



COVID 19, Paxlovid and the lesson from rare genetic diseases with naturally occurring protection from SARS-CoV-2 infection

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The coronavirus disease 2019 (COVID-19) pandemic, resulting from infection with SARS-CoV-2 has focused intense scientific interest on Angiotensin Converting Enzyme (ACE)2, as it is expressed in the respiratory epithelium, the heart, the kidney and the vascular wall and is used by the SARS-CoV-2 as an entry point into the cells [1].

The SARS-CoV-2 entry and replication-transcription mechanism is based in fact on the binding with glycosylated ACE2, whose glycosylation is dependent on the acidic pH environment of the trans Golgi network/post Golgi pathways in the endosomes, and by several proteases including Cathepsin (Cat)-L, whose activity is also dependent on the acidic endosomal pH [1].

Various therapies have been tested to date to fight the infection, the most effective of which have been the vaccines, monoclonal antibodies, remdesivir and the recently introduced Paxlovid. Of specific note is Paxlovid, which exerts its action by altering; the efficacy of intracellular proteins involved in the processes of SARS-CoV-2 entry into the cell, the functional viral protein release, and SARS-CoV-2 replication [2].

These effects of Paxlovid on virus entry and replication mechanisms draw attention to some rare genetic diseases, which have been reported to have naturally occurring protection from SARS-CoV-2 infection via similar mechanisms to those used by this drug.

We have reported that patients affected by rare genetic tubulopathies, Gitelman and Bartter syndromes seem to be protected from COVID-19. This protection has been observed in three surveys repeated in our cohort of Gitelman

and Bartter patients carried out during various waves of the pandemic in April 2020, April 2021 and January 2022. These surveys found that none of our 128 patients was hospitalized with COVID-19 and the very few patients who tested positive were either asymptomatic or had very minor symptoms [3, 4]. This despite the fact that Gitelman and Bartter syndrome patients have higher ACE2 levels than healthy subjects in addition to renin-angiotensin system activation, yet normo/hypotension and chronic metabolic alkalosis [1, 5]. Chronic metabolic alkalosis in Gitelman and Bartter patients could be the basis for the possible presence of a specific intracellular environment not favorable to SARS-CoV-2 infection [4, 6].

In a follow-up study we found that patients with Gitelman and Bartter syndromes have significantly higher non-glycosylated ACE2 levels and lower Cat-L activity compared with healthy individuals [4]. In addition, their Cat-L activity was inversely correlated to their blood bicarbonate levels [4]. Thus, alteration of ACE2 glycosylation and Cat-L activity, key elements for virus cell entry and viral replication-transcription, which is likely due to their chronic metabolic alkalosis-dependent alteration of the acidic pH environment in the endosome, provides the rationale for their protection from SARS-CoV-2 infection and/or severe complications [4, 6].

Patients with another rare disease, Fabry disease, also seem to be protected from SARS-CoV-2 infection.

Fabry disease is an X-linked rare metabolic disease caused by mutations in the gene coding for the lysosomal enzyme alpha-galactosidase A. The consequently reduced or altered lysosomal alpha-galactosidase A activity causes a progressive accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3) and lyso-Gb3, within lysosomes of cardiac, renal, vascular and pulmonary cells. This leads to impairment of lysosomal functions including endosomal maturation, autophagy processes and endosomal-lysosomal acidic pH [7]. These abnormal lysosomal functions thus likely produce an unfavorable host cellular environment

