

Furin Protease: From SARS CoV-2 to Anthrax, Diabetes, and Hypertension

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Perm J 2020;24:20.187

E-pub: 09/16/2020

<https://doi.org/10.7812/TPP/20.187>

ABSTRACT

Furin is a protease that is ubiquitous in mammalian metabolism. One of the innovations that make sudden acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) more infectious than its ancestor viruses is the addition of a furin cleavage site. Conditions associated with elevated furin levels, including diabetes, obesity, and hypertension, overlap greatly with vulnerability to the severe form of coronavirus disease 2019 (COVID-19). We suggest that diet and lifestyle modifications that reduce the associated comorbidities may prevent the development of severe COVID-19 by, in part, lowering circulating furin levels. Likewise, natural and pharmaceutical inhibitors of furin may be candidate prophylactic interventions or, if used early in the COVID-19, may prevent the development of critical symptoms.

INTRODUCTION

The sudden acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has a spike protein that binds to a cell's angiotensin-converting enzyme 2 (ACE2) receptor, locking it on the cell membrane. To enter the cell, however, the virus must leave the spike protein behind. Coutard et al¹ recently proposed that the SARS-CoV-2 spike glycoprotein (S) contains a furin cleavage complex (FCC). The FCC adds to SARS-CoV-2 infectivity and pathogenicity in multiple ways.

VIRAL HIJACKING OF FURIN PROTEASE

Furin is a protease essential to the mammalian host's biochemistry, but in this instance, it is hijacked by SARS-CoV-2 to facilitate the separation preliminary to entering the cell. The FCC greatly enhances the virus's infectivity, and it is a strong candidate as the gain-of-function² mutation that enabled SARS-CoV-2 to jump from animals to humans and rapidly spread to pandemic levels.

In addition to using furin to gain entry into the host cell, SARS-CoV-2 also uses endogenous furin to cleave the S protein in the trans-Golgi network right after virion assembly. This latter mechanism separates furin from other virally hijacked proteases (eg, TM-RPCC2),² potentially increasing the pathogenicity of SARS-CoV-2.² Infection with a variant of SARS-CoV-2 that omits the FCC site resulted in a blunted illness in hamsters.³ Braun and Sauter⁴ note that the ability of viruses to exploit furin may have major effects on their pathogenicity. In fact, as observed in the hamster study by Lau et al,³ the same virus without the FCC might be avirulent, whereas the addition of the FCC can allow the virus to spread systemically and cause higher rates of mortality. Furin is present in most tissues and is highly expressed in the lungs.⁵

We already know that furin plays a role in the potent virulence of dengue fever and other aggressive infections, including HIV and various avian influenzas.⁶ Anthrax toxin is liberated by furin

from *Bacillus anthracis*, and furin cleavage allows the anthrax toxin to flood the body *before* innate immunity kicks in effectively,⁷ greatly increasing lethality. Similarly, the SARS-CoV-2 viral load can overwhelm the system before innate immunity can bring it under control.⁸ It is well known that underlying comorbidities have a pronounced effect on the lethality of coronavirus disease 2019 (COVID-19). Here, we explore the possibility that baseline inflammation contributes to a delayed response from the innate immune system, and that furin itself might hold a key role in both the virus-initiated delayed immune response and the influence of comorbidities.

ROLE OF FURIN IN DISEASE

Furin is a key protease in humans. It is ubiquitous in nature, including other mammals, where it is found in the Golgi apparatus and on the cell surface of most tissue cell types. Furin exists in both membrane-bound and secreted forms. Furin cleaves and activates a diverse group of more than 100 proproteins and peptides in normal human physiology. Higher plasma furin levels have been identified in individuals on the cardiometabolic continuum years before the onset of diabetes. Furin, independent of all other risk factors, is associated with an increased risk of diabetes, hyperinsulinemia, hypertension, hyperlipidemia, obesity, and all-cause mortality.^{9,10}

Fernandez and colleagues⁹ explain: "*Regarding potential mechanisms, as furin is responsible for the maturation of the insulin pro-receptor, one could speculate that more furin in circulation reflects a compensatory mechanism to increase the synthesis of active insulin receptors. Another possible mechanism of action of furin in [diabetes mellitus] development may be via pancreatic β -cells; furin has been demonstrated to control the proliferation and differentiation of pancreatic β -cell lines and to be involved in the maturation of insulin secretory granules.*"

Why has the US been overwhelmed with COVID-19 cases? More than 1 in 3 Americans have cardiometabolic disease,¹¹ and individuals on the cardiometabolic continuum are hardest hit by the virus. A reason for this finding may be the presence of elevated furin levels identified in this population, even well before the onset of disease, making them particularly vulnerable to the SARS-CoV-2 cellular entry and replication.

