GUT—the Trojan Horse in Remote Organs’ Autoimmunity

Aaron Lerner¹,² and Torsten Matthias²
¹B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
²AESKU-KIPP Institute, Wendelshiem, Germany

Accepted date: March 22, 2016

Abstract

Human beings assemble and maintain a diverse but host-specific gut microbial community along the longitudinal axis of the intestines. Helped by a functional tight junction, the default response to commensal microbes is tolerance, whereas the default response to pathogens is an intricately orchestrated immune response, resulting in pathogen clearance. Nutrients and industrial food additives were suggested to impact the intestinal ecosystem and to breach tight junction integrity. Taken together, certain nutritional components, increased intestinal permeability, disease specific dysbiotic pathobionts and their capacity of post translation modification of proteins, are luminal events that impact autoimmunogenesis. The present review expands on the multi gut originated axes and their relationship to remote organ autoimmune diseases. Brain, joint, bone, endocrine, liver, kidney, heart, lung and skin autoimmune diseases are connected to the intestinal luminal compartmental deregulated events to form the gut-systemic organs axes.

Keywords: Gut; Intestine; Autoimmune disease; Microbiome; Nutrient; Intestinal permeability; Post translational modification of protein; Gut-axis

Introduction

Material and methods

A PubMed search was performed using the following search words: gut, intestine, autoimmunity, autoimmune disease, incidence, microbiome, nutrient, intestinal permeability, leaky gut, post translational modification of protein, gut-axis, spanning the period 2000-2015.

Special emphasis was given to identify manuscripts that dealt with the various gut-remote organs (brain, joint, bone, thyroid, pancreas, endocrine, liver, kidney, heart, lung and skin) axes. Suitable publications were identified by screening PubMed, Google, and the Cochrane Library databases. Original papers, in the English language, especially those on the gut ecosystems’ events involved in the local autoimmune processes and peripheral organs autoimmunity, were identified. Entities were validated and used when directly stating at least one of the above mentioned key word indices.

The surge in ADs incidence

Autoimmune diseases (ADs) are spreading worldwide. Epidemiological data provide strong evidence of a steady rise in ADs throughout westernized societies over the last five decades [1]. In fact, the rise in ADs mimics the surge in allergic and cancerous conditions while infections are less frequent at least in the Western societies, creating the basis for the hygiene hypothesis [2]. Multiple sclerosis, type 1 diabetes, inflammatory bowel diseases (mainly Crohn’s disease), systemic lupus erythematosus, primary biliary cirrhosis, myasthenia gravis, autoimmune thyroiditis, autoimmune hepatitis, rheumatic diseases, bullous pemphigoid, and celiac disease (CD) are several examples [1,3-5]. Geoepidemiologically, their relationship to socioeconomic status, their rapid increase in developed countries, the selected populations migrating from under developed to the westernized territories and the relatively low concordance rate for most of the ADs between monozygotic twins, indicate some form of environmental impact, rather than long-term genetic influences which are driving these recent evolutionary processes [1-6]. Such rapid change invokes a causal role for environmental factors associated with modern life-improved public health, use of antibiotics in medicine and agriculture, and changes in diet. This view is corroborated by the striking increase of autoimmune diseases in recent decades, whereas the genetic basis in affected populations has remained arguably constant [2]. It seems that the lifestyle of humans has changed so rapidly that the human genetics have been unable to catch up.

Among many others, three major environmental factors, strongly related to socioeconomic status are suspected to drive these phenomena: infections, ecology and nutrition. At the same time, profound environmental changes such as global warming, urbanization, air pollution, novel food additives, nutrient engineering and food processing technologies, dietary habits and ageing populations, are suspected to drive this surge. The present review will not deal with the multifaceted interrelationship between AD and infections or environmental ecology [1,7], but will expand on the cross-talks between the nutrients, dysbiotic modification of peptides, tight junction performance, putting the human gut in the center of systemic autoimmunogenesis. More specifically, aiming to describe the multiple gut-organs axes, which spread the consequences of the intestinal nutritional-microbial-immunogenic events, seeding autoimmunity in remote organs.
Nutrients and autoimmunity

