Enhanced inflammation and suppressed adaptive immunity in COVID-19 with prolonged RNA shedding

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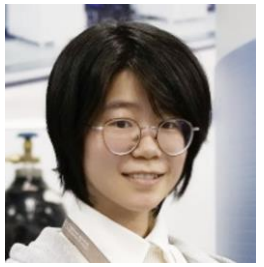

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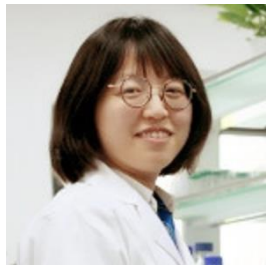

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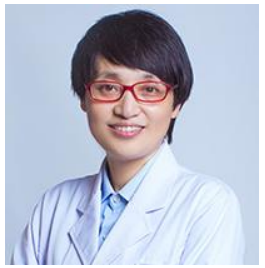

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迪安诊断

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康洲阳

毛婷婷, 黄重庆

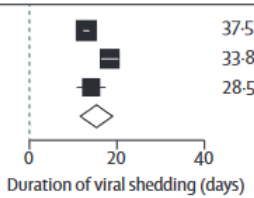
OUTLINE

- Background and research gap
- Overview of clinical patients, samples and study design
- Immunological analysis between the LC and SC groups
- Differentially expressed proteomes and metabolomes between the LC and SC groups
- Integration of proteomic and metabolomic data
- Risk factors for COVID-19 prognosis

BACKGROUND

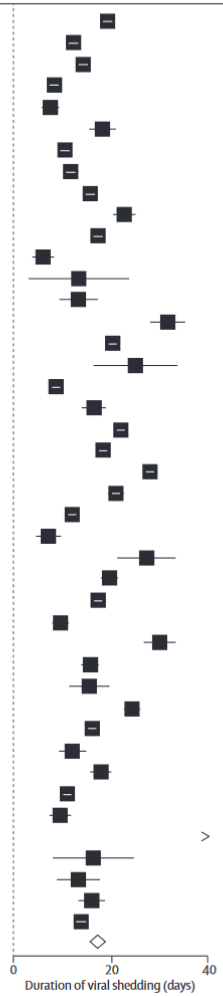
The duration of viral RNA shedding

	Mean duration of viral shedding (95% CI), days	SE	Variance	Total duration of viral shedding, days	Relative weight
Al-Jasser et al (2019)[99]	13·2 (12·3–14·0)	0·4	0·2	249	37·58
Alkendi et al (2019)[100]	18·5 (16·3–20·7)	1·1	1·2	58	33·85
Park et al (2018)[101]	14·3 (10·8–17·7)	1·8	3·2	17	28·57
Overall	**15·3 (11·6–19·0)**	**1·9**	**3·6**	**324**	



The mean duration of MERS-CoV shedding is less than 20 days

	Mean duration of viral shedding (95% CI), days	SE	Variance	Total duration of viral shedding, days	Relative weight
Fang et al (2020)[79]	19·3 (18·8–19·7)	0·2	0	32	2·53
Cai et al (2020)[24]	12·3 (11·9–12·6)	0·2	0	298	2·53
Hu et al (2020)[35]	14·3 (12·9–15·6)	0·7	0·5	59	2·48
Kim et al (2020)[4]	8·3 (6·9–9·8)	0·7	0·5	28	2·48
Le et al (2020)[57]	7·5 (5·6–9·4)	1·0	0·9	12	2·44
Lo et al (2020)[68]	18·2 (15·3–21·1)	1·5	2·1	10	2·34
Ling et al (2020)[45]	10·5 (9·4–11·6)	0·6	0·3	66	2·50
Qian et al (2020)[71]	11·7 (10·1–13·2)	0·8	0·6	24	2·47
Wu et al (2020)[38]	15·7 (14·2–17·2)	0·8	0·6	74	2·47
Xiao et al (2020)[43]	22·8 (20·4–25·1)	1·2	1·4	56	2·40
Xu et al (2020)[36]	17·3 (16·1–18·5)	0·6	0·4	113	2·49
Xu et al (2020)[17]	6·0 (3·6–8·4)	1·2	1·5	10	2·39
Yongchen et al (2020)[34]	13·3 (2·8–23·9)	5·4	28·9	21	1·18
Young et al (2020)[70]	13·3 (9·2–17·3)	2·1	4·2	18	2·17
Zhou et al (2020)[40]	31·7 (27·9–35·4)	1·9	3·6	41	2·21
Zhou et al (2020)[33]	20·3 (19·6–21·1)	0·4	0·1	191	2·52
Zhu et al (2020)[82]	25·0 (16·2–33·8)	4·5	20·2	10	1·41
Sakurai et al (2020)[41]	8·7 (7·8–9·5)	0·4	0·2	90	2·52
To et al (2020)[58]	16·5 (14·0–19·0)	1·3	1·7	23	2·38
Huang et al (2020)[49]	22·0 (20·9–23·1)	0·6	0·3	200	2·50
Liang et al (2020)[47]	18·3 (16·9–19·8)	0·8	0·6	120	2·48
Shi et al (2020)[31]	28·0 (26·6–29·4)	0·7	0·5	246	2·48
Talmy et al (2020)[67]	21·0 (19·4–22·6)	0·8	0·7	119	2·47
Chen et al (2020)[26]	12·0 (11·3–12·7)	0·4	0·1	284	2·52
Hu et al (2020)[53]	7·1 (4·3–9·8)	1·4	2·0	24	2·35
Song et al (2020)[75]	27·3 (21·2–33·5)	3·1	9·8	21	1·83
Yang et al (2020)[54]	19·7 (17·9–21·5)	0·9	0·8	45	2·45
Wu et al (2020)[29]	17·3 (15·8–18·9)	0·8	0·6	91	2·47
Zhang et al (2020)[77]	9·5 (7·8–11·2)	0·9	0·7	23	2·46
Fu et al (2020)[64]	30·0 (26·5–33·5)	1·8	3·1	50	2·26
Tan et al (2020)[37]	15·8 (13·9–17·6)	1·0	0·9	67	2·44
Kujawski et al (2020)[16]	15·5 (11·2–19·8)	2·2	4·9	12	2·12
Yan et al (2020)[32]	24·3 (22·4–26·2)	1·0	0·9	120	2·44
Yang et al (2020)[83]	16·1 (14·9–17·3)	0·6	0·4	213	2·50
Xu et al (2020)[80]	12·0 (9·1–14·9)	1·5	2·2	14	2·33
Huang et al (2020)[23]	17·9 (15·6–20·2)	1·2	1·4	33	2·40
Chen et al (2020)[25]	11·0 (10·8–11·2)	0·1	0	249	2·53
Chang et al (2020)[61]	9·5 (7·1–11·9)	1·2	1·5	16	2·39
Li et al (2020)[66]	53·9 (50·7–57·1)	1·6	2·7	36	2·29
Pongpirul et al (2020)[70]	16·3 (7·8–24·9)	4·3	18·9	11	1·45
Tan et al (2020)[10]	13·3 (8·6–17·9)	2·4	5·5	10	2·08
Wang et al (2020)[77]	16·0 (13·1–18·9)	1·5	2·2	18	2·33
Zha et al (2020)[46]	13·8 (12·6–15·1)	0·6	0·4	31	2·49
Overall	**17·0 (15·5–18·6)**	**0·8**	**0·6**	**3229**	

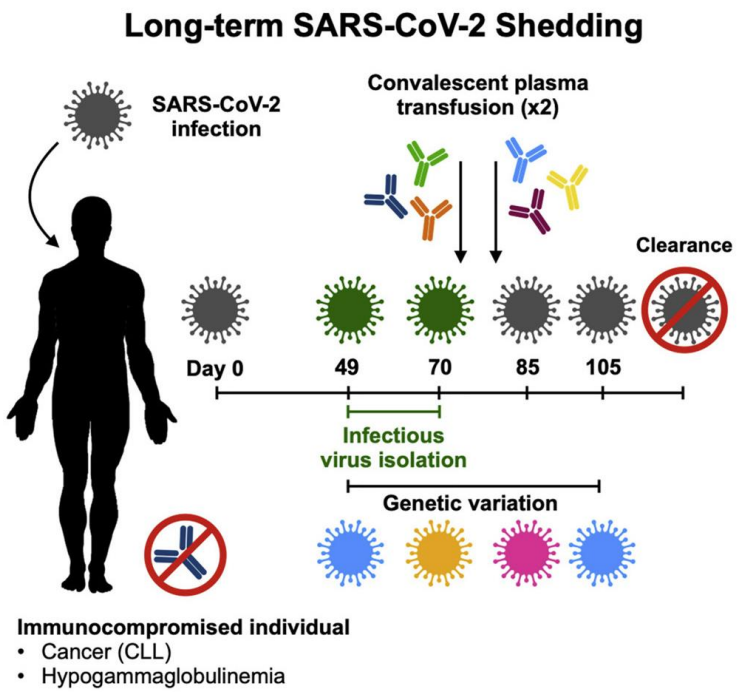


The mean duration of SARS-CoV-2 RNA shedding is usually from 10-25 days.

