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Review Article

Unraveling the mechanisms behind iron overload and ineffective hematopoiesis in myelodysplastic syndromes

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ABSTRACT

Myelodysplastic syndromes (MDS) are a group of clonally-acquired blood disorders characterized by ineffective hematopoiesis leading to cytopenias. Red blood cell transfusions are an important component of supportive care in patients with MDS. Prolonged exposure to transfusions can lead to iron overload, which results in iron-induced toxicity caused by the production of reactive oxygen species (ROS). ROS accumulation has detrimental effects also on hematopoietic stem cells and may contribute to MDS progression. The observation that iron chelation improves hematologic parameters and reduces transfusion dependence further indicates that iron overload impairs hematopoiesis. Over the past decade, the mechanisms regulating iron homeostasis and the complex interplay between iron overload and toxicity, ineffective hematopoiesis, and transformation to leukemia have become clearer. In this narrative review, we provide an overview of recent findings pertaining to iron overload in patients with MDS and its effects on hematopoiesis. We also briefly discuss the position of chelation therapy in the context of the new developments.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonally acquired blood disorders characterized by bone marrow failure and a variable tendency to progress to acute myeloid leukemia (AML) [1–3]. According to the 2016 revision of the World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues, MDS are classified based on the evaluation of peripheral blood and bone marrow morphology, cytogenetic and molecular analysis. Categories include: MDS with single lineage dysplasia, MDS with ring sideroblasts, MDS with multilineage dysplasia, MDS with excess blasts, MDS with isolated del(5q), and unclassifiable MDS [1]. Several mechanisms are involved in the pathogenesis of MDS, including acquired somatic mutations, cytokine abnormalities, immune dysregulation, changes in the bone marrow microenvironment, altered RNA splicing, telomere erosion and dysfunction, and epigenetic alterations [4]. Somatic mutations in genes involved in pre-messenger RNA (mRNA) splicing have been described in more than 50% of patients with MDS [3,4]. The gene encoding splicing factor SF3B1 is the most frequently mutated gene in patients with MDS (20–28% of all cases) [5]. SF3B1 mutations have been shown to be significantly associated with a disease phenotype, characterized by the presence of ring sideroblasts (erythroblasts with iron-loaded mitochondria) [6]. SF3B1 mutations occur more frequently in low-risk MDS and are independent predictors of better overall survival and lower risk of evolution to AML [6]. MDS are characterized by ineffective hematopoiesis leading to peripheral blood cytopenias, with anemia being the most frequent [7]. Supportive care including red blood cell (RBC) transfusion is frequently necessary in anemic patients; however, prolonged exposure to RBC transfusions results in the accumulation of iron, which is due to the absence of a specific mechanism for iron excretion in humans [8]. Ineffective hematopoiesis also contributes to increased iron accumulation [8]. In patients with thalassemia, excess iron is associated with increased morbidity and mortality, caused by iron loading into cardiac, hepatic,

Abbreviations: GDF11, growth differentiation factor 11; LCI, labile cellular iron; NTBI, non-transferrin-bound iron

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and endocrine tissues [8,9]. The toxic effects of iron are due to the production of reactive oxygen species (ROS) catalyzed by Fe^{2+}. Iron overload and ROS have also been shown to have detrimental effects on bone marrow stroma and hematopoietic stem cells, which can further impair hematopoiesis [10–12]. The notion that excess iron has detrimental effects on hematopoiesis is supported by the observation that effective iron chelation therapy in iron-overloaded MDS patients in some instances improves peripheral blood counts and reduces transfusion dependence [13–17]. However, the exact mechanisms underlying these effects and their reversal by iron chelation therapy have not been fully elucidated.

In recent years, important advances have been made in our understanding of iron homeostasis and MDS pathogenesis. These are likely to change and improve the therapeutic approach to these complex diseases. In this narrative review, we provide an overview of our current understanding of iron overload in transfusion-dependent patients with MDS and its effects on hematopoiesis; we also briefly review the evidence supporting the role of iron chelation in hematologic improvement. Recent developments in the field of MDS are discussed in an attempt to define their implications for the management of iron overload in patients with MDS.

2. Iron overload in MDS

Although most data come from studies in ß-thalassemia, recent advances have contributed to improving our understanding of the mechanisms underlying iron overload in MDS. Repeated RBC transfusions are the main cause of iron accumulation in MDS. Other factors contributing to iron overload include: ineffective erythropoiesis with associated anemia; increased gastrointestinal iron absorption; and inconsistent but generally reduced production of hepcidin, the major regulator of iron export from cells into the plasma [18].

