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Supplemental information

Multi-omics personalized network analyses highlight progressive disruption of central metabolism associated with COVID-19 severity

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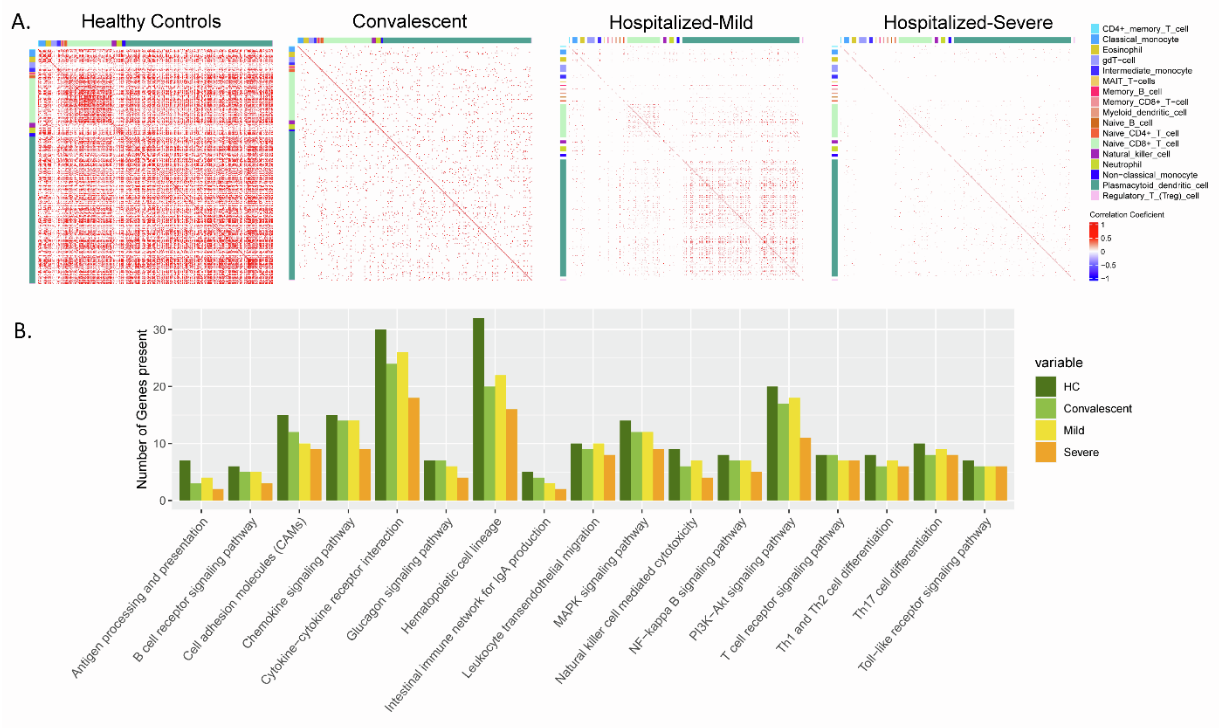

Figure S1: Association between marker genes and pathways related to lost marker genes. (A) Heatmap of significant correlations among marker genes inhealthy (adj p<0.001), convalescent (adj p<0.001), hospitalized mild (adj p<0.001), and hospitalized severe samples (adj p<0.2). Column annotation represents corresponding cell types. (B) Bar graph showing the number of genes present in healthy, convalescent, hospitalized, mild hospitalizedsevere in each of the significant pathways identified in lost marker gene associations.

