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Review Article

Gut Microbiome: An Intersection between Human Genome, Diet, and Epigenetics

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The composition and diversity of gut microbiome are in crosstalk with the genetic makeup and diet of an individual. Under normal health conditions, the gut commensals are in homeostasis with the host; while they inhabit the gut for their normal growth, they protect against invading pathogens through anticolonization mechanisms and contribute largely to the metabolism of several macromolecules in the gut. Specific genetic variants in genes that are responsible for maintaining the composition of the gut commensal, such as genes of the immune system, are described to result in gut dysbiosis that can lead to the development of several autoimmune diseases such as inflammatory bowel disease and type-1 diabetes. Similarly, the diet of an individual shapes the gut microbiota by allowing the predominance of microbes that metabolize an abundant macromolecule in the diet. Epigenetically, the microbial metabolites produced by these microbes can be beneficial in the treatment of cancer or deteriorating by serving as carcinogens. Therefore, the complex association of the gut microbiome with the genetic makeup and diet of an individual plays a significant role in the development of several diseases and health conditions. Recently, the association between the human genome and the gut microbiome has been analyzed and considered a multiomic approach, and extensive genome-wide association studies were conducted to further understand the complex relationship.

1. Introduction

The human genome and its genetic factors play a core role in determining the composition and diversity of both commensal and pathogenic microbial communities in the human body, especially the gut [1–3]. Specific genetic variations can affect the abundance of some microbial species, either by allowing or limiting their existence in the microbiota, and thus, the microbiota composition of an individual varies relatively depending on the genetic makeup of that individual [4, 5]. Thus, a genetic defect in a gene considered crucial in controlling the abundance of specific taxa may result in dysbiosis. Dysbiosis refers to the disruption of homeostatic balance in the microbiota composition. The commensal microbiota is symbiotic with the human body [6]; it is involved in a wide range of activities such as vitamin synthesis, immune system maturation, digestion of complex sugars, and energy homeostasis [7–9]. Much research has been done to thoroughly investigate the role of human genetics in the microbiome's diversity. The aid of genome-wide association studies (GWAS) and the vast availability of large genomic consortia enable the link and association between some specific genetic loci, autoimmune diseases, and the risk of developing such diseases, with an individual microbiota composition [10]. Most of these genes associated with microbiome composition and function that are identified through GWAS are immune genes that protect pathogenic microbes [11, 12]. Consequently, with a significant mutation in these immune genes, the immune system becomes defective and cannot clear pathogenic microbes, thereby increasing their abundance and decreasing or eliminating the commensal microbes. This entails the existence of a complex relationship between human genetic factors, the immune system, the microbiome, and possibly environmental factors

Table 1: Gene variants and their associated microbiota.

Gene	Microbiota	Related condition	References
NOD2	Increase *Escherichia* spp. and decrease *Faecalibacterium spp.*	IBD	[35]
NOD2/ATG16L1	Increase *Bacteroides fragilis*	IBD	[51]
UBR3	Increase *Rikinellaceae spp.*	Dysregulation of the protein ubiquitination pathway	[72]
PLD1 & LINGO2	Increase *Akkermansia* and *Blautia spp.*	Obesity	[72]
SLIT3	Increase *Clostridiaceae* and *Dermococcus spp.*	Inflammation and obesity	[2]
VDR3	Increase *Parabacterioides spp.*	Dysregulation of bile synthesis	[94]
ALDH1AL1	Increase *Christensenelleceae spp.*	Dysregulation of xenobiotic metabolism	[2]
PTN2 & PTN22	Increase *Faecalibacterium*, *Bilophilia*, and *Coprococcus spp.*	T1D	[83, 85]
DR3/4	Increase Bacteroides, *Parabacteroides*, *Clostridium*, *Klebsiella*, and *Akkermansia spp.*	T1D	[89]

in the development of many autoimmune diseases, such as inflammatory bowel diseases (IBD) and type-1 diabetes (T1D) [13, 14]. The exact molecular mechanism of this complex relationship is not yet fully understood; however, it is known that these genes encode for various components of the immune system, specifically that which function to recognize and distinguish between a commensal and a pathogen, then target, and eliminate the microbial pathogens. It is worthy of note that the gut microbiota is known as a mediator of several inflammatory responses, which can be useful in explaining its involvement in the progression of autoimmune diseases, although few genes that are not directly involved with the immune system are also indicated to affect the gut microbiota composition, such as the *VDR3* gene [2, 15, 16].

Additionally, the human gut microbiota composition is also affected by diet, such that the amount of a given macromolecule in a diet can result in the increased abundance of microbiota that metabolizes the macromolecule. Interestingly, some of this diet-induced microbiota can produce carcinogens that contribute to the development of cancer, or the microbiota may lead to epigenetic changes that can be beneficial in the treatment of cancer [17]. This review is aimed at discussing the relationship between the human genome and gut microbiome in the pathogenesis of autoimmune diseases, diet and gut microbiome interaction and epigenetics, and the involvement of the gut microbiota in maintaining gut immunity.

2. Human Genome and Microbiome Interaction

Some common genetic variants within the human genome that have been associated with gut microbiota dysbiosis are discussed below, and Table 1 and Figure 1 summarize and give an overview of the interaction.

2.1. MHC Gene Variants. The human leukocyte antigens (HLA) are encoded by major histocompatibility complex (MHC) class I and II genes and are considered to be one of the most polymorphic genes in humans [18–20]. HLA molecules are important components of the immune system involved in the differentiation between "self" and "non-self," ensuring appropriate immune response. Hence, specific polymorphisms observed in the MHC class II genes have been associated with an increased risk of occurrence of inappropriate immune responses, leading to the inability of the immune system to identify self-antigens, and thus attacking them as seen in autoimmune diseases such as ulcerative colitis (UC), T1D, Crohn disease (CD), rheumatoid arthritis (RA), and celiac disease [18, 21]. The gut microbiota has been described to be involved in the onset, further development, and pathogenesis of these autoimmune diseases [22]. To support this claim, arthritis was not developed in germ-free mice until intestinal microbiota were introduced [23]. However, the MHC class II polymorphisms simultaneously affect the ability of the immune system to recognize antigens of the commensal microbiota, thereby destroying them [18, 21, 24], and resulting in dysbiosis. This further results in an increased level of an immunoregulator at the mucosal level, T helper cell (Th17), and a disrupted intestinal permeability [25–28]. This explains the involvement of gut microbiota in the development of autoimmune diseases. Furthermore, specific polymorphisms in the HLA alleles have also been associated with a defective production of the predominant antibody in the mucosal surface, immunoglobulin A (IgA) [27]. IgA is a crucial component of the adaptive immune system and also the first line of defense against mucosal microbial pathogens. Defective IgA is shown to lead to the abundance of specific bacterial taxa such as *Bacteroides species* in the development of colitis [27, 29]. Conversely, *Bacteroides* and *Bifidobacterium* species level decreases in RA individuals while *Prevotella* species increase [30].

