Multiple Myeloma Pathogenesis and The Existing Therapies

Subjects: Hematology
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Multiple myeloma (MM) is a mature B-cell neoplasm that is characterized by uncontrolled growth of plasma cells (PCs) in bone marrow (BM) which leads to excessive secretion of antibodies. The progression of MM is a multistep process that starts with an asymptomatic premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS), in which BM produces abnormal PCs and secretes M protein instead of normal antibodies.

multiple myeloma | B-cell malignancy | bone marrow microenvironment

1. The Pathogenesis of Multiple Myeloma

Multiple myeloma (MM) is a mature B-cell neoplasm that is characterized by uncontrolled growth of plasma cells (PCs) in bone marrow (BM) which leads to excessive secretion of antibodies. The progression of MM is a multistep process that starts with an asymptomatic premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS), in which BM produces abnormal PCs and secretes M protein instead of normal antibodies [1]. With the increase in oncogenic mutations, MGUS evolves into smoldering MM (SMM), which is characterized by a higher serum level of M protein and a higher percentage of clonal PCs. About 50% of patients with SMM show a constant increase of M protein and develop MM [2]. While both MGUS and SMM are asymptomatic, complications of accumulated proteins may start to affect the kidneys [3]. Almost 20–40% of MM patients have renal disease by the time of diagnosis [4].

The complexity of MM is attributed to the clinical and biological heterogeneity of the disease that further genetically evolves during its progression [5]. MM cells have a wide range of genetic changes including point mutations, insertions, deletions, multiploidy, and chromosomal translocations [6]. For example, trisomic MM and patients with t(11;14) are considered standard-risk patients. On the other hand, MM patients with t(4;14), t(14;16), t(14;20), p53 mutation, gain 1q, or del(17p) are considered to be high-risk [7][8]. Moreover, the bone marrow microenvironment (BMM) plays an important role in disease development, progression, and resistance [9]. All these factors enhance different signaling pathways that contribute to proliferation, survival, invasion, angiogenesis, and osteoclastogenesis [10]. There are many signaling pathways that protect against apoptosis and support MM growth which become activated through the adhesion of MM to the BMM. These activated pathways include phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), and nuclear factor kappa B (NF-κB), janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3), which support MM growth and protect against apoptosis (**Figure 1**). The activation of these pathways leads to upregulation and secretion of several cytokines and factors from both MM and BMM cells such as interleukin-6 (IL-6), insulin-like growth factor-1, VEGF, tumor necrosis factor alpha (TNF-α), and transforming growth factor-β [11][12].

