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Do Intestinal Microbiota and Thyroid Travel in Tandem?

Editorial

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The gut microbiota exerts some pivotal metabolic functions in digestion and absorption of nutrients [1], detoxification and synthesis of vitamins [2]. Furthermore, it is essential in correct development of lymphoid tissue associated with intestine (GALT) [3], the largest component of the lymphoid system, which contains over 70% of the total immune system. Although the characterization of the "healthy microbiota" is not an easy task, the disruption of the homeostatic and mutualistic relationship between the gut microbiota and the host, called dysbiosis, is defined as "the altered composition and function in the microbiota are driven by a series of environmental and host-related factors, which perturb the microbial ecosystem to a greater extent than its capacity for resistance and resilience "4. The condition of dysbiosis, which can be linked to the excess of pathobionts, the reduction of the concentration of commensals and the microbial diversity [4] have been related to various gastrointestinal and systemic disorders, such as dysmetabolic diseases (obesity, type 2 diabetes mellitus) [5,6], allergic [7] (asthma), inflammatory [8] (IBD) and autoimmune. Among the latter, the most studied were type 1 diabetes mellitus [9], rheumatoid arthritis [10], multiple sclerosis [11], systemic lupus erythematosus [12] and Hashimoto's thyroiditis [13].

Effect of the microbiota on development and actions of the immune system.

The proper functioning of the immune system depends on the balance between tolerance towards auto-symbiotic bacteria and the correct targeting of the immune response against external harmful agents. The relationship between the host's immune system and microbiota is bidirectional: in fact, if the host's immune system is crucial for influencing the composition of gut microbiota, it has been shown that the microbial community could directly modulate innate and adaptive host immunity [14]. GF animals show impaired development of primary and secondary lymphoid organs, a reduction in CD4 + and CD8 + T cells and an imbalance in the Th1 and Th2 differentiation pathway, in favor of the latter, evidenced by the overproduction of IL-4 and the reduction of IFN-γ production at the splenic level [15]. Most of these alterations can be reversed by colonization with the microflora of conventional animals. Studies conducted outside of mono-colonized animals have shown the specific role of some bacterial species in immunological imbalance. For example, the Th1 to Th2 imbalance was reversed by mono-colonization with Bacteroides fragilis due to the presence of the Polysaccharide A molecule [16]. In addition, GF mice show the absence of Th17 production in the small intestine, which can be restored by the presence of segmented filamentous bacteria (SBF); similarly, the concentration of regulatory T cells (Treg), which is reduced in the colon of GF mice, can be normalized by some colonization of Clostridium species [17]. Even the relationship between effector and regulatory lymphocyte concentrations appear to be controlled by the microbiota, through the production of SCFA and innate signals: rather, TLR9 and TLR5 knock-out mice show an increase in regulatory lymphocytes, associated with the reduced response of cytokine effector [18]. The microbiota is also involved in the activation and differentiation of B cells: although the total number of B cells in GF mice is comparable to that of conventional mice, fewer B cells in the small intestine, producing IgA and IgG1, can be detected and this condition can be restored to normal by the conventionalization of the flora [19]. Recently, the involvement of the microbiota in the differentiation of regulatory B cells (Breg) in the spleen and mesenteric lymphonoids has also been demonstrated [20].

Innate immunity is also influenced by the intestinal microbiota. The local and systemic concentration of metabolites produced by the microbiota seems to influence the development of the myeloid compartment in the bone marrow, guiding its

differentiation and functions, and the lymphoid arm of innate immunity with different mechanisms [21], as widely reviewed. In several animal models GF, macrophages and dendritic cells, as well as intestinal epithelial cells and ILC (innate lymphoid cells), both in their cytotoxic and non-cytotoxic subgroups, show alterations in number and/or function [22]. The microbiota has also been involved in the modulation of epigenetic changes in mammals: for example, through the production of diet-dependent (SCFA vitamins and polyamines) or independent (lipopolysaccharide and peptidoglycan) substances, the microflora is able to inhibit or activate enzymes, influencing the epigenetic state of whole organism. For example, SCFA has been shown to inhibit histone deacetylase, can reduce the production of interferon-γ [23] and increase naive CD4 + T cells and Treg cells [24].