Thus, accordingly, the inability to recognize antigens of the commensal microbiota and a defective IgA antibody production due to MHC and HLA gene-specific polymorphism weakens the immune system's ability to protect against the tons of microbial pathogens the gut is exposed to, thereby attacking commensal microbiota and increasing the abundance of several gut pathogens. This eventually led to inflammatory responses that contribute to the prevalence and development of different enteric disease conditions.

2.2. NOD2 Variants. NOD2 (nucleotide binding oligomerization domain-2) gene encodes for a pattern recognition receptor (PRR) which is located intracellularly and is

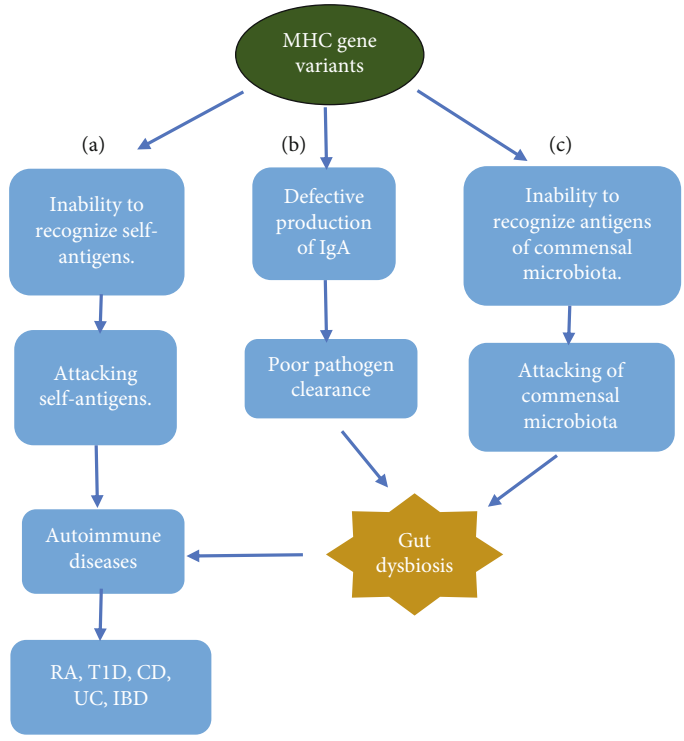

Figure 1: Relationship between MHC gene variants and gut dysbiosis and some. (a) A variant in the MHC gene is associated with the inability of the immune system to recognize self-antigens, thereby attacking them and progressing to the development of autoimmune diseases such as T1D, IBD, RA, UC, and CD. This pathway is independent of gut microbiota. (b) The MHC gene is involved in the production of IgA, and a genetic variant in the gene is shown to result in defective IgA production. As the most common immunoglobulin in the gut, defective IgA results in a poor clearance of gut pathogens which eventually develop into gut dysbiosis. Dysbiosis was described to contribute to the development of autoimmune diseases. (c) Lastly, similar to the inability to recognize self-antigens, the gene variant is also associated with the inability to recognize the antigens of gut commensals. This eventually led to the attacking of the commensals and resulting in gut dysbiosis. The dysbiosis developed in this case is also known to be involved in the development of autoimmune diseases.

responsible for the recognition of pathogen-associated molecular patterns (PAMPs), specifically the peptidoglycan motifs of bacteria [31–33]. In IBD patients, *NOD2* gene variants are involved in the development of the disease [34, 35]. The mechanism is not fully understood; however, it is illustrated that there is ineffective clearance of bacterial pathogens in the gut, in IBD patients [35–37]. Therefore, since the *NOD2* gene encodes for a PRR that recognizes peptidoglycan motifs of bacteria, it can be suggested that the poor clearance of bacterial pathogens in the gut as seen in IBD patients is due to a defective form of the PRR, which cannot efficiently recognize the peptidoglycan motifs of pathogenic bacteria. Accordingly, defective PRR due to the *NOD2* gene variant is not limited to poor recognition of pathogenic bacteria, as some studies have indicated that the gene variant also results in the increased abundance of nonpathogenic bacterial species, specifically *Escherichia coli*, and a spontaneous decrease in another nonpathogenic species of bacteria, the *Faecalibacterium species* [12, 38, 39]. The mechanism that led to this unusual association between these two bacterial species in this case is not clearly understood. This is because *E. coli* is a gram-negative bacterium and *Faecalibacterium* is a gram-positive bacterium; in the case of poor recognition of peptidoglycan motifs, the gram-positive bacterium is expected to be more abundant due to the high content of peptidoglycan motifs in the cell membrane of gram-positive bacteria as compared to gram-negative bacteria. Nonetheless, since the PRR is defective, an unusual composition of the gut microbiome is expected and other microbial factors such as quorum sensing or antibacterial toxins might contribute to fluctuations in the level of nonpathogenic strains.

In addition, distinctive to the involvement of the *NOD2* gene variant in defective PRR, several studies using *NOD2* gene defective mice observed gut dysbiosis and the risk of development of colitis, which resulted due to a defective mucosal barrier [40–43]. However, this observation can be explained owing to the understanding that poor pathogen clearance that can occur due to a defective PRR system is sufficient to result in an increased abundance of mucus-degrading pathogens or a decrease in commensal microbiota that stimulates mucosal production. Therefore, the defective mucosal barrier observed in some studies can still be linked to the involvement of the *NOD2* gene in the production of PRR. Conversely, a different observation was made in other studies using the same *NOD2* defective mouse, where they illustrated an increased level of a commensal microbe, *Bacteroides vulgatus* [44–46]. They added that the bacteria led to the abnormal expression of inflammatory genes, including IFN gamma. Fundamentally, IFN gamma is known to

