Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
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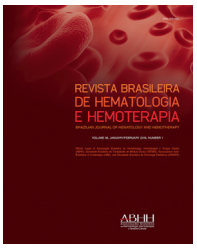

Scientific Comment

New developments in the understanding and diagnosis of myelodysplastic syndromes with ring sideroblasts☆

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Myelodysplastic syndromes (MDS) represent a group of clonal hematopoietic stem cell disorders in which cytopenias of variable severity are associated with dysplastic changes of hematopoietic precursors, and a higher risk of progression to acute myeloid leukemia (AML).[1] Besides dysplasia, the presence of ring sideroblasts (RS) has long been recognized as an important morphologic feature of MDS; it used to define a subset of patients within this group. Accordingly, the World Health Organization (WHO) criteria revised in 2008 defined refractory anemia with ring sideroblasts (RA-SR) as a specific MDS subgroup, morphologically characterized by erythroid dysplasia and the presence of at least 15% RS in bone marrow smears.[2]

However, seminal studies published within the last five years have changed concepts and diagnostic definitions in the field of myeloid malignancies swiftly. Among these studies, made possible by the development of high-throughput sequencing technologies, the description of mutations associated with MDS and AML in large patient cohorts,[3–5] followed by the demonstration that some of these mutations are also present (though with a lower allele burden) in individuals without evident hematologic alterations,[6–8] led to the proposal of a new pathological category termed clonal hematopoiesis of indeterminate potential (CHIP).[9] This could be conceptually viewed for myeloid neoplasms, as monoclonal gammopathy of undetermined significance is for multiple myeloma. Furthermore – as explored in a study in this edition of the Revista Brasileira de Hematologia e Hemoterapia (RBHH)[10] – these studies also resulted in the description of the first association between an acquired mutation and a specific morphologic abnormality of hematopoietic precursors in MDS.

High-throughput whole genome sequencing studies revealed that mutations in genes involved in RNA splicing are found in ~45–85% of patients with MDS. In particular, somatic mutations of *splicing factor3b subunit 1* (*SF3B1*) have been identified in ~60–80% of MDS-RS patients[4,5] with an extremely high predictive value for the disease phenotype with RS, as *SF3B1* is emerging as the first gene to be strongly associated with a specific morphological feature of MDS.[11] Moreover, MDS patients carrying *SF3B1* mutations present a fairly homogeneous disease phenotype often characterized by isolated erythroid dysplasia, significant erythroid dysplasia, and high proportion of RS. Even more importantly, these patients present significantly better survival and lower risk of progression to AML.[11,12] Together, these data supported a significant change in the revised WHO classification of MDS in 2016, which established that, in the presence of a *SF3B1* mutation, a diagnosis of MDS-RS may be defined with RS in as few as 5% of nucleated erythroid cells, with the former threshold of 15% RS reserved for cases lacking a demonstrable *SF3B1* mutation.[13] These patients will be classified

DOI of original article: http://dx.doi.org/10.1016/j.bjhh.2016.06.002.

☆ See paper by Donaires et al. in Rev Bras Hematol Hemoter. 2016;38(4):320–324.

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http://dx.doi.org/10.1016/j.bjhh.2016.08.003

as 'MDS with single lineage dysplasia and ring sideroblasts (MDS-RSSLD)' or 'MDS with multilineage dysplasia and ring sideroblasts (MDS-RSMLD)'.[13]

It is in this changing context that Donaires et al. present a study in which *SF3B1* mutations were screened in 91 MDS patients from two distinct geographical areas of Brazil, using a strategy targeting the most frequently mutated exons of *SF3B1* by direct Sanger sequencing.[10] In total, 7% of patients presented heterozygous *SF3B1* mutations, all of them with RS. The proportion of patients presenting *SF3B1* mutations was somewhat lower than reported in Europe and North America, a finding that the authors speculate to be associated with the heterogeneous background of the Brazilian population, or to the fact that only mutation hotspots were evaluated in the *SF3B1* gene using their screening strategy. The authors also provide a detailed review of the cellular and molecular mechanisms by which *SF3B1* mutations lead to RS, and an *in silico* simulation of the putative consequences of each mutation that they found in the function of SF3B1 protein.

The quick impact of the identification of the association of *SF3B1* mutations with RS on classical diagnostic criteria for MDS illustrate how fast new molecular biology findings can influence the practice of the general hematologist. Well-known challenges in the differential diagnosis of MDS,[14] and the prospects that new molecular data also pave the way to improve risk stratification and treatment strategies[15] corroborate the importance of studies addressing the molecular pathogenesis of myeloid malignancies and in particular of MDS.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Cazzola M, Malcovati L. Myelodysplastic syndromes – coping with ineffective hematopoiesis. N Engl J Med. 2005;352:536–8.
2. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114:937–51.
3. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368:2059–74.
4. Yoshida K, Sanada M, Shiraishi Y, Nowak D, Nagata Y, Yamamoto R, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011;478:64–9.
5. Papaemmanuil E, Cazzola M, Boultwood J, Malcovati L, Vyas P, Bowen D, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011;365:1384–95.
6. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–98.
7. Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371:2477–87.
8. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20:1472–8.
9. Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126:9–16.
10. Donaires FS, Martellia F, Alves-Paiva RM, Magalhães SM, Pinheiro RF, Calado RT. Splicing factor SF3B1 mutations and ring sideroblasts in myelodysplastic syndromes: a Brazilian cohort screening study. Rev Bras Hematol Hemoter. 2016;38:320–4.
11. Malcovati L, Papaemmanuil E, Bowen DT, Boultwood J, Della Porta MG, Pascutto C, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood. 2011;118:6239–46.
12. Malcovati L, Cazzola M. Recent advances in the understanding of myelodysplastic syndromes with ring sideroblasts. Br J Haematol. 2016;174(6):847–58.
13. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.
14. Dos Santos TE, de J, Gonçalves RP, Duarte FB. Myelodysplastic syndrome versus idiopathic cytopenia of undetermined significance: the role of morphology in distinguishing between these entities. Rev Bras Hematol Hemoter. 2013;35:438–9.
15. Traina F, Visconte V, Elson P, Tabarroki A, Jankowska AM, Hasrouni E, et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. Leukemia. 2014;28:78–87.