ISSN:2790-1688 Volume-15-(2025)

Synthetic biology in the gut microbiota for obesity treatment

Zengyue Geng

BDA School The High School Affiliated to Renmin University of China, Beijing 100176, China

Abstract. Obesity is a global problem that has had a serious impact on the health of many people around the world. Recently, scientists have discovered that the gut microbiome has a significant influence on human obesity. The objective of this article is to synthesize and examine the existing state of research, evolving trends, and critical problems related to the relationship between gut microbiota and obesity. This review summarizes the intestinal flora species that have an impact on obesity discovered in recent studies, the metabolic products of the intestinal flora that have a direct impact on obesity and their mechanisms of action, the therapies for modifying the intestinal flora based on synthetic biology for the treatment of obesity, their limitations, and prospects.

Keywords: synthetic biology; obesity; gut microbiota.

1. Introduction

Today, it has been reported that overweight or obesity affects 40% of the global population. Based on the data from the Obesity Federation, it is expected that overweight or obesity will have an impact on more than 4 billion people by 2035. Clearly, obesity poses a significant threat to public health. It leads to metabolic disorders in the human body. For example, excessive accumulation of fat has a destructive effect on glucose metabolism, leading to dysfunction of multiple metabolic pathways involving adipose tissue, liver, heart, pancreas, and muscle [1]. Concentration of fat also leads to chronic inflammation, which continuously affects fat storage and metabolism[2]. Although numerous studies have sought to elucidate the physiopathologic mechanisms of obesity, the exact workings of this condition remain unclear, particularly regarding the connection of the intestinal microbiome and obesity. In previous studies, an increase in phylum Firmicutes, the genus Clostridium, as well as the species Clostridium coccoides, Eubacterium rectale, Lactobacillus reuteri, Clostridium histolyticum, Akkermansia muciniphila, and Staphylococcus aureus was often found to be associated with obesity.[3], which will influence energy metabolism through countless methods. In the following article, we will introduce the types of bacteria that can regulate obesity, specifically the metabolic products of the gut microbiota used to regulate obesity, as well as the therapies for obesity developed based on the gut microbiota.

2. The intestinal microbiota affects host obesity through specific metabolic products or metabolic pathways.

Increasing research suggests that microbiota is related to obesity. For example, in obese children, the Firmicutes in the gut increased, while that of Bacteroidetes went down.[4] Another research revealed that the Firmicutes/Bacteroidetes ratio rose with increasing BMI.[5] However, contrary results have emerged from some studies—scientists detected no substantial variation in Bacteroidetes abundance between obese populations and individuals with a normal body weight.[6]

It has been recently discovered that the Christensenellaceae is related to weight-loss.[7] Akkermansia muciniphila serves as a crucial bacterium when it comes to weight loss. Supplementing with Akkermansia muciniphila can enhance metabolic parameters among overweight and obese individuals.[8] Obesity is negatively correlated with the Lactobacillus paracasei (L. paracasei), while the abundances of L. reuteri and L. gasseri are significantly associated with obesity. Evidence of the anti-obesity effect of Bifidobacterium has been obtained. In dietary obesity animal models, its administration showed strain-dependent obesity effects.[9] Nevertheless, obesity is linked to a reduction in the abundance of Bifidobacterium in the gut.[10] Million et al. discovered that M. smithii and B. animalis were linked to normal weight, whereas Lactobacillus reuteri was related to

obesity.[11] What these findings reveal is that microorganisms linked to obesity have species specificity: even bacteria in the same genus may exert opposing effects, which is presumably tied to the complex metabolic mechanism that drives obesity. Additionally, scientists found that Clostridium argentinoides can produce a relatively high level of 4-hydroxyphenylacetic acid (4HPAA), which inhibits obesity in mice bearing a diet with high-fat.[12]

