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Scientific Comment

Utility of the p53 mutant protein in patients with low-risk myelodysplastic syndrome

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In this issue of the Revista Brasileira de Hematologia e Hemoterapia, Duarte et al.[1] present data on the role of p53 protein expression and prognosis of patients with low-risk myelodysplastic syndrome (MDS). In a cohort of 38 patients, the authors demonstrated an association between mutant p53 protein expression and shortened survival.

MDS is a clinically heterogeneous disorder.[2] Patients with this condition demonstrate clonal hematopoietic expansion, cytopenias, myelodysplasia, ineffective hematopoiesis and an increased propensity to develop acute myeloid leukemia. Not surprisingly, prognosis is related to severity of cytopenias, presence of cytogenetic abnormalities and clonal evolution demonstrated by blast counts, and other 'traditional' prognostic elements. There is heterogeneity even among patients diagnosed with lower-risk disease, since a subset of these patients have more aggressive disease. Recent efforts have demonstrated that several molecular parameters linked to the pathophysiology of MDS may affect overall survival.[3,4] Thus, identification of additional prognosticators that more accurately characterize subgroups and their outcomes are essential.

Current understanding of the pathophysiology of MDS indicates that there are founding mutations in a hematopoietic stem cell that ultimately offer a survival advantage to the affected cell(s). These mutations occur in genes encoding protein products that are involved typically in either RNA splicing or DNA methylation, which in turn leads to genomic instability and further mutations.[5] The survival advantage in mutated cells usually leads to a dominant bone marrow progenitor clone. This clone can subsequently acquire additional driver mutations that lead to the development of multiple subclonal populations. The accumulation and combination of these genetic lesions likely contribute to the phenotypes observed in MDS patients. *TP53* gene mutations are particularly interesting given the fact that its protein product has tumor suppression activity.

TP53 encodes a cytoplasmic protein p53 that regulates cell growth and death. Mutations have been identified in a variety of cancers.[6] In MDS, *TP53* mutations have been found mainly in intermediate- to high-risk patients. Patients often present with complex cytogenetic abnormalities, severe thrombocytopenia, increased risk of leukemia progression, and have shorter survival.[7,8] While it has been well documented that genetic lesions in *TP53* carry an independent poor prognostic value, mostly amongst advanced stage patients,[9,10] the role of *TP53* mutations in low-risk MDS remains unclear. Duarte et al. examined whether intracellular accumulation of mutant p53 correlates with clinical characteristics and prognosis among 38 patients with low-risk MDS (defined by current scoring system).[1] Patients with mutant p53 were older, anemic and leukopenic at the time of diagnosis, and had a shorter median survival compared to those carrying wild-type p53.

Duarte et al. concluded that molecular identification of mutant p53 contributes to risk stratification of patients with low-risk MDS, which may alter the treatment approach.[1] The authors provide a compelling argument for further characterization of the role of p53 in a larger cohort of low-risk MDS patients.

Interpreting p53 mutation role in MDS is not a trivial task, however, since there are often complicating interactions

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with other intracellular regulators.[11] A recent effort to characterize genetic lesions in MDS showed that each patient frequently harbors mutations in multiple genes simultaneously.[8] In another study, mutations in genes *ASXL1*, *EZH2*, *RUNX1*, *NRAS* and others were associated with shorter overall survival in lower-risk MDS.[12] Interestingly, interactions among these gene products and p53 have been documented extensively.[13,14]

Over the past 5–10 years a variety of technologies have improved and enabled high-throughput analysis of entire MDS genomes, leading to the identification of several new potentially targetable genes implicated in MDS pathogenesis. The challenge is how to incorporate these into new prognostic systems. In addition, it is expected that these approaches will lead to therapeutic insights that are desperately needed for MDS patients.

Conflicts of interest

The authors declare no conflicts of interest.

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