GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

The role of the gut micro biota in kidney disease

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GSC Advanced Research and Reviews, 2023, 14(03), 292–299

Publication history: Received on 21 February 2023; revised on 28 March 2023; accepted on 31 March 2023

Article DOI: https://doi.org/10.30574/gscarr.2023.14.3.0106

Abstract

There is increasing evidence of the influence of the gut microbiota on kidney diseases and precursors such as hypertension, diabetes, cardiovascular diseases and its complications, such as stroke, heart failure, and myocardial infarction. This is no surprising considering that the most common risk factor for hypertension, such as age, sex medication, and diet, can also impact the gut microbiota.

For example, sodium and fermentable fiber have been studied in relation to both hypertension and the gut microbe Inflammation and fibrosis are the important pathophysiologic processes in diabetic kidney disease (DKD), which is induced by epigenetics, especially histone posttranslational modification (HPTMs). Have been indicated to play different roles in the repair of DNA damage.

Recent reports highlighted that butyrate, one of the short-chain fatty acids (SCFAs) primarily originated from the fermentation of dietary fiber in the gut, attenuates inflammation and fibrosis in the prevention and treatment of DKD, however the molecular mechanisms are still unclear.

Histone lysine butyrylation (Kbu), a novel histone modification marker induced by butyrate, has been found to be involved in the regulation of pathophysiological processes. To reveal the mechanisms of butyrate-induced histone (Kbu), in the prevention and treatment of DKD, both DKD models *in vivo* and in vitro were treated with sodium butyrate (NaB). The results confirmed that exogenous NaB improved the disorder of glucose and lipid metabolism, prevented proteinuria and renal failure, and inhibited renal inflammation and fibrosis

New treatment options in the form of prebiotics (dietary fiber), probiotics (lactobacillus spp) and postbiotics (the short-chain fatty acids acetate, propionate, and butyrate) have all been demonstrated to be beneficial in the kidney disease.

We should include short-chain fatty acids such as butyric acid in our patients with kidney disease regardless of the etiology to maintain the intestinal microbiota and avoid dysbiosis that causes inflammation, proteinuria, endothelial dysfunction.

Keywords: DKD (diabetic kidney disease); HPTMs (histone posttranslational modification); SCFAs (short-chain fatty acids); KBU (histone lysine butyrylation) NaB(sodium butyrate); Histone deacetylases (HDACs); Proliferator-activated receptors (PPARs); Glucagon-like peptide 1 (GLP1); CKD (chronic kidney disease); AKI (acute kidney injury)