2.1 Short-chain fatty acids(SCFAs)

Intestinal microbiota allow humans to obtain energy from indigestible foods. They convert those indigestible foods into SCFAs, which supply 10% of the daily energy requirement for humans.[13] Scientists found that germ-free mice weighed less and excreted more calories in feces and urine than ordinary mice. This finding supports idea that the intestinal microbiota can assist humans in extracting more energy, achieving better energy balance, and maintaining weight.[14]. In another study, it shows that normal-weight adults who follow high-calorie diets have more stool energy loss than those who are overweight [15]. In a previous study, SCFAs were involved in several pathways that affect metabolism. One of the pathways is that SCFAs function as signaling molecules. In this way, they can modulate the secretion of various hormones[16]. Moreover, SCFAs can interact with G-protein-coupled receptors, stimulating the secretion of gut peptides [16], and induce intracellular signaling pathways that ultimately affect energy metabolism, insulin sensitivity, and inflammation.[17]. For instance, SCFA supplementation can improve insulin resistance and obesity in mice with diet-induced obesity[18]. Interestingly, there is contradictory evidence regarding the function of SCFAs. For example, a study shows that individuals with obesity have more SCFAs than normal weight individuals, thus suggesting that obesity contributes to increased energy harvest. Some studies have shown that humans can benefit from SCFAs as they function. However, the specific mechanism underlying how gut microbiota affects energy harvest is still unknown.

2.2 LPS and other pathogen-associated molecules

One characteristic of obesity and metabolic disorders is Low-grade inflammation[19], which was initially found to be related to gut microbiota because of the occurrence of metabolic endotoxaemia[20]. Metabolic endotoxaemia refers to an elevation in the levels of circulating lipopolysaccharides (LPS) in the blood resultting in low-grade chronic inflammation as well as metabolic dysfunction [21]. LPS are some Gram-negative bacteria's outer membrane molecules. Ordinarily, FPS' transportation from gut to blood can be prevented by the gut barrier[21, 22]. However, numerous factors are capable of undermining the integrity of the gut barrier, such as a high-fat diet[23], common infections or inflammatory bowel diseases, excessive alcohol consumption[24], a lack of dietary fiber [25], and obesity[23]. Those factors result in a multitude of changes, involving modifications in the position and arrangement of tight proteins, fluctuations in antimicrobial peptides production, and mucus layer transition[26, 27].

Many mechanisms can account for how the compounds secreted by the gut influence the adipose tissue mechanism. The first one involves the activation of inflammatory pathways by TLR4 together with CD14, which then initiates the immune responses of the adipose tissue. [20]. Upon exposure to LPS, changes will occur in adipocytes and preadipocytes, disrupting the normal course of adipogenesis. LPS can modulate gene expression and the secretion of cytokines to suppress the diversification of mouse preadipocytes into mature adipocytes.[20].

Nevertheless, the interplay among LPS, fat tissue, and metabolic disorders is intricate and continues to be an area that is under intense research. To ascertain whether LPS in the gut can induce glucose and insulin resistance and macrophage accumulation in white adipose tissue (WAT). A research found that once the gut of the mice was colonized by this bacterium capable of generating LPS, it gave rise to disrupted glucose metabolism, augmented macrophage accumulation, and a tendency towards the M1 phenotype in the WAT. In contrast, when GF mice were mono-colonized with an E. coli strain that expresses LPS but has reduced immunogenicity, it did not cause macrophage accumulation or inflammation in the WAT[28]. Also, statistic suggests that LPS from specific

bacteria can have an antagonistic effect on TLR4 but still contribute to endotoxaemia. Anhê et al. Found that LPS from E.coli injures the gut barrier and aggravates glycaemic control in mice. But the LPS, which is secreted by other bacteria, doesn't have the same negative effects in obese mice; they can even counteract the dysglycaemia caused by LPS from E.coli[29]. Those discoveries suggest that metabolic endotoxaemia ought to go beyond just the LPS load and take into account the specific features of LPS molecules.

