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Multiple myeloma in the marrow: pathogenesis and treatments

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Abstract

Multiple myeloma (MM) is a B-cell malignancy resulting in osteolytic lesions and fractures. In the disease state, bone healing is limited due to increased osteoclastic and decreased osteoblastic activity, as well as an MM-induced forward-feedback cycle where bone-embedded growth factors further enhance tumor progression as bone is resorbed. Recent work on somatic mutation in MM tumors has provided insight into cytogenetic changes associated with this disease; the initiating driver mutations causing MM are diverse due to the complexity and multitude of mutations inherent in MM tumor cells. This manuscript provides an overview of MM pathogenesis by summarizing cytogenic changes related to oncogenes and tumor suppressors associated with MM, reviewing risk factors, and describing the disease progression from MGUS to overt MM. It also highlights the importance of the bone marrow microenvironment (BMM) in the establishment and progression of MM, as well as associated MM-induced bone disease, and the relationship of the bone marrow to current and future therapeutics. This review highlights why understanding the basic biology of the healthy and diseased BMM is crucial in the quest for better treatments and work toward a cure for genetically diverse diseases such as MM.

Keywords

multiple myeloma; bone marrow niche; treatments; bone marrow

Introduction

Multiple myeloma (MM) is a fatal, malignant B-cell neoplasm characterized by uncontrolled, destructive growth of mutated plasma cells within the bone marrow (BM). Patients over age 65 are most commonly affected by this disease[1] and, as indicated by its name, MM is characterized by dissemination of multiple tumor cells throughout the BM. A mnemonic sometimes used for the common MM pathologies is CRAB: C (calcium, elevated), R (renal failure), A (anemia), B (bone lesions). Additionally, a hallmark of MM is heterogeneous chromosomal aberrations and numerous mutations in a range of genes, both of which make the disease very difficult to target therapeutically.[2]

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MM begins as monoclonal gammopathy of undetermined significance (MGUS), progresses to smoldering (asymptomatic) myeloma and finally becomes overt (symptomatic) myeloma, resulting in BM infiltration and osteolytic lesions. During MM progression the normal equilibrium between osteoblastic (bone building) and osteoclastic (bone breakdown and resorption) activity is skewed toward net bone loss. MM-induced osteolysis releases growth factors embedded inside the bone matrix, fueling MM progression and expansion in the BM niche and resulting in greater osteoclastic activity in a process known as the *vicious cycle*.[3,4] During this MM-induced cycle, osteoclastic bone breakdown releases bone-embedded growth factors to promote tumor growth which, in turn, stimulates greater osteoclast activity. MM progression and drug resistance depend on interactions with the local microenvironment; therapies that target the marrow microenvironment rather than the tumor cells directly, such as bisphosphonates, have proven to be effective in inhibiting tumor growth and osteolysis, suggesting that targeting of the marrow can be an effective therapeutic avenue to pursue.[5–10] In addition to osteoblasts and osteoclasts, other BM niche cells, including mesenchymal stem cells (MSCs), BM adipocytes, immune cells, and osteocytes, also likely affect MM progression.[7] BM cells exist in a dynamic, stress-sensing environment where they release soluble signaling molecules to communicate with one another; how these signals are processed by MM cells invading the BM niche remains a key area of investigation.

Recent advances in genetic technologies have provided additional insight into mutations and chromosomal abnormalities associated with MM.[11] We now know that the majority of MM cases are associated with an initiating somatic mutation and are frequently accompanied by additional oncogenic mutations. This genetic complexity makes the treatment of MM problematic. Thus far, MM treatments primarily rely on chemotherapies in conjunction with proteasome inhibitors,[12,13] anti-resorptive agents such as bisphosphonates[14], corticosteroids and bone marrow transplantation.[12–14] Immunostimulatory agents are also being investigated as potential treatments for MM; however, a better understanding of the MM BM niche and cell-cell interactions is crucial in providing novel, more effective treatments for MM patients. This review aims to describe the nature of somatic mutations as they relate to MM disease prognosis. It also outlines the interactions of MM with the various cell types in the BM niche and describes current treatments as they relate to microenvironmental components.

Epidemiology, cytogenetics, and risk stratification in MM

Over 22,000 new cases of MM were diagnosed in 2013, and the number of cases of MM increases steadily each year.[15] It appears that nearly all patients have MGUS during the 2 years before they develop MM, most patients have MGUS 4 years before MM, and ~82% of MM patients have MGUS 8 years before MM develops.[16] Other known risk factors for MM include being of male sex, older age, and African American racial background.[17] However, as the number of MM cases continues to increase annually,[1] stratification of secondary risk factor assessment to encourage early diagnosis will become clinically significant. These secondary risk factors include exposure to chronic, low-grade inflammation, pre-existing and/or chronic immunodeficiency, and, potentially, the presence of known inflammatory diseases or conditions (eg. obesity, cardiovascular disease, or type II diabetes

mellitus).[1,18–20] Of growing interest are the pathogenic links between MM and obesity-related chronic, low-grade inflammation, BM/tumor microenvironment hypoxia, and genetic instability.[21–23] Research into how each of these components support malignant transition is ongoing.[24,25]

Overt MM is often characterized by mutations in *KRAS* (particularly in previously treated patients), *NRAS, BRAF, FAM46C, TP53, and DIS3*. Often mutations affecting proteins within the same pathway are also observed (e.g., *KRAS*, *NRAS* and *BRAF*).[26] Common mutations include loss at 1p and inactivation of the tumor suppressor p53, resulting in an abundance of immunoglobulin production.[11] Somatic mutations associated with the development of MM can be characterized as either non-hyperdiploid disease (NHD) or hyperdiploid disease (HD).[27] Both classes of mutations involve large chromosomal structural events which result in the dysregulation of G_1/S cell cycle and cyclin D gene transcription.[11,28,29] NHD is characterized by chromosomal translocations at 14q32, including t(4;14), t(11;14), t(14;16), and t(14;20), which involve early translocation of immunoglobulin heavy chain (IgH) genes.[30] This results in increased expression of IgH in the clinical presentation of MM.[11,28,29] NHD is linked with an increased likelihood of disease progression and poor overall prognosis.[11,28,31] By contrast, HD is characterized by the presence of trisomies, specifically chromosomes 3, 5, 7, 9, 11, 15, 19 and 21. Excess cyclin D in the absence of elevated IgH is the main signature of HD.[1] Additional cytogenetic aberrations in MM patients with refractory disease include 13q deletion and 1q21 gains in approximately 47.4% and 52.2% of MM patients, respectively.[29]