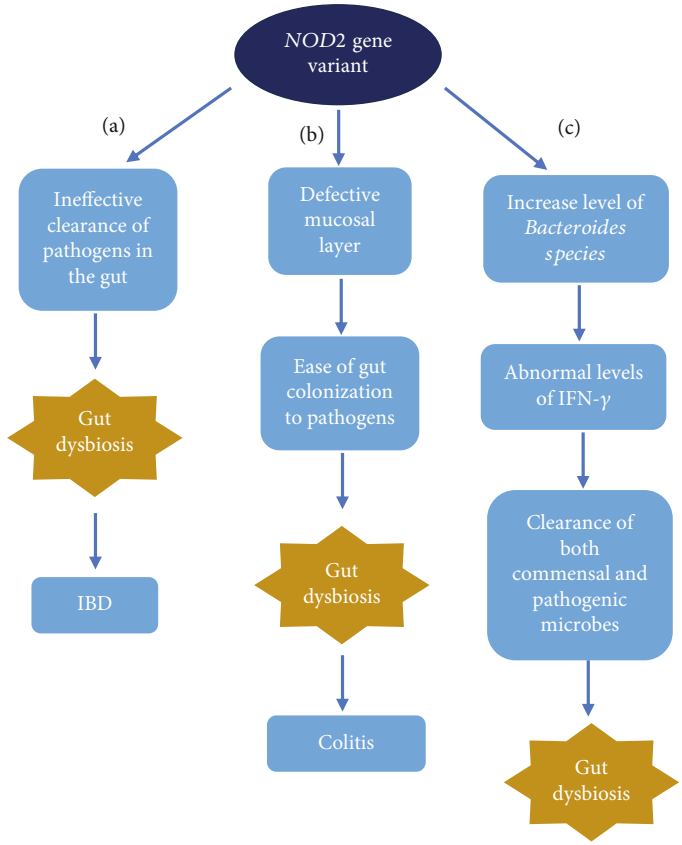

Figure 2: Relationship between NOD2 gene variant and gut microbiota. (a) The NOD2 gene is crucially involved in the PRR system, and a genetic variant in the gene has been associated with ineffective clearance of gut pathogens, resulting in gut dysbiosis that contributes to the development of IBD. (b) The development of a defective mucosal layer is linked to a genetic defect of the NOD2 gene. Consequently, the gut is easily colonized by pathogens and progresses to gut dysbiosis which is associated with the development of colitis. (c) The abundance of Bacteroides species is often connected to the NOD2 gene variant. The bacteria is known to increase the expression level of IFN-γ. This inflammasome activates pathways that clear both commensals and pathogens from the gut and cause gut dysbiosis.

be involved in the intracellular destruction of pathogenic bacteria and fungi, among other immune functions. Consequently, abnormal expression of the inflammatory genes, such as IFN gamma, is thought to decrease the level of both pathogenic and nonpathogenic bacteria, and this can also explain the development of defective mucosal barrier. Overall, the *NOD2* gene variant can be seen to lead to the abundance of both pathogenic and nonpathogenic strains of bacteria, arising mainly from a defective PRR system. On the other hand, abnormal IFN gamma is associated with the *NOD2* gene variant, further studies will be required to propose specifically the molecular mechanism of how the *NOD2* gene resulted in gut dysbiosis. The overview of this gene variant is summarized in Figure 2.

2.3. ATG16L1 Variants. *ATG16L1* (autophagy related 16 like 1) gene is among the gene variants associated with the development of CD and is involved in the regulation of autophagy [18]. Autophagy is essential in mediating lysosomal degradation and the clearance of bacteria intracellularly [47, 48]. The role of the gene in the regulation of autophagy explains the dysbiosis that resulted in the development of CD, where the *ATG16L1* gene variant is commonly found. Interestingly, the interaction between *NOD2* and *ATG16L1* is crucial, and genetic variants that hinder this association, as seen in CD patients, lead to impaired bacterial clearance and poor antigen presentation by immune cells such as dendritic cells [49–51]. This implies that individuals with either *NOD2* or *ATG16L1* gene variant can develop dysbiosis that progresses to CD; further investigation can be done to clearly understand the association between the genes.

Moreover, the *ATG16L1* gene is crucial in modulating several immune responses that protect pathogenic microbes. *ATG16L1* hypomorphic mice were demonstrated to show a microbiota-dependent risk of the development of colitis due to defective production of antimicrobial peptides in Paneth cells and altered toll-like receptor (TLR) signaling [18]. Similarly, disruption of the *ATG16L1* gene was reported to affect CD4+ T cell regulation, and hence T-regulatory cells and T-helper 2 cell-mediated responses in the intestine [52, 53]. In a separate but similar study, it was added that the disruption of the gene resulted in an impaired T cell function and subsequent destruction of the mucosa due to the loss of efficient recognition of intestinal antigens and the subsequent increased production level of immunoglobulin G (IgG) and IgA that eventually target the commensal

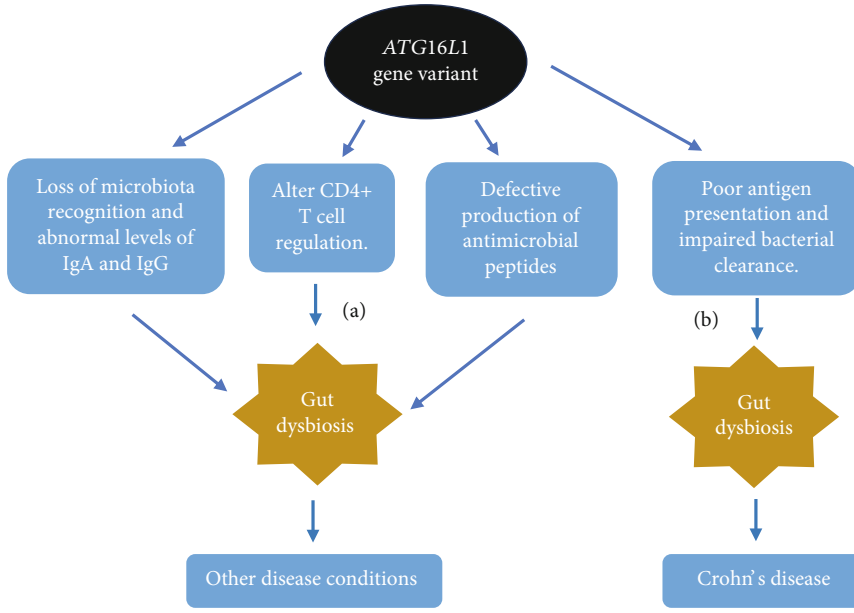

Figure 3: Relationship between ATG16L1 and gut microbiota. (a) ATG16L1 gene variant has been associated with loss of microbiota recognition, abnormal levels of IgA and IgG, altered CD4+ T cell recognition, and a defective production of antimicrobials. These are known to develop gut dysbiosis that causes several disease conditions. (b) The same gene variant is known to cause poor antigen presentation and impaired bacterial clearance which results in gut dysbiosis that has been associated with Crohn's disease.

microbiota [52, 54, 55]. These findings demonstrated the interaction between the *ATG16L1* gene with several immune conditions from both adaptive and innate immune systems that led to dysbiosis, as shown in Figure 3.

