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REVIEW

T Cells Dysfunction in Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a kind of plasma cell hematologic malignancy. Notable advancements in patient survival have been achieved due to the clinical application of anti-CD38 monoclonal antibody, chimeric antigen receptor T cells (CAR-T) and bispecific T cell engagers (TCEs). However, the immunosuppressive microenvironment of the bone marrow hinders the effectiveness of these novel immunotherapies, consequently restricting their efficacy. Hence, it is imperative to clarify the exact mechanisms to devise strategies aimed at improving the efficacy of immunotherapy. In this review, we provide a systematic overview of recent research concerning the different T cell subtypes in the immune evasion mechanisms of MM. The review emphasizes the imbalance between the immune surveillance and the immune suppression, and highlight recent studies about unconventional T cells, the metabolic control of immune reactions, and novel therapeutic strategies aimed at addressing immune evasion mechanisms that promote the progression of MM.

Keywords: multiple myeloma, immune escape, immunosuppressive cells, Th17, CTL, Treg

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Introduction

Multiple myeloma (MM)—the second most prevalent hematologic malignancy—is characterized by clonal expansion of antibody-secreting plasma cells within the bone marrow microenvironment. Global epidemiological data from GLOBOCAN 2020 reveal an annual incidence of 176404 cases (0.9 per 100 000), with rising trends strongly correlated with population aging.[1,2] The inevitable development of drug resistance and disease recurrence, coupled with enhanced tumor invasiveness, continue to unfavorable outcomes, underscoring the incurable nature of MM.

Existing studies have demonstrated the integral role of the immune system in cancer biology. In MM, immune dysregulation has been associated with disease development, recurrence, and resistance to medication. The bone marrow niche promotes myeloma cell survival and fosters an immunosuppressive microenvironment. This is partly facilitated by suppressive hematopoietic cells, such as regulatory T cells and myeloid-derived suppressor cells. These immunosuppressive mechanisms contribute to flaws in T cell distribution and function in MM, including altered frequency of CD8+ and CD4+ T cell, an imbalanced Th1/Th2 ratio, and impaired T cell response.[3] It is crucial to thoroughly elucidate the mechanisms underlying the immunosuppressive microenvironment in MM. By doing so, it is possible to discern strategies to reverse this immunosuppression, overcome therapeutic resistance, and reduce recurrence. This review aims to delineate the different subtypes of T cells involved in the immune evasion mechanism of MM, emphasize the potential role of metabolism, and accentuate the areas requiring clarification and prospective resolutions.

Cytotoxic T Lymphocytes

The predominant adaptive immune cells accountable for immune surveillance are cytotoxic T lymphocytes(CTLs). During the initial stages of MM infiltration into the bone marrow, there is an elevation in the proportion of CTLs within the bone marrow microenvironment, resulting in a heightened anti-tumor immune reaction. As the tumor burden expands, the effector functions of CTLs become profoundly suppressed.[4] Several factors contribute to the impaired

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function of CTLs. Based on distinct T cell phenotypic states, these deficiencies can be broadly categorized as anergy, senescence, or exhaustion (Figure 1).

T Cell Anergy

T cell anergy is a state characterized by diminished responsiveness of T cells and their inability to generate IL-2. Anergy arises when T cells receive inadequate co-stimulation and/or excessive co-inhibitory signals, leading to their functional impairment.[5] This secondary signaling is mediated by the binding of co-stimulatory receptors, such as CD28, or co-inhibitory receptors with B7 family ligands. Prior studies have shown that a majority of T cells lack CD28 expression in the bone marrow of both healthy and diseased patients.[6] The absence of co-stimulatory signaling molecules in the bone marrow of MM patients, which are necessary for immune surveillance, may indicate that T cells in these patients are in a state of anergy. Additionally, divergent results have been obtained regarding the expression of CTLA-4 on T cells within the bone marrow of MM patients.[5,6] B7 family molecules are ubiquitously expressed by tumor cells in MM.[7,8] In the context of receptor and ligand expression, the second signaling pathway crucial for activating T cells seems to be impaired in the onset and progression of MM. Despite this, the absence of distinct surface markers for T cell anergy makes studying T cell anergy a challenge for immunologists. Currently, there are no explicit reports on how T cell anergy mediates immune evasion by tumor cells in MM. In summary, further exploration is warranted to ascertain the contribution of T cell anergy to the immunosuppressive tumor microenvironment (TME).

T Cell Senescence

Senescence is a potential cause of CTL dysfunction in MM. Previously, it was believed that senescence involved telomere shortening, cell cycle arrest, and phenotypic alterations. Nevertheless, senescent T cells within the immune microenvironment of MM seem to exhibit unique characteristics. On one hand, a recent study found a subset of senescent T cells in MM that do not depend on telomere shortening, which challenges the previous understanding of telomere length in senescent T cells, emphasizing the necessity for additional exploration. On the other hand, in cell cycle arrest, the typical signaling pathways that induce senescence, such as p38 MAPK, p16, and p21, do not increase in MM. In contrast, the level of SMAD related to T cell inactivation increases, which could be an important process leading to senescent T cell cycle arrest.[5] These distinct characteristics, differing from those typically seen in conventional senescence, imply that the senescence process in the MM microenvironment is not age-related. This phenomenon is more likely attributed to the pathological changes initiated by tumor cells.

In recent years, research on the phenotypic changes of senescent T cells has advanced significantly. Initially, it was believed that the phenotypic feature of senescent T cells was the expression of CD57+CD28-. Subsequently, as research progressed, the involvement of molecules such as CD160, KLRG1, Tim-3, and others in the senescent phenotype of T cells was elucidated.[5,6] Several additional molecules, including TIGIT and Helios, were identified as signature markers of senescent T cells. Of significance, these two molecules also seem to correlate with T cell exhaustion,[9] with TIGIT specifically acknowledged as an immune checkpoint.[10,11] Guillerey et al discovered that TIGIT+CD8+ T cells in patients with MM exhibited reduced abilities for TNF-α and IFN-γ secretion, as well as impaired cytotoxicity and proliferation. They further demonstrated that blocking TIGIT with monoclonal antibodies enhances the effector function of CD8+ T cells and inhibits the progression of MM. However, further research is needed to determine whether TIGIT+CD8+ T cells are indicative of senescent T cells and to elucidate whether these effects occur by reversing exhaustion or senescence pathways.[12] A recent omics study also observed increased expression of TIM3 and TIGIT in CD8+ T cells in the TME of MM patients, which added confidence to the research on developing corresponding target inhibitors.[13]

T Cell Exhaustion

T cell exhaustion represents a dysfunctional state commonly observed in various cancer processes. It is characterized by impaired function of effector cells, sustained expression of inhibitory receptors, and alterations in transcriptional regulation. The state of exhaustion impedes the effective control of tumors by effector T cells. Beltra et al proposed a four-stage model outlining the developmental trajectory of exhausted T cells based on the expression of Ly108 (a surrogate marker for TCF1) and CD69 (Ly108+CD69+, Ly108+CD69-, Ly108-CD69-, Ly108-CD69+). This model

