The yin–yang effects of immunity: From monoclonal gammopathy of undetermined significance to multiple myeloma

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Multiple myeloma (MM) is the third most common malignant neoplasm of the hematological system. It often develops from monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) precursor states. In this process, the immune microenvironment interacts with the MM cells to exert yin and yang effects, promoting tumor progression on the one hand and inhibiting it on the other. Despite significant therapeutic advances, MM remains incurable, and the main reason for this may be related to the complex and variable immune microenvironment. Therefore, it is crucial to investigate the dynamic relationship between the immune microenvironment and tumors, to elucidate the molecular mechanisms of different factors in the microenvironment, and to develop novel therapeutic agents targeting the immune microenvironment of MM. In this paper, we review the latest research progress and describe the dual influences of the immune microenvironment on the development and progression of MM from the perspective of immune cells and molecules.

KEYWORDS
multiple myeloma, immune microenvironment, yin–yang, immune cells, immune molecules

Introduction

Multiple myeloma (MM) is a hematological neoplasm with abnormal proliferation of clonal plasma cells (PCs), resulting in the production of large amounts of monoclonal M proteins (1). Common symptoms of MM include impairment of myeloma-related organ function manifestations such as “CRAB” symptoms (hypercalcemia, renal insufficiency,
anemia, and bone lesions) and secondary amyloidosis (2). MM accounts for approximately 1% of total malignant tumors and is the third most common hematological malignancy after lymphoma and leukemia, with an estimated 176,404 new cases and 117,077 new deaths in 2020 (3). The median age at diagnosis was approximately 66–70 years in the majority of patients, with 37% of them under 65 years of age (4). In recent years, with the widespread use of new chemotherapy drugs, immunotherapy and autologous stem cell transplantation (ASCT), median survival has significantly improved (5, 6). However, most of the patients remain largely incurable and even suffer from relapse, drug resistance, and death, which brings great burden to the patients and the society. Therefore, treatment still faces huge challenges. It is extremely urgent to study the mechanism of the occurrence and development of MM, improve the cure rate of patients, and minimize the disease recurrence and drug resistance.

As we all know, MM has two important biological characteristics. One is that genetics is highly volatile (7). There are a series of genetic events in the progression of MGUS, SMM to active MM. Initially, post-germinal center B cells are subjected to a series of primary genetic events that progressively progress to MGUS, mainly immunoglobulin heavy chain (IGH) translocations [t(11;14), t(4;14), t(6;14), t(14;16), t(14;20)] and hyperdiploidy (chromosomes 3, 5, 7, 9, 11, 21). Compared to other translocation subgroups, t(14;16) and t(14;20) had significantly higher number of mutations. Moreover, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC)-related mutations in (t14;16) and (t14;20) translocation groups were significantly higher than other translocation groups (8). APOBEC mutations cause DNA damage and promote genomic instability in MM (9). Conversely, DNA damage closely associated with inflammation may cause abnormal expression of APOBEC family enzymes and altered DNA methylation, leading to altered hematopoietic gene expression (10). As the disease progresses, MGUS clones gain a clonal advantage after being struck by secondary genetic events (such as KRAS mutations, NRAS mutations, and TP53 deletion) and stimulated by drug treatment pressure, and continue to evolve more competitive clones that further drive disease progression. The eventual transformation from inert to aggressive tumor may be an internal factor for MM recurrence, drug resistance, and refractory disease (11–14). Second, the occurrence and development of MM highly depended on the immune microenvironment; these interactions between MM cells and the immune microenvironment, including direct contact and indirect promotion through matrix molecules or various cytokines, lead to MM cell proliferation (15, 16). Thus, approximately 1% of patients with MGUS and 10% of patients with SMM will develop active MM every year (17, 18). Studies have found that abnormalities in the immune microenvironment possibly participate in or even determine the disease progression of MGUS to MM (19). In addition, this interaction forms an immunosuppressive microenvironment, leading to the body’s inability to remove minimal residual disease (MRD) after treatment, which is an external factor for MM recurrence, drug resistance, and refractory (20). However, the immune microenvironment serves different purposes, exerting a tumor cell suppressive effect on the one hand and promoting tumor progression on the other. This role is similar to the yin and yang effects in Chinese traditional medicine. In this review, we update the yin-yang effects of immunity from MGUS to MM, so as to provide a basis for more accurate targeted therapy.

The yin and yang effects of multiple myeloma progression

With the in-depth study of the tumor immune mechanisms, the theory of immunoediting was formally proposed by Schreiber (21, 22). Immunoediting is divided into three stages, immune elimination, immune equilibrium, and immune escape. During immune elimination stage, the body quickly eliminates tumor cells before the tumor appears clinically symptomatic. However, if the mutation of tumor cells is not eliminated in the eradication stage, a few malignant cells are likely to escape the eradication and enter the immune equilibrium stage, during which the malignant cells and immune systems shape each other but the body does not show clinical symptoms. Persistent immune pressure selection results in tumor cells mutating in a state of genetic instability and imbalance that is no longer recognized by adaptive immunity and insensitivity to antitumor immune effector mechanisms, inducing tumor microenvironment into an immunosuppressive state and resulting in tumor cells entering the escape stage, where tumor growth is no longer blocked by the immune system, thus presenting immune tolerance (23). Studies have found that similar to solid tumors, the MM progression also occurs throughout the immunoediting processes (Figure 1) (24, 25).

