Blood Cells, Molecules and Diseases 55 (2015) 76–81

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Review

Genetics factors associated with myelodysplastic syndromes

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ARTICLE INFO

Article history:
Submitted 7 April 2015
Accepted 16 April 2015
Available online 17 April 2015

Keywords:
MDS
Genetics
Cytogenetic abnormalities
Epigenetic
Diagnosis

ABSTRACT

The myelodysplastic syndromes (MDS) are a clinically and cytogenetically heterogeneous group of clonal diseases. Clonal chromosomal abnormalities are observed in 30–50% of patients with MDS. The deletions are among the most common alterations, and often involve the long arms of chromosomes 5, 7, 8, 13, and 20 and the short arms of chromosomes 12 and 17. The advent of new technologies for the detection of genetic abnormalities led to the description of a new set of recurrent mutations, leading to new insights into the pathophysiology of MDS. The recent recognition that genes involved in the regulation of histone function (*EZH2*, *ASXL1*, and *UTX*) and DNA methylation (*DNMT3A*, *IDH1*/*IDH2*, and *TET2*) are frequently mutated in MDS, has led to the proposal that there is an important link between genetic and epigenetic alterations in this disease. In fact, regulatory factors have also been considered as miR-143/miR-145, miR-146a, miR-125a and MiR-21. Somatic mutations may influence the clinical phenotype but are not included in current prognostic scoring systems. In recent years research has brought new insights into these diseases, but few of the findings are sufficiently robust to be incorporated into the clinical routine at this time. Thus, the aim of this study was to review the role of genetic factors involved in the diagnosis and development of the different phenotypes of MDS.

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1. Introduction

The myelodysplastic syndromes (MDS) belong to a heterogeneous group of clonal hematological disorders resulting from changes in progenitor bone marrow cells with clinical variables and laboratory characteristics. They originate from somatic mutations of hematopoietic progenitor cells (stem cells) that induce blocking cell differentiation which reflects in one or more dysplastic hematopoietic lineages [1]. The development of a genetically unstable and abnormal clone of stem cells that has maturation and proliferation changes, will feature ineffective hematopoiesis by increased apoptosis. This event promotes cytopenias in one or more hematopoietic lineages. Symptoms, when present, are related to failure of the affected lines and will eventually lead to leukemic transformation, which occurs in about one third of the cases [2]. However, the signs and symptoms of MDS are nonspecific, and when the erythroid lineage is affected, normally patients show signs of anemia, such as pallor, pale conjunctiva, tachycardia, hypotension and headache [3].

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http://dx.doi.org/10.1016/j.bcmd.2015.04.003
1079-9796/

The MDS affect mainly elderly individuals, with an incidence of 2–12/100,000 habitants/year in the general population, and increases to 50/100,000 habitants/year in the group above 70 years old. This age group is most affected due to the gradual and lifelong accumulation of genome damage caused by endogenous and exogenous carcinogens. It is suggested that the apparent increase in the number of cases is a result of increasing population longevity [2–4].

Due to the heterogeneity of the disease's pathogenesis, the clinical course and prognosis are highly variable [5]. The pathogenesis of MDS is still poorly understood, since there is an involvement of abnormal complex events [6]. This clinical phenotype diversity can be partially explained by the type of acquired chromosomal abnormalities and the presence of some molecular markers.

In recent years, the molecular classification of MDS stood and opened new horizons not only for diagnosis and classification, but also for prognosis, enabling an impact on treatment. This major step was mainly driven by the use of new molecular techniques [7]. The prevalence of MDS is growing with the increase in life expectancy and the expansion of knowledge about the different mechanisms related to MDS make this an opportune time to discuss the molecular aspects of the pathogenesis of these syndromes. Given the complexity of biological events associated with MDS, the goal of this search was to conduct a literature review to assess the importance of molecular markers and the cytogenetic aspects involved in the diagnosis and development of different phenotypes disease.

2. Cytogenetic aspects

There is a variable risk of progression to acute myeloid leukemia (AML) that appears to be induced by somatic genomic instability and epigenetic modifications. Allelic disequilibrium caused by structural or numerical chromosomal aberrations and DNA repair defects are closely linked to the pathophysiology of disease [8].

