Multiple Myeloma Mesenchymal Stem Cells: Characterization, Origin, and Tumor-Promoting Effects

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Abstract

Hematologic malignancies rely heavily on support from host cells through a number of well-documented mechanisms. Host cells, specifically mesenchymal stem cells (MSC), support tumor cell growth, metastasis, survival, bone marrow colonization, and evasion of the immune system. In multiple myeloma, similar to solid tumors, supporting cells have typically been considered healthy host cells. However, recent evidence reveals that many MSCs derived from patients with multiple myeloma (MM-MSC) show significant defects compared with MSCs from nondiseased donors (ND-MSC). These abnormalities range from differences in gene and protein expression to allelic abnormalities and can initiate after less than 1 day of coculture with myeloma cells or persist for months, perhaps years, after removal from myeloma influence. Alterations in MM-MSC function contribute to disease progression and provide new therapeutic targets. However, before the scientific community can capitalize on the distinctions between MM-MSCs and ND-MSCs, a number of confusions must be clarified, as we have done in this review, including the origin(s) of MM-MSCs, identification and characterization of MM-MSCs, and downstream effects and feedback circuits that support cancer progression. Further advances require more genetic analysis of MM-MSCs and disease models that accurately represent MSC-MM cell interactions.

Introduction

Mesenchymal stem cells (MSC) are a dynamic population of cells capable of self-renewal, differentiation, tumor and wound homing, and immunomodulation. Harvested from bone marrow, adipose tissue, cord blood, or a variety of other sites, MSCs play multiple roles in tumor progression, as previously reviewed (1). Complications in comparing studies and drawing conclusions arise because of different stem cell isolation, characterization, and culture protocols and the inherent variability in stem cells within and between donors. MSCs can have both tumor supportive (protumor) and inhibitory (antitumor) effects (2), but most myeloma-specific studies show a stimulatory, protective, and protumor effect of MSCs on myeloma cells, suggesting that novel drugs could counteract these tumor-supporting effects in the bone marrow.

Local bone microenvironment activates many pathways leading to lesion growth and disease progression, including the following: the phosphoinositide 3-kinase (PI3K)/Akt/mTOR/p70S6K cascade, the IKK-α/NF-κB pathway, Ras/Raf/mitogen-activated protein kinase (MAPK), and Janus-activated kinase (JAK)/STAT3, as reviewed extensively (3, 4). Many clinical and preclinical trials are aimed specifically at developing inhibitors of these pathways. Moreover, findings are emerging that alterations in the local microenvironment may be not only supportive of tumor growth but also required for tumorigenesis. For example, deletion of DICER in osteoprogenitor mesenchymal cells can disrupt hematopoiesis and cause myelodysplasia and acute myelogenous leukemia in mice. This, among other studies, shows the concept of microenvironment-induced oncogenesis (5–9). MSCs can also increase multiple myeloma cell adhesion to bone marrow, protecting the cells from chemotherapy and helping them accumulate within the bone. Adhesion is mediated by molecules, including CD44, very late antigen (VLA)4, VLA5, leukocyte function-associated antigen 1 (LFA1), neuronal adhesion molecule (NCAM), intercellular adhesion molecule (ICAM1), syndecan 1, and MCP1, as reviewed previously (10). Binding of CD40, located on multiple myeloma cells, with its ligand (CD40L) on MSCs can further increase expression of adhesion molecules such as LFA1 and VLA4. Subsequently, multiple myeloma cell adhesion is further increased, stimulating cytokine [interleukin 6 (IL-6) and VEGF] secretion by MSCs, creating a forward feedback loop for tumor growth (11, 12). In sum, stromal dysfunction is tied to neoplasia progression, implicating local stromal cells as coconspirators in tumor development.