Nutrients are only a part of the exposome that human body is facing. The human intestine has to cooperate with 100 mg of foreign protein ingested per day and with trillions of luminal microorganisms. During evolution our mucosal and systemic immune systems learned to discriminate between harmful invaders while remaining tolerant to potentially harmful antigens such as food proteins. However, when this equilibrium is breached, tolerance is affected, paving the way for immune dysregulations resulting in autoimmunity. The association between diet and the risk of developing ADs was proposed half a century ago and was reviewed lately [8,9]. Despite our increasing knowledge, little is known about the interplay of diet and gut microbiota in human immune-mediated diseases. Dietary milk, carbohydrates, fats, protein, fiber, fruit, vegetables or animal proteins have been studied as potential etiological factors in IBD. Cow milk, fruit and berry juices, and n3-PUFA were studied in T1D. MS incidence was positively associated with the consumption of milk, animal fat and meat, total energy intake and resulting obesity. Comparable pattern of dietary risk factors was also suggested by RA. Nevertheless, the majority of studies have been equivocal or circumstantial and do not yet support any of these macronutrients as causal factors [9]. Several more specific nutritional factors like; vitamin A, D, selenium, zinc, omega-3 fatty acids and flavonols were associated with immune responses involved in ADs [9]. Like mentioned above, the exact role of diet as a risk factor in these conditions is less clear-cut. Even the more beneficial nutrients like polysaturated fatty acids, plant fiber, fish oils or the intake of vegetables and fresh fruits are far from establishing causality in ADs’ prevention or therapy [8,9]. It seems that the nutritional exposome is far from explaining human reactome. Most recently, the hypothesis that changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of ADs was forwarded [3]. In fact, glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles, extensively and increasingly used by the food processing industries, are breaches of the intestinal tight junction integrity. The leaky gut as discussed below, is a well-known pathway that drives not only allergy, but also systemic autoimmunity [10].

The microbiome and autoimmunity

A mass of 1-2 Kg, numbering 100 trillion and possessing 100 times the human gene number, is the microbiome profile. Intricate host-microbe symbiotic relationships in the human gut have evolved during the long-term coevolution between the two. It resulted in fine-tuned inter-Kingdom molecular adaptations that benefit both sides, in an ideal symbiotic way [11]. This led to remarkable co-dependence and blurred the distinction between self and non-self. Advantages for the host organism include metabolic, nutritive, structural, protective and other immune beneficial functions exerted by the commensal microbiota. It processes food, digests complex host-indigestible polysaccharides, protects against pathogen invasion, performs essential metabolic functions, delivers essential nutrients, vitamins and energy to the host and activates immune, enteric nervous and enteric-endocrine gut mucosal systems. The contribution of commensal microbiome for development and functioning of the host immune system is also well recognized [12]. Recent studies show that the complex communities of commensal species that occupy our mucosal tissues influence not only the development and homeostasis of the host’s immune system but also confer susceptibility to immune-mediated disease. Alterations in the fine-tuned but fragile microbiome-host relationship can result in community inhabitant change, whereby the dysbiota is overriding the microbiota, setting the stage for immune dysregulation and potential autoimmunogenesis [13-15]. Multiple animal models of human ADs suggest a direct involvement of the commensal microbiota, when invaded with the pathogenic dysbiota, in disease development. Under germ-free conditions no disease is developing in the animal models of inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis, supporting the notion of “no bags, no disease”, while in some others they are only attenuated [16]. Causality is strengthened by the reintroduction of specific pathbiont restoring the AD severity. Most recently, we reviewed the microbial species used in defined animal models of specific ADs and their functions [17]. Some of them are associated with human ADs [17] even though, established causality is far from being substantiated.

Evidence exists that certain microbes and their products regulate the differentiation of multiple subsets of lymphocytes like Th17, T regulatory, iNKT and B cells and modulate immune responses at mucosal tissues that contribute to tissue-specific autoimmunity in genetically susceptible individuals [12].

