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Review Article

Gut microbiota in immunomodulation and infection prevention among multiple myeloma patients after chemotherapy: current evidence and clinical prospects

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Abstract: Multiple Myeloma (MM) is the second most common hematological malignancy, with its pathogenesis involving complex cytogenetic variations, tumor clonal evolution, and dynamic interactions between tumor cells and bone marrow stromal microenvironment. Recent studies highlight the role of the intestinal microbiota, a key component of the tumor-associated microenvironment, in regulates MM occurrence, progression, and treatment response via the "gut-bone marrow axis". Under physiological conditions, it protects the local microenvironment by regulating host metabolism and maintaining immune homeostasis. However, intestinal dysbiosis causes metabolic disorders and immune surveillance defects, promoting tumor growth, drug resistance, and poor prognosis. Though traditional treatments such as chemotherapy and hematopoietic stem cell transplantation have been optimized, chemotherapy disrupts intestinal mucosal integrity and impairs immunity, significantly increasing post-chemotherapy infections. These infections can interrupt treatment, worsen conditions, and reduce quality of life, leaving MM still intractable. Notably, microbiota-targeted interventions (e.g., probiotics, fecal microbiota transplantation [FMT]) have shown potential to reduce infection risk by restoring microbiota balance and repairing intestinal barriers. These interventions may also exert potential anti-tumor effects through immune microenvironment regulation and alleviate chemo/radiotherapy-related adverse reactions (e.g., nausea, diarrhea), offering a new direction for relapsed/refractory MM. This article summarizes the molecular regulatory network of the intestinal microbiota in the pathogenesis of MM and the research progress of microbiota-based interventions, aiming to provide a foundation for developing novel microbiome-oriented precision treatment regimens and improving chemotherapy tolerance and patient prognosis.

Keywords: Multiple myeloma, gut microbiota, bone marrow microenvironment

Introduction

Overview of multiple myeloma and challenges in chemotherapy

Multiple myeloma (MM) is a hematological malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow [1]. Its pathogenesis is driven by interactions between genetic and environmental factors [2, 3], with risk factors including advanced age, family history, chronic antigen stimulation, occupational exposure, and obesity [4]. Epidemiologically, MM exhibits significant geographical, age, and gender disparities: globally, there are approximately 176,000 new cases and 117,000 related deaths annually, accounting for 1% of all new cancer diagnoses and 1.5% of cancer-related deaths [5]. Among hematological malignancies, its incidence is second only to non-Hodgkin lymphoma [6]. The peak incidence occurs between ages 65 and 75 year, with fewer than 2% of cases in individuals under 40 [7]. MM's incidence is consistently higher in males than in females across all age groups [8], and age-standardized incidence rates are higher in developed countries such as North America and Europe (6-8 cases per 100,000 population) compared to Asian and African countries (2-4 cases per 100,000 population) [5]. In China, the incidence of MM shows an obvious upward trend. In 2016, the

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incidence rate was 1.6 cases per 100,000 population, with a mortality rate of 1.0 case per 100,000. Notably, urban-rural disparities exist, likely due to aging population, improved diagnostics, and environmental changes [5]. Given MM's insidious onset, frequent late-stage diagnosis, and high recurrence rate, early diagnosis and standardized treatment are crucial for improving prognosis.

Contemporary treatment of MM has evolved into multimodal precision therapy, combining chemotherapy, targeted therapy, immunotherapy, hematopoietic stem cell transplantation (HSCT), and supportive care [9, 10]. As a traditional cornerstone, chemotherapy remains vital for newly diagnosed and relapsed patients, particularly suitable for controlling tumor burden in advanced stages. It inhibits the proliferation of malignant plasma cells by interfering with DNA replication or cell division of tumor cells through cytotoxic drugs. First-line regimens focus on proteasome inhibitors (e.g., bortezomib) and immunomodulatory drugs (e.g., lenalidomide) [11]. These targeted agents precisely inhibit tumor growth by acting on key pathways. Combination regimens containing proteasome inhibitors can significantly improve complete response rates and prolong progression-free survival (PFS) and overall survival (OS).

However, the cytotoxicity of chemotherapy can suppress normal bone marrow hematopoiesis, leading to neutropenia and immune impairment, which significantly increases infection risk (especially in elderly or frail patients). Additionally, the development of drug resistance leads to relapse or progression to refractory MM, limiting long-term treatment efficacy. Thus, optimizing chemotherapy regimens to maximize efficacy while minimizing toxicity (especially infection risk) remains a critical challenge.

Prevalence of post-chemotherapy infections and their impact on patient prognosis

Post-chemotherapy infections are common and severe complications in MM patients, closely associated with chemotherapy-induced immune dysfunction [12]. While inhibiting tumor cells, chemotherapeutic drugs significantly suppress bone marrow hematopoietic function, leading to reduced numbers and impaired function of neutrophils - core immune cells responsible for defending against pathogens such as bacteria and fungi [13]. Studies have shown that the incidence of neutropenia increases significantly in MM patients after chemotherapy [14, 15]. The lungs are the most common site of infection, accounting for 40%-50% of infected cases, followed by urinary tract and bloodstream infections [16, 17]. Pathogenically, Gram-negative bacteria (e.g., *Escherichia coli*, *Klebsiella pneumoniae*) and Gram-positive bacteria (e.g., *Staphylococcus aureus*, *Streptococcus*) are the primary causative agents [18]. In recent years, fungal infections (e.g., Candida, Aspergillus) have also risen, particularly in patients receiving long-term broad-spectrum antibiotics or corticosteroids [19]. Overall, the risk of infection after chemotherapy in MM patients is significantly elevated, with a five-fold increase, rising to seven-fold in the first year and remaining five-fold higher within five years of diagnosis [12]. Approximately 13.8% of patients develop severe infections within the first six months of treatment (mostly within the first 4 months), and 21.1% experience grade ≥3 infections within 18 months. Infection-related mortality in the first year ranges between 27 and 32% [20]. Among these, bacterial infections are the most common, predominantly involving Gram-negative bacilli and Gram-positive cocci. Furthermore, fungal infections are more prevalent in patients with severe immune impairment [21]. Factors influencing infection risk include age ≥80 years, intensive treatment regimens, advanced disease stage, and neutropenia. Infections mostly occur early in the treatment but pose a persistently elevated risk, remaining a major contributor to patient mortality [22].

Infections adversely affect patient prognosis in multiple ways: first, they can force interruption or dose reduction of chemotherapy regimens, delaying anti-tumor treatment and increasing the risk of disease progression [23]; second, severe infections such as sepsis and severe pneumonia can directly threaten life [24]; additionally, infections prolong hospital stays, increase medical costs, and recurrent infections can deteriorate patients' nutritional status and further impair immune function, forming a "vicious cycle of infection-immune deficiency-increased susceptibility to infection", which significantly reduces patients' quality of life and

long-term survival rates [25]. Therefore, effective prevention and control of post-chemotherapy infections are crucial for improving the prognosis of MM patients.

