BAOJ Biotechnology

Chun Loong HO, et al., BAOJ Biotech 2018, 4: 2
4: 036

Mini review

The Role of Proteins and Peptides in Human Microbiome Modulation

Zhao LIU[1] and Chun Loong HO[1*]

[1]*Department of Biomedical Engineering, Southern University of Science and Technology (SUSTech), Shenzhen, China*

Abstract

Protein and peptides play an essential role in controlling the host microbiome. The microbiome is the collective genomic response of the microbiota to the host organism. The microbiota is the collection of microbes that dwell within the host body, that plays an important role in managing the host metabolism. Here, we discuss the role of polypeptides in controlling the microbiome through direct and indirect means. The microbiome is affected by internal and external factors. The external factor includes the use of prebiotics and probiotics help to stimulate the growth of certain microbial populations in the microbiota, while internal factors cover the host biochemical response and the native microbiota in response to changes in the host. The direct interactions are where the polypeptides play a direct role in stimulating or inhibiting the growth of certain microbes, thus changing the composition of the microbiota and therein reshaping the landscape of the microbiome. The indirect interaction, on the other hand, is the interference of the microbial-microbial or microbial-host interaction, that results in the change of biochemical response. This may cause changes in the microbial population, but the biochemical changes stem from the changes in the microbiota response. While the microbiome and its microbiota composition differ in various parts of the host (i.e., skin, respiratory tract, gastrointestinal tract, and urinary tract), we believe by understanding the role of peptides and how it affects the host health, we can use peptides to modulate the microbiome for therapeutic means.

Key Words: Therapeutic Peptides; Microbiome, ; Microbiota, ; Prebiotics; Probiotics, ; Quorum-Sensing

Introduction

Polypeptides have been used for modulating the microbiota population and affecting the microbiome. These polypeptides, through direct or indirect interactions, results in microbiome changes that affect the host health [1]. The microbiota refers to the host-associated microorganisms and viruses, while the microbiome is the mutual interaction of the host with its microbiota's collective genome [2]. Microbes co-evolve with its host playing an essential role in the host development. The number of microorganisms in the human body accounts to more than a trillion commensal microorganisms, deeming it as an "essential organ". In recent years, much research has been dedicated to understanding the role manner of the microbiome in facilitating host biochemical changes and its impact on therapeutic responses. It has been shown that the variance of human microbiome differs significantly in different populations, age groups, and lifestyles [3]. This delicate balance is easily perturbed by changes in host behavior, diet and host biochemistry. Interestingly, the introduction of peptides as a form of prebiotics or microbial secretome alters the host's biological processes [1] . Thus, we intend to discuss the manner how polypeptides affect the microbiome and its potential role as a form of therapeutics. Here, we will discuss the use of polypeptides in microbiota modulation (direct interaction) and the use of polypeptides in interfering with the microbial-microbial/host-microbial interactions (indirect interaction).

***Corresponding Author:** Chun Loong HO, Department of Biomedical Engineering, Southern University of Science and Technology, 1088 Xueyuan Blvd, Nanshan District, Shenzhen Guangdong, People's Republic of China, Tel: +86-0755-88015283, E-mail: hejl@sustc.edu.cn

Sub Date: October 16th 2018 , **Acc Date:** October 22nd 2018, **Pub Date:** October 24th 2018

Citation: Chun Loong HO, Zhao LIU (2018) The Role of Proteins and Peptides in Human Microbiome Modulation. BAOJ Biotech. 4: 036.

The Use of Peptides for Microbiota Modulation

Gut microbiome modulation could be controlled by altering the population of the human microbiota [2]. The human microbiota exists in a homeostatic balance, where the microbiota population depends on the host biochemistry and its interacting microbes. As the host biochemistry changes, so do the population of these microbes. It is evident that the changes in these population do cause changes in the host metabolism. For example, the use of fecal matter transplantation (FMT) in obese and diabetic patients changes in recipient's biochemistry [4]. Thus, to facilitate a sustainable manner of maintaining this balance, the use of peptides could help in promoting the growth of certain classes of microbes or suppressing the growth of other less desirable microbes.

