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Microbiome-Microbolome And Disease: A Covert Nexus

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Abstract

The microbial diversity associated with all life forms, including humans, plants, and animals, is magnificent. Different regions of the body are inhabited by different species and forms of microbes. Such transient interaction with the microbiome affects all organisms concerning their physiological functioning as well as disease. Inherent functions of the body, like immune reactions, developmental pathways, metabolic and endocrinological attributes coupled with genetics, lifestyle factors, diet, and introduction of antibiotics in the system, and other metabolites, all play an important integrative role in the maintenance or loss of health. Research indicates that the occurrence of diverse types of health conditions, like autoimmune disorders, neurological problems like Alzheimer's, mood alterations, cancer, and even social behavior, are related to the changes in the microbial population in the human gastrointestinal tract. This paper highlights the different effects of the gut microbiome-metabolome conjugate and its effect on health conditions, with a brief reflection on the diverse modes of advanced treatment and future research using nanotechnology and artificial intelligence.

Keywords: Gut Microbiome –Metabolome, Diseases, Treatment, Nanotechnology

1. Introduction

The distribution and diversity of microorganisms in the human body are fascinating with an estimated human flora to exceed the total number of cells by a factor of ten [1]. Since the activity of the human microflora has been less appreciated and understood over the years, the collaborative interactions between the human flora and the living human body needed elaboration. The shotgun sequencing experiments coupled with microarrays contributed immensely to the characterization of the microbial diversity in the human body that relied on the 16S rRNA, 18S rRNA, marker genes that allowed the determination of the microbial diversity of an area with a genome in multiple of 150 in comparison to the human genome [2, 3, 4].

The main concentration of microbes packed into the gastrointestinal tract measures about 1011–1012 bacteria/1cm^3 [5] where a plethora of these tiny organisms play fundamental role in the functioning of the digestive tract and aids other functions like the metabolic degradation of xenobiotics, metabolism of vitamin b12 and Vitamin K.

Reports indicate that the absence or lack of the microbial diversity are potentially capable of producing autoimmune diseases like type I diabetes, rheumatism , coagulation problems, muscular dystrophy and hindrance in neural transmission pathways due to Vitamin K malfunction. It can also produce cancer, loss of memory, depressive conditions,, autism, and even Alzheimer's disease [4]. Microbial interaction with human cells and health appears to pass on to the progeny. It is proposed that there are multiple

ways by which the human flora interacts with human physiology. In addition to the genetic and developmental regulations, the canvas of interaction includes environmental interactions that cause remodeling of certain parameters of the interconnected physiology of immune system. The impact also extends to metabolism, hormonal pathways, and brain function coupled with the tendency of epigenetic modulation of the genome.

Research points to the fact of an interactive crosstalk between the microbial populations, environment, plants and health in man [6]. This microbial diversity functions in a broader perspective of the terrestrial and microbial ecosystems and their niches. Factors like agricultural developments, industrial influences and others continuously challenge the balance of these interactive systems as consequences of the lifestyle modification leading to unhealthy conditions [7]. There are various types of gut microbiota interactions associated with different diseases [8]. The metabolic products produced by the gut mircrobiota includes a host of different substances like bile acids, indoles, short chain fatty acids that have specific regulatory and inflammatory responses leading to a diversity of health issues like colitis [9], hepatic steatosis[10], Parkinson's disease [11] Multiple sclerosis, obesity schizophrenia and a host of others[8, 11, 12,13, 14]. The present paper highlights the nexus between the microbiome population of the gut, and its implications in disease orchestrated by the metabolomics with highlights on treatments and future prospects.

2. Microbial composition of the human gut

The gut microbiome is composed of a plethora of bacterial types associated with diverse types of functions. Encoding over 3 million genes, the gut microbiome perhaps has the greatest microbiological density. Genetic sequencing tools employed for analysis of the gut microbiome have identified bacteria, yeast along with viruses [15]. The microbial diversity consists of a few phyla encompassing 160 species including Actinobacteria, Proteobacteria, Fusobacteria, Firmicutes, and Verrucomicrobia. Almost a staggering 90% of the microbial diversity is represented by Firmicutes and Bacteroidetes [16]. There are over 200 genera in the phylum Firmicutes, including Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus. Of the Firmicutes phylum, 95% is composed of the genus Clostridium. Additionally, prominent genera like Prevotella and Bacteroides make up the Bacteroidetes. Proportionally less common is the Actinobacteria phylum, which is primarily represented by the genus Bifidobacterium. [16].

3. Functional dynamics of gut microbiome

The gut microbiome is an essential component of the digestive system, although there is an association between the commensal microbiota and the gut. From a functional standpoint, gut microbiota aid in synthesizing and extracting metabolites as well as nutrients like short-chain fatty acids, amino acids, vitamins, etc. In addition, they also exhibit immunological parameters by restricting the growth of pathogenic microbes as well as the production of bacteriocins [17].

Additionally, they perform several unique functions in the immune system's regulation, the host's nutrition and metabolism, the integrity of the intestinal mucosa barrier, and the defence of the gut against infections. Everybody has a unique profile of gut microbiota [18] .The gut microbiota of each individual is formed early in life. Various parameters like the baby's delivery style date of birth, appropriate milk-feeding technique, duration of the weaning period, and external variables like antibiotic use affect the gut microbiota composition of an individual.

