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Infection, Genetics and Evolution 86 (2020) 104602

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Short communication

Overlapping host pathways between SARS-CoV-2 and its potential copathogens: An in silico analysis

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ARTICLE INFO

Keywords:
SARS-CoV-2
Coinfection
Systems biology
Transcriptomics
Viral infection

ABSTRACT

Background: SARS-CoV-2 coinfection with other viral and bacterial pathogens and their interactions are increasingly recognized in the literature as potential determinants of COVID-19 phenotypes. The aim of this study was to determine infection induced, host transcriptomic overlap between SARS-CoV-2 and other pathogens.

Materials and methods: SARS-CoV-2 infection induced gene expression data were used for gene set enrichment analysis (GSEA) via the Enrichr platform. GSEA compared the extracted signature to VirusMINT, Virus and Microbe perturbations from Gene Expression Omnibus (GEO) in order to detect overlap with other pathogen induced host gene signatures. For all analyses, a false discovery rate (FDR) <0.05 was considered statistically significant.

Results: GSEA via Enrichr revealed several significantly enriched sub-signatures associated with HSV1, EBV, HIV1, IAV, RSV, P.Aeruginosa, Staph. Aureus and Strep. Pneumoniae infections, among other pathogens (FDR $<$ 0.05). These signatures were detected in at least 6 infection-induced transcriptomic studies from GEO and involved both bronchial epithelial and peripheral blood immune cells.

Discussion: SARS-CoV-2 infection may function synergistically with other viral and bacterial pathogens at the transcriptomic level. Notably, several meta-analyses of COVID-19 cohorts have furthermore corroborated viral and bacterial pathogens reported herein as coinfections with SARS-CoV-2. The identification of common, perturbed gene networks outlines a common host targetome for these pathogens, and furthermore provides candidates for biomarker discovery and drug design.

1. Introduction

Several studies have outlined the potential contribution of SARS-CoV-2 coinfection with other viral and bacterial pathogens in determining COVID-19 outcomes and clinical phenotypes.(Kim et al., 2020; Lin et al., 2020) A meta-analysis of 24 studies of concomitant bacterial infections (both concurrent and secondary to SARS-CoV-2 infection) indicated that COVID-19 complicated with bacterial infections affected 6.9% (95% CI 4.3–9.5%) of the pooled patient population (n = 3338 patients), and was higher (8.1%) in critically ill patients.(Langford et al., 2020) Notably, up to 70% of the included studies reported on the use of broad-spectrum antimicrobials regardless of laboratory confirmed coinfection.(Langford et al., 2020) A meta-analysis by Davis and colleagues, reporting on 18 retrospective and 1 prospective study estimated a pooled prevalence of 16.8% (95% CI = 8.1–27.9) in SARS-CoV-2 coinfection with viral and bacterial respiratory tract pathogens, when considering studies with 100% copathogen testing (n = 1210 patients). (Davis et al., 2020) Overall, despite difference in reporting, pathogen (viral, bacterial, fungal) screening panels, study size and design (retrospective vs. prospective), these aforementioned studies have outlined the coinfection as a recurring complication of COVID-19.

A direct implication of coinfection is whether and which copathogens function synergistically on the transcriptomic level with SARS-CoV-2. The aim of this study was to determine overlapping host gene signatures between SARS-CoV-2 and other viral and bacterial potential copathogens.

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https://doi.org/10.1016/j.meegid.2020.104602
Received 3 July 2020; Received in revised form 10 October 2020; Accepted 18 October 2020
Available online 24 October 2020

2. Materials and methods

A study by Bojkova and colleagues provided data on the SARS-CoV-2 - induced modulations on the host's transcriptome.(Bojkova et al., 2020) Gene set enrichment analysis (GSEA) of differentially expressed genes extracted from this study was performed via the Enrichr(Kuleshov et al., 2016) web service; subsequently, via Enrichr, the VirusMINT(Chatraryamontri et al., 2009), Virus and Microbe Perturbations libraries (Kuleshov et al., 2016) were scrutinized to compare infection – derived, Gene Expression Omnibus (GEO) extracted gene signatures overlapping with the gene set extracted from Bojkova et al.'s experiment. For all analyses, an FDR <0.05 was considered statistically significant.