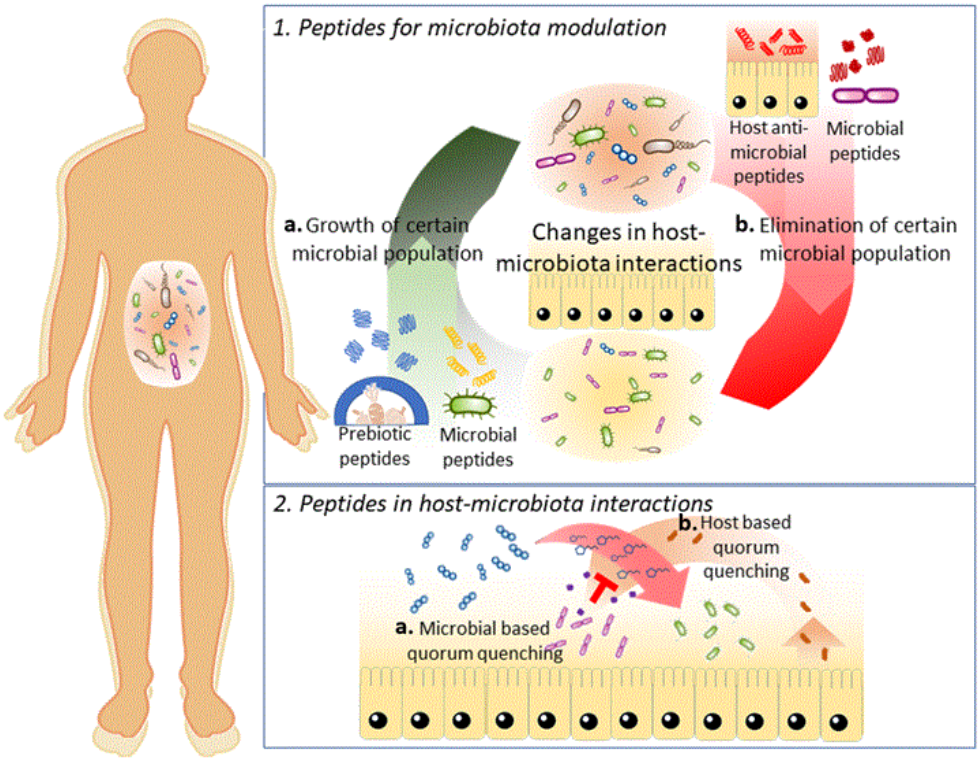

Figure 1:

The use of prebiotics has been used to encourage the re-population of a healthy microbiota and thus a healthy microbiome (Figure 1.1.a). Prebiotics has been studied intensively over the last decade, in which prebiotics (such as high-dietary fibers, oligosaccharides [5] and altering the composition of food-derived peptides [6] could encourage the growth of certain types of healthy microbes. The whey-isolated peptide was found to encourage the growth of probiotic bacteria in vitro. These peptide isolates orally introduced to mice promoted the abundance of *Lactobacillus* spp., *Bifidobacterium* spp., and Bacteriodetes by gastrointestinal tract acidification; further encouraging these microbes to produce organic acids such as lactic acid and acetic acid [6]. Additionally, certain commensal microbes found in the gut have a widely distributed non-ribosomal peptide synthase (NRPS) gene cluster that encodes for pyrazinones and dihydropyrazinones [7]. These NRPS produce peptide aldehydes that function as a potent protease inhibitor. The production of these peptide aldehydes helps in maintaining the microbial balance in the microbiome space [7].

The alternative to this is the suppression of certain microbial types by peptides (Figure 1.1.b). Various peptides that are expressed either by the host metabolism or the interacting microbiota suppresses the growth of certain classes of microbes. The host body naturally produces specific peptides that suppress the growth of pathogenic microbes and establishing a homeostatic balance in the host. Examples include lactoferrin that controls microbiota by sequestering metal ions [8], bactericidal/permeability-increasing proteins [9], cathelicidins [10] and defensins [11]. The host body biochemistry deploys the

antimicrobial peptides (AMP) to modulate the microbiota that would help in re-establishing balanced homeostasis, favoring microbes that would help in the restoration. In the human gut, it has been shown that these selections take place at the mucosal, where the deployment of different isomeric forms of defensin facilitates the selection of either gram-positive or gram-negative bacteria [12]. The changes in the host biochemistry also promote specific behavior in microbes, giving them the advantage to grow. This stimulation results in the production of microbial AMPs to outcompete other microbes in the host [13]. An example of this is the changes of oral microbiome, where the introduction of an antimicrobial peptide to clear *Streptococcus mutans* resulted in changes in the microbiota population [14].