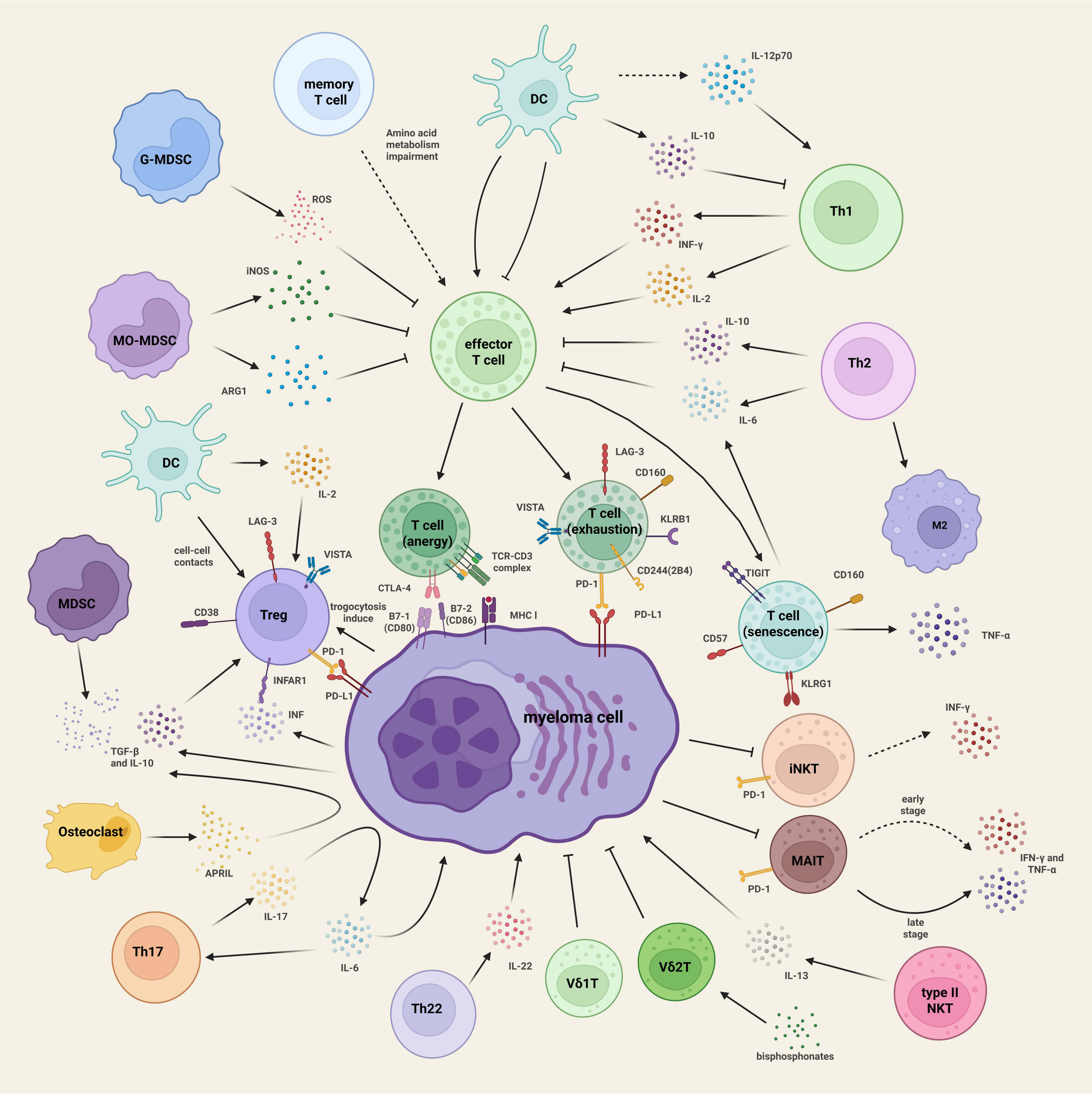

Figure 1 T cells in immunosuppressive microenvironment in MM. Various dysfunctions of T cells exist in the immunosuppressive tumor microenvironment of MM. Impaired amino acid metabolism in the late stages of the disease leads to deficient differentiation of memory T cells into effector T cells. Myeloid-derived suppressor cells (MDSCs) inhibit the function of effector T cells through the actions of ROS, iNOS, and Arg1. DCs play a dual role in CTL activation: they activate CTLs by presenting antigens, while also inhibiting their activation through the CD28-CD80/86 axis. The tumor microenvironment in MM is characterized by an imbalanced Th1/Th2 ratio, with reduced secretion of INF-γ and IL-2 (which activate CTLs) and increased secretion of IL-6 and IL-10 (which inhibit CTLs), influenced by DCs. These intricate factors interact synergistically to induce dysfunction in CTLs. T cells exhibit various dysfunctions: anergic T cells have low CD28 expression and high CTLA-4 expression; senescent T cells express senescence surface markers (CD28-CD57+, CD160+, KLRG1+, and TIGIT+) and secrete inhibitory cytokines (IL-6 and TGF-β); exhausted T cells express immune checkpoints (PD-1, CTLA-4, and LAG-3) and exhaustion surface markers (Vista, CD160, CD244(2B4), and KLRB1). Cytokines including IL-2, IL-10, TGF-β, and type I INF, secreted by DCs, MDSCs, and MM cells, can enhance the function of Tregs MM cells can also induce the production of Treg through trogocytosis. Osteoclasts can further enhance Treg activity by stimulating MM cells to secrete inhibitory cytokines. Secretion of IL-17 and IL-22 by Th17 and Th22 cells contributes to the formation of an immunosuppressive tumor microenvironment and facilitates the growth of MM cells. Among unconventional T cells, γδ T cells can suppress MM cells through diverse mechanisms, but their quantity and function are altered within the tumor microenvironment. Both iNKT and MAIT cells exhibit high expression of PD-1 and are inhibited by MM cells, leading to decreased secretion of INF-γ and TNF-α. Conversely, type II NKT cells may promote MM progression via the IL-13 pathway. Created in BioRender. f_, f_. (2025)https://BioRender.com/c5se8y7.

offers a more comprehensive insight into the transition of T cells from tissue-resident to peripheral blood circulation, encompassing their activation to gradual loss of biological effects. Although the precise mechanisms involving critical steps, transcription factors, and epigenetic modifications underlying exhaustion necessitate further investigation, this model provides valuable insights into the processes driving T cell exhaustion.[14]

The abnormal expression of immune checkpoints characterizes T cell exhaustion. Among the numerous immune checkpoint studies, research on PD-1 (programmed cell death protein 1) has been conducted most extensively. It was initially considered to be highly expressed on exhausted T cells in MM.[6] Several substances have been identified as inducers of T cell exhaustion, resulting in increased expression of PD-1.[15] For instance, elevated levels of cytokines and metabolites such as IFN-γ, and kynurenine have been shown to upregulate PD-1 expression.[16,17] Conversely, elevated levels of lactic acid in the TME suppresses PD-1 expression in CD8+ T cells, potentially conferring resistance against PD-1 blockade.[18] In stark contrast to the advancing mechanistic studies, early clinical trials found little single-agent efficacy for immune checkpoint inhibitors in MM.[19] Furthermore, the coadministration of PD-1 blockade with immunomodulatory drugs have yielded unsuccessful outcomes.[20,21] These disappointing results prompted a re-examination of PD-1 expression. In a subsequent study, it was revealed that PD-1+ CD8+ T cells in MM bone marrow are predominantly effector or memory T cells. However, although exhibiting PD-1 positivity, these cells showed an inability to degranulate against autologous myeloma targets. This observation implies a deficiency in tumor specificity, which may elucidate the limited clinical effectiveness.[22] The disappointing outcomes of clinical trials also suggest that our comprehension of the role of immune checkpoints in the development of T cell exhaustion in MM remains insufficient.