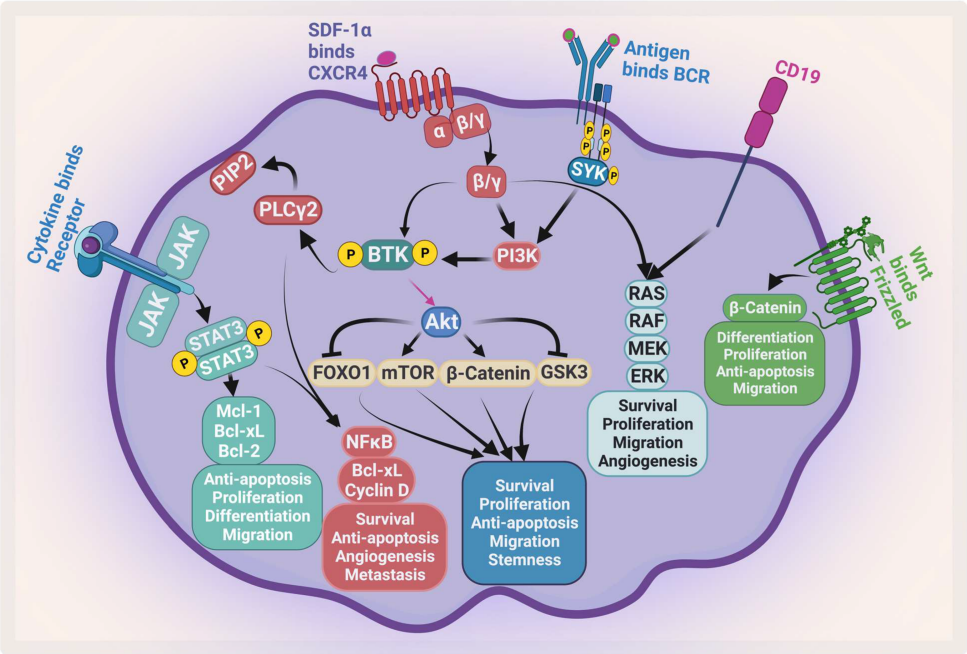

Figure 1. Major signaling pathways in MM. MM receives several survival and proliferation signals: JAK2/STAT3 pathway activates antiapoptotic proteins and activates NF-κB, the PI3K/AKT/mTOR pathways become activated when stromal-derived factor 1 α (SDF-1α) binds to CXCR4 and/or antigen binds to B-cell receptor (BCR). The RAS/MEK/ERK pathway becomes activated by BCR and CD19. Wnt/β-catenin pathway activation enhances differentiation, survival, migration, and antiapoptotic signals. Ras: rat sarcoma; Raf: rapidly accelerated fibrosarcoma; MEK: mitogen-activated protein kinase kinase. Created by Biorender.com.

The BMM contains several specialized cells that are responsible for skeletal integrity, immunity, and blood formation [13][14] (**Figure 2**). Its compartments are classified into niches: the immune niche, the vascular niche and the endosteal niche [15]. Each niche contains various cell types such as B-cells, T-cells, myeloid-derived suppressor cells, osteoclasts, natural killer (NK) cells, mesenchymal stem cells, BM stromal cells (BMSCs), osteoblasts, and endothelial progenitor cells [16].

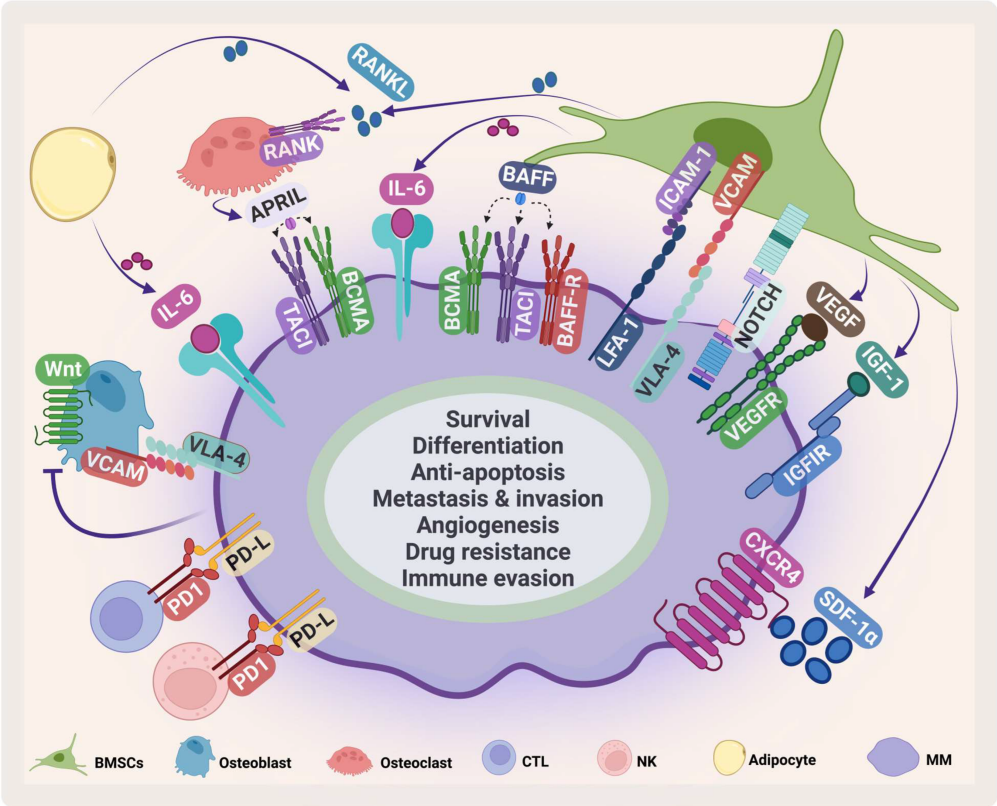

Figure 2. MM microenvironment. MM cells interact with several cells in the BMM such as BMSCs, osteoclasts, osteoblasts, cytotoxic T-cell (CTLs), natural killer (NK) cells, adipocytes. This interaction enhances MM survival and inhibits immune cells. VCAM: vascular cell adhesion protein; LFA-1: lymphocyte function-associated antigen-1; ICAM-1: intercellular adhesion molecule 1; IGF-1: insulin-like growth factor-1. Created by Biorender.com.

