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Exploring the cell-free transcriptome as biomarker source in IgM gammopathies: new insights from the FIL "BIO-WM" trial

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Introduction

IgM gammopathies encompass a heterogeneous group of hematological conditions, ranging from IgM monoclonal gammopathies of uncertain significance (IgM-MGUS) to asymptomatic Waldenström's Macroglobulinemia (aWM) and symptomatic WM (WM). This study aimed to investigate the potential of cell-free RNA (cfRNA) as a biomarker source in IgM gammopathies.

Materials and methods

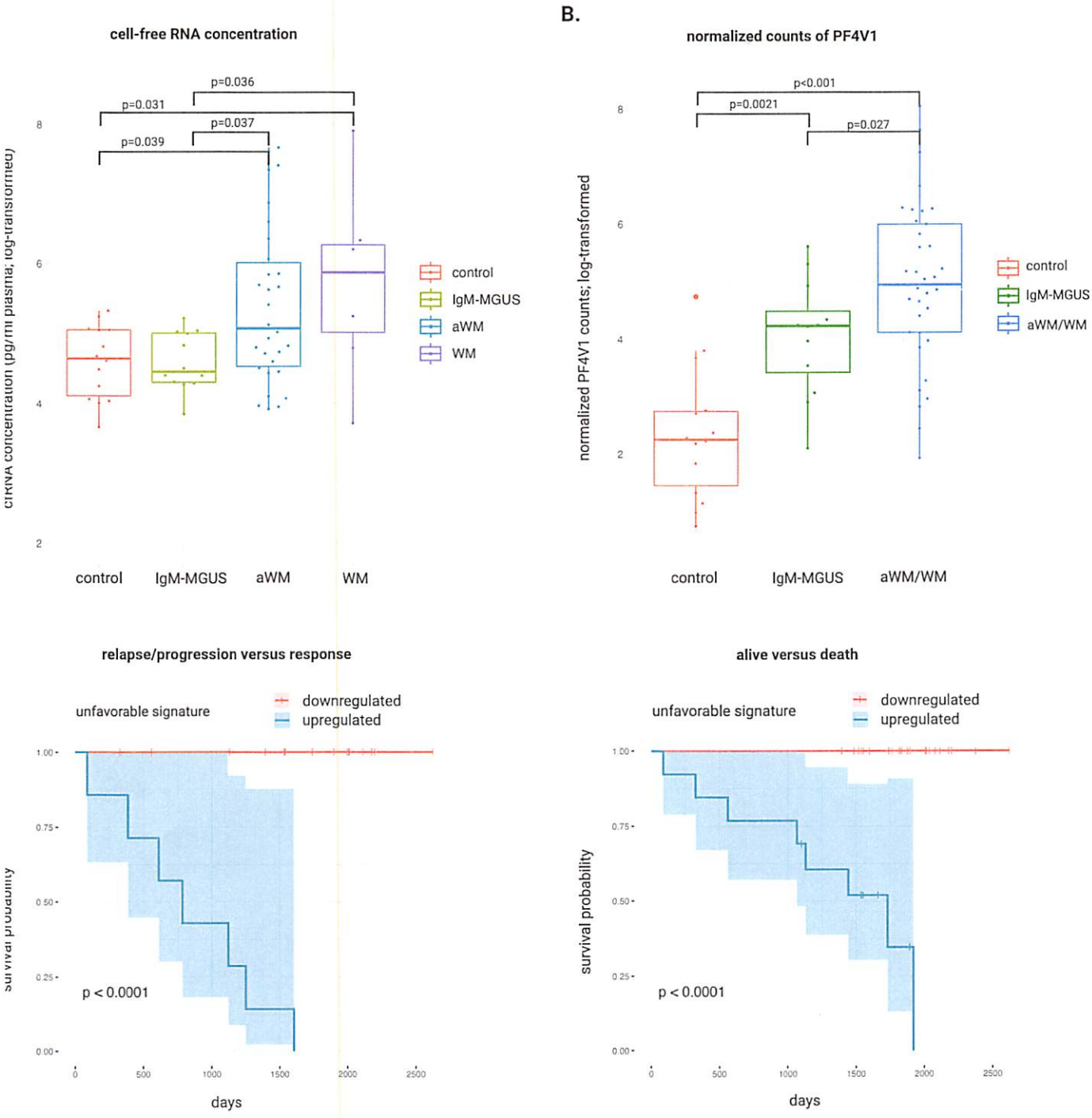
Biological specimens and clinical data were collected from a retrospective and prospective series of IgM gammopathy patients enrolled in the Fondazione Italiana Linfomi (FIL) "BIO-WM" trial (NCT03521516). Diagnostic blood plasma samples were included from 60 patients with IgM-MGUS (n=15), aWM (n=32), and WM (n=13), along with plasma from healthy controls (HC) (n=28), collected using EDTA or cfDNA Streck tubes. RNA was extracted from 200 µl of plasma using the miRNeasy serum/plasma kit and sequenced on a NovaSeq 6000 instrument with the SMARTer Stranded Total RNA-seq pico v3 library preparation kit. Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome pathways enrichment analyses were performed using the clusterProfiler and ReactomePA packages, respectively. Bulk deconvolution was performed using the Tabula Sapiens v1 basis matrix. Flow cytometry and $MYD88^{L265P}$ mutational ddPCR data were also available. Due to superior quality of cfRNA in EDTA tubes, only data from 49/60 patients (12 IgM-MGUS, 30 aWM, 7 WM) and 14 HC were reported.

