Symbiosis

www.symbiosisonline.org
www.symbiosisonlinepublishing.com

Mini Review | Journal of Nutritional Health & Food Science | Open Access

Special Issue: Food Safety & Hygiene

Diet, Gut Microbiota and Obesity

Hongjie Li[1,4]* and Chuanxian Wei[2,3]*

[1]*Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94945-1400, USA*
[2]*State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, the Chinese Academy of Sciences, 15 Datun Road, Beijing 100101, China*
[3]*University of Chinese Academy of Sciences, Beijing, 100080, China*
[4]*Department of Biology, University of Rochester, River Campus Box 270211, Rochester, NY, 14627, USA*

Received: July 15, 2015; Accepted: September 09, 2015; Published: September 20, 2015

***Corresponding authors:** *Hongjie Li, Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94945-1400, USA, Tel: + 1-585-290-0085; Emails: hli@buckinstitute.org*

Chuanxian Wei, State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, the Chinese Academy of Sciences, 15 Datun Road, Beijing 100101, China, Tel: 86-10-64880162; Fax: + 86-10-64888474; Emails: weichuanxian@moon.ibp.ac.cn

Abstract

Increasing evidence suggests that alteration of gut microbiota ('dysbiosis') can lead to a number of diseases, including obesity, which affects a large population in the world and is now a global health issue. The mechanisms of gut microbiota-mediated obesity are just being explored and characterized in recent years. It has been suggested that dysbiosis of gut microbiota contributes to obesity development mainly in three ways: affecting energy harvest, altering host gene expression, and triggering chronic inflammation. Among the factors that determine and influence gut microbiota composition, diet is one of the best characterized in human and animal studies, and has been long linked with weight gain or loss. In this review, we will discuss recent advances of mechanisms through which gut microbiota dysbiosis leads to obesity. We will further discuss the underlying causes of obesity-related gut microbiota, highlighting dietary effects.

Keywords: Diet; Gut microbiota dysbiosis; Obesity

Introduction

Obesity is a medical condition with excess body weight, increasing the risk of a number of diseases, such as Type 2 Diabetes (T2D), heart disease, liver disease, and stroke. In clinic, obesity is described as Body Mass Index (BMI) [1] higher than 30kg/m^2, which is a general standard for defining obese individuals. It is believed that consumption of high-calorie diet and reduced physical activity are the causes of high prevalence of obesity in high-income countries, where sedentary lifestyles are becoming predominant [2]. Emerging evidence now suggests that gut microbiota plays a key role in mediating diet- and lifestyle-caused obesity (Figure 1) [3].

The human Gastrointestinal (GI) tract is estimated to be colonized by over 100 trillion (10^{14}) microbes, ten times more than the number of human cells in the body [4]. The term gut microbiota describes all the commensal microbial species living in the intestine. It is becoming evident that gut microbiota plays critical roles in maintaining human health on many aspects, including fermenting unused energy substrates, training the immune system, maintaining epithelial integrity, regulating gut development, and preventing the invasion of pathogenic bacteria [4,5]. Recent studies based on 16S ribosomal-RNA gene sequencing and metagenomic analysis have started to explore the species diversity of gut microbiota within and between individuals [6,7]. It is estimated that about 1000 species can colonize the human gut. Although there is a big range of variation in the species level from different individuals, one recent study showed that the gut microbiota of most individuals can be classified into one of three clusters ('enterotypes') based on the three dominant bacterial genera, Bacteroides, Prevotella, and Ruminococcus [8].

The composition of the gut microbiota is determined and influenced by a number of factors, such as genetics, age, geographic origin, diet and the use of antibiotics [4,5]. One study has compared bacterial species of fecal samples from 531 individuals of different ages (0-70 years) and geographic origins (three populations from US and Malawi) [9]. It was found that the diversity of the gut microbiota within individuals is much higher in adults than in children, but that the interpersonal differences are significantly higher in children. The composition of the bacterial community converges towards an adult-like microbiota by the end of the first 3-5 years of life. These features are shared in all three populations.