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1. Introduction

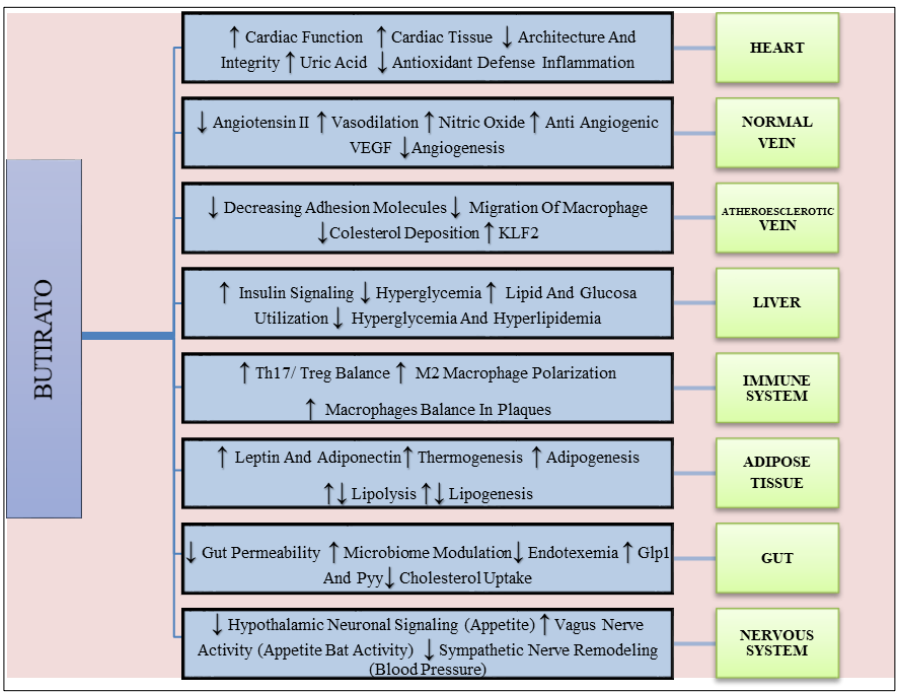
The gut microbiota comprises trillions of microbes that play beneficial roles in gut and immune homeostasis and health. Beneficial bacterial metabolites include the short -chain fatty acids (SCFAs), In particular, acetate propionate, and butyrate, which are bioproducts of bacterial fermentation of indigestible dietary fibers[1-2], very high amount of SCFAs is produced in the colon, where most gut commensal bacteria reside, but some SCFAs are transported to blood and the periphery, SCFAs promote intestinal homeostasis, including IgA and mucus production, expansion of colonic T regulatory cells, and epithelial integrity[3]. SCFAs are also detectable in serum and urine[4], although at much lower concentrations than in the gut. The beneficial effect of SCFAs at extraintestinal sites has been established for type 1 and type 2[5-6] asthma[7-8], obesity[9], appetite suppression and hypothalamic neuronal activation[10-11] and hypertension[12.]

Butyrate is a four-carbon SCFAs, mainly known as a fuel for colonocytes. In addition to dietary fibers especially resistant starch. The key aspects of butyrate mechanism of action can be listed as follows. First, butiryc acid has an immunomodulatory and anti-inflammatory effect has reported to be an epigenetic modifier by acting as a histone deacetylases (HDACs) inhibitor. Many studies show a positive correlation in the capacity of butyrate in the inhibition of HDACs, induction of apoptosis and/or detection of the cell cycle in colon cancer cells[13].

Second, Free Fatty acid receptor 2 (FFAR2) also known as GPR43 belongs to this group of GPCRs and has been shown to participate in a number of important biological activities. FFAR2 is activated by short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate. have been shown to play vital role in the immune regulation and metabolic homeostasis, Butyrate is known to be a pleiotropic molecule that as well as binding to FFARs, also has the ability to bind peroxisome proliferator-activated receptor (PPARs).

PPARs are a family of ligand-activated transcription factors that recognized to have a significant impact on metabolism related pathway[14-15]. Butyrate could induce adipogenesis by activating PPARγ, and Adipogenesis is associated with reduced inflammatory and oxidative molecules production in adipose tissue, organs lipotoxicity an insulin resistance[16].

Diabetes and cardiometabolic diseases are low-grade inflammatory diseases and knowing that butyric acid inhibits some pathways that are involved in inflammation, decreases oxidative stress, an cause an increase in insulin sensitivity by increasing activity of insulin receptors, protective , that supplementation of diet with 1% butyrate could reduce atherosclerotic lesions in ApoE knockout mice by decreasing adhesion molecules production and reducing migrations of macrophage to the lesion site[17-18]. See **figure 1**



FFAR: free fatty acid receptor, HDAC: Histone deacetylase, KLF2: Kruppel Like Factor 2, VEGF: vascular endothelial growth factor, GLP-1: glucagon-like peptide 1, PYY, peptide YY

Figure 1 The key aspects of butyrate mechanism of protective effects in CVD and CVD risk factors

Chronic kidney disease (CKD) has a worldwide increasing prevalence of 8–16% (14). In most aspects, CKD hasmany features of a Western life style disease, namely an altered gut microbiota[19] Recent data support a link between altered gut microbiota composition a kidney disease[20-21] The butyric acid inhibits oxidative stress and inflammatory gene expression and then ameliorates inhibits oxidative stress and inflammatory DKD via inhibition of histone deacetylases (HDACs)[22]

Furthermore, NaB also alleviates glucolipid metabolism disorders by increasing glucagon-like peptide 1 (GLP1)

HDACs inhibitors are emerging as a promising approach to attenuate tissue damage, although the potential of synthetic HDACs inhibitors may be limited because of side effects or toxicity, the butiryc acid is natural inhibitor[23].