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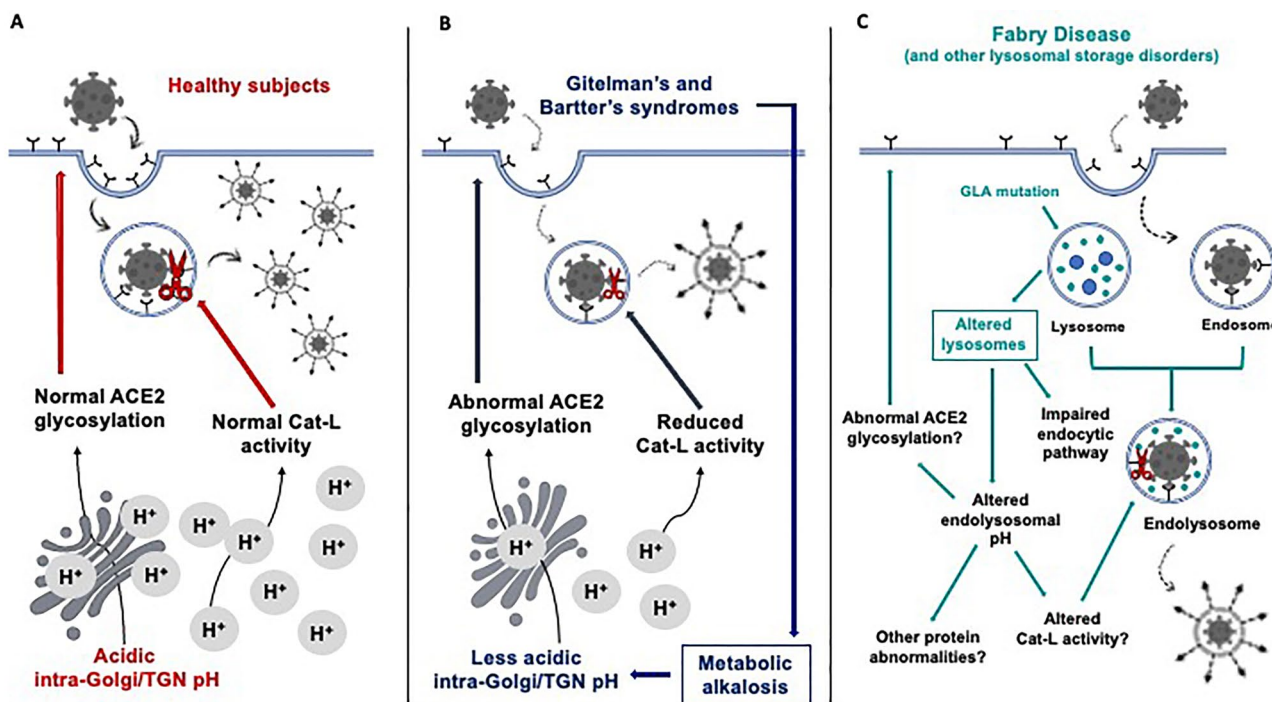


Fig. 1 Possible mechanism of altered ACE2 glycosylation and reduced Cat-L activity in Gitelman and Bartter Syndromes (B), Fabry Disease and other lysosomal storage disorders (C) compared to

healthy subjects (A), in causing reduced SARS-CoV-2 entry into the cell and reduced proteolytic cleavage of SARS-CoV-2 into the cell

thereby interfering with SARS-CoV-2 infection and propagation, which does not seem to be influenced by enzyme replacement treatment (ERT). Protection from COVID-19 of Fabry disease patients has been confirmed by a survey involving more than 200 Fabry disease patients between February and April 2020, which found that only 3 patients resulted positive for COVID-19, 1 with mild symptoms and 2 asymptomatic [8]. These findings were mirrored by a survey in our cohort of 40 ERT-treated Fabry patients, which found that only 1 tested positive for COVID-19 with only minor symptoms (personal unpublished data).

Interestingly, impairment of lysosomal functions, notably the alteration of intralysosomal pH, is a hallmark of another genetic lysosomal storage disease, Niemann-Pick disease type C (NPC) [9]. In NPC, altered cholesterol and sphingomyelin lysosomal trafficking induces intralysosomal accumulation and alteration of lysosomal functions, including impaired Cat-L and other hydrolytic enzyme activity [9]. These alterations led Ballout et al., to speculate that these NPC-related alterations in lysosomal activities, including intralysosomal acidic pH and reduction of Cat-L activity, could prevent SARS-CoV-2 cell entry and its intracellular processing by proteases such as Cat-L, thereby reducing virus infectivity [9].

