Seminars in Immunopathology (2019) 41:655–664
https://doi.org/10.1007/s00281-019-00769-w

REVIEW

Resolution of acute intestinal graft-versus-host disease

Sindhu Thiagarajan[1,2] · Markus F. Neurath[1,2] · Kai Hildner[1,2]

Received: 12 October 2019 / Accepted: 15 October 2019 / Published online: 31 October 2019

Abstract

Allogeneic transplantation of hematopoietic stem cells (allo-HCT) represents an increasingly employed therapeutic approach to potentially cure patients suffering from life-threatening malignant and autoimmune disorders. Despite its lifesaving potential, immune-mediated allo-reactivity inherent to the allogeneic transplantation can be observed within up to 50% of all allo-HCT patients regularly resulting in the manifestation of acute and/or chronic graft-versus-host disease (GvHD). Mechanistically, especially donor T cells are assumed to chiefly drive inflammation that can occur in virtually all organs, with the skin, liver, and gut representing as the most frequently affected anatomic sites. Especially in the presence of intestinal manifestations of GvHD, the risk that the disease takes a life-threatening, potentially fatal course is significantly increased. In the light of a rapid gain of knowledge in respect to decode innate and adaptive immunity related mechanisms as, e.g., cytokine networks, intracellular signaling pathways or environmental triggers as, e.g., the intestinal microbiota and the development of novel therapeutic approaches, detailed insight into endogenous mechanisms seeking to counterbalance the proinflammatory machinery or to proactively foster signals promoting the resolution of allo-driven intestinal inflammation is emerging. Here, we seek to highlight the key aspects of those mechanisms involved in and contributing to the resolution of GvHD-associated intestinal inflammation. Concomitantly, we would like to briefly outline and discuss promising future experimental targets suitable to be therapeutically employed to directionally deflect the tissue response from a proinflammatory to an inflammation-resolving type of intestinal GvHD after allo-HCT.

Keywords Allogeneic hematopoietic stem cell transplantation · Intestinal graft-versus-host disease · T cells · resolution of intestinal GvHD

Introduction

Clinical background and definition of graft-versus-host-disease

Malignancies of the hematopoietic stem cell compartment, but also complex and therapy-refractory autoimmune diseases, are frequently associated with high mortality and hence represent the most common indications to perform allogeneic hematopoietic stem cell transplantation (allo-HCT) [1, 2]. Adaptations and novel strategies of the conditioning and transplantation process have steadily improved patients' outcomes and led to hence wide-spread usage of this potentially life-saving therapy over the last few decades [3, 4]. However, intrinsic to the procedure, allo-HCT represents a double-edged sword in respect to the functional consequences in transplanted individuals: While upon transplantation allo-reactive donor immune cells detect and eliminate malignancy defining recipient immune cells presumably residing in many patients postconditioning—an overall beneficial process called graft-versus-leukemia (GvL)-effect-, donor immune cells likewise have the potential to unpredictably attack host tissues by mounting a highly proinflammatory immune response upon sensing recipient body cells as foreign and thereby initiating a detrimental cascade finally resulting in the development of graft-versus-host-disease (GvHD)[1, 5]. Therefore, besides the risk of recurrence of the underlying

This article is a contribution to the special issue on Resolution of Inflammation in Chronic Diseases – Guest Editor: Markus Neurath

✉ Kai Hildner
Kai.Hildner@uk-erlangen.de

[1] Department of Medicine 1, University Hospital Erlangen, University of Erlangen-Nuremberg, Kussmaul Campus for Medical Research, Erlangen, Germany

[2] University Hospital Erlangen, Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany

malignant disorder, patients are threatened by two-dreaded outcomes associated with GvHD manifestations overall accounting for the majority of nonrelapse mortality (NRM) cases: (i) hampered tissue homeostasis through immune-mediated barrier disruption and (ii) stepping up of the immunosuppressive regimen to counteract GvHD activity with both scenarios resulting in an increased probability to develop and succumb to severe, fatal infections.

Central pathogenesis of GvHD

Although still only partially understood, the pathophysiological key event preceding the manifestation of GvHD is the expression and presentation of recipient-derived, genetically defined allo-proteins and allo-peptides. These "foreign" antigens are presented directly or indirectly by immune cells, i.e., professional antigen-presenting cells (APC) of donor or recipient origin or nonhematopoietic recipient cells (e.g., epithelial or stromal cells) with APC functionality resulting in the activation, priming, differentiation, and expansion of proinflammatory donor T lymphocytes (Fig. 1). The most important antigens identified to drive allo-reactivity are human leukocyte antigens (HLA) or major histocompatibility complex (MHC) antigens in mice. In fact, the degree of the HLA mismatch determines the frequency of the development of acute GvHD. However, despite HLA identity up to 40% of allo-HCT recipients manifest an acute form of systemic GvHD indicating the presence of HLA-unrelated, so called minor histocompatibility antigens (MiHA)[2, 6–8].

GvHD subtypes and characteristics

Generally, two types of GvHD can be distinguished in allo-HCT patients–acute and chronic GvHD. The acute form affects about 30–60% of all allo-HCT patients and is defined as a systemic, inflammatory disease state that particularly affects the gut, skin, and/or liver. Clinical signs of acute GvHD can occur both within and after 100d after allo-HCT [1, 5]. Chronic GvHD is characterized by a delayed onset, but usually constant progression of clinical manifestations that can virtually affect all organs with the mucosal surfaces of the oro-gastro-intestinal and genital tract, eyes, liver, and skin being the tissue sites mostly attacked. While about 50% of patients show clinical characteristics of chronic GvHD, first signs can be usually detected around 2–18 months posttransplantation [1]. Overall, roughly 25% of allo-HCT patients suffering from either acute or chronic forms of GvHD are at risk to directly or indirectly (e.g., by uncontrolled infections due to intensified immunosuppressive drug regimens) succumb to these severe, life-threatening complications post allo-HCT [1].

Epidemiology, challenges, and current in clinical use therapy of gastrointestinal GvHD management

Allo-HCT patients with acute GvHD often show clinical signs of gastrointestinal tract affection like diarrhea and abdominal pain sensations. Individuals with clinical signs of intestinal inflammation that is not caused by a defined pathogen (e.g., primary or reactivated cytomegalovirus infection) or cannot be attributed to drug-related side effects (e.g., mycophenolate mofetil, MMF), are diagnosed with so called intestinal GvHD [1, 5, 7]. Patients with intestinal GvHD face the highest risk to succumb to this dreaded complication especially when the clinical manifestations are severe. Various strategies to a priori prevent the induction and manifestation of GvHD have been employed. For examples, optimization of the tissue compatibility between donor and recipient is pursued, e.g., by preferred usage of relatives rather than foreigners as HCT donors to overall reduce disparity. Also, reduced intensity conditioning protocols are employed when possible to reduce tissue damage and release of T cell activating and hence disease-promoting cytokines prior transplantation [1].

