Review

Dysbiosis promotes Gastric Diseases and Impede Therapies by hijacking Gut Immune Homeostasis

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Abstract: Perturbation in the microbial population / colony index has harmful consequences on human health. Both biological and social factors influence the composition of the gut microbiota and promote gastric diseases. Changes in the gut microbiota manifest in disease progression owing to epigenetic modification in host which influences differentiation and function of immune cells adversely. Uncontrolled use of antibiotics; chemotherapeutic drugs and change in the diet pattern usually contribute to the changes in the colony index of sensitive strains known to release microbial content in the tissue micromillieu. Ligands released from dying microbes induce TLR mimicry on interaction with TLR abnormally which skew hypoxia and sterile inflammation contributing to severity of disease like IBD autoimmunity and cancer. Various modalities / interventions practiced across the globe and future strategies for microbiota based therapeutic approaches with special emphasis on tumor and inflammatory diseases are reviewed here. Therefore the major aim and scope of this manuscript is to both discuss various modalities / interventions across the globe and to design future microbiota based therapeutic approaches for mitigating the burden with special emphasis on tumor and Inflammatory diseases.

Keywords: Gut microbiota; macrophages; TLR mimicry; Immunoepigenetics; metabolism; sterile inflammation

1. Introduction

Despite of being the most sophisticated and successful animal of ecosystem, *Homo sapiens* is obliged to various other ecological partners on which it depends for normal life. Among various partners, human and bacteria have evolved together during the course of evolution and symbiosis in between human with various bacteria which live in human gut are vital for a healthy life style of human in many aspects. Human health greatly depends upon its symbiotic association with commensal microorganisms which consists of different species of bacteria; fungi and virus are present in our gut. These microbiota contribute to the metabolic and nutrition which are important for human health and a balance in the composition of these commensal organisms[1]for the homeostasis. Exact composition of human microbiome which is important for the homeostasis still remains largely elusive so far. The best studied Gastro intestinal tract (GI tract) microbiota, which comprises of viruses, bacteria, fungi and protozoa, estimated to be about 100 trillion in numbers. Human body harbors large number of microbiota on skin, gut and / or genital tissues which are beneficial and involved in variety of vital functions. They protect the body from the penetration of pathogenic microbes. These beneficial microbial colonies compete with each other for space and resources. Intestinal or Gut microbes also assist with endogenous turnover of vitamin B complex and other nutrients like minerals and amino acid metabolism and turnover[2].Recent studies have

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provided compelling evidences that good microbiota also interact with immune system and keep their activity at bay contributing to the homeostatic mechanism however bad gut microbiota interact with immune system differentially and promote non immunogenic / sterile inflammatory reaction which break homeostasis and promote various gastric diseases. Frequent or uncontrolled use of antibiotics, chemotherapeutic drugs and change in dietary pattern has shown to disrupt the microbiome and leads to dysbiosis or dysbacteriosis [3]which is characterized with the imbalance of life supportive microbes. Among various organs, gastrointestinal tract are the most sensitive organs which gets affected by dysbiosis.

Recent meeting of WHO has suggested that degree of dysbiosis can control the severity of various disease ranging from metabolic, obesity, malnutrition, diabetes, chronic inflammatory diseases such as *inflammatory bowel disease* (IBD), encompassing *ulcerative colitis* (UC) and Crohn's disease (CD)[4]. Although various advance technology platforms like High throughputs sequencing technologies (HTS) as well as nongenomic techniques have enabled us to understand the influence of the gut Microbiome on human health and disease, however our knowledge in regard of Dysbiosis driven pathogenesis of gastric disease still remained elusive so far. Therefore in view of this and clinical significance, in this article we have discussed various molecular and immunological aspects of dysbiosis with special emphasis on gastrointestinal (GI) disease. We have also uncovered the state-of-the-art tools that can be exploited to study the gut Microbiome and look to future therapeutic options, such as the manipulation of the gut microbiota by probiotics and various immunoregulatory mechanisms[5] for the management of dysbiosis.

