Thyroid Diseases and Intestinal Microbiome

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ABSTRACT

The human microbiome plays an integral role in health. In particular, it is important for the development, differentiation, and maturation of the immune system, 70 % of which resides in the intestinal mucosa. Microbiome studies conducted to date have revealed an association between disturbances in the microbiota (dysbiosis) and various pathological disorders, including changes in host immune status. Autoimmune thyroid diseases are one of the most common organ-specific autoimmune disorders, with a worldwide prevalence higher than 5 %. The predominant autoimmune thyroid diseases are Hashimoto's thyroiditis and Grave's disease. Several factors, such as genetic and environmental ones, have been studied. In accordance with recent studies, it is assumed that the gut microbiome might play a significant role in triggering autoimmune diseases of the thyroid gland. However, the exact etiology has not yet been elucidated. The present review aims to describe the work carried out so far regarding the role of gut microflora in the pathogenesis of autoimmune thyroid diseases and its involvement in the appearance of benign nodules and papillary thyroid cancer. It appears that future work is needed to elucidate more precisely the mechanism for gut microbiota involvement in the development of autoimmune thyroid diseases.

Introduction

In recent years, numerous publications have referred to the human microbiome and its biological significance for the human organism. The term "microbiome" describes all the diverse normal microbial flora along with their genetic material [1, 2]. Human microbial flora includes all the major groups of microbes (bacteria, viruses, fungi, and protozoa), with bacteria and viruses being the most numerous [3–5]. The clinical and experimental data available highlight the role of bacteria, as most clinical studies refer to this group of germs. In particular, four bacteria genera predominate in the intestinal flora: *Firmicutes* (including Gram-positive cocci, bacilli and *clostridia*), *Bacteroidetes* (including *Bacteroides* and *Porphyromonas*), *Actinobacteria* (including *Mycobacteria*, *Nocardia* spp and *Corynebacterium* spp) and *Proteobacteria* (including *Enterobacteriaceae, Vibrio* spp and *Helicobacter* spp) [6, 7]. Normal microbial flora is found in different numbers and composition depending on its location, namely the gastrointestinal tract (the most colonized area of the human body), skin, oral cavity, and respiratory system (upper and lower) and the placenta and uterus in women. Based on recent clinical findings, germs can also be detected in areas that were previ-

ously considered sterile, such as the amniotic cavity in the fetus, the breasts, and the central nervous system [8].

It has been estimated that normal flora includes about 10–100 trillion microbes belonging to about 35 000 different species [9] and amounting to approximately 2.5–3 million expressed genes [10, 11]. For comparison, the total number of human cells is estimated to be around 10 trillion, with a genetic expression of approximately 20 000–30 000 genes [12]. This difference arises from the fact that only 2–3 % of the genome of human cells is expressed, in contrast with bacteria where their genetic expression amounts to 95–98 %. This data supports the view that 99 % of the expressed genes in humans are of microbial origin [12, 13].

According to these data, the definition of man as a superorganism [13–17] is correct; the old belief that "you are what your genes express" does not seem to apply. It has also become very clear that the genes of the microbes in our normal flora can alter the expression of our own genes, and that disorders of the microbial flora in a specific area (e. g., intestine) affect human functions even in remote anatomical areas (e. g., brain, lungs, adipose tissue, endocrine system, etc.). Thus, in reality, man is a guest in the universe of microbes.

However, it should also be mentioned that the composition and function of normal microbial flora (e. g., intestine) are affected by other organs (e. g., brain) [17, 18]. The communication-conversation between the normal microbial flora of various organs is bidirectional, humoral and takes place through the exchange of chemical messaging substances [17, 18]. It has been reported in a number of studies that the conversation between the gut flora and the brain takes place to such an extent that the term "gut–brain axis" is justified [18]. More recently, with the clinical and experimental data accumulating during the COVID-19 epidemic, the gut–lung microbial flora conversation came to the forefront and allowed the term "gut–lung axis" to be introduced [19].

