Myelodysplastic Syndromes

Subjects: Others

Contributor: Valeria Visconte

The molecular pathogenesis of myelodysplastic syndrome (MDS) is complex due to high rate of genomic heterogeneity. Significant advances have been made in the last decade in elucidating the landscape of molecular alterations (cytogenetic abnormalities, gene mutations) in MDS. Seminal experimental studies have clarified the role of diverse gene mutations in the context of disease phenotypes, but the lack of faithful murine models and/ or cell lines spontaneously carrying certain gene mutations have hampered the knowledge on how and why specific pathways are associated with MDS pathogenesis.

Keywords: Myelodysplastic Syndromes ; cytogenetic abnormalities ; Genomics

1. Introduction

Myelodysplastic syndromes (MDS) are a group of disorders characterized by the dysregulation in hematopoiesis leading to uni/ multi-lineage dysplasia in the bone marrow, peripheral blood cytopenias, and increased risk of progression to acute myeloid leukemia (AML) [1][2][3]. Significant advances have been made in the last decade which elucidated the pathobiology of MDS. However, the molecular pathogenesis of MDS remains complex due to the high rate of genomic heterogeneity. The intricacy is possibly due to the interaction of genetic mutations in hematopoietic stem cells (HSCs), bone marrow milieu, and extrinsic factors e.g., dysregulated immunity and chemoradiation therapy [4][5][6]. The incidence of MDS is more common in elderly individuals, highlighting the increased risk of acquired mutations in HSCs and progenitor cells (HSPCs), which keep on accumulating with age and reach on average 5–10 mutations [7][8]. The recurrent genomic mutations affect diverse pathways such as RNA splicing, epigenetics, transcription, signaling, and metabolism [4][9].

Studies suggest that genomic aberrations in MDS are most commonly due to somatic mutations followed by chromosomal abnormalities and less often due to germline mutations [4][10][11]. In children, several rare genetic bone marrow failure syndromes predispose to an increased risk of MDS, such as Fanconi anemia, dyskeratosis congenita or telomeropathies, and Shwachman-diamond syndrome [12]. Besides, we have more evidence of increased risk of MDS with germline mutations affecting genes such as ANKRD26, CEBPA, DDX41, ETV6, GATA2, and RUNX1 [4][13]. Therapy-related MDS (t-MDS) is another spectrum of MDS attributed to the widespread of radiation therapy and treatment with high dose chemotherapy (cyclophosphamide, melphalan, busulfan, and ifosfamide), and topoisomerase II inhibitors (anthracyclines) [14][15]. This MDS subtype is frequently associated with chromosomal abnormalities/complex karyotypes [16]. Broadly, the most common genes with recurrent somatic mutations in MDS include ASXL1 (10–20%), EZH2 (5–10%), NRAS (5–10%), RUNX1 (10–15%), SF3B1 (20–30%), SRSF2 (10–15%), STAG2 (5–10%), TET2 (20–30%), TP53 (10–12%), and U2AF1 (5–12%) [4][9][11][13]. Given the high complexity of MDS, it is critical to understand the genomic landscape of patients for disease classification, risk prognostication, and response to therapies. Here, we aim to review the comprehensive genomic profiles and understand the pathobiology of MDS by giving an overview of the recent advances in the field.

2. Molecular Targeted Therapies

MDS is characterized by the occurrence of somatic mutations in several cellular pathways as previously described. Hence, these pathways and their key genes represent proposed targets for pharmacologic therapy.

Therapeutic interventions for splicing factor mutations have been based on the development of pan-splicing modulators. Bacterially derived products and analogs have shown to bind the SF3B complex and disrupt spliceosome assembly. Those compounds include a class at low (FR901463, FR901464, FR901465, herboxidienes, pladienolides) and high stability [E7107 (an analog of pladienolide B), spliceostatin A (SSA; from FR901464), and the sudemycins]. Recently, H3B-8800, a selective and orally bioavailable modulator of wild type and mutant SF3b, showed a dose-dependent modulation of splicing. H3B-8800 is a small molecule that was designed on the scaffold of pladienolide with a potency of

binding to SF3b complexes. Oral administration of H3B-8800 demonstrated preferential induction of apoptosis in several xenograft models bearing spliceosomal mutations. Data from the phase 1/2 study evaluating the pharmacokinetics/pharmacodynamics in MDS and related disorders (NCT02841540) were recently reported [17].