BMSCs are a heterogeneous cell population that supports hematopoiesis in normal conditions. They play an important role in supporting the survival, proliferation, and drug resistance of MM [17]. They communicate with MM in several ways. The direct cell adhesion contact through adhesion molecules such as very late antigen 4 (VLA-4), vascular cell adhesion protein, lymphocyte function-associated antigen-1, and intercellular adhesion molecule 1 stimulates IL-6 secretion by BMSCs [18] and mediates drug resistance through cellular-adhesion-mediated drug resistance (CAM-DR) [19]. Stromal cell-derived factor-1α (SDF-1α), a chemokine produced by BMSCs, plays an important role in embryogenesis, angiogenesis, hematopoiesis, and inflammation [20][21]. It stimulates homing and migration of cells through G protein-coupled receptor C-X-C chemokine receptor type 4 (CXCR4) [22]. The SDF-1α/CXCR4 axis plays an important role in survival, angiogenesis, metastasis, invasion, and adhesion in MM (**Figure 2**) [23]. It has been shown that the SDF-1α level in MM is elevated and this elevation contributes to activating several signaling pathways and induces mitogen-activated protein kinase kinase1/2, AKT phosphorylation, mitogen-activated protein kinase (MAPK), and NF-κB in MM cell lines and patient samples [24][25]. The SDF-1α/CXCR4 axis mediates drug resistance through different pathways that are involved in CAM-DR, affecting adhesion molecules, enhancing IL-6 mediated drug resistance, and stimulating pathways including MAP/extracellular signal-regulated kinase (ERK), wingless/integrated3 (Wnt3)/Ras homolog family member A/Ras homologous -associated protein kinase, and Ras homologous/Ras homologous -kinase [26][27][28][29][30].

Other cytokines and growth factors secreted from BMSCs suppress the immune response and facilitate MM immune evasion. One of the most important cytokines in MM is IL-6, which is secreted by different BM cells including BMSCs,

osteoclasts, and macrophages [31]. IL-6 secretion stimulates the JAK/STAT3 pathway, which leads to increased survival and proliferation through the upregulation of Mcl-1, Bcl-xL, Bcl-2, c-Myc, and cyclin D1 [32][33][34][35]. As MM progresses, osteoclast activity increases, which in turn causes bone lesions. During disease progression, an imbalance occurs in receptor activator of NF-κB ligand (RANKL), and osteoprotegerin [36].

In autologous hematopoietic progenitor cell (HPC) transplantation, plerixafor, a specific antagonist of SDF-1α binding to CXCR4, was approved in 2008 to induce hematopoietic stem cells (HSCs) and progenitor cells (HPCs) trafficking. It has been shown that it augments granulocyte colony-stimulating factor (G-CSF)-induced mobilization of HSCs and HPCs [37][38].

2. The Existing Therapies for MM

In the 1960s, oral melphalan, an alkylating agent, in combination with prednisone was considered the frontline treatment for MM [39][40]. Then, FDA-approved thalidomide, an immunomodulatory agent (IMiDs), was introduced in MM therapy. Thalidomide enhanced the overall survival (OS) and showed longer progression-free survival (PFS) regardless of patient age when used in combination with melphalan and prednisolone (clinical trial # NCT00232934, and ISRCTN90692740) [41][42]. Additionally in the 1980s, autologous stem cell transplantation (ASCT) followed by a high dose of therapy was introduced and became the standard of care among younger patients with normal renal function [43][44].

The discovery and the introduction of proteasome inhibitors (PIs) in 2003 has tremendously improved PFS in patients [45]. Bortezomib became the first line of treatment for MM in newly diagnosed MM (NDMM) patients. For relapsed and refractory MM (RRMM) patients, it was used in combination with melphalan and prednisone (**Table 1**) [46]. After the success of bortezomib, other PIs such as carfilzomib and ixazomib were approved for the MM treatment. In the TOURMALINE-MM1 trial (NCT01564537), oral ixazomib was tested in combination with lenalidomide and dexamethasone (IRd) on RRMM patients and it has significantly improved the PFS (20.6 months in the IRd group vs. 14.7 months in the Rd group (lenalidomide and dexamethasone) at a median follow-up of 14.7 months). The overall response rate (ORR) was 78% in the IRd group and 72% in the Rd group. The median OS was not reached at a median follow-up of approximately 23 months. The additional adverse effects between the two groups were limited and there was a similar quality of life between the IRd and the Rd groups [47].

Table 1. FDA-approved medications for MM from 2006 to 2013.

