Correlation Analysis Between Microbes And Human Diseases

Fangzheng Zhou *

Shcool of Food and Nutritional Sciences, University College Cork, Cork City, Ireland

* Corresponding Author Email: 119102393@umail.ucc.ie

Abstract. The pathophysiology of human diseases has been shown to be strongly connected to a variety of microorganisms. The microbiome that inhabits the human bodies has a significant impact on our health, yet its relationship to disease remains poorly understood. Now, various microbial-based human illness networks have been created, examining the micro-to-macro link between microorganisms and disease. In addition, microbial-based disease analysis can anticipate new disease-microbe-drug correlations and processes. The prediction techniques and scientific achievements given could be used to solve intractable medical problems. On the basis of evidence that microbes have either been demonstrated to play pathogenic roles in promoting obesity, NAFLD, and cardiovascular illnesses, a link has been established between gut bacteria and the development of numerous diseases, both positively and negatively. How to better systematically comprehend the intricate connections between bacteria and hosts within the human body and develop novel tailored medications to tackle metabolic illnesses. Reduce the number or activity of dangerous microorganisms by encouraging the reconfiguration of the gut microbiota, or utilizing their activity to stimulate the growth of beneficial bacteria. Analyzing the pathogenic logic chain of microbes in various diseases, identifying the metabolic mechanism at the micro level, and developing more accurate methods for disease prediction.

Keywords: Microbes, Human Diseases, Microbe-Disease Association.

1. Introduction

The human body is home to a staggering number of different kinds of microorganisms, including but not limited to bacteria, archaea, fungi, and viruses. The overwhelming majority of these inhabitants are bacterial in nature. These microorganisms can be found in a variety of human organs, including the respiratory system, the skin, the digestive tract, the mouth, and the stomach. These microorganisms play an essential role in human health and disease because of the functions that they perform. The interaction that takes place between the microbe and the host is not a one-way street but rather a two-way street that is beneficial to both parties involved [1]. The microbiota that is typically found in the body will colonize different organs and will establish either a symbiotic or a commensal relationship with the human body. The make-up of the microbial population is significantly impacted by a wide variety of factors, with the environment and genetics being two of the most important. In recent years, the rapid development of methodologies for new generation DNA sequencing has made it possible for the revelation of connections between human microbes and a wide range of diseases [1]. This was made possible as a result of the discovery that human microbes can cause disease. These discoveries may result in the creation of new treatments for the aforementioned conditions in the future. The disordered central nervous system, cancer diseases, cardiovascular diseases, obesity, and diabetes are all included in this category.

A greater understanding of the processes that underlie the development and progression of diseases is a step toward being made possible by the discovery of potential connections between microorganisms and diseases. The task of making predictions regarding the connection that exists between microorganisms and diseases has already been successfully carried out using a variety of different automated learning techniques in the present day. There has been a meteoric rise in the amount of time spent conducting research on the microbe-disease associations as a direct result of the rapid advancements in diagnostic modern biotechnology and genetic testing that have revealed an increasing number of microbe-disease associations. These rapid advancements have revealed an increasing number of microbe-disease associations (MDAs). However, in order to identify MDAs

utilizing conventional wet methodological approaches, a substantial amount of both financial and time investment is required. In 2017, the Human Microbe-Disease Association Database (HMDAD) was established as the very first database of its kind. The known connections between microorganisms and diseases that have been uncovered through studies of the microbiome served as the basis for the creation of this database. On the basis of the findings of previous studies, a large number of scientists have since developed new methods of prediction or improved upon those that already existed. The MSLINE, a novel computational model for predicting the relationship between microbes and various diseases, was developed this year by a group of researchers working in the field [2]. Despite the significant progress that has been made, there are still some important things to keep in mind when it comes to computing predictions of the connections between microbes and diseases. These things should be kept in mind because they are important.

2. The connection between the body's microbes and Inflammatory bowel disease

The set of chronic inflammatory gastrointestinal illnesses known as inflammatory bowel disease (IBD) affects people all over the world. Campylobacter concise and Helicobacter pylori are some of the species that have an association with inflammatory bowel disease (IBD) [3]. Using next-generation sequencing, researchers compared the fungal microbiome of newly diagnosed juvenile inflammatory bowel disease patients to that of adult IBD patients and healthy controls [3]. The biological aspects of inflammatory bowel disease are heavy reliance on associated bacteria at the mucosal-luminal interface of the intestine (MLI). To investigate this, conduct a number of researches that combine the examination of the microorganisms and metaproteome at the MLI in people with intestinal diseases and human gut health controls. Some researchers believe that a lack of "defensive" bacteria and an excess of "aggressive" bacteria in the gut contribute to IBD [4]. Safe and effective prevention and therapy for IBD may lie in the manipulation of gut microbes' flora.

