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OBM Transplantation

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Short Communication

Promising Tactics with Certain Probiotics for the Treatment of Nephropathy in Hematopoietic Stem Cell Transplantation

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Academic Editor: Thomas R. Chauncey

Special Issue: Advances in Hematopoietic Stem Cell Transplantation

OBM Transplantation
2022, volume 6, issue 3
doi:10.21926/obm.transplant.2203165

Received: May 02, 2022
Accepted: August 08, 2022
Published: August 30, 2022

Abstract

Hematopoietic stem cell transplantation (HSCT) is a standard form of cellular therapy for patients suffering from malignant hematological diseases. However, graft-versus-host disease (GVHD) is a very serious complication and a major cause of morbidity and mortality after allogeneic HSCT. Calcineurin inhibitors, such as cyclosporine, are widely used to enhance the survival of patients who have undergone HSCT. Unfortunately, both GVHD and cyclosporine occasionally cause nephropathy. Several studies have shown that the gut-kidney axis is associated with nephropathy. Dysbiosis of the gut microbiota might aggravate renal damage by increasing systemic micro-inflammation, suggesting that diet might affect the risk of GVHD. Here, we summarized the recent findings regarding the association between the alteration of gut microbiota and nephrotoxicity. The results suggested that treatment with certain probiotics benefits the symbiosis in the gut-kidney axis and makes HSCT safer.

Keywords

Gut microbiota; hematopoietic stem cell; reactive oxygen species; allogeneic hematopoietic stem cell transplantation; graft-versus-host disease; gut microbiota; gut-kidney axis

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is performed commonly for treating various hematological diseases. HSCT involves the intravenous infusion of hematopoietic stem cells from human leukocyte antigen (HLA)-matched donors (allogeneic) or from the patients themselves (autologous) [1] (Figure 1). However, HSCT procedures are limited by life-threatening complications, and acute graft-versus-host disease (GVHD) is one of them [2]. GVHD is a systemic pathogenic condition that occurs when the graft's immune cells might identify the host as a foreign agent and attack the recipient's cells/tissues. Several organs might be affected by GVHD. Acute kidney injury is a common complication of allogeneic HSCT [3], which might significantly increase patient morbidity and/or mortality. Therefore, the patient needs to undergo rigorous chemotherapy and/or radiotherapy to eliminate residual malignant cells and reduce immunological resistance before HSCT is performed. GVHD can be initiated by several risk factors such as aging and/or intestinal inflammation [4], following which immune recovery occurs and eventually leads to complete recovery. However, GVHD might also progress as a late phase complication at about six months after the HSCT. Chronic kidney injury is a long-term complication of allogeneic HSCT. Calcineurin inhibitors, which are used for prophylaxis treatment of GVHD, can also lead to the development of nephropathy [5]. Cyclosporine, a strong immunosuppressant belonging to the group of calcineurin inhibitors, is recommended as prophylaxis treatment for patients receiving allogeneic HSCT; however, it exhibits nephrotoxicity [5]. Modifiable targets of the gut microbiota might reduce the risk of GVHD and nephrotoxicity [4, 6]. The prevention and/or treatment of GVHD and the adverse effects of cyclosporine are important issues that need to be addressed to improve the efficacy of HSCT. Research on these topics has recently become popular [7].

