 to disclose the existing correlations between the Gas6/TAM axis and disease evolution. To date, most of the available studies in the literature on this topic date back to the first wave of the pandemic and show some important limits. The most significant limitations of these studies are represented by the wide difference in disease severity at admission and the hospital management of patients, as no clear therapeutic guidelines were available at that time, so, in many cases, information about pharmacological treatment is missing in published reports.

In their study, Morales and coworkers evaluated plasma Gas6 and sTAM expression at admission to emergency care units and observed a direct correlation between basal Gas6 and sAxl levels and disease severity [23]. Similar results were obtained also by Huckriede and colleagues, who studied a cohort of patients admitted to the ICU with severe disease, observing that plasma Gas6 levels were significantly higher in nonsurvivors compared to patients recovering from the disease, allowing good discrimination of patients who will develop irreversible acute lung injury. On the other hand, they did not find any correlation between sAxl levels and organ damage, further highlighting the importance of Gas6 in predicting disease evolution [22]. De Bruin's research group also obtained similar results in a cohort of patients admitted to the ICU and general wards, where a correlation between plasma Gas6 levels and negative disease evolution was observed [21].

It is important to note that almost all reports in the literature about the involvement of the Gas6/TAM axis in COVID-19 focus on the adult population. To date, only one study [24] evaluated this issue in pediatric patients, highlighting that, in contrast to what was observed in adults, both Gas6 and MerTK levels are lower in infected individuals than in healthy individuals, an observation that further supports the different disease evolution according to the age of the infected patients.

2. Axl Role in SARS-CoV-2 Infection

Even if the majority of the research papers are focused on the Gas6/TAM axis involvement in COVID-19, interesting results also come from in vitro research. Since the first decade of this century, different studies demonstrated, in vitro, that TAM receptors and their ligands, by acting as a bridge with PtdSer, could promote different enveloped virus infections (i.e., filovirus such as Ebola, and flaviviruses such as Dengue and West Nile) [35][39][40][41]. In particular, the Axl role in lung viral infections has also been studied in a murine model, where it has been demonstrated that its inhibition by monoclonal antibodies locally enhanced innate and adaptive immunity, suggesting Axl-targeted inhibition as an interesting clinical approach to treat viral lung diseases [42]. It is noteworthy that, according to available in vitro and in vivo evidence, Axl is not indispensable for enveloped virus entry, but might reasonably act as a "facilitator" in some cell types rather than others [39].

According to such evidence, Axl has also been investigated in the context of COVID-19 and in vitro results have highlighted an unsuspected role of Axl in the SARS-CoV-2 infection process, even if its exact mode of action has not yet been clarified. In particular, some reports demonstrated that the Axl receptor can specifically interact with the N-terminal domain of SARS-CoV-2 spike protein in an ACE2-independent manner, thus representing a potential alternative receptor for viral entry in pulmonary and bronchial epithelial cells, where Axl and ACE2 receptors are not co-expressed. These in vitro studies highlighted that knocking down Axl or its addition in the soluble recombinant form to cell culture is effective in reducing the viral infection of pulmonary epithelial cells, while its biological ligands (Gas6 and protein S) do not bind to SARS-CoV-2 [25][36]. According to this evidence, Axl may be involved in the viral endocytosis mechanism by interacting with virion-associated PtdSer residues [26][37]. Consistently, the inhibition of the intracellular Axl signaling pathway with bemcentinib reduced receptor-mediated viral internalization and new virions production in a dose-dependent manner [26].

This ability of SARS-CoV-2 to exploit different cellular receptors to infect host cells not only offers a reasonable explanation for its high infectivity and its wide tropism but also represents a new therapeutic target to limit COVID-19 spreading. Although Axl's involvement in tumor progression has been known for many years, different drugs targeting this receptor have already been developed and commercialized, fostering studies about their repurposing in COVID-19 management. As preclinical studies using Axl inhibitors such as bemcentinib and gilteritinib showed promising results [27][28][29][30][38], bemcentinib is under clinical trials to evaluate its effectiveness in treating SARS-CoV-2 infection [31][32], while it has been reported that gilteritinib administration in an acute myeloid leukemia patient ameliorated COVID-19 symptoms [33].

In addition to these studies investigating Axl's role as an alternative receptor for SARS-CoV-2 cell entry, a recent study focused on Axl involvement in COVID-19 pathogenesis, especially in the epithelial-to-mesenchymal transition (EMT) process [34]. The SARS-CoV-2 infection has been shown to upregulate different oncogenic pathways, including EMT [34][43]. Such an alteration in the adhesive properties of epithelial cells, especially in the lung district could thus be involved in altering air/blood barrier permeability, finally resulting in impaired respiratory function, typical of severe COVID-19. Considering Axl's role in regulating EMT, Stewart and coworkers hypothesized that

reverting EMT using Axl inhibitors such as bemcentinib, which displays a proven in vitro antiviral efficacy against SARS-CoV-2, could represent an attractive option to limit COVID-19 severity [34].

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