Autoimmune disorders of the thyroid gland

Autoimmune thyroid disorders are the most common organ-specific autoimmune diseases, involving about 5% of the world population [25], with Hashimoto's thyroiditis (HT) being the most prevalent. Although the factors underlying the genesis of HT have not been fully clarified, it is now certain that the disease derives from the interaction of a predisposed genotype with endogenous and environmental triggers. The contribution of these problems in the pathophysiology of HT is not fully elucidated, but studies on sibling patients, as well as on monozygotic and dizygotic twins, support a relevant genetic influence on the development of the disease [26]. Environmental factors include: iodine consumption [27], the use of certain drugs, such as α-interferon [28], lithium [29] or immune checkpoint blocking molecules [30] and vitamin D deficiency [32]. A role of Yersinia enterocolitica and Helicobacter pylori infections have been hypothesized in the pathogenesis of thyroid autoimmunity, but only HCV infection, so far, has been associated with an increased risk for the development of Hashimoto's thyroiditis [32]. Among endogenous factors, female sex [33] and polymorphism of the vitamin D receptor gene are involved [34].

Studies on genetic predisposition have revealed that both thyroid-specific polymorphisms and immune-regulatory genes may be involved in the onset of autoimmune thyroid disease. Polymorphisms of single nucleotides of TSH receptor [35] and of the thyroglobulin molecule [36] have been associated with HT, as they can increase their self-antigenic potential or due to the variation of their expression at the thymic level, thus reducing central tolerance towards them. Concerning the immuno-regulatory genes, alongside correlation with specific HLA class II haploids, which present antigens for recognition by CD4 + T helper cells, the involvement of CTLA-4 and PTPN-22 has been demonstrated [37]. These genes regulate certain characteristics of the immunological synapse, namely the presentation of the antigen, bound to HLA molecules, by presenting TCR antigen (T cell receptor) cells on T lymphocytes. Furthermore, the polymorphisms of IL2RA and FOXP3, genes pivotal in peripheral tolerance, mechanisms mediated by regulatory T lymphocytes, have been linked to the development of HT [38]. Recently, the hypothesis of post-transcriptional or post-translational events in the genesis of HT has been proposed: recent studies have focused on epigenetic modifications, such as methylation and histone modifications of DNA, as well as abnormal expression of microRNA and RNA long non-coding [39]. All these factors are actors in the regulation of gene expression, in turn involved in the maintenance of immune homeostasis [39].

The combined effect of environmental and genetic factors basically causes loss of tolerance towards self-antigens and determines the activation of T lymphocytes, which can undertake different differentiation paths, depending on the polarization of cytokines. Mainly involved in the genesis of HT are those characteristic pathways of the Th1 and Th17 effector, respectively involved in stimulation of cellular immunity and neutrophilic granulocytes [40]. However, when HT is concomitant with other autoimmune disorders, an in IL-4 percentage increase has also been described [41]. Additional elements of the immune system, involved in the genesis of thyroid autoimmunity, are represented by B and T cells, whose malfunction has been demonstrated in patients with HT [41]. The imbalance between anti- and pro-inflammatory effector cells is in favor of the latter, resulting in the collapse of self-tolerance and in direct attack from T lymphocytes to thyrocytes. Inflammation of the gland can result from the exposure of normally hidden antigens to which specific autoantibodies are produced, but not necessarily pathogens.

Intestine, microbiota and thyroid function:

The link between thyroid function and gastrointestinal system has been known for some time: T3 is considered one of the most important regulators of the development and differentiation of epithelial cells of the intestinal mucosa [42]. Clinically, the change in blood concentration of thyroid hormones is responsible for gastrointestinal symptoms, as evidenced by frequent gastrointestinal disturbances documented in the hypo- and hyper-function of the gland [43]. This effect may be due to the alteration of neuro-motor function of the gastrointestinal tract, which is expressed in different speed of propagation of the concentration in the musculature intestinal and in the possible edema of the muscular layer, due to the local infiltration of glycosaminoglycans [44]. Conversely, more recent studies have shown that changes in thyroid function may affect the intestinal microbial population. In particular, a study conducted in 2007 showed that, subjects with hypothyroidism have a greater chance of developing bacterial overgrowth of the small intestine. This can reach a concentration of microorganisms higher than 106 CFU/mL of intestinal aspirate or colonic-type bacteria in the small intestine [45]. This excess of bacteria appears to contribute to impaired gastrointestinal neuromuscular function and consequent gastrointestinal symptoms complained of by patients: in fact, the decontamination obtained, through appropriate antibiotic therapy, led to the improvement of these symptoms [45]. Also hyperthyroidism seems contribute to intestinal dysbiosis [46], such as demonstrated by real-time PCR analysis, a significant reduction of Bifidobacterium e Lactobacillus and an increase in Enterococcus strains in fecal specimens from hyperthyroid subjects, than the euthyroid. Although this problem has been little studied, variations in the composition microbial have been shown to be responsible for changes in thyroid function. The analysis of the radioactive iodine uptake in GF or kanamycin-treated rats, compared to control population, revealed reduced thyroid function in GF rats [47]. A study conducted in 1996 also showed that TSH increased by 25% in GF mice, compared to those with normal intestinal flora [48]. Furthermore, intestinal flora seems to have a role in the recycling and enterohepatic metabolism of thyroid hormones [49]: in fact, both beta-glucuronidase and sulfatase [50], which could lead to intestinal deconjugation and reabsorption of thyroid hormones in small

