Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Host – virus – drug interactions as determinants of COVID-19's phenotypes: A data-driven hypothesis

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A B S T R A C T

There is a growing body of evidence on the significance of interactions between comorbidities, their treatments and COVID-19 clinical phenotypes. The hypothesis explored herein is that pharmaceutical compounds currently in use are affecting COVID-19 susceptibility and phenotypes by overlapping transcriptional networks.

Using two distinct SARS-CoV-2 – host interactomes, gene set enrichment analysis is used to discover compounds and assorted gene signatures derived from SARS-CoV-2 interactomes. Micronutrients, antiplatelets, ACE2 inhibitors, NSAIDs, corticosteroids and tyrosine kinase inhibitors are among the compounds discovered. Considering the implication of their associated comorbidities such as diabetes and cardiovascular disease that are associated with severe COVID-19, this study outlines the need to consider specific compounds as modulators of the observed COVID-19 spectrum. Furthermore, given that micronutrient trafficking may be targeted by viral processes, and display synergism with other enriched compounds, such as statins, studies assessing their levels prior and during infection are more than warranted.

Introduction

There is a growing body of evidence on the significance of interactions between comorbidities and COVID-19 clinical phenotypes [1]. Correspondingly, observational studies that have attempted to link concomitant drugs with COVID-19 outcomes [2]. Recent advances in mapping the perturbations of SARS-CoV-2 infection on the host's transcriptome [3,4] may allow a more in-depth approach, enabling the discovery of overlapping gene signatures at the host – drug – gene interface. The significance of these signatures lies in the potential modulation of COVID-19 outcomes, as well as determining the drug – modified host susceptibility prior to infection.

Hypothesis

The hypothesis explored herein is that pharmaceutical compounds currently in use are affecting transmission dynamics and COVID-19 phenotypes by host – virus – drug overlapping transcriptional networks.

Evaluation of the hypothesis

For the evaluation of this hypothesis, host – virus – drug interactions on the transcriptomic level were considered by interrogating a previously generated dataset [5]. For the generation of the host – virus – drug dataset, gene set enrichment analyses (GSEA) were performed on two SARS-CoV-2 associated signatures: (a) differentially expressed genes extracted from pathway lists made available by Bojkova et al [3] – **Interactome A** ($\mathbf{I_A}$) and (b) master regulator analysis-derived SARS-CoV-2 / human interactors made available by Guzzi et al [4] – **Interactome B** ($\mathbf{I_B}$). The purpose of utilizing both lists was to assess the potential human interactome of SARS-CoV-2 in a complimentary manner.

Following the reconstruction of the two interactomes, drug – gene set enrichment analyses (D-GSEA) were performed via the Enrichr web service [6], screening (a) the DSigDB, a database of human gene – drug interactions [7] and gene signatures extracted from drug perturbation experiments available on Gene Expression Omnibus (GEO) [8]. For all analyses, p-values and false discovery rates (FDR) < 0.05 were considered statistically significant.

Results

Antihypertensives, NSAIDs, Corticosteroids, statins, specific kinase receptor inhibitors and anticoagulants were among salient drug classes significantly enriched by both SARS-CoV-2 gene signatures; Furthermore, trace metals and vitamins were also included in the list of significantly enriched compounds (Table 1 and Supplementary Materials 1). Of note, valproic acid was associated with the largest gene signature, comprised of 157 genes from I_A (Adjusted p-value = $2.16e^{-7}$).

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Table 1
Compounds identified by interrogating the DSigDB database, using two distinct SARS-CoV-2 – Host interactomes (I_A and I_B).

Compound	Hits		Adjusted p-value	
	I_A	I_B	I_A	I_B
Acetaminophen	95	5	$2.03e^{-4}$	0.044
Amantadine	7		0.019	
Amikacin	30		$1.44e^{-12}$	
Aspirin	21	12	0.003	0.004
Baclofen	15		$1.64e^{-4}$	
Benserazide	6	5	0.002	0.021
Captopril	30	3	$2.98e^{-4}$	0.023
Cimetidine	40		$4.60e^{-7}$	
Clindamycin	95	18	$4.36e^{-29}$	0.023
Colchicine	10		0.001	
Copper	52		$3.27e^{-5}$	
Dexverapamil	18		$1.42e^{-4}$	
Enalapril	5		0.010	
Fluvastatin	5		0.001	
Imatinib		5		0.013
Lonafarnib		3		0.018
Losartan		4		0.045
Metoclopramide	11		$8.34e^{-6}$	
Metronidazole	29		$1.65e^{-4}$	
N-Acetyl-Cysteine		7		0.030
Primidone	5	4	0.017	0.026
Selenium	57	22	$3.69e^{-8}$	0.001
Valproic Acid	175		$2.16e^{-7}$	
Vitamin E	53	22	$5.11e^{-7}$	0.001
Warfarin		4		0.027
Zinc		17		0.043

