E Poster 50-

Transcriptomic Analysis of Host Immune Response for Precision Drug Prediction for SARS-CoV-2 Infected Patients- An Evidence Based Approach

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Introduction

SARS CoV-2 Virus can trigger severe pneumonia and lead to acute respiratory distress syndrome. Data from clinical, in vitro and in vivo suggest that virus-induced cytokine dysregulation is a contributory factor to the pathogenesis. Drugs targeting the same are being tried.

Methodology

We obtained transcriptomic data of the peripheral blood mononuclear cells (PBMCs) from BioProject PRJNA6333931 from the NCBI Portal. A PBMC is any peripheral blood cell having a round nucleus. These cells consist of lymphocytes (T cells, B cells, NK cells) and monocytes which are the drivers of disease pathogenesis in COVID-19. Further, it is depicted in Figure 1

Results- Pathwa Analysis

Gene-Set Enrichment Analysis on the transcriptome of SARS Cov-2 infected macrophages demonstrated distinct changes in numerous cellular pathways. Eleven sets of major pathways were found to be remarkably affected, viz. Metabolism, Signal Transduction, Immune System, Metabolism of Proteins, Infectious Disease, Hemostasis, Neuronal System, Metabolism of Steroids, Programmed Cell Death, Cellular Responses to External Stimuli, and Reproduction. The highest Reactions ratio was 0.183 and the lowest was 0.002. Metabolism (0.249), Signal transduction (0.232), and Immune System (0.197) were found to have high reactions ratio.

.Notable findings of Gene Set Enrichment Analysis are:

- Many pathways of Innate Immune System were significantly upregulated, with notable changes in phagocytosis and complement activation. The higher phagocytosis could be attributed to the marked increase in degranulation and upregulation of the neutrophilic interaction pathways. Upregulation of the Lectin receptors seems to be contributing to the upregulated complement cascade.
- In the Adaptive Immune System, MHC Class 2 Presentation and B Cell Receptor signalling were significantly increased.
- The cross talk between the mediators of the immune system i.e. the cytokines is upregulated. Signalling by Interferons Gamma was highest followed by Interferons Alpha and Beta. Interleukins 4, 13, 1, 12, and 10 were significantly upregulated, whereas the increased signalling by Interleukin 6 waslater found to be statistically insignificant.
- MAPK6/MAPK4 Signalling and Signalling by NOTCH were significantly upregulated among Signal Transduction pathways.
- Amongst Hemostasis pathways, Platelet activation, signalling, and aggregation and Cell surface interactions were found to be widely impacted.
- Neuronal pathways were downregulated, especially the protein-protein interaction at synapses.
- Interestingly Protein translation, Unfolded protein response and Protein folding were significantly upregulated. Amyloid fibre formation was found to be increased but later was proved to be statistically insignificant.
- Cellular response to stress was increased but, to metal ions was found insignificant. Both the modalities of Programmed Cell Death, Regulated Necrosis and Apoptosis were significantly upregulated.
- Reproduction was found to be impacted due to decreased Fertilization.
- Disease shares inflammatory signatures with other diseases namely Leishmania, HIV, HCMV, and Mycobacterium tuberculosis.

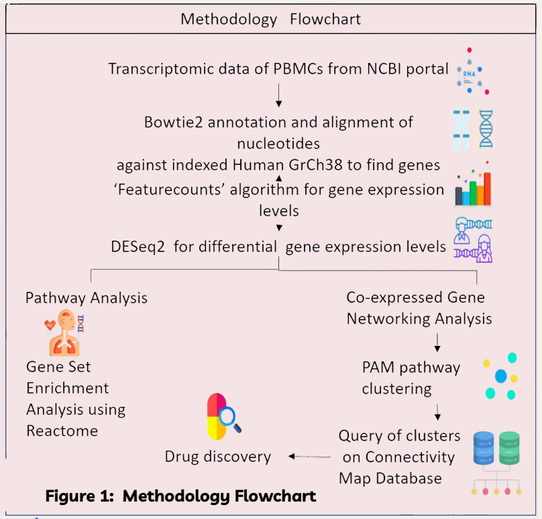

Figure 1: Methodology Flowchart

Results- Drug Analysis

From the normalized DEGs, totally 1970 differentially expressed genes with significance cutoff -1 <log2FC >1 and p-value <0.05 were selected. 309 genes were upregulated and 1661 genes were downregulated in the list. Cogena analysis was performed and the enriched pathways (Reactome dataset) in each cluster were identified (Figure 4).