Is a promising and nontoxic alternative. Augmented butyrate levels could be achieved through direct delivery, or through a medicinal food approach Mediterranean diet, or a high-fiber butyrate-yielding diet may be strategies to prevent CKD.[24]

2. Intestinal microbiota and chronic kidney disease

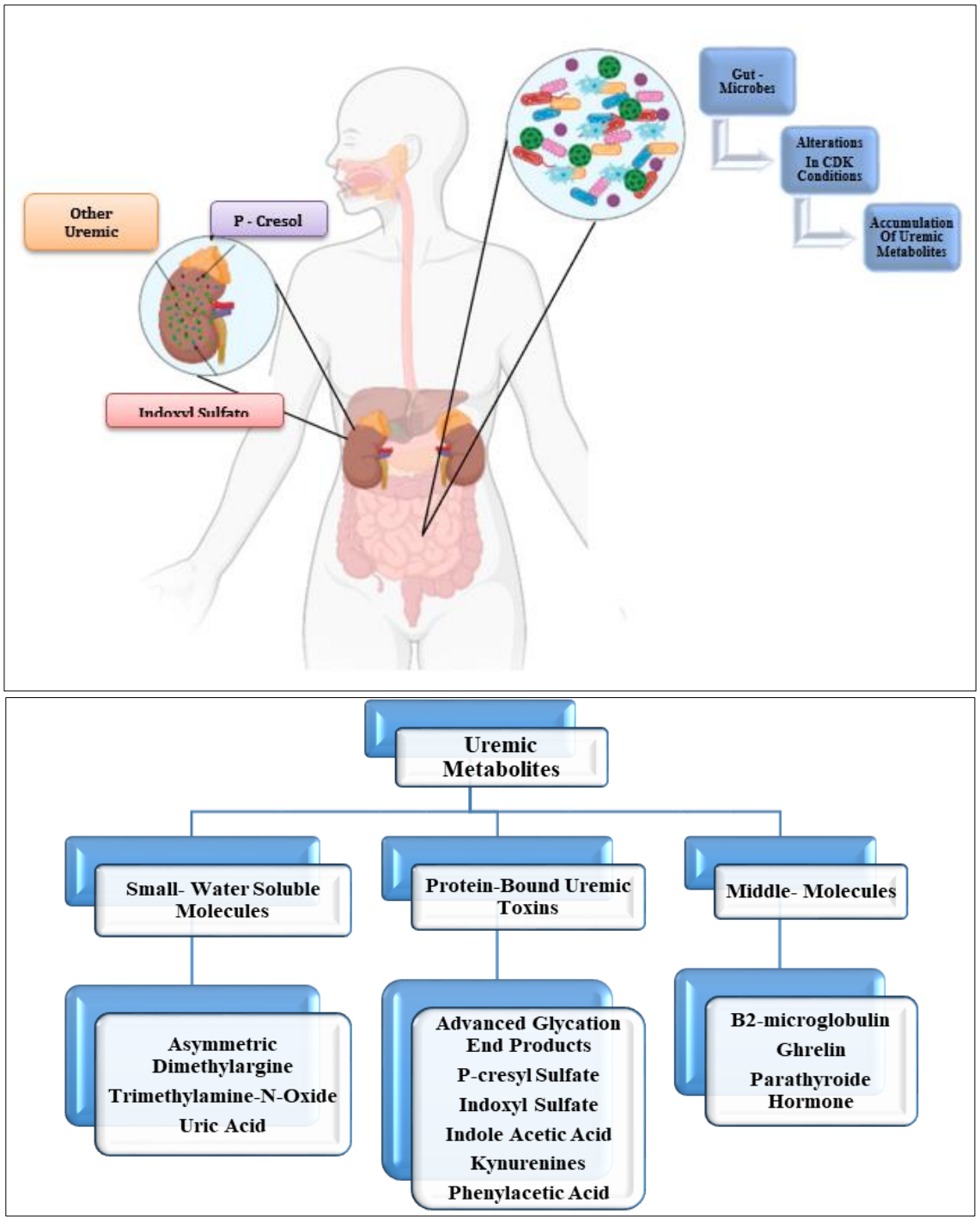
Several studies have shown the presence of dysbiosis in animal models and humans with chronic kidney disease (CKD)[24] In an early study, found significant differences in the abundance of 190 bacterial operational taxonomic units between end-stage kidney disease (ESKD) and healthy controls.

