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Invited review

Bone marrow niche in the myelodysplastic syndromes

Christopher R. Cogle[a], Najmaldin Saki[b,*], Elahe Khodadi[b], June Li[c], Mohammad Shahjahani[b], Shirin Azizidoost[b]

[a] Division of Hematology and Oncology, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, USA
[b] Health Research Institute, Research Center of Thalassemia & Hemoglobinopathy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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ABSTRACT

The myelodysplastic syndromes (MDS) are a diverse group of clonal hematopoietic malignancies characterized by ineffective hematopoiesis, progressive bone marrow (BM) failure, cytogenetic and molecular abnormalities, and variable risk of progression to acute myeloid leukemia (AML). The BM microenvironment in MDS plays an important role in the development of this disorder. The BM stromal cells of MDS patients often harbor distinct chromosomal aberrations than the hematopoietic elements, suggesting different genetic origins. Perturbed cytokine secretions from BM stromal cells such as multipotent mesenchymal stem cells (MSCs) and endothelial cells are associated with increased proliferation and survival of malignant hematopoietic cells. Within the MDS BM there are also alterations in stromal cell composition, signaling and angiogenesis between Low- and High-risk MDS patients. Several open lines of investigation into the MDS niche remain, including the timing of stromal defects in context to dysplastic hematopoiesis. Another important, unanswered question is the impact of age on BM stroma function and regulation (or dysregulation) or hematopoietic stem/progenitor cells. With a better understanding of the MDS niche, new therapeutic strategies will emerge.

Contents

1. Introduction

The myelodysplastic syndromes (MDS) comprise a group of clonal hematological malignancies resulting in bone marrow (BM) failure and increased risk for progression to acute myeloid leukemia (AML) [1,2]. Next generation DNA sequencing of hundreds of MDS patients has revealed that MDS is a highly heterogeneous multigenetic disease with sub clonal architecture [2,3]. Recent studies of the general population found that 5–10% of older, apparently healthy individuals had acquired ≥1 myeloid gene mutation, whereas younger individuals were much less likely to have acquired clonal hematopoiesis with somatic mutations [4,5]. Together, these results support the notion that the origin of MDS is tied to cellular senescence and provide biological rationale for why MDS most often presents in the seventh and eight decades of life [6,7]. Clinically, MDS is often diagnosed after recognizing

* Corresponding author. Tel.: +98 9161133369; fax: +98 6133738330.
E-mail address: najmaldinsaki@gmail.com (N. Saki).

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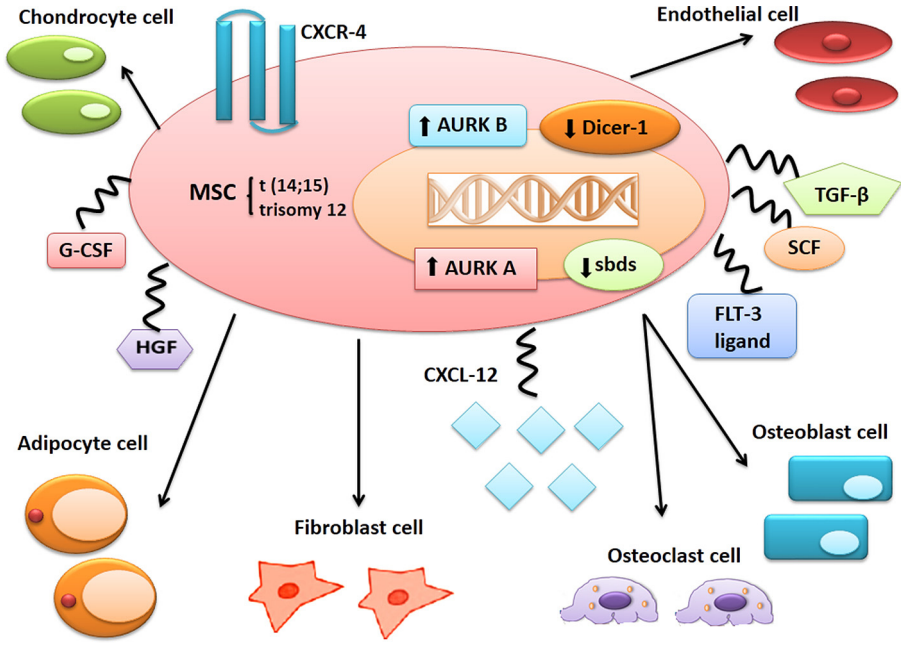