Besides these preventive measurements, therapeutically, immunosuppressive treatment regimens represent nowadays the main stay in the standard drug protocol to prevent GVHD. Here, especially inhibition of T cell functions (e.g., cytokine production, T cell proliferation) is assumed to underlie efficacy shown for calcineurin inhibitors (e.g., sirolimus) that are used in combination with classic immunosuppressive agents (e.g., methotrexate or MMF) [1, 5]. In case, prophylactic, preventive measurements and standard immunosuppression fail and GvHD types clinically manifest, immunosuppression is intensified usually by switching to i.v. application regimens and adding corticosteroids as the still mainstay of all attempts to limit tissue inflammation. Hence, there is an urgent need for the establishment of novel upfront and/or second line therapeutic regimen given the current standard and its limited clinical success [5].

Despite the still so far incomplete understanding of the pathophysiologic cascade initiating and promoting intestinal GvHD, evidence from both murine and human studies strongly suggest that donor lymphocytes represent the major mediator of immune-mediated tissue damage [1, 4, 8]. Experimental evidence exists especially for a functional role of IFN-gamma (IFNg)-producing donor lymphocytes, i.e., T helper cells 1 (Th1) or cytotoxic $CD8^+$ T cells (Tc1) in the pathogenesis of intestinal GvHD [9]. The overall magnitude and functional characteristics of the GvHD-mediating T cell response is highly dependent on the degree of the HLA mismatch on the one hand but also on the quality and quantity of additional signals derived from other especially innate immune cells like APC, neutrophilic granulocytes, and innate lymphoid cells (ILC) [10]. Furthermore, it has been identified that signals stemming from intestinal microbiota but also from

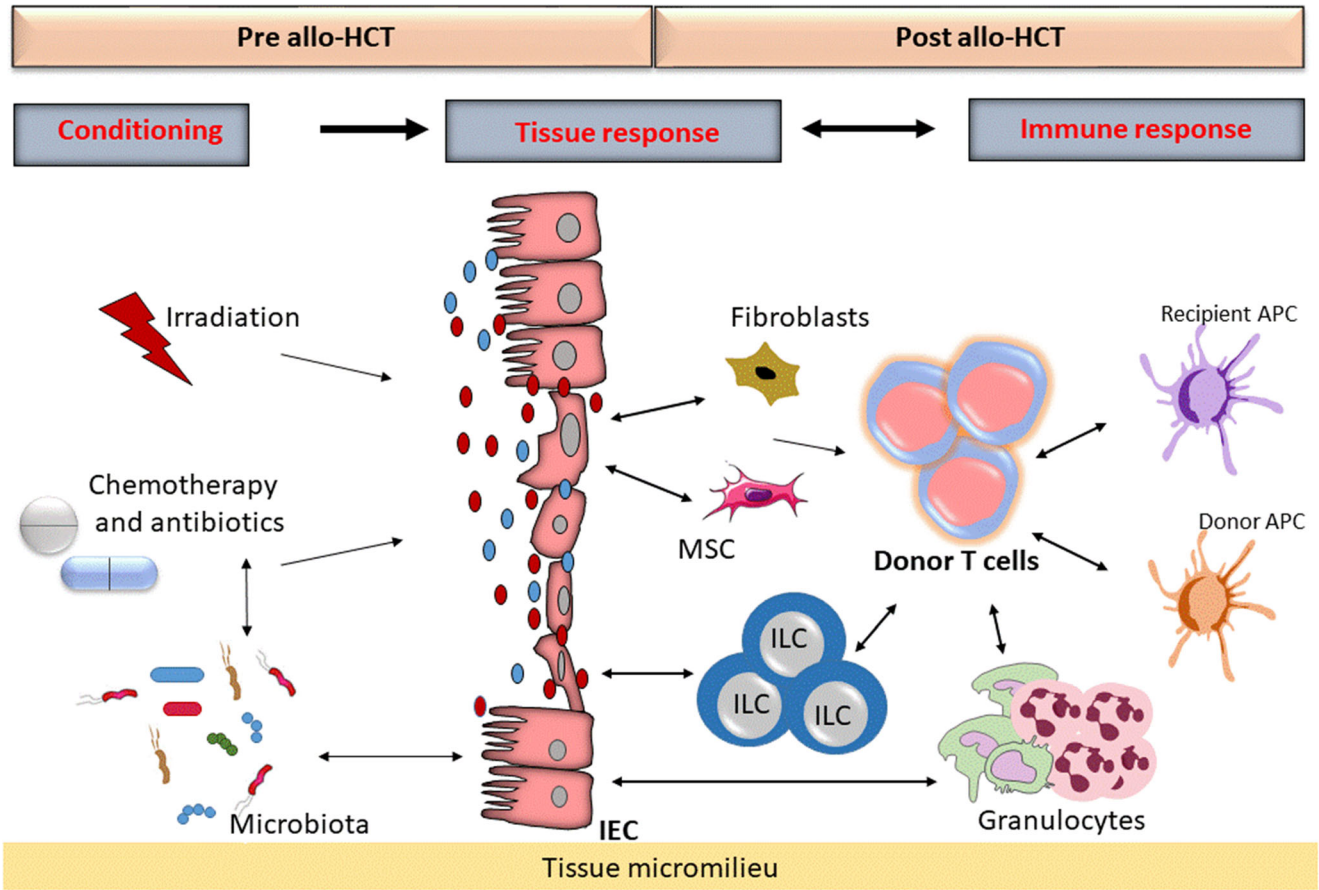

Fig. 1 Pathophysiology of acute intestinal GvHD highlighting crucial cell types, compartments, and interventions involved in the regulation of intestinal inflammation. In the pre-HCT phase, various modalities as part of state-of-the-art conditioning regimens including total body irradiation, chemotherapy, and antibiotics are severely compromising the intestinal tissue homeostasis through directly damaging intestinal epithelial cells (IEC) and significant changes of quality and quantity of the intestinal microbiota. IECs release significant amounts of effector molecules (as, e.g., cytokines, antimicrobial peptides, etc.) in response to its own damage and the defective intestinal barrier resulting. This and the consecutive translocation of luminal content (i.e., food-derived antigens, commensals, and pathogens) lead to an massive recruitment and expansion of immune cells including donor T cells, innate lymphoid cells (ILC), neutrophilic granulocytes and professional antigen-presenting cells (APCs), and phenotypical and functional adaptations of stromal cells (as, e.g., mesenchymal stromal cells, MSC). Overall, all aspects contribute to the dramatic shift of the tissue micromilieu representing the setting in which the intestinal GvHD underlying detrimental, donor T cell–dominated immune response is initiated and promoted in the post allo-HCT phase

nonhematopoietic recipient cell types like intestinal epithelial cells (IEC) and stromal cells like mesenchymal stromal cells (MSC) critically impact and shape the induction of the cytotoxic T cell response underlying acute GvHD (Figs. 1 and 2) [11, 12].