Research on the intestinal microbiome in other chronic inflammatory disorders that is mediated by the immune system can be able to help us comprehend the gut microbiota in IBD. Researcher presented a summary of the evidence connecting microorganisms to the etiology of gut inflammation in inflammatory bowel diseases and a summary of the evidence supporting the use of antibiotics to treat IBD [5]. Intestinal homeostasis is governed by an intricate web of host genetic factors, microorganisms and their metabolites, causing it difficult to categorize and mechanistically unravel the various processes. As shown in Figure 1, some researchers discussed the environmental and genetic factors that impact the functions of intestinal bacteria and their metabolites in the clinical progression of inflammatory bowel disease, and methods that can be applied with microbiome-based therapeutics to avoid, treat, and finally cure IBD [6].

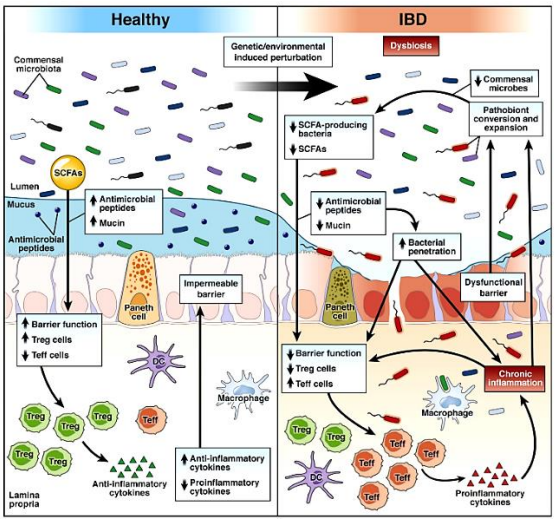

Figure 1. Influencing factors of dysbiosis and chronic inflammatory state in IBD [6]

3. The connection between body's microbes and cancer

Cancer is a multidimensional disease in which an aging cell starts to divide irregularly as a result of DNA damage and inflammation, among other reasons. The recent advances in our knowledge of microorganisms in diseases, also their possible contribution to the development of cancer, were reviewed. Inflammation is not often considered carcinogenic, yet a considerable proportion of malignancies are caused by chronic microbial infections and inflammation-induced damage [7]. There is proof that suggests microbes are blamed for roughly 10–20% of human cancer. The International Agency for Cancer Research has identified 10 microorganisms as carcinogenic to yet, among which is Helicobacter pylori because of its link to gastrointestinal cancer. The interaction that occurs between bacteria and cancer cells contributes to the progression of cancer, and researchers are attempting to control the targeting of bacteria and cancer cells in order to develop novel approaches to the treatment of cancer.

Digital karyotyping microbe identification (DK-MICROBE) is a method that was invented for detecting bacterial and viral genomic DNA in human illness tissues. Colorectal cancer has been linked to Fusobacterium species, according to metagenomic research. Further sequencing of a considerably larger sample size (n=130) of colorectal cancer and matched normal control tissues are presented in, which expands upon this earlier research [6]. The role of host-microbe interactions in colorectal cancer and the possible advantages of microbe-targeted therapeutics from happening and how to treat them are discussed. Researchers presented an overview of recent research and molecular explanations for the link between the gastrointestinal microbiota and the emergence of malignancies, which sheds light on potential therapeutic approaches for cancer detection, therapy, or avoidance. Among the most commonly utilized cancer chemotherapeutic medicines are microbe-derived antitumor antibiotics focused mostly on microbe-derived anticancer medications while considering their derivatives, biological mechanism, separation techniques, limits, and what kind of cancers they target [8]. The clinical significance of plasma cfRNAs produced from humans and microbes, as well as their prospective applications in the diagnosis of cancer and the localization of tumors, are demonstrated in a paper [9], as shown in Figure 2. There is some evidence that suggests that cancer cells and dangerous bacteria can both benefit from receiving an abundance of energy. Even though some bacteria can boost the fitness of cancer cells, others may provide protection against the disease. The intricate dynamic interactions between cancer cells and microorganisms across time, in both healthy individuals and cancer patients, should be the investigation orientation of future research.

