

Review

Dysregulation of the Bone Marrow Immune Microenvironment and Clinical Outcomes in Multiple Myeloma

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Abstract

Multiple myeloma (MM) is characterized not only by malignant plasma cell proliferation but also by progressive dysregulation of the bone marrow immune microenvironment (BMIME). Increasing evidence suggests that disease progression, therapeutic resistance, and clinical outcomes are associated with dynamic interactions between tumor cells, immune populations, stromal elements, and inflammatory signaling pathways within the marrow niche. Although many of these observations derive from high-dimensional immune profiling, spatial transcriptomics, and single-cell transcriptomic studies, emerging mechanistic and functional evidence supports an important role for immune dysregulation in shaping disease evolution, immune escape, and therapeutic responsiveness. Recent advances in spatial profiling, immune phenotyping, and multi-omic approaches have revealed profound remodeling of the immune ecosystem across the evolution from monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) to symptomatic MM. This remodeling is characterized by progressive T-cell exhaustion, immunosenescence, dysfunction of natural killer (NK) cells, expansion of immunosuppressive myeloid populations, and altered cytokine and ligand–receptor signaling networks associated with adverse clinical outcomes. Importantly, emerging studies demonstrate that immune signatures derived from the BMIME may improve prognostic stratification beyond conventional tumor cytogenetics and staging systems. In this review, we discuss the mechanisms underlying immune dysregulation in MM, summarize recent discoveries regarding immune remodeling associated with clinical outcomes, and explore the translational implications of immune-based biomarkers and therapeutic strategies. Understanding



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the dynamic interplay between tumor genetics, immune-cell states, immunosenescence, and microenvironmental remodeling may facilitate the development of clinically actionable biomarkers and more personalized immunotherapeutic approaches and novel risk-adapted treatment strategies in MM.

Keywords: multiple myeloma; bone marrow immune microenvironment; immune dysregulation; T-cell exhaustion; immunosenescence; single-cell RNA sequencing; tumor-associated macrophages; myeloid-derived suppressor cells; immune signatures; immunotherapy

1. Introduction

MM is the second most prevalent hematological cancer, and its incidence continues to rise globally, characterized by the clonal proliferation of plasma cells within the bone marrow (BM) [1–3]. Although substantial advances in therapy, including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapies, have improved survival outcomes, MM remains largely incurable for most patients [4]. Disease progression and therapeutic resistance are increasingly recognized as consequences not only of tumor-intrinsic genomic abnormalities [2,5] but also of progressive dysregulation of the bone marrow immune microenvironment (BMIME) [6–8]. Cancer immunoediting has been conceptualized as occurring through three dynamic phases: elimination, equilibrium, and immune escape [9,10]. In precursor plasma cell disorders such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), immune surveillance may initially constrain malignant transformation through coordinated innate and adaptive immune responses [11,12]. However, progressive immune dysfunction is increasingly associated with clonal expansion, immune evasion, and symptomatic disease progression. Although the available evidence strongly supports an association between immune remodeling and disease evolution, definitive causal relationships remain incompletely established and continue to be actively investigated.

Unlike prior reviews that primarily focus on individual immune-cell populations within the MM microenvironment, the present review emphasizes recent advances in single-cell immune atlases, immune-aging biology, mechanistic studies of immune dysfunction, and the translational implications of immune remodeling for modern immunotherapies, including bispecific antibodies, antibody-drug conjugates, CELMoDs, and CAR-T-cell therapies.

Recent advances in single-cell RNA sequencing, spatial transcriptomics, and multi-omic immune profiling have transformed the understanding of the MM microenvironment [13,14]. A recent large-scale single-cell atlas of newly diagnosed MM identified profound immune remodeling associated with disease progression and clinical outcomes, including T-cell exhaustion, inflammatory myeloid activation, interferon-associated signatures, and senescence-associated immune phenotypes [14].

Emerging evidence suggests that the BMIME is an important contributor to disease biology, treatment responsiveness, and clinical outcomes in MM. However, much of the current understanding of BMIME remodeling derives from cross-sectional immune-profiling studies, including single-cell RNA sequencing, spatial transcriptomics, CyTOF, and other high-dimensional technologies. Although these approaches provide unprecedented insight into immune-cell heterogeneity and intercellular communication networks, they do not necessarily establish functional relevance or causal biological relationships. In this review, we summarize current evidence regarding immune dysregulation in MM, critically examine

recent advances in immune profiling and mechanistic studies of immune dysfunction, and discuss the translational implications of immune signatures, clinically actionable biomarkers, and emerging immune-based therapeutic strategies. Prospective longitudinal studies and functional investigations remain essential to determine whether specific immune alterations actively contribute to disease progression and treatment resistance or primarily reflect evolving tumor biology.

2. Architecture of the Bone Marrow Immune Microenvironment in Multiple Myeloma

The BM microenvironment consists of a highly complex and dynamic cellular ecosystem (see Figure 1) composed of immune cells, stromal cells, endothelial cells, osteoclasts, osteoblasts, extracellular matrix components, cytokines, and chemokines [7,15–18]. These components collectively regulate plasma cell survival, immune homeostasis, hematopoiesis, and treatment response [7,16,18]. Multiple myeloma (MM) develops and progresses within the bone marrow (BM), where malignant plasma cells reside in a highly specialized and dynamic tumor microenvironment (TME). Rather than altering the intrinsic biology of the disease, this complex ecosystem provides the cellular and molecular context that supports tumor survival, immune escape, treatment resistance, and the clonal selection underlying disease evolution. The BM microenvironment acts as an evolving ecosystem with interconnected cellular and non-cellular compartments that continuously interact with malignant plasma cells through direct cell–cell contact, cytokine signaling, metabolic exchange, extracellular vesicles, and extracellular matrix remodeling [7,15–18]. These bidirectional interactions not only support plasma cell survival and proliferation but also promote immune escape, clonal evolution, angiogenesis, osteolytic bone disease, dissemination, and resistance to therapy (Figure 1).

The cellular compartment of the MM microenvironment comprises both immune and non-immune populations (Figure 2). Immune cells include myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), dendritic cells, T lymphocytes, regulatory T cells (Tregs), NK cells, neutrophils, mast cells, and B regulatory cells. Non-immune elements include bone marrow stromal cells (BMSCs), osteoblasts, osteoclasts, endothelial cells, fibroblasts, adipocytes, and mesenchymal stem cells [7,15–17]. Together, these populations create a permissive immunosuppressive niche that progressively shifts the marrow environment from immune surveillance to immune tolerance and tumor support. Within the immune compartment, T lymphocytes, NK cells, macrophages, dendritic cells, MDSCs, neutrophils, and Tregs play critical roles in shaping antitumor immunity [7,9,19–23]. Recent single-cell studies have demonstrated that the baseline BMIME in newly diagnosed MM is predominantly composed of CD8⁺ T cells, CD4⁺ T cells, myeloid cells, NK cells, B cells, erythroid populations, and residual plasma cells. Importantly, each of these major cellular compartments comprises numerous transcriptionally and functionally distinct subpopulations (cell states or clusters), revealing remarkable cellular heterogeneity and complex intercellular communication networks that shape immune surveillance, disease progression, therapeutic resistance, and clinical outcomes [14,17].

Among the stromal components, BMSCs play a central organizing role in MM pathobiology. Adhesion of malignant plasma cells to stromal cells through integrins, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and the chemokine receptor type 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis activates critical survival pathways, including nuclear factor kappa B (NF-κB), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling [15,16,18]. These interactions promote the secretion of interleukin 6 (IL-6), vascular

endothelial growth factor (VEGF), B-cell activating factor (BAFF), a proliferation-inducing ligand (APRIL), and insulin-like growth factor 1 (IGF-1), thereby enhancing malignant plasma cell proliferation, inhibiting apoptosis, and promoting resistance to proteasome inhibitors, corticosteroids, and immunotherapies [15,16]. Importantly, stromal-mediated signaling also contributes to cell adhesion-mediated drug resistance (CAM-DR), a key mechanism of therapeutic escape in MM [24].

