Macrophages in multiple myeloma

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Abstract

Macrophages are one of the important cells constituting in the tumor microenvironment and are also a key driving factor in tumor progression. Increasing evidence suggests that the infiltration of macrophages is associated with a low overall survival rate in patients with multiple myeloma. In fact, macrophages can affect many pathways that are crucial for the occurrence and development of multiple myeloma, including the homing of malignant cells to the bone marrow, the growth and survival of tumor cells, drug resistance, angiogenesis, and immunosuppression. Therefore, therapeutic strategies targeting macrophages in the bone marrow microenvironment have certain prospects for clinical application. This review will discuss the recent findings on the functions elicited by macrophages throughout different stages of MM and provide a comprehensive evaluation of potential macrophage-targeted therapies.

Keywords: Multiple myeloma (MM), Tumor-associated macrophages (TAMs), Tumor microenvironment (TME), Mesenchymal stem cells (MSC), Therapeutic strategies

Introduction

Multiple myeloma is a type of malignant tumor involving plasma cells. In this condition, monoclonal plasma cells proliferate excessively in bone marrow. (Opperman et al., 2021) Multiple myeloma recently represents 1% of all new cancer diagnoses and is still considered nearly universally fatal. (Kumar et al., 2017; Moreau et al., 2015; Opperman et al., 2021) It represents a frequent hematological disease. Despite the development of therapies that have been observed including proteasome inhibitors (bortezomib, carfilzomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) monoclonal antibodies(daratumumab, isatuximab, elotuzumab). The required drug resistance lead to relapsed/refractory disease (R/R) disease and it reduce progression-free survival (PFS) and overall survival (OS) at last (Minakata et al., 2023). The mechanisms of drug resistance include intrinsic factors, such as mutations in the proteasome and downregulation of the drug target, as well as extrinsic factors in the bone marrow microenvironment, including interactions with stromal cells, mesenchymal stem cells (MSCs), endothelial cells, and tumor-associated macrophages (TAMs) (Gozzetti et al., 2022; Leung-Hagesteijn et al., 2013).

Macrophages, especially tumor-associated macrophages (TAMs), are abundant in the microenvironment of multiple myeloma and play a crucial regulatory role in tumor progression. They promote angiogenesis, immune evasion, cell survival, and the drug resistance of myeloma cells (Asimakopoulos et al., 2013; Opperman et al., 2021).Due to their central role in shaping the tumor microenvironment, TAMs have become promising therapeutic targets. This review will discuss the most recently research findings from 2009 to 2025 on the functions elicited by macrophages throughout different stages of MM and provide a comprehensive evaluation of potential macrophage-targeted therapies.

1. TAMs in the Myeloma Microenvironment:

TAMs are immune cells that infiltrate the tumor microenvironment (TME) and contribute to the progression of multiple myeloma. Macrophages have gradually become an important regulatory factor for cancer-related inflammation, which is also the seventh hallmark of cancer. The role of

tumor-associated macrophages in the development of hematological malignancies including multiple myeloma has recently received increasing attention(Petty & Yang, 2019). Studies have shown that removing macrophages in the polycythemia vera model alleviate disease symptoms, such as spleen size and red blood cell levels(Nasillo et al., 2021). Which indicates that even in circulating blood cancers, macrophages help tumor cells survive, whether in the bone marrow or lymphoid organs (Asimakopoulos et al., 2013; Leopold Wager et al., 2015).

Mesenchymal stem cells (MSC), in combination with TAM and endothelial cells, can foster an immunosuppressive TME and form a "vascular niche", which can shield MM cells from antineoplastic drugs like bortezomib (Sun et al., 2022). It is key for designing personalized precision therapeutic strategies and ameliorating disease prognosis by understanding of myeloma bone marrow microenvironment cell interplay (Boulogeorgou et al., 2025; Cencini et al., 2023)

2. M1 vs. M2 Macrophages in Multiple myeloma

TAMs can be broadly categorized into M1 (classically activated, antitumor) and M2 (alternatively activated, protumor) macrophages. TAM are recognized by the CD68 marker but are further characterized by remarkable plasticity and were divided in the current classification into M1 (classically activated) and M2 (alternatively activated). The M1 subtype of tumor-associated macrophages (TAMs) can trigger Th-1 mediated immune response and exert anti-tumor effects. In contrast, the M2 subtypes of TAMs has low antigen-presenting ability and promotes, tumor progression by facilitating immunosuppression and angiogenesis. From biological perspective, human macrophages that are mature can be identified by specific surface markers, such as the CD11b, CD11c, CD14, CD16, CD68, CD115, and CD312. It is worth noting that the M1 subtypes of TAMs within the macrophage's helper type exhibits high levels of activation markers, including CD38, CD40, CD64, CD80, and CD86. While the M2 subtypes within TAMs has high levels of CD163, CD204, and CD206 (Guerriero, 2018; Sun et al., 2022).