Cevik, et al. ***Lancet Microbe***. 2021

BACKGROUND

The relationship between the phenotype and viral RNA shedding



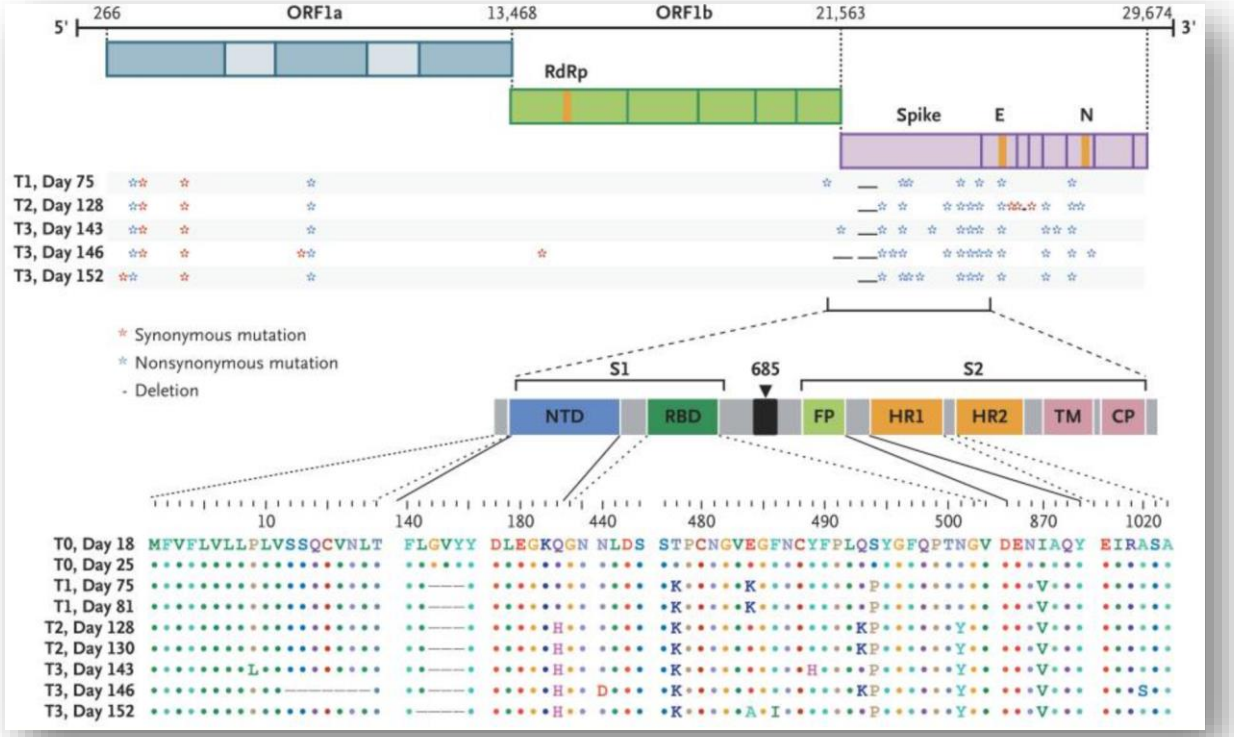
Avanzato, et al. ***Cell***. 2020

Table 1.
Comparison of Clinical Characteristics and Treatment Responses Between Groups With Different Shedding Durations

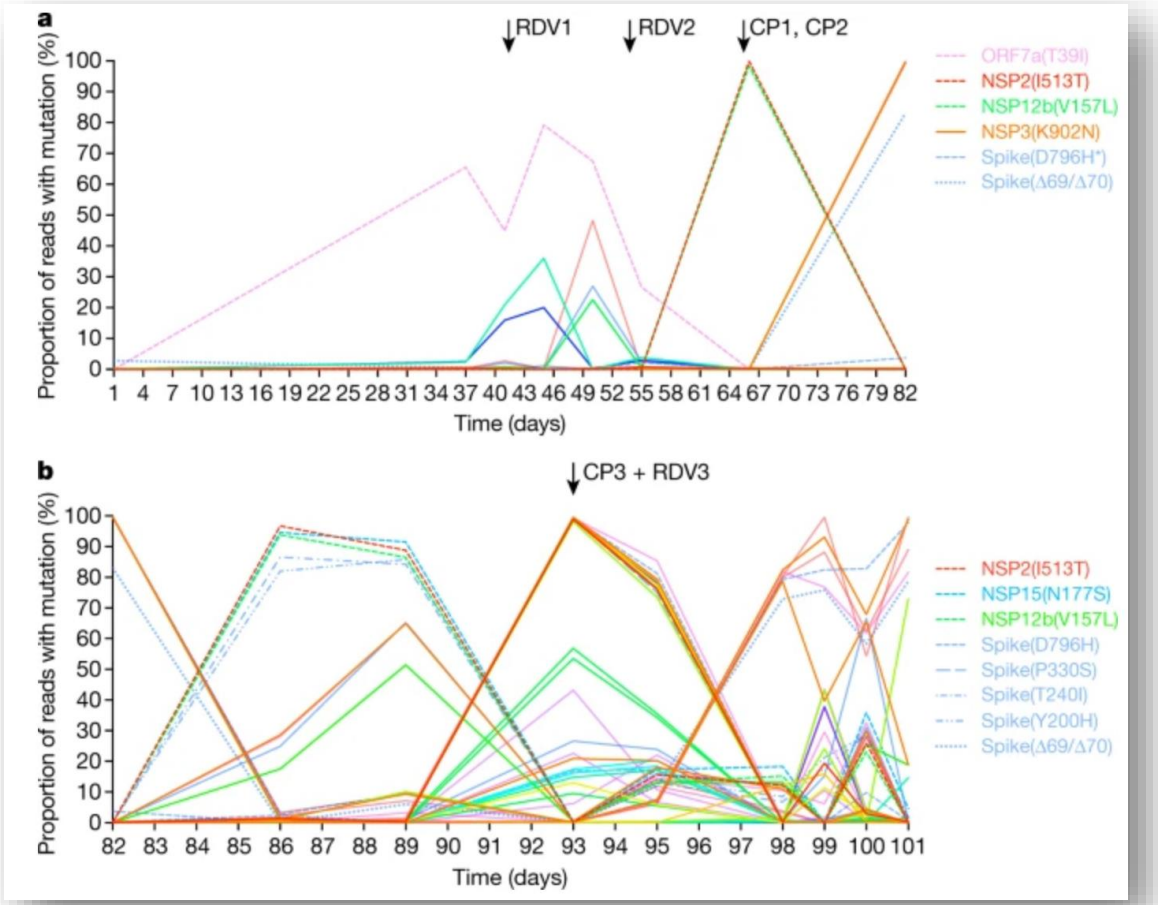
	All Patients (N = 113)		Viral Shedding Duration After Illness Onset				
	n	Values	n	<15 Days (n = 37)	n	≥15 Days (n = 76)	P^a
Age, years, median (IQR range)	113	52 (43, 63)	37	48 (34, 61)	76	54.5 (45, 63)	.033
Male sex, % (n)	113	58.4 (66)	37	40.5 (15)	76	67.1 (51)	.009
Exposure history in Hubei, % (n)	113	62.8 (71)	37	67.6 (25)	76	60.5 (46)	.467
Exposure history to confirmed patients, % (n)	113	40.7 (46)	37	51.4 (19)	76	35.5 (27)	.108
Duration from illness onset to hospital admission, median (IQR), days	113	5 (3, 8)	37	4 (2, 6)	76	6 (4, 9)	.001
Patients with severe disease at admission, % (n)	113	28.3 (32)	37	16.2 (6)	76	34.2 (26)	.049
Comorbidity, % (n)							
Hypertension	113	23.0 (26)	37	8.1 (3)	76	30.3 (23)	.009
Diabetes	113	8.0 (9)	37	5.4 (2)	76	9.2 (7)	.715
Coronary heart disease	113	5.3 (6)	37	5.4 (2)	76	5.3 (4)	1
Current smoker	113	7.1 (8)	37	8.1 (3)	76	6.6 (5)	.715
Treatment, % (n)							
Corticosteroid	113	56.6 (64)	37	40.5 (15)	76	64.5 (49)	.025
Umifenovir	113	48.7 (55)	37	43.2 (16)	76	51.3 (39)	.420
Ribavirin	113	16.8 (19)	37	8.1 (3)	76	21.1 (16)	.084
Invasive mechanical ventilation	113	15.9 (18)	37	2.7 (1)	76	22.4 (17)	.006