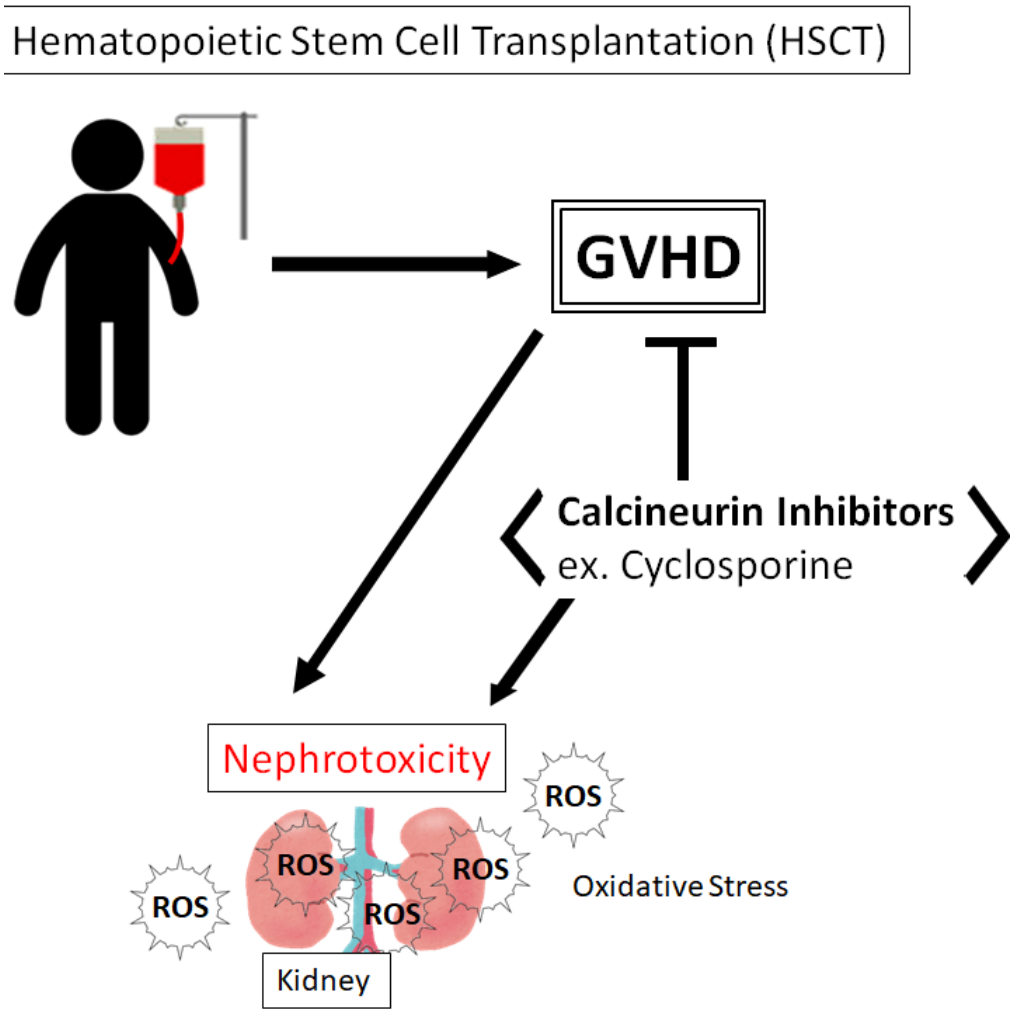

Figure 1 The HSCT patients might suffer from GVHD (graft-versus-host disease), which also increases the risk of developing kidney complications. An immunosuppressant, such as cyclosporine, is commonly administered to HSCT patients to prevent GVHD. However, nephrotoxicity is frequently induced by the use of cyclosporine. Arrowhead represents stimulation and/or augmentation. Hammerhead represents inhibition. Some critical pathways have been omitted for clarity. Abbreviation: ROS, reactive oxygen species; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

2. Nephropathy Induced by the Use of Cyclosporine and GVHD

Cyclosporine is a powerful immunosuppressant used in HSCT or solid organ transplantation for preventing transplant rejection and for treating autoimmune diseases. However, its application is limited because of its severe toxicity to the kidneys [8] (Figure 1). The kidneys are susceptible to hypoxic injury. Calcineurin inhibitors can induce vasoconstriction and reduce the oxygenation of the kidneys [9]. They might also induce arterial hypertension and worsen nephropathy [10]. Cyclosporine can increase the production of reactive oxygen species (ROS) [11], thus inducing glomerular dysfunction and the associated nephrotoxicity [12]. The association between oxidative stress and kidney tubular cell death is a well-known problem that needs to be addressed [13]. Cyclosporine can induce a dose-dependent increase in some oxidants and lipid peroxidation [14], which can exacerbate proximal tubular destruction in the kidneys [15]. Antioxidants, including

vitamin C, vitamin E, and polyphenolic compounds, might inhibit the peroxidation of cyclosporine-induced nephrotoxicity [16]. Also, studies have shown the protective effects of 2-deoxy-D-glucose on nephrotoxicity induced by cyclosporine [17], suggesting a strong role of oxidative stress in cyclosporine-induced renal damage. Therefore, the use of cyclosporine might also be restricted due to its toxicity to other organs, including the liver, via cyclosporine-induced oxidative stress [18].

