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REVIEW

Cytogenetic changes of mesenchymal stem cells in the neoplastic bone marrow niche in leukemia

Shirin Ferdowsi[1], Shirin Azizidoost[2], Nasim Ghafari[3], Najmaldin Saki (✉)[2,3]

[1] *Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran*
[2] *Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[3] *Golestan Hospital Clinical Research Development Unit, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

BACKGROUND: Bone marrow mesenchymal stromal cells (BM-MSCs) are an essential cell type in the hematopoietic microenvironment. The question of whether MSCs from patients with different leukemias have cytogenetic abnormalities is controversial. In this study, we attempted to review the cytogenetic profiles of MSCs in patients with leukemia, and verify whether these profiles were related to different *ex vivo* culture conditions or to chronic or acute disease states. This information could be useful in clarifying the origin of MSCs and developing clinical applications for this cell type.
METHODS: A systematic literature search was performed using the PubMed search engine. Studies published over the past 15 years, i.e., between 1995 and January 2015, were considered for review. The following keywords were used: "cytogenetic," "leukemia," "bone marrow," and "mesenchymal stromal cells."
RESULTS: Some studies demonstrated that BM-MSCs are cytogenetically normal, whereas others provided evidence of aberrations in these cells.
CONCLUSIONS: Studying cytogenetic changes of MSCs in a variety of leukemias will help researchers understand the nature of these tumors and ensure the safety of human stem cells in clinical applications.

Keywords bone marrow, mesenchymal stromal cells, leukemia, cytogenetic, niche

Introduction

Mesenchymal stromal cells (MSCs) are a central component of the bone marrow (BM) microenvironment that contributes to the structure and function of the BM niche, controlling homing, self-renewal, differentiation, and proliferation of hematopoietic stem cells (HSC) (Keating, 2006; Borovski et al., 2011; Saki et al., 2011; Azizidoost et al., 2014). There are a number of studies showing that MSCs are a major contributor to the formation of tumor stroma. For example, Haniffa *et al*. (2007) suggested that mesenchymal fibroblasts within solid tumors originate from bone marrow MSCs. In fact, these findings indicate that MSCs have the ability to form a cancer stem cell niche (Ramasamy et al., 2007). Existing data on the cytogenetic and functional integrity of MSCs are controversial, and whether MSCs influence the development and progression of leukemia is still a matter of discussion (Blau et al., 2007; Choumerianou et al., 2008; Dimitriou et al., 2008; Lopez-Villar et al., 2009; Menendez et al., 2009; Klaus et al., 2010). Several studies have identified cytogenetic aberrations in the MSCs of a significant proportion of patients with leukemia (Flores-Figueroa et al., 2005; Blau et al., 2007; Lopez-Villar et al., 2009; Klaus et al., 2010). However, several other authors have been unable to identify specific cytogenetic changes in MSCs obtained from different hematological malignancies (Bhatiaet al., 1995; Soenen-Cornu et al., 2005; Arnulf et al., 2007; Carrara et al., 2007; Garayoa et al., 2009; Klaus et al., 2010; Achille et al., 2011; Kastrinaki et al., 2011) (Table 1). Whether chromosomal aberrations lead to functional alterations in BM-MSCs and how this might influence the development and outcome of leukemia remain to be elucidated. Blau et al. (2011) reported that the presence of chromosomal aberrations in BM-MSCs correlated with poor overall survival and disease-free survival outcomes. Therefore, in this study, we wanted to review the cytogenetic profiles of MSCs in patients with leukemia and to verify whether these profiles were related to

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Correspondence: Najmaldin Saki
E-mail: najmaldinsaki@gmail.com

the different cell expansion conditions in vitro or to chronic or acute disease states. This information could be useful to determining the origin of MSCs and the development of clinical applications for MSCs. In addition, characterizing BM-MSCs may help us better understand the biology of leukemia.

Cytogenetic changes of MSCs in myelodysplastic syndrome and acute myeloid leukemia

