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Biology of the Bone Marrow Microenvironment and Myelodysplastic Syndromes

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Abstract

Myelodysplastic syndromes (MDS) are characterized by cytopenias resulting from ineffective hematopoiesis with a predisposition to transform to acute myeloid leukemia (AML). Recent evidence suggests that the hematopoietic stem cell microenvironment contributes to the pathogenesis of MDS. Inflammation and hypoxia within the bone marrow are key regulators of hematopoietic stem and progenitor cells that can lead to several bone marrow failure syndromes, including MDS. In this brief review, we provide an overview of the clinical and molecular features of MDS, the bone marrow microenvironment, and specific pathways that lead to abnormal blood cell development in MDS. Characterization of key steps in the pathogenesis of MDS will lead to new approaches to treat patients with this disease.

Keywords

myelodysplastic syndromes; bone marrow microenvironment; signaling pathways; hypoxia; ribosomal deficiency; inflammation

Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis in the bone marrow leading to cytopenias in the blood and a predisposition to acute myeloid leukemia (AML) (1–4). The categorization of subclasses of MDS is based on the percentage of leukemia blasts in the peripheral blood and

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the bone marrow, the number and type of dysplastic cell lineages, the presence of ringed sideroblasts, and cytogenetic abnormalities. Low, intermediate or high-risk MDS is classified using the revised International Prognostic Scoring System (5, 6). The majority of MDS patients are diagnosed at greater than 70 years of age. A number of factors including environmental, genetic and prior exposure to chemotherapy or radiation therapies are associated with the development of MDS (7). In addition, there are a number of inherited bone marrow failure syndromes including Fanconi anemia (FA), Shwachman-Diamond syndrome (SDS), and dyskeratosis congenital (DC) that often develop during childhood and predispose patients to the development of MDS at an early age (7, 8).

A variety of morphological, genetic, and clinical features have been identified that distinguish pediatric MDS from adult MDS and have been previously discussed in detail (9). Although relatively uncommon in children, de novo and secondary MDS is often the first presentation of an inherited bone marrow failure syndrome. Unlike in adults, pediatric MDS is more often associated with monosomy 7 and a hypocellular bone marrow. Refractory cytopenia is more common than refractory anemia, which is seen in the elderly (9). Thus, there are biological and clinical aspects of pediatric MDS that are different from adult MDS.

Significant advances have been made to understand the pathogenesis of MDS to explain the spectrum of this disease. In addition to cytogenetic abnormalities including del(5q), −7 or del(7q), and +8, defects have been identified in RNA splicing machinery, epigenetic regulation of gene expression, and specific signaling pathways, including p38 Mitogen Activated Protein Kinase (MAPK) and Tissue Necrosis Factor alpha (TNFalpha) (3). Somatic mutations have been identified in hematopoietic stem cells from MDS patients and most likely contribute to the pathogenesis of the disease. Approximately 80% of MDS patients have a somatic mutation in their hematopoietic stem cells. Mutations in p53, EZH2, ETV6, RUNX1, and ASXL1, in MDS patients have been associated with a poor prognosis (4). In particular, p53 mutations predict patients who will progress to AML.

Treatment of MDS depends on the severity of the disease. For low-risk MDS, supportive care has been the primary mode of treatment, including growth factors, transfusions, and antibiotic therapy (4). For high risk disease, hypomethylating agents (decitabine and 5-azacytidine), immunomodulatory drugs (lenalidomide), and chemotherapy (daunomycin, cytarabine) are often used. High dose chemotherapy and stem cell transplantation can produce long-term remission in high-risk MDS patients.

Bone marrow microenvironment and MDS

The bone marrow is comprised of hematopoietic stem cells (HSC) existing within a complex and dynamic microenvironment with multiple cellular and molecular factors that regulate hematopoiesis under physiologic and pathophysiologic conditions. The delicate interplay between the hematopoietic stem and progenitor cells, stromal cells, and cytokines or chemokines secreted within the microenvironment is needed to maintain hematopoiesis. Multiple cellular components of the bone marrow microenvironment including osteoblasts/osteoprogenitor cells, vascular endothelial cells, mesenchymal stem cells, monocytes, and macrophages support the hematopoietic stem cell niche (for a recent review (10)). It is likely