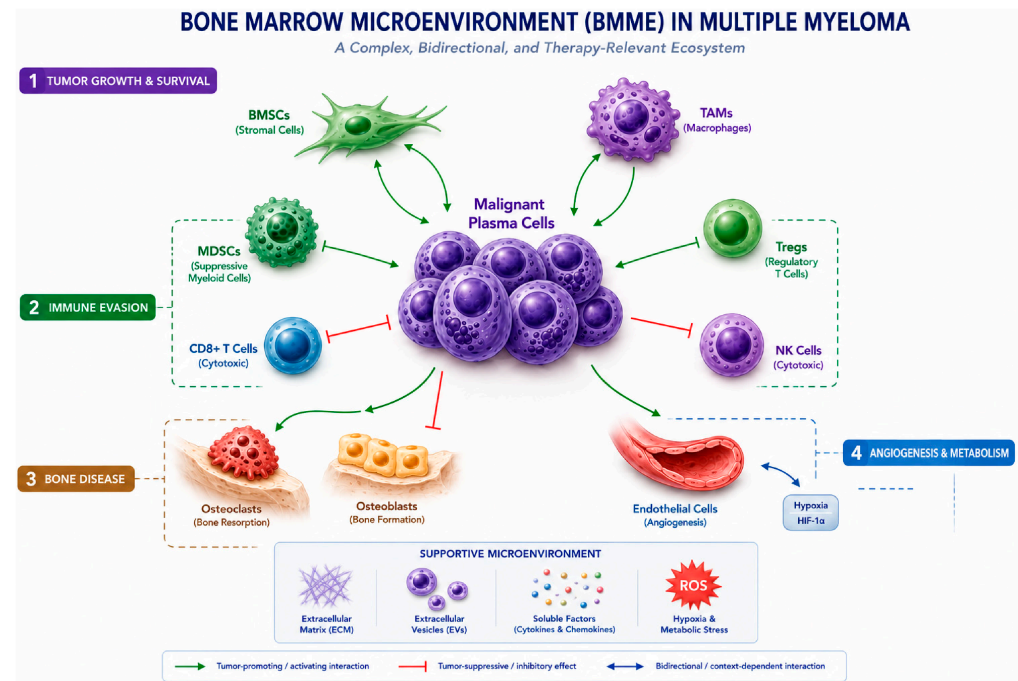


Figure 1. Bone Marrow Microenvironment (BMME) in multiple myeloma: Schematic representation of the bone marrow microenvironment in multiple myeloma, highlighting the bidirectional interactions between malignant plasma cells and surrounding cellular and non-cellular compartments. Bone marrow stromal cells, tumor-associated macrophages, myeloid-derived suppressor cells, regulatory T cells, endothelial cells, osteoclasts, osteoblasts, cytotoxic CD8⁺ T cells, and natural killer cells contribute to tumor growth, immune evasion, bone remodeling, angiogenesis, metabolic adaptation, and therapeutic resistance. The supportive non-cellular niche includes extracellular matrix, extracellular vesicles, soluble cytokines and chemokines, hypoxia-related signaling, and reactive oxygen species.

Bone remodeling is profoundly dysregulated within the MM microenvironment. Osteoclasts' activity is markedly increased by receptor activator of nuclear factor kappa-B ligand (RANKL), macrophage inflammatory protein 1 alpha (MIP-1α), IL-6, tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), VEGF, and activin. This signaling pathway drives excessive bone resorption and the release of growth factors stored within the bone matrix, which further stimulates myeloma cell growth [15,16,25]. Simultaneously, osteoblast differentiation and bone formation are suppressed, in part through inhibition of Wnt signaling pathways and increased production of molecules such as dickkopf-related protein 1 (DKK1) and sclerostin [26,27]. This uncoupling of bone remodeling establishes a self-reinforcing osteolytic niche that promotes tumor expansion and skeletal destruction [15].

Immune dysfunction is another defining characteristic of the MM TME. Myeloid populations, particularly MDSCs and TAMs, exert potent immunosuppressive activity through the production of arginase-1, nitric oxide, reactive oxygen species, IL-10, and TGF-β [19–21,28]. These mechanisms suppress cytotoxic T-cell and NK-cell activity, impair antigen presentation, and facilitate immune escape. TAMs, predominantly polarized toward an M2-like phenotype, additionally promote angiogenesis, plasma cell survival,

osteoclast activation, and resistance to therapy through the secretion of IL-6, VEGF, and BAFF [22,23,28].

Component	Key Mediators	Main Functions	Therapeutic Relevance
 Osteoclasts	RANKL, IL-6, MIP-1α	Bone resorption; plasma cell survival	RANKL inhibitors; bone-targeted therapy
 Osteoblasts	DKK1, sclerostin	Suppressed bone formation	Wnt pathway modulation
 MDSCs	IL-10, TGF-β, arginase-1	Immune suppression; angiogenesis	MDSC depletion; checkpoint synergy
 Macrophages (TAMs)	IL-6, VEGF, BAFF	Survival; angiogenesis; drug resistance	CSF1R inhibitors; macrophage reprogramming
 Dendritic Cells	IL-10, Reduced CD80/CD86	Immune tolerance	DC restoration; vaccines
 Neutrophils	ROS, VEGF	Immune modulation; angiogenesis	Targeting neutrophil plasticity
 Mast Cells	Histamine, Proteases	Angiogenesis; plasma cell support	Anti-angiogenic strategies
 T Cells	PD-1, TIGIT	Exhaustion; reduced cytotoxicity	Checkpoint inhibitors; bispecific antibodies
 NK Cells	Decreased NKG2D; Decreased ADCC	Impaired tumor killing	NK-cell-engaging antibodies
 BMSCs	IL-6, CXCL12	Survival; CAM-DR	CXCR4/Adhesion targeting
 Endothelial Cells	VEGF	Angiogenesis	Anti-angiogenic therapy
 ECM	Fibronectin, Collagen	Adhesion; CAM-DR	Integrin targeting
 EVs	miRNAs, Proteins	Immune suppression; resistance	EV-based biomarkers
 Soluble Factors	IL-6, BAFF, APRIL	Growth; resistance	Cytokine pathway inhibition

Figure 2. Cellular and non-cellular components of the multiple myeloma bone marrow tumor microenvironment. This table summarizes the principal cellular and non-cellular components of the multiple myeloma bone marrow tumor microenvironment, highlighting their key mediators, biological functions, and therapeutic relevance. Together, these compartments support malignant plasma cell survival, immune evasion, angiogenesis, bone remodeling, and treatment resistance, underscoring the bone marrow niche as a critical driver of disease progression and an important therapeutic target. Abbreviation: MM = multiple myeloma; TME = tumor microenvironment; RANKL = receptor activator of nuclear factor kappa-B ligand; IL = interleukin; MIP-1α = macrophage inflammatory protein-1 alpha; DKK1 = dickkopf-related protein 1; MDSCs = myeloid-derived suppressor cells; TGF-β = transforming growth factor beta; TAMs = tumor-associated macrophages; VEGF = vascular endothelial growth factor; BAFF = B-cell activating factor; CSF1R = colony-stimulating factor 1 receptor; DC = dendritic cell; ROS = reactive oxygen species; PD-1 = programmed cell death protein 1; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; NK = natural killer; NKG2D = natural killer group 2 member D; ADCC = antibody-dependent cellular cytotoxicity; BMSCs = bone marrow stromal cells; CXCL12 = C-X-C motif chemokine ligand 12; CXCR4 = C-X-C chemokine receptor type 4; CAM-DR = cell adhesion-mediated drug resistance; ECM = extracellular matrix; EVs = extracellular vesicles; miRNAs = microRNAs; APRIL = a proliferation-inducing ligand.