2.3 Bioactive lipids

Bioactive lipids are a category of signaling molecules and they play vital roles in a multitude of both physiological and pathological processes [30]. Besides, they take part in many biological activities, including regulating blood pressure, influencing inflammation, facilitating cell growth, and participating in immune responses[31, 32]. Bioactive lipids are secreted by both the host and gut microbiota, and such lipids have the ability to impact the microbiota's composition and activity, along with multiple metabolic processes of the host.[33, 34]. We will introduce several kinds of bioactive lipids.

Although bile acids are produced by the liver, the activities and composition of the microbiota have an impact on their production. [35]. When humans consume foods, the bile acids stored in the gallbladder will be released into the gut to assist in the digestion and absorption of dietary fat.

Endocannabinoids(eCB) are produced by digestive tract cells when on a high-fat diet. They are capable of modulating glucose, appetite, and lipid metabolism, and contributing to immunity.[33, 36].

Research proves that when our tongue tastes the fat in food, it produces a signal that is transmitted to the cerebrum. Then the cerebrum separates the signal to the gut through the vagus, and the signal in the gut stimulates eCB's productivity. In the role of the eCB system, the human body begins to secrete digestive substances, which cause the feeling of hunger, leading to a greater urge for high-fat foods.[37] This process is essentially an addictive response caused by eCB. This finding provides a method for humans to solve the problem. For instance, controlling the cell reception of eCB through drugs to interfere with addiction signal transmission[38]. Although people will feel anxious and upset when eCB is blocked in the cerebrum, it causes an addictive response outside the cerebrum, so the block of eCB won't trigger other side effects. Furthermore, scientists have uncovered another finding which suggests that the eCB system contributes to the function of the gut barrier, the regulation of intestinal microbiota, and the metabolism of adipose tissue. Specifically, an increase in anandamide in obesity or diabetes mice leads to increased gut permeability based on CB1[36]. Moreover, when the eCB system was activated by means of a powerful eCB agonist, adipogenesis was boosted, and the integrity was impaired[39]. These changes go on to enhance the levels of LPS in the blood, disrupt the gut barrier, and have an impact on both the endocannabinoid system in adipose tissue and the whole intestine. ultimately shaping a harmful circulation and altering the metabolism of adipose tissue. This finding demonstrates that adipogenesis is influenced by the backfeed loop of LPS and the eCB system.

2.4 Tryptophan derivatives

Tryptophan is capable of being metabolized into a variety of metabolites within the intestinal microbiota and tissue cells. Compared to healthy people, the levels of tryptophan metabolites in the blood samples of obese individuals are lower. Nevertheless, kynurenine (Kyn), which is another metabolite of tryptophan, presents a high level in obese individuals. This is likely due to the elevated enzymatic activity of indoleamine 2,3-dioxygenase 1 (IDO1).[40] Studies have shown that an increase in the enzyme activity of IDO1 has been witnessed in obesity, implying that obesity is related to the enzyme activity of IDO1 in the intestine. Deleting or inhibiting IDO1 can maintain the gut mucosal barrier, enhance insulin sensitivity, modify lipid metabolism in the liver and adipose tissues and alleviate metabolic endotoxaemia and inflammation.[41]

Some enzymes encoded by the intestinal microbiota are homologous to the ones in the eukaryotic Kyn pathway. These enzymes can regulate the aryl hydrocarbon receptor (AHR) pathway by means

of tryptophan derivatives and indole, promoting the specialization of preadipocytes into mature adipocytes in order to regulate the growth of adipose tissue. Moreover, the AHR pathway plays a part in regulating adipogenesis and adipocyte metabolism.[42, 43] Consequently, it inhibits weight gain in mice fed a high-fat diet and enhances glucose tolerance.[44] Kyna and GPR5 increased the expression of PGC1α, thereby enhancing the expression level of the Rgs14 gene, which resulted in an increase in signal conduction of β-adrenergic receptors. Instead, the deletion of the GPR5 gene led to an increase in weight, glucose intolerance, and greater susceptibility to a fatty diet. Moreover, it was revealed that GPR5-knockout mice had a functional deficiency in the browning of adipose tissue that was induced by exercise. This discovery reveals a new pathway that can modulate energy homeostasis via the interaction among gut microbiota-derived metabolites.[44]