Graft-versus-host disease is characterized by the activation, expansion, cytokine production, and migration of alloreactive donor T cells. Oxidative stress increases in the recipients of allogeneic HSCT and contributes to the development of GVHD [19]. Patients who undergo HSCT are susceptible to many risk factors that contribute to the development of acute kidney injury [20]. Specifically, GVHD is a major independent risk factor for the development of acute kidney injury (AKI) in HSCT recipients [21]. The occurrence of GVHD might lead to the reprogramming of immune cells, which is associated with the differentiation of CD4-positive cells into type 1 T helper (Th1) and type 17 T helper (Th17) cells along with the dysfunction of regulatory T cells (Tregs) [22]. The Th17 cells affect the immunopathology of lupus nephritis [23]. These cells might be a controller of inflammation in renal injury [24]. An imbalance in the Th17/Treg cells might be the immunological basis of the nephritic syndrome [25].

3. Probiotics as Therapeutic agents against GVHD in HSCT

The microbiota consists of functional microorganisms, including bacteria that reside in the digestive tract and provide benefits to the host [26]. Gut microbiota consists of a multispecies community that might have a symbiotic relationship with the host. Alterations in the microbiota are affected by dietary and/or environmental factors, which can initiate redox signaling in the cells of the gut mucosa [27]. Redox signaling might lead to inflammation. Thus, the gut microbiota has a delicate balance. Perturbations in the microbial balance in the gastrointestinal tract might lead to inflammatory bowel disease. The gut microbiota, ROS, oxidative stress, inflammation, and several diseases might be closely associated. Diet influences the composition of the gut microbiota. Some microbial metabolites, such as short-chain fatty acids (SCFAs), protect the host against GVHD by adjusting immune reactions [28]. Therefore, the loss of intestinal commensals that produce SCFAs might affect the severity of GVHD. Modifying microbial metabolites can strongly affect the prognosis of GVHD [29]. Certain therapeutic methods might alter the composition of the gut microbiota and promote the treatment of nephrotoxicity induced by cyclosporine (Figure 2). Altering the gut microbiota by using probiotics can delay the progression of renal injury and reduce inflammation and/or oxidative stress [30]. For example, the administration of *Lactobacillus plantarum* can decrease the risk of developing a gut-mediated condition in children undergoing HSCT [31]. Prebiotics stimulate the growth of certain microorganisms in the gut for health benefits and even for modulating the aging process [32]. Certain strains of microbiota can decrease GVHD due to the high production of butyrate (an SCFA) [29]. Disrupting the diversity of the gut microbiota can exacerbate GVHD [33]. Interestingly, low diversity of microorganisms can decrease the beneficial effects of prebiotics [34]. Elucidating the structures and activities of the gut microbiota in the host might provide valuable information and contribute to the safety of various treatment strategies in HSCT. The intervention strategies targeting the gut microbiota, including prebiotics, probiotics, postbiotics, and/or fecal microbiota transplantation (FMT), might be used for the treatment of GVHD (Figure 2).

