Towards a genetically inspired classification of MDS

MDS Foundation Satellite Meeting @ ASH 2021

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No disclosures
Question

Which one of the following criteria is part of the current WHO classification to define a specific disease group:

A. *NPM1*-mutated myeloid neoplasms
B. Myeloid neoplasms with germline or somatic mutations in *DDX41*
C. MDS with bi-allelic *TP53* mutation or with complex karyotype and mutated *TP53*
D. MDS with unrecognized driver mutation
E. None of the above
Current principles of MDS classification

WHO classification based on an integrated approach combining morphology, immunophenotype, clinical and genetic features.

Apart from del(5q), no distinction of genetic etiology in the WHO categorization

Arber et al Blood 2016
Challenge: MDS genetic heterogeneity

More than 50 genes recurrently mutated in MDS | 10-15 in more than 5% of patients
Patients have in average 3 to 4 driver mutations
Challenge: MDS genetic heterogeneity

More than 50 genes recurrently mutated in MDS | 10-15 in more than 5% of patients
Complex diagnostic boundaries with other myeloid neoplasms or conditions
A genetic driven classification of MDS is a tangible goal

Non random patterns of co-mutations and mutual exclusivity

Strong genotype-phenotype associations
Systematic approaches to study MDS classification

AML

MPN

MDS

Papaemmanuil et al NEJM 2016 | Grinfeld et al NEJM 2018 | Bersanelli et al JCO 2021
Systematic approaches to study MDS molecular classification

Papaemmanuil et al NEJM 2016 | Grinfeld et al NEJM 2018 | Bersanelli et al JCO 2021
Systematic approaches to study MDS molecular classification

IWG MDS

Validation Cohort

n=3,328

Training Cohort

n=1,100

J-MDS

Classification

Cytogenetics

Allelic Imbalances

121 genes
Systematic approaches to study MDS molecular classification

IWG MDS

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J-MDS

Classification

Cytogenetics
Allelic Imbalances
121 genes

Molecular composition & Clonality
Molecular rules amenable to clinical adoption
Clinical presentation
Relationship with WHO & morphology
Outcomes


IWG-PM data | ASH abstract #61 session 637
Biomarker discovery for MDS classification

- Single gene biomarker
- Single genetic feature biomarker
- Combinations of multiple alterations

Increased complexity of disease-defining genetic features

- UBA1
- NPM1
- DDX41
- SF3B1

- Co-mutation

- Mutual exclusivity

- bi-allelic TP53
De novo identification of molecular classes in MDS

85% of patients classified across 17 non-overlapping molecular subgroups
Wide range in size (1 to 15%)
De novo identification of molecular classes in MDS

86% of patients classified across 17 non-overlapping molecular subgroups

Wide range in size (1 to 15%)

Clinical relevance of molecular classes (e.g. variation of marrow blasts)
De novo identification of molecular classes in MDS

86% of patients classified across 17 non-overlapping molecular subgroups
Wide range in size (1 to 15%)
6% of MDS without recognizable oncogenic lesions
MDS with no recognizable oncogenic lesions

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Younger age | Female bias | Favorable outcome
Enriched for MDS-SLD/MLD
MDS with no recognizable oncogenic lesions

6% of MDS without recognizable oncogenic lesions
Younger age | Female bias | Favorable outcome
Enriched for MDS-SLD/MLD

No lesions and MDS-SLD/MLD (n=130)
Screening for UBA1 mutations

No lesions but excess blasts (n=22)
Whole genome sequencing ongoing
VEXAS syndrome
(Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic)

Autoinflammatory syndrome with somatic mutations of *UBA1*

Vacuolization of hematopoietic precursors

Risk of hematologic neoplasia
25% of VEXAS patients have MDS

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<thead>
<tr>
<th>Diagnostic or classification criteria that were met</th>
<th>no. (%)</th>
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<tr>
<td>Relapsing polychondritis</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Sweet’s syndrome</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Multiple myeloma or monoclonal gammopathy of undetermined significance</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Polyaneritis nodosa</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Giant-cell arteritis</td>
<td>1 (4)</td>
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VEXAS syndrome
(Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic)