Furthermore, research indicates that gut microbiota influences energy expenditure and insulin resistance by regulating the expression of the miR-181 family via the tryptophan-derived metabolite they generate. Besides, the improper regulation of the miR-181 axis plays a part in obesity, insulin resistance, and inflammation in WAT. Among a group of children categorized according to their weight percentiles (19 vs 19 children being obese), it was discovered that the expression of miR-181 in WAT and the plasma levels of tryptophan-derived metabolites were abnormally regulated in cases of obesity.[45].

Serotonin is a derivative of tryptophan. In research, scientists have observed that mice on a fatty diet exhibit two different phenotypes (one fat and one thin). It was discovered that Bacteroides common plays a key regulatory role in the body weight of mice. The content of serotonin in Bacteroides vulnificus was significantly changed by immunofluorescence detection. On this basis, they treated mice on a high-fat diet with serotonin and found that the mice lost weight.[46]

2.5 Aromatic metabolites

Aromatic compounds constitute a category of compounds possessing a benzene ring structure. They have a stable structure and are not easy to decompose. and some of the members (mainly 4HPAA, 3HPP, 4HPP and Tyrosol) can regulate the occurrence of obesity. In a recent study, scientists analyzed body fat, blood lipids, and fecal microbiome in a large-scale cohort study (with over 4,000 samples from Guangzhou), and found that the aromatic metabolites of microorganisms (mainly 4HPAA, 3HPP, 4HPP, and Tyrosol) were associated with the accumulation of body fat. Afterwards, they conducted animal experiments based on this discovery, feeding the same group of mice either a regular diet or a fatty diet. Among them, some mice from the fatty diet group were also extracted and treated with one of the substances, respectively. It was noticed that the weights of the mice to which a single substance was added were all lower than those of the mice on the high-fat diet without any substance added.[12]

Afterwards, they analyzed the mechanism of action of these four substances. It turned out that the addition of these four substances had no impact on the appetite of mice and scarcely influenced the energy consumption of mice, but the absorption of food by mice was significantly affected (the absorption rate was lower compared to untreated mice), and scientists found that mice that were treated with these four substances for a long time would also show symptoms of insulin resistance. In addition, they found that these four substances could upregulate the B-cell immune response, thereby reducing the inflammatory response in mice.[12]

Through extensive metabolomics analysis, scientists have discovered that Bacteroides and Clostridium butyricum are closely related to the weight changes of mice. Scientists artificially altered the content of two types of bacteria in the intestines, observed the weight changes of mice, and conducted product analysis. They found that para-aminobenzoic acid could limit the weight gain of mice.[47]

3. The method of synthetic biology for modifying the intestinal flora to treat obesity

Because the gut microbiota has many influences on obesity, scientists have developed probiotic therapy. However, traditional probiotic therapies often have inconsistent effects and cause adverse reactions.[48] This restriction prompted scientists to seek a new pathway for treating the disease.

Recently, Scientists have carried out gene reprogramming on the bacteria in the gut microbiome, equipping them with new enzyme activities or regulatory circuits so that they are capable of executing enhanced or novel biochemical functions which are advantageous to the host. In this manner, therapeutic effects surpassing those that the natural microbiota can attain have been realized.[49] Compared to unmodified microbiota therapy, live bacteria therapy methods have several obvious advantages: it is possible to design them to carry out functions that are absent in natural gut bacteria, like rapid detoxification, decomposition of metabolites, or the delivery of human cytokines.[49]