that aberrant interactions between hematopoietic stem cells and the microenvironment also contribute to the pathogenesis of MDS. Indeed genetic studies in mice have shown that manipulation of the osteoblastic niche is sufficient to promote MDS and AML phenotypes. Genetic disruption of DICER, an RNAase III endonuclease that is essential for miRNA biogenesis and RNA processing resulted in the development of myelodysplasia and AML progression (11). Interestingly, microarray analysis of dysregulated gene expression in DICER deficient osteoblasts revealed significant down regulation of the Shwachman-Diamond-Bodian Syndrome gene (Sbds). Inactivating mutations in Sbds are associated with both skeletal abnormalities as well as bone marrow failure and a predisposition to develop MDS and AML (12). These findings indicate that dysregulation of Sbds in cells of the osteoblastic lineage may contribute to the pathogenesis of SDS. Further evidence to support a role for cells in the osteoblastic lineage in the pathogenesis of MDS was observed in mice with a single activating mutation of B-catenin in osteoblasts. These mice accumulated common chromosomal aberrations in myeloid cells as well as MDS features and the rapid development of AML (13). In this model, constitutive activation of beta-catenin in osteoblasts lead to increased expression of the Notch ligand, Jagged-1 that activated Notch signaling in HSCs. Importantly, nuclear accumulation and increased beta-catenin signaling in osteoblasts was also identified in 38% of patients with MDS/AML suggesting that this model may recapitulate cellular and molecular features within a subset of MDS/AML patients (13). In addition to murine models of MDS/AML, patient-derived bone marrow stromal cells have also been shown to promote the malignant behavior of human MDS cells *in vivo*. While human MDS cells injected into mice intrabone results in very little engraftment of the stem cells (14), co-injection of MDS cells with MDS MSCs significantly enhanced the engraftment rate of MDS cells within the bone marrow of immunocompromised mice (15). Previous studies have demonstrated that expression of CD146 on stromal cells is associated with enhanced engraftment of MDS cells. Additionally, overproduction of niche factors including N-Cadherin, IGFBP2, VEGFA, and LIF were also associated with the enhanced engraftment mediated by patient derived MDS MSC cells (14, 15). Despite the advances in this field, very little is known regarding the molecular basis of interaction between MDS cells and specific stromal cells in humans that could lead to development of dysplasia in the bone marrow.

Hypoxia and MDS

In addition to the cellular components of the HSC/MDS niche mentioned above, hypoxia, or low oxygen availability, is a prominent molecular feature of the bone marrow microenvironment that contributes to both normal and malignant hematopoiesis. Relative to most tissues, the bone marrow resides in a particularly hypoxic microenvironment. Oxygen tensions within the bone marrow cavity range from 0.6% to 4.2% O_2, whereas oxygen tensions in most other adult tissues range from 2–9% O_2 (16, 17). Hypoxia develops as a result of an imbalance between oxygen delivery and oxygen consumption. The bone marrow is thought to be particularly hypoxic tissue due to the low blood flow rate within bone marrow sinusoids and the high oxygen consumption rate of hematopoietic cells. It is estimated that the blood flow rate within bone marrow sinusoids is 1/10 to 1/20 of that found within bone marrow arterioles (18). In addition, it has been estimated using mathematical

modeling that a layer of three myeloid progenitors is sufficient to utilize all oxygen delivered by a neighboring sinusoid cell (19).

The hypoxia inducible transcription factors HIF-1 and HIF-2 are the key molecular mediators of the cellular response to hypoxia. In response to oxygen tensions below 5% O_2, the transcription factors HIF-1 and HIF-2 are stabilized and activate gene expression programs including angiogenesis, glycolytic metabolism, erythropoiesis, differentiation and apoptosis that help cells adapt to low oxygen (20). While HIF-1 and HIF-2 bind similar target DNA sequences, they have both overlapping and distinct functions (21, 22).

Recent studies have defined an important functional role for hypoxia and HIF signaling in the regulation of HSC metabolism and maintenance. In particular, HIF-1 is highly expressed in HSCs where it regulates glycolytic metabolism (23). Genetic inactivation of HIF-1 in HSCs resulted in loss of cell cycle quiescence and decreased HSC numbers during stress conditions of bone marrow transplantation, myelosuppression, and aging (24). In contrast, loss of HIF-2 in HSCs had no significant effect on HSC maintenance or post-transplantation renewal indicating a predominant role for HIF-1 in the maintenance of HSC function (25).