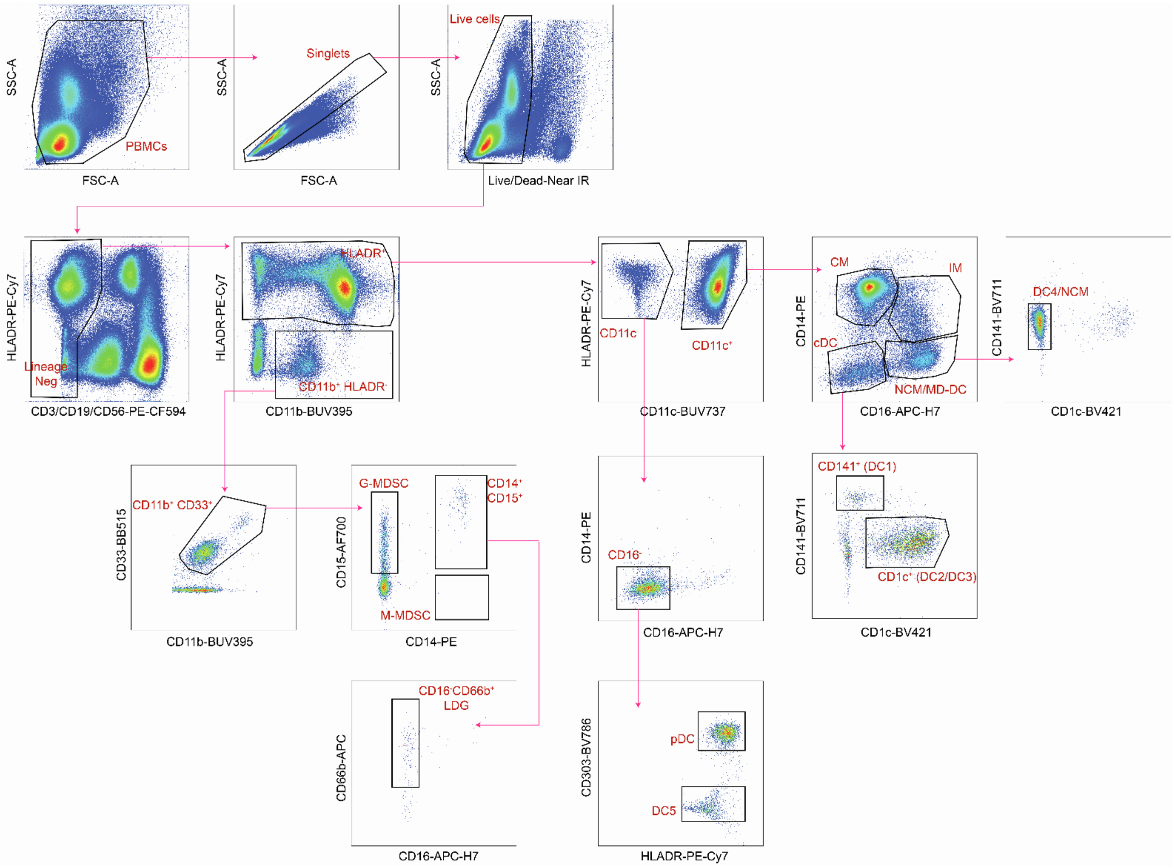

Figure S2: Gating strategy of the mononuclear phagocytes (MNPs).