Lymphoid dysfunction emerges early during progression from MGUS to overt MM and is characterized by progressive T-cell exhaustion and impairment of NK-cell cytotoxicity [7,12,17,29]. CD8⁺ T cells demonstrate increased expression of inhibitory immune checkpoints, such as programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte activation gene 3 (LAG-3), accompanied by reduced cytokine production and impaired proliferative capacity. NK cells exhibit downregulation of activating receptors, including natural killer group 2D (NKG2D) and DNAX accessory molecule 1 (DNAM-1/CD226), further compromising antitumor immune surveillance [7,17]. These changes collectively establish an immunologically exhausted environment that favors persistence and expansion of malignant clones.

The non-cellular compartment of the MM microenvironment is equally important in sustaining disease progression. The extracellular matrix (ECM), which is composed of

fibronectin, collagen, laminin, and proteoglycans, provides structural support while simultaneously regulating adhesion signaling, migration, and survival of plasma cells [15,16]. Interactions between plasma cells and ECM proteins activate integrin-dependent pathways that contribute to CAM-DR and facilitate dissemination within the marrow niche.

In addition, extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as critical mediators of intercellular communication within the MM ecosystem. Plasma cell-derived EVs transport oncogenic proteins, microRNAs, cytokines, and metabolic mediators that can reprogram stromal and immune cells toward tumor-supportive phenotypes [15,17]. EVs also contribute to angiogenesis, osteoclast activation, immune suppression, and resistance to therapy, while potentially enabling systemic remodeling of distant marrow niches prior to disease dissemination.

The BM extracellular fluid is enriched with soluble mediators, including IL-6, interleukin 10 (IL-10), transforming growth factor beta (TGF- β), CXCL12, VEGF, BAFF, APRIL, and TNF- α , which collectively activate pro-survival and anti-apoptotic pathways in malignant plasma cells while promoting immune suppression, angiogenesis, osteolytic disease, metabolic reprogramming, and therapeutic resistance [7,15–18]. In parallel, direct cell–cell interactions mediated by ligand-receptor pathways such as PD-L1/PD-1, CD47/signal regulatory protein alpha (SIRP α), BCMA/APRIL, and TIGIT/CD155 further contribute to immune escape, T-cell exhaustion, and resistance to immune-mediated cytotoxicity [7,17,30]. Emerging evidence further suggests that obesity-associated metabolic inflammation and insulin resistance may further amplify this tumor-supportive niche by promoting chronic low-grade inflammation, adipokine dysregulation, immune-cell dysfunction, and metabolic reprogramming, thereby creating conditions that favor plasma cell survival, immune escape, and disease progression [30–34]. Consequently, MM should be understood not solely as a plasma cell malignancy but as a co-evolving ecosystem in which malignant clones and the bone marrow microenvironment dynamically shape one another throughout disease progression and treatment exposure, ultimately leading to progressive loss of immune surveillance and emergence of treatment-resistant tumor clones [2,7,15–18,29].

3. Immune Dysregulation Across Multiple Myeloma Evolution

3.1. Immunosurveillance in MGUS and Smoldering Multiple Myeloma

MGUS and SMM represent precursor plasma cell disorders characterized by asymptomatic clonal plasma cell expansion with variable risk of progression to symptomatic MM [2,12,18,29]. During these early disease stages, immune surveillance mechanisms may establish a state of equilibrium capable of constraining malignant transformation through coordinated innate and adaptive immune responses [9,29] (Figure 3).

Several studies have demonstrated that patients with MGUS retain more effective cytotoxic T-cell responses and NK-cell activity compared with patients with symptomatic MM, supporting the concept that early immune control may delay disease progression [7,9,29,35]. In a single-cell RNA-sequencing analysis of bone marrow from healthy donors and patients with MGUS, SMM, or MM, Zavidij et al. identified changes in both the relative abundance of immune populations and stage-associated transcriptional programs within specific cell subsets [35]. Importantly, these findings distinguish compositional and transcriptional alterations from directly measured immune function. Functional validation in that study included selected monocyte–T-cell suppression experiments and experimental analyses related to GZMK⁺ T-cell biology; however, human NK-cell cytotoxicity was not directly assessed. Thus, changes in NK-cell abundance or activation-associated transcriptional programs should not, in isolation, be interpreted as evidence of impaired NK-cell cytotoxic function. Nevertheless, evidence from complementary studies supports progres-

sive impairment of antitumor immune competence during disease evolution. Persistent antigenic stimulation, chronic inflammatory signaling, genomic evolution, and progressive immunosenescence may collectively contribute to immune dysfunction and facilitate immune escape [2,7,11].

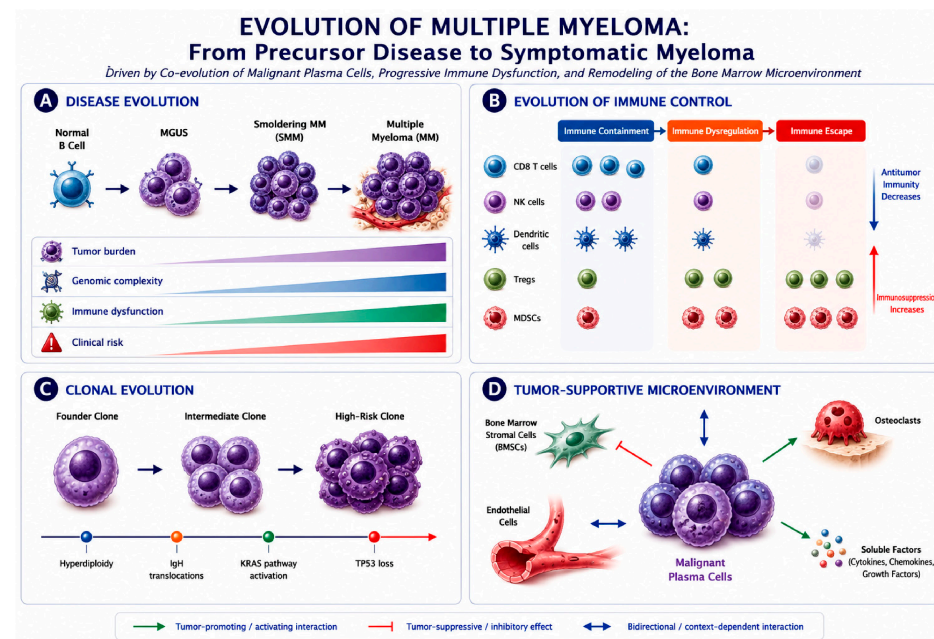


Figure 3. Evolution of multiple myeloma from precursor disease to symptomatic multiple myeloma. Schematic representation of multiple myeloma (MM) evolution from normal B cells to monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and symptomatic MM. Disease progression is depicted as a dynamic process associated with increasing tumor burden, genomic complexity, immune dysfunction, and clinical risk. The figure highlights the progressive loss of immune control, transitioning from immune containment to immune dysregulation and immune escape, with declining antitumor immune activity and increasing immunosuppression mediated by regulatory T cells and myeloid-derived suppressor cells. In parallel, clonal evolution is represented by the emergence of progressively higher-risk plasma cell clones associated with early genomic events, such as hyperdiploidy and immunoglobulin heavy-chain translocations (IgH), followed by the acquisition of diverse secondary molecular alterations that may include KRAS-pathway activation and TP53 abnormalities and other genomic events associated with disease progression. The tumor-supportive bone marrow microenvironment further contributes to disease progression through bidirectional crosstalk between malignant plasma cells, bone marrow stromal cells, endothelial cells, osteoclasts, and soluble mediators, promoting plasma cell expansion, immune escape, angiogenesis, bone remodeling, and transition to clinically active disease.