Numerous novel immunosuppressive targets have also shown potential in MM. Molecules like KLRB1, VISTA, and LAG-3 have been found to be overexpressed on exhausted CD8+ T cells within the bone marrow microenvironment of MM, potentially correlates with disease relapse and adverse post-transplant prognosis.[4,6,23] However, this study solely performed a correlation analysis, indicating the necessity for additional research to explore the underlying mechanisms.[24]

Given the phenotypic overlap between senescence and exhaustion, it is a pertinent inquiry to ascertain which of the two factors plays a more significant role in immune evasion in MM. With the failure of several clinical trials of PD-1 inhibitors, the current balance of knowledge on this issue seems to be shifting towards immune senescence. An early study considered that T cells in the bone marrow of MM patients exhibit elevated PD-1 expression.[25] However, Suen et al compellingly challenged this paradigm by demonstrating that dysfunctional clonal T cells in the MM bone marrow microenvironment show minimal or nonsignificant alterations in PD-1 and CTLA-4 expression levels. Previous study has concluded that elevated PD-1 expression in T cells is often associated with overall T cells or CD8+ T cells, rather than cloned T cells that are more likely to respond to tumors, in the patient's bone marrow. This distinction could potentially account for the divergent findings observed.[5] A recent study also did not find a statistically significant difference in the proportion of CD8+COTL1-exhausted T cells between the MM group and the healthy donors (HDs) group, aligning with prior research findings.[4,25,26] These findings suggest that immune senescence and immune exhaustion coexist in T cell dysfunction in MM, with immunosenescence likely playing a dominant role, based on cellular phenotypic changes.

T Helper and Treg Cell

Th1 & Th2

Helper T cell 1 (Th1) and helper T cell 2 (Th2) are the originally discovered helper T cell subsets, and they promote the progression of adaptive immunity by secreting different cytokines. In MM, there is an alteration in the equilibrium of Th1/Th2. At the level of cell quantity, previous reports have shown an increased ratio in the disease, closely associated with the disease state.[27,28] However, at the functional level, the production of Th1 cytokines like IL-2 and IFN-γ was decreased, alongside an overexpression of Th2 cytokines such as IL-10 and IL-4.[29] Some studies have aimed to investigate the cause of Th1/Th2 imbalance in MM. Dendritic cells (DCs) serve as a pivotal component in immune responses. Distinct stimulation can induce divergent cytokine secretion profiles in DCs, among which high-level IL-12 production by DCs constitutes a critical determinant for effective Th1 cell activation. However, Shinde et al discovered that dysfunctional monocyte-derived DCs (Mo-DCs) show decreased IL-12p70 expression and increased IL-10 production, resulting in compromised Th1 responses.[30] Moreover, the polarization of macrophages towards M2 and Th2 responses both play a role in creating an immunosuppressive microenvironment.[31] Nevertheless, additional research is required to explore the causal relationship between these two factors and the precise regulatory mechanisms. Currently, the functional impact of Th1/Th2 dysregulation on immune evasion in MM remains unclear. Further analysis of the interplay between T helper subsets and dysfunctional CTLs may help uncover essential strategies to rebalance this dynamic.

Treg

In recent years, regulatory T cells and Th17 cells have attracted growing attention alongside the classic Th1 and Th2 cells, owing to their potential involvement in the immune evasion mechanism of MM.

Treg cells are a subset of CD25+CD4+ T cells differentiated from Th0 induced by high concentrations of TGF-β and IL-2, and specifically express the Forkhead box protein P3 (FoxP3). In MM patients, reports of changes in the quantity of Tregs both in peripheral blood and in bone marrow are still conflicting.[32–38] The conflicting studies on Tregs in MM patients in recent years have been well reviewed by Hadjiaggelidou et al.[39] These inconsistencies may be attributed to the heterogeneity of samples, the diversity of identification methods, differences in reporting forms for Tregs (eg, percentage frequency or absolute value of numbers),[40] and changes in the quantity that may occur in MM progression. These observations suggest that Treg cells constitute a heterogeneous group of cell subsets with complex functions in TME. One of these subtypes, CD8+ CD28− regulatory T cells, according to a recent study, have a prognostic value after induction therapy.[41]

Recent co-culture studies demonstrate myeloma cells have the ability to enhance the expansion of mouse and human Tregs through both contact-dependent and independent mechanisms.[33,42] Additionally, myeloma cells can transfer membrane proteins to T cells through trogocytosis to generate acquired regulatory T cells.[43] Apart from myeloma cells, DCs induce Tregs through direct cell-cell contacts (including CD80/CD86-mediated interactions) and the production of IL-2.[44] Although the exact mechanism remains incompletely understood, various molecules, including arginase, CD40, and cytokines (such as TGF-β, IFN-γ, and IL-10), have been implicated in the crosstalk between myeloid-derived suppressor cells (MDSCs) and Treg cells.[45,46] Osteoblasts are also one of the participants in the MM immunosuppressive microenvironment. A proliferation-inducing ligand (APRIL) produced by them stimulates the upregulation of TGF-β and IL-10, thereby fostering Treg survival through TACI signaling.[47] While Tregs may play a significant immunosuppressive role in MM, there is currently no literature documenting the specific molecular mechanisms by which Tregs exert detrimental effects.

Tregs have also been found to be associated with the prognosis of MM patients. Alrasheed et al found that MM patients with higher frequency of Tregs had poorer survival and elevated immune checkpoint profiles (ie, PD-1, LAG-3) on Tregs.[48] Huang et al have also corroborated this, and further found that the heightened expression of VISTA on Tregs in MM may promote the activation of Tregs.[23] The inhibitory effect of Treg in autologous transplantation has also been confirmed. During stem cell mobilization, Treg cells expressing immunosuppressive molecules are mobilized from the bone marrow to the peripheral blood and inhibit the long-term control of CD8+ T cells against MM in grafts. This suppression is relieved when Treg is depleted.[49] Elevation of immune checkpoints on Tregs also significantly affects the efficacy of immune checkpoint inhibitors.[50] In numerous animal models of solid tumors, it has been confirmed that small molecule drugs or monoclonal antibodies against VISTA are beneficial to directly inhibit Tregs, promote the invasion and proliferation of tumor effector T cells, and stimulating cytokine secretion, thereby enhancing the anti-tumor response, but there is a lack of relevant reports in MM.

Beyond the conventional CD4+ Treg cells, additional subgroups of CD8+ Treg cells and CD4 CD8 double negative (DN) Treg cells have also been defined; however, their investigation in MM remains severely limited. Two types of CD8+ Treg cells exist within tumors. One type is CD8+CD25+ Treg cells that mediate non-specific immunosuppression, which have been found to be significantly elevated in two studies compared to HDs.[51,52] Nevertheless, given their non-tumor specificity, it remains unclear whether this subgroup contributes to tumor-related immune regulation in MM. The other type is CD8+CD28- Treg cells that mediate antigen-specific immune suppression. Research findings indicate their elevation in both peripheral blood and bone marrow, in contrast to HDs. Lymphocyte function-associated antigen 1 (LFA-1) likely serves as their functional phenotype for immunosuppression. These cells may exert immune suppression through the secretion of inhibitory cytokines and potential interactions with the IL-10 regulatory network.[53] Leone et al identified two heterogeneous CD8+ cell subgroups in MM patients. IFNγ-producing CD8+ T cells stimulated by professional APCs to mediate anti-tumor activity, and may be the conventional CTLs we believe in, versus immunosuppressive Foxp3+ CD8+ T cells induced by bone marrow endothelial cells that produce abundant IL-10 and TGF-β to inhibit the former cytotoxic subset.[54] We believe that this subgroup may also be CD8+CD28- Treg cells. In addition, some studies have found that DN Treg cells are significantly reduced in MGUS and MM patients.[36] It is not yet known whether this is related to the immune evasion mechanism in MM. In summary, our current understanding of CD8+ Treg and CD4 CD8 double negative Treg cells is still very limited.

