Similarities and Differences in the Transcriptomic Host Response between SARS-CoV-2 and Other Viral Infections

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Introduction

- The COVID-19 pandemic caused by SARS-CoV-2 has resulted in >35M infections/ >1M deaths globally to date
- This pandemic has closed labs, clinical enrollment of patients difficult due to PPE shortages, rolling waves of halting life across the globe
- Leveraging computational approaches as a strength during these limited times we combine large amounts of data from currently circulating viruses for comparison to the prospective collection of COVID-19 patients
- Early in a pandemic it is
  1) Imperative to understand pathophysiology that is similar to circulating viral infections for immediate repurposing of possible treatments
  2) Clearly identified novel differences may yield new drug targets

To our knowledge this is the largest whole blood RNAseq cohort of COVID-19 patients to date, for rapid dissemination of initial finding and data with the global research community.

Methods

Publicly Available Microarray
23 datasets
1075 non-COVID-19 respiratory viral infections
780 Healthy Controls (HC)

RNAseq
62 COVID-19
Hospitalized Patients
24 Healthy Controls (HC)

VOOM TRANSFORMATION + COCONUT CONORMALIZATION

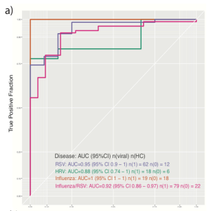
635 genes

Multicohort meta-analysis
14 datasets
652 influenza, RSV, HRV versus 672 HC
|ES|≥1 FDR ≤ 0.05%

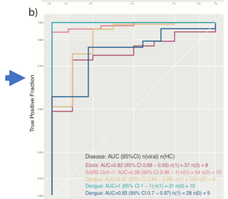
RNAseq analysis
62 COVID-19 Patients versus 24 HC
|ES| ≥1 FDR ≤ 0.05%

2002 genes

RESPIRATORY VALIDATION
4 datasets
178 influenza, RSV, HRV
58 HC



OTHER VIRUSES VALIDATION
5 datasets
245 SARS1, Ebola, Dengue
50 HC



COVID-19 (62) versus non-COVID-19 (652)
|ES|≥1 FDR ≤ 0.05%

416 genes

Results

Gene signatures |ES| ≥ 1 FDR ≤ 0.05%

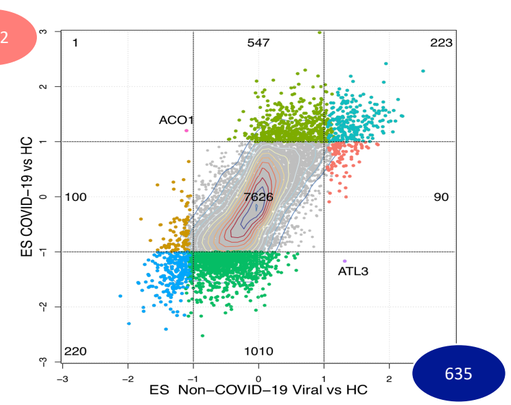
2002 genes — COVID-19 vs HC (2002 genes) ***(COVID-19 signature)***

635 genes — non-COVID-19 vs HC (635 genes) ***(non-COVID-19 signature)***

416 genes — COVID-19 vs non-COVID-19 (416 genes) ***(COVID-19 SPECIFIC signature)***

Differential gene expression of COVID-19 vs HC is highly correlated with non-COVID-19 vs HC (r=0.74, p<0.001) while two genes are oppositely regulated

