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The Drug Resistance Mechanism and Overcoming Strategies of Immunotherapy for Multiple Myeloma: A Comprehensive Review

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Abstract: ***Immunotherapy for multiple myeloma (MM) has emerged as a significant breakthrough in the treatment of the disease, despite significantly improving remission rates in patients with relapsed or refractory MM (R/R MM), but still faces challenges such as drug resistance and toxic side effects. Characteristic changes in the immune microenvironment are the main cause of resistance, including T-cell exhaustion, inhibitory factors secreted by bone marrow stromal cells, abnormal expression of immune checkpoints, and tumor antigen escape, etc. Countermeasures include combined targeted therapy, epigenetic regulation, novel immunotherapies, etc. In the future, single-cell technology will be needed to analyze the heterogeneity of resistance. Develop dynamic monitoring markers and formulate individualized regimens. This article reviews the mechanisms of resistance and strategies for overcoming immunotherapy in multiple myeloma, aiming to analyze the key influencing factors and potential therapeutic targets and provide relevant ideas for overcoming immunotherapy resistance.***

Keywords: Multiple myeloma, Bone marrow microenvironment, Immunotherapy resistance, CAR-T cell therapy.

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell proliferative disorder that ranks second among hematological malignancies and is more common in the elderly [1]. Based on GLOBOCAN 2022 data and population projections, studies have analyzed the global prevalence and mortality of multiple myeloma (MM) and predicted up to 2045. There were an estimated 188,000 new cases and 121,000 deaths worldwide in 2022, with significant regional and gender differences in morbidity and mortality (male > female). East Asia and North America have the highest number of cases, while North America and Australia/New Zealand have the highest incidence. If the incidence rate remains unchanged, the number of MM cases and deaths is projected to increase by 71% and 79% respectively by 2045 compared to 2022. The study pointed to a significant global imbalance in the diagnosis and treatment of MM and called for enhanced surveillance and disease control in the context of an aging population to reduce its global burden [2].

Immunotherapies such as monoclonal antibodies, CAR-T cell therapy, and immunomodulators significantly improved the remission rate in 8 patients with R/R MM, but still faced challenges such as drug resistance and toxic side effects. Therefore, an in-depth study of the characteristics of the bone marrow microenvironment of MM and its drug resistance mechanism is of great significance for the development of new therapeutic strategies. This article presents a review of the latest research progress on the mechanisms of immunotherapy resistance in MM and related mechanisms in overcoming strategies.

2. Characteristics of the Immune Microenvironment in Multiple Myeloma

2.1 The Tumor-Supportive and Immunosuppressive Core Niche

The immune microenvironment of multiple myeloma is a highly complex and dynamically changing ecosystem. In the bone marrow, bone marrow stromal cells (BMSC), defined as a population of mesenchymal cells located between the outer surface of the bone marrow vessels and the bone surface, are key components of this environment [3]. BMSC has the functions of repairing damaged tissue, inhibiting macrophage polarization and promoting angiogenesis. Bone marrow stromal cells with defective differentiation of osteoclasts, vascular endothelial cells and osteoblasts create a cellular microenvironment suitable for the growth and survival of myeloma cells [4,5].

Extracellular vesicles (EVs) derived from bone marrow stromal cells (BMSCS), including exosomes and microvesicles, have been shown to be a key factor in the progression and drug resistance of multiple myeloma (MM) and confer resistance to MM cells [6]. Tumor-associated macrophages (Tams) are a rich source of pro-angiogenic cytokines and growth factors, which are also crucial in promoting tumor progression and treatment resistance, and can influence angiogenesis, metastasis behavior of tumor cells (TCS) and lead to multidrug resistance [7,8].

