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Unbiased plasma proteomics in Waldenström Macroglobulinemia

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Background

The clinical presentation of Waldenström Macroglobulinemia (WM) is highly heterogeneous. Differences in underlying biology, including molecular abnormalities, bone marrow (micro)environment and IgM properties, may contribute to this heterogeneity. In addition, it has recently been postulated that inflammation plays an important modulatory role in the clinical presentation of WM and the response to treatment. Unbiased mass spectrometry (MS) plasma proteomics is a powerful technique that allows for the comprehensive analysis of protein systems in plasma. To this end, we applied our MS based plasma proteomics workflow to WM patients in various stages of disease and treatment. Here, we provide an interim analysis based on initial findings.

Method

We selected plasma samples and clinical data from WM patients in the B-cell Biobank at Amsterdam University Medical Centers. Patients were classified based on WHO diagnostic classification, with disease staging at sample collection following consensus staging and response criteria. All participants signed informed consent. Age-matched plasma samples from healthy individuals were obtained from Sanquin as controls. MS-based plasma proteomics consisted of digestion the plasma proteins into peptides, followed by analysis on an Evosep One – timsToF HT system operated by an in-house developed DIA-PASEF method. Data analysis was performed in DIA-NN and Rstudio.

Results

We included 229 plasma samples of 88 WM patients and 43 plasma samples from healthy individuals. We identified 880 proteins and quantified 750 proteins per sample, allowing for a comprehensive overview of the humoral systems as well as cell-specific signatures. Standard laboratory values for immunoglobulin levels correlated well with MS-based values, indicating a high accuracy of our workflow. The initial analysis was performed on samples from distinct disease stages from patients that were not on any treatment at the time of sampling; IgM MGUS (n=36), smouldering (n=26), and symptomatic (n=15). Principal component analysis distinguished healthy controls from WM patients (figure 1a). This categorization was mainly driven by a combination of IgM, other immunoglobulins, inflammation and acute phase proteins. Next we compared protein abundances. As expected, IgM levels increased with disease progression. Interestingly, both acute phase and inflammation proteins (SAA1/2 and CRP) were

amongst the most significantly different proteins in symptomatic WM compared to the controls and other disease stages. In contrast, two apolipoproteins APOC2 and APOC4 were uniquely downregulated in symptomatic WM. Additionally, LRP5, a lipoprotein receptor involved in canonical WNT pathway signaling, was the only protein significantly downregulated in all disease stages compared to healthy controls (figure 1b).

Conclusions

We found inflammation and apolipoprotein pathways gradually dysregulated in symptomatic WM compared to healthy controls, IgM MGUS and smouldering WM. Additionally, LRP5 decrease could indicate a possible involvement of WNT signaling, as has been observed in other hematological malignancies (e.g. CLL and MCL). These findings might provide a basis for further research for exploration and validation. Next, we will extend our data analysis to study the effect of treatment in patients with longitudinal sampling, the relation to somatic mutations to further identify possible modulators of heterogeneity in WM patients.

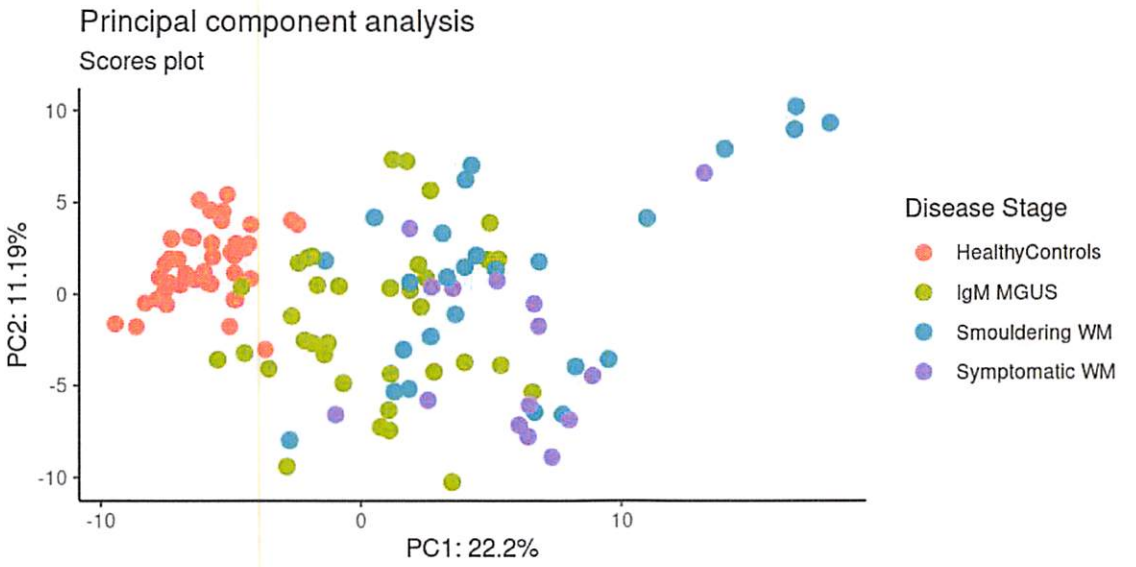

Figure 1 – a) Principle component analysis (PCA) of the plasma proteomes of Healthy Controls, IgM MGUS and WM patients (smouldering & symptomatic). PCA was performed on proteins with no missing values to avoid imputation.