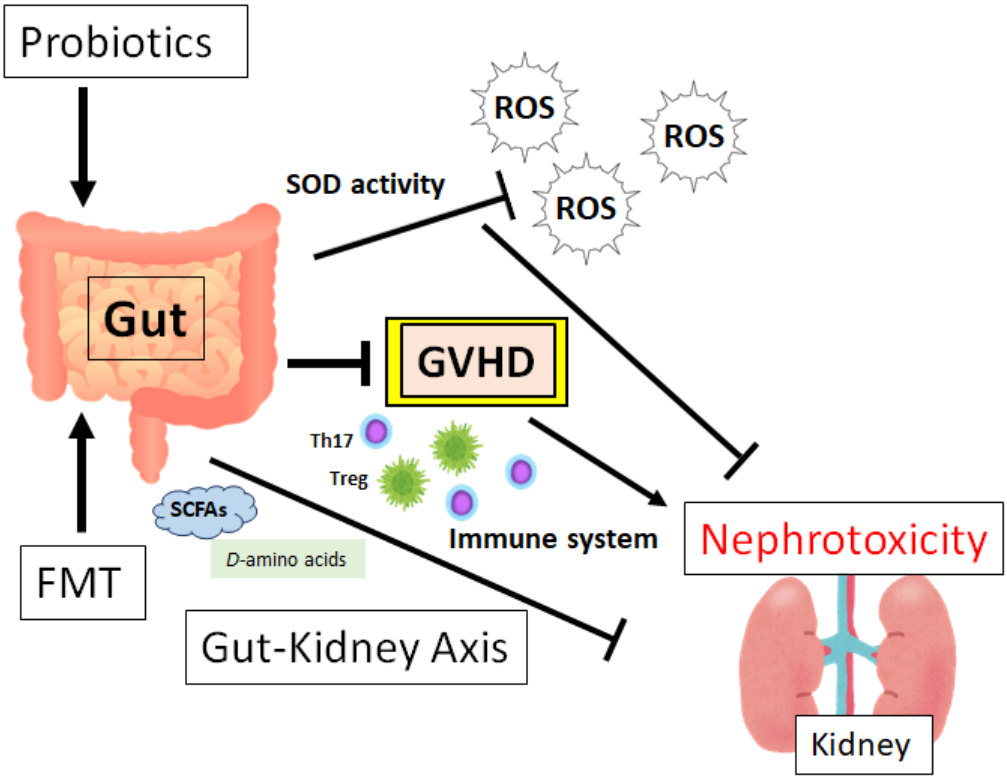

Figure 2 The gut microbiota prevents the progression of nephrotoxicity and GVHD partially by inhibiting ROS. Besides probiotics, in fecal microbiota transplantation (FMT), microorganisms are introduced into a recipient for the safe and successful supplementary treatment of nephrotoxicity and/or GVHD. Arrowhead indicates stimulation and/or augmentation. Hammerhead indicates inhibition. Some critical events, such as cytokine induction, have been omitted for clarity. Abbreviation: FMT, fecal microbiota transplantation; ROS, reactive oxygen species; GVHD, graft-versus-host disease; SOD, superoxide dismutase; SCFAs, short-chain fatty acids; Th17, type 17 T helper cell; Treg, regulatory T cell; GVHD, graft-versus-host disease.

4. Favorable Roles of the Gut-Kidney Axis for the Protection of the Kidneys

The gut microbiota can protect and/or damage host cells/organs, including kidney cells, contributing to the homeostasis of the health-disease balance in the host [35]. Generally, ROS are released by cells as a result of ATP synthesis and can damage cellular DNA [36, 37]. Some important physiological roles of ROS include the regulation of enzymes involved in autophagy, DNA synthesis, and DNA repair [38]. The ROS comprise oxygen-containing energetic molecules capable of reacting with various organic molecules produced due to inflammatory reactions [39]. Certain levels of ROS can alter the signaling pathways to control mRNA and/or protein expression, and in turn, influence cell survival [36, 40]. Gut microbiota might also influence cell survival in some cases. For example, acetate and/or butyrate, produced by the gut microbiota via fermentation protect against oxidative stress in many cell types [41]. Additionally, some microorganisms in the gut can counteract the activity of genotoxic compounds, such as food-related DNA-reacting mutagens [42]. Therefore, understanding redox regulation of physiological processes is important for developing treatment strategies based on the modification of the gut microbiota. Recent advancements in technologies

for the isolation of nucleic acids from feces and DNA sequencing have helped to identify previously unknown beneficial and/or pathological microorganisms in the human gut [43].