Gut Microbiota and Obesity

Studies from the past decade have provided strong evidence of the association between obesity and gut microbiota [10-14]. For example, by transplanting human whole fecal microbiota from obese (Ob) and lean (Ln) twins to germ free mice, one recent study showed that the gut microbiota modulates host metabolism to regulate body mass [13]. Mice that received fecal microbiota from the Ob twins had increased total and fat mass and showed obesity-associated metabolic disorders, phenotypes that were not observed in mice receiving fecal microbiota from

the Ln twins. The mechanisms of microbiota dysbiosis on obesity development are just being explored, and we will discuss them as below (Figure 1).

Energy harvest

Gut microbiota could promote host energy harvest from the diet, which is supported by the observation that conventionally raised mice show more body weight gain than germ free mice. Fecal microbiota transplantation experiments show that transfer of the gut microbiota from obese mice ('obese microbiota') to germ free and wild type recipients led to an increase in body weight in the recipients, supporting the proposal that obese microbiota is more efficient in extracting energy from the diet than that of lean individuals [15]. Furthermore, in obese microbiota, the relative abundance of two dominant bacterial phyla Firmicutes and Bacteroidetes shifted to a status with high metabolic potential, i.e., fewer Bacteroidetes and more Firmicutes, compared to normal microbiota [15,16], resulting in increased fermentation to enhance the hydrolysis of indigestible food and production of Short-Chain Fatty Acids (SCFAs), such as butyrate, acetate and propionate[17-19]. Particularly, butyrate is the main energy substrate for cellular metabolism in colonic epithelium; acetate and propionate are utilized by liver and act as substrates for hepatic lipogenesis and gluconeogenesis. SCFAs, especially butyrate and propionate, also activate gut gluconeogenesis [20]. In germ free mice, the colon epithelium is energy deprived and undergoes autophagy due to lack of butyrate produced by gut microbiota [21]. Studies showed that the fecal concentration of SCFAs was higher in obese compared with obese and normal-weight adult and children [17,22]. Additionally, diet induced mice obesity models have revealed the role of SCFA receptors in obesity. For example, mice with the null mutation of free fatty acid receptor 2 (FFAR2), FFAR2$^{-/-}$ mice, fed a high fat diet had less weight gain than FFAR2 wild type mice [23], while there is no difference in weight gain in FFAR3$^{-/-}$ mice compared with WT mice maintained on either a normal food or high fat diet over a 5-month time period [24]. Furthermore, several studies indicated that SCFAs supplementation treatment may protect against diet-induced obesity, as observed that mice fed a high fat diet along with SCFAs supplementation gained less body weight than the control high fat diet-fed mice [24-26]. Thus, these data suggest that differences in the metabolic capacity of an individual's gut microbiota may contribute to the development of obesity at least in certain conditions.

Roux-en-Y Gastric Bypass (RYGB) is one of the most common and effective bariatric surgeries for treatment of severe obese patients [27] and the mechanisms of RYGB-mediated weight loss include reduced food ingestion, change of appetite, release of satiety-promoting hormones and shift in bile acid metabolism [28]. Recent studies from RYGB patients [29] and RYGB-mouse model [30] have begun to characterize the gut microbiota as a mediator for RYGB-induced metabolism effects. Both studies have shown not only that the gut microbiota composition shifted to a different status after RYGB surgery, correlating with a sustained weight loss, but also that transplantation of RYGB-microbiota to germ-free mice can induce significant weight loss of the recipients compared to mice receiving control microbiota. It was observed in one study [29] that the concentrations of SCFAs (acetate, propionate and butyrate) were decreased in RYGB patients, and thus the reduced energy harvest was proposed to contribute to weight loss. In the other study [30], however, it was found that the proportions of SCFAs in RYGB mice were changed (acetate decreased, propionate increased), but the net energy intake was not significantly different. With previous findings [31], the authors proposed that RYGB-microbiota induces weight loss through increasing energy expenditure [30]. In summary, it is evident that gut microbiota plays a pivotal role on RYGB-induced weight loss, but the mechanisms are needed to be clarified from future studies.