Hypoxia and activation of HIF signaling is also associated with the development and pathogenesis of a variety of hematologic diseases (26–30). In MDS patients, HIF-1 expression correlates with poor patient survival and disease progression (31). Functionally, the role of HIF signaling in MDS remains to be elucidated. However, studies indicate that there may be both direct and indirect roles for hypoxia and HIF signaling in the pathogenesis of MDS. In vitro assays have demonstrated that culturing MDS cells in hypoxic conditions enhances the colony-forming unit (CFU) yield from MDS mononuclear cells (32). Additionally, gene expression profiling of supportive MDS MSCs in comparison to healthy MSCs revealed a strong hypoxic signature indicating that hypoxia and HIF signaling may also influence the malignant behavior of MDS MSCs (15). Future studies are needed to carefully dissect the role of HIF signaling within both MDS and key supportive cells of the MDS niche.

Inflammation and Immune Suppression in MDS

The role of inflammation and immune suppression is becoming increasingly recognized as an important factor in the pathogenesis of bone marrow failure syndromes, including MDS, DBA, and FA (33, 34). Dysregulation of cytokine expression in MDS bone marrow contributes to suppression of both ineffective hematopoiesis and malignant clone immune escape. The expression of TNFalpha, TGFbeta, IFNgamma, IL-4, IL-6, IL-7, and IL-10 are abnormally regulated in some MDS patients (1, 35)., TNFalpha has been implicated as a factor contributing to the increased apoptosis of stem cells in MDS, DBA and FA patients (33, 34). Additionally, TNFalpha, TGFbeta, and IFNgamma exhibit myelosuppressive activities within MDS marrow (36). IL-10 is an immunosuppressive cytokine is elevated in CD3+ peripheral blood cells in high risk compared to low risk MDS patients (37, 38). Polymorphisms within the IL10 promoter are also present associated with poor patient prognosis in MDS patients, further indicating a role for IL10 in the pathogenesis of MDS (39).

Recent studies have began to identify key cellular components of the MDS bone marrow microenvironment that contribute to altered cytokine production, the development of ineffective hematopoiesis, and immune escape in MDS patients. Chen and colleagues discovered that myeloid-derived suppressor cells (MDSCs) are expanded in MDS patients and can actively suppress hematopoiesis through the production of IL-10 and TGFbeta (40). In addition to myeloid suppressor cells, regulatory T cells (Tregs) are also expanded in MDS patients. The activation of Treg cells in MDS is thought to promote immune tolerance and allow for the expansion of blasts harboring genetic mutations (41, 42). Along with the increase in suppressive immune populations, patients with high risk MDS also exhibit impaired natural killer (NK) cells function and expansion of autoreactive CD8+ T cells (43).

There is now significant evidence that activation of the innate immune system, e.g. macrophages and neutrophils, contributes to HSC senescence and MDS pathogenesis (1). Signaling pathways of the toll-like receptors (TLRs) are among the important mediators of the inflammatory response. TLR4 is overexpressed in MDS HSCs, which leads to apoptosis and cytopenias (44). Increased TLR1, 2, and 6 and downstream immune modulating kinase IRAK1 have also been reported in MDS HSCs. There are now inhibitors of IRAK1 that have been demonstrated to induce cell cycle arrest and apoptosis of the MDS HSCs *in vitro* (1, 45). Several other immune signaling molecules downstream of TLRs such as TRAF6 and NFκB have also been shown to mediate the proinflammatory response and have increased activation in low- and high-risk MDS stem cells (1, 46).

Proinflammatory signaling pathways have recently been shown to be critical for normal hematopoietic stem cell fate (47, 48). In zebrafish, TNFalpha signaling through TNFR2 expressed on HSCs resulting in activation of the Notch and NFkappaB signaling pathways is required for definitive but not primitive hematopoiesis (47). Interestingly, TNFalpha is produced by neutrophils in the microenvironment, not macrophages or monocytes suggesting the innate immune systems plays a crucial role in HSC production. Another study demonstrated that interferon-gamma (IFNgamma) and its receptor Crfb17 regulates HSC development in zebrafish (49). IFNgamma does not regulate HSC proliferation or survival, but rather transition from endothelial cells to HSCs in the hemogenic endothelium or aorta-gonad-mesonephros region. IFNgamma appears to activate Stat3 signaling pathways downstream of Notch and blood flow to regulate HSC fate (49). Therefore, inflammatory signals are not only critical for pathogenesis of MDS, but also for normal HSC development (48).