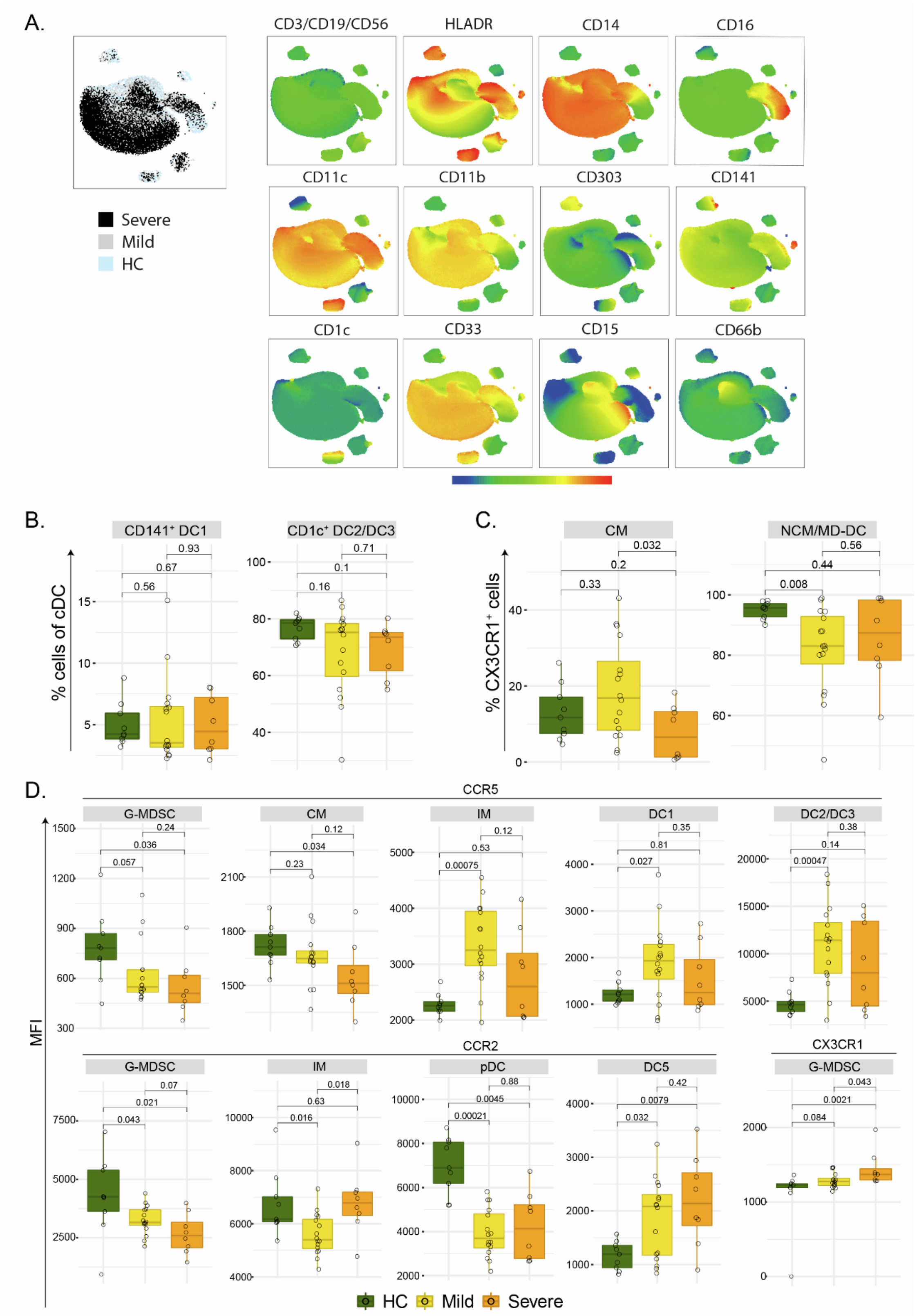

Figure S3: (A) UMAP showing differences in cell populations between HC, mild, and severe COVID-19 patients (left); cell identity was based on marker expression (right). (B) Box plots showing the percentage of CD141$^+$ DC1 cells and CD1c$^+$ DC2/DC3 cells of cDCs. (C) Box plots showing the percentage of CX3CR1$^+$ CM and NCM/MD-DC cells. (D) Box plots showing median fluorescence intensity (MFI) of chemokine the receptors CCR5, CCR2, and CX3CR1 in different MNPs. P-values were determined by the Mann-Whitney U test.