Drug	Year	Treatment	Adverse Effects	Refs.
Thalidomide	2006	NDMM	somnolence, constipation, neuropathy, VTE, and rash	[48] [49]
Lenalidomide	2006	Received one prior therapy	neutropenia, thrombocytopenia, leukopenia, lymphopenia, febrile neutropenia, deep vein thrombosis, pulmonary embolism, atrial fibrillation, constipation, diarrhea, fatigue, pneumonia, hypokalemia, hypocalcemia, muscle weakness, neuropathy, and depression	[50]
Doxorubicin	2007	RRMM	thrombocytopenia, neutropenia, anemia, fatigue, pyrexia, nausea, vomiting, mucositis/stomatitis diarrhea, and hand foot syndrome	[49] [51]

Drug	Year	Treatment	Adverse Effects	Refs.
Bortezomib	2008	NDMM	asthenic conditions, diarrhea, constipation, PSN, vomiting, nausea psychiatric disorders, pyrexia, anorexia, thrombocytopenia, leukopenia, neuralgia, neutropenia, and anemia	[49] [52]
Plerixafor	2008	MM	diarrhea, vomiting, nausea, fatigue, headache, injection site reactions, dizziness, and arthralgia	[49] [53]
Carfilzomib	2012	RRMM	fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, pyrexia, pneumonia, ARF, pyrexia, and CHF	[54]
Pomalidomide	2013	RRMM	asthenia, fatigue, neutropenia, anemia, constipation, diarrhea, nausea, URTI, dyspnea, back pain, and pyrexia	[55]

NDMM: newly diagnosed multiple myeloma; **RRMM**: relapsed/refractory multiple myeloma; **NTE**: non-transplant-eligible; **TE**: transplant-eligible; **Td**: thalidomide, dexamethasone; **Rd**: lenalidomide, dexamethasone; **V**: bortezomib; **PLD-V**: pegylated liposomal doxorubicin, bortezomib; **MP**: melphalan, prednisone; **VMP**: bortezomib, melphalan, prednisone; **G-CSF**: granulocyte-colony-stimulating factor; **Plerix-G-CSF**: plerixafor, granulocyte-colony-stimulating factor; **Pd**: pomalidomide, dexamethasone; **VTE**: venous thromboembolism; **PSN**: Peripheral sensory neuropathy; **ARF**: acute renal failure; **CHF**: congestive heart failure; **URTI**: Upper respiratory tract infection.

The introduction of a new generation of IMiDs such as lenalidomide in 2005, in combination with PIs, increased survival from 14.8 to 30.9 months [56]. Currently, a triple therapy (PI, IMiD, and corticosteroids) is the first line of treatment for MM followed by autologous stem cell transplant (ASCT). Lenalidomide is usually recommended as a maintenance therapy for MM patients [57]. A combination of bortezomib, lenalidomide, and dexamethasone (VRd) was tested on NDMM in the SWOG-S077 phase III clinical trial (NCT00644228) versus Rd. There was a significant improvement in median PFS (43 months in VRd group vs. 30 months in Rd group) and in median OS (75 months in VRd vs. 64 months in the control group). The ORR was 82% in the VRd group vs. 72% in the Rd group [58]. The next generation IMiD, pomalidomide is shown to be effective and is one of the treatment options that is usually considered in combination after the first relapse for patients who are refractory to lenalidomide [59]. It was first approved in 2013 in combination with dexamethasone for RRMM patients [60]. Then, it was approved in combination with anti-CD38 monoclonal antibody and a steroid for RRMM patients who have previously received two therapies including lenalidomide and bortezomib [60][61][62][63].

Introducing daratumumab, an anti-CD38, in clinical trials (MAIA, ALCYONE, CASTOR, and POLLUX) with different combinations improved minimal residual disease negativity (MRD), and PFS [64] (**Table 2**). In 2019, daratumumab, lenalidomide, and dexamethasone (DRd) treatment was approved in NDMM patients who are ineligible for transplant after phase III MAIA trial (NCT02252172). In this study, DRd showed significant improvement in PFS (not reached) compared with lenalidomide and dexamethasone (Rd) (31.9 months). The median OS was not reached at a median follow-up of 56.2 months. The common adverse effects of this treatment are neutropenia, pneumonia, anemia, and lymphopenia. Treatment-related-death was 4% in the DRd group compared to 3% in the Rd control group [65][66]. In addition, daratumumab was tested in combination with bortezomib and melphalan-prednisone (D-VMP) in a phase III ALCYONE trial (NCT02195479) in NDMM patients. The 18-month PFS was 71.6%. At a median follow-up of 16.5 months, 22.3% of the patients were negative for MRD. The common adverse effects were neutropenia, thrombocytopenia, and anemia [67]. After the CASSIOPEIA phase III trial (NCT02541383) on ND transplant-eligible MM patients, daratumumab was approved to be used in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) in 2019. At a median follow-up of 35.4 months, PFS was not reached versus 46.7 months with the control group. The most common adverse effects were lymphopenia, hypertension, and neutropenia [68].