Stromal cell–induced chemotherapy resistance in myeloma cells is well documented (13, 14), yet many drug screens are still done in the absence of stromal cells and, therefore, produce deceiving findings. Novel drug screens...
using stromal cell–myeloma cell cocultures are now being developed to produce more clinically relevant modeling tools (15, 16). Pharmaceutical developers are also now attacking tumor cells through stromal-affected drugs, such as bortezomib, perifosine, and an array of bisphosphonates, that target stromal cell–tumor cell interactions. Perifosine induces apoptosis even in multiple myeloma cells attached to bone marrow stromal cells through the c-jun-NH2-kinase (JNK) pathway (17), and bortezomib, a proteasome inhibitor, was recently found to directly induce osteoblastic differentiation in MSCs to combat osteolysis through the transcription factor RUNX-2 (18). As a last example, the CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells and MSCs and enhances multiple myeloma cell sensitivity to therapy (19). This work and other studies reveal that CXCR4 inhibitors or other therapies that detach tumor cells from the bone matrix can increase chemosensitivity of multiple myeloma cells. These pharmaceuticals were developed based on in vitro studies of healthy donor stroma cells and multiple myeloma cells. We hypothesize that more effective and specific chemotherapeutic strategies will be identified using in vitro models containing MSCs from patients with multiple myeloma. The questions that arise are then the following: Are there differences between nondenuded (ND-MSC) and myelomatous MSCs [MSCs derived from patients with multiple myeloma (MM-MSC)]? How do these relate to differing interactions with multiple myeloma cells? Lastly, how can we target these interactions for a therapeutic effect? These questions are addressed below. The MM-MSCs that are discussed were obtained from untreated patients with multiple myeloma, unless otherwise noted; often, the status of age matching was not reported in the studies.

Origin and Derivation of the Multiple Myeloma Mesenchymal Stem Cells

The development of MM-MSCs is poorly understood, and their phenotypic and genotypic characteristics are disputable (Fig. 1). Some results suggest that MM-MSCs are inherently abnormal and will remain abnormal, despite being removed from the myeloma cell influence, whereas others argue that MM-MSCs are only temporarily modified in their gene expression in response to multiple myeloma cells. For example, many patients survive for years with bone lesions or pathologic fractures that never heal because of disrupted osteogenesis and osteoblast function, even in the absence of tumor, suggesting permanent defects within MM-MSCs (20). However, within hours of coculture with multiple myeloma cells, normal MSCs can become in vitro MM-MSCs, displaying a phenotype similar to that of patient-derived MM-MSCs (21). Furthermore, cell–cell contact may be necessary to create in vitro MM-MSCs, or soluble factors may be sufficient, showing our lack of knowledge about MM-MSC evolution. Chromosomal aberrations (e.g., deletions, translocations) in MM-MSCs remain once the cells are removed from multiple myeloma cell coculture (22). However, the origin of these aberrations is unclear, and in vitro multiple myeloma cell priming of MSCs shows that genetic alterations are not necessarily the source of, or required for, phenotypic variation in MM-MSCs (22). The theory that MM-MSCs and multiple myeloma cells are derived from a common progenitor (23) has been disproved by chromosomal aberration comparisons (22, 24, 25). Another report suggests that a contamination of CD11b+ myeloid cells within patient-derived tumor-associated stromal cells is responsible for the observed effects on tumor cells (26). Although this study used lung carcinoma cell lines, the same results may be true in myeloma studies. As many groups isolate “MSCs” by plastic adherence, a strong possibility exists that what are thought to be MSCs are actually a diverse population containing myeloid cells. A final complication is that injection of ND-MSCs into osseous tumor lesions has returned mixed results in terms of tumor growth inhibition. Although some of these MSCs retained their differentiation potential and increased osteoblastic activity and bone formation, others were functionally converted into MM-MSCs, supported tumor growth, and showed decreased osteogenesis. The development of MM-MSCs is likely a consequence of multiple factors, and alterations may vary between individuals, lesion locations, coculture myeloma cell types (in vitro), and subpopulations of cells within the MSC population. Identifying the governing mechanisms in the transition from normal MSC to MM-MSC and how these cells provide feedback to multiple myeloma cells is vital for improved myeloma therapy (21).
Phenotype Aberration Characteristics of Multiple Myeloma Mesenchymal Stem Cells

Cytokine and matrix metalloproteinase expression

MM-MSCs differ from ND-MSCs in many aspects (Fig. 2), including spontaneous or myeloma cell–induced cytokine production. Many multiple myeloma stimulatory growth factors, such as stem cell factor (SCF), VEGF, and IL-6, are secreted at higher levels by MM-MSCs than by ND-MSCs (24, 25, 27–30). Adhesion of multiple myeloma cells to ND-MSCs can increase IL-6 production and downstream NF-κB pathway stimulation, suggesting direct cell–cell contact as an initiator of the MM-MSC phenotype (31). Importantly, MSC-derived IL-6 supports multiple myeloma growth, showing one of many forward feedback mechanisms in myeloma (32).