4. The connection between body's microbes and cardiovascular disease

Heart disease and the gut microbiota have a complicated relationship. Human atherosclerotic plaques were found to include bacterial DNA in early sequencing investigations, which suggested a possible relationship between microbiome and atherosclerosis; however, it was not clear whether or not the DNA came from actively growing bacteria within the arterial wall [10]. Recent research has given insight into the intricate web of connections between microorganisms, their metabolic by-products, and the risk of cardiovascular disease. First evidence that IH/HC induces functional alterations in the intestinal bacteria, opening the door to further study of the gut microbiome's involvement in cardiometabolic disorders. Multiple metaorganismal mechanisms influence CVD in experimental animals and show striking symptomatic connections in human studies [11]. Trimethylamine-N-oxide (TMAO) and uremic toxins are metabolites originating from the intestinal microbes that have an impact in cardiorespiratory fitness and illness. In terms of daily foods, some researchers addressed why specific bacteria are present in people and the reason why they can affect the human cardiovascular system [12].

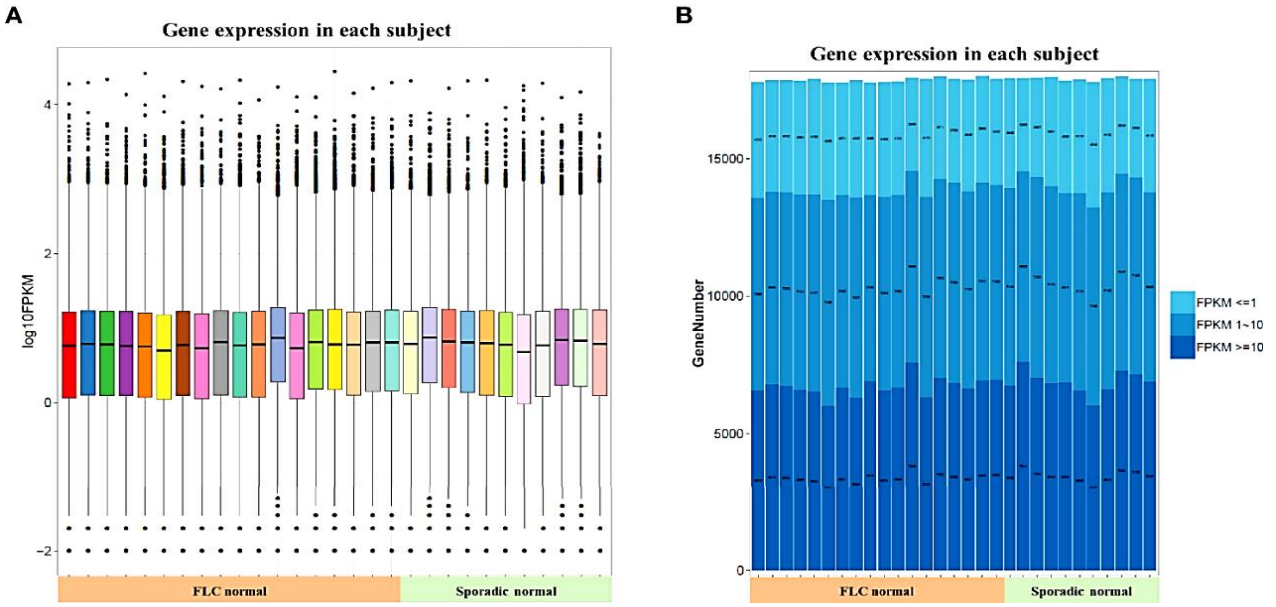

Figure 2. Global expression of genes in normal lung tissue [9]

In a review, the authors compiled the most recent research on how the microbiome is linked to cardiovascular disease and how probiotics might help. As a potentially beneficial alternative product, a Ganoderma lucidum mycelium-fermented liquid (GLFL) has not yet been studied in people, although its effects on intestinal microorganisms and factors that increase the chance of cardiovascular disease are intriguing [13]. There were few volunteers who were fed GLFL while its polysaccharide content was examined to determine its effect on gut bacteria and cardiovascular risk variables. The meta-organismal route has provided compelling evidence in the etiology of CVD, as evidenced by several clinical studies of patient cohorts and animal models [13].