3. Results

Epstein Barr Virus infection (EBV; FDR = $2.9*e^{-16}$) was the most salient viral infection signature identified by VirusMINT from Bojkova et al.'s signature, followed by Human immunodeficiency Virus 1 (HIV-1; FDR = $1.97*e^{-4}$) and Herpes Simplex Virus 1 (HSV1; FDR = 0.041). Microbe perturbations GSEA revealed significant overlap with multiple pathogens, including influenza A virus, Streptococcus Pneumonia and *Staphylococcus aureus* among others (Table 1; FDR < 0.05; Genes comprising each signature are available from DOI: 10.17632/m4zdf3mg8c.1 and Supplementary Files 1).

Table 1
Significantly enriched, pathogen signatures retrieved from the Virus MINT and GEO Microbe Perturbations databases.

VirusMINT			
Term		Hits	Adjusted *P*-value
Epstein-Barr virus (strain GD1)		23	$2.90E^{-16}$
Human immunodeficiency virus 1		22	$1.97E^{-4}$
Human herpesvirus 1 (strain 17)		5	0.041
GEO Microbe perturbations			
Term	Cell type	Hits	Accession	Adjusted *P*-value
Respiratory syncytial virus (RSV)	Human bronchial epithelial cells	30	GDS2606	$5.47e^{-14}$
Streptococcus pneumoniae	Human pharyngeal epithelial cells	27	GDS3041	$1.022e^{-12}$
Rhinovirus	Human bronchial epithelial cells	27	GDS4832	$8.038e^{-11}$
Respiratory syncytial virus (RSV)	Human bronchial epithelial cells	28	GDS2023	$8.718e^{-11}$
Pseudomonas aeruginosa	Human bronchial epithelial cells	23	GDS2606	$4.205e^{-10}$
Staphylococcus aureus	Human bronchial epithelial cells	26	GDS2606	$1.261e^{-9}$
H1N1 influenza virus (seasonal strain BN/59)	Human primary lung bronchial epithelial cells	28	GDS4855	$6.663e^{-13}$
Staphylococcus aureus	Human macrophage	21	GDS4931	$1.307e^{-8}$
H1N1 influenza virus (pandemic strain KY/136)	Human primary lung bronchial epithelial cells	21	GDS4855	$4.055\ e^{-8}$

"Term" refers to each pathogen signature significantly enriched via Enrichr scrutiny of each respective database (i.e. Virus Mint, GEO Perturbations UP and DOWN). "Hits" refers to the number of genes comprising the signature. "Accession" refers to the GEO datasets accession for each study. VirusMINT reports on all significantly enriched viruses, whereas those presented under "GEO Microbe Perturbations" are selected among the total of those significantly enriched. The complete list, along with the genes comprising each signature are available from DOI: 10.17632/m4zdf3mg8c.1

4. Discussion

Coinfection with SARS-CoV-2 and other viruses and bacteria has recently become increasingly recognized as a clinical concept, the outlines of their interactions however are consequently only recently emerging.

In the analyses presented herein, EBV, HSV1, H1N1, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were identified as potential copathogens in a data-driven manner, denoted by overlapping gene signatures, induced by SARS-CoV-2 infection. (Table 1; Genes comprising each signature are available from DOI: 10.17632/m4zdf3mg8c.1 and Supplementary Files 1).

Collectively, these pathogens were identified as COVID-19 coinfections in several previously mentioned meta-analyses and cohorts, (Zhu et al., 2020; Massey et al., 2020; Lai et al., 2020) with S.Aureus and EBV being significantly higher in the SARS-CoV-2+ vs. the SARS-CoV-2- group in one of the largest cohorts in the literature (n_1 = 12,075 total tested patients; n_2 = 1690 SARS-CoV-2 positive patients).(Massey et al., 2020)

Currently, there are limited evidence on SARS-CoV-2's mechanistic interactions with each of these pathogens.(Lai et al., 2020) In the case of Herpesviridae, aside from well characterized syndromes such as a case of EBV-associated lymphoproliferative syndrome complicated with COVID-19,(Hu et al., 2020) it is likely that indolent EBV and HSV1 infections may be conceptually underdiagnosed in the setting of laboratory confirmed COVID-19.