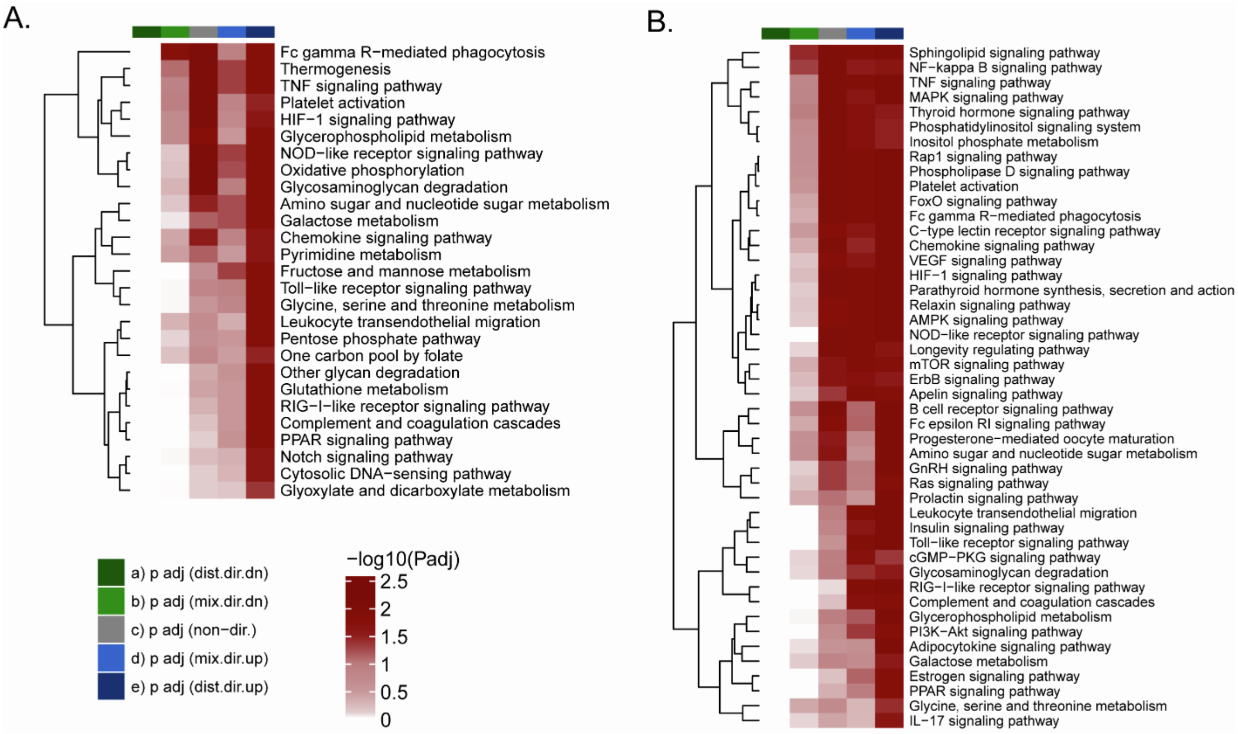

Figure S4. Gene set enrichment analysis. (A) Heatmap visualizing significantly regulated KEGG pathways (adj p<0.05) in COVID-19 mild compared to healthy individuals. The color scale represents adjusted p-values of different directionality classes of regulation. (B) Heatmap visualizing significantly regulated KEGG pathways (adj p<0.05) in COVID-19 severe in comparison with healthy individuals. The color scale represents adjusted p-values of different directionality classes of regulation.

Figure S5: Gene set enrichment analysis: KEGG gene set enrichment analysis results of communities identified in transcriptomics metabolomics association network topology analysis.