Table 2. FDA-approved medications for MM from 2014 to 2019.

Drug	Year	Treatment	Adverse Effects	Name and NCT Number	Refs.
Panobinostat	2015	RRMM	pneumonia, diarrhea, arrhythmias, hypophosphatemia and hypokalemia, ECG change, thrombocytopenia, neutropenia fatigue, and sepsis	PANORAMA1 NCT01023308	[69]
Carfilzomib	2015	RRMM	CVE, VTE, ARF, pulmonary toxicities, hypertension, and thrombocytopenia	ASPIRE NCT01080391	[70]
Daratumumab	2015	RRMM	fatigue, nausea, back pain, pyrexia, URTI, cough, IRs, lymphopenia, neutropenia, anemia, and thrombocytopenia	SIRIUS NCT01985126	[71]
Ixazomib	2015	RRMM	diarrhea, constipation, thrombocytopenia, PSN, nausea, peripheral edema, vomiting, and back pain	TOURMALITOURMALINE NCT01564537	[47]
Elotuzumab	2015	RRMM	ARF, pneumonia, nasopharyngitis pyrexia, anemia, pulmonary embolism, and PSN	ELOQUENT-2 NCT01239797	[72] [73]
Daratumumab	2016	RRMM	URTI, cough, diarrhea, fatigue, nausea, pyrexia, muscle spasm, and dyspnea, neutropenia, anemia	POLLUX NCT02076009	[74]
Daratumumab	2016	RRMM	URTI, IRs, diarrhea, peripheral edema, Neutropenia, and thrombocytopenia, anemia	CASTOR NCT02136134	[75] [76]
Daratumumab	2019	NTE NDMM	IRs, URTI, diarrhea, constipation, peripheral edema, nausea, fatigue, asthenia, dyspnea, pyrexia, muscle spasms, and PSN	MAIA NTC02252172	[66] [77] [78]
Selinexor	2019	RRMM	Thrombocytopenia, fatigue, nausea, anemia, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and URTI	STORM KCP-330-012 NCT02336815	[79] [80]
Daratumumab	2019	TE NDMM	IRs, PSN, constipation, asthenia, nausea, neutropenia, thrombocytopenia, peripheral edema, pyrexia and paresthesia	CASSIOPEIA NCT02541383	[81]

NDMM: newly diagnosed multiple myeloma; **RRMM**: relapsed/refractory multiple myeloma; **NTE**: non-transplant-eligible; **TE**: transplant eligible; **ORR**: overall response rate; **Vd:** bortezomib, dexamethasone; **PAN-Vd:** panobinostat, Treatment choices differ according to age, cytogenic abnormalities, and eligibility for transplantation. Maintenance bortezomib, dexamethasone; **Rd**: lenalidomide, dexamethasone; **KRd:** carfilzomib, lenalidomide, dexamethasone; **DVd:** therapy for standard-risk MM patients is lenalidomide. However, bortezomib is used as a maintenance therapy for high-daratumumab, bortezomib, dexamethasone; **DRd**: daratumumab, lenalidomide, dexamethasone; **IRd:** ixazomib, risk ND patients who are determined to be eligible for ASCT. ND high-risk patients who are eligible for ASCT start with lenalidomide + dexamethasone; **VTd**: bortezomib, thalidomide, and dexamethasone; **DVTd:** daratumumab, bortezomib, three to four cycles of VRd or three to four cycles of quadruplet regimen of daratumumab, bortezomib, lenalidomide, and thalidomide, dexamethasone; **ERd**: elotuzumab, lenalidomide, dexamethasone; **Sd**: selinexor, dexamethasone; **m**: dexamethasone (DVRd) [59].

2.1. Mechanism of Action of Proteasome Inhibitors

Acute: **URTI**: Upper respiratory tract infection; **PSN**: Peripheral sensory neuropathy; **IRs**: Infusion reactions; **VTE:** venous thromboembolic events; **CVE**: Cardiovascular events, **ARF**: acute renal failure.