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are clonal disorders affecting pluripotent stem cells that are defined by ineffective hematopoiesis (Bernasconi, 2008). Recent studies have shown cytogenetic aberrations in BM-MSCs from patients with MDS (Flores-Figueroa et al., 2005; Lopez-Villar et al., 2009; Klaus et al., 2010;Blau et al., 2011) and adult AML (Blau et al., 2007;Blau et al., 2011; Huang et al., 2015) that were distinct from those with leukemia. Lopez-Villar et al. (Lopez-Villar et al., 2009) showed for the first time that MSCs from patients with MDS had genomic aberrations, and that some of these patients exhibited a particular MDS subtype, 5q- syndrome. Blau et al. (2011) demonstrated that MSCs of patients with MDS and AML had genetic abnormalities that were distinct from those of leukemic blasts. No statistically significant differences were observed in an outcome of complete remission or the relapse rate of patients with and without MSCs with aberrations. However, this study determined that overall mortality and leukemia-related mortality were more frequent in patients with aberrations in MSCs. In another study, Blau et al. (2007) showed that not only numerical but also structural cytogenetic aberrations were detected in BM-MSCs in a significant percentage of patients with MDS (44%) and AML (54%). Most of the structural abnormalities were observed in chromosomes 1, 7, and 10. These researchers never found identical chromosomal aberration in hematopoietic cells and BM-MSCs from the same patient. The lack of overlap between the karyotypes in BM-MSCs and hematopoietic cells suggests a non-hematopoietic origin for BM-MSCs. Flores-Figueroa et al. (2005) observed karyotype alterations in BM-MSCs in 55% of patients with MDS. Interestingly, they detected numerical aberrations almost uniquely in patients with an abnormal karyotype in hematopoietic cells. The fact that BM-MSCs showed typical chromosomal changes may suggest enhanced genetic susceptibility and an impact from these changes on the pathophysiology of MDS and AML. Recent evidence suggests that the presence of chromosomal abnormalities (mainly aneuploidy) in MSCs is associated with higher levels of (Aurora kinase). Evidence of AURKA expression supports the hypothesis that chromosomal abnormalities in MSCs of patients with MDS are not a consequence of the method used for preparation of the chromosomes before testing. It may reflect genomic instability in the bone marrow microenvironment of patients with MDS. In fact, the presence of genomic abnormalities in MSCs indicates that an unstable BM microenvironment facilitates the expansion of MDS/leukemic cells (Oliveira et al., 2013). Pimenova et al. (2013) also showed that the stromal microenvironment does not contribute to abnormal clone in MDS; however, it may be of great importance in the pathogenesis of this disease.

Cytogenetic changes of MSCs in acute and chronic lymphoid leukemia

There are a few reports on the cytogenetic profiles of BM-derived MSCs in patients with chronic lymphoid leukemia (CLL) (Campioni et al., 2012), whereas contradictory findings have been reported for patients with acute lymphoid leukemia (ALL) (Choumerianou et al., 2008; Menendez et al., 2009). Campioni et al. (2012) showed that the BM-MSCs of patients with ALL and CLL have a normal karyotype, thus supporting the idea that hematopoietic cells have an origin that is distinct from that of BM-MSCs. In particular, MSCs from infants with MLL-AF4 + B-ALL were reported to harbor and express the MLL-AF4 fusion gene. Unlike leukemic blasts, MLL-AF4 + BM-MSCs did not exhibit monoclonal immunoglobulin gene rearrangements. The absence of monoclonal rearrangements in these cells excludes the possibility of cellular plasticity or de-differentiation of B-ALL blasts and implies that MLL-AF4 might arise in a population of pre-hematopoietic precursors (Menendez et al., 2009).

Cytogenetic changes of MSCs in myeloproliferative neoplasms

Polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myeloid leukemia (CML), are all considered classic myeloproliferative neoplasms (MPNs). According to the World Health Organization (WHO) classification system, the presence of BCR-ABL indicates a diagnosis of CML and its absence indicates another MPN. The BCR-ABL fusion gene results from a t (9;22) translocation, the so-called Philadelphia chromosome (Jootar et al., 2006; Shahrabi et al., 2014). Results of previous studies indicate that cultured MSCs in patients with BCR-ABL + CML do not harbor this specific translocation (Jootar et al., 2006; Carrara et al., 2007; Wöhrer et al., 2007). However, the influence of MSCs on hematopoiesis in CML patients is a matter for further investigation. BCR-ABL – MPNs are most commonly distinguished by the JAK^{2V617F} mutation, but several studies have shown that JAK^{2V617F} may not be the initiating event (Nussenzveig et al., 2007; James, 2008; Pieri et al., 2008). Very little is known about BM-MSCs of these patients (Pieri et al., 2008). A study by Avanzini et al.

Table 1 Cytogenetic aberrations in BM-MSCs from leukemia patients.