Results

Compared to IgM-MGUS and HC, higher cfRNA concentrations were found both in aWM (p=0.037, 95% CI [3.5, 250 pg/ml]; p=0.039; 95% CI [2.3, 240 pg/ml]) and WM patients (p=0.036, 95% CI [30, 470 pg/ml]; p=0.031, 95% CI [13, 450 pg/ml]) (Figure1A). CfRNA concentration significantly correlated with IgM serum levels (p=0.0047, R=0.40) and bone marrow infiltration (p=0.0019, R=0.43). $MYD88^{L265P}$ plasma levels showed a weak negative correlation with normalized cfRNA counts of MYD88 (p=0.015, R=-0.36). Numerous differentially abundant coding and non-coding genes (DAGs) were identified between the cfRNA profiles of the subgroups. PF4V1 emerged as a potential marker to distinguish between HC, IgM-MGUS, and aWM/WM, with One-vs-Rest multiclass ROC AUCs of 0.98, 0.82, and 0.88, respectively (Figure1B). A comparison between aWM and WM to IgM-MGUS patients revealed 259 and 510 DAGs, respectively, with aWM/WM patients showing enrichment in neurodegeneration, platelet activation, signaling, and aggregation, as well as neutrophil degranulation pathways. A higher blood plasma abundance of a 3-gene unfavorable signature (PAFAH1B1, ARAF, SMG7) was associated with time to relapse or progression in aWM/WM patients (p<0.0001), and a 6-gene unfavorable signature (ECH1, EIF3B, DHX9, EPRS1, ATP5PF, HIST1H1C) was linked to all-cause mortality in aWM/WM patients (p<0.0001) (Figure1C). Bulk deconvolution indicated an increased circulating plasma cell fraction in aWM/WM compared to IgM-MGUS (p=0.035) and HC (p=0.0042). Deconvolution and flow cytometric peripheral blood results were correlated for plasma cells (p<0.001; R=0.59) and B-cells (p<0.001; R=0.68), with the former also showing a correlation with extent of bone marrow involvement (p<0.001; R=0.48).

Conclusion

This is the first reported evidence that a cell-free transcriptome signature, observed in plasma, can differentiate between distinct subgroups of IgM gammopathies, guiding the indication for bone marrow examination. Moreover, it might assist in prognostication and therapy response prediction, and elucidate underlying biological pathways.



ure 1. (A) Cell-free RNA concentrations and (B) normalized PF4V1 counts in healthy controls (control), IgM-MGUS, aWM, and WM patients. (C) Kaplan-Meier vival curves depicting shorter time to relapse or progression (left) and increased all-cause mortality (right) in aWM/WM patients with higher plasma ındance of the unfavorable gene signature. aWM: asymptomatic Waldenström's Macroglobulinemia; IgM-MGUS: IgM monoclonal gammopathy of unknown nificance; WM: Waldenström's Macroglobulinemia.