MM may also be characterized through molecular genetic (gene expression) profiling.[2] High-throughput sequencing of MM patient samples has identified novel driver mutations beyond classical cancer mutations (NRAS, KRAS, and TP53). These include mutations in transcription factors BRAF, FAM46C, DIS3, XBP1, IRF4, and PRDM1, as well as various histone modifying enzymes MLL, MLL2, MLL3, UTX, MMSET (WHSC1), WHSC1L1, and recent inference toward HOXA-9.[30] Whole genome sequencing of MM patient samples from the COSMIC database also identified mutations in AFF1, c12*orf*42, CSMD3, LRRC4C, PCDH7, PTPRD, PPFIBP1, RB1, and ZKSCAN3.[32,30] Identification and investigation of these mutations may aid in the diagnosis of MM cases and potentially identify patients who may be genetically predisposed or susceptible to development of this disease.

MM clonality and tumor heterogeneity also limit the identification of effective therapeutic drugs that target this array of mutations. Secondary genetic mutations are associated with, and thought to determine, the longevity of mutated MM cells, where cells with the greatest resilience and survival likelihood are selectively expanded.[2] Notably, intraclonal heterogeneity is considered to be non-uniform among individual cases as well as within MM cell populations,[2,5] presenting a particular clinical challenge in the context of chemosensitivity and drug resistance. The focus of a substantial amount of research effort is therefore aimed at identifying critical BM microenvironmental and systemic variables contributing to intraclonal, heterogeneic malignancy and subsequent refractory disease.

While the above mutations and phenotypic correlations have been identified as primary risk factors for MM, additional risk stratification has been implemented in populations with MGUS. Risk factors for the progression of MGUS to MM include: 1) increased serum myeloma protein (M-protein); 2) type of M-protein present (e.g., IgG, IgM, IgA)[33]; 3) abnormal ratio of free kappa to lambda light chain immunoglobulins (<0.26, >1.26);[33] 4) presence of >95% (clonal) plasma cells present in the BM;[34] and 5) presence of circulating plasma cells.[16,35] In patients with MGUS, the presence of three or more risk factors is considered "high risk" (approximately 58% 20-year progression within MGUS patient population), two risk factors represents "high-intermediate risk" (37%), one risk factor is "low-intermediate risk" (21%) and the absence of risk factors is considered "low risk" (5%).[16] Approximately 3% of the adult population over the age of 50 are expected to have MGUS.[16] However, due to the absence of symptoms and the lack of standardized MGUS/MM screening procedures, MGUS is often under-diagnosed. Progression of MGUS to MM is discussed in further detail throughout the subsequent sections.

Pathogenesis of MM

The progression of MM begins with the asymptomatic, precursor pathogenic state of MGUS. Evidence indicates that MGUS, previously characterized by myeloma cell growth without bone destruction or other organ involvement, is in fact associated with alterations in the bone. Epidemiologic evidence has shown that patients with MGUS suffer from a significantly increased fracture risk, and that the prevalence of MGUS is increased in patients with osteoporosis.[36] Recent findings by Drake *et al.* have demonstrated that the onset of MGUS is concurrent with the deterioration of both auxiliary and appendicular microarchitecture leading to skeletal fragility.[36] The relationship between bone loss in MGUS and the progression to MM is an area of current interest, as a correlation may suggest that treating bone loss in MGUS could not only decrease fracture risk in these patients, but could also delay the onset of MM, a theory currently under investigation in our labs and others.

In the absence of clinical symptoms, MGUS is diagnosed by quantifying the amount of immunoglobulin present in both the bloodstream and BM, specifically with a plasma cell population of <10% in the BM. With a plasma cell content exceeding 10%, the disease state transitions into either smoldering MM (SMM) or MM (if clinically manifested).[16] MGUS progresses to MM at a rate of 1–2% of patients per year and this transition is likely influenced by the presence of mutational diversity or clonality of MM cell populations as well as changes in the local BM and other systemic factors.[17,31,37,38] MM cells are thought to initially create a plasmacytoma, a single tumor, and then develop into multiple lesions to form the disease of multiple myeloma.[39] Smoldering multiple myeloma (SMM) is an intermediate clinical stage between MGUS and MM. It is classified as having high serum or urinary monoclonal protein as well as clonal BM plasma cells in the range of 10–60%, in the absence of additional myeloma-defining events[40] such as hypercalcaemia, renal insufficiency, anemia, or bone lesions.[41]

With the evasion techniques of clonal evolution and drug resistance, MM may progress to an aggressive, bone-marrow independent disease known as plasma cell leukemia (PCL).[23,37] In

PCL, MM cells proliferate and spread into circulation, causing an increase in plasma cells (≥20%) in the blood and often creating plasmacytomas at other places outside the BM throughout the body.[42] Efforts to fully understand the pathogenesis of both precursor, symptomatic, and terminal-stage MM should aim to identify mechanisms that cause somatic mutations, drug resistance, immune evasion, or relapse as potential drug targets. Treatments that interfere with MM growth and osteolysis in the bone marrow microenvironment (BMM) to slow disease progression and improve patient quality of life and life expectancy are already in use with additional treatments in development.[43]

