The Insider: Impact of the Gut Microbiota on Cancer Immunity and Response to Therapies in Multiple Myeloma

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The human microbiota is a unique set of microorganisms colonizing the human body and evolving within it from the very beginning. Acting as an insider, the microbiota provides nutrients, and mutualistically interacts with the host's immune system, thus contributing to the generation of barriers against pathogens. While a strong link has been documented between intestinal dysbiosis (i.e., disruption to the microbiota homeostasis) and diseases, the mechanisms by which commensal bacteria impact a wide spectrum of mucosal and extramucosal human disorders have only partially been deciphered. This is particularly puzzling for multiple myeloma (MM), a treatable but incurable neoplasia of plasma cells that accumulate in the bone marrow and lead to end-organ damage. Here we revise the most recent literature on data from both the bench and the bedside that show how the gut microbiota modulates cancer immunity, potentially impacting the progression of asymptomatic monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) to full blown MM. We also explore the effect of the gut microbiome on hematopoietic stem cell transplantation, chemotherapy, immunomodulating therapy and cancer immunotherapy in MM patients. Additionally, we identify the most cogent area of investigation that have the highest chance to delineate microbiota-related and pathobiology-based parameters for patient risk stratification. Lastly, we highlight microbiota-modulating strategies (i.e., diet, prebiotics, probiotics, fecal microbiota transplantation and postbiotics) that may reduce treatment-related toxicity in patients affected by MM as well as the rates of undertreatment of SMM patients.

INTRODUCTION

The very moment we open our eyes to the world, our body has already been colonized by symbiotic microorganisms that will increase in number and species and become established through the first years of life into our own microbiota [1]. This also is the time in which the immune system gets forged to recognize and eliminate pathogens [2] while acquiring tolerance to the self [3] and the host

microbiota that becomes an extended self (4). Of note, children share a stereotypic immune system development that is microbiota-driven (5). A strong link between gut microbiota and immune dynamics is also found in adults undergoing immune reconstitution after hematopoietic stem cell transplantation (HSCT) (6). The mechanisms by which the microbiota interacts with the host immune system, and eventually modulates and/or gets modulated by the immune system is under investigation (7–30). The modulatory effects of the microbiota on the immune system are not only local, but also systemic and affect distant organs (31). Therefore, disruption to the microbiota homeostasis (i.e., dysbiosis) associates with diseases that span from allergy (32) and other immune-mediated diseases (33) to obesity (34), psychiatric disorders (35) and cancer (36). The microbiota also directly impacts human pathologies. As few examples, selected species of *Escherichia coli* alkylate DNA on adenosine residues and induce double strand breaks, eventually favoring mutations in colorectal cancer (37); intestinal commensal bacteria lead to androgen biosynthesis, thus promoting endocrine resistance in prostate cancer (38). Additionally, the gut microbiota influences susceptibility of cancer patients to surgery (39), chemotherapy (40), radiotherapy (41) and immunotherapy (42). Indeed, fecal microbiota transplant (FMT) from donors who achieved complete response to anti-PD-1 monotherapy into anti-PD-1-refractory melanoma patients resulted safe, feasible and associated with clinical responses and improved cancer control by the immune system (43). Modulation of the gut microbiome has also been attempted in patients affected by hematologic malignancies because the microbiota is highly susceptible to most of the treatments proposed to these patients (44), and microbiota translocation into the bloodstream of patients with therapy-induced immunosuppression contributes to morbidity and mortality (45). In turn, treatment-induced dysbiosis can be corrected by probiotics, prebiotics and FMT (46).

We focused here on multiple myeloma (MM), a treatable but incurable neoplasia of plasma cells that mainly accumulate in the bone marrow (BM) causing anemia, hypercalcemia, renal insufficiency, and bone lesions (47). Full blown MM is often preceded by two potentially curable asymptomatic diseases: monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) (48). Thus, identifying mechanisms by which MGUS and SMM patients progress to full-blown MM would represent a substantial clinical advancement. Microbiota-modulated immunity has been proposed as a mechanism of progression from SMM to MM (49). Additionally, several clinical and preclinical studies have highlighted the role of the gut microbiota in MM patients' response to therapies (50, 51). Therefore, MM and its asymptomatic phases are examples of diseases in which alteration of the gut flora impacts disease progression, response to therapy and treatment-related toxicities. Information gathered in MM can be translated to other human diseases.

