Editorial Commentary

Proteome profiling to advance management of metabolic dysfunction-associated fatty liver disease

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Metabolic dysfunction-associated fatty liver disease (MAFLD) is a complex, heterogenous and progressive disease that is characterised by substantial phenotypic variability, which results in disparate clinical presentations and outcomes (1-4). Notably, only a proportion of patients with MAFLD progress to the more advanced stages of the disease. Therefore, the identification of the subgroups that have a high risk of disease progression is of paramount importance for clinical care, as well as drug development and clinical trials (5).

In a recent study, Abozaid *et al.* (6) analyzed the proteome alterations linked to hepatic steatosis and fibrosis. The objective was to discover new biomarkers that might indicate the severity of FLD and gain novel insights into its pathogenesis. In order to achieve this objective, they employed multiplex platforms to measure a panel of proteins associated with either cardiometabolic stress or inflammation pathways in blood samples collected from 2,578 individuals who took part in the extensive population-based Rotterdam study and were diagnosed with non-alcoholic FLD (NAFLD) or MAFLD. They then correlated the results with liver steatosis or fibrosis severity (quantified via ultrasound or elastography, respectively), adjusting for confounding factors such as type 2 diabetes, body mass index (BMI), smoking and alcohol consumption.

The study revealed that 9.6% (8 out of 83) of the proteins associated with inflammation and 21.6% (19 out of 88) of the proteins associated with cardiometabolic risk correlated with the existence of steatosis and degree of fibrosis, respectively. A signalling pathway analysis identified noncanonical NF-κB signalling and coagulation pathways as the most enriched pathways that correlated with the observed proteomic changes.

In a subsequent experiment within the same study, the levels of interleukin 18 receptor 1 (IL18-R1) and carboxylesterase 1, 2 of the 15 conserved disease-associated proteins, were found to be significantly altered in hepatocyte spheroids treated with fatty acids to simulate lipotoxic stress. These findings suggest that these proteins may be produced by fatty hepatocytes in patients with MAFLD.

The current study revealed that fibroblast growth factor 21 (FGF21) had the most pronounced association with the severity of liver disease, which is intriguing. Although it is assumed to have a hepatoprotective role in MAFLD, various other studies have shown that hepatic FGF21 levels are elevated in patients with MAFLD compared to healthy individuals; this suggests the presence of FGF21 resistance (7). A recent study revealed that FGF21 resistance is mediated by mistranslation of FGF21, which is further regulated by

the *FGF21* rs838133 variant (7).

In order to examine the translational implications of their findings, the authors (6) showed that utilizing plasma proteomic data was more effective than using the fibrosis-4 index in predicting significant fibrosis. However, it was not superior to using a sonogram or the fatty liver index in identifying steatosis. Collectively, these results indicate that circulating proteins have the potential to serve as innovative biomarkers for FLD.

The study has multiple noteworthy strengths. The authors utilized a large, well-defined population-based cohort. They employed assays to systematically examine plasma proteins associated with inflammation and cardiometabolic stress, which are relevant pathways in the development of MAFLD. Additionally, they explored the clinical utility of the findings by comparing the diagnostic accuracy of the proteome-based protein panel with the currently used blood-based algorithms for detecting FLD severity.

The authors appropriately acknowledged the following main limitations of their study. The blood samples used for the proteomic analysis were collected many years prior to conducting tests for diagnosing liver disease, and the confirmation of the condition by histology was not obtained. Despite the intention to utilise a systematic approach, ultimately the study only included the use of two multiplex platforms that could detect proteins involved in two pathways. Finally, hepatic spheroids are not optimal tools for confirming the pathobiological basis of disease, as they do not sufficiently mimic characteristic of hepatic tissues or adequately represent physiologically relevant metabolic stress.

Further research is needed to determine (I) the clinical utility of the protein biomarkers identified in the present study; (II) whether alteration in the plasma proteome can be indicative of the changes in liver histopathology and underlying pathobiology of the disease; and (III) a causal role for the identified proteins in MAFLD pathogenesis. Clarifying these aspects may open new therapeutic avenues. It will be particularly interesting to examine whether the proteomic signature observed in this study is conserved across various cohorts, ethnicities and geographic regions, and even among other related metabolic diseases. Notably, two recent reports that used different proteomics assays in small cohorts of patients with biopsy-proven FLD (8,9) failed to discern an overlapping signature between these studies.

Additionally, given the complexity of MAFLD pathogenesis, future studies should integrate multiple omics data, for example plasma proteomic data, with genetic and transcriptomic analyses to ensure proper risk stratification of patients and the application of a more personalised approach to disease management (10). For instance, a recent study (11) integrated proteomic discoveries with the hepatic transcriptome profile and genetic data obtained from genome-wide association studies. The study showcased that by combining proteomic data, polygenic risk scores, and clinical data, a distinctive signature could be used to accurately distinguish between FLD and cirrhosis.

In conclusion, hepatology research is entering a new and exciting era of discovery driven by the growing accessibility of extensive datasets containing detailed information on large groups of individuals with liver disease, as well as advanced techniques that allow comprehensive and unbiased profiling of bio-samples. The acquired knowledge will contribute to shaping our understanding of disease pathophysiology, facilitating the identification of novel diagnostic and prognostic biomarkers. This, in turn, will aid in the creation of personalized care strategies for patients with MAFLD.

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Footnote

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