2.4. SLIT3 Variants. *SLIT3* (slit guidance ligand 3) gene is known to be involved in bacterial lipopolysaccharide (LPS) pattern recognition [2]. However, the protein encoded, SLIT3, is also essential in the degradation of sitosterol, a microbial pathway to the production of androstenedione [56, 57]. This microbial catabolic pathway is a sidechain degradation that leads to energy production in the form of ATP from sterol compounds. Goodrich et al. illustrated the link between the *SLIT3* variant and a relative abundance of an unclassified bacterium, *Clostridiaceae* [58]. In another study, a distinct variant of *SLIT3* from the Goodrich et al.'s study was associated with an abundance of *Dermococcus species* in the nasal microbiome [59]. Interestingly, two separate studies demonstrated that the SLIT3 ligand is central in modulating immune signals in response to bacterial LPS, apart from its significance in the degradation of sterols [60, 61]. Although the association of the *SLIT3* gene with response to bacterial LPS is understood as supported by existing reports, the mechanism is not fully elucidated. Yet, it can be suggested that the increased abundance of the aforementioned bacterial species may be due to poor recognition of the bacterial LPS antigen by the immune system or due to the accumulation of sitosterol or a metabolite that serves as a modulator or substrate for *Clostridiaceae* and *Dermococcus species*. The *SLIT3* gene variant plays a role in the recognition of the bacterial LPS by the immune system, and thus the clearance of bacteria, however, the gene variant has not been associated with the development of any autoimmune diseases.

2.5. MUC Genes. The intestinal epithelium lining is physically protected by the intestinal mucosal layer, serving as a barrier separating luminal microbiota from the intestinal epithelium. *MUC* (mucin) genes encode protein components of the mucosal glycoproteins produced and secreted by goblet cells [62, 63]. Mucin is a glycoprotein and a major component of the mucus that serves as an energy source for several gut commensals. Since the mucus is a physical barrier protecting the epithelium, the amount of the gut commensal utilizing the mucin must be maintained to avoid the thinning of the mucus. Moreover, mucus production must be regulated and maintained in a fashion that the amount of mucus produced is not lower than the amount of mucus degraded by the commensal mucus-degrading bacteria. Accordingly, abnormal expression of *MUC2*, *MUC6*, and *MUC5AC* was seen in patients with ulcerative colitis; also, deletion of the *MUC2* gene in mice shows increased risk due to dysbiosis, as shown in several studies [64–66]. In the case of a defective mucosal layer due to deformity in mucin production, the gut epithelial cells will be exposed to pathogens and even nonpathogenic microbes, which eventually lead to the development of autoimmune diseases such as UC. Illustratively, the gut will be inflamed, and commensal microbes will be attacked by the immune system while invading pathogens can still resist the anticolonization mechanisms by the immune system, and subsequently colonize the gut, as seen in UC patients. Nonetheless, the disruption or mutation in the *IL10* gene in patients with ulcerative colitis resulted in a thin mucosal layer, increasing the vulnerability and the abundance of pathogenic microbes in the gut [67, 68]. The specific molecular mechanisms for both the *MUC gene* and *IL10* gene variants in the development of UC are not fully understood yet.

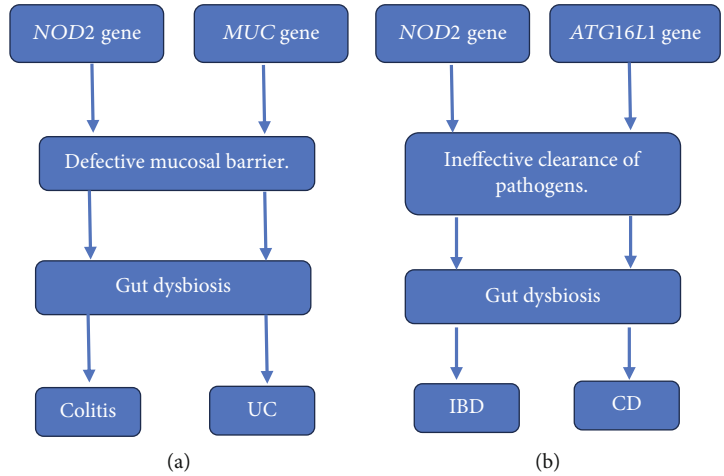

Figure 4: Common pathways between gene variants. (a) Both the NOD2 gene and MUC gene variants are known to cause defective mucosal barriers that result in gut dysbiosis. However, the gut dysbiosis resulting from the NOD2 gene is associated with colitis, while that of the MUC gene is associated with UC. (b) Similarly, the NOD2 gene and ATG16L1 gene variants both cause an ineffective clearance of pathogens in the gut that leads to gut dysbiosis. Although NOD2 is associated with IBD, ATG16L1 is associated with CD.

2.6. Other Genes. Some IBD-susceptible genes including *CCL2*, *DAP2*, and *IL23R* genes are demonstrated by Goodrich et al. to be involved in mediating the microbiome composition in IBD patients [2]. A large cohort study by Turpin et al. showed the correlation between the *UBR3* variants and the relative increased abundance of *Rikenellaceae species* [69]. The *UBR3* gene is known to encode a crucial protein in the protein ubiquitination pathway and also plays a significant role in apoptosis; the phenomenon between the *UBR3* gene resulting in the increased abundance of *Rikenellaceae species* is not understood. However, since the gene is involved in the modulation of apoptosis, it is possible that the gene variant led to increased intestinal cell death which in turn increases the permeability of microbes in the intestines. Similarly, the same suggestion was made to explain the relationship between *PLD1* and *LINGO2* genes in individuals with obesity [70–73]. Separate studies further linked a significant genetic variation in the two genes with increased abundance of *Akkermansia species* [74, 75] and *Blautia species* [76–78]. In T1D patients, various SNPs in immune genes, including *CTLA4*, *IFIH1*, *INS*, *IL2*, *IL10, PTPN2*, and *PTPN22*, have been associated with gut dysbiosis and the development of the disease [79–82]. Also, SNPs in *PTPN2* and *PTPN22* genes have been shown to lead to the decreased abundance of several commensal microbiota, such as *Faecalibacterium species*, *Coprococcus species*, and *Bilophila species*, with a spontaneous increase in abundance of *Bacteroides* in individuals with autoimmune diseases [83–87]. *PTPN2* and *PTPN22* genes are primarily known to be involved in the production of an enzyme and protein tyrosine phosphatases, and the phosphatase is involved in signal transduction in immune cells such as T cells. Lastly, an increased abundance of *Erysipelotichacea*, *Parabacteroides*, *Akkermansia*, *Clostridium*, *Bacteroides*, *Klebsiella*, and *Veillonella species* was associated with the *DR3/4* risk genotype [81, 84, 88–91]. Interestingly, the *DR3/4* risk alleles make the immune system hyperactive and increase susceptibility to infection [92, 93]. The common pathways shared between genetic variants are shown in Figure 4.