5. The connection between body's microbes and obesity

It has recently been brought to people's attention that the microbiota that is found in the gut is another factor that contributes to the development of obesity. In point of fact, obese people and animals have a microbiome community that is distinct from that of their leaner counterparts [14]. As shown in Figure 3, there is a possibility that the microbiota in the intestinal tract play an important role in the shifts in hedonic dietary patterns that are factors associated with a higher prevalence of obesity [14]. The authors of this article provided a summary of research on the effect that hydrolysates have on the microbes that live in the intestinal tract, which ultimately leads to obesity. In spite of this, the primary focus of the article is on the way in which hydrolysates modify the intestinal microbiota in a way that appears to help improve current weight. The alterations in intestinal physiology and lipid metabolism that are caused by gut microbes ultimately result in the breakdown of the intestinal epithelial barrier, which leads to obesity [1].

Microorganisms that offer protection against obesity and the metabolic problems that frequently accompany it have been uncovered by researchers. For instance, it has been demonstrated that supplementation with Akkermansia muciniphila can lower the amount of body fat seen in mice that are obese [15]. This was accomplished by reducing the amount of Akkermansia muciniphila that the mice consumed. Resveratrol's effect of preventing obesity is most likely mediated by processes of controlling gut bacteria, which, in turn, improve fat storage and metabolism [16]. Resveratrol is found in red grapes and other dark-skinned plants. The research into the possible relationship between intestinal bacteria and bariatric surgery, the goal of which is to provide convincing evidence for the enhancing effect of intestinal flora in enhancing the therapeutic benefit of bariatric surgery. Because of this, the microbiota of the gut has become a primary focus of research for the development of new therapeutics to combat the rising rates of obesity.

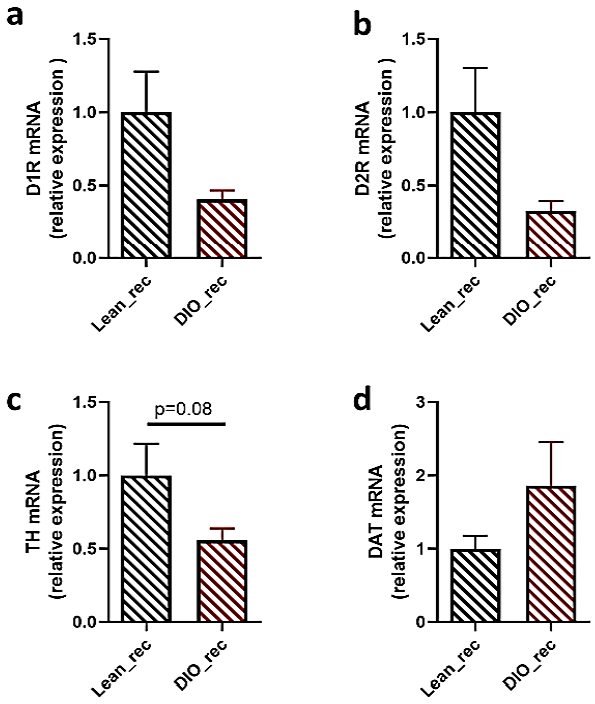

Figure 3. Effects of dopaminergic signaling in obese gut microbiota receptor mice [14]

6. The connection between body's microbes and diabetes

Both Type 1 and Type 2 diabetes exist, with type one diabetes (T1D) being caused by autoimmune destruction of the human islet cells, which leads to an inability to make insulin. Nearly all new instances of diabetes are of the type 2 variety. characterized by an inability on the part of the body to make adequate use of insulin [1]. Tobacco use, excess body fat, increased blood pressure, and elevated levels of cholesterol are highly connected to type 2 diabetes. Those factors for diabetes-related complications may be exacerbated by unhealthy lifestyle choices. However, addressing these issues head-on through measures like exercise and weight management might assist [1].