Potential role of gut microbiota in immune function and infection onset

The intestinal microbiota, a complex microbial community within the host's gut, maintains a dynamically balanced symbiotic relationship with the human body. Through multiple pathways such as secreting metabolites, regulating immune cell activity, and modulating cytokine secretion, the microbiota plays a critical role in the maturation of the intestinal mucosal immune system and the maintenance of intestinal barrier function, thereby enhancing the body's anti-infective capacity [26]. Disruption of this balance, known as dysbiosis, directly leads to immune dysfunction and significantly increases the risk of infection. Recent studies confirm that a stable intestinal microbiota is a crucial for host immune homeostasis, and its disorder can impair the immune system's ability to clear pathogens. This occurs by disrupting the Treg/Th17 balance, inhibiting natural killer (NK) cell activity, and other mechanisms, making dysbiosis a key inducer of increased infection susceptibility.

A core pathological feature of MM is immune dysregulation and elevated infection risk. Due to clonal proliferation of malignant plasma cells, MM patients exhibit abnormal immunoglobulin synthesis and T-cell exhaustion. Coupled with chemotherapy-induced suppression of the hematopoietic system, the incidence of infection in MM patients is significantly higher than in the general population. Notably, intestinal dysbiosis is clearly linked to these MM features: *Klebsiella pneumoniae* accelerates disease progression by enhancing glutamine synthesis to provide metabolic support for MM cells [27, 28]. Additionally, *Citrobacter freundii* is specifically enriched in MM patients, and FMT experiments have shown that this bacterium increases circulating ammonium ion levels, which incudces drug resistance in MM patients. Specifically, ammonium ions enter MM cells to stabilize NEK2 protein, promoting chromosomal instability, and enhancing cellular drug resistance [29]. These findings reveal that intestinal dysbiosis may exacerbate immune deficiencies and contribute to disease progression in MM.

In summary, the intestinal microbiota plays a pivotal role in regulating the pathological process of MM by linking host immune homeostasis and infection susceptibility. It not only affects MM cell proliferation and drug resistance through metabolic interactions but also amplifies patients' infection risk by reshaping the immune microenvironment. Even in emerging therapies such as CAR-T therapy, dynamic changes in the microbiota and its metabolites can serve as indicators for evaluating treatment responses [30].

MM patients are at high risk of post-chemotherapy infections, which severely impairs patient prognosis. Given the limited preventive and control measures available, it is crucial to conduct in-depth research into the underlying infection mechanisms to explore new prevention and treatment strategies. Although existing studies have mentioned the association between intestinal microbiota, immunity, and infections, research on the role of intestinal microbiota in MM remains insufficient. This review systematically explores the relationship between the intestinal microbiota and MM, revealing that intestinal dysbiosis exacerbates immune deficiencies, promotes disease progression, and increases infection risk through mechanisms such as disrupting immune homeostasis, providing metabolic support, and inducing drug tolerance. This not only provides a novel insight into the pathological process of MM but also offers comprehensive theoretical and practical references for developing new infection prevention and treatment strategies based on intestinal microbiota regulation, potentially improving the prognosis of MM patients.

Role of gut microbiota in multiple myeloma

The microbiota characteristics of MM patients

The human gut microbiota is predominantly composed of the phyla *Bacteroidetes* and *Firmicutes* [31]. However, MM patients exhibit distinctive gut dysbiosis that differs significantly from that of healthy individuals. In patients with MM, the intestinal microbiota exhibits significant abnormalities, including an increase in opportunistic pathogens (such as *Pseudomonas aeruginosa*, *Klebsiella*, and *Streptococcus*), a decrease in *Actinobacteria*, and elevated levels of *Faecalibacterium prausnitzii*, with higher

levels of *Faecalibacterium prausnitzii* being associated with poor prognosis in patients [27, 32]. Although studies report conflicting conclusions regarding microbial diversity, for instance, Zhang et al. [32] analyzed 40 MM patients and 17 healthy controls through high-throughput sequencing of fecal samples and found that MM patients had lower intestinal microbial diversity compared to healthy controls. MM patients showed a higher abundance of *Proteobacteria* and a lower abundance of *Actinobacteria* at the phylum level, as well as significantly increased proportions of *Bacteroides*, *Faecalibacterium prausnitzii*, and *Roseburia* at the genus level. In contrast, Jian et al. [33] studied 19 newly diagnosed MM patients and 18 healthy controls, revealing higher bacterial diversity in MM patients, significant changes in symbiotic microbiota composition, and an increase in opportunistic pathogens. These findings collectively confirm that the intestinal microbiota structure in MM patients differs significantly from that of healthy individuals.

Previous studies have indicated that intestinal microbiota imbalance is closely associated with the occurrence and development of various diseases, particularly in oncology, where microbiota can participate in disease progression by regulating immune function, metabolic pathways, and the tumor microenvironment. For example, the enrichment of opportunistic pathogens is often related to impaired host immune function, which may increase the risk of infection and exacerbate inflammation [34]. Furthermore, the abnormal proliferation of nitrogen-cycling bacteria may affect cellular signaling pathways through metabolites, thereby promoting tumor cell survival and drug resistance. These findings underscore the clinical significance of the intestinal microbiota in MM.

In summary, the intestinal microbiota of MM patients exhibits significant abnormalities, characterized by an increase in opportunistic pathogens and dysbiosis in the proportions of specific phyla or genera. Despite some conflicting conclusions about microbial diversity, the specific structural alterations in the microbiota of MM patients have been consistently confirmed. Combined with the regulatory effects of intestinal microbiota on immunity and metabolism highlighted in previous studies, it is speculated that these microbiota characteristics may contribute to MM progression by influencing immune function and metabolic pathways, providing important references for subsequent exploration of microbiota-targeted interventional strategies for MM.

Regulatory effects of gut microbiota on host immune system

MM can be divided into two major subtypes: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Its immune regulation involves multiple key processes, including immune surveillance evasion and the differentiation and functional regulation of immune cells. In the pathological state, MM can evade immune surveillance by inhibiting T cell activity and increasing the number of immunosuppressive cells [35, 36]. The interaction between dendritic cells (DCs), B cells, and T cells is central to immune regulation. After migrating to lymph nodes or Peyer's patches, DCs present specific antigens to T cells, prompting T cells to screen B cells carrying adaptive antigens. These B cells differentiate into plasma cells through proliferation, mutation, and class switching, leading to immunoglobulin secretion. Mutated plasma cells in a favorable microenvironment can drive the progression of MGUS to SMM, MM, or plasma cell leukemia (PLC), highlighting the critical role of the immune system in MM progression.