While we refer all interested readers to a more comprehensive review on this topic (52), in our short and more clinically-oriented paper we will start reporting data from both the bench

and the bedside that show how the gut microbiota modulates MM. We will define the role of IL-17 in the crosstalk between MM and the intestinal microbiota. We will highlight how the gut microbiota is modified and can modify patients' susceptibility to treatments. We will conclude with experimental and clinically strategies that can modulate the gut microbiota in patients affected by MGUS, SMM or MM.

GUT MICROBIOTA AND MULTIPLE MYELOMA

Diet can profoundly affect the gut microbiota. While a link between diet an MM has been investigated for decades (53), only recently a correlation between microbiome and progression of MM has been searched for. As for other human diseases (4), the gut microbiota from MM patients has a reduced richness in bacterial species (54). *Bacteroides*, *Clostriudium leptum* and *Rothia* are enriched in MM patients when compared to family members, who usually share the microbiome (55). Interestingly, the level of *Clostridium leptum* positively correlates with ISS stage in MM patients. Because *Clostridium leptum* and *Rothia* are butyric acid-producing bacteria, the authors hypothesized dysregulation of the sugar metabolism in the intestine of MM patients (54). Whether short-chain fatty acids (SCFAs) have direct effects on neoplastic plasma cells or anti-MM immunity (56) needs to be investigated.

Opportunistic nitrogen-recycling bacteria such as *Klebsiella* and *Streptococcus* are enriched in the gut microbiota of MM patients (57). Accordingly, MM patients showed increased urease and glutamine synthetase activity in their feces and more urea and less ammonia in their blood than healthy subjects. Mice treated with FMT from MM patients and challenged with 5TGM1 MM cells experienced accelerated tumor burden that associated with elevated L-glutamine levels in their blood (57). Thus, gut colonization by nitrogen-recycling bacteria accelerates MM by making available L-glutamine. Building on this knowledge, fluoroglutamine might work as PET tracer in MM (58).

Altogether, these findings suggest that metabolites produced by a dysbiotic microbiota impact MM progression. Indeed, genetic diversity in the microbiome provides a wide variety of enzymes that convert polysaccharides and oligosaccharides into SCFAs like acetate, propionate, and butyrate (59). In mice, acetate, butyrate and pentanoate exert partially overlapping effects on T cells, B cells and dendritic cells (60, 61). By activating receptors expressed on intestinal epithelial cells and hematopoietic cells, SCFAs reduce inflammation (62, 63). In the context of autologous HSCT, the presence of the butyrate-producing bacteria *Eubacterium hallae* or *Faecalibacterium prausnitzii* in the gut microbiota of MM patients positively correlates with increased rates of minimal residual disease negativity (64). In rats, butyrate administration ameliorates colitis by increasing numbers of regulatory T cell (Treg) and suppressing levels of the pro-inflammatory cytokine IL-17A in both plasma and colonic mucosa (65). Conversely, commensals favoring the expansion of intestinal T helper-17 (Th17) cells may

accelerate MM progression in mice (66). Thus, a strong link exists among commensal bacteria, Treg/Th17 cell balance and MM.

IL-17 SWINGS THE BALANCE BETWEEN GUT MICROBIOTA AND MULTIPLE MYELOMA

A different composition of the gut microbiota induces different immune responses locally and systemically (67). By producing IL-17, Th17 lymphocytes maintain a healthy intestinal mucosa and limit bacteria over-growth (68). Conversely, Treg cells allow tolerance to the extended self and limit excessive inflammation (69). Imbalance in the crosstalk between the host and the microbiota leads to excessive immune activation and expansion of Th17 cells.