The gut microbiota plays a beneficial role in the development of chronic kidney disease [44]. For example, probiotics such as *Akkermansia* and *Lactobacillus* can alleviate renal metabolism in chronic kidney disease through the gut-kidney axis [45]. Altering the composition of the gut microbiota can reduce inflammation in the kidneys. Thus, it is an innovative therapeutic strategy that functions by modifying or remodeling the gut microbiota [46]. The pathogenic role of the gut-kidney axis in the development of chronic kidney disease is also associated with chronic fatty liver disease [47]. Altering the levels of short-chain fatty acids, D-amino acids, and ROS biosynthesis in the gut can influence the pathogenesis of nephrotoxicity [48]. The microbiota associated with the gut-kidney axis plays a key role in the development and/or prevention of diabetic nephropathy [48]. This suggests that the gut microbiota is involved in the nephrotoxicity of GVHD and/or the use of cyclosporine. For example, *Salvia miltiorrhiza* can alleviate renal fibrosis and the effects on metabolism caused by cyclosporine-induced chronic nephrotoxicity in HSCT patients by acting on the gut-kidney axis [45, 49] (Figure 2).

5. Future Perspectives

The details regarding the effects of the alterations in the gut microbiota on the prognosis of GVHD in HSCT patients are not clear. However, protecting the intestinal microenvironment might be a novel strategy to manage GVHD [50]. Additionally, the gut microbiota can modify the pharmacokinetics of cyclosporine [51]. Even if it remains unclear whether modifying the microbiota indirectly affects the severity of GVHD, it might still be used to prevent GVHD in HSCT recipients. A disturbance in the communication between the epithelial cells of the intestine and the gut microbiota might generate immunologically pathogenic responses in the host [52]. For example, the abundance of the gut microbiota, which increases the content of SCFAs, can decrease the permeability of the colon epithelium and affect the balance of Th17/Treg cells [53]. Additionally, a high-calorie diet can reset the gut microbiota and disrupt the balance of Th17/Treg cells, disturb the immune homeostasis, and aggravate inflammatory damage [54]. Several studies on humans have shown that the loss of diversity of the gut microbiota following HSCT might be associated with severe gut injury [55]. The prolonged use of antibiotics might also decrease microbial diversity and increase the risk of GVHD [56]. These findings suggest potential adjustable targets for decreasing the risk of GVHD and/or improving the survival rate after HSCT. Further detailed studies are necessary to determine the immune responses caused by the gut microbiota that lead to the development of inflammatory responses after HSCT and/or the administration of cyclosporine.

Abbreviations

ATP	adenosine triphosphate
DNA	deoxyribonucleic acid
FMT	fecal microbiota transplantation
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplantation
HLA	human leukocyte antigen
ROS	reactive oxygen species

SCFAs	short-chain fatty acids
Th1	type 1 T helper cell
Th17	type 17 T helper cell
Treg	regulatory T cell

Author Contributions

KT and SM contributed conception of the study. KT, HS, YI, AT and SM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and had given final approval of the version to be submitted.

Competing Interests

The authors declare that they have no competing financial interests.

References

1. Orrantia A, Terrén I, Astarloa-Pando G, Zenarruzabeitia O, Borrego F. Human NK cells in autologous hematopoietic stem cell transplantation for cancer treatment. Cancers (Basel). 2021; 13: 1589.
2. Neves JF, Marques A, Valente R, Barata D. Nonlethal, attenuated, transfusion-associated graft-versus-host disease in an immunocompromised child: Case report and review of the literature. Transfusion. 2010; 50: 2484-2488.
3. Miyata M, Ichikawa K, Matsuki E, Watanabe M, Peltier D, Toubai T. Recent advances of acute kidney injury in hematopoietic cell transplantation. Front Immunol. 2021; 12: 779881.
4. Kumari R, Palaniyandi S, Hildebrandt GC. Microbiome: An emerging new frontier in graft-versus-host disease. Dig Dis Sci. 2019; 64: 669-677.
5. Karolin A, Escher G, Rudloff S, Sidler D. Nephrotoxicity of calcineurin inhibitors in kidney epithelial cells is independent of calcineurin and NFAT signalling. Front Pharmacol. 2022; 12: 789080.
6. Zou YT, Zhou J, Zhu JH, Wu CY, Shen H, Zhang W, et al. Gut microbiota mediates the protective effects of traditional Chinese medicine formula Qiong-Yu-Gao against cisplatin-induced acute kidney injury. Microbiol Spectr. 2022: e0075922. doi: 10.1128/spectrum.00759-22.
7. Sadeghi S, Kalantari Y, Seirafianpour F, Goodarzi A. A systematic review of the efficacy and safety of topical cyclosporine in dermatology. Dermatol Ther. 2022; 35: e15490.
8. Woo M, Przepiorka D, Ippoliti C, Warkentin D, Khouri I, Fritsche H, et al. Toxicities of tacrolimus and cyclosporin A after allogeneic blood stem cell transplantation. Bone Marrow Transplant. 1997; 20: 1095-1098.
9. Cippà PE, Grebe SO, Fehr T, Wüthrich RP, Mueller TF. Altitude and arteriolar hyalinosis after kidney transplantation. Nephrology. 2016; 21: 782-784.
10. Hošková L, Málek I, Kopkan L, Kautzner J. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. Physiol Res. 2017; 66: 167-180.
11. Wang QS, Liang C, Jiang S, Zhu D, Sun Y, Niu N, et al. NaHS or lovastatin attenuates cyclosporine A–induced hypertension in rats by inhibiting epithelial sodium channels. Front Pharmacol. 2021; 12: 665111.

