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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Comparative Analysis of Bone Marrow Microbiome and Proteome Differences between Essential Thrombocythaemia and Prefibrotic Primary Myelofibrosis

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Background

Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are hematologic malignancies with a hallmark feature of chronic inflammation. MPNs mainly include polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) and prefibrotic primary myelofibrosis (pre-PMF). In contrast to ET, an accurate morphological diagnosis of pre-PMF is a key issue due to its worse prognosis. However, it is difficult to accurately diagnose pre-PMF, mainly relying on pathological diagnosis. The heavy reliance on morphology for accurate diagnosis poses a challenge to the professional abilities of physicians. The uneven expertise of physicians can lead to improper diagnosis and delay patient treatment. Therefore, accurate diagnosis of these two disease subtypes is of great importance.

It is increasingly recognized that the bone marrow microenvironment, including inflammation and metabolic imbalances, influences disease progression. So far, there have been few studies focusing on the combined analysis of the bone marrow microbiome and proteome in MPN patients. We aim to describe the changes of bone marrow microbiome and proteome and their association with pathogenesis in ET and pre-PMF patients

Method

We analyzed the formalin-fixed, paraffin embedded (FFPE) tissue slide of bone marrow from six patients with untreated pre-PMF (median age: 64 years, m/f=4/2) and ET (n=7, median age: 53 years, m/f=2/5). Proteomic analysis of FFPE tissue slides of bone marrow from 13 patients was performed using 4D-direct DIA. The bone marrow microbiota was analyzed by using 2bRAD-M sequencing technology.

Result

The clinical and laboratory characteristics of ET and pre-PMF patients are summarized in Table 1. The *JAK2* ^{V617F} mutations were detected in all patients, and the mutations were more frequent in patients with pre-PMF than in those with ET (17.9% vs. 55.8%, p=0.001). All patients in the ET group are at MF grade 0, while all in the pre-PMF group are at MF grade 1. The lactate dehydrogenase in pre-PMF group patients is higher than in ET group patients, and the difference is statistically significant (p=0.007). In addition, the neutrophil-to-lymphocyte ratio (NLR), an inflammation-related indicator, is significantly increased in the pre-PMF group. The neutrophil-to-lymphocyte ratio in the pre-PMF group is significantly higher than in the ET group, which is statistically significant (p=0.015). High density lipoprotein cholesterol (HDL) in the pre-PMF group is significantly reduced, and the difference is statistically significant (p<0.001). This suggests a difference in lipid metabolism between pre-PMF and ET. Figure 1A shows a significant correlation between NLR and HDL, with a statistical difference (p= 0.013).

Proteomics analysis identified a total of 177 differential proteins in the bone marrow of ET and pre-PMF, of which 108 were up-regulated and 69 were down-regulated in the pre-PMF group (Figure 1B and 1C). Through functional enrichment analysis,

we found that the differentially expressed proteins upregulated in the pre-PMF group (such as: CXCR4, CXCR2, GBP5, etc.) are mainly enriched in immune and inflammation-related GO (Gene Ontology) terms, such as immune response (GO:000695). The differentially expressed proteins downregulated in the pre-PMF group (such as APOA4, FABP4, etc.) are mainly enriched in lipid metabolism-related GO terms, such as lipoprotein metabolic process (GO: 0042157), and positive regulation of fatty acid biosynthetic process (GO: 0045723). Association analysis revealed a significant relationship between differential proteins and clinical markers (Figure 1D). We identified 223 differential microbes in the bone marrow, which were classified into 88 genera. The α diversity of the microbiota in bone marrow calculated by Chao1 showed that there was significant difference in species diversity between the two groups (Figure 1E). Microbiome composition showed statistically significant differences between pre-PMF and ET ($p<0.001$, $R^2=0.302$, PERMANOVA). Microbial diversity and richness was higher in pre-PMF, and reaching statistical significance in this small cohort (Figure 1F).

Conclusion

We have shown that there are multi-level differences, including the proteome and microbiome, between ET and pre-PMF patients.This could potentially provide new insights for distinguishing and treating these two disease subtypes.