They showed that the abundance of saccharolytic microorganisms such as Lactobacillus and Bifidobacteria decreases in CKD, whereas that of proteolytic microorganisms such as Clostridium and Bacteroides increases[25]

Urea directly provokes a decrease in transepithelial resistance of cultured enterocytes, and intestinal edema and regional ischemia in CKD could lead to development of leaky gut[26]. At the molecular level, intestinal barrier disruption has been associated with decreased expression of heat shock protein 70 (HSP70) and claudin-1, increased expression of pore-forming claudin-2, and epithelial apoptosis in the colon of a mouse model of CKD [27] approximately 10 g of protein reaches the colon daily, where they degraded by intestinal bacteria to metabolites such as ammonium, amines, thiols, phenols, and indoles. These products of fermentation in the colon are eliminated by the faeces, although a part is absorbed and is eliminated by the kidney.

Toxins derived from the gut are associated with poor outcomes of CKD. Protein-bound uremic toxins such as p-cresyl sulfate or indoxyl sulfate, produced by fermentation of tyrosine or tryptophan by intestinal bacteria, are excreted by tubular secretion in the kidney, leading to elevated blood levels in patients with CKD. Indoxyl sulfate has been reported to increase transforming growth factor-β expression and oxidative stress, promote smooth muscle cell calcification, and cause endothelial cell dysfunction. These protein-bound uremic toxins ultimately lead to increased risk of cardiovascular diseases, mortality, and CKD progression[28] , Trimethylamine N-oxide (TMAO), another uremic toxin derived from bacterial metabolism of quaternary amines, has been reported to be associated with increased mortality in patients with CKD [29-30] (See **figure 2**)

Based on these findings, therapeutic strategies targeting the microbiota, including prebiotics, an indigestible food ingredient that induces activation of microorganisms; probiotics, living microorganisms; symbiotic, a combination of prebiotics and probiotics; and adsorbents, which adsorb toxic substances, might be useful in the treatment of CKD. AST-120, an insoluble enteric carbon adsorbent that can suppress the accumulation of indoxyl sulfate, has been shown to delay dialysis initiation and to slow the reduction in glomerular filtration rate despite negative results shown in a recent double-blind controlled trial[31]



The uremic metabolites had been Classified into three categories based on their solubility and molecular weight: small water-soluble molecules, protein-bound uremic toxins (PBUTs) and middle molecules. Each category has characteristic representatives which have the highest global toxicity score in terms of the number of biological systems affected and overall experimental and clinical evidence

