GvHDHub

EHA 2019 | The role of intestinal microbiota in graft-versus-host disease

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At the 24th European Hematology Association (EHA) Congress in Amsterdam, Professor Ernst Holler from the University Medical Center, Regensburg, Germany, gave an educational talk on Saturday 15 June, entitled "Microbiota and graft-*versus*-host disease: a double-edged sword". He spoke about current approaches in microbiota research and how the view of researchers has changed on the pathophysiology of hematopoietic stem cell transplantation (HSCT)-related complications in recent years.[1]

Graft-*versus*-host disease (GvHD) remains the most prominent cause of mortality post-allogeneic HSCT. It has been shown that GvHD affects predominantly the gastrointestinal (GI) system and it is therefore not surprising that recent studies highlighted the important role of the gut microbiota in HSCT outcomes and in the development of GvHD.[1]

Key highlights

- The influence of intestinal bacteria on inflammation in GvHD was first described by van Bekkum: germfree mice showed reduced GvHD[2] while the presence of bacterial lipopolysaccharide enhanced the GvHD reaction[3]
- The 16s molecular sequencing of gut microbiota in patients undergoing allo-HSCT was first described by researchers from the Memorial Sloan Kettering Cancer Center[4] and later on by Holler's group as well[5]. It helped to identify a large group of anaerobic commensal bacteria that had not been integrated into the microbiota-host interaction before
    - Both studies concluded that the loss of commensal bacteria, as well as bacterial diversity in the first two weeks post-HSCT, are associated with a higher risk of GvHD development and transplant mortality
    - Antibiotic prophylaxis, used as a standard of care for prophylaxis of infections and also in GvHD, often leads to loss of microbiota diversity and is now considered as the major cause of dysbiosis and causes an abundance of single pathogenic bacteria[6]
    - However, certain antibiotics seem to spare commensal bacteria such as rifaximin and vancomycin
- Changes in the microbiota during the first two weeks after HSCT can exert a long-lasting impact on the outcome as dysbiosis negatively affect the rebuilding of the immune system by donor cells and their tolerance to host cells. This is similar to the development of the immune system in newborn where dysbiosis predisposes to autoimmune disease[7]
- Swimm *et al.*, found that there is strong protection in GvHD-related pathology and improved survival in mice receiving indole-carbaldehyde prophylaxis without interference with GvL effects[8]
- The axis of microbiota, microbiota-derived metabolites, and GI regulatory T cells seems to be a predominant mechanism in the regulation of GvHD and may equally affect graft-*versus*-leukemia response
- The presence of specific bacteria protects against relapse and thus supports the general concept that intestinal microbiota also regulate antitumor immunosurveillance[1,9]

Antibiotics	Prebiotics	Probiotics	Postbiotics
Complete gut decontamination	Non-digestible carbohydrates	Fecal microbiota transplant (FMT)	Short-chain fatty acids
Rifaximin	Avoidance or encouragements of certain food	Engineered microbes	Indole derivates
Commensal regimens		Rationally selected strains	Avoidance of food that compromises the mucus barrier
Timing of initiation or discontinuation of prophylaxis and empiric treatment			

Table 1: Microbiota based prophylaxis and treatment[1]

Take home messages

- Currently, the most direct approach to restore commensal bacteria and microbiota diversity is FMT[1]. FMT seems to be safe and effective for patients undergoing HSCT[9,10], however, further clinical trials are required
- It should be further evaluated whether the mechanism of healthy donor FMT is based on unknown bacterial strains or works via other metabolic effects provided by a healthy microbiota
- Antibiotic stewardship needs to consider microbiota modulation in the future by:
  - Protecting the intestinal microbiome by antibacterial peptides
- Neutralizing antibiotics in the gut using oral enzymes
- Further studies needed on chronic GvHD occurring at sites with specific microbiota or epithelial interactions

References

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