Disclosures No relevant conflicts of interest to declare.

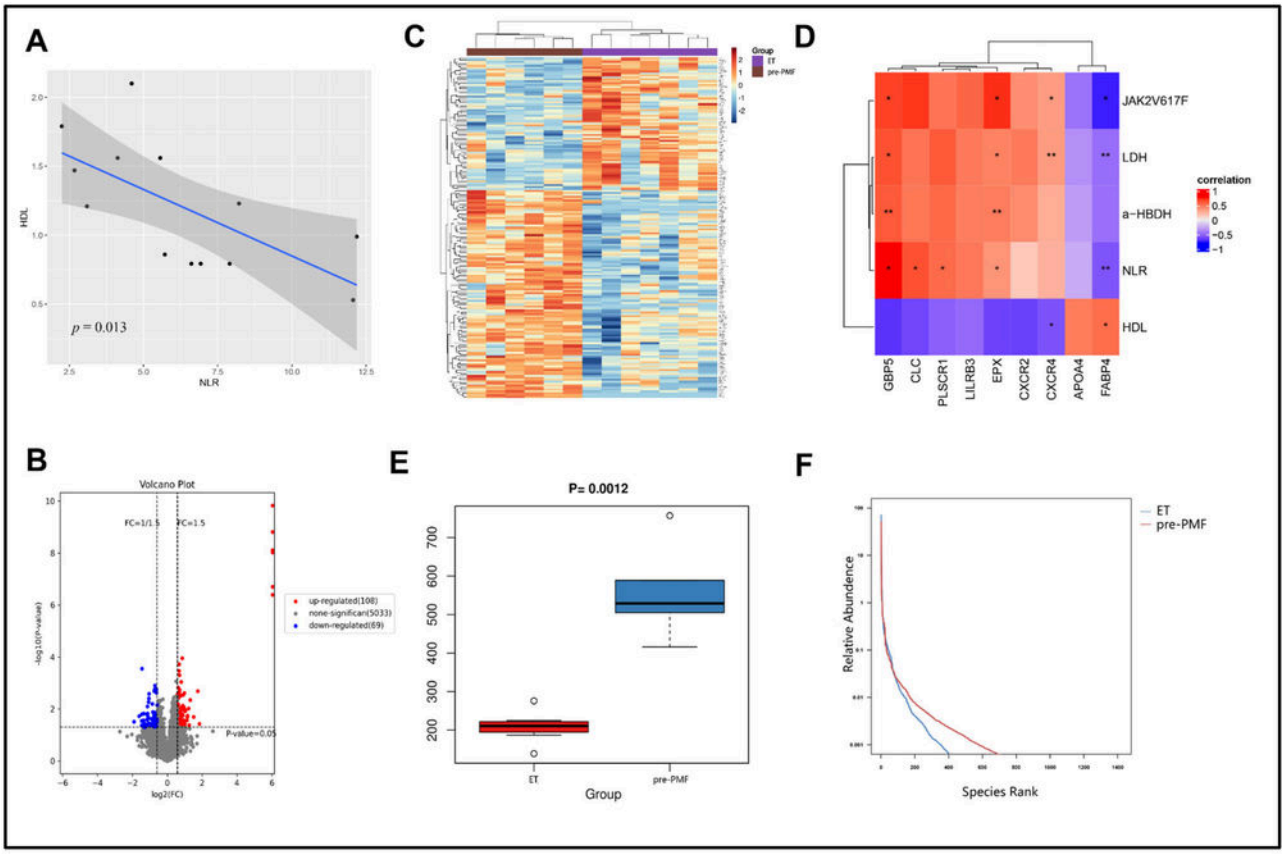

Figure 1. (A) Correlation between HDL and NLR . (B) Volcano plot of differential proteins between ET and pre-PMF. (C) Heatmap of differential proteins between ET and pre-PMF. (D) Association between differential proteins and clinical biomarkers in ET and pre-PMF. (E) Chao 1 Index for comparing alpha diversity between ET and pre-PMF. (F) Rank abundance between ET and pre-PMF.

Figure 1

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