Figure 2 Chronic kidney disease and uremic toxins

3. Intestinal microbiota and nephrolithiasis

The genetic predisposition or environmental conditions shared by family members can influence disease pathophysiology. The concentrations of urinary calcium, oxalate, phosphate, and uric acid play an important role in stone formation, and emerging evidence indicates active participation of the gut/microbiome in the pathogenesis of nephrolithiasis. Oxalate, which is a constituent of the most common type of kidney stone, is excreted via the urine after

absorption in the intestine. Lack of commensal bacteria with oxalate-degrading activity has been shown to be associated with stone formation. In uric acid excretion, one-third of the uric acid is degraded by intestinal uricolysis, also suggesting the possible role of intestinal microbiota in the pathogenesis of uric acid stones. Observations have shown that the overall microbial composition in patients with kidney stones is considerably different from that in healthy controls, which further support the intestinal microbiota as an important contributor to stone formation[32]

Prevention and treatment of dysbiosis in recent years, there has been a growing interest in restoring the symbiosis of the intestinal microflora in CKD in order to reduce the generation of uremic toxins, oxidative stress and the inflammation

3.1. Diet rich in fiber

A diet rich in fiber increases the production of short-chain fatty acids, which provide energy to the intestinal flora. And allows amino acids that reach the colon to be incorporated into bacterial proteins and excreted in instead of being fermented to uremic solute furthermore, the furthermore, the SCFAs (short-chain fatty acids) are used as a substrate by the intestinal mucosa and maintain its functionality and integrity. The fiber increases intestinal transit, reducing the fermentation time of amino acids and improves the composition of the microflora, reducing the production of undesirable solutes.

In healthy subjects, a vegetarian vs. an omnivore reduces the generation of Indoxyl sulfates (IS) which was related to higher fiber intake and lower of protein from the fisrt .A very low protein diet (0,3 g/kg/weight/day) supplemented with keto analogues of amino acids also reduces IS level in patient with ckd[33]

3.2. Prebiotics, probiotics and symbiotics: Probiotics are defined as “live microorganisms”

Which when administered in adequate amounts provide a health benefit to the host. A recent review evaluates the possible benefits of probiotics in general and especially in ckd the effectiveness of probiotics to lower toxin levels uremic disorders and delaying the progression of ckd has been investigated in in vitro models, animal models and in patients. Symbiotic are probiotic supplements combined with prebiotics. In hemodialysis patients the treatment with a symbiotic decreased the levels of IS

The generation of toxins uremic could be reduced by selectively increasing saccharolytic bacteria (which digest dietary fiber) and reducing proteolytic bacteria (fermenters of proteins and amino acids) in the colon. The main regulator of the metabolism of colonic bacteria is the availability of nutrients and, specifically, the rate of hydrates fermentable carbon vs. nitrogen.

Prebiotics are indigestible food components that, selectively fermenting, allow changes specific in composition or activity on microflora gastrointestinal that confers benefits to the health and well-being of the host. Probiotics stimulate growth or the activity of one or a limited number of bacteria in the colon, may increase the rate of carbohydrates[34]

3.3. Adsorptive therapies: the use of oral sorbents could decrease circulating uremic toxins or endotoxins

Of intestinal origin. AST-120 Oral Sorbent Decreases IS levels in a dose-dependent manner[35].

In addition, a reduction in IS levels has been described, PCS or phenyl sulfate and oxidative stress in patients on hemodialysis[36]

Other authors have described that the administration of AST-120 improves the erythropoietic response.

AST-120 improves barrier dysfunction intestine and decreases plasmatic levels of endotoxins, markers of inflammation and oxidative stress in a CKD model in rats[37]

4. Conclusion

Uremic metabolites exhibit cell-damaging properties, damage the intestinal epithelial cell wall, increase gut permeability and lead to the translocation of bacteria and endotoxins from the gut into the circulatory system. To limit CKD progression, it is imperative to address the changes in the gut microbiome; therefore, it is necessary to identify and characterize the role of different microbes in the progression of CKD.

Advances in high-throughput sequencing technology have provided unprecedented insights into the complex microbial communities of the various mucosal surfaces. Similar to several other metabolic and chronic inflammatory conditions including diabetes, obesity, or rheumatoid arthritis, emerging data have demonstrated that alteration of intestinal microbiota is associated with a variety of kidney diseases.