The M1 subtype of tumor-associated macrophages (TAMs) can be activated by granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), and microbial products, thereby triggering an inflammatory response. These M1 TAMs produce cytokines such as IL-1, IL-6, IL-12, IL-23, tumor necrosis factor-alpha (TNF-α), and nitric oxide (NO), as well as chemokines such as CXCL9, CXCL10, and CXCL11. These factors can promote Th1-mediated anti-tumor immunity (Ushach & Zlotnik, 2016).

In contrast, cytokines M-CSF generated the M2 TAMs, (Ushach & Zlotnik, 2016). They secrete the IL-4, IL-10 IL-13 and transforming growth factor-beta (TGF-β) which are associated with anti-inflammatory molecules, as well as secrete and chemokine ligands such as CCL17, CCL18, and CCL22, and express high levels of surface markers including CD204 (class A scavenger receptor), CD206 (mannose receptor), and CD163 (hemoglobin scavenger receptor). These characteristics contribute to tumor development, functioning by promoting immune escape, and promoting angiogenesis, and driving tissue remodelling (Cencini et al., 2023).

While tumor-associated macrophages (TAMs) have traditionally been classified into two subtypes: M1 and M2, this binary framework—established over 20 years ago. It may oversimplify the multiple functional states of diverse of macrophages. A more precise classification can identify at least five macrophage subtypes: M1, M2a, M2b, M2c, and M2d. M2a macrophages, induced by IL-4 and/or IL-13, are primarily involved in anti-inflammatory responses and tissue repair. M2b macrophages, activated by IL-1β. It exhibits immunoregulatory functions. Also, M2b plays an immunoregulatory role. M2c macrophages, driven by IL-10, are associated with immunosuppression and tissue remodeling. Finally, M2d macrophages, which can be stimulated by IL-6, express angiogenic markers that further contribute to tumor blood vessel formation. (Mantovani et al., 2002; Ricketts et al., 2021; Xue et al., 2014).

3. Pro-tumorigenic Effects of M2 Macrophages

In multiple myeloma, M2 macrophages are often associated with tumor growth, angiogenesis, and resistance to therapy. Macrophages support myeloma cell growth, survival, and drug resistance through both contact-mediated and non-contact-mediated mechanisms. (Cencini et al., 2023; Yang et al., 2025; Zheng et al., 2009).Although they possess ability of pro-inflammatory and tumoricidal functions, in tumor microenvironment, macrophages play the roles that promote tumor progression Multiple myeloma can increased CD47, a signal of “don’t eat me” on the surface to avoid macrophage-mediated myeloma cell killing (Kim et al., 2012; Yue et al., 2022). Through macrophages and MSCs interacting, MSCs can change macrophages to support multiple myeloma survives and proliferation(Garcia-Sanchez et al., 2023; Xu et al., 2012). There is a huge treatment potential under these interactions (Gong et al., 2012; Oronsky et al., 2020).

4. TAMs and Drug Resistance

Studies have shown that TAMs can contribute to drug resistance in MM, particularly to proteasome inhibitors and immunomodulatory drugs. Multiple myeloma observed drug resistance including proteasome inhibitors (bortezomib, carfilzomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) monoclonal antibodies(daratumumab, isatuximab, elotuzumab) The required drug resistance lead to relapsed/refractory disease (R/R) disease and it reduce progression-free survival (PFS) and overall survival (OS) at last.(Minakata et al., 2023)The mechanisms of drug resistance are two parts intrinsic and extrinsic. Intrinsic mechanism including (1) The mutation of proteasome subunits, up-regulation of pumps of efflux. (2) Decreased target expression on MM plasma cells such as B-cell maturation antigen (BCMA). (3) Downregulation or mutation of cereblon or IKZF1. Extrinsic mechanism including (1) Endothelial cells as drug barrier through increased angiogenesis. (2) The stromal cells and mesenchymal stem cells inhibit the differentiation of osteoblast, resulting in increased expression of BCL2 and enhanced the activity of NF-κB activity. (3) Tumor-associated macrophages (TAMs) promote the proliferation, homing, angiogenesis and immune escape of multiple cancer types such as multiple myeloma(MM), prostate cancer (PC) (Gozzetti et al., 2022; Leung-Hagesteijn et al., 2013).