These personal, healthy core native gut microbiota stay relatively stable throughout adulthood. However, different enterotypes, BMI, exercise, and lifestyle all contribute to the variation in gut microbiota composition. Therefore, there is standard ideal gut microbiota composition because each individual's gut microbiota composition is unique. The gut microbiome ecosystem is a specialized mechanism of interspecific interaction stabilized by the selection process that plays diverse roles in health and disease (Fig1)

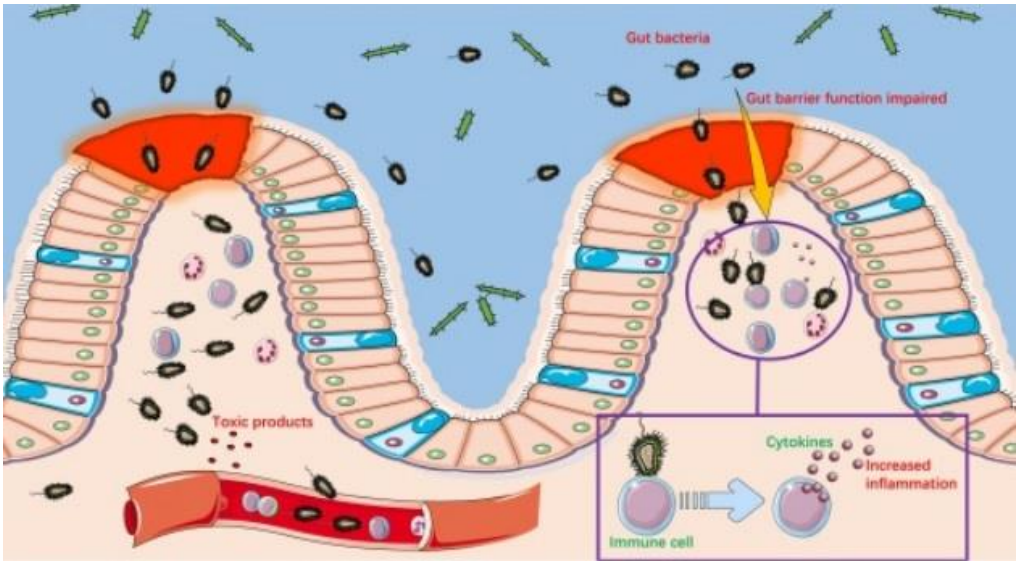

Figure1. Loss of barrier function of gut microbiota leads to infection (Reeved from Lu et al, 2020)

The primary function of the gut ecosystem is the provision of a portal for the digestive as well as absorptive processes to function optimally, and it also acts as a barrier to pathogenic substances or otherwise harmful ones, preventing them from passing from the gut into other systems, organs, or the circulatory system. In addition, the human gut is the locale of a multitude of bacterial species, in addition to other body region species [19].

Anatomical location in the gut, type of delivery, breast feeding, lifestyle, food, age and other factors cause sequential alteration in gut microbiome composition

The microbial composition of the gut is a dynamic entity showing modifications or alterations with various factors, including anatomical location in the colon, gestational age, and presence of normal or medically assisted delivery, feeding methods, and other parameters. Considering the anatomical location of the microbiome in the colon, the colon of the gut is populated mainly by Bacteriodetes and Firmicutes, with minute amounts of Proteobacteria and no Fusobacteria (Fig2).

The microbial population differs even in a normal and C-section birth, with members of different genera like Bifidobacterium spp., Bacteroides fragilis, Prevotella spp., Lactobacillus spp., Staphylococcus spp., Streptococcus spp., Escherichia spp., and Sneathia spp. increasing in a normal vaginal birth, while a baby born before 37 weeks of pregnancy has a lower preponderance of Bifidobacterium spp. In a C-section delivery, the number of Corynebacterium spp. and Propionibacterium spp. increases while the population of Bacteroides spp., Shigella spp., Escherichia spp., and Staphylococcus spp. are reduced. Breastfeeding increases the number of Bifidobacterium spp., Lactobacillus spp., Staphylococcus spp., and Enterococcus spp.; however, artificial milk increases the number of Clostridium difficile, Lactobac-

illus spp., Escherichia spp., and other microorganisms. Age also appears to impact the microbial composition. Above 70 years, there is a noticeable difference in the bacterial Proteobacteria (increment), while Bifidobacteriaceae and Clostridium get reduced [19]

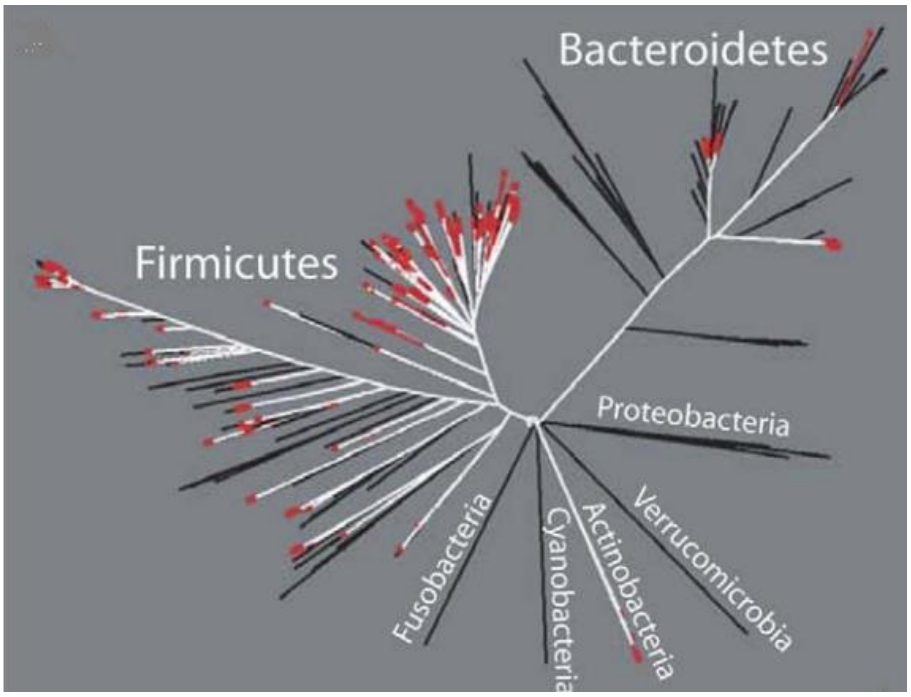

Figure 2.phylogenetic tree depict Microbial diversity in human colon Red, blue and yellow branches indicate unique diversity of the individual itself. (Retrieved from Ley et al, 2006, Cell. 2006 Feb 24; 124(4):837-48).