Xu, et al. ***Clinical infectious diseases***. 2020

The relationship between the viral RNA shedding prolonged and evolution



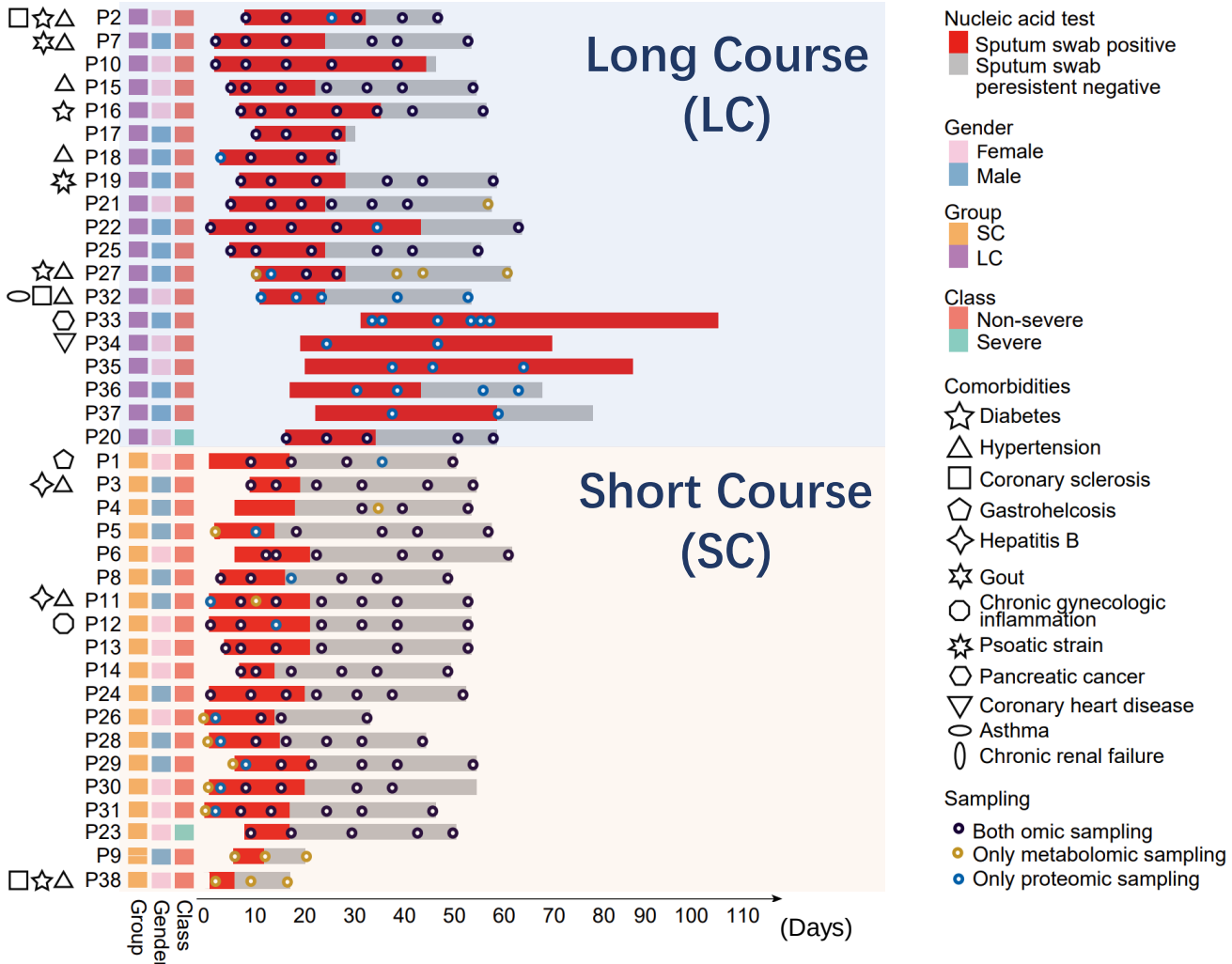
Bina, et al. ***N Engl J Med***. 2020



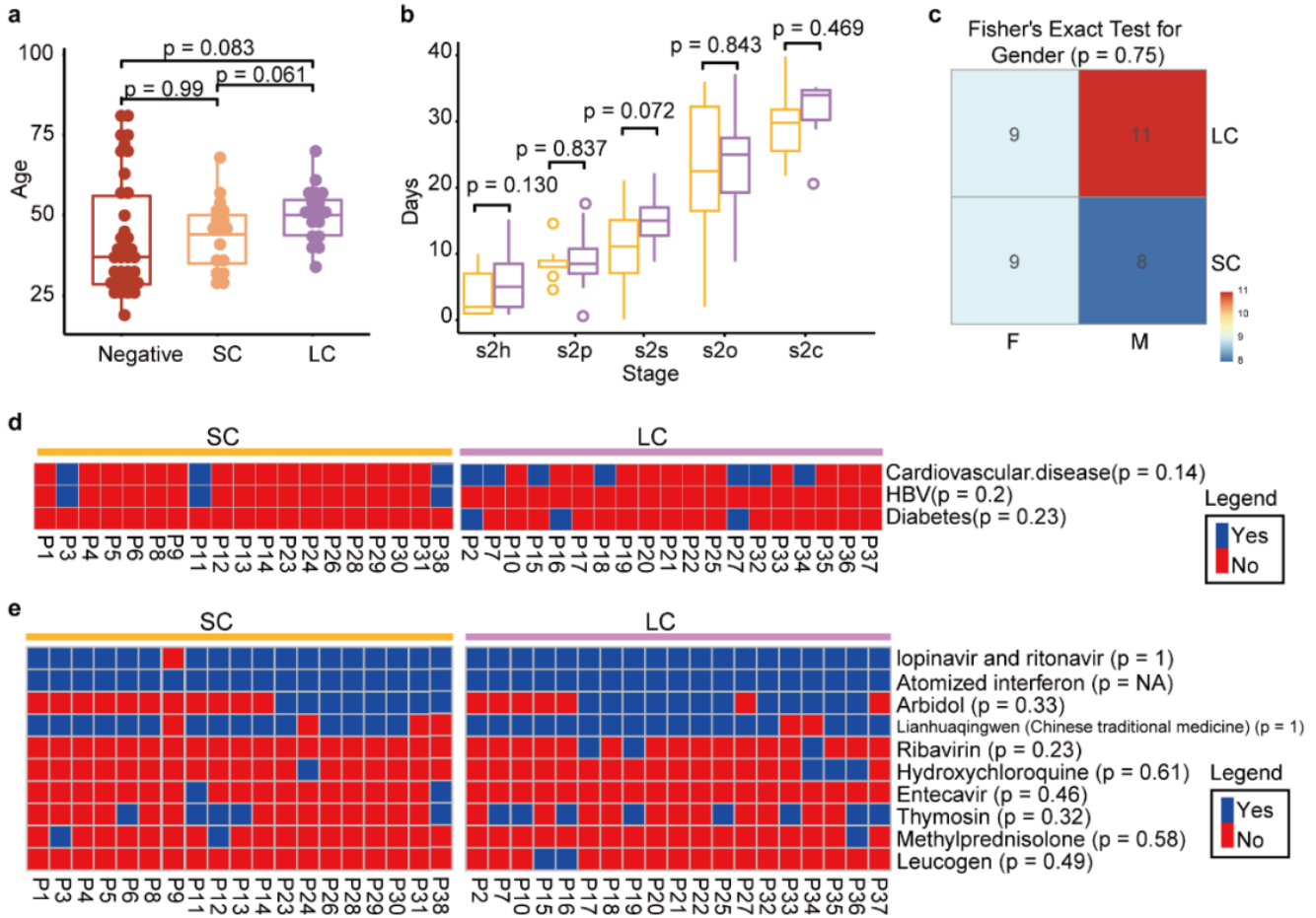
Kemp, et al. ***Nature***. 2021

Few studies have characterized host responses of patients with long viral RNA shedding at the molecular level.