The intestinal microbiota can influence MM immune regulation by affecting the these immune processes. The excessive proliferation of specific bacteria caused by intestinal dysbiosis can activate DCs, thereby regulating their interaction with B cells and T cells, as well as the antigen presentation process. This, in turn, affects B cell differentiation into plasma cells and immunoglobulin secretion. Additionally, the intestinal microbiota also plays a role in immune checkpoint blockade therapy [37]. For example, *Bifidobacterium* and *Akkermansia muciniphila* can enhance DC activity and $CD8^+$ T cell responses in the tumor microenvironment [38], directly acting on T cell function regulation. These findings indicate that the intestinal microbiota can modulate critical processes in MM by regulating the functions of immune cells such as DCs, T cells, and B cells, poten-

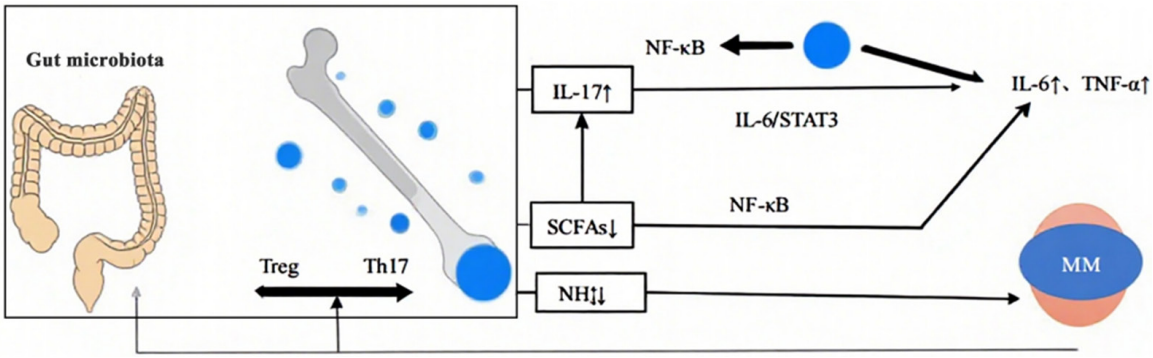

Figure 1. The impact of gut microbiota on multiple myeloma (MM) via the gut-bone marrow axis. Note: Gut microbiota dysbiosis leads to reduction in short-chain fatty acids (SCFAs) and accumulation of ammonium ions (NH_4^+), disrupting the balance between regulatory T cells (Treg) and Th17 cells (with enhanced Th17 differentiation). Activated Th17 cells secrete IL-17, which stimulates the NF-κB and IL-6/STAT3 inflammatory signaling pathways, resulting in the upregulation of proinflammatory cytokines (IL-6, TNF-α), ultimately driving the progression of MM.

tially influencing the immune status in MM patients.

Relationship between gut microbiota, immune tolerance, and immune responses

Immune tolerance and immune response in patients with MM involve multiple key processes that significantly affect chemotherapy efficacy and prognosis. In immune tolerance, the balanced differentiation of regulatory T cells (Tregs) prevents excessive immunity-mediated tissue damage, and their dysfunction may lead to immune homeostasis imbalance. In immune responses, the cytotoxicity of NK cells, the activation status of Th17 cells, and the secretion of related cytokines, such as IL-17, are directly involved in anti-tumor immunity and regulation of bone marrow microenvironment. Additionally, the activation of signaling pathways, such as mTOR, NF-κB, and STAT3, as well as the secretion of osteoclast differentiation-related factors, such as RANKL, are not only associated with myeloma cell proliferation and chemotherapy resistance but also closely linked to immune cell functions [39-42].

The intestinal microbiota plays a crucial role in regulating immune tolerance and immune response in MM patients through metabolites and the "gut-bone marrow axis" (**Figure 1**). Short-chain fatty acids (SCFAs), key metabolites produced by the microbiota, promote the differentiation of Tregs by inhibiting histone deacetylases (HDACs), enhancing immune tolerance [43]. SCFAs also enhance the cytotoxicity of NK cells by activating G protein-coupled receptor 43 (GPR43), with propionic acid and acetic acid being particularly effective in this process [44]. Universidad de Zaragoza, 50009 Zaragoza, Spain; Departamento de Farmacología, Fisiología y Medicina Legal y Forense, Facultad de Veterinaria, Universidad de Zaragoza, 50013 Zaragoza, Spain; Instituto de Investigación Sanitaria de Aragón (IIS Aragón. In contrast, nitrogen-cycling bacteria, such as *Klebsiella pneumoniae* and *Streptococcus,* are abnormally enriched in the intestines of MM patients. Their metabolites, incldiung ammonia (NH_3), activate the mTOR pathway, promoting the proliferation of myeloma cells and inducing chemotherapy resistance [40]. The research team from Central South University confirmed that NH_4^+ produced by *Citrobacter freundii* stabilized NEK2 protein, leading to bortezomib resistance, while supplementation with *Clostridium butyricum* partially reversed this process [29]. Furthermore, SCFAs can circulate to bone marrow through the bloodstream, inhibiting the NF-κB pathway to reduce RANKL secretion, thereby suppressing osteoclast differentiation [41, 42]. Conversely, microbiota dysbiosis can cause excessive activation of Th17 cells in the bone marrow; IL-17 secreted by Th17 cells promotes the proliferation of myeloma cells by activating the STAT3 pathway and inhibits Treg function. This process has been verified in IL-17 gene knockout mouse models of MM [45].

Furthermore, immune cells that interact with the gut microbiota are mainly present in the lamina propria, among with the most common

