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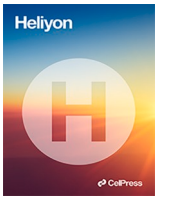

Review article

Pathways to therapy resistance: The sheltering effect of the bone marrow microenvironment to multiple myeloma cells

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A B S T R A C T

Multiple Myeloma (MM) is a malignant expansion of plasma cells in the bone marrow (BM), resulting in a disease characterized by symptoms of end organ damage from light chain secretion, crowding of the BM, and bone lesions. Although the past two decades have been characterized by numerous novel therapies emerging, the disease remains incurable due to intrinsic or acquired drug resistance. A major player in MM's drug resistance arises from its intimate relationship with the BM microenvironment (BMME). Through stress-inducing conditions, soluble messengers, and physical adhesion to BM elements, the BMME activates numerous pathways in the myeloma cell. This not only propagates myeloma progression through survival and growth signals, but also specific mechanisms to circumvent therapeutic actions. In this review, we provide an overview of the BMME, the role of individual components in MM survival, and various therapy-specific resistance mechanisms reported in the literature.

1. The perfect match: myeloma and the bone marrow

Multiple Myeloma (MM) is a cancerous proliferation of plasma cells within the bone marrow (BM). It accounts for 1 % of all cancer cases and is the second most prevalent blood cancer after non-Hodgkin's lymphoma [2]. The disease is distinguished by manifestations of end organ damage caused by the release of light chains, the accumulation of cells in the BM, and the presence of bone lesions. It predominantly affects older individuals, with the typical age of onset being between 66 and 70 years. Due to the reduced physiological capacity and chemotherapeutic tolerance of senior individuals, treating this disease is challenging. Despite the emergence of various innovative medications in the previous two decades, the disease remains incurable due to the development of drug resistance [3].

The malignant plasma cells originate in the BM, progressing from monoclonal gammopathy of unknown significance (MGUS) to MM [5]. The bone marrow microenvironment (BMME) plays a crucial role in the advancement and expansion of myeloma, mostly because it contains growth factors, cytokines, and stem cells [6,7]. The BM's feeding, compartmentalized, and producing characteristics are essential for the resistance of MM to therapy [3].

The BMME is composed of a diverse range of cells including hematopoietic cells, mesenchymal stem cells, mesenchymal stromal cells, osteoblasts, osteoclasts, endothelial cells, endothelial progenitor cells, fibroblasts, pericytes, and combination of immune cells

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[7–10]. The extracellular matrix (ECM) contains proteins, such as fibronectin, as well as other cytokines, growth factors, and chemokines [10,11]. Myeloma cells are known to occupy a specialized space in the BM, referred to as a "niche". This niche provides a conducive environment for the growth and sustenance of myeloma cells, while simultaneously providing protection against the effects of chemotherapy [11] (Fig. 1). The bone marrow stromal cells (BMSCs) of MM patients exhibit significantly elevated amounts of growth factors, such as stem cell factor (SCF), vascular endothelial growth factor (VEGF), and interleukin-6 (IL-6), in comparison to BMSCs seen in healthy individuals [12–18].

1.1. Immune components in microenviromentment

BMME is crucial in the emergence of treatment resistance in MM, with immune cells playing a significant role [8]. Within the BMME, different types of immune cells, such as macrophages, T cells, regulatory T cells (Treg), natural killer (NK), and myeloid-derived suppressor cells (MDSCs), interact with myeloma cells to provide a protective environment [19]. Macrophages, namely M2-polarized macrophages, release cytokines and growth factors including IL-6 and transforming growth factor- β (TGF-β). These substances enhance the survival and expansion of myeloma cells while preventing apoptosis. The Tregs inhibit anti-tumor immune responses, creating an immunological-tolerant environment that enables myeloma cells to avoid immune recognition and elimination [8,19]. The MDSCs contribute to the suppression of the immune system by generating arginase and reactive oxygen species, which further reduce the efficiency of immune-mediated anti-tumor responses [20]. These interactions not only promote the life of myeloma cells, but also lead to drug resistance by activating signaling pathways that increase cell survival and the removal of drugs, so lowering the effectiveness of therapeutic medicines. Due to the constraints of space, we will not be able to provide a comprehensive discussion on the role that each immune cell plays in drug resistance. However, there are numerous devoted reviews that cover the role of immune cells in MM and resistance in a comprehensive manner [8,21,22].

1.2. Myeloid-derived suppressor cells

The BMME members have diverse roles and exert ramifications on resistance to MM medication therapy. One of these members is a type of cells called MDSCs. In typical circumstances, there are a few immature myeloid lineage cells present in the BM that have the ability to rapidly transform into macrophages, dendritic cells, or granulocytes [23].

Nevertheless, in the context of MM, the BMME has the potential to disrupt the process of differentiation and impact the growth of

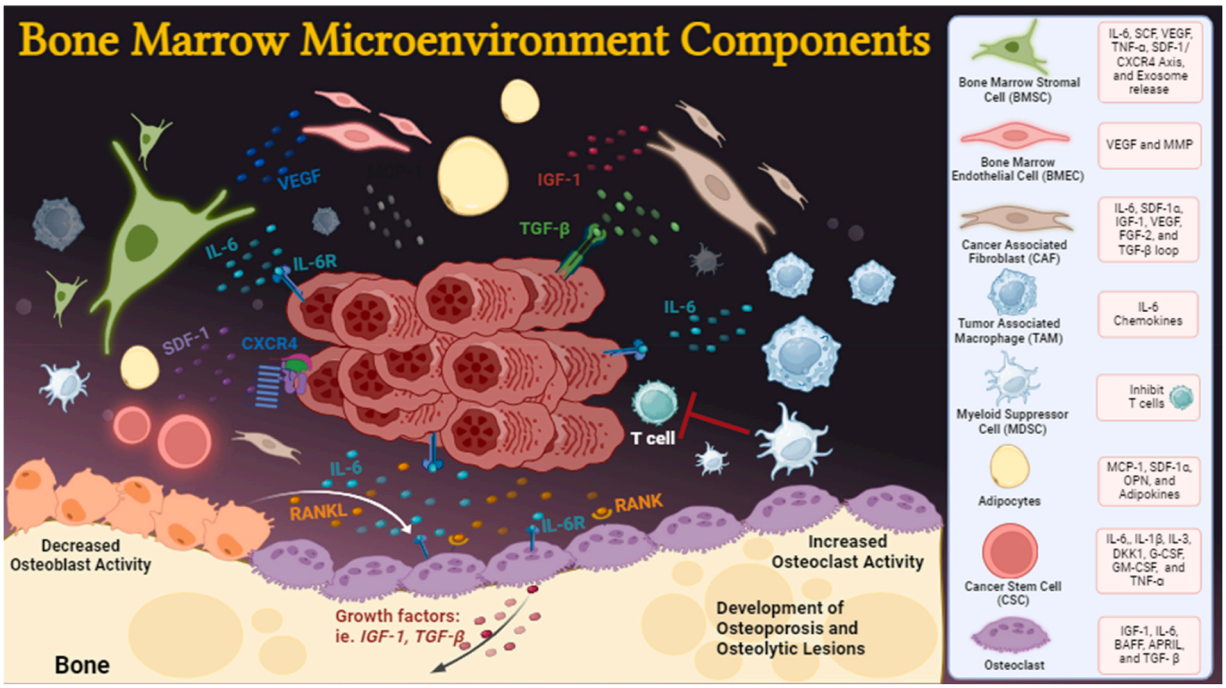

Fig. 1. The constituents of the BMME. Signal transduction via paracrine and autocrine messengers are imperative for myeloma pathogenesis, growth and ultimate survival. IL-6: Interleukin-6; CXCR4: Chemokine receptor type 4; SDF-1: Stromal cell-derived factor 1, IGF1; Insulin Like Growth Factor 1; VEGF: Vascular endothelial growth factor; TNFα: Tumor necrosis factor alpha; MMP: Matrix metalloproteinase; FGF2: fibroblast growth factor 2; TGFβ: Transforming growth factor-beta; MCP1: Monocyte chemoattractant protein 1; OPN: osteopontin; DKK1: Dickkopf-related protein 1; G-CSF: granulocyte colony-stimulating factor; BAFF: B-cell activating factor; APRIL: A proliferation-inducing ligand. Figure made utilizing BioRender.com.

the MDSC lineage through the action of substances including VEGF, GM-CSF, and IL-6 [23,24]. MDSCs possess a notable capacity to inhibit T-cell activity by triggering the generation of arginase 1 (ARG1), inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and peroxynitrite [24]. As a result, they let malignant myeloma cells avoid the immune system and promote the advancement and spread of the disease [23,25,26]. IL-18 is a possible therapeutic target that can be used to overcome resistance caused by MDSCs. Nakamura et al. demonstrated that IL-18 enhances the function of MDSCs, and that the effectiveness of bortezomib treatment was linked to an elevated ratio of $CD8^+$ T-cells to MDSCs [27].