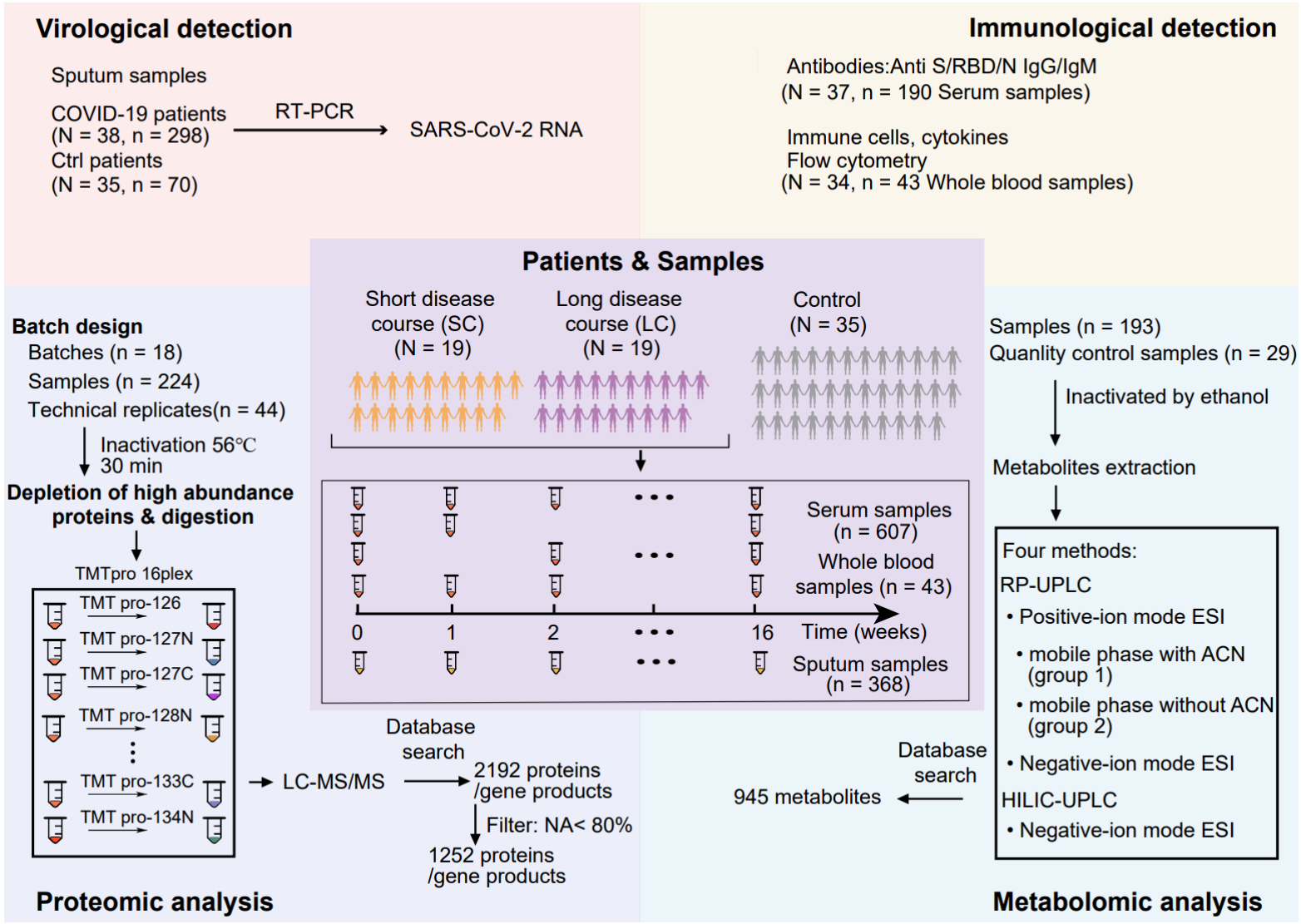
THE OVERVIEW OF CLINICAL PATIENTS



NO SIGNIFICANT CLINICAL DIFFERENCES



STUDY DESIGN



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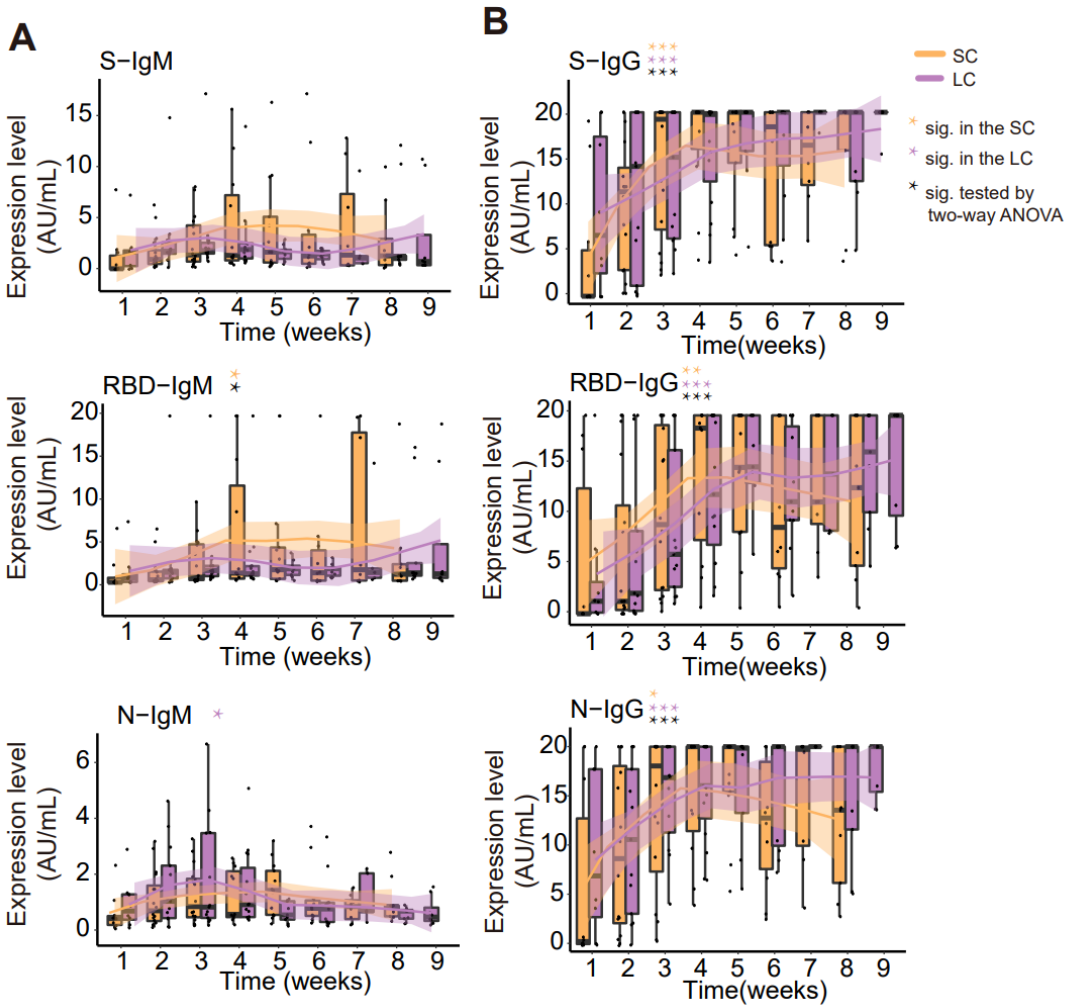
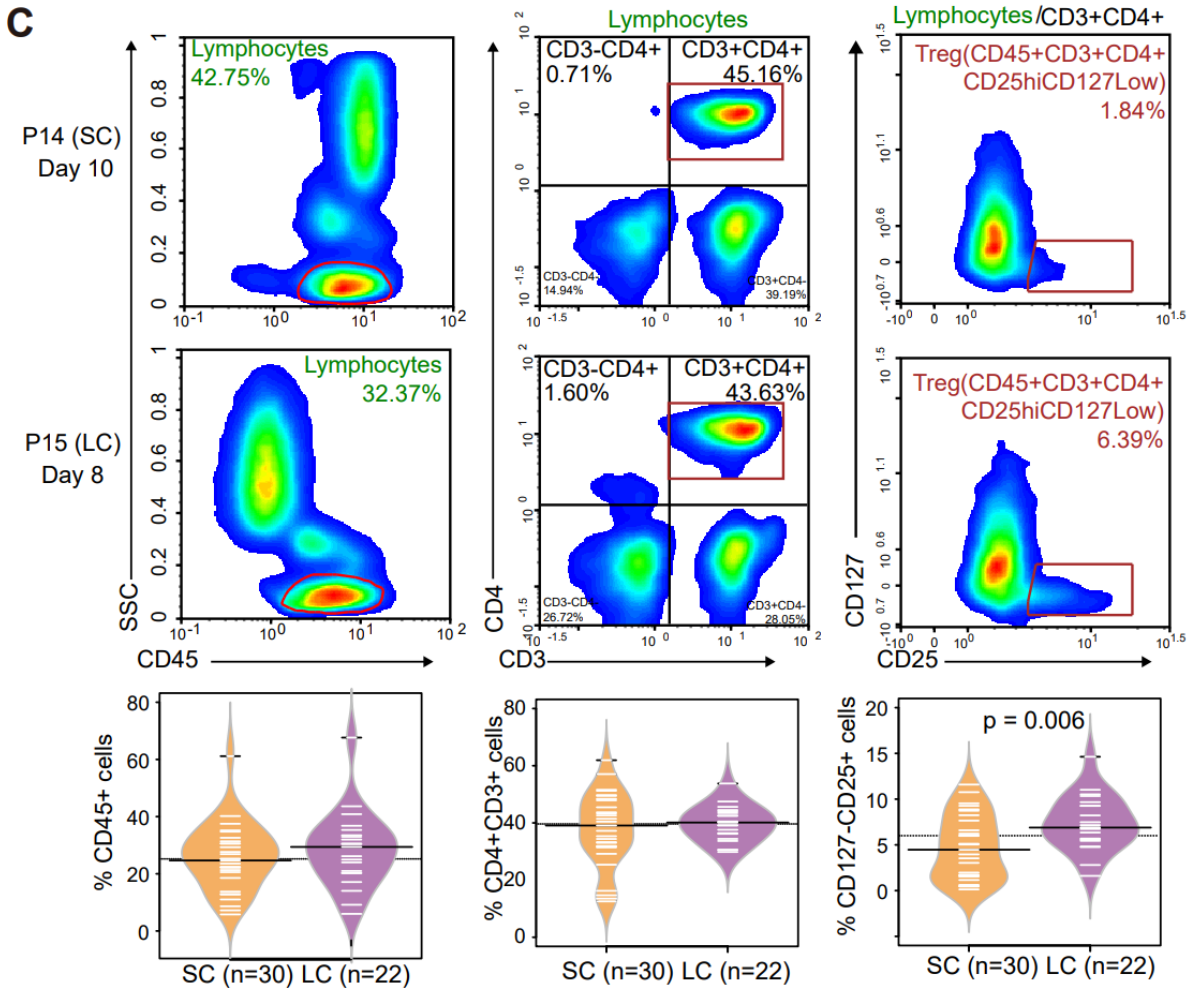
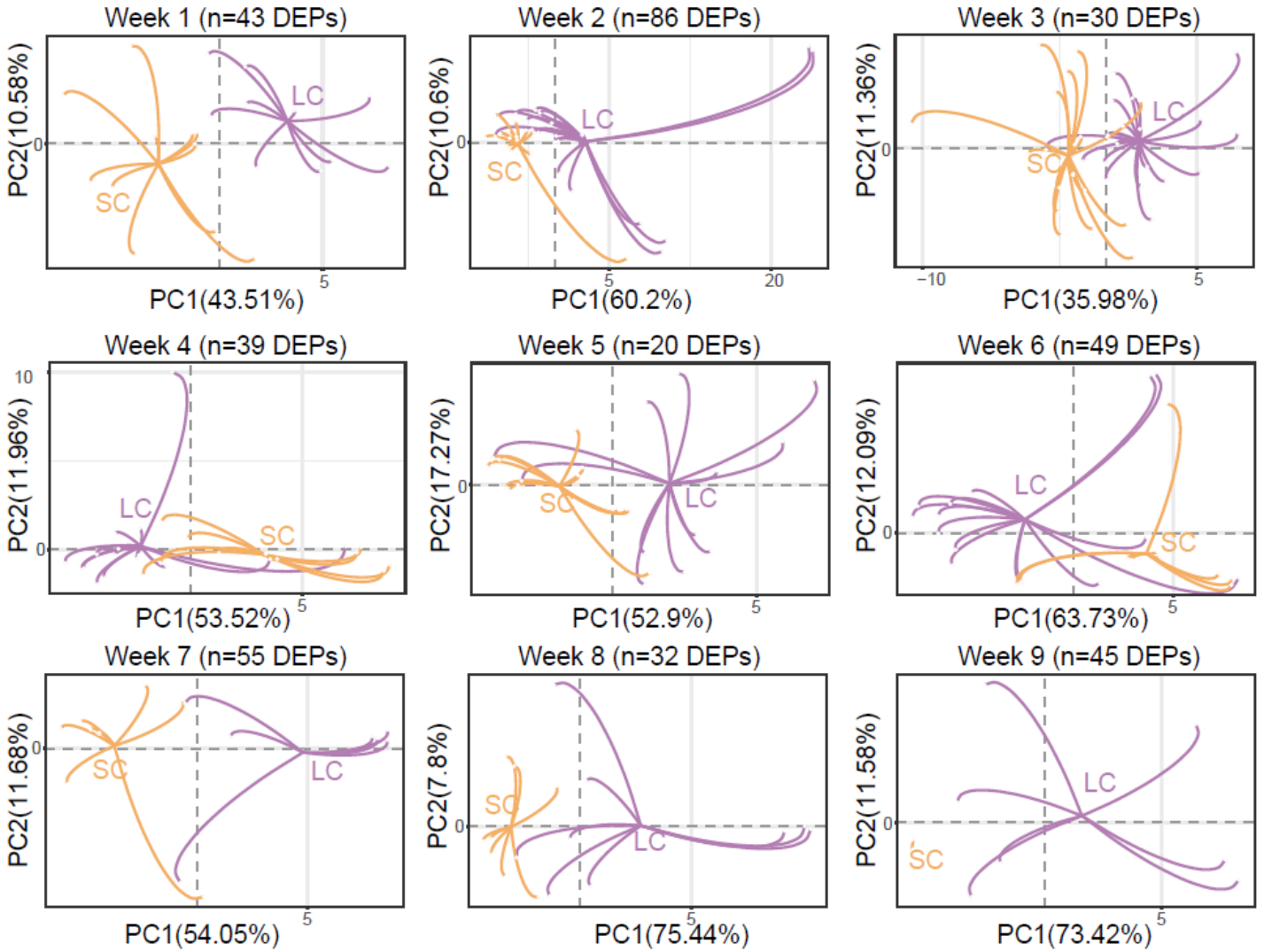
THE TIME-SERIES IMMUNOLOGICAL DETECTION