Autoinflammatory syndrome with somatic mutations of *UBA1*  

Vacuolization of hematopoietic precursors  

Risk of hematologic neoplasia  
25% of VEXAS patients have MDS

- 10 to 25% of MDS patients have manifestations of autoimmunity and autoinflammation symptoms  
- MDS cohort selected for male and the co-occurrence of autoinflammatory disease (Zhao et al 2021): *UBA1* mutations identified in 12% (4/33)
ddPCR assays for UBA1 hotspots mutations on male MDS patients with no identified drivers 10% positive (7/64)

Presence of UBA1 mutations resolves 10% of MDS without recognizable oncogenic lesions
SF3B1-mutant MDS
A paradigm for a genetically driven classification

Early event in MDS pathogenesis

Genotype-phenotype
Ringed sideroblasts

Favorable outcome

SF3B1 mut
SF3B1 wt

**SF3B1-mutant MDS**

A paradigm for a genetically driven classification

**SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS**

Luca Malcovati,1 Kristen Stevenson,2 Elli Papaemmanuili,3 Donna Neuberg,5 Rafael Bejar,4 Jacqueline Boulwood,3 David T. Bowen,6 Peter J. Campbell,7 Benjamin L. Ebert,6 Pierre Fenaux,8 Torsten Haferlach,10 Michael Heuser,11 Joop H. Jansen,12 Rami S. Kornegay,13 Jaroslaw P. Maciejewski,14 Matthew J. Walter,13 Michaela Fontenay,14 Guillermo Garcia-Manero,17 Timothy A. Graubert,14 Aly Karsan,19 Manja Maggendorfer,26 Andrea Pelligatti,26 David A. Sallman,23 Michael R. Savona,26 Mikkael A. Sekeres,14 David P. Steensma,8 Sudhir Tauro,7 Felicitas Thol,11 Paresh Vyas,22 Arjan A. van de Loosdrecht,23 Detlef Haase,24 Heinz Tüchler,21 Peter L. Greenberg,26 Seishi Ogawa,27,a Eva Hellstrom-Lindberg,28,a and Mario Cazzola19

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Hematologic and morphology requirements

Exclusion criteria with other cytogenetics or gene mutations

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**Table 3. Proposed diagnostic criteria for the MDS with mutated SF3B1**

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<td>Isolated erythroid or multilineage dysplasia*</td>
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<td>Any additional somatically mutated gene other than RUNX1 and/or EZH2†</td>
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*RS are not required for the diagnosis.

†Additional JAK2V617F, CALR, or MPL mutations strongly support the diagnosis of MDS/MPN-RS-T.
Mutations in *NPM1* found predominantly in MDS-EB but also in other subtypes
Mutations in \textit{NPM1} found predominantly in MDS-EB but also in other subtypes

Same patterns of co-mutations and clonality in \textit{NPM1}-mutated MDS or AML

NPM1-mutated MDS (1.5%)  
Poor outcome & high risk of AML transformation

NPM1-mutated MDS (1.5%)

Implications for therapeutic decision making

Figure 5. Kaplan-Meier estimate of survival based on therapy and allogeneic stem cell transplantation in patients with NPM1-mutated MDS and MDS/MPN.

Need for prospective studies on treatments for NPM1-mutated MDS

Germline and somatic *DDX41* mut. in MDS/AML (3%)

Characteristic pattern of germline LOF mutations with secondary somatic (R525)
Late onset disease >60y with male bias
DDX41

Germline and somatic *DDX41* mut. in MDS/AML (3%)

Table 17. Classification of myeloid neoplasms with germ line predisposition

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<td>Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction</td>
</tr>
<tr>
<td>AML with germ line <em>CEBPA</em> mutation</td>
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<td>Myeloid neoplasms with germ line <em>DDX41</em> mutation*</td>
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Germline recognition can be challenged by inconclusive personal or family history review and the late onset of disease (>60y)

Germline and somatic *DDX41* mut. in MDS/AML (3%)

Diverse patterns of molecular presentation

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Makishima et al, EHA 2021: 5,856 cases screened for *DDX41* mut.
Germline and somatic $DDX41$ mut. in MDS/AML (3%)

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Makishima et al, EHA 2021: 5,856 cases screened for $DDX41$ mut.