Based on these recent insights, a series of innovative targeting strategies are under clinical investigation with only few that have become routine care so far. While most attempts seek to predominately limit intestinal inflammation through the blockage of putatively pro-inflammatory molecules or pathways, some approaches are in fact intending to initiate and mediate resolution of intestinal GvHD mostly through a significant modulation of the tissue micromilieu composed of epithelial cells, stromal cells, immune cells both of donor and recipient origin, and intestinal microbiota as described in the next sections.

Tissue adaptation and homeostasis restoring, inflammation-resolving mechanisms in intestinal GvHD

Targeting innate immune mechanisms

The IL-10 cytokine family member IL-22 is predominately produced by T cells and innate immune cells, here foremost innate lymphoid cells (ILCs) [13, 14]. Intestinal epithelial cells (IEC) including progenitor and intestinal stem cells are IL-22 responsive due to the expression of the IL-22R [15]. Effects downstream of the IL-22R are mediated via Jak/Stat signaling resulting in the transmission of proliferation-inducing and anti-apoptotic signals. Interestingly, antimicrobial peptides are among the most strongly induced genes within IEC upon stimulation with IL-22 implying that IL-22

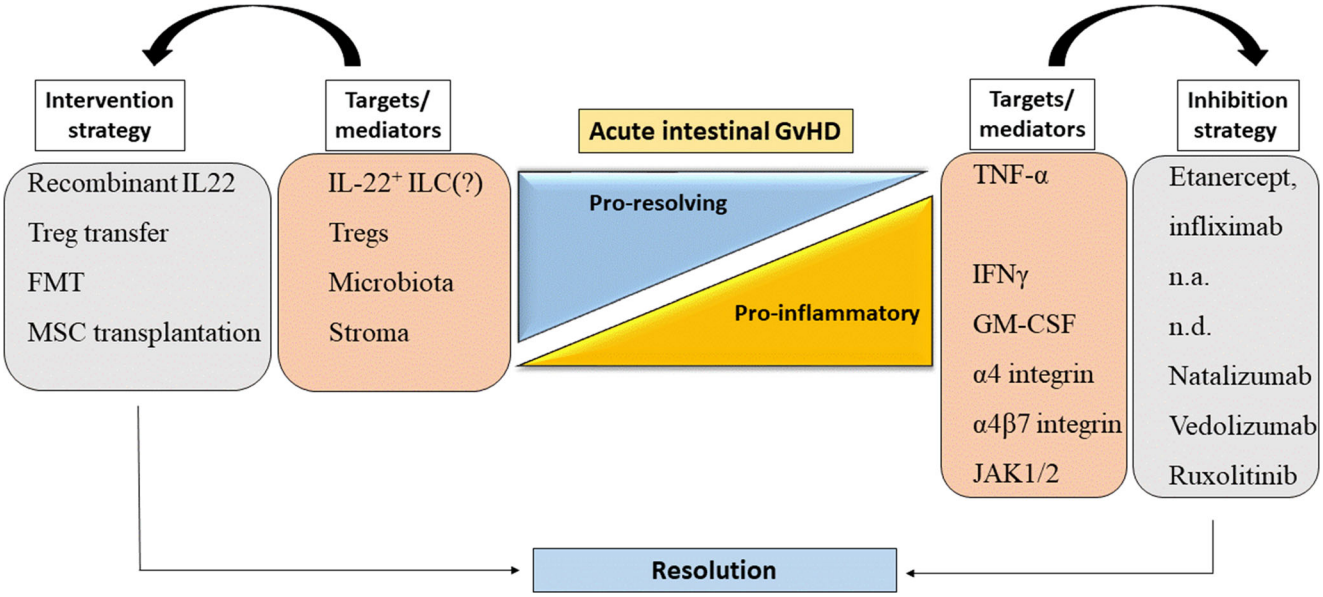

Fig. 2 Therapeutic strategies to achieve resolution of intestinal GvHD-associated tissue inflammation. The phenotype and course of acute intestinal GvHD can be modulated by individual mediators (e.g., IL-22), homing, and/or functional abilities of selected cell types (e.g., alpha4/ beta7 [α4/ β7] integrin expression on the cell surface of donor leukocytes) or even distinct compartments (e.g., intestinal microbiota). While targeting bona fide pro-inflammatory mechanisms usually requires blocking of the specific molecule or pathway (e.g. through neutralizing antibodies), to augment or even install a priori inflammation, pro-resolving mechanisms usually requires a complementation (e.g. Treg transfer) or exchange approach (e.g. FMT) to reach the therapeutic goal of induced resolution of uncontrolled intestinal inflammation frequently observed in patients with acute intestinal GvHD.

might serve barrier-protective functions on the one-hand and could contribute to tissue regeneration of the gut wound healing on the other hand [13, 16, 17]. However, the first wave of studies primarily focused on the effects of lymphocyte-derived IL-22 and reported that IL-17a as its signature cytokine expressing Th17 cells and a related; however, distinct T helper cell subset, so called Th22 cells, are the subsets among T cells that express IL-22 [16]. In fact, IL-22 deficient donor T cells lead to an attenuation of murine acute graft-versus-host disease mortality thereby ascribing IL-22 a role in T cell–mediated immunity propelling the idea that neutralization of IL-22 may represent a valuable approach to counteract IL-22–mediated tissue pathology [18]. However, the fact that allo-HCT recipient mice lacking IL-22 expression—here suspected to be largely provided by radio-resistant and hence post conditioning preserved IL-22 expressing ILCs that are, however, also target cells of allo-reactive T cells—displayed a more severe course of acute GvHD largely reversed the until then assumed to be rather proinflammatory to a globally more protection-conferring role during intestinal GvHD [19]. Mechanistically, IL-22 was shown to be involved in the maintenance of the intestinal epithelial stem cell upon tissue damage thereby promoting the recovery of acute GvHD-mediated intestinal tissue damage [15]. In line with the assumption of an overall protective role in acute GvHD, mice treated with rec. IL-22 showed a more favorable outcome and reduction of intestinal GvHD signs. Consequently, clinical trials assessing the efficacy of add-on IL-22 treatment alongside with corticosteroid administration in allo-HCT patients with newly diagnosed intestinal GvHD are under way.