Increasing studies suggest that MGUS/SMM may be representative of immune equilibrium and subsequent disruption of equilibrium during the progression in MM (25, 26). A single-cell RNA sequencing revealed an increase in the quantity of NK cells, T cells, CD16+ cells, and non-classical monocytes, and a decreased number of plasmacytoid dendritic cells (pDCs), immature neutrophils, and CD14+ monocytes in the MGUS stage. Several of the alterations have already been observed in the early stages of MGUS. Meanwhile, the accumulation of regulatory T cells (Tregs) and ‘8T1’ cells was observed, with a subsequent loss of CD8+ memory populations and elevated IFN signaling in the SMM stage. Conversely, they found that MM cells caused a loss of antigen presentation and induced T cells’ suppressor phenotype (16). The CD8+ memory T cells play an important role in tumor immunity (27). In MM, CD8+ central memory T cells were moderately reduced, while there was a marginally higher ratio of CD8+ effector/effector memory T cells. T-cell factor 1 (TCF1) expression levels were significantly elevated in memory CD8+ T cells from MGUS.
patients, while no alterations were observed in the expression of T-bet, EOMES, and GATA-3. In addition, the percentages of TCF1hi cells were obviously elevated in MGUS patients while TCF1- cells were elevated in the MM group. In MGUS and MM, the most obvious differences in T cells are related to two different T-cell types of clusters (T2 and T3). In the T2 cluster, there was an over-representation of MGUS and an under-representation of MM, and the expression of stem-like genes (TCF1/TCF7) was notably increased. The T3 cluster enriched in MM significantly increased the expression of KL RG1 (senescence-associated gene), PRDM1 (a marker of exhaustion), and Fos, and downregulated granulysin and lysozyme (28).

Immune checkpoints are a class of immunosuppressive molecules whose high expression causes depletion of T cells, thereby reducing immune surveillance and killing of tumor cells, and eventually lead to immune evasion of tumor cells. The programmed cell death protein (PD)-1/PD-ligand (PD-L1) axis, the most representative immune checkpoint, controls the antitumor immune response to solid tumors and malignant hematologic diseases (29). Federica et al. found that in comparison to MGUS patients, PD-L1 expression was elevated in CD138+ MM cells in both MM and SMM patients. Moreover, there was an inversion of the CD4+/CD8+ ratio in patients with relapsed MM, followed by increased levels of IL-6 expression. There was a remarkable positive correlation between % CD14+PD-L1+ and %CD8+PD-1+ cells in relapsed patients compared to the patients with SMM and newly diagnosed MM (NDMM) (30). Therefore, MGUS and MM obviously exhibit the immune yin-yang effects.

Host-associated immunodeficiency contributes to the development of MM from MGUS/SMM (31). The depletion in peripheral blood (PB) B cells and the upregulation in T cells were found in MM progression. This alteration of immune status is strictly related to immune paralysis during the progression of MM. They also observed the same trends in B, T, and NK cells in SMM non-progressors versus SMM progressor patients. This variation specifically shows that SMM progressor patients reduced the proportion of CD57 lymphocyte subsets (including the CD57-CD16+ and CD57-CD56+). Moreover, the expression of PD-L1 in CD138+ MM cells was higher compared to MGUS and SMM patients. The above signs indicate a state of immune depletion and exhaustion during the progression of MM.

The tumor immune microenvironment favored angiogenesis and related to the progression of MM from asymptomatic to symptomatic, with poor prognosis and therapy resistance (32). In MM VκMYC mice, microvessel density (MVD) was almost twice that of SMM mice, and highly correlated with the level of monoclonal antibodies in the blood. Two cytokines for angiogenesis [vascular endothelial growth factor (VEGF-A) and IL-18] were significantly increased in VκMYC mice at the stage of MM (33). Meanwhile, in VκMYC mice bearing oncogene-driven PC proliferative barriers, immune microenvironment changed, including progressively decreased T helper (Th1) and continuously increased Th2 cytokine secretion, which related to the accumulation of CD206CTie2C macrophages. Therefore, angiogenesis in the tumor immune microenvironment also performs a critical role in the progression of tumor cells.
The yin and yang effects of immune cells associated with multiple myeloma progression

Innate immune cells

Dendritic cells

Dendritic cells (DCs) are extensively presented antigen-presenting cells (APCs) that efficiently uptake, process, and deliver antigens and have the ability to promote the activation and differentiation of naive T lymphocytes (34, 35). Generally, DCs are broadly divided into two major types: plasmacytoid DCs (pDCs) and myeloid DCs (mDCs). Results regarding the number, phenotypic status, and function of DCs are controversial during progression from MGUS to MM. Compared to healthy donors (HDs), pDCs were significantly reduced in MM PB and bone marrow (BM) patients. More importantly, the prominently reduced pDCs were also found in MGUS vs. MM patients. A similar study has found that the proportion of both mDCs and pDCs are decreased from MGUS/SMM to MM (36). In addition, the frequency of mDCs and pDCs is negatively associated with disease progression in MM patients (37). Another research has reported that DCs from MM patients are functionally impaired, although they are numerically normal. They cannot increase the expression of CD86 and CD83 showed an elevated trend. At same time, the ability of DCs to stimulate the proliferation of CD4+ and CD8+ T cells is impaired in MM patients. After chemotherapy and ASCT, HLA-DR and HLA-A, B, and C expression in mDCs and pDCs was higher than in patients with MM at diagnosis (41). In conclusion, the yin and yang effects of DCs in the progression of MM are obviously distinct (Figure 2, Table 1).