The importance of TAM-associated granumonocytes in the pathogenesis and clinical outcomes of multiple myeloma, such as the emergence of the CD47-SIRPα axis as a key immune checkpoint, has raised the prospect of effective new therapies [9]. Regulatory T (Treg) cells are a small but significant subpopulation of naturally inhibitory CD4+ T cells that can suppress anti-cancer immune responses and thereby promote tumor progression [10]. Studies have found that responders (partially or better) have a lower proportion of immunosuppressive regulatory T cells (Tregs) and T cells expressing co-suppressive receptors (CD38, PD-1, and PD-1/TIM-3) compared to non-responders [11]. Bone marrow-derived suppressor cells (MDSCS) are composed of a group of heterogeneous immunosuppressive myeloid cells that originated from common myeloid progenitor cells and whose amplification is also an important feature of the MM immune microenvironment, which inhibits T cell function by consuming arginine and nitric oxide synthase pathways [12]. A significant increase in MDSC was found in the peripheral blood and bone marrow (BM) of multiple myeloma (MM) patients, suggesting that MDSC plays a role in disease progression and drug resistance [13].

2.2 The Core Functional Hallmark Driving Disease Progression

The immune microenvironment of MM also shows distinct features of angiogenesis and hypoxia. Studies have found that CREB can recruit MMSET, leading to HIF-1α protein stabilization and increased dimethylation of histone H3 at lysine 36 on the DKK1 promoter, with circ_0111738 functioning as a competitive endogenous RNA (ceRNA), And by inactivating the HIF-1 pathway, it inhibits the oncogenic function of miR-1233-3p in MM [14,15]. Mascitetan blocking ET-1 rs targets not only MM cell proliferation/viability (downregulated by ERK1/2), but also MM cell angiogenic activity (downregulated by HIF-1α) [16].

Targeting HIF-1α, ERK1/2, Akt and NF-κB has the potential to be used for the treatment of drug-resistant MM [17]. The bone marrow microenvironment is a complex structure consisting of cells, extracellular matrix (ECM) proteins and cytokines, and ECM genes are repeatedly mutated. The expression level of ECM molecules may be a related prognostic marker or therapeutic target for MM [18]. This provides a physical barrier for tumor cells and limits the infiltration and function of immune cells.

3. Immunotherapy

3.1 Innovations in Imaging Diagnostic Techniques

In recent years, immunotherapy has emerged as a major breakthrough in the treatment of multiple myeloma, significantly improving the clinical prognosis of patients. In clinical practice, a variety of immunotherapy strategies have shown significant efficacy. Monoclonal antibody drugs such as daratumumab, which have shown good anti-tumor activity in clinical trials by targeting the CD38 antigen, have been included in first-line treatment regimens. Another class of monoclonal antibodies, such as elotuzumab, enhances the anti-tumor immune response by activating NK cells [19,20]. CAR-T cell therapy shows encouraging efficacy in patients with relapsed/refractory disease. In particular, CAR-T products targeting BCMA such as idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have received FDA approval [21]. Bispecific antibody technology has also made breakthroughs, such as teclistamab (BCMA×CD3) and talquetamab (GPRC5D×CD3), which effectively activate the immune system by simultaneously binding tumor cells and T cells [22,23].

In addition, novel immunomodulators and antibody-drug conjugates (ADCs) such as belantamab mafodotin have shown therapeutic potential in clinical trials [24]. These innovative therapies are reshaping the treatment landscape for multiple myeloma and bringing new hope for improving patient outcomes. Although immunotherapy for multiple myeloma (MM) has shown good efficacy in refractory relapsed patients, it still faces safety and drug resistance challenges, and synergies need to be achieved through technological innovation and combination therapy in the future.

