Unlocking Plasma Proteomics at Scale: A multi nanoparticle approach to improve the depth of coverage

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Proteograph™ Product Suite Delivers Unbiased, Deep and Rapid Plasma Proteomics

Blood plasma is the ideal biospecimen to assess the health and diseased states of humans since it passes by almost all tissues and is accessible from a large number of individuals at different time points. However, the challenging wide dynamic range of the plasma proteome comprising thousands of proteins and their proteoforms (e.g., PTMs, isoforms) limits unbiased proteomics at depth in large-scale with current technologies. To overcome this limitation, we have developed a fast and scalable technology that employs intricate protein-coronas formed on the surface of engineered nanoparticles (NPs) to interrogate the depth of plasma proteomes. A combination of the selected 5 NP allows rapid quantification of over 2,000 proteins across 7 orders of magnitude from a set of plasma with high precision. The key to expand the capability of the NPs in proteomics is to characterize physicochemical properties driving protein corona formation while exploring biological pathways interrogated with each NP.

Proteograph Core Technology

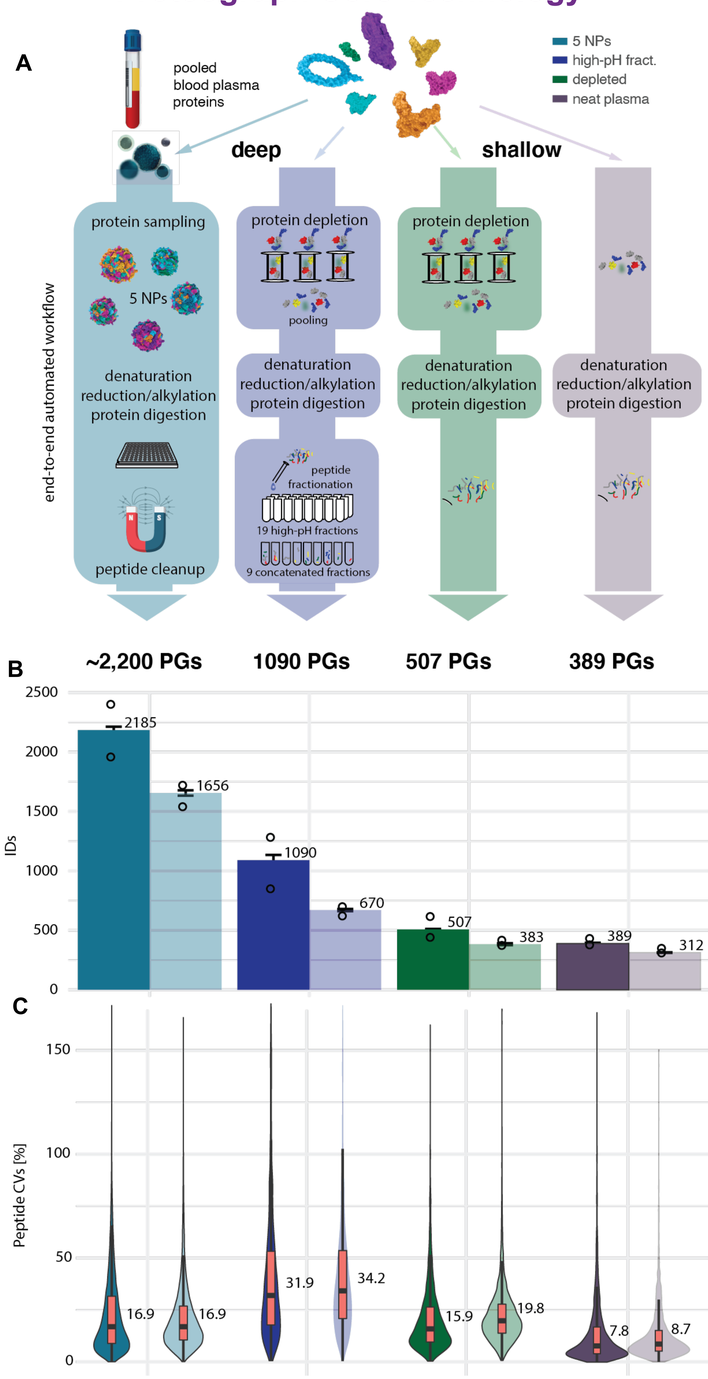

Figure 1. Depth of coverage and analysis precision achieved with different label-free plasma proteomics workflows. A) Conventional label-free plasma proteomics workflows compared to Proteograph Product Suite with a 30 minutes DIA analysis for each 5 NP and total analysis time of 2.5 hrs. B) Proteograph data resulted in ~2200 protein groups identification (1% FDR at protein and peptide level) across 7 orders of magnitude dynamic range with further improvement with DIA-NN (left bars) compared to baseline Spectronaut result (Right) bars). C) Proteograph Assay precision showed improved replicate CV compared to depletion and fractionation methods.