The rapid development of gut microbiota design is attributed to the discoveries of synthetic biology techniques and enzyme engineering. In the field of synthetic biology, scientists have successfully precisely edited microorganisms through the CRISPR-Cas system. For instance, a genome editing approach targeting various Bacteroides species in the human gut, based on CRISPR/Cas12, has been demonstrated. Moreover, researchers are able to simulate the metabolic network of bacteria by making use of sophisticated genome-scale metabolic models of gut bacteria and microbiota. Through this method, they can anticipate which gene deletions or additions will lead to production that corresponds to the expected result.[50] In the field of enzyme engineering, a study conducted in 2024 offered a series of molecular tools for the protein secretion of Bacteroides. These tools aided in identifying signal peptides and secretion pathways that can enhance the process of exporting therapeutic proteins.[51] Moreover, researchers utilized directed evolution and computational enzyme design to boost the catalytic efficiency within the gastrointestinal environment.

3.1 Modify a single strain to produce beneficial substances.

Lacto-N-triose II (LNT II) has garnered significant attention due to its potential as a nutraceutical, as it facilitates the production of more intricate foods at levels analogous to those in human milk.[52] Owing to these remarkable traits, there is a strong inclination to utilize engineered microorganisms for the production of LNT II. By modifying the metabolic engineering of E. coli Nissle 1917 (EcN), such as overexpressing the lgtA glycosyltransferase, intensifying the supply of UDP-GlcNAc, mitigating feedback inhibition, and eliminating competing pathways, scientists obtained high-yield LNT II strains.[53] Scientists have proved through computer models that eliminating specific fermentation pathways in Escherichia coli will divert carbon to enhance butyrate synthesis. This provided information for the generation of strains knocked out in the lactic acid and succinic acid production pathways, thereby increasing the yield of butyrate in the experiment.[54] Praveschotinunt et al. made modifications to E.coli Nissle to enable it to secrete biologically active anti-TNF nanobodies that are linked to the cell surface via matrix-binding domains. In the model of Inflammatory Bowel Disease , this customized anti-TNF administration mitigated the inflammatory signal in the colonic mucosa, thereby reducing the severity of the disease.[55] Wang et al. engineered Escherichia coli Nissle to secrete a parasitic worm protein known as Sj16, which is capable of inducing regulatory immune cells. When this strain is administered orally, it can help restore butyrate-producing commensal bacteria and boost the level of retinoic acid, consequently improving colitis in mice.[56] Palmer et al. made modifications to E.coli Nissle so that it could produce microamycin H47 in response to the biomarker tetrathionate of Salmonella infection.[57] In the mouse intestinal infection model, this modified strain selectively eliminated Salmonella, leading to a significant reduction in the pathogen load.[51] To address metabolic syndrome, Ma et al. altered E.coli Nissle to enable it to secrete glucagon-like peptide 1 mimics. As a result, this led to a reduction in weight gain among obese mice and an improvement in glucose tolerance.[55]

3.2 Modify multiple strains for combined treatment.

Scientists have developed a genetically modified yeast strain capable of detecting and binding to Clostridium difficile toxin protein in the colon, thereby reducing its impact. Riglar et al. introduced two strains within a two-strain system. One of the strains is an Escherichia coli strain secreting anti-inflammatory effectors, while the other strain serves as a live diagnostic to monitor inflammation. It is likely that one strain can identify inflammatory markers and then trigger the other strain to dispense the drug.[58]

3.3 Degrading harmful compounds or eliminating harmful bacteria

The utilization of targeted active biological therapy is capable of specifically eliminating antibiotic-resistant bacteria or harmful pathogens while safeguarding the integrity of the rest of the microbiota. In this way, it can lessen the dependence on broad-spectrum antibiotics.[59] Scientists have developed a genetically modified yeast strain for detecting and binding Clostridium difficile toxin protein in the colon, thereby reducing its effects.[58]

Synlogic's strain SYNB8802 is a type of E.coli that has been modified to metabolize oxalate （Excessive accumulation of oxalate can cause kidney stones).[60] In contrast, Novome 's strain (NB1000) with an oxalic acid degradation pathway and a dependent circuit, which could stably implant in the intestine when specific polysaccharides were given.[55] Engineered bacteria have been developed to absorb excessive trimethylamine or choline in the gut, thereby reducing trimethylamine-N-oxide.[61]