intestine. Some recent reports have suggested that intestine may also be involved in synthesis of endogenous compounds, such as thyronamine 3-T1AM, a decarboxylate derivative of thyroxine, and diiodiothyronine 3.5T2, a derivative of triiodiothyronine. The key enzymes for their production (isoforms deiodinase and ornithine decarboxylase), in fact, were detected in the wall of the murine intestine [51]. Based on their effects in animal models, has been hypothesized that they may also exert some of the non-genomic effects of thyroid hormones in humans [52]. Some species of microbial flora have been defined as "probiotics", according to their ability to contribute to microbial homeostasis [53]. Few studies have evaluated the effects of probiotic supplementation, reporting an increase in the thyroxine [54] and triiodothyronine [55] level in broilers. Furthermore, a study published in 2014 examined the beneficial effect of Lactobacillus reuterii on thyroid gland homeostasis in mice [56]. In fact, the supplemented mice showed a higher follicular epithelium and a greater mass of the thyroid gland, compared to the age-matched control group. Functionally, these mice showed higher levels of T4 in line with more active behavior and a slimmer shape. It is interesting to note that these beneficial effects on the mouse thyroid are mediated by the action of Lactobacillus reuterii on the production of interleukin-10 and the consequent enhancement of Treg cells: the effects of this integration, in fact, were no longer detectable in mice depleted in CD25+ [56].

Microbiota and thyroid autoimmunity

Similarly to other autoimmune disorders, attention to the link between microbial composition and thyroid autoimmunity has increased more and more. The involvement of dysbiosis in the genesis of inflammatory bowel disease has been well documented. Population variations of the gut microbiota have been reported in inflammatory [57] and autoimmune diseases, involving organs outside the gastrointestinal system. There are several mechanisms that link dysbiosis at the onset of autoimmune disease, such as molecular mimicry [58] from the activation of bystanders [59], and the spread of the epitheus [60]. These phenomena have been studied much more for diseases such as multiple sclerosis, rheumatoid arthritis, type 1 mellitus diabetes and systemic erythematosus lupus [61], but in recent years, alterations in the intestine microbial composition have also been reported in patients with Hashimoto's thyroiditis. Interestingly, ultrastructural morphological changes in enterocytes of distal duodenum were detected in HT patients [62]. In fact, a variation in the thickness of the microvilli and the increased space between adjacent microvilli were observed by examination with a transmission electron microscope [62]. In these patients, intestinal permeability was also assessed by a lactulose/mannitol test: a leaky intestinal condition was diagnosed in this category of patients, compared to the control group [62]. Since greater intestinal permeability allows the passage of toxins, antigens or bacterial metabolites from the intestine to the bloodstream, a role for this condition in the onset of autoimmune thyroid disease has been hypothesized [63].

The possible role of microbiota in influencing susceptibility to autoimmune thyroiditis has been demonstrated since 1988, where conventional and GF, genetically identical rats were compared: the administration of homogenized intestinal contents of conventionalized rats to GF animals increased their susceptibility to experimental autoimmune thyroiditis. This discovery suggested the importance of environmental factors, namely the intestinal microbiota, in the pathogenesis of this disease [64]. It should be noted that, in an in vitro and in silico study, some components of specific strains of the genera Bifidobacterium and Lactobacillus share amino acid sequences with thyroid peroxidase and thyroglobulin and selectively bind human autoantibodies [65]. On the contrary, a study in mice has shown that daily ingestion of probiotics Lactobacillus rhamnosus HN001 and Bifidobacterium Lactis HN019 does not induce or help in the development of experimental autoimmune thyroiditis [66].

The implications on man:

The gut microbiota [67,68,69] shapes the thyroid mainly through the following microbial mechanisms:

- Dysbiosis damages the intestinal barrier and increases intestinal permeability, allowing antigens (molecules recognized as foreign by our immune system) to pass into circulation and activate the immune system;
- Circulating antibodies can react with the bacterial antigen and enhance the activation of inflammasome (the inflammasome is a cytoplasmic intracellular signaling multiprotein complex which is known as a mediator of innate immunity, i.e. of that natural immunity not specific that is present from birth and is the body's first immune defense barrier, responsible for the inflammatory response to infections and diseases) in the thyroid gland. Some scientists demonstrated that the expression of the inflammasome in patients with Hashimoto's thyroiditis was significantly increased and that it can be regulated by the intestinal microbiota and its metabolism;
- Short-chain fatty acids (SCFA), metabolites of the fermentation of commensal bacteria in dietary fiber, are hypothesized to play a crucial role in development, functioning and modulation of immune system.