1.3. Osteoclasts

Osteoclasts play a crucial part in the development of bone disease in MM and have been discovered to contribute to the resistance of MM drugs. They exert a substantial impact on the tumor microenvironment through a mutually reinforcing loop with MM cells. When myeloma cells come into contact with BMSCs, it triggers the production of growth factors and cytokines. These substances activate osteoclasts, causing them to break down bone and release stored growth factors derived from bone, such as insulin-like growth factor 1 (IGF-1) and TGF-β. The growth factors attach to receptors on the surface of tumor cells and trigger SMAD and MAPK signaling. Additionally, extracellular calcium binds and activates calcium pumps, which promotes the proliferation of tumor cells [28]. In addition, this connection stimulates the RANK/receptor activator of nuclear factor-κB ligand (RANKL) pathway, leading to an increased differentiation of osteoclasts from MDSCs. Research has demonstrated that osteoclasts can promote the survival of myeloma cells by direct contact, involving the participation of IL-6 and osteopontin [29].

1.4. Tumor associated macrophages

Tumor associated macrophages (TAMs) are essential elements of tumor microenvironments, exerting influence on the advancement of several solid and hematologic malignancies [30]. TAMS contribute to the processes of angiogenesis, invasion, and proliferation [31,32]. They enhance the survival of myeloma cells by producing more IL-6 [31]. A study discovered that the existence of TAMs led to resistance against melphalan by inhibiting caspase-3 activation and poly(ADP-ribose) polymerization (PARP), while also maintaining Bcl-xL levels [33].

1.5. Bone marrow endothelial cells

Bone marrow endothelial cells (BMECs) have a significant function in the dynamic and vascular environment of the BMME [7,34]. BMECs have been involved in the autocrine loops of both VEGF and HGF/cMET in MM patients, which allows for the proliferation of plasma cells and the progression of the disease [35,36].

When comparing the BMECs of patients with MM to healthy HUVEC cells, researchers Vacca et al. observed that BMECs had more angiogenic activity and displayed higher amounts of angiogenic markers VEGFR-2, Tie-2/Tek, bFGFR-2, CD61, CD105, and CD133. In addition to promoting both angiogenesis and vasculogenesis, BMECs were discovered to facilitate adhesion and invasion of malignant plasma cells by secreting bFGF, VEGF, MMP-2, and MMP-9 [37].

Patients with relapsed/refractory MM have shown increased expression of stabilized hypoxia inducible factor-1α (HIF-1α) in their BMECs, which is associated with higher levels of ROS generation. The blood-brain barrier endothelial cells that had increased levels of stable HIF-1α showed resistance to the drugs bortezomib and lenalidomide. However, when HIF-1α was inhibited using siRNA or Panobinostat, the resistance was eliminated. This was accompanied by decreases in several proteins associated with drug resistance and cell adhesion, including GSTP1, HSP70, LASP-1, and GRP [38]. In addition, multiple clinical trials have provided evidence that the addition of panobinostat to bortozomib and dexamethasone improves response and progression-free survival in patients with bortezomib-refractory MM. However, it does not have a significant impact on overall survival [39,40].

1.6. Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) constitute a significant proportion of the microenvironment in several solid and hematologic malignancies [10,41]. Cancer-associated fibroblasts (CAFs) contribute to the advancement, survival, and movement of MM by producing various factors including TGF-β, IL-6, SDF-1α, IGF-1, VEGF, and FGF-2 [42]. Frassanito et al. showed that bortezomib-resistant CAFs can shield myeloma cells from the effects of bortezomib when they are grown together by producing various substances, including IGF-1, IL-6, IL-8, TGF-β, and exosomes [43]. Their examination of bortezomib-resistant CAFs revealed a connection between cellular stress and a self-regulating TGF-β loop, leading to the amplification of the autophagy pathway [43].

CAFs have a significant impact on the development of resistance to MM and the formation of an immunosuppressive microenvironment [44]. Therefore, they are a promising target for immunotherapy. Sakemura et colleagues demonstrated that the creation of dual chimeric antigen receptor T (CAR-T) cells, which target both B-cell maturation antigen (BCMA) and CAFs, resulted in increased survival rates and long-lasting remissions in mice compared to CAR-T cells that either targeted BCMA or CAFs individually [45]. Furthermore, their work indicates that cancer-associated fibroblasts CAFs create an immunosuppressive microenvironment by producing TGF-β [45].

1.7. Adipocytes

Obesity is a global epidemic, and increasing research is establishing a link between adipose tissue and the development of cancer. Bone marrow adipose tissue (BMAT) contributes to the BMME by releasing adipokines and participating in metabolic processes [46–48]. Studies have demonstrated that adipokines promote the formation of prostate cancer and other solid tumors. However, their involvement in hematologic malignancies is not as well-defined [23,49]. However, studies have demonstrated that obesity increases the likelihood of MGUS progressing to MM [28,50]. Adipokines encompass the hormones leptin, adiponectin, resistin, and visfatin. Leptin is recognized for its role in regulating feelings of fullness and promoting the breakdown of fats. However, it has also been demonstrated to promote the growth of MM cells [28]. Yu et al. discovered that elevated levels of leptin can enhance resistance to chemotherapy by activating AKT and STAT3. Furthermore, they observed an additional correlation between overexpression of Bcl-2 and inhibition of caspase-3 [28,51]. Leptin has been demonstrated to enhance autophagy and prevent caspase cleavage and apoptosis, hence promoting chemoresistance [52].

Trotter et al. demonstrated that both preadipocytes and mature adipocytes enhance the growth and aggressiveness of MM through distinct mechanisms [53]. The cells release different chemoattractants and soluble substances that encourage the advancement of MM, including monocyte chemotactic protein (MCP)-1, stromal cell-derived factor (SDF)-1α, and osteopontin (OPN). Preadipocytes stimulate Wnt/β-catenin signaling, which enhances the ability of cancer cells to evade the immune system, migrate, and survive.