3.4 Inhibit the proliferation of harmful bacteria.

Hwang et al. modified E.coli Nissel specifically against Pseudomonas aeruginosa. The modified Escherichia coli is equipped with a genetic circuit that can recognize the population signal of Pseudomonas aeruginosa and then produce customized bacteriocins and lysate peptides to eliminate Pseudomonas. This probiotic can eliminate Pseudomonas aeruginosa infection present and prevent its formation during preventive administration.[62] Meanwhile, the safety, dose standardization, and host-specific variability of microbial therapy still need further optimization and confirmation.[59]

4. Conclusion

Although scientists have discovered many cases of intestinal microbiota regulating obesity, there are still many unclear mechanisms of action, and changes in many substances may have opposite effects in different individuals. However, therapies for obesity developed based on the gut microbiota also face numerous challenges, including poor viability and persistence of strains, as well as reduced therapeutic effects due to differences between humans and experimental animals. On this path, further exploration by scientists is still needed.

Although engineered bacteria are more controllable and adjustable compared to traditional therapies, engineered strains are also facing severe challenges. One of the principal problems is the variable implantation and persistence of microorganisms in the gastrointestinal environment, which are influenced by factors, the makeup of the natural microbiota, and diverse immune responses among individuals. This variability affects the reproducibility and treatment outcomes among various populations.[59]

References

[1] Yazici, D. and H. Sezer, Insulin Resistance, Obesity and Lipotoxicity. Adv Exp Med Biol, 2017. 960: p. 277-304.

[2] Kawai, T., M.V. Autieri, and R. Scalia, Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol, 2021. 320(3): p. C375-C391.

[3] Gomes, A.C., C. Hoffmann and J.F. Mota, The human gut microbiota: Metabolism and perspective in obesity. Gut Microbes, 2018. 9(4): p. 308-325.

[4] Indiani, C.M.D.S., et al., Childhood Obesity and Firmicutes/Bacteroidetes Ratio in the Gut Microbiota: A Systematic Review. Child Obes, 2018. 14(8): p. 501-509.

[5] Koliada, A., et al., Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. BMC Microbiol, 2017. 17(1): p. 120.

[6] Zhang, H., et al., Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A, 2009. 106(7): p. 2365-70.

[7] Waters, J.L. and R.E. Ley, The human gut bacteria Christensenellaceae are widespread, heritable, and associated with health. BMC Biol, 2019. 17(1): p. 83.

[8] Depommier, C., et al., Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med, 2019. 25(7): p. 1096-1103.

[9] Yin, Y., et al., Effects of four Bifidobacteria on obesity in high-fat diet-induced rats. World J Gastroenterol, 2010. 16(27): p. 3394-401.

[10] Waldram, A., et al., Top-down systems biology modeling of host metabotype-microbiome associations in obese rodents. J Proteome Res, 2009. 8(5): p. 2361-75.

[11] Million, M., et al., Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii. Int J Obes (Lond), 2012. 36(6): p. 817-25.

[12] Jiang, Z., et al., Human gut microbial aromatic amino acid and related metabolites prevent obesity through intestinal immune control. Nat Metab, 2025. 7(4): p. 808-822.

[13] Rosenbaum, M., R. Knight and R.L. Leibel, The gut microbiota in human energy homeostasis and obesity. Trends Endocrinol Metab, 2015. 26(9): p. 493-501.

[14] Lupp, C., M. Skipper and U. Weiss, Gut microbes and health. Nature, 2012. 489(7415): p. 219.

[15] Jumpertz, R., et al., Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr, 2011. 94(1): p. 58-65.

[16] Blaak, E.E., et al., Short chain fatty acids in human gut and metabolic health. Benef Microbes, 2020. 11(5): p. 411-455.

[17] Dalile, B., et al., The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol, 2019. 16(8): p. 461-478.

[18] Perry, R.J., et al., Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome. Nature, 2016. 534(7606): p. 213-7.