Peptide-Mediated Host-Microbial/Microbial-Microbial Interference

The microbiome is regulated by the inter-microbial interaction within the host microbiome space. In regulating the microbiome, peptides are employed by the host or other competing microbes alter the function of the microbiota by interfering with the signaling processes. In this section, we discuss the different microbial-microbial and host-microbial interferences.

The microbes in an established microbiota communicate with each and other members using quorum sensing (QS) molecule. These QS molecules comprise of acyl-homoserine lactones (AHL) from gram-negative bacteria, auto inducing peptides (AIP) from certain gram-positive bacteria and farnesol in yeast [15]. However, there are certain microbes produce polypeptides to quench these quorum sensing signals, altering the microbial behavior that affects the microbiome in general. This quorum quenching either result from the hydrolysis of the QS-molecules or competitive binding of QS-inhibitors to the receptor. Microbes such as *Pseudomonas aeruginosa* PAO1, *Variovorax*sp. and certain *Streptomyces* sp. produces AHL-acylase that hydrolyzes AHL, thus interrupting QS [16]. In competitive binding, AIP of different *Staphylococcus* sp. produced from the expression of AgrD with different sequence resulted in the quorum quenching in two-component QS system. This indicates that between the differing *Staphylococci,* AIP is used as a QS competitive inhibitor [17]. Among *Staphylococcus aureus,* the non-pathogenic microbe competes with their pathogenic cousins by producing an RNAIII inhibiting peptide, that interferes with the RNAIII activating proteins required from AIP-mediated QS [18].

Similarly, in the host-microbial interference, the host biochemistry disrupts the microbial QS by hydrolysis of the QS molecules. In mice, the introduction of hapten AP4-5 resulted in the production of anti-AP4 monoclonal antibodies, that binds to AIP rendering the QS molecule redundant [19]. Additionally, the expression of paraoxonase enzymes from mammalian epithelial cells results in the hydrolysis of AHL, on top the other synthetic chemicals introduced into the host [20,21]. Studies showing the deficiency of the host to produce paraoxonase enzymes result in the enhancement of gram-negative QS, thus supporting the proof that the mammalian host counters the microbial pathogenesis by hydrolysis of QS molecules [22,23].

Thus, polypeptides are used by both microbes and the host biochemistry to regulate the behaviour of certain populations of the microbiota. These changes in behaviour result in the change of the microbiome and affecting the host biochemistry.

Conclusion

Polypeptides play an essential role in changing the microbiome landscape, thus affecting the host health. By understanding how these polypeptides function, we could further use them as therapeutic tools to mold the microbiome to increase the therapeutic efficacy of treatments administered to patients. Additionally, a better understanding of these polypeptides can further increase the available synthetic biology tools.

Acknowledgments

This manuscript is supported by the Department of Biomedical Engineering, Southern University of Science and Technology. We would like to acknowledge Miss Jingyu Xiao and Miss Chen Xinyi for their administrative assistance. We would also like to offer our appreciation to Mr. Nikhil Aggarwal, Ms. Niying Chua, Mr. Felix Meier, Mr. Kai Sheng Lim, Mr. Liu Feng and Mr. Qiu Yuanxin for their input on this manuscript.

References

1. Miller GW (2014) In Miller, G. W. (ed.), The Exposome. Academic Press, San Diego 27-37.

2. Dewar M, IzawaJ, Li F, Chanyi RM, Reid G, Burton JP (2018) In Ku, J. H. (ed.), Bladder Cancer. Academic Press 615-628.

3. Taneja V (2017) In Legato, M. J. (ed.), Principles of Gender-Specific Medicine (Third Edition). Academic Press, San Diego 569-583.

4. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, et al. (2012) Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome. Gastroenterology 143(4): 913-916.e917.

5. García-Cayuela T, Díez-Municio M, Herrero M, Martínez-Cuesta MC, Peláez C, et al. (2014) Selective fermentation of potential

prebiotic lactose-derived oligosaccharides by probiotic bacteria. International Dairy Journal 38(1): 11-15.