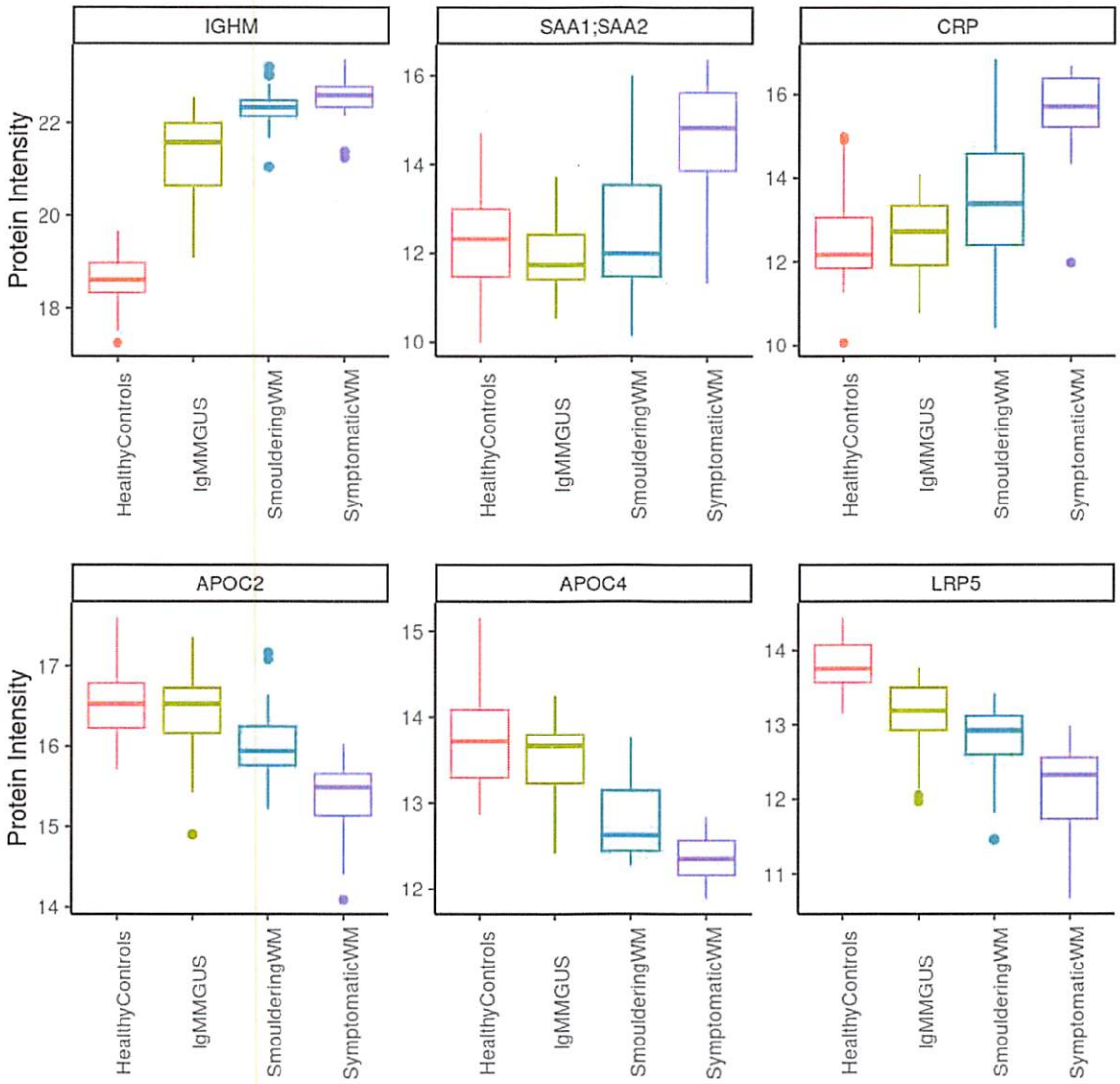

Figure 1b – Protein levels of the most significantly *upregulated* proteins (IGHM, SAA1:SAA2 and CRP) and of significantly *downregulated* proteins (APOC2, APOC4 and LRP5) at distinct staging of disease.