Increased expression of IL-1β, TNF-α, and a range of other factors that can inhibit normal progenitor cell growth has also been detected in MM-MSCs compared with ND-MSCs (29, 33–35). Recent studies document increased IL-10, B-cell–activating factor of the TNF family (BAFF), and hepatocyte growth factor (HGF) by MM-MSCs compared with ND-MSCs, in response to RPMI8226 myeloma cells (29). These cytokines can induce osteoclast stimulation, tumor angiogenesis, and increased multiple myeloma cell adhesion, proliferation, and migration (29). Other studies have described differences in matrix metalloproteinase (MMP), TGF-β family members, receptor activator of nuclear factor kappa B ligand (RANKL), and FasL expression and increases in cytokine production when stimulated with lipopolysaccharide or Newcastle disease virus (34, 36, 37). These data suggest that therapeutic interventions specifically targeting these cytokines or their downstream pathway components may be more important for patients with multiple myeloma than in vitro experiments involving no MSCs or MSCs from healthy patients have shown. For example, anti–IL-6 therapies, such as tocilizumab or other downstream JAK/STAT or NF-κB inhibitors, may be more effective than currently realized as anticancer therapies when delivered specifically to areas of MSC–multiple myeloma cell interactions (38).

Chemotherapy resistance

ND-MSCs and, to a greater extent, MM-MSCs can suppress bortezomib-induced multiple myeloma cell growth inhibition in a cell–cell contact-dependent manner by increasing Bcl2 expression in multiple myeloma cells (27). MM-MSCs, but not ND-MSCs, are also able to activate bortezomib resistance through enhanced NF-κB activity in multiple myeloma cells, induced by soluble MM-MSC–derived IL-8 (39). However, these MM-MSCs were from uncharacterized patients who lacked classification about stage or treatment and, hence, may not represent the typical MM-MSC phenotype. Still, the work suggests a closer examination of the potential of inhibitors of NF-κB and IL-8 within myeloma bone lesions. For example, sunitinib, a potent inhibitor of the proto-oncogene RET, was recently shown to decrease IL-8 expression, but it is not commonly given to patients with multiple myeloma. Hence, sunitinib...
may be effective for patients with multiple myeloma and may have fewer off-target side effects if delivered directly to the bone marrow.

It is well known that adhesion of multiple myeloma cells to bone marrow provides the cancer cells with protection against chemotherapies. Multiple myeloma cells have been found to become chemosensitized when their adhesion to marrow stromal cells via the CXCR4 receptor is inhibited (19). Moreover, expression of CXCR4 was increased in multiple myeloma side populations (the more stem-like tumor cell population). We propose that more studies into methods of de-adhesion of tumor cells via CXCR4 inhibitors or other therapeutic interventions may be effective for patients with multiple myeloma and may have fewer off-target side effects if delivered directly to the bone marrow.

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ND-MSCs can also upregulate survivin in multiple myeloma cells through direct cell–cell contact, although the ability for MM-MSCs to do this has not been investigated (41). Lastly, MSCs from acute myeloid leukemia, Hodgkin disease, and multiple myeloma showed similar capacities to protect multiple myeloma cells from IL-6 receptor antagonist therapies, although the ability of ND-MSCs was not studied (32).

Extracellular matrix protein expression

Fifteen years ago, multiple myeloma stromal cells were found to deposit fewer extracellular matrix proteins (ECM) with simpler organization than ND stromal cells, specifically in fibronectin, laminin, and collagen IV (42). More recently, however, MM-MSCs were found to have increased fibronectin and collagen IV expression compared with ND-MSCs (33, 43). These proteins provide feedback to multiple myeloma cells, as they express moieties for adhesion and survival through cell adhesion–mediated drug resistance (CAM-DR). Research shows fibronectin adhesion is mediated through integrins such as VLA-4 and VLA-5, among many others (44, 45). Fibronectin binding upregulates p27, induces NF-κB activation, and has been shown to alter expression of 469 gene products in multiple myeloma cells (46).

