IL-27: a new target for GVHD prevention

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In this issue of Blood, Belle et al have identified a key role for interleukin-27 (IL-27) in acute graft-versus-host disease (GVHD), which is a complex process orchestrated by donor immune T cells and antigen-presenting cells of both donor and host origin.

IL-27 is a heterodimeric, pleiotropic cytokine that somewhat paradoxically provides pro- or anti-inflammatory cues depending on the particular in vivo context. Given these complexities, it is noteworthy that the work of Belle et al has both dissected the role of IL-27 in acute GVHD and provided an initial rationale for IL-27 blockade as a new approach for GVHD prevention.

As summarized, Belle et al have demonstrated that genetic deficiency of the IL-27 receptor or monoclonal antibody (mAb) blockade of the IL-27p28 cytokine subunit reduces acute GVHD by shifting donor T-cell immunity away from pathogenic Tbet+ CD4+ Th1 and CD8+ Tc1 cells and toward CD4+ and CD8+ FoxP3-expressing regulatory T cells (Tregs) (see figure panels A-B).

The results presented by Belle et al are unique relative to some previous models that identified an anti-inflammatory role of IL-27 signaling. However, this apparent discrepancy can be resolved because such models were characterized by Th17-driven autoimmunity that was amenable to regulation by IL-27-mediated promotion of Tbet- T cells that secreted tissue-protective IL-10. In an analogous manner, the severity of acute GVHD can fluctuate depending on the reciprocal balance of fate defining transcription factors; however, as illustrated by Belle et al., IL-27 signaling seems to only further drive the inherent predisposition of posttransplant T cells toward the pathogenic Tbet+ Th1/Tc1 subsets. In the absence of posttransplant IL-27 signaling, the drive for Tbet+ effectors was diminished, thereby allowing protective Treg cell reconstitution.

It is important to note that IL-27 represents a cytokine capable of promoting IL-10 secretion in effector T cells and Treg subsets. As such, one might have concern that therapeutic blockade of IL-27 could abrogate the known beneficial effect of Treg cell-derived IL-10 in preventing acute GVHD. To the contrary, Belle et al demonstrated that IL-27 therapeutic blockade not only fully preserved Treg cell IL-10 secretion but also enhanced Treg cell stability in vivo during GVHD.

In future investigations, it will be important to extend the current disease prevention studies and determine the effect of IL-27 blockade on established GVHD, which is characterized by ongoing Tbet+ T-cell–mediated inflammation in the skin, gut, and liver. In other inflammatory models, Treg cell efficacy for the treatment of inflammatory disease is dependent upon the expression of Tbet, which in turn dictates a chemokine receptor expression profile that allows Treg cell migration into the diseased tissue. As such, it remains to be determined whether Treg cells starved of the Tbet-inducing cytokine IL-27 will have a transcriptional machinery sufficient for infiltration into active GVHD sites.

It will also be critical to determine the effects of IL-27 blockade on the key immunologic reaction that typically necessitates allogeneic bone marrow transplantation, that is, the graft-versus-tumor (GVT) effect. On this point, there may be reason for concern, because IL-27 promotes the antitumor effect of CD8+ T cells; and, IL-27 directly inhibits the growth of human acute myeloid leukemia cells. However, because IL-27 can increase the expression of IL-10 and programmed death ligand-1, it is possible that IL-27 blockade might promote antitumor effects in settings driven by these immunosuppressive factors. In conclusion, Belle et al have clearly demonstrated that IL-27 blockade can favorably skew the balance of TCONV to Treg cells for effective GVHD prevention and have set the stage for further studies to determine whether an anti–IL-27 approach can be used to treat established GVHD, or to favorably balance GVHD and GVT effects.

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REFERENCES


4. Yi T, Chen Y, Wang L, et al. Reciprocal differentiation between a loss of diversity and GVHD-related mortality. Vice versa, an abundance of protective bacteria such as Blautia or further Clostridiales is associated with absence of GVHD and improved survival. Experimental and clinical studies suggested 2 major mechanisms contributing to loss of microbiota diversity: prophylactic and therapeutic use of broad-spectrum antibiotics interfering with commensal clostridia and Paneth cell destruction and subsequent loss of antimicrobial peptides by GVHD itself. Changes of bacterial metabolites in the intestinal cell wall are likely to contribute to the strong effect of microbiota damage and loss of intestinal immunoregulation, which in turn enhances inflammation and tissue damage.

