PLENARY LECTURE

Molecular basis of myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by dysplasia in one or more cell lines, ineffective hematopoiesis and variable risk of progression to acute myeloid leukemia. In the past few years, important steps have been taken in characterizing the molecular basis of MDS. More recently, somatic mutations in genes encoding core components of the RNA splicing machinery have been detected in high proportions of MDS patients, and are shown to be founding mutations in many instances. These mutations have different clinical significance, and their incorporation into current stratification systems might improve risk assessment in MDS.

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Myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by dysplasia in one or more cell lines, ineffective hematopoiesis and variable risk of progression to acute myeloid leukemia (AML).¹ The World Health Organization (WHO) classification criteria² for MDS diagnosis require evaluation of peripheral blood and bone marrow morphology, combined with cytogenetic analyses, and define the following categories:³ refractory cytopenia with unilineage dysplasia, refractory anemia with ring sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (RAEB) type 1 (RAEB-1) and 2 (RAEB-2), and MDS with isolated (del 5q)).

These conditions are heterogeneous in terms of life expectancy,⁴ and risk-based stratification systems have been developed to improve their prognostication, including the International Prognostic Scoring System (IPSS)⁵ and the WHO classification-based Prognostic Scoring System (WPSS).⁶ Both IPSS and WPSS are currently being revised by the International Working Group for Prognosis in MDS to improve their ability to predict the outcome of MDS patients. As comorbidities have a significant impact on clinical outcome, accounting for both disease status and comorbid conditions considerably improves risk stratification in MDS.⁷

In the past few years, important steps have been taken in characterizing the molecular basis of MDS, and in developing novel molecular tools for diagnosis and prognostic evaluation of these myeloid neoplasms. Acquired somatic mutations of *TET2* have been detected in approximately 25% of MDS patients.^{8,9} *TET2* mutations represent a useful marker of clonal proliferation, although they do not carry prognostic relevance.¹⁰ Additional mutant genes, including *TP53*, *EZH2*, *ETV6*, *RUNX1* and *ASXL1*, have been identified in smaller proportions of patients, but mutations in these latter genes have been shown to be independently associated with decreased overall survival in MDS.¹¹

More recently, somatic mutations in genes encoding core components of the RNA splicing machinery have been detected in high proportions of MDS patients.^{12–17} The close association between mutations in one of these genes, *SF3B1*, and disease phenotype with ring sideroblasts is consistent with a causal relationship.¹⁸ In addition, *SF3B1* mutations are independent predictors of favorable clinical outcome, especially of low risk of leukemic evolution.¹⁸ On the contrary, mutations of *SRSF2* or

U2AF1, other genes encoding spliceosome components, are associated with unfavorable clinical outcome and a high risk of progression to (AML).^{14–17} Incorporation of these mutant genes into current stratification systems might improve risk assessment in MDS.

The recent advances in our understanding of the molecular basis of MDS have also allowed to decipher, at least in part, the pathophysiology of myelodysplastic/myeloproliferative neoplasms,¹⁹ such as refractory anemia with ring sideroblasts associated with marked thrombocytosis and chronic myelomonocytic leukemia.^{20–22}

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

- 1 Cazzola M, Malcovati L. Myelodysplastic syndromes—coping with ineffective hematopoiesis. *N Engl J Med* 2005; **352**: 536–538.
- 2 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H *et al.* *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC: Lyon, 2008.
- 3 Brunning RD, Orazi A, Germing U, Le Beau MM, Porwit A, Bauman I *et al.* Myelodysplastic syndromes/neoplasms, overview. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.* (eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC: Lyon, 2008, pp 88–93.
- 4 Malcovati L, Della Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglini E *et al.* Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol* 2005; **23**: 7594–7603.

- 5 Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G *et al.* International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997; **89**: 2079–2088.
- 6 Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R *et al.* Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007; **25**: 3503–3510.
- 7 Della Porta MG, Malcovati L, Strupp C, Ambaglio I, Kuendgen A, Zipperer E *et al.* Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica* 2011; **96**: 441–449.
- 8 Delhommeau F, Dupont S, Della Valle V, James C, Trannoy S, Masse A *et al.* Mutation in TET2 in myeloid cancers. *N Engl J Med* 2009; **360**: 2289–2301.
- 9 Langemeijer SM, Kuiper RP, Berends M, Knops R, Aslanyan MG, Massop M *et al.* Acquired mutations in TET2 are common in myelodysplastic syndromes. *Nat Genet* 2009; **41**: 838–842.
- 10 Smith AE, Mohamedali AM, Kulasekararaj A, Lim Z, Gaken J, Lea NC *et al.* Next-generation sequencing of the TET2 gene in 355 MDS and CMML patients reveals low-abundance mutant clones with early origins, but indicates no definite prognostic value. *Blood* 2010; **116**: 3923–3932.
- 11 Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G *et al.* Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med* 2011; **364**: 2496–2506.
- 12 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**: 64–69.
- 13 Papaemmanuil E, Cazzola M, Boultonwood J, Malcovati L, Vyas P, Bowen D *et al.* Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med* 2011; **365**: 1384–1395.
- 14 Graubert TA, Shen D, Ding L, Okeyo-Owuor T, Lunn CL, Shao J *et al.* Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. *Nat Genet* 2012; **44**: 53–57.
- 15 Makishima H, Visconte V, Sakaguchi H, Jankowska AM, Abu Kar S, Jerez A *et al.* Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. *Blood* 2012; **119**: 3203–3210.
- 16 Damm F, Kosmider O, Gelsi-Boyer V, Renneville A, Carbuccia N, Hidalgo-Curtis C *et al.* Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. *Blood* 2012; **119**: 3211–3218.
- 17 Thol F, Kade S, Schlarmann C, Löffel P, Morgan M, Krauter J *et al.* Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. *Blood* 2012; **119**: 3578–3584.
- 18 Malcovati L, Papaemmanuil E, Bowen DT, Boultonwood J, Della Porta MG, Pascutto C *et al.* Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood* 2011; **118**: 6239–6246.
- 19 Hyjek E, Vardiman JW. Myelodysplastic/myeloproliferative neoplasms. *Semin Diagn Pathol* 2011; **28**: 283–297.
- 20 Malcovati L, Della Porta MG, Pietra D, Boveri E, Pellagatti A, Galli A *et al.* Molecular and clinical features of refractory anemia with ringed sideroblasts associated with marked thrombocytosis. *Blood* 2009; **114**: 3538–3545.
- 21 Muramatsu H, Makishima H, Maciejewski JP. Chronic myelomonocytic leukemia and atypical chronic myeloid leukemia: novel pathogenetic lesions. *Semin Oncol* 2012; **39**: 67–73.
- 22 Cazzola M, Malcovati L, Invernizzi R. Myelodysplastic/myeloproliferative neoplasms. *Hematol Am Soc Hematol Educ Prog* 2011; **2011**: 264–272.