Relatively recently, neutrophilic granulocytes were identified to critically impact the pathogenesis of acute intestinal GvHD [10]. While usually exerting classic front-line innate immune cell functions by targeting commensals or pathogens thereby hindering their translocation from the intestinal luminal to invade the host upon barrier disruption as, e.g., after irradiation prior allo-HCT, recent experimental evidence suggest that neutrophils might promote allo-reactive T cell activation by upregulating MHC class II expression and antigen presentation to T cells in draining lymph nodes during onset of intestinal GvHD [20]. Furthermore, by releasing, e.g., reactive oxygen species (ROS) neutrophils are also directly contributing to GvHD-driven tissue damage [21]. Pathologic effects exerted by neutrophils were dependent on the presence of microbial signals. Interestingly, so far, it has not been studied whether or not certain components of intestinal microbiota are particularly involved in the promotion of direct (e.g., release of ROS) or indirect (e.g.. MHC class II upregulation and enhanced antigen presentation abilities) effects executed by neutrophilic granulocytes, presumably representing an additional link between intestinal microbiota, immune cell function, and its mutual relationship central to the immunological pathogenesis of acute intestinal GvHD. Regardless, however, in a murine acute GvHD model, system depletion of neutrophils reduced the severity of intestinal GvHD–associated symptoms overall suggesting that targeting or modulating neutrophils in

fact might represent a target structure within the innate immune cascade for therapeutic interventions helping to prevent detrimental progression of acute GvHD or to even induce its resolution [20, 21].

Targeting the stromal compartment

As in other fields of research of intestinal biology (e.g., colorectal cancer) nonhematopoietic cell types, especially stromal cells, are increasingly being recognized and acknowledged for their abilities to significantly impact the tissue micromilieu (e.g., by releasing cytokines, participation in antigen-presentation processes, etc.) and thereby affect the tissue response during infections, cancer cell formation, or severe intestinal inflammation as observed in intestinal GvHD [12]. Reversely, inflammatory conditions as in the case of intestinal GvHD has been shown to strongly impact stromal cells' abilities to exert putatively beneficial immunomodulatory activities. Among stromal cells, mesenchymal stromal cells (MSC) have been identified to possess significant immune regulatory properties and thereby exerting inhibitory effects on both adaptive and innate immune cells [22]. MSC can be maintained and expanded ex vivo starting from bone marrow cells highlighting MSCs in that respect to be a suitable cell population that can be employed for cellular therapy attempts via MSC transplantation to restore tissue homeostasis and induce resolution of inflammation [23]. Consecutively, a series of clinical trials—albeit each investigating rather small cohorts—failed to identify severe MSC treatment–related side effects while these studies provided overall critical evidence for the potential of MSCs to substantially mitigate signs of intestinal GvHD [12, 23, 24].

Targeting the intestinal microbiota

The differentiation of allo-reactive effector T cells and their functional abilities is critically influenced by the prevalent tissue micromilieu in which donor T cell priming takes place. The immunologically sensed tissue milieu is composed of released proteins (cytokines/chemokines, anti-microbial peptides, etc.) and signals provided by surface receptors expressed on APC, other myeloid cells like innate lymphoid cells (ILCs), nonhematopoietic stromal cells, and epithelial cells in response to the intensive conditioning measurements prior allo-HCT and as a result of the onset of the allo-immune response after allo-HCT. In addition to this so called damage-associated molecular pattern (DAMPs), it has become increasingly clear especially within the last 5–10 years that signals, i.e., microbe- and pathogen-associated molecular pattern (MAMPS and PAMPs) and metabolites derived from intestinal microbiota, have a major impact on the nature and functionality of the evolving immune response [25]. In 1974, a seminal study demonstrated the impact of microbial signals on allo-reactivity as mice fully devoid of microbial colonization, so called germ-free mice, is essentially lacking clinical signs of intestinal GvHD [26]. This finding paved the way for numerous attempts to purposefully and vigorously decontaminate patients prior allo-HCT procedure [25]. However, though, this approach yielded in clinical practice and follow-up studies variable results putting this concept of prophylactic administration of antibiotics again into question. In fact, consecutively several studies found that conditioning, i.e., radiotherapy and/or chemotherapy and prophylactic or infection-triggered administration of antibiotics routinely resulted in a dramatic shift of the intestinal microbiota in allo-HCT recipients [11, 27]. This shift is foremost characterized by the reduction of the diversity of the microbial community, a pathophysiologic state that is often named dysbiosis [11, 25, 27, 28]. The dysbiotic state, however, is thereby unstable und rather dynamic given the observation that following allo-HCT, immune reconstitution by itself and inflammatory signals derived from evolving intestinal GvHD account for additional alterations of the intestinal microbiota [11, 27]. Reversely, continuous changes in the composition of the microbial communities directly or indirectly modulate the quality and quantity of the ongoing immune response thereby putatively initiating a self-preserving vicious circle due to the putatively detrimental cross-talk of a highly colitogenic microbiota and a ramping immune response potentially further shaping the microbiota in the direction of enhanced immunogenicity [11].

Adding to these novel insights into the pathophysiologic role of intestinal microbiota in intestinal GvHD pathogenesis, several studies have described a detrimental prognosis and outcome of dysbiotic allo-HCT patients following intensive antibiotic pretreatment while the presence of a preserved diversity of the intestinal microbiota has been associated with a better outcome and survival post allo-HCT[28]. Interestingly, the intestinal presence of members of the genus Blautia have been shown to be associated with reduced GvHD-related deaths in allo-HCT patients whereas the detection and accumulation of, e.g., enterococci after systemic administration of broad-spectrum antibiotics were associated with active GvHD [28, 29]. Also, certain microbial metabolites were identified to be able to modulate and importantly limit GvHD, presumably, e.g., via fostering the regulatory T cell (Tregs) response [30, 31]. Hence, based on these results, future studies can be envisioned to investigate targeted supplementation of, e.g., specific metabolites, distinct microbiota (e.g., clostridiae as these were also shown to expand Tregs in murine mouse models) or even whole fecal microbiota transplantation (FMT) as an intervention strategy to restore immune homeostasis and thereby to induce resolution of intestinal inflammation in allo-HCT patients [32]. Due to the significant infectious and immunological risk inherent to the irreversible transfer of allogeneic fecal material into highly immune-incompetent recipients upon or after allo-HCT, a recent study reported autologous FMT in allo-HCT patients to result in

successful reconstitution of the preexisting microbial diversity [33]. This study may represent a crucial technical milestone on the path to therapeutically employ FMT to restore immune homeostasis and prevent and/or resolve intestinal GvHD in allo-HCT patients in the future.

Targeting regulatory T cell responses

The existence of inflammation-limiting T suppressor cells has been conceptually suspected for a long time, but its validity and especially the underlying mechanisms were controversially discussed among leading immunologists over decades. In fact, it lasted until the identification of the transcription factor forkhead box protein 3 (FoxP3) and the description of its functional role to firmly establish that T cells with suppressive properties, thereafter called regulatory T cells (Tregs), indispensably represent the central cellular backbone of the endogenous machinery ensuring proper regulation of effector T cell responses in vivo [34, 35]. Mice deficient for FoxP3 routinely develop a rapidly progressing immune mediated inflammatory disease phenotype that is characterized by multi-organ inflammation including severe affection of the intestinal compartment with the development of detrimental wasting disease [34, 35]. Human genetic studies revealed that patients with similar clinical symptoms in fact carry a functionally relevant mutation in the FoxP3 gene. Clinically these patients consecutively develop a systemic, inflammatory disease syndrome called immunodysregulation polyendocrinopathy enteropathy x-linked, IPEX [36].