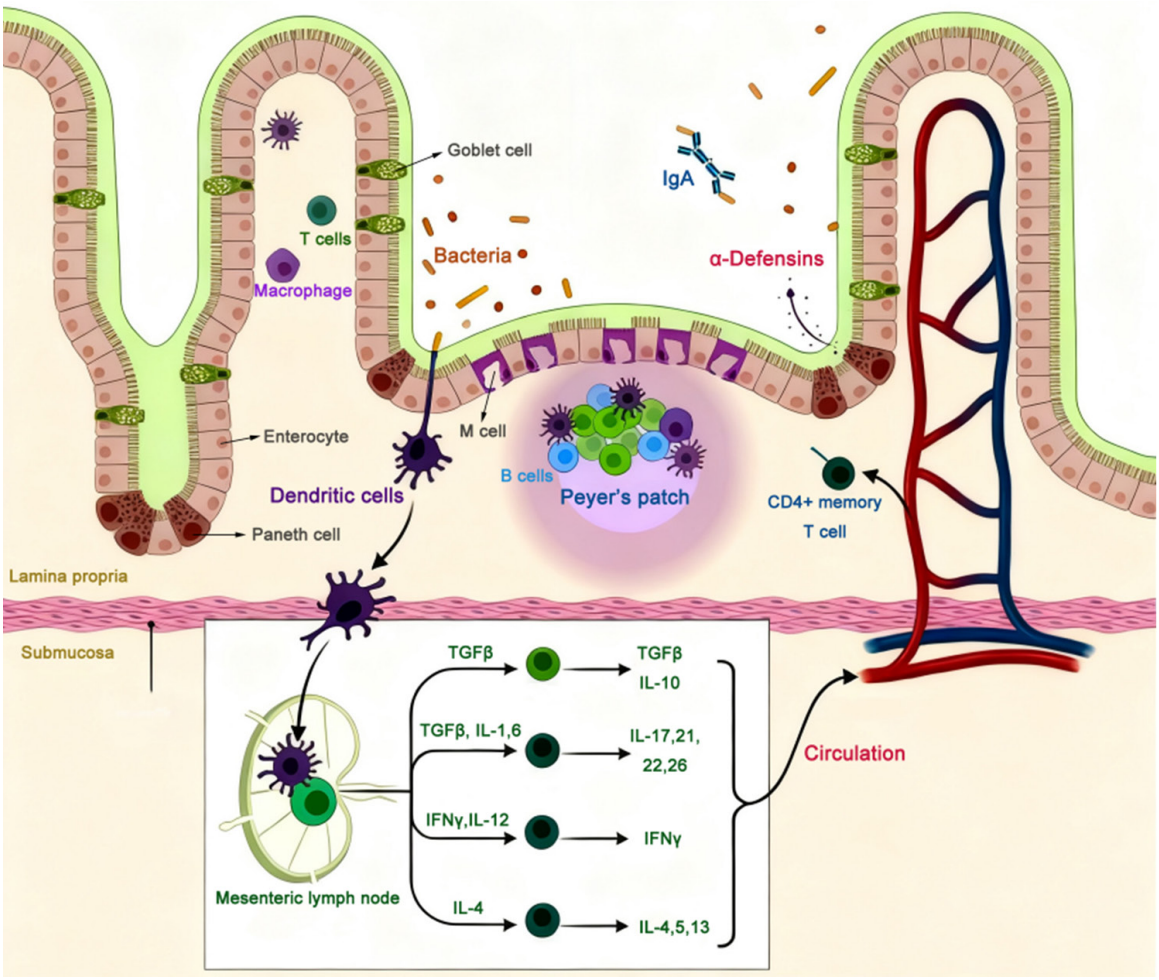

Figure 2. The intestinal immune system. Note: Bacteria colonizing the gut are recognized by dendritic cells (DCs), which capture and present bacterial antigens in mesenteric lymph nodes or Peyer's patches. In lymph nodes, DCs direct the differentiation of T cells into Treg, Th17, Th1, and Th2 cells, thereby shaping a pro- or anti-inflammatory cytokine milieu. From the perspective of multiple myeloma pathophysiology, the balance between Treg/Th17 cells is particularly critical. Th17 cells secrete pro-inflammatory cytokines such as IL-17, which are known to promote chronic inflammation and facilitate the progression of multiple myeloma.

being regulatory T cells, NK cells, and invariant T cells [46]. Additionally, DCs infiltrate deeply into the villi and maintain close contact with intestinal epithelial cells (IECs) (**Figure 2**). Through its metabolites (e.g., SCFAs, tryptophan metabolites) and signaling pathways, the gut microbiota precisely regulates the functions of these immune cells, including DCs, T cells, and B cells, thereby influencing the immunoregulatory process in MM. SCFAs, for instance, can activate DC maturation and upregulate the expression of surface costimulatory molecules CD80/CD86 to enhance the efficiency of MM-related antigen presentation, laying the foundation for subsequent T cell activation [47]. Additionally, they promote the proliferation of $CD4^+$ effector T cells, enhance their cytotoxicity, and induce moderate differentiation of regulatory T cells to balance the immunosuppressive state in the MM microenvironment. For B cells, the gut microbiota activates them via Toll-like receptor (TLR) signaling, driving their differentiation into plasma cells that produce anti-MM antibodies, while also regulating B cells to secrete cytokines like IL-10, thus reducing the accumulation of immunosuppressive factors that MM cells rely on for survival [48]. Ultimately, through multiple mechanisms, including antigen presentation, effector cell activation, and humoral immune regulation, the

gut microbiota helps address the immunoregulatory disorders in MM and inhibits tumor immune escape.

In summary, the intestinal microbiota directly affects the immune tolerance and immune response in MM patients by regulating immune cell differentiation, signaling pathway activation, and bone marrow microenvironment remodeling through metabolites. Its bidirectional regulation of Tregs, NK cells, Th17 cells, and other immune functions, as well as its regulatory role in the "gut-bone marrow axis", highlights the crucial role of the intestinal microbiota in maintaining immune homeostasis. This highlights the potential of microbiota-targeted interventions to improve post-chemotherapy immune dysfunction and optimize treatment efficacy.

Impact of gut microbiota dysbiosis on immune system function

The immune system function in MM patients involves multilevel regulation, including immune cell activity, metabolic balance, and homeostasis of the inflammatory microenvironment. These components collectively constitute the core mechanisms of anti-tumor immunity: $CD4^+$ T cells coordinate immune responses by secreting cytokines; NK cells directly kill tumor cells; and metabolites such as SCFAs maintain immune cell differentiation and function through epigenetic regulation [49-51]. Additionally, as a key "organ" regulating host immunity, the composition and metabolic activity of the intestinal microbiota directly affect the balance of these immune components.

Post-chemotherapy intestinal dysbiosis impairs immune function in MM patients through dual pathways. First, dysbiotic changes in microbiota composition - such as over-proliferation of *Klebsiella pneumoniae* and *Streptococcus*, and a reduction in *Bifidobacterium* - lead to impaired capacity of SCFAs synthesis [52]. Among SCFAs, butyrate and propionate are key metabolites that maintain immune cell homeostasis: butyrate deficiency inhibits dendritic cell maturation, resulting in impaired antigen-presenting function, while reduced propionate directly weakens NK cell cytotoxicity against myeloma cells by downregulating the expression of NKG2D receptors on NK cell surfaces [50]. Second, dysbiosis triggers abnormal metabolic pathways, such as hyperactive tryptophan metabolism producing excessive kynurenine, which induces an immunosuppressive microenvironment by activating the aryl hydrocarbon receptor (AHR), further reducing the proportion of cytotoxic T cells [53, 54]. Clinical data show that post-chemotherapy patients exhibit over 30% reduction in intestinal microbial diversity and an increased ratio of Proteobacteria to Firmicutes, which is significantly associated with reduced peripheral blood $CD4^+$ T cells and decreased NK cell activity [49, 55] (**Figure 3**).