The transition from MGUS or SMM to active MM is associated with profound remodeling of the BMIME, including depletion of naïve and memory T-cell populations, reduced NK-cell cytotoxicity, expansion of immunosuppressive MDSCs and TAMs, and increased expression of inhibitory immune checkpoint pathways associated with T-cell exhaustion [7,19–22,28,36–38]. Recent immune-profiling and single-cell transcriptomic studies have further demonstrated that inflammatory immune populations and dysfunctional immune signatures strongly correlate with disease progression, relapse risk, and inferior survival outcomes in MM [14,17,29].

Collectively, these findings support the hypothesis that disruption of immune equilibrium and progressive immune dysregulation are closely associated with transformation from precursor disease to symptomatic MM [7,9,18,29]. However, because much of the available evidence remains observational, additional mechanistic studies are required to

determine the extent to which these immune alterations directly contribute to disease progression.

3.2. T-Cell Dysfunction and Exhaustion

T-cell dysfunction represents one of the central hallmarks of immune dysregulation in MM and plays a critical role in disease progression, immune escape, and therapeutic resistance [7,14,17,29]. Recent single-cell transcriptomic studies have demonstrated profound remodeling of CD8⁺ T-cell states throughout MM evolution, particularly in patients with rapidly progressive disease and inferior clinical outcomes [6,14].

Rapid progressors exhibit enrichment of terminally differentiated cytotoxic effector T-cell populations, including granzyme (GZM) K⁺ and TIGIT⁺ exhausted CD8⁺ T cells, accompanied by depletion of naïve and central memory T-cell compartments that are essential for durable immune surveillance and sustained antitumor responses [6,35]. These dysfunctional T-cell populations display reduced expression of cytolytic mediators such as PRF1, GZMB, and granulysin (GNLY), suggesting impaired immune-mediated tumor control [6].

In particular, expansion of activated HLA-positive CD8⁺ effector populations and increased expression of inhibitory and exhaustion-associated molecules, including PD-1, TIGIT, LAG-3, thymocyte selection-associated high mobility group box protein (TOX), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), have been consistently associated with high tumor burden, accelerated disease progression, and inferior survival outcomes [6,14,17,29]. The progressive accumulation of these exhausted T-cell phenotypes reflects chronic antigen stimulation, persistent inflammatory signaling, and continuous exposure to immunosuppressive mediators within the BMIME [7,14].

Trajectory along with immune-aging analyses additionally demonstrated expansion of terminally differentiated CD27[−]CD28[−] cytotoxic T-cell populations in aggressive disease, accompanied by features of immunosenescence and reduced immune adaptability [8,14]. Collectively, these data strongly support the conclusion that biologic “immune age”, and T-cell functional status may better predict clinical outcomes compared to chronological age alone, particularly in patients receiving modern immunotherapies [8,39].

Regulatory T cells (Tregs) represent an additional and clinically relevant component of immune dysregulation in MM. Multiple studies have demonstrated increased frequencies of Tregs in active MM compared with MGUS, smoldering multiple myeloma (SMM), and healthy controls, suggesting progressive expansion of immunosuppressive networks during disease evolution [7,17,29,35]. Tregs suppress antitumor immunity through secretion of interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), inhibition of cytotoxic CD8⁺ T-cell responses, suppression of natural killer (NK)-cell activity, and promotion of immune tolerance [7,17,19,20]. Importantly, Kawano et al. demonstrated that IFNAR1 signaling directly contributes to MM-driven Treg expansion and immunosuppressive activity, providing mechanistic evidence linking interferon signaling and immune suppression in MM [40]. These findings suggest that Tregs are not merely biomarkers of immune dysfunction but may actively contribute to the establishment of a permissive immunosuppressive microenvironment associated with disease progression, immune escape, and resistance to immunotherapy [17,29,40]. Although much of the evidence regarding Treg expansion derives from immune-profiling studies, the IFNAR1 blockade experiments reported by Kawano et al. provide functional support for a direct role of Tregs in MM-associated immune suppression [40].

The origin of immune-aging phenotypes in MM is probably multifactorial and cannot be inferred from chronological age alone. In age-matched MGUS and NDMM cohorts, Potdar et al. observed greater immune-aging scores and enhanced basal inflammatory

signaling in NDMM, while stimulated T cells retained cytokine production and proliferative capacity [41]. These findings support disease-associated inflammatory remodeling rather than universal T-cell exhaustion. Consistent with this interpretation, Bailur et al. showed that bone marrow immune alterations, including terminal effector differentiation of memory T cells and changes in innate and myeloid compartments, are already detectable in MGUS and evolve further in MM [42]. Single-cell studies across healthy donors, MGUS, SMM, and MM similarly indicate that immune remodeling emerges during precursor disease, although compositional and transcriptional findings should not be equated with direct functional impairment [35]. Nevertheless, cross-sectional comparisons cannot fully separate physiological aging, duration of clonal stimulation, disease burden, prior infections, or treatment exposure. Definitive attribution will require age-matched, treatment-naïve longitudinal sampling from precursor disease through MM, with repeated functional and molecular measurements.

These observations indicate that progressive T-cell exhaustion and immunosenescence are strongly associated with disease progression and therapy resistance. Recent studies suggest that biologic immune age, characterized by T-cell differentiation, senescence, and functional immune fitness, may provide prognostic information beyond chronological age, particularly among patients receiving immune-based therapies [8,14]. Consequently, immune-aging biomarkers represent promising candidates for future risk stratification and treatment-selection strategies, although prospective validation remains necessary [39,43].

3.3. Myeloid-Mediated Immunosuppression

The myeloid compartment also undergoes profound remodeling in MM. Increased levels of inflammatory monocytes, MDSCs, TAMs, and neutrophil populations contribute to immunosuppressive signaling and tumor progression.

3.3.1. Myeloid-Derived Suppressor Cells

MDSCs are major immunosuppressive components of the MM bone marrow microenvironment (BMME) and play an important role in disease progression, immune escape, angiogenesis, bone remodeling, and therapeutic resistance [19,20,36,38]. MDSCs are a heterogeneous population of immature myeloid cells that expand under chronic inflammatory and tumor-driven conditions, with accumulation detected even in precursor stages such as MGUS and smoldering MM, indicating that immune dysregulation develops early during myelomagenesis [19,20,29,35].

In MM, MDSCs are expanded within the bone marrow microenvironment and can suppress antitumor immunity while supporting myeloma-cell growth [20,44–46]. In patient-derived and experimental systems, MM cells promoted MDSC development, whereas MM-associated MDSCs demonstrated immunosuppressive and tumor-promoting activity, supporting a bidirectional interaction between malignant plasma cells and the myeloid compartment [20,44–48]. Mechanistically, arginase-1 (ARG1) has direct MM-specific functional support, with pharmacologic inhibition and genetic deletion restoring T-cell responses and/or attenuating myeloma progression; iNOS has also been implicated in MDSC-mediated T-cell suppression, although the MM-specific causal evidence is less extensive [20,49,50]. Increased reactive oxygen species (ROS) production has also been observed in MM-associated myeloid populations, and ROS can contribute to granulocyte-mediated T-cell suppression, although this mechanism should not be considered uniformly established across all MM MDSC subsets [20,51]. Expression of individual inhibitory mediators varies according to MDSC subset and clinical context; for example, increased ARG1 and PD-L1 expression has been reported in monocytic MDSCs from patients with progressive

disease [52], while clinical studies have demonstrated preferential expansion of M-MDSCs in active or progressive MM compared with remission states [45,53].

Beyond immune suppression, MM-associated MDSCs can directly support malignant plasma-cell growth and survival, indicating that their contribution to disease biology extends beyond suppression of adaptive immunity [20,44,47,48]. Bidirectional interactions between MM cells and the myeloid compartment have been demonstrated experimentally, with MM cells promoting the development and survival of suppressive myeloid populations, while MDSCs can enhance myeloma-cell proliferation and survival [20,47,48]. These tumor-supportive effects extend to other components of the bone marrow microenvironment. In preclinical MM models, granulocytic/PMN-MDSCs demonstrated proangiogenic activity, whereas monocytic MDSCs and tumor-associated Gr-1⁺CD11b⁺ myeloid populations were shown to differentiate into functional osteoclasts and contribute to osteolytic bone disease [54,55]. Experimental targeting of MDSC-associated pathways, including ARG1, can restore T-cell responses and attenuate MM progression, providing a biological rationale for therapeutic strategies directed at suppressive myeloid populations [50]. However, the contribution of MDSCs to resistance to individual contemporary immunotherapeutic modalities remains incompletely defined and should not be inferred solely from their general immunosuppressive properties.