Ribosomal deficiency, MDS, and inflammatory response

One of the most common chromosomal abnormalities in adult MDS is (del)5q. Somatic chromosomal deletions in 5q leads to the development of MDS that is characterized by a defect in erythroid differentiation. Ebert et al. employed an siRNA approach to identify downregulated genes that would phenocopy the hematopoietic defects associated with 5q deletion. These studies revealed that partial loss of the ribosomal protein subunit 14 (RPS14) was sufficient to phenocopy the disease in hematopoietic progenitor cells. Moreover, RSP14 expression was sufficient to rescue the erythroid defect in patient derived progenitors (50). The mechanism by which RSP14 regulated erythroid differentiation was linked to a defect in

the processing of pre-RNA (50). Interestingly, this defect was analogous to the ribosomal biogenesis defects found in Diamond-Blackfan Anemia (DBA) providing a functional link between MDS in somatic 5q del with a congenital bone marrow failure syndrome (50). Indeed, inherited mutations in several other proteins involved in ribosomal synthesis are associated with the development of pediatric bone marrow failure syndromes including Diamond-Blackfan Anemia (DBA), SDS, dyskeratosis congenital, and cartilage hair hypoplasia (51, 52).

DBA is characterized by a selective erythroid defect leading to anemia at an early age in childhood (53). In 1999, mutations in the ribosomal protein subunit, RPS19, was first described in patients with DBA (54). Approximately 25% of patients with DBA have mutations in RPS19. We recently described that knockdown of RPS19 in cord blood CD34+ cells results in decreased GATA1 protein levels and increased TNFalpha production by CD71+ (nonerythroid) cells including stromal cells, such as macrophages (33). The induction of TNFalpha was mediated by p53 activation and phosphorylation of p38 Mitogen Activated Protein (MAP) kinase. The erythroid defect was corrected *in vitro* by treatment with TNFalpha (33). This was the first report linking ribosomal deficiency to inflammatory responses in human hematopoietic stem and progenitor cells. In addition, these data suggest that perhaps other bone marrow failure syndromes, including RPS14 deficient del(5q) MDS, could lead to stress hematopoiesis that activates p53 and p38MAPkinase, and decreased levels of GATA1. The precise mechanism by which ribosomal insufficiency in hematopoietic stem and progenitor cells produces inflammation is not known and is a focus of investigation in the future.

Targeting the microenvironment for treatment of MDS

Several approaches to decrease inflammation in the bone marrow of MDS patients have been taken. Unfortunately, immune modulators have variable responses in MDS patients. Antithymocyte globulin and cyclosporine alone or in combination have responses between 0 and 30% (1). One study showed that lenalidomide is effective in 83% of patients with del(5q) MDS, while hypomethylating agents seem to be more effective in MDS patients with greater numbers of blasts in the bone marrow (55). An obvious approach to treating MDS would be to target TNFalpha or its receptor. In one pilot study with 12 MDS patients treated with Etanercept, four patients had improvement in their blood counts or transfusion requirements while others had decreased cell counts. Although baseline TNFalpha levels did not correlate with response, the HSCs from these patients showed an increase in myeloid progenitor cells *in vitro* (56). Clearly, more studies are required to determine the optimal administration or MDS patient populations who might respond to Etanercept (2). The TNFalpha antibody, infliximab, treatment in low-risk MDS patients yielded a low response rate (3/22 patients compared to 0/21) (57). Thus, TNFalpha blockade alone may not be optimal therapy for MDS patients. Other components of the microenvironment that are potential targets for therapy include Dicer, where targeted deletion of Dicer in the osterix-expressing osteoprogenitor cells affected proliferation, survival, and differentiation of HSCs of MDS patients (1, 58). Greater understanding of the relationship between inflammation in the bone marrow microenvironment of MDS patients and their HSCs will provide novel approaches to treat this disease.