Collectively, intestinal dysbiosis systematically impairs the anti-tumor immune capacity of MM patients by disrupting immune cell activity, disturbing metabolic balance, and exacerbating the inflammatory microenvironment. Such dysbiosis not only directly reduces the function of immune effector cells (e.g., NK cells and T cells) but also forms a vicious cycle through abnormal regulation of metabolites like SCFAs and kynurenine, aggravating post-chemotherapy immunosuppression. Given the bidirectional regulatory relationship between the microbiota and immunity, targeted regulation of intestinal microbiota - such as probiotic supplementation or fecal microbiota transplantation - may represent a novel strategy to improve immune function, reduce infection risk, and overcome drug resistance in MM patients, with its clinical value warranting further verification.

Effects of chemotherapy on intestinal microbiota

Mechanisms of chemotherapy-induced damage to intestinal microbiota

Chemotherapeutic drugs damage intestinal microbiota through multi-dimensional effects, with core mechanisms including direct killing of microorganisms and disruption of intestinal microenvironment homeostasis. Chemotherapeutic drugs can directly act on intestinal microbiota. For example, fluoropyrimidine-based drugs such as capecitabine inhibit DNA synthesis, exerting cytotoxicity not only on tumor cells but also on rapidly proliferating intestinal commensal bacteria, leading to a significant reduction in their abundance [56]. A study on patients with colorectal cancer showed that after capecitabine treatment, the number of *Lactobacilli* in the intestinal tract decreased,

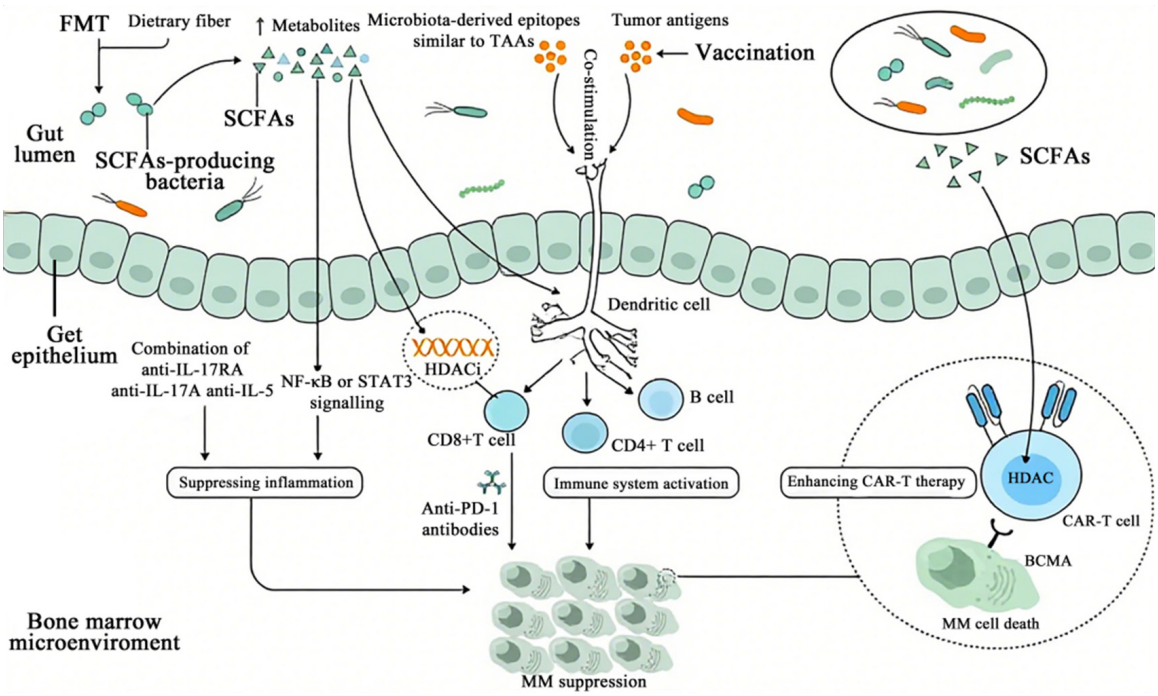

Figure 3. Applications of gut microbiota in multiple myeloma. Note: Gut microbiota dysbiosis leads to a reduction in short-chain fatty acid (SCFA)-producing bacteria, which in turn causes decreased SCFA levels. This metabolic disturbance triggers excessive activation of inflammatory mediator pathways such as IL-6 and NF-κB, thereby promoting the progression of multiple myeloma. Selective enrichment of nitrogen-cycling microbiota in the intestinal lumen enhances glutamine synthesis, thereby accelerating myeloma progression.

while the proportion of drug-resistant *Enterococci* increased [57].

Additionally, chemotherapeutic drugs indirectly exacerbate dysbiosis by damaging the intestinal barrier. Platinum-based drugs, such as cisplatin and oxaliplatin, induce apoptosis of IECs, increase intestinal permeability, and cause translocation of intestinal microbiota from the intestinal lumen to the mucosal layer and bloodstream, triggering local inflammatory responses [58]. The inflammatory microenvironment selectively promotes the proliferation of opportunistic pathogens, such as *Enterobacteriaceae,* by enriching nitrates and creating hypoxic conditions. This process is accompanied by decreased microbial diversity and depletion of beneficial flora. Meanwhile, reactive oxygen species (ROS) and reactive nitrogen species (RNS) released by immune cells further remodel microbial metabolism and composition, inducing intestinal dysbiosis [59]. Yuan et al. [60] demonstrated that an increase in *Bacteroidetes* and a decrease in *Prevotella* in the intestinal community may be associated with oxaliplatin-induced intestinal injury.

The mechanisms by which chemotherapeutic agents damage the intestinal microbiota in patients with MM exhibit multi-dimensional characteristics. In terms of direct effects, fluoropyrimidine-based drugs, while killing tumor cells by inhibiting DNA synthesis, directly damage rapidly proliferating intestinal commensal bacteria, leading to a decrease in the number of beneficial bacteria such as *Lactobacillus* and the enrichment of drug-resistant *Enterococcus*. Indirect mechanisms are mediated through the disruption of the intestinal barrier: platinum-based drugs, such as cisplatin and oxaliplatin, induce apoptosis of IECs, increase intestinal permeability, and promote the migration of microbiota to the mucosal layer and bloodstream, triggering local inflammatory responses. The inflammatory microenvironment selectively promotes the proliferation of opportunistic pathogens, such as *Enterobacteriaceae,* by enriching nitrates and creating hypoxic conditions. This process is accompanied by reduced microbial diversity and depletion of beneficial microbiota, while ROS and RNS released by immune cells further remodel the microbiota composition.

