TITLE: An anti-SARS-CoV-2 metabolite is reduced in diabetes

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Standfirst: A glucose-like metabolite, reduced in the serum of diabetic patients, inhibits the entry of SARS-CoV-2 into key cellular targets. The work led by Prof. Cheng and colleagues provides a molecular explanation for the increased risk of severe COVID-19 in patients with diabetes.

From the very beginning of the SARS-CoV2 pandemic, patients with diabetes and other comorbidities were shown to be more prone to COVID-19 severe progression, probably due to a complex and multifactorial complication of their metabolic disease. Since then, understanding which risk factors increase the severity of COVID-19 in patients with diabetes has become a priority for improving their clinical management[4].

Identifying those factors that increase the probability of developing severe COVID-19 and its associated mortality upon infection is still a critical need for clinical practice and public health management. Patients at higher risk of severe complications and hospitalizations could benefit from early treatments[1], but they need to be diagnosed in a timely manner.

Several large genetic screenings have found distinct factors associated with severe clinical outcomes of COVID-19, enabling the identification of molecular pathways that could serve as targets for the development of novel treatments[2]. The best example of the success of this approach is Baricitinib, an inhibitor of the Janus kinase identified by genetic screening that has shown anti-inflammatory efficacy in preclinical models[3] and more recently also in clinical trials[1]. However, many other -omic platforms could be extremely useful in underscoring and revealing new pathways associated to critical disease, offering the possibility to find novel therapeutic targets to benefit those at higher risk.

It has been long suspected that prior metabolic disorders such as diabetes in COVID-19 patients may predispose to a severe course of viral infections[5]. However, how can a particular metabolic signature impact the course of COVID-19 remains largely unexplored. Tong *et al.* addressed in this paper if serum metabolites found in humans could modulate SARS-CoV-2 infection (Figure 1)[6]. Nontargeted metabolomic profiles of serum samples were used to identify a list of small molecules filtered via the Human Metabolome Database (https://hmdb.ca) with *in vitro* anti-SARS-CoV-2 activity. Almost three hundred of these metabolites were commercially available and individually screened for antiviral activity. These efforts revealed one such metabolite, 1,5-anhydro-D-glucitol (1,5-AG), which was able to block viral infection at physiological concentrations not only in cellular models, but also in more complex biological systems such as organoids. The authors also provided a mechanistical explanation showing how 1,5-AG inhibits viral fusion with the cellular membrane by binding to the S2 subunit of the SARS-CoV-2 spike protein. Intriguingly, this antiviral activity was also observed for other coronaviruses such as MERS-CoV, but not for other respiratory viruses.

A key finding of this study is that the levels of the antiviral metabolite identified here were significantly lower in diabetic patients as compared to non-diabetic individuals. In addition, the serum 1,5-AG levels in severe COVID-19 patients were lower than in those with milder disease or uninfected. This later observation may link COVID-19 severe progression to metabolic

complications associated to disease deterioration. When supplementing this metabolite to db/db mice, an animal model used to study diabetes type II, the pathological outcome caused by COVID-19 was reduced suggesting that modulation of 1,5-AG might be a new therapeutic avenue in this particular population.

These results for SARS-CoV-2 correlate with prior studies where diabetes was also found to be a poor prognosis marker for MERS and SARS infections[7,8], highlighting that 1,5-AG might be an indicator of disease progression. Importantly, in these infectious contexts, 1,5-AG supplementation could be favorable for patients with diabetes. While understanding the role of metabolites in the pathogenesis of COVID-19 and other coronavirus-related diseases holds a great potential, there are several challenges that need to be addressed which are currently common limitations in most metabolomic studies. The major technical problem identified here is the difficulty to obtain large sample cohorts that represent populations. Also, there is a high variation among laboratories in sample collection and analysis[9]. Furthermore, many of the molecular mechanisms by which viruses induce changes in host metabolism remain unidentified.

Metabolomics can provide insights into the interactions between pathogens and hosts and shed light on viral tropism. In fact, evidence has shown that host susceptibility to a viral infection might be related to the presence of endogenous metabolites[10]. Other factors including increased or reduced receptor expression, altered immune responses, and viral mutations in the receptor binding domain may also contribute to SARS-CoV-2 pathogenesis in patients with comorbidities. In this recent study, the role of 1,5-AG in disease progression and its antiviral effect was shown. Yet, the feasibility to administer this metabolite in diabetic patients will require future clinical trials. Thus, future steps will be: (i) to develop 1,5-AG derivate(s) with a long-term metabolic kinetics, (ii) to determine the anti-SARS-CoV-2 activity of the newly identified metabolites in humans, and (iii) to assess the role of 1,5-AG and other metabolites as biomarkers to identify disease outcome and patient prognosis. Altogether these future steps will help to implement timely and individualized therapeutic strategies.

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Figure 1. Identification and screening of human serum metabolites with anti-SARS-CoV-2 activity. Serum samples were collected from three individuals and measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). A total of 222 metabolites were selected and evaluated for their anti-SARS-CoV-2 activity in cell culture. From the metabolites with antiviral activity, 1,5-AG was present at lower concentration in diabetic patients. Diabetes is a risk factor for severe COVID-19, and *in vitro*, 1,5-AG was demonstrated to play a role during viral entry. Finally, db/db mice, a model of type 2 diabetes mellitus, showed lower amounts of 1,5-AG in serum and mice, but the levels of this metabolite were enhanced when a 1,5-AG-releasing osmotic pump was implanted subcutaneously in the animals.