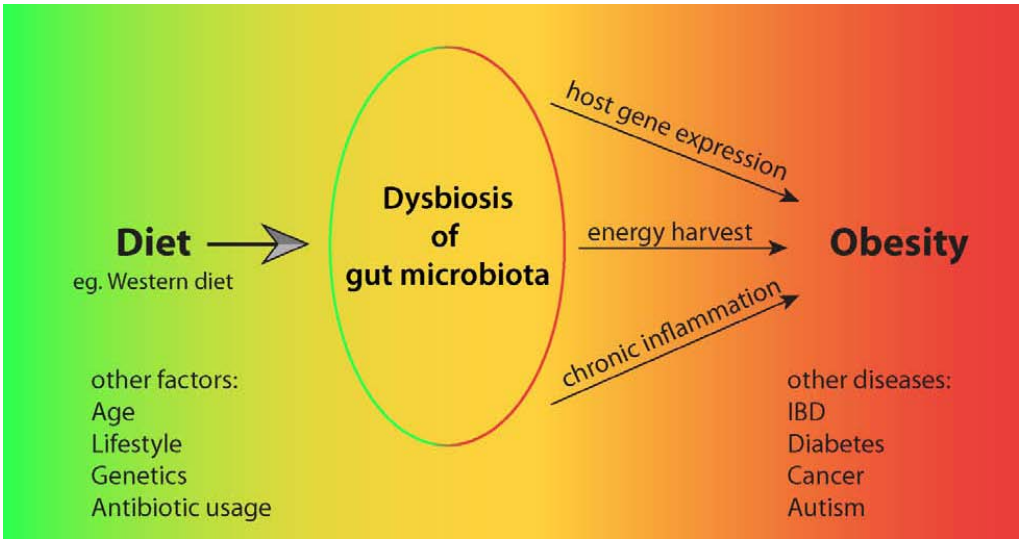

Figure 1: Specific diets, such as Western diet, can cause dysbiosis of gut microbiota, from 'normal microbiota' to 'obese microbiota', which leads to obesity development by altering the host gene expression, influencing the energy harvest from diet, and triggering low-grade chronic inflammation.

Host gene expression

Gut microbiota not only directs the fermentation of indigestible dietary polysaccharides into absorbable monosaccharides in gut lumen, but also shapes the host metabolism status by affecting the expression of host genes that regulate energy storage and expenditure. It has been revealed that gut microbiota instructs the host to increase hepatic lipid accumulation, which is associated with the development of insulin resistance and T2D [18]. The expression of fasting-induced adipose factor, Fiaf, a circulating Lipoprotein Lipase (LPL) inhibitor, is suppressed by conventionalized microbiota. Through suppressing Fiaf, the gut microbiota increases lipoprotein lipase activity, thus enhancing the uptake of fatty acids in gut epithelial cell and deposition of lipids in adipose [18,32]. Consistently, germ free Fiaf-/- mice show 67% higher LPL activity in epididymal fat pad than germ free littermates harboring the wild type Fiaf allele. SCFAs, a family of fermentation end-products by gut microbiota, as mentioned above, may influence host susceptibility to T2D through epigenetic regulation of gene expression as a histone deacetylase inhibitor [33].

Studies have also shown gut microbiota may promote obesity through preventing host excess energy expenditure. AMP-Activated Protein Kinase (AMPK), a "fuel gauge" that monitors cellular energy status, has been implicated in the regulation of glucose and lipid homeostasis, and its activation leads to maintaining cellular energy stores, mostly by enhancing oxidative metabolism. It has been revealed that AMPK activity is diminished or impaired in skeletal muscle of individuals with obesity and diabetes [34]. Compared to conventionally reared mice, germ free mice show persistent resistance to obesity induced by Western diet with high fat and high sugar, which is linked to its increased AMPK activity in liver and skeleton muscle, suggesting that the presence of gut microbiota suppresses host AMPK activity to prevent excess energy expenditure [35]. Thus, gut microbiota and its products interact with molecules expressed by gut epithelium and thereby regulate the balance between energy storage and expenditure at the host side.