4. Mechanism of Resistance

4.1 Immune Dysfunction and Suppression

The mechanism of resistance in immunotherapy is a complex process involving multiple factors, mainly T-cell dysfunction, bone marrow microenvironment-mediated immunosuppression, abnormal expression of immune checkpoints, and tumor antigen escape. Persistent antigen stimulation in the tumor microenvironment leads to CD8+T cell exhaustion, manifested as upregulation of inhibitory receptors such as programmed death receptor 1 (PD-1), T-cell immunoglobulin mucin molecule-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), along with reduced secretion of interferon -γ (IFN-γ) and decreased proliferation ability. The dysfunctional T cells are heterogeneous, and their different states may be associated with disease progression. It is crucial to precisely analyze the exhausted T cell subpopulations and their associations with specific disease contexts, which are mainly driven by long-term antigen exposure and the immunosuppressive microenvironment [25,26]. BMSC promotes resistance through multiple mechanisms, including secreting hypoxia-induced miR-140-5p and miR-28-3p, activating the MAPK pathway by targeting SPRED1 to produce CXCL12γ subtypes to enhance tumor cell adhesion, and recruiting Tregs and MDSCs to construct an immunosuppressive microenvironment [27,28,29].

4.2 Tumor Adaptive Escape and Heterogeneity

Abnormal expression of immune checkpoint molecules is another key mechanism. Studies have shown that high expression of the PD-L1/PD-1 pathway is associated with disease progression. DNp73 can serve as a biomarker for predicting the efficacy of PD-L1 inhibitors in MM, significantly inducing myeloma cell proliferation, drug resistance, and immune escape [30], Sawasdee et al [31]. Using bispecific αPD-L1×αCD3 T cell-conjugated arm T cells (BAT) to block PD-L1 signaling and activate T cells represents a promising strategy for treating MM, including cases resistant to bortezomib. In addition to PD-L1/PD-1, other checkpoint molecules such as CD47 and CD38 are also involved in immune escape. Overexpression of CD47 evades immune clearance through the “Don’t eat me” signal, while CD38 inhibits T cell functionby consuming NAD+ [32,33].

In addition, antigen escape is one of the important reasons for CAR-T cell therapy resistance. Tumor cells evade immune recognition by down-regulating the expression of target antigens such as BCMA or secreting soluble BCMA, while the subclonal diversity caused by tumor heterogeneity further increases the difficulty of treatment [34]. Multi-omics analyses show that different phenotypic clusters have unique clinical characteristics and resistance patterns [35]. These mechanisms together form a complex network of immunotherapy resistance in MM, suggesting the need to develop combination therapy strategies targeting multiple targets in the future. The complexity and diversity of immunotherapy resistance mechanisms also reflect the evolutionary outcome of the long-term “game” between tumor cells and the immune system, an area that faces both major challenges and breakthrough opportunities from a clinical translational perspective.

5. Overcoming Drug Resistance Strategies

5.1 Synergistic Targeting and Combination Blockade of Immune Checkpoints

Although significant progress has been made in immunotherapy for multiple myeloma, the problem of drug resistance mediated by mechanisms such as abnormal activation of immune checkpoints, formation of immunosuppressive microenvironments, and antigen escape in tumor cells remains a major clinical challenge. To overcome this challenge, researchers are actively exploring innovative combination therapy strategies.

A variety of combination therapy strategies not only offer new ideas for cracking the drug resistance mechanism, but also bring hope for improving the prognosis of patients. Lenalidomide can enhance the activity of T cells and natural killer (NK) cells while downregulating immunosuppressive cells. Immune checkpoints can negatively regulate the immune system and are closely related to immune escape. In terms of immune checkpoint regulation, CD47-SIRPα axis blocking shows great promise, and gene-edited BCMA-CAR-T cells secrete CD47-SIRPα blockers simultaneously, significantly enhancing the anti-tumor effect [36]. The CRISPR/Cas9 gene-editing system developed a BCMA-directed universal CAR-T (UCAR-T) BC404-UCAR-T that secretes CD47-SIRPα blockers and significantly inhibits myeloma cell growth in xenograft models [37]. TIM-3 as an immune checkpoint molecule, blocking it can significantly enhance the cytotoxic effect of NK cells on MM. However, bispecific antibody (BsAb) treatment targeting BCMA (such as teclistamab) or GPRC5D (such as talquetamab) activates T cells, while upregulating exhaustion markers (PD-1, TIM-3, etc.) leads to impaired T cell function and thus acquired resistance. A combination of TIM-3 inhibitors or other immunomodulatory strategies is needed to overcome resistance [38].