The human microbiome plays an important role not only for the physiological mechanisms of the human body, but also for various pathological conditions [20–22]. In particular, it is of great importance for the synthesis of vitamins (K, B12, and folic acid), while also contributing to the metabolism of carbohydrates, fats, proteins, bile acids, and insoluble fiber. Based on its complex activity, normal microbial flora is metabolically characterized as an organ, equivalent to the liver [23]. It is also crucial for the development, maturation and training of natural and acquired immunity (70–80 % of the immune system is located in the intestinal mucosa) [11], while it is also necessary to prevent the gut being colonized by pathogenic microorganisms and to regulate motility of the intestine. It is interesting to note that clinical observations, experimental data and clinical studies converge on the view that disorders of the human microbiome are associated with many diseased entities such as malignancies (e. g., stomach cancer, cervical cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, etc.), chronic infections (stomach ulcer, atherosclerosis), cardiovascular disease, obesity, metabolic syndrome, inflammatory bowel disease (irritable bowel syndrome, ulcerative colitis, Crohn's disease), type 2 diabetes, non-alcoholic steatohepatitis, neurological diseases such as Parkinson's disease, autism, multiple sclerosis, and mental disorders (e. g., depression) or behavior change [24].

Of particular importance is the well-established communication between microorganisms and their hosts through an array of hormonal signals. In 1992, the term "microbial endocrinology"was introduced due to the proliferative effect of catecholamines on the growth of coliforms [25]. Moreover, clinical studies have revealed the existence of hormone receptors in microorganisms, facilitating cross-kingdom cell-to-cell signaling. Additionally, microbial flora appears to evoke autoimmune conditions, such as in the case of the thyroid gland, along with morphological changes [26].

Regarding the evaluation of the human microbiota, two strong considerations arise: a), which is exactly the normal microbial flora of every individual and b) ethical and framework and regulations in human microbiome research are urgently needed with respect of informed concept , privacy, return of results, commercialization, and data protection [27] .

Thyroid diseases in relation to the human microbiome

Autoimmune thyroid diseases

Autoimmune thyroid diseases (ATD) are one of the most common organ-specific autoimmune diseases. Specifically, Hashimoto's thyroiditis (TH) and Grave's disease (GD) are considered the most common. The gastrointestinal tract, considered nowadays to be the largest endocrine organ, often plays a distinct role in the development of autoimmune thyroid diseases. In particular, molecular mimicry between microbial and human antigens can turn a defensive immune response into autoimmunity under particular conditions in genetically predisposed persons [28]. Although there is no direct link between normal intestinal microbial flora and autoimmune thyroid disease, clinical studies provide evidence that the "Gut–Thyroid Axis" modulates thyroid physiology, while the gut microbiome is also affected by thyroid function [29–31].

Hashimoto's disease(thyroiditis) (HT)

HT is one of the most common organ-specific T-cell mediated diseases, with a reported frequency ranging from 5 to 20 %, worldwide [32]. Moreover, greater prevalence has been reported in the elderly and in the female population [33]. It is characterized histologically as a chronic lymphocytic infiltration, with high titers of autoantibodies against peroxidase (anti-TPO) and thyroglobulin (anti-Tg) [34].

Lymphocyte infiltration of the thyroid presents as swelling of the gland with the gradual replacement of the parenchyma by fibrous tissue and the destruction of the architecture of the gland. The process results in clinical hypothyroidism. The altered functional state, if not corrected with hormonal replacement (administration of thyroid hormones), leads to a variety of clinical manifestations such as cardiovascular disorders, decrease gastrointestinal motility, reduced fertility and musculoskeletal and psychological changes. It is worth noting that HT also predisposes to thyroid cancer [35].

The pathogenetic mechanism of HT remains unknown. However, many data support the view that it is caused by interactions of both genetic and environmental factors [36]. Genetic predisposition refers to the loss of tolerance to self-antigens associated with immunomodulatory genes (HLA class I and II antigens) and cytotoxic lymphocyte protein-4 (CTLA-4) [37].

Environmental factors include deficiency of selenium, iron, zinc, and vitamin D, along with excessive iodine intake. Various bacterial infections (e. g., *Helicobacter pylori*, *Yersinia enterocolitica*) and viral infections (hepatitis C virus, Epstein–Barr virus, enteroviruses), as well as factors such as stress, smoking, climate, sex, age and air pollution, are also implicated [29, 38].