[19] Hotamisligil, G.S., Inflammation and metabolic disorders. Nature, 2006. 444(7121): p. 860-7.

[20] Cani, P.D., et al., Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes, 2007. 56(7): p. 1761-72.

[21] Cani, P.D., Human gut microbiome: hopes, threats and promises. Gut, 2018. 67(9): p. 1716-1725.

[22] Regnier, M., et al., Gut microbiome, endocrine control of gut barrier function and metabolic diseases. J Endocrinol, 2021. 248(2): p. R67-R82.

[23] Cani, P.D., 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): p. 1470-81.

[24] Leclercq, S., et al., Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Natl Acad Sci U S A, 2014. 111(42): p. E4485-93.

[25] Chassaing, B., et al., Lack of soluble fiber drives diet-induced adiposity in mice. Am J Physiol Gastrointest Liver Physiol, 2015. 309(7): p. G528-41.

[26] Everard, A., et al., Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci U S A, 2013. 110(22): p. 9066-71.

[27] Paone, P. and P.D. Cani, Mucus barrier, mucins and gut microbiota: the expected slimy partners? Gut, 2020. 69(12): p. 2232-2243.

[28] Caesar, R., et al., Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. Gut, 2012. 61(12): p. 1701-7.

[29] Anhe, F.F., et al., Metabolic endotoxemia is dictated by the type of lipopolysaccharide. Cell Rep, 2021. 36(11): p. 109691.

[30] Park, J., et al., Bioactive Lipids and Their Derivatives in Biomedical Applications. Biomol Ther (Seoul), 2021. 29(5): p. 465-482.

[31] Leuti, A., et al., Bioactive lipids, inflammation and chronic diseases. Adv Drug Deliv Rev, 2020. 159: p. 133-169.

[32] Ayub, M., H. Jin and J. Bae, Novelty of Sphingolipids in the Central Nervous System Physiology and Disease: Focusing on the Sphingolipid Hypothesis of Neuroinflammation and Neurodegeneration. Int J Mol Sci, 2021. 22(14).

[33] Cani, P.D., et al., Endocannabinoids--at the crossroads between the gut microbiota and host metabolism. Nat Rev Endocrinol, 2016. 12(3): p. 133-43.

[34] Russo, R., et al., Gut-brain Axis: Role of Lipids in the Regulation of Inflammation, Pain and CNS Diseases. Curr Med Chem, 2018. 25(32): p. 3930-3952.

[35] Collins, S.L., et al., Bile acids and the gut microbiota: metabolic interactions and impacts on disease. Nat Rev Microbiol, 2023. 21(4): p. 236-247.

[36] Muccioli, G.G., et al., The endocannabinoid system links gut microbiota to adipogenesis. Mol Syst Biol, 2010. 6: p. 392.

[37] DiPatrizio, N.V., Endocannabinoids and the Gut-Brain Control of Food Intake and Obesity. Nutrients, 2021. 13(4).

[38] Scheyer, A., et al., Endocannabinoids at the synapse and beyond: implications for neuropsychiatric disease pathophysiology and treatment. Neuropsychopharmacology, 2023. 48(1): p. 37-53.

[39] Geurts, L., et al., Chronic endocannabinoid system stimulation induces muscle macrophage and lipid accumulation in type 2 diabetic mice independently of metabolic endotoxaemia. PLoS One, 2013. 8(2): p. e55963.

[40] Favennec, M., et al., The kynurenine pathway is activated in human obesity and shifted toward kynurenine monooxygenase activation. Obesity (Silver Spring), 2015. 23(10): p. 2066-74.

[41] Laurans, L., et al., Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health. Nat Med, 2018. 24(8): p. 1113-1120.

[42] Dou, H., et al., Aryl hydrocarbon receptor (AhR) regulates adipocyte differentiation by assembling CRL4B ubiquitin ligase to target PPARgamma for proteasomal degradation. J Biol Chem, 2019. 294(48): p. 18504-18515.