2. Eco-physiological balance of Gut Microbiota with gut associated lymphoid tissues

Normal gut microbiota comprises mostly of several genera of Gram positive Firmicutes and many different Gram negative bacteroidetes like Bacteroides, Prevotella, Parabacteroides and Alistipes. In addition several other phyla including the Proteobacteria, Actinobacteria, Fusobacteria, Verruco microbia, methanogenic archaea, Eukarya *(protists and fungi),* and other more transient colonizers are found to be part of human GI microbiome. Under normal physiological conditions, symbiotic association of gut microbiota with Gut Associated Lymphoid Tissue (GALT) contributes to immune homeostasis. Both macrophages and M cells of payer's patches play an important role in sensing antigens and transport to mucosal lymphoid nodes for immune responses[6]. Interestingly, gut microbiota colony index contributes to the overall health of the host by promoting the maturation and activation of myeloid cells of GALT involved in patrolling to restrict invaders in gut thus prevent disease progression. Many studies have documented that changes in the composition of microbial communities disrupts gut homeostasis which promotes leaky gut, inflammatory bowel disease and allergic inflammation predisposing affected individuals sensitive to develop cancer. Many pre clinical studies suggest that intake of broad spectrum antibiotic efficiently depletes / changes the composition of faecal microbiota and impairs GALT architecture and functions[7]. Among various social factors like age, ethnicity, dietary habit and regional environment etc. diet is one of the major factors that affect the composition of the microflora of the intestines[8]. Diet is now established to alter the gut microbiota, M cell hyperplasia and gut infiltration of activated macrophages to induce Th1 immune response in the gut which ultimately leads to malfunction of gut[9]. Chronic and recurrent inflammation in gut triggers oxidative stress which depletes sensitive microbes leaving resistant strains unaffected. This dysbiosis continuously agitate GALT adversely to promote sterile inflammatory response and sensitize the host for chronic gastric disease. Various evidence[10],[11],[12], [13]suggests that changes in intestinal microbiota drive changes in the intercellular tight junctions like desmoglins facilitate the leaky Gut and enhance the interaction of various danger signals (like) released from the dying bacterial cells with immune cells thus promote sterile inflammation. Increasing evidences suggest that dysbiosis is associated with inflammatory bowel disease and wide range of malignancies.

3. Change in the Gut Microbiome triggers sterile inflammation and promotes gastric inflammatory disease

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The gut microbiota and mucosal immunity constantly interact with each other to maintain intestinal homeostasis. However, if this balance is broken, dysfunction of the intestinal immune system occurs that triggers a variety of diseases including IBD. Several studies indicated that intestinal dysbiosis causes an abnormal immune response leading to IBD inflammation and destruction of the gastrointestinal tract. Dysbiosis driven chronic inflammatory and autoimmune diseases is associated with altered expression of pattern-recognition receptors (e.g. TLRs) and downstream signaling. Inside the gut, innate immune cells and non-immune cells, such as intestinal epithelial and stromal cells sense the pathogen-associated molecular patterns on microbial components mediated by their TLRs. Innate immune cells such as dendritic cells and macrophages sense PAMPs through TLRs initiating rapid and effective inflammatory responses against microbial invasion.

Next generation sequencing technology has enabled us to decipher information about the changes in the microbiome composition of intestinal microflora genome associated with development of the disease. Dysbiosis play an important role in development of inflammatory bowel disease (IBD) development, mainly due to decline in *Firmicutes* and *Bacteroidetes*, and an increase in detrimental bacteria, such as *Proteobacteria* and *Actinobacteria*[14]. Due to altered microbial index in IBD, the ability of microbiota to adapt to environmental changes and to defend against natural disturbances has been impaired. Therefore, manipulation of intestinal microflora has been a powerful preventive and therapeutic intervention for the management of this disease. These responses may be used as markers for immunomodulation in therapeutic intervention in IBD. A deficiency in IL-10 has been observed with cases of early-onset IBD[15].

Decrease in dietary fibers containing short chain fatty acids (SCFAs) which are produced by the fermentation of gut bacteria in the Fecal samples from IBD patients[16]provide a correlation of dysbiosis with the onset and progression IBD. The SCFAs are known to regulate inflammatory responses in different ways, such as binding of short chain fatty acid receptors (GPR43) regulation of colonic Treg cell homeostasis by restoring the colonic size and function of the Treg cell pool in germ-free mice. Gut microbiota also secrete several immunogenic substances such as complex lipopolysaccharides present on the cell surface of Gram-negative bacteria involved in gut immune homeostasis maintenance. *Bacteroides fragilis* represent one class of bacteria found in the human intestine contributes to immune homeostasis by promoting Foxp3+T cells activity in GALT[17].