Th17 cells are pathogenic in MM (70–72). Alexandrakis et al. (73) originally observed higher IL-17A levels in the peripheral blood of MM patients of stage II and III compared to stage I and a positive correlation with VEGF and microvessel density in the BM, thus hypothesizing a proangiogenic role for IL-17A in MM. Th17 cells are enriched in the BM of MM patients (70), where they support local inflammation and favor bone disease by promoting osteoclast differentiation (71). IL-17A, whose levels are increased in the BM of MM patients, contributes to neoplastic plasma cell survival and proliferation through the autocrine release of IL-6 (74). Also mouse neoplastic plasma cells express functional 17RA/RC (66), and *in vivo*, MM plasma cells upregulate cell proliferation and cell-cycle progression pathways if stimulated with IL-17A (75); while genes related to antigen processing and presentation and leukocyte trafficking and activation are downregulated in response to IL-17A (75). Neoplastic plasma cells can produce IL-17A, and treatment with antibodies specific for human IL-17A delayed growth of human MM in immunodeficient mice (76). These findings spurred a clinical trial with anti-IL-17A antibodies in MM patients (NCT03111992). IL-17A also resulted detrimental in the context of allogeneic-HSCT (77, 78). These works also identified IL-17A as the main path linking microbiota to Graft-Versus-Host Disease (GVHD). Indeed, in the absence of donor IL-17A, HSCT was more effective in controlling mouse MM (75).

While IL-17A is also elevated in some MGUS patients (79), a direct link has been reported between gut microbiota, IL-17A and progression of asymptomatic MM to full-blown MM (66). In Vk*MYC mice developing *de novo* MM that invariably evolves from asymptomatic to symptomatic MM (80), *Prevotella heparinolytica*, a human commensal (81), induces expansion of Th17 cells in the intestinal mucosa. Gut-born Th17 cells migrate to the BM, where they promote neoplastic plasma cell proliferation and progression from asymptomatic to symptomatic MM. At odds, *P. melaninogenica* restrain MM progression by limiting expansion of Th17 cells. Similarly, in SMM patients, high levels of BM IL-17 predicted faster progression to active MM (66). Lack of IL-17A in MM mice, or treatment with antibiotics or antibodies blocking IL-17/IL-

17R interactions delayed disease progression (66). Thus, targeting the microbiota-IL17A axis in SMM patients might block disease progression.

ROLE OF THE GUT MICROBIOTA IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

HSCT is a primary treatment for hematological malignancies and can be subdivided into autologous or allogeneic based on the use of self or donor-compatible HSCs, respectively (82). While the standard of care for MM patients is to receive high-dose chemotherapy followed by autologous-HSCT, allogeneic-HSCT can be proposed as part of a clinical trial and often associates with drawbacks like GVHD, a clinical condition in which the grafted immune system attacks tissues of the transplant recipient (83–85). The gut microbiota appears directly linked to allogeneic-HSCT success (86) and risk of GVHD (87). A large study including 111 MM patients across multiple clinical centers reported that lower diversity of intestinal microbiota associates with higher risk of transplant- and GHVD-related deaths (88).

Khan and colleagues highlighted interesting similarities in gut microbiota dysbiosis after both autologous- and allogeneic-HSCT in MM patients (89). Changes in the bacteriome and mycobiome also modulate early toxicity and the rate of neutrophil engraftment after autologous-HSCT (90). Generally, changes in bacterial abundances and species were linked to conditioning regimen or patient's treatments (91, 92). Reduced bacterial diversity associates with increased immune activation, probability of relapse, GVHD and overall mortality (88, 91, 93–98). *Enterobacteria* and *Proteobacteria* abundance correlates with increasing probability of GVHD, pulmonary or gastro-intestinal complications and infection (92, 96, 98, 99). More in depth, enrichment in *Clostridium difficile* and *Rothia* associated with both autologous- and allogeneic-HSCT-related adverse events in MM patients (100), while colonization of species like *Akkermansia muciniphila* or *Enterococcus faecium* predispose to the dominance of other bacteria and further detrimental systemic consequences for patients (101). On the other hand, enrichment in *Ruminococcaceae*, *Lachnospiraceae* and *Clostridiales* correlates with higher transplantation efficiency and reduced GVHD (93, 102). Others identified *Blautia*, *Actinomyces*, *Prevotella* and *Eubacterium limosum* as commensals with protective effects (91, 98, 101).

