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Minireview

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.

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Contents

1. 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 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 are 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

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in children, de novo and secondary MDS are often the first presentation of an inherited bone marrow failure syndrome. Unlike in adults, pediatric MDS are 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.

2. Bone marrow microenvironment and MDS

The bone marrow is comprised of hematopoietic stem cells (HSCs) 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.

3. 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.

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