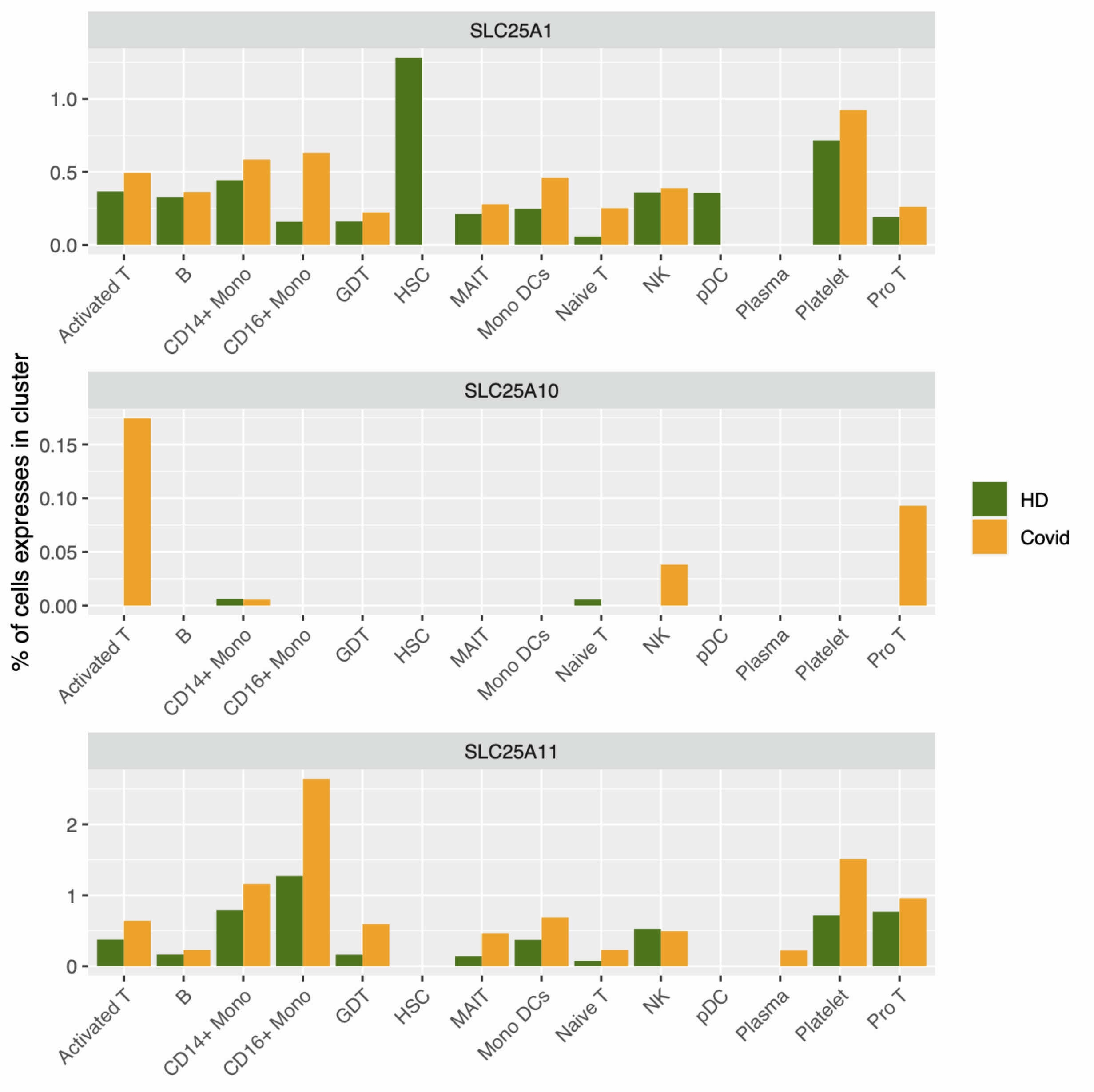

Figure S6. Expression of the members of the mitochondrial carrier family (SLC25) (*SLC25A1, SLC25A10,* and *SLC25A11*) in different cell types.