Reports also show increased osteopontin production from MM-MSCs compared with ND-MSCs in response to myeloma cells (29). Interestingly, MM-MSCs also displayed increased hyaluronan synthase 1 (Has1) expression, decreased Has2 expression, and increased total hyaluronan production (47). Multiple myeloma adhesion to hyaluronan also confers CAM-DR to multiple myeloma cells (48).
Osteopontin has been shown to mediate multidrug resistance in other cancers by enhancing hyaluronate binding and may act similarly in multiple myeloma (49). Moreover, MM-MSCs have been found to express higher levels of intracellular receptor for hyaluronan-mediated motility compared with ND-MSCs, suggesting an increased dependence on hyaluronan for MM-MSC migration (33).

**Adhesion, phenotype, and biomechanics**

Differences in MM- versus ND-MSC adhesion molecule expression may facilitate multiple myeloma cell entrapment in the bone marrow. MM-MSCs express adhesion molecules that bind multiple myeloma cells ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) at higher levels than ND-MSCs (27, 33, 39). Beta-1 and beta-2 integrin-mediated multiple myeloma cell adhesion may also be stronger to MM-MSCs than to ND-MSCs, although these MM-MSCs were from uncharacterized patients (50).

Most reports describe a similar phenotypic appearance and MSC marker expression profile in MM-MSCs and ND-MSCs (25). However, MM-MSCs may be significantly stiffer than ND-MSCs (51). Forward feedback mechanisms through focal adhesion kinase activation between MM-MSCs and multiple myeloma cells (specifically, the multiple myeloma cancer stem cell population) may govern stiffening of both cell types (51).

**Proliferation and differentiation capacity**

MM-MSC proliferation and rate of osteogenic differentiation is much slower, in part due to reduced expression of growth factor receptors and increased expression of inflammatory cytokines, such as TNF-α, relative to their normal counterparts (24, 52, 53). Dysregulated ephrinB2/EphB4 signaling in MM-MSCs may also decrease their osteogenic potential and increase their multiple myeloma cell support (54). MM-MSCs have also shown a 5-fold higher expression of the osteoblast inhibitor DKK1 at transcript and protein levels, suggesting a direct role in osteolytic lesion propagation through autocrine and paracrine signaling (52). In contrast, others have found similar proliferative and differentiation potentials in MM- and ND-MSCs, although this is not commonly found and is often not quantified (25, 28).

**Immunomodulation and downstream effects on tumor stem cells**

MM-MSCs show an impaired ability to inhibit T-cell proliferation compared with ND-MSCs, but they show no difference in their ability to support hematopoiesis (24, 25). The ability to stimulate osteoblastic differentiation is also decreased in T cells isolated from patients with myeloma and in ND-MSCs cocultured with multiple myeloma cells (34).

Corre and colleagues report enhanced support of tumor cell proliferation by MM-MSCs compared with ND-MSCs, suggesting that the abnormal niche created by MM-MSCs may be more efficient at supporting myeloma progression (24). Multiple myeloma cells also show low baseline microRNA (miRNA)-15a, increased miRNA-15a expression after bortezomib treatment, and a subsequent decline in expression after coculture with MM-MSCs, suggesting another potential protective mechanism of MM-MSCs (27). In ovarian cancer, carcinoma-associated MSCs (CA-MSC) derived from patients with cancer significantly promoted tumor cell growth compared with MSCs from healthy individuals (55). Overexpression of bone morphogenetic protein (BMP)-2, BMP-4, and BMP-6 in CA-MSCs compared with ND-MSCs and subsequent promotion of the cancer stem cell population was deemed the underlying mechanism of increased tumor growth (55). Of course, in multiple myeloma other factors are likely involved because BMP signaling would likely promote osteogenesis, not tumor growth. MM-MSCs may also enhance cancer stem cell colony-forming ability (in vitro) and proliferation (in vitro and in vivo) compared with ND-MSCs (40, 51). MM-MSCs also seem to support proliferation of the stem-like population of multiple myeloma cells to a greater extent than ND-MSCs do, suggesting that MM-MSCs are more specifically selective for the growth of tumor-initiating cells than ND-MSCs (40). Indeed, the theory that the less mature, more resistant CD138-negative myeloma cell fraction develops in response to interactions with local mesenchymal cells is becoming increasingly credible and suggests an urgent need to unlock the underpinnings of their association (36).