2.7. Nonimmune System-Mediated Genes. As mentioned earlier, most of the genes reported to modulate the microbiota composition are involved in mediating immunity, yet some genes that are not directly involved in mediating immune response but may be indirectly involved with the immune system are illustrated to affect the abundance of some microbes. Blekhman et al. reported that SNPs in a gene that codes for the vitamin D receptor (VDR) increased the abundance of *Parabacteroides* [4]. This was further investigated in *VDR* gene knockout mice, and increased levels of *Parabacteroides species* were observed compared to the wild-type mice [4, 94]. The mechanism is not clearly understood; nonetheless, VDR is commonly known as a receptor for secondary bile acids [95]; therefore, its activation is known to negatively inhibit bile acid synthesis [96]. Bile is a digestive secretion involved in the emulsification of fats and excretion of several hepatic metabolites such as cholesterol. Interestingly, apart from the digestive functions, bile acid/salts also serve as microbial anticolonization factors that limit the gut colonization of some microbes. This possibly supports the association between the VDR gene variant and the increased abundance of *Parabacteroides species*. Lastly, SNPs in the *UBAP2* that are involved in the ubiquitin pathway are reported to affect the gut microbiota composition [97].

3. Diet and Microbiome Interaction

An individual's diet can affect the gut microbiome in terms of the distribution and composition of the microbiota. Some of these diet-induced microbiotas are known to cause significant epigenetic changes that can alter the existing homeostasis responsible for maintaining the regulation of cell apoptosis

Table 2: Macromolecules and microbial substrates in the development of epigenetic changes.

	Microbial substrates	Metabolites produced	Epigenetic changes	Cancer activity
Carbohydrates	Nonstarch carbohydrates, resistant starch, and oligosaccharides from plants	SCFA such as acetate, butyrate, and propionate	Butyrate inhibits the activity of histone deacetylase (HDAC) activity, thus inducing apoptosis and inhibiting cell proliferation.	Anticancer activity
Phytochemicals	Polyphenols such as curcuminoids, lignans, polyphenol ellagitannins, flavonoids, anthocyanins, and epigallocatechin-3-gallate	Ellagic acid, urolithins, and valerolactone	Ellagic acid and urolithins inhibit the activity of histone acetyltransferase (HAT) activity. Valerolactone modulates DNA methylation and histone modifications resulting in anti-inflammatory activities.	Anticancer activity
Fats	Polyunsaturated fatty acids (PUFA)	Linoleic acids	Inhibit fatty acid synthase. Inhibit cancer cell metastasis. It also induces DNA methylation and histone modifications to induce apoptosis and anti-inflammatory activities.	Anticancer activity
Fats	Undigested fats and unabsorbed bile	Ursodeoxycholate (UDCA) and deoxycholate (DCA)	Modulation of expression of several genes at mRNA levels and the production of reactive oxygen species (ROS), resulting in DNA damage and alteration in the expression of chromosomal maintenance and mitosis genes. Moreover, DCA induces apoptosis through HDAC.	Cancer and anticancer activity
Fats	Alcohol	Acetaldehyde	Distort DNA repair system causes chromosomal damage and hence alters gene expression.	Cancer activity
Proteins	Valine, leucine, and isoleucine	SCFA such as acetate, butyrate, and propionate	Butyrate inhibits the activity of histone deacetylase (HDAC) activity, thus inducing apoptosis and inhibiting cell proliferation.	Anticancer activity
Proteins	Undigested amino acids such as methionine, arginine, phenylalanine, and tryptophan	Polyamines, phenols, and indoles	Cocarcinogens	Cancer activity

and proliferation. Eventually, carcinogenic changes occur in the cell due to the diet-induced epigenetic changes [98, 99].

Epigenetics includes heritable changes in a gene activity that do not originate from changes in the DNA sequence [99, 100]. This includes post-translational and post-transcriptional modifications of amino acids in histone proteins and microRNA (miRNA). This histone modification can be achieved through methylation, phosphorylation, acetylation, or ubiquitination [101–104]. Enzymes catalyzing these chemical reactions are described to be affected by diet-induced microbiotas through the production of certain microbial metabolites that interfere with their enzymatic activities. Table 2 gives an overview of the association between diet and epigenetic changes concerning cancer.

3.1. Dietary Carbohydrates. Digestion of carbohydrates mainly starts in the mouth by amylases and later in the gut by a factory of digestive enzymes. However, some dietary carbohydrates contain fibers—such as nonstarch carbohydrates, resistant starches, and oligosaccharides from plants—that remain undigested and are passed to the large intestine. In the large intestine, these macromolecules, such as xylan and pectin, are metabolized by microbes in different microbial pathways producing different types of short-chain fatty acids (SCFA) [103, 105, 106]. The concentration of SCFA produced in the colon is not the same throughout its length; there is 70-140 mmol in the proximal colon and about 20-70 mmol in the distal colon [107]. Acetate, butyrate, and propionate predominate in the pool of SCFA produced, with trace amounts of lactate, formate, and caproate. Gut microbiota consisting of *Faecalibacterium* spp., *Roseburia* spp., and *Coprococcus* spp. predominate in the colon producing SCFA from the complex sugars via glycolysis and other microbial pathways [108–111].

Butyrate is produced in high concentrations by the gut microbes and serves as a major energy source to the epithelial cells of the colon via beta-oxidation; several studies have illustrated that in a healthy gut, the concentration of butyrate and other SCFA produced in the gut is sufficient enough to influence the regulation of gene expression of the epithelial cells [112–114]. The butyrate concentration gradient decreases from the lumen to the bottom of the colon. The butyrate's normal concentration in the bottom is in homeostasis, with the amount of butyrate needed for influencing cell turnover and normal colonic epithelial cell growth through a beta-oxidation pathway, as mentioned earlier. An increase in the butyrate levels in the bottom of the colon above the homeostasis level can inhibit the activity of histone deacetylases (HDAC) activity in the epithelial cells, inducing apoptosis and inhibiting cell proliferation.

Intriguingly, for cancer growth, cancerous cells prefer glucose over butyrate as a substrate for aerobic glycolysis, and this eventually leads to the accumulation of butyrate in the colon. It was shown that the build-up of butyrate in the colon due to the preference of glucose over it by the rapidly growing cancerous cells results in the inhibition of HDAC activity, thus promoting cell apoptosis and inhibition of cell proliferation in the cancerous cells and neighboring cells [115–117]. Currently, the use of butyrate-producing bacteria in the colon to inhibit HDAC activity and hence halt colorectal cancer growth is an active area of research in colon cancer bacteriotherapy [118, 119].

In contrast, individuals on a significantly low-fiber diet, as in the Western diet, are at risk of developing dysbiosis in the gut due to weakening mucosal integrity and growth. Insufficient production of SCFA will deprive the normal colonic epithelial cells of substrate for their growth. In cases where an individual on a persistent western diet developed colon cancer, the HDAC activity will not be inhibited due to extremely low levels of SCFA, despite the preference for glucose by the cancerous cells. While individuals on a healthy high-fiber diet produce SCFA in the gut and the presence of cancer cells, the homeostasis level of the SCFA may inhibit cancer growth due to the accumulation of SCFA, specifically butyrate, in the colon.