Interestingly, a genus of bacteria may harbor species with opposing effects on the immune system (4). One example is *Clostridium difficile* that may increase risk of GVHD, disease relapse or mortality, contrary to other family members (6, 93, 99, 100). Different effects by different strains belonging to the same genus correlate to different metabolic activities. Butyrate and propionate can reduce GVHD, improve HSCT outcomes but also protect mice against radiation-induced injuries of the hematopoietic compartment (103). The microbiome also regulates energy uptake to improve allogeneic-HSCT outcomes in mice (97, 104), or lactose metabolism whose reduction,

through diet or variation in microbial composition, limits pathological bacteria expansion and adverse effects in patients (105).

IMPACT OF THE GUT MICROBIOTA IN THERAPIES FOR MM PATIENTS

Because the gut microbiota can influence response to therapy and toxicity across different treatments (40), also in MM patients a link between gut microbiota and response to therapies has been investigated.

Proteasome Inhibitors and Immunomodulating Drugs

MM patients benefit from combinations of proteasome inhibitors (PIs; bortezomib, carfilzomib, ixazomib) and immunomodulating drugs (IMiDs; thalidomide, lenalidomide, pomalidomide, dexamethasone) (106). PI treatment is burdened with gastrointestinal toxicity (107) that may also depend on gut microbiota (51). While the work by Pianko and colleagues did not investigate gastrointestinal toxicity in MM patients treated with PIs and/or IMiDs followed by autologous-HSCT, it showed an association between deep treatment response and enrichment in *Eubacterium hallii* and *Faecalibacterium prausnitzii* (64). *F. prausnitzii* usually associates with gut health, and both bacteria are SCFA producers (108), thus suggesting a potential link between SCFA producing bacteria a reduced gastrointestinal toxicity.

A higher prevalence of beneficial bacteria belonging to Bifidobacterium and Lactobacillus genus has been found in mice exposed to dexamethasone (109). Significantly decreased IL-17 levels in the intestinal mucosa and reduced colitis susceptibility were observed in mice receiving FMT from dexamethasone-conditioned donor mice (109). Thus, the immunosuppressive effect of dexamethasone may in part be supported by the induction of an anti-inflammatory microbiota (110).

Chemotherapies

Cyclophosphamide (CTX) is an alkylating agent that stimulates type I interferon response and Th1/Th17 lymphocyte polarization (111). Because of the dual role of Th17 cells in MM pathogenesis and gut homeostasis, the effect of CTX on intestinal microbiota is relevant to understand the therapeutic outcomes in MM patients. *Bacteroidetes* and *Verrucomicrobia* are significantly reduced in mice treated with CTX (112). CTX treatment also increases intestinal barrier permeability and translocation of Gram-positive commensals, which favor Th1 and Th17 cell differentiation and anti-tumor immunity (113, 114).

Similarly, melphalan administration in rats causes severe injury to the small intestine, weight loss and infections (115). These effects recapitulate the toxicity observed in patients and limit melphalan administration to elderly subjects (116). Indeed, melphalan induces dysbiosis, reduction of SCFA production and bacterial translocation (115). Thus, replenishing SCFA or