I_A refers to the SARS-CoV-2 – host interactome extracted from Bojkova *et al*'s study; I_B refers to the SARS-CoV-2 – host interactome extracted from Guzzi *et al*'s study. The order of selection was alphabetical, based on first author name. "Hits" refers to the number of genes comprising each drug – associated signature.

Discussion

The compounds identified via D-GSEA of host pathways affected by SARS-CoV-2 generally outline three major aspects of host – virus – drug interactions: (a) Host immune fitness, codetermined by an adequate homeostasis of trace metals and other micronutrients (b) modulation of the host – virus interaction interface during viral latency (c) amelioration of the host's inflammatory and stress responses.

Host immune fitness as determined by micronutrient status

As a host factor, tissue micronutrient availability presents a major modifiable parameter affecting immune fitness. Several studies have shown that both trace metals and vitamins are implicated in maintaining crucial aspects of immunosurveillance and mounting an effective antiviral response [9].

Effective intracellular latency depends on the subversion of Cu and Zn trafficking from the host during the course of viral infections, with the efflux of these ions diverted to virion assembly and as cofactors to viral proteins [10,11]. Aside from latency mechanisms, a perturbed intracellular copper trafficking axis furthermore amounts to impaired phagocytosis and thus susceptibility to pathogens requiring phagosomal copper repletion [11]. A deeper layer of interplay can be found in host – virus interactions on the transcriptional level [12,13], as well as the conjugation of viral lifecycles, mutagenesis and their virulence with cellular micronutrient stores, as is the case with Cu [10] and Se [14].

Malnutrition as a substrate for the development of both severe COVID-19 and susceptibility to SARS-CoV-2 was among the earliest hypotheses in the literature [15]. Currently, a recent study by Zhang and colleagues has indicated that Se nutritional status may be associated with COVID-19 outcomes [16]. Given selenium's role in platelet aggregation and endothelial interactions [17], its role in the development of severe disease manifestations such as coagulopathy [18] may account for these observations.

Modulation of the host – virus interactions following infection

ACEi are perhaps the most salient compounds governing this aspect of the host – virus – drug interactions. As ACE2 is indispensable for SARS-CoV-2's cellular entry [19], ACEi are currently under evaluation as potential therapeutic compounds against COVID-19 [20]. In a similar manner, statins have been previously evaluated in numerous RNA viruses as potential perturbators of lipid raft hijacking during the viral lifecycle [21]. Considering the transcriptomic evidence supporting SARS-CoV-2's modulation of the host's metabolic cascades, it is likely that this strategy is also utilized by the novel coronavirus [22]. Notably, selenium supplementation and statins may function synergistically in downregulating HMG-CoA reductase [23], indicating that micronutrient status may furthermore affect host-drug interactions aside from immune fitness.

A major implication of this study's findings is that in the setting comorbidities associated with severe COVID-19 phenotypes, i.e. metabolic and cardiovascular disease, the risk may be mitigated by medications already received by these patients. In this sense, the potential host – virus – drug interactions should be considered both in risk stratification, but also in determining whether their cumulative effect results in positive outcomes.

As a case in point, the risk of developing severe COVID-19 in patients receiving concomitant anticoagulant therapy may be mitigated between said anticoagulant use and concomitant cardiovascular comorbidities [24,25]. In the setting of COVID-19 phenotypic spectrum, it becomes evident that concomitant medication are already contributing to the observed outcomes.

Host inflammatory and stress responses as determinants of COVID-19 morbidity

Aside from the detrimental effects of infection, comorbidities and the drug-modulated pathways of the host, the immune response and the effect of stress cascades may be contributing to what is perceived as severity and outcomes for COVID-19. The elevation of systemic stress and inflammation biomarkers indicates that the host's response may contribute to overall tissue and organ detriment [26]. Considering preliminary reports on the efficacy of dexamethasone in limiting mortality in severe COVID-19 [27], agents limiting the host's stress and inflammatory responses may be correspondingly mitigating outcomes. Considering that dysregulated cytokine responses may emerge even from moderate disease stages and result in organ damage [28], successful inflammation restriction whether host or host – drug mediated has been outlined a determinant of COVID-19's spectrum.