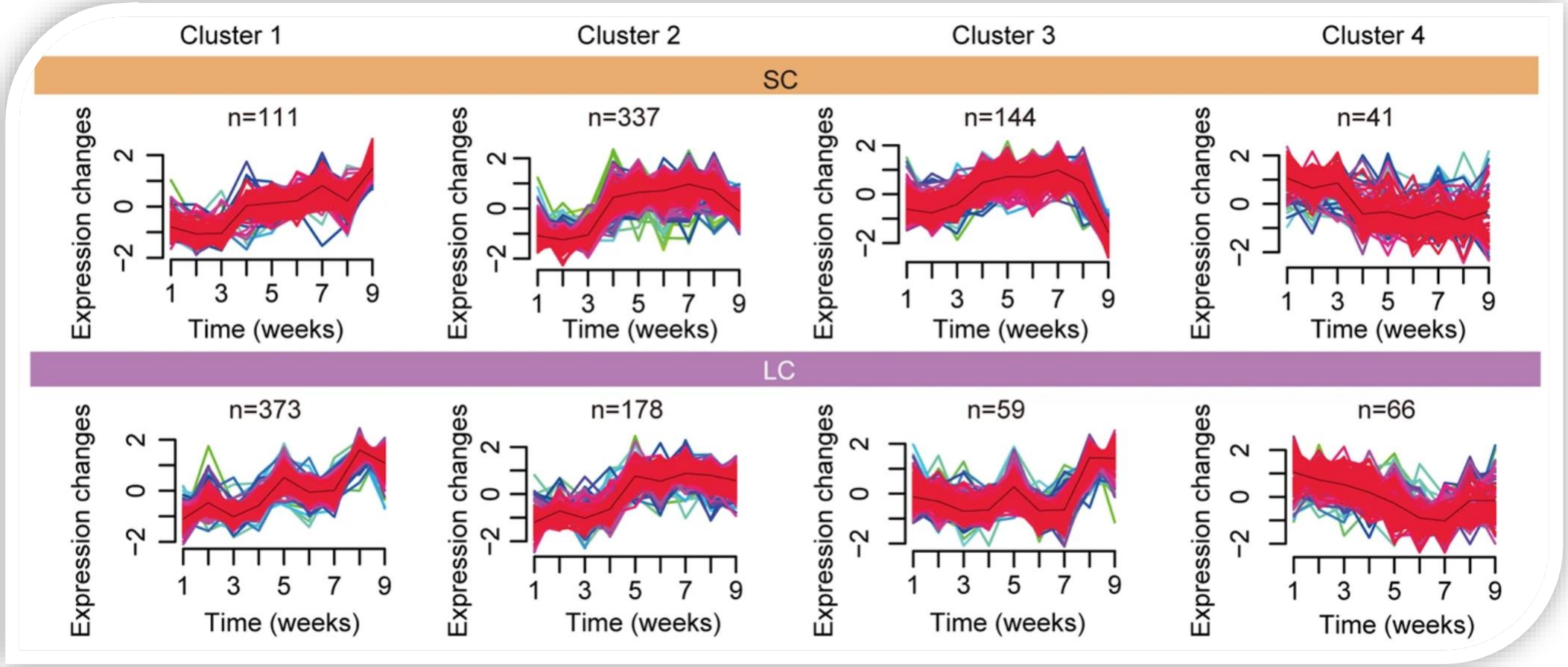
DOWNREGULATION OF TREG CELLS



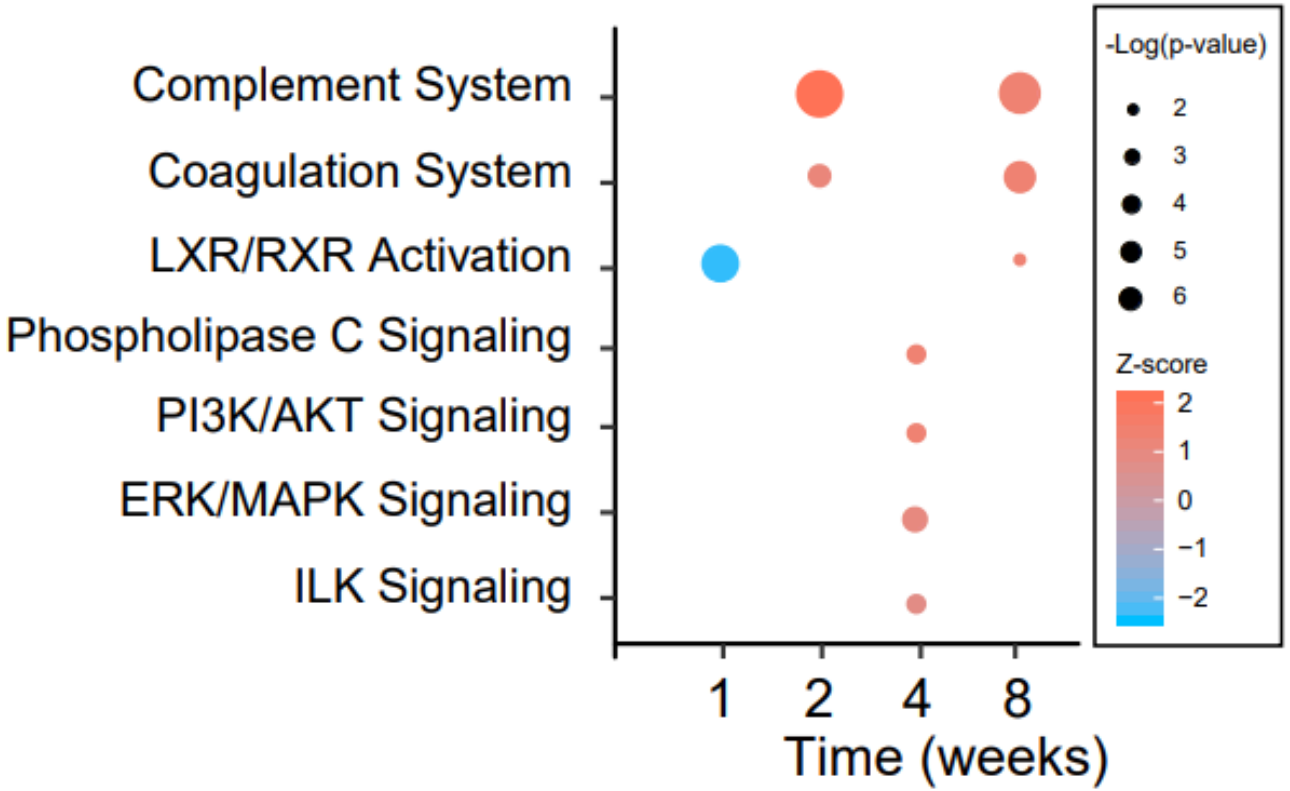
DIFFERENCE BETWEEN THE LC AND SC



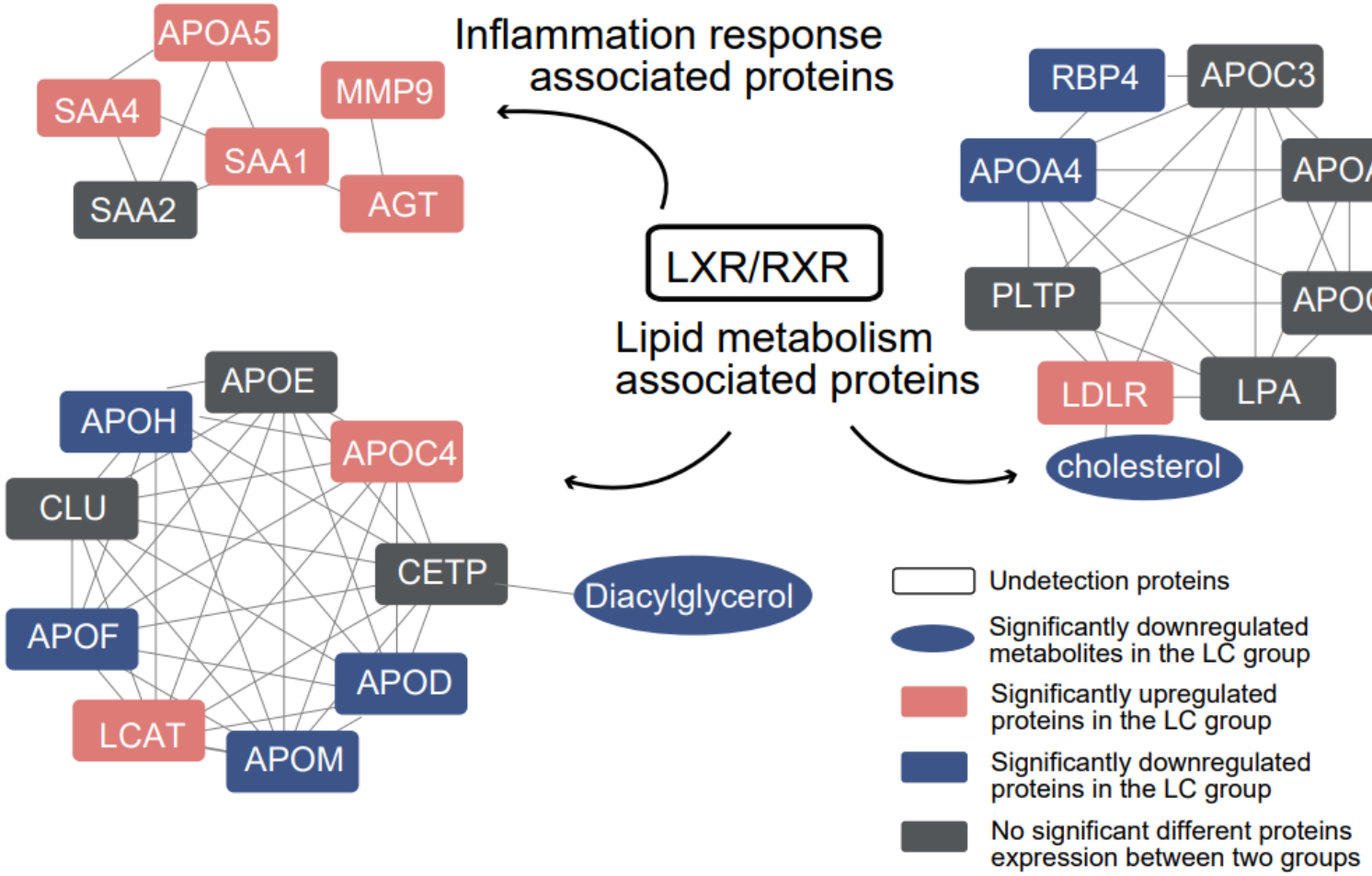
DELAYED IMMUNE RESPONSE IN THE LC GROUP