2.1. Red blood cell transfusion-induced iron overload

In normal conditions, iron homeostasis is maintained by enterocytes controlling iron dietary uptake and macrophages recycling iron from erythrocytes. The mechanisms involved in iron homeostasis have been comprehensively reviewed elsewhere [8,19]. At the cellular level, such control is ensured by the tight regulation of the production and function of proteins involved in iron transport and metabolism. Transferrin is the main plasma iron transporter and its saturation is an important sensor of systemic iron. Under normal conditions, transferrin-bound iron is the main source of iron available to cells. In the cytosol, free iron, referred to as labile cellular iron (LCI), binds ferritin, a storage protein that stores iron in the non-toxic Fe^{3+} form and whose main function is to protect cells from iron toxicity. LCI is exported to the plasma via ferroportin, the only known cellular iron exporter. Ferroportin is the target of hepcidin, a peptide hormone produced by the liver that acts by inducing the internalization and degradation of ferroportin [20]. Hepcidin is the primary negative regulator of iron export from cells into the plasma. In conditions of iron deficiency, hepcidin levels are very low, leading to increased transport of iron via ferroportin from enterocytes and macrophages into the plasma. In the presence of iron overload, hepcidin levels are elevated. This results in decreased dietary iron absorption by enterocytes and decreased release of cellular iron into the plasma.

Repeated RBC transfusions result in iron overload, as physiologic mechanisms for the excretion of iron are not present in humans. When senescent endogenous or transfused RBC are phagocytised by reticuloendothelial macrophages, hemoglobin is degraded and iron is exported into the plasma via ferroportin, to be recycled for hemoglobin production. In the plasma, iron binds to transferrin which, under normal conditions, is saturated with iron by up to 30%. In the presence of iron accumulation in the plasma, due to repeated transfusions and ineffective erythropoiesis, transferrin saturation increases. When it reaches 70–80%, non-transferrin-bound iron (NTBI) serum levels significantly increase [21]. A fraction of NTBI, referred to as labile plasma iron (LPI), is poorly bound to protein and is redox-active. During controlled iron homeostasis, iron enters cells bound to transferrin, via the transferrin receptor 1. This receptor is expressed in most cells; however, its expression is higher in cells and tissues with higher iron requirements, such as liver and erythroid precursors. When transferrin saturation is elevated, iron begins to enter cells through transferrin-independent routes (ion channels and transporters), which, unlike the transferrin receptor 1-mediated route, are not tightly controlled by cellular iron levels; this leads to increased levels of toxic LCI. Transferrin-independent entry of NTBI/LPI has also been described in erythrocytes, reticulocytes and erythroid precursors under elevated NTBI plasma levels [22]. Of relevance, these forms of iron do not contribute to the synthesis of heme [22].

2.2. Contribution of ineffective erythropoiesis to iron overload

Elevated transferrin saturation has been reported in non-transfused patients with MDS before erythroid failure leading to transfusion dependence [2,23,24]. In patients with MDS, iron accumulation is self-sustained because iron released from macrophages upon hemoglobin degradation is inadequately used, and increased bone marrow activity driven by ineffective erythropoiesis and anemia results in hepcidin suppression and increased iron absorption [8,12,25]. Evidence from ß-thalassemia suggests that the decrease in hepcidin mediated by increased marrow activity prevails over the increase in hepcidin associated with excess iron [8,12].The existence of an “erythroid factor” regulating iron metabolism has been suggested. Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-ß (TGF-ß) super-family that suppresses hepcidin production by liver cells and is regarded as a potential candidate for this regulatory role [26]. However, a correlation between GDF-15 and hepcidin in MDS has not been conclusively demonstrated and mechanisms of hepcidin suppression may be disease-specific [8,12,18]. In this regard, it should be noted that serum hepcidin levels in patients with MDS have been found to vary considerably across MDS subtypes [18]. The lowest hepcidin levels were reported in patients with refractory anemia with ring sideroblasts (RARS, or MDS with ring sideroblasts according to the WHO 2016 classification) and the highest in refractory anemia with excess blasts (RAEB, or MDS with excess blasts according to the 2016 WHO classification).

3. Effects of iron overload on hematopoietic cells

Iron toxicity is mediated by the production of ROS. Increased oxidative stress has been implicated in cell senescence and malignant transformation. Iron excess and oxidative stress cause disturbances in the hematopoietic niche that result in impaired hematopoiesis.

3.1. Iron overload causes oxidative damage

Iron-induced oxidative stress is mainly caused by hydroxyl radicals produced in the reaction of Fe^{2+} with H_2O_2. The hydroxyl radical is a potent oxidant that reacts with most cellular components including DNA, thereby causing permanent damage to cells and their genetic material. The extent of iron-induced oxidative damage varies considerably among MDS subtypes and among patients with the same disease subtype and same degree of iron overload; this suggests that beside tissue iron concentration, other factors are involved, such as genetic and environmental factors, and the duration of the exposure to oxidative stress [8].

Among the possible mechanisms underlying ROS-mediated iron toxicity relevant for the development and progression of MDS, telomere erosion leading to genome instability, aneuploidy and malignant transformation has been extensively studied [27]. In a retrospective