normalization of microbiota composition might re-establish intestinal homeostasis and improve drug tolerability.
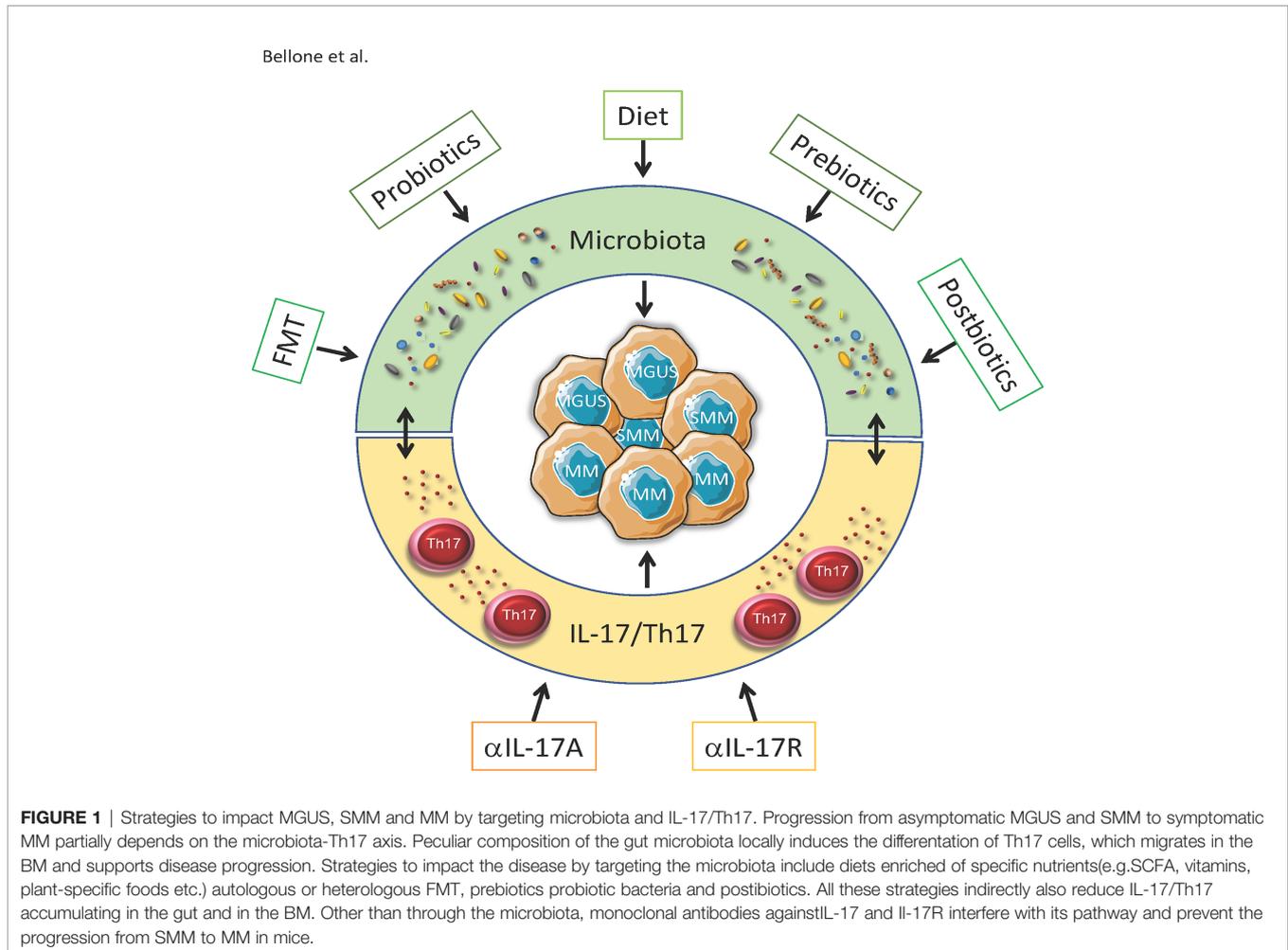
Cancer Immunotherapies

A strong correlation exists between gut microbiome and response to immune checkpoint inhibitors (ICIs) (43, 117–123). Interestingly, PD-L1 is expressed on malignant plasma cells, and PD-L1 predicts progression of SMM patients to MM (124). However, early-phase clinical trials with ICI as single agent showed modest activity in MM patients, whereas the combination with PIs ignited toxic events (125, 126). The latter might be linked to PI gastrointestinal toxicity (107). Andrews et al. associated defined microbiota signatures and abundance of *Bacteroides intestinalis* with upregulation of mucosal IL-1β and IL-17 in patients with ICI-related gastrointestinal adverse events (127). Administration of *Bifidobacterium* was sufficient to ameliorate ICI-related immunopathology in mice without dampening antitumor immunity (128). This strategy might also be adopted in MM patients.