The gut microbiota has been implicated in different physiological conditions and diseases (Fig 3). It is postulated that gut microbiota composition is intricately linked to the biological aging of the gut and is not non-chronological. Exercise and mobility, dietary habits, and social customs all affect the healthy composition of the gut microbiome, aiding in longer life spans. In mobility-deprived or very meagre workout regimens, there appears to be an alteration of the gut microbiome leading to an increase in immobility, digestion, and other physiological parameters like the immune system and muscular system, involving sarcopenia and motor neural issues [20].

In ethnic communities, forced changes in diet have resulted in changes in the microbial composition of the gut, and modern lifestyles are being regarded as sources of multiple diseases. Microbial compositions of the gut are of different types in certain ethnic groups, like Irish travellers, resembling pre-industrialized communities or societies. Thus, microbial composition and health have been implicated in public health parameters under the pressure of lifestyle modifications [21]. The environment also plays a significant role in the development of the gut microbiome in association with cohabitation, health conditions, and microbiome compositions. It has also been linked to socioeconomics, early and present-day vulnerability to microbiome that has been intricately linked to functionality and diseases [22].

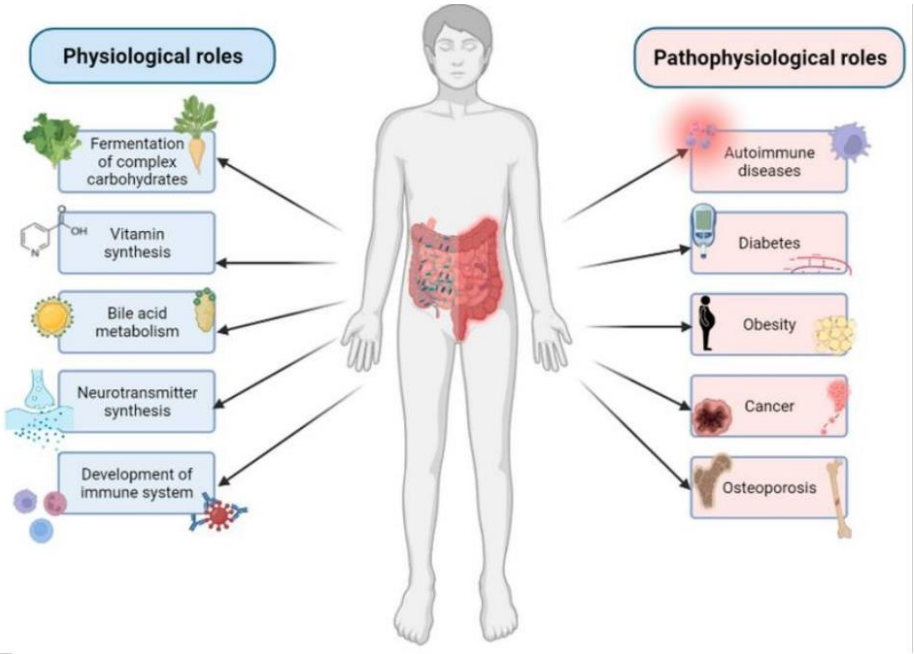

Figure 3 .Role of gut microbiome in health and disease, (Retrieved from Zemanova et al, 2022)

4. Impact of alteration in microbiome composition and metabolome on Diseases

It has been implicated in different research studies that the gut microbiome is intimately related to a wide spectrum of disease conditions, lifestyles, and even social behavior via its metabolome. There is a statistically significant difference in the taxonomy of the gut microbiome composition between a healthy and a diseased individual [23].According to available data, the microbiome is more stable in later childhood and adulthood after being relatively variable during infancy and early childhood. Microbiota effects can modify risk mechanisms and predispose to the development of diseases by altering the host's metabolism in later life and during early development [24] (Fig4)

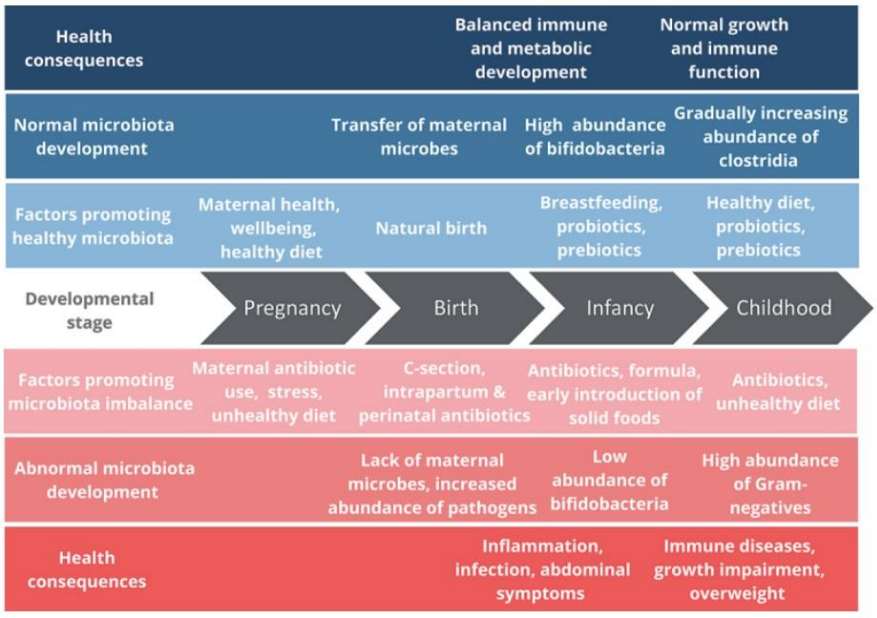

Figure 4. Age related dependence of health, immune development, growth on microbiome (used under CC 4.0 Copyright © 2022 Korpella & Vos, 2022)

The gut microbiota plays an important role in human functional metabolic pathways by contributing enzymes that are not produced by the human genome [25]. Introduction of Polyphenols in diet has been linked to the changes in the gut microbiome in relation to diseases [26]. Gut microbiome composition has also been significantly dependent on the diet and metabolites [27, 28]

4.1The cardiac diseases and the heart –gut axis

Researches indicate that alterations in the gut microbiome and the metabolome alternations pose significant risks for the development of cardiovascular diseases via the influence of the altered metabolome on the host metabolism [29]. Recent evidence suggests that the alteration of the gut microbiota and its metabolites, like indole-3 propionic acid (IPA), significantly alters the function of the cardiomyocyte mitochondria, leading to cardiomyocyte mitochondrial dysfunction that has been extensively linked to cardiovascular diseases (CVD).