Studies in *Bacteroides* have revealed multiple biochemical mechanisms involved in change of gut microbiota index to overcome several challenges posed by the dysbiosis. This may range from variable pH of GI tract, differential oxygen gradients and host immune surveillance, *Bacteroides* depend on other microbes especially Ruminococcus obeum in the gut to fulfill their need for corrinoid (Vitamin B12 class like co-factors) for their survival suggesting that corrinoid producers seem to determine the diversity of gut microbial community, particularly Bacteroides. Germ free mice exhibit Immune defects like imbalanced Th1 vs Th2 response and reduced serum levels of IgA in the gut are ameliorated by colonization with Bacteroides[18]suggests that host-microbiome interaction has an important health implications.

Altered composition of Bacteroidetes and Firmicutes has been reported in both animal models and in human subjects under disease conditions. Abundance of Bacteroides, have been found in Estonian and Finnish children suffering from type 1 diabetes (T1D) compared with Russian children who have lower T1D prevalence[19] however were shown to have abundance of *Bifidobacterium*. This study also demonstrated that Lipopolysaccharide (LPS) from *Bacteroidesdorei*, the most common Bacteroides sp in Finnish cohorts, promoted immune tolerance and fails to protect Non obese Diabetic (NOD) mice from developing T1D as compared with LPS of *E.coli* origin. Metabolism of gut microbiota can also have adverse consequences, as shown by the facilitation of growth of entero hemorrhagic E. coli (EHEC), by *Bacteriodese*e specially *B. thetaiotamicron* and *B. vulgatus*, which cleave fucose and sialic acid moieties and other sugars from mucosal glycoproteins that are then consumed by EHEC, leading to enhanced expression of its virulence genes[20].

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4. Change in the Gut Microbiome triggers TLR mimicry and promote cancer related inflammation

Since gut microbiota lives in close proximity with colonic mucosa, there dysbiosis not only influence inflammatory response but also digestion and other vital functions of the gut. Dysbiosis driven breakage of tolerance mechanism often leads to chronic inflammation and sensitize gut for chronic disease other then IBD like cancer which depend upon the desmoplastic reactions which are mimicked by various microbial products. During dysbiosis, commensal are remodelled by / toward pathogenic bacteria by Th17 immune response which are heterogeneous in nature and believed to promote cancer related inflammation as seen in colorectal cancer (CRC) pathogenesis. Pathogenic bacteria like *Enterotoxigenic B. fragilis* promotes inflammation and produce genotoxins leading to cell proliferation and mutations causing adenoma which enhanced the colonization of bacterial species like *Fusobacterium* species that promote tumor progression[21]. All these process are facilitated by the increased permeability of mucosal surfaces which allows bi directional movement of the gut microbiota and their interaction with immune cells like CD169+ /TCR-1+ lumen macrophages, Type 2 neutrophiles and regulatory T cells. This special interaction of these gut microbiota with refractory immune cells promote desmoplastic reactions which further enhances sterile inflammation and sensitize the host for cancer progression. Most of these events are reported to promote epigenetic changes in neighboring cells.

Activation of (pattern recognition receptors) PRRs like TLRs (especially TLR2 and TLR4) and NLRs both by specific and non specific mechanisms leads to TLR mimicry which confer chemo / radio resistance in tumor cells, are influenced by the presence of pathogen derived genotoxic factors like cyclomodulins which favors cellular proliferations and differentiation. During dysbiosis, activation of M1 macrophages contributes to the production of genotoxins in the form of ROS / RNI having toxic properties[21]. Fusobacterium species promote the upregulation of non canonical NF-kB driven inflammatory genes, has also been found to be enriched in colonic tumors. Much of these mechanisms are similar to the pathogenesis of *H.pylori* driven gastric cancer including methylation oflysyl oxidase tumor suppressor gene which promotes tumor generation. Dysbiosis not only induces bacteria induced cancer but also support virus induced cancer like cervical cancer. The expression of cancer causing E6 and E7 protein of HPV is affected by estrogen and it has been shown that gut microbiota greatly modulates the blood estrogen level thus contributing to tumor development[22],[23]. Accumulating data suggest that dysbiosis induced carcinogenesis is multifactorial in nature. Gut microbiota can pervasively dictate cancer progression by inducing desmoplastic reaction which includes sterile inflammation, epigenetic modification of DNA and subsequent genomic instability of host cells[24].