12. O'Connell S, Tuite N, Slattery C, Ryan MP, McMorrow T. Cyclosporine A–induced oxidative stress in human renal mesangial cells: A role for ERK 1/2 mapk signaling. Toxicol Sci. 2012; 126: 101-113.
13. Kim J, Jang HS, Park KM. Reactive oxygen species generated by renal ischemia and reperfusion trigger protection against subsequent renal ischemia and reperfusion injury in mice. Am J Physiol Renal Physiol. 2010; 298: F158-F166.
14. Longoni B, Boschi E, Demontis GC, Marchiafava PL, Mosca F. Regulation of Bcl-2 protein expression during oxidative stress in neuronal and in endothelial cells. Biochem Biophys Res Commun. 1999; 260: 522-526.
15. Moon D, Kim J. Cyclosporin A aggravates hydrogen peroxide-induced cell death in kidney proximal tubule epithelial cells. Anat Cell Biol. 2019; 52: 312-323.
16. Longoni B, Migliori M, Ferretti A, Origlia N, Panichi V, Boggi U, et al. Melatonin prevents cyclosporine-induced nephrotoxicity in isolated and perfused rat kidney. Free Radic Res. 2002; 36: 357-363.
17. Ouyang Z, Cao W, Zhu S, Liu X, Zhong Z, Lai X, et al. Protective effects of 2-deoxy-D-glucose on nephrotoxicity induced by cyclosporine A in rats. Int J Clin Exp Pathol. 2014; 7: 4587.
18. Bingul I, Olgac V, Bekpinar S, Uysal M. The protective effect of resveratrol against cyclosporine A-induced oxidative stress and hepatotoxicity. Arch Physiol Biochem. 2021; 127: 551-556.
19. Sofi MH, Wu Y, Schutt SD, Dai M, Daenthanasanmak A, Voss JH, et al. Thioredoxin-1 confines T cell alloresponse and pathogenicity in graft-versus-host disease. J Clin Invest. 2019; 129: 2760-2774.
20. Wanchoo R, Stotter BR, Bayer RL, Jhaveri KD. Acute kidney injury in hematopoietic stem cell transplantation. Curr Opin Crit Care. 2019; 25: 531-538.
21. Krishnappa V, Gupta M, Manu G, Kwatra S, Owusu OT, Raina R. Acute kidney injury in hematopoietic stem cell transplantation: A review. Int J Nephrol. 2016; 2016: 5163789.
22. Mhandire K, Saggu K, Buxbaum NP. Immunometabolic therapeutic targets of graft-versus-host disease (GvHD). Metabolites. 2021; 11: 736.
23. Paquissi FC, Abensur H. The Th17/IL-17 axis and kidney diseases, with focus on lupus nephritis. Front Med. 2021; 8: 654912.
24. Lee H, Lee JW, Yoo KD, Yoo JY, Lee JP, Kim DK, et al. Cln 3-requiring 9 is a negative regulator of Th17 pathway-driven inflammation in anti-glomerular basement membrane glomerulonephritis. Am J Physiol Renal Physiol. 2016; 311: F505-F519.
25. Li YY, Wei SG, Zhao X, Jia YZ, Zhang YF, Sun SZ. Th17/Treg cell expression in children with primary nephritic syndrome and the effects of ox-LDL on Th17/Treg cells. Genet Mol Res. 2016; 15. doi: 10.4238/gmr.15027669.
26. Hacıoglu S, Kunduhoglu B. Probiotic characteristics of lactobacillus brevis KT38-3 isolated from an artisanal tulum cheese. Food Sci Anim Resour. 2021; 41: 967-982.
27. Alam A, Leoni G, Quiros M, Wu H, Desai C, Nishio H, et al. The microenvironment of injured murine gut elicits a local pro-restitutive microbiota. Nat Microbiol. 2016; 1: 15021.
28. Riwes M, Reddy P. Short chain fatty acids: Postbiotics/metabolites and graft versus host disease colitis. Semin Hematol. 2020; 57: 1-6.
29. Mathewson ND, Jenq R, Mathew AV, Koenigsknecht M, Hanash A, Toubai T, et al. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. Nat Immunol. 2016; 17: 505-513.