Chronic inflammation

Obesity is associated with low-grade chronic systemic inflammation, which has been implicated in insulin resistance and the development of T2D [36]. High Fat Diet (HFD) induced obesity is tightly associated with increased expression of several pro-inflammatory cytokines, such as IL-1, IL-6, TNF-α, and MCP-1 [37-39]. Studies show that obese mice and humans have significantly elevated bacteria-derived plasma lipopolysaccharide (LPS) levels, termed as "metabolic endotoxemia" [40,41], which contribute to the low-grade inflammation through the signal cascade involved in LPS binding to Toll-Like Receptor 4 (TLR4) and subsequent activation of innate immune response. Subcutaneous infusion of LPS could lead to the increase of body fat to a similar extent as in high fat diet-fed mice [40], a phenotype that was not present in LPS unresponsive $TLR4^{-/-}$ or $CD14^{-/-}$ mice [40,42-44]. Similarly, elimination of gram-negative bacteria by antibiotics reduced metabolic endotoxemia and the LPS levels in obese mice, alleviating the obesity phenotype [45]. In addition to LPS, the circulating fatty acids, other ligands of TLR4 signaling, could also activate host immune response, contributing to obesity-related chronic inflammation [44]. Two other Toll-like receptors, TLR2 and TLR5, have also been implicated in gut microbiota dysbiosis-induced immune activation, although the mechanisms remain elusive [46,47]. Besides, the obese microbiota may also cause chronic inflammation by breaking the gut barrier integrity, leading to leaky gut symptoms [48]. A recent study in HFD-induced rodent obesity model added further insights in the association of gut microbiota dysbiosis, chronic inflammation, and metabolic disorders. Through analyzing the changes of gut immune system in HFD-induced T2D mice, they found that HFD-fed mice impaired the T cell homeostasis in the gut, i.e., a loss of IL-17/RORγt CD4 T cells (Th17 cells). Normal food-fed $ROR\gamma t^{-/-}$ mice, which lack gut mature Th17 cells, spontaneously developed T2D phenotypes, such as glucose intolerant, hyperinsulinemic, and slightly insulin resistant. Further studies revealed that HFD-induced decrease in relative abundance of the *Porphyromonadaceae* and increase of *Bacteroidaceae* and *Comamonadaceae* are responsible for the dysregulated gut immune response through affecting the gene expression profiles of gut Antigen Presenting Cells (APCs) and reducing their ability to induce Th17 cell differentiation. Symbiotic treatment that modulates the abundance of these bacterial species protected mice from HFD-induced metabolic disorders through prevention of the loss of Th17 cells. In turn, the impaired gut immune homeostasis further enhances the deleterious gut microbiota composition, thus preceding the onset of metabolic disorders [49]. These studies suggest a vital role of gut immune system in linking gut microbiota dysbiosis to metabolic disorders.

Diet and Gut Microbiota

Diet is one of the factors that can shape the gut microbiota structure, and certain types of diets have been associated with obese microbiota (Figure 1) [50,51]. For example, the Bacteroides genus is highly associated with the consumption of animal proteins, amino acids and saturated fats, which are typical components of Western diet, while the Prevotella genus is associated with the consumption of carbohydrates and simple sugars, which are typical for agrarian societies. People with a Bacteroides-dominated gut microbiome will gain a Prevotella-dominated microbiome by switching from a Western diet to a carbohydrates-based diet for an extended period of time. Consistently, another study found that the European microbiome is dominated by taxa typical of the Bacteroides, whereas the African microbiome is dominated by the Prevotella [52].

To gain more details how diet calories influence gut microbiota, one human study investigated the dynamic changes of gut microbiota in 12 lean and 9 obese individuals in response to diets with different caloric contents, and found that the nutrient load can rapidly influence the composition of gut microbiota [53]. Meanwhile, by monitoring ingested calories (energy consumption) and stool calories (energy loss) using bomb calorimetry, it was found that stool energy loss in lean individuals was directly correlated with changes of Firmicutes and Bacteroidetes (two dominant bacterial phyla in the distal

gut): an increase in Firmicutes and a corresponding decrease in Bacteroidetes contribute to reduced energy loss, that is to say, elevated energy harvest. In another study on obese and overweight subjects, microbial gene richness, instead of the bacterial composition, was used as readout for gut microbiota status, and it was found that 18 (40%) individuals are with Low Gene Count (LGC) and 27 (60%) are with High Gene Count (HGC) [54]. The LGC group showed more noted systemic dysmetabolism (such as high insulin resistance) and low-grade inflammation compared to the HGC group, and 6-week dietary intervention, which was shown to increase the microbial gene richness in LGC individuals, significantly improved the metabolic status. The low-grade inflammation, however, appeared to be relatively refractory to dietary intervention. To characterize how quickly the human gut microbiota can respond to the changes of diet, David et al. [55], found that it took only one day for the changes to occur after the intervention diet reached distal gut microbiota and that the gut microbiota went back to original structure two days after the intervention ended, suggesting that gut microbiota can be altered by diet in a very acute manner.