**Gene signature and chromosomal aberrations**

Microarray gene expression data have identified 104 transcripts upregulated in rat MSCs exposed to conditioned media from human colorectal cancer cells for 24 hours versus control medium, showing tumor cell–induced MSC gene expression modifications (37). Two gene expression profiling studies have extracted many genes differentially expressed by human MM- and ND-MSCs. One study used human U133 plus 2.0 GeneChip microarrays and identified 145 genes differentially expressed, including IL6, DKK1, and "growth and differentiation factor-15" (GDF15; ref. 24). The other study examined expression profiles of multiple myeloma–associated bone cells in relation to osteolytic disease. Using microarray analysis, the study examined MM-MSCs and MM-osteoblasts (OB) in osteolytic and nonosteolytic samples from patients with multiple myeloma and from healthy donors. ND-MSCs and MM-MSCs displayed distinct transcriptional patterns in 78 genes. ND-OBs versus MM-OB samples had 29 specifically modulated genes. Many of the HOXB genes were highly expressed in both MSCs and OBs of patients with myeloma, although the significance of this finding remains elusive (37). MSCs from osteolytic versus nonosteolytic patients also displayed different expression of 45 genes, but no difference in OB gene expression was found between these groups (37). However, whole-genome array-comparative genomic hybridization analysis identified no chromosomal abnormalities in MM-MSCs or MM-OBs (37).

In contrast, others have reported genomic imbalances in MM-MSCs absent in ND-MSCs (22). The researchers note, however, that these genomic imbalances were more evident in passage 3 MSCs compared with passage 0 MSCs, suggesting that this may be due to MSC adaptation to culture conditions.
MSCs report severe chromosomal alterations in MDS-MSCs (22). Similarly, studies examining chromosomal differences conditions and/or clonal selection for abnormal MM-MSCs (58). MDS-MSCs also secrete more IL-1β and, after treatment with TNF-α, secrete more SCF compared with their normal counterparts (58). Of note, ND-MSCs and MDS-MSCs had no difference in adhesion molecule or ECM protein expression or in differentiation ability, suggesting that dramatic chromosomal abnormalities may not cause drastic changes in function. Hence, although disputed, the results suggest potential MM-MSC genomic alterations.

Lastly, in all studies that positively identify chromosomal differences in MM- versus ND-MSCs, the specific abnormalities of MM-MSCs were unique from the mutations and/or abnormalities observed in patient-matched myeloma cells, implying the absence of a common progenitor cell for MM-MSCs and multiple myeloma cells (24, 25). Rather, the data suggest a coevolution of genomic alterations in juxtatumoral MSCs during tumorigenesis in response to the same carcinogens or mutagens responsible for plasma cell transformation (22). In summary, although chromosomal aberrations may be present between normal and MM-MSCs, they do not explain most of the functional and gene expression differences observed.

Disease Models for Reproduction of the Multiple Myeloma Mesenchymal Stem Cell Phenotype

Understanding how MM-MSCs evolve from healthy ND-MSCs requires in vitro experiments and models of ND-MSCs cocultured with multiple myeloma cells. With those tools, we can determine parameters that initiate this phenotypic switch that may include the following: (i) time periods of coculture, (ii) soluble or direct cell–cell contact requirements, (iii) other cell types, and (iv) mutagens, among other parameters. Whether the transition involves intermediate phenotypes or one dramatic switch and whether the phenotype change is an initiator of, or a downstream reaction to, genetic alterations or myeloma disease progression can be elucidated.