The diversity of clinical features present in patients with MDS can be partly explained by the type of chromosomal abnormalities acquired, and can be observed in approximately 30–50% of primary MDS and 80% of secondary. Deletions, monosomy and trisomy trigger clonal proliferation of hematopoietic progenitor cells in the bone marrow, and these events are observed in most patients with MDS [9]. Many specific abnormalities are closely linked to prognosis and genomic instability increases the propensity to develop AML [10]. However, none of them is fully specific for MDS and many of these recurring changes can be observed in other myeloid neoplasms, which hinders the inclusion of molecular tests to diagnosis [11].

Most patients with recurrent MDS have karyotypic abnormalities. The deletions are among the most common alterations, and often involve the long arms of chromosomes 5, 7, 20, 11, and 13 and the short arms of chromosomes 12 and 17. When these emerge as the only cytogenetic defect, these deletions are considered low risk, however, when they occur in conjunction with other changes, they could be considered as an advanced risk for MDS [12].

In order to improve the risk assessment for MDS, the International Prognostic Scoring System (IPSS) proposed in 1997 the classification for MDS based on the combination of cytogenetics, cytomorphology and clinical aspects. In this system, the proposed parameters were evaluated by the French–American–British (FAB) classification prioritizing a more refined classification of bone marrow cytogenetic findings. Many recent studies have applied 3 cytogenetic risk categories defined by the IPSS (good, intermediate, and poor), however, in 2012 there was a revision of IPSS (IPSS-R) analyzing the impact of cytogenetics on survival in patients with MDS which indicated a distinction of 5 cytogenetic risk groups (very good, good, intermediate, poor, and very poor) as described in Table 1 [13].

The classification proposed by the World Health Organization (WHO) in 2008 also highlighted the importance of cytogenetic features for diagnosis. In cases where the clinic is consistent with MDS and the morphological features are not fully conclusive, a presumptive diagnosis may be performed when one considers the presence of specific cytogenetic abnormalities [14]. Fig. 1 shows the main karyotypic abnormalities associated with the disease prognosis by IPSS-R and MDS frequency found in different studies in the literature [15].

A cytogenetic study including 491 patients with MDS showed that 40% of the patients had normal karyotype, 8.7% had a deletion of the long arm of chromosome 5 (del 5q−), and 4.5% had trisomy 8, among other changes [12].

The most frequent chromosomal alteration in MDS is the partial or complete deletion of the long arm of chromosome 5 (del5q) [2]. The del 5q is associated with the homozygous loss of several genes involved in the regulation of hematopoiesis, including genes for cytokines and their receptors, cell cycle regulators, transcription factors and signaling mediators. This isolated deletion is characterized by refractory macrocytic anemia blast excess, with/without other cytopenias, presence of thrombocytosis and typical mononuclear megakaryocytes. The loss of the genes between the regions 5q13 and 5q33 suggest a significant correlation between the genetic defect and the clinical features of the del5q syndrome [7,8]. Abnormalities of chromosome 5 were related to exposure to inorganic gases and vapors, including ammonia, hydrogen peroxide and mineral acids [16].

Another frequent alteration is the monosomy of chromosome 7, which is generally characterized by severe and refractory cytopenia and the susceptibility to infection and occurs in 10% of patients with MDS. Inactive regions of tumor suppressor genes (7q22 and 7q36)

Table 1
Cytogenetic classification according to the IPSS and the new 5-group classification [13]

Classification/prognostic group	Abnormalities		
	Single	Double	Complex
IPSS			
Good	Normal; −Y del5q; del20q	–	–
Intermediate	Other	Any	–
Poor	7[a]	–	≥3[b]
5-Group			
Very good	−Y; del11q	–	–
Good	Normal; del5q; del20q; del12p	Including del5q	–
Intermediate	del7q; +8; i(17q); +19; any other	Any other	–
Poor	−7;inv(3)/t(3q)/del3q	Including −7/ del7q	3[b]
Very poor	–	–	3[b]

– Indicates not applicable.
[a] Any chromosome 7 abnormality.
[b] Number of clonal abnormalities.