3.2. Fat Diet. A high-fat diet can alter the microbiota composition of the gut by favoring the abundance of microbes that metabolize undigested fats and unabsorbed bile. This diet decreases the abundance of SCFA-producing bacteria, such as *Faecalibacterium* spp., due to bile toxicity. For instance, a Western diet mostly rich in saturated fatty acids and low in fiber content will lead to the accumulation of bile in the gut and eventually decrease the abundance of nonbile metabolizing microbes including SCFA-producing bacteria. Accordingly, the metabolism of undigested fats and unabsorbed bile by microbes, mostly *Bacteroides species*, was shown to produce carcinogenic metabolites [104, 120, 121]. Several other studies further demonstrated that carcinogenic metabolites such as ursodeoxycholate (UDCA) and deoxycholate (DCA) produced during the metabolism of unabsorbed bile are involved in the pathogenesis of gastrointestinal cancer and some cases, breast cancer [122–125]. Moreover, Weir et al. reported that *Ruminococcus gnavus* abundance increases in high-fat diet individuals and is responsible for the elevated levels of UDCA in alcoholic subjects [126]. Thus, a high-fat diet shaped the gut microbiota into producing higher concentrations of UDCA, DCA, and other carcinogenic metabolites, which can lead to the development of cancer. This explains one of the roles of gut microbiota in the development and progression of gastrointestinal and breast cancer.

Additionally, apart from the production of carcinogenic metabolites by the fat and bile-digesting microbes, their persistent existence in the gut can directly or indirectly be involved in the development of cancer. For example, the persistent abundance of *Helicobacter pylori* in the gut due to a high-fat diet can induce epigenetic changes in the gastric mucosa due to its prolonged adhesion to the mucosal surfaces resulting in a prolonged inflammatory response [127]. In the same report, it was shown that a decrease in the abundance of commensal microbiota, *Methylbacterium*, in the gut is related to the invasiveness and aggressiveness of breast cancer, even though the mechanism is not clearly understood.

Alcohol-induced microbiota produces simple metabolites that may interfere with DNA repair systems, resulting in an altered expression of genes. This claim was demonstrated in several studies involving alcohol drinkers, where the oral microbiota metabolizes alcohol to produce a simple short-lived metabolite, acetaldehyde; high levels of acetaldehyde are known to interfere with the activity of DNA repair systems in the oral cavity, thus, chromosomal damage [104, 128–130]. Conversely, good fats, such as polyunsaturated fatty acids (PUFA), have been shown to increase the abundance of *Roseburia* spp., *Bifidobacterium* spp., and *Lactobacillus* spp. in the gut; these commensal microbiotas metabolize the PUFA into conjugated linoleic acids [131, 132], and the biotransformation of PUFA through microbial pathways was shown to negatively affect the growth of cancer cells. This phenomenon is not fully elucidated yet; thus, further studies are required to establish the connection between PUFA and cancer.

3.3. Phytochemicals. Polyphenols, including curcuminoids, anthocyanins, flavonoids, and lignans, are a class of phytochemicals subjected to complex microbial pathways in the colon to produce metabolites that can induce epigenetic changes [103], significant in the treatment and or prevention of cancer. For instance, most berries have polyphenol ellagitannins that are metabolized by microbes such as *Clostridium species* and *Actinobacterium species* to urolithins [103, 133, 134]. They illustrated that urolithins, ellagic acid, other microbial metabolites, and even ellagitannins are found to induce epigenetic modifications, more specifically urolithins and ellagic acids are shown to affect the activity of histone acetyltransferase (HAT) negatively. These studies also align with the observation by Green et al., which suggested that ellagitannins may have anti-inflammatory activity [135]. In the same studies, they also showed that urolithin levels are associated with an increased abundance of commensal microbes, *Bifidobacterium* spp. and *Lactobacillus* spp.

In separate studies, epigallocatechin-3-gallate (EGCG), a green tea polyphenol and a substrate for microbial metabolism, were shown to demonstrate a significant antioxidant activity, anticancer, and lowering of blood sugar and cholesterol levels [136–139]; these activities are suggested to be due to the biotransformation of ECGC by the microbes. Precisely, EGCG undergoes extensive biotransformation into important metabolites known to modulate gene expression, such as valerolactone. To further establish the relationship between ECGC and its metabolites, such as valerolactone with gut microbiota and cancer, Arab and Il'yasova investigated different doses of ECGC on microbiota and reported that there is a change in the microbiota composition in the gut due to increased doses of EGCG, even though the shift in the microbiota is not clearly defined to specific taxa [140]. Mechanistically, the anticancer activity of EGCG and its metabolites are active investigation areas, due to their

ability to induce DNA methylation and/or histone modification, thus mediating gene expression [103, 141] that can be beneficial in the treatment of cancer and other anti-inflammatory responses.

3.4. Protein Diet. Similar to the metabolism of other macromolecules, gut microbiomes are also essential in the metabolism of protein molecules in both small and large intestines. Most dietary proteins in our meals are hydrolyzed to single amino acids and peptides with the aid of proteases and peptidases [142]. The single amino acids or peptides produced serve as metabolic substrates and are thus utilized by some gut microbes. Interestingly, gut microbes also play a significant role in the metabolism of undigested amino acids in the large intestines and also partake in the dietary protein and nitrogen recycling process in the small intestines [143, 144]. The undigested amino acids are fermented into several microbial metabolites and or end-products such as SCFA and ammonia, respectively [145]. Depending on an individual's dietary protein source and intake, the content and composition of the gut microbiota are known to adjust to accommodate microbes that digest the complex and undigested proteins and amino acids. For instance, peanuts and soybeans were revealed to contain a significant amount of low digestible crude protein because of the presence of molecules such as glycinin and β-conglycinin in them; therefore, a significant abundance of microbes such as *Bacteroides*, *Clostridium*, and *Streptococcus* species are found in the colon [146]. In the small intestines, a high protein diet was shown to lead to the accumulation of microbes that metabolize proteins and or produce and secrete important enzymes such as proteases and peptidases, including *Klebsiella* spp., *E. coli*, *Dextrinosolvens*, *Anaerovibrio lipolytic*, and *Streptococcus bovis* [143].