We [25], and others [26] have previously demonstrated that many pathogenic microbes which has high correction with cancer, have the capacity of reprogramming macrophages which are decisive at infection and cancer interface. Apart from this, many pathogenic bacteria / virus like Helicobacter pylori, Fusobacterium nucleatum and Chlamydia sp. in the microbiota potentially alter cell cycle progression and inhibit apoptosis[27]thus conferring cancer like phenotype in persistently infected tissue micromilieu. Moreover, cross reactivity of gut microbiome or its metabolites with PRRs /TLRs are anticipated to promote TLR mimicry[28] and believed to influence sterile inflammatory response for promoting cancer progression. Infection with H. pylori is associated with early onset of disease however, associates with a favorable prognosis. Conversely *F. nucleatum* can alter chemotherapeutic response in colorectal cancer. Recent studies have illustrated several bacteria species such as members of *Proteobacteria, Firmicutes*, *Actinobacteria* and *Fusobacteria* phyla have been detected in gastric cancer biopsies[29]which may serve as prognostic factor thus reinforcing the association of dysbiosis with cancer.

Evidence illustrates that many such bacteria like *H. pylori* modulates the host genome, altering different signaling pathways such as TLRs. Toll like receptors (TLRs) categorized as trans membrane proteins recognize pathogen-associated molecular patterns (PAMPs) are critical for of innate and adaptive immunity . Lipids, nucleic acids, and proteins from dying bacterial, viral, or fungal cells are potent ligands or PAMPS and interact preferentially with TLR-2,4, 5 and 9[28]to trigger TLR mimicry

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and activate distinct signaling pathways. H.pylori upregulates TLR4 to facilitate its adherence to gastric epithelial cells and activates NF-κB via TLR5 interaction along with AP-1 and MAP kinases resulting in expression and secretion of pro-inflammatory cytokines. Interestingly hyper activation of MAPK signalling has been associated with polarization of effector macrophage toward cancer promoting phenotype. Besides altering regulatory pathways, numerous studies proposed that host genetic makeup can influence the interaction of various microbiota with host cells. For instance, genetic variants rs1640827 and rs17163737 of TLR5 lead to enhanced interactions with H.pylori therefore increasing gastric cancer susceptibility[30]. A similar mechanism during dysbiosis is anticipated to lead to the similar response in various diseases.

Many bacterial species like *S. bovis, Bacteroidesfragilis, Escherichia coli, Enterococcus Shigella, Klebsiella, Streptococcus, Peptostrepto coccus* etc which are present in human gut microbiota, have been associated with progression of colorectal cancer (CRC). About 25–80% of patients with *S. bovis* bacteremia exhibit CRC[31]like symptom and their stool samples had shown a higher population of bacteria belonging to the *Bacteroides-Prevotella* group. Intra gastric circulation of Th-17 cells like CD169+/TCR-1+ myeloid cell, CD4/fOXp3 Treg and macrophages and immature DC's mount Th17 response including proinflammatory cytokines and pro angiogenic factors during dysbiosis which potentially promote neoplastic transformation of infected or inflamed gut during development of cancer.

Thus, it is intriguing to understand the molecular / immunological mechanism and the causal relationship between immune system with microflora in development of CRC. Studies using cyclophosphamide suggest that selective enrichment of gut with Gram+ bacteria can enhance Th1 immune responses and offer therapeutic benefit suggesting that the gut microbiota certainly help anticancer immune response[32].