PIs kill myeloma cells through different pathways (**Figure 3**). Inhibition of proteosomes leads to the accumulation of ubiquitinated proteins that would otherwise be degraded in the proteosome. This leads to the accumulation of these proteins in the endoplasmic reticulum (ER), which in turn causes ER stress, which leads to ER stress-dependent apoptosis and activation of the Jun amino-terminal kinases (JNKs) pathway, increasing the Fas ligand, caspase 8, and caspase 3 [82][83]. Furthermore, mitochondrial injury occurs due to the direct effect of ubiquitinated proteins and the indirect effect of the ER stress that releases reactive oxygen species (ROS) [84]. The direct apoptosis effect of PIs can also occur through accumulation and phosphorylation of P53, which stimulates pro-apoptotic proteins such as Bcl-2-associated X protein (Bax), NADPH oxidase activator (NOXA), cytochrome-c release, and inhibition of the antiapoptotic protein Mcl-1 [85][86].

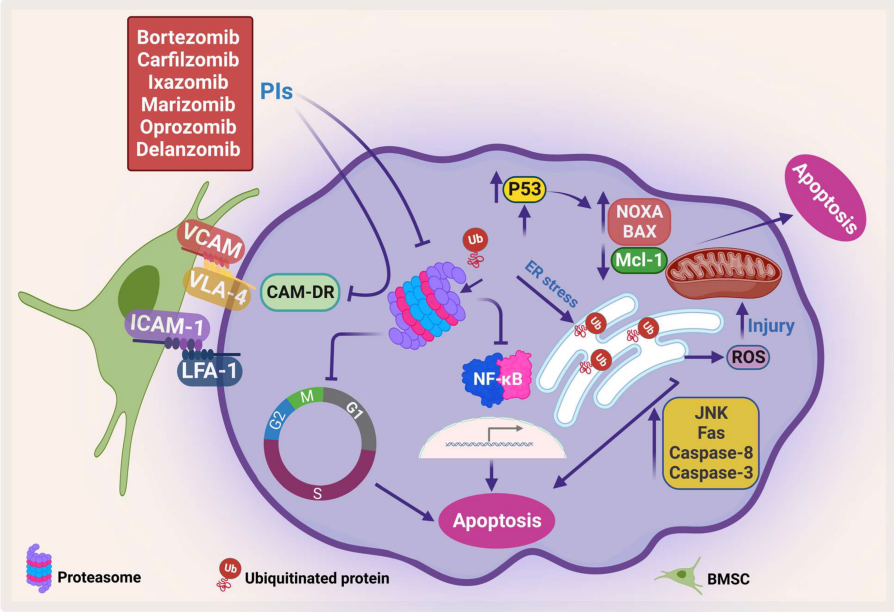

Figure 3. Proteasome inhibitors (PIs) induce apoptosis and inhibit CAM-DR. PIs induce protein accumulation, which leads to ER stress and activates JNK, which in turn activates caspase-8 and caspase-3, increases Fas, and generates ROS. In addition, PI enhances pro-apoptotic proteins, NOXA and BAX, and inhibits Mcl-1, which leads to apoptosis. Moreover, PI inhibits CAM-DR through inhibition of adhesion molecules (adapted from [86]). Created by Biorender.com.

Bortezomib is the first-generation FDA-approved PI that reversibly inhibits the chymotrypsin-like activity of the proteasomes [87]. Bortezomib has been shown to inhibit NF-κB, which in turn inhibits its downstream pathways and their products, including IL-6, vascular endothelial growth factor (VEGF), c-Myc, and cyclin D1 [88]. On the other hand, bortezomib has been shown to induce constitutive NF-κB activity which could be due to the difference in response among different cell clones [89][90] (reviewed in [86]). In addition, bortezomib ameliorates CAM-DR by inhibiting the expression of adhesion molecules such as VLA-4. Therefore, it resensitizes MM cells to treatment [91]. Even though introducing bortezomib has numerous benefits for patients, several side effects such as peripheral neuropathy may occur. The second-generation PI, carfilzomib, which does not cross the blood–brain barrier may have lower incidence of neuropathy. However, caution should be taken in using carfilzomib in elderly patients as it has shown cardiovascular side

effects (reviewed at [92]). Similarly, ixazomib showed lower neurotoxicity than bortezomib as well as more efficacy in clinical trials [93].

