

Proteomic and metabolomic profiling of urine uncovers
immune responses in patients with COVID-19

尿液的蛋白质组和代谢组分析揭示了COVID-19
患者的免疫反应

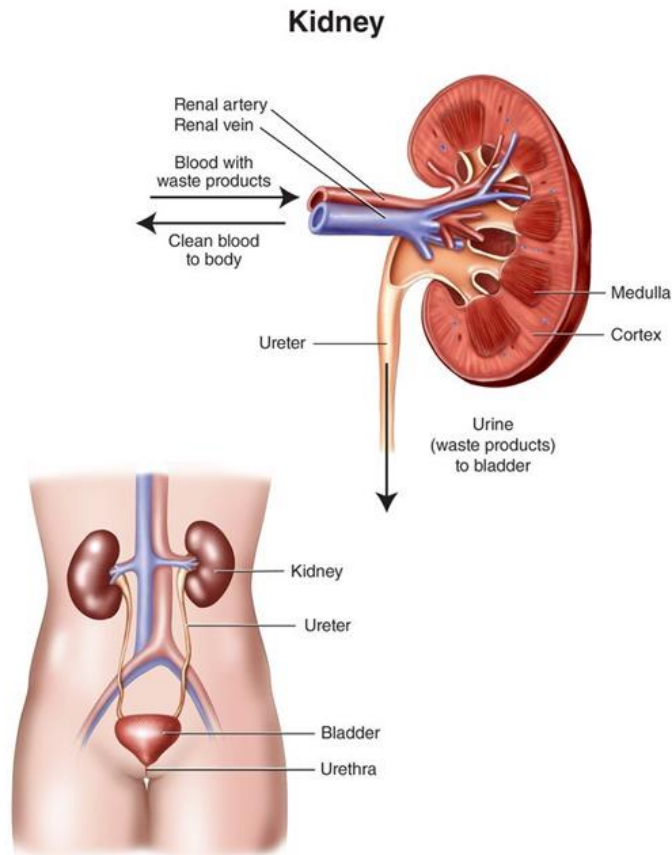
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Urine as potential source for protein biomarkers



Pros:

1. Non-invasive
2. Informative biological information: proteins, metabolites.

Cons:

1. Highly variable: sex, age, physiological or pathological status, etc.
2. Normalization

[1] Mansoori B. et al. Adv. Pharm. Bull. 2017;7:339–348
[2] Milojkovic D. et al. Clin. Cancer Res. 2009;15:7519–7527

Serological and urinary biochemical analytes of COVID-19



Serology indicators for predicting severity of COVID-19:

interleukin-6, d-dimer, thrombin time, C-reactive protein, blood lymphocyte count¹⁻³

Molecular changes of COVID-19:

complement system, macrophages, platelet degranulation⁴



urine indicators for predicting severity of COVID-19:

urine glucose, proteinuria, β 2-macroglobulin, liver-type fatty acid-binding proteins^{5,6}

Molecular changes of COVID-19:

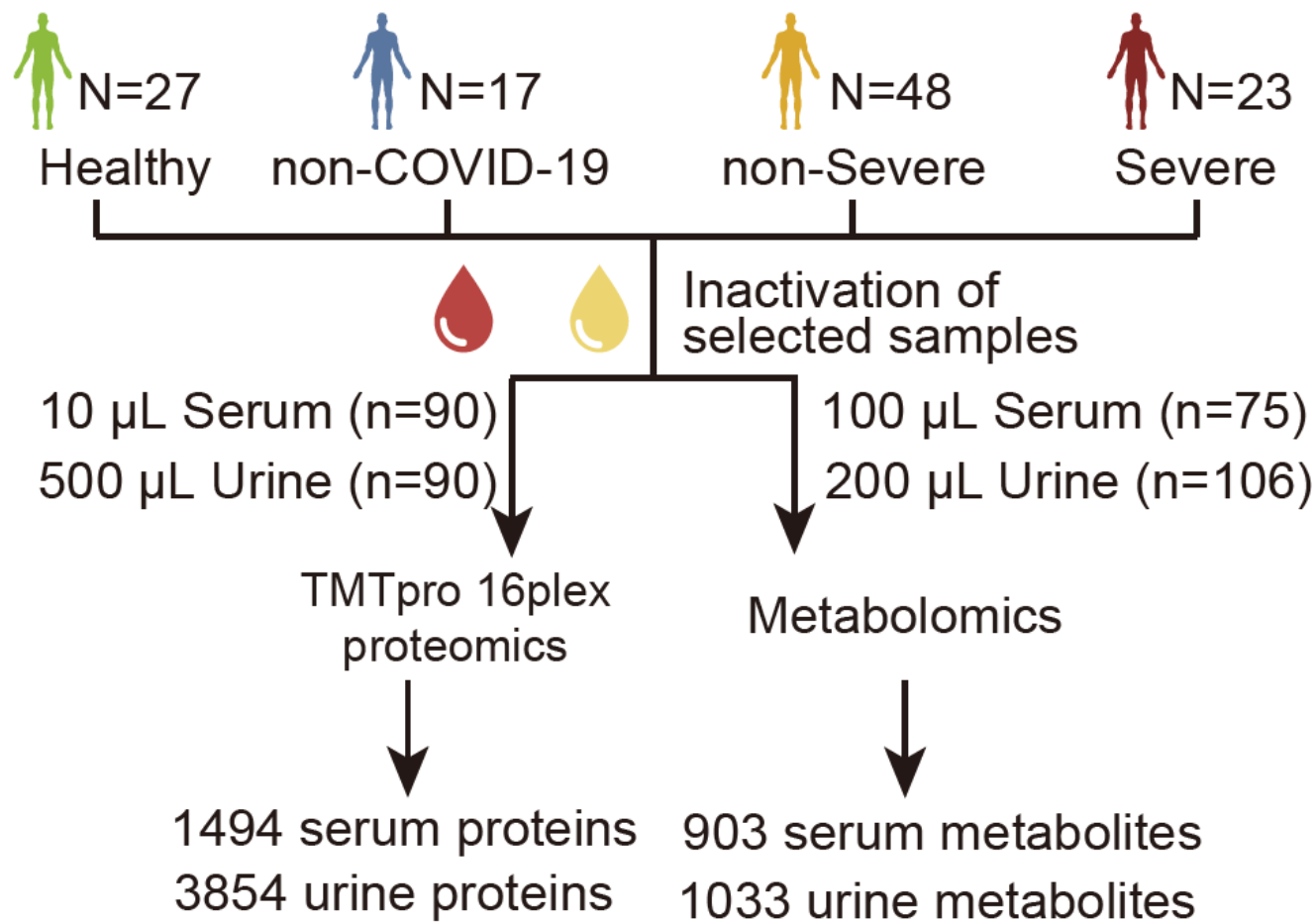
immune response, complement activation, platelet degranulation, lipoprotein metabolic process^{7,8}

[1] Gao Y. et al. J. Med. Virol. 2020; 92: 791-796 [2] Qin C. et al. Clin. Infect. Dis. 2020 [3] Tan L. et al. Signal Transduct. Target Ther. 2020; 5: 33 [4] Shen B. et al. Cell. 2020 [5] Rui L. et al. Clin. Chem. Lab. Med. 2020; 58: 1121-1124 [6] Katagiri D. et al. Crit. Care Explor. 2020; 2: e0170 [7] Li Y. et al. Urine. 2020; 2: 1-8 [8] Tian W. et al. Nat. Commun. 2020; 11: 5859

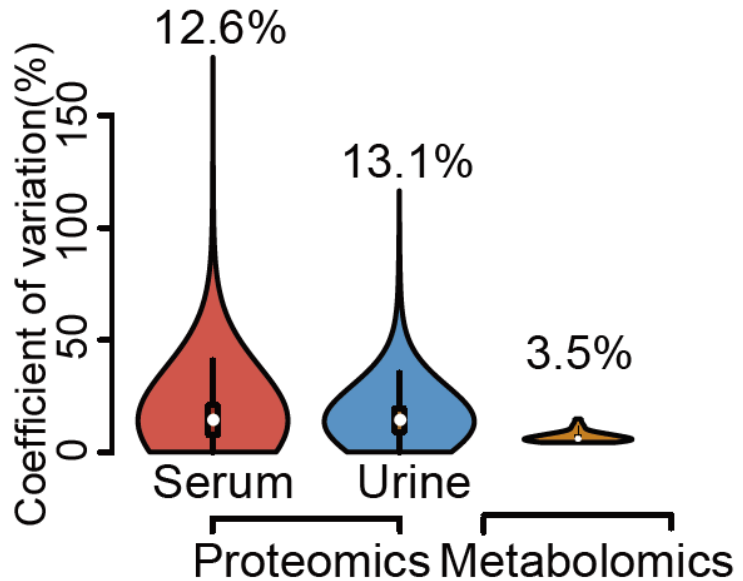
Objectives

- A comprehensive and in-depth analysis of COVID-19 molecular changes in biofluids level
- Exploring the value of urine in infectious diseases research