Several mechanisms of the microbial involvement in the promotion of autoimmunity have been suggested [18]. Molecular mimicry, bystander activation during infection, or the “amplification of autoimmunity by cytokines” elicited by microbial activation of professional antigen-presenting cells and the innate lymphoid cells to produce proinflammatory cytokines by T cells. The fourth suggested mechanism, involving the dysbiota originated post translational modification of protein (PTMP), generating various neo-epitopes, will be discussed in the next paragraph.

Intestinal post-translation of peptides and autoimmunity

The immune system carefully distinguishes between self and non-self-components. Therefore, any small deviation of this balanced function may result in an autoimmune activity and harm against self-antigens (autoantigens). One of the ways to transform self-tolerated antigen to non-self autoantigen is PTMP. The microbiota, the dysbiota and the ingested probiota secrete multiple enzymes, the activity of which spans a plethora of chemical and biochemical reactions that can change naïve peptide to a neo-peptide. Peptides crossing, de-amination/deamidation, de/phosphorylation, deacetylation, de/tirosination, de/glutamylation, de/glycylation, ubiquitination, palmitoylation, glycosylation, galactosylation, arginylation, methylation, citrullination, sumoylation and carbamylation are some examples of PTMP taking place in the intestine [17]. The spectrum and activities of enzymes, which are normally involved in PTMPs, become biased when the intestinal microbiota ecosystem is replaced by dysbiotic microbial communities. Two well established examples are given, demonstrating how these activities may affect PTM of host proteins thus generating new aberrant epitopes. These novel, non-self-epitopes may generate host autoimmune responses and trigger autoimmune diseases. In CD, the autoantigen is tissue transglutaminase (tTG), capable of deamidating or transamidating gliadin peptides [19,20]. The result is neo-epitopes of gliadin docking on the tTG, inducing anti-tTG or anti neo-epitope tTG autoantibodies. These are the well-known serological markers of CD [21,22]. More recently, a family member of tTG, the microbial Tg that is heavily used in the food industry, has been shown to induce specific antibodies in CD patients [3,4,23]. Interestingly, the same food additive has been suggested as a new environmental trigger and potential inducer of CD.
[4,23]. The second example is rheumatoid arthritis, where citrullination is a major posttranslational modification of arginine, which converts naïve peptides into the immunogenic neo-epitopes. This PTMP constitutes the basis for the specific prediction of disease activity due to the production of anti-citrullinated protein antibodies [24]. Recently, it has been suggested that infectious agents that release toxins such as lipopolysaccharides at mucosal surfaces may trigger the inflammatory response with a potential to cause citrullination of various proteins such as fibronectin, fibrinogen and collagen [25].

The PTMP contribute substantially to the adaptability, cell cycle regulation and survival of the microbes [26]. On the other hand, the microbial PTMP has a paramount pathogenic potential to the host. Their enzymatic machinery is capable to transform naïve self or non-self-peptides to autoimmunogenic one, as shown in CD and rheumatoid arthritis.

The leaky gut and autoimmunity

Increasing evidence, both functional and morphological, supports the concept of increased intestinal permeability as an intrinsic characteristic of several ADs in both humans and animal models of the disease. Often referred to as a ‘leaky gut’, its mechanistic impact on the pathogenesis of ADs remains unclear. Is it a cause, consequence or co-evolutionary phenomenon? [10,27-29]. Data is accumulating that intestinal luminal environmental factors might perturbate the regulatory mechanisms of the tight junction, resulting in a leaky gut thus breaking equilibrium between tolerance and immunity to non-self-antigens. Nutrients, toxins, allergens, carcinogens, intestinal infections, dysbiotic bacteria, drugs and stress and the recently described industrial processed food additives, can breach the tight junction integrity [3,4,7-10,12,13,15-18,23,24,28,29]. In fact, TJ dysfunction seems to be a primary defect in AD [28-30]. Intestinal permeability is increased in many AD: Ulcerative colitis, Crohn’s disease, CD, inflammatory joint disease, ankylosing spondylitis, juvenile onset arthritis, psoriatic arthritis, type 1 diabetes mellitus and primary biliary cirrhosis. The end result of the passage of those non-self-proteins, from the luminal compartment to the subepithelial one, initiates the autoimmune cascade. The richness of the mucosal milieu in immune components, cells and systems, blood and lymphatic vessels, entero-neural and endocrine network and muraledomesoderm cohabitation, constitute an ideal place to initiate, maintain and propagate the autoimmune cascade.

