Abstract title

A combined imaging and proteomic approach identifies inflammatory response proteins upregulated in MASH: results from the UK Biobank

Authors

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Background

MASH (Metabolic dysfunction-associated steatohepatitis) is a severe form of liver disease characterized by presence of cardiometabolic risk factors, liver inflammation and damage due to fat accumulation. Multiparametric MRI (mpMRI) with LiverMultiScan is recommended in MASH guidelines as imaging biomarkers cT1 and liver fat content (LFC) can quantify disease activity and steatosis in the liver, respectively. A multi-modality approach that combines imaging with proteomic analysis could significantly enhance our understanding of metabolic alterations in MASH. The UK Biobank, with its newly released extensive proteomic data linked to imaging data, provides an ideal resource for employing this approach. We aimed to identify the proteomic signature of MASH, shedding light on the proteins involved in fibro-inflammation and fat infiltration.

Methods

We analysed a total of 1,464 proteins in plasma samples from 1,172 individuals from the UK Biobank, who had paired mpMRI data (46% male, median age 58 years, BMI 26 kg/m^2, 4% diabetes). Protein expression was measured using proximity extension assays. MASH was defined as LFC >5% and cT1 >800ms. Statistical analyses included t-test to assess significant protein dysregulation in the MASH group compared to controls, and hazard ratios (HR) for risk of clinical events or diagnoses from hospitalisation and death records.

Results

377 proteins were differentially expressed in participants with MASH from controls without steatotic liver disease; 86 of these (23%) have known roles in inflammatory pathways. Amongst those significantly upregulated in MASH ($p < 0.001$) were targets of drugs that are FDA-approved for other diseases. Notably, seven of those proteins **had associations with chronic liver disease and cirrhosis and with all-cause mortality ($p < 0.001$):** COL6A3 (HR: 2.2), IL-6 (HR: 1.3), VEGFA (HR: 1.4), CD4 (HR: 2.9), CD79B (HR: 1.9), PGF (HR: 2.7) and CD22 (HR: 1.77).

Conclusion

This study presents a proteomic signature for MASH associated with inflammation and poor outcomes in the UK Biobank. An approach combining imaging and proteomics offers new insights into the pathophysiological mechanisms underlying MASH and provides potential targets for therapeutic intervention.

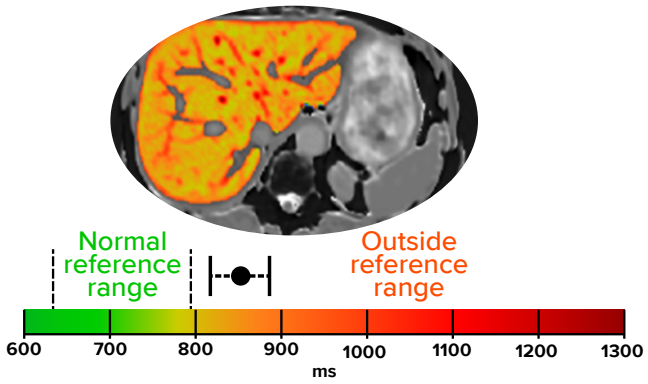

Figure 1: cT1 map of a participant with MASH showing a notable liver disease activity (cT1 = 834 ms).

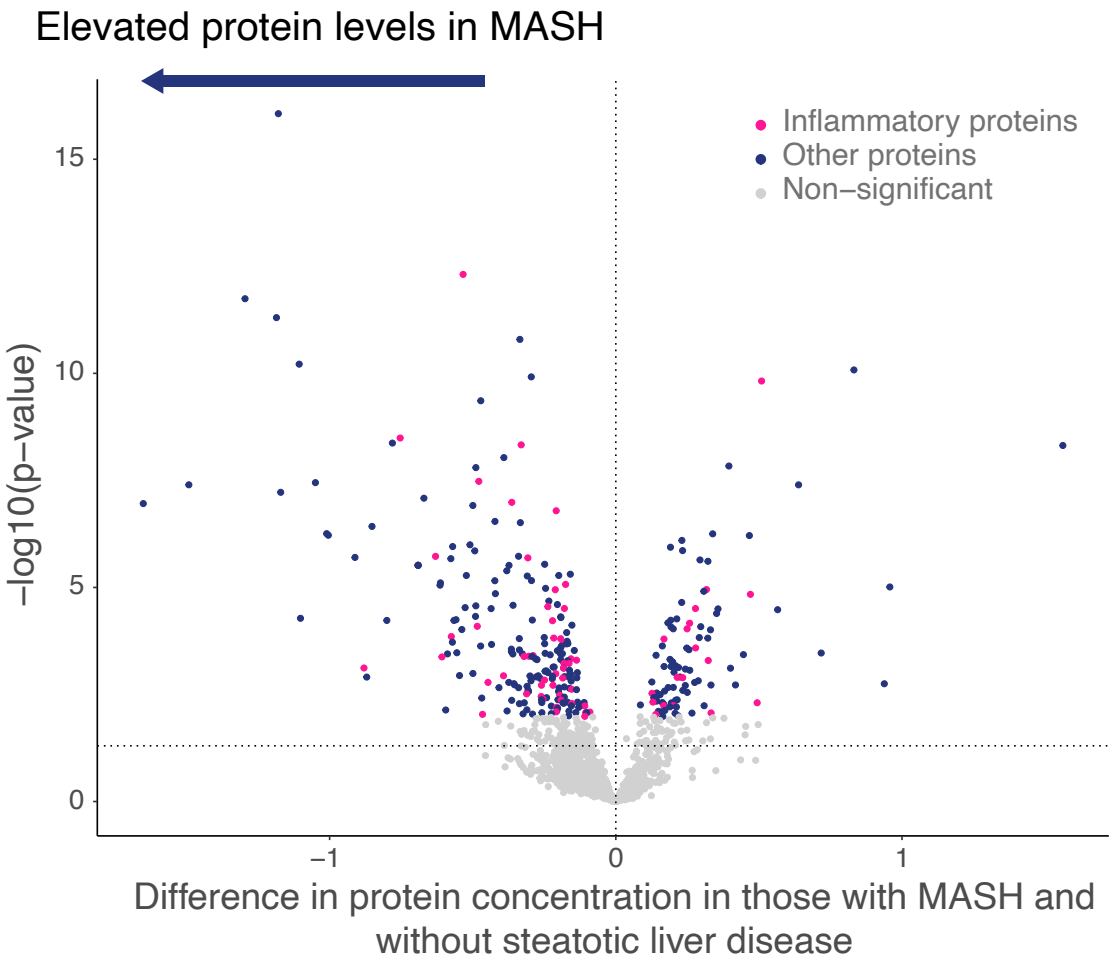

Figure 2: Volcano plot showing difference in protein concentration for 1,464 proteins in participants with MASH compared to controls without steatotic liver disease. Blue and pink dots represent proteins and inflammatory markers significantly dysregulated in MASH ($p < 0.05$).