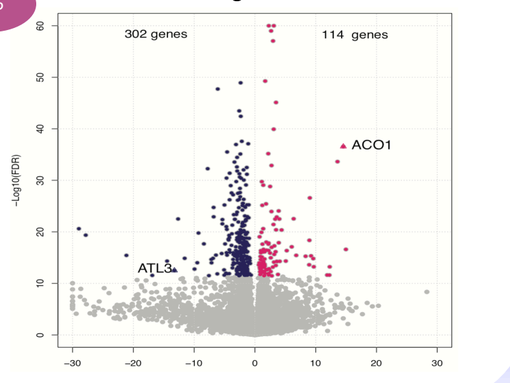
2002



635

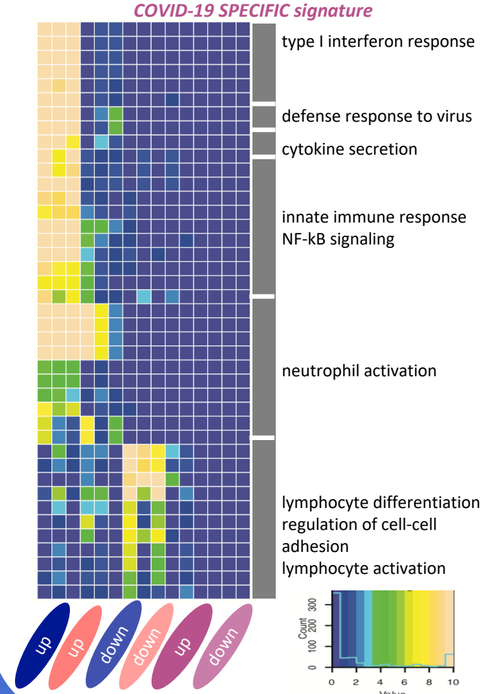
Using COCONUT to co-normalize across disease, study and platform: COVID-19 versus non- COVID-19 yields 416 gene signature

416



GO term pathway enrichment analysis

COVID-19 signature and ***non-COVID-19 signature*** are enriched for viral infection related terms but not for the ***COVID-19 SPECIFIC signature***



immunoStates
Bulk RNA
Cell Proportion
Deconvolution

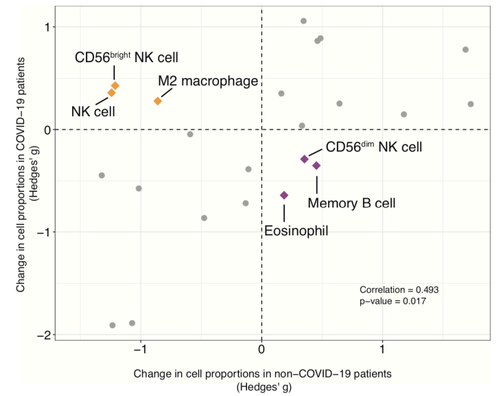
Concordant shifts in cell population

Large portion of shifts in cell proportion correlated

Discordant shifts in cell proportion

COVID-19 relative to non-COVID19

- Increased CD56bright NK cells, M2 macrophages
- Decreased CD56dim NK cells, memory B cells, eosinophils



Summary

The concordant and discordant responses mapped here provide a window to explore the pathophysiology of COVID-19 vs other viral infections and show clear differences in signaling pathways and cellularity as part of the host response to SARS-CoV-2

SIMILARITIES

- The ***COVID-19 signature*** and ***non-COVID-19 signature*** have highly correlated gene expression and GO term enrichment analysis, which allows for rapid gains in pathophysiology understanding, key at the onset of a pandemic

DIFFERENCES

- COCONUT co-normalization enables comparison of COVID-19 to non-COVID-19 viral infections for the ***416 COVID-19 SPECIFIC signature***
- The lack of GO term enrichment is a possibly a product of the novel combination of genes, and warrants further research as to how this influences the pathophysiology

IMMUNE CELL PROPORTIONS

- Method allows for repurposing RNA from precious COVID-19 samples for immune cell proportional shifts
- Shifts in several cell types are common to both viral types, as well as notable shifts in cell types in COVID-19 patients

Further Reading
Thair SA, He YD, Hasin-Brumshtein Y, et al. Transcriptomic Similarities and Differences in Host Response between SARS-CoV-2 and Other Viral Infections. medRxiv. June 2020:2020.06.18.20131326. doi:10.1101/2020.06.18.20131326

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