Diagnosis	Cytogenetic markers in MSCs	Molecular change	Reference
AML	•t(1;2)(p32;q31), t(1;6)(p32;p12), del(7)(q11.2q32), del (7)(q22), t(3;20)(p13;p11.2), del(11)(q23), -X, del(13) (q12q22), inv(X)(q12p22), + 5, -4, -X, -Y •t(2;11)(q33;q13), del(4)(q12q21), der(5;17)(p10;q10), del(7) (q22q34),-6, + 8,+ 16,-18,-20,-22, dd(5)(q13) •t(1;10)(p36;p12), t(7;9)(q11.2;q34), t(7;10)(q11.2;q21), del(3)(p21), del(11)(q23),-22, del(8)(q11), + 13, t (2;13),-12 •t(3;9)(q25;q31), del(1)(q42)	↓ MCP-1,GM-CSF,IL-6 ↑ FOS,MYB	Blau et al., 2007; Blau et al., 2011; Yeh et al., 2012; Huang et al., 2015
MDS	•del(7)(q22), inv(X)(q12p22),+ 5, -4, -Y •der(7)t(1;7), del(17)(p11.2), t(4;7)(p14;q22), dic(6;16), -16,-17, t(7;19)(q22;q13), t(15;17)(q26;q12), t(1;3)(p12; q13), del(2)(q31),	↑ AURKA	Blau et al., 2007, 2011
Pro-B-All	•t(4;11) MLL-AF4	- - - -	Menendez et al., 2009
CLL	•Normal	- - - -	Campioni et al., 2012
ALL	•Normal& der(13;14)(q10;q10)	- - - -	Campioni et al., 2012; Yeh et al., 2012
MPN	•Loss 7pter-p22.2, loss 7p21.3, loss 7p21.3-p15.2, loss 7p12.3-p12.1, loss 7q11.22, gain 7q11.23-qter, Gain 7q22.1-qter, 5 +, 7 +, Loss 11q13.2-q13.4, loss 1q42.11-q44, loss 3p21.31-p11.1, loss 17q11.1-q11.2 •Normal for JAK^{2V617F} positive	↓G-CSF, IL-7	Pieri et al., 2008; Mercier et al., 2009; Avanzini et al., 2014
CML	•Normal for t(9;22)	- - - -	Jootar et al., 2006; Carrara et al., 2007; Wöhrer et al., 2007
MM	•Normal & Chromosomal loss at 4p14-4p13 and 3q13.13	↑ AREG, DKK1, IL-1β ↓IGF-1, SDF-1	Garayoa et al., 2009

↑ and ↓ shows up-regulation and down-regulation, respectively. Abbreviation: CML: chronic myeloid leukemia; MPN: myeloproliferative neoplasms; MDS: myelodysplastic syndrome; ALL: acute lymphoid leukemia; CLL:chronic lymphoid leukemia; AML: acute myeloid leukemia ; MM: Multiple myeloma; AURKA: Aurora Kinase A; G-CSF: Granulocyte colony-stimulating factor;IGF-1: Insulin-like growth factor 1; SDF-1: Stromal cell-derived factor 1; AREG: amphiregulin; IL-7: Interleukin 7; MCP-1: Monocyte Chemoattractant Protein-1;GM-CSF: Granulocyte macrophage colony-stimulating factor; DKK1: Dickkopf WNT signaling pathway inhibitor 1; IL-1β: Interleukin-1 beta; IL-6: Interleukin 6.

(Avanzini et al., 2014) detected functional and genetic aberrations of BM-MSCs cultured *in vitro* from patients with Philadelphia − MPNs. These results support the hypothesis that a primary MSCs defect leads to MPNs and represent a mechanism for leukemogenesis. However, the contribution of this genetic aberration to the different phenotypes of MPNs is not clear. Mercier et al. (2009) found that MSCs of most patients with MPNs had a phenotype and differentiation capacity comparable to that of MSCs derived from healthy donors. They did not find the JAK^{2V617F} mutation in any of the MSC samples. These results indicate that in MPNs, MSCs do not originate from mutated hematopoietic progenitor clones. A study by Bacher et al. (2010) showed that in myelofibrosis, the JAK^{2V617F} mutation is restricted to hematopoietic cells, and that it cannot explain the stromal aberrations also detected in this disorder.

Cytogenetic changes of MSCs in multiple myeloma

Multiple myeloma (MM) is defined by an accumulation of clonal plasma cells in the BM. The genetic basis for the disease includes complex genetic abnormalities in myelomatous cells (Zhan et al., 2006). In addition, the involvement of the BM microenvironment in the pathophysiology of the disease is well accepted (Mitsiades et al., 2007; Podar et al., 2007). Indeed, a difference between MSCs derived from patients with MM and those from healthy donors has been reported (Wallace et al., 2001; Arnulf et al., 2007; Corre et al., 2007; Garderet et al., 2007; Zdzisińska et al., 2008). Some genes are differentially expressed in the MSCs of patients with MM and in subjects with normal BM-MSCs. Three examples are amphiregulin (AREG), DKK1, and IL-1β, which are overexpressed in MMBM-MSCs compared to that in normal subjects. Two other examples are IGF-1 and SDF-1, which were underexpressed in MMBM-MSCs. Moreover, MMBM-MSCs produce larger amounts of IL-6 than normal MSCs (Corre et al., 2007). Notably, AREG can stimulate the production of IL-6 by BM-MSCs (Mahtouk et al., 2005). Thus, the simultaneous expression of AREG by cells in the microenvironment and by malignant plasma cells might enhance the survival of the tumor cells. MM cells may also block the differentiation of BM-MSCs into osteoblasts by producing the Wnt inhibitors DKK1 and sFRP2 (Tian et al., 2003; Oshima et al., 2005) or the EGF family member amphiregulin (Mahtouk et al., 2005). A number of studies have found that MSCs from patients with MM did not show the chromosomal alterations detected in myeloma plasma cells (Arnulf et al., 2007; Garayoa et al., 2009). In a study by Garayoa et al. (Garayoa et al., 2009), a chromosomal loss at