Pathogenesis of MM within the bone marrow microenvironment

The contributions of the bone marrow microenvironment (BMM) to MM are a focal area of research. The BMM is a highly dynamic niche, capable of renewing damage and responding to systemic energy levels, inflammatory mediators, and endocrine signals.[44–47] The BMM is a primary modulator of both malignant transformation and MM disease progression.[6,48] Along with activated inflammatory agents, reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) are also present in the hypoxic state within the BMM.[49–51] Properties of the BMM allow for infiltration, growth, proliferation, adhesion, and migration of MM cells, while providing the structural and nutritional sustenance to harbor quiescent, drug-resistant MM cells.[2] In addition to providing an optimal substrate for MM initiation and progression, the BMM can also provide activated inflammatory agents including cytokines, chemokines, adipokines (e.g. adiponectin and leptin), and growth factors (e.g. IL-6, IGF-1, VEGF, TNF-α, and SDF-1) secreted by macrophages, neutrophils, and other cells in the BM. These factors then support malignant cell growth, drug resistance and cytotoxicity of healthy cells.[23,52]

Interestingly, ROS formation via cells in the BM niche has been implicated as a potential primary, tumor-initiating event in leukaemogenesis in mice,[53] demonstrating the complexities of understanding oncogenesis in the BMM. Additionally, other BM inflammatory components such as SDF1, a chemoattractant for CXCR4, expressed on MM cells, are also known to promote MM tumor cell BM homing and engraftment;[23] increased expression of CXCR4 in clonal cells supported epithelial-to-mesenchymal transition (EMT)-like transcriptional patterns.[23,54] A hypoxic microenvironment can further enhance the genomic instability for cells within the BM, select for dormant clones, and also contribute to MM cell drug resistance.[23,55,56] Still, the effects of hypoxia on MM remain under investigation as novel model systems to measure or induce hypoxia and quantify cellular responses in the BMM are being engineered and optimized.

The tumor microenvironment is ever evolving in response to changes in the molecular biochemistry, genetic profile, and diversity in type and number of cell populations. Tumors and the surrounding microenvironment are thought to communicate in a highly bi-directional, parasitic manner, each with the potential to alter inherent characteristics of the other.[57] A typical MM tumor microenvironment contains several cellular mediators/cell subtypes, including MM mesenchymal stromal cells, osteoblast (OB) and osteoclast (OC) bone cells, BM adipocytes, and a variety of immunomodulatory cell types (e.g., macrophages, NK cells, regulatory T cells etc.). This type of diverse microenvironment

contributes to the dynamic characteristics of healthy BMM as well as to the growth and survival of a tumor.[6] The roles of these cell types in MM progression are outlined below.[5]

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are of key importance in the BM as they serve as the common progenitor to a variety of BMM cells including osteoblasts (OBs), osteocytes (OCs), and adipocytes. MSCs found in BM are a dynamic cell type with many capabilities including self-renewal, differentiation, cell signaling, injury- and tumor-homing, and immunomodulation.[7,58] MSC function is highly influenced by the surrounding BMM, and is thus altered in many disease states.[6] MSCs from MM patients (MM-MSCs)[7] interact with MM tumor cell clusters,[6,59] and are altered by this interaction but are not genetically compromised. MM-MSCs have also been shown to produce exosomes that specifically contain proteins and microRNAs that promote tumor growth. The role of pharmacological treatments in targeting MM-MSCs are under current investigation, as previously reviewed.[60]

Twenty years ago, it was first shown that MM-MSCs were altered and "hijacked" by myeloma cells to change their expression of certain cytokines (TGF-β1, MIP-1β, and IL-7);[61] this led to a feedback loop enhancing tumor growth by inhibiting pre-B cells to create a more immunosuppressed environment for MM cells to grow. Since then, many abnormalities in MM-MSCs in terms of gene and microRNA expression have been found, some of which enhance drug-resistance of MM cells in the BMM or contribute to decreases in osteoblastic activity.[62] MM-MSCs have been shown to induce bortezomib resistance in MM cells through secretion of IL-8 and other factors that increase MM NF-κB signaling.[63] IL-6, IGF-1, VEGF, TNF-α, SDF-1 and BAFF constitute other stromal elements that promote the survival, migration, and drug resistance of MM cells.[64] IL-6 is of particular importance, as it acts both in paracrine and autocrine manners[65] and targeting MSC-derived IL-6 using siRNAs has recently been proven effective pre-clinically to inhibit MM cell growth.[66]

Osteoblasts

Osteoblasts (OBs) line the bone surface in basic multicellular units (BMUs), separated from the BM by a layer of canopy cells in what has been termed a "bone remodeling compartment (BRC)" (in the trabeculae) or behind a cutting zone led by osteoclasts (in the cortex).[67] Within this compartment, osteoblasts produce and mineralize bone osteoid as osteoclasts resorb bone.[68] In healthy conditions, once activated by coupling-factors released during osteoclast maturation and activity, osteoblasts mineralize and rebuild healthy bone matrices.[69] In MM, osteoblast growth is significantly repressed, resulting in unbalanced osteoclastic bone resorption and abnormal bone turnover.[4,6] The role of osteoblasts in MM and MM drug resistance is still unclear, but osteoblasts appear to suppress MM growth or induce dormancy via paracrine signaling.[70–73] Decorin is one proteoglycan produced by osteoblasts that has been demonstrated to directly inhibit growth and survival of MM cells *in vitro* by inducing apoptosis and subsequent arrest of MM cell cycle.[6,74,75] By contrast, osteoblasts may also promote growth and survival of MM cells through the production of various growth factors or providing a niche to harbor quiescent MM cells, inducing chemotherapy resistance. Factors such as osteocalcin, osteopontin, FGF and TGFβ, which

are synthesized and secreted by osteoblasts, have been identified as factors which modulate the growth and survival of MM cells.[6] Direct osteoblast support, inhibition, or effects on drug resistance of MM cells may be dependent on the characteristics of the surrounding BMM. More remains to be examined in this realm, and three-dimensional models of osteoblasts and MM cells may help us explore these interactions in a more physiologically relevant model than possible in two-dimensional co-cultures.[6,70,76]

Osteoclasts

Osteoclasts (OCs), the major target of bisphosphonate therapies, are the primary mediators of bone resorption in both healthy and pathological bone turnover.[4,76] Clinically, the presence of lytic bone lesions in MM manifests with severe bone pain, pathological fractures, increased bone turnover serum markers, and hypercalcemia.[6] In MM, OC's are increasingly prominent in the BMM due to their activation by various cytokines and signaling pathways.[77–79] With excessive bone resorption overpowering the protective "rebuilding" effects of OBs, the integrity of bone structure becomes compromised by the presence of lytic bone lesions. Pathological lysis of bone tissue activates a vicious cycle, resulting in the ongoing release of calcium, growth factors, and ECM proteins, all of which enhance tumor growth and survival.[80] Osteoclasts may also reactivate dormant MM cells by remodeling the endosteal niche, releasing MM cells from their physical and temporal hibernation.[73] Moreover, osteoclasts, as well as stromal cells, have been shown to protect MM cells from dexamethasone-induced apoptosis.[81] Osteoclasts also support angiogenesis through secretion of proangiogenic factors,[82] hence, targeting osteoclasts through bisphosphonates is efficacious through numerous avenues.

