International Journal of Celiac Disease, 2016, Vol. 4, No. 3, 92-94
Available online at http://pubs.sciepub.com/ijcd/4/3/12

DOI:10.12691/ijcd-4-3-12

Nutrients, Bugs and Us: The Short-chain Fatty Acids Story in Celiac Disease

Aaron Lerner[1,2,*], Jeremias Patricia[2], Torsten Matthias[2]

[1]B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[2]AESKU.KIPP Institute, Wendelsheim, Germany
*Corresponding author: aaronlerner1948@gmail.com

Abstract The gut ecosystem with myriads of microorganisms and the high concentration of immune system cells can be considered as a separate organ on its own. The balanced interaction between the host and microbial cells has been shaped during the long co-evolutionary process. In dysbiotic conditions, however, this balance is compromised and results in abnormal interaction between the host and microbiota. Celiac disease is such an example were dysbiotic and metabolic signature are shaping the disease progression in genetically susceptible individuals. Short chain fatty acids are bacterial originated metabolic messenger between the pathobionts and the intestinal mucosa. Their local luminal effects and systemic ones were just recently unraveled. Accumulating data attribute multiple beneficial effects to them. Changes in microbiota and their short-chain fatty acids production is clearly related to the pathogenesis of celiac disease and might open new therapeutic strategies to combat the disease.

Keywords: *celiac disease, stool, microbiota, dysbiota, bacteria, short-chain fatty acids*

Cite This Article: Aaron Lerner, Jeremias Patricia, and Torsten Matthias, "Nutrients, Bugs and Us: The Short-chain Fatty Acids Story in Celiac Disease." *International Journal of Celiac Disease*, vol. 4, no. 3 (2016): 92-94. doi: 10.12691/ijcd-4-3-12.

1. Introduction

The gut ecosystem with myriads of microorganisms and the high concentration of immune system cells is considered as a separate organ on its own. Intricate host–microbe symbiotic relationships in the human gut have evolved during the long-term coevolution between the two. It resulted in fine-tuned inter kingdom molecular adaptations that benefit both sides. The microbiome is essential for food digestion, generation of anti-inflammatory substances, drug activation, immune induction, training and function and finally, zooming on the present topic, production of short-chain fatty acids (SCFAs). Being an integral part of our immune makeup, the microbiota mitigates against untoward effects, by establishing a biotic barrier against the hostile environment.

In dysbiotic conditions, however, this balance is compromised and results in abnormal interaction between the host and the microbiota [1]. Some members of the gut microbiota have been linked to various autoimmune diseases. Changing a single bacterial species and/or the entire commensal community can alter the outcome of a specific condition due to the imbalance of pathological/protective immune responses. In this regards, a summary of specific microbial species in relation to defined animal models of autoimmune diseases and their functions, in relation to disease progression, was recently published [1]. In celiac disease (CD), increased diversity of the following microbial species: *Lachnoanaerobaculum*, *Prevotella*, *Actinomycetes*, *Lachnoanaerobaculum umeaense* was detected. In human CD, however, genetic factors, antibiotic usage and breast feeding were related to microbiota changes, representing risk factors that might induce dysbiosis [2]. Decrease in *Bifidobacterium ssp*, *Bacteroides*, *Parabacteroides* and increases in *Candida albicance*, *Escherichia* and *Helicobacter* were observed. Due to the complexity of the 100 trillion gut microbiota and the additional alteration occurring in CD dysbiome, the eternal question of a hen or an egg is still ongoing [3]. If it is the cause, consequence or co-evolution, is still obscure.

Not less important is the transcriptome, proteinome and the metabolome associated with those changes. Those components are the direct messengers between the bugs and us. One of the most characterized metabolic products group is the SCFAs, recently explored in the stools of CD children [4]. The authors studied the correlations between selected stool microbiota/dysbiota and the faecal concentrations of SCFAs, in pediatric CD. They found clear changes in the faecal bugs and in SCFAs concentrations and concluded that those changes relate to CD pathogenesis. Furthermore, the pro-inflammatory SCFAs, namely acetic and propionic acids, can potentially represent disease related markers. Interestingly, their bacterial origin was not conclusive and rest debatable. Due to the importance of the above mentioned topics, the new observations on the luminal and systemic function of SCFAs and the continuing efforts for new therapeutic strategies, the present editorial will update and expand on them.

