Allogeneic Hematopoietic Stem Cell Transplantation

Subjects: Oncology

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a well-established treatment for a variety of hematologic malignancies, immune disorders and metabolic diseases. Allo-HSCT often represents the only possible curative therapy, however it is hampered by high morbidity and mortality rates for an array of complications, including bloodstream infection and graft-versus-host disease (GvHD).

Keywords: gut microbiome ; hematopoietic stem cell transplantation

1. Introduction

Recently, the gut microbiome (GM) has emerged as a major contributor to the genesis of the complications of Allo-HSCT and to transplant outcomes [1][2][3]. While this relationship has been extensively studied in terms of clinical correlations, the underlying biological processes still remain poorly understood [4]. A growing body of evidence is now focused on the role of metabolomics in the immune response regulation and in other host biochemical processes [5]. Interestingly, among the factors that modify fecal, plasmatic and urinary metabolites, the GM, alongside with diet, have emerged as the major determinants [6]. Analogously, metabolic activities of GM are affected by environmental factors and host activities. The latter include a complex crosstalk taking place in the intestinal mucosa, with the secretion of mucus, secretory IgA, antibacterial peptides and microRNA [7]. Hence it has been suggested that microbiome-derived metabolites could provide some insights in the complex relationship between the GM, immune system and intestinal microenvironment, particularly in the HSCT setting [8]. To address this issue, we conducted a narrative literature review of studies addressing the role of gut microbiota derived metabolites in allo-HSCT. Electronic databases, including PubMed, Google Scholar and EMBASE, were searched to identify relevant studies published up to December 2020. The search was restricted to English-language studies involving both humans, mice and pre-clinical models. Papers were selected independently by two authors independently, and a third author supervised the selection. Herein, we provide a comprehensive overview on the current knowledge of gut microbiome-derived metabolites and their role in determining relevant biological processes in HSCT (Table 1 and Table 2).

Table 1. Summary of studies investigating the role of microbiome-derived metabolites in HSCT setting in mouse model.

Metabolites	Results	References
Fiber-Derived Metabolites—Short-Chain Fatty Acids		
Butyrate	**Butyrate can improve IEC integrity, decrease apoptosis and mitigate GvHD. Administration of Clostridiales strain leads to higher butyrate levels.**	**[9]**
Butyrate	**Post-transplant enterococcal domination and loss of Clostridiales were associated with a reduction in butyrate in mice developing GvHD.**	**[10]**
Butyrate, propionate	**Butyrate and propionate improve GvHD in mouse model. This effect is dependent on the presence of SCFA receptor GRP43.**	**[11]**
Amino Acid-Derived Metabolites		
Tryptophan-derived AhR ligand		
Indoles and derivatives	**GM derivatives, such as indole, limit intestinal inflammation and damage associated with myeloablative chemotherapy or radiation exposure and acute GvHD. Treatment with indole-3-carboxaldehyde can protect from gut damage in HSCT recipients.**	**[12]**
Tyrosine-derived metabolites		
Tyrosine	**Mice with aGvHD present lower levels of tyrosine. Oral administration of tyrosine can ameliorate aGvHD and modify GM configuration.**	**[13]**

Metabolites	Results	References
Choline-derived metabolites		
TMAO	**TMAO augments allo-reactive T-cell proliferation and Th1 subtype differentiation mediated by the polarized M1 macrophages. This results in higher severity of GvHD.**	[14]
Bile Acids		
Tauroursodeoxycholic acid (TUDCA)	**BAs were altered after HSCT. Administration of exogenous TUDCA protects intestinal epithelium by inflammatory cytokines. TUDCA did not influence GM composition.**	[15]

Table 2. Summary of studies investigating the role of microbiome-derived metabolites in HSCT setting in human.