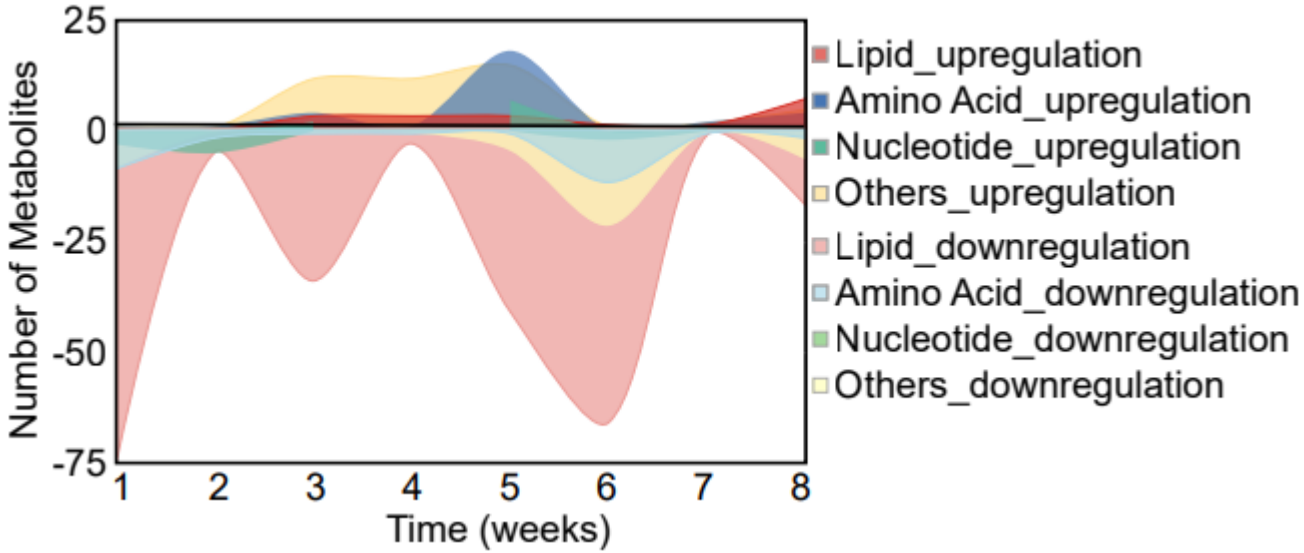
LXR/RXR WAS INHIBITED IN THE LC GROUP

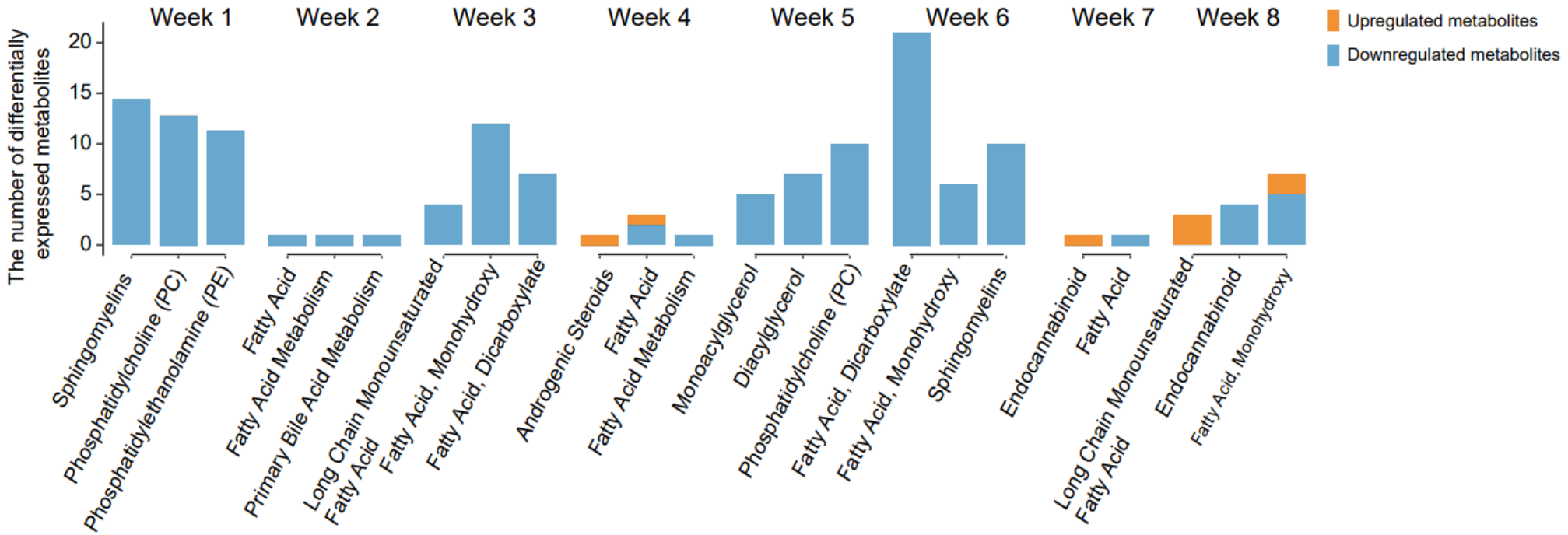


LXR/RXR MEDIATED LIPID REGULATION AND IMMUNITY IN THE LC GROUP



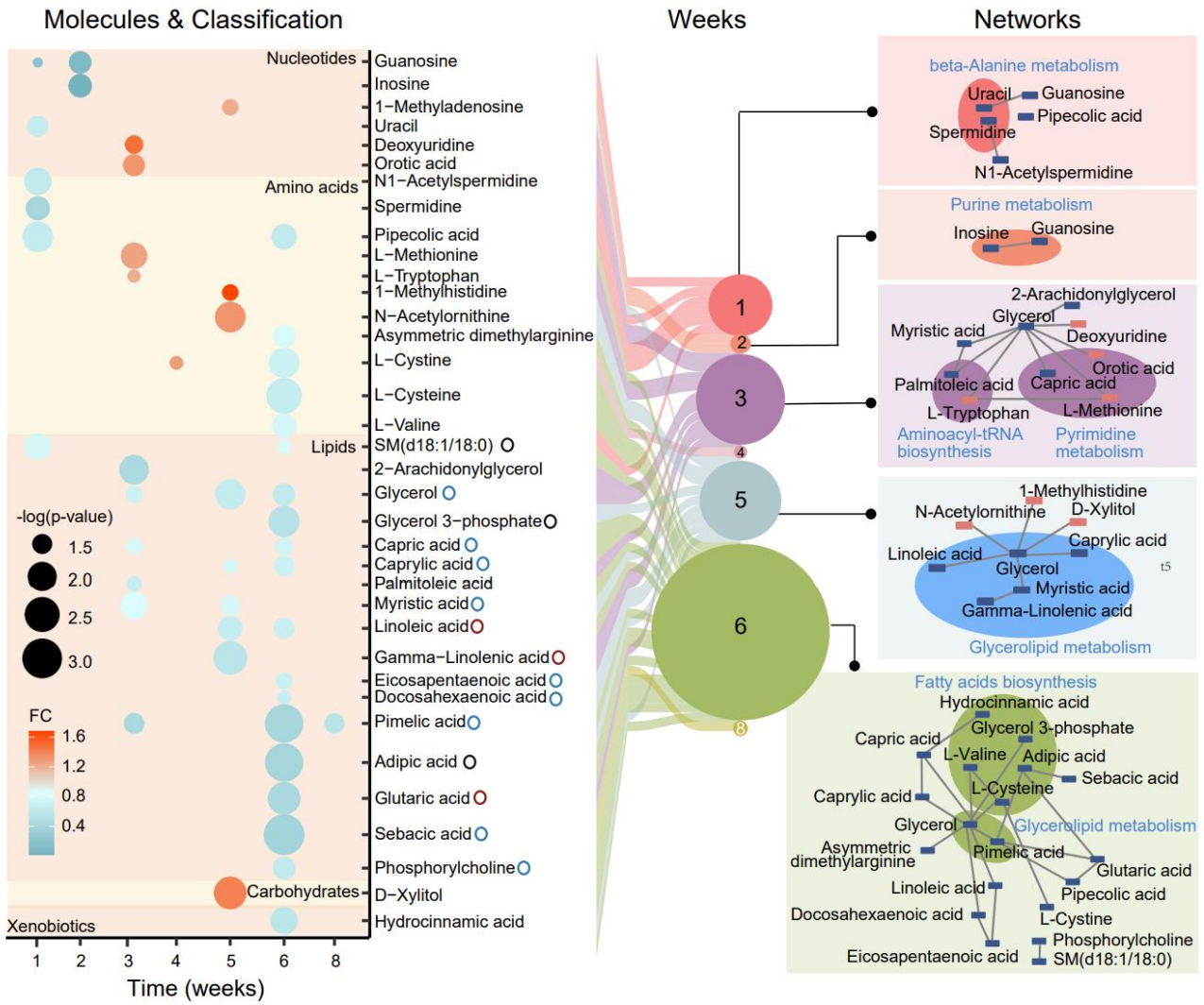
DOWNREGULATED LIPID IN THE LC GROUP