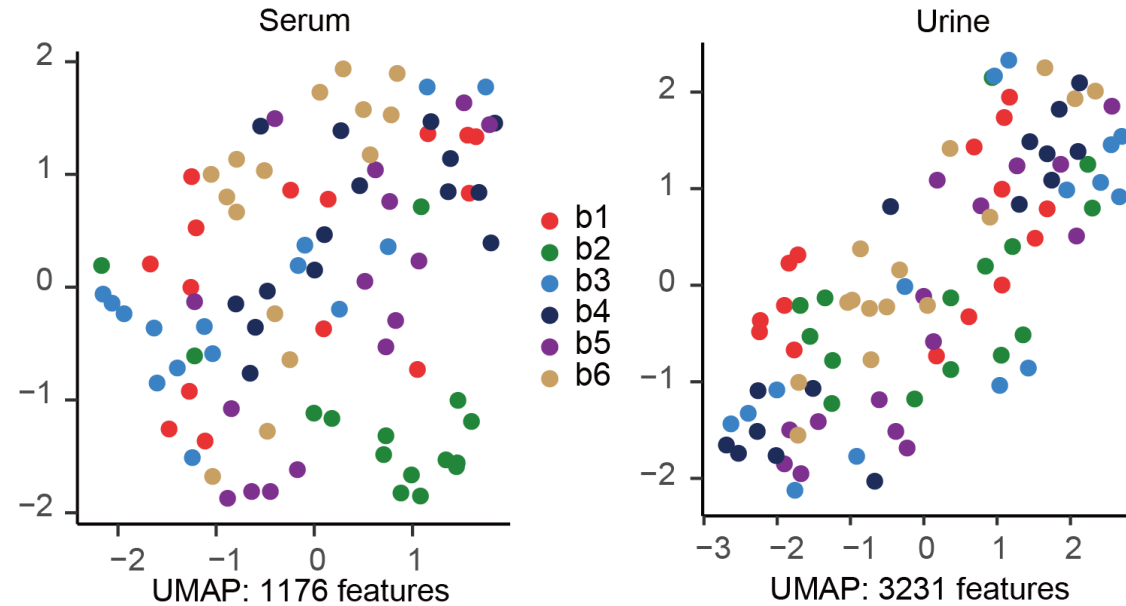
Study design



Quality control of proteomic and metabolomic data set

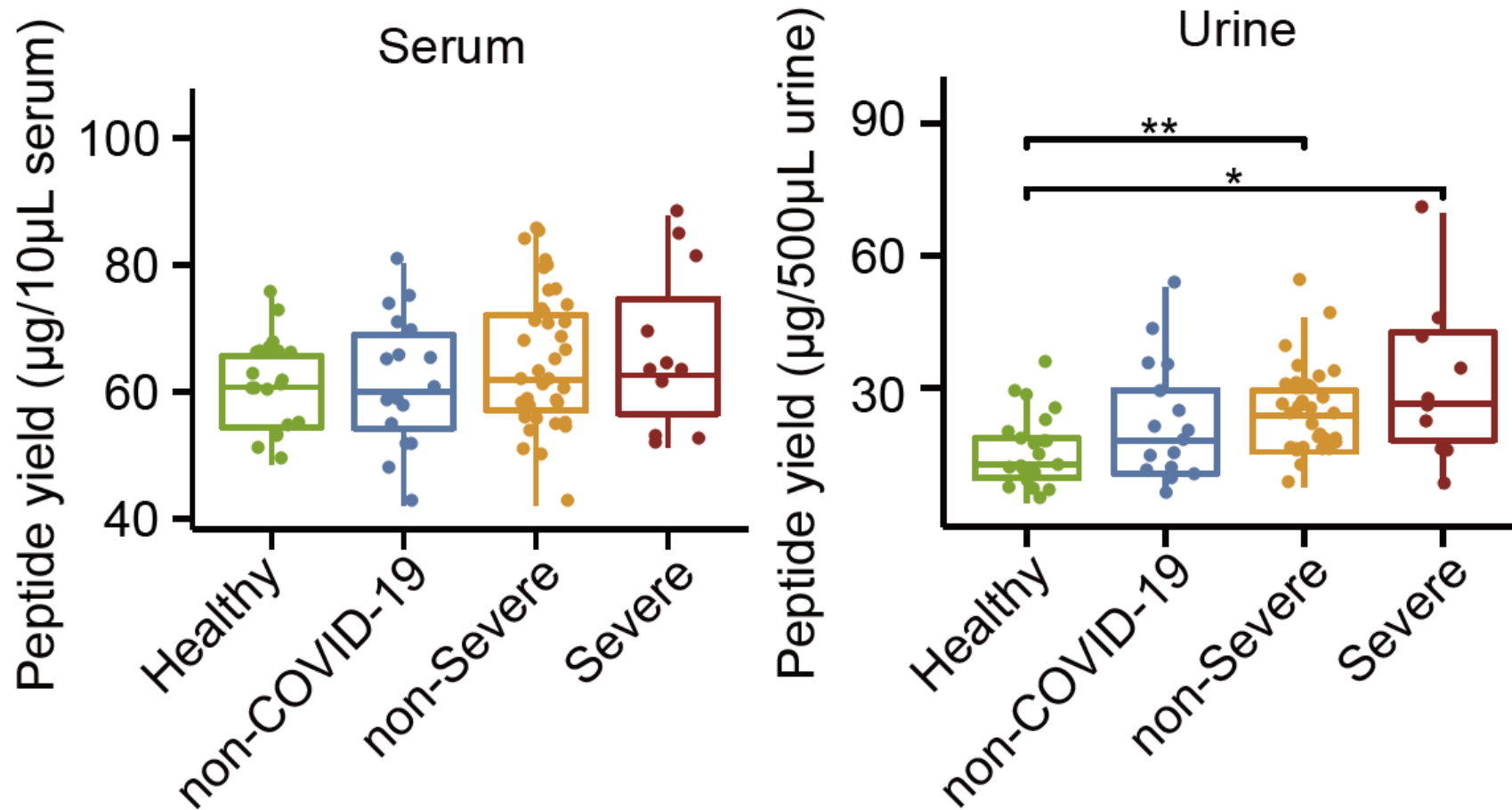


CVs of the protein or metabolites abundance from control samples by proteomics and metabolomics.



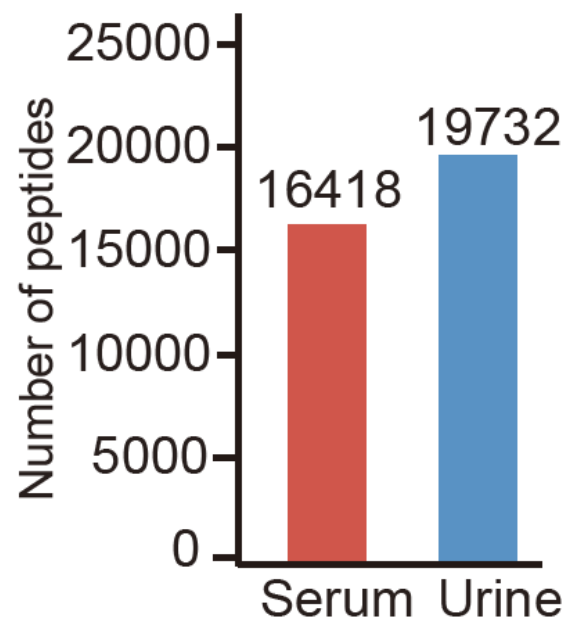
UMAP analysis of the serum and urine proteomics data distribution in 6 batches

