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Introduction. Dysregulation of hepcidin, a key iron regulating hormone, is important in the pathogenesis of iron overload in patients with myelodysplatic syndromes (MDS), heterogeneous clonal myeloid disorders characterized by ineffective hematopoiesis, especially erythropoiesis, cytopenia and deregulated iron homeostasis. Recently, Erythroferrone (ERFE) was discovered as a new erythroid-regulator of hepcidin in the context of erythropoietic stress. ERFE, encoded in humans by the *FAM132B* gene, induces increased iron availability by downregulation of hepcidin in the liver and therefore represents an important new factor in iron homeostasis to be explored as a potential diagnostic or therapeutic target in the context of anemia and iron overload. In order to determine the specific role of ERFE in MDS, we analyzed the gene expression of *FAM132B* in MDS patients and controls and correlated the differential expression data with clinical parameters and expression level of others iron genes.
Methods. Bone marrow samples from 65 newly diagnosed MDS and 8 non-malignant hematological patients were collected. The diagnosis of MDS was based on the 2008 World Health Organization (WHO) classification. Total RNA was extracted with Trizol reagent. Reverse transcription and PCR amplification were performed according to manufacturer's instruction. The expression level of each gene was normalized to the housekeeping gene ABL1 and analyzed by $2^{-\Delta\Delta CT}$ relative quantitative method. Statistical analyses were performed using GraphPad 4.0 software. P-values of $<0.05$ were considered statistically significant. Unpaired t-test or Mann Whitney test was used to study difference between two groups. Correlation analysis was performed using the Spearman's rank correlation coefficient $r_s$.
Results. We first evaluated the expression of *FAM132B* in total bone marrow (BM) cells of 65 newly diagnosed MDS patients. *FAM132B* expression had a more variable expression pattern in MDS than controls and was highly expressed in 31 out of 65 patients. In BM cells, expression levels of *FAM132B* correlated inversely with those of *HAMP* and positively with those of FPN1 and EPOR. We next evaluated *FAM132B* expression in the different subgroups of WHO classification. ERFE expression was significantly higher in RA ($p=0.0013$) and RAEB-1 ($p=0.001$) subtypes when compared with controls, but not in RAEB-2 or in RCMD. To investigate the potential role of ERFE in a clinical setting, we next conducted Spearman's correlation analysis on the mRNA expression of *FAM132B* and laboratory parameters. Our results showed that FAM132B was positively correlated with serum iron, ferritin, bone marrow erythroblasts and MCV and inversely correlated with peripheral RBC.
Discussion and Conclusion. This study analyzes the *FAM132B* expression in MDS, clonal conditions of the bone marrow with impaired hematopoiesis, especially erythropoiesis. The observed high overexpression of *FAM132B* in MDS patients, its positive correlation with BM erythroblasts but its negative correlation with peripheral RBC might be related to an abnormal and ineffective erythropoiesis. Moreover, the inverse correlation between *FAM132B* and BM *HAMP* confirms that ERFE is able to modulate, through hepcidin suppression, the iron homeostasis, not only at systemic level as shown by the correlation with the laboratory markers of iron metabolism, but also at the BM level. These finding suggest that ERFE may play an important role in the physiopathology of the dysfunctional erythropoiesis and it could be assessed as new biomarker in MDS.