30. Dai Y, Quan J, Xiong L, Luo Y, Yi B. Probiotics improve renal function, glucose, lipids, inflammation and oxidative stress in diabetic kidney disease: A systematic review and meta-analysis. Ren Fail. 2022; 44: 862-880.
31. Ladas EJ, Bhatia M, Chen L, Sandler E, Petrovic A, Berman DM, et al. The safety and feasibility of probiotics in children and adolescents undergoing hematopoietic cell transplantation. Bone Marrow Transplant. 2016; 51: 262-266.
32. Chenhuichen C, Cabello-Olmo M, Barajas M, Izquierdo M, Ramírez-Vélez R, Zambom-Ferraresi F, et al. Impact of probiotics and prebiotics in the modulation of the major events of the aging process: A systematic review of randomized controlled trials. Exp Gerontol. 2022; 164: 111809.
33. Ma T, Chen Y, Li LJ, Zhang LS. Opportunities and challenges for gut microbiota in acute leukemia. Front Oncol. 2021; 11: 692951.
34. Yoshifuji K, Inamoto K, Kiridoshi Y, Takeshita K, Sasajima S, Shiraishi Y, et al. Prebiotics protect against acute graft-versus-host disease and preserve the gut microbiota in stem cell transplantation. Blood Adv. 2020; 4: 4607-4617.
35. Ferreira RDS, Mendonça LABM, Ribeiro CFA, Calças NC, Guimarães RCA, Nascimento VAD, et al. Relationship between intestinal microbiota, diet and biological systems: An integrated view. Crit Rev Food Sci Nutr. 2022; 62: 1166-1186.
36. Ikeda Y, Nagase N, Tsuji A, Taniguchi K, Kitagishi Y, Matsuda S. Comprehension of the relationship between autophagy and reactive oxygen species for superior cancer therapy with histone deacetylase inhibitors. Oxygen. 2021; 1: 22-31.
37. Ikeda Y, Taniguchi K, Nagase N, Tsuji A, Kitagishi Y, Matsuda S. Reactive oxygen species may influence on the crossroads of stemness, senescence, and carcinogenesis in a cell via the roles of APRO family proteins. Explor Med. 2021; 2: 443-454.
38. Tsitsipatis D, Martindale JL, Ubaida-Mohien C, Lyashkov A, Yanai H, Kashyap A, et al. Proteomes of primary skin fibroblasts from healthy individuals reveal altered cell responses across the life span. Aging Cell. 2022; 21: e13609.
39. Wu S, Liu X, Cheng L, Wang D, Qin G, Zhang X, et al. Protective mechanism of leucine and isoleucine against H_2O_2-induced oxidative damage in bovine mammary epithelial cells. Oxid Med Cell Longev. 2022; 2022: 4013575.
40. Arfin S, Jha NK, Jha SK, Kesari KK, Ruokolainen J, Roychoudhury S, et al. Oxidative stress in cancer cell metabolism. Antioxidants (Basel). 2021; 10: 642.
41. Hu S, Kuwabara R, de Haan BJ, Smink AM, de Vos P. Acetate and butyrate improve β-cell metabolism and mitochondrial respiration under oxidative stress. Int J Mol Sci. 2020; 21:1542.
42. Garcia-Gonzalez N, Prete R, Perugini M, Merola C, Battista N, Corsetti A. Probiotic antigenotoxic activity as a DNA bioprotective tool: A minireview with focus on endocrine disruptors. FEMS Microbiol Lett. 2020; 367: fnaa041.
43. Kanangat S, Skaljic I. Microbiome analysis, the immune response and transplantation in the era of next generation sequencing. Hum Immunol. 2021; 82: 883-901.
44. Hobby GP, Karaduta O, Dusio GF, Singh M, Zybailov BL, Arthur JM. Chronic kidney disease and the gut microbiome. Am J Physiol Renal Physiol. 2019; 316: F1211-F1217.
45. Han C, Jiang YH, Li W, Liu Y. Astragalus membranaceus and Salvia miltiorrhiza ameliorates cyclosporin A-induced chronic nephrotoxicity through the "gut-kidney axis". J Ethnopharmacol. 2021; 269: 113768.

