

Comprehensive analysis of plasma protein profiles in distinct stages of IgM Gammopathies

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Abstract (word count = 466/500)

Abstract

IgM Gammopathies represent a broad disease spectrum ranging from IgM MGUS to asymptomatic WM (AWM) and symptomatic WM. These conditions are characterized by a poorly understood heterogenous clinical presentation and disease course. Plasma proteins provide an integrated molecular readout of the entire body and thus might offer insights into the biological processes underlying this heterogeneity. To this end, we investigated plasma protein profiles in IgM gammopathy patients at distinct disease stages using unbiased mass spectrometry (MS)-based plasma proteomics and targeted cytokine profiling using Luminex assays.

Methods

We selected plasma samples of WM patients in the B-cell Biobank at Amsterdam University Medical Centers. Patients were classified based on WHO diagnostic classification and disease stages according to IWWM-11 response criteria. Inflammatory WM (iWM) was defined as a CRP >20 mg/L. All participants signed informed consent. Age-matched plasma samples from healthy individuals were obtained from Sanquin as controls. MS-based plasma proteomics comprised of digestion of the plasma proteins into peptides, followed by LC-MS/MS analysis. Targeted cytokine profiling was performed using Luminex assays on targets based on literature and proteomics results involved in inflammatory and B-cell pathways.

Results

We included 101 plasma samples from 18 IgM MGUS, 18 AWM and 22 symptomatic WM patients and 43 controls. Using principal component analysis (PCA) of the plasma proteomic profiles patients were clearly separated from controls, but this did not fully recapitulate the current disease classification, supporting the notion of a biological continuum (Fig 1A). Differential abundance analysis revealed a cluster of acute phase/inflammatory proteins, including CRP, increasing with distinct disease stages (Fig 1B). The increased CRP levels were confirmed using Luminex assays and independently validated the concept of iWM. In our cohorts iWM was observed in 50% of symptomatic WM patients and 11% of AWM patients, consistent with previous reports. Further characterization with targeted cytokine profiling revealed elevation of CCL5 and CXCL13 in iWM patients, amongst others (Fig 1C). A novel finding was the levels of CCL18, which progressively increased across the disease spectrum. CCL18 is a chemokine that is typically produced by macrophages associated with an immunosuppressant effect and has been linked to adverse prognosis in B-cell lymphomas. CCL18 correlated strongly with IgM levels (Fig 1D), suggesting that it may originate from lymphoplasmacytic tumor cells. Yet these proteins did not correlate with CRP (Fig 1E), suggesting that inflammation is a distinct process. Finally, plasma

proteomic analysis identified a progressive decrease in triglyceride homeostasis with distinct disease stages (Fig 1B).

Conclusions

To our knowledge, this is the first comprehensive plasma proteomic study in this patient population providing a framework for understanding disease heterogeneity in IgM gammopathies. Using these approaches, we demonstrated a clear, yet poorly understood complex inflammatory signature in the disease stages that trigger further evaluation in relation to LPL cell characteristics as well as TME. While this approach allows for the unbiased analysis of > 800 proteins from only 0.01 ml of plasma, it is readily scalable and can be seamlessly implemented in large prospective cohorts and clinical trials.

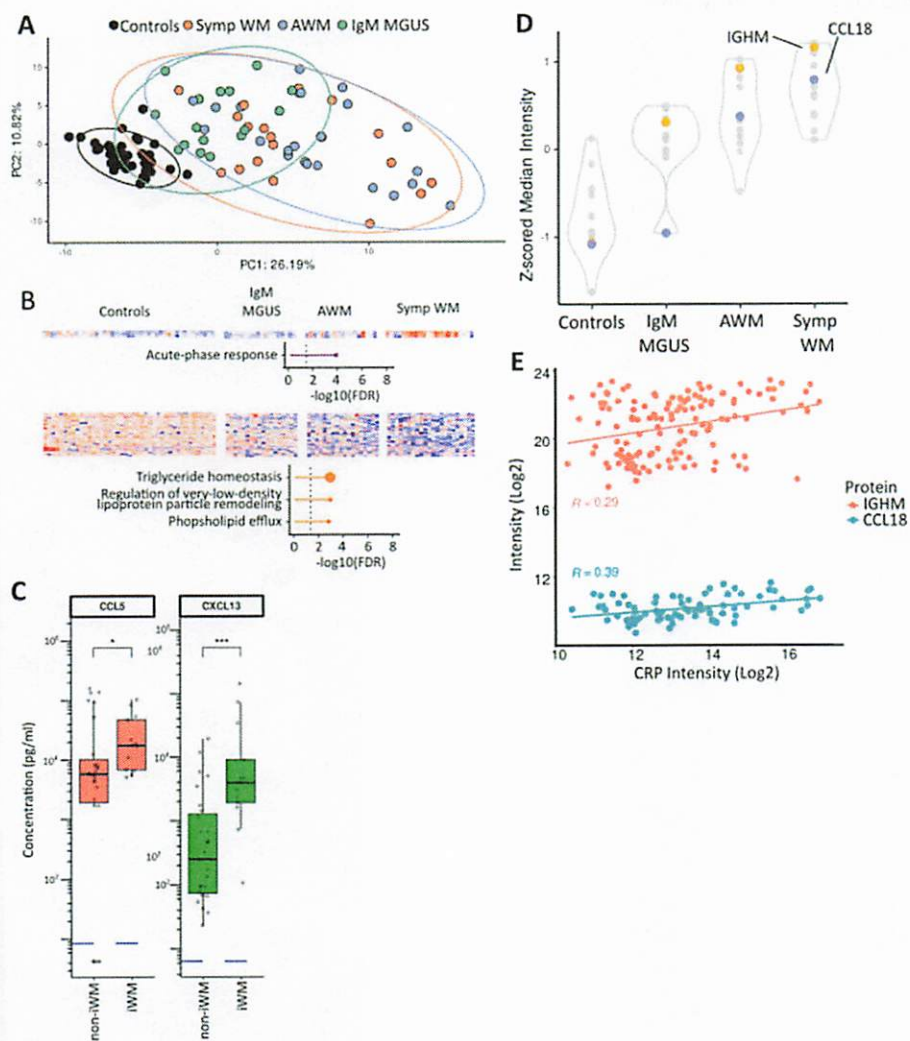


Figure 1 – Protein signatures in IgM gammopathy distinct disease stages. (A) PCA of global proteomic plasma profiles in controls (black), IgM MGUS (green), asymptomatic WM (AWM, purple) and symptomatic WM (Symp WM, orange) patients. (B) heatmap of clustered protein profiles related to acute-phase response (top) and Triglyceride homeostasis (bottom) across disease groups. Blue denotes relatively decreased abundances and red increased (z-scored). (C) Concentration of CCL5 and CXCL13 was significantly increased in iWM patients compared to non-iWM patients. Dotted line indicates limit of quantification and significance was calculated by using Kruskal Wallis *ad hoc* Dunn testing and indicated by *(p value > 0.05)/***(p value > 0.0005). (D) Z-scored median intensity of IGHM (orange) and

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CCL18 (purple) across samples at distinct disease stages. Other co-clustering proteins are denoted in grey. (E) Spearman-correlation of IGHM (Red) and CCL18 (blue) to CRP (y-axis).



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