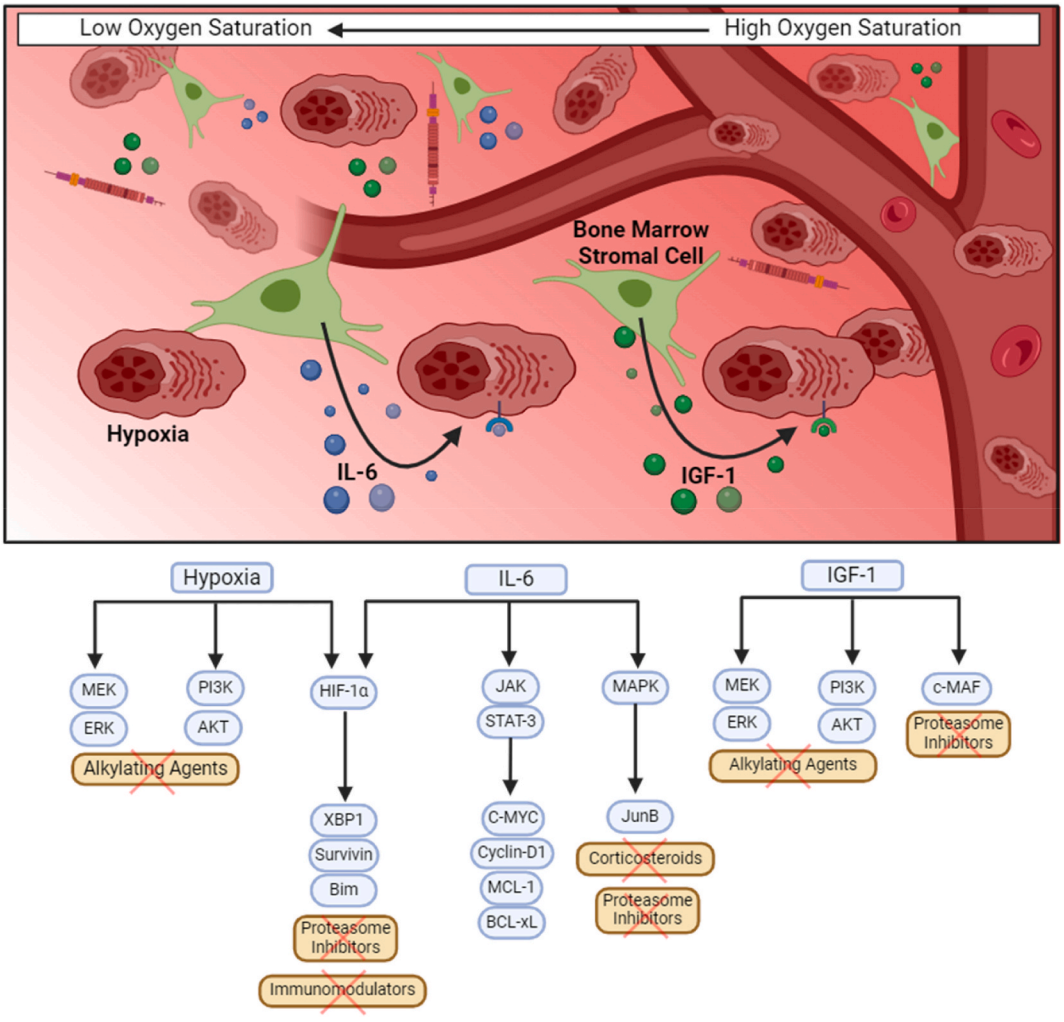

Fig. 2. The BMME contains both growth and stress signals. IL-6, IGF-1 and hypoxia are three signals within the bone marrow microenvironment that can contribute to multiple myeloma drug resistance. At the heart of MM pathogenesis is IL-6, which has proven to promote survival through various mechanisms. IL-6: Interleukin-6; IGF1; Insulin Like Growth Factor 1; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase ½; PI3K: phosphoinositol-3-kinase; AKT: Protein kinase B; HIF-1α: Hypoxia-inducible factor 1-alpha; XBP1: X-box-binding protein 1; Bim: Bcl-2-like protein 11; JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3; c-myc: cellular Myc; MCL-1: Induced myeloid leukemia cell differentiation protein; BCL-xL: B-cell leukemia/lymphoma extra large; MAPK: mitogen-activated protein kinase; junB: JunB proto-oncogene; AP-1 transcription factor subunit; c-Maf: proto-oncogene c-Maf. Figure made utilizing BioRender.com.

Preadipocytes also suppress MM apoptosis by reducing amounts of cleaved caspase-3. Concurrently, mature fat cells promote the progression of MM by activating the ERK signaling pathway [53].

Adipose tissue serves as the main energy reservoir in our bodies. As people age, fat typically builds up in BM. It has been proposed that MM can specifically target this fat and use fatty acid metabolism as a potential energy source to support the growth of MM [54]. Fairfield and colleagues have recently documented that MM decreases the amount of lipids in adipocytes [46] and also affects the senescence-associated secretory phenotype (SASP). Additionally, they demonstrated that MM cells shown resistance to dexamethasone when co-cultured with BMAT. Furthermore, they discovered that patients with a smaller BMAT volume fraction achieved a full response when treated with high dosage melphalan and dexamethasone [46].

1.8. Cancer stem cells

Cancer stem cells (CSCs) are a minority group of versatile cells within a tumor population that has the ability to renew themselves, initiate tumor growth, and resist the effects of drugs.These cells play a significant role in the recurrence of the disease [55–60]. These cells are likely to continue surviving even after a complete response to chemotherapy, and they represent a significant part of minimum residual disease (MRD) [61]. The CSCs in MM exhibit frequent activation of the Hedgehog (Hh), Wnt, and Notch pathways, which play a role in their ability to self-renew [62]. They exhibit unusually elevated levels of IL-6, DKK1, IL-1β, IL-3, G-CSF, GM-CSF, stem cell factor, and TNF-α [13,14,63–65]. The BMME, which is already recognized for its involvement in supporting the survival of hematopoietic stem cells, is likely involved in providing nourishment to these CSCs [66]. Nevertheless, these CSCs continue to exhibit abnormalities after they are extracted from the BMME niche [67].

2. Bone marrow: a specialty that fosters growth

As mentioned earlier, the BM plays a crucial role in providing a unique and specialized environment that promotes the growth and survival of MM cells. Various cytokines, chemokines, and growth factors are released by the BM stroma. These include IL-6, VEGF, and SDF-1. These substances play a crucial role in supporting the growth and viability of myeloma cells (Fig. 2). Furthermore, the low oxygen conditions within the BM not only enhance the adaptability of myeloma cells, but also provide them with a favorable environment that shields them from chemotherapy drugs and immune recognition. The intricate interplay between myeloma cells and the BMME highlights the complex nature of MM progression and underscores the challenges in eradicating these malignant cells.

2.1. Hypoxia

Stress is one of the signals that the BMME imposes on myeloma cells, and it can have an effect on their proliferation. Hematopoietic stem cells flourish in the naturally low-oxygen environment of the BM [68]. The cells of the BM frequently exhibit the presence of HIF-α, which serves as a central controller of cellular reactions to low oxygen levels. Gaining insight into the function of HIF-1α in the development of MM and its resistance to therapy is highly significant. Pharmacological inhibition of HIF-1α has been shown *in vivo* investigations to effectively reduce the disease burden of myeloma [69]. The research undertaken by Borsi et al. has shown that the stability of HIF-1α has a vital role in the survival of myeloma. Suppression of HIF-1α resulted in reduced cytokine production and impaired adherence of MM cells to microenvironment components. Interestingly, research demonstrated that the stimulation of MAPK phosphorylation in myeloma co-culture with BMSCs may be interrupted by blocking HIF-1α with EZN-2968 [70].

The expression of HIF-1α has been found to have a role in the development of resistance to lenalidomide and melphalan [71,72]. ERK 1/2, AKT, and NF-κB were found to be consistently activated in melphalan-resistant myeloma cells. Research has demonstrated that the concurrent suppression of all three variables leads to a reduction in HIF-1α mRNA levels [71]. Research has shown that hypoxic circumstances can cause a higher level of resistance to bortezomib and carfilzomib [73]. Tsubaki et al. demonstrated that the expression of Survivin and Bim, which is regulated by HIF-1α, may be responsible for this phenomenon [71].

2.2. Interleukin- 6

IL-6 has a crucial role in the development and functioning of MM. IL-6 was first cloned in 1988 as a factor that differentiates B cells. It plays a crucial role in the proliferation and survival of myeloma cells [74]. These survival benefits include multiple mechanisms of resistance to chemotherapy. The BMME secretes it, with contributions from osteoclasts, macrophages, and BMSCs [23]. IL-6 activates several downstream targets, such as HIF-1α, JAK/STAT3, RAS/MAPK, and other transcription factors [75].

JAK/STAT3 is a specific downstream target of IL-6. In MM, the normal control exerted by the repressors SHP-1, SHP-2, and SOCS1 over IL-6 signaling is disturbed, resulting in excessive activation of the JAK-STAT pathway [76]. STAT3 activation leads to the increased expression of c-myc, cyclin D1, Mcl-1, Bcl-xL, and Bcl-2 [76]. In addition, studies have demonstrated that STAT3 has a role in helping cells avoid detection by the immune system, as seen by the downregulation of CD8 [76–79].

The AP-1 family comprises a group of transcription factors that play a role in cellular proliferation, survival, and apoptosis [80]. Recently, JunB has been studied to determine its involvement in MM. It has been discovered that JunB is activated by IL-6 in a manner that depends on both the duration and dosage of IL-6 exposure [81]. Fan et al. have shown that the soluble substances released by BMSCs, particularly IL-6, stimulate the production of JunB through a MEK/MAPK and NF-κB-dependent mechanism. JunB was linked to the proliferation of MM cells, and specifically provided protection against the effects of dexamethasone and bortezomib. The study discovered that there were elevated levels of baseline JunB expression in cells that were resistant to dexamethasone and bortezomib.

Furthermore, they observed that the use of shRNA to knock down JunB resulted in the restoration of drug sensitivity [81].