6. Yu YJ, Amorim M, Marques C, Calhau C Pintado M (2016) Effects of whey peptide extract on the growth of probiotics and gut microbiota. Journal of Functional Foods 21: 507-516.

7. Guo CJ, Chang FY, Wyche TP, Backus KM, Acker TM, et al. (2017) Discovery of Reactive Microbiota-Derived Metabolites that Inhibit Host Proteases Cell 168(3): 517-526.e518.

8. Ho CL, Hwang IY, Loh K, Chang MW (2015) Matrix-immobilized yeast for large-scale production of recombinant human lactoferrin. MedChemComm 6(3): 486-491.

9. Canny G, Cario E, Lennartsson A, Gullberg U, Brennan C, et al. (2006) Functional and biochemical characterization of epithelial bactericidal/permeability-increasing protein. American journal of physiology. Gastrointestinal and liver physiology 290(3): G557-567.

10. Bucki R, Leszczynska K , Namiot A, Sokolowski W (2010) Cathelicidin LL-37: a multitask antimicrobial peptide. Archivum immunologiae et therapiae experimentalis 58(1): 15-25.

11. Ericksen B, Wu Z, Lu W, Lehrer RI (2005) Antibacterial activity and specificity of the six human {alpha}-defensins. Antimicrobial agents and chemotherapy 49(1): 269-275.

12. Wei G, de Leeuw E, Pazgier M, Yuan W, Zou G, et al. (2009) Through the looking glass, mechanistic insights from enantiomeric human defensins. The Journal of biological chemistry 284(42): 29180-29192.

13. Zhang L, Hu W, Ho J, Fitzgerald RJ, GinT, (2018) In Cho, C. H. (ed.), Antimicrobial Peptides in Gastrointestinal Diseases. Academic Press 21-33.

14. Guo L, McLean JS, YangY, Eckert R, Kaplan CW, et al. (2015) Precision-guided antimicrobial peptide as a targeted modulator of human microbial ecology. Proceedings of the National Academy of Sciences of the United States of America 112(4): 7569-7574.

15. Hornby JM, Jensen EC, Lisec AD, Tasto JJ, Jahnke B, et al. (2001) Quorum Sensing in the Dimorphic FungusCandida albicans Is Mediated by Farnesol. Applied and Environmental Microbiology 67(7): 2982-2992.

16. Dong YH, Wang LH, Zhang LH (2007) Quorum-quenching microbial infections: mechanisms and implications. Philosophical Transactions of the Royal Society B: Biological Sciences 362(1438): 1201-1211.

17. Ji G, Beavis R, Novick RP (1997) Bacterial Interference Caused by Autoinducing Peptide Variants. Science 276(5321): 2027-2030.

18. Balaban N, Goldkorn T, Nhan RT, Dang LB, Scott S, et al. (1998) Autoinducer of Virulence As a Target for Vaccine and Therapy Against Staphylococcus aureus. Science 280(5362): 438-440.

19. Park J, Jagasia R, Kaufmann GF, Mathison JC, Ruiz DI, Moss JA, et al. (2007) Infection control by antibody disruption of bacterial quorum sensing signaling. Chemistry & biology 14(10): 1119-1127.

20. Draganov DI, Teiber JF, Speelman A, Osawa Y, Sunahara R, et al. (2005) Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities. Journal of lipid research 46(6): 1239-1247.

21. Ozer EA, Pezzulo A, Shih DM, Chun C, Furlong C, et al. (2005) Human and murine paraoxonase 1 are host modulators of Pseudomonas aeruginosa quorum-sensing. FEMS microbiology letters 253(1): 29-37.

22. Stoltz DA, Ozer EA, Ng CJ, Yu JM, Reddy ST, et al. (2007) Paraoxonase-2 deficiency enhances Pseudomonas aeruginosa quorum sensing in murine tracheal epithelia. American journal of physiology. Lung cellular and molecular physiology 292(4): L852-860.

23. Teiber JF, Horke S, Haines DC, Chowdhary PK, Xiao J, et al. (2008) Dominant role of paraoxonases in inactivation of the Pseudomonas aeruginosa quorum-sensing signal N-(3-oxododecanoyl)-L-homoserine lactone. Infect Immun 76(6): 2512-2519.