The RANK/RANKL/OPG signaling pathway, deregulated in MM, is one of the important regulatory pathways involved in maintaining the balance between bone remodeling and resorption.[83–85] Receptor activator of NF-κB ligand (RANKL) is produced by osteoblast-progenitor cells as well as MM cells, and signals by binding to its receptor on the surface of the osteoclast-progenitors to stimulate osteoclast differentiation. RANKL also binds osteoprotegerin (OPG) which inhibits RANK/RANKL signaling and, in turn, osteoclastogenesis.[76] In metastatic bone disease, such as MM, this system is dysregulated, leading to increased osteolysis and bone resorption. MM cells directly stimulate osteoclastogenesis through their own production of RANKL but also indirectly manipulate this system by driving increased RANKL expression and decreased OPG in both BM stromal cells and osteoblast.[76] Denosumab, a RANKL neutralizing antibody, was found to be non-inferior and trending towards superior versus zoledronic acid (a bisphosphonate) in one randomized, double-blind study in delaying time to first on-study skeletal related event (SRE) in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.[86] However, overall survival and disease progression were similar between groups and hypocalcemia occurred more frequently with denosumab. Another clinical study, in the recruiting stage, will compare denosumab to zoledronic acid in the treatment of bone disease in subjects with MM.

Osteocytes

A subset of osteoblasts that slow in their building bone activities become buried by their more active osteoblast neighbors until they are fully embedded in bone matrix and differentiate into osteocytes. Osteocytes sit within lacunae, tiny crevices within bone, and make up ~95% of bone cells.[87] These cells regulate the response of bone to mechanical stress through the secretion of factors including sclerostin and RANKL into the BMM to modulate osteoblast and osteoclast activity.[88–90] Sclerostin, a Wnt inhibitor,[91] decreases OB differentiation from MSCs,[92,93] and is also secreted from some MM cells to suppress OB differentiation *in vitro*.[94] Interestingly, osteocyte number is decreased and osteocyte apoptosis is increased in MM,[95] while circulating sclerostin levels are positively correlated with bone disease severity in MM patients.[96] Sclerostin is also upregulated in the BMM of MM patients versus healthy people and sclerostin is overexpressed by plasma cells from MM patients.[97,98] These findings implicate sclerostin as a novel target corrupting the BMM, skewing the balance away from osteoblastogenesis and toward osteolysis.

Adipocytes

In addition to bone cells, adipocytes in the BMM also interact with MM cells. In the classical model of lineage commitment, adipocytes arise from MSCs and are the major cell type found in adipose tissue. Lipid-laden adipocytes serve as an energy reserve in the BM and also serve an endocrine function through the expression and secretion of hormones known as adipokines (e.g., leptin and adiponectin), and growth factors (e.g., IL-6, TNF-α, MCP-1, and insulin), which may promote myelomagenesis or disease progression.[18] Bone marrow adipose tissue (BMAT) has been characterized as yellow adipose tissue, which has gene expression patterns that overlap with both white and brown fat.[99] This suggests that BMAT can serve as an important regulator of energy maintenance in the BM niche during times of stress.[99] Clinical studies have suggested an association between BMAT and an increased likelihood of MM[100,101] but the direct relationship and potential mechanisms remain largely unexplained. Adipocytes isolated from MM patient femoral biopsies can support myeloma growth *in vitro*,[102] and a recent study suggests that they may protect MM cells from chemotherapy-induced apoptosis.[103]

Obesity has been established as a physiological risk factor for MM development, and obese individuals have shown a 1.5–2 fold elevated risk for developing MM when compared to individuals of normal weight.[18,22] Circulating adiponectin, which is inversely proportional to fat mass,[104] has been shown to inhibit proliferation of MM and reduce tumorigenic angiogenesis.[105,106] Inhibition via adiponectin occurs through several signaling pathways, including cyclic AMP-dependent protein kinase A (PKA), signal transducer and signal activator 3 (STAT3), mitogen-activated protein kinase (MAPK), β-catenin, and phosphatidylinositol 3-kinase (PI3K/AKT).[106] This results in the anti-proliferative and anti-tumorigenic effects seen in MM, breast, prostate, colon, and liver epithelial cell cancers.[18,106] From a mechanistic perspective, deficiency in adiponectin (as seen in obesity) limits the biological actions of several signaling pathways that are essential to preventing growth, proliferation, migration, and drug resistance in MM cells.[22] Additionally, leptin may play a role in the transition from MGUS to MM through the regulation of the osteoprotegrin/RANKL signaling pathway. Elevated serum leptin levels have been documented in MM

patient populations when compared to healthy individuals.[107,108] Together these results suggest that adipocytes may support advancement of MM in the BM niche; however, additional studies are required to evaluate this hypothesis.