MDSCs comprise phenotypically and functionally heterogeneous populations, including monocytic (M-MDSC) and polymorphonuclear/granulocytic (PMN-MDSC/G-MDSC) subsets, whose relative abundance and suppressive phenotype vary according to disease stage and clinical context [45,46,52,53]. MM-associated granulocytic populations have demonstrated suppressive activity associated with ARG1- and ROS-related pathways, although phenotypic definitions differ among studies, and some suppressive granulocytic populations, such as high-density neutrophils, do not correspond strictly to conventionally defined PMN-MDSCs [46,49,51]. In contrast, monocytic MDSCs are preferentially expanded in active or progressive MM, and increased ARG1 and PD-L1 expressions have been reported in M-MDSCs during progressive disease [45,52,53]. Experimental studies further support a functional role for myeloid ARG1 in MM-associated immune suppression and disease progression [20,50]. Collectively, these findings demonstrate substantial biological heterogeneity among MM-associated suppressive myeloid populations but do not support a universal M-MDSC–iNOS versus PMN-MDSC–ROS functional dichotomy across all stages and clinical settings of MM.

3.3.2. Macrophages

Tumor-associated macrophages (TAMs) represent an abundant and functionally heterogeneous component of the MM bone marrow microenvironment. Rather than constituting discrete M1/M2 populations, MM-associated macrophages display a spectrum of activation states, with tumor-supportive phenotypes contributing to malignant plasma-cell survival and adverse clinical behavior. In experimental systems, macrophages protected MM cells from chemotherapy-induced apoptosis through direct interactions with malignant plasma cells, providing functional evidence for macrophage-mediated tumor support [22]. Consistent with these experimental observations, increased bone marrow macrophage infiltration has been associated with adverse clinical features and inferior survival in patients with MM [23]. These findings support a role for TAMs in MM progression but do not establish macrophage-mediated resistance uniformly across proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, bispecific antibodies, and cellular therapies.

PD-L1 expression within the MM bone marrow microenvironment should also be interpreted according to the cellular compartment in which it is measured. In a flow-cytometric analysis spanning precursor and active plasma-cell disorders, Costa et al. demonstrated

differential PD-L1 expression among myeloid populations, with higher expression on CD14⁺CD16⁺ nonclassical monocytes than on classical monocytes [56]. Separately, PD-L1 expression has been demonstrated on malignant CD138⁺ plasma cells and myeloma-propagating pre-plasma-cell populations [57]. In newly diagnosed MM, higher PD-L1 expression on bone marrow plasma cells was associated with poorer clinical outcomes [58]. Collectively, these studies demonstrate that PD-L1 is expressed across distinct myeloid and malignant plasma-cell compartments in MM; however, expression and prognostic association should not be interpreted as direct evidence that PD-L1 independently drives disease progression or macrophage-mediated immune suppression.

Recent single-cell studies further demonstrate substantial heterogeneity within the myeloid compartment of clinically aggressive MM. In a cross-center single-cell RNA-sequencing analysis, Pilcher et al. identified distinct immune-microenvironmental features associated with rapidly progressing disease, including alterations in monocyte/macrophage populations and inflammatory signaling networks [6]. Because these findings were derived primarily from cross-sectional transcriptional profiling, enrichment of particular myeloid populations or inflammatory programs should be interpreted as an association with rapid progression rather than direct evidence of their causal contribution to aggressive disease. These observations nevertheless support further investigation of myeloid populations as potential biomarkers and therapeutic targets in MM while emphasizing that transcriptionally defined macrophage states cannot be reduced to a universal binary M1/M2 classification.

3.4. NK Cell Dysfunction

Natural killer (NK) cells are key components of innate antitumor immunity and represent one of the earliest immune defenses against malignant plasma cells in MM [7,9,17]. Unlike T cells, NK cells recognize tumor cells independently of antigen presentation through a balance of activating and inhibitory receptor signaling. During early disease stages, NK cells may retain partial antitumor activity; however, MM progression is associated with progressive NK-cell dysfunction characterized by reduced cytotoxicity, impaired cytokine production, and defective antibody-dependent cellular cytotoxicity (ADCC) [7,17,29].

A major mechanism of NK-cell impairment involves downregulation of activating receptors such as NKG2D, DNAM-1, NKP30, and NKP46, together with enhanced signaling through inhibitory receptors, including killer immunoglobulin-like receptors (KIRs) and NKG2A, within the bone marrow microenvironment [7,59,60]. Immunosuppressive cytokines such as TGF- β and IL-10, as well as suppressive interactions with MDSCs, TAMs, and regulatory T cells, further inhibit NK-cell activation, proliferation, and cytotoxic function [19,20,28,29,61]. Chronic inflammation, hypoxia, and metabolic stress within the bone marrow niche additionally promote NK-cell exhaustion and bioenergetic dysfunction [15,17,51,60].

NK-cell dysfunction has important therapeutic implications because several modern MM therapies, including monoclonal antibodies, bispecific antibodies, and cellular immunotherapies, depend at least partially on preserved NK-cell activity and ADCC mechanisms [4,59,60,62,63]. In addition to reduced expression of activating receptors and enhanced inhibitory signaling, dysfunctional NK-cell populations demonstrate impaired cytotoxic activity, altered cytokine production, and reduced immune surveillance capacity [59,60].

Single-cell analyses have identified dysregulated NK-cell subsets characterized by altered expression of genes involved in cytotoxicity and immune activation, including PRF1, GNLY, NKG7, GZMB, and FCGR3A, suggesting progressive impairment of effector-cell function during disease evolution [6,13,14,35]. These transcriptional alterations are

associated with impaired tumor-cell elimination and adverse clinical outcomes. However, because these observations derive primarily from transcriptomic analyses, additional functional studies are required to confirm their biological significance and determine the extent to which they directly contribute to disease progression and therapeutic resistance [14,19]. Collectively, these findings suggest that reduced NK-cell fitness may represent both a biomarker of immune dysfunction and a potential therapeutic target in MM [59,60,62,63].

3.5. Interferon Signaling and Immune Remodeling

3.5.1. Type I Interferon Signaling

Type I interferons (IFN-I), including IFN- α and IFN- β , are key regulators of innate immune activation, antigen presentation, antiviral responses, and tumor immune surveillance [64,65]. Early studies demonstrated that interferons exert direct cytotoxic effects on primary myeloma cells, supporting their potential antitumor activity in MM [66]. More recently, high-dimensional immune-profiling and immune atlas studies have identified enrichment of type I interferon (IFN-I)-associated immune signatures in specific genomic subgroups, particularly patients harboring TP53 abnormalities, whereas 1q21 gain is associated with reduced interferon activity and a more immunosuppressive microenvironment [14]. These findings suggest that distinct genomic subtypes may engage in different immune and inflammatory programs during disease evolution.

Mechanistically, IFN-I signaling is linked to innate immune activation, DNA damage responses, and cellular senescence pathways. Experimental studies have demonstrated interactions between IFN-I signaling, DNA-damage responses, apoptosis pathways, and cellular senescence. However, direct evidence supporting these mechanisms specifically in MM remains limited, and additional disease-specific mechanistic studies are warranted [67,68]. In MM, activation of the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway has emerged as an important regulator of innate immune sensing and IFN-I production within the TME [65]. Preclinical and translational studies have demonstrated that bortezomib can activate cGAS/STING signaling, induce IFN-I secretion, and promote immunogenic cell death, potentially contributing to antimyeloma immune responses [69,70]. These observations provide a potential mechanistic framework linking interferon activation, innate immune signaling, and treatment responsiveness in MM. Although the precise contribution of IFN-I signaling to clinical outcomes remains incompletely understood, interferon-associated immune programs may contribute to the improved outcomes observed with bortezomib-containing regimens in some high-risk patients, including those with del(17p) [69–71].