Peptide yield from serum and urine

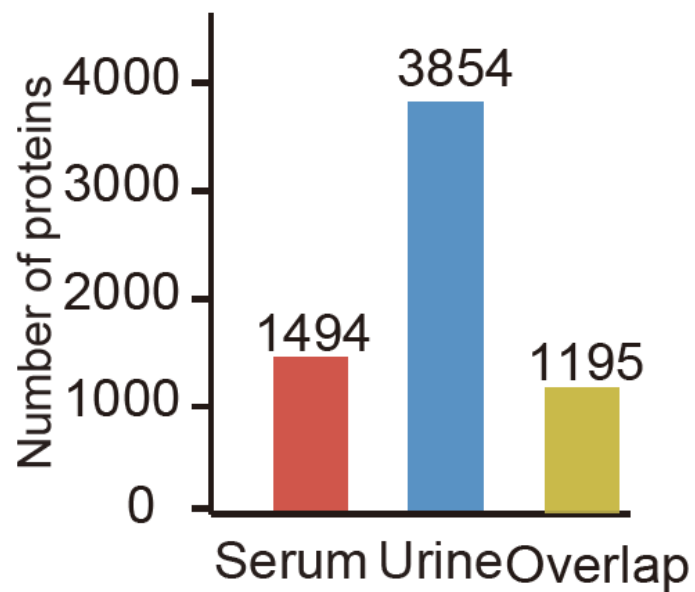


Urine and serum quantified peptide and protein

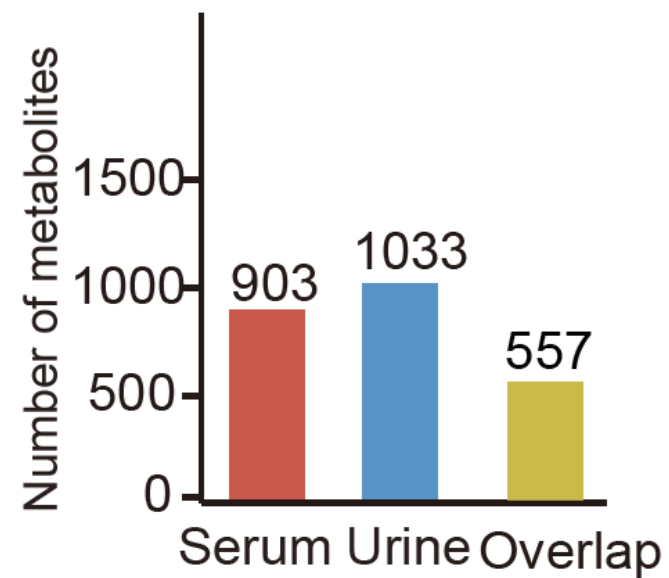
C



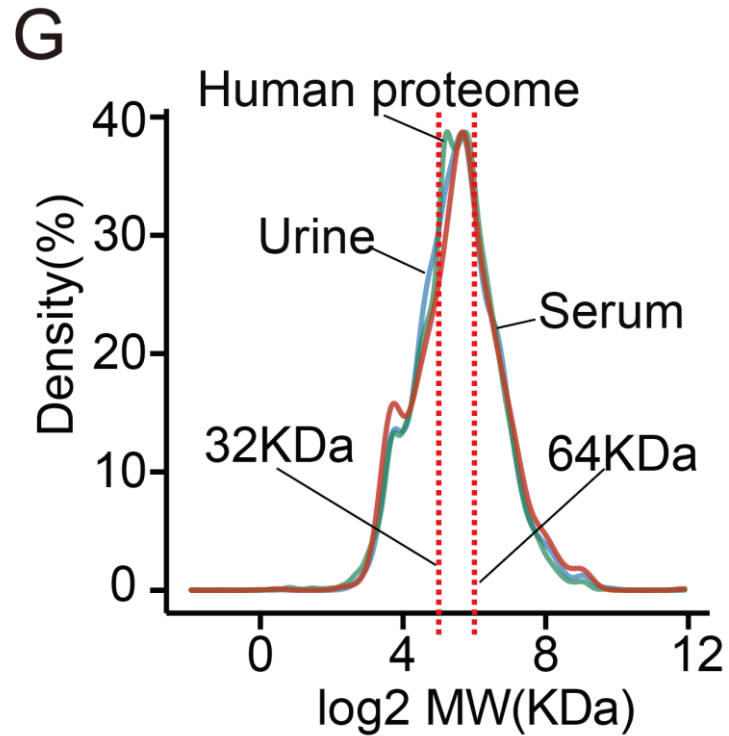
D



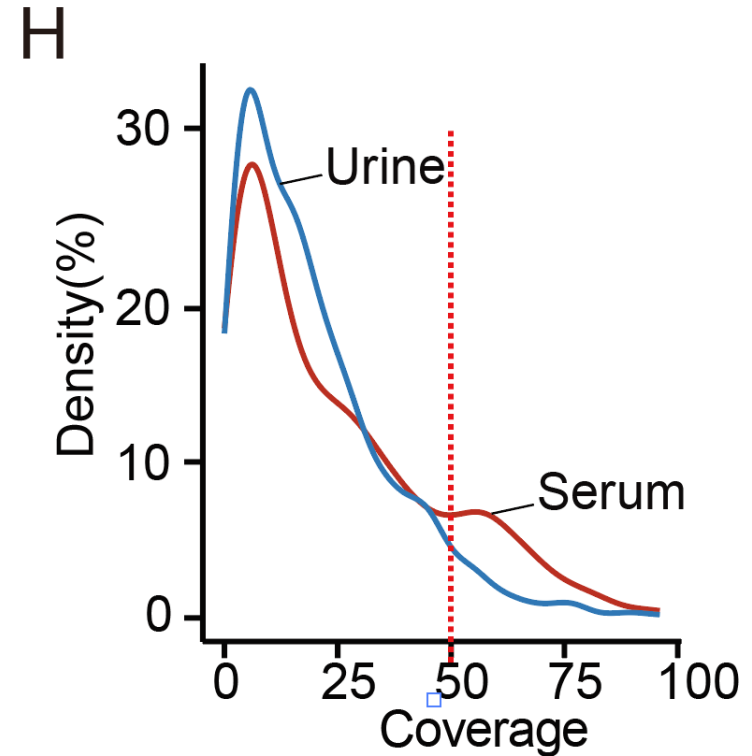
E



Urine and serum protein distribution

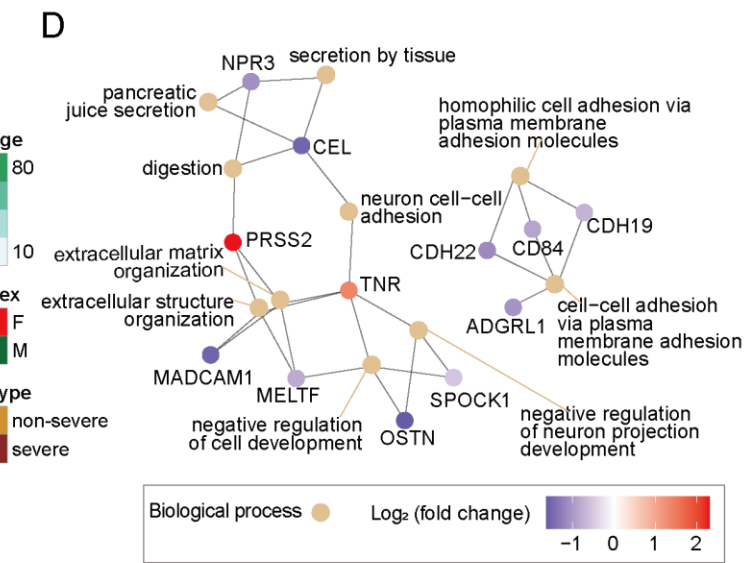
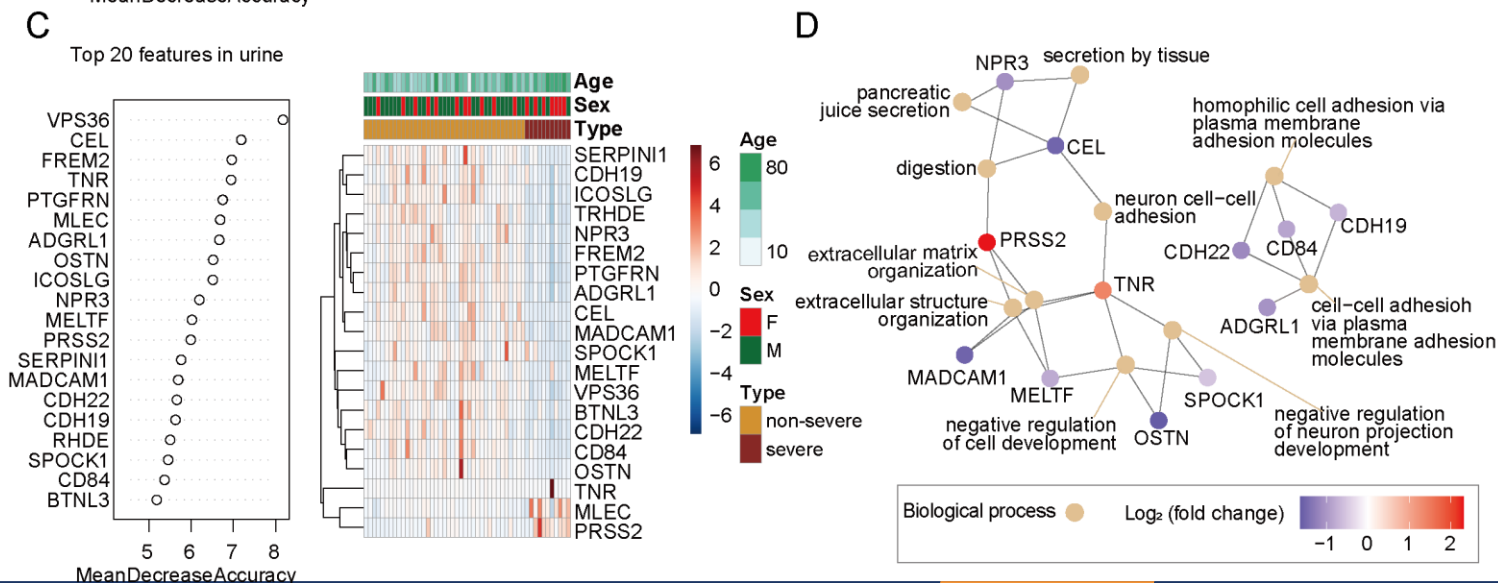
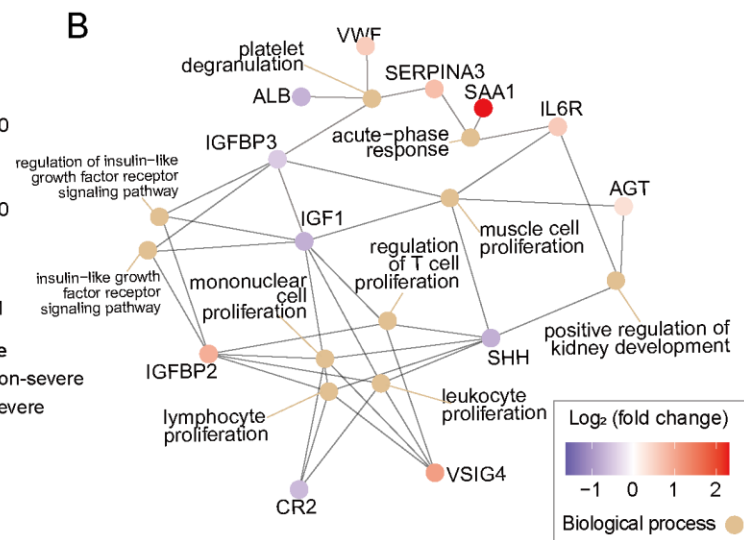
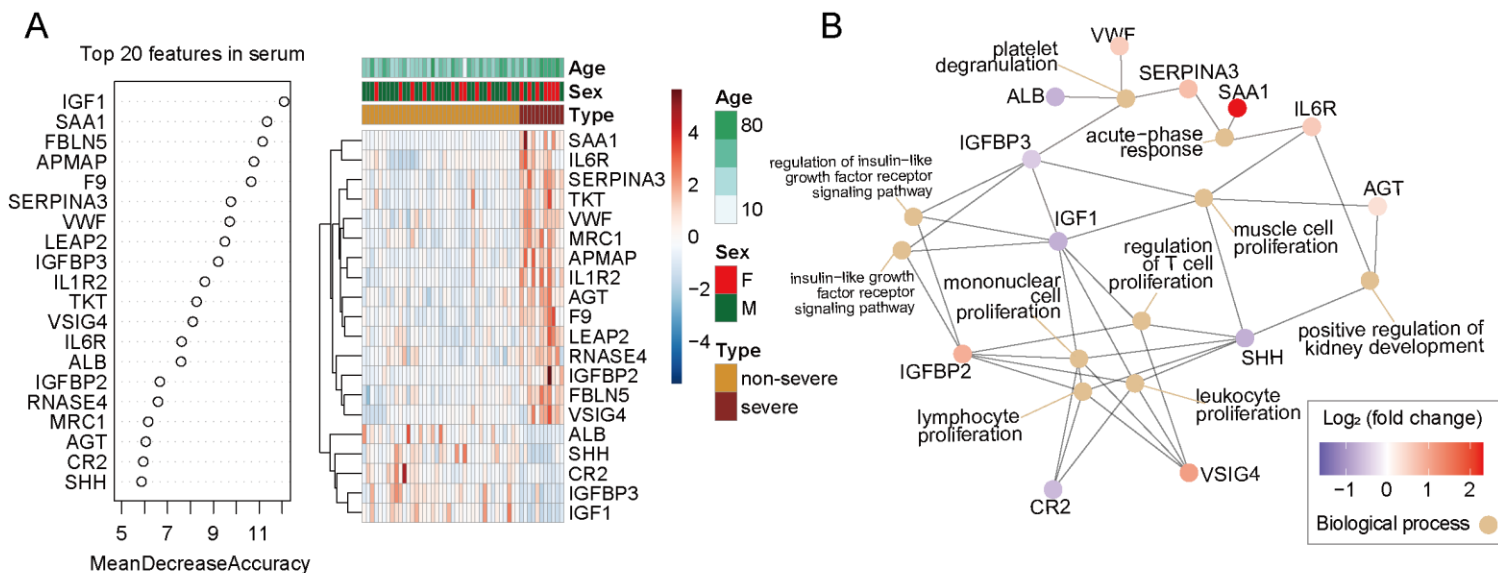