[43] Alexander, D.L., et al., Aryl-hydrocarbon receptor is an inhibitory regulator of lipid synthesis and of commitment to adipogenesis. J Cell Sci, 1998. 111 (Pt 22): p. 3311-22.

[44] Agudelo, L.Z., et al., Kynurenic Acid and Gpr35 Regulate Adipose Tissue Energy Homeostasis and Inflammation. Cell Metab, 2018. 27(2): p. 378-392.e5.

[45] Virtue, A.T., et al., The gut microbiota regulates white adipose tissue inflammation and obesity via a family of microRNAs. Sci Transl Med, 2019. 11(496).

[46] Wen, X., et al., B. vulgatus ameliorates high-fat diet-induced obesity through modulating intestinal serotonin synthesis and lipid absorption in mice. Gut Microbes, 2024. 16(1): p. 2423040.

[47] Qiao, S., et al., Cross-feeding-based rational design of a probiotic combination of Bacterides xylanisolvens and Clostridium butyricum therapy for metabolic diseases. Gut Microbes, 2025. 17(1): p. 2489765.

[48] Biazzo, M. and G. Deidda, Fecal Microbiota Transplantation as New Therapeutic Avenue for Human Diseases. J Clin Med, 2022. 11(14).

[49] Charbonneau, M.R., et al., Developing a new class of engineered live bacterial therapeutics to treat human diseases. Nat Commun, 2020. 11(1): p. 1738.

[50] Esvap, E. and K.O. Ulgen, Advances in Genome-Scale Metabolic Modeling toward Microbial Community Analysis of the Human Microbiome. ACS Synth Biol, 2021. 10(9): p. 2121-2137.

[51] Yeh, Y., et al., A molecular toolkit for heterologous protein secretion across Bacteroides species. bioRxiv, 2023.

[52] Fang, X., et al., Preclinical Safety Evaluation of the Human-Identical Milk Oligosaccharide Lacto-N-Triose II. Int J Toxicol, 2024. 43(1): p. 27-45.

[53] Zhu, Y., et al., Metabolic Engineering of Escherichia coli for Lacto-N-triose II Production with High Productivity. J Agric Food Chem, 2021. 69(12): p. 3702-3711.

[54] Ciocan, D. and E. Elinav, Engineering bacteria to modulate host metabolism. Acta Physiol (Oxf), 2023. 238(3): p. e14001.

[55] Ma, J., et al., Engineered probiotics. Microb Cell Fact, 2022. 21(1): p. 72.

[56] Wang, L., et al., An engineered probiotic secreting Sj16 ameliorates colitis via Ruminococcaceae/butyrate/retinoic acid axis. Bioeng Transl Med, 2021. 6(3): p. e10219.

[57] Palmer, J.D., et al., Engineered Probiotic for the Inhibition of Salmonella via Tetrathionate-Induced Production of Microcin H47. ACS Infect Dis, 2018. 4(1): p. 39-45.

[58] Riglar, D.T., et al., Engineered bacteria can function in the mammalian gut long-term as live diagnostics of inflammation. Nat Biotechnol, 2017. 35(7): p. 653-658.

[59] Sadhu, S., T. Paul and N. Yadav, Therapeutic engineering of the gut microbiome using synthetic biology and metabolic tools: a comprehensive review with E. coli Nissle 1917 as a model case study. Arch Microbiol, 2025. 207(9): p. 213.

[60] Lubkowicz, D., et al., An engineered bacterial therapeutic lowers urinary oxalate in preclinical models and in silico simulations of enteric hyperoxaluria. Mol Syst Biol, 2022. 18(3): p. e10539.

[61] Romano, K.A., et al., Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. mBio, 2015. 6(2): p. e02481.

[62] Hwang, I.Y., et al., Engineered probiotic Escherichia coli can eliminate and prevent Pseudomonas aeruginosa gut infection in animal models. Nat Commun, 2017. 8: p. 15028.