Tumor-associated macrophages

Tumor-associated macrophages (TAMs) are the most enriched immune cells in the tumor immune microenvironment, which are derived from circulating monocytes and tissue-resident macrophages (TRMs) (42, 43). Activated macrophages are classified into two different types: M1 and M2. M1 macrophages are activated by IFN-γ, lipopolysaccharide (LPS), and granulocyte macrophage-colony stimulating factor (GM-CSF) and then secrete IFN-γ, IL-6, IL-12, tumor necrosis factor-alpha (TNF-α), reactive oxygen species (ROS), and nitric oxide synthase (NOS), exhibiting pro-inflammatory features such as promoting the destruction of tumor cells, recruiting tumor-killing leukocytes, or directly phagocytosing tumor cells (44). On the contrary, M2 macrophages promote tumor cell proliferation, distant metastasis, drug resistance, and angiogenesis and suppress immunity, which is stimulated by IL-10, transforming growth factor beta (TGF-β), and neovascularization agents VEGF and fibroblast growth factor-2 (FGF-2) (45). M2 macrophages express high levels of CD206, CD163, and TGF-βR, while M1 macrophages express high levels of CD40, CD80, and CD86 (43). Both M1 and M2 macrophages are highly plastic and can be interconverted in response to changes in the tumor microenvironment or therapeutic intervention.

![FIGURE 2](image-url)

The yin and yang effects of immunity cells and non-cellular components. Immune cells (including CD56bright NK cells, DC cells, CD4+ T cells, CD8+ T cells, M1-like macrophages, and Th1 cells) suppress malignant PCs by secreting IFN-γ, TNF-α, and cytotoxic effects. Meanwhile, malignant PCs can form an immunosuppressive microenvironment (including M2-like macrophages, MDSC, Treg cells, Th17 cells, suppressor DC cells, CD56dim NK cells, and Bregs) by secreting IL-10, TGF-β, and IL-6. The immunosuppressive microenvironment in turn can be suppressed by VEGF, IL-17, IGF-1, IL-10, and TGF-β, which promotes multiple myeloma progression. See text for detailed explanation.
In recent years, a large amount of research evidence has demonstrated that macrophages have an essential role in the progression of MM, such as promoting BM PC homing and proliferation, angiogenesis, and angiogenic mimicry (46–49). Macrophages in the blood effectively supported the proliferation of MM cell lines through contact-mediated and non-contact-mediated mechanisms, and contributed to the in vitro growth of primary CD138+ cells in the BM of MM patients. Importantly, co-culture with macrophages protects MM from chemotherapeutic drug-induced cell death and significantly promotes IL-1β, chemokine C-C motif ligand-2 (CCL2), CCL5, and IL-8 expression in MM cells at the mRNA level. Moreover, MM cells educate macrophages and promote M2 polarization (50). In the BM of MM patients, CD163+CD206+ M2 macrophages were significantly increased compared with SMM and MGUS patients. The function, phenotype, and morphology of active MM were distinct from patients with stable disease and MGUS (50). Furthermore, the study found that overall survival (OS) was obviously shorter in patients with CD68+ macrophages (85). Wang et al. showed that patients with higher CD163+ M2 macrophage expression at MM diagnosis had worse progression-free survival (PFS) and OS, and achieved lower rates of complete remission (CR)/near-CR rate, particularly relapsed and aggressive MM patients (86).

MM is a highly vascularized tumor, with increased neovascularization leading to tumor progression. CD163+ M2 macrophages were found to be correlated with MVD. In a xenograft mouse model of MM, binding of clodronate liposomes (Clo) to VEGFA siRNA significantly suppresses tumor growth. The expression of angiogenesis and VEGFA expression were obviously higher in the control than in Clo and Clo+ si. In addition, the number of neovascularization upregulated the number of M2 macrophages. CD163+ cells were clearly more numerous in the Clo+ M2 group than in the Clo+ M1 group (87). Scavelli et al. indicated that macrophage expression with VEGF and bFGF obtained endothelial cell (EC) markers when MM is in an active state of disease. Meanwhile, macrophages adapted functionally, phenotypically similar to MM patient-derived endothelial cells (MMECs). This cannot occur in MGUS or benign anemia patients, likely minimal in nonactive MM (46). Thus, neo-angiogenesis and angiogenesis play a vital role in MM progression, supporting the idea that macrophages may promote MM growth by stimulating MM-associated neo-angiogenesis through paracrine secretion. MM-associated macrophages also

### Table 1: Yin and yang effects of immune cells associated with multiple myeloma progression.

| Immune cells | Effects in different stages of the disease | MGUS/SMM | MM |
|--------------|---------------------------------------------|----------|----|
| DCs          | Yang (Antitumor)                            |          | Yin (Pro-tumor): suppressive |
| TAMs         | Yang: M1 macrophages, promoting the destruction of tumor cells, recruiting tumor-killing leukocytes, or directly phagocytosing tumor cells | Yin: M2 macrophages, promoting tumor cell proliferation, distant metastasis, and suppressing immunity |
| NKs          | Yang (Antitumor)                            |          | Yin (Pro-tumor): |
| MDSCs        | –                                           |          | Yin (Pro-tumor): |
| CD4+/CD8+ T  | Increased: Yang (Antitumor)                |          | Yin (Pro-tumor): |
| Tregs        | –                                           |          | Yin (Pro-tumor): |
| Th17         | –                                           |          | Yin (Pro-tumor): |
| Bregs        | –                                           |          | Yin (Pro-tumor): |

DCs: dendritic cells, TAMs: tumor-associated macrophages, NKs: natural killer (NK) cells, MDSCs: myeloid-derived suppressor cells, Tregs: regulatory T cells, Th17: T helper 17 cells, Breg: regulatory B cells.
have the capacity to be directly involved in MM-associated neo-
angiogenesis. Therefore, M1-like macrophages have an immune
yang effect and M2-like macrophages have a yin effect in the
progression of MM (Figure 2, Table 1).