In the context of intestinal inflammation, Fiona Powrie's group provided direct experimental evidence that $CD4^+CD25^+$ splenic T cells enriched for Tregs are sufficient to suppress effector T cell driven intestinal tissue inflammation in syngeneic murine colitis [37]. Consecutive studies employed the disease mitigating and hence intestinal inflammation resolving properties of regulatory T cells in the context of allo-HCT [38]. Here, depletion of Tregs from the transplanted donor T cell pool led to an aggravation while transfer of bona fide Tregs along with effector T cells to an inhibition of intestinal GvHD symptoms [39–41]. More recently, especially Tregs located at mucosal surfaces have been recognized to represent not a uniform population but to essentially consist of two major $FoxP3^+$ Treg subsets: thymically derived, so called natural Tregs (nTregs) on the one hand and peripherally imprinted, so called induced Tregs (iTregs) on the other hand [42, 43]. In fact, most if not any of those studies showing Tregs to be sufficient to limit or even prevent intestinal GvHD directly used freshly isolated nTregs or after ex vivo expansion protocols for the therapeutic intervention [39, 41]. nTregs develop in a largely microbiota-independent fashion are the predominant Treg population in lymphoid-resident tissues, and their T cell receptor (TCR) is largely detecting endogenous (self-) antigens [42]. In contrast, iTregs differentiate into distinct iTreg subsets in a microbiota-dependent manner, represent the prevailing Treg population within non-lymphoid tissues like mucosal surfaces and their TCRs sense peptides predominately derived from of food sources, microbiota, or pathogens [30, 31]. Interestingly, certain Clostridium spp. was identified to positively regulate the colonic Treg pool [32]. Overall, there is an increasing body of experimental evidence that development, maintenance, and functionality of Tregs and intestinal microbiota are closely linked and even intertwined. Hence, experimental approaches and clinical trials currently assessing efficacy of Treg-based cellular therapy to resolve intestinal GvHD need to take the potential modulation of Treg biology in the presence of distinct microbiota components into account while conversely FMT requires in depth-considerations regarding the impact of transferred microbial signals on the composition and functionality of intestinal Treg subsets in situ.

Inflammation-promoting mechanisms counteracting resolution of intestinal GvHD

Targeting recruitment, migration, and homing of allo-reactive T cells

Due to the efficacy in murine studies, depletion of donor T cells from the graft prior or upon transplantation has been one of the most vigorously tested approaches to limit donor T cell driven manifestation of acute GvHD [44]. However, although, e.g., administration of anti-thymocyte globulin (ATG) lead to a significant reduction of acute GvHD incidence, overall improved patient survival was not observed due to both relapse of the underlying malignancies and, e.g., increased infection rates thereby elevating non-relapse mortality (NRM) cases [1].

Hence, rather than trying to fully eliminate donor T cells from the transplant, the concept of limiting the influx of intestinal and putatively inflammatory T cells into the target tissue by interfering with homing and chemokine receptors has gained tremendous attention . In IBD, blockade of intestinal T cell homing can be achieved by administration of an *alpha4/beta7* integrin-blocking antibody, vedolizumab, that has been approved for both Crohn's disease and ulcerative colitis [45, 46].

Interestingly, preclinical studies employing murine models of acute GvHD suggest that targeting T cell homing might be effective to limit intestinal GvHD. Especially alpha4/beta7 integrin-dependent lymphocyte homing may impact severity and survival of acute intestinal GvHD while genetic inactivation of *chemokine receptor 9* (CCR9), another chemokine receptor also described to mediate intestinal T cell homing in steady-state mice, failed to have a positive impact on acute GvHD-related survival despite altering T cell homing pattern [47, 48]. Consequently, the efficacy of alpha4/beta7-integrin blockage using the monoclonal antibody vedolizumab was evaluated in allo-HST patients, and, although not consistently, so far,

retrospective studies reported clinical benefit. Currently, a phase 3 trial (ClinicalTrials.gov identifier: NCT03657160) is under way to assess in how far vedolizumab treatment is able to mediate resolution of ramping up acute intestinal GvHD when added to standard GvHD prophylactic measurements. Similarly, natalizumab, a related humanized monoclonal antibody directed against alpha4 integrin, is currently explored in clinical trials for its protective effects in intestinal GvHD (NCT02176031, NCT02133924). Finally, a small molecule compound, maraviroc, shown to interfere with *chemokine receptor 5* (CCR5) and approved for HIV treatment, inhibits lymphocyte chemotaxis in vitro and more importantly was demonstrated to be effective in the treatment of acute forms of visceral GvHD including the gut [49]. Results of further clinical studies (NCT02737306) also taking an alternative approach by using a CCR5 blocking humanized monoclonal antibody *PRO 140* are awaited.

Targeting proinflammatory-signaling pathways

Cytokines and chemokines released predominately but not exclusively by immune cells as outlined in greater detail in the next paragraph function as key mediators of intestinal GvHD manifestations [4]. In addition to T cells, innate immune cells and non-hematopoietic recipient cells like stromal cells and epithelial cells express and release significant amounts of cytokines thereby collectively shaping the as "tissue micromilieu" denominated pool of signals that critically impacts the functional abilities of differentiating allo-reactive T cells. Mechanistically, upon binding of a distinct cytokine to its respective cytokine receptor, intracellular signaling of more than 60 cytokines (e.g., γ_c cytokine family) is mediated by the *Janus kinases* (Jak)*/signal transducers and activators of transcription* (Stat) signaling pathway ultimately resulting in the phosphorylation of Stat transcription factor molecules upon which these proteins translocate into the nucleus and induce or repress gene expression through binding at distinct regulatory genetic loci (e.g., promotor region) [50]. Interference with Jak/stat signaling has become a therapeutic option due to the identification of chemical compounds with Jak inhibitory activities, and, e.g., treatment with the Jak1/Jak3 inhibitor tofacitinib has been approved for the treatment of ulcerative colitis patients [51]. Of note, however, none of the available and in-clinical trials tested kinase inhibitors act by selectively inhibiting a single Jak kinase alone [50]. In fact, many if not all kinase inhibitors are suspected to potentially interfere with signaling pathways other than Jak/Stat, .i.e., exert off-target effects due to lacking binding specificity to a single Jak kinase. Furthermore, Jak/Stat-dependent cytokine signaling occurs both in T cells as well as in non-T cell immune cells as e.g. APC making data from studies investigating the mechanism of action of Jak-inhibitors and immunological effects observed after systemic treatment in the context of intestinal GvHD difficult to interpret [50]. Overall, cumulative evidence from murine studies suggest that of the four Jak family members especially Jak1, Jak2, and Jak3 seem to be functionally involved in transmitting cytokine-induced signals relevant in the pathogenesis of acute GvHD. Especially, the effects of the unselective Jak1/Jak2 inhibitor ruxolitinib have been intensively evaluated in preclinical and clinical studies resulting in its recent approval by the US Food and Drug administration (FDA) as oral medication for patients suffering from steroid-refractory acute GvHD [52]. Mechanistically, ruxolitinib was shown to inhibit Th1 cell differentiation while regulatory T cell frequencies were enhanced overall elevating intestinal GvHD severity and prognosis [52]. In addition, signaling downstream of the IFN-gamma receptor was identified to be affected by ruxolitinib treatment while this effect was not restricted to T cells indicating that non-T cell cells appear to be targeted by ruxolitinib treatment as well. In line with this assumption, ruxolitinib was demonstrated to directly modulate antigen presentation abilities of dendritic cells resulting in hampered differentiation of allo-reactive lymphocytes into acute GvHD-mediating cytotoxic T cells [53]. Overall, the efficacy of ruxolitinib treatment is seemingly based on pleiotropic effects affecting multiple cell types and cytokine signaling pathways. Hence, currently, additional and putatively more selectively acting Jak inhibitors as, e.g., itacitinib are currently under preclinical and clinical investigation pursuing the goal to identify novel treatment options to block immune cell signaling in order to perpetuate resolution of acute intestinal GvHD.