Molecular weight (MW)
Distributions of quantified proteins



Sequence coverage distribution
of each quantified protein.

Machine learning model identified severe COVID-19 cases

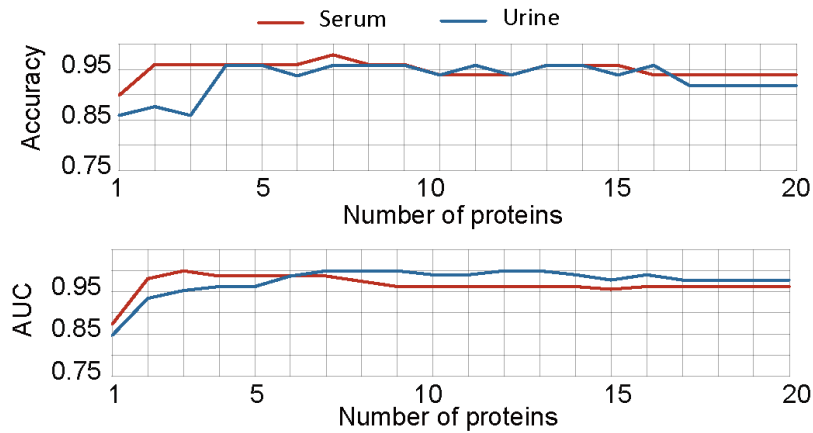


The top 20 feature proteins in serum (A) or urine (C) proteomics data selected by random forest analysis and ranked by the mean decrease in accuracy.

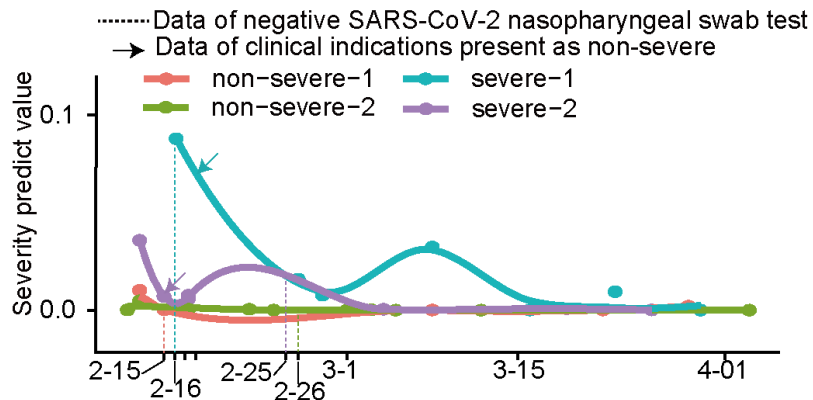
The biological process involved in the top 20 urine (B) or serum (D) proteins