Different other compounds, like Trimethylamine N-oxide (TAMO), short-chain fatty acids, etc., have been found to impact the gut-heart axis, leading to heart failure due to the consumption of indigestible components in meals [30].

4.2Gut microbiome and the Gut -brain axis

Maintenance of health is dependent on the interplay between the gut microbiota and the brain, and disruption of the gut-brain axis leads to the distortion of the normal activity of interaction, producing diseases. The role of gut microbiota alteration as a causative agent in IBD has been implicated in recent studies, contributing to the development of several factors leading to irritable bowel syndrome. Alteration of the microbiota has been linked to various issues, like disruption of the gut-brain axis (GBA), changes to visceral hypersensitivity, alteration of the mobility of the gastrointestinal tract, impairment of the function of the epithelial barrier of the gut, and activation of the immune response, etc.[24,31].

Similar microbial interventions have been reported in other intestinal problems like Crohn's disease, ulcerative colitis, and chronic inflammatory disorders of the gut, where lysogenic prophage components have been incorporated and integrated into the bacterial genome of the gut [32]. Such signals are presumed to cause the excision of phage components from the bacterial genome, leading to an increase in phage activities during inflammation [9].Research indicate changes in the gut microbiome composition between healthy an schizophrenia patients , the latter having a lesser diversity (alpha diversity) and different unique bacterial taxa like Veillonellaceae, Lachnospiraceae and others are found to be related to the degree of schizophrenia as well as different conditions of anxiety, depressive conditions and trauma in patients [14,33].\

4.3Gut microbiome gut- bone axis

Bone health, regeneration, and degeneration of the bone are extremely important in the maintenance of bone structure homeostasis and disease prevention. Evidence indicates that the gut microbiome has a strong influence on the health of the bones and appears to be a potent regulator of bone homeostasis. Data also indicate that there is a significant relationship between the development of different diseases like osteoarthritis, rheumatoid arthritis [34], bone cancer, etc., by influencing factors like calcium absorption, production of short-chain fatty acids, and immune-endocrine control [35].There are also evidences of involvement of oral and gut microbiome in periodontal ailments[36].

4.4Gut microbiome and gut- immune axis

The optimal functionality of the immune system is based on the delicate balance between the crosstalk between the different arms of the immune system, namely the humoral and cell-mediated immune syste-

ms. The gut microbiome has been found to have a strategic and significant impact on the fine-tuning of the immune system of the body, leading to a change in consistent status. This balance is strictly regulated by the delicate interaction between regulator and responder molecules that play a fundamental role in impaired lymphocyte function under disease conditions. It has been indicated that the inhibition of the protest microbiome along with derived metabolites significantly alters the adaptive immune response component of the immune system [37].

5. Application of microbiome and its related metabolome in disease treatment

With the implications and discovery of the potential impact of alteration of the gut microbiome and metabolome on diseases, it is an obvious possibility that restoration of the microbiome-metabolome axis may possess the potential for a new domain of treatment for multiple disease conditions. Thus, the microbiome-metabolome axis has extensive potential for therapeutic applications in the restoration of the normal microbiome-metabolome constitution of the body as a treatment since the impact of the microbiome-metabolome axis is widespread, broad-spectrum, and integrated into multiple axes of the body like the gut immune axis, the gut brain, the gut cardiac axis, etc.

Workers have pointed to the therapeutic application of microbiomes in disease conditions [38]. Research indicates that the use of microbiota can alter the status of the body from a sub-health (condition progressing to an unhealthy status) to a healthy status by altering and readjusting the balance and interaction of the gut microbiota. The application of Bacillus licheniformis as a mature probiotic regulated the microbiota balance. B. licheniformis decreased factors like tumor necrosis factor-alpha, serum corticosterone, and cytokines that are programmed for inflammation to a considerable level. It was observed that changes in the microbiota altered the state of behavior linked to anxiety by remodeling the gut microbiome, altering it from a sub- health to a healthy status. The application of the bacillus also altered the state of behavior linked to anxiety by remodeling the gut microbiome, altering it from a sub- health to a healthy status [39] .Lifestyle alteration has also been linked to alterations of the gut microbiome plasticity and microbiome metabolome interactions [21].

Bacteria and yeast included in probiotics have been successfully used extensively to treat various types of disease conditions, and the use of probiotic bacteria is under continuous research as an adjuvant in the treatment of intestinal diseases. Probiotics have been utilized to enhance the prognosis and management of diseases. Microbiota has been used extensively against antibiotic-associated diarrhea, inflammatory bowel disease, Crohn’s disease, colorectal cancer, ulcerative colitis, and a host of other disease conditions [40].