Beyond entry and replication, furin also activates a number of peptides in normal human physiology that may influence COVID-19 pathogenesis. For example, furin modulates the renin

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Keywords: furin, furin cleavage complex, furin protease, SARS-CoV-2

angiotensin aldosterone system (RAAS)¹² by activating the prorenin receptor, which mediates formation of vasoconstrictor angiotensin. Recall angiotensin promotes release of aldosterone, sparing sodium at the expense of potassium. Hypokalemia (and RAAS interference through ACE2) are present in COVID-19,¹³ although whether furin plays a key role here remains to be elucidated.

Coagulopathy and associated hypoxia involving von Willebrand factor and clotting factor VIII appear to play a central role in COVID-19 pathology. Furin is necessary for activation of clotting factor VIII.¹⁴ Notably, furin expression is potently induced by hypoxia,⁴ as all 3 *FUR* promoters harbor binding sites for the hypoxia inducible factor-1 (HIF-1). Severe hypoxia is, of course, a hallmark finding in the most severe COVID-19 cases.

The following questions remain to be answered:

1. Do individuals with the comorbidities associated with COVID-19 have higher baseline furin levels that increase SARS-CoV-2 infectivity and pathogenicity?
2. Given the ubiquitous nature of furin proteases in normal human physiology, could this coincide with known SARS-CoV-2 pathogenic mechanisms?
3. Could these coincidences increase when the baseline furin level is increased?

TREATMENT OPTIONS

Nonspecific furin inhibition may be associated with substantial side effects given the myriad roles furin plays in human physiology. Heparin, however, is a furin inhibitor⁵ with a known and generally accepted risk-benefit ratio. Given the risk of coagulopathy seen in some patients with COVID-19, it isn't surprising that heparin use has been associated with lower mortality in hospitalized patients.¹⁵ Furin expression is potently induced by hypoxia, as all 3 *FUR* gene promoters harbor binding sites for hypoxia-inducible factor-1 (HIF-1). Berberine is an HIF-1 inhibitor, and may therefore be a treatment consideration for COVID-19 patients.¹⁶ Resolving cardiometabolic diseases through diet, lifestyle modifications, and pharmaceutical interventions should reduce furin levels and baseline inflammation, which could reduce viral entry and replication, allowing the innate immune system to better respond and leading to a more benign course of illness. Natural compounds with *in vitro* evidence of potential effectiveness and a good safety profile include 4 flavonoids that appear to inhibit furin catalytic activity: (1) luteolin (> 95% inhibition *in vitro*),¹⁷ (2) baicalein, (3) chrysin, and (4) oroxylin.¹⁸

LABORATORY TESTING

If furin proves to play an important role in COVID-19 pathogenesis, serum furin measurement could be useful. However, furin testing is currently limited to the research setting only.

CONCLUSION

Comorbidities associated with COVID-19 include those that comprise cardiometabolic disease, including obesity, diabetes, and hypertension. These conditions are associated with increased circulating furin levels. Because SARS-CoV-2 uses elevated furin to both gain cellular entry (through the FCC gain-of-function mutation) and to propagate with a high level of efficiency, it overwhelms the body's ability to orchestrate an effective immune response. Addressing comorbidities (and associated elevated furin levels)

through diet, lifestyle modifications, and pharmacologic management is a logical strategy for reducing COVID-19 pathogenicity. Natural and pharmacologic furin inhibitors may prove highly useful to inhibit viral entry and propagation. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

Kathleen Loudon, ELS, of Loudon Health Communications performed a primary copyedit.

How to Cite This Article

Fitzgerald K. Furin protease: From SARS CoV-2 to anthrax, diabetes, and hypertension. *Perm J* 2020;24:20.187. DOI: <https://doi.org/10.7812/TPP/20.187>.