Model performance

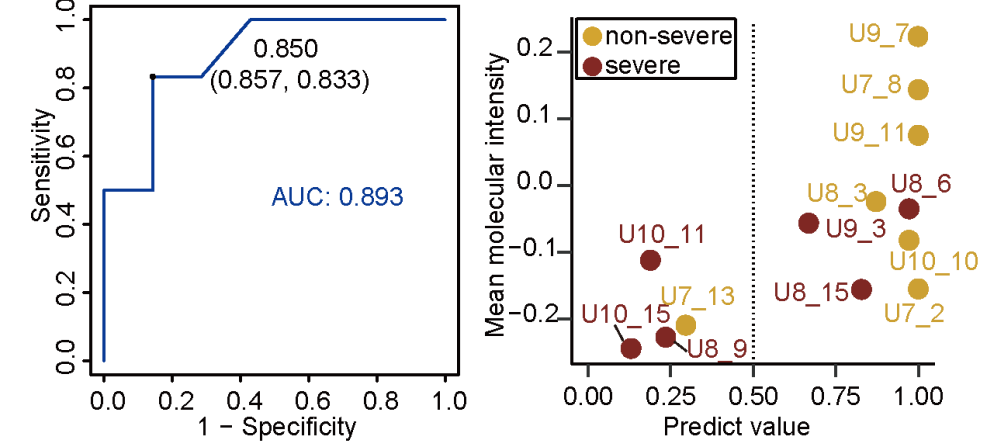
A



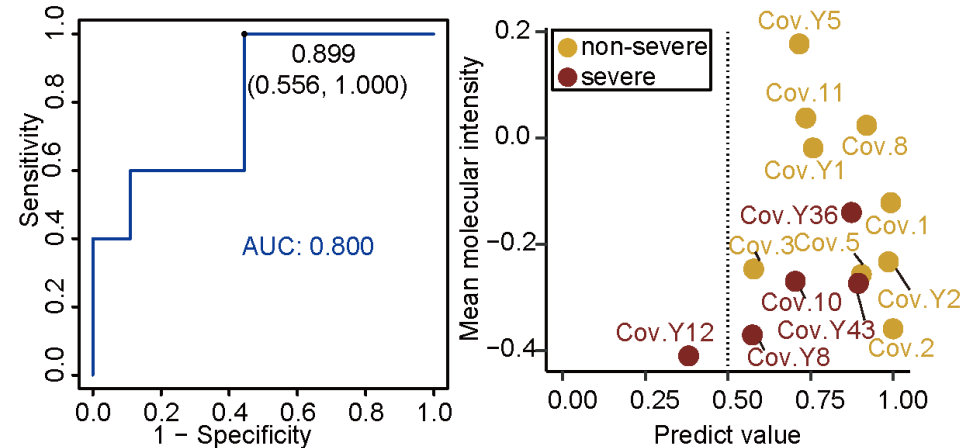
B



C

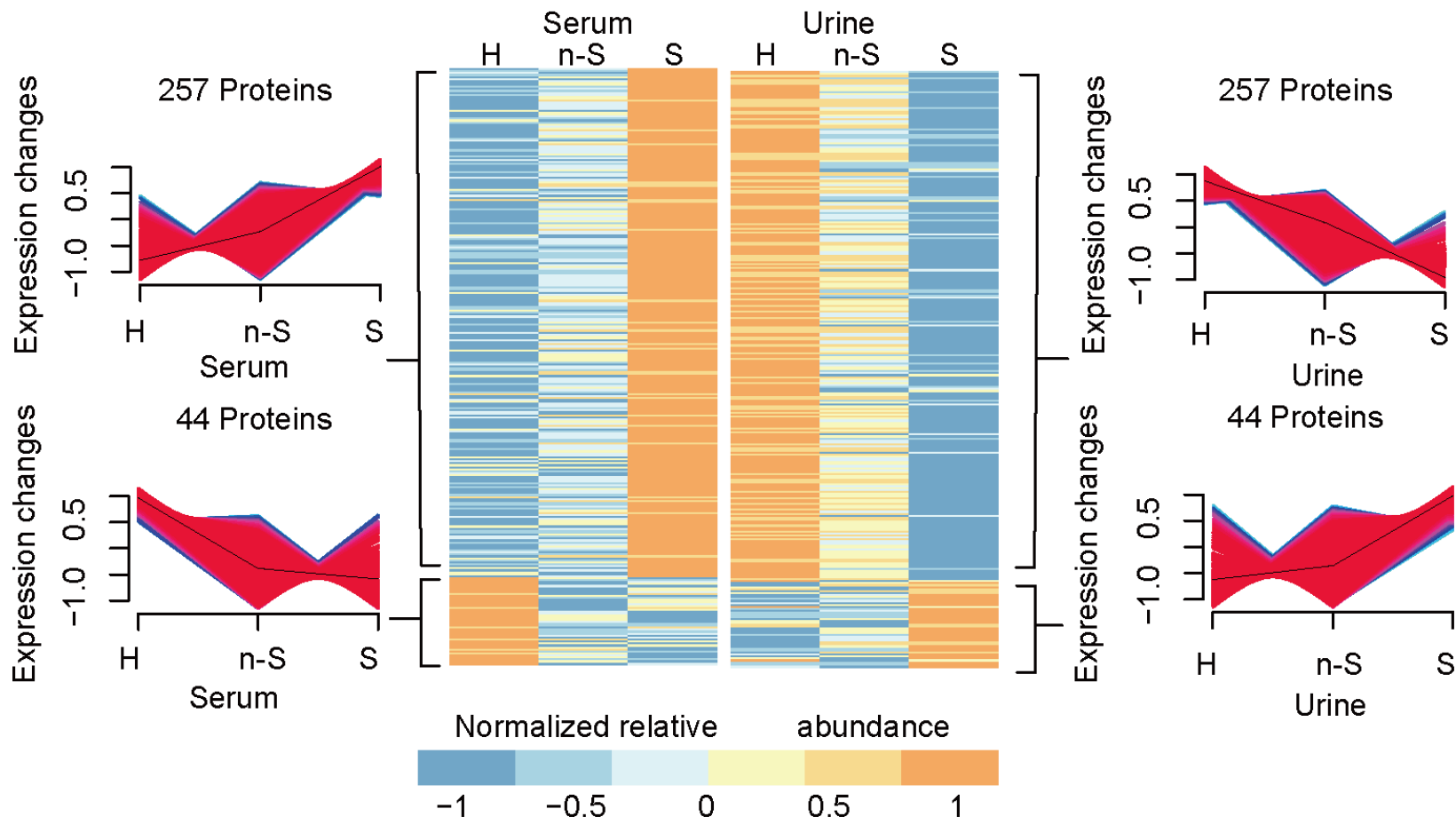


D



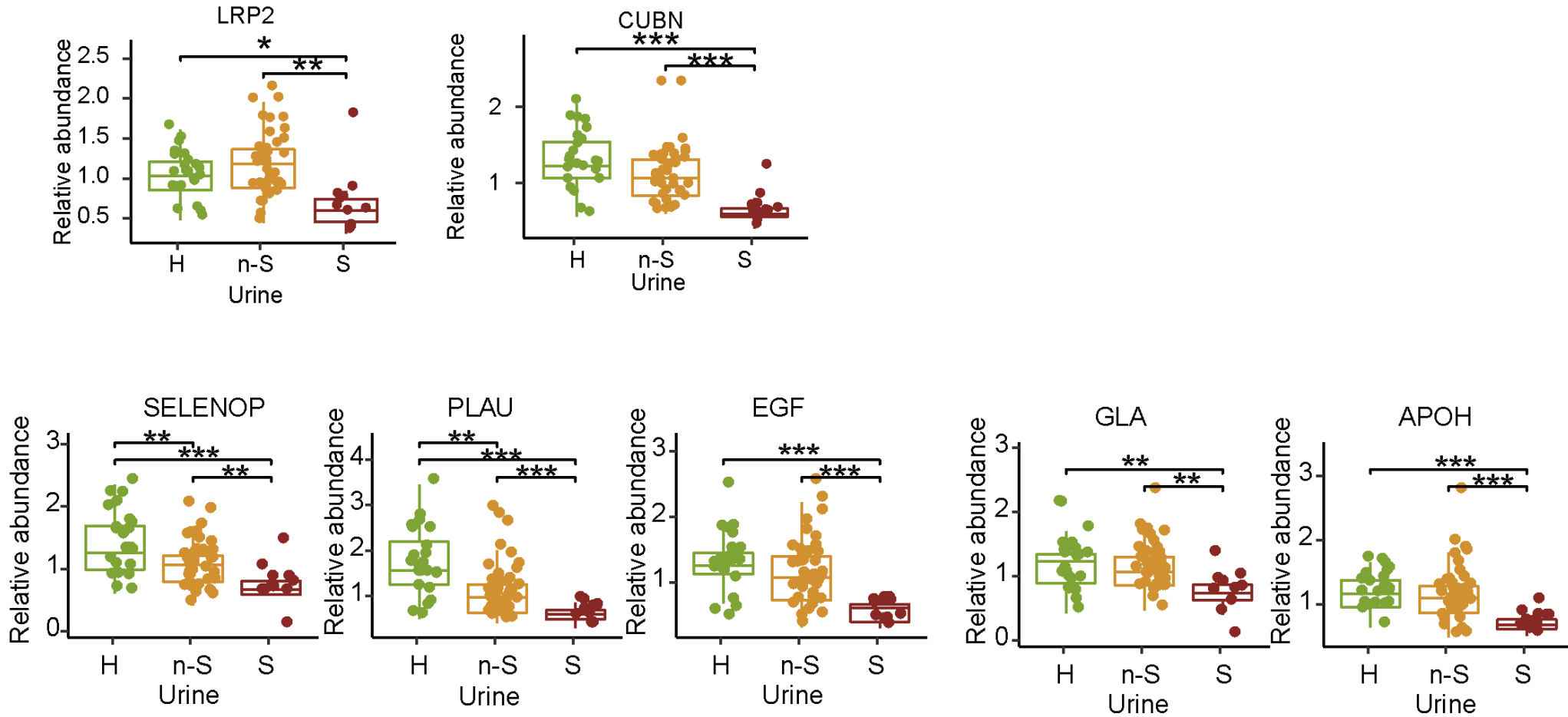
(A) The AUC and accuracy values of the 20 serum or urine models. (B) Severity prediction value of 4 patients with COVID-19 at different urine sampling times. Model performance in the independent TMT-labelled (C) and the label-free DIA data set (D).

301 proteins showed opposite expression patterns in urine and sera

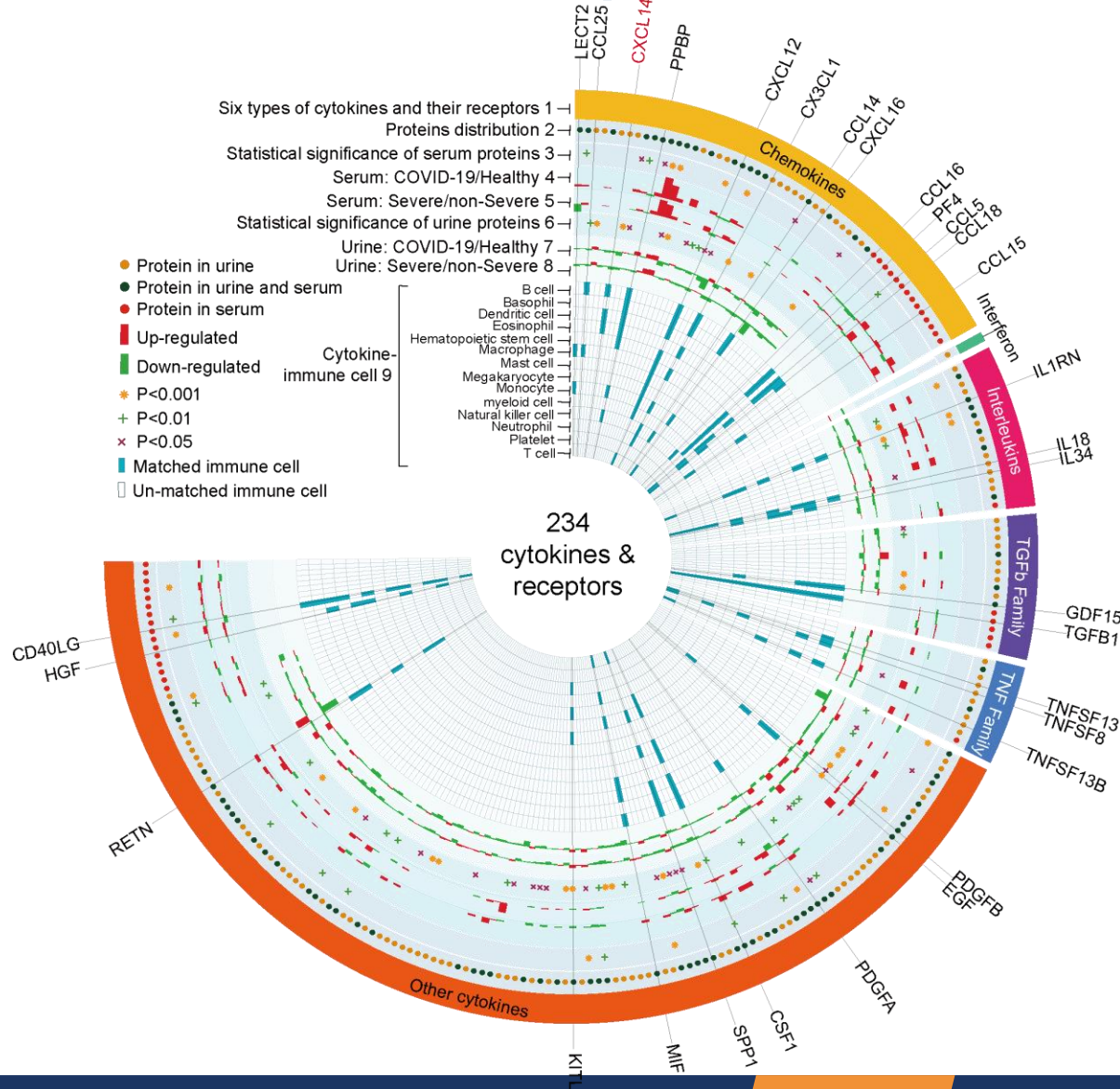


301 proteins identified in both serum and urine with opposite expression patterns in different patient groups.