5. Immune pharmaceutics as next generation modalities for breaking dysbiosis

Diet and geographical location plays a major role in determining the microbial diversity in the gut. Uncontrolled use of antibiotics often (both prescribed and indiscriminate usage) kills a broad variety of sensitive gut microbes and leads to dysbiosis which warrant the inclusion of Pro and / or Prebiotics to re-populate the gut and modulate the gut microbiome[33]. More than 1200 clinical trials investigating the effect of Probiotics either alone or in combination for various diseases are listed in the clinical trials database, with several studies completed and in the data analysis stage[34],[35]. Probiotics are live microorganisms generally belonging to the genera most commonly found in fermented foods. Species like *Bifidobacterium* and *Lactobacillus*.Probiotics modulate gut micromillieu mainly by modulating intestinal epithelial signaling pathways, influencing the titre of sIgA and other Th2 effector cytokines and by enhancing the intestinal epithelial barrier function by their virtue of increased mucin secretion[36]. It is interesting to note that every probiotics follow a particular mechanism for promoting balance or reconstituting health. Certain probiotics like Lactobacilli and Bifidobacterium have shown to compete with cariogenic species like Streptococcus mutans. In a clinical trial, twice daily orally or once weekly intra-vaginally administration of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri, has shown to reduce recurrences of UTI and restored a normal lactobacilli dominated vaginal flora over anaerobes in patients[37]. This is due to their potential to produce more lactose which is an important nutrient that gets metabolized to glucose and galactose in most neonates. However intolerance tolactose and its metabolism lead to the alterations in colonic microbiota. In such cases probiotic supplementation could alleviate lactose intolerance. Such intervention is quite effective in preventing diseases like Eczema, diarrhea, upper RTI, necrotizing enterocholitis, pulmonary exacerbation in children. Recently a randomized, double blind, placebo controlled trial of *Lactobacillus acidophilus* and Inulin has shown the efficacy in reducing free and LDL bound cholesterol by 7.84 and 9.27% respectively in a cohort of obese patients[38]. It is becoming evident that gut microbiome can actually have a role in obesity and Irritable bowel syndrome (IBS) as well. A study reported, if mice are reared in germ free environment and have no microorganisms in their gut, such mice are protected from obesity and metabolic disorders like insulin resistance, glucose intolerance, even when fed with western style diet loaded with high fat or

high calorie. In the similar lines another recently study has established the link of specific gut microbiota on the therapeutic efficacy of metformin in the cohort of obese patients over lean cohort[39]. This is which is anticipated to be due to immunometabolic programming of M1 or Th1 macrophages[40]of obese patients towards M2 and / or scavenging macrophages by metformin which is believed to change the specific gut microbiota in obese people contributing to the outcome

This is very interesting aspect of the dysbiosis related disease progression and shed new light in microbiome modulation of human health outcomes. These studies reinforce the involvement of the gut immune axis in dictating good or bad gut microbiota therefore warrant further investigations for establishing biological correlation of concept which has been discussed in this study.

6. Future perspective

Although numerous animal and human studies so far have acclaimed the safety and health benefits of probiotics, however this area of research in still in its infancy and warrant more rigorous studies for claiming its impact on expected outcome on health. Utilization of microbial based strategies is expected to afford help in the management of large number of haemolytic / metabolic diseases. Industrial application of Microcins, Colicins, plantaricin, vibriocin etc. which are bateriocins toxins and produced by E. coli, *Lactobacillus sp.* have been explored against various bad gut microbiota which are associated with many diseases.Fecal material transplantation (FMT) represents one such intervention which is explored for the management of *various* infections and cancer. Transplantation of gut microbiota of "normal" mice, into such germ free mice led to significant weight gain even in the face of normal diet, suggesting that microbiome is contributing to this weight gain. This approach has decisive influence on cancer directed immune therapies thus certainly represent novel biological entity for affording better treatment option. Finally it would be essential to identify the set of gut microbiota which are responsible which promote gut Immune homeostasis mainly deciphering their immunomodulatory impact on gut on the component of innate and adaptive immunity for homeostasis.

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References

1. Pathogenesis., T. human microbiome: from symbiosis to, NIH Public Access, **2014** 145–163.
2. Leblanc, J.G., Milani, C., Giori, G.S. De, Sesma, F., Sinderen, D. Van, Ventura, M., Bacteria as vitamin suppliers to their host : a gut microbiota perspective, *Curr. Opin. Biotechnol.* 24 **2013** 160–168.
3. Gareau, M.G., Sherman, P.M., Walker, W.A., probiotics and the gut microbiota in intestinal health and disease, *Nat. Publ. Gr.* 7 **2010** 503–514.
4. Kamada, N., Seo, S.U., Chen, G.Y., Núñez, G., Role of the gut microbiota in immunity and inflammatory disease, 13 **2013**.
5. Fraser, C.M., Ringel, Y., Sanders, M.E., Sartor, R.B., Sherman, P.M., Versalovic, J., Young, V., Finlay, B.B., Perspective Defining a Healthy Human Gut Microbiome : Current Concepts , Future Directions , and Clinical Applications, **2012** 611–622.
6. Silva, C. Da, Wagner, C., Bonnardel, J., Gorvel, J., Lelouard, H., The Peyer ' s Patch Mononuclear Phagocyte System at Steady State and during Infection, 8 **2017**.
7. Chemouny, J.M., Gleeson, P.J., Abbad, L., Lauriero, G., Bredel, M., Bex-coudrat, J., Boedec, E., Roux, K. Le, Daugas, E., Vrtovsnik, F., Gesualdo, L., Leclerc, M., Berthelot, L., Mkaddem, S. Ben, Lepage, P., Monteiro, R.C., Modulation of the microbiota by oral antibiotics treats immunoglobulin A nephropathy in humanized mice, **2018** 1–10.
8. Conlon, M.A., Bird, A.R., The Impact of Diet and Lifestyle on Gut Microbiota and Human Health, **2015** 17–44.
9. Arrazuria, R., Pérez, V., Molina, E., Juste, R.A., Khafipour, E., Diet induced changes in the microbiota and cell composition of rabbit gut associated lymphoid tissue (GALT), **2018** 1–11.