Type I interferons also exert broad immunomodulatory effects on T-cell function and immune homeostasis within the BMME [65]. However, chronic IFN-I signaling may paradoxically contribute to immune dysregulation and tumor-associated immunosuppression. Kawano et al. demonstrated that IFNAR1 signaling promotes regulatory T-cell (Treg) expansion and immunosuppressive activity in MM, whereas IFNAR1 blockade reduced MM-driven immune suppression [40]. These findings reinforce the dual role of interferon signaling in MM, functioning both as a mediator of antitumor immunity and, under chronic inflammatory conditions, as a contributor to immune exhaustion and tolerance.

3.5.2. Type II Interferon Signaling

Type II interferon (IFN- γ) exerts distinct biological effects and is produced predominantly by activated T cells and natural killer (NK) cells. Unlike IFN-I signatures, which are generally associated with enhanced immune surveillance and antigen presentation, IFN-II-associated programs have been linked to inflammatory remodeling, immunosenescence, and adverse clinical outcomes in MM [14,43].

Patients with poor clinical outcomes exhibit enrichment of IFN-II-dominant immune programs characterized by immunosenescent CD8⁺ T cells, inflammatory myeloid activation, and increased APRIL signaling [14,43]. Conversely, patients with better outcomes are associated with IFN-I-associated monocyte populations, enhanced antigen presentation, preservation of naïve and central-memory T-cell compartments, and increased BAFF signaling [14,43]. These contrasting interferon-associated immune states may partially explain the marked heterogeneity observed in disease progression and treatment response [14]. From a translational perspective, IFN-associated immune signatures may ultimately serve as promising candidate biomarkers for risk stratification and therapeutic selection [14,72].

Cell-cell communication analyses identified BAFF (TNFSF13B) and APRIL (TNFSF13) as pivotal myeloid-derived mediators in the BMIME [73]. IFN-I-associated monocyte populations observed in patients with more favorable outcomes demonstrate increased BAFF expression, whereas APRIL expression is enriched in IFN-II-associated macrophage and monocyte populations observed in rapidly progressing disease [14]. Because BAFF and APRIL signaling influence plasma-cell survival, immune regulation, and microenvironmental interactions, these pathways may contribute to differences in disease behavior and clinical outcomes [14,73].

Integration of BMIME signatures with conventional cytogenetic risk factors markedly enhances prognostic stratification and prediction of clinical outcomes in MM [2,72]. Recent immune atlas studies have revealed that differentiated, exhausted, and immunosenescent immune cell populations within the BMIME are independently associated with poorer prognosis, even in patients with otherwise favorable cytogenetics [14]. These observations suggest that immune remodeling within the bone marrow microenvironment contributes importantly to disease heterogeneity and clinical outcomes, independent of conventional cytogenetic risk classification. Integration of immune-state variables, immune age, interferon signatures, inflammatory myeloid activation, and T-cell functional status may ultimately improve prognostic assessment and identify patients most likely to benefit from specific immunotherapeutic strategies. Nevertheless, prospective validation studies remain necessary before these biomarkers can be incorporated into routine clinical practice.

4. Translational and Therapeutic Implications

The growing understanding of immune dysregulation in multiple myeloma (MM) has important translational and therapeutic implications. MM is no longer viewed solely as a plasma-cell malignancy driven by tumor-intrinsic genetics; it is increasingly recognized as a disease sustained by dynamic interactions between malignant plasma cells and an immunosuppressive bone marrow microenvironment. These interactions begin early, can already be detected in precursor states such as MGUS and smoldering multiple myeloma (SMM), and intensify during progression to active disease, ultimately shaping both immune escape and treatment resistance [74–76].

This evolving framework helps explain why many of the most effective modern therapies in MM depend, at least in part, on immune-mediated mechanisms of action. Monoclonal antibodies such as daratumumab and isatuximab do not simply target tumor cells directly; they also induce complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, phagocytosis, apoptosis, and broader immunomodulatory effects within the marrow niche [77]. T-cell-redirecting bispecific antibodies represent an important therapeutic strategy in MM by simultaneously engaging a tumor-associated antigen on malignant plasma cells and CD3 on T cells, thereby promoting immune-synapse formation and redirected T-cell cytotoxicity [78,79]. Mechanistic evidence for this approach has been demonstrated with Teclistamab, a BCMA×CD3 bispecific antibody. In preclinical studies, Pillarisetti et al. showed that Teclistamab specifically engaged BCMA-expressing

MM cells and CD3-positive T cells, resulting in T-cell activation, cytokine release, and dose-dependent killing of BCMA-positive myeloma cells. Antimyeloma activity was demonstrated across MM cell-line systems, ex vivo patient-derived bone marrow samples, and whole-blood assays, with additional antitumor activity observed in xenograft models [80]. These findings provide direct mechanistic evidence for BCMA-directed T-cell redirection while distinguishing the experimentally demonstrated mechanism of action from clinical efficacy outcomes.

In a translational analysis of the MajesTEC-1 study, Cortes-Selva et al. evaluated the relationship between baseline immune characteristics and clinical response to Teclistamab in patients with relapsed/refractory MM. Better clinical outcomes were associated with higher baseline peripheral T-cell counts, lower proportions of regulatory T cells (Tregs) and T cells expressing selected coinhibitory receptors, and an immune profile characterized by greater cytolytic potential [81]. These findings support an association between preserved baseline immune fitness and response to BCMA $\times$ CD3 T-cell-redirecting therapy; however, because these analyses were correlative, they do not establish that any individual T-cell subset or immune phenotype independently determines response or resistance to Teclistamab.

Other emerging or expanding immune-based platforms also fit this paradigm. The antibody-drug conjugates, such as belantamab mafodotin, target B-cell maturation antigen (BCMA) expressed on malignant plasma cells and deliver the cytotoxic payload monomethyl auristatin-F (MMAF). In addition to direct tumor-cell killing, belantamab may promote antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and immunogenic cell-death pathways that can enhance antitumor immune responses [82,83]. Cereblon E3 ligase modulators (CELMoDs), including iberdomide and mezigdomide, likewise extend beyond direct anti-myeloma effects: by enhancing degradation of Ikaros and Aiolos, they reshape immune-cell composition and function, increase activated T-cell and NK-cell populations, and may help restore anti-tumor immune pressure in heavily pretreated disease [84–87].

CAR-T-cell efficacy in MM reflects several biologically distinct dimensions that should be considered separately, including cellular expansion, characteristics of the apheresis starting material and manufactured product, post-infusion persistence, and the condition of the endogenous T-cell compartment. In a post hoc analysis of idecabtagene vicleucel (idecel), Lin et al. reported that CAR-T-cell expansion in peripheral blood and bone marrow was associated with clinical efficacy and post-infusion reductions in soluble BCMA; patients with more durable responses also had higher proportions of naïve and fewer exhausted T cells in apheresis material, together with a more favorable functional phenotype in the manufactured CAR-T-cell product [88]. Longitudinal single-cell multi-omic analysis further demonstrated compartment-specific differences between circulating and bone marrow CAR-T cells, with marrow CAR-T cells exhibiting a more activated and exhausted phenotype, while impaired effector-to-memory transition was associated with terminal differentiation and reduced persistence [89]. Complementary population cellular-kinetic modeling of ide-cel incorporated cellular expansion, effector-to-memory conversion, and elimination and showed that greater expansion and lower elimination rates of effector and memory CAR-T-cell populations were associated with longer progression-free survival [90]. These observations identify expansion, starting-cell and product phenotype, and post-infusion persistence as related but distinct features of CAR-T biology and should not be interpreted as evidence that any single parameter independently determines treatment outcome.