5.2 Remodeling the Immunosuppressive Microenvironment by Targeting TAMs MDSCs and Tregs

Therapy targeting immunosuppressive cells is also a promising direction. TAMs, MDSCs and Tregs are key factors mediating immunotherapy resistance, and targeting these cells has become an important direction to break through the resistance bottleneck. In the tumor microenvironment, M2-type TAMs promote immune escape by secreting immunosuppressive factors such as interleukin-10 (IL-10) and transforming growth factor -β(TGF-β), and the anti-CSF-1R antibody pexidartinib specifically blocks the CSF-1/CSF-1R signaling pathway Induce apoptosis of M2-type TAMs and promote their transformation to anti-tumor M1 type [39]. Targeting TAMs has become an important strategy for cancer immunotherapy by inhibiting their pro-tumor function or activating anti-tumor activity, and has synergistic potential with conventional therapies and other immunotherapies. Myeloma cells express chemokine receptor type (CCR2) at high levels. CCR2 inhibitors such as PF-04136309 can effectively block bone marrow migration of MDSCs mediated by CCL2/CCR2; Tregs highly express CD25(IL-2Rα), and CD25-targeted monoclonal antibodies (basiliximab) or ADCs selectively clear Tregs while preserving effector T cell function [40]. Treatment requires a balance between efficacy and safety, avoiding adverse reactions such as cytokine storm, and future development of bone marrow-targeted delivery systems and dynamic immune monitoring technologies to optimize Tregs-targeted therapy strategies, reshape the immune microenvironment, and enhance anti-tumor immune responses [41]. These strategies aim to reshape the immune microenvironment and enhance the anti-tumor immune response.

5.3 Epigenetic Regulation and Novel Immunotherapies through HDAC DNMT Inhibitors and Engineered Cells

Epigenetic modulators have unique advantages in overcoming drug resistance. Several Histone Deacetylase (HDAC) inhibitors, such as SAHA and panobinostat, have been approved by the FDA for the treatment of hematological malignancies and have shown good anti-cancer potential. A BIS Phase 1a study (NCT03618602) found that Bisthianostat, a novel HDAC inhibitor evolved from the natural HDACi largazole, was well tolerated. No grade 3 of 4 non-hematological adverse events (AEs) occurred in 8 patients with R/R MM, and the pharmacokinetic characteristics were good [42]. DNA Methyltransferase inhibitors (DNMTi) offer a new strategy to overcome immunotherapy resistance in multiple myeloma by reversing epigenetic silencing of immune-related genes. These drugs can target heterogeneous MM cell populations, including more drug-resistant immature subpopulations. Among them, Zebularine, as a representative DNMTi, promotes dendritic cell (DC) maturation and up-regulates the expression of major histocompatibility complex class I (MHC I) molecules, thereby enhancing tumor antigen presentation efficiency and activating anti-tumor immune responses. This epigenetic regulatory mechanism opens up new avenues for improving the efficacy of MM immunotherapy [43]. Bispecific antibodies (BsAb) show remarkable efficacy in R/R MM by simultaneously targeting BCMA antigens of CD3+T cells and MM cells. Key clinical trial MajesTEC-1 (NCT04557098) showed that BCMAxCD3 bispecific antibody teclistamab led to an ORR of 63% and still induced deep and durable remission in patients who failed multiple lines of treatment, providing strong evidence for efficacy data at a median follow-up of 13.8 months [44]. In addition, UCAR-T technology brings new hope for drug-resistant MM. Studies have successfully developed dasatinib-resistant UCAR-T cells (KM UCAR-T) by introducing the T316I mutation at the LCK locus using a cytosine base editor (CBE) and combining it with CRISPR-Cas9 to knockout the TRAC/B2M gene. The cell can resist host immune rejection while retaining its anti-tumor function and selectively expand through dasatinib regulation, showing good therapeutic potential [45]. Research on immunotherapy for MM has made breakthrough progress, offering a diverse range of solutions to overcome drug resistance through innovative strategies such as targeting immune checkpoints, reshaping the tumor microenvironment, epigenetic regulation, and developing novel CAR-T cells. These frontier explorations not only deepen the understanding of resistance mechanisms, but also bring new hope for clinical treatment. In the future, through the optimization of combination therapy strategies and individualized precision medicine, it is expected to significantly improve the survival prognosis of patients with relapsed/refractory disease.