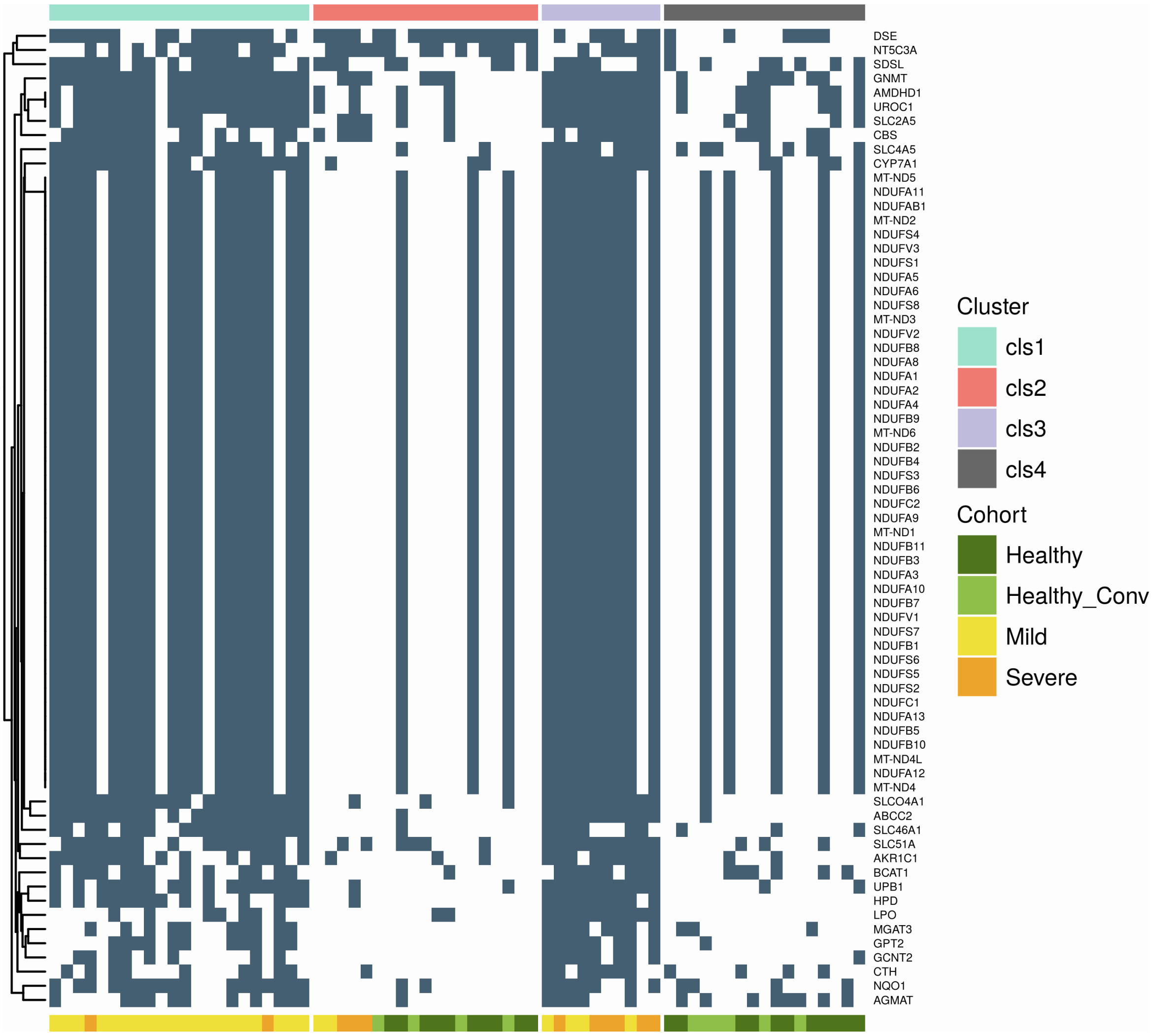

Figure S7. Gene essentiality: Genes identified as essential in more thanhalf of the SNF-1 and SNF-3 cluster samples. The top column annotation represents SNF-clusters and the bottom column annotation represents the original cohort definition. An empty cell denotes a non-essential gene in the corresponding sample.

Figure S8. Expression of the mitochondrial carrier family (SLC25). Bar graph showing percentage cells in each of the cell typeclusters where the corresponding gene is expressed.

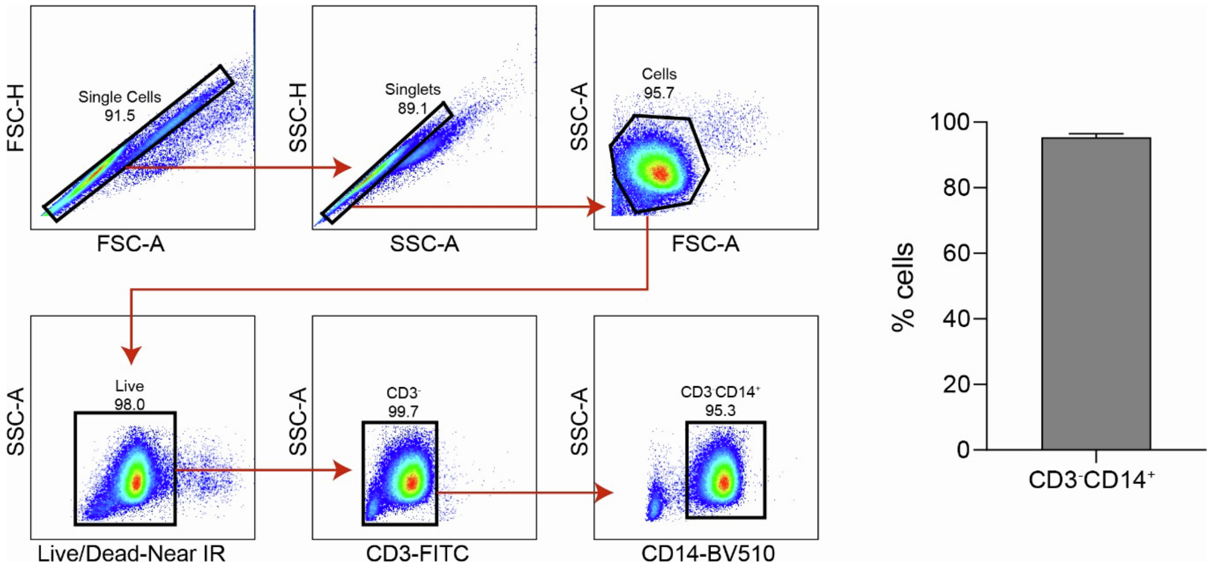

Figure S9. Monocyte's purity following negative selection.

Table S1. Markers used for immune phenotyping of MNPs

Abbreviation of cell population	**Markers that define this population**
Live cells	Live/Dead stain$^-$
Lin$^-$	CD3$^-$CD19$^-$CD56$^-$
G-MDSC	Lin$^-$HLADR$^-$CD11b$^+$CD33$^+$CD14$^-$CD15$^+$
M-MDSC	Lin$^-$HLADR$^-$CD11b$^+$CD33$^+$CD14$^+$CD15$^-$
LDG	Lin$^-$HLADR$^-$CD11b$^+$CD33$^+$CD14$^+$CD15$^+$CD16$^-$CD66b$^+$
CM	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^+$CD16$^-$
IM	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^+$CD16$^+$
NCM / MD-DC	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^-$CD16$^+$
cDC	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^-$CD16$^-$
DC1	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^-$CD16$^-$CD141$^+$
DC2/DC3	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^-$CD16$^-$CD1c$^+$
DC4	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^+$CD14$^-$CD16$^+$CD141^{low}CD1c$^-$
DC5	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^-$CD14$^-$CD16$^-$CD303$^-$
pDC	Lin$^-$HLADR$^+$CD11b$^{+/-}$CD11c$^-$CD14$^-$CD16$^-$CD303$^+$

