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PU.1 expression correlates with patient disease status in the myelodysplastic syndromes, a new prognostic marker

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Background: Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell disorders characterized by ineffective haematopoiesis and dysplasia, manifesting as variable degrees and combinations of peripheral blood cytopenia. The result is often transfusion-dependent anemia, increased risk of infection, bleeding complications, and an increased potential of progression to acute myelogenous leukemia (AML). In recent years treatment with 5-azacytidine (AZA) has seen an increase in patient survival for intermediate and high-risk group MDS patients, although the precise mechanism of action is not yet fully understood. Previous studies have demonstrated down regulation of the PU.1 transcription factor in high-risk MDS patients, which can be reversed by administration of AZA. However, it is not currently known if PU.1 levels correlate with MDS disease severity and/or prognosis.

Aims: Assess if PU.1 expression levels in MDS patients correlate with disease prognosis as determined by risk group stratification using the Revised International Prognostic Scoring System (IPSS-R). In addition, we will use commercially available cell lines (SKM-1, MOLM-13, K562 and HL60) to explore the potential of AZA in correcting down-regulated PU.1 expression that is seen in high-risk MDS.

Methods: BM specimens were collected from 13 patients diagnosed with MDS who were stratified according to IPSS-R guidelines (5-low, 3-int, 2-high risk) and from 13 hematological normal controls. Samples were enriched for the mononuclear fraction by Ficoll separation. Total RNA was extracted and analyzed by Real Time PCR for PU.1 expression relative to the housekeeping gene GAPDH using the 2-ΔΔCT method. *In vitro* models of MDS, SKM-1 and MOLM-13 were treated with 1 μM AZA for 24, 48, or 72 hr followed by analysis of PU.1 expression analysis by RT-qPCR.

Results & Conclusion: Analysis of patient samples revealed that PU.1 expression is significantly lower in high-risk patients compared controls. In addition, preliminary data suggests that PU.1 expression also correlates with disease severity and could provide insight as a prognostic marker. PU.1 expression was significantly increased upon treatment with 1 μM AZA in commercially available cell lines.

Biography

Ciro Roberto Rinaldi has completed his MD from University Federico II Naples, Italy. He did his PhD in Biotechnology and during his PhD he moved to Chicago where he worked in Giuseppina Nucifora's Lab at the University of Illinois. He is a Consultant Hematologist at United Lincolnshire Hospital Trust and specialized in MPN, MDS and Myeloma. He has been a Visiting Professor in Biomedical Science at University of Lincoln in 2015, where he led the MPN/MDS Molecular Biology Lab focusing on Philadelphia-negative MPN and abnormal pathways in MDS. In 2014, he became the Hematology Expert Clinical Advisory Group (ECAG) Lead for the East Midland.

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