The majority of myeloma cell lines rely on Mcl-1 to prevent apoptosis, however, a small subgroup of myeloma cells depend on Bcl-2/Bcl-xL for this purpose [82]. In 2017, Gupta et al. conducted a study to examine the impact of the presence of stromal cells on the expression of anti-apoptotic proteins [83]. The researchers discovered that myeloma cells grown with BMSCs exhibited reduced reliance on Bcl-2/Bcl-xL. However, when IL-6 was inhibited while the cells were still in the presence of BMSCs, their sensitivity to Bcl-2/Bcl-xL was restored. Subsequently, they discovered that IL-6 has the ability to trigger a reliance on Mcl-1. Additionally, they reported that inhibiting Jak, a protein downstream of IL-6, would counteract these observations [83]. Venetoclax is an authorized Bcl-2 inhibitor for the treatment of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). It is also being studied for its effectiveness in patients with MM who have a specific genetic abnormality called t (11; 14) translocation. This translocation is associated with increased levels of Bcl-2 and decreased levels of Mcl-1, making Venetoclax a potential treatment option for these patients [83]. The study conducted by Gupta et al. indicates that treatment with Venetoclax or comparable medications should be combined with IL-6 inhibition in some manner [84].

2.3. *Insulin-like growth factor-1 (IGF-1)*

IGF-1 is crucial in the emergence of treatment resistance in MM in the BMME. IGF-1 is synthesized by BMSCs and functions as a powerful stimulant and survival factor for myeloma cells. IGF-1 binds to its receptor (IGF-1R) on myeloma cells, triggering important signaling pathways such as PI3K/Akt and MAPK [85–87]. These pathways play a critical role in cell growth, survival, and the ability to fight apoptosis [10,88]. This signaling pathway not only stimulates the proliferation of myeloma cells but also increases their resistance to the effects of chemotherapy drugs [85]. Furthermore, the stimulation of these pathways by IGF-1 leads to an increase in the expression of anti-apoptotic proteins including Bcl-2 and Mcl-1, which strengthens the drug-resistant characteristics. IGF-1 has been shown to stabilize MAF expression via inhibition of GSK3β [85]. Silencing of c-MAF results in increased bortezomib response [89].This highlights the significance of focusing on the IGF-1/IGF-1R pathway as a therapeutic approach to address drug resistance and enhance treatment results in individuals with MM.

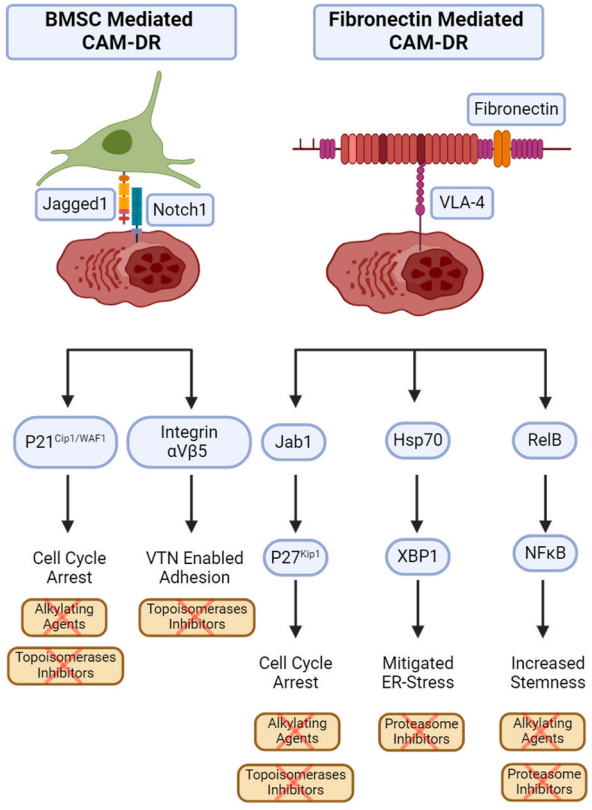

Fig. 3. Depiction of two multiple myeloma cell adhesion molecule drug resistance pathways. Fibronectin and BMSCs are abundant in the BMME and physical interactions between them and multiple myeloma cells activate numerous drug resistance pathways. VLA-4: Alpha4beta1 (VLA-4) integrin; p21waf/cip1: cyclin-dependent kinase inhibitor 1; VTN: Vitronectin; JAB1:Jun activating binding protein; P27kip1:Cyclin-dependent kinase inhibitor 1B; Hsp70: Heat shock protein 70; XBP1: X-box-binding protein 1; RelB: RELB Proto-Oncogene, NF-κB Subunit; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells. Figure made utilizing BioRender.com.

3. Mechanisms of drug resistance and survival

The complex interplay between drug resistance and survival in MM is deeply impacted by the BMME. It is fascinating to observe how the adhesion of myeloma cells to BMSCs can lead to the secretion of anti-apoptotic factors and the activation of signaling pathways like NF-κB, PI3K/Akt, and MAPK. Gaining a deep understanding of these mechanisms is absolutely essential in order to develop innovative therapeutic strategies that can effectively disrupt this protective niche and ultimately enhance patient outcomes in MM.

3.1. Cell adhesion mediated drug resistance (CAM-DR)

Myeloma cells are able to adhere to components of the BMME, such as BMSCs and fibronectin, which triggers upregulation of various pathways and soluble factor secretion. Damiano and Dalton et al. termed this phenomenon cell adhesion-mediated drug resistance (CAM-DR) after noticing that myeloma adhesion offered protection from two mechanistically different chemotherapeutic drugs [90]. Cell adhesion is performed via members of the integrin family, including CD138 (syndecan-1), CD44, VCAM1, LFA-1, MUC-1, ICAM-1, VLA4 (α4β1), and VLA5 [10]. VLA-4, of note, is an integrin that is very strongly expressed in MM and is the only one capable of both adhesion to ECM elements and BMSCs via separate binding sites [10,91].

Myeloma cells achieve homing and retention in the BM via the SDF-1/CXCR4 axis [92]. SDF-1 is a chemokine secreted by BMSCs and BM fibroblasts that is recognized by membrane-expressed CXCR4. Parts of the BM that house myeloma cells express notably higher levels of SDF-1 compared to the rest of the BM [93]. Importantly, knockout of SDF-1 has been shown to impair MM adhesion to BMSCs, and co-culture with BMSC would not activate downstream pathways normally seen [93–95].

HMG-CoA has also been implicated in CAM-DR mediation via the HMG-CoA/GG-OO/Rho/Rho-kinase pathway [96]. Wnt signaling is active in MM and contributes to proliferation and survival, and its activity can be due to overexpression of β-catenin [97]. HMG-CoA also plays a role via activation of Rho, a stimulator of Wnt3 activity [96,98]. It has been shown that the Wnt3/Rho signal is associated with a state in myeloma cells in which they bind to BMSCs via β1-integrin [96,98]. Simvastatin has been shown to overcome CAM-DR in MM [99].

CAM-DR to a wide variety of drugs has been reported with VLA-4-mediated fibronectin adhesion, including resistance to bortezomib, vincristine, doxorubicin, and dexamethasone [99–103] (Fig. 3). One downstream player of fibronectin adhesion is heat shock protein 70 (Hsp70), a known mediator of drug resistance [104]. The Hsps are family of chaperone proteins which are induced in response to stress. They support cell survival and proliferation through maintenance of proper folding of oncogenes. Hsp70 is known to increase splicing of XBP1, a transcription factor that activates stress-managing genes, including hypoxia-related genes, oxidoreductases, foldases, and chaperones [89]. This plays an important role in staving off ER stress-induced by proteasome inhibitors (PI).

Adhesion to fibronectin has also been shown to induce cessation of the cell cycle [96]. $p27^{kip1}$ is a cyclin dependent kinase inhibitor that is responsible for cell cycle arrest. Myeloma binding to fibronectin down-regulates Jab1, resulting in increased nuclear localization of $p27^{kip1}$ [105]. $p27^{kip1}$ overexpression is associated with cell cycle arrest, and a likely protection from apoptosis, offering protection from cell-cycle-dependent therapy [90,102,105]. Fei et al. further demonstrated *in vitro* resistance to mitoxantrone and doxorubicin in their experiments [105].

NF-κB is a well-defined transcription factor family that promotes growth, survival, and drug resistance in MM [106,107]. MM cell adhesion to fibronectin has been shown to activate RelB, a regulator of NF-κB [96]. Further, MM binding to BMSCs has been shown to induce TNF-α secretion by myeloma cells, leading to NF-κB activation in BMSCs [96,108]. V1810, an NF-κB inhibitor, not only induces apoptosis in MM cells, but also reverses drug resistance to melphalan [106].