Immunomodulatory factors

In addition to osteoclasts, other HSC-derived cells populate the BM niche, including tissue-specific macrophages known as *osteomacs* and other immune cells.[48] Osteomacs are responsible for the regulation of HSCs in the BM niche by directing their homing and colonization, as well as their transition between active stem cell status and dormancy.[109] Other immune cells that populate the BM include additional macrophages, neutrophils, and myeloid-derived suppressor cells, all of which may respond to stress, affect tumor growth, and affect bone turnover and other BM cells.[110,111] Regulatory T cells in the BM niche create an immune-privileged[112] or immunosuppressive environment that can be corrupted by the colonization of foreign entities including cancer cell types.[48,111] Importantly, immune cells in the microenvironment can be modulated by the tumor to provide favorable conditions for MM tumors. Specifically, myeloid-lineage progenitor cells have been demonstrated to support tumor cells both *in vitro* and *in vivo*.[113,114] Immune cell populations are often skewed by MM cells, with increased regulatory T cells (immune-inhibiting) and decreased activity and/or number of effector T cells (tumor killing) present in the BM.[115] Upon tumor invasion, mononuclear cells begin to produce and secrete VEGF, which stimulates mobilization of endothelial cells and subsequent tumor vascularization.[116]

Endothelial cells

The BMM is conducive to MM cell homing and proliferation in part due to unique BM endothelial cells that express adhesion proteins that specifically enable the rolling and intravasation of MM cells through fenestrated BM capillaries.[57] Angiogenic cytokines and growth factors are primarily modulated through BM stromal cells.[6,54] Endothelial cells and endothelial progenitor cells, which are associated with BM stromal cells, mobilize in response to microenvironment stress, such as MM invasion, to stimulate vasculogenesis of the BM niche.[117] In addition to stimulating VEGF secretion from mononuclear cells, tumor cells also secrete extremely high amounts of VEGF to stimulate the production and release of IL-6 from endothelial cells and BM stromal cells.[116] This creates a feedback stimulus of IL-6 signals from the endogenous endothelial cells to increase VEGF, indirectly promoting vascularization of MM-infiltrated bone. Studies suggest that vasculogenesis as mediated by endothelial and endothelial progenitor cells may represent an early disease event that takes place during the transition from either MGUS or smoldering MM to overt MM.[118]

Treatments

While MM remains incurable, new therapies have substantially improved patient quality of life and survival rates. Treatment of MM has substantially progressed in the last decade, with the development of novel pharmaceutical agents and the use of bisphosphonate drugs in conjunction with autologous stem cell transplantation (ASCT). New approaches have focused on the co-treatment of specific proteasome inhibitors (PIs) with immunomodulatory drugs (IMiDs), the use of monoclonal antibodies, and histone deacetylase inhibitors.

Nonetheless, chemotherapy and steroids remain effective treatments for most MM patients. Highlighted below and in Table 1 is a compilation of the most common treatments currently used for MM.

Chemotherapy

MM is often treated with classical chemotherapies to target and destroy cancer cells.[95] Chemotherapeutics commonly used for MM include: melphalan, vincristine, doxorubicin and liposomal doxorubicin.[119] These are used primarily in the treatment of overt MM, as patients with asymptomatic, smoldering MM do not benefit from chemotherapy.[16,120] Chemotherapeutics are often used in conjunction with ASCT, which is able to both replenish stem cells and potentially induce BM remodeling.[121] This treatment combination has been shown to increase progression-free survival and overall survival in MM patients, and may be used in the treatment of relapsed, refractory MM.[122,123] Additional combination treatments that utilize the cancer targeting aspects of chemotherapy drugs as well as agents that target and modulate bone remodeling such as proteasome inhibitors and bisphosphonates are now used to treat MM. Specifically, doxorubicin has been combined with the proteasome inhibitor, bortezomib, to treat patients with refractory MM. This dual treatment resulted in a greater myeloma-suppressive effect than bortezomib alone.[124,125] Combination therapies utilizing chemotherapy and bisphosphonates have response rates as high as 80% in newly diagnosed patients[126], and up to 75% in patients with relapsed disease.[127]

Proteasome inhibitors

Proteasome inhibitors such as bortezomib or the second-generation carfilzomib block the proteasome, leading to the accumulation of proteins in MM cells, causing their destruction.[128,129] Specifically, bortezomib has been shown to promote apoptosis in MM cells as well as osteoclasts (attenuating bone loss) and induce osteoblast differentiation[80,130,131] Bortezomib has been shown to enhance the activity of certain concurrent therapies (e.g., lenalidomide and dexamethasone) and is often prescribed in combination with other anti-MM drugs due to its chemosensitizing effects.[132–138] However, there are clinical challenges associated with bortezomib therapy including drug resistance and off-target effects including peripheral neuropathy.[139,140] Carfilzomib has been demonstrated to also be effective when used with lenalidomide and dexamethasone by significantly reducing the minimal residual disease in patients that are newly diagnosed with MM.[141–143] Due to the effectiveness of bortezomib, next-generation proteasome inhibitors are currently being developed (e.g., oprozomib, ixazomib, marizomib, and delanzomib). Many of these new proteasome inhibitors are being used after treatment with bortezomib, where MM progresses to bortezomib resistance or becomes relapsed and refractory MM.[144]

Bisphosphonates

Bisphosphonates are a class of drugs that inhibit resorption of bone by blocking osteoclasts and decrease osteolytic bone pain.[145,146] It is well known that MM is able to increase the number of OCs within the BMM,[147,148] leading to bone pain, hypercalcemia, and increased bone fractures in patients.[149–151] Therefore treatment with bisphosphonates is commonly used in conjunction with proteasome inhibitor drugs[152–154] or chemotherapy to kill tumor cells and inhibit bone destruction.[155,156] Several studies suggest that bisphosphonates may

not have direct anti-tumor effects, despite their bone-protective effects.[157–159] Specifically, nitrogen-containing bisphosphonates alendronate, pamidronate and zoledronate are all FDA approved and are often administered as a crucial aspect of MM patient pain and bone disease management.[160]

Immunomodulatory drugs and monoclonal antibodies

Endogenous immunomodulatory actions and/or immunodeficiency can significantly impact the dynamics of the BMM to either promote or suppress MM tumor cell growth.[23,115] Recent drug therapies for many cancer types, including MM, continue to support a paradigm shift in using an immunomodulatory approach for the management and treatment of malignant disease. As recently reviewed by Kawano et al., MM tumor cells can induce pronounced immunosuppression both systemically as well as locally at the BMM.[115] Immunodeficiency in the BMM is characterized by an increase in immunosuppressive cell populations, including regulatory T cells and myeloid derived suppressor cells (MDSCs).[161] In the pathogenesis of MM, the ability of MDSCs to differentiate into immune-protective macrophages and granulocytes is inhibited.[115,162] Thus, restoration of tumor-suppressor immunomodulation is a crucial component in the development of anti-MM drug therapies.