Proteins involved in renal tubular reabsorption



Cytokines and their receptors identified in urine and sera



197 cytokines and their receptors identified in urine, while 124 identified in sera. Circos plot integrating the relative expression and cytokine-immune cell relationship of 234 cytokines and their receptors.

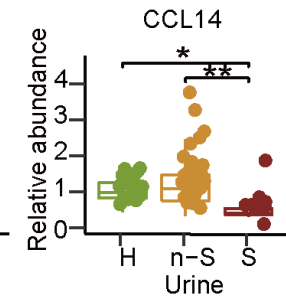
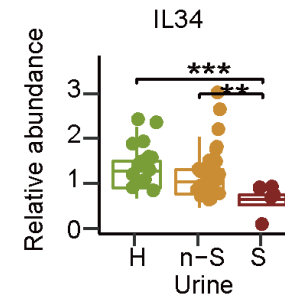
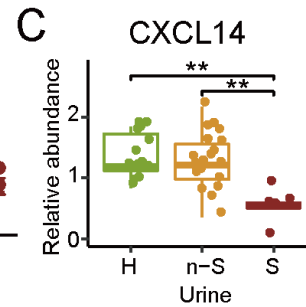
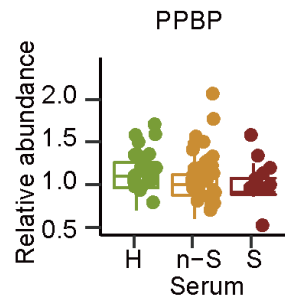
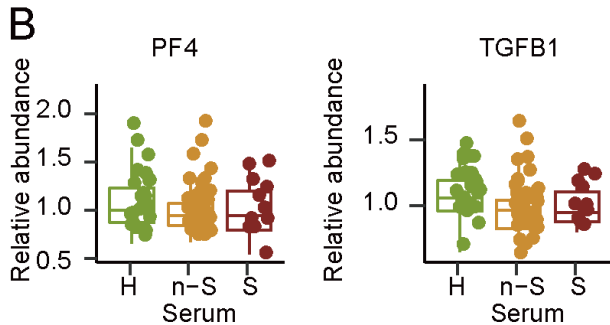
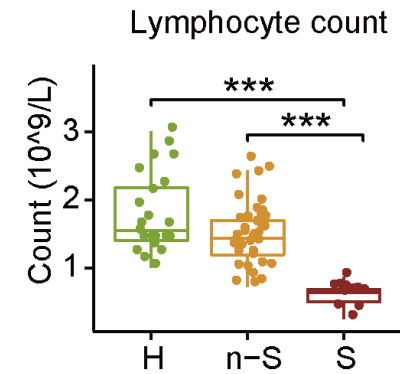
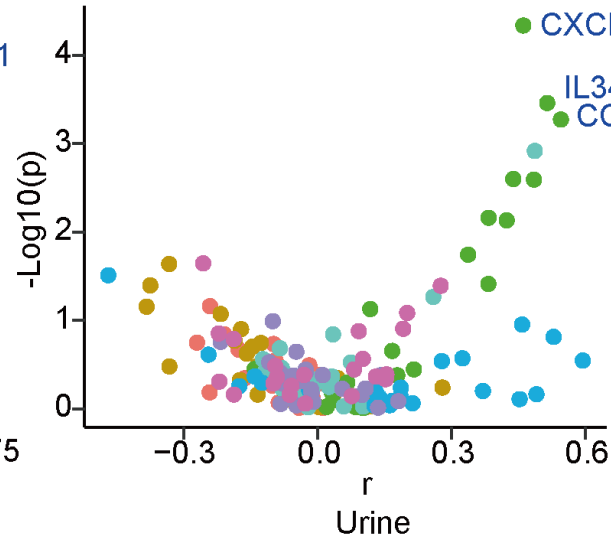
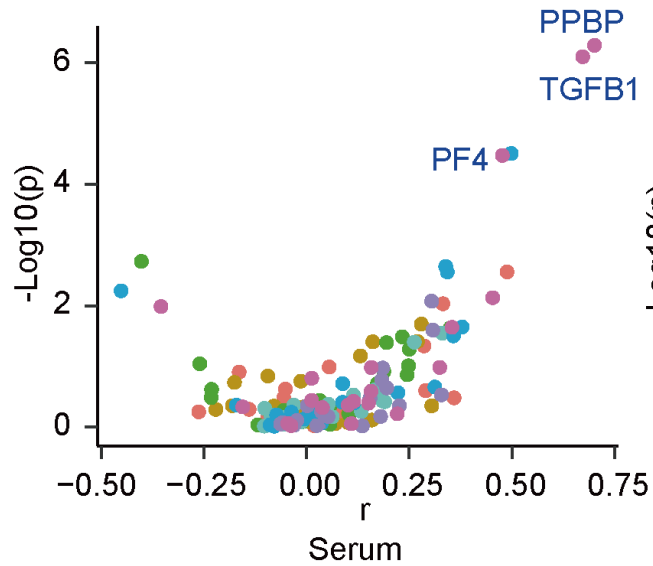
[1] Kveler K. et al. Nat. Biotechnol. 2018; 36: 651-659

[2] Yu Y. et al. Bioinformatics. 2018; 34: 1229-1231

Cytokines and immune cells

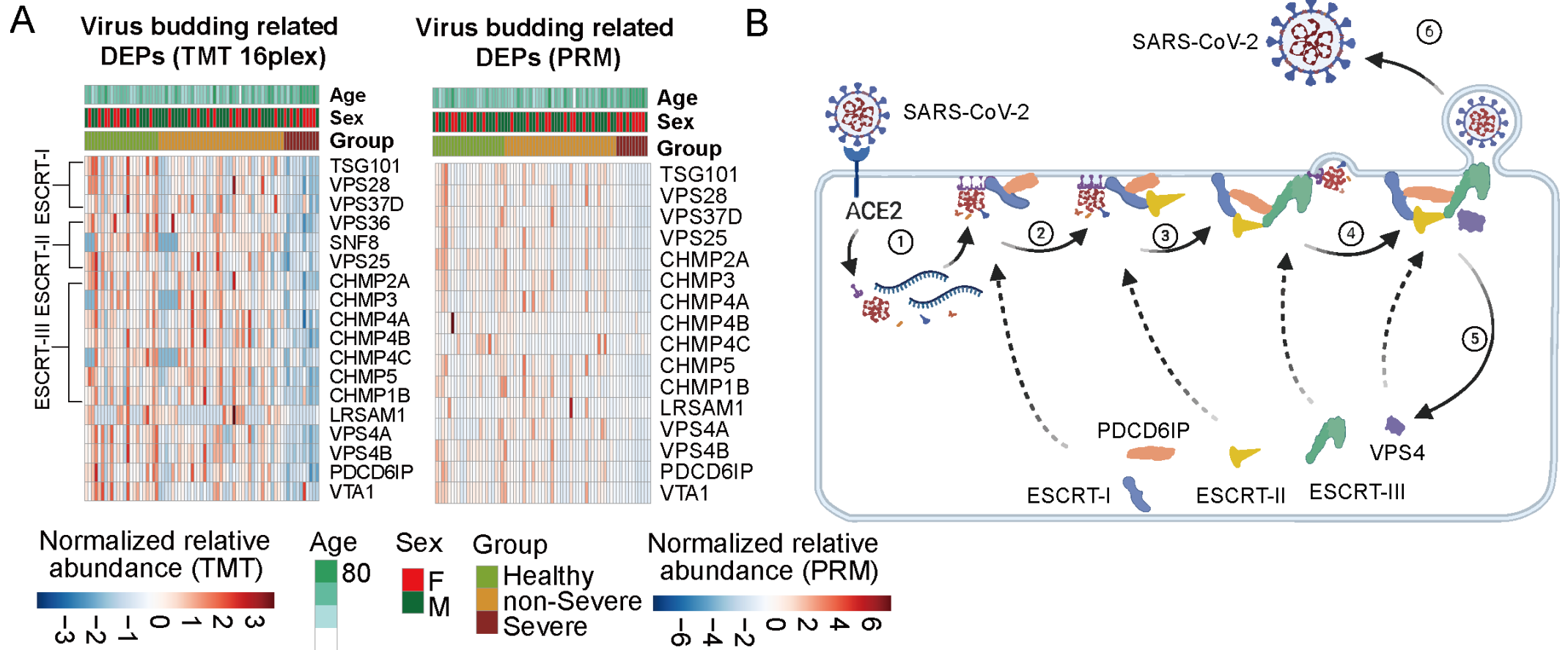
A

- Platelet
- Monocyte
- Basophilic
- Neutrophil
- Eosnophils
- White blood cell
- Lymphocyte