Th17

Th17 cells represent a subset of helper T cells that are synergistically induced by TGF-β along with IL-6 or IL-21, originating from Th0 cells. They primarily secrete IL-17, IL-17F, and IL-22, accompanied by the expression of the lineage-specific transcription factor nuclear retinoic acid receptor (RAR) related orphan receptor C (RORC). It has been reported that the proportion of Th17 cells is increased in the peripheral blood and bone marrow of MM patients,[32,55] which may be attributed to the enrichment of Th17 cells in the bone marrow of MM patients induced by dendritic cells. Furthermore, the level of IL-17 in the bone marrow microenvironment of MM patients is also increased. It has the potential to induce myeloma cell proliferation and inhibit immune function by activating the IL-6/STAT3 signaling pathway.[56]

The concept of a Treg/Th17 balance has garnered increased attention in recent years due to the differentiation-inducing effects of TGF-β and IL-6 on the two types of cells in the periphery. In MM, the disturbance of this equilibrium may be an important feature of immune dysregulation.[57] Studies have demonstrated that the Treg/Th17 ratio is elevated in MM patients and lower in long-term survivors. An increase of the Treg/Th17 ratio is associated with a decrease in the overall survival of MM patients and a higher Treg/Th17 ratio suggests a more suppressive immune environment in MM patients.[58] These results suggest that we should pay attention to the imbalance of the overall homeostasis of immune cells in MM patients rather than solely on changes in individual cell types.[59]

Th22

Th22 is a newly discovered human inflammatory T helper subtype characterized by the high secretion of IL-22 and TNF-α, without the secretion of IFN-γ, IL-4, or IL-17A. The aryl hydrocarbon receptor (AHR) is considered as a pivotal transcription factor for the Th22 subtype and is involved in the expression of IL-22. The current study shows that the proportion of Th22 and Th17 is increased in MM patients, and there is a notable positive correlation between Th22 and Th17.[60] Furthermore, heightened frequencies of IL-22 and IL-13 dual-producing T cells have been observed in the peripheral blood and bone marrow of patients with relapsed and advanced MM, potentially contributing to the maintenance of MM pathology by promoting cell proliferation and drug resistance in specific MM cell lines.[61] Elevated levels of Th22 cells in the bone marrow are also linked to poor prognosis.[62] All of these findings point to a crucial role Th22 cells play in MM, but the research in this field is still in its infancy. The interaction of Th22 cells with other cells in TME and the mechanism of IL-22 in MM merit further investigation.

Tfh

Follicular helper T (Tfh) cells represent a subset of CD4+ T cells distinguished by the expression of CXCR5, PD-1, and ICOS in germinal centers (GCs). Tfh cells provide co-stimulatory factors, such as ICOS, which facilitate B cell proliferation and differentiation. A subversive study found that plasma cells can serve as APCs to engage with Tfh cells and negatively feedback inhibit the ability of effector Tfh cells to produce IL-21.[63] Zhou et al found that levels of Tfh cells, ICOS, PD-1, and IL-21 were notably elevated in newly diagnosed MM (NDMM) patients compared to HDs. Conversely, in CR or PR patients, Tfh cells, ICOS, and PD-1 expression levels were significantly decreased, although they did not reach normal levels. This suggests that Tfh works in some unknown ways in the pathogenesis of MM, which may be related to the destruction of the negative feedback mechanism mentioned above.[64] Furthermore, it has been noted that the Tfh17/Tfh ratio is significantly higher in MM patients, especially relapsed patients compared with HCs. And the

Tfh17/Tfh ratio is decreased in post-ASCT patients compared with non-ASCT patients. These results imply that Tfh17 (CXCR3-CCR6+) cells may be essential to the clinical development of MM.[65]

Unconventional T Cells

Unconventional T cells encompass a heterogeneous group of recently defined T cells. Their greatest characteristics are limited TCR diversity, recognition of non-peptide antigens, and rapid response by virtue of their innate immune characteristics. Unconventional T cells mainly include three subgroups: CD1-restricted T cells, MR1-restricted mucosa-associated invariant T cells (MAIT cells), and γδ T cells (Figure 1).

CD1-Restricted T Cells

CD1d-restricted T cells, namely natural killer T (NKT) cells, were originally defined as cells co-expressing CD3 and NK cell-specific proteins, but there is now a consensus that this cell population is characterized by restricted recognition of lipid molecules presented by CD1d. NKT cells are divided into two types. Type I NKT cells express constant TCRα chain and limited but not constant TCRβ chain, also known as “invariant NKT cells” or “iNKT cells”; cells with expression of other αβTCRs are classified as type II NKT cells, also known as “diverse NKT cells”.

Dhodapkar et al found advanced MM patients have significantly lower iNKT cell frequency compared with HDs, and their ligand-dependent INF-γ production was significantly insufficient. Dendritic cells loaded with the iNKT ligand α-GalCer can overcome this quantitative and functional deficit in vitro. The data indicate that the clinical progression in patients with MM is associated with acquired dysfunction of iNKT cell that are likely to be reversible and suggest that iNKT cells may exert positive effects on tumor immunity.[66] In contrast, type II NKT cells may facilitate the inflammatory response within the tumor microenvironment by secreting IL-13, causing fibrosis and angiogenesis, thereby promoting the growth of MM cells.[67] The CD1d antigen-presenting molecule recognized by NKT cells, which is not expressed in MM cell lines, is highly expressed in precancerous and early myeloma cells, and its expression gradually decreases with the progression of MM, which may indicate advanced MM cells develop immune evasion against NKT cells. Currently, the specific mechanism underlying the down-regulation of CD1d molecular expression remains unclear and warrants further investigation.[68,69]

MR1-Restricted Mucosa Associated Invariant T Cells (MAIT Cells)

MAIT cells express unique TCR molecules, including a TCRα chain (Vα7.2–Jα33) and a TCRβ chain (Vβ2 or Vβ13), and recognize vitamin B metabolites presented by MHC class 1b (MR1) molecules.

Compared with the NKT cells, the research of MAIT cells in MM is still in an early stage. The earliest report found that compared with HDs, the percentage of MAIT cells in NDMM patients is significantly reduced. The ability to secrete IFN-γ and TNF-α after stimulation is also significantly impaired. This means that the anti-tumor effect of this cell population could be impaired in MM. This study also analyzed the correlation between iNKT cells and impaired MAIT cells, and found that the PD-1 pathway may mediate MAIT cell dysfunction and disrupts MAIT-iNKT immune interactions in MM.[70] A subsequent study verified the conclusion that the percentage of MAIT cells decreased in NDMM patients, and further discovered that the ability of MAIT cells to secrete IFN-γ is restored in relapsed refractory MM (RRMM) patients, possibly due to the heightened inflammatory capacity of T cells in RRMM patients.[71] However, whether MAIT cells have a direct or indirect effect on killing MM cells or promoting tumors has not yet been studied. Its role in the MM immune microenvironment deserves further exploration.