Type 2 diabetes has been associated with change in gut flora, and these alterations have been shown to have an effect not only on the progression of the disease but also on resistance to it. Gut dysbiosis and the resulting breakdown of epithelial barriers, as well as an increase in inflammatory bacterial by-products like lipopolysaccharide (LPS), are among the factors that contribute to metabolic inflammation. According to a paper, in T1D, the microbiome of the gut can drive and promote inflammation. Translocation of microbial antigens to the pancreas, as demonstrated by the authors, may result in inflammation leading to T1D [17]. Microorganisms frequently migrate from luminal and mucosal areas and continue to disrupt cytokines required for autoimmune cells and humoral responses, therefore eliminating beta cells that produce insulin [17]. Vaccination against high microbial surface antigens with poly-N-acetylglucosamine (PNAG) controls this inflammation [17].

In the past decades, there are more people suffering from type 2 diabetes and prediabetes worldwide, making type 2 diabetes a fast-rising public health concern. In addition to genetic susceptibility, poor lifestyles and dietary habits are key contributors to impaired insulin sensitivity and chronic inflammation, including diabetes complications. Research on the changes in the intestinal microbiomes of people with type 2 diabetes has been analyzed in depth, which focused on the disease model for type 2 diabetes and how it might be predicted, diagnosed, and monitored in the future. In particular, gut microorganisms digest anything they can obtain from the host's diet, producing metabolites that can influence different cells. As shown in Figure 4, the authors discuss how common dietary components contribute to the advancement of type 2 diabetes by influencing microbial secretion [18]. The gut microbiota functions as an endocrine organ, significantly impacting the

development and progression of type 2 diabetes via metabolically independent and dietary metabolite-driven pathways.

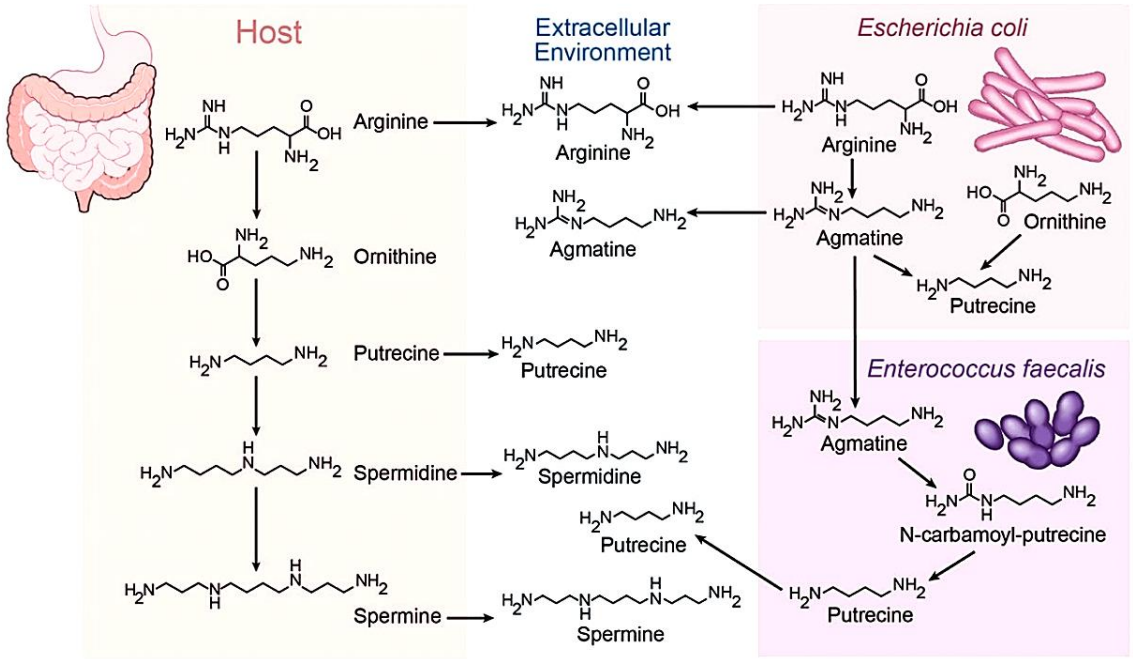

Figure 4. Production mode of polyamines [18]