The gut microbiota can promote the expansion and persistence of adoptively transferred cytotoxic T cells (CTLs) both in humans and mice (129). In mice, pentanoate and butyrate enhance anti-tumor activity of CTLs and chimeric antigen receptor (CAR)-T cells through metabolic and epigenetic reprogramming (130). A preliminary study on hematological patients receiving CAR-T cell therapy showed enrichment in *Ruminococcaceae*, and *Lachnospiraceae*, which produce SCFA, in patients achieving complete remission (131). Because CAR-T cells are proposed to MM patients (132), it will be interesting to investigate how modulation of the gut microbiota can impact this treatment (133, 134).

CONCLUSIONS

The information gathered so far strongly suggest that interfering with the insider (i.e., modifying the intestinal microbiota) may limit MM progression and increase susceptibility to therapies. These strategies include dietary intervention, administration of prebiotics, probiotics and postbiotics, but also FMT (**Figure 1**). While the concept of nutritional support is well established in the clinical practice (135), a more precise modulation of the gut microbiota has been attempted only recently, thanks to the acquisition of technologies for microbiome identification (36). Interestingly, unique microbial signatures can also be found in the peripheral blood within and between several cancer types (136).

Clinical trials aimed at modulating the gut microbiome to improve therapeutic response in hematopoietic malignancies are ongoing (**Table 1**) (137). Many of these trials propose administration of 1-6 different commensals with or without dietary intervention, and several of them focus on FMT. Major outcomes for patients undergoing HSCT are safety and GVHD control. Recently, a randomized trial has been launched to assess FMT efficacy in preventing allogeneic-HSCT complications in MM patients (NCT04935684). In other ongoing clinical trials,

FIGURE 1 | Strategies to impact MGUS, SMM and MM by targeting microbiota and IL-17/Th17. Progression from asymptomatic MGUS and SMM to symptomatic MM partially depends on the microbiota-Th17 axis. Peculiar composition of the gut microbiota locally induces the differentation of Th17 cells, which migrates in the BM and supports disease progression. Strategies to impact the disease by targeting the microbiota include diets enriched of specific nutrients(e.g.SCFA, vitamins, plant-specific foods etc.) autologous or heterologous FMT, prebiotics probiotic bacteria and postibiotics. All these strategies indirectly also reduce IL-17/Th17 accumulating in the gut and in the BM. Other than through the microbiota, monoclonal antibodies againstIL-17 and Il-17R interfere with its pathway and prevent the progression from SMM to MM in mice.

the microbiota is investigated in correlation to taste function (NCT03276481); to the supplementation of probiotic fermented milk product (NCT04530812); and to combined therapies (i.e., Selinixor, carfizomib and daratumumab or pomalidomide; NCT04661137). Many more studies deal with dietary intervention. As few examples, NCT04920084 will investigate whether a plant-rich diet is feasible and prevent MM in overweight individuals with MGUS or SMM. Another trial will determine if a specific mycobiome supporting diet can reduce gut inflammation in patients undergoing autologous-HSCT (NCT04685525). Resistant starch versus maltodextrin will be compared in a randomized trial involving candidates to autologous-HSCT (NCT05135351).

The natural tropism of bacteria for tumors have been exploited to design bacterial therapy for cancer (138). Commensals can be engineered to deliver drugs into tumors (36), and strategies have been devised to implement bacterial lysis with release of genetically encoded cargo within tumors only when a predefined population density of bacteria is reached (139–141).