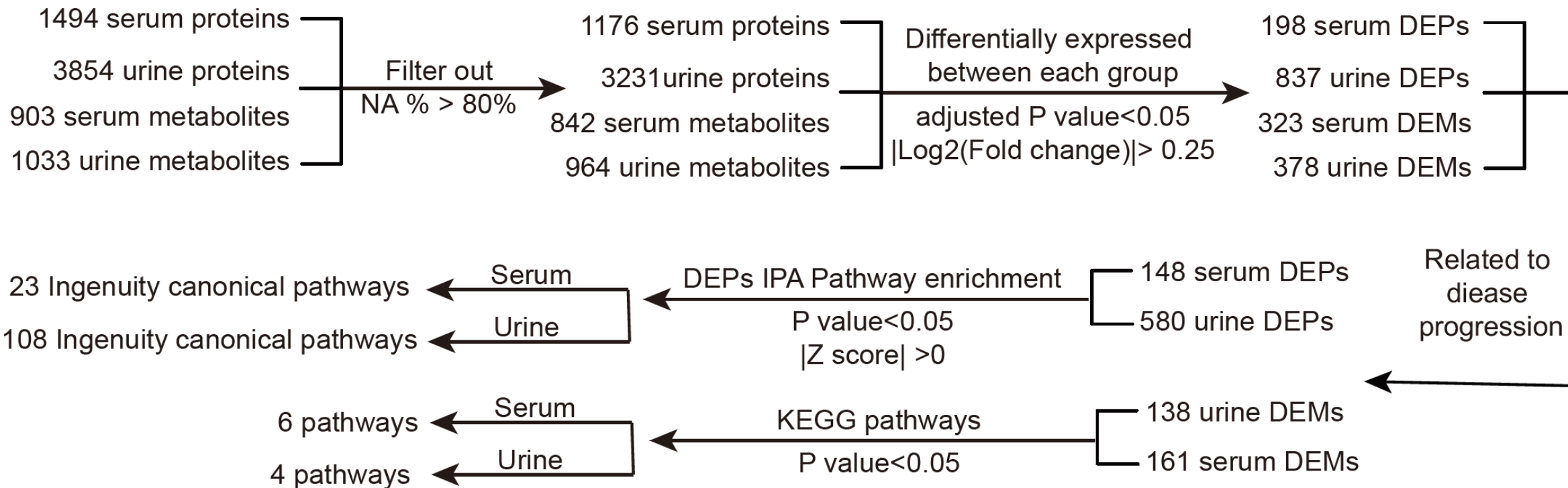
Spearman's rank correlation coefficients between serum or urine cytokines and immune cells.

Dysregulated ESCRT super-complex



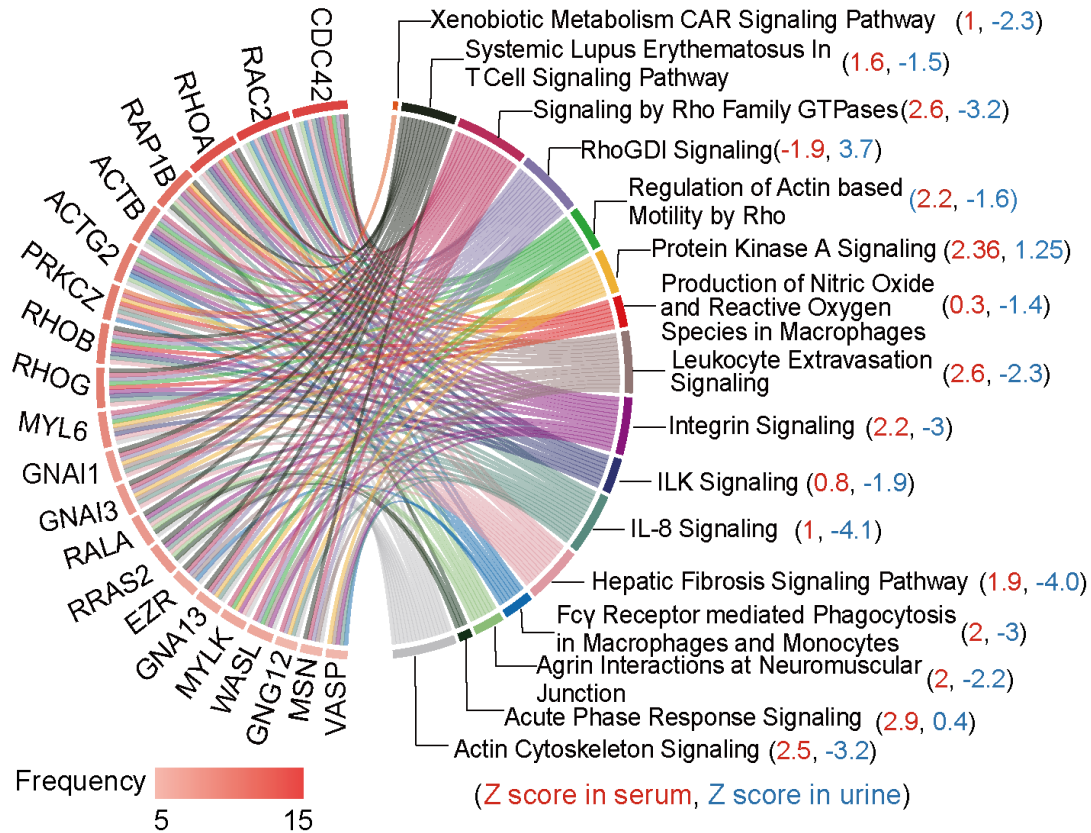
(A) Virus budding-related DEPs uniquely regulated in the urine were identified by untargeted TMT 16plex proteomics and confirmed by PRM. (B) Schematic diagram of the virus budding process.