4p14-4p13 and another loss at 3q13.13 were detected in in vitro-expanded MSCs derived from patients with MM. In general, these alterations did not recur within the patients. These findings indicate that BM-MSCs from patients with MM can create an efficient niche to allow survival and proliferation of myeloma stem cells.

Impact of anti-leukemic therapy on the cytogenetic changes of BM-MSCs

Alteration in the cytogenetic of BM-MSCs with anti-leukemic therapy remains unknown so far. In a study by Yeh et al. (2012), karyotypes of BM-MSCs from patients with leukemia were investigated before and after anti-leukemic therapy. Cytogenetic abnormalities were found in BM-MSCs after transplantation in three cases. In one patient who had a clonal del (1) (q42) mutation in BM-MSCs at the time of diagnosis, an additional del (5) (q13q22) mutation appeared after total body irradiation (TBI)-based allogeneic transplantation. These researchers also showed cytogenetic abnormalities in BM-MSCs that were completely different from those in BM hematopoietic cells. In another study, Kemp et al. (2011) showed that melphalan and cyclophosphamide cause functional injury to human BM-MSCs in vitro. In ALL and CLL cases, Campioni et al. (2012) showed that their BM-MSCs had a normal karyotype, thus supporting a distinct origin of hematopoietic cells (HC). They concluded that the presence of *in vitro* hMSC, human MSCs, aneuploidy is associated with lymphoid neoplasias with chromosome abnormalities, suggesting that hMSCs should be characterized before they are applied in clinical therapies. In addition, hMSCs are reported to be key regulators in normal B lymphopoiesis and in protecting CLL cells from spontaneous or drug-induced *in vitro* apoptosis, thus playing a crucial role in disease progression and resistance to therapy (Balakrishnan et al., 2010; Ferretti et al., 2011).

Discussion and future perspective

Previous studies have shown that the cancer microenvironment directly contributes to the pathogenesis, treatment resistance, and relapse of various malignancies (Saki et al., 2011). Although it is now well accepted that the BM microenvironment is the key determinant of malignant progression in leukemia, it is unclear whether the BM microenvironment plays the same role in genomic alterations of MSCs that can co-evolve during leukemogenesis (Dimitriou et al., 2008). The detection of cytogenetic aberrations in MSCs indicates that unstable MSCs may help in the expansion of malignant cells. Therefore, genetic alterations in MSCs may be one mechanism of leukemogenesis (Campioni et al., 2012). The functional implications of cytogenetically modified MSCs should be further examined to determine whether autologous MSCs should be used or excluded for clinical purposes and to identify a potential common origin of MSCs and hematopoietic cells (Blau et al., 2011). Campioni et al. (2012) analyzed the cytogenetic profiles of hMSCs in patients with ALL and CLL to verify whether these profiles were related to different ex vivo culture conditions or to chronic or acute disease states. They concluded that *in vitro* culture conditions may play a critical role in defining these profiles, because MSC samples from hematological malignancies that are cultured in M5100 medium may allow long-term survival of CD45 + pathologic lymphocytes, thus rendering the identification of hMSC nuclei more difficult. In these samples, a higher proportion of adherent cells may have been erroneously reported as MSC carriers of leukemia-associated cytogenetic alterations. The studies reviewed here indicate that in a subset of patients with leukemia, MSCs bear chromosomal abnormalities that do not correspond to abnormalities found in the hematopoietic cells of that patient (Blau et al., 2007). It is unknown why BM-MSCs can have distinct cytogenetic abnormalities.

In conclusion, we believe that it is important to test for chromosomal aberrations of MSCs to ensure the safety of human stem cells for clinical applications. The possibility that karyotype aberrations in BM-MSCs may define different disease stages should also be considered. In fact, the study of cytogenetic changes of MSCs in a variety of leukemias may help researchers to clarify the nature of these tumors. In addition, characterizing the karyotypes of these stromal cells in a variety of leukemias may be useful in developing markers to determine leukemia prognosis. It is equally important to see how the BM-MSCs change in response to anti-leukemic therapy. Further studies are needed to evaluate these changes in MSCs.

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Compliance with ethics guidelines

Authors declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by the any of the authors.

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