Natural killer cells

Natural killer (NK) cells are a vital component of the innate
immunity and have an important role in tumor immunity,
especially in hematological tumors (88–91). Unlike T cells, NK
cells can directly kill cancer or infected cells without antigenic pre-
stimulation, major histocompatibility complex (MHC) class I
molecule presentation, and antibody recognition (92). Moreover,
also produces a large number of cytokines, which regulate the
adaptive immune responses and are involved in other
related pathways (93, 94). NK cells are divided into CD56bright
and CD56dim types based on the surface density of CD56 changes,
which exhibit different phenotypic characteristics. The CD56bright
NK cells can directly produce a large amount of cytokines, while
CD56dim NK cells have a stronger cytotoxicity and express
significantly more immunoglobulin-like receptors and FCγRIII
(FCγ receptor III, also named CD16) (95). As the first line of
defense, NK cells rapidly remove pathogens and tumor cells from
the body. The triggering of NK cells depends on two modes of
“missing self” and “induced self” (51). In the event of viral
infection or cellular carcinogenesis, MHC-I molecules’
expression on the cell surface is either absent or low, resulting
in a loss of function of the NK cell surface killer activation
receptors by “missing self”. In addition to downregulating MHC
class I molecule expression, some neoplasms and virus-infected
cells may also combine and reactivate killer activation receptors
on the surface of NK cells, which is called “inducing self” (52, 53).

The correlation between NK cells and MM progression
remains controversial. Numerous studies have found NK cell
dysfunction from MGUS/SSM to MM (Figure 2, Table 1). A
recent single-cell RNA sequencing study reveals that NK cell
abundance is frequently increased in patients with MGUS,
associated with a more immature NK cell subpopulation and
subsequent phenotypic shift in MM progression, suggesting a
possible compromised immune system. Furthermore, they also
observed that the NK cells’ enrichment in MGUS patients had a
significant enrichment for the C-X-C motif chemokine receptor
(CXCR) 4 CXCR4+ subset, while lower NK cells’ frequencies
displayed the low CXCR4 and CX3CR1+ subset (16). Another
study found that the SMM and MM patients had higher
percentages of CD56dim NK cells in PB compared with HDs,
while the relapsed/refractory multiple myeloma (RRMM)
and especially post-autologous stem cell transplant (pSCT)
patients had obviously lower CD56dim NK cells. By comparison,
the CD56bright NK cells of RRMM and pSCT had higher
percentages, and this increased accumulation may be the result
of NK cell reactivation after previous treatment or chemotherapy
drugs and stem cell transplant (SCT) depletion.

In addition, the expression receptors on the surface of NK
cells such as CD57, FcγRIII, CD226, NKG2D, SLAM family
member 7 (SLAMF7), and natural cytotoxicity receptors
(NCRs) have been found to be altered (54). Bernal et al. found
that the MM PCs had the highest MHC-I molecules, followed by
MGUS PCs and the lowest expression on cells without
monoclonal gammapathy. The activated NKG2D ligand MICA
followed a reverse order (55). However, Carbone et al. had a
different conclusion that early-stage MM patients express a
lower level of MHC-I molecules and higher levels of NKG2D,
MICA, and MICB, but an opposite expression level in the late
stage (56). Decreased expression of ligands or activated NK cell
receptors led to the functional quiescence of NK cells and immune
evasion (57). Moreover, several studies revealed that the
expressions of 2B4 and DNAM-1 were decreased in MM, but
NCRs had no changes (54, 58). The NK cells’ capacity for
antibody-dependent cellular cytotoxicity (ADCC) declined,
especially in advanced disease (96). This response depended on
the expression of activation receptors and the respective ligands
on myeloma cells (97). The degranulation response of NK cells
could also assess NK cell function. Compared to HDs, MM
patients showed significantly decreased expression of the NK
cell degranulation marker CD107a. In RRMM and pSCT
patients, CD107a expression was lower under ADCC conditions
(54). Therewith, the elevated expression of the inhibitory receptor
[such as PD-1/PD-L1, T-cell immunoglobulin and ITIM domains
(TIM2/3) interacting with the ligand expressed on MM cells and
mediates NK cell depletion. Meanwhile, NK cell recovery is
achieved until 30 days after autologous hematopoietic stem cell
transplantation (auto-HSCT). Importantly, at +30 and +100 days
after auto-HSCT, MM patients with a lower frequency of mature,
well-differentiated NKG2A-CD57+ NK cell subset had a better
PFS to the next treatment than those with a higher frequency (98).
This provides new insights into the importance and degree of
differentiation in NK cell reconstitution, which may have a better
prognosis of MM patients after auto-HSCT.

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a
heterogeneous group of BM-derived cells that are precursors
to DCs, macrophages, and/or granulocytes (59). Under normal
conditions, BM hematopoietic stem cells firstly differentiate into
myeloid precursor cells (MPCs), and then rapidly into mature
granulocytes, DCs, and macrophages, which enter the
appropriate organs to perform immune functions (60).
However, in pathological conditions such as tumor infection
and inflammation, the maturation of MPCs is hindered by
inflammatory factors or tumor-derived cytokines, and they
acquire immature and dysfunctional myeloid suppressor cells
(MDSCs) (61). There are two major subsets of MDSCs,
monocyte-like MDSCs (Mo-MDSCs) and granulocyte-like
MDSCs (G-MDSCs) (62). In mice, Mo-MDSCs present a
CD11b+ Ly6G<sup>high</sup> Ly6C<sup>high</sup> phenotype and G-MDSCs present a CD11b+ Ly6G<sup>high</sup> Ly6C<sup>low</sup> phenotype, while in humans, Mo-MDSCs exhibit CD11b+ CD33+ HLA-DR<sup>low</sup> CD14+ and G-MDSCs exhibit CD11b+ CD33+ HLA-DR<sup>low</sup> CD14+ (63).