In summary, through direct toxic effects and indirect barrier disruption, chemotherapeutic agents systematically exacerbate microbiota dysbiosis, thereby contributing to impaired immune function and increasing the risk of infectious complications.

Effects of chemotherapy on intestinal dysbiosis

Chemotherapy induces significant intestinal dysbiosis in MM patients through dual pathways: directly disrupting microbial structure and indirectly interfering with the intestinal microenvironment. For instance, cyclophosphamide, a commonly used clinical agent exerts anti-tumor effects but also damages the intestinal epithelial barrier, leading to the collapse of intestinal microbial homeostasis [61]. Studies by State et al. [62] further confirmed that caloric restriction attenuates the response of mice to cyclophosphamide and stabilizes their intestinal microbiota, indirectly verifying the drug's destructive effects on the intestinal barrier and microbiota.

This chemotherapy-induced dysbiosis is not only closely associated with complications of MM treatment but also profoundly impacts therapeutic efficacy through microbiota-drug interactions. A typical example is the proteasome inhibitor bortezomib, whose efficacy is tightly linked to specific microbial compositions. Zhu et al. [29] confirmed that nitrogen-cycling bacteria, such as *Citrobacter freundii*, enriched in the intestines of patients with relapsed MM, produce ammonium salts. These ammonium salts enter tumor cells, exacerbate chromosomal instability, and directly enhance bortezomib resistance. More broadly, intestinal dysbiosis and the presence of specific microbiota can indirectly affect therapeutic response to proteasome inhibitors (including bortezomib) by regulating immune system function [63].

Current research suggests that while the microbiota is not considered to directly induce initial mutations in normal cells to form abnormal clones, it can indirectly participate in key links of tumor clonal evolution by regulating the tumor microenvironment. In the early stage of abnormal clone formation following normal cell mutation, gut microbial metabolites (e.g., reduced SCFAs or increased lipopolysaccharides [LPS]) can alter the intensity of immune surveillance in the local microenvironment. A deficiency in SCFAs may weaken the ability of effector T cells to eliminate abnormal clones, enabling these clones to bypass immune barriers and achieve initial proliferation [64]. As mutations persist, subclones form and intratumoral heterogeneity is established. The microbiota can provide survival advantages for different subclones by regulating nutrient supply (e.g., increased abundance of glutamine-producing microbiota) and activating signaling pathway (e.g., NF-κB/IL-6). For instance, inflammation-tolerant subclones are more likely to expand in the microbiota-induced chronic inflammatory microenvironment, further exacerbating heterogeneity [65]. During therapeutic intervention, the high expression of inflammatory factors caused by microbiota dysbiosis can activate anti-apoptotic pathways (e.g., PI3K/Akt) in drug-resistant clones, helping them resist therapeutic damage and survive. These microenvironment-regulating effects ultimately enhance the proliferative advantage of drug-resistant clones and indirectly promote the exacerbation of intratumoral heterogeneity and the continuous development of drug resistance (**Figure 4**).

In summary, chemotherapeutic agents systematically exacerbate intestinal dysbiosis in MM patients by disrupting the intestinal barrier, altering microbial metabolic activity, and inducing immune microenvironment disorders. This dysbiosis not only increases the risk of infection but also affects chemotherapy sensitivity through the metabolic-immune axis, forming a "dysbiosis-decreased efficacy-enhanced drug resistance" vicious cycle.

Characteristics of intestinal microbiota changes after chemotherapy in existing studies

Existing studies have shown that chemotherapy can induce significant intestinal microbiota dysbiosis, and this dysbiosis in MM patients exhibit both common characteristics of chemotherapy-induced dysbiosis and specific manifestations. In terms of common features, across different chemotherapy regimens and tumor types, microbiota dysbiosis is characterized by an imbalance at the phylum level and remodeling of microbiota structure. For example, after cisplatin chemotherapy, the abun-

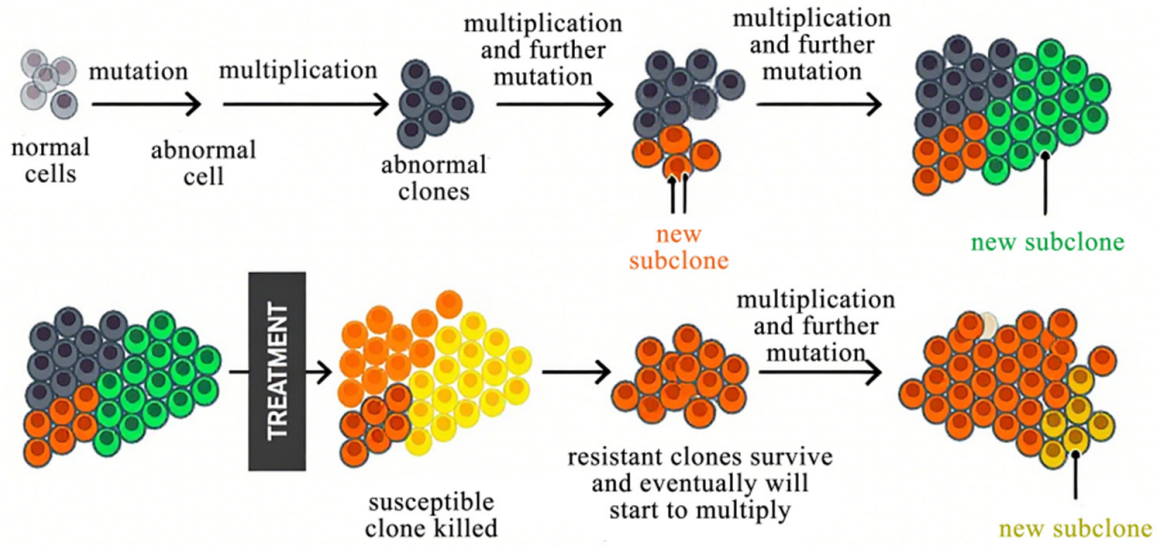

Figure 4. The dynamic process of tumor clonal evolution and the emergence of drug resistance. Note: Normal cells acquire mutations that give rise to abnormal clonal populations. With the accumulation of additional mutations, these clones generate diverse subclones, establishing intratumoral heterogeneity. During therapeutic intervention, drug-sensitive clones are eliminated, whereas resistant clones survive, further proliferate, and acquire new mutations to form novel subclones. These processes drive the enhancement of tumor heterogeneity and the progression of drug resistance.

dance of *Bacteroidetes* and *Firmicutes* significantly decreases, while that of *Proteobacteria* and *Deferribacteres* significantly increases [66]. In patients with non-Hodgkin lymphoma, the abundance of *Firmicutes* and *Actinobacteria* in the intestinal microbiota significantly decreases after chemotherapy [67]. Similarly, 5-fluorouracil-based combination regimen causes a reduction in beneficial bacteria such as *Lactobacillus* and an increase in pathogenic bacteria such as *Clostridium difficile* and *Enterococcus* [68]. Meanwhile, chemotherapy often reduces the diversity and abundance of the gut microbiota, and this effect is particularly prolonged in pediatric and adolescent patients, manifesting as significantly reduced microbial species abundance even one year after the completion of treatment [69].