5.1. Fecal microbiota transplantation (FMT) and vaginal seeding

It has been well documented that different interventions like C-section, breastfeeding, etc. are significant factors for microbial colonization of the infant gut, and the mechanism of development of the infant gut microbiome dominance is obscure. Infant gut microbiota is also affected by various parameters like intrapartum antibiotics, mode of birth (caesarian section), lactic acid bacteria, breastfeeding, and vaginal seeding, which involves the transfer of the vaginal flora to the mouth of the newborn after C-section. The most dominant populations of microbes normally undergoing material-to-fetal transportation are Bifidobacteria and Bacterioid strains possessing the capacity to utilize the oligosaccharide in milk. Infant gut microbiota is affected by maternal stress, maternal asthma, gestational diabetes, maternal diet etc. Treatments to reestablish the infant microbiome has been researched and applied in various ways including microbiota targeting treatments, probiotic lactic acid bacteria supplementations, vaginal seedi-

ng and maternal FMT or Maternal Fecal microbiota transplantation delivering healthy donor stool to the C section infant through various methods like colonoscopy, nasogastric tube etc.[41]
Gut microbiome restoration played a significant role in reversing the state of liver injury. Similar results have been obtained for alteration of gut microbiota by probiotics in treatment of bone related disorders [42, 35]. Thus, there are ample opportunities for the use of microbiome restoration for not only identifying the disease condition in sub-health conditions but also treatment and prevention.

6. Advanced methods of treatment of altered microbiome and metabolome influx in disease by use of nanomedicine

With the advent of nano-biotechnology as well as robotics and metabolome engineering, it has become possible to substantially develop treatments for gut microbiome-metabolome-related diseases. Recent advances in nanomedicine have emerged as one of the most promising technologies, with a specific focus on the application of nanomaterial for the modulation of the gut microbiota by enhancing the anti-cancer theory. Engineering the gut microbiome is paving the pathway for the most advanced treatment options [43]. Nanotechnology, including diverse application parameters, can operate both at the in vitro platform level and in diagnosis and treatment in a complementary fashion. Different metabolic pathways synthesize different nanomaterials, which, when studied and modified concerning considerations such as survival period, decreased cell diffusion rates, and insignificant reduction abilities, are being well explored.(Fig5) Different diagnostic and therapeutic mediators have already been developed using nanomaterials being deployed against inflammatory bowel disease, intestinal cancer, etc. A wide spectrum of nanomaterials have already been developed and successfully used, which includes metal-based nanoparticles, nanogels, nanofibres, and nanoclays possessing diversified functional domains like antibacterial activity, tissue engineering, removal of antibiotic-resistant bacteria, drug diversity, enzymatic catalysts, food delivery, ionic adsorption, etc.[44] Successful intervention in cancer immunotherapy has been fabricated through the development and use of nanoparticle-coated bacteria as a DNA vaccine.[45] (Fig 6).

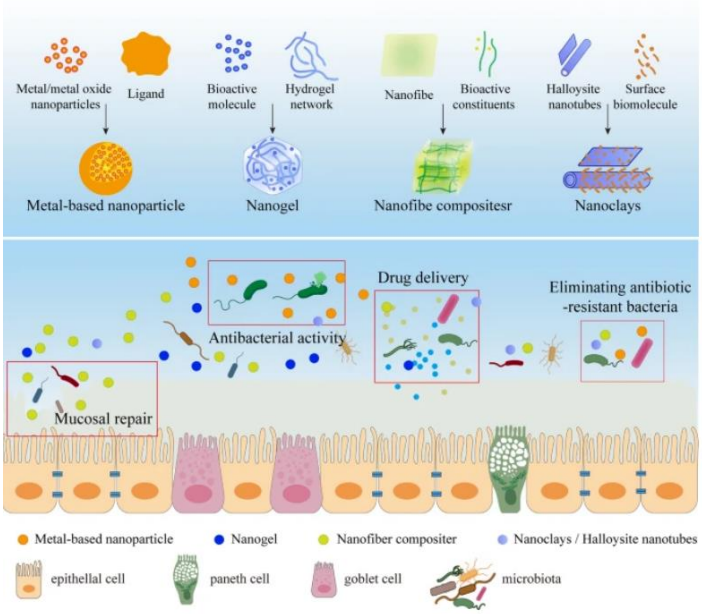

Figure: 5 Role of diverse nanomaterials and their impact on gut and its microbiome (Retrieved from Fei et al, 2022)

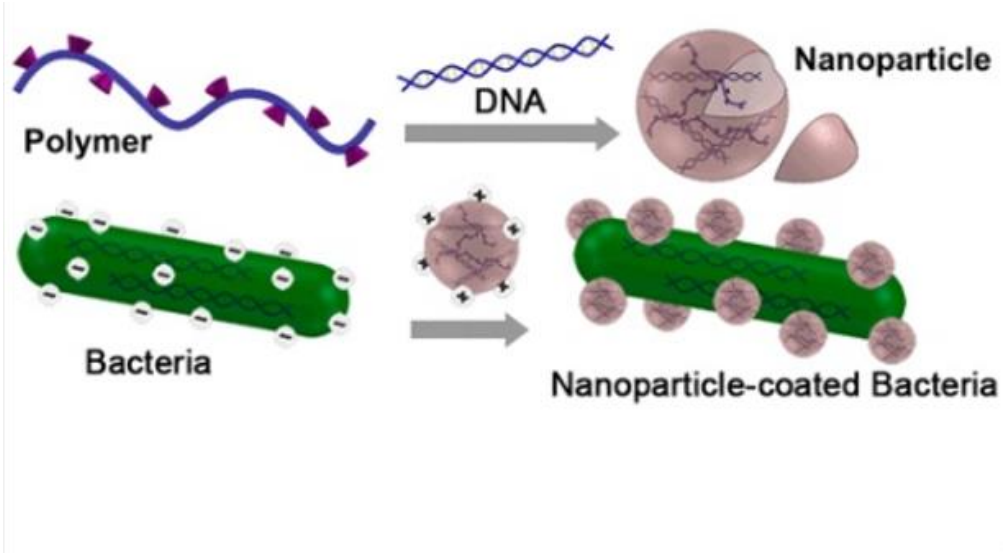

Figure: 6 Nanoparticle coated bacteria as DNA vaccine in cancer immunotherapy (Retrieved from Hu et al, 2015).