Recently, many researchers [70,71,72,73] have observed that patients with Autoimmune Thyroid Disease (AITD) have a reduction in the so-called α diversity (diversity that takes into account the number of species in a more or less uniform small area) and an abundance of some microorganisms compared to to the patients considered who were not affected by AITD. Furthermore, the current results have revealed the correlation between the clinical parameters of AITD, such as TRAb (Anti TSH Receptor) or TPOAb (Anti-thyroid peroxidase antibodies) and the microbiota.

For example:

- Some researchers found that the proportion of Synergistetes (a phylum of anaerobic bacteria) was negatively correlated with TRAb;
- Other researchers found that the Lactobacillus genus of bacteria was positively correlated with TRAb;
- Regarding the phylum (i.e. the type), some researchers found a higher ratio of intestinal bacteria.

Firmicutes/Bacteroidetes in patients with Graves'disease (GD) than in the control group, which may be relevant for inflammatory disease; while other researchers found that the ratio was significantly decreased in AITD patients.

To better understand the potential role of the gut microbiota in pathogenesis of Autoimmune Thyroid Disease, a meta-analysis70

was performed to evaluate the alteration in the microbial population between patients with Autoimmune Thyroid Disease and healthy controls (i.e. people who did not have autoimmune thyroid disease).

Thanks to the development of 16S ribosomal RNA gene sequencing technologies, significant alterations in the abundance and composition of the gut microbiota have been found between AITD and healthy controls, suggesting that the gut-thyroid axis may play a pivotal role in the development and in the progress of the AITD.

Although Hashimoto's thyroiditis (HT) and Graves' disease (GD) [74,75] are considered the two most common forms of Autoimmune Thyroid Disease (AITD), the pathogenesis and hallmark of Hashimoto's and Graves' disease are quite different. The hallmark of Hashimoto's thyroiditis is the high rate of Ab-TPO and Ab-TG, while the hallmark of Graves' disease is a high level of Ab-TR.

Furthermore, the alteration of some compositions of the intestinal microbiota can be different in Hashimoto's thyroiditis and Graves' disease. For example, the richness species index was significantly elevated in samples from patients with Hashimoto's thyroiditis while it was low in patients with Graves' disease. Richness species is an important feature of ecological composition and structure of microbial community.

Autoimmune Thyroid Disease is linked to intestinal microbiota dysbiosis through several mechanisms, such as: bacterial overgrowth, hyperactivation of the inflammasome, increase in intestinal permeability, alteration of microbiota metabolities and immune homeostasis. However, the mechanisms of the gut-thyroid axis [76,77] complex have not been fully elucidated.

Firmicutes and Bacteroidetes are the main microorganisms that predominate as regards, from a taxonomic point of view, the type. Traditionally, the relationship between Firmicutes and Bacteroidetes has been implicated in the predisposition of pathological conditions. In this meta-analysis, the relationship of Firmicutes and Bacteroidetes in patients with Autoimmune Thyroid Disease showed a lower level than their healthy counterparts.

Furthermore, patients with Autoimmune Thyroid Disease (AITD) showed a noticeable alteration in composition of gut microbiota compared to controls. A 'random effect model' indicates that people with AITD showed a significantly increased relative abundance of pathogenic bacteria and a reduced percentage of beneficial bacteria such as Lactobacillus and Bifidobacterium. The latter could be used as probiotics to modulate immune response without negative effects on development of an experimental mouse model of autoimmune thyroiditis [78]. Furthermore, Lactobacillus has been shown to protect TH17 cells and support the integrity of the barrier by secreting IL-22 cytokines and pro-inflammatory IL-17cytokine. The Th17/Treg imbalance can cause inflammatory disorders, indicating that Lactobacillus participates in the balance of the immune system. Overall, Bifidobacterium and Lactobacillus have shown anti-inflammatory effects and protect our body from pathogens.

Furthermore, the increase in Bacteroides fragilis species can explain the upregulation of the IL-18 cytokine, IL-1β and caspase-1 by promoting the inflammatory response. Furthermore, B. fragilis can activate the expression of the NLRP3 inflamosome, which has been found to be over-expressed in patients with Hashimoto's thyroiditis. However, the interaction between intestinal microbiota and inflammasome is not yet clear.

In conclusion, there is a reciprocal influence between the microbiota composition and thyroid homeostasis [79], but the evidence still emerges only from animal studies, in humans this has not been fully characterized.

Another reasonable hypothesis of the role that the microbiota plays in the advancement of AITD is molecular mimicry. The antigenic properties of the proteins of some intestinal bacteria can bind Ab-TPO and Ab-TG, which are the main clinical diagnostic parameters of Autoimmune Thyroid Disease.

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