Contrary to herpesviridae, the interaction between HIV-1 and SARS-CoV-2 may be more complex, given the effect of HIV-1 on immunity and conversely, considering the potential efficacy of antiretroviral therapy on SARS-CoV-2.(Roncati et al., 2020) Currently, salient differences in infection rates and outcomes between HIV – negative and HIV – positive SARS-CoV-2 patients have not been detected.(Ford et al., 2020) By contrast, H1N1 coinfection with SARS-CoV-2 was initially considered rare(Xu et al., 2020) with phenotypically distinct presentations even when comparing the occurrence of ARDS.(Konala et al., 2020) Interestingly, immune responses against both viruses present similarities on the cellular and organism level, with prior immunization to influenza representing a potentially exploitable mechanism of immune fitness versus SARS-CoV-2.(Tang et al., 2020) Aside from exploitable, bystander immune responses, antiviral and antimicrobial drug repurposing are the current mainstay of treatment approaches(Tu et al., 2020) – rendering the importance of mapping pathogen interactions indispensable.

5. Conclusion

Multiple overlapping pathways were detected between SARS-CoV-2 and several viral and bacterial pathogens. SARS-CoV-2 infection may thus function synergistically with other viral and bacterial pathogens at the transcriptomic level. The results of this study support thorough testing for coinfection particularly in severe COVID-19 patients, and highlights the need to evaluate combinatory antiviral and antimicrobial strategies when considering these patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable/single author.

Availability of data and materials

Not applicable.

Funding

No funding source.

Authors' contributions

GV was the sole author of this study, responsible for its inception, data analysis and writing the original and final draft

Declaration of Competing Interest

None declared.

Acknowledgements

To my colleagues at the Athens Naval Hospital, holding the line against the pandemic.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2020.104602.

References

Kim, D., Quinn, J., Pinsky, B., Shah, N.H., Brown, I., 2020. Rates of coinfection between SARS-CoV-2 and other respiratory pathogens. JAMA. https://doi.org/10.1001/jama.2020.6266.

Lin, D., et al., 2020. Coinfections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients. Sci. China Life Sci. 63, 606–609. https://doi.org/10.1007/s11427-020-1668-5.

Langford, B.J., et al., 2020. Bacterial coinfection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin. Microbiol. Infect. S1198-743X(20)30423-7 https://doi.org/10.1016/j.cmi.2020.07.016.

Davis, B., et al., 2020. Viral and atypical respiratory coinfections in COVID-19: a systematic review and meta-analysis. J. Am. Coll. Emerg. Phys. Open 1 (4), 533–548. https://doi.org/10.1002/emp2.12128.

Bojkova, D., et al., 2020. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature. https://doi.org/10.1038/s41586-020-2332-7.

Kuleshov, M.V., et al., 2016. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Res. 44, W90–W97. https://doi.org/10.1093/nar/gkw377.

Chatr-aryamontri, A., et al., 2009. VirusMINT: a viral protein interaction database. Nucleic Acids Res. 37, D669–D673. https://doi.org/10.1093/nar/gkn739.

Zhu, X., et al., 2020. Coinfection with respiratory pathogens among COVID-2019 cases. Virus Res. 285, 198005. https://doi.org/10.1016/j.virusres.2020.198005.

Massey, B.W., Jayathilake, K., Meltzer, H.Y., 2020. Respiratory microbial coinfection with SARS-CoV-2. Front. Microbiol. 11, 2079.

Lai, C.C., Wang, C.Y., Hsueh, P.R., 2020. Coinfections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? J. Microbiol. Immunol. Infect. 53, 505–512.

Hu, Y., et al., 2020. Positive detection of SARS-CoV-2 combined HSV1 and HHV6B virus nucleic acid in tear and conjunctival secretions of a non-conjunctivitis COVID-19 patient with obstruction of common lacrimal duct. Acta Ophthalmol. https://doi.org/10.1111/aos.14456.

Roncati, L., Lusenti, B., Nasillo, V., Manenti, A., 2020. Fatal SARS-CoV-2 coinfection in course of EBV-associated lymphoproliferative disease. Ann. Hematol. https://doi.org/10.1007/s00277-020-04098-z.

Ford, N., et al., 2020. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. J. Int. AIDS Soc. 23, e25489. https://doi.org/10.1002/jia2.25489.

Xu, Z., Zhang, Z., Wang, F., 2020. COVID-19 in people with HIV. Lancet HIV. https://doi.org/10.1016/S2352-3018(20)30163-6.

Konala, V.M., et al., 2020. Coinfection with Influenza A and COVID-19. Eur. J. Case Rep. Intern. Med. 7, 001656. https://doi.org/10.12890/2020_001656.

Tang, X., et al., 2020. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. Chest. https://doi.org/10.1016/j.chest.2020.03.032.

Tu, Y.F., et al., 2020. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int. J. Mol. Sci. 21 https://doi.org/10.3390/ijms21072657.