Luspatercept (ACE-536) is a TGF-α sequester and a suppressor of the SMAD2/3 levels that had improved response in low-grade MDS carrying SF3B1 mutations by increasing erythroid maturation and hemoglobin levels. In a double-blind, placebo-controlled, phase 3 trial in patients with very-low-risk, low-risk, or intermediate-risk MDS, 93% of the treated patients harbored an SF3B1 mutation [18].

HSC showed sensitivity to treatment with aryl sulfonamides (e.g., indisulam). In fact, drug sensitivity correlated with increased DCAF15 expression levels. Indisulam and other sulfonamides seem to induce the degradation of RBM39 (RNA binding motif protein 39), causing abnormal mRNA splicing changes such as intron retention and exon skipping [19]. Moreover, protein arginine methyltransferases (PRMTs) inhibitors (MS023, GSK591) influenced the growth of SRSF2 mutant cells [20].

Early-phase clinical trials (NCT03433781, NCT03397173) are underway to test the effects of ascorbic acid on MDS patients with TET2 deficiency in vivo. Vitamin C was reported to restore the hematopoiesis in mouse models and primary cells with TET2 deficiency [21].

Targeting IDH1/2 mutants using small-molecule inhibitors is another active area of investigation. Enasidenib (AG-221) is an oral inhibitor of IDH2 mutant proteins that are involved in the citric acid cycle and catalyze the conversion of isocitrate to α-ketoglutarate (α-KG). When IDH2 mutations occur, mutant IDH2 proteins elicit neomorphic activity that reduces α-KG to the oncometabolite (R)-2-hydroxyglutarate (2-HG). Increased 2-HG levels inhibit α-KG proteins (histone demethylases, TET family-DNA methylcytosine dioxygenases) inducing hypermethylation of histones and arresting cellular differentiation. AG-221 treatment restores 2-HG levels to normal and unblocks the differentiation of IDH2 mutant cells. Ivosidenib (AG-120) is a highly specific and reversible inhibitor of mutant IDH1 [22]. AG-120 works through the allosteric competition with the magnesium ion, which prevents the generation of a catalytically active site.

Novel therapeutic agents, mostly activators, have been generated for mutant p53. PRIMA-1Met (APR-246, APR) is an investigational small molecule which restores the conformation of p53 and rescues p53 function [23]. More recently, it was reported that low doses of APR-246 alone or with 5-azacitidine, reactivate p53 and induce apoptosis in TP53 mutant MDS and AML cell lines and primary cells [24].

Finally, allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment option; however, relapse occurs in 10–50% of patients with MDS after allo-HCT [25][26]. High-risk cytogenetics is associated with early relapse, and most relapses after allo-HCT are postulated to be due to regrowth of the pre-transplant MDS clones or emergence of new MDS clones [26]. Donor cell MDS and donor cell leukemia are a very rare and complex phenomenon and are only described in the literature as case reports and case series [27][28]. The underlying pathogenesis for donor cell MDS is unknown. Treatment options for these patients are limited and associated with poor prognosis [29]. Chromosome 7 monosomy is the most common karyotype abnormality reported in patients with donor cell MDS/DCL [30][31].

3. Conclusions

MDS is a complex disease with a fascinating origin. A plethora of molecular pathway disruptions have been postulated to explain the heterogeneity of the disease phenotype, but no exclusive genetic drivers are capable of recapitulating all its aspects. The recent advances in next-generation sequencing were crucial and hallmarked specific gene mutations that are now part of disease risk stratification and targeted therapeutic modalities. This is the case of SF3B1 mutations, as a part of the 2016 World Health Organization diagnostic criteria of MDS-RS and TP53 mutations which identify a distinct disease entity of poor prognosis. Future advancements in the understanding of MDS molecular mechanisms will further enhance the guidance of clinical decisions to help move forward into individualized therapeutic approaches.

References

1. Tefferi, A.; Vardiman, J.W. Myelodysplastic Syndromes. N. Engl. J. Med. 2009, 361, 1872–1885.
2. Nimer, S.D. Myelodysplastic syndromes. Blood 2008, 111, 4841–4851.
3. Montalban-Bravo, G.; Garcia-Manero, G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. Am. J. Hematol. 2018, 93, 129–147.