Dysbiosis and associated barrier dysfunction, bacterial translocation, and an altered immune response were shown to play important roles in both AKI and CKD. Several strains of bacteria participating in degradation of oxalate have been shown to be associated with oxalate stone formation, and recent studies also suggest the presence of more complex interactions between the microbiota and kidney in transplantation recipients.

However, many of these studies only show a correlation, and causal relationship remains largely unclear. To develop microbiota-targeted therapeutics, further studies unraveling the mechanisms underlying the shifts of microbiota, metabolites, and their impact on disease pathogenesis are needed. Despite promising data from several clinical trials testing the effect of pre-, pro-, and symbiotic in various kidney diseases, they are derived from studies that enrolled only small numbers of patients; also, the results are inconsistent and limited. Various factors such as individual genetic characteristics, race, and environmental factors complicate the interaction between the microbial community and the host, and targeting a single microbial community might not provide sufficient control over complex host and microbial interactions.

Compliance with ethical standards

Acknowledgments

Acknowledgments to the anonymous reviewers of the article for providing constructive criticism throughout the development of the article.

Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

References

[1] Koh, A., De Vadder, F., Kovatcheva-Datchary, P., and Backhed, F. ¨ (2016) From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 165, 1332–1345

[2] Tan, J. K., McKenzie, C., Mariño, E., Macia, L., and Mackay, C. R. (2017) Metabolite-sensing G protein-coupled receptors-facilitators of diet-related immune regulation. Annu. Rev. Immunol. 35, 371–402

[3] Thorburn, A. N., Macia, L., and Mackay, C. R. (2014) Diet, metabolites, and "western-lifestyle" inflammatory diseases. Immunity 40, 833–842

[4] Verbeke, K., Ferchaud-Roucher, V., Preston, T., Small, A. C., Henckaerts, L., Krempf, M., Wang, H., Vonk, R. J., and Priebe, M. G. (2010) Influence of the type of indigestible carbohydrate on plasma and urine short-chain fatty acid profiles in healthy human volunteers. Eur. J. Clin. Nutr. 64, 678–684

[5] Mariño, E., Richards, J. L., McLeod, K. H., Stanley, D., Yap, Y. A., Knight, J., McKenzie, C., Kranich, J., Oliveira, A. C., Rossello, F. J., Krishnamurthy, B., Nefzger, C. M., Macia, L., Thorburn, A., Baxter, A. G.,Morahan, G.,Wong, L. H., Polo, J.M.,Moore, R. J., Lockett, T. J., Clarke, J.M., Topping, D. L., Harrison, L. C., andMackay, C. R. (2017) Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. Nat. Immunol. 18, 552–562, erratum: 1271

[6] Zhao, L., Zhang, F., Ding, X.,Wu, G., Lam, Y. Y.,Wang, X., Fu, H., Xue, X., Lu, C., Ma, J., Yu, L., Xu, C., Ren, Z., Xu, Y., Xu, S., Shen, H., Zhu, X., Shi, Y., Shen, Q., Dong, W., Liu, R., Ling, Y., Zeng, Y., Wang, X., Zhang, Q., Wang, J., Wang, L., Wu, Y., Zeng, B., Wei, H., Zhang, M., Peng, Y., and Zhang, C. (2018) Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 359, 1151–1156

[7] Thorburn, A. N., McKenzie, C. I., Shen, S., Stanley, D., Macia, L., Mason, L. J., Roberts, L. K., Wong, C. H., Shim, R., Robert, R., Chevalier, N., Tan, J. K., Mariño, E., Moore, R. J., Wong, L., McConville, M. J., Tull, D. L., Wood, L. G., Murphy, V. E., Mattes, J., Gibson, P. G., and Mackay, C. R. (2015) Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. Nat. Commun. 6, 7320