MM cells also induce CAM-DR by binding BMSCs directly. MM cells can bind BMSCs utilizing a variety of receptors including integrin β1 and β2 receptors and by CD21/CD23 interactions via a mechanism yet to be determined [109]. MM cells express Notch receptors that bind BMSC Jagged-1 ligands, resulting in the activation of Notch-1 in MM. This Notch-1 activation protected MM cells from treatment with melphalan and mitoxantron by upregulating the CDK inhibitor $p21^{WAF/Cip}$, thereby halting the cell cycle [110]. MM induced Notch-1 also leads to expression of integrin αvβ5 which enables MM adhesion to vitronectin (VTN), a protein abundant in ECM and plasma. This interaction with VTN has been shown to protect MM cells from apoptosis and confer resistance against doxorubicin treatment [111]. Furthermore, cell-to-cell contact between MM cells and BMSCs increases the paracrine section of IL6, which goes on to alter MM cell gene expression [112].

3.2. Angiogenesis and its role in drug resistance

The formation of new blood vessels from pre-existing ones, known as angiogenesis, plays a vital role in the BMME and has a significant impact on drug resistance in MM [113,114]. Angiogenesis plays a crucial role in ensuring a steady provision of oxygen and nutrients, essential for the proliferation and survival of myeloma cells. Pro-angiogenic factors such as VEGF, fibroblast growth factor (FGF), and angiopoietins are secreted by myeloma cells and the surrounding stromal cells [115]. These factors promote the development of new blood vessels, improving the vascular network within the BME. The enhanced blood vessel formation not only facilitates the growth of myeloma cells but also establishes a dynamic setting that enables these cells to flourish, even when subjected to therapeutic interventions.

The increased vascular network within the BMME also plays a role in drug resistance through various mechanisms. Firstly, the newly formed blood vessels can be irregular and dysfunctional, which can affect blood flow and the delivery of drugs to the myeloma cells [116]. This leads to less than ideal levels of therapeutic agents reaching the tumor cells, which in turn decreases their effectiveness. Furthermore, factors related to angiogenesis, such as VEGF, trigger signaling pathways that enhance the survival, growth, and

movement of myeloma cells [117]. As an expert in the field, it is fascinating to observe how VEGF interacts with receptors on myeloma cells, leading to the activation of the PI3K/Akt and MAPK pathways [118]. These pathways play a crucial role in promoting cell survival and providing protection against apoptosis. In addition, as discussed above, the hypoxic conditions commonly linked to rapid angiogenesis can trigger the expression of HIF-1α, which enhances the survival of myeloma cells and contributes to their resistance to treatment. Thus, the exploration of angiogenic pathways alongside traditional therapies shows promise as a means to combat drug resistance and enhance treatment results in MM.

3.3. *Bruton's tyrosine kinase signaling and drug resistance*

Bruton's tyrosine kinase (BTK) is a major player of the bone marrow microenvironment (Fig. 4). It has gained much attention over the past decade as more information emerges about its role in MM. It is found to be overexpressed in both MM plasma cells and BM stem cells and have been heavily implicated in MM progression and drug resistance [57,119,120].

BTK is a non-receptor tyrosine kinase that is part of the five-membered TEC family of kinases [121]. It is a metalloprotein enzyme, dependent on zinc for optimal activity and stability [122]. There are five different protein interaction domains: Amino terminal

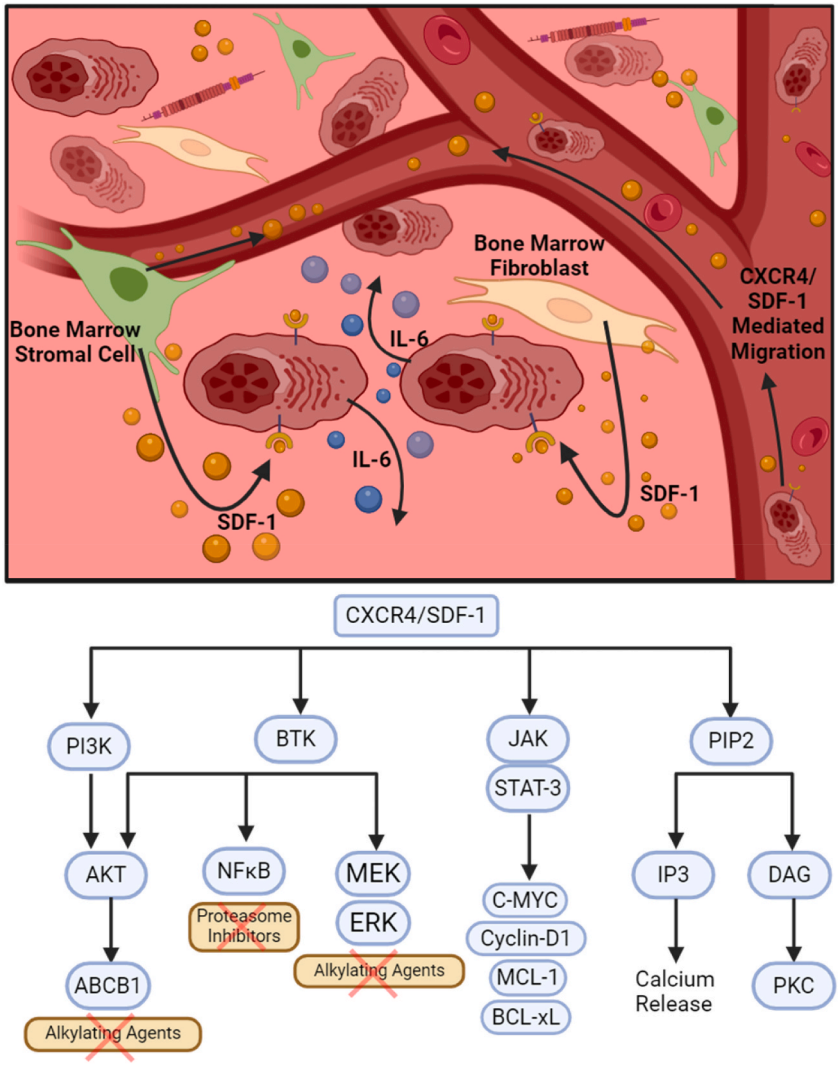

Fig. 4. SDF-1, released by BM stromal cells and fibroblasts, stimulates MM CXCR4 signaling and homing to the BMME. CXCR4 binding SDF-1 both activates several pathways that confer resistance and promotes MM secretion of IL-6. CXCR4: Chemokine receptor type 4; SDF-1: Stromal cell-derived factor 1; IL-6: Interleukin-6; PI3K: phosphoinositol-3-kinase; AKT: Protein kinase B; ABCB1: P-glycoprotein 1; BTK: Bruton's tyrosine kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase ½; JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3; c-myc: cellular Myc; MCL-1: Induced myeloid leukemia cell differentiation protein; BCL-xL: B-cell leukemia/lymphoma extra large; PIP2: Phosphatidylinositol 4,5-bisphosphate; IP3: Inositol trisphosphate; DAG: Diacylglycerol; PKC: Protein kinase C. Figure made utilizing BioRender.com.

Pleckstrin Homology domain (PH), proline-rich TEC homology domain (TH), SRC homology domains (SH2, SH3), and a kinase domain. BTK phosphorylates PLC-γ2, which goes on to hydrolyze PIP3 into IP3 and DAG. This pathway will go on to activate AKT, NFAT, FOXOs, and NF-κB-mediated pathways [121]. There have also been reports of BTK involvement in WNT/β-catenin signaling [123]. Yang et al. demonstrated that BTK overexpression was associated with increased levels of β-catenin, phospho-AKT, and phosphor-GSK3β. Conversely, they showed that BTK knockout reduced the aforementioned protein levels [123].

One component of BTK-mediated drug resistance as well as MM progression appears to be through the SDF-1/CXCR4 axis. de Gorter et al. demonstrated that not only was SDF-1 controlled migration impaired in B cells deficient in LYN and SYK, but selective inhibition of PLC-γ2 abolished migration altogether [124]. The results strongly suggest that BTK mediates MM migration through phosphorylation of PLC-γ2. Bam et al. further showed that shRNA-mediated knockdown of BTK would inhibit chemotaxis toward SDF-1, and therefore disrupt homing to the BM [120].