Lenalidomide and pomalidomide, second generation immunomodulatory drugs (IMiDs), enhance the sensitivity of MM cells to both bortezomib and dexamethasone. They also promote the tumor suppressor actions of host immune defense mechanisms.[163] For this reason, multiple combination therapies are often utilized in clinical practice to improve treatment response by delaying progression or recurrence and improving symptom management.[164–168] A Phase 3 trial found pomalidomide therapy combined with low-dose dexamethasone to be safe and effective in patients with relapsed MM disease, who had previously been treated with bortezomib or thalidomide.[169] Richardson and colleagues have recently published Phase 2 clinical trial outcomes exploring the maximum tolerated dose (MTD) of lenalidomide in patients with relapsed or refractory MM disease.[165] Findings from this investigation revealed that the MTD of lenalidomide (15 mg/day) administered alongside low-dose dexamethasone (40 mg/week) on the first 21 of 28 total days of treatment was tolerable and resulted in favorable results in response and 2-year survival rates.[165] Thalidomide, the first generation IMiD, is still commonly used for managing MM by inhibiting angiogenesis, inducing apoptosis of MM cells, and inhibiting the secretion of IL-6 and VEGF by MM cells during adhesion to BM stromal cells.[170] Like other IMiDs, thalidomide is currently being used with PIs (bortezomib or carfilzomib) and corticosteroids (e.g., dexamethasone, prednisone, prednisolone, and methylprednisone).[171–175] Developments in MM drug therapies will likely continue to maximize selectivity through antibody-mediated mechanisms combined with proteasome inhibitors, IMiDs, bisphosphonates and traditional chemotherapy.[117,161]

Monoclonal antibodies are increasingly being utilized to treat myeloma patients, both to target the myeloma cells directly and to modulate the immune response and microenvironment.[176] Recent work with daratumumab, a human monoclonal antibody that binds CD38,[177] has shown target-cell killing of tumor cells.[178] CD38 is a transmembrane glycoprotein that is highly expressed by myeloma cells, making this a desirable, myeloma-

specific target.[179] Importantly, single agent daratumumab treatment, which has recently been approved by the FDA, was effective in patients with refractory disease, including those who had previously been treated with lenalidomide and bortezomib.[178] Radioimmunotherapy (RIT), which combines radiation with immunotherapy, is in preclinical stages as a treatment for MM. Perhaps the most promising RIT in respect to MM treatments is the use of indatuximab ravtansine, an antibody targeting CD138 antigen, which is expressed in greater than 95% of MM cells.[180,181] Recent work has shown that coupling this antibody to radioactive isotopes significantly increased survival in animal models of MM.[181] The targeting of antigens and other cell-surface proteins in the treatment of cancers is rapidly expanding through the use of antibody-drug conjugates, which combine the specificity of a monoclonal antibody with a small anti-cancer drug molecule. Pre-clinical *in vitro* and *in vivo* work with these conjugates has demonstrated promise in the treatment of MM and other hematological cancers.[182]

Another promising new approach to MM treatment is the addition of an immunostimulatory agent, elotuzumab, to the now standard treatment of lenalidomide and dexamethasone therapy.[1,30] Elotuzumab, a FDA approved humanized immunoglobulin G1 monoclonal antibody, targets signaling lymphocytic activation molecule F7 (SLAMF7).[183] SLAMF7, expressed by both natural killer (NK) and MM cells, plays an integral role in the activation of NK cells through binding with the EAT-2 adapter protein.[161,184] In MM cells, EAT-2 is significantly under-expressed, resulting in poor SLAMF7 signaling. Elotuzumab is able to reduce tumor burden through the activation of NK cells that induce antibody-mediated apoptosis of MM cells, with little effect on healthy cells.[161,184]

In addition to bisphosphonates, other bone anabolic and anti-resorption agents such as anti-DKK1, anti-sclerostin, and anti-activin A antibodies are being explored for stimulating bone healing and regrowth in MM patients, and may also have anti-tumor effects.[94,96–98,185–192] Specifically, antibodies used to target and suppress DKK1 in pre-clinical trials have been shown to prevent the development of MM-induced osteolysis and increased bone formation in animal models.[193] SOST-neutralizing antibodies (anti-SOST), which have been shown to increase bone formation and bone volume in both experimental models of and patients with osteoporosis, are also under development as a potential treatment for MM.[194,195] Two recent studies have indicated the efficacy of anti-SOST antibody to prevent MM induced bone loss and inhibit MM growth in mouse myeloma models.[192,196]

The use of monoclonal antibodies and their effectiveness to treat MM both in early experimental models and in clinical trials has demonstrated the importance of understanding the molecular mechanisms of MM progression, including MM interaction with other cell types within the BM niche. For more information on the potential of monoclonal antibodies in the treatment of myeloma, please refer to the review by Sondergeld *et al.*[197]

Histone deacetylase inhibitors

Epigenetic modifications have been shown to play a major role in cancer development resulting in aberrant histone modifications.[198] Histone acetylation is a major regulatory mechanism of gene transcription, where histone deacetylases remove acetyl groups from the histone lysine residues, resulting in repressed transcription.[199] Histone deacetylase inhibitors

(HDACi) have been shown to inhibit cell growth and induce apoptosis in MM cells as both a single treatment or in conjunction with bortezomib treatment.[200,201] Furthermore, HDACi are able to overcome the bortezomib resistance that is commonly seen in MM cells.[202] There are several HDACi that are currently under evaluation.[203] The first FDA-approved HDAC inhibitor was suberoylanilide hydroxamic acid (SAHA), which is commonly used in combination with bortezomib or lenalidomide.[204–206] MM treatment with the HDACi vorinostat or panobinostat, with bortezomib or bortezomib/dexamethasone, has been shown to prolong MM patient survival for 0.8 months and 3.9 months, respectively.[204,207] Yet, further studies are needed in order to fully elucidate the epigenetic modifications and interactions in MM and the role of epigenetics in MM progression and pathogenesis.

