Deep, unbiased and quantitative mass spectrometry-based plasma proteome analyses of personalized response to mRNA COVID-19 vaccine

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Global vaccination efforts against COVID-19 have immunized a significant portion of the world population in recent years, with the mRNA vaccines playing a pivotal role in combating the COVID-19 pandemic. However, individual responses to these vaccines vary, leading to diverse vaccination efficacy. Despite significant progress, full understanding of the molecular mechanisms driving the personalized immune response to COVID-19 vaccine remains elusive. To bridge this knowledge gap, we employed an innovative nanoparticle-based plasma proteomic workflow coupled with tandem mass tag (TMT) labeling. This approach allowed us to quantitatively analyze plasma proteomic changes in a cohort of 12 volunteers after receiving two doses of the Pfizer-BioNTech mRNA COVID-19 vaccine, yielding insights into individual variations in vaccination responses. Plasma samples were collected before and after first and second dose of COVID-19 vaccine from each volunteer, and processed by a nanoparticle-based workflow (Proteograph). A total of 48 samples were analyzed in Orbitrap Fusion Lumos MS equipped with FAIMS Pro Interface. Peptides were separated using an analytical C18 Aurora column into 24 fractions, employing a two-hour gradient with four FAIMS-Pro compensation voltages. This method enabled the identification of 23,372 peptides corresponding to 3,094 proteins from a cohort of 48 human plasma samples. To our knowledge, this represents the deepest access to the plasma proteome for studies related to the COVID-19 vaccine. Our analysis delineated a subset of 69 proteins manifesting a dose-responsive pattern to vaccination, with enhanced magnitudes of response following the administration of the second dose. Significantly, in a subgroup of seven individuals who contracted COVID-19 post full vaccination (COVID subgroup), these proteins showed attenuated responses, hinting at a putative link between protein regulation and vaccine efficacy. Conversely, in the NONCOVID subgroup, which includes five individuals who remained uninfected post-vaccination, 74 differentially expressed proteins were discovered that discernibly segregate COVID from NONCOVID subgroups, underscoring the utility of our extensive plasma proteomic profiling. Further bioinformatics exploration via pathway enrichment analysis identified 47 and 46 gene ontology biological processes (GOBP) pathways that were modulated post-vaccination in the ALL and NONCOVID subgroups, respectively. Notably, 18 pathways, accounting for approximately 40% of the total, were common to both subgroups, implicating critical immunity-associated pathways such as the acute phase, adaptive immune and humoral immune responses. Specifically, the humoral immune response pathway was upregulated in both subgroups, corroborating existing literature on its activation by the COVID-19 vaccine. Our data suggest that deeper access to the plasma proteome allows for a more nuanced understanding of individual responses to vaccination.

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