Although all data point to a high likelihood that strategies interfering with intestinal microbiota may improve outcome after stem cell transplantation, the current report is the first to report the therapeutic effect of FMT not only in an individual patient but also in a small series of patients suffering from steroid-refractory GVHD: With a day 28 response in 3 of 4 patients, allowing reduction of steroids and a restoration of commensal bacteria, this approach holds the promise to contribute to long-term stabilization of intestinal GVHD, which is still the major cause of acute treatment-related mortality. FMT has been established as a highly efficient treatment of refractory Clostridium difficile infections, but is currently under development to treat other microbiota-related diseases such as inflammatory bowel disease, or even metabolic syndromes. If confirmed in larger and multicenter trials with a longer follow-up, the efficacy of FMT in GVHD would be 1 of the best clinical examples of the strong interaction of microbiota with innate and adaptive immunity, as even strong reactions against allo-antigens may be controlled by a tolerogenic and anti-inflammatory environment provided and supported by a diverse intestinal microbiota.

In spite of this first positive report, FMT is still to be considered a highly experimental treatment approach that should be developed in the context of carefully designed clinical trials. Given the risk for transfer of unrecognized infectious agents and the lack of current knowledge about the exact role of the intestinal microbiome and virobiome, larger studies need to carefully answer these questions and analyze long-term adverse effects. In addition, the optimal way of microbiota modulation including the use of pre-/pro- and postbiotics has to be addressed as well. The observations also raise a series of further questions to basic science: What is the role of pathogenicity factors of specific noncommensal bacteria, such as recently shown for the mucolytic activity of the species Akkermansia muciniphila, and are there further strain specific differences in GVHD vs non-GVHD patients that can only described by shotgun metagenomic sequencing? What is the role of antigen-specific T-cell responses against bacterial antigens? Bacterial antigen specificity

Comment on Kakihana et al, page 2083

Fit for cure? Microbiota and GVHD

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In this issue of Blood, Kakihana et al report for the first time successful and safe application of related fecal microbiota transplants (FMTs) via nasoduodenal tubes in a small series of patients suffering from steroid-resistant acute intestinal graft-versus-host disease (GVHD). In spite of concomitant cytomegalovirus and Aspergillus infections at the start of treatment, adverse effects were limited and mainly related to the mode of application. Three of 4 patients responded at the end of the observational period of 28 days after first FMT, allowing reduction of concomitant steroid dose by 69%. Four-week response was associated with restoration of commensal microbiota and accompanied by an increase of the effector regulatory T-cell/CD8 T-cell ratio in 3 of 4 patients. In the 3 responding patients, improvement of gut symptoms persisted after the last FMT, with 1 patient being alive 2 years after FMT and 2 patients finally relapsing from underlying disease 106 days and 1 year, respectively, after FMT without recurrence of GVHD. Since van Bekkum et al’s report on a role of the intestinal microbiota in pathogenesis of GVHD, the interaction of intestinal microbiota and epithelial inflammation in allogeneic stem cell transplantation has always been the focus of immunological research and preventive clinical approaches, such as decontamination. Recently, modern techniques of molecular 16s rDNA sequencing of intestinal microbiota or metabolomics of microbial metabolites confirmed this hypothesis by showing a dramatic association between a loss of diversity and GVHD-related mortality. Vice versa, an abundance of protective bacteria such as Blautia or further Clostridiales is associated with absence of GVHD and improved survival. Experimental and clinical studies suggested 2 major mechanisms contributing to loss of microbiota diversity: prophylactic and therapeutic use of broad-spectrum antibiotics interfering with commensal clostridia and Paneth cell destruction and subsequent loss of antimicrobial peptides by GVHD itself. Changes of bacterial metabolites in the intestinal cell wall are likely to contribute to

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