Recently, the roles of MDSCs have been reported in different cancer types, especially MM (64, 65). Several studies have found that MDSCs differ in number function and phenotype in MM patients compared with MGUS patients and HDs. Favaloro et al. discovered an absolute and relative increase in the number of G-MDSCs in both PB and BM in MM patients. Meanwhile, both patients with progressive disease and stable disease had significantly higher proportions of G-MDSCs compared to age-matched controls. Similar to the G-MDSC, patients with progressive disease also had higher BM Mo-MDSC levels than those with NDMM. High Mo-MDSC levels had significantly poorer prognosis than patients with lower Mo-MDSCs. High Mo-MDSC can be used as an important poor prognostic indicator (66). In addition, the MDSC burden is closely related to MM stages, therapeutic response to bortezomib-based treatment, and pool clinical outcome (67). Similar to other solid tumors, MM cells have a bidirectional interaction with other cells of the immune microenvironment: regulating tumor development on the one hand, and transforming the BM microenvironment into an immunosuppressive environment on the other. The phenotype and frequency of MDSCs in BM and PB of patients with NDMM or RRMM were analyzed such that the frequency of MDSCs in RRMM increased with disease progression compared to HDs. The inhibitory molecules reactive species of oxygen (ROS) and arginase-1 (ARG1) significantly increased. More importantly, MM-MDSCs can directly induce MM cell proliferation, and conversely, MM cells can also trigger the development of MDSCs by inhibited activity against autologous T cells. This immunosuppression is manifested by downregulation targeting CD4<sup>+</sup> T, CD8<sup>+</sup> T, and NKT cell-mediated antitumor immune responses. In addition, neither lenalidomide nor bortezomib changed this effect. Meanwhile, Tregs can also be inhibited (62, 66). Mesenchymal stromal cells (MSCs) have strong immunosuppressive effects. MSCs stimulate the proliferation of MDSCs and suppress their apoptosis. Additionally, MSCs enhanced MDSCs by suppressing T-cell proliferation and IFN-γ production. Furthermore, both the Arg1 and NOS2 mRNA and protein levels were upregulated in MDSCs. These findings demonstrate that MSCs may perform immunomodulatory effects on MDSCs through the upregulation of Arg1 and NOS2 (99).

In MM-bearing mice models, MDSCs accumulate mainly in the spleen and lymph nodes, which promote MM growth. During the progression of MM in the 5TMM mouse model, the accumulation of MDSCs in the BM was observed in the early stages of disease progression, while an increase in circulating myeloid cells was observed in the later stages (100). Another research showed that polymorphonuclear/granulocytic (PMN)-MDSCs displayed a higher suppressive potential and a pro-angiogenic role by the expression and upregulation of vasculegenic-related factors. Interestingly, they observed Mo-MDSCs as osteoclast precursors (68). In summary, MDSCs play a yin immunological role in the progression of MM.

Other myeloid cell lineages also participated in the development of MM, for example, neutrophils in the absolute number between MM, MGUS, and HDs, but they found that neutrophils isolated from MM had a reduced phagocytic activity and an immunosuppressive function of T cells, indicating that neutrophils may contribute to the impairment of MM immune function. Petersson et al. found that BM neutrophils of MM patients exhibited MDSC function (69). However, high-density neutrophils (HDNs) have been found in MM and, to a lesser extent, in MGUS. HDNs from MM have induced the upregulation of FcγRI (also known as CD64) and the downregulation of structural FcγRIa, as well as decreased phagocytic activity and oxidative burst (70). HDNs may promote MM progression through increased susceptibility to infection and immune dysfunction. Human PB monocytes are a population of heterogeneous cells. They are generally divided into three categories, classical (CD16<sup>+</sup>CD14<sup>+</sup>), non-classical (CD16<sup>+</sup>CD14<sup>dim</sup>), and intermediate (CD16<sup>+</sup>CD14<sup>+</sup>+) (71). Compared with HDs, the proportion of CD16<sup>+</sup>CD14<sup>+</sup> monocytes was remarkably lower in MM patients, while the proportion of CD16<sup>+</sup>CD14<sup>dim</sup> and CD16<sup>+</sup>CD14<sup>+</sup> monocytes was significantly higher. CD16<sup>+</sup>CD14<sup>dim</sup> and CD16<sup>+</sup>CD14<sup>+</sup> monocyte ratios were positively correlated with serum PCa, M-protein, calcium, creatinine, and lactate dehydrogenase (LDH) levels and negatively correlated with serum albumin levels. The proportion of CD16<sup>+</sup>CD14<sup>+</sup> monocytes was positively correlated with albumin levels and negatively correlated with serum M-protein, PCa, calcium, creatinine, and LDH levels (72). Sponaas et al. found that as tumor load increases, the quantity of CD16<sup>+</sup>CD14<sup>dim</sup> monocytes has been shown to increase (73). Meanwhile, another study found that in MM and SMM patients, PD-L1 was expressed at higher levels in CD14<sup>+</sup>CD16<sup>+</sup> monocytes than CD14<sup>+</sup>CD16<sup>+</sup> cells, independent of disease stage (30). Therefore, other types of cells also play an important role in MM progression (Figure 2, Table 1).