Targeting proinflammatory effector cytokines

Numerous studies seeking to identify a possible association between elevated systemic cytokine levels, and the presence and severity of acute GVHD consistently found increased IFNg, IL-6 and tumor necrosis factor alpha (TNF-alpha) levels in patients with acute GvHD compared with allo-HCT patients without GvHD [54]. Consecutive follow-up studies were designed to further explore the presence of a functional link between distinct effector cytokines and the more severe manifestation phenotype of acute GvHD. In case of IFNg, especially work from G. Hill's group established in murine GvHD models, the concept that Th1 cells functionally account for the manifestation of acute intestinal GVHD [9]. In fact, in this study, it was shown that *IFNgR*$^{-/-}$ recipients, i.e., in the absence of host tissue's ability to respond to IFNg, are protected against intestinal GVHD while lung manifestations exacerbated. Interestingly, as "data not shown", it was reported in this study that *IFNg*$^{-/-}$ donor T cells, i.e., T cells lacking the signature cytokine of Th1 cells, induced GVHD manifestations in the liver, the skin, and importantly the gut indistinguishably from WT cells [9]. Further studies confirmed this protective, inflammation-dampening and putatively resolving

role of IFNg in acute GvHD. Collectively these data show that IFNg responsiveness of the gut tissue is required, but T cell–derived IFNg does not seem to represent a prerequisite to drive intestinal GVHD. Systemic inhibition of IFNg is a rather double-edged sword in respect to the potential risk of aggravating GvHD on the one hand and the risk to compromise the well-established contribution of IFNg to the desired GvL effect on the other hand.

TNF-alpha levels were also reported to be elevated after conditioning measurements, i.e., prior allo-HCT. Importantly, increased sera levels have been associated with a higher probability to develop acute GvHD and with poor outcomes [55, 56]. Hence, systemic TNF-alpha blockade achieved by administering TNF-alpha neutralizing agents like infliximab, a mainstay in the treatment of IBD, or etanercept, a central therapeutic drug for the management of rheumatoid arthritis, has been explored in clinical studies [57]. Overall, these studies yielded rather disappointing results in respect to clinical efficacy while, however, in some of the reports clinical control of acute intestinal GvHD in response to TNF-alpha blockade could be observed in some patients. Interestingly, TNF-alpha seems to foster regulatory T cell responses suggesting a bidirectional role of TNF-alpha implying that this circumstance could be functionally relevant for the observed failure to control intestinal GvHD in non-responding patients [58, 59]. In summary, however, at least subgroups of patients with steroid-refractory acute GvHD, although currently rather undefined, seem to clinically benefit from TNF-alpha blockade [60].

Shortly after the identification of Th17 cells as a helper cell subset functionally and developmentally clearly distinct from other T helper cells like Th1 and Th2 cells, IL-17a-producing Th17 cells were identified to be critical promotors of chronic inflammatory disease states in murine model systems of, e.g., psoriasis, arthritis, and syngeneic colitis [60, 61]. However, negative clinical trial outcomes investigating the efficacy of IL-17R blocking antibodies in Crohn's disease along with preclinical studies demonstrating that IL-23 driven inflammatory Th17 cells co-expressing GM-CSF and IL-17a rather than IL-17a only expressing and through IL-6/TGF-beta–induced Th17 cells are the T cell subset preferentially driving acute inflammatory tissue disease states as, e.g., in the central nervous system fostered the concept that IL-17a and IL-17a secreting Th17 cells might overall exert rather barrier-protective than disease-promoting functions in the gut [62, 63]. In allo-HCT, published preclinical studies reported in respect to intestinal GvHD outcomes upon modulation of Th17 cells rather inconclusive and partially contradictory results further supporting the conclusion that bona fide Th17 cells play less of a role than Th1 cells but may synergize with Th1 in GVHD induction [64–68].

More recently, in fact, two independent reports described Granulocyte-macrophage colony stimulating factor (GM-CSF)-expressing T helper cells, Th_{GM}, as critical promotors of acute intestinal GvHD in the murine system [69–71]. Functionally, T cells lacking Th17 cell differentiation potential through the inactivation of the transcription factor of retinoic acid receptor related orphan receptor gamma t (Rorγt) following which however Th_{GM} differentiation is preserved were compared with T cells deficient for the transcription factor of basic leucine zipper transcriptional factor ATF-like (Batf), thereby essentially unable to differentiate into both Th17 and Th_{GM} cells, in respect to their functional abilities to induce acute GvHD. While wildtype and RoR$\gamma t^{-/-}$ T cells caused virtually indistinguishable intestinal GvHD, $Batf^{-/-}$ T cells protected from developing severe intestinal GvHD suggesting that indeed Th17 cells but no THGM cells are dispensable in that matter [69, 70]. Direct genetic inactivation of GM-CSF within the donor T cell compartment recapitulated that this finding overall clearly supported the conclusion that GM-CSF^{+} T cells are functionally relevant drivers of intestinal GvHD [69, 71]. Future studies though need to determine the precise mechanism and circumstances underlying GM-CSF-driven GvHD propagation to provide further experimental support to pursue GM-CSF blockage as a putatively novel future therapeutic intervention strategy to harness acute intestinal GvHD.

Concluding remarks

In summary, rising numbers of patients eligible for allo-HCT and hence increased use of unrelated donors, higher frequency, and increased severity of acute intestinal GvHD are inevitable consequences representing a significant therapeutic challenge complicating the management of those patients. Given this scenario, gaining novel insight into mechanisms promoting and/ or hampering resolution of acute intestinal GvHD-related tissue inflammation provides a promising opportunity to reduce morbidity and mortality and increases overall quality of life of allo-HCT patients.