7. The connection between the body's microbes and disorders of the central nervous system

Multiple pieces of research point to the microbiome as the factor responsible for regulating both the central nervous system (CNS) and the immune system. The microbiome gut-brain axis is a novel concept that has emerged as a result of the growing body of research demonstrating that the microbiome is essential to the proper functioning of the intestinal tract. The production of metabolites by microbes can, over the course of time, lead to the development of diseases that are either life-threatening or debilitating. Both the central nervous system, which controls the signals that are transmitted to the stomach, and the stomach, which is the organ that receives signals from the central nervous system, are impacted by these metabolites [19], as shown in Figure 5. Researchers have developed the concept of the diseases axis in order to more thoroughly investigate the dynamic relationship that exists between the digestive tract and the central nervous system. This concept is built around the idea of a two-way interaction, with separate mechanisms governing each of the possible outcomes that can occur as a result of that interaction. The homeostasis of energy, glucose, and lipids can be altered by intestinal microorganisms through the regulation of metabolic channels such as the endocrine, enteric, and central neurological systems [19]. However, the specific role that microbiota play in neurological diseases is still not completely understood.

8. Prediction methods for microbe-disease associations

In spite of the fact that numerous types of human diseases have been demonstrated to be caused by microbes, a significant number of clinically relevant microbial infections have not yet been discovered. According to the hypothesis, bacteria that perform comparable roles tend to have comparable association or non-association patterns with diseases that perform analogous duties, and vice versa. This also holds true for diseases that perform analogous duties for bacteria. This is also true for diseases that perform functions that are analogous to those of bacteria. This collaborative structure is the first one of its kind. In order to arrive at these conclusions, information was extracted

from the Human Microbe-Disease Association Database, which is referred to by its abbreviation, HMDAD. The methodology known as Networks Consistent Projection for Human Microbe-Disease Association predictions (NCPHMDA) combines previously established links between microbes and diseases with the application of the Gaussian distribution model in order to conduct an analysis of the connection between bacterial pathogens and diseases [2]. Another component of this methodology is the merging of previously established links between microbes and diseases. The Binary Matrix Completion Microbe Disease Association is a one-of-a-kind method for making predictions (BMCMDA). The principle of Binary Matrix Completion serves as the foundation for this approach. This strategy can be implemented in a number of different ways, one of which involves placing a collection of MDAs into a binary MDA matrix. This matrix can then be used to make predictions regarding potential MDAs. The researchers looked at the differences in the faecal microbiota of approximately 40 children who had been diagnosed with autism spectrum disorder [2], and they found that only 6 of the children had been determined to have typical development. The researchers proposed using dimension decomposition and label spreading for HMDA based on the similarity test for metabolic disorders and microbes, disease symptom familiarity, and a dataset of recognized microbe-disease affiliations acquired from the HMDAD database. a plan for enhancing disease and microbe networks as well as predicting new correlations based on similarities. This method is referred to by the acronym BRWMDA [20], which was created specifically for this purpose. Throughout the course of the past few years, an ever-increasing number of academics have developed a variety of computational models in an effort to forecast the existence of bacteria that are possibly associated with diseases [20].