The mucosal committed immune cells, post translation modified proteins, proinflammatory cytokines and lymphokines have the capacity to circulate via the local vessels, to bring the autoimmune message to remote organs, thus creating a gut-extraintestinal organ axes. Following are some capsular summaries on gut-organ axes.

Gut-human Organs Axes and Autoimmunity

**Gut-brain axis**

The fields of bacteriology, mucosal and systemic immunology, brain and gut neurology, intestinal endocrinology and nutrition are rapidly converging. Bugs, guts, brains and behavior were once believed to be separate territories clinically and scientifically. However, recent observations in our understanding of the microbiome indicate that the boundaries between domains are becoming permeable. The cross-talks and communications are multidirectional: Biological systems are operating simultaneously in a vastly complex and interconnected net [31]. The Microbiota-brain interaction is bidirectional, namely through signaling from the gut microbiota to brain and vice versa by means of neuronal, endocrine, metabolomic, immune and humeral links. Most of the data were acquired using microbial challenged germ free animals, probiotics, antibiotics, infections and specific disease animal models [32-35]. They suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition, memory, learning, pain, sleep, hunger/satiety, emotional, exploratory, stress and eating behaviors. In clinical practice, evidence of microbiome-brain interactions comes from the associations between dysbiota and the central nervous system disorders like: autism, anxiety, depression (melancholic microbes), schizophrenia, multiple sclerosis, neuromyelitis optica, Guillain-Barre syndrome, meningitis, chronic fatigue syndrome, and most lately Parkinson’s disease [32,36-38]. Even functional gastrointestinal disorders, like irritable bowel syndrome or non-celiac gluten sensitivity, can be considered an example of the disruption of these complex relationship [32,39,40].

Several mechanistic pathways were suggested to explain the cross-talks in the gut-brain axis [32,35,41-44]:

**From gut microbiota to brain:** Production, expression and turnover of neurotransmitters (i.e. serotonin, GABA), neurotrophic factor (BDNF), enterocoeuronic peptides (cholcystokinin, glucagon-like peptide-1, peptide YY), cytokines, tryptophan metabolites and bacterial-derived cell wall components (peptidoglycans), protection of intestinal barrier and tight junction integrity, maturation, activation and regulation of the microglia (the brain-gut macrophages), the bacterial metabolome/proteome (SCFA) and mucosal immune regulation.

**From brain to gut microbiota:** Alteration in mucus and biofilm production, alteration in gut motility, alteration of tight junction performance and intestinal permeability, alteration in immune functions, the newly discovered meningeal lymphatic system relaying peripheral immune system and brain.

In summary, understanding the microbiome-gut-brain axis will entail fleshing out the mechanisms by which transduction across each domain occurs, allowing us ultimately to appreciate the role of commensal and dysbiotic organisms in shaping and modulating host brain functions and human behavior. It seems that over 100 years has elapsed since Metchnikoff, founded the microbiota and today’s knowledge of those biota regulating our brain and life, have come together.

**Gut-joint axis**

Multiple observations strengthen the gut–joint axis in rheumatologic and gastrointestinal diseases. It appears that autoimmune inflammation starts in the gut mucosa, years prior to the onset of detectable joint manifestations suggesting that rheumatoid arthritis and spondyloarthritis are a gut initiated inflammatory state [45-47]. Gut inflammation is associated with age, sex, disease activity and degree of MRI inflammation on sacroiliac joints, and is predictive for disease course, therapeutic decision-making and prognosis [46,47]. Except for epidemiological similarities between gut and joint conditions, IBD shares dysbiotic similarities with spondyloarthritis. Decreased numbers of *Firmicutes*, a major phyla of gut commensals, especially the species *Faecalibacterium prausnitzii* and *Clostridium leptum* have been found in the two conditions and could be an important link in the gut–joint axis. Multