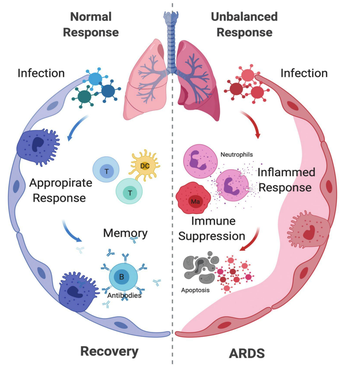
Quantitative proteomic characterization of respiratory viruses-exposed human primary T cells reveals host-pathogen interactions and therapy targets

Jiapei Yu[1,3], Hui Li[2,3,4], Zhisheng Huang[2,3], Bin Cao[2,3,4*]

[1] Department of Basic Medical Sciences, School of Medicine, Tsinghua University, Beijing, China
[2] Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China
[3] Laboratory of Clinical Microbiology and Infectious Diseases, China-Japan Friendship Hospital, National Clinical Research Center of Respiratory Diseases, Beijing, China
[4] Institute of Respiratory Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Introduction

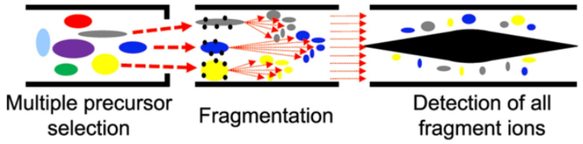
Respiratory viruses include influenza A virus and SARS-CoV-2 are responsible for the serious epidemics. Decreased peripheral lymphocyte counts have been observed in severe patients with influenza and COVID-19[1]. The host antiviral immune response is orchestrated by multiple molecules and cells, but the longitudinal variation and detailed features of respiratory virus-specific CD4$^+$ and CD8$^+$ T-cell response remain uncertain. Here we are using proteomics combined with biochemistry to dissect the lymphopenia and virus-specific T-cell responses.



Methods

Peripheral blood was collected from recruited healthy people at specific times. Different subsets of T cells were obtained and purified then infected with influenza A virus for further research.

The average top three filtered peptides which passed the 1% Q value cutoff were used to calculate[2]. After student's t-test, different expressed proteins were filtered if their Q value < 0.05 and absolute AVG log2 ratio > 0.58. The relevant experiments of SARS-CoV-2 are underway.

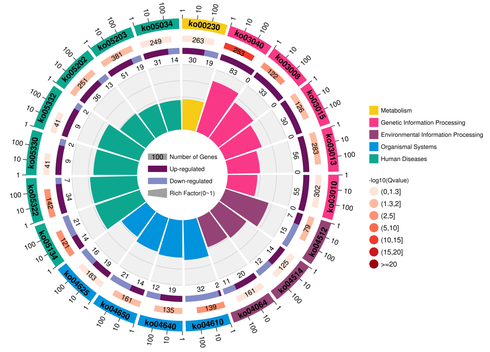


Results

Based on clustering analysis, for CD4$^+$ T cells, the signalling pathways of genetic information processing are up-regulated after infection obviously, such as spliceosome, ribosome biogenesis, mRNA surveillance, and RNA transport.

Besides, the pathways of complement/coagulation cascades and platelet activation are down-regulated, which suggests the coordination functions of CD8$^+$ T cells can be weakened by the virus. The cell-to-cell mapping of SARS-CoV-2-T cells will be drawn shortly.

A



B

Figure 1. Proteins enrichment loop graph of KO-KEGG (A, CD4$^+$ T cells; B, CD8$^+$ T cells). 1st lap, top 20 pathways of proteins enrichment; 2nd lap, the number of pathways in the background genes and Q value; 3rd lap, Up-down proteins proportion bar chart (deep purple, up-regulation; light purple, down-regulation); 4th lap, rich factor value (differential proteins divide total proteins in the relevant pathway).

Gene set enrichment analysis was also used because it derives more power by focusing on gene sets, which groups of genes that share common biological function and regulation[3].

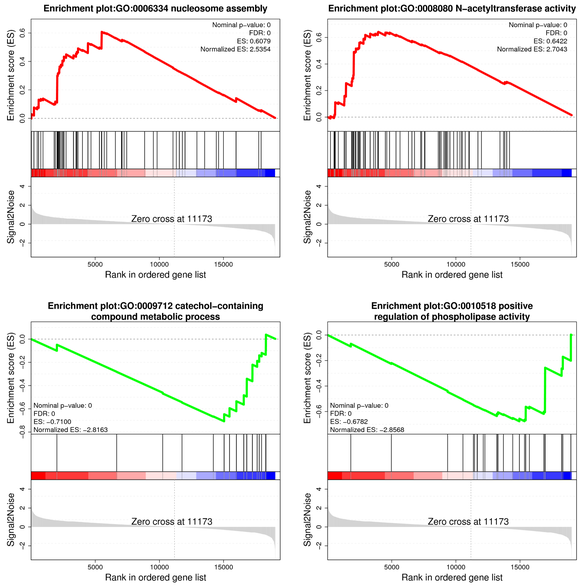


Figure 2. Gene set enrichment analysis of four pathways for human CD4$^+$ T cells. Use the expression information of all genes in human CD4$^+$ T cells and the most common Signal2 Noise as the standard to sort genes. The calculation formula of Signal2Noise is: $(\mu\alpha-\mu\beta)/(\sigma\alpha+\sigma\beta)$, which μ represents the mean, σ represents the standard deviation, and both α and β represent the different groups.

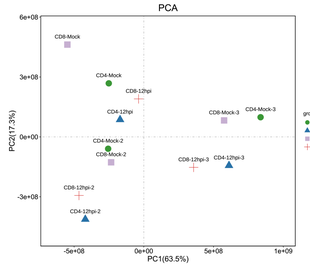
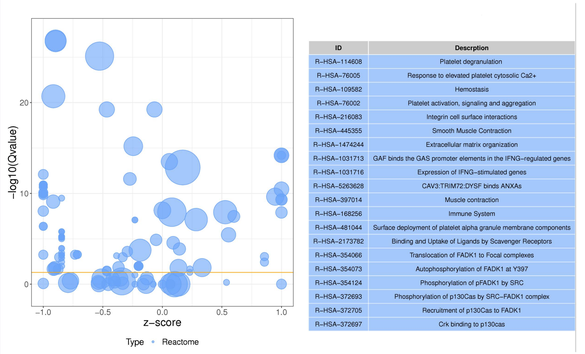


Figure 3. PCA analysis of T cell samples.



ID	Descrption
R-HSA-114608	Platelet degranulation
R-HSA-76005	Response to elevated platelet cytosolic Ca2+
R-HSA-109582	Hemostasis
R-HSA-76002	Platelet activation, signaling and aggregation
R-HSA-216083	Integrin cell surface interactions
R-HSA-445355	Smooth Muscle Contraction
R-HSA-1474244	Extracellular matrix organization
R-HSA-1031713	GAF binds the GAS promoter elements in the IFNG–regulated genes
R-HSA-1031716	Expression of IFNG–stimulated genes
R-HSA-5263628	CAV3:TRIM72:DYSF binds ANXAs
R-HSA-397014	Muscle contraction
R-HSA-168256	Immune System
R-HSA-481044	Surface deployment of platelet alpha granule membrane components
R-HSA-2173782	Binding and Uptake of Ligands by Scavenger Receptors
R-HSA-354066	Translocation of FADK1 to Focal complexes
R-HSA-354073	Autophosphorylation of FADK1 at Y397
R-HSA-354124	Phosphorylation of pFADK1 by SRC
R-HSA-372693	Phosphorylation of p130Cas by SRC–FADK1 complex
R-HSA-372705	Recruitment of p130Cas to FADK1
R-HSA-372697	Crk binding to p130cas

Figure 4. Reactome analysis of CD8$^+$ T cells. The ordinate is -log10 (Qvalue), and the abscissa is the z-score value (the ratio of the difference between the number of up-regulated genes and the number of down-regulated genes in the total differential genes), and the yellow line represents the threshold of Q value = 0.05. On the right is the list of Reactome channels with the top 20.

Conclusion

On the one hand, viruses are very crafty and they can escape and kidnap host-immune pathways through virus-host interactions to avoid being wiped out by the host immune system. On the other hand, the initial innate immune responses to pathogens have to restrict virus spread before the adaptive immune responses thoroughly develop.

Our unbiased and high-throughput quantitative proteomics study provides crucial novel insight into the human primary T-cell response against respiratory virus infection.

References:

1. Jiuyang Xu, et al. *Semin Respir Crit Care Med*, 2020, 41(4):555-567.
2. Yeoun Jin Kim, et al. *J Proteomics*, 2018, 189:91-96.
3. Subramanian A, et al. *Proc Natl Acad Sci USA*, 2005, 102(43):15545-50.