2.2. Mechanism of Action of Immunomodulatory Drugs

IMiDs target some proteins for ubiquitination and proteasomal degradation through binding with cereblon ubiquitin ligase, forming an E3 ubiquitin ligase complex with DNA damage-binding protein 1, Cullin-4A, and RING box protein-1 (**Figure 4**). They target IKAROS family zinc finger 1 and 3 (IKZF1 and IKZF3), which are transcription factors that play an important role in lymphocyte biology. IKZF3 is an essential transcription factor in plasma cell development and therefore its degradation affects MM progression [94].

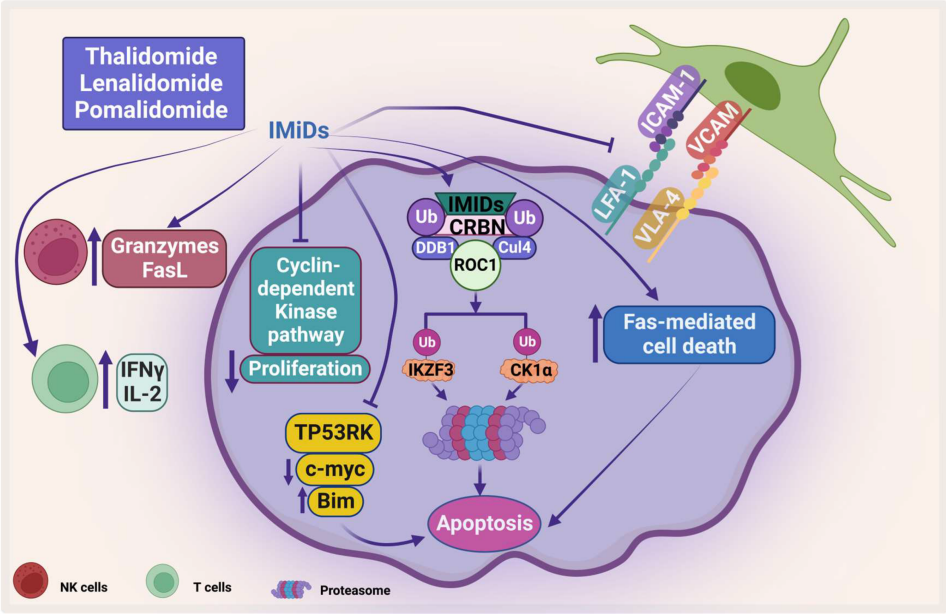

Figure 4. The direct and indirect effect of IMiDs on MM. IMiDs enhances apoptosis and inhibits MM proliferation through the cyclin-dependent pathway. IMiDs works indirectly through activating the immune cells. CRBN: Cereblon, DDB1: DNA damage-binding protein 1, CUL4: Cullin-4A, and ROC1: RING box protein-1. Created by Biorender.com.

Another protein that has been shown to be degraded by IMiDs is casein kinase 1 alpha (CK1α), which plays an important role in the pathogenesis of MM. CK is one of the serine/threonine kinases that is important in cell survival and has been shown to be important in different types of cancer including MM [95]. Manni et al. have shown that CK1α is overexpressed in most patients' samples and its inhibition leads to apoptosis, a decrease in β-catenin and AKT expression, and an increase in p53 and p21 expression. In addition, the same group showed that CK1α inhibition enhances the cytotoxicity of bortezomib and lenalidomide on MM [96]. Interestingly, both CK1α and CK2 have been shown to sustain activation of important signaling pathways such as JAK/STAT, NF-κB, and PI3K/AKT [95][97][98]. IMiDs also inhibit the proliferation of PCs by inhibiting the cyclin-dependent kinase pathway through inducing P21 [99]. Moreover, IMiDs induce direct apoptosis in PCs by activation of Fas-mediated cell death [100][101]. Moreover, Hideshima et al. showed that IMiDs inhibit the kinase activity of p53-related protein kinase (TP53RK), which correlate negatively with MM patients' survival. TP53RK phosphorylate serine 15 of p53, which in turn affects MM growth. The binding of IMiDs to TP53RK triggers

apoptosis by inducing pro-apoptotic protein Bim. It also affects the metastasis of MM cells by inhibiting c-Myc protein [102].