Cluster 1 is broadly comprised of Immune System Pathways and Cluster 2 and 3 are comprised of Neuronal System Pathways. Cluster1 and Cluster 3 were selected for drug analysis. Cluster 2 had similar pathways as Cluster 3 and therefore, was not used. Drugs with enrichment scores above 4.32 have been ranked in a descending manner.

As shown in figure 3, using Cluster 1, 20 drug targets were identified of which 9 are available as licensed drugs, namely Sulindac, Pancuronium, Etamsylate, Cyclosporin, Crotamiton, Ciprofloxacin, Valproic acid, Triamcinolone, and Tretinoin.

As shown in figure 4, using Cluster 3, 4 drug targets were identified of which 3 are available as licensed drugs, namely Scopolamine, Captopril, and Thalidomide.

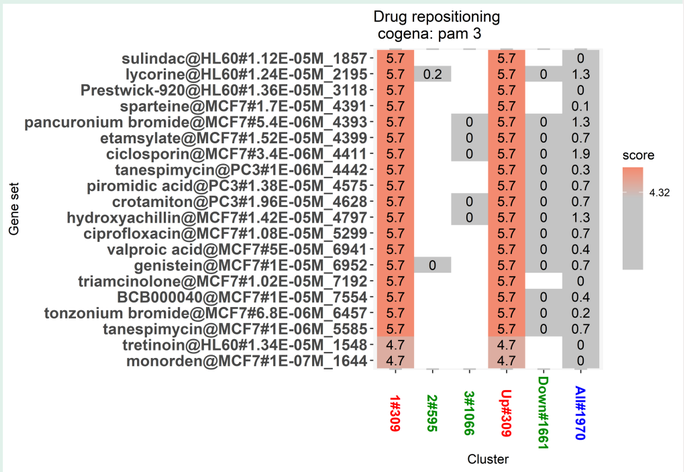

Figure 3: Drug repositioning based on cluster 1. Enriched drugs with the cell line, dose, and instance number are shown on the y axis based on the immune-related cluster

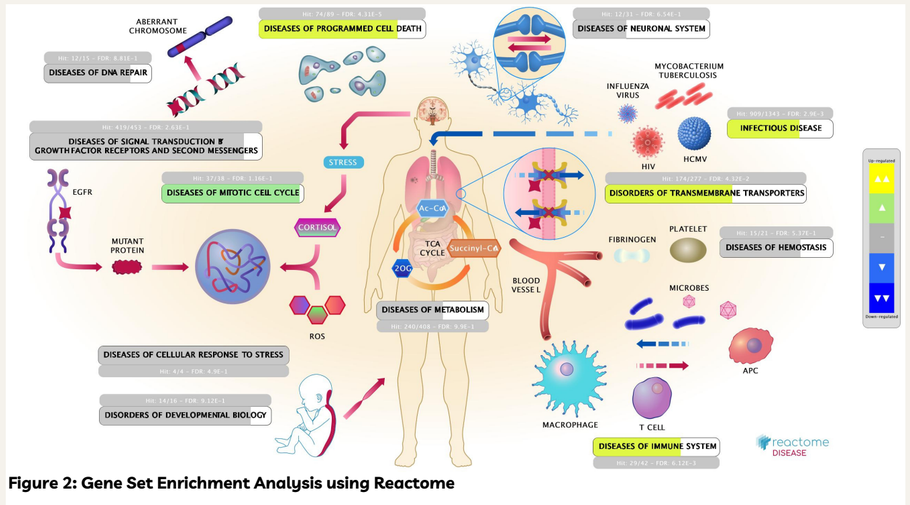

Figure 2: Gene Set Enrichment Analysis using Reactome

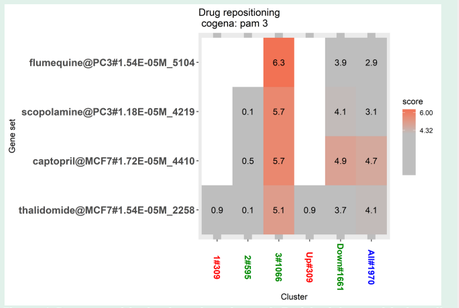

Figure 4: Drug repositioning based on cluster 3. Enriched drugs with the cell line, dose, and instance number are shown on the y axis based on the Neuronal System-related cluster

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