For MM patients, the core characteristics of intestinal microbiota dysbiosis after chemotherapy are more distinct. The typical manifestations include a significant reduction in *Firmicutes* and abnormal proliferation of *Proteobacteria* [32]. In addition, melphalan, a commonly used drug in MM treatment, induces microbiota dysbiosis, particularly through excessive proliferation of pathogens, which is closely associated with impaired intestinal barrier function and bacterial translocation. Moreover, melphalan may further alter microbiota composition by affecting bile acid absorption [70]. These changes collectively reveal that intestinal microbiota dysbiosis in MM patients after chemotherapy not only follows the general patterns of chemotherapy's impact on microbiota but also exhibits unique structural and functional abnormalities due to treatment drugs and disease characteristics.

Relationship between intestinal microbiota and post-chemotherapy infections

Evidence from current studies: association between intestinal microbiota and infection onset

Research has firmly established that intestinal microbiota is closely associated with infection onset in patients with MM. This association is mediated through the dysregulation of intestinal flora homeostasis and a series of consequent pathophysiological changes, supported by multiple clinical studies. Under normal conditions, intestinal microecological "homeostasis" is maintained by competitive inhibition and mutualism among commensal microorganisms, which together form a natural anti-infective barrier that prevents colonization of pathogenic bacteria [71]. However, in MM patients,

the intestinal microbiota composition often undergoes significant alterations. These abnormalities are not only disease-related but also closely associated with chemotherapeutic and antibiotic use - among which antibiotics are key drivers of intestinal dysbiosis. Ramirez et al. [72] clearly pointed out that antibiotic use disrupts the microbiota in multiple dimensions, reducing microbial diversity, altering metabolic activity, and increasing the prevalence of drug-resistant bacteria, thereby predisposing patients to subsequent infections.

The application of chemotherapy further exacerbates this imbalance. While effectively killing tumor cells, chemotherapeutic drugs simultaneously cause a sharp reduction in commensal flora and excessive proliferation of opportunistic pathogens, increasing the risk of infection through dual mechanisms. On one hand, the deficiency of short-chain SCFAs directly impairs the integrity of the intestinal barrier. Clinical studies have confirmed that fecal butyrate concentration in MM patients decreases significantly after chemotherapy [73], and the serum butyrate level is inversely correlated with disease progression. This directly downregulates the expression of tight junction proteins (e.g., occludin) in intestinal epithelium, greatly increasing the risk of bacterial translocation. On the other hand, the disruption of flora structure creates ecological niches for antibiotic-resistant bacteria (ARB) colonization - a process that can be induced by antibiotics, chemotherapeutic drugs, or immunosuppressants [8]. Jasiński et al. [74] investigated 138 MM patients undergoing 141 autologous stem cell transplantations and found that 15% exhibited ARB predominantly with extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacilli. More importantly, the infection rate (especially bloodstream infections) in patients with intestinal ARB colonization was significantly higher than that in non-colonized individuals, directly confirming the association between ARB colonization and increased infection risk.

In summary, intestinal dysbiosis in MM patients, induced by the combined effects of the disease itself, chemotherapy, and antibiotic use, significantly increases infection susceptibility by impairing intestinal barrier function and promoting ARB colonization. These findings underscore the central role of the intestinal microbiota in MM-related infections and provide a theoretical basis for developing clinical strategies to reduce infection risk through microbiota-targeted regulation.

Role of specific microbiota in infection onset

In the context of MM chemotherapy, specific intestinal microbiota play a critical role in the occurrence of infections. Studies have pointed out that intestinal *Klebsiella pneumoniae* can cause pneumonia in MM patients by synthesizing glutamine, revealing the association of specific pathogenic bacteria with pulmonary infections [18]. This indicates that specific microbiota may not only contribute to infections through direct or indirect mechanisms but also increase infection risk by altering host immune function. In the intestinal microbiota of relapsed MM patients, *Citrobacter freundii (C. freundii)* is significantly enriched [29]. As a nitrogen-cycling bacterium, *C. freundii* produces large amounts of NH_4^+ by expressing deaminase, leading to elevated systemic NH_4^+ levels. High concentrations of NH_4^+ accelerate MM progression and induce resistance to bortezomib (BTZ). Both *in vitro* and *in vivo* experiments demonstrated that ammonium chloride (NH_4Cl) concentrations ≥0.5 mM promote the proliferation of bone marrow-derived mesenchymal stem cells and may stimulate tumor-supporting cells in MM by activating the Akt/mTOR/S6K signaling pathway, thereby enhancing cell proliferation and survival [75]. MM mice supplemented with NH_4Cl exhibit a higher tumor burden. Collectively, these findings indicate that harmful microbiota, represented by *C. freundii,* indirectly increase the infection risk by altering metabolic profiles, accelerating disease progression, and reducing drug efficacy.

In addition, chemotherapy reduces the abundance of beneficial bacteria such as *Bifidobacterium* and *Faecalibacterium prausnitzii* while increasing the proportion of harmful bacteria such as *Enterobacteriaceae*. This dysbiosis impairs intestinal barrier function, facilitating the translocation of microorganisms and their products into the circulatory system and triggering systemic infections. Overall, specific microbiota play a key role in infection occurrence during MM chemotherapy through multiple mechanisms, including directly causing infections, affecting disease progression and

drug efficacy, and damaging the intestinal barrier.

Potential of intestinal microbiota in preventing post-chemotherapy infections

Microbiota as a target for infection prevention

The sharply increased infection risk in MM patients after chemotherapy is closely associated with disrupted intestinal microbiota homeostasis. Chemotherapeutic drugs and antibiotics damage the integrity of the intestinal mucosal barrier, leading to imbalances in dominant flora such as *Bacteroidetes* and *Firmicutes*, a reduction in total microbial count, and increased susceptibility to pathogenic bacterial translocation and subsequent infections. Meanwhile, decreased synthesis of key microbiota metabolites (e.g., SCFAs) disrupts the Th17/Treg immune balance, further impairing the body's defense mechanisms. This dysregulation of the microbiota-immune axis represents a major factor contributing to post-chemotherapy infections. Owing to its controllable nature, the intestinal microbiota has emerged as a target for infection prevention. A clinical study by Cruz et al. [74] confirmed that regulating the intestinal microbiota can serve as a potential intervention for pulmonary infections, providing important insights applicable to MM.