4. Sperling, A.S.; Gibson, C.J.; Ebert, B.L. The genetics of myelodysplastic syndrome: From clonal haematopoiesis to secondary leukaemia. Nat. Rev. Cancer 2017, 17, 5–19.
5. Raaijmakers, M.H.G.P.; Mukherjee, S.; Guo, S.; Zhang, S.; Kobayashi, T.; Schoonmaker, J.A.; Ebert, B.L.; Al-Shahrour, F.; Hasserjian, R.P.; Scadden, E.O.; et al. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature 2010, 464, 852–857.
6. Medyouf, H. The microenvironment in human myeloid malignancies: Emerging concepts and therapeutic implications. Blood 2017, 129, 1617–1626.
7. Magee, J.A.; Piskounova, E.; Morrison, S.J. Cancer stem cells: Impact, heterogeneity, and uncertainty. Cancer Cell 2012, 21, 283–296.
8. Welch, J.S.; Ley, T.J.; Link, D.C.; Miller, C.A.; Larson, D.E.; Koboldt, D.C.; Wartman, L.D.; Lamprecht, T.L.; Liu, F.; Xia, J.; et al. The origin and evolution of mutations in acute myeloid leukemia. Cell 2012, 150, 264–278.
9. Nguyen, P.L.; Hasserjian, R.P. 18—Myelodysplastic Syndromes. In Hematopathology, 3rd ed.; Hsi, E.D., Ed.; Foundations in Diagnostic Pathology; Elsevier: Amsterdam, The Netherlands, 2018; pp. 539–563.e2. ISBN 978-0-323-47913-4.
10. Bejar, R.; Levine, R.; Ebert, B.L. Unraveling the molecular pathophysiology of myelodysplastic syndromes. J. Clin. Oncol. 2011, 29, 504–515.
11. Ogawa, S. Genetics of MDS. Blood 2019, 133, 1049–1059.
12. Bannon, S.A.; DiNardo, C.D. Hereditary Predispositions to Myelodysplastic Syndrome. Int. J. Mol. Sci. 2016, 17, 838.
13. Bejar, R.; Greenberg, P.L. The Impact of Somatic and Germline Mutations in Myelodysplastic Syndromes and Related Disorders. J. Natl. Compr. Cancer Netw. 2017, 15, 131–135.
14. Andersen, M.K.; Christiansen, D.H.; Pedersen-Bjergaard, J. Centromeric breakage and highly rearranged chromosome derivatives associated with mutations of TP53 are common in therapy-related MDS and AML after therapy with alkylating agents: An M-FISH study. Genes Chromosomes Cancer 2005, 42, 358–371.
15. Pedersen-Bjergaard, J. Radiotherapy- and chemotherapy-induced myelodysplasia and acute myeloid leukemia. A review. Leuk. Res. 1992, 16, 61–65.
16. Smith, S.M.; Le Beau, M.M.; Huo, D.; Karrison, T.; Sobecks, R.M.; Anastasi, J.; Vardiman, J.W.; Rowley, J.D.; Larson, R.A. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: The University of Chicago series. Blood 2003, 102, 43–52.
17. Steensma, D.P.; Wermke, M.; Klimek, V.M.; Greenberg, P.L.; Font, P.; Komrokji, R.S.; Yang, J.; Brunner, A.M.; Carraway, H.E.; Ades, L.; et al. Results of a Clinical Trial of H3B-8800, a Splicing Modulator, in Patients with Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML) or Chronic Myelomonocytic Leukemia (CMML). Blood 2019, 134, 673.
18. Fenaux, P.; Platzbecker, U.; Mufti, G.J.; Garcia-Manero, G.; Buckstein, R.; Santini, V.; Díez-Campelo, M.; Finelli, C.; Cazzola, M.; Ilhan, O.; et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N. Engl. J. Med. 2020, 382, 140–151.
19. Han, T.; Goralski, M.; Gaskill, N.; Capota, E.; Kim, J.; Ting, T.C.; Xie, Y.; Williams, N.S.; Nijhawan, D. Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. Science 2017, 356.
20. Fong, J.Y.; Pignata, L.; Goy, P.-A.; Kawabata, K.C.; Lee, S.C.-W.; Koh, C.M.; Musiani, D.; Massignani, E.; Kotini, A.G.; Penson, A.; et al. Therapeutic Targeting of RNA Splicing Catalysis through Inhibition of Protein Arginine Methylation. Cancer Cell 2019, 36, 194–209.e9.
21. Cimmino, L.; Dolgalev, I.; Wang, Y.; Yoshimi, A.; Martin, G.H.; Wang, J.; Ng, V.; Xia, B.; Witkowski, M.T.; Mitchell-Flack, M.; et al. Restoration of TET2 Function Blocks Aberrant Self-Renewal and Leukemia Progression. Cell 2017, 170, 1079–1095.e20.
22. Becker, J.S.; Fathi, A.T. Targeting isocitrate dehydrogenase mutations (IDH) in AML: Wielding the double-edged sword of differentiation. Curr. Cancer Drug Targets 2020.
23. Kaur, R.P.; Vasudeva, K.; Kumar, R.; Munshi, A. Role of p53 Gene in Breast Cancer: Focus on Mutation Spectrum and Therapeutic Strategies. Curr. Pharm. Des. 2018, 24, 3566–3575.
24. Maslah, N.; Salomao, N.; Drevon, L.; Verger, E.; Partouche, N.; Ly, P.; Aubin, P.; Naoui, N.; Schlageter, M.-H.; Bally, C.; et al. Synergistic effects of PRIMA-1Met (APR-246) and Azacitidine in TP53-mutated myelodysplastic syndromes and acute myeloid leukemia. Haematologica 2019.
25. Kröger, N.; Brand, R.; van Biezen, A.; Zander, A.; Dierlamm, J.; Niederwieser, D.; Devergie, A.; Ruutu, T.; Cornish, J.; Ljungman, P.; et al. Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with