Microbiota-derived metabolites (142) and microorganism-associated molecular patterns (143) can protect the BM from ionizing radiation toxicity. Additionally, recovery of lymphocytes and neutrophils after irradiation largely depends

on gut microbiota, which also supports nutrients and caloric uptake (97). Because disruption of the intestinal microbiota occurs frequently in HSCT recipients as consequence of the conditioning regimens and wide-spectrum antibiotic use, peri-transplant treatment with simple nutrients, commensal-derived metabolites, selected bacterial species, or even FMT (144) should support optimal immune reconstitution and protection from GVHD and transplant-associated nutritional alterations (135). Of note, FMT in allogeneic-HCT recipients induced protection from intestinal GVHD that associated with increased abundance of butyrate-producing bacteria (144). Butyrate and propionate levels also associate with protection from chronic GVHD in patients affected by MM (145). Administration of resistant starch and prebiotics to allogeneic-HSCT recipients reduced the incidence of acute GVHD that associated with preservation of butyrate-producing commensals (146).

Modulation of the gut microbiota and its derivatives should be time and context dependent. While propionate can provide radioprotection (142), butyrate might limit the immunostimulatory activity of radiotherapy by decreasing dendritic cell antigen presentation (147). In the same vein, melanoma patients resistant to anti-CTLA-4 blockade showed high blood propionate and butyrate levels and higher proportion of Tregs (56). Thus, an excess of SCFAs,

TABLE 1 | Clinical trials in MM patients.

Trial ID	Patient population	Patients (n)	Intervention	Outcome	Result	Status (location)
Prebiotics						
NCT05135351	MM and Lymphoma patients undergoing autologous HSCT	30	Randomized, double-blind, placebo-controlled trial of resistant starch versus placebo	Primary: feasibility; secondary: hospital duration, rate of neutropenic fever, rate of broad-spectrum antibiotic exposure and rate of gastrointestinal symptoms	–	Not yet recruiting (University of Nebraska, USA)
NCT04629430	Patients affected by hematologic cancer and undergoing HSCT	29	Single group assignment, open label trial of prebiotics and HSCT	Primary: frequency of participants ingesting the required diet; secondary: incidence and severity of acute GVHD and acute GI GVHD, C. difficile infection, patient weight and days to neutrophil engraftment	–	Recruiting (University of Virginia, USA)
Probiotics						
NCT00946283	Patients undergoing donor allogenic HSCT for hematologic cancer or myelodysplastic syndrome	30	Single group assignment, open label trial of Lactobacillus rhamosus GG and HSCT	Primary: safety; secondary: none	Terminated due to slow accrual	Terminated (Rutgers Cancer Institute of New Jersey, USA)
NCT03057054	Patients undergoing alternative donor allogeneic HCT	500	Randomized, parallel assignment, placebo-controlled trial of Lactobacillus plantarum and HCT	Primary: Incidence of GI acute GVHD; secondary: none	–	Recruiting (Children's Oncology Group, CA; National Cancer Institute, USA)
NCT04530812	Asymptomatic MM patients	13	Randomized, parallel assignment, open label trial of Kefir and best practice	Primary: changes in biomarkers of metabolism, patient-reported pain, fatigue, gut health, and quality of life; Secondary: gut microbial community structure	–	Completed (Roswell Park Cancer Institute, USA)
Diet						
NCT00003077	Advanced cancer patients who have significant weight loss and not amenable to curative therapy	63	Randomized, single group assignment, open label trial of high dose omega-3 fatty acids	Primary: survival; secondary: patient weight, maximum tolerated dose and antitumor response	Only 16% of patients has weight stabilization or weight gain	Completed (Holden Comprehensive Cancer Center, USA)
NCT00469209	Primary refractory, relapsing after prior therapy MM patients	60	Randomized, parallel assignment, open label trial of vitamin c, arsenic trioxide, bortezomib and melphalan	Primary: toxicity and safety, efficacy and pharmacokinetics; secondary: time to toxicity	–	Completed (MD Anderson Cancer Center, USA)
NCT00171925	MM and asymptomatic Stage I MM patients	143	Randomized, parallel assignment, open label trial of zolendronic acid, calcium and vitamin D	Primary: progression free survival; secondary: number of patients with skeletal-related events and complications	Reduced overall disease progression and skeletal events	Terminated (Novartis Investigative Site, DE)
NCT00317811	MM and plasma cell neoplasm patients	35	Single arm, open label trial of ascorbic acid, bortezomib and melphalan	Primary: overall response, safety and tolerability, time to disease progression; secondary: time to response, PFS, OS	Disease controlled in 94% of patients	Completed (Oncotherapeutics, USA)
NCT00661999	Anemic patients undergoing chemotherapy for nonmyeloid malignancies	502	Randomized, parallel assignment trial of ferrous sulfate, darbepoetin alfa and sodium ferric gluconate	Primary: hematopoietic response; secondary: hemoglobin levels, time to RBC transfusion, overall quality of life	No significant improvement	Completed (Mayo Clinic, USA)
NCT00951626	Patients affected by hematologic cancer and undergoing allogenic HSCT	282	Randomized, parallel assignment trial of diet intervention	Primary: quality of life; secondary: time-to-complication, number of complications, mortality	–	Completed (City of Hope Comprehensive Cancer Center, USA)