In summary, the findings from these rare diseases point out the essential role of the endosomal-lysosomal functions

in SARS-CoV-2 infection (Fig. 1A). This is likely the case for the observed protection from SARS-CoV-2 infection in Gitelman and Bartter patients as a result of their chronic metabolic alkalosis via a mutation-driven alteration of the acidic pH of the trans Golgi network/post Golgi pathway in the endosome [3, 4, 6] (Fig. 1B). Impaired lysosomal functions, including the alteration of endo-lysosomal pH due to lysosomal storage disorders, seem to be the reason for protection from SARS-CoV-2 infection of Fabry disease patients [8] (Fig. 1C) and is likely to be the case also for NPC [9] (Fig. 1C).

These observations in human models of naturally occurring protection from SARS-CoV-2 infection provide a robust mechanistic rationale for the beneficial effects of the new antiviral Paxlovid, which exerts its effect via inhibition of proteins involved in lysosomal processes, key for SARS-CoV-2 cell entry and replication-transcription [2]. Studies are ongoing in our laboratory to establish whether, in addition to those shown in Gitelman and Bartter patients, these proteins are also altered in Fabry disease patients. The results provided by these studies could help further the search for new drug targets either of specific proteins involved in and/or specific lysosomal processes, that might prove useful in dealing with the evolving nature of SARS-CoV-2 infection.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

References

1. Stefanelli LF, Gobbi L, Ravarotto V, Bertoldi G, Calò LA (2022) The counter-regulatory arm of the renin-angiotensin system and COVID-19: insights from Gitelman's and Bartter's syndromes. *J Hypertens* 40:648–649. <https://doi.org/10.1097/HJH.00000000000003090>
2. Resnick SJ, Iketani S, Hong SJ, Zask A, Liu H, Kim S, Melore S, Lin F-Y, Nair MS, Huang Y, Lee S, Tay NES, Rovis T, Yang HW, Xing L, Stockwell BR, Ho DD, Chavez A (2021) Inhibitors of coronavirus 3CL proteases protect cells from protease-mediated cytotoxicity. *J Virol* 95:e0237420. <https://doi.org/10.1128/JVI.02374-20>
3. Calò LA, Rigato M, Sgarabotto L, Ianesello L, Bertoldi G, Ravarotto V, Davis PA (2021) ACE2 and SARS-CoV-2 infection risk: insights from patients with two rare genetic tubulopathies. Gitelman's and Bartter's syndromes. *Front Med* 8:647319. <https://doi.org/10.3389/fmed.2021.647319>
4. Bertoldi G, Ravarotto V, Sgarabotto L, Davis PA, Gobbi L, Calò LA (2022) Impaired ACE2 glycosylation and protease activity lowers COVID-19 susceptibility in Gitelman's and Bartter's syndromes. *J Intern Med* 291:522–524. <https://doi.org/10.1111/joim.13426>
5. Calò LA, Davis PA, Rossi GP (2014) Understanding the mechanisms of angiotensin II signaling involved in hypertension and its long-term sequelae: insights from Bartter's and Gitelman's syndromes, human models of endogenous angiotensin II signaling antagonism. *J Hypertens* 32:2109–2119. <https://doi.org/10.1097/HJH.0000000000000321>
6. Calò LA, Davis PA (2021) Far di Necessità Virtù, using rare tubulopathies, Gitelman's and Bartter's syndromes, to inform the fight against COVID-19. *J Nephrol* 34:281–283. <https://doi.org/10.1007/s40620-020-00951-6>
7. Ivanova MM, Changsila E, Iaconou C, Goker-Alpan O (2019) Impaired autophagic and mitochondrial functions are partially restored by ERT in Gaucher and Fabry diseases. *PLoS One* 14:e0210617. <https://doi.org/10.1371/journal.pone.0210617>
8. Pieroni M, Pieruzzi F, Mignani R, Graziani F, Olivetto I, Riccio E, Ciabatti M, Limongelli G, Manna R, Bolognese L, Pisani A (2021) Potential resistance to SARS-CoV-2 infection in lysosomal storage disorders. *Clin Kidney J* 14:1488–1490. <https://doi.org/10.1093/ckj/sfab045>
9. Ballout RA, Sviridov D, Bukrinsky MI, Remaley AT (2020) The lysosome: a potential juncture between SARS-CoV-2 infectivity and Niemann-Pick disease type C, with therapeutic implications. *FASEB J* 34:7253–7264. <https://doi.org/10.1096/fj.202000654R>

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