The treatment of IMiDs helps in restoring the immune homeostasis. Several mechanisms have been proposed for IMiDs-mediated immune restoration, for example thalidomide stimulates the proliferation of T-cells and increases the secretion of interferon-gamma (IFN-γ) and interleukin-2 (IL-2) [103][104]. Along these lines, lenalidomide has been shown to stimulate T-cell-mediated cytotoxicity, induction of T-cell proliferative responses to allogeneic dendritic cells, and suppresses expression of programmed cell death protein-1 (PD-1) [105][106]. In addition, lenalidomide and pomalidomide suppress forkhead box P3 transcription factor and T regulatory cell expansion [107]. Moreover, lenalidomide enhances the expression of Fas ligand on NK cells and increases granzyme secretion which correlates to an increase in Ab-dependent cellular cytotoxicity (ADCC) [100]. Lenalidomide and pomalidomide inhibit the expression of adhesion molecules and inhibit the RANKL/osteoprotegerin ratio, which leads to inhibition of osteoclast formation [108].

2.3. Mechanism of Action of Histone Deacetylase Inhibitors

Dysregulation in epigenetics including histone acetylation has been shown in different types of cancer including MM [109] [110]. Mithraprabhu et al. have shown that class I histone deacetylase (HDAC) is significantly upregulated in MM patients' samples compared with normal PCs [111]. Moreover, upregulation of HDAC1 was correlated with poor prognosis and shorter OS [111].

Removal of the acetyl group from the lysine residue on histone by HDACs causes transcription repression (**Figure 5**). HDACs affect different proteins via deacetylation either directly or indirectly by affecting the function of the chaperone protein that is needed for their stabilization. HDACs cause hyperacetylation and therefore destabilization for the chaperone protein heat shock protein 90 (HSP90), which inhibits its association with CXCR4 leading to proteasomal degradation of CXCR4 in acute myeloid leukemia (AML) cells [112][113]. HDACs also cause degradation of protein phosphatase 3 catalytic subunit alpha (PPP3CA), which is overexpressed in MM, and patients show poor prognosis when it is overexpressed. As HDAC6 plays an important role in the aggresomal protein degradation, its inhibition significantly synergizes with proteasomal inhibition in MM [114]. Hideshima et al. have shown that a selective HDAC6 inhibitor increased the cytotoxicity of bortezomib in vitro and overcame its resistance through JNK activation and ER stress [115]. In 2015, panobinostat was approved for treatment of RRMM patients in combination with dexamethasone. HDAC inhibitors (HDACis) have been shown to affect the acetylation of histone and non-histone proteins; they therefore affect different cell processes including apoptosis, survival, angiogenesis, and the cell cycle [116][117].

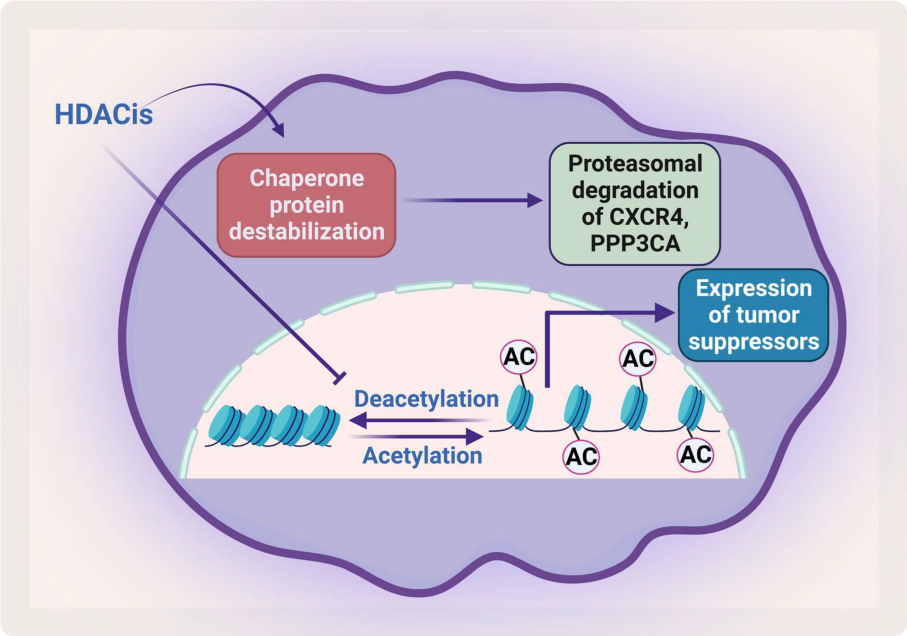

Figure 5. The effect of HDACis on MM. HDACis cause proteasomal degradation of CXCR4 and PPP3CA and enhance the expression of tumor suppressors. Created by Biorender.com.

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