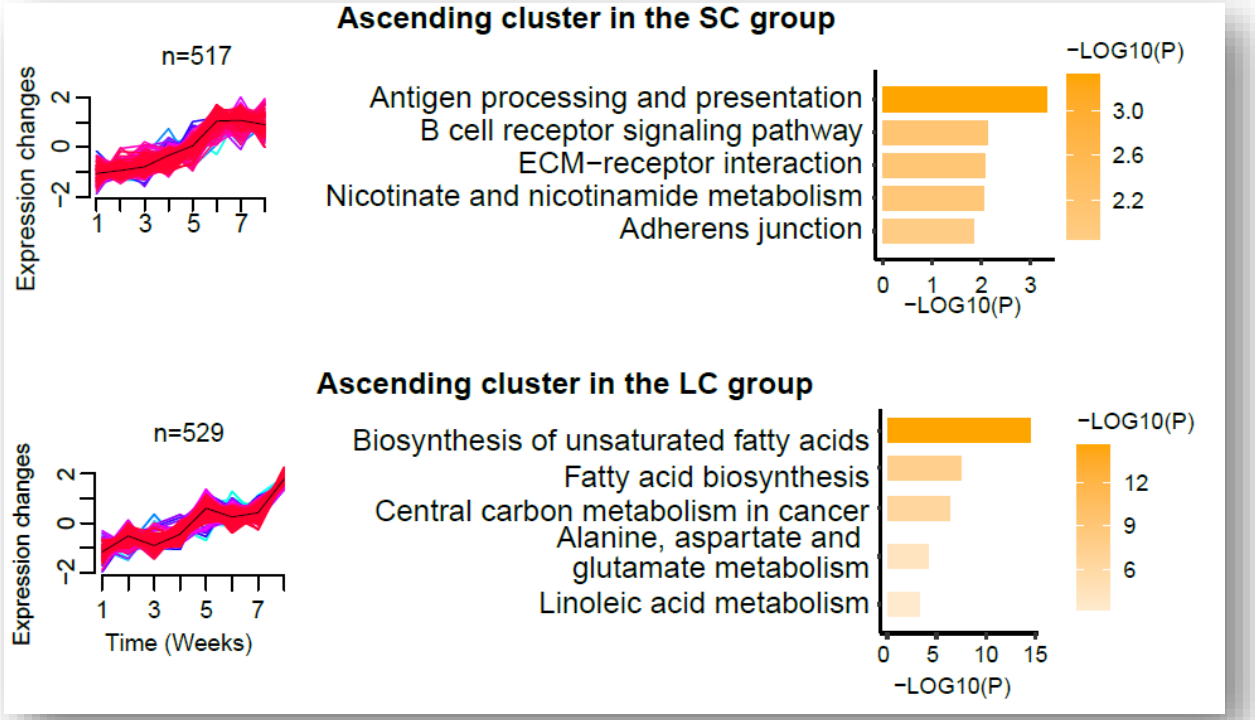


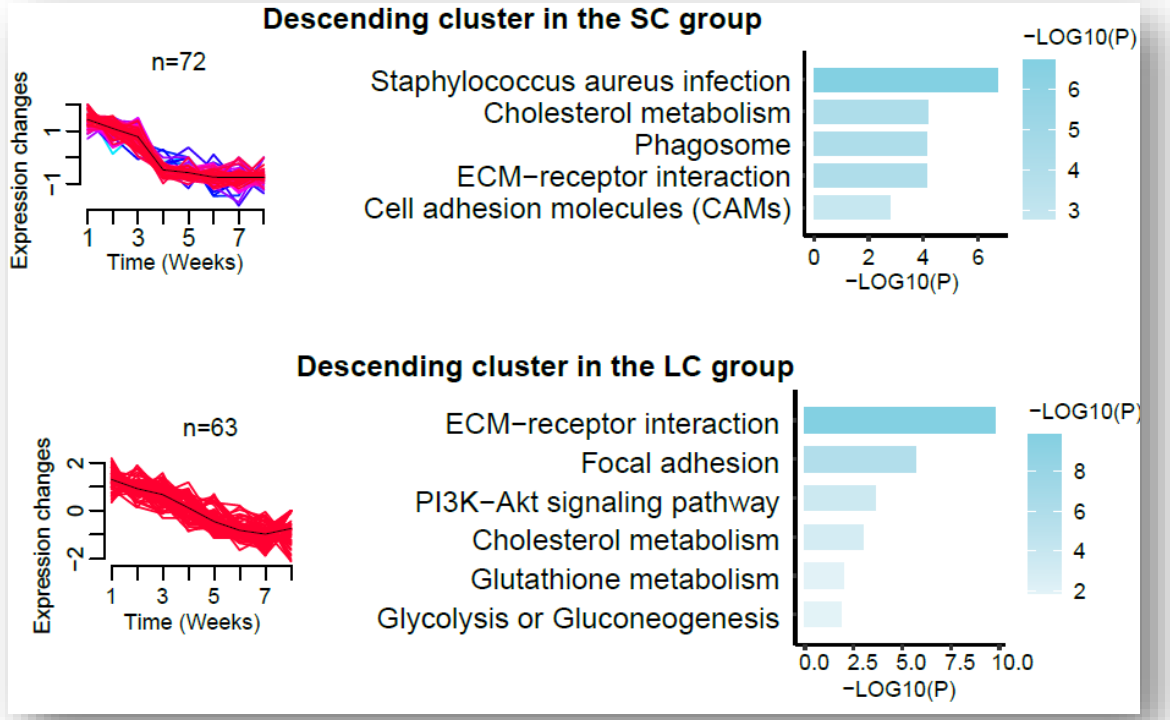
The most significantly downregulated lipids in the LC group are sphingomyelins, phosphatidylcholine (PC), and PC is a well-known as a kind of anti-inflammation factor.