(Continued)

TABLE 1 | Continued

Trial ID	Patient population	Patients (n)	Intervention	Outcome	Result	Status (location)
NCT04530812	MM patients	13	Randomized, parallel assignment, open labeled trial of kefir and best practice	Primary: biomarkers of metabolism, pain and fatigue, gut health, quality of life; secondary: gut microbial phylotype, bacterial metabolic function	–	Completed (Roswell Park Cancer Institute, USA)
NCT04685525	MM patients undergoing autologous HSCT	40	Single group assignment, open labeled trial of mycobiome supporting diet	Primary: adherence; secondary: none	–	Not yet recruiting (University Hospitals Cleveland Medical Center, Case Comprehensive Cancer Center, USA)
NCT04920084	MGUS, SMM patients	20	Single group assignment, open labeled trial of a plant-based diet	Primary: adherence, weight loss, BMI reduction; secondary: none	–	Recruiting (Memorial Sloan Kettering Cancer Center, USA)
FMT						
NCT04935684	Patients affected by hematologic cancer and undergoing allogenic HSCT	150	Randomized, parallel assignment, open-label, multi-center trial of FMT	Primary: GVHD and RFS rate; secondary: OS, PFS, mortality	–	Not yet recruiting (University Hospital, Clermont-Ferrand, F)

MM, multiple myeloma; SMM, smoldering multiple myeloma; HSCT, hematopoietic stem cell transplantation; GVHD, graft versus host disease; GI, gastrointestinal; C. difficile, Clostridium difficile; HCT, hematopoietic cell transplantation; PFS, progression free survival; OS, overall survival; RBC, red blood cells; BMI, body mass index; RFS, relapse free survival; FMT, fecal microbiota transplantation.

while protective in some contexts (60–63, 65, 93, 108), may be detrimental for the induction of efficient anti-cancer CTL responses (56, 147, 148). The situation is even more complex in MM patients, in which modulation of the gut microbiota and its metabolic derivatives should aim at restraining Th17 cell numbers in favor of optimal CTL responses (4). It will be interesting to investigate in animal models of MM if resistant fiber or SCFA supplementation in combination with immune checkpoint blockade limit the expansion of Th17 cells in favor of a potent anti-tumor immunity.

Manipulation of the gut microbiota is not without risks (149). Probiotic strains (e.g., *Lactobacilli*) can cause bacteriemia although the mechanism of transmission from probiotic to blood is unclear (150). Probiotics may also impair microbiota reconstitution after antibiotic-induced dysbiosis (151). Thus, further investigation is warranted to better understand the mechanistic links between prokaryotic and eukaryotic cells sharing our body space.

AUTHOR CONTRIBUTIONS

MB designed the review. MB, AB, LC, ML, and BM performed the literature review and wrote the manuscript. AB designed and created the table and the figure. All authors reviewed and edited the manuscript. All authors also approved the final version of the manuscript.

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