2. The Dysbiotic Origin of SCFA in CD is Debatable

Microbe-generated metabolites are intertwined with the enteral mucosa cell biology and functions, and SCFAs-mediated signaling pathways are essential for gut microbe's communication with the host. Acetate, propionate, butyrate, and pentanoate, having respectively, 2, 3, 4, and 5 carbon atoms are SCFAs, largely produced by microbial fermentation of complex non-digestible polysaccharides like starches and fibers in the colon. They are absorbed by the colonic epithelium where the preferred fuel source of colonocytes is butyrate. Microbiota-produced SCFAs enter the bloodstream through the portal vein of the host and/or the distal colon. Then, they are distributed to remote organs where they are taken up, metabolized and used in a variety of cellular responses [5]. Similarly to the variability in the loss of diversity of the microbiome repertoire in CD, not a lot is known about the origin of the luminal metabolic compounds. It is well established that SCFAs production is heavily related to the diet, but the specific bacterial species rate of SCFAs production is yet, unknown. Several groups observed a metabolic signature in CD lumen and stools of specific and total SCFAs [6,7,8]. Interestingly, as shown by the parallel microbiology and metabolome approach, the long-term gluten-free diet did not completely restore the microbiota and, consequently, the metabolome of CD children [7]. This points to a genetic CD predisposition that influences those intestinal events. Despite the suggestion that probiotic bacteria (e.g., *Lactobacillus* and *Bifidobacterium*) may modify the metabolism in the large intestine by increasing the synthesis of SCFAs, we are far from "Rebiosis" or the answer to the question: how to restore the microbial diversity and functionality in CD [8]?

3. Luminal and Systemic Function of SCFAs

Food intake regulates energy balance, and its dysregulation leads to metabolic disorders such as obesity and/or diabetes. Free fatty acids are not only essential nutrients they can also act as signaling molecules in various cellular processes. Table 1 summarizes the luminal, as well as, the systemic effects attributed to SCFAs. Their functions span numerous biological domains and pathways, attesting to their essentiality, evolutionary conservation and biological importance.

Table 1. Luminal and systemic function of SCFAs

Luminal effects	Systemic effects
• stimulate Na^+ and water absorption from the large intestine • colonocyte fuel (butyrate) • gut immune homeostasis • activate G-protein-coupled receptors: regulation of gut hormones, obesity, and gut inflammation • potential protection for ulcerative colitis, Crohn's disease, antibiotic associated diarrhea • induce production of antimicrobial peptides	• energy homeostasis, source of energy • regulate epigenetics, histone deacetylase inhibitor • immunomodulation • activate G-protein-coupled receptors: regulation of systemic hormones, obesity, inflammation • decrease IL-12, increase IL-23 • activate dendritic cells • pro-apoptosis and cell proliferation regulation • potential protection from diabetes • regulation of fatty acid, glucose, cholesterol metabolisms • improvement of insulin sensitivity • appetite regulation • influence allergic airway disease and hematopoiesis • regulate blood pressure

Adapted from references: [9-15].

4. Is SCFA a Potential Therapeutic Target for CD?

Accumulating evidence established the microbiotic and the metabolic signature in CD. Further elucidation of the role and functions of the metabolic products produced by the CD associated dysbiosis, might open a new line of therapeutical strategies. Until today efforts were concentrated on bacterial degradation of gluten in the bakery or in the intestinal lumen [16]. Even probiotics didn't deliver the goods, since once pathogenic dysbiosis sets in, probiotics have not proven to be remedial. Based on the above, one can foresee several new alternatives, based on the synthetic biology [17]. "Living pills" are engineered bacteria having the potential to be an effective mean for delivering, enhancing, or themselves acting as therapeutic agents to treat certain diseases, including CD [18]. Such a pill, harboring the enzymatic activity with high through output of SCFAs synthesis and delivery, might be beneficial. Ongoing efforts are being made to adapt a variety of commensal microbial species for remodeling the gut ecobiotics in disease-treating indications [19]. One can consider it as a science fiction, but, engineered viruses can also selectively destroy pathogenic bacteria [20]. In CD we are not at this stage, but scientific visions can always fasten medical solutions.