γδ T Cells

Unlike mainstream T cells, γδ T cells express TCRγ chains and TCRδ chains, and recognize antigens without MHC restriction. However, due to the lack of diversity of TCRγ and δ chains, these cells can recognize fewer types of antigens. According to variations in the V region of the δ chain, human γδT cells are divided into three types: Vδ1T cells, Vδ2T cells and Vδ3T cells. Currently research on Vδ1T cells, and Vδ2T cells is more prevalent, because the quantity of Vδ3T cells is not enough.[72]

In MM research, γδ T cells have received more extensive attention compared to MAIT cells. Nevertheless, current reports on γδ T cells in MM are very rare and show contradictory results. Earlier studies did not identify any notable variances in the overall frequencies of γδ T cells in the bone marrow or peripheral blood of MM patients versus HDs.[73,74] But a recent literature reported that the peripheral blood Vδ1 T cells and Vδ2 T cells and the total Vδ1 and Vδ2 frequencies of MM patients are significantly lower than those of HDs, but the total γδ T cell frequencies were higher than those of HDs. These contradictory results deserve more experimental verification and interpretation.[75] Researchers have long discovered that bisphosphonates, such as pamidronate and zoledronate, can activate Vδ2T cells via MHC class I-related chains A (MICA) to exert anti-MM effects, and further discovered that ICAM-1/ LFA-1 interaction is necessary in this process, as ICAM-1 facilitates the recognition of myeloma cells by γδ T cells.[76] Th1-like Vγ9Vδ2 T cells can exert cytotoxic effects on MM cells, and with the participation of SLAMF7 monoclonal antibody elotuzumab, this group of cells can kill MM cells and osteoclasts through antibody-dependent cellular cytotoxicity (ADCC).[77] Vδ1T can also mediate anti-MM through Natural killer-G2D molecule (NKG2D), DNAX accessory molecule-1 (DNAM-1), intracellular cell adhesion molecule (ICAM)-1, CD3 and CD2 receptors and some TCR-mediated killing effect on MM.[78] Furthermore, Niu et al showed low-dose bortezomib upregulates NKG2D and DNAM-1 on tumor cells to boost γδ T cell cytotoxicity against MM.[79] A recent study, however, showed that hypoxia-adapted myeloma stem cells resist γδ T cell-mediated cytotoxicity by modulating the mevalonate pathway.[80] This phenomenon poses a challenge that needs to be addressed in order to enhance the activation of γδ T cells for the treatment of MM. Another earliest study discovered that bone marrow stromal cells prompt MM cells to secrete CXCL10 to recruit γδ T cells into the tumor microenvironment and change their function, thereby creating an immunosuppressive milieu that is conducive to the survival of tumor cells.[81] So how to make γδ T cells enrich around tumor cells but exert normal anti-tumor immune function has become a new task worth exploring.

Memory T Cells

Memory T cells (TMEM) are the reserve army of cytotoxic T cells and continue to participate in the immune response to tumors, and their quantity and functional status reflect the state of immunity. Memory CD8+ T cells comprise a heterogeneous population, encompassing circulating memory (TCIRC) subsets: central memory (TCM), effector memory (TEM) and stem cell memory T cells (TSCM), and a non-circulating subset: Resident memory T cells (TRM). Multiple studies examining memory T cells in patients with early-onset MM have reported decreased levels of all four TMEM subtypes in the bone marrow of MGUS and SMM/MM patients compared to HDs, suggesting that a large number of memory cells differentiate into effector cells in the early stage of the disease to exert anti-tumor effect.[25,26,82,83] Conversely, during disease progression, this differentiation process seems to be impaired, as demonstrated by two studies showing an expanded presence of TMEM in the bone marrow of MM patients compared to non-tumor control subjects. These findings suggest that the quantity of these cells is progression-dependent, potentially due to hindered differentiation of memory T cells into effector T cells linked to impaired amino acid metabolism.[4,84,85] Recently, Minnie et al found that lenalidomide treatment altered the phenotype of memory T cells and increased expression of the gene encoding IL-7R. Notably, the combined administration of a TIGIT inhibitor and lenalidomide significantly augmented the effector function of CD8+ T cells and elevated the frequency of memory T cells in the BM.[11] In a related study conducted by the same research team, it was determined that alloantigens, rather than myeloma antigens, were responsible for inducing donor T cell exhaustion following alloBMT. This exhaustion subsequently contributed to the resistance of MM patients to GVT after alloBMT. The utilization of post-transplant cyclophosphamide (PT-Cy) can depletion alloantigen-driven T cell exhaustion and redirect it toward myeloma antigen-driven T cells. Furthermore, the administration of PT-Cy can also enhance the abundance of Tscm, offering insights into the potential application of alloBMT in MM.[86] These two studies also open new avenues for modulating the quantity and function of memory T cells in MM patients.

Effects of Other Cells in Microenvironment on T Cells

MM Cells

The precise cause of T cell dysfunction in MM patients remains uncertain, however, emerging research indicates that MM cells play a prominent role in this process. At present, it is widely accepted that MM cells predominantly impact the functionality of T cells through two mechanisms: modifying the expression of surface antigens to evade immune surveillance and directly suppressing the activity or cytotoxicity of T cells by expressing specific molecules.

During the progression from MGUS to MM, the function of antigen processing-presenting machinery (APM) is impaired due to the APM components alternation.[87] Subsequently, it is observed that the dynamic modulation of MHC class-I molecules' expression on the membrane surface of MM cells, enabling them to evade immune surveillance by CTL or NK cells.[88] Recently, the expression of cancer-germline antigens (CGA) is considered to be related to the expression and mutation of MHC molecules, suggesting the potential involvement of CGA in immune evasion.[89] Furthermore, instances of B cell maturation antigen (BCMA) down-regulation and resistance to CAR-T and bispecific antibody (BsAb) have been reported with the advent of BCMA target immunotherapy and the emergence of drug resistance. The mechanism at play may involve clonal selection under therapeutic stress, wherein myeloma cells exhibiting high BCMA expression are eradicated while tumor cells displaying low BCMA expression are favored for survival.[90–92]

In another aspect, carcinoembryonic antigen-associated cell adhesion molecule-6 (CEACAM-6) expressed in MM cells was found to impede T cell activation and its cytotoxic response towards MM cells.[93] The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene is expressed in a part of extramedullary myeloma cells. And TRAIL may bind to the TRAIL receptor on T cells and trigger abnormal activation.[94] Extramedullary myeloma also exhibits up-regulation of the hypoxia-inducible factor-1α (HIF1A) gene, and hypoxia can promote the production of PD-L1, thereby increasing the resistance of tumor cells to CTL-mediated killing.[95]

As understanding of the tumor microenvironment continues to deepen, the distance between T cells and tumors has begun to attract the attention of researchers. Through multiplex immunohistochemistry, Ninkovic et al found that CLT cells in the bone marrow of NDMM patients were closer to MM cells than MGUS and RRMM.[96] In another spatial transcriptome study on extramedullary myeloma, researchers found that exhausted phenotype Tim3+/PD-1+ T cells were diffusely co-localized with MM cells in extramedullary myeloma lesions, while functional and activated CD8+ T cells were confined to niches lacking PCs.[97] These results suggest that T cells play a protective role in the early stages of the disease, but as the disease progresses and relapses, they are not only functionally impaired, but also gradually move away from tumor cells in space.