Accordingly, the most common microbial metabolites in the protein metabolisms include SCFA, ammonia, polyamine, phenol, hydrogen sulfide, and indole. However, polyamines, phenols, and indoles are characterized by promoting cancer [147]. Amino acid precursors such as methionine and arginine are hydrolyzed to polyamines by colonic cells, while the colonic microbes can produce even more polyamines such as cadaverine, histamine, putrescine, and tyramine from the metabolism of histidine, tyrosine, and arginine [148]. These polyamines play a significant role in bacterial secretion and transport, growth, and proliferation in the colon. Interestingly, neoplastic cells in the colon also utilize these polyamines for their continuous mitosis; therefore, isolation of colonic epithelium from a colon cancer individual shows high concentrations of polyamines [147, 148]. Some of the microbes commonly isolated in this case include *Bifidobacteriu*m, *Bacteroides*, and *Clostridium* species [148]. On the other hand, phenols and indoles are considered to be cocarcinogens and are also involved in the promotion of cancer [149]. They are derived from the metabolism of phenylalanine and tryptophan by gut microbes such as *Bifidobacterium*, *Clostridium*, *Bacteroides*, and *Lactobacillus* species. Phenols and indoles are produced in high concentrations in the distal colon, indicating a significantly high amino acid and peptide metabolism in the large intestines [148, 150]. This implies that a diet rich in amino acids that are metabolized to polyamines, phenols, and indoles shapes the gut microbiota mostly in the small and large intestines, producing these metabolites in high concentrations and thus promoting cancer growth in the colon.

4. Gut Microbiome and Immunity

The commensal microbiota and the human body are in a homeostatic relationship under normal health conditions, known as Eubiosis. The microbiota composition varies between individuals depending on many factors mentioned in this paper, but about 40% of the microbiome is similar in all individuals [149]. The composition and role of microbiota are not generally the same throughout the gut such that the composition at any point of the gut is the same; rather, some of these microbes are localized to a particular part of the gut depending on the function they provide. The gut commensal microbiome can provide metabolic function and or immune function, depending on the microbe. For example, some metabolites from the microbiome may have metabolic and antimicrobial functions, such as the SCFA, which serves as an energy source to the gut epithelial cells and is also known to be bioactive molecules that interfere with bacterial metabolic and lower the intracellular pH, thereby demonstrating an antibacterial activity. The role of the gut microbiome in protecting against invading pathogens through several layers of colonization resistance mechanisms, such as quorum sensing, bacteriocins production, and nutrient competition, has been intensively studied. This protection against invading pathogens by the gut microbiome can be achieved through the mediation of the host immune system or microbiome-specific immune protection [151].

4.1. Host Immune System-Mediated Protection. The gut commensal microbiota plays an essential role in mediating both the adaptive and innate immune systems by inducing the activation of T cells and B cells, differentiation of T cells, antimicrobial production, and regulation of antibody production. A study by Atarashi et al. illustrated that the gut microbiota plays an essential role in differentiating T cells into T regulatory cells and T helper cells, including Th1s, Th2s, and Th17s [152]. The role of gut microbiota in the differentiation of T cells into helper cells was also demonstrated in separate studies, where segmented filamentous bacteria were reported to induce the Th17s production and also involved in mediating the immune system in the initial production of antimicrobials against *Citrobacter rodentium* infections [153, 154]. The differentiation of T cells is critical in advancing and maturing an adaptive immune response; the T-dependent activation of B cells requires stimulation from T helper cells. Accordingly, Fan et al. demonstrated that the commensal microbiota stimulates the innate immune system in the production of antimicrobial peptides by initiating the transcriptional factor H1F-1α, which provides protection against *Candida albicans*, a fungal infection [153]. Interestingly, *C. albicans* infection can also be arrested by *Lactobacillus reuteri* through the stimulation of type 3

innate lymphoid cell expansion, which is subsequently accompanied by the production of a cytokine, interleukin 22 (IL-22) [155].

Moreover, the SCFA produced by fibrinolytic microbiota was shown by El-Sayed et al. to activate B cells in the production of IgA and thus improve the local mucosal immunity; they also added that the SCFA produced can modulate gene expression epigenetically by inhibiting the activity of HDAC as mentioned previously in this paper [104]. Further studies may be required to understand the mechanism of SCFA-induced production of IgA. In another separate but similar study, Zeng et al. reported that commensal microbiota, *Escherichia coli*, systemically induces the production of IgG by plasma cells and protects the body from *Salmonella typhimurium* infection [156]. The mechanism is not fully understood.

Interestingly, the fungal cell wall of some fungi or yeast, such as *C. albicans* contains mannose oligosaccharides (MOS) and β-glycan, which are active substances that can modulate innate and adaptive immune systems [157]. Distinctively, MOS contains mannan residues that trap pathogens by mimicking the cellular receptors of these pathogens on epithelial cells, thereby reducing their gut colonization and aiding in their clearance from the gastrointestinal tract. Studies have indicated that *E. coli*, *Shigella* spp., *Salmonella spp*., *Vibrio spp*., and *Pseudomonas* spp. infection can be reduced in the presence of MOS; the MOS serves as a colonization resistance mechanism against the invading microbes [158–160]. The efficacy and side effects of utilizing MOS from *C. albicans* in treating bacterial infection can be further studied, contributing to therapeutic applications of MOS.

Furthermore, the β-glycan component of the fungal cell wall has been reported to have immunomodulatory effects through the modulation of adaptive immune response via the amplification of both inflammatory and cytotoxic T cells against *S. typhimurium* infection [161, 162]. The same studies reported that the β-glycan also induced the production of antimicrobial peptides against *Salmonella* spp. These findings imply that some fungi's cell walls can be used to treat several bacterial infections.

4.2. Microbiome-Specific Immune Protection. Without activating the immune system, the commensal microbiota can protect the body against pathogenic microbes through other mechanisms, including quorum sensing, nutrient competition, production of bacteriocins, inducing mucus production and antimicrobials, and an inhospitable environment for pathobionts. The detailed explanation of these mechanisms is beyond the scope of this paper.

Nonetheless, a gut commensal can hinder gut colonization of a pathobiont through quorum sensing, as seen between *Ruminococcus obeum* and *Vibrio cholerae*. It was illustrated that *R. obeum* blocks the mucosal colonization of *V. cholerae* through quorum sensing by interfering with the expression of virulence genes which are vital in the successful colonization of the bacteria [163–165]. The *R. obeum* produces autoinducers sensed by *V. cholerae* at high cell density, thus limiting subsequent expression of biofilm structures and facilitating the detachment of the pathogen from the intestinal epithelial cells. This anticolonization mechanism is highly specific such that the autoinducers must be sensed by the pathogen to halt its further colonization. This is an active research area in the management of enteropathogens such as *V. cholerae*.

Through nutrient competition, the gut commensal microbes may compete with the pathobionts for the available nutrients which can be crucial for the growth or colonization of the pathogens, thus starving them and inhibiting their growth and pathogenesis. Deriu et al. demonstrated that pathogenic *E. coli* (E. coli O157) and *C. rodentium* growth can be controlled via nutrient competition by *S. typhimurium* for the available sugars in the gut or iron requirement [166]. Nutrient competition tightens between strains of the same species because they require similar substrates and metabolites for their growth and, therefore, must compete for survival.