6. Future Research Directions and Challenges

The application of single-cell technology will deepen the understanding of the immune microenvironment of MM. Single-cell RNA sequencing reveals heterogeneity and dynamics of different cell subpopulations in the microenvironment A prospective, multicenter, single-arm clinical trial (NCT04065789) combined longitudinal single-cell RNA sequencing (scRNA-seq) to investigate the molecular dynamics of the mechanism of MM resistance and found that peptideylprolyl isomerase A (PPIA) is a potential new target for drug-resistant MM The deletion of CRISPR-Cas9 in PPIA or the inhibition of PPIA by the small molecule inhibitor cyclosporine makes MM tumor cells sensitive to proteasome inhibitors [46].

Reliable biomarker development is the foundation of precision immunotherapy, and in addition to traditional PD-L1 expression levels, T-cell receptor library diversity, immune gene profiling, and microbiome analysis may predict treatment responses. T cells, as pillars of adaptive immunity, play a key role in infection immunity, autoimmunity, anti-tumor and immunomodulation, and it is estimated that one T cell receptor (TCR) can recognize up to 10 6different epit opes [47]. Based on the characteristics of the immune microenvironment, two immune subtypes with significant clinical differences, namely the immune dysfunction type and the immune active type, were identified in a study that analyzed the transcriptome of 859 MM patients. The immune classification system specifically pointed out that only patients with the immune active type might respond to existing immunotherapy. Dysfunctional patients need to develop combination therapy strategies targeting specific targets such as the CXCL pathway to overcome drug resistance [48].

Liquid biopsies (such as ctDNA) can dynamically monitor the clonal evolution of R/R MM. (NCT03433001) studies showed that TP53/KRAS mutations detected by ctDNA were more predictive of prognosis than bone marrow samples. The 2-year PFS of patients with ≥2 mutations was 0%, and the dynamic changes in mutations reflected clonal selection under treatment stress [49]. Ai-driven multi-omics integration is revolutionizing individualized treatment for multiple myeloma. Whole-body tumor quantitative analysis based on WB-DWI (ttDV/ttADC parameters) can precisely predict high-risk genetic abnormalities and prognostic risks. Reprogramming of the immune microenvironment is key to long-term disease control, and immunosuppression can be mitigated by targeting metabolic pathways or the physical microenvironment. The mechanisms of resistance in MM to novel therapies such as immunomodulatory drugs involve ABC transport-mediated drug efflux, SLC transporter dysfunction, and adenosine signaling pathway-mediated immune microenvironment remodeling [50]. These studies provide a solid theoretical basis and clinical translational pathways for achieving immune microenvironment reprogramming through multi-target interventions. Future research should focus on developing precise biomarker-guided combination therapy strategies to overcome drug resistance and achieve durable disease control.

7. Conclusion

In conclusion, the bone marrow microenvironment plays a central role in the formation of immunotherapy resistance in MM. From the protective effect of stromal cells to the accumulation of immunosuppressive cells, from the expression of checkpoint molecules to the loss of antigens, these mechanisms together form a complex network of drug resistance. Despite the huge challenges, the prospect of overcoming drug resistance is becoming clearer as understanding of the bone marrow microenvironment deepens and new therapeutic strategies are developed. Future research will need to focus more on the dynamic changes in the microenvironment and individual differences, and ultimately improve the long-term prognosis of MM patients through multidisciplinary collaboration and precision medicine strategies.

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