Studies from animal models have also provided rich insights into the interaction between diet and changes of gut microbiota. One study took advantage of gnotobiotic mice harboring a community of 10 sequenced human gut bacteria to explore the response of the microbiota to the changes of diet [56]. A series of diets with defined concentrations of four macronutrient gradients (casein for protein, corn oil for fat, starch for polysaccharide, and sucrose for simple sugar) were administrated to these mice, and shotgun sequencing of total fecal DNA was performed to determine the absolute abundance of each bacteria. It was shown that total community abundance and the abundance of each species were best associated with casein level: seven out of ten species (such as *Bacteroides caccae*) are positively correlated with casein concentration and three remaining species (such as *Eubacterium rectale*) are negatively correlated with casein concentration. The authors further generated a linear statistical model, which, to some extent, can predict the abundance of each bacterial species from each of the perturbed diet components. Besides extrinsic factors (such as diet), intrinsic factors (such as genetics) can also shape the structure of gut microbiota in mammals, but whether they contribute equally is not clear. A recent study reported that diet can overrule the differences of gut microbiota that are associated with different genotypes, including inbred, transgenic and outbred mice, suggesting that diet plays a dominant role in shaping gut microbial ecology [57].

Obesity is strongly associated with specific diets (e.g., Western diet), which, as discussed above, can influence the composition of gut microbiota. Thus, an association between changes in the diet induced-gut microbiota and the development of obesity has been proposed [58]. Accordingly, an epidemiological study shows that yogurt consumption can prevent age-associated weight gain, which may be due to the effects of probiotics in the yogurt [59]. Indeed, one study with 10-year follow up records after child birth have tested the impact of the probiotic intervention on the development of obesity, and the results suggest that modulation of gut microbiota can modify the growth pattern of child by preventing weight gain during the first year of life [60].

Conclusion and Outlook

More and more findings have pointed to the critical roles of gut microbiota on obesity development and its related complications, leading to the idea of targeting gut microbiota for obesity treatment. Although it has become evident that certain types of microbiota dysbiosis can lead to obesity, it is still not well known whether this impact is due to the change in the amount of single or multiple bacterial species, or it is due to the ratio changes of certain species. Thus, future studies should put efforts on the more accurate quantitative analysis of each species in one bacterial community, but also on the exploration of effects from individual bacterial species (like mono-association studies). In addition, identification of gut bacteria-derived molecules which trigger the downstream events leading to the development of obesity will greatly facilitate strategies for interventions.

References

1. Keys A, Karvonen MJ, Kimura N, Fidanza F, Taylor HL. Indexes of Relative Weight and Obesity. Journal of Chronic Diseases. 1972; 25(6-7): 329-43.
2. Cox AJ, West NP, Cripps AW. Obesity, inflammation and the gut microbiota. Lancet Diabetes Endocrinol. 2015; 3(4): 207-15. doi: 10.1016/S2213-8587(14)70134-2.
3. Graham C, Mullen A, Whelan K. Obesity and the gastrointestinal microbiota: a review of associations and mechanisms. Nutr Rev. 2015; 73(6): 376-85. doi: 10.1093/nutrit/nuv004.
4. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003; 361(9356): 512-19.
5. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012; 148(6): 1258-70. doi: 10.1016/j.cell.2012.01.035.
6. Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006; 312(5778): 1355-9.
7. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science. 2005; 308(5728): 1635-8.
8. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011; 473(7346): 174-80. doi: 10.1038/nature09944.
9. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486(7402): 222-7. doi: 10.1038/nature11053.
10. Bajzer M, Seeley RJ. Physiology: obesity and gut flora. Nature. 2006; 444(7122): 1009-10.
11. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444(7122): 1022-3.
12. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. Nature. 2009; 457(7228): 480-4. doi: 10.1038/nature07540.
13. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut

microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013; 341(6150): 1241214. doi: 10.1126/science.1241214.

14. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005; 102(31): 11070-5.

15. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444(7122): 1027-31.

16. Turnbaugh PJ, Baeckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008; 3(4): 213-23. doi: 10.1016/j.chom.2008.02.015.

17. Schwiertz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring). 2010; 18(1): 190-5. doi: 10.1038/oby.2009.167.

18. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004; 101(44): 15718-23.

19. Layden BT, Angueira AR, Brodsky M, Durai V, Lowe WL Jr. Short chain fatty acids and their receptors: new metabolic targets. Transl Res. 2013; 161(3): 131-40. doi: 10.1016/j.trsl.2012.10.007.

20. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014; 156(1-2): 84-96. doi: 10.1016/j.cell.2013.12.016.

21. Donohoe DR, Garge N, Zhang XX, Sun W, O'Connell TM, Bunger MK, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. 2011; 13(5): 517-26. doi: 10.1016/j.cmet.2011.02.018.

22. Payne AN, Chassard C, Zimmermann M, Muller P, Stinca S, Lacroix C. The metabolic activity of gut microbiota in obese children is increased compared with normal-weight children and exhibits more exhaustive substrate utilization. Nutr Diabetes. 2011; 1: e12. doi: 10.1038/nutd.2011.8.

23. Bjursell M, Admyre T, Goransson M, Marley AE, Smith DM, Oscarsson J, et al. Improved glucose control and reduced body fat mass in free fatty acid receptor 2-deficient mice fed a high-fat diet. Am J Physiol Endocrinol Metab. 2011; 300(1): E211-20. doi: 10.1152/ajpendo.00229.2010.

24. Lin HV, Frassetto A, Kowalik EJ, Nawrocki AR, Lu MFM, Kosinski JR, et al. Butyrate and Propionate Protect against Diet-Induced Obesity and Regulate Gut Hormones via Free Fatty Acid Receptor 3-Independent Mechanisms. PLoS One. 2012; 7(4): e35240. doi: 10.1371/journal.pone.0035240.

25. Gao ZG, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, et al. Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. Diabetes. 2009; 58(7): 1509-17. doi: 10.2337/db08-1637.

26. Yamashita H, Fujisawa K, Ito E, Idei S, Kawaguchi N, Kimoto M, et al. Improvement of obesity and glucose tolerance by acetate in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biosci Biotechnol Biochem. 2007; 71(5): 1236-43.

27. Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the weight loss response to gastric bypass surgery. J Clin Endocrinol Metab. 2011; 96(10): E1630-3. doi: 10.1210/jc.2011-1130.

28. Miras AD, le Roux CW. Mechanisms underlying weight loss after bariatric surgery. Nat Rev Gastroenterol Hepatol. 2013; 10(10): 575-84. doi: 10.1038/nrgastro.2013.119.

29. Tremaroli V, Karlsson F, Werling M, Stahlman M, Kovatcheva-Datchary P, Olbers T, et al. Roux-en-Y Gastric Bypass and Vertical Banded Gastroplasty Induce Long-Term Changes on the Human Gut Microbiome Contributing to Fat Mass Regulation. Cell Metab. 2015; 22(2): 228-38. doi: 10.1016/j.cmet.2015.07.009.

30. Liou AP, Paziuk M, Luevano JM, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved Shifts in the Gut Microbiota Due to Gastric Bypass Reduce Host Weight and Adiposity. Sci Transl Med. 2013; 5(178): 178ra41. doi: 10.1126/scitranslmed.3005687.

31. Stylopoulos N, Hoppin AG, Kaplan LM. Roux-en-Y gastric bypass enhances energy expenditure and extends lifespan in diet-induced obese rats. Obesity (Silver Spring). 2009; 17(10): 1839-47. doi: 10.1038/oby.2009.207.

32. Kim HK, Youn BS, Shin MS, Namkoong C, Park KH, Baik JH, et al. Hypothalamic Angptl4/Fiaf is a novel regulator of food intake and body weight. Diabetes. 2010; 59(11): 2772-80. doi: 10.2337/db10-0145.