BTK is also involved with CXCR4 signaling, as expression is positively correlated with cell membrane CXCR4 expression as well [120]. In fact, Wang et al. described an interesting role, in that BTK expression was inversely correlated with the rate of CXCR4 ubiquitination [125]. Using laser confocal microscopy, they found that CXCR4 exhibited strong co-localization with BTK, and suspected that BTK may directly bind to CXCR4. They then went on to investigate rates of ubiquitination in MM cell lines overexpressing BTK compared to wildtype and found far higher rates of ubiquitination in wildtype cells. The results indicate that BTK overexpression, as in MM, can stabilize CXCR4 expression through prevention of ubiquitin-mediated degradation [125].

NF-κB, a cellular transcription pathway that is related to cytokine production and cell survival, is downstream of BTK signaling. One of the consequences of NF-κB activation due to BTK overexpression is bortezomib-resistance [126]. Murray et al. found higher basal levels of NF-κB p65 activity in nuclei of bortezomib-resistant cells compared to bortezomib-naive cells. This was suggestive of clonal selection in the face of constant bortezomib exposure. However, they were able to resensitize these cells to bortezomib with ibrutinib treatment, as well as lenti-viral—mediated knockdown of NF-κB p65 [126].

BTK can promote drug resistance through drug efflux pumps. BTK overexpression leads to increased expression of the ABCB1 efflux pump. Yang et al. demonstrated that ABCB1 required upstream AKT signaling to operate properly, showing another benefit in targeting the BTK/AKT pathway [123].

BTK has been shown to actively suppress cellular senescence in myeloma [127]. Gu et al. demonstrated that inhibition of BTK would result in large proportions of a myeloma population left in G0/G1 arrest, while overexpression would induce resistance to senescence. They demonstrated that this was done through activation of AKT/P27/RB signaling. Interestingly, elevated BTK is a feature of MMSCs, the expression of which is significantly higher than in bulk myeloma cells [57]. BTK overexpression leads to upregulation of NANOG, MYC, SOX2 and other stemness genes [123]. Yang et al. went on to find that knockdown of BTK activated PARP and caspases 3, 8, and 9, suggesting that BTK plays a role in inhibiting the intrinisic and extrinsic apoptotic pathways. They also demonstrated that NANOG levels could be decreased in MM cell lines overexpressing BTK with selective inhibition of β-catenin, suggesting a role in WNT/β-catenin signaling [123]. Our research has shown that BTK inhibitor effectively suppresses the survival of multiple myeloma stem-like cells (MMSCs), inhibits osteoclastogenesis, and overcomes resistance to bortezomib. This suggests that BTK inhibitors could be beneficial in addressing resistance and recurrence in MM [128,129].

3.4. Epigenetic regulation and its role in resistance

Epigenetic control inside the BMME plays a crucial role in the development of treatment resistance in MM [130]. Epigenetic alterations, including DNA methylation, histone modifications, and non-coding RNA activity, have the ability to significantly impact gene expression without changing the actual DNA sequence [131]. These alterations are of utmost importance in the survival, multiplication, and defense mechanisms of myeloma cells. For example, the process of hypermethylation can prevent the expression of tumor suppressor genes like p16 and p21 [132]. This can lead to uncontrolled cell proliferation and resistance to apoptosis, which are important factors in the development of drug resistance in MM [132].

Histone modifications, such as acetylation and methylation, are important for controlling the structure of chromatin and the expression of genes. Altered patterns of histone modifications have been reported in MM, resulting in alterations in the expression of genes related to treatment response [133,134]. Myeloma cells often have high levels of histone deacetylases (HDACs), which causes the chromatin to become tightly packed. This leads to the suppression of genes that play a role in apoptosis and cell cycle regulation [130,135]. The process of epigenetic suppression has a role in the resistance of myeloma cells to both chemotherapeutic drugs and targeted therapy. HDAC inhibitors have demonstrated potential in correcting these epigenetic alterations, reinstating the expression of crucial genes, and enhancing the susceptibility of myeloma cells to treatment [130,135,136].

Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play a role in regulating gene expression and are involved in the development of medication resistance in MM [137]. The dysregulation of microRNAs, such as miR-15a/16, has been associated with the inhibition of genes that promote cell death and the activation of pathways that promote cancer formation [138,139]. The miRNA-21 is downstream of the NF-κB and IL-6/STAT3 axis and thereby inducible via soluble factors and cell adhesion [89]. Unsurprisingly, it is overexpressed in MM, and its abundance is associated with protection from dexamethasone, doxorubicin, and bortezomib [89]. Increased expression of miRNA-21 has been shown to reduce levels of tumor suppressor phosphatase and tensin homolog (PTEN), while also upregulating RhoB, a player in CAM-DR [89]. miRNA-125a-5p has been shown to be elevated in patients with t (4; 14) translocation [89]. It is induced by adhesion to BMSCs and is shown to downregulate the p53 pathway [89]. In the presence of BMSCs, selective inhibition of miRNA-125a-5p was able to reduce viability [89]. miRNA-451 has had a more unique role with its association with stemness. Constitutive expression is associated with disruption of PI3K/AKT/mTOR signaling by targeting downstream of tuberous sclerosis 1 (TSC1), an important finding for stem cell biology [140]. In a similar manner, long non-coding

RNAs (lncRNAs) have the ability to interact with complexes that change chromatin and transcription factors in order to control the expression of genes that are linked to drug response [137]. These epigenetic regulators establish a sheltered environment within the BM, enabling myeloma cells to avoid therapeutic approaches. Gaining a comprehensive understanding of the intricate interaction between epigenetic mechanisms in the BMME is essential for the development of innovative therapeutic approaches that target medication resistance and enhance outcomes for patients with MM.

3.5. Role of exosomes in drug resistance

Exosomes, tiny vesicles released by different cells in the BMME, have a crucial role in facilitating drug resistance in multiple myeloma [141,142]. These vesicles function as transporters of bioactive molecules, such as proteins, lipids, and nucleic acids, enabling communication between cells and impacting the behavior of the cells they interact with. Exosomes derived from BMSCs and myeloma cells are of great significance in the study of MM [143]. They possess a wide range of signaling molecules, including cytokines, growth factors, and miRNAs, that have the ability to modify the characteristics of myeloma cells and bolster their ability to survive and resist treatment [143].

Exosomes play a crucial role in drug resistance by transferring specific miRNAs that control gene expression in myeloma cells. As an example, exosomal miRNAs have the ability to decrease the expression of genes that promote cell death or increase the expression of pumps that remove drugs from cells [144]. This can result in a decrease in the effectiveness of chemotherapy drugs. In addition, exosomes have the ability to transport proteins that can activate important signaling pathways related to cell survival and growth, including the PI3K/Akt and MAPK pathways. Exosomes released by tumors promote angiogenesis by releasing various factors such as angiogenin, HGF, MMP-9, Serpin E1, TIMP, Thrombospondin 1, and VEGF [10]. They contain significant quantities of IL-6, CCl2, γ-catenin, and fibronectin [10]. Experiments have demonstrated that exosomes derived from BMSCs provide a safeguard against bortezomib by activating certain proteins (c-Jun, p38, p53, AKT) and influencing the expression of Bcl-2, caspase 9, caspase 3, and PARP [145]. In addition, exosomes have the ability to influence the immune response in the BMME, creating a suppressive environment that enables myeloma cells to avoid detection by the immune system and continue to survive even after treatment [146]. Furthermore, exosomes play a role in the survival of MDSCs by activating STAT3 and enhancing their immunosuppressive characteristics [147,148].

In addition, exosomes derived from myeloma cells that are resistant to drugs have the ability to transfer traits of resistance to cells that are sensitive to drugs, thereby facilitating the spread of resistance among the population of tumor cells [143]. The transfer of resistance mechanisms occurs horizontally by transporting drug-resistant proteins like ABC transporters or miRNAs that target drug sensitivity pathways [143]. Due to this, myeloma cells that were once sensitive become resistant, which makes treatment strategies more complex and contributes to the recurrence of the disease. Exploring the function of exosomes in facilitating drug resistance emphasizes the intricate nature of the BMME and emphasizes the importance of innovative treatment strategies that focus on exosomal communication to overcome resistance and enhance patient outcomes in MM.