5. Conclusions

Intestinal lumen microbiotic and metabolic signature is well established in CD. SCFAs are only part of these events, but accumulating data attribute multiple beneficial effects to them. Changes in microbiota and SCFAs production are clearly related to the pathogenesis of CD. However, the origin of the specific CD microbiota that secrete and influence CD initiation or progression is still unknown. Understanding the eco-events that drive CD genesis and the function of the luminal SCFAs might open new horizon for future remedies. The data outlined herein provide encouraging road-map toward new therapeutical strategies to help the gluten intolerant populations.

References

[1] Lerner A, Aminov R, Matthias T. Dysbiosis may trigger autoimmune diseases via inappropriate posttranslational modification of host proteins. Frontiers in Microbiology. 2016; 7: Article 84.

[2] Nagao-Kitamoto H, Kitamoto S, Kuffa P, Kamada N. Pathogenic role of the gut microbiota in gastrointestinal diseases. Intest Res. 2016; 14: 127-38.

[3] Cenit MC, Olivares M, Codoñer-Franch P, Sanz Y. Intestinal Microbiota and Celiac Disease: Cause, Consequence or Co-Evolution? Nutrients. 2015; 7: 6900-23.

[4] Maša Primec, Martina Klemenak, Irene Aloisio, Mario Gorenjak, Diana Di Gioia, Dušanka Mičetić-Turk, Tomaž Langerholc. Faecal Concentrations of Short-chain Fatty Acids and Selected Bacteria in Healthy and Celiac Children. Internat J of Celiac Disease. 2016; 4: 95-101.

[5] Walter H. Moos, Douglas V. Faller, David N. Harpp, Iphigenia Kanara,Julie Pernokas, Whitney R. Powers, nKosta Steliou. Microbiota and Neurological Disorders: A Gut Feeling. Biores Open Access. 2016; 5: 137-145.

[6] Nistal E, Caminero A, Vivas S, Ruiz de Morales JM, Sáenz de Miera LE, Rodríguez-Aparicio LB, Casqueiro J. Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. Biochimie. 2012; 94: 1724-9.

[7] Di Cagno R, De Angelis M, De Pasquale I, Ndagijimana M, Vernocchi P, Ricciuti P, et al. Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. BMC Microbiol. 2011; 4; 11: 219.

[8] Di Cagno R, Rizzello CG, Gagliardi F, Ricciuti P, Ndagijimana M, Francavilla R, et al. Different fecal microbiotas and volatile organic compounds in treated and untreated children with celiac disease. Appl Environ Microbiol. 2009 ; 75: 3963-71.

[9] Sun Y, O'Riordan MX. Regulation of bacterial pathogenesis by intestinal short-chain Fatty acids. Adv Appl Microbiol. 2013; 85: 93-118.

[10] den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013; 54: 2325-40.

[11] Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients. 2015; 7: 2839-49.

[12] Byrne CS, Chambers ES, Morrison DJ, Frost G. The role of short chain fatty acids in appetite regulation and energy homeostasis. Int J Obes (Lond). 2015; 39: 1331-8.

[13] Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med. 2014; 20: 159-66.

[14] Miyamoto J, Kasubuchi M, Nakajima A, Irie J, Itoh H, Kimura I. The role of short-chain fatty acid on blood pressure regulation. Curr Opin Nephrol Hypertens. 2016; 25: 379-83.

[15] Natarajan N, Pluznick JL. From microbe to man: the role of microbial short chain fatty acid metabolites in host cell biology. Am J Physiol Cell Physiol. 2014; 307: C979-85.

[16] Lerner A., Matthias T. Food Industrial Microbial Transglutaminase in Celiac Disease: Treat or Trick. International J Celiac Dis. 2015; 3: 1-6.

[17] Moos WH, Faller DV, Harpp DN, Kanara I, Pernokas J, Powers WR, et al. Microbiota and Neurological Disorders: A Gut Feeling. Biores Open Access. 2016; 5: 137-45.

[18] Eisenstein M. Living factories of the future. Nature. 2016; 531: 401-3.

[19] Garber K. Drugging the gut microbiome. Nat Biotechnol. 2015; 33: 228-31.

[20] Madhusoodanan J Viral Soldiers. The Scientist 2016; 30: 27-33.