The gut commensals also produce important bioactive compounds known as bacteriocins. Bacteriocins are biologically active compounds produced by microbes to inhibit growth and colonization or kill other microbes. For example, *Bacillus thuringiensis* is a gram-positive bacterium that produces a bacteriocin with bactericidal activity against *Clostridium difficile*, while commensal *E. coli* (Nissle 1917 strain), a gram-negative bacterium, produces microcins that are effective against the growth of *S. typhimurium* infections [167]. Intriguingly, bacteriocins have a wide range of activity such that bacteriocins from gram-negative bacteria can affect gram-positive bacteria; the reverse is more interesting because of the existence of an outer membrane on the surface of gram-negative bacteria. Several in vitro studies have demonstrated the effect of bacteriocins from gram-positive bacteria such as *Streptococcus lactis* 11541 and *Pediococcus acidilacticii* QC38 against a gram-negative bacterium, *V. cholerae* [168–170].

The gut commensal microbiota is essential in producing mucus that provides the first line of defense against pathogens in the gut; it also produces significant SCFA that can lower the pH of the gut. The lower pH in the gut is known to affect the growth of several enteric pathogens by inhibiting the expression of their virulence genes or affecting the overall gene expression, thus limiting their growth and colonization. Zipperer et al. showed that the virulence genes of *S. typhimurium* are downregulated at lower pH due to SCFA in the gut, while *C. difficile* survival is significantly reduced in the presence of *Clostridium sciders* that convert primary bile acids into secondary bile acids in the gut [171]. Additionally, the deconjugating of bile by some gut commensals such as *B. obeum*, due to the enzymatic activity of bile salt hydrolase (BSH), has been shown in many studies to limit the colonization of *V. cholerae* [151, 172, 173].

4.3. Future Perspective. Further in-depth studies are required to establish a clear molecular mechanism on how the genetic variants result in gut dysbiosis and to obtain more evidence that the observed dysbiosis in such cases is clearly due to that specific genetic variant. Multiomic approaches can be useful in identifying novel genes that are previously reported to be

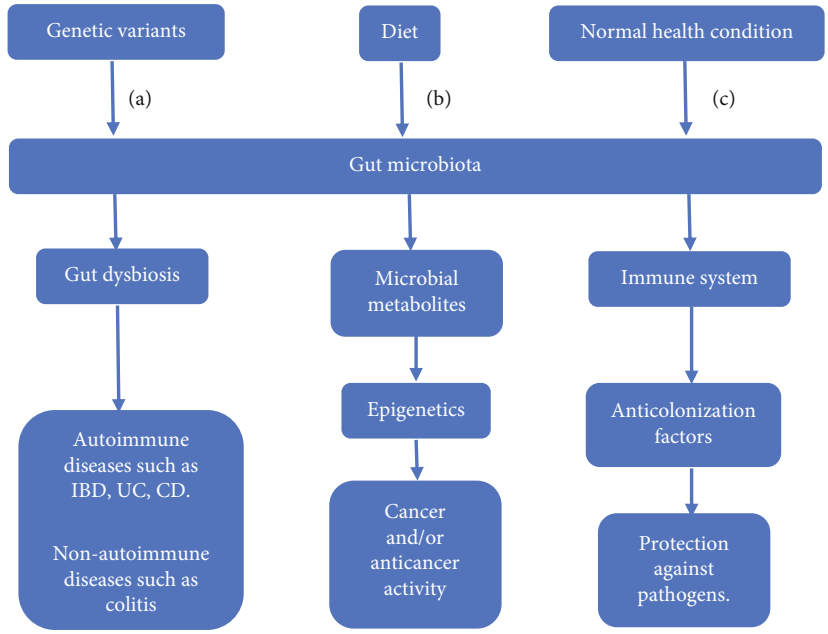

Figure 5: Relationship between gene variants, diet, normal health conditions, and the gut microbiota. (a) The gene variants interact with the gut microbiota to induce dysbiosis that results in the development of both autoimmune diseases and nonautoimmune diseases. (b) Also, microbial metabolites are generated when the diet interacts with the gut microbiota. These microbial metabolites can cause several epigenetic changes that can be crucial in the development of cancer or its treatment. (c) Under normal health conditions, the gut microbiota is in homeostasis with the human body, and directly or indirectly, the gut microbiota modulates the immune system in protecting it against invading pathogens, through several layers of anticolonization factors.

involved in shaping the content and composition of the gut microbiome, determining the strength of the association, and enabling the development of new diagnostic and therapeutic tools. Several GWAS have been performed to identify and study the interaction between human genetic variation and microbiota composition and how that affects an individual's health. In the future, as the genome-microbiome field is still nascent, metagenomic-wide association studies (MGWAS) can be used to further analyze and reveal complex associations, with the aid of the available human microbiome project (HMP) and modern advancements in bioinformatics tools.

Furthermore, some important factors are often unaccounted for when studying and establishing the relationship between diet, genome, epigenome, and microbiome in disease and health. These factors include hygiene, vaccination history and status, medications, immune status, drinking water, age, smoking, lifestyle, overall health status, and geographic location [45]. Most of the already established studies exclude these factors, and therefore, more thorough studies are required to consider as many factors as possible that may directly or indirectly result in dysbiosis or pathogenesis of a disease.

5. Conclusion

Specific genetic variants in immune-related genes are capable of distorting the homeostatic relationship between gut commensals and the human gut. These immune genes play a significant role in maintaining the composition of the gut commensals while protecting the body from pathogens. The inability of the immune system to carry out this function effectively due to a given genetic variant in the immune genes will result in dysbiosis which in some cases contributes to the development of autoimmune diseases such as T1D, IBD, and CD.

Additionally, the composition of the gut microbiome can be affected by the diet, such that the relative abundance of particular microbes that metabolize macromolecules that are high in the diet are found in high concentrations in the gut. Although the majority of the macromolecules in the diet can be metabolized by human enzyme machinery, some complex molecules remain undigested, and thus the gut microbiota acts on them and metabolizes them. In most cases, the diet-induced microbiota produces intermediary or end-products from the metabolism of the complex molecules in the diet, and these metabolites can be useful or detrimental to the host. Polyphenols from phytochemicals and SCFA from complex polysaccharides are considered useful in the treatment of cancer through epigenetic changes, while phenols and indoles from complex proteins and UDCA from undigested bile are considered carcinogenic molecules and hence play a role in the development of different type of cancers.

Conclusively, under normal conditions, the gut commensals directly stimulate the human immune system into protecting against pathogens or indirectly through microbiota-dependent mechanisms, and the gut commensals can provide several layers of anticolonization mechanisms. All these findings indicate the complex relationship that exists between the human genetic variant, diet, and the gut microbiome, as shown in Figure 5. The gut microbiome is considered, an intersection point between the human genetic variants and diet, in disease and health conditions.

Conflicts of Interest

The authors declare that there are no competing interests.

Authors' Contributions

Abdullahi Y. Muhammad designed and wrote the first version of the manuscript. Malik Amonov, Atif A. Amin, and Farrukh J. Alvi revised and finalized the manuscript.

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