3.6. Nuclear factor erythroid-derived-2-like 2 (NRF2) and its role in resistance

Nuclear factor erythroid-derived-2-like 2 (NRF2) is a transcription factor with roles of antioxidant and detoxifying maintenance through expression of Heme Oxygenase-I, NQO1, Catalase, Superoxide Dismutase, Glutamate Cysteine Ligase, Glutathione S Transferase [149]. Yen and Hsiao have produced an excellent review of NRF2 involvement in MM, and a few key points will be discussed

Table 1
Established pathways of resistance in therapies for Multiple Myeloma.

Drug class	Resistance Pathways
Proteasome Inhibitors	HIF-1α
	JunB
	IGF-1
	BTK
	CAF
	CAM-DR
	miRNA-21
	XBP1
Corticosteroids	JunB
	Receptor mutation
	CAM-DR
	miRNA-21
IMiDs	CRBN mutations
	AGO2
Antibodies	Survivin
	CD-38 downregulation
Traditional Chemotherapy	HIF-1α
	TAMs
	CAM-DR
	miRNA-21

here [149]. Their findings show that NRF2 has opposing roles in the BMME and myeloma cells. In the BMME, NRF2 activation results in NF-κB suppression, seen in fibroblasts, adipocytes, and osteoblasts [149–151]. Downstream effects of NF-κB were observed to be inhibited in different pathologic models, such as induction of VCAM-1 and ICAM-1 [152–154]. Furthermore, NRF2 was found to inhibit MDSC activity through antioxidant activity and downregulation of iNOS, NOX2, and IL-6 [149]. Therefore, NRF2 activity in the BMME promotes sensitivity to chemotherapy through downregulation of survival pathways, a reduced capacity for CAM-DR, and increased susceptibility to $CD8^+$ T-cells. Conversely, NRF2 induction in myeloma cells contributes to survival effects. Yu Sun et al. demonstrated that bortezomib and carfilzomib could induce NRF2 activity, which resulted in increased pro-survival signaling. Furthermore, knockout of NRF2 reversed these findings [155].

4. Specific drug class resistance

The therapy paradigm for MM has undergone tremendous advancements in recent decades, with several categories of drugs playing crucial roles in enhancing patient outcomes. Nevertheless, despite the progress made in therapeutic approaches, the issue of resistance to these medicines continues to be a significant obstacle. Gaining knowledge about the interaction between various drug classes and BMME, as well as understanding the development of resistance, is essential for optimizing treatment plans and overcoming challenges in therapy. Below we will explore the importance of distinct categories of drugs, such as proteasome inhibitors, immunotherapies, corticosteroids, and others, in the management of MM. The review will also investigate the causes of resistance linked to each medication category, emphasizing the interaction between the BMME and myeloma cells that leads to treatment ineffectiveness (Table 1).

4.1. Resistance against proteasome inhibitors

Proteosomes inhibitors (PIs) are the main weapon to treat MM. The first proteosome inhibitor, bortezomib was approved in 2003 to treat MM. Later several other advanced PIs have been approved namely, carfilzomib, marizomib, oprozomib and delanzomib for the MM treatment. Theoretically, PIs are favorable targets in MM therapy owing to the propensity of myeloma cells to hyperproduce immunoglobulin.

The unfolded protein response (UPR) is a complex array of responses to endoplasmic reticulum stress in cells, and overcoming this response is paramount to success in PI therapy [89]. Overexpression of certain players in the response, such as Grp78/Bip, XBP1s, and HSPs may confer decreased sensitivity to proteasome inhibition [89]. XBP1s, as discussed above, is an adaptation to hypoxia, a physiologic finding of the BMME. The stressful BMME activates IRE1α, a sensor of ER stress, that leads to activation of XBP1s.

Bortezomib resistance is correlated with a degree of NF-κB activation, though the strict mechanism of which is under debate [156]. It follows that BMME support in activation of NF-κB via adhesion or soluble factors can support resistance to PIs [156,157].

It is not surprising that low Ig-secretory phenotypes of MM are inherently resistant to PI therapy [156,158]. Interestingly, expression of CYP26 in BMSCs promotes low retinoic-acid environment that prevents differentiation of B cells to plasma cells, translating to reduced sensitivity to PI therapy [156,159].

Combining PIs with immunotherapies has demonstrated encouraging results in countering resistance and improving therapeutic outcomes [160,161]. Immunotherapeutic strategies, such as daratumumab and elotuzumab, monoclonal antibodies, immune checkpoint inhibitors, and CAR T-cell therapies, have been combined with proteasome inhibitors to take advantage of their complementary mechanisms of action [162,163]. As an example, daratumumab focuses on CD38 found on myeloma cells. When used alongside bortezomib, it amplifies the cytotoxic effects by utilizing processes like antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [164,165]. This combination has the ability to disrupt proteasome function and also enhances the immune system's ability to identify and eliminate myeloma cells more effectively. Further studies are ongoing to explore the potential of combining immune checkpoint inhibitors, like pembrolizumab, with proteasome inhibitors to enhance the immune response against myeloma cells by counteracting the immunosuppressive microenvironment of the bone marrow [166].

4.2. Resistance against corticosteroids

Corticosteroids, such as dexamethasone and prednisone, are essential elements of treatment regimens for MM because of their strong anti-inflammatory and immunosuppressive effects. These drugs trigger programmed cell death in myeloma cells by altering the expression of several genes that promote or inhibit apoptosis. Corticosteroids exert an inhibitory effect on cytokine production, diminish inflammation, and limit the growth of myeloma cells [167]. Corticosteroids, when combined with proteasome inhibitors and immunomodulatory medicines, improve the effectiveness of treatment and help reduce tumor size in patients with MM [168].

Nevertheless, the emergence of resistance to corticosteroids is a substantial obstacle in the management of MM. Resistance mechanisms are complex and encompass both inherent and acquired elements. A primary factor contributing to corticosteroid resistance is the reduction or alteration of the glucocorticoid receptor (GR), which hinders the capacity of corticosteroids to attach and produce their desired outcomes [156,169]. Such resistance could be induced via transcription elongation block in the gene NR3C1 and epigenetic inactivation of RASD1 [156,170,171]. In addition, changes in the signaling pathways that occur after the activation of the GR, such as the PI3K/Akt and MAPK pathways, can also contribute to resistance by boosting the survival and growth of cells even when treated with corticosteroids [172]. Furthermore, the BMME itself has a crucial function in facilitating corticosteroid resistance [173]. The interactions between myeloma cells and the surrounding stromal cells, together with the production of protective cytokines and growth factors, form a specialized environment that protects myeloma cells from the cell death-inducing effects of corticosteroids

[173].

Moreover, exosomes are widely acknowledged as significant agents in the development of corticosteroid resistance in MM. Exosomes possess components that can regulate corticosteroid signaling pathways, increase the production of anti-apoptotic genes, and facilitate medication efflux. For example, the transfer of miRNAs through exosomes, which decrease the expression of GR or target apoptotic pathways downstream, can make myeloma cells less sensitive to corticosteroids [174]. In addition, exosomes have the ability to regulate the immunological milieu, which can diminish the efficacy of corticosteroid-induced immunosuppression and exacerbate medication resistance.

Gaining insight into the mechanisms that cause corticosteroid resistance is crucial in order to devise novel therapeutic approaches to address this obstacle. Potential strategies to restore corticosteroid sensitivity and improve treatment results for MM patients include targeting the BMME, disrupting exosomal communication, and enhancing GR signaling. By examining the intricate relationship between myeloma cells, the BMME, and exosomal pathways, it may be feasible to create improved combination treatments that reduce resistance and boost the effectiveness of corticosteroids in the treatment of MM.

4.3. Resistance against traditional chemotherapy

Alkylating agents and DNA intercalators are among the older approved therapies for MM. Currently, four drugs are approved: cyclophosphamide (1959), doxorubicin (1974), carmustine (1977), and melphalan (2016).

In 2002, Spanswick et al. described that resistance to alkylation therapy occurred from increased rate of DNA inner strand cross-link repair, owing to the FA/BRCA pathway [156,175,176]. Chen et al. went on to demonstrate that knockout of this pathway could reverse drug resistance, while overexpression could enhance drug resistance [156,176]. Cho et al. further showed that MAGE-A expression modulated Bcl-2 expression, conferring resistance to melphalan, as well as vorinostat and bortezomib [177].

