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Comment on Kakhiana et al, page 2083

Fit for cure? Microbiota and GVHD

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In this issue of Blood, Kakhiana 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.1

Since van Bekkum et al’s2 report on a role of the intestinal microflora 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 microbiota2 or metabolomics of microbial metabolites3 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 Blautia4 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 clostridia4,6 and Paneth cell destruction and subsequent loss of antimicrobial peptides by GVHD itself7,9. 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.8

Although all data point to a high likelihood that strategies intervening 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,10 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 virome, 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,4 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...
was recently postulated for some of the regulatory T cells controlling intestinal inflammation. If antigen specificity against bacterial antigens holds true, it will also be important to analyze the relevance of the specific donor T-cell vs host T-cell repertoires that might decide on occurrence of intestinal GVHD. Do microbiota not only influence intestinal inflammation but also exert systemic immunoregulatory effects, and thus have an effect not only on other manifestations of GVHD but also on graft-versus-leukemia effects? What are the driving mechanisms of epithelial stabilization, ranging from interleukin 22 to epithelial effects of metabolites such as short chain fatty acids, indoles, and others? And finally, which immunoregulatory cell types (eg, regulatory T cells, indoleamine 2,3-dioxygenase–producing dendritic or myeloid-derived suppressor cells, innate lymphoid cells) are involved in microbiota-mediated restoration of balanced intestinal and systemic immune responses?

Today, the triad of microbiota, immune effector cells, and epithelial cells has to be considered whenever epithelial inflammation is addressed, and the report on successful FMT in patients with GVHD adds a strong piece of evidence.

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