Table S2. Individual patient data

ID	Clinical Definitions	SARS-CoV-2 PCR positive	SARS-CoV-2 Serology positive	SNF_cluster	Age (as of 2020)	Gender	BMI	Comorbidities
COVID19_20	HC	No	No	2	55	Female	27,16	no
COVID19_21	HC	No	No	2	48	Male	24,15	no
COVID19_1	HC	No	No	4	55	Male	20,9	no
COVID19_11	HC	No	No	4	44	Male	21,46	no
COVID19_31	HC	No	No	4	61	Male	21,22	no
COVID19_2	HC	No	No	2	46	Male	24,49	no
COVID19_22	HC	No	No	4	59	Male	20,99	no
COVID19_24	HC	No	No	2	48	Male	32,1	no
COVID19_4	HC	No	No	4	45	Female	22,73	no
COVID19_25	HC	No	No	2	46	Male	24,97	no
COVID19_5	HC	No	No	4	62	Female	31,99	no
COVID19_16	HC	No	No	2	52	Male	39,68	no
COVID19_6	HC	No	No	4	41	Male	18,71	no
COVID19_17	HC	No	No	2	46	Male	25,17	no
COVID19_27	HC	No	No	2	48	Male	24,31	no
COVID19_7	HC	No	No	4	49	Male	22,31	no
COVID19_8	HC	No	No	2	45	Male	31,35	no
COVID19_28	HC	No	No	4	38	Male	23,12	no
COVID19_9	HC	No	No	2	60	Male	25,17	no
COVID19_19	HC	No	No	4	46	Male	24,38	no
COVID19_29	HC	No	No	4	46	Male	19,71	no
COVID19_10	Conv	No	Yes	2	65	Male	22,59	no
COVID19_18	Conv	No	Yes	2	49	Male	29,34	no
COVID19_23	Conv	No	Yes	2	41	Male	28,06	no
COVID19_32	Conv	No	Yes	2	43	Male	23,84	no
COVID19_12	Conv	No	Yes	4	49	Female	25,28	no
COVID19_13	Conv	No	Yes	4	48	Female	21,15	no
COVID19_14	Conv	No	Yes	4	51	Male	21,98	no
COVID19_15	Conv	No	Yes	4	66	Male	21,8	no
COVID19_26	Conv	No	Yes	4	54	Female	24,92	no
COVID19_3	Conv	No	Yes	4	50	Female	22,99	no
COVID19_004	Mild	Yes	ND	1	66	Male	21,08	no
COVID19_005	Mild	Yes	ND	1	38	Female	28,73	no
COVID19_008	Mild	Yes	ND	1	60	Male	28,55	yes
COVID19_010	Mild	Yes	ND	1	74	Male	26,83	yes
COVID19_011	Mild	Yes	ND	1	64	Male	25,51	no
COVID19_012	Mild	Yes	ND	1	48	Male	31,46	no
COVID19_014	Mild	Yes	ND	1	63	Male	25,21	no
COVID19_015	Mild	Yes	ND	1	44	Male	28,4	no
COVID19_017	Mild	Yes	ND	1	47	Male	34,72	no
COVID19_018	Mild	Yes	ND	1	38	Female	21,37	no
COVID19_019	Mild	Yes	ND	1	66	Male	23,85	yes
COVID19_022	Mild	Yes	ND	1	61	Male	30,42	no
COVID19_023	Mild	Yes	ND	1	59	Male	29,86	yes
COVID19_024	Mild	Yes	ND	1	32	Male		no
COVID19_027	Mild	Yes	ND	1	57	Male	28,01	yes
COVID19_029	Mild	Yes	ND	1	50	Male	27,71	no
COVID19_032	Mild	Yes	ND	1	59	Male	31,02	no
COVID19_036	Mild	Yes	ND	1	69	Male	30,08	yes
COVID19_039	Mild	Yes	ND	1	64	Female	23,94	no
COVID19_041	Mild	Yes	ND	1	34	Male	32,25	no
COVID19_001	Mild	Yes	ND	2	45	Female	23,73	no
COVID19_006	Mild	Yes	ND	2	59	Male	31,35	yes
COVID19_002	Mild	Yes	ND	3	44	Female	54,14	yes
COVID19_013	Mild	Yes	ND	3	53	Male		yes
COVID19_016	Mild	Yes	ND	3	72	Male	21,91	yes
COVID19_030	Mild	Yes	ND	3	59	Male	34,88	yes
COVID19_009	Severe	Yes	ND	1	52	Male	30,97	yes
COVID19_034	Severe	Yes	ND	1	76	Male	26,83	no
COVID19_028	Severe	Yes	ND	2	71	Male	26,57	no
COVID19_033	Severe	Yes	ND	2	52	Male	34,56	yes
COVID19_037	Severe	Yes	ND	2	62	Male	40,14	yes
COVID19_007	Severe	Yes	ND	3	39	Male	24,49	no
COVID19_020	Severe	Yes	ND	3	75	Male	28,31	yes
COVID19_021	Severe	Yes	ND	3	65	Male	25,66	yes
COVID19_026	Severe	Yes	ND	3	58	Male	24,94	no
COVID19_031	Severe	Yes	ND	3	55	Male	19,2	yes
COVID19_035	Severe	Yes	ND	3	57	Male	33,26	yes