7. Discussion

The influence of gut microbiome and metabolome in human disease is undeniably established. A wealth of data suggests that changes in the gut microbiome and metabolome are responsible for disease conditions. A broad range of factors, including C-section deliveries, breast milk, diet, and lifestyle, have been associated with alterations in the gut microbiome and metabolome. These modifications have an impact on various physiological and biochemical aspects of the body, and may even influence social behavior. The majority of common diseases, like issues with the immune system, cardiovascular and cardiomyocyte mitochondrial diseases, and psychological and neurological conditions like schizophrenia and depressive disorders, are correlated with microbial changes or alterations of their metabolome in the system. Hence, with the extensive role of gut microbiota in diseases, new treatment technologies and methods are being invented and applied. The wide spectrum of treatment protocols, like the use of fecal microbiota, genetically engineered microbiota, nanotechnology-associated drug delivery systems involving microbes, and the use of nanobots and artificial intelligence, are focused on ushering in a new era of treatment and health.

8. Future prospects: Nano-robotics and AI

The pathway for future research involving the gut microbiome and disease nexus will potentially focus on the identification of prospective disease conditions by screening the gut microbiome and metabolome of the individual. This will lead to a much faster prognosis and preventive measures. The application of nanobots and artificial intelligence appears to be most suited for this purpose. Presently, the application of nanobots is widespread in different disease conditions as potential drug delivery vehicles [46,4748] and when integrated with artificial intelligence it may empower the feasibility to scan, accurately predict the disease possibility, and render treatment in terms of tissue engineering, programmable antibiotics, microbolome engineering, and microbiome -metabolome restoration [49,50,51] .With proper research and application, it may be possible to use programmed nanobots to enter into the human system as scanning, maintenance and repair unit (SMR) unit, to scan, maintain and or repair microbiome-metabolome malfunction for optimum heath on a long term basis.

REFERENCES

1. Savage, D. C. (1977). Microbial ecology of the gastrointestinal tract. Annual Review of Microbiology, 31, 107–133. https://doi.org/10.1146/annurev.mi.31.100177.000543
2. Relman, David A. (2002). New Technologies, Human-Microbe Interactions, and the Search for Previously Unrecognized Pathogens. The Journal of Infectious Diseases, 186(s2), S254–S258. https://doi.org/10.1086/344935
3. Feng, Q., Chen, W.-D., & Wang, Y.-D. (2018). Gut Microbiota: An Integral Moderator in Health and Disease. Frontiers in Microbiology, https://doi.org/10.3389/fmicb.2018.00151
4. Altves, S., Yildiz, H. K., & Vural, H. C. (2020). Interaction of the microbiota with the human body in health and diseases. Bioscience of Microbiota, Food and Health, 39(2), 23–32. https://doi.org/10.12938/bmfh.19-023
5. Ley, S. H., Pan, A., Li, Y., Manson, J. E., Willett, W. C., Sun, Q., & Hu, F. B. (2016). Changes in Overall Diet Quality and Subsequent Type 2 Diabetes Risk: Three U.S. Prospective Cohorts. Diabetes Care, 39(11), 2011–2018. https://doi.org/10.2337/dc16-0574
6. Tu, P., Chi, L., Bodnar, W., Zhang, Z., Gao, B., Bian, X., Stewart, J., Fry, R., & Lu, K. (2020). Gut Microbiome Toxicity: Connecting the Environment and Gut Microbiome-Associated Diseases. Toxics, 8(1). https://doi.org/10.3390/toxics8010019
7. Peterson, J., Garges, S., Giovanni, M., McInnes, P., Wang, L., Schloss, J. A., Bonazzi, V., McEwen, J. E., Wetterstrand, K. A., Deal, C., Baker, C. C., Di Francesco, V., Howcroft, T. K., Karp, R. W., Lunsford, R. D., Wellington, C. R., Belachew, T., Wright, M., Giblin, C., & David, H. (2009). The NIH Human Microbiome Project. Genome Research, 19(12), 2317–2323. https://doi.org/10.1101/gr.096651.109
8. Lu, D., Huang, Y., Kong, Y., Tao, T., & Zhu, X. (2020). Gut microecology: Why our microbes could be key to our health. Biomedicine & Pharmacotherapy, 131, 110784. https://doi.org/10.1016/j.biopha.2020.110784
9. Duerkop, B. A., Kleiner, M., Páez-Espino, D., Zhu, W., Bushnell, B., Hassell, B., Winter, S., Kyrpides, N. C., & Hooper, L. V. (2018). Murine colitis reveals a disease-associated bacteriophage community. Nature Microbiology, 3(9), 1023–1031. https://doi.org/10.1038/s41564-018-0210-y
10. Hoyles, L., Fernández-Real, J.-M., Federici, M., Serino, M., Abbott, J., Charpentier, J., Xifra, G., & Ricart, W. (2018). Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nature Medicine, 24(7), 1070–1080. https://doi.org/10.1038/s41591-018-0061-3
11. Perez-Pardo, P., Dodiya, H. B., Engen, P. A., Forsyth, C. B., Huschens, A. M., Maliha Shaikh, Voigt, R. M., Ankur Naqib, Green, S. J., Kordower, J. H., Shannon, K. M., Johan Garssen, Kraneveld, A. D., & Keshavarzian, A. (2019). Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut, 68(5), 829–843. https://doi.org/10.1136/gutjnl-2018-316844
12. Ruiz, F., Vigne, S., & Pot, C. (2019). Resolution of inflammation during multiple sclerosis. Seminars in Immunopathology, 41(6), 711–726. https://doi.org/10.1007/s00281-019-00765-0
13. Sankararaman, S., Noriega, K., Velayuthan, S., Sferra, T., & Martindale, R. (2022). Gut Microbiome and Its Impact on Obesity and Obesity-Related Disorders. Current Gastroenterology Reports, 25,. https://doi.org/10.1007/s11894-022-00859-0
14. Zheng, P., Zeng, B., Liu, M., Chen, J., Pan, J., Han, Y., Liu, Y., Cheng, K., Zhou, C., Wang, H., Zhou, X., Gui, S., Perry, S. W., Wong, M.-L., Licinio, J., Wei, H., & Xie, P. (2019). The gut

microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Science Advances, 5(2), eaau8317. https://doi.org/10.1126/sciadv.aau8317