10. Thanabalasuriar, A., Koutsouris, A., Hecht, G., Gruenheid, S., independent of its putative PDZ binding domain, 1 **2010** 114–118.
11. Capaldo, C.T., Powell, D.N., Kalman, D., Layered defense : how mucus and tight junctions seal the intestinal barrier, **2017** 927–934.
12. Mohan, M., Chow, C.T., Ryan, C.N., Chan, L.S., Dufour, J., Aye, P.P., Blanchard, J., Moehs, C.P., Sestak, K., Dietary Gluten-Induced Gut Dysbiosis Is Accompanied by Selective Upregulation of microRNAs with Intestinal Tight Junction and Bacteria-Binding Motifs in Rhesus Macaque Model of Celiac Disease, *Nutrients***2016**,*8*, 11**.**
13. Hamilton, X.M.K., Boudry, G., Lemay, D.G., Raybould, H.E., Changes in intestinal barrier function and gut microbiota in high-fat diet-fed rats are dynamic and region dependent, **2018** 840–851.
14. Inohara, N., Nun, G., Mechanisms of inflammation-driven bacterial dysbiosis in the gut, 10 **2017**.
15. Salzer, E., Kansu, A., Sic, H., Dogu, F.E., Prengemann, N.K., Santos-valente, E., Pickl, W.F., Demir, A.M., Ensari, A., Colinge, J., Bilic, I., Ban, S.A., Rizzi, M., Eibel, H., Boztug, K., Early-onset inflammatory bowel disease and common variable immunodeficiency – like disease caused by IL-21 deficiency, *J Allergy Clin Immunol*. **2014**, *6*,133 .
16. Desai, M.S., Seekatz, A.M., Koropatkin, N.M., Stappenbeck, T.S., Martens, E.C., Article A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Article A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility, **2016** 1339–1353.
17. Telesford, K.M., Yan, W., Ochoa-reparaz, J., Pant, A., Kircher, C., Christy, M.A., Begum-haque, S., Kasper, D.L., Kasper, L.H., Telesford, K.M., Yan, W., Ochoa-reparaz, J., Kircher, C., Christy, M.A., Begum-haque, S., Kasper, D.L., Telesford, K.M., Yan, W., Ochoa-reparaz, J., Pant, A., Kircher, C., Christy, M.A., A commensal symbiotic factor derived from Bacteroides fragilis promotes human CD39 C Foxp3 C T cells and T reg function, 0976 **2015**.
18. Kozakova, H., Schwarzer, M., Tuckova, L., Srutkova, D., Czarnowska, E., Rosiak, I., Hudcovic, T., Schabussova, I., Hermanova, P., Zakostelska, Z., Aleksandrzak-piekarczyk, T., Koryszewska-baginska, A., Tlaskalova-hogenova, H., Colonization of germ-free mice with a mixture of three lactobacillus strains enhances the integrity of gut mucosa and ameliorates allergic sensitization, 13 **2015** 180–190.
19. Vatanen, T., Kostic, A.D., Hennezel, E., Cullen, T.W., Knip, M., Xavier, R.J., Huttenhower, C., Gevers, D., Cullen, T.W., Szabo, S.J., Porter, J.A., La, H., Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans Article Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans, **2016** 842–853.
20. Wexler, A.G., Goodman, A.L., into the microbiome, *Nat. Publ. Gr.* 2 **2017** 1–11.
21. Sheflin, A.M., Whitney, A.K., Weir, T.L., Cancer-Promoting Effects of Microbial Dysbiosis, **2014**.
22. Spurgeon, M.E., Boon, J.A. Den, Horswill, M., Barthakur, S., Forouzan, O., Rader, J.S., Human papillomavirus oncogenes reprogram the cervical cancer microenvironment independently of and synergistically with estrogen, **2017**.
23. Chen, K.L., Madak-erdogan, Z., Estrogen and Microbiota Crosstalk : Should We Pay Attention ?, *Trends Endocrinol. Metab.* 27 **2016** 752–755.
24. Bhat, M.I., Kapila, R., Dietary metabolites derived from gut microbiota : critical modulators of epigenetic changes in mammals, 0 **2017** 1–16.
25. Darfeuille-michaud, A., Intracellular colon cancer-associated Escherichia coli promote protumoral activities of human macrophages by inducing sustained COX-2 expression, 95 **2018** 296–307.
26. Prakash, H., Inhibitors of Apoptosis Protein Antagonists (Smac Mimetic Compounds) Control Polarization of Macrophages during Microbial Challenge and Sterile Inflammatory Responses, 8 **2018** 1–21.
27. Gagnaire, A., Nadel, B., Raoult, D., Neefjes, J., Gorvel, J., Collateral damage : insights into, *Nat. Publ. Gr.***2017**.
28. Frosali, S., Pagliari, D., Gambassi, G., Landolfi, R., Pandolfi, F., Cianci, R., How the Intricate Interaction among Toll-Like Receptors , Microbiota , and Intestinal Immunity Can Influence Gastrointestinal Pathology, 2015 **2015**.
29. Coker, O.O., Dai, Z., Nie, Y., Zhao, G., Cao, L., Nakatsu, G., Wu, W.K.K., Wong, S.H., Chen, Z., Sung, J.J.Y., Mucosal microbiome dysbiosis in gastric carcinogenesis, **2018** 1024–1032.
30. Xu, T., Fu, D., Ren, Y., Dai, Y., Lin, J., Tang, L., Ji, J., Genetic variations of TLR5 gene interacted with Helicobacter pylori infection among carcinogenesis of gastric cancer, 8 **2017** 31016–31022.