Interventions targeting microbiota have opened new avenues for infection prevention. Probiotic-derived metabolites (e.g., butyrate) can enhance intestinal epithelial barrier function and regulate immune activity, directly compensating for chemotherapy-induced metabolite deficiencies. Strategies including probiotic supplementation, FMT, and dietary fiber intervention have shown preliminary efficacy in reducing infection rates and restoring immune function. Their core mechanisms involve reshaping microbiota homeostasis, repairing intestinal barrier integrity, and restoring immune balance.

In summary, the intestinal microbiota, by regulating intestinal barrier integrity, immune balance, and metabolic homeostasis, has become a core target for preventing infections in MM patients after chemotherapy. In-depth exploration of related intervention strategies is expected to significantly improve the effectiveness of infection prevention and control in these patients.

Role of probiotics and intestinal microbiota modulation in infection prevention

Probiotics are beneficial microorganisms that contribute to maintaining intestinal health and enhancing immune function. Probiotic interventions have demonstrated significant potential in reducing infections risk in MM patients by reestablishing intestinal microecological balance. Recent studies suggest that probiotics may influence MM progression and treatment response by regulating intestinal microbiota, enhancing immune responses, and influencing drug metabolism [76]. For example, probiotics may reduce inflammatory responses and enhance the activity of immune cells (e.g., T cells and NK cells) through microbiota-mediated immune regulation, thereby strengthening antitumor immune responses [77]. MM patients, due to compromised immune function, are prone to opportunistic pathogens colonization [78], and probiotics may mitigate infection risk by suppressing pathogenic overgrowth and stabilizing the gut microbiota. Specifically, *Lactobacillus* and *Saccharomyces boulardii* have been shown to modulate intestinal microbial composition and improve immune function [76].

Although current research on the clinical application of probiotics in MM remains at an early stage, accumulating evidence indicates that probiotics may enhance therapeutic efficacy and reduce side effects by regulating intestinal microbiota and immune function. For example, probiotics can potentially alleviate chemotherapy- and immunosuppressant-induced toxicity, and enhance treatment outcomes by modulating intestinal microbiota [77]. Future research should focus on the specific mechanisms through which probiotics exert protective effects in MM, determining optimal probiotic strains, dosages, and administration methods, and identifying differential responses across different patient populations.

Association between intestinal microbiota restoration and immune function

Restoration of the gut microbiota represents a pivotal strategy for improving immune function in patients with MM, providing critical mecha-

nistic support for correcting disease- and treatment-induced immunodeficiency through multi-dimensional modulation of immune homeostasis. At the level of fundamental immune architecture, appropriate microbiota reconstitution activates pattern recognition receptors (PRRs) on intestinal epithelial cells and immune cells, thereby promoting the maturation of gut-associated lymphoid tissue (GALT). This process is crucial for rebuilding the chemotherapy-compromised intestinal immune system in MM patients, fostering populations of IgA-producing plasma cells, $CD4^+$/$CD8^+$ T cells, and Tregs, thereby re-establishing the structural foundation for immune responses [79]. Regarding immune response regulation, beneficial microbes and their metabolites bind to PRRs via microbe-associated molecular patterns (MAMPs), triggering cytokine production and immune cell differentiation. Specifically, this interaction promotes the expansion of anti-inflammatory Tregs while inhibiting the excessive activation of pro-inflammatory Th17 cells, thereby precisely balancing the dysregulated immune tolerance and defense mechanisms commonly seen in MM patients [80]. At the level of barrier defense and systemic immunity, restored healthy microbiota enhances intestinal barrier integrity. By maintaining mucosal homeostasis and activating immune surveillance, it effectively prevents pathogen colonization and systemic dissemination, reducing the high infection risk prevalent among MM patients [81]. Concurrently, gut microbiota influences the function of distal immune organs via microbial metabolites and signaling molecules, indirectly impacting the efficacy of chemotherapy and immunotherapy [82].

Therefore, clinically feasible gut-directed interventions, such as probiotic supplementation and prebiotic modulation, can recalibrate immune homeostasis by re-establishing microbial balance, directly ameliorating immune dysfunction in MM patients caused by the disease itself or chemotherapy [79].

In summary, gut microbiota restoration systematically promotes immune repair in MM patients by reconstructing the foundation of immune development, rebalancing immune response, and reinforcing barrier defenses. This provides a key therapeutic target for enhancing treatment efficacy and bolstering anti-infective capacity.

Clinical prospects and challenges of microbiota interventions

Microbial intervention shows significant potential in the treatment of MM, but its clinical translation faces multiple challenges. Although existing studies lack large-scale clinical validation, accumulating evidence indicates that the intestinal microbiota indirectly influences MM occurrence, progression, and therapeutic response by regulating T cell function and activating signaling pathways such as TLR/NF-κB [49, 83], providing a theoretical basis for intervention.

The clinical prospects of microbiota modulation are reflected in two aspects. First, microbiota characteristics may serve as novel biomarkers for MM risk stratification; second, targeted regulation is likely to improve immunotherapy sensitivity, reverse drug resistance, and enhance immune surveillance while reducing infection risk by restoring microbiota homeostasis (e.g., increasing SCFA-producing bacteria).

However, clinical translation faces three major challenges. Mechanistically, microbe-host interaction networks and specific molecular pathways remain unelucidated; Technically, microbiota detection lacks standardized protocols, with limited predictive value of biomarkers, which are also susceptible to interference from factors such as antibiotics and diet; At the intervention level, the long-term safety, optimal timing, and strain-specific effects of probiotics and FMT all lack evidence-based support.

Future efforts should focus on integrating multi-omics approaches to deepen mechanistic understanding, establish a standardized microbiota assessment system, and conducting large-scale randomized controlled trials to validate individualized intervention strategies. Ultimately, incorporating microbiota regulation into comprehensive supportive care systems will drive innovation in MM treatment paradigms.

Conclusion

The intestinal microbiota plays a crucial role in immune reconstitution and infection prevention in patients with MM after chemotherapy, primarily through its metabolites and interactions with the host immune system. Maintaining

or restoring a healthy intestinal microecology can alleviate chemotherapy-induced immunosuppression, reduce the risk of infection, and potentially enhance the efficacy of chemotherapy. Future clinical studies should focus on developing targeted microecological intervention strategies, such as probiotic supplementation and FMT, and integrating them as adjuvant therapies to conventional chemotherapy. This represents a promising new direction for advancing the comprehensive treatment of multiple myeloma.

Disclosure of conflict of interest

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

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