15. Laterza, L., Rizzatti, G., Gaetani, E., Chiusolo, P., & Gasbarrini, A. (2016). The Gut Microbiota And Immune System Relationship In Human Graft-Versus-Host Disease. Mediterranean Journal of Hematology and Infectious Diseases, 8(1), 2016025. https://doi.org/10.4084/mjhid.2016.025
16. Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J.-M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., & Kurokawa, K. (2011). Enterotypes of the human gut microbiome. Nature, 473(7346), 174–180. https://doi.org/10.1038/nature09944
17. Khosravi, A., & Mazmanian, S. K. (2013). Disruption of the gut microbiome as a risk factor for microbial infections. Current Opinion in Microbiology, 16(2), 221–227. https://doi.org/10.1016/j.mib.2013.03.009
18. Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. Biochemical Journal, 474(11), 1823–1836. https://doi.org/10.1042/bcj20160510
19. Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G., Gasbarrini, A., & Mele, M. (2019). What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms, 7(1), 14. https://doi.org/10.3390/microorganisms7010014
20. Strasser, B., Wolters, M., Weyh, C., Krüger, K., & Ticinesi, A. (2021). The Effects of Lifestyle and Diet on Gut Microbiota Composition, Inflammation and Muscle Performance in Our Aging Society. Nutrients, 13(6), 2045. https://doi.org/10.3390/nu13062045
21. Keohane, D. M., Ghosh, T. S., Jeffery, I. B., Molloy, M. G., O'Toole, P. W., & Shanahan, F. (2020). Microbiome and health implications for ethnic minorities after enforced lifestyle changes. Nature Medicine, 26(7), 1089–1095. https://doi.org/10.1038/s41591-020-0963-8
22. Gacesa, R., Kurilshikov, A., Vich Vila, A., Sinha, T., Klaassen, M. a. Y., Bolte, L. A., Andreu-Sánchez, S., Chen, L., Collij, V., Hu, S., Dekens, J. a. M., Lenters, V. C., Björk, J. R., Swarte, J. C., Swertz, M. A., Jansen, B. H., Gelderloos-Arends, J., Jankipersadsing, S., Hofker, M., & Vermeulen, R. C. H. (2022). Environmental factors shaping the gut microbiome in a Dutch population. Nature, 604, 1–8. https://doi.org/10.1038/s41586-022-04567-7
23. Ma, Z., Li, L., & Gotelli, N. J. (2019). Diversity-disease relationships and shared species analyses for human microbiome-associated diseases. The ISME Journal, 13(8), 1911–1919. https://doi.org/10.1038/s41396-019-0395-y
24. Carroll, I. M., Ringel-Kulka, T., Keku, T. O., Chang, Y.-H., Packey, C. D., Sartor, R. B., & Ringel, Y. (2011).Molecular analysis of the luminal- and mucosal-associated intestinal microbiota in diarrhea-predominant irritable bowel syndrome. American Journal of Physiology-Gastrointestinal and Liver Physiology, 301(5), G799–G807. https://doi.org/10.1152/ajpgi.00154.2011
25. Chaudhari, S. N., McCurry, M. D., & Devlin, A. S. (2021).Chains of evidence from correlations to causal molecules in microbiome-linked diseases. Nature Chemical Biology, 17(10), 1046–1056. https://doi.org/10.1038/s41589-021-00861-z
26. Molinari, R., Merendino, N., & Costantini, L. (2021). Polyphenols as modulators of pre-established gut microbiota dysbiosis: State-of-the-art. BioFactors. https://doi.org/10.1002/biof.1772