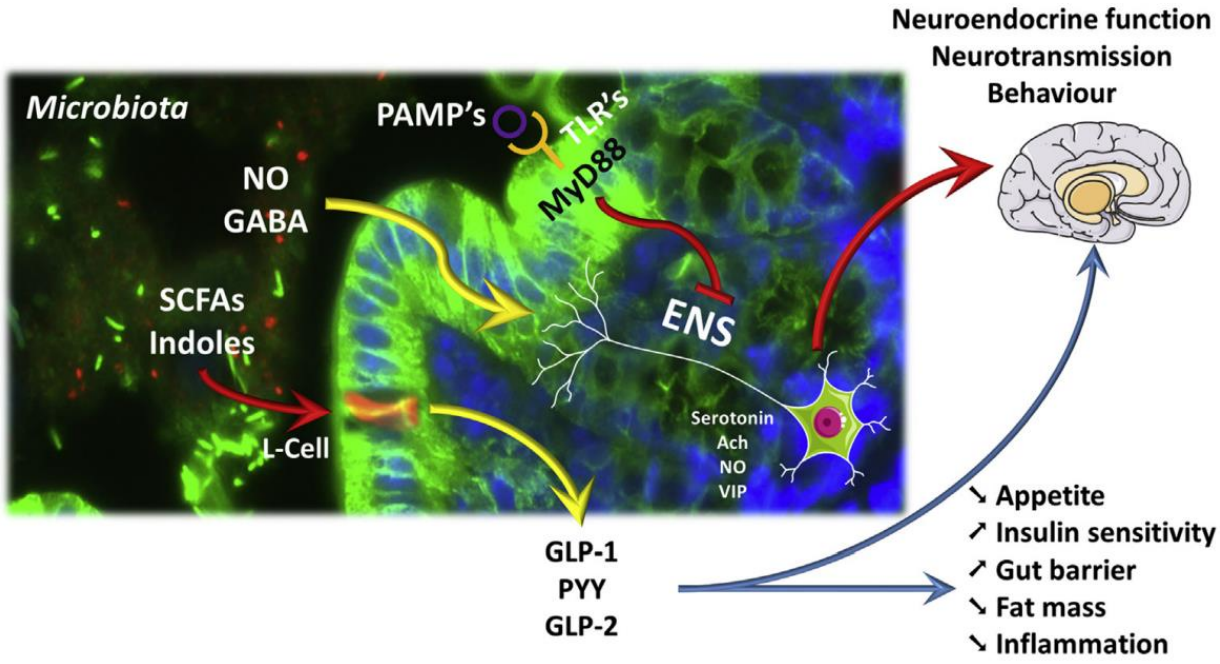

Figure 5. Interactions among microbial metabolites, endocrine and neural pathways [19]

Using a model that has been constructed with the help of deep neural networks is one way that it has been proposed that one might be able to make predictions regarding the components of matrices. The multi-similarities factorization of the bilinear matrix remains a closely guarded secret. The Markov model disease association prediction, also known as MSBMFHMDA, is an innovative method that was developed to make predictions regarding the potential connections that may exist between pathogens and diseases. The goal of this method is to determine whether or not there is a relationship between pathogens and diseases. The technique referred to as multi-view feature aggregation (MVFA), which has the potential to be utilized in the process of locating bacteria that are the cause of disease [21]. In order to achieve this goal, linear and nonlinear data must be integrated into the analysis. A multi-view graph augmentation convolutional network, which, for the sake of

ease of use, they abbreviated as MVGCNMDA. The network was established with the purpose of determining whether or not particular microorganisms are linked to particular diseases. Some researchers proposed developing predictions regarding the linkages between microorganisms and diseases by utilizing a network of networks that were built on a metapath aggregated graph neural network (MAGNN) [9]. These researchers believed that this would be the most effective way to do so. After this, the establishment of canonical depictions of pathogens proceeded with the introduction of characteristics that were similar to illnesses and bacteria. In order to accomplish this goal, the MDADP is an innovative webserver that will host both a new MDA database as well as prediction methods for the purpose of MDA research. This was done so that the MDADP could achieve this objective. The aforementioned objective will serve as the motivation for carrying out these specific steps. In order to investigate the possibility of a connection between microbes and illness, the researchers developed a one-of-a-kind computer model that they call MSLINE. The "LINE," which is an acronym that stands for Multiple Similarities and Large-scale Information Network Embedding, serves as the foundation for the work that they do [2].

9. Conclusions

Multiple lines of evidence support a connection between changes in gut bacteria and the advent of metabolic illness. Most bacteria can be found in one's digestive system, where they generate or change substances or activate host reactions that influence physiological processes as diverse as immunology, neurology, and metabolism. New treatments for metabolic diseases may be possible once the complex connections between gut microorganisms and their hosts are uncovered. More knowledge is required for dynamics study of the gut microbiome. However, most studies have focused on microbiome macro manifestations. What's more, scientific studies can be adapted into policies that direct public health or clinical practice. The intricacy of the intestinal microbiome, which includes more than simply bacteria and archaea, can be overwhelming. There should be an emphasis on encouraging the reorganization of the intestinal microbiota, with the goal of decreasing the number or activity of dangerous germs and increasing the number or activity of good bacteria.

Numerous in vitro investigations on the targeting mechanism of certain microbial compounds have been undertaken on suspected target tissues or cells, and many ongoing studies use rodents as experimental subjects due to the unavailability of experimental animals that are physiologically similar to humans. Many experimental attempts have fallen short in elucidating the connection between the gut microbiome and pathogenicity. Given the high inter-individual variability in the gut microbiome, a human study should ideally involve repeated, randomized, cross-over interventions on a single participant over a prolonged period of time. This suggests that well-designed, extended randomized controlled trials are the only practical option to learn how the gut microbiome influences human disease. For this purpose, a sufficient number of individuals must be recruited to conduct statistical tests of associations.

