Myelodysplastic syndromes are a heterogeneous group of disorders characterized by ineffective hematopoiesis accompanied by morphologic dysplasia [1]. The underlying genetic lesions responsible for the pathogenesis of the disease remain largely elusive. In addition, the diagnosis of low-grade dysplastic process such as refractory anemia (RA) poses a challenge to the clinician as well as to the hematopathologist. This issue of Leukemia and Lymphoma carries a small but significant study by Li and colleagues [2] that might improve our understanding of the biology of MDS and provide a useful diagnostic tool for the diagnosis of low-grade MDS such as RA.

Li and colleagues investigated WT1 expression in nucleated bone marrow cells from patients with established diagnosis of MDS. The authors used a somewhat unusual approach of simultaneous FISH and immunohistochemistry using the phosphatase anti-alkaline phosphatase to study WT1 expression in cells with clonal cytogenetic abnormalities demonstrable by FISH. This approach permitted them to compare WT1 expression not only between normal and MDS samples but also between cytogenetically clonal and non-clonal cells from an individual patient with MDS. The authors confirm higher WT1 expression in MDS patients when compared with normal controls as reported in previous studies using RT-PCR [3]. In addition, they demonstrate that within a sample from a patient with MDS, the clonal cells have higher WT1 expression when compared with non-clonal cells. Furthermore, WT1 expression even in the non-clonal cells in these patients was higher than that seen in the 12 normal controls. Interestingly, the authors did not observe a difference in the WT1 expression levels between the various sub-types of MDS examined (RA vs. RAEB vs. CMML).

While definitive conclusions cannot be drawn from a small study, the study explores the possibility of looking at WT1 expression at a cellular level. This approach has the advantage of demonstrating not just the amount of the protein expressed, but also the fraction, morphology and cytogenetic clonality of cells expressing the protein. The authors also make the intriguing observation that the non-clonal cells in MDS patients had higher percentage of WT1 expressing cells when compared with the controls. While this needs to be confirmed in larger studies, there are two possible implications of this observation – one, WT1 over expression precedes the acquisition of the cytogenetic abnormality and may be an early event in the pathogenesis of MDS. Alternatively, WT1 expression in these cells could be a bystander effect of the marrow environment in these patients.

In spite of these interesting observations, the study suffers from some drawbacks. The expression of WT1 was detected in a very small fraction of the cells (mean positivity in MDS was 4%). Furthermore, the sub-cellular localization was almost entirely cytoplasmic – somewhat unusual for a transcription factor. The lack of differences between various groups of MDS is also intriguing and contradictory to some older studies where the WT1 expression was studied using qRT-PCR [3]. It remains to be seen if these findings are merely a consequence of the detection method used and the specific epitope recognized by the antibody or if indeed, this is the true expression profile of WT1 in MDS. These are important questions and the answers are important not only for our understanding of the biology of MDS, but also on the development of WT1 targeted therapies for MDS [4].

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References