Future directions and conclusions

The pathogenesis of multiple myeloma is influenced by alterations, aberrations, and/or dysregulation in endocrine, vascular, genetic, and metabolic factors. Thus, identifying and targeting the corresponding molecular pathways is crucial in working toward the optimal delivery of individualized pharmacologic therapies in MM. Increases or excess in adiposity may contribute to MM risk via systemic pro-inflammatory effects or BM specific adiposity; this requires further investigation in patient populations as well as in both *in vitro* and *in vivo* models. Multiple myeloma is characterized by the presence of osteolytic bone lesions, resulting from prolonged declines in osteoblast-mediated bone mineralization, increases in bone resorption by osteoclasts, and propagation of the vicious cycle.[208] While this review has focused mainly on the effects of the BM niche on MM pathogenesis, neuro-endocrine regulation of bone metabolism could also play a role in MM progression. For example, sympathetic nervous system (SNS) fibers, known to innervate cortical bone, modulate a number of outcomes, including regulating homeostatic hormonal control of bone turnover.[208] Please refer to the elegant review by Elefteriou *et al.*[209] for more information on the effects of the SNS on bone remodeling in response to many factors including oncogenesis. The complex regulation of MM from multiple systems (the BMM and beyond) makes understanding and combatting disease initiation and progression difficult. Integration of these effects is necessary to provide better therapeutics and work toward a cure.

Myeloma is now being treated by therapies aimed at either directly killing tumor cells or normalizing the aberrant tumor microenvironment. Treatments such as bisphosphonates, which inhibit osteolysis, and IMiDs that stimulate immune cell activation have been implemented with success. As we gain better understanding of the bone, BM, and blood biology disrupted by MM, we are developing safer, more efficacious treatment strategies. Exciting, novel strategies to inhibit the vicious cycle and osteolysis and heal osteolytic lesions based on a better understanding of the basic biology of the disease and the BMM are in development.[6,210–212] These microenvironment-targeting treatments, in conjunction with ASCT will induce better patient outcomes, and are leading the way in the treatment of relapsed, refractory MM.[123] Interesting new directions may target osteocytes and osteoblasts, as we learn more about the roles of these and other cells in the BM.

Novel strategies are also being explored in the preclinical setting targeting NF-κB, JAK, MEK, Pim, PYK2, Src, mTor, PDPK1/RSK2, PERK, and other kinases and

pathways.[213–223] Targeting hypoxia (e.g., HIF1α) and double-strand break repairs are other avenues being explored. Moreover, many novel strategies are being employed using chimeric antigen receptor T cells[224–226] and other engineered immune responses against MM in preclinical models that may soon make their way to the clinic. Combinatorial strategies, as with all cancers, are inevitably required for the most efficacious treatments. More targetable and prognostically significant genomic alterations are continually arising as our bioinformatics, sequencing, and preclinical validation capacities grow, and high-throughput drug screens are enabling more rapid, accurate identification of novel natural and synthetic anti-MM therapies.

A crucial aspect in the fight against MM and other cancers is the prevention of the disease, an issue arguably underrepresented in cancer research due to challenges in proving effectiveness. The integration of multi-system regulatory factors through the use of better disease models is crucial for continued understanding of MM pathogenesis for better prevention, as well as treatment approaches. In the meantime, more thorough characterization of patient tumors through genetic and epigenetic sequencing, and other profiling techniques, as well as increased sharing of patient data among centers, will provide critical information about potential causations linking systemic health, genetics, epigenetics, and environment, to cancers including myeloma. Lastly, we suggest one of the greatest strategies in accelerating effective myeloma research may be a collaborative, transparent “pre-competitive” space for researchers and pharmaceutical companies alike. We envision that transparent sharing of data and results will push the myeloma research field forward in a novel, patient-centric manner towards a cure, or, more realistically, patient-specific cures. Such a space and cooperative agreement would optimize our global scientific journey towards a greater understanding of this and other diseases, and accelerate research and discoveries relevant for those who rely on rapid development of effective therapies.