Adaptive immune cells T cells

The aberrant function and number of T cells present in the progression of MM. The normal CD4/CD8 T-cell ratio in BM was as follows: age ≤ 1 year [0.9 (0.5–1.2)]; 1 year < age ≤ 4 years [0.5 (0.4–0.6)]; 4 years < age ≤ 15 years [0.4 (0.3–0.6)]; age > 15 years [0.4 (0.3–0.5)] (74). The CD4<sup>+</sup>/CD8<sup>+</sup> T-cell ratio was abnormal in MGUS or MM patients. In untreated myeloma patients, the CD4<sup>+</sup> cells were downregulated in both percentage and absolute numbers, while the CD8<sup>+</sup> T cells were slightly upregulated (75). Additionally, the CD28, CD152, ZAP-70, and PI3K involved in T-cell signaling and the signal transduction
molecules are significantly reduced in CD4+ and CD8+ T cells, especially in the advanced MM stage (101). The decrease in the number of CD4+ cells was associated with the clinical stage, a shorter survival, high β2-microglobulin (B2M), and anemia. Another study found a strong T-cell response to autologous precancerous cells in MGUS patients. This pre-tumor-specific CD4+ and CD8+ T-cell response was detected in T cells freshly isolated from BM. MM-BM-derived T cells are deficient in this tumor-specific fast effector function. This phenomenon could be explained by the fact that the increased tumor burden from MGUS to MM leads to T-cell exhaustion.

Inflammation is one of the characteristics of MM, as it is highly dependent on inflammation during disease progression. A variety of inflammatory molecules are involved in this process, such as IL-6, IL-10, and TGF-β. Meanwhile, MM being an age-related disease, the senescent body has decreased immune cell function and is unable to perform biological functions, leading to a gradual accumulation of senescent cells in the body, causing the body to enter a specific chronic inflammatory state. Not only is inflammation a symptom of senescence, it may also drive the key factors of diseases associated with the aging process (76). During the process of senescence, the expression of pro-inflammatory factors is caused by an imbalance between the innate and acquired immune systems of the body. Their long-term stimulation leads to chronic, low-grade, inflammatory senescence and increases the development of age-related diseases. Multiple signaling pathways are involved in the above processes, such as NF-κB, JNK, and RIG-1 pathways (77). Thus, inflammation and senescence interact in the development of MM and together contribute to the progression of the disease. Zelle-Rieser et al. found that T cells from MM displayed the characteristics of exhaustion and senescence in the tumor area. There was an increased expression of PD1, cytotoxic-T-lymphocyte-antigen-4 (CTLA-4), CD160, and 2B4 on CD8+ T cell from BM of MM patients (78). Importantly, CTLA4 is expressed not only on the surface of T cells, but also on CD4+ and CD8+ T cells (79). Thus, inflammation and senescence interact in the development of MM and together contribute to the progression of the disease. Zelle-Rieser et al. found that T cells from MM displayed the characteristics of exhaustion and senescence in the tumor area. There was an increased expression of PD1, cytotoxic-T-lymphocyte-antigen-4 (CTLA-4), CD160, and 2B4 on CD8+ T cell from BM of MM patients (78). Importantly, CTLA4 is expressed not only on the surface of T cells, but also on CD4+ and CD8+ T cells, but its expression in the immune microenvironment of MM has not been reported in relevant studies (79). Under continuous antigenic stimulation, the expression of CD28 gradually and irreversibly decreases, while CD57 expression increases, manifesting a state of replicative senescence. In both HDs and MM patients, most of the T cells deleted CD28 expression while CD57 expression was notably upregulated in MM-BM T cells. Thus, compared to HDs’ BM, the total amount of CD57+ CD28- CD8+ T cells was obviously increased. Furthermore, after therapy with immunomodulatory drugs and dexamethasone, the proportion of senescent CD57+CD28−CD8+ T cells was reduced (78).

Regulatory T cells (Tregs), which are generated by the thymus and exported to the periphery, inhibit in a positive regulatory manner the activation and proliferation of potentially self-reactive T cells present in the normal body, thereby significantly suppressing immune action. Tregs are clearly classified into thymus-derived tTregs, peripherally induced pTregs in vivo, and in vitro induced iTregs. CD4+CD25+Foxp3+ is considered to be the classical combination marker for Tregs (80). The proportions of CD4+CD25+ cells were significantly elevated in MGUS and MM patients compared with HDs. The Foxp3 and CTLA4 expression also decreased in MGUS and MM patients. Moreover, Tregs did not inhibit anti-CD3-mediated T-cell proliferation in MGUS or MM patients (102). The local changes are manifested such that the proportion of Tregs is higher in MRD-positive patients than in MRD-negative patients. In a mouse model of MM based on MOPC cells, the BM section showed that Tregs highly accumulated at the site of tumor growth. Tregs from BM MOPC-MM mice expressed higher levels of activation markers of CD25, CD69, and CD44 and inhibitory receptors T-cell immunoglobulin mucin-3 (Tim-3), lymphocyte-activation gene 3 (Lag3), and TIGIT compared with healthy mice. In mice, Treg depletion rapidly leads to the activation of CD8+ T cells and NK cells as major effector cells against MM (103). The evolution from MGUS to MM is related to alterations in Tregs and terminal effector CD8+ T cells (TTE). This may be associated with the expression of CD39 and CD69, influencing the adenosine metabolic pathway and its residence in the BM microenvironment, as well as the oligochonal expansion of CD8+ TTE cells (104). Conversely, studies also reported an association between the presence of BM-infiltrating regulatory T cells and dysfunctional CD4+PD-1+ cells and inferior survival in NDMM patients (81).