In one model, primary ND-MSCs were differentiated down the osteoblastic lineage and then cultured with multiple myeloma cells for 7 to 10 days (21). In this model system, each cell type was grown on opposite sides of a 1-μm pore membrane. Although some osteoblast samples supported tumor growth, others inhibited it, and it was determined that multiple myeloma proliferative response to MSCs was based on traits within the multiple myeloma cells themselves, not the MSCs (21).

Coculture of ND-MSCs with multiple myeloma cells can also induce changes in MSCs. Multiple myeloma cells can induce VEGF and IL-6 upregulation and basic fibroblast growth factor downregulation in MSCs, giving these a similar phenotype to that of patient-derived MM-MSCs (59). Affymetrix microarray analysis of multiple myeloma and MSC RNA after 18 hours of coculture revealed rapid induction of gene expression changes in both cell types, but results have not been peer reviewed (60). Still, the work suggests that 2-dimensional (2D) culture of MSCs with multiple myeloma cells may be able to produce MM-MSC–like cells very rapidly. Advantages of using induced MM-MSCs rather than patient-derived MM-MSCs include reproducibility, controllability, greater cell numbers and proliferation rates, the ability to analyze development of the MM-MSCs outside the body, and better controls (i.e., the same MSC population cultured without multiple myeloma cells).

Although long recognized in the field of tissue engineering, the importance of using 3D rather than 2D models to elucidate biologically relevant interactions has only recently been recognized in MSC–myeloma cell interaction modeling. Cytokine production was compared in 2D and 3D cultures of MM-MSCs in response to RPMI8226 myeloma cells using a gelatin sponge and showed that MSCs in the 3D culture produce more IL-11 and HGF and less IL-10 than in the 2D cultures (61). Furthermore, multiple myeloma cells responded with increased production of soluble IL-6 receptor after contact with MM-MSCs in 3D compared with 2D. Other researchers have also described models for 3D cell culture, but the models lack mineralization and they poorly mimic the strength, rigidity, or complexity of bone (62).

Several in vivo multiple myeloma models have been described to study stromal cell–myeloma cell interactions. One model, the severe combined immunodeficient (SCID)-hu model, improves upon previous mouse models by humanizing the bone compartment using xenograft human fetal bone chips implanted into CB-17 SCID mice. The model reproduces homing of myeloma cells to these bone chips and the subsequent bone–tumor cell interactions observed in myeloma (14). A drawback to this model is that MSCs and osteoblasts in this bone are healthy and not necessarily representative of MM-MSCs or MM-OBs found in patients. Subsequent models have used 3D poly-e-caprolactone polymeric scaffolds seeded with MM-MSCs and multiple myeloma cells, providing a more realistic microenvironment model (63).

Conclusions

MM-MSCs show a number of functional differences, many of which allow them to specifically support multiple myeloma cells. Transient protein and/or mRNA-based differences and long-term chromosomal differences were identified between ND-MSCs and MM-MSCs, but the cause of these alterations remains largely unknown. More research is necessary to understand the evolution of allelic imbalances and the nonchromosomal-based differences between healthy and tumor-associated cells, which have been identified not only in myeloma but also in many other tumors (23, 64–66). Specifically, it would be beneficial to characterize and study MSCs from a variety of patients with well-defined clinical data. Little to no data are available on MM-MSCs from high-risk patients with monoclonal gamopathy of undetermined significance and/or smoldering myeloma. There is rarely any clinical follow-up or characterization of the MSCs from patients with myeloma, and age- or sex-matched comparisons are rare. Hence, more data
need to be collected on the properties of MSCs from broader, well-documented populations of both healthy donors and donors who have myeloma to more fully and accurately understand the evolution and interactions of myeloma and myeloma MSCs.

Disclosure of Potential Conflicts of Interest

M.R. Reagan declares no competing financial interests. I.M. Ghobrial received research funding from Millennium, Bristol-Myers Squibb, and Novartis and is on the advisory board or consultant for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Novoxon, and Polyphor.

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Authors’ Contributions

M.R. Reagan researched and wrote the article and created the figures. I.M. Ghobrial reviewed and edited. Both identified the theme of the review.

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