[8] Trompette, A., Gollwitzer, E. S., Yadava, K., Sichelstiel, A. K., Sprenger, N., Ngom-Bru, C., Blanchard, C., Junt, T., Nicod, L. P., Harris, N. L., and Marsland, B. J. (2014) Gut microbiotametabolism of dietaryfiber influences allergic airway disease and hematopoiesis. Nat. Med. 20, 159–166

[9] Den Besten, G., Bleeker, A., Gerding, A., van Eunen, K., Havinga, R., van Dijk, T. H., Oosterveer, M. H., Jonker, J. W., Groen, A. K., Reijngoud, D. J., and Bakker, B. M. (2015) Short-chain fatty acids protect against high-fat diet-induced obesity via a PPARg-dependent switch from lipogenesis to fat oxidation. Diabetes 64, 2398–2408

[10] Frost, G., Sleeth, M. L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., Anastasovska, J., Ghourab, S., Hankir, M., Zhang, S., Carling, D., Swann, J. R., Gibson, G., Viardot, A., Morrison, D., Louise Thomas, E., and Bell, J. D. (2014) The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 5, 3611

[11] Psichas, A., Sleeth, M. L., Murphy, K. G., Brooks, L., Bewick, G. A., Hanyaloglu, A. C., Ghatei, M. A., Bloom, S. R., and Frost, G. (2015) The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int. J. Obes. (Lond) 39, 424–429

[12] Pluznick, J. L., Protzko, R. J., Gevorgyan, H., Peterlin, Z., Sipos, A., Han, J., Brunet, I., Wan, L. X., Rey, F., Wang, T., Firestein, S. J., Yanagisawa, M., Gordon, J. I., Eichmann, A., Peti-Peterdi,

[13] Thangaraju M, Carswell KN, Prasad PD, Ganapathy V. Las células de cáncer de colon mantienen niveles bajos de piruvato para evitar la muerte celular causada por la inhibición de HDAC1 / HDAC3. La revista bioquímica. 2009, 417 : 379–389.

[14] Den Besten, G., Bleeker, A., Gerding, A., van Eunen, K., Havinga, R., van Dijk, T. H., et al. (2015). Short-Chain Fatty Acids Protect against High-Fat DietInduced Obesity via a PPARγ-dependent Switch from Lipogenesis to Fat Oxidation. Diabetes 64 (7), 2398–2408. doi:10.2337/db14-1213

[15] Du, Y., Li, X., Su, C., Xi, M., Zhang, X., Jiang, Z., et al. (2020). Butyrate Protects against High-Fat Diet-Induced Atherosclerosis via Up-Regulating ABCA1 Expression in Apolipoprotein E-Deficiency Mice. Br. J. Pharmacol. 177 (8), 1754–1772. doi:10.1111/bph.14933

[16] Evans, J. L., Maddux, B. A., and Goldfine, I. D. (2005). The Molecular Basis for Oxidative Stress-Induced Insulin Resistance. Antioxid. Redox Signal. 7 (7-8), 1040–1052. doi:10.1089/ars.2005.7.1040

[17] Gao, Z., Yin, J., Zhang, J., Ward, R. E., Martin, R. J., Lefevre, M., et al. (2009). Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. Diabetes 58 (7), 1509–1517. doi:10.2337/db08-1637

[18] Hulten, E. A., Bittencourt, M. S., Preston, R., Singh, A., Romagnolli, C., Ghoshhajra, B., et al. (2017). Obesity, Metabolic Syndrome and Cardiovascular Prognosis: from the Partners Coronary Computed Tomography Angiography Registry. Cardiovasc. Diabetol. 16 (1), 14–11. doi:10.1186/s12933-017-0496-8

[19] Vaziri, N. D., Wong, J., Pahl, M., Piceno, Y. M., Yuan, J., DeSantis, T. Z., Ni, Z., Nguyen, T. H., and Andersen, G. L. (2013) Chronic kidney disease alters intestinal microbial flora. Kidney Int. 83, 308–315