Effect of intestinal microbial flora disorder on HT

There is a significant amount of evidence to suggest that changes in the intestinal flora, bacterial overgrowth, and increased intestinal permeability favor the development of HT. Thus, the functional term "thyroid–gut" axis has come into use [30]. The effect of the intestinal microbial flora on HT formation, which has been established in experimental animals since 1970, is supported by the following data: a) Intestinal dysbiosis is found to affect thyroid hormone concentrations by altering enterohepatic circulation and the absorption of iodide from the gut lumen, b) Gut microbiota is able to alter CNS neurotransmitters' circulation and function and thus the physiology of the "hypothalamic–pituitary–thyroid" axis, and c) Through its metabolic action on bile acids, the intestinal microbial flora is implicated in the secretion of TSH [39] and the regulation of deiodinase type 2 of iodothyronine and, finally, through alterations in normal intestinal flora gut via dysbiosis occurring in patients with HT. Particularly, in patients with HT, an increase was observed both in bacteria belonging to the genera *Bacteroides, Parasutterella* and in those belonging to the group *Escherichia-Shigella*, with a parallel decrease observed in those belonging to the genera *Bifidobacterium*, *Lactobacillus*, *Prevotella*, and *Dialister* [40, 41]. These results are consistent with the results of a recent study of HT patients from Brazil [33], where an increase in bacteria belonging to the genus *Bacteroides* was observed, with a parallel decrease in bacteria belonging to the genus *Bifidobacterium*. However, more data are needed as different results have been published in previous studies. On the other hand, clinical studies in patients with HT have reported an increase in bacteria belonging to the genera *Blautia*, *Roseburia*, *Ruminococcus*, *Rombutsia*, *Dorea*, *Fusicatenibacter*, and *Eubacterium* with a parallel reduction in bacteria belonging to the genera *Bacteroides*, *Faecalibacterium*, and *Prevotella* [39]. Interestingly, a positive correlation between *Helicobacter pylori* colonization and HT was detected through activation of NLRP3 inflammatory cascade system, caspase-1, and an increase in IL-1β secretion was also seen to be activated by the TLR-4, MyD88 and NF-κB pathway ,as it happens with *Proteus mirabilis* [42, 43].

Grave's disease (GD)

Grave's disease is considered to be the most common cause of hyperthyroidism. The main pathophysiological feature of the disease is the production of autoantibodies against the thyroid-stimulating hormone receptor (TSHR), resulting in the overproduction of thyroid hormones. This condition is clinically manifested by hyperthyroidism, goiter and occasionally bulging eyes or exophthalmos. Although the etiology and pathogenesis of the disease are still elusive, genetic, immunological and environmental factors are believed to be important [44]. Among the environmental factors, the microbial flora of the gastrointestinal tract is currently under investigation, with the aim of elucidating the molecular pathophysiological mechanisms.

Effect of gut microbiome on GD

In recent years, interventions including antibiotics, probiotics, and diet modification that modulate the gut microbiota, have been actively investigated in preclinical models and, to some extent, in clinical settings in patients with GD in order to reveal pathophysiological had an increased number of bacteria belonging to the genera *Bacteroides* and *Lactobacillus*, while a decrease was observed in bacteria belonging to the genera *Blautia*, *Anaerostipes*, *Collinsella*, and *Dorea* [45]. It is well known that bacteria belonging to the genera *Bacteroides* produce volatile fatty acids such as succinic, propionic, and acetic acid [46] that do not induce the synthesis and secretion of mucus, a substance that strengthens the binding of epithelial cells and lubricates the gastrointestinal mucosa. This condition facilitates the increased permeability of the intestinal mucosa to a large amount of metabolic pro-inflammatory products that cause dysfunction of the immune system [47]. By this process, it is believed that *Bacteroides* could play at least a permissive role in the pathogenesis of GD [48]. Bacteria belonging to the genus *Blautia*, the number of which was found to be reduced in individuals with GD [42], have well-known probiotic properties and thus they maintain the health of the macro-organism [49, 50]. Interestingly, bacteria of the genus *Blautia* have butyric acid as their final metabolic end product. Bacteria belonging to the genus *Anaerostipes* also produce the same short chain fatty acid through the assimilation of lactic acid (a metabolic product of lactobacilli) [51]. This substance, known as the intestinal mucosa protector, stabilizes the integrity of the intestinal mucosa by activating the β-oxidation of fatty acids and inhibiting nitric oxide synthetase through the signal transduction system of PP-signal (PPAR) and also by its action in the differentiation of T-regulatory lymphocytes, preventing the entry of pro-inflammatory agents into general circulation [52, 53]. Butyric acid has also been shown to reduce TNF-α, IL-6 levels and to suppress the NLRP3 inflammasome through the expression of the hGPR109 gene [54].