MDSCs

Besides MM cells, the influence of other cells within the TME on T cells has gradually been increasingly elucidated. Particularly, immune cells within the TME have garnered significant interest from researchers in recent years.

Among these, MDSCs have been the most known, and a study has shown that such cells can mediate immunodeficiency in MM by impeding the activity of anti-tumor CTL in an antigen-specific manner. In the existing knowledge, MDSCs are divided into two types, granulocytic MDSCs (G-MDSCs) hinder CTL function through reactive oxygen species (ROS), while monocytic MDSCs (MO-MDSCs) inhibits via inducible nitric oxide synthase (iNOS) and arginase. Görgün et al confirmed that the inhibitory factors iNOS and ARG1, along with the inhibitory cytokines IL-6 and IL-10, are associated with the immunosuppressive effects in MM. They further elucidated the inhibitory mechanism of MDSCs on CTL in MM and observed that the administration of bortezomib and lenalidomide resulted in the suppression of these cytokines without affecting the frequency and inhibitory function of MDSCs. Hence, it is imperative to anticipate the discovery of novel drugs or combinations that can effectively alter the immunosuppressive role of MDSCs.[98] Xiong et al confirmed the inhibitory function of MDSCs to CTL in 5TGM1model and discovered MDSCs playing a role in resistance to PD-1 antibody therapy.[99]

DCs

DCs are vital antigen-presenting cells, categorized into myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) based on their lineage. Currently, limited advancements have been made regarding the influence of DCs on T cells within the MM bone marrow microenvironment. A recent article presented a succinct summary of this subject, and its results delved deeper into the complexities of this relationship. On one hand, bone marrow-resident mDCs and pDCs can fully mature and stimulate tumor-specific CD8+ T cells through CD91-calreticulin-mediated phagocytosis of apoptotic MM cells. On the other hand, mDCs can also influence on the expression of proteasome subunits in MM cells through a contact-dependent process involving CD28. (Figure 1) This direct interaction with tumor plasma cells renders them resistant to CD8+ T cell cytotoxicity.[100] Given that the study relies on in vitro experiments, further research is required to understand the function of DCs in the real environment and their impact on T cells. With the rise of DCs vaccines, comprehending the dysfunction of DCs could be a crucial piece of the immunotherapy puzzle for MM.

A recent study suggested that CD71+ erythroid cells (CECs) inhibit T cell proliferation by expressing arginase 2 (ARG2) in the VK*MYC mouse model, providing a new insight into the immunosuppressive microenvironment of MM.[101] On the one hand, the importance of CECs in this process deserves further exploration in clinical samples; on the other hand, the cell types that were originally thought not to be involved in immunosuppression but actually act as something remain to be discovered.

In the current understanding of drug resistance and relapse of MM, T cell dysfunction in the immune microenvironment occupies a core position. Understanding which cells impair T cell function and exploring how to reverse it are crucial issues. The function of these environmental cells and their crosstalk in the TME in the formation of the immunosuppressive microenvironment of MM is complex, but opportunities and challenges coexist. An in-depth elucidation of the contribution of various immune cell populations and stromal cells in the mechanisms of immunosuppression will provide a deeper understanding of the disease and open new doors for MM immunotherapy.

Metabolism and T Cells

In recent years, the influence of metabolism on tumors has received more attention, and the key role of metabolism associated tumor immunity has gradually been revealed.

Glucose Metabolism and Oxidative Phosphorylation

Compared with HDs, CD8-GNLY effector T cells and CD8-XCL2 memory T cells in the high tumor infiltration group showed enhanced glycolysis/gluconeogenesis, oxidative phosphorylation (OXPHOS), and lipid metabolism, according to a single-cell sequencing study analyzing the metabolism of immune cells in the bone marrow of MM patients. Moreover, the high tumor infiltration group showed increased activity in the tricarboxylic acid cycle (TCA cycle) of CD8-GNLY effector T cells, while the CD8-XCL2 memory T cells exhibited a decrease.[4] This high-throughput analysis study comprehensively depicts the metabolic changes occurring in effector T cells and memory T cells in MM, laying the foundation for further in-depth research.

Lipid Metabolism

MM bone marrow CD8+ T cells express fatty acid transport protein 1 (FATP1), which causes CD8+ T cells to uptake long-chain fatty acids from the bone marrow, consequently inhibiting the function of CD8+ T cells.[102] This uptake may be mediated by CD36. Indeed, Ma et al found that tumor-infiltrating CD8+ T cells in MM patients expressed higher CD36 compared with MGUS, which may activate lipid peroxidation and ferroptosis of T cells, so that the function of CD8+ T cells to produce cytotoxic cytokines is impaired.[103] These two studies suggest that lipid peroxidation in MM may play a significant role in T cell dysfunction, highlighting the need for further research in this area(Figure 2).

Amino Acid Metabolism

T cells located in the bone marrow of MM patients had extensive amino acid metabolism impairment including arginine.[4] Wan, Y. et al found that the unfolded protein response (UPR) signature protein XBP1 in CTL in MM inhibits SLC38A2 by directly binding to the promoter of the glutamine transporter SLC38A2, resulting in reduced glutamine uptake and immune dysfunction in T cells. This study partially elucidates the possible mechanism of T cell dysfunction and provides insights into reversing the dysregulated amino acid metabolism of T cells in MM.[104]