[20] Felizardo, R. J., Castoldi, A., Andrade-Oliveira, V., and Camara, N. O. ˆ (2016) The microbiota and chronic kidney diseases: a double-edged sword. Clin. Transl. Immunology 5, e86

[21] Felizardo, R. J. F., Watanabe, I. K. M., Dardi, P., Rossoni, L. V., and Camara, N. O. S. (2019) The interplay among gut microbiota, ˆ hypertension and kidney diseases: the role of short-chain fatty acids. Pharmacol. Res. 141, 366–377

[22] Wong, J., Piceno, Y. M., DeSantis, T. Z., Pahl, M., Andersen, G. L., and Vaziri, N. D. (2014) Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. Am. J. Nephrol. 39, 230–237

[23] C. Moreno-Yruela, D. Zhang, W. Wei et al., "Class I histone deacetylases (HDAC1-3) are histone lysine delactylases," Science Advances, vol. 8, no. 3, p. eabi6696, 2022.

[24] C. Moreno-Yruela, D. Zhang, W. Wei et al., "Class I histone deacetylases (HDAC1-3) are histone lysine delactylases," Science Advances, vol. 8, no. 3, p. eabi6696, 2022.

[25] Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int 2103, 83:308–315.

[26] 21. Chaves LD, McSkimming DI, Bryniarski MA, et al. Chronic kidney disease, uremic milieu, and its effects on gut bacterial microbiota dysbiosis. Am J Physiol Renal Physiol 2018, 315:F487– F502.

[27] Yang J, Lim SY, Ko YS, et al. Intestinal barrier disruption and dysregulated mucosal immunity contribute to kidney fibrosis in chronic kidney disease. Nephrol Dial Transplant 2019, 34:419– 428.

[28] Miyazaki T, Ise M, Hirata M, et al. Indoxyl sulfate stimulates renal synthesis of transforming growth factor-beta 1 and progression of renal failure. Kidney Int Suppl 1997, 63:S211–S2114.

[29] Tang WH, Wang Z, Kennedy DJ, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res 2015, 116:448–455.

[30] Missailidis C, Hällqvist J, Qureshi AR, et al. Serum trimethylamine-N-oxide is strongly related to renal function and predicts outcome in chronic kidney disease. PloS One 2016, 11:e0141738.

[31] Ueda H, Shibahara N, Takagi S, Inoue T, Katsuoka Y. AST-120, an oral adsorbent, delays the initiation of dialysis in patients with chronic kidney diseases. Ther Apher Dial 2007, 11:189–195.

[32] 5. Stern JM, Moazami S, Qiu Y, et al. Evidence for a distinct gut microbiome in kidney stone formers compared to non-stone formers. Urolithiasis 2016, 44:399–407.

[33] Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol. 2014, 25:657–70.

[34] Meijers BK, de Preter V, Verbeke K, Vanrenterghem Y, Evenepoel P. p-cresyl sulfate serum concentrations in haemodialysis patients are reduced by the prebiotic oligofructose enriched inulin. Nephrol Dial Transplant. 2010, 25:219–24.

[35] Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. Am J Kidney Dis. 2006, 47:565–77.

[36] Yamamoto S, Kazama JJ, Omori K, Matsuo K, Takahashi Y, Kawamura K, et al. Continuous reduction of protein-bound uraemic toxins with improved oxidative stress by using the oral charcoal adsorbent AST-120 in haemodialysis patients. Sci Rep. 2015, 5:14381, doi: 10.1038/srep14381.

[37] Vaziri ND, Yuan J, Khazaeli M, Masuda Y, Ichii H, Liu S. Oral activated charcoal adsorbent (AST-120) ameliorates chronic kidney disease-induced intestinal epithelial barrier disruption. Am J Nephrol. 2013, 37:518–25.