References

[1] Beg, R., Gonzalez, K. and Martinez-Guryn, K. (2022) Implications of microbe-mediated crosstalk in the gut: Impact on metabolic diseases [J]. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1867(8), pp. 159180.

[2] Wang, L. et al. (2022) MDADP: A Webserver Integrating Database and Prediction Tools for Microbe-Disease Associations [J], IEEE journal of biomedical and health informatics, 26(7), pp. 3427–3434.

[3] Mukhopadhya, I. et al. (2015) The fungal microbiota of de-novo paediatric inflammatory bowel disease [J]. Microbes and Infection, 17(4), pp. 304–310.

[4] Kumar, S. and Kumar, A. (2022) Microbial pathogenesis in inflammatory bowel diseases. Microbial Pathogenesis [J], 163, pp. 105383.

[5] Ledder, O. (2019) Antibiotics in inflammatory bowel diseases: do we know what we're doing? [J]. Translational Pediatrics, 8(1), pp. 42–55.

[6] Lee, M. and Chang, E.B. (2021) Inflammatory Bowel Diseases (IBD) and the Microbiome—Searching the Crime Scene for Clues [J]. Gastroenterology, 160(2), pp. 524–537.

[7] Armstrong, H. et al. (2018) The Complex Interplay between Chronic Inflammation, the Microbiome, and Cancer: Understanding Disease Progression and What We Can Do to Prevent It [J]. Cancers, 10(3), pp. 83.

[8] Kapoor, R., Saini, A. and Sharma, D. (2022) Indispensable role of microbes in anticancer drugs and discovery trends [J]. Applied Microbiology and Biotechnology, 106(13–16), pp. 4885–4906.

[9] Chen, Ying et al. (2022) A Multi-Omics Study of Familial Lung Cancer: Microbiome and Host Gene Expression Patterns [J]. Frontiers in Immunology, 13, pp. 827953.

[10] Koren, O. et al. (2011) Human oral, gut, and plaque microbiota in patients with atherosclerosis [J]. Proceedings of the National Academy of Sciences, 108(supplement_1), pp. 4592–4598.

[11] Tripathi, A. et al. (2018) Intermittent Hypoxia and Hypercapnia, a Hallmark of Obstructive Sleep Apnea, Alters the Gut Microbiome and Metabolome [J]. mSystems, 3(3), pp. e00020-18.

[12] Sawicka-Śmiarowska, E., Moniuszko-Malinowska, A. and Kamiński, K.A. (2021) Which Microbes Like My Diet and What Does It Mean for My Heart? [J]. Nutrients, 13(11), pp. 4146.

[13] Ettinger, G. et al. (2014) The influence of the human microbiome and probiotics on cardiovascular health [J]. Gut Microbes, 5(6), pp. 719–728.

[14] de Wouters d'Oplinter, A. et al. (2021) Gut microbes participate in food preference alterations during obesity [J]. Gut Microbes, 13(1), pp. 1959242.

[15] Depommier, C. et al. (2019) Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study [J]. Nature Medicine, 25(7), pp. 1096–1103.

[16] Qiao, Y. et al. (2014) Effects of resveratrol on gut microbiota and fat storage in a mouse model with high-fat-induced obesity [J]. Food & Function, 5(6), pp. 1241–1249.

[17] Kostic, A. (2021) 115-OR: Microbiome Antigens as a Vaccination Strategy in Type 1 Diabetes [J]. Diabetes, 70(Supplement_1), pp. 115-OR.

[18] Massey, W. and Brown, J.M. (2021) The Gut Microbial Endocrine Organ in Type 2 Diabetes [J]. Endocrinology, 162(2), pp. bqaa235.

[19] Cani, P.D. and Knauf, C. (2016) How gut microbes talk to organs: The role of endocrine and nervous routes [J]. Molecular Metabolism, 5(9), pp. 743–752.

[20] Yang, X. et al. (2021) Multi-Similarities Bilinear Matrix Factorization-Based Method for Predicting Human Microbe-Disease Associations [J]. Frontiers in Genetics, 12, pp. 754425.

[21] Peng, W. *et al.* (2021) Multi-View Feature Aggregation for predicting microbe-disease association [J]. *IEEE/ACM transactions on computational biology and bioinformatics*, doi: 10.1109/TCBB.2021.3132611.