Table S3. Flux balance analysis

HMR ID	Flux Direction	Equation
r2377	Neg flux HC	AKG[c] + cis-aconitate[m] <=> AKG[m] + cis-aconitate[c]
r2378	Neg COVID	cis-aconitate[m] + succinate[c] <=> cis-aconitate[c] + succinate[m]
HMR_4855	Pos COVID	fumarate[c] + malate[m] <=> fumarate[m] + malate[c]
HMR_4852	Neg COVID Pos HC	AKG[c] + malate[m] <=> AKG[m] + malate[c]
HMR_8741	Neg COVID	fumarate[c] + sulfite[m] <=> fumarate[m] + sulfite[c]
HMR_4872	Neg COVID	malonate[c] + sulfite[m] <=> malonate[m] + sulfite[c]
HMR_6522	Neg COVID	malate[c] + thiosulfate[m] <=> malate[m] + thiosulfate[c]
HMR_4851	Pos COVID	AKG[c] + succinate[m] <=> AKG[m] + succinate[c]
HMR_4864	Pos COVID	succinate[c] + sulfite[m] <=> succinate[m] + sulfite[c]
HMR_4868	Pos COVID	malate[c] + sulfite[m] <=> malate[m] + sulfite[c]
HMR_4863	Pos COVID	succinate[c] + sulfate[m] <=> succinate[m] + sulfate[c]
HMR_4867	Neg COVID	malate[c] + sulfate[m] <=> malate[m] + sulfate[c]
HMR_4871	Pos COVID	malonate[c] + sulfate[m] <=> malonate[m] + sulfate[c]
HMR_8742	Neg COVID	fumarate[c] + sulfate[m] <=> fumarate[m] + sulfate[c]
HMR_6521	Pos COVID	fumarate[c] + thiosulfate[m] <=> fumarate[m] + thiosulfate[c]

Table S4. MRM transitions for GC-QQQ-MS analysis. RT=retention time; CE = Collision Energy.

Compound	**RT (min)**	**Quantifier**	**CE**	**Qualifier**	**CE**
aconitic acid	5.24	375→147	10	375→211	10
alpha-keto-glutaric acid	4.75	288→73	20	288→198	10
alpha-ketoglutaric acid (IS)	4.75	308→147	10	-	-
citric acid	5.42	183→73	10	183→183	10
citric acid (IS)	5.42	276→185	10	-	-
fumaric acid	4.00	245→73	20	245→245	10
fumaric acid (IS)	4.00	249→147	10	-	-
glucose	5.7	319→129	10	319→157	10
glucose (IS)	5.7	323→132	10	-	-
glucose 6-phosphate	6.73	387→387	10	387→73	40
isocitric acid	5.47	245→73	20	245→83	20
lactic acid	2.72	219→147	10	219→191	10
malic acid	4.5	335→147	10	335→73	10
malic acid (IS)	4.5	339→147	20	-	-
methyl stearate (IS)	6.2	298→101	20	-	-
shikimic acid	5.4	462→204	10	462→254	20
succinic acid	3.9	262→73	10	262→113	10
succinic acid (IS)	3.9	251→147	20	-	-
sucrose	7.31	437→257	20	437→303	10
sucrose (IS)	7.31	442→262	10	-	-
Urea	3.35	261→147	20	261→245	10