Based on mechanistic studies, several signaling pathways to target the microenvironment to treat MDS patients have been identified. Recently the RPS19 and RPS14 deficient HSCs were demonstrated to be responsive to the amino acid and translational enhancer, L-Leucine, by activating the mTOR pathway (59). P38 MAP kinase is constitutively activated in MDS HSCs and an inhibitor of the p38MAPK alpha isoform increases proliferation of MDS stem cells *in vitro.* A Phase I/II clinical trial for low- and intermediate-risk MDS with the small molecule, SCIO-469, demonstrated a 30% response in cytopenia (2). Another p38MAPK inhibitor known as ARRY-614 also targets the Tie-2 ligands are overexpressed in MDS patients and are associated with a worse prognosis (36). A phase I study of ARRY-614 demonstrated decreased platelet transfusion requirements in a subset of patients with low- and intermediate-risk MDS (60). Correlative studies demonstrated decrease in p38MAPK activation and apoptosis in the bone marrow cells from MDS patients who responded. Additional targeted therapies have been developed for TGFbeta ligand Activin (2). A ligand trap developed for TGFbeta receptor, ACE-536, stimulates erythropoiesis in preclinical studies and is presently in phase I/II clinical trials for MDS (61). Sotatercept is a fusion protein of Activin receptor type IIa and IgG, inhibits SMAD2/3 signaling (62, 63). Clinical trials with other multi- kinase inhibitors and mTOR inhibitors, e.g. tensirolimus, for MDS patients are currently in progress. MEK inhibitors, farnesyl transferase inhibitors, EGF inhibitors, glutathione-S-Transferase-1 inhibitors are all under investigation (2).

In conclusion, the bone marrow microenvironment plays a critical role in the fate of HSCs and contributes to the pathogenesis of MDS. Recent work has demonstrated that key cellular factors within the bone marrow microenvironment including cells of the osteoblast lineage, immune, and mesenchymal stromal cells produce signaling molecules that promote the initiation and progression of MDS (Figure 1). Hypoxia in the bone marrow also controls normal hematopoiesis and when altered likely contributes to the pathogenesis of MDS (Figure 1). Future studies will be necessary to better define the interactions between stromal cells, cytokines/chemokines, and their specific effects on HSC proliferation, survival, and differentiation. This information will be crucial for development of novel therapies to treat MDS.

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Research Highlights

The bone marrow microenvironment plays a critical role in the pathogenesis of MDS.

Characterization of molecular pathways that contribute to MDS could lead to identification of novel approaches to treat MDS.

Inflammatory signals in the bone marrow determine hematopoietic stem cell fate and are aberrantly regulated in MDS hematopoietic stem cells.

Hypoxia is important for normal hematopoietic stem cell development and potentially plays a role in MDS.

Dysregulation of inflammatory signaling, including upregulation of TNFalpha, is associated with the development of acquired and inherited bone marrow failure syndromes. Dysregulation of inflammatory signaling contributes to the pathogenesis of MDS through both direct mechanisms on HSCs and by altering the bone marrow microenvironment.

Several targeted therapies have been developed, which inhibit molecules that are abnormally regulated in MDS patients.

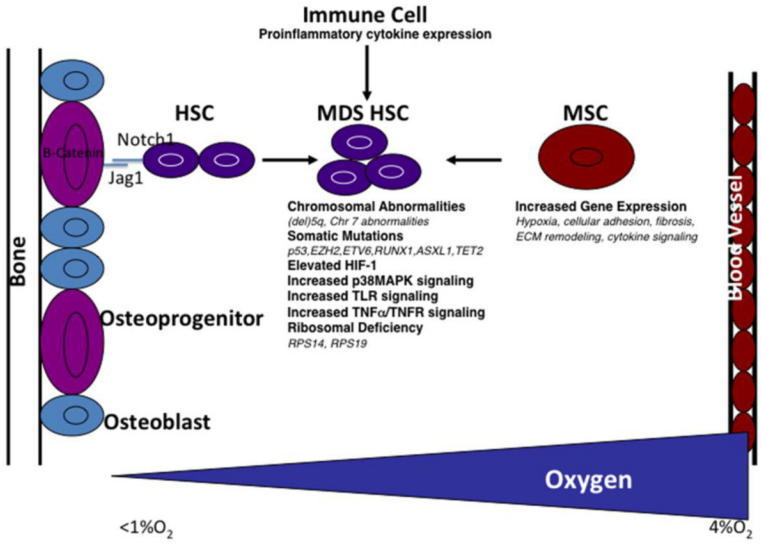

Figure 1. Cellular and molecular mechanisms of MDS

Immune cells, osteoblasts, and mesenchymal stromal cells (MSCs) express signaling molecules that influence MDS HSC signaling and function. Hypoxia also has the capacity to directly and indirectly influence the behavior of MDS HSCs.