Funding information This study was supported by the Collaborative Research Center 1181 (DFG-CRC1181, project B05), University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (to K.H) and the Collaborative Research Center 221 (DFG-CRC221, project B03 [K.H.].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373(9674):1550–1561

2. Blazar BR, Murphy WJ, Abedi M (2012) Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 12(6):443–458
3. Vadakekolathu J, Rutella S (2017) T-cell manipulation strategies to prevent graft-versus-host disease in haploidentical stem cell transplantation. Biomedicines 5(2):33
4. Ferrara JL (2000) Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors. J Hematother Stem Cell Res 9(3): 299–306
5. Zeiser R, Blazar BR (2017) Acute graft-versus-host disease — biologic process, prevention, and therapy. N Engl J Med 377(22): 2167–2179
6. Holtan SG, Pasquini M, Weisdorf DJ (2014) Acute graft-versus-host disease: a bench-to-bedside update. Blood advances 124(3): 363–373
7. Ferrara JLM, Chaudhry MS (2018) GVHD: biology matters. Blood Advances 2(22):3411
8. Markey KA, MacDonald KP, Hill GR (2014) The biology of graft-versus-host disease: experimental systems instructing clinical practice. Blood 124(3):354–362
9. Burman AC, Banovic T, Kuns RD, Clouston AD, Stanley AC, Morris ES, Rowe V, Bofinger H, Skoczylas R, Raffelt N, Fahy O, McColl S, Engwerda CR, McDonald K, Hill GR (2007) IFNgamma differentially controls the development of idiopathic pneumonia syndrome and GVHD of the gastrointestinal tract. Blood 110(3):1064–1072
10. Zeiser R (2015) Activation of innate immunity in graft-versus-host disease: implications for novel targets? Oncol Research and Treatment **38**(5):239–243
11. Jenq RR et al (2012) Regulation of intestinal inflammation by microbiota following allogeneic bone marrow transplantation. J Exp Med 209(5):903–911
12. Elgaz S, Kuçi Z, Kuçi S, Bönig H, Bader P (2019) Clinical use of mesenchymal stromal cells in the treatment of acute graft-versus-host disease. Transfus Med Hemother 46(1):27–34
13. Zindl CL et al (2013) IL-22–producing neutrophils contribute to antimicrobial defense and restitution of colonic epithelial integrity during colitis. Proc Natl Acad Sci USA 110(31):12768–12773
14. Takatori H, Kanno Y, Watford WT, Tato CM, Weiss G, Ivanov II, Littman DR, O'Shea JJ (2009) Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. J Exp Med **206**(1):35–41
15. Aparicio-Domingo P et al (2015) Type 3 innate lymphoid cells maintain intestinal epithelial stem cells after tissue damage. J Exp Med 212(11):1783–1791
16. Basu R, O'Quinn DB, Silberger DJ, Schoeb TR, Fouser L, Ouyang W, Hatton RD, Weaver CT (2012) Th22 cells are an important source of IL-22 for host protection against enteropathogenic bacteria. Immunity 37(6):1061–1075
17. Pickert G et al (2009) STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J Exp Med 206(7): 1465–1472
18. Couturier M et al (2013) IL-22 deficiency in donor T cells attenuates murine acute graft-versus-host disease mortality while sparing the graft-versus-leukemia effect. Leukemia 27(7):1527–1537
19. Pan B, Xia F, Wu Y, Zhang F, Lu Z, Fu R, Shang L, Li L, Sun Z, Zeng L, Xu K (2018) Recipient-derived IL-22 alleviates murine acute graft-versus-host disease in association with reduced activation of antigen presenting cells. Cytokine 111:33–40
20. Hülsdünker J (2018) et al, Neutrophils provide cellular communication between ileum and mesenteric lymph nodes at graft-versus-host disease onset. Blood **131**(16):1858–1869
21. Schwab L et al (2014) Neutrophil granulocytes recruited upon translocation of intestinal bacteria enhance graft-versus-host disease via tissue damage. Nat Med 20:648
22. Buron F, Perrin H, Malcus C, Héquet O, Thaunat O, Kholopp-Sarda MN, Moulin FT, Morelon E (2009) Human mesenchymal stem cells and immunosuppressive drug interactions in allogeneic responses: an in vitro study using human cells. Transplant Proc 41(8):3347–3352
23. Prasad VK, Lucas KG, Kleiner GI, Talano JA, Jacobsohn D, Broadwater G, Monroy R, Kurtzberg J (2011) Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal™) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. Biol of Blood and Marrow Transplant 17(4):534–541
24. Le Blanc K et al (2004) Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 363(9419):1439–1441
25. Holler E, Weber D (2016) Fit for cure? Microbiota and GVHD. Blood 128(16):2004–2005
26. van Bekkum DW et al (1974) Mitigation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora. J Natl Cancer Inst 52(2):401–404
27. Shono Y, van den Brink MRM (2018) Gut microbiota injury in allogeneic haematopoietic stem cell transplantation. Nat Rev Cancer 18:283
28. Weber D, Jenq RR, Peled JU, Taur Y, Hiergeist A, Koestler J, Dettmer K, Weber M, Wolff D, Hahn J, Pamer EG, Herr W, Gessner A, Oefner PJ, van den Brink M, Holler E (2017) Microbiota disruption induced by early use of broad-spectrum antibiotics is an independent risk factor of outcome after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 23(5): 845–852
29. Jenq RR et al (2015) Intestinal blautia is associated with reduced death from graft-versus-host disease. Biol Blood Marrow Transplant 21(8):1373–1383
30. Sefik E, Geva-Zatorsky N, Oh S, Konnikova L, Zemmour D, McGuire A, Burzyn D, Ortiz-Lopez A, Lobera M, Yang J, Ghosh S, Earl A, Snapper SB, Jupp R, Kasper D, Mathis D, Benoist C (2015) MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of RORgamma(+) regulatory T cells. Science 349(6251):993–997
31. Ohnmacht C et al (2015) MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORgammat(+) T cells. Science 349(6251):989–993
32. Atarashi K et al (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331(6015):337–341
33. Taur Y et al (2018) Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. Sci transl med 10(460):eaap9489
34. Fontenot JD, Gavin MA, Rudensky AY (2003) Foxp3 programs the development and function of CD4 + CD25+ regulatory T cells. Nat Immunol 4(4):330–336
35. Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. Science 299(5609): 1057–1061
36. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27(1):20–21
37. Mottet C, Uhlig HH, Powrie F (2003) Cutting edge: cure of colitis by CD4 + CD25+ regulatory T cells. J Immunol 170(8):3939–3943
38. Edinger M, Powrie F, Chakraverty R (2009) Regulatory mechanisms in graft-versus-host responses. Biology of Blood and Marrow Transplantation 15(1, Supplement):2–6
39. Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S (2002) Donor-type CD4(+)CD25(+) regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation. J Exp Med 196(3):389–399
40. Taylor PA, Lees CJ, Blazar BR (2002) The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells

inhibits graft-versus-host disease lethality. Blood 99(10):3493–3499
41. Edinger M, Hoffmann P, Ermann J, Drago K, Fathman CG, Strober S, Negrin RS (2003) CD4 + CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation. Nat Med **9**(9):1144–1150
42. Panduro M, Benoist C, Mathis D (2016) Tissue Tregs. Annu Rev Immunol 34:609–633
43. Schiering C, Krausgruber T, Chomka A, Fröhlich A, Adelmann K, Wohlfert EA, Pott J, Griseri T, Bollrath J, Hegazy AN, Harrison OJ, Owens BMJ, Löhning M, Belkaid Y, Fallon PG, Powrie F (2014) The alarmin IL-33 promotes regulatory T-cell function in the intestine. Nature 513(7519):564–568
44. Coghill JM, Sarantopoulos S, Moran TP, Murphy WJ, Blazar BR, Serody JS (2011) Effector CD4+ T cells, the cytokines they generate, and GVHD: something old and something new. Blood 117(12):3268–3276
45. Feagan BG et al (2013) Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 369(8):699–710
46. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A, GEMINI 2 Study Group (2013) Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 369(8):711–721
47. Beilhack A et al (2008) Prevention of acute graft-versus-host disease by blocking T-cell entry to secondary lymphoid organs. Blood 111(5):2919–2928
48. Schreder A, Moschovakis GL, Halle S, Schlue J, Lee CW, Schippers A, David S, Bernhardt G, Ganser A, Pabst O, Förster R, Koenecke C (2015) Differential effects of gut-homing molecules CC chemokine receptor 9 and integrin-β7 during acute graft-versus-host disease of the liver. Biology of Blood and Marrow Transplantation 21(12):2069–2078
49. Reshef R, Luger SM, Hexner EO, Loren AW, Frey NV, Nasta SD, Goldstein SC, Stadtmauer EA, Smith J, Bailey S, Mick R, Heitjan DF, Emerson SG, Hoxie JA, Vonderheide RH, Porter DL (2012) Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. N Engl J Med 367(2):135–145
50. O'Shea JJ (2004) Targeting the Jak/STAT pathway for immunosuppression. Ann Rheum Dis 63(suppl 2):ii67–ii71
51. Panés J et al (2017) Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 66(6):1049–1059
52. Spoerl S et al (2014) Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood 123
53. Heine A, Held SA, Daecke SN, Wallner S, Yajnanarayana SP, Kurts C, Wolf D, Brossart P (2013) The JAK-inhibitor ruxolitinib impairs dendritic cell function in vitro and in vivo. Blood 122(7):1192–1202
54. Imamura M, Hashino S, Kobayashi H, Kubayashi S, Hirano S, Minagawa T, Tanaka J, Fujii Y, Kobayashi M, Kasai M (1994) Serum cytokine levels in bone marrow transplantation: synergistic interaction of interleukin-6, interferon-gamma, and tumor necrosis factor-alpha in graft-versus-host disease. Bone Marrow Transplant 13(6):745–751
55. Holler E et al (1995) Modulation of acute graft-versus-host-disease after allogeneic bone marrow transplantation by tumor necrosis factor alpha (TNF alpha) release in the course of pretransplant conditioning: role of conditioning regimens and prophylactic application of a monoclonal antibody neutralizing human TNF alpha (MAK 195F). Blood 86(3):890–899
56. Remberger M, Ringden O, Markling L (1995) TNF alpha levels are increased during bone marrow transplantation conditioning in patients who develop acute GVHD. Bone Marrow Transplant 15(1):99–104
57. Yalniz FF, Hefazi M, McCullough K, Litzow MR, Hogan WJ, Wolf R, Alkhateeb H, Kansagra A, Damlaj M, Patnaik MM (2017) Safety and efficacy of infliximab therapy in the setting of steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 23(9):1478–1484
58. Leclerc M et al (2016) Control of GVHD by regulatory T cells depends on TNF produced by T cells and TNFR2 expressed by regulatory T cells. Blood 128(12):1651–1659
59. Pierini A et al (2016) TNF-α priming enhances CD4 < sup > +</sup > FoxP3 < sup > +</sup > regulatory T-cell suppressive function in murine GVHD prevention and treatment. Blood 128(6):866–871
60. Ivanov II, McKenzie B, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR (2006) The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126(6):1121–1133
61. Leppkes M et al (2009) RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F. Gastroenterology **136**(1):257–267
62. Codarri L, Gyülvészi G, Tosevski V, Hesske L, Fontana A, Magnenat L, Suter T, Becher B (2011) RORgammat drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. Nat Immunol 12(6):560–567
63. Becher B, Tugues S, Greter M (2016) GM-CSF: from growth factor to central mediator of tissue inflammation. Immunity 45(5):963–973
64. Yi T, Zhao D, Lin CL, Zhang C, Chen Y, Todorov I, LeBon T, Kandeel F, Forman S, Zeng D (2008) Absence of donor Th17 leads to augmented Th1 differentiation and exacerbated acute graft-versus-host disease. Blood 112(5):2101–2110
65. Yu Y, Wang D, Liu C, Kaosaard K, Semple K, Anasetti C, Yu XZ (2011) Prevention of GVHD while sparing GVL effect by targeting Th1 and Th17 transcription factor T-bet and RORgammat in mice. Blood 118(18):5011–5020
66. Kappel LW, Goldberg GL, King CG, Suh DY, Smith OM, Ligh C, Holland AM, Grubin J, Mark NM, Liu C, Iwakura Y, Heller G, van den Brink M (2009) IL-17 contributes to CD4-mediated graft-versus-host disease. Blood 113(4):945–952
67. Iclozan C et al (2010) T helper17 cells are sufficient but not necessary to induce acute graft-versus-host disease. Biol of blood and marrow transplant 16(2):170–178
68. Fulton LM et al (2012) Attenuation of acute graft-versus-host disease in the absence of the transcription factor RORgammat. J Immunol 189(4):1765–1772
69. Ullrich E et al (2018) BATF-dependent IL-7RhiGM-CSF+ T cells control intestinal graft-versus-host disease. J Clin Invest 128(3):916–930
70. Buchele V et al (2018) Targeting inflammatory T helper cells via retinoic acid-related orphan receptor gamma t is ineffective to prevent allo-response-driven colitis. Front Immunol 9:1138
71. Tugues S et al (2018) Graft-versus-host disease, but not graft-versus-leukemia immunity, is mediated by GM-CSF–licensed myeloid cells. Sci Trans M 10(469):eaat8410