PNAS LETTER

Rebound increase in circulating dipeptidyl peptidase 4 (DPP4) enzyme activity after acute COVID-19

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I have read with great interest the paper by Yang et al. who assessed the plasma metabolome and cytokine profile in the blood obtained from convalescent-phase COVID-19 patients (1). They reported that glycylproline (gly-pro) strongly accumulated in individuals with rapidly declining antibody levels defined as no detectable SARS-CoV-2–specific IgG antibodies 40 to 70 d after the COVID-19 onset (1). Experimental evidence also demonstrated that gly-pro directly suppressed the immune responses upon SARS-CoV-2 infection. Gly-pro is a known product of enzymatic dipeptide cleavage from the N-terminal of different proteins catalyzed by the dipeptidyl peptidase 4 (DPP4) that in many cases results in the biological inactivation of proteins as well (1–3).

We published earlier that the reduction of circulating DPP4 activity was associated with the worsening severity of acute COVID-19 disease and was one of the strongest prognostic biomarkers of mortality, deserving interest for potential future application in the clinical care (4, 5). The serum DPP4 enzyme activity—measured by gly-pro/paranitroaniline (pNA) hydrolysis—was significantly increased in the convalescent phase in individuals who donated plasma after acute SARS-CoV-2 infection compared with those still hospitalized with acute COVID-19 (4, 5). Moreover, we also found an increase in the serum DPP4 activity of plasma donors in the convalescent phase compared with SARS-CoV-2–naive individuals who never had been exposed to this virus (4, 5). The pattern of change in serum DPP4 activities according to the disease course and virus exposure (acute vs convalescent COVID-19 phases and convalescent vs SARS-CoV-2 naive) (Table 1) suggests a rebound increase evolving in the convalescent phase after a significant decrease in the acute phase. Rebound increases above the normal range are known medical phenomena that occur after an acute pathologic condition is resolved. Perhaps the most well-known example for a rebound increase is the posthypoglycemic hyperglycemia, i.e., the Somogyi effect in diabetes care (6, 7).

The significant rebound increase in circulating DPP4 activity in the convalescent phase of COVID-19 explains the strong accumulation of gly-pro in individuals with rapidly fading

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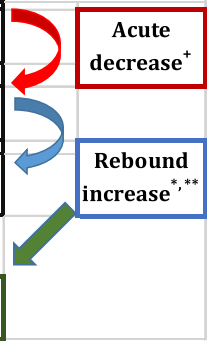
Table 1. Circulating sDPP4 enzyme activities in different study groups stratified by SARS-CoV-2 virus exposure and phase of COVID-19 disease

Circulating biomarker	Study groups startified by SARS-CoV-2 virus exposure and phase of COVID-19 disease	Valid N	Mean	Confidence -95%	Confidence 95%	Std. Dev.	Median	Lower Quartile	Upper Quartile
sDPP4 activity (U/L)	SARS-CoV-2 naïve controls	39	**33.83**	31.54	36.13	7.08	**33.2**	30.01	39.27
sDPP4 activity (U/L)	Hospitalized patients with acute COVID-19	100	**24.83**	23.06	26.6	8.93	**23.24**	17.8	30.34
sDPP4 activity (U/L)	Plasma donors (convalescent phase)	43	**40.55**	37.91	43.18	8.56	**40.16**	34.28	49.49



Plasma donors were at least 14 d after complete recovery from PCR-confirmed SARS-CoV-2 infection and had presence of anti-SARS-CoV-2 antibodies in the testing performed on the day of screening for convalescent plasma donation that was subsequently used for the treatment of severe cases with acute COVID-19 disease.
+Mann–Whitney U test, P < 0.0001, acute (hospitalized) Covid-19 cases vs SARS-CoV-2–naive individuals.
*Mann–Whitney U test, P < 0.0001, convalescent-phase vs acute (hospitalized) Covid-19 cases.
**Mann–Whitney U test, P = 0.0003, convalescent-phase Covid-19 vs SARS-CoV-2–naive individuals.
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antibodies and suggests a highly coordinated regulatory process of the immune system that employs the aminopeptidase function of the multifunctional DPP4 protein. It is especially intriguing that DPP4 has also been predicted to have a weak interaction with the receptor-binding domain of SARS-CoV-2 and emerged as a coreceptor candidate in physical proximity to the attachment sites of the spike protein on the host cell membrane (8, 9).

The question, whether this multifaceted interaction between DPP4 and SARS-CoV-2 evolved to help the patients to decrease the virus-specific antibody levels that are no longer sustainable/needed after recovering from an acute coronavirus infection such as COVID-19 (and potentially MERS also ref. 10) urges further studies. Taken together, DPP4 may be involved in a novel regulatory mechanism that drives the fading of the immune response against these particular pathogens after the acute infection.

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1. Z. Yang *et al.*, Plasma metabolome and cytokine profile reveal glycylproline modulating antibody fading in convalescent COVID-19 patients. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2117089119 (2022).
2. C. F. Deacon, Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. *Front. Endocrinol. (Lausanne)* **10**, 80 (2019).
3. R. Mentlein, Dipeptidyl-peptidase IV (CD26)–role in the inactivation of regulatory peptides. *Regul. Pept.* **85**, 9–24 (1999).
4. A. Nadasdi *et al.*, Decreased circulating dipeptidyl peptidase-4 enzyme activity is prognostic for severe outcomes in COVID-19 inpatients. *Biomark. Med.* **16**, 317–330 (2022), 10.2217/bmm-2021-0717.
5. G. Firneisz, Z. Prohászka, I. Vályi-Nagy, "Methods for prediction of severity and risk of mortality of Covid-19 disease and pre-screening of acute SARS-CoV-2 infections." (PATENTSCOPE: WO/2022/180415, WIPO IP PORTAL) (2022), International Patent Application No. PCT/HU2022/050016.
6. G. Reyhanoglu, A. Rehman, "Somogyi Phenomenon" in *StatPearls* (Treasure Island (FL), 2022).
7. M. Watts, Somogyi phenomenon – Rebound hyperglycemia (Diabetes.co.uk, 2019), https://www.diabetes.co.uk/blood-glucose/somogyi-phenomenon.html (22 December 2022).
8. K. Cameron, L. Rozano, M. Falasca, R. L. Mancera, Does the SARS-CoV-2 spike protein receptor binding domain interact effectively with the DPP4 (CD26) receptor? A molecular docking study. *Int. J. Mol. Sci.* **22**, 7001 (2021).
9. N. Kotani, T. Nakano, R. Kuwahara, Host cell membrane proteins located near SARS-CoV-2 spike protein attachment sites are identified using proximity labeling and proteomic analysis. *J. Biol. Chem.* **298**, 102500 (2022).
10. H. Zeberg, S. Pääbo, The MERS-CoV receptor gene is among COVID-19 risk factors inherited from Neandertals. bioXriv [Preprint] (2020). 10.1101/2020.12.11.422139 (22 December 2022).