46. Snelson M, Clarke RE, Nguyen TV, Penfold SA, Forbes JM, Tan SM, et al. Long term high protein diet feeding alters the microbiome and increases intestinal permeability, systemic inflammation and kidney injury in mice. Mol Nutr Food Res. 2021; 65: e2000851.
47. Raj D, Tomar B, Lahiri A, Mulay SR. The gut-liver-kidney axis: Novel regulator of fatty liver associated chronic kidney disease. Pharmacol Res. 2020; 152: 104617.
48. Nagase N, Ikeda Y, Tsuji A, Kitagishi Y, Matsuda S. Efficacy of probiotics on the modulation of gut microbiota in the treatment of diabetic nephropathy. World J Diabetes. 2022; 13: 150-160.
49. Cai H, Su S, Li Y, Zhu Z, Guo J, Zhu Y, et al. Danshen can interact with intestinal bacteria from normal and chronic renal failure rats. Biomed Pharmacother. 2019; 109: 1758-1771.
50. Zhou Z, Shang T, Li X, Zhu H, Qi YB, Zhao X, et al. Protecting intestinal microenvironment alleviates acute graft-versus-host disease. Front Physiol. 2020; 11: 608279.
51. Yang Y, Hu N, Gao XJ, Li T, Yan ZX, Wang PP, et al. Dextran sulfate sodium-induced colitis and ginseng intervention altered oral pharmacokinetics of cyclosporine a in rats. J Ethnopharmacol. 2021; 265: 113251.
52. Zeiser R, Warnatz K, Rosshart S, Sagar, Tanriver Y. GVHD, IBD, and primary immunodeficiencies: The gut as a target of immunopathology resulting from impaired immunity. Eur J Immunol. 2022. doi: 10.1002/eji.202149530.
53. Sun P, Zhang C, Huang Y, Yang J, Zhou F, Zeng J, et al. Jiangu granule ameliorated OVX rats bone loss by modulating gut microbiota-SCFAs-Treg/Th17 axis. Biomed Pharmacother. 2022; 150: 112975.
54. Liu H, Bai C, Xian F, Liu S, Long C, Hu L, et al. A high-calorie diet aggravates LPS-induced pneumonia by disturbing the gut microbiota and Th17/Treg balance. J Leukoc Biol. 2022; 112: 127-141.
55. Weber D, Hiergeist A, Weber M, Dettmer K, Wolff D, Hahn J, et al. Detrimental effect of broad-spectrum antibiotics on intestinal microbiome diversity in patients after allogeneic stem cell transplantation: Lack of commensal sparing antibiotics. Clin Infect Dis. 2019; 68: 1303-1310.
56. Romick-Rosendale LE, Haslam DB, Lane A, Denson L, Lake K, Wilkey A, et al. Antibiotic exposure and reduced short chain fatty acid production after hematopoietic stem cell transplant. Biol Blood Marrow Transplant. 2018; 24: 2418-2424.