4.4. Resistance against immunomodulatory drugs (IMiDs)

Among the immunomodulatory drugs (IMiDs) approved for MM are thalidomide (1998) and its analogs: lenalidomide (2005) and pomalidomide (2013). Cereblon (CRBN) is the main mediator of thalidomide analog effectiveness against MM. CRBN forms an E3 ligase complex with DDV1 and Cul4A, collectively known as CRL4 (CRBN). Thalidomide analogs promote ubiquitination of the lymphoid transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) by the CRL4 (CRBN) complex [156,178,179]. It follows that MM lines with decreased expression of CRBN are intrinsically resistant to lenalidomide and pomalidomide therapy [156,180]. Further, *in vitro* studies have documented the effects of CRBN mutations in MM responsiveness to these therapies [156,181]. Xu et al. identified AGO2 as a potential drug target to overcome IMiD resistance. AGO2 is a CRBN-binding protein, the silencing of which is attributed to high levels of CRBN expression [182].

4.5. Resistance against antibodies

CD38 is an important transmembrane glycoprotein responsible for multiple functions, including migration, adhesion, and even generation of nucleotide metabolites [183–187]. Under normal conditions, CD38 is held at low levels of expression, but is overexpressed in myeloma cells [183,184]. CD38 therapy is therefore an attractive target. Daratumumab, an anti-CD38 antibody, is currently FDA approved for MM. Anti-CD38 antibodies destroy myeloma cells via Fc-dependent mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) [183]. As expected, CD38-overexpressing myeloma cells are more susceptible to ADCC and CDC therapy compared to cells with lower expression [183,188]. While this may imply that an acquired phenotype of CD38-downregulation confers anti-CD38 resistance, this has not necessarily been seen. Reduction in CD38 levels were both found in patients with diminishing response as well as a sustained response [183]. Anti-CD38 therapy may confer a pressure for myeloma cells to remain in a low-CD38 state, an unfavorable phenotype due to reduced capacity for adhesion [183]. In addition, BMSCs offer protection from daratumumab-induced ADCC, possibly via upregulation of survivin and Mcl-1 [183,189].

Another transmembrane glycoprotein that is highly expressed in MM is SLAMF7 (CD319, CS1,and CRACC). It is targeted by Elotuzumab (An FDA approved IgG1 monoclonal antibody). It affects MM by enhancing NK cell–mediated ADCC and macrophage-mediated antibody-dependent cellular phagocytosis (ADCP).

4.6. CAR-T therapy and resistance

CAR-T therapy has emerged as a groundbreaking treatment for MM, providing a ray of hope for patients facing relapsed or refractory disease [162,190]. Genetically modifying a patient's own T cells to express a chimeric antigen receptor that specifically targets a surface antigen on myeloma cells is a key aspect of CAR-T therapy. One of the primary focuses of CAR-T therapy in MM is B-cell maturation antigen (BCMA), as it is found in abundance on myeloma cells [191]. After being reintroduced into the patient, these modified CAR-T cells actively target and eliminate myeloma cells that express BCMA. This results in a notable decrease in tumor size and, in numerous instances, long-lasting and impactful responses.

The effect of CAR-T therapy on MM has been revolutionary, as clinical trials have shown remarkable response rates and prolonged progression-free survival in patients who have undergone extensive prior treatment [192]. For example, BCMA-targeted CAR-T therapies, like idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have demonstrated impressive effectiveness,

resulting in complete or near-complete remissions for numerous patients [190,193]. This groundbreaking discovery has opened up a fresh path for patients who have tried all available treatment options, showcasing the immense potential of CAR-T therapy in revolutionizing the treatment of MM.

Although CAR-T therapy has shown impressive effectiveness, overcoming resistance is still a major obstacle that needs to be addressed. There are various factors that contribute to the resistance of CAR-T treatment in MM. One crucial aspect to consider is antigen escape, where myeloma cells decrease or completely stop expressing BCMA. This results in CAR-T cells being unable to identify and eradicate these cells. In addition, the BMME can have a suppressive effect on CAR-T cell function and longevity. The secretion of immunosuppressive cytokines, such as TGF-β and IL-10, by myeloma cells and stromal cells, along with the recruitment of regulatory T cells and MDSCs, collectively hampers the activity of CAR-T cells and fosters an immune-privileged environment.

In addition, there are intrinsic factors within CAR-T cells that can contribute to resistance. Over time, the effectiveness of CAR-T cells can be reduced due to T cell exhaustion. This is marked by the increased expression of inhibitory receptors like PD-1 and LAG-3, as well as the decline in effector functions. The challenging BMME, combined with continuous exposure to antigens, can expedite the development of T cell exhaustion, which hampers the long-term efficacy of CAR-T therapy.

Ongoing research is dedicated to finding ways to improve the effectiveness and long-term success of CAR-T therapy in treating multiple myeloma. These involve enhancing CAR-T cell design to enhance their longevity and effectiveness, integrating CAR-T therapy with other substances that influence the immune microenvironment, and utilizing dual-targeting CAR-T cells to prevent antigen evasion. In addition, researchers are investigating various approaches to address T cell exhaustion and improve the effectiveness of CAR-T cells against myeloma. These include the exploration of checkpoint inhibitors and metabolic reprogramming techniques. Ultimately, a comprehensive grasp of the resistance mechanisms is crucial in order to fully harness the therapeutic capabilities of CAR-T therapy for the treatment of MM. By studying the complexities of the BMME and finding ways to boost the resilience of CAR-T cells, we can potentially improve the results for individuals with MM and lay the foundation for longer-lasting and more efficient treatments.

5. Conclusion and future direction

The majority of individuals with MM commonly undergo a recurrence following treatment, often due to the development of drug resistance and antigen escape [5,190]. The presence of genomic instability during the development of the disease contributes to the intricacy of disease progression [194]. Additionally, there are numerous mutational factors that might cause MM illness and contribute to its heterogeneity [195]. Multiple pathways in MM can be disturbed, leading to activation or repression of other pathways through cross talk. Hence, it is crucial to integrate several therapies to address various feedback loops that may negate the efficacy of some inhibitors, overcome resistance, and mitigate the adverse effects of specific drugs [190].

When tackling the dilemma of drug resistance, it is important to consider the shelter and signals provided by the BMME. The niche's residents and richness in growth and survival signals are important for myeloma progression, survival, and resistance to therapy. The countless safeguards and hurdles in place therefore necessitate the need for further research into the interactions of myeloma cells and their surroundings.

Advancements in the treatment of MM are ongoing, with a particular focus on immunotherapy in combination with other treatments. The future of this approach involves studying MMSCs and identifying potential tumor-associated antigens that can be targeted with immunotherapy and small molecules (Table 2). The goal is to enhance the effectiveness and specificity of immunotherapy by targeting the BMME, such as BMSCs, to overcome the protective environment provided by the BMME. In the last ten years, immunotherapy has been introduced and has demonstrated encouraging outcomes. Additional clinical studies are required to investigate treatment sequences and determine the impact of immunotherapy on patients with newly diagnosed MM. Given the varied phenotype of MM, it is important to additionally take personalized therapy into consideration. Novel chemicals should be used to research new targets in order to reduce toxicity and adverse effects and enhance patients' overall survival and quality of life.

Table 2
Identifying pathways of therapy resistance may be critical to achieving sustained remission in MM.

Member	Strategy	Refrecnes
CAFs	Target tumor stromal barrier to enhance drug delivery Target factors secreted by CAFs Target CAF-ECM interactions Shift CAF phenotype to quiescent fibroblast	Ohlund et al. [1]
miRNA	miRNA sponges Anti-miRNA Oligonucleotides (AMO) Small Molecular Inhibitors of Specific miRNAs (SMIR)	Simonson et al. [4]
MDSC	Anti-GMCSF, CSF1R, VEGF, CXCR4, CCL2 5-Fluorouracil Phosphodiesterase-5 inhibitors	Shay et al. [16]
Osteoclasts	Anti-RANKL Bisphosphonates	Shay et al. [16]
TAMs	Anti-CSF1R TLR9 agonists Anti-CD40 agonist	Shay et al. [16]

Availability of data and materials

Not applicable.

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Consent for publication

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CRediT authorship contribution statement

Kuntal Bhowmick: Writing – original draft, Methodology. **Max von Suskil:** Writing – review & editing, Methodology. **Omar S. Al-Odat:** Writing – review & editing, Methodology. **Weam Othman Elbezanti:** Writing – review & editing, Methodology. **Subash C. Jonnalagadda:** Writing – review & editing, Resources, Conceptualization. **Tulin Budak-Alpdogan:** Writing – review & editing, Resources. **Manoj K. Pandey:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

All authors declared that there are no conflicts of interest.

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