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Myelodysplastic Syndromes

FLOW CYTOMETRIC CHARACTERIZATION OF MYELODYSPLASTIC SYNDROME STEM CELLS: A NEW PROGNOSTIC TOOL

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Introduction: Myelodysplastic Syndromes (MDS) are clonal hematopoietic disorders characterized by ineffective hematopoiesis, and high risk of transformation to Acute Myeloid Leukemia (AML). While extensive research has elucidated the role of leukemic stem cells (LSCs) in AML pathogenesis, the stem cell compartment driving MDS remains less defined. Current evidence suggests that MDS originates from immature malignant stem and progenitor cells (MDS-SCs) that serve as a reservoir for leukemic evolution. These cells share phenotypic features with normal Hematopoietic Stem Cells (HSCs) but aberrantly express AML-associated markers such as CD123, CD371 (CLL1), and CD366 (TIM-3).
Aims and Methods: Bone marrow (BM) samples from MDS patients (pts) at diagnosis were collected and a flow cytometry antibodies panel including CD34, CD38, CD90, CD45RA, CD123, CLL-1, and TIM-3 was designed. The entire CD34+ compartment was analyzed, focusing on CD34+CD38-CD90+ (HSC-like) and CD34+CD38-CD45RA+ (LSC-like) subsets. The aims are to determine whether AML-like LSCs are already detectable in MDS samples; to define a distinct MDS-SC phenotype within the patient cohort. The final goal is to identify phenotypic signatures that could facilitate the prognostic stratification and therapeutic monitoring of MDS pts.
Results: 60 pts with diagnosis of MDS were studied. Using a flow cytometry gating strategy, we analyzed the CD34+CD38- compartment, focusing on 2 distinct subsets: CD34+CD38-CD90+ HSCs and CD34+CD38-CD45RA+ LSCs. Based on the presence/absence of these 2 populations, the 60 MDS pts were stratified as follows: Group 1 (18/60; 30%) – Negative for both HSCs and LSCs; Group 2 (6/60; 10%) – Positive only for HSCs; Group 3 (11/60; 18%) – Double positive for both HSCs and LSCs; Group 4 (25/60; 42%) – Positive only for LSCs; notably, 6/25 (24%) pts in this group progressed to AML. To date, Next-Generation Sequencing (NGS) has been performed in 20/60 (33%) cases, revealing mutations in genes involved in RNA splicing (SRSF2, SF3B1, U2AF1), DNA methylation (IDH2, TET2, DNMT3A), transcription regulation (KRAS, RUNX1), histone modification (EZH2), and chromatid cohesion (STAG2). Interestingly, Groups 1 and 2 predominantly harbored initiating MDS-associated mutations, whereas Groups 3 and 4 already displayed AML-like molecular alterations.
Conclusions: We developed a flow cytometry–based approach to stratify MDS pts by their stem cell compartment, identifying a subset (Groups 3 and 4) with AML-like LSCs and higher risk of leukemic transformation, distinct from those with an MDS-like phenotype and only initiating mutations (Groups 1 and 2). Combining flow cytometry, cytogenetic, and NGS data offers new insight into MDS clonal evolution, emphasizing mutated MDS-SCs as key drivers of progression. Ongoing work aims to expand the cohort and validate findings against normal BM, to establish this strategy as a predictive tool for early detection and monitoring of high-risk MDS pts.