Fig. 1. *The role of MSCs in MDS BM niche.* MSCs are crucial cells in B.M niche. These cells can differentiate to osteoblast, osteoclast, adipocyte, chondrocyte and epithelial cells that are the main cells involved in hemtopoietic microenvironment. Up regulation or down regulation of molecules involved in hematopoiesis in MSCs can lead to the proliferation and survival of malignant HSCs. **Abbreviation:** MSC, mesenchymal stem cell; AURK A,B, Aurora kinases; HGF, Hepatocyte growth factor; TGF-β, tumor growth factor-β; CXCL-12, Chemokine (C-X-C Motif) Ligand 12; CXCR-4, Chemokine (C-X-C Motif) Receptor 4; Dicer1, Double-Stranded RNA-Specific Endoribonuclease; sbds, Shwachman–Bodian–Diamond syndrome; FLT-3 ligand, Fms-Related Tyrosine Kinase 3 ligand; SCF, Stem cell factor; G-CSF, growth colony stimulating factor.

symptoms related to BM failure and cytopenias (e.g. fatigue, pallor, infections, bruising, bleeding). MDS has a multi-step pathogenic process. Early stages of the disease (Low to Intermediate-risk MDS) harbor rare, multipotent stem cells with somatic genomic mutations [1,2]. This clone is associated with dysplastic hematopoiesis, excessive release of myelosuppressive cytokines, defective differentiation and genomic instability. MDS transformation to AML is a result of continuation of this process, hypermethylation, silencing of tumor suppressor genes (e.g. p15) and activation of oncogenes (e.g. Ras) [2]. Although the MDS BM is hyperproliferative, the net balance is ineffective hematopoiesis due to increased apoptosis of malignant progenitors. Apoptosis in progenitor cells is increased due to cell-intrinsic signals like BCL-2 family proteins, but BM niche signaling also promotes apoptosis via TNF-α, Fas ligand, and TGF-β [1,3].

Whereas the majority of current MDS studies focus on genetic and epigenetic events required for normal HSC transformation into malignant hematopoietic cells, there is mounting evidence of a BM niche-based model for MDS genesis that predisposes normal HSCs to genomic mutations [4,5].

In normal hematopoiesis, the BM niche controls hematopoietic cells via paracrine regulation, cell–cell contact and extracellular matrix (ECM) deposition. Within the BM niche, multipotent mesenchymal stromal cells (MSCs) serve an important role in regulating HSC self-renewal and differentiation [6–8]. Other important BM stromal cells include osteoblasts, osteoclasts, endothelial cells, fibroblasts, adipocytes and chondrocytes (Fig. 1) [9,10]. Close cooperation between the BM niche and HSC balances the dynamic needs for hematopoiesis and tissue turnover [9,11].

As for the MDS niche, the picture is ill-defined. However, emerging data provide enough concepts to allow for a framework of understanding. In a most basic frame, a cluster of atypical located immature precursors (ALIPs) physically and chemically interact with a unique orchestration of BM stromal elements (Fig. 2) [6,7,12].

In terms of paracrine regulation by BM stroma, the MDS niche is rife with myelotoxic cytokine imbalances compared to normal BM (Table 1) [13]. Not only do the imbalances in cytokine release depress hematopoiesis, they further perturb BM angiogenesis, ECM deposition, facilitate progressive genomic instability and contribute to the immune evasion of MDS cells [14].

2. MSCs in MDS BM niche

MSCs serve important roles in hematopoiesis and immune regulation. Several studies have indicated that impaired MSCs propagate MDS [8]. Among the MSC impairments is altered expression of Aurora kinases genes (AURK). AURKs are mitotic kinases with an important role in the regulation of G2/M phase of cell cycle, centrosomes and cytokinesis. Upregulation of AURK in cells causes dysregulation of mitosis and meiosis, which results in increased ontogenesis [14,15]. Recent studies have indicated the role of AURK A and AURK B upregulation in MSCs in MDS development. Aurora-A gene is located on 20q13.2 chromosome. The expression level of AURK mRNA is highly increased in MSCs in MDS patients. Dysregulated expression of AURK leads to increased number of centrosomes, gain or loss of chromosomes causing cell death in normal cells and survival of malignant cells [16–18]. However, upregulation of AURK A is not sufficient for disease transformation to AML, and further cytogenetic and chromosomal rearrangements as well as Ras signaling are needed. The latter in turn activates mitogen-activated protein kinase pathway (MAPK) and causes malignant transformation. AURK A upregulation phosphorylates p53, reducing its stability, increasing transcription and thus enhancing the proliferation of malignant cells [17–19]. AURK B is located on 17p13.1 chromosome. Although the overexpression of AURK B has been demonstrated in MSCs, it is not known how this upregulation affects the development of malignant cells (Table 1) (Fig. 1) [16,19].

Studies show that although HSCs and MSCs undergo changes in response to induction factors like TNF-α, Fas and TGF-β in the BM niche of MDS, they do not originate from the same neoplastic clone, and this supports the notion that that these two cell types may bear different chromosomal disorders [1,3,15]. In fact, within the