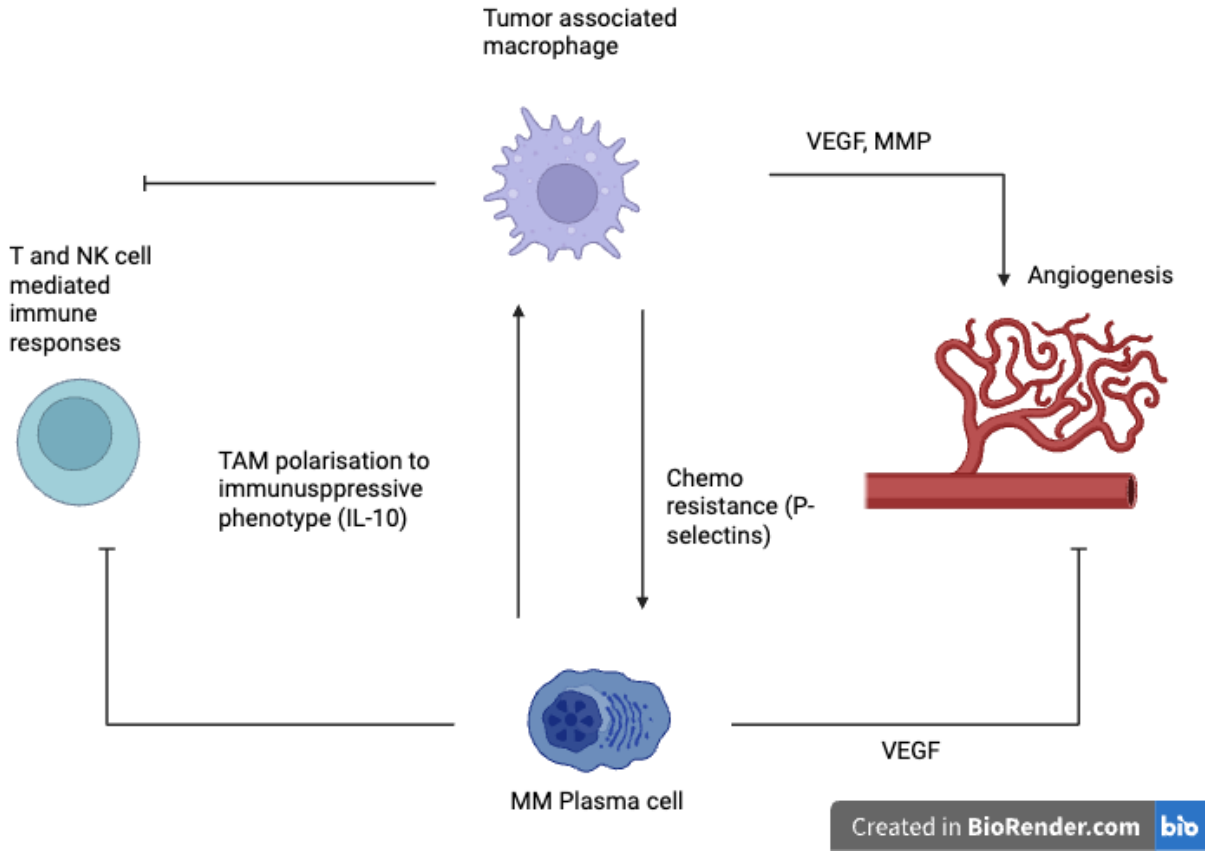
5. TAMs and Angiogenesis

TAMs can promote angiogenesis, the formation of new blood vessels, which is crucial for tumor growth and metastasis in MM(Opperman et al., 2021). TAMs mostly transform into M1 (classical activated type, with anti-tumor activity) and M2 (alternative activated type, with pro-tumor activity) subtypes. Numerous studies have shown that in lymphoproliferative tumors (including multiple myeloma), there is an association between TAMs, disease progression, drug resistance, and reduced survival rates(Cencini et al., 2023). In vitro co-cultures bone marrow derived macrophages with multiple myeloma cells, there is a tendency to transform into M2-type TAMs. Additionally, there is a hypothesis suggesting that the pro-tumor effect of M2-type TAMs is related to the reduced resistance to proteasome inhibitors and immunomodulatory drugs(Cencini et al., 2023). Multiple clinical studies have confirmed that CD68/CD163 double-positive M2- type TAM are associated with increased micro vessel density, enhance chemotherapy resistance, and reduced survival rates, and are not related to the stage of multiple myeloma(Opperman et al., 2021).