T helper 17 (Th 17) cells are a group of IL-17-secreting T cells that require co-induced differentiation by IL-6 and TGF-β. They play a very important role in host defense, inflammation, and autoimmunity (82). Th17 cells were altered with different therapy stages of MM. The percentage of Th17 cells in peripheral blood mononuclear cells (PBMCs) was significantly increased in NDMM, partial remission (PR), and disease relapse multiple myeloma patients, but significantly decreased in CR (83). Prabhala et al. found that Th17-associated cytokines (such as IL-17, IL-23, and IL-13) were significantly elevated in MM patients compared with HDs. Moreover, IL-17 promotes MM cell growth and suppresses immune function. Downregulation of Th1 cell responses by Th17-secreted cytokines in myeloma. Several studies have identified an abnormal ratio of Th17 and Tregs cells in the progression of MM (84). Remarkable differentiation of Treg/Th17 ratio was observed between normal and MM patients. The absolute number of Th17 cells is elevated and Treg cells are reduced in MM patients, which results in a significant imbalance in the Th17/Treg cell ratio. This change normalizes with disease stabilization (105, 106). In addition to the abnormal Th17/Treg ratio, there were also aberrant Th1 and Th2 ratios. Thus, the yin and yang effects of T cells appear to be particularly pronounced in the pathogenesis of MM (Figure 2, Table 1) (107).
Regulatory B cells

Regulatory B cells (Bregs) are a subset of B lymphocytes that have immunomodulatory functions and maintain immune tolerance. Through secretion of IL-10, IL-35, and TGF-β, Bregs inhibit immunopathology (108). Recent studies have demonstrated that the inflammatory environment of different diseases induces different Breg populations (109, 110). In MM, Bregs–myeloma cell interactions enable immunosuppression and promote their survival in the BM environment. In MM, regulatory CD19+CD24highCD38high B cells, which have immunosuppressive properties, are more clearly defined in BM than in PB. The proportions of BM-Bregs within CD19+ cells are remarkably increased in NDMM patients compared to patients who responded to treatment (maintenance). However, BM-Bregs from NDMM patients are dramatically reduced 1 day after CD138+ myeloma cell deletion. In CD138-depletion of BM mononuclear cells (BMMCs) (CD138-BM), the frequency of apoptosis BM-Bregs was notably increased as compared to freshly harvested BMMC (BM) and with the addition of CD138+ myeloma cells (111). Zhou et al. found that the proportion of CD19+CD24highCD38high Bregs within CD19+ B cells significantly differed at different stages of MM. Namely, in MGUS patients, the percentage of CD19+CD24highCD38high Bregs was markedly higher compared to MM. In addition, the B-cell percentage in NDMM was positively correlated with Breg percentage. Patients with Bregs < 10% had significantly shorter OS and PFS (112). Another study showed that the proportion of Bregs with CD19+CD24highCD38high was higher than in HDs. While the percentage of CD19+CD24highCD38high Bregs in MM patients decreased after treatment with daratumumab (113). Furthermore, the Breg combination with PET/CT can predict the therapeutic response and survival in contemporary patients with NDMM (114). Thus, Bregs also display the yin and yang effect in MM (Figure 2, Table 1).

The yin and yang effects of noncellular components associated with multiple myeloma progression

Non-cellular components mainly include cytokines, growth factors, pro-angiogenesis factors, and chemokines. Cytokines, growth factors, pro-angiogenesis factors, and chemokines are secreted into the fluid environment of the BM, and the interaction of MM cells with the BM microenvironment is of paramount importance in the progression of MM (115–117).

IL-6 plays a pathogenic role in MM and promotes the growth of MM cells (118). The levels of IL-6 in the MM group were higher than those in HDs and associated with Durie-salmon (DS) stages and treatment cycle. Elevated serum IL-6 levels are factors in the poor prognosis of MM patients (119). However, another research revealed that the high expression level of IL-6 is linked to low tumor burden and low proliferation scores in MM (120). Frassanito et al. found that the production of autocrine IL-6 in MM patients paralleled the clinical stage of disease. The highest percentage of IL-6+ cells was detected in resistant relapse or primary refractory patients. Then, in the absence of exogenous IL-6, the MM cells were characterized by a high susceptibility to spontaneous apoptosis (121). Systemic levels of IL-6 may be useful as prognostic factors of MM bone disease (122). BM IL-6 levels in MM patients are highly correlated with bone resorption rates and serum C-terminal telopeptide of collagen I (ICTP) and urinary N-telopeptide (uNTx) (122, 123).

IL-10 is a key anti-inflammatory mediator that protects the host from pathogen and microbiota overreaction, while playing an active role in other environments such as sterile wound healing, autoimmunity, and cancer (124). Serum IL-10 levels were obviously increased in MGUS patients compared to HDs and lower than those observed in MM patients (125). Wang et al. found that high IL-10 levels lead to significantly worse PFS and OS in patients, suggesting that the serum IL-10 levels are a novel predictor of prognosis in MM (126). IL-10 can also induce PC proliferation and angiogenesis in MM. Serum levels of IL-10 correlated positively with VEGF, angiopoietin-2 (Ang-2), B cell-activating factor (BAFF), and infiltration. Furthermore, increased IL-10 expression parallels disease progression and advanced international staging system (ISS) stage (127). Minnie et al. found that CD8+ T cells derived from MM relapsed mice showed high IL-10 secretion, which was related to the increase in the expression of TIGIT and PD-1 (128).