In severe COVID-19, this niche would be addressed by empiric approaches such as NSAIDs, corticosteroids, glycemic control and secondary ischemic prevention measures [29].

In this study, the empirical approach is corroborated by transcriptomic evidence; specifically, pathways associated with the later compounds have already been targeted during the course of SARS-CoV-2's latency, and presumably function to precipitate each corresponding complication.

Concluding remarks

In accordance to epidemiological observations, multiple gene signatures associated with significantly enriched compounds were identified by this study. These compounds would affect COVID-19 phenotypes in three interconnected concepts: host immune fitness, the modulation of viral – host interactions and finally the modulation of the host's stress and immune cascades.

Contrary to common interpretations of pharmacogenomic studies, the purpose of the current analysis is to provide a list of virus – host – drug interactions that will serve accurate phenotyping of the COVID-19 clinical spectrum. While any of these compounds could be theoretically repurposed, such as i.e. antiplatelets, considering COVID-19 associated coagulopathy, transmission dynamics indicate that SARS-CoV-2 infection occurs in patients already receiving these agents.

This observation, along with the concept of specific compound (rather than arbitrary drug class) – virus – host interactions, outline an imminent need for a paradigm shift in phenotyping. Interestingly, gene signatures associated with each compound may be complimentary, and thus, interacting comorbidities (i.e. cardiovascular and metabolic disease) may also share interacting compounds with respect to the SARS-CoV-2 – host interface.

Whether this matter is addressed or not, transmission dynamics are inevitably affected, as well as the biological behavior of SARS-CoV-2 itself, by pre-existing drug – host interactions. As a case in point, it worth considering the effects on Se depletion in inducing provirulent genomic changes [30] in otherwise avirulent latent viruses [31] – especially when considering that its role in SARS-CoV-2 infection has not yet been fully elucidated.

Furthermore, considering that the compounds identified in this analysis are widely used and often in patients with the constellation of comorbidities associated with severe COVID-19, further scrutiny is required in identifying their modulatory effects on disease outcomes. Phenotyping studies should furthermore consider that even comorbidities associated with worse outcomes may be treated with medications that could actually mitigate severe COVID-19 outcomes, both based on mechanistic effects (i.e. coagulopathy averted by anticoagulants) and the transcriptional interactions detected in this study. Micronutrient status and the possibility of cryptogenous malnutrition regarding key trace metals mandates further exploration both by clinical and population based studies. Given that regional nutritional status has previously been associated viral transmission dynamics [32] and disease severity [16] and the micronutrient associated gene signatures detected in this study, further scrutiny is necessary to determine their associations with relative to disease severity, outcomes, as well as their effect in combination with other compounds targeting the SARS-CoV-2 –host interface. Finally, less elucidated relationships those detected with valproate and benserazide may indicate that the emerging neuroinvasive potential of SARS-CoV-2 may too be modified by concomitant medication affecting the CNS, albeit towards currently unknown outcomes.

Ethics approval and consent to participate

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Consent for publication

Not applicable/single author.

Availability of data and materials

Not applicable.

Competing interests

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Appendix A. Supplementary data