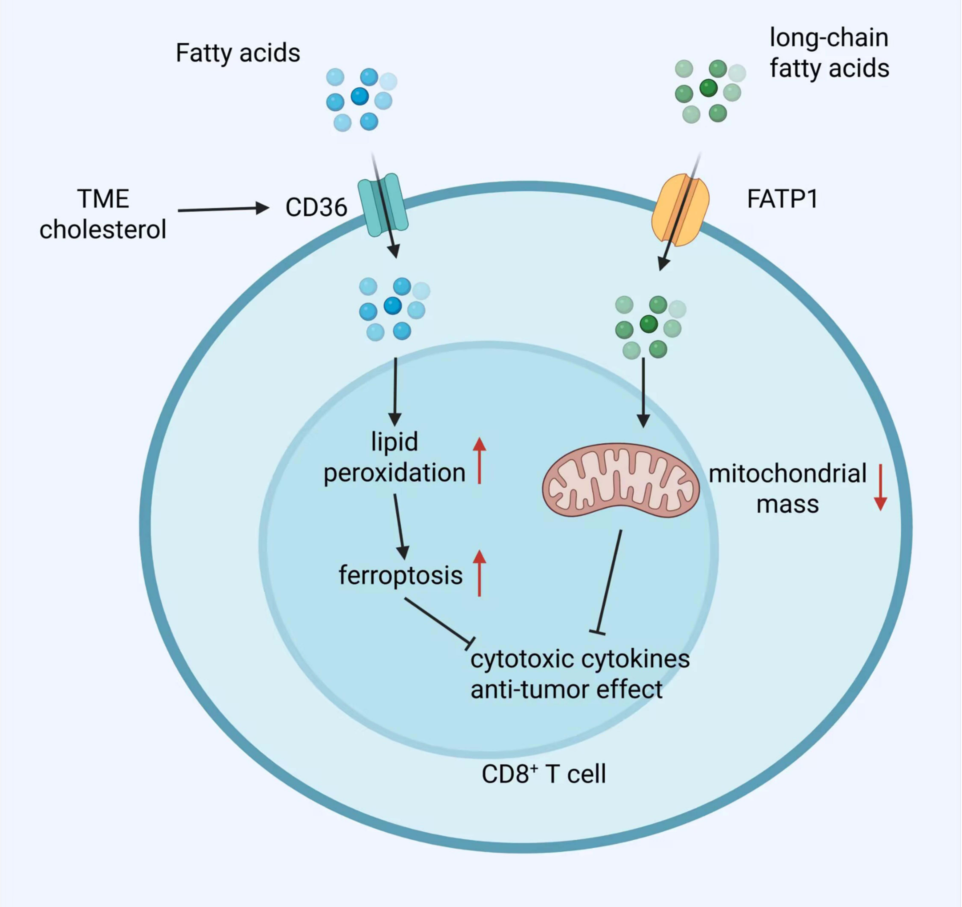

Figure 2 Fatty acid metabolism disorder of CD8+T cells in MM. On one hand, the uptake of fatty acids via CD36 triggers lipid peroxidation and ferroptosis. On the other hand, the entry of long-chain fatty acids through FATP1 impairs mitochondrial mass. Collectively, these processes contribute to a reduction in CD8+ T cell secretion of cytotoxic cytokines and diminish the anti-tumor effect in multiple myeloma. Red arrows indicate: Red arrows indicate: (upper left) increased lipid peroxidation, (lower left) elevated ferroptosis, and (right) reduced mitochondrial mass. Created in BioRender. f,f. (2025) https://BioRender.com/xcs0gr8.

Although significant progress has been made in studying the role of metabolism on tumor immune modulation, it is important to note that the exploration of MM in this framework is relatively recent. Moreover, various regulatory mechanisms have been identified in non-pathological conditions or in other tumor types, but their validation in MM remains incomplete. A crucial aspect is understanding the underlying causes of these metabolic disorders. Are these effects attributed to the unique metabolic microenvironment or do they arise from direct or indirect attacks on T cells by immunosuppressive cells, such as tumor cells? Overall, this line of inquiry shows promise.

Coping Strategies

Given the multifaceted dysfunction of T cells within the tumor microenvironment, it is imperative to explore novel strategies for reversing the immunosuppression. Fortunately, we are not clueless.

Targeting immune checkpoints, inhibiting the loss of MM cell surface antigens, reversing the immunosuppressive tumor microenvironment, and enhancing T cell metabolic activity represent promising strategies for controlling disease progression.

Despite the disappointing performance of the immune checkpoint PD-1 in clinical trials, recent mechanistic studies have shown a growing interest and preference for the new immune checkpoint TIGIT and LAG-3. Early studies demonstrated that targeting TIGIT expression in DNAM-1+ CD8+ T cells represents the most effective strategy for anti-TIGIT therapy. Subsequent investigations further revealed that combined anti-TIGIT and lenalidomide treatment exhibits significant anti-MM efficacy, providing strong rationale for ongoing clinical trials of this combination regimen.[11,105,106] In the MyCheckpoint clinical trial, 13 RRMM patients were randomized to receive either anti-TIGIT or anti-LAG-3 antibody monotherapy followed by combination treatment with pomalidomide and dexamethasone. This study generated preliminary clinical data on these two immune checkpoint inhibitors in MM, demonstrating acceptable overall tolerability and safety profiles. However, the observed response rates underscore the need for further optimization of therapeutic combinations to enhance clinical outcomes.[107]

To address the decreased antigen expression in MM, in addition to NK cell therapy, recent studies have shown that γ-secretase inhibitors (GSIs) can effectively inhibit the GS cleavage process, preventing the release of soluble BCMA

