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Myelodysplastic Syndromes

SPALT LIKE TRANSCRIPTION FACTOR 4 DEREGULATION IN LOW RISK MYELODYSPLASTIC SYNDROME SF3B1 MUTATED PATIENTS

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Introduction: : Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis, peripheral cytopenias, and variable risk of progression to AML. Mutations in splicing machinery genes, in particular SF3B1, play a key role in the pathogenesis of low-risk MDS (LR-MDS), especially in ring sideroblast-associated forms.
Recent studies suggest that SALL4, an epigenetic regulator of stemness and oncogenic transformation, may be deregulated in hematological malignant contexts.
Methods: We enrolled 72 LR-MDS patients (as per IPSS-R) from the 'Gruppo Romano Laziale Mielodisplasie (GROM-L)' and the oncohaematology laboratory of the University of Rome 'Tor Vergata' (M/F: 37/35, median age 77, range 46-93). This population included: SF3B1 mutants (n=21), non-SF3B1 splicing factor (SF) mutants (n=7), SFwt (n=42) and co-mutated for SF3B1 and other SF genes (n=2). Ten healthy donors (HD) were used as control. We performed on these samples a genetic screening (t-NGS), SALL4 expression assay (Q-rt-PCR) and epigenetic analysis (Pyrosequencing).
Results: A total of 119 mutated genes were identified in the entire study cohort (1.65 mutations per patient) with a median VAF of 30% (range 1-100%).
With the exclusion of SF3B1 mutation itself, we observed in SF3B1mut vs SFwt subgroup a similar mutational burden (1.1 vs 1.2 mutations per pts). In the same line, we detected a similar mutational landscape, with DNMT3A, TET2 and ASXL1 as most frequently mutated genes (33,3% vs 23,8%, 19,0% vs 16,6% and 14,2% vs 16,6%, respectively).
The analysis of SALL4 total mRNA expression showed a trend towards upregulation in LR-MDS vs HD (p=0.099), while MDS harboring SF3B1-K700E mutations presented higher expression when compared to both HD (p=0.0151) and SFwt patients (p=0.0019).
Looking for alternative splicing events (ASE) in SALL4, SALL4A splicing isoform resulted up-regulated in both the overall LR-MDS population and the subgroup of SF3B1-K700E MDS when compared to HD (p=0.0006 and p=0.0001, respectively).
In contrast, we observed no differences in SALL4B isoform expression between LR-MDS patients and HD. However, SF3B1-K700E LR-MDS showed SALL4B upregulation when compared to both SFwt and HD (p=0.0043 and p=0.0067, respectively).
Since epigenetic regulation in specific CpGs has been previously identified by our group in HR-MDS, we tested DNA methylation in a subgroup of 18 patients (SF3B1-K700E=9 and SF3B1wt=9). Unexpectedly, we found an increased methylation in SF3B1-K700E vs SFwt LR-MDS patients (p=0.0003), indicating a direct correlation between DNA methylation levels and gene expression.
Conclusions: SALL4 and its isoforms' expression levels are deregulated in LR-MDS, particularly SF3B1-K700E. Although the mechanisms of epigenetic regulation remain to be fully elucidated, these evidence suggest the potential role of SALL4 as biomarker and/or therapeutic target in this subset of patients.