allogeneic stem cell transplantation. Haematologica 2009, 94, 542–549.

26. Yeung, C.C.S.; Gerds, A.T.; Fang, M.; Scott, B.L.; Flowers, M.E.D.; Gooley, T.; Deeg, H.J. Relapse after Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes: Analysis of Late Relapse Using Comparative Karyotype and Chromosome Genome Array Testing. Biol. Blood Marrow Transpl. 2015, 21, 1565–1575.
27. Dietz, A.C.; DeFor, T.E.; Brunstein, C.G.; Wagner, J.E. Donor-derived myelodysplastic syndrome and acute leukaemia after allogeneic haematopoietic stem cell transplantation: Incidence, natural history and treatment response. Br. J. Haematol. 2014, 166, 209–212.
28. Komrokji, R.; Ifthikharuddin, J.J.; Felgar, R.E.; Abboud, C.N.; Wedow, L.A.; Connaughton, A.; Bennett, J.M. Donor cell myelodysplastic syndrome after allogeneic stem cell transplantation responding to donor lymphocyte infusion: Case report and literature review. Am. J. Hematol. 2004, 76, 389–394.
29. Engel, N.; Rovo, A.; Badoglio, M.; Labopin, M.; Basak, G.W.; Beguin, Y.; Guyotat, D.; Ljungman, P.; Nagler, A.; Schattenberg, A.; et al. European experience and risk factor analysis of donor cell-derived leukaemias/MDS following haematopoietic cell transplantation. Leukemia 2019, 33, 508–517.
30. Farina, M.; Bernardi, S.; Gandolfi, L.; Zanaglio, C.; Morello, E.; Turra, A.; Zollner, T.; Gramegna, D.; Rambaldi, B.; Cattina, F.; et al. Case Report: Late Onset of Myelodysplastic Syndrome From Donor Progenitor Cells After Allogeneic Stem Cell Transplantation. Which Lessons Can We Draw From the Reported Case? Front. Oncol. 2020, 10, 564521.
31. Wang, E.; Hutchinson, C.B.; Huang, Q.; Lu, C.M.; Crow, J.; Wang, F.F.; Sebastian, S.; Rehder, C.; Lagoo, A.; Horwitz, M.; et al. Donor cell-derived leukemias/myelodysplastic neoplasms in allogeneic hematopoietic stem cell transplant recipients: A clinicopathologic study of 10 cases and a comprehensive review of the literature. Am. J. Clin. Pathol. 2011, 135, 525–540.