TGF-β is an important modulator of cell growth and differentiation, which has been demonstrated to suppress the proliferation of dormant hematopoietic stem cells and induce the differentiation of late progenitor cells into red blood cells and BM cells (129). TGF-β plays a vital role in hematological malignancies, including leukemia, lymphoma, and MM (130). TGF-β1 is produced in MM by tumor cells and bone marrow mesenchymal stem cells (BMSCs), and associated with tumor cell growth. In addition, the inhibitory effect of tumor cell resistance to TGF-β1 on normal B-cell proliferation and immunoglobulin secretion may have promoted MM cell growth (131). Serum TGF-β1 levels were in the normal range in patients without immunoparesis, whereas they were increased in patients with immunoparesis (132). Thus, patients with higher TGF-β1 levels appeared to have functional immune impairment in MM. TGF-β receptor (TβRII) expression is reduced or absent in most MM specimens. Functionally, restoration of TβRII expression in MM cells significantly suppressed cell proliferation and motility, mainly independent of its ligand-presenting action (133). TGF-β also promotes osteolytic bone disease associated with MM. Inhibition of TGF-β activation delays tumor progression and bone
Angiogenesis plays an essential role in the development of MM. VEGF is a key molecule involved in the angiogenic process of MM. Alexandrakis showed that VEGF was increased in MM patients and was distinctively higher in stage III disease compared to stage I and stage II. In addition, there were positive correlations of VEGF and IL-6, TNF-α, β2M, C-reactive protein (CRP), and LDH (137). Another research found that most of the MM cases exhibited strong VEGF expression. Also, VEGF expression is positively correlated to MVD (138). VEGF and its type 2 receptor (VEGFR2) polymorphisms are related to the increased risk and aggressiveness in MM (139).

Insulin-like growth factor-1 (IGF-1) is a group of factors that promote cell growth and have insulin-like metabolic effects. In recent years, its role in the regulation of normal and malignant hematopoietic growth has received increasing attention (140, 141). IGF-1 promotes vascular endothelial cell and BM stromal cell lineage trafficking. The mechanism is through activation of PI3K/PKC and PI3K/RhoA pathways independent of Akt to promote myeloma cell migration (142). Peng et al. demonstrated that the acquisition of mesenchymal characteristics is enhanced by IGF-1 in a time-dependent manner. In vitro studies showed that the IGF-1-mediated mesenchymal phenotype contributes to the migration, invasion, and colony formation of MM. Mechanistic studies suggested that IGF-1 induces epithelial–mesenchymal transition (EMT) in MM cells by the PI3K/Akt signaling pathway (143). IGF-1 is also a growth and survival factor in MM cell lines (144). In clinical trials, Standal et al. found that serum IGF-1 levels were not different between MM and healthy age- and sex-matched controls. Nevertheless, MM patients with low IGF-1 level had not reached median survival (145). This suggests that IGF-1 is a prognostic factor.

The C-X-C motif chemokine ligand 12 (CXCL12) is also called stromal cell-derived factor-1 (SDF-1), which is selectively overexpressed in several tissues and organs, and functions as the ligand for C-X-C motif chemokine receptor 4 (CXCR4). The CXCR12/CXCR4 axis has emerged as a potential therapeutic target through the activation of multiple signaling pathways, such as ERK1/2, Ras, p38 MAPK, PLC/MAPK, SAPK/JNK, and regulation tumor stem cells, which play a vital role in tumor initiation and progression (146, 147). Their antagonists have been generated and show encouraging results in terms of anti-cancer activity. The level of CXCR4 expression was increased in BM of MM patients compared to HDs (148). On the contrary, several studies found that CXCR4 expression was inversely correlated with disease status and survival of MM patients. Patients with active MM exhibited a significantly lower expression of CXCR4 compared to those with inactive disease (149). CXCR4 is a good prognostic indicator of survival for MM patients (150). PM PCs produce significant levels of SDF-1 protein and shows higher level of expression compared with normal subjects, and elevated serum SDF-1 levels are associated with an increased osteoclast activity, bone destruction, and tumor angiogenesis in MM patients (151, 152). Tumor PCs also increased CX43 expression in MSCs, and led to an elevated CXCL12 expression and stimulated CXCR4 expressed on MM cells. The resulting CX43/CXCL12/CXCR4 interaction boosted mitochondrial trafficking in MSCs and protected tumor cells from the effects of anti-myeloma drugs (153). Furthermore, blockade of the SDF-1/CXCR4 axis reduces adhesion-mediated resistance to chemotherapy in MM cells through interaction with IL-6 (154). The CXCR4-specific inhibitor AMD3100 and the antibody against CXCR4 MAB171 inhibit MM cell migration in vitro. The CXCR4 knockout assay showed that SDF-1-dependent migration was mediated through PI3K and ERK/ MAPK pathways, but not p38 MAPK (155). Moreover, MM cells recruit tumor-supporting macrophages by the CXCR4/CXCL12 axis and drive their polarization towards the M2 phenotype (50). In a murine model, injection of RPMI-8226 caused an osteolytic lesion proximal to the tumor, leading to a 5% reduction in bone volume (BV) compared with control. Importantly, systemic application of the CXCL12/CXCR4 antagonist T140 significantly inhibited bone loss (156). Thus, different immune molecules play different yin and yang roles in the development of MM (Figure 2).

Conclusion

The immune microenvironment is critical to the development and progression of MM. In recent years, with the rapid development of immunotherapy, researchers have begun to focus on the role of the immune microenvironment in the pathogenesis and treatment of MM, with the expectation that new therapeutic targets will be identified. In this article, we provide a comprehensive overview on how the immune microenvironment regulates the development of MM, both in its negative role of promoting the immune escape of tumor cells and in its positive role of limiting tumor growth through the activation of antitumor immunity. However, the immune microenvironment is a dynamic and complex process, which is one of the root causes of MM recurrence and refractory to treatment. At the same time, we are faced with the question of when to use immunotherapy, for which patients, and how to use more efficacious immune-targeted therapies. Therefore, a more precise understanding of the interactions between MM and the immune microenvironment will help provide a scientific basis for
better immunotherapy. In the future, as research continues to progress, we believe that increasingly precise immunotherapy approaches will emerge to achieve maximum survival time for MM patients.

**Author contributions**

All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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