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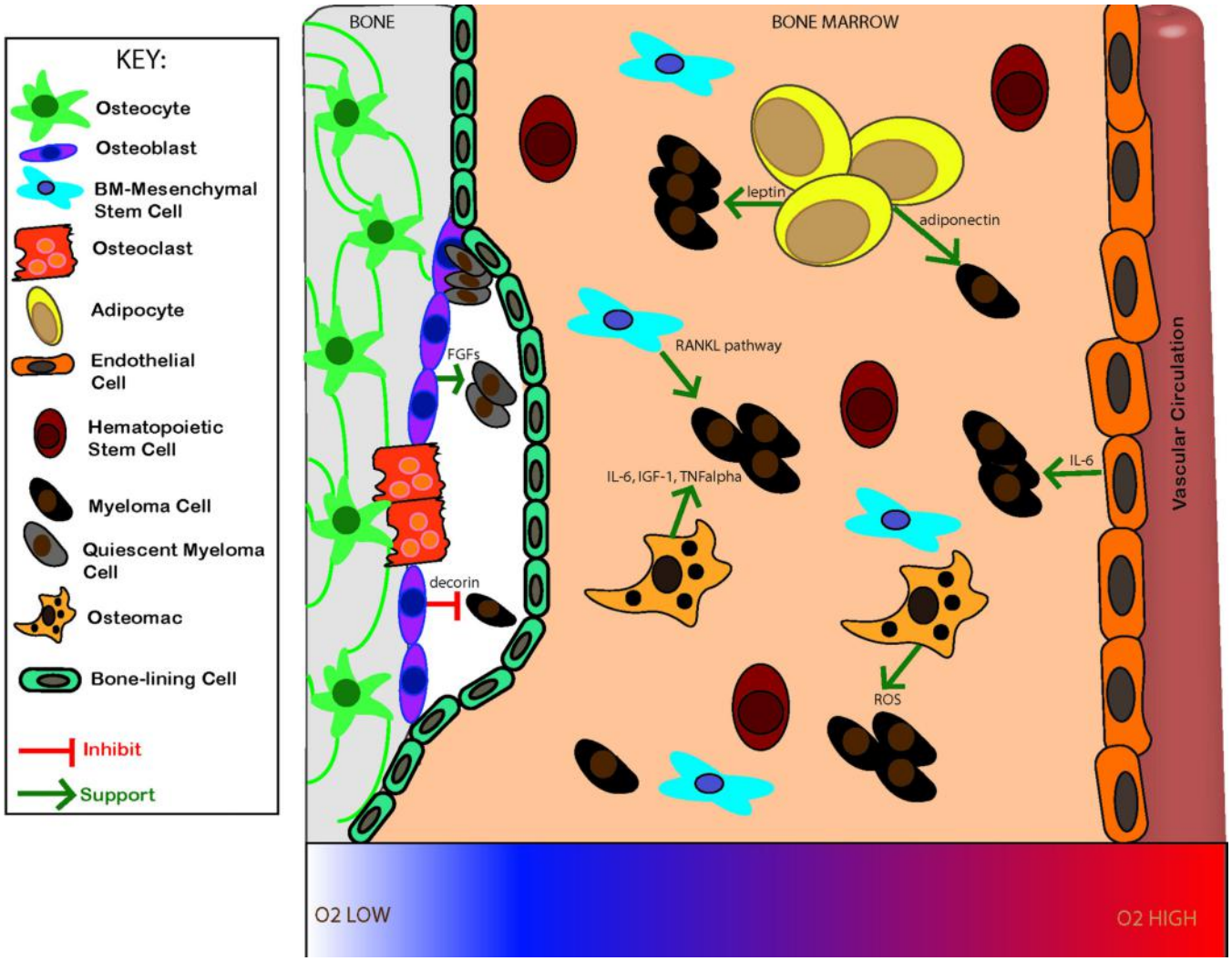

FIGURE 1.

The bone marrow microenvironment: osteoclastic and vascular niches. Schematic of the bone marrow microenvironment and its role in multiple myeloma. Pathogenesis and progression of MM is carried out via pathological bone resorption, resulting in the formation of lytic bone lesions and the degradation of bone density. Additionally, cells within the BMM may contribute to MM cell migration, adhesion, quiescence and tumor formation, which triggers the release of soluble growth factors, collectively promoting invasion of the microvasculature by the MM tumor.

Table 1

Current treatments used to treat multiple myeloma

Drug	Type of drug	Clinical trial phase	References and/or trial identification numbers
BORT	PI	FDA approved	
BORT/LEN/DEX	PI/IMiD/steroid	III	NCI-2010-02211, IFM/DFCI 2009, NCT01208662
BORT/LEN/DEX/LEN	PI/IMiD/steroid/IMiD	II	Roussel *et al.*[227]
CARF	PI	FDA approved	
CARF/LEN/DEX	PI/IMiD/steroid	III	Stewart *et al.*[228]; E1A11, NCI-2012-02608, ECOG-E1A11, NCT01863550
CARF/POM/DEX	PI/IMiD/steroid	I/II	AMyC 10-MM-01, NCI-2012-01279, IST-CAR-521, PO-MM-PI-0034, NCT01464034
THAL/DEX	IMiD/steroid	III	MT2003-13, NCI-2010-01413, 0312M54569, 2004LS001, NCT00293306, UMN-2004LS001, UMN-MT2003-13, UMN-0312M54569, NCT00177047
Oprozomib	PI	Pre-clinical	Hurchla *et al.*[229]
Ixazomib/LEN/DEX	PI/IMiD/steroid	III	NCI-2012-02752, 2011-005468-10, C16011-CTIL, NL41603.028.12, U1111-1164-7621, NCT01659658
Delazomib	PI	I	Gallerani *et al.*[230]
Melphalan/THAL/PRED/DEF	Chemo/IMiD/steroid/antic	I/II	Palumbo *et al.*[231]
Vincristine	Chemo	III	Kyle *et al.*[232]
CYCLO/THAL/DEX	Chemo/IMiD/steroid		Garcia-Sanz *et al.*[127]
DOX/LEN/BORT	Chemo/IMiD/PI	I/II	Jakubowiak *et al.*[168]
Liposomal DOX/DEX/LEN	Chemo	II	Baz *et al.*[233]
Bendamustine	Chemo	I	Michael *et al.*[234]
Etoposide	Chemo	Pre-clinical	Wood *et al.*[235]
LEN	IMiD	FDA approved	
POM	IMiD	FDA approved	
POM/DEX	IMiD/steroid	III	San Miguel *et al.*[205]
ELO	IMiD	FDA approved	Starr[236]
LEN/BORT/DEX/ELO	IMiD/PI/steroid/Ab	I/II	Usmani *et al.*[237]
Daratumumab	Ab	FDA approved	
BI-505	Ab	I/II	Hansson *et al.*[238]
Rituximab	Ab	II	Baz *et al.*[239]; Bergua *et al.*[240]; Korte *et al.*[241]
SAHA	HDACi	I	Mitsidades *et al.*[242]; Richardson *et al.*[243]
LBH589	HDACi	III	San-Miguel *et al.*[207]
AR-42	HDACi	Pre-clinical	Canella *et al.*[200]
Vorinostat	HDACi	I	Vesole *et al.*[244]
Ricolinostat (ACY-1215)	HDACi	Ib/II	Yee *et al.*[245]

BORT, bortezomib; LEN, lenalidomide; DEX, dexamethasone; CARF, carfilzomib; POM, pomalidomide; ELO, elotuzumab; Ab, antibody; PI, proteasome inhibitor; IMiD, immunomodulatory drug; HDACi, histone deacetylase inhibitor; Chemo, chemotherapy; CYCLO, cyclophosphamide; DOX, doxorubicin; PRED, prednisone; DEF, defibrotide; antic, anticoagulant