DOWNREGULATED ANTI-INFLAMMATORY LIPIDS IN THE LC GROUP

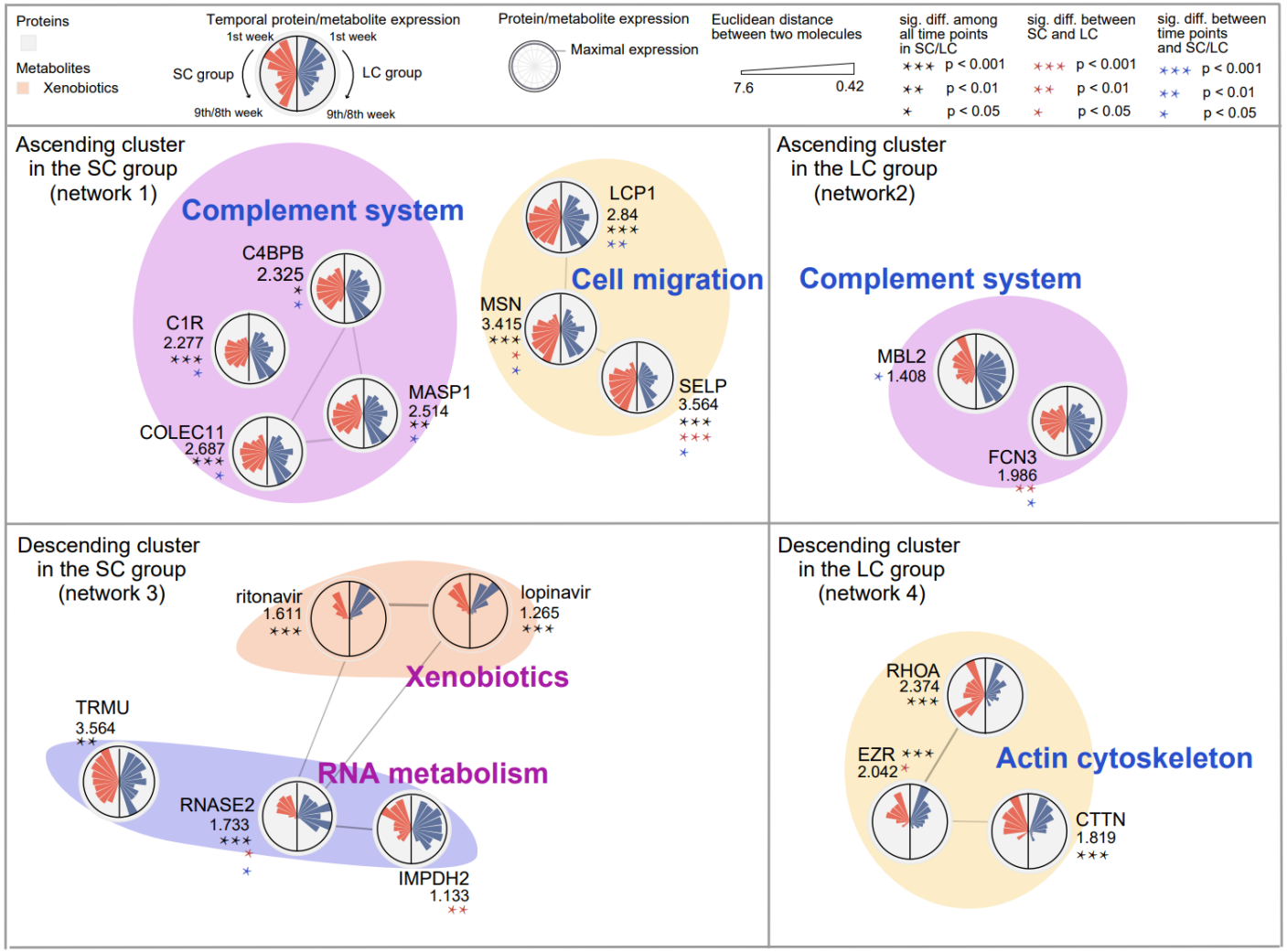


PROTEOMICS AND METABOLOMICS INTEGRATION



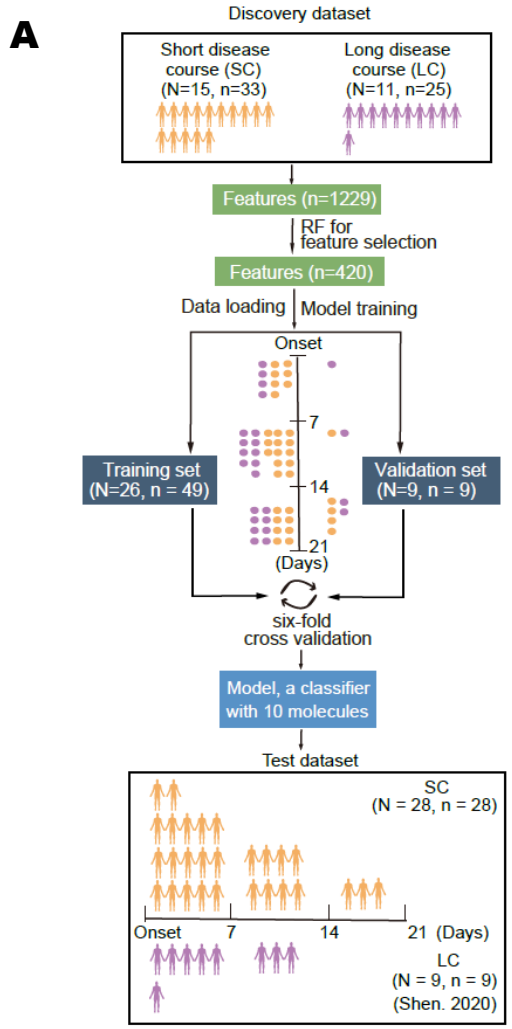


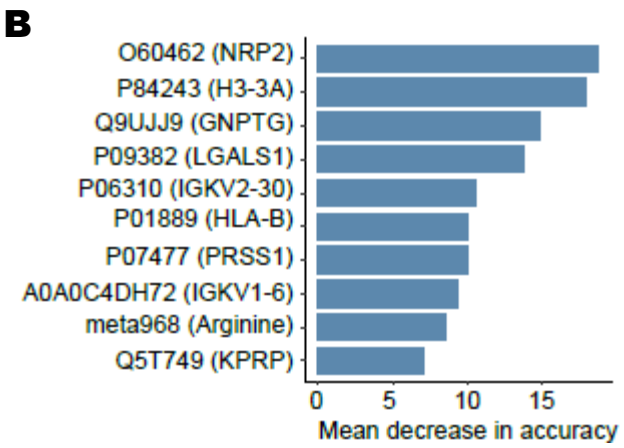
KNN-BASED NETWORK ANALYSIS

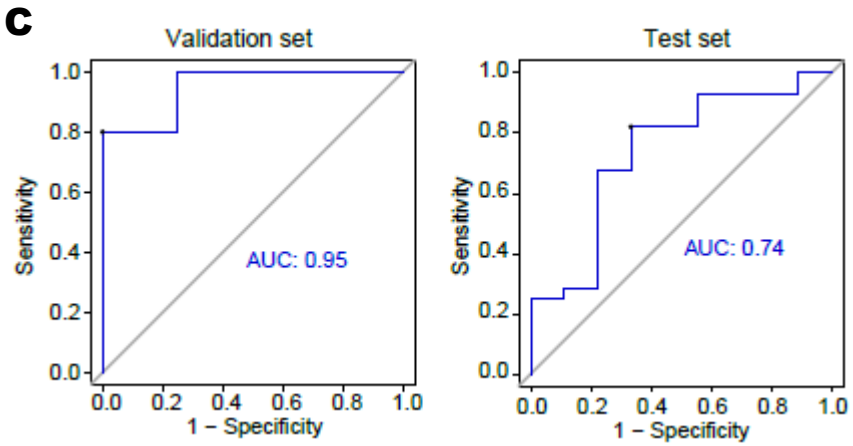


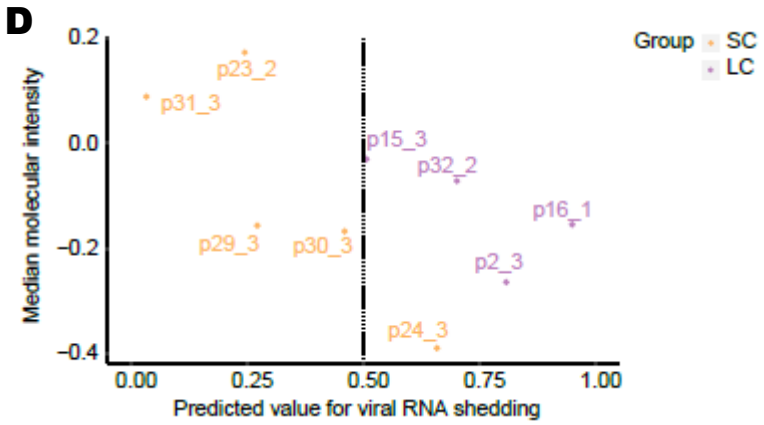
Activated lectin pathway, suppressed cell migration, and enhanced viral replication plausibly contribute to prolonged RNA shedding.

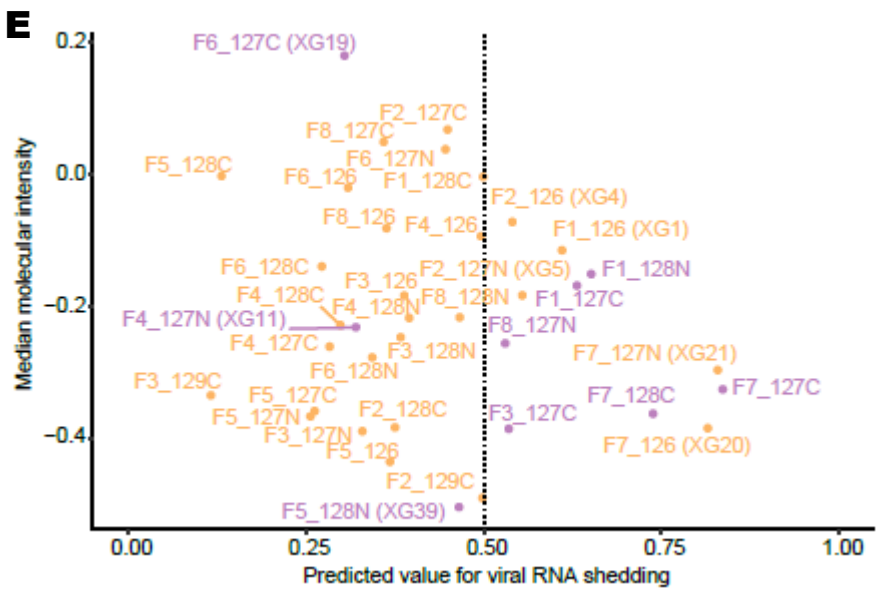
MOLECULAR RISK FACTORS FOR PROLONGED VIRAL RNA SHEDDING PERIOD











CONCLUSION

- To understand the molecular mechanisms underlying prolonged viral RNA shedding in COVID-19 patients, we profiled a deep and time-resolved landscape of their plasma proteome and metabolome.
- These patients exhibited prolonged inflammation and suppressed adaptive immunity.
- Prolonged viral RNA shedding was associated with ten potential risk factors, including NRP2, H3-3A, GNPTG, LGALS1, IGKV2-30, HLA-B, PRSS1, IGKV1-6, KPRP, and arginine.