33. Davie JR. Inhibition of histone deacetylase activity by butyrate. J Nutr. 2003; 133(7 Suppl): 2485S-2493S.

34. Xu XJ, Gauthier MS, Hess DT, Apovian CM, Cacicedo JM, Gokce N, et al. Insulin sensitive and resistant obesity in humans: AMPK activity, oxidative stress, and depot-specific changes in gene expression in adipose tissue. J Lipid Res. 2012; 53(4): 792-801. doi: 10.1194/jlr.P022905.

35. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A. 2007; 104(3): 979-84.

36. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011; 29(1): 415-45.

37. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor-necrosis-factor-alpha - direct role in obesity-linked insulin resistance. Science. 1993; 259(5091): 87-91.

38. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112(12): 1796-808.

39. Cai DS, Yuan MS, Frantz DF, Melendez PA, Hansen L, Lee J, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappa B. Nat Med. 2005; 11(2): 183-90.

40. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. Diabetes. 2007; 56(7): 1761-72.

41. Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, et al. Energy intake is associated with endotoxemia in apparently healthy men. Am J Clin Nutr. 2008; 87(5): 1219-23.

42. Tsukumo DML, Carvalho-Filho MA, Carvalheira JBC, Prada PO, Hirabara SM, Schenka AA, et al. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. Diabetes. 2007; 56(8): 1986-98.

43. Kim KA, Gu W, Lee IA, Joh EH, Kim DH. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. PLoS One. 2012; 7(10): e47713. doi: 10.1371/journal.pone.0047713.

44. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links

innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006; 116(11): 3015-25.

45. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008; 57(6): 1470-81. doi: 10.2337/db07-1403.

46. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010; 328(5975): 228-31. doi: 10.1126/science.1179721.

47. Caricilli AM, Picardi PK, de Abreu LL, Ueno M, Prada PO, Ropelle ER, et al. Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. Plos Biol. 2011; 9(12): e1001212. doi: 10.1371/journal.pbio.1001212.

48. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009; 58(8): 1091-103. doi: 10.1136/gut.2008.165886.

49. Garidou L, Pomie C, Klopp P, Waget A, Charpentier J, Aloulou M, et al. The gut microbiota regulates intestinal CD4 T cells expressing RORgammat and controls metabolic disease. Cell Metab. 2015; 22(1): 100-12. doi: 10.1016/j.cmet.2015.06.001.

50. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011; 334(6052): 105-8. doi: 10.1126/science.1208344.

51. Salonen A, de Vos WM. Impact of diet on human intestinal microbiota and health. Annu Rev Food Sci Technol. 2014; 5(1): 239-62. doi: 10.1146/annurev-food-030212-182554.

52. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010; 107(33): 14691-6. doi: 10.1073/pnas.1005963107.

53. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr. 2011; 94(1): 58-65. doi: 10.3945/ajcn.110.010132.

54. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, et al. Dietary intervention impact on gut microbial gene richness. Nature. 2013; 500(7464): 585-8. doi: 10.1038/nature12480.

55. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014; 505(7484): 559-63. doi: 10.1038/nature12820.

56. Faith JJ, McNulty NP, Rey FE, Gordon JI. Predicting a human gut microbiota's response to diet in gnotobiotic mice. Science. 2011; 333(6038): 101-4. doi: 10.1126/science.1206025.

57. Carmody RN, Gerber GK, Luevano JM, Jr., Gatti DM, Somes L, Svenson KL, et al. Diet dominates host genotype in shaping the murine gut microbiota. Cell Host Microbe. 2015; 17(1): 72-84. doi: 10.1016/j.chom.2014.11.010.

58. Ley RE. Obesity and the human microbiome. Curr Opin Gastroenterol. 2010; 26(1): 5-11. doi: 10.1097/MOG.0b013e328333d751.

59. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011; 364(25): 2392-2404. doi: 10.1056/NEJMoa1014296.

60. Luoto R, Kalliomaki M, Laitinen K, Isolauri E. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. Int J Obes (Lond). 2010; 34(10): 1531-7. doi: 10.1038/ijo.2010.50.