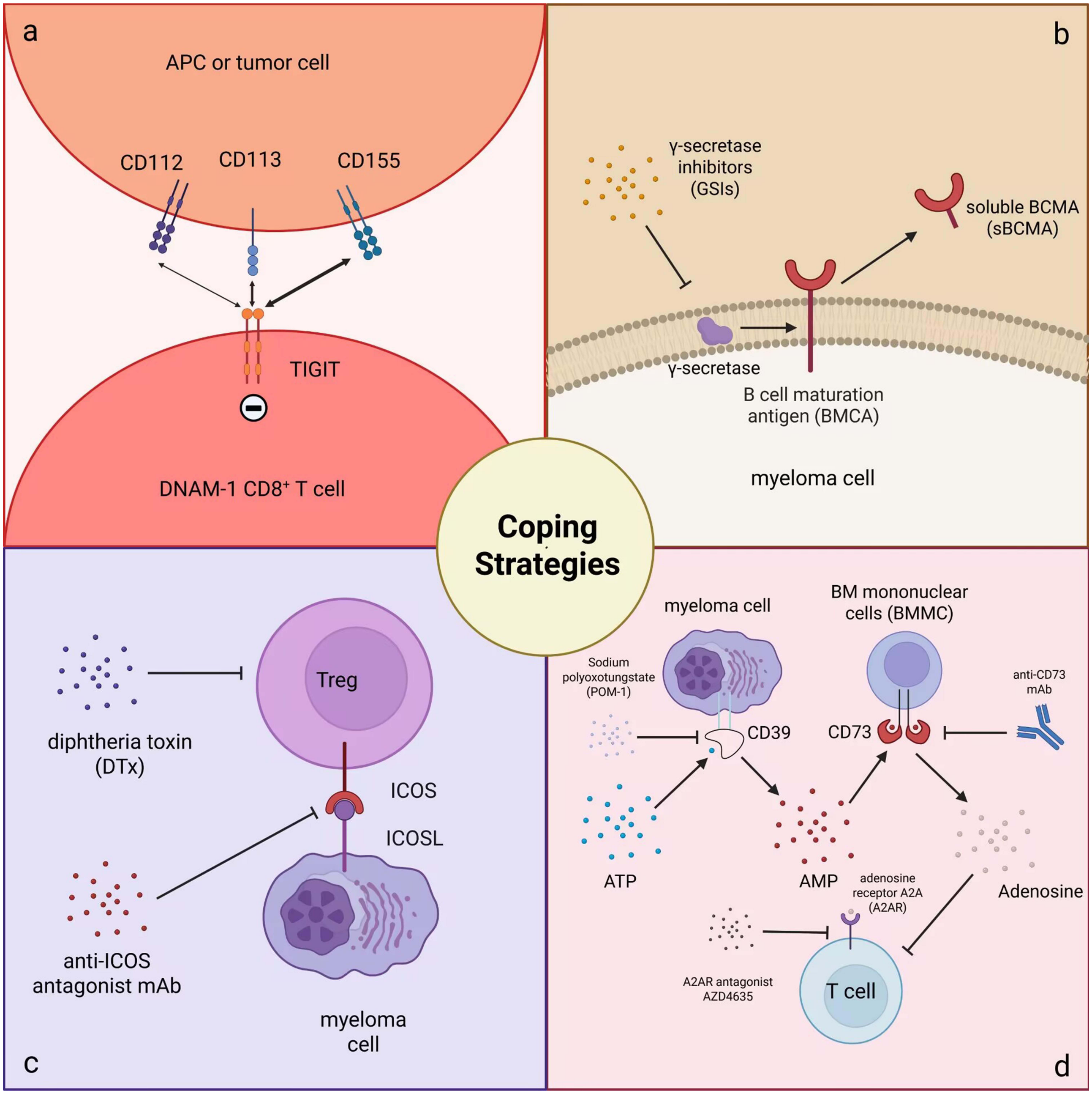

Figure 3 Coping Strategies to reverse the immunosuppressive microenvironment. (**a**) Targeting the expression of TIGIT in DNAM-1 CD8+ T cells could be an effective approach for anti-TIGIT immunotherapy; (**b**) γ-secretase inhibitors (GSIs) can inhibit the γ-secretase cleavage process, leading to the release of soluble BCMA (sBCMA) into bone marrow mononuclear cells in MM patients. This restoration of BCMA on the MM cell membrane enhances the targeting of MM cells and the efficacy of BCMA×CD3 BsAb; (**c**) Short-term depletion of Tregs using diphtheria toxin elicits an effective CD8 T cell and NK cell-mediated immune response, resulting in complete and stable remission of multiple myeloma, myeloma cells induce the generation of Treg cells through the ICOS/ICOSL pathway, and anti-ICOS therapy can block this process; (**d**) MM cells can inhibit T cell function by increasing the concentration of adenosine in the TME through CD39 and CD73 molecules on their cell membrane surface. POM-1 and anti-CD73 antibodies can block the adenosine pathway in the microenvironment and partially relieve the immunosuppression. Created in BioRender. f_, f_. (2025)https://BioRender.com/m2ax468.

(sBCMA) into circulation. This restoration of BCMA on the MM cell membrane enhances the targeting of MM cells and the efficacy of BCMA×CD3 BsAb. Furthermore, this discovery offers promising prospects for other BCMA-targeting medications and therapies.[108] In the MajesTEC-2 trial (NCT04722146), combination therapy with a BCMA×CD3 BsAb and γ-secretase inhibitors demonstrated modest improvements in overall response rate and complete response rates. However, this regimen was associated with unacceptable toxicity profiles and mortality rates.[109]

The regulation of both anti-tumor and pro-tumor immunity is essential as they represent opposing ends of the spectrum. Consequently, investigations are underway to explore the mechanisms that modulate the function of Tregs. Studies have shown that MM cells can induce the generation of Treg through the ICOS/ICOSL pathway. Thus, blocking this process to weaken the power of pro-tumor immunity deserves attention.[110] This is strongly demonstrated in the study by Dahlhoff et al, where they transiently depleted Treg cells in mice to halt the onset and progression of MM. The next step is to develop efficient and safe targeted therapies for Treg cells.[111]

Table 1 Frequency Change of T Cell Subsets in MGUS and MM

		Peripheral Blood		**Bone Marrow**	
Cell type		MGUS	MM	MGUS	MM
CD4		↔[32,74]	↓[32]		↑[27]
CD8		↔[32] or ↑[74]	↑[74]		
CD4/CD8		↔[32] or ↓[74]	↓[32,74]		↔[27]
CTL					↑in early stage↓in late stage[4]
$CD8^{+}T_{MEM}$				↔ or↓[82,83]	↓[25,82] in early stage↑[4] or ↔[83] in late stage
Th1				↑[27]	↑[27]
Th2					
Th1/Th2			↑[32]		
CD4+Treg		↑[36,37]	↑[34–38]		↔[34,37]
CD8+Treg	$CD8^{+}CD25^{+}$ Treg		↑[51,52]		
	$CD8^{+}CD28^{-}$ Treg	↑[53]	↑[53]		
DNTreg		↓[36]	↓[36]		
Th17			↑[28,32]		↑[28,55]
Treg/Th17		↔[59]	↑[58,59]		
Th22		↔[61]	↑[60,61]	↔[61]	↑[60,61]
Tfh			↑[64]		
NKT	Type I NKT (iNKT)	↔[66,118]	↔[66,119] or ↓[118]		
	Type II NKT		↑[67]		
γδ T		↔[74]	↔[73,74] or ↑[75]	↔[74]	↔[73,74]
MAIT			↓[70,71]		↓[70]

Notes: ↑, ↓ and ↔ indicate increase, decrease or no changes, respectively, in absolute or relative frequency of corresponding T cell subsets in the peripheral blood or bone marrow of MGUS or MM patients compared with HDs. Blank cells indicate unavailable or insufficient data on the corresponding T cell subsets upon review of the current literature.

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; CTL, cytotoxic T lymphocytes; TMEM, memory T cell; Th, T helper; Treg, regulatory T cell; DNTreg, double negative regulatory T cell; Tfh, Follicular helper T cell; NKT, natural killer T cell; MAIT, MR1-restricted mucosa associated invariant T cell.

In relation to metabolism, there is currently a scarcity of research on T cell metabolic dysfunction in MM. This may be due to the nascent phase of studying immunometabolism in this context. As knowledge in this field continues to advance, the discovery of effective targets is imminent. Two recent studies suggest that MM cells can inhibit T cell function by increasing the concentration of adenosine in the TME through CD39 and CD73 molecules on their cell membrane surface. Although the actual situation and regulation of adenosine metabolism remain ambiguous, the findings of these two studies laid the groundwork for understanding the metabolic profile of adenosine in the MM TME. Additionally, they have underscored the impact of other metabolisms in the TME on immune cells.[112,113] Currently, research on lipid metabolism, lactic acid metabolism, and mitochondrial function has been conducted in various other tumor studies. The aforementioned studies are inspiring, and have the potential to offer valuable insights for metabolic and immune research in the realm of MM.[15,114–117](Figure 3)

Conclusions

We have summarized numerous studies regarding the changes in the quantity of T cell subsets (Table 1), despite occasional contradictions in their findings. In stark contrast, we know little about the factors contributing to these alterations. Elucidating the underpinnings of the observed immunophenotypic changes will be an integral research focus moving forward.

The advent of high-throughput technologies, particularly single-cell RNA sequencing, has revolutionized our understanding of T cell biology in MM, unveiling previously unrecognized heterogeneity in immune dysfunction. This technological breakthrough coincides with the clinical transition to an immunotherapy era dominated by CAR-T cell therapies and bispecific T cell engagers (TCEs). Such paradigm shift necessitates the development of next-generation staging systems that integrate tumor-intrinsic factors with immune competence metrics, as emerging evidence confirms that intrinsic T cell functional status critically determines therapeutic responses to T cell-redirecting modalities.

Notably, the current lack of standardized protocols for assessing T cell fitness creates substantial clinical ambiguity. There is an urgent need to establish multidimensional assessment frameworks that synergistically evaluate: 1) T cell receptor repertoire diversity, 2) exhaustion marker profiles, 3) metabolic fitness, and 4) spatial distribution within the bone marrow niche. Such comprehensive immune monitoring could enable predictive modeling of treatment responses and guide personalized sequencing of immunotherapies.

Our review synthesizes current knowledge on MM-associated T cell dysfunction, elucidating the complex interplay between malignant plasma cells and immune effectors through soluble factors, checkpoint interactions, and metabolic competition. While significant progress has been made, critical knowledge gaps persist regarding the reversibility of T cell exhaustion and optimal strategies for restoring anti-myeloma immunity. Future research directions should prioritize combinatorial approaches targeting both tumor vulnerabilities and immune rejuvenation, ultimately advancing towards precision immunotherapy paradigms in MM management.

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