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References

[1] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5).
[2] Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 2020;43(7):1399–407.
[3] Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 2020.
[4] Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM. Master regulator analysis of the SARS-CoV-2/human interactome. J Clin Med. 2020;9(4).
[5] Vavougios GD. Selenium – associated gene signatures within the SARS-CoV-2 – host genomic interaction interface. Free Radic Biol Med. 2020;S0891–5849(20):31150–3. https://doi.org/10.1016/j.freeradbiomed.2020.07.014.
[6] Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z, et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Res 2016;44(W1):W90–7.
[7] Yoo M, Shin J, Kim J, Ryall KA, Lee K, Lee S, et al. DSigDB: drug signatures database for gene set analysis. Bioinformatics 2015;31(18):3069–71.
[8] Clough E, Barrett T. The gene expression omnibus database. Methods Mol Biol 2016;1418:93–110.
[9] Elmadfa I, Meyer AL. The role of the status of selected micronutrients in shaping the immune function. Endocr Metab Immune Disord Drug Targets 2019;19(8):1100–15.
[10] Rupp JC, Locatelli M, Grieser A, Ramos A, Campbell PJ, Yi H, et al. Host cell copper transporters CTR1 and ATP7A are important for Influenza A virus replication. Virol J 2017;14(1):11.
[11] Li C, Li Y, Ding C. The role of copper homeostasis at the host-pathogen axis: from bacteria to fungi. Int J Mol Sci 2019;20(1):175. https://doi.org/10.3390/ijms20010175.
[12] Yamamoto M, Koga R, Fujino H, Shimagaki K, Ciftci HI, Kamo M, et al. Zinc-binding site of human immunodeficiency virus 2 Vpx prevents instability and dysfunction of the protein. J Gen Virol 2017;98(2):275–83.
[13] Beck MA. Selenium and vitamin E status: impact on viral pathogenicity. J Nutr 2007;137(5):1338–40.
[14] Taylor EW, Ruzicka JA, Premadasa L, Zhao L. Cellular selenoprotein mRNA tethering via antisense interactions with ebola and HIV-1 mRNAs may impact host selenium biochemistry. Curr Top Med Chem 2016;16(13):1530–5.
[15] Briguglio M, Pregliasco FE, Lombardi G, Perazzo P, Banfi G. The malnutritional status of the host as a virulence factor for new coronavirus SARS-CoV-2. Front Med (Lausanne) 2020;7:146.
[16] Zhang J, Taylor EW, Bennett K, Saad R, Rayman MP. Association between regional selenium status and reported outcome of COVID-19 cases in China. Am J Clin Nutr. 2020;111(6):1297-1299; Vitoux D, Chappuis P, Arnaud J, Bost M, Accominotti M, Roussel AM. [Selenium, glutathione peroxidase, peroxides and platelet functions]. Ann Biol Clin (Paris). 1996;54(5):181-187.
[17] Ricetti MM, Guidi GC, Tecchio C, Bellisola G, Rigo A, Perona G. Effects of sodium selenite on in vitro interactions between platelets and endothelial cells. Int J Clin Lab Res. 1999;29(2):80–4.
[18] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with covid-19. N Engl J Med 2020;382(17):e38.
[19] Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367(6485):1444–8.
[20] Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of angiotensin II receptor blockers and ACE (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. Hypertension 2020;76(1):51–8.
[21] Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. Nat Rev Immunol 2019;19(2):104–17.
[22] Vavougios GD. A data-driven hypothesis on the epigenetic dysregulation of host metabolism by SARS coronaviral infection: potential implications for the SARS-CoV-2 modus operandi. Med Hypotheses 2020;140:109759.
[23] Dhingra S, Bansal MP. Modulation of hypercholesterolemia-induced alterations in apolipoprotein B and HMG-CoA reductase expression by selenium supplementation. Chem Biol Interact 2006;161(1):49–56.
[24] Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K.

Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol 2020;189(5):846–7. https://doi.org/10.1111/bjh.16727.
[25] Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents [published online ahead of print, 2020 Jun 25]. Br J Haematol. 2020;10.1111/bjh.16968. doi:10.1111/bjh.16968Vargas-Vargas M, Cortes-Rojo C. Ferritin levels and COVID-19. Rev Panam Salud Publica. 2020;44:e72.
[26] Song Y, Zhang M, Yin L, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2) [published online ahead of print, 2020 Jul 4]. Int J Antimicrob Agents. 2020;106080. doi:10.1016/j.ijantimicag.2020.106080.
[27] RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. N Engl J Med. 2020;10.1056/NEJMoa2021436. doi:10.1056/NEJMoa2021436.
[28] Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol 2020;108(1):17–41. https://doi.org/10.1002/JLB.3COVR0520-272R.
[29] Chen ZR, Zhou Y, Liu J, et al. Pharmacotherapics advice in guidelines for COVID-19. Front Pharmacol 2020;11:950.
[30] Beck MA. Increased virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency. J Nutr 1997;127(5 Suppl):966S–70S.
[31] Beck MA. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice. Biomed Environ Sci 1997;10(2–3):307–15.
[32] Fang LQ, Goeijenbier M, Zuo SQ, et al. The association between hantavirus infection and selenium deficiency in mainland China. Viruses 2015;7(1):333–51.