27. Requena, T., Martínez-Cuesta, M. C., & Peláez, C. (2018). Diet and microbiota linked in health and disease. Food & Function, 9(2), 688–704. https://doi.org/10.1039/c7fo01820g
28. Redondo-Useros, N., Nova, E., González-Zancada, N., Díaz, L. E., Gómez-Martínez, S., & Marcos, A. (2020). Microbiota and Lifestyle: A Special Focus on Diet. Nutrients, 12(6), 1776. https://doi.org/10.3390/nu12061776
29. Gabriel, C. L., & Ferguson, J. F. (2023). Gut Microbiota and Microbial Metabolism in Early Risk of Cardiometabolic Disease. Circulation Research, 132(12), 1674–1691. https://doi.org/10.1161/circresaha.123.322055
30. Hemmati, M., Kashanipoor, S., Mazaheri, P., Alibabaei, F., Babaeizad, A., Asli, S., Mohammadi, S., Gorgin, A. H., Ghods, K., Yousefi, B., & Eslami, M. (2023). Importance of gut microbiota metabolites in the development of cardiovascular diseases (CVD). Life Sciences, 329, 121947. https://doi.org/10.1016/j.lfs.2023.121947
31. Bhattarai, Y., Muniz Pedrogo, D. A., & Kashyap, P. C. (2017). Irritable bowel syndrome: a gut microbiota-related disorder? American Journal of Physiology-Gastrointestinal and Liver Physiology, 312(1), G52–G62. https://doi.org/10.1152/ajpgi.00338.2016
32. Feiner, R., Argov, T., Rabinovich, L., Sigal, N., Borovok, I., & Herskovits, A. A. (2015). A new perspective on lysogeny: prophages as active regulatory switches of bacteria. Nature Reviews Microbiology, 13(10), 641–650. https://doi.org/10.1038/nrmicro3527
33. Malan-Müller, S., Valles-Colomer, M., Palomo, T., & Leza, J. C. (2023). The gut-microbiota-brain axis in a Spanish population in the aftermath of the COVID-19 pandemic: microbiota composition linked to anxiety, trauma, and depression profiles. Gut Microbes, 15(1). https://doi.org/10.1080/19490976.2022.2162306
34. Park, H.-K., & Lee, S. J. (2022). Treatment of gouty arthritis is associated with restoring the gut microbiota and promoting the production of short-chain fatty acids. Arthritis Research & Therapy, 24(1). https://doi.org/10.1186/s13075-022-02742-9
35. Zemanova, N., Omelka, R., Mondockova, V., Kovacova, V., & Martiniakova, M. (2022). Roles of Gut Microbiome in Bone Homeostasis and Its Relationship with Bone-Related Diseases. Biology, 11(10), 1402. https://doi.org/10.3390/biology11101402
36. Martínez, M., Postolache, T. T., García-Bueno, B., Leza, J. C., Figuero, E., Lowry, C. A., & Malan-Müller, S. (2022). The Role of the Oral Microbiota Related to Periodontal Diseases in Anxiety, Mood and Trauma- and Stress-Related Disorders. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.814177
37. Łukasz Wojciech, Chin Wen Png, Koh, E. Y., Yan, D., Deng, L., Wang, Z., Wu, L., Hamidinia, M., Desmond, Zhang, W., Pettersson, S., Chun, E., Zhang, Y., Kevin, & Gascoigne, N. R. J. (2023). A tryptophan metabolite made by a gut microbiome eukaryote induces pro-inflammatory T cells. The EMBO Journal, 42(18). https://doi.org/10.15252/embj.2022112963
38. Bai, X., Huang, Z., Duraj-Thatte, A. M., Ebert, M. P., Zhang, F., Burgermeister, E., Liu, X., Scott, B. M., Li, G., & Zuo, T. (2023). Engineering the gut microbiome. Nature Reviews Bioengineering, 1(9), 665–679. https://doi.org/10.1038/s44222-023-00072-2
39. Feng, S., Meng, C., Hao, Z., & Liu, H. (2022). Bacillus licheniformis reshapes the Gut Microbiota to Alleviate the Subhealth. Nutrients, 14(8), 1642. https://doi.org/10.3390/nu14081642
40. Kim, S.-K., Guevarra, R. B., Kim, Y.-T., Kwon, J., Kim, H., Cho, J. H., Kim, H. B., & Lee, J.-H. (2019). Role of Probiotics in Human Gut Microbiome-Associated Diseases. Journal of Microbiology

and Biotechnology, 29(9), 1335–1340. https://doi.org/10.4014/jmb.1906.06064
41. Korpela, K., & de Vos, W. M. (2022). Infant gut microbiota restoration: state of the art. Gut Microbes, 14(1). https://doi.org/10.1080/19490976.2022.2118811
42. Li, Y., Hu, H., Yang, H., Lin, A., Xia, H., Cheng, X., Kong, M., & Liu, H. (2022). Vine Tea (Ampelopsis grossedentata) Extract Attenuates CCl 4 -Induced Liver Injury by Restoring Gut Microbiota Dysbiosis in Mice. Molecular Nutrition & Food Research, 66(9), 2100892. https://doi.org/10.1002/mnfr.202100892
43. Abduladheem Turki Jalil, Thabit, S. N., Hanan, Z. K., Mohammed Qasim Alasheqi, Kareem, A., Zabibah, R. S., & Fadhil, A. A. (2023). Modulating gut microbiota using nanotechnology to increase anticancer efficacy of the treatments. Macromolecular Research, 31. https://doi.org/10.1007/s13233-023-00168-z
44. Fei, Y., Ma, Y., Zhang, H., Li, H., Feng, G., & Fang, J. (2022). Nanotechnology for research and treatment of the intestine. Journal of Nanobiotechnology, 20(1). https://doi.org/10.1186/s12951-022-01517-3
45. Hu, Q., Wu, M., Fang, C., Cheng, C., Zhao, M., Fang, W., Chu, P. K., Ping, Y., & Tang, G. (2015). Engineering Nanoparticle-Coated Bacteria as Oral DNA Vaccines for Cancer Immunotherapy. Nano Letters, 15(4), 2732–2739. https://doi.org/10.1021/acs.nanolett.5b00570
46. Hortelão, A. C., Patiño, T., Perez-Jiménez, A., Blanco, À., & Sánchez, S. (2017). Enzyme-Powered Nanobots Enhance Anticancer Drug Delivery. Advanced Functional Materials, 28(25), 1705086. https://doi.org/10.1002/adfm.201705086
47. Li, P., Roos, S., Luo, H., Ji, B., & Nielsen, J. (2023). Metabolic engineering of human gut microbiome: Recent developments and future perspectives. Metabolic Engineering, 79, 1–13. https://doi.org/10.1016/j.ymben.2023.06.006
48. Suhail, M., Khan, A., Rahim, M. A., Naeem, A., Fahad, M., Badshah, S. F., Jabar, A., & Janakiraman, A. K. (2021). Micro and nanorobot-based drug delivery: an overview. Journal of Drug Targeting, 1–10. https://doi.org/10.1080/1061186x.2021.1999962
49. Jitendra, G., Reena, G., & Abhishek, T. (2021). Nanobot: Artificial Intelligence, Drug Delivery and Diagnostic Approach. Journal of Pharmaceutical Research International, 33(59B), 189–206. https://doi.org/10.9734/jpri/2021/v33i59b34369
50. Liu, Y., Yu, W., Wang, Q., Cao, Z., & Li, J. (2023). Artificially engineered bacteria to treat gastrointestinal disease and cancer. Drug Discovery Today, 28(8), and 103667. https://doi.org/10.1016/j.drudis.2023.103667
51. Zhou, J., Li, M., Chen, Q., Li, X., Chen, L., Dong, Z., Zhu, W., Yang, Y., Liu, Z., & Chen, Q. (2022). Programmable probiotics modulate inflammation and gut microbiota for inflammatory bowel disease treatment after effective oral delivery. Nature Communications, 13(1), 3432. https://doi.org/10.1038/s41467-022-31171-0