Review Article

Stem Cell INVESTIGATION

Mesenchymal stem cells in pathogenesis of myelodysplastic syndromes

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Abstract: Myelodysplastic syndromes (MDS) are clonal malignant stem cell disorders characterized by inefficient hematopoiesis. The role of the marrow microenvironment in the pathogenesis of the disease has been controversial. Emerging evidence indicated that mesenchymal stem cells (MSC) derived from MDS patients were cytogenetically abnormal, and they showed a deficient hematopoietic-supportive capacity and increased production of cytokine such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interferon γ (IFN-γ). From the point of some evidence, the abnormal microenvironment seems to participate in the progression of the disease by contributing to the selective expansion of the malignant clone. In this review, we will discuss the most recent progress related to identification of normal MSC and the importance of the stem cell niche in development and maintenance of MDS.

Keywords: Mesenchymal stem cell (MSC); myelodysplastic syndromes (MDS); pathogenesis

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Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematopoietic disorders characterized by inefficient hematopoiesis, peripheral blood cytopenia and risk of progression to acute leukemia (1). The clinical heterogeneity of MDS is a reflection of the various pathogenic mechanisms responsible for their development. It is commonly thought that MDS are a neoplasm caused by the neoplastic transformation of hematopoietic stem or myeloid progenitor cells (2,3). However, this hematopoietic cell-centered approach to explain deregulation in MDS has some limitations. It has been very difficult to duplicate disease in *in vivo* models by transplanting hematopoietic cells from MDS patients into immunodeficient mice (4). This observation has developed a long-standing debate about a potential causative or facilitating role for marrow microenvironment in the pathogenesis of this disease.

Mesenchymal stem cells (MSC), the most important component of marrow microenvironment, have been defined as primitive, non-hematopoietic cells residing primarily in bone marrow, and capable of giving rise to different cell lineages, including fat, muscle, cartilage, bone, and fibroblasts (5-7). Although there are no unique cell surface markers for the identification of MSC, minimal criteria to define human MSC, including plastic-adherent; ≥95% of the adherent population must express CD105, CD90 and CD73; they must lack expression of CD45, CD34 and CD14; and they must show *in vitro* differentiation capabilities into osteoblasts, adipocytes and chondroblasts have been published (8).

Is the MSC biologically normal in MDS? In terms of morphology, as well as the expression of certain cell markers, no differences were observed between MSC from MDS patients and those derived from normal marrow (9). Initial studies looking at adherent cell layers in Dexter-type long-term cultures indicated that the composition and function of such cells were similar to those of their normal counterparts, suggesting that the MDS-derived MSC is normal (10,11). Soenen-Cornu *et al*. (12) tested the osteoblastic differentiation potential of MDS-derived MSC and found that such cells have intact differentiation

ability for that particular lineage. Using co-culture studies they also found that MDS-derived MSC have the ability to sustain the growth of MDS-derived $CD34^+CD38^-$ and $CD34^+CD38^+$ cells, with either normal or abnormal karyotypes. In another study Flores-Figueroa *et al*. (13) have demonstrated that MDS-derived MSC had the capability of differentiating towards osteoblasts, chondrocytes and adipocytes; secreting normal levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), SCF, GM-CSF and VEGF; secreting normal levels of collagen and fibronectin; supporting the growth of normal UCB-derived early progenitors ($CD34^+CD38^-Lin^-$ cells) and sustaining the adhesion of progenitor cells.

In contrast several studies have shown a significant proportion (44-55%) of cytogenetic alterations in MDS-derived MSC (9,14), and more recent studies involving the use of genomic tools have demonstrated alterations at the gene expression level in these cells (15). Both the hematopoietic cells and MSC can probably be altered in response to damage-inducing factors and harbor independent chromosomal aberrations. Several additional alterations lead to the development of a leukemic clone, which is known to exhibit genomic instabilities and a DNA repair deficiency (16).

