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A glucose-like metabolite deficient in diabetes inhibits cellular entry of SARS-CoV-2

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The severity and mortality of COVID-19 are associated with pre-existing medical comorbidities such as diabetes mellitus. However, the underlying causes for increased susceptibility to viral infection in patients with diabetes is not fully understood. Here we identify several small-molecule metabolites from human blood with effective antiviral activity against SARS-CoV-2, one of which, 1,5-anhydro-D-glucitol (1,5-AG), is associated with diabetes mellitus. The serum 1,5-AG level is significantly lower in patients with diabetes. In vitro, the level of SARS-CoV-2 replication is higher in the presence of serum from patients with diabetes than from healthy individuals and this is counteracted by supplementation of 1,5-AG to the serum from patients. Diabetic (db/db) mice undergo SARS-CoV-2 infection accompanied by much higher viral loads and more severe respiratory tissue damage when compared to wild-type mice. Sustained supplementation of 1,5-AG in diabetic mice reduces SARS-CoV-2 loads and disease severity to similar levels in nondiabetic mice. Mechanistically, 1,5-AG directly binds the S2 subunit of the SARS-CoV-2 spike protein, thereby interrupting spike-mediated virus–host membrane fusion. Our results reveal a mechanism that contributes to COVID-19 pathogenesis in the diabetic population and suggest that 1,5-AG supplementation may be beneficial to diabetic patients against severe COVID-19.

The outcomes of a viral infection and disease progression are determined by complex host–virus interactions[1,2]. Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), presents highly heterogeneous clinical manifestations in humans[3,4]. The majority of individuals infected with SARS-CoV-2 have asymptomatic, mild or moderate disease; however, elderly individuals and patients with comorbidities such as type 2 diabetes mellitus are at a much higher risk of serious illness and even death[5]. Although complex immunological changes may underlie the vulnerability of these populations, metabolic disorders are also evident in patients with comorbidities[5,6] and could predispose them to severe viral infections[5,7]. Nonetheless, the role of metabolic factors in COVID-19 pathogenesis is still largely unknown.

Serum metabolites vary significantly in terms of quantity and compositions among individuals[8]. Therefore, we assessed whether the metabolites in human serum might regulate SARS-CoV-2 infection. Human serum samples were separated by centrifugation with a 3-kDa filter. Either the filtrates containing small-molecule metabolites or the upper retentate with serum proteins was incubated with Vero cells and infected with SARS-CoV-2 (Fig. 1a and Supplementary Table 1a). The amount of viral RNA was significantly reduced in cells treated with the serum filtrates compared to the infected control (Fig. 1b). Notably, incubation with the upper retentate also impaired viral infection, which may be attributed to virucidal proteinaceous factors, such as complements[9] (Fig. 1b). We next aimed to identify the metabolic component(s) with antiviral activity in human serum. A total 484 metabolite compounds, which were pooled from either our experiment of three donors or a published metabolites profile[10] (Supplementary Table 1b), were filtered using the Human Metabolome Database (HMDB) (https://hmdb.ca). A total of 298 small-molecule metabolites were identified for further investigation; notably, 222 were commercially available (Fig. 1c and Supplementary Table 2). We incubated Vero cells with 100 μM solutions of each metabolite and then infected them with SARS-CoV-2. Seven metabolites reduced the amount of viral RNA with an inhibition rate higher than 95% (Fig. 1d). *N*-oleoyl glycine was excluded from further analyses because of its potent cytotoxicity (Extended Data Fig. 1a). The antiviral activity of the remaining six metabolites was validated by immunofluorescence staining with a monoclonal antibody against the SARS-CoV-2 nucleocapsid (N) (Fig. 1e(i),(ii)). The 50% maximal inhibitory concentration (IC_{50}) of these metabolites ranged from 7.18 μM to 43.10 μM in Vero cells (Fig. 1f). Three metabolites,

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