Proprietary Engineered Nanoparticles Enables Deep Plasma Proteomics at Scale

Modeling Protein Intensity Across Samples as a Function of Nanoparticle Properties

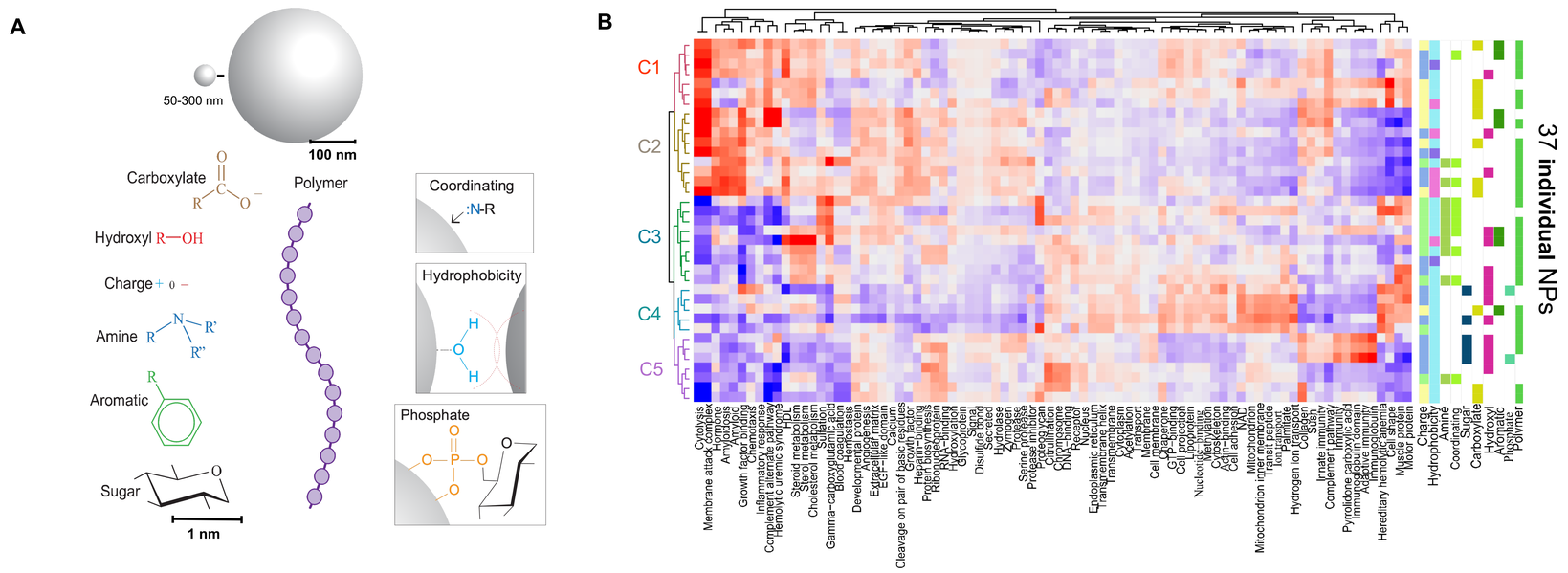

Figure 2. Intricate relation of protein properties, physicochemical makeup of NPs, and protein-corona composition. A) Example of physiochemical and functional design elements. B) Enrichment analysis (1D enrichment) indicates protein class and function (Uniprot Keywords) specific corona composition in relation to NP-properties.

Figure 3. Dissecting association of specific NP-properties and individual protein abundance in the corona. A) Based on variance decomposition analysis of normalized protein intensities individual contributors to observed protein corona differences are estimated using a linear mixed effects model. On average, more than 50 %of the variance in protein corona composition for a particular protein can be explained by NP properties (green) B) Exploring to what degree individual NP-properties explain variation of a protein in the protein corona.

Conclusions

- Using machine learning (linear mixed-effects) models, we identified significant relationships between physicochemical NP properties (including zeta potential, amine, and carboxy functionalization) and differential abundance of individual proteins and protein classes within NP corona.
- 23% of the abundance of C-reactive protein (CRP) as an example in a protein corona was associated with NP zeta potential, and 22% could be allocated to polymeric and sugar surface functionalization. In contrast, we observed the abundance of plasma kallikrein (KLKB1) to be unaffected by NP zeta potential but more than 50% driven by sugar functionalization.
- Our results suggest that we can model the relationship between NP surface functionalization and specific proteins or protein classes in complex biological samples and use this information to guide future NP design to further increase the utility of the Proteograph Product Suite in proteomics research and biomarker discovery.

Proteograph Product Suite

Sample ready to be analyzed on most LC/MS instruments

References

1. Blume et al. Nat. Comm. (2020)

Publications

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