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ORIGINAL ARTICLE

Impact of Inactivated SARS-CoV-2 Vaccines on Serum Glycan Profiles and Protein N-Glycosylation

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SUMMARY

Background: **This study aimed to investigate the effect of inactivated SARS-CoV-2 vaccines and booster shots on serum glycan profiles and protein N-glycosylation, specifically how vaccination influences glycan synthesis over time, how booster shots differentially impact populations with varying antibody titers, and which specific glycoproteins exhibit altered glycosylation. The goal was to explore a novel mechanism by which COVID-19 vaccines might exert antiviral effects through indirect inhibition of host glycosylation.**
Methods: **Serum glycan profiles were analyzed in individuals receiving two primary doses and a booster shot of inactivated SARS-CoV-2 vaccine, categorized by symptomatic status and antibody titers. Serum proteins were immobilized on AminoLink plus coupling resin, followed by sequential derivatization of α2,6- and α2,3-linked sialic acids. Glycans were released using PNGase F and analyzed by MALDI-TOF-MS with maltoheptaose as an internal standard. Glycoproteomics via LC-MS/MS identified site-specific protein glycosylation changes.**
Results: **Significant alterations in serum glycan profiles were observed. Overall glycan synthesis showed substantial suppression one-month post-vaccination, followed by gradual recovery. The booster vaccine inhibited glycan synthesis, and high-titer individuals exhibited a more pronounced N-glycan profile and faster recovery. Symptomatic status had no significant impact on glycan abundance. Glycoproteomic analysis revealed substantial alterations in glycosylation of stress and immune response proteins, including CP, HPX, SERPINA1, FN1, IgG, AGP, and C3, after vaccination.**
Conclusions: **This study demonstrates a novel mechanism: inactivated COVID-19 vaccines indirectly inhibit host glycosylation pathways. Vaccination significantly suppresses N-glycosylation, primarily reducing N-glycan abundance, with recovery influenced by antibody titer. These results highlight the intricate relationship between immune response, host glycosylation, and viral infection, suggesting avenues for developing novel therapeutic strategies targeting both the virus and host response to enhance antiviral protection.**
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Supplementary Data

Supplementary Methods

Serum sample preparation for glycan analysis

The samples were mixed according to the criteria outlined in the "Tab #" column of Table S1. Each individual or mixed serum sample required a total volume of more than 50 µL. To create a mixed serum sample, serum from multiple patients or volunteers was combined. For instance, Mixed Sample 1 comprised serum from four individuals who experienced post-vaccine fatigue, with each individual contributing 13 µL of serum to the final mixture. Table S1 details the specific samples used for each figure in the paper. Please note that Tab #14 to 28 represent individual, unmixed samples.

Table S1. List of Patient information and samples collected from each Patient for glycan analysis.

Tab #	Titer	Symptom	Collection time (month)	No. of sample	Volume (µL)	Remark
1	low	Fatigue	one	4	15	patient 1 - 1 to 1 - 4, figure 3, figure 5, figure 6
2	high	Fatigue	one	2	25	patient 2 - 1 and 2 - 2, figure 3, figure 6
3	low	Pain	one	6	10	patient 3 - 1 to 3 - 6, figure 3, figure 5
4	high	Pain	one	3	20	patient 4 - 1 to 4 - 3, figure 3
5	low	Sleepiness	one	12	5	patient 5 - 1 to 5 - 12, figure 3, figure 5, figure 6
6	high	Sleepiness	one	2	25	patient 6 - 1 and 6 - 2, figure 3, figure 6
7	high	NS	one	15	4	patient 7 - 1 to 7 - 15, figure 3, figure 6
8	low	NS	one	18	3	patient 8 - 1 to 8 - 18, figure 3, figure 5, figure 6
9	N/A	N/A	N/A	27	2	patient 9 - 1 to 9 - 27, figure 1 - A, figure 5
10	high	mixed	one	16	4	patient 10 - 1 to 10 - 16, figure 1 - B, 2A, figure 3
11	low	mixed	three	16	4	patient 10 - 1 to 10 - 16, figure 2 - B, figure 3
12	low	mixed	six	16	4	patient 10 - 1 to 10 - 16, figure 2 - C, figure 3
13	high	mixed	booster	17	4	patient 10 - 1 to 10 - 16, with addition of 13 - 17 (extremely high titer for non-booster), figure 2 - D, figure 3
14	low	NS	one	1	50	patient 14 (no symptom), figure 3
15	low	NS	one	1	50	patient 14 (no symptom), figure 3
16	low	NS	three	1	50	patient 14 (no symptom), figure 3
17	low	NS	six	1	50	patient 14 (no symptom), figure 3
18	low	NS	booster	1	50	patient 18 (low titer), figure 3, figure 4
19	low	NS	three	1	50	patient 18 (low titer), figure 3, figure 4
20	low	NS	six	1	50	patient 18 (low titer), figure 3, figure 4
21	low	NS	booster	1	50	patient 18 (low titer), figure 3, figure 4
22	high	NS	one	1	50	patient 22 (high titer), figure 3, figure 4
23	high	NS	three	1	50	patient 22 (high titer), figure 3, figure 4
24	high	NS	six	1	50	patient 22 (high titer), figure 3, figure 4
25	low	MS	one	1	50	patient 25 (most symptom), figure 3, figure 6
26	low	MS	three	1	50	patient 25 (most symptom), figure 3, figure 6
27	low	MS	six	1	50	patient 25 (most symptom), figure 3, figure 6
28	low	MS	booster	1	50	patient 25 (most symptom), figure 3, figure 6
29	high	mixed	one	20	3	patient 29 - 1 to 29 - 20, age ≤ 30, figure 3
30	high	mixed	one	42	2	patient 30 - 1 to 30 - 42, age > 30, figure 3
31	high	mixed	one	23	3	male patient 31 - 1 to 31 - 23, figure 3
32	high	mixed	one	39	2	female patient 32 - 1 to 32 - 39, figure 3
33	high	NS	booster	1	50	patient 22 (high titer), figure 4, figure 3
34	N/A	N/A	no vaccine	4	15	male patient 34 - 1 to 34 - 3, no vaccine
35	N/A	N/A	no vaccine	23	3	female patient 35 - 1 to 35 - 23, no vaccine

NS No symptom, MS Multiple symptom. High titer > 10, low titer < 10.