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Short communication

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

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\textbf{ABSTRACT}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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.\cite{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.\cite{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.\cite{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 co-infection with viral and bacterial respiratory tract pathogens, when considering studies with 100% copathogen testing ($n = 1210$ patients).\cite{Davis et al., 2020} Overall, despite difference in reporting, pathogen (viral, bacterial, fungal) screening panels, study size and design (retropective 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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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 (Chatr-aryamonti 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–8) 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/m4zd3mg8c.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   | GDS3004   | 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–9         |
|                            | H1N1 influenza virus (pandemic strain KY/ 136) | Human primary lung bronchial epithelial cells | 21 | GDS4855   | 4.055e–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/m4zd3mg8c.1 and Supplementary Files 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/m4zd3mg8c.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 (n1=12,075 total tested patients; n2=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 herpessviridae, 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.

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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.

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Appendix A. Supplementary data

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

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