31. Zou, S., Fang, L., Lee, M., Dysbiosis of gut microbiota in promoting the development of colorectal cancer, 6 **2018** 1–12.
32. Viaud, S., Saccheri, F., Mignot, G., Yamazaki, T., Hannani, D., Enot, D.P., Pfirschke, C., Engblom, C., Pittet, J., Schlitzer, A., Ginhoux, F., Apetoh, L., Chachaty, E., The intestinal microbiota modulates, 342 **2014** 971–976.
33. Neuman, H., Forsythe, P., Uzan, A., Avni, O., Koren, O., Medicine, F., Szold, H., St, H., Israel, S., College, Z.A., St, J., Joseph, S., Hamilton, L.N., Antibiotics in early life : dysbiosis and the damage done, **2018** 1–11.
34. Kristensen, N.B., Bryrup, T., Allin, K.H., Nielsen, T., Hansen, T.H., Pedersen, O., Alterations in fecal microbiota composition by probiotic supplementation in healthy adults : a systematic review of randomized controlled trials, *Genome Med.***2016**.
35. Sáez-lara, M.J., Robles-sanchez, C., Ruiz-ojeda, F.J., Plaza-diaz, J., Gil, A., Effects of Probiotics and Synbiotics on Obesity , Insulin Resistance Syndrome , Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease : A Review of Human Clinical Trials, *Int J Mol Sci.* **2016**,*6*, 1–15.
36. Villena, J., Kitazawa, H., Modulation of intestinal TLR4-inflammatory signaling pathways by probiotic microorganisms : lessons learned from Lactobacillus jensenii TL2937, 4 **2014** 1–12.
37. Falagas, M.E., Betsi, G.I., Tokas, T., Athanasiou, S., Probiotics for Prevention of Recurrent Urinary Tract Infections in Women A Review of the Evidence from Microbiological and Clinical Studies, 66 **2006** 1253–1261.
38. Ooi, L., Ahmad, R., Yuen, K., Liong, M., Lactobacillus acidophilus CHO-220 and inulin reduced plasma total cholesterol and low-density lipoprotein cholesterol via alteration of lipid transporters, *J. Dairy Sci.* 93 **2010** 5048–5058.
39. Brunkwall, L., Orho-melander, M., The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes : from current human evidence to future possibilities, **2017** 943–951.
40. Lumeng, C.N., Bodzin, J.L., Saltiel, A.R., Obesity induces a phenotypic switch in adipose tissue macrophage polarization, 117 **2007**.