In the pathogenesis of GD , the growth of bacteria of the genus *Lactobacillus* has also been implicated in the sense that these bacteria can activate the NF-κB signal transduction mechanism and thus be involved in the occurrence of GD. It is of interest that some patients with GD show elevated peroxidase (TPO) antibody titers, apparently due to molecular mimicry as certain amino acid sequences in certain lactobacilli proteins are homologous to TPO and thyroglobulin amino acid sequences [55]. Also, the breakdown of immune tolerance against TSHR exacerbates the GD phenotype [56, 57] .Based on these findings, it is argued that *lactobacilli* activate pro-inflammatory metabolic signal transduction pathways, a process that further exacerbates the existing dysbiosis of the intestinal flora, forming part of a vicious cycle of thyroid dysfunction and dysbiosis of the intestinal microbiome.

In the pathogenesis of GD, the growth of bacteria belonging to the genera *Fusobacteria*, *Sutterella*, and *Prevotella* are also shown to be involved. In particular *Sutterella* (some species) have an immunomodulatory effect through their ability to adhere to intestinal cells [58, 59]. For *Prevotella* it is postulated that there is a similarity with human TSHR as it happens with rheumatoid arthritis [60].

Nodules and thyroid cancer

Based on a methodologically rigorous clinical study published in 2007 [53], the incidence of thyroid nodules in the adult population ranges from 20 to 76 % worldwide, with about 10 % of these nodules being malignant. Predisposing factors include age, metabolic syndrome and accumulation of certain genes, with TRPM3, EPB41L3, and AP005059 appearing to be of particular importance [61, 62]. The amount of iodine present in the environment plays a significant role, as people living in iodine-deficient areas showed an increased incidence of developing nodules [26]. This phenomenon is explained, at least in part, by the fact that iodine has antioxidant and anticancer properties, inhibits cellular proliferation and is generally cytotoxic to neoplastic proliferation [63, 64].

While it has been accepted for many years that thyroid function is essential for the regulation of the metabolism, the exact mechanism of the pathogenesis of thyroid nodules has not been fully elucidated. In the last two years, the relationship between microbial intestinal flora, nodules, and thyroid cancer has begun to be investigated as it is described below. These results clearly indicate that both thyroid nodules and cancer are associated with gut microbial flora and help developing potential probiotics to facilitating the treatment of thyroid cancer and nodules [65].

Effect of intestinal microbial flora on the formation of thyroid nodules

There is relatively little existing literature. It is not until recently that a clinical study [50] investigated the composition of the gut microbiome in patients with thyroid nodules. The study was based on the genome-wide association of the gut microbes, and parallel measurements of thyroid hormones such as free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). It is interesting to note that in individuals with thyroid nodules, a decrease in butyric acid-producing bacteria was observed as the main metabolic product of carbohydrate fermentation (*Butyrivibrio, Roseburia hominis, Faecalibacterium prausnitzii, Eubacterium eligens*). Additionally, butyric acid can also act as an inhibitor of histone deacetylation, an inhibitor of cell proliferation, while it can also increase iodine uptake by follicular thyroid cells [66].

Effect of intestinal microbial flora on the development of thyroid cancer

In recent studies [67], a large quantitative and qualitative change in the composition of the intestinal microbial flora was documented in people with thyroid cancer. In particular, patients with thyroid cancer showed an increased number of bacteria belonging to the groups *Clostridiaceae*, *Neisseria*, and *Streptococcus*, with a decrease in bacteria belonging to the genus *Lactobacillus*. It is worth noting that the metabolic products of bacteria belonging to the groups *Clostridiaceae* and *Streptococcus* have well-known carcinogenic effects [68]. Bacteria of the genus *Neisseria* have been associated with inflammatory bowel disease and pancreatic disease [69]. The reduction of *lactobacilli* is important for the uptake of trace elements such as selenium, which has antioxidant and protective action on the thyroid gland [59]. Based on the above data, the hypothesis that changes in the intestinal microbiome contribute to the occurrence of thyroid cancer was formed.

Conclusion

Healthy gut microbiota is a prerequisite for an adequate function of the complex network of intricate stages and pathways in the body described as the immune system. Based on immunomodulation studies, microbiota gut alterations are able to cause impaired immunoregulation, leading to specific immune responses against thyroid antigens, contributing to the pathogenesis and progression of autoimmune thyroid diseases. Further studies are needed to elucidate the exact pathogenetic role of the gut microbiota on the development of thyroid autoimmunity, providing also the functional immunoregulatory foci for possible therapeutic interventions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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