IWG data consistent: 90% likely-germline, among which 60% 2nd somatic. No detected difference in age between subgroups
Germline and somatic *DDX41* mut. in MDS/AML (3%)

Clinical presentation and outcomes of *DDX41*-mutated MDS

*DDX41* mutations are associated with excess blasts and risk of AML-t, but conversely favorable OS.
Germline and somatic $DDX41$ mut. in MDS/AML (3%)

Favorable outcomes following treatment with HMA

$DDX41$ mut. are emerging as a marker of favorable outcome following HMA.

Need large and prospective studies

Sebert et al., Blood 2019

Nannya et al., under review
Biomarker discovery for MDS classification

Increased complexity of disease-defining genetic features

Single gene biomarker
- UBA1
- NPM1
- DDX41
- SF3B1

Single genetic feature biomarker
- bi-allelic TP53

Combinations of multiple alterations
- Co-mutation
- Mutual exclusivity
- SF3B1
Myeloid neoplasms with bi-allelic TP53 alteration

TP53-AML & complex karyotype  
TP53-MDS & complex karyotype

TP53 mutations are associated with aneuploidies, high-risk disease, dismal prognosis and resistance to therapy

Mutations, deletions and cnLOH result in bi-allelic targeting of **TP53**

In **MDS**, association with complex karyotype specific to bi-allelic **TP53**

High rate of AML progression and dismal OS across all modes of bi-allelic targeting
Myeloid neoplasms with bi-allelic TP53 alteration

Evolution to secondary AML from TP53-mutated MPN, with acquisition of second biallelic TP53 hit
**Therapeutic targeting of mutant TP53 MDS/AML**

Emerging therapeutic approaches for mutant TP53 myeloid disease:

**APR-246 stabilizing mutant p53 function | anti-CD47 monoclonal antibody**

NCT03072043/NCT03588078: Azacytidine + APR-246

Cluzeau et al. JCO 2021 | Sallman et al. JCO 2021
(Ir)relevance of WHO classification in bi-allelic TP53 subset

No distinction in outcomes per WHO subtypes among cases with bi-allelic TP53/CK
bi-allelic TP53

No distinction in outcomes per WHO subtypes among cases with bi-allelic TP53/CK and across primary/therapy-related MDS
WHO defines therapy-related myeloid neoplasms as a distinct entity
Therapy-related myeloid neoplasms

Therapy-related MDS is enriched for complex monosomal karyotype, isolated -7, mutations in TP53 and in PPM1D

The role of genetic context in the outcomes of t-MDS

Diverse genetic etiology in t-MDS
Similar outcomes for primary versus t-MDS when genetic context is considered
Genetic context matters: *SF3B1*-mutant MDS

**Table 3. Proposed diagnostic criteria for the MDS with mutated SF3B1**

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Hematologic and morphology requirements
Exclusion criteria with other cytogenetics or gene mutations

Malcovati et al. Blood 2011;2015;2021
Genetic context matters: *SF3B1*-mutant MDS

 Subset of mutant-\textit{SF3B1} based on patterns of co-mutation

1. \textit{SF3B1}^{5q} (7\%)
   Concomitant isolated del(5q)

2. \textit{SF3B1}^{\beta} (15\%)
   Part of molecular classes with patterns of co-mutations with RUNX1:BCOR/L1 or STAG2

3. \textit{SF3B1}^{\alpha} (78\%)
   Isolated \textit{SF3B1} mutations simple co-mutation patterns (DTA)
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Epistatic interactions SF3B1:isolated del(5q)

Meggendorfer et al. Haematologica 2017
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Strong modulation of the favorable outcome associated with mutant \textit{SF3B1}  
with its pattern of co-mutations
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Variation of *SF3B1* VAF between subsets and association with ringed sideroblasts

Woll et al. Cancer Cell 2014
**Summary**

**UBA1** mutations frequent in MDS with no otherwise recognized driver

**NPM1** mutated MDS no different from AML

**DDX41** mutations define a distinct entity with therapeutic implications

bi-allelic **TP53** is a universal marker of aggressive disease across myeloid neoplasms

mutant-**SF3B1** is more meaningful than MDS-RS, but a role for the genetic context

Importance of genetic etiology in t-MDS
Acknowledgement

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Eva Hellström-Lindberg | Seishi Ogawa
Luca Malcovati | Mario Cazzola
Robert Hasserjian | Raf Bejar
Peter Greenberg | Ben Ebert | Heinz Tuechler

Tracey Iraca

MDS patients and families

All IWG members