Additional studies by different groups showed a deficient hematopoietic-supportive capacity by MDS-derived MSC. Aizawa *et al*. (17) found that in some cases of MDS-refractory anemia, the stromal cells lack a hematopoietic supportive function.

Moreover, several defects in the bone marrow microenvironment may contribute to the pathogenesis of MDS including the aberrant secretion of angiogenic cytokines by monocyte and MSC. Numerous studies, both *in vitro* and *in vivo*, have demonstrated increased levels of cytokine production in the marrow microenvironment of MDS patients, such as TNFα, IL-6, interferon γ (IFN-γ) (18-22). Furthermore, a recent data have provided a disease-progression model in which overproduction of IFN-γ and TNFα in the microenvironment is the primary event. This causes B7-H1 molecule expression on MDS blasts, which generates a bifunctional signal inducing T-cell apoptosis and enhancing blast proliferation (23).

MSC have immunomodulatory properties, exerted by cell-to-cell contact and in a paracrine pattern (24,25). Several clinical and immunological studies suggest a significant deregulation of the immune system in the complex pathogenesis of MDS. This deregulation may even promote the progression of early MDS to advanced MDS (26). This raised the question of whether MSC play a definite role in the immune abnormalities of MDS. One previous study by Zhao *et al*. (27) demonstrated that the immunoregulatory function of MDS-MSC were impaired, suggesting the involvement of MSC in the pathogenesis of MDS. In their recent study the MSC from low-risk MDS patients and high-risk MDS patients were compared, and they demonstrated that high-risk MDS-MSC exhibited lower inhibition effect on T cells apoptosis and higher immunosuppressive rate on T-cell proliferation than that of low-risk MDS-MSC. The secretion of cytokines as well as the ability of hematopoietic support was different between the two groups (28). These results illuminated the different immunoregulatory role of MSC in low- and high-risk MDS, which may be important for understanding the pathogenesis of MDS and develop the immunomodulatory treatment of MDS.

Recently, other evidence was provided that primary alterations in the bone marrow microenvironment can drive oncogenesis in hematopoietic system. These findings suggest that a specific deletion of DICER1 in MDS-derived osteoprogenitors triggers blood cytopenias, high apoptosis rate, myelodysplasia and subsequent AML development in a murine model (29). Then Santamaría *et al*. (30) demonstrated an impaired microRNA biogenesis in human MSC from MDS patients, where DICER1 and DROSHA gene and protein downregulation correlated to a gene and microRNA abnormal expression profile, validating the animal model results previously described. These findings support the mechanism of malignancy resulting from the interaction of cell autonomous and microenvironmentally determined events, and point to the microenvironment as the site of the initiating event that leads to secondary genetic changes in other cells.

Overall, there still remains one key question: what is the origin of such abnormalities of MSC? Three explanation of MSC contribution in MDS initiation and progression are possible. First, it may be hypothesized that marrow microenvironment acts as an initiator of oncogenesis. The disruption of hematopoiesis integrity induced by the microenvironment may enable the hematopoietic progenitor cells initiating genetic events or clonal transformation (4). A second possible explanation is that the same agent that caused the initial genetic damage in myelodysplastic hematopoietic cells (radiation exposure, aromatic compounds, viruses, etc.) also affected MSC, although not necessarily inducing the same type of alterations. And the abnormal microenvironment may provide a selective milieu

for clonal expansion of hematopoietic stem cells. Thirdly, recent data support the view that in MDS, reciprocal heterotypic signaling between disease-propagating hematopoietic cells and MSC within the bone marrow environment is required to drive disease initiation and progression. "Reprogramming" of MSC by hematopoietic cells may be the initiative step and subsequently followed by a cascade of yet-to-be-defined events facilitating disease progression (31,32). Up to now, we do not yet have the precise answers to the above question; however, there is no doubt that actual explanation to this issue will come out in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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