Metabolites	Study Design	Results	References
Fiber-Derived Metabolites—Short-Chain Fatty Acids			
Butyrate	**1325 allo-HSCT adult patients**	**Post-transplant enterococcal domination and loss of Clostridiales were associated with a reduction in butyrate in patients developing GvHD.**	[10]
Butyrate, propionate, acetate	**35 allo-HSCT adult aGvHD patients**	**Butyrate, propionate and acetate levels were lower in patients experiencing GvHD 2–3 compared to the control. Butyrate was low even in patents with GvHD 1.**	[16]
Butyrate, propionate, acetate, formate	**42 allo-HSCT pediatric patients**	**Butyrate, propionate, acetate decrease within the first 14 days after HSCT and are lower in patients developing GvHD. Formate is a possible marker for the *Enterobacteriaceae* family. Expression of butyrate transporters in GvHD is altered. Greater number of days of antibiotic was associated with lower levels of butyrate and propionate.**	[17]
Butyrate, propionate, hexanoate, isobutyrate	**10 allo-HSCT adult cGvHD patients**	**Plasma concentration of SCFAs reflects fecal content. Patents developing cGvHD present lower plasma concentration of butyrate, propionate, hexanoate, isobutyrate.**	[18]
Butyrate	**44 allo-HSCT adult patients**	**Butyrate levels were correlated with Shannon index and were low in patients experiencing bloodstream infections within 30 days after HSCT.**	[19]
Butyrate, propionate, acetate, desaminotyrosine	**360 allo-HSCT adult patients**	**Butyrate-producing bacteria and fecal SCFAs were associated with a protection from viral lower respiratory tract infections**	[20]
Butyrate	**99 allo-HSCT adult patients**	**Oral supplementation with resistant starch and commercially available prebiotic mixture, GFO, resulted in higher post-HSCT butyrate-producing bacteria and a maintained or increased fecal butyrate concentration.**	[21]
Butyrate, propionate, acetate	**20 allo-HSCT pediatric patients**	**Enteral nutrition resulted in higher fecal concentration of butyrate, propionate and acetate.**	[22]
Amino Acid-Derived Metabolites			
Tryptophan-derived AhR ligand			
3-IS	**131 allo-HSCT adult patients**	**Lower 3-IS urinary levels are associated with higher transplant-related mortality and worse outcome. 3-IS urinary levels are correlated with GM diversity and with a higher presence of *Eubacterium rectale* and *Ruminococcaceae*.**	[23]
3-IS	**13 allo-HSCT adult patients receiving FMT**	**FMT results in higher 3-IS urinary levels.**	[24]
Indoxyl sulfate	**Two cohort of 43 and 56 allo-HSCT adult patients**	**Tryptophan-derived AhR ligand 3-indoxyl sulfate was involved in the GvHD-related metabolic alterations.**	[25]
Tyrosine-derived metabolites			

Metabolites	Study Design	Results	References
Tyrosine	86 allo-HSCT adult patients	In patients who develop aGvHD tyrosine metabolism was found to be altered. Other microbiome-derived metabolites (tryptophan, lysine, phenylalanine and secondary bile acids) were altered.	[26]
Riboflavin (Vitamin B2)-Derived Metabolites			
Riboflavin	121 allo-HSCT adult patients receiving CBT	Patients with post-HSCT MAIT cells reconstitution had a GM with higher expression of genes involved in the riboflavin synthesis pathway.	[27]
Polyamines and Breath Metabolites			
N-acetylputrescine, agmatine	184 allo-HSCT adult patients	Salivary metabolic profile of HSCT patients with and without severe oral mucositis (grade 0–1 vs. 3–4) was found to be different. Metabolites such as urea, 5-aminovalerate, N-acetylputrescine and agmatine, also show differences between the pre-transplant and the time of mucositis onset.	[28]
2-propanol, acetaldehyde, dimethyl sulfide, isoprene, and 1-decene	19 allo-HSCT adult patients	Comparing patients with and without GI GvHD, the former show modification in the levels of volatile organic compounds, namely 2-propanol, acetaldehyde, dimethyl sulfide, isoprene, and 1-decene.	[29]

2. Microbiome-Derived Metabolites in Allogeneic Hematopoietic Stem Cell Transplantation

GM-derived metabolites have emerged as crucial players in mediating crosstalk between GM and host in allo-HSCT recipients. Several questions should still be addressed in the upcoming studies. Firstly, the different metabolic profiles should be more precisely characterized and the relationship between specific bacterial strains and derived metabolites should be investigated. These data should be accomplished with '–omics' approaches, including metabolomics, metagenomics and metatranscriptomics. Alongside with the aforementioned metabolites, many others have been demonstrated to have a role in human homeostasis and should thus be investigated in the HSCT setting [8][30]. Future collaborative studies on larger cohorts will also clarify whether specific metabolic profiles could be associated with allo-HSCT outcomes as it has been demonstrated for GM diversity [1]. Lastly, the different metabolic patterns between children and adults should be directly addressed, considering the differences in GM configuration [31] and HSCT outcomes [32]. Certainly, these data pose a new intriguing field of research and substantial opportunities for the near future. GM-derived metabolites might serve as a feasible surrogate marker for microbiome characterization that may be clinically useful to predict HSCT-related risk [23]. Furthermore, the modulation of GM-derived metabolites should also appear as a target for therapeutic interventions. These should include diet, which is known to represent the main strategy to modulate microbial products m[8], emphasizing the importance of nutritional support during HSCT [22][33][34][35]. Other strategies should also be tested in order to modulate metabolites, such as probiotics, prebiotics and other oral supplements alongside FMT. In conclusion, GM-derived metabolites have proven to be an important field of research in the HSCT setting, also appearing as a promising therapeutic target for the nearfuture.

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