Differential expression analysis proteins and metabolites

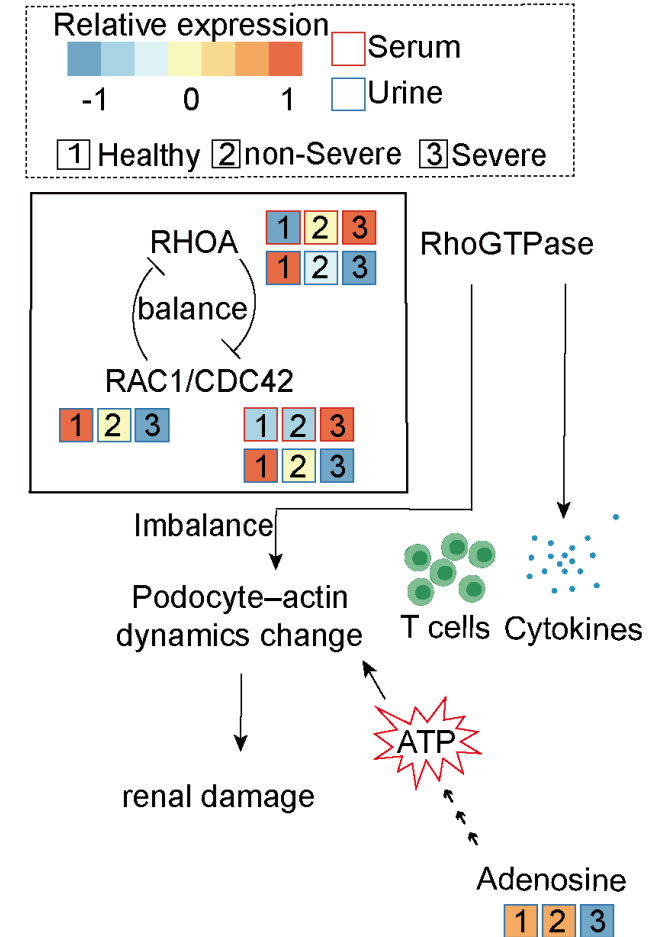


Imbalanced CDC42-RHOA-RAC1 molecular switches

A

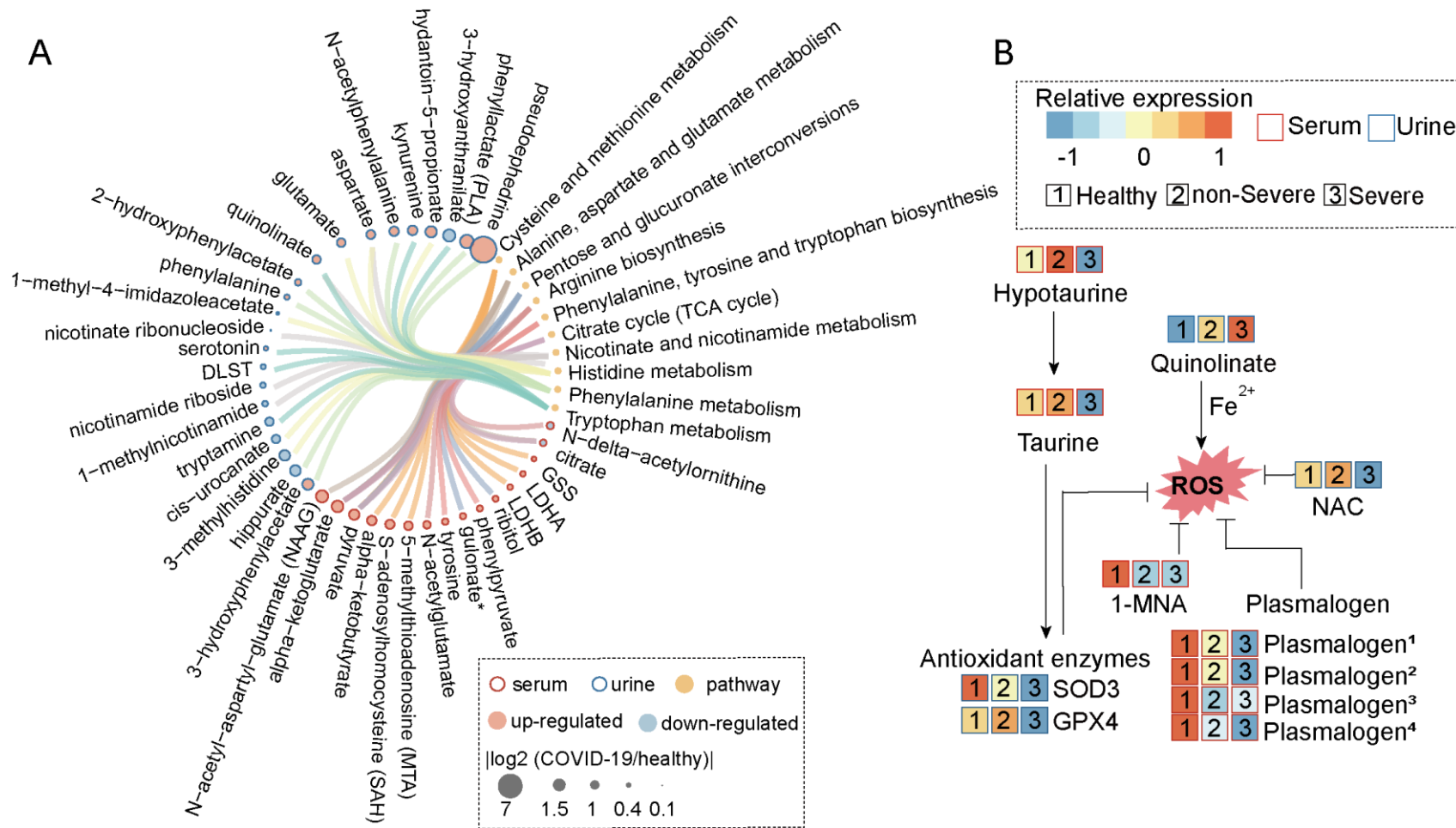


B



(A) The top 21 regulated proteins which they are enrolled in the overlapped 16 out of 20 pathways. (B) Schematic diagram of the dynamic balance of Rho GTPases. The imbalance affects the functional integrity of glomerular podocytes and results in renal damage.

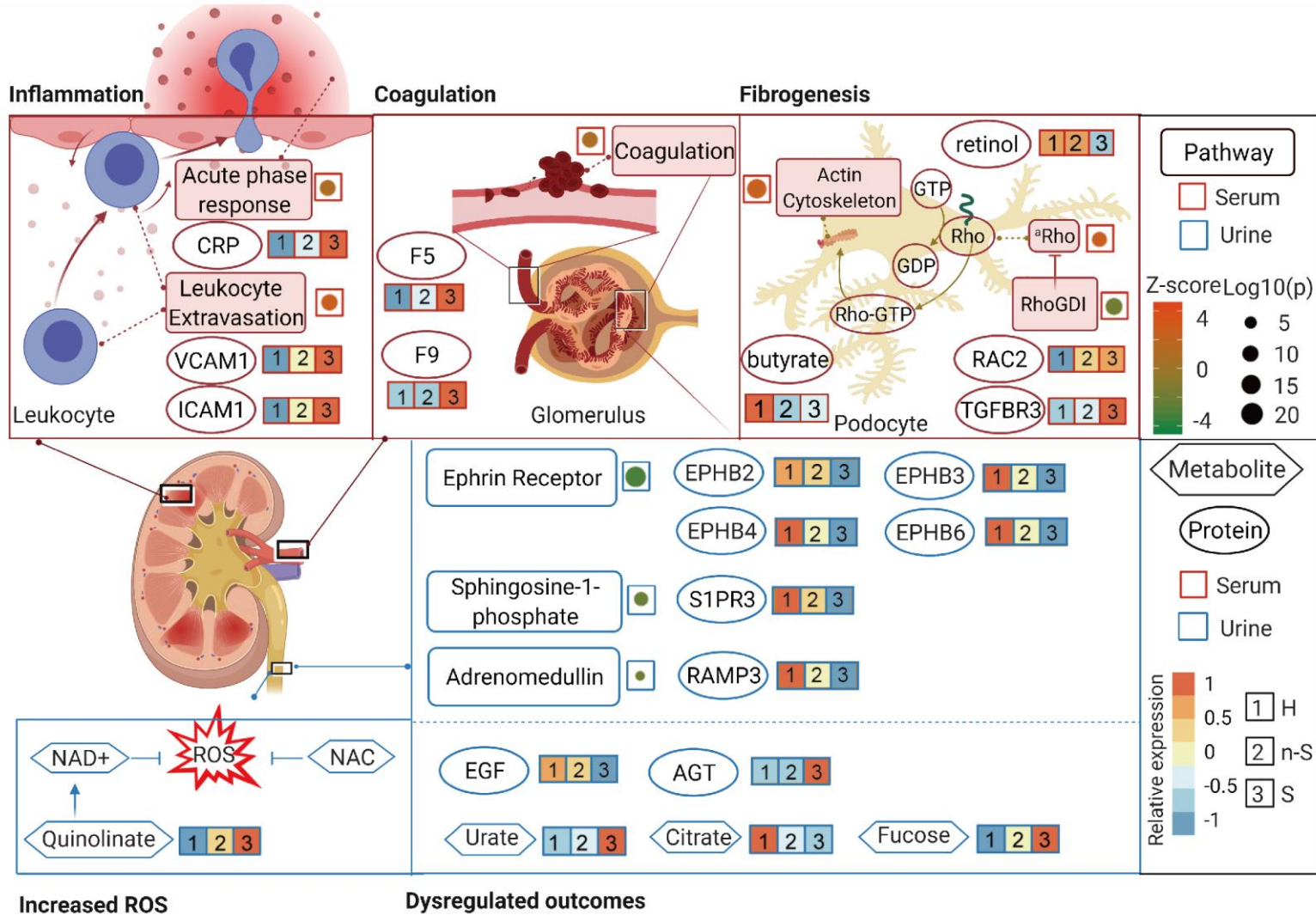
Activation ROS and impaired immune cells in COVID-19



(A) DEPs and differentially expressed metabolites (DEMs) were involved in the 10 KEGG pathways.

(B) Schematic diagram of metabolites participating in the oxidative stress in COVID-19.

Inflammation-induced renal injuries as revealed by multiomics data



Take-home messages

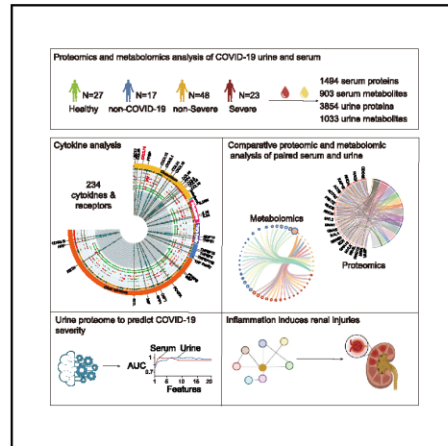
- More cytokines and their receptors are detected in urine than in serum
- Machine learning models based on urinary proteins equal the ones using sera proteins
- Dysregulated inflammatory processes induce renal injury as revealed by multiomics data



Cell Reports

Proteomic and metabolomic profiling of urine uncovers immune responses in patients with COVID-19

Graphical abstract



Highlights

- More cytokines and their receptors are detected in urine than in serum
- Machine learning models based on urinary proteins equal the ones using sera proteins
- Dysregulated inflammatory processes induce renal injury as revealed by multiomics data

Article

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In brief

The value of the urine proteome is largely underestimated compared to the blood proteome. Bi et al. systematically compare proteins and metabolites in COVID-19 urine and sera and show the urine proteome to be a valuable source of biomarkers, offering unique insights into the pathogenesis of infectious diseases.

Proteomic and metabolomic profiling of urine uncovers immune responses in patients with COVID-19

Xiaojie Bi#, Wei Liu#, Xuan Ding#, Shuang Liang#, YufenZheng#, Xiaoli Zhu#, Sheng Quan#, Xiao Yi, Nan Xiang, JupingDu, Haiyan Lyu, Die Yu, Chao Zhang, Luang Xu, Weigang Ge, Xinke Zhan, Jiale He, Zi Xiong, Shun Zhang, Yanchang Li, PingXu, Guangjun Zhu, Donglian Wang, Hongguo Zhu, ShiyongChen, Jun Li, Haihong Zhao, Yi Zhu*, Huafen Liu*, Jiaqin Xu*, Bo Shen*, Tiannan Guo*



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