6. TAMs and Immunosuppression

TAMs can suppress the immune response against myeloma cells, contributing to immune evasion. Figure 1. Showed the multiple myeloma (MM) plasma cells interact with the tumor-associated macrophages (TAMs). MM plasma cells can cause TAMs to enter an immunosuppressive state(Opperman et al., 2021). Conversely, TAMs enhance the chemotherapy resistance of MM cells

through the P-selectin signaling pathway(Sun et al., 2022). In summary, TAMs and MM cells promote angiogenesis and inhibit anti-tumor immune responses by inhibiting the activity of T cells and natural killer (NK) cells. Abbreviations: NK = natural killer cell; VEGF = vascular endothelial growth factor; IL-10 = interleukin 10; MMP = matrix metalloproteinase.



7. Targeting TAMs

Tumor-associated macrophages (TAMs) are crucial immune cells in the microenvironment of multiple myeloma (MM). Depending on their subtypes, TAMs can either inhibit tumor growth or promote it: M1 subtype macrophages facilitate anti-tumor immune responses, however M2 subtype macrophages create an immunosuppressive environment that promotes tumor growth. Due to this dual effect, TAMs have become a promising target for immunotherapy(Sun et al., 2022). One main strategy is to reduce the number of tumor-associated macrophages (TAMs), especially the M2 subtype, to weaken their supportive role towards the tumor. For instance, administering liposomal clodronate directly can eliminate bone marrow macrophages, thereby interfering with the homing and growth of myeloma cells. Another approach is to reprogram TAMs to transform from the M2 subtype to the anti-tumor M1 subtype(Sun et al., 2022; Sun et al., 2021; Zhou et al., 2020). The activation of CD40 on macrophages is an example of this method, which can enhance the immune response against myeloma. The activation of CD40 on macrophages is an example of this method, which can enhance the immune response against myeloma(Wang et al., 2022).

Furthermore, therapeutic approaches aim to block immune-suppressive signaling pathways. For instance, immune checkpoints such as CD47/SIRPα can be inhibited, thereby triggering an immune attack against myeloma cells(Sun et al., 2022). Similarly, blocking the interaction of IL-10/IL-10R or using inhibitors like Ruxolitinib, a JAK1/2 inhibitor, can suppress the tumor-promoting function of macrophages and help reverse drug resistance. Additionally, in preclinical models, selective elimination of macrophage subpopulations such as CD163+ shows promising results(Sun et al., 2022).

The regulation of the development of myeloma is by tumor promoting locus 2(TPL2) kinase though both tumor cell autonomous and non-autonomous mechanisms. Among which the later involves myeloma-associated macrophages (Hope et al., 2014). TPL2 serves as a key function of cytokine secretion by these macrophages. In malignant plasma cells, TPL2 also responds to growth and inflammatory signals to activate the downstream mitogen-activated protein kinase pathway. Therefore, targeting and inhibiting TPL2 may disrupt the necessary signal interactions between macrophages and myeloma cells, which provide a potential therapeutic strategy for interfering with the tumor-supporting communication in the myeloma microenvironment (Asimakopoulos et al., 2013)

8. Clinical Significance

TAMs may be a promising target for future treatment strategies to combat the common drug resistance phenomenon in relapsed/refractory multiple myeloma cases, but there are still many issues to be studied, including clarifying the molecular mechanisms regulating the interactions between TAMs, multiple myeloma cells, and other components within the tumor microenvironment(Sun et al., 2022). Finally, these promising results must be verified in clinical studies to provide increasingly personalized treatment plans for each patient.
Summary: Tumor-associated macrophages (TAMs) play a significant role in the multiple myeloma (MM). M1-type macrophages can promote anti-tumor immune responses, while M2-type macrophages dominate in multiple myeloma, promoting cell proliferation, angiogenesis, immune evasion, and drug resistance(Guerriero, 2018; Sun et al., 2022).

CD68/CD163 double-positive M2-type tumor-associated macrophages (TAMs) are closely associated with a worse clinical prognosis, including higher micro vessel density, chemotherapy resistance, and lower survival rate (Ricketts et al., 2021; Xue et al., 2014). Targeting TAMs through reprogramming from M2 to M1, CD47 blockade, or inhibition of TPL2 kinase may become an important therapeutic strategy for relapsed/refractory multiple myeloma (MM)(Asimakopoulos et al., 2013; Hope et al., 2014; Sun et al., 2022).

Although therapies targeting macrophages hold promise, further research is needed to comprehensively explain the interaction between tumor-associated macrophages and multiple myeloma. To verify the effectiveness of these treatments in clinical trials. Ultimately, a deeper understanding of the biology of tumor-associated macrophages will help develop more effective and personalized treatments for multiple myeloma (Opperman et al., 2021)

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