References

1. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res* 2020 Feb;176:104742. DOI: <https://doi.org/10.1016/j.antiviral.2020.104742>.
2. Li H, Wu C, Yang Y, et al. Furin, a potential therapeutic target for COVID-19 [Chinese]. *ChinaXiv* 2020 Feb 23;202002.00062 [cited 2020 Aug 24]. Available from: www.chinaxiv.org/abs/202002.00062.
3. Lau S-Y, Wang P, Mok BW-Y, et al. Attenuated SARS-CoV-2 variants with deletions at the S1/S2 junction. *Emerg Microbes Infect* 2020 May 4;175:1-15. DOI: <https://doi.org/10.1080/22221751.2020.1756700>.
4. Braun E, Sauter D. Furin-mediated protein processing in infectious diseases and cancer. *Clin Transl Immunol* 2019 Aug 5;8(8):e1073. DOI: <https://doi.org/10.1002/cti2.1073>.
5. Belen-Apak FB, Sarialioglu F. The old but new: Can unfractionated heparin and low molecular weight heparins inhibit proteolytic activation and cellular internalization of SARS-CoV2 by inhibition of host cell proteases? *Med Hypotheses* 2020 Sep;142:109743. DOI: <https://doi.org/10.1016/j.mehy.2020.109743>.
6. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020 Apr 16;181(2):281-92.e6. DOI: <https://doi.org/10.1016/j.cell.2020.02.058>.
7. Stubbs MT II. Anthrax X-rayed: New opportunities for biodefence. *Trends Pharmacol Sci* 2002 Dec;23(12):539-41. DOI: [https://doi.org/10.1016/S0165-6147\(02\)02127-2](https://doi.org/10.1016/S0165-6147(02)02127-2).
8. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020 Mar;38(1):1-9. DOI: <https://doi.org/10.12932/AP-200220-0772>.
9. Fernandez C, Rysä J, Almgren P, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. *J Intern Med* 2018 Oct;284(4):377-87. DOI: <https://doi.org/10.1111/joim.12783>.
10. Ji H-L, Zhao R, Matalon S, Matthay M. Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. *J Physiol Rev* 2020 Jul;100(3):1065-75. DOI: <https://doi.org/10.1152/physrev.00013.2020>.
11. Prediabetes—Your chance to prevent type 2 diabetes. Atlanta, GA: Centers for Disease Control and Prevention. Reviewed 2020 Jun 11 [cited 2020 Sep 2]. Available from: <https://www.cdc.gov/diabetes/basics/prediabetes.html>.
12. Cilhoroz BT, Schifano ED, Panza GA, et al. FURIN variant associations with postexercise hypotension are intensity and race dependent. *Physiol Rep* 2019 Feb;7(3):1-13. DOI: <https://doi.org/10.14814/phy2.13952>.
13. Chen D, Li X, Song Q, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. *JAMA Netw Open* 2020;3(6):e2011122. doi: <https://doi.org/10.1001/jamanetworkopen.2020.11122>.
14. Mazurkiewicz-Pisarek A, Plucienniczak G, Ciach T, Plucienniczak A. The factor VIII protein and its function. *Acta Biochim Pol* 2016;63(1):11-16. DOI: https://doi.org/10.18388/abp.2015_1056.
15. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. *J Thromb Thrombolysis* 2020 Aug;50(2):298-301. DOI: <https://doi.org/10.1007/s11239-020-02162-z>.
16. Lin S, Tsai S-C, Lee C-C, Wang B-W, Liou J-Y, Shyu K-G. Berberine inhibits HIF-1 α expression via enhanced proteolysis. *Mol Pharmacol* 2004 Sep;66(3):612-19.
17. Peng M, Watanabe S, Chan K, et al. Luteolin restricts dengue virus replication through inhibition of the proprotein convertase furin. *Antiviral Res* 2017 Jul;143:176-85. DOI: <https://doi.org/10.1016/j.antiviral.2017.03.026>.
18. Majumdar S, Mohanta BC, Chowdhury DR, Banik R, Dinda B, Basak A. Proprotein convertase inhibitory activities of flavonoids isolated from *oroxylum indicum*. *Curr Med Chem* 2020;17(19):2049-58. DOI: <https://doi.org/10.2174/092986710791233643>.