The endogenous, non-CAR T-cell compartment represents a related but distinct component of immune fitness. Longitudinal profiling has shown that CAR-T-cell therapy

can reshape the endogenous T-cell landscape in MM and that features of these non-CAR T-cell populations are associated with subsequent treatment response [91]. Accordingly, endogenous T-cell states should be distinguished from the phenotype of apheresis starting cells, the manufactured CAR-T product, and circulating or bone marrow CAR-positive cells when evaluating biomarkers of response and persistence.

More broadly, the immune dysfunction that characterizes MM may limit the efficacy and durability of these therapies. Resistance after BCMA-directed CAR-T-cell therapy is multifactorial and has been associated not only with antigen escape and product-related factors but also with T-cell dysfunction, limited CAR-T-cell persistence, prior treatment exposure, and immunosuppressive pressures within the bone marrow microenvironment [78,92–94]. These mechanisms should be considered complementary rather than interchangeable, and their relative contribution to treatment failure is likely to vary among patients and across disease and treatment contexts.

This is particularly relevant when considering the quality of the endogenous T-cell compartment. Contracted or dysfunctional memory T-cell pools, particularly stem cell-like and central-memory populations, may represent unfavorable features for sustained cellular immunity. In MM, stem cell-like memory T-cell populations have been reported to be reduced in newly diagnosed disease compared with healthy controls or patients in complete response, while emerging evidence indicates that the composition and functional state of memory T-cell compartments are associated with the efficacy and durability of CAR-T-cell therapy [91,95]. These observations support pretreatment endogenous T-cell fitness and memory composition as promising candidate biomarkers for predicting the response and durability of immune-based therapies. However, these associations do not establish that any individual memory T-cell subset independently determines CAR-T-cell efficacy, persistence, or toxicity, and prospective validation remains necessary.

In addition to T-cell dysfunction, inflammatory myeloid signaling and stromal-mediated suppression represent major barriers to durable response. The MM marrow niche contains suppressive myeloid-derived populations, dysfunctional dendritic and NK-cell networks, mesenchymal stromal cells, osteoclast-related signaling, soluble cytokines, and extracellular matrix interactions that together blunt anti-tumor immunity and support plasma-cell survival. This means that relapses after immunotherapy should not be interpreted only as tumor escape but often as the result of persistent or reconstituted microenvironmental immune suppression [74,76,96].

Taken together, these insights create a strong rationale for immune profiling as a translational tool in MM. High-dimensional profiling of bone marrow and peripheral blood may help identify which patients are most likely to benefit from a given immunotherapy, particularly when comparing T-cell-redirecting modalities with other options. The same profiling approaches may also help predict response depth and durability by identifying exhausted T-cell phenotypes, inflammatory cytokine environments, suppressive myeloid signatures, or antigen-related escape patterns before treatment begins. More importantly, serial immune profiling may reveal why patients relapse after an initial response, allowing resistance to be classified as primarily tumor-intrinsic, T-cell-intrinsic, or microenvironment-driven [17,74,78,92].

These translational applications have practical therapeutic consequences. First, immune profiling may improve patient selection for immunotherapy by identifying patients with preserved T-cell fitness or less severely immunosuppressed marrow environments. Second, it may support prediction of treatment response, especially for bispecific antibodies and CAR-T therapies, where baseline immune function appears closely tied to outcome. Third, it may allow for earlier identification of resistance mechanisms, such as antigen loss, chronic T-cell stimulation, checkpoint-mediated exhaustion, or suppressive myeloid

expansion. Fourth, it may enable adaptive treatment strategies, including therapy sequencing, treatment switching, incorporation of immune-restoring partners, or modification of treatment intensity over time. These concepts are now highly relevant because expert groups increasingly emphasize that sequencing of immunotherapies matters, and prior exposure to one T-cell-redirecting platform can influence the efficacy of the next [4,78,97,98].

A particularly important frontier is the application of these principles to precursor disease. Because immune alterations arise early during myeloma evolution, immune profiling may eventually complement current risk-stratification models in MGUS and SMM and help distinguish biologically stable precursor conditions from those already experiencing loss of effective immune control. While observation remains the current standard for SMM outside specific high-risk investigational contexts, emerging prospective data and systematic reviews suggest that early intervention is an active area of clinical development. In this setting, immune biomarkers could be especially valuable—not merely to predict progression, but to identify patients in whom immune-interceptive strategies might delay or prevent transformation to symptomatic MM [74,75,99,100].

Looking ahead, the most promising therapeutic strategies in MM will likely combine tumor-directed cytoreduction with microenvironment-directed immune restoration. This could include rational combinations of monoclonal antibodies, CELMoDs, bispecific antibodies, checkpoint or costimulatory approaches, dual-target or sequential T-cell redirection, γ -secretase inhibition to enhance antigen density, and interventions aimed at reducing suppressive myeloid or stromal signaling. The broader goal is not simply to eliminate plasma cells but to restore durable immune competence and reverse the exhausted, immunoparetic state that allows the disease to recur [78,84,85,92,96].

In that sense, a deeper understanding of immune regulation is reshaping MM therapy from a purely disease-control model into a more integrated strategy of immune restoration, resistance prevention, and earlier disease interception. As immune and multi-omic biomarker platforms mature, they are likely to shape a more personalized treatment paradigm in which the optimal therapy is defined not only by the tumor clone but also by the condition of the host immune ecosystem in which that clone evolves.

5. Future Perspectives

Future progress in MM will likely depend on moving beyond static disease classification toward a more dynamic understanding of the tumor–immune ecosystem, integrating tumor genomics with longitudinal immune and microenvironmental profiling. Emerging data suggest that immune contexture in both marrow and peripheral blood is linked to treatment response, resistance, and disease evolution, supporting the incorporation of immune monitoring into clinical decision-making and trial design [91,98].

A major next step will be the development of biomarker-guided immunotherapy selection. Rather than choosing therapy solely according to line of treatment or prior exposure, future strategies may incorporate baseline T-cell fitness, memory T-cell composition, inflammatory cytokine patterns, suppressive myeloid signatures, and antigen-density profiling to identify the patients most likely to benefit from CAR-T cells, bispecific antibodies, monoclonal antibodies, or CELMoDs-based combinations [101–103].

Another important direction is the design of therapies that do not merely redirect immunity but actively restore immune competence. Rational combinations of tumor-targeted agents with immune-enhancing partners—such as CELMoDs, CD38-directed antibodies, checkpoint or co-stimulatory modulators, and agents that disrupt stromal or myeloid suppression—may help reverse exhaustion, improve T-cell persistence, and deepen the durability of response [98,101,104–107].

Overcoming antigen escape and post-immunotherapy relapse will remain a central research priority. Likely approaches include dual-target or sequential targeting strategies, trispecific constructs, γ -secretase inhibition to enhance BCMA expression, and optimized sequencing across BCMA- and non-BCMA-directed platforms such as GPRC5D-targeted therapies. International expert recommendations already emphasize that treatment order matters, and clinical experience increasingly suggests that better sequencing may improve both efficacy and long-term disease control [77,82,101,102,108].

The timing of immunotherapy may also shift earlier in the disease course. Because immune dysregulation begins in precursor states and may worsen with repeated treatment exposure, there is increasing interest in using immune-based therapies when endogenous immune fitness is more intact. This concept raises the possibility that earlier intervention in selected patients—not only in relapsed MM, but potentially in biologically high-risk SMM—could improve long-term outcomes, especially if guided by immune biomarkers rather than conventional clinical risk models alone [91,109].

Because immune dysregulation emerges early during progression from MGUS and SMM to symptomatic MM, there is increasing interest in identifying opportunities for immune interception before the development of clinically active disease [29,56,57]. Improved understanding of precursor-stage immune remodeling may facilitate the development of biomarker-guided preventive strategies and early therapeutic interventions designed to preserve immune surveillance and delay disease progression.

A particularly promising area is the integration of serial immune profiling with measurable residual disease (MRD) assessment. In the future, combining MRD status with immune-state metrics may help distinguish patients with durable immune control from those at high risk of immunologic relapse, allowing adaptive treatment intensification, maintenance, de-escalation, or therapy switching [91,102].

An additional and increasingly relevant area of investigation is the role of host metabolic health in shaping the bone marrow immune microenvironment and influencing myeloma evolution. Emerging epidemiologic, translational, and preclinical evidence suggests that obesity-associated chronic inflammation, insulin resistance, and adipose tissue dysfunction may contribute to immune dysregulation, inflammatory cytokine production, metabolic reprogramming, and remodeling of the bone marrow niche, creating conditions that favor plasma cell survival and disease progression [30–34,110]. These observations raise the possibility that metabolic interventions—including sustained weight reduction, optimization of insulin sensitivity, lifestyle modification, and potentially the use of metabolically active agents such as metformin or GLP-1 receptor agonists—may complement existing myeloma therapies by restoring a more favorable immune and metabolic milieu [30,31,33,110,111]. Although direct clinical evidence that obesity treatment alters the natural history of multiple myeloma remains limited, this concept represents an important area for future translational and prospective clinical investigation [32–34,111]. Emerging evidence further suggests that lifestyle and metabolic interventions may influence immune and microenvironmental pathways relevant to myeloma evolution. Recent prospective studies, including dietary intervention approaches in precursor plasma-cell disorders, have demonstrated favorable immune and metabolic changes, supporting the investigation of non-pharmacologic strategies as potential complements to future immune-interception programs [112]. However, additional prospective studies are required to determine whether these interventions translate into reduced progression risk or improved clinical outcomes.

Finally, future progress will require that modern immunotherapy development be paired with improved supportive care and real-world implementation strategies. As T-cell-redirecting therapies move earlier and are used more sequentially, infection prevention, immune reconstitution monitoring, and toxicity mitigation will become increasingly im-

portant determinants of outcome. Thus, the future of MM therapy will likely be defined not only by more potent immune agents but also by more sophisticated frameworks for selecting patients, sequencing therapies, monitoring immune recovery, and preserving long-term host immunity [82,101,102].

In summary, future therapeutic development in MM is expected to move toward a model of immune-informed precision therapy, in which treatment selection, timing, and sequencing are guided by the interaction between tumor biology and immune fitness. The goal will not only be deeper remissions but also restoration of durable immune surveillance and prevention of relapses through more comprehensive targeting of both the myeloma clone and its permissive microenvironment [91,98,101,102] (Figure 4).

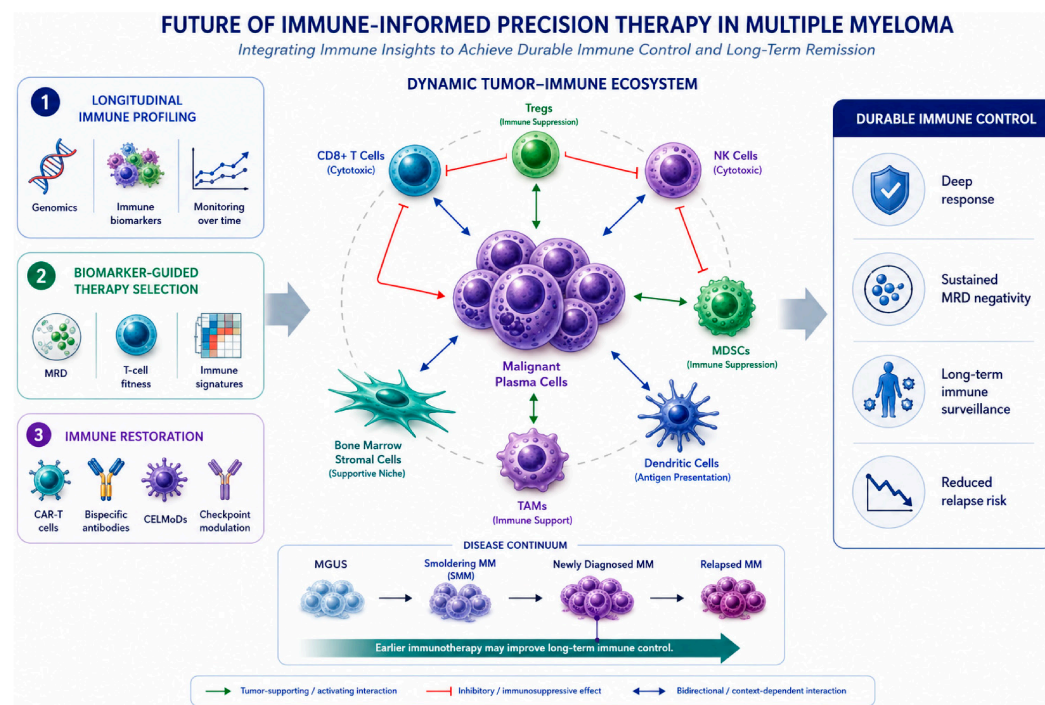


Figure 4. Future of immune-informed precision therapy in multiple myeloma. This figure illustrates a future therapeutic framework for multiple myeloma centered on dynamic integration of tumor biology, immune fitness, and the bone marrow immune microenvironment. Longitudinal immune profiling, including genomic assessment, immune biomarkers, and serial monitoring over time, may enable more precise characterization of tumor–immune interactions across the disease continuum from MGUS and smoldering multiple myeloma to newly diagnosed and relapsed disease. Biomarker-guided therapy selection, incorporating MRD status, T-cell fitness, and immune signatures, may support personalized treatment decisions and adaptive therapeutic strategies. Potential biomarker domains include immune age, T-cell fitness, interferon-associated immune states, inflammatory myeloid signatures, measurable residual disease (MRD), and genomic risk variables. The central tumor–immune ecosystem highlights the bidirectional and context-dependent crosstalk between malignant plasma cells, cytotoxic CD8⁺ T cells, NK cells, regulatory T cells, myeloid-derived suppressor cells, dendritic cells, tumor-associated macrophages, bone marrow stromal cells, and soluble mediators. Immune-restorative approaches, including CAR-T cells, bispecific antibodies, CELMoDs, and checkpoint modulation, are positioned as strategies to restore antitumor immunity and overcome immune suppression. Together, these approaches aim to achieve durable immune control, characterized by deep response, sustained MRD negativity, long-term immune surveillance, and reduced relapse risk.

6. Conclusions

Multiple myeloma is increasingly recognized as a disease shaped not only by tumor-intrinsic genetic alterations but also by dynamic interactions between malignant plasma

cells and the bone marrow immune microenvironment. Accumulating evidence demonstrates that progressive immune remodeling accompanies disease evolution from precursor conditions through active and relapsed disease and is associated with clinical outcomes, therapeutic responsiveness, and resistance to treatment.

Advances in single-cell, spatial, and multi-omic technologies have substantially improved our understanding of the cellular and molecular networks that govern immune regulation within the myeloma microenvironment. These studies have identified immune states and microenvironmental features that may complement traditional genomic risk assessment and provide new opportunities for biomarker development and therapeutic stratification. However, many current observations remain primarily derived from correlative profiling studies and require prospective validation and mechanistic confirmation.

As immunotherapies become increasingly integrated across the myeloma treatment continuum, a deeper understanding of the relationship between tumor biology, immune fitness, and the marrow microenvironment will be essential. Future progress will likely depend on integrating longitudinal immune monitoring, functional immune studies, and biomarker-driven clinical trials to develop more individualized therapeutic strategies. Ultimately, incorporation of immune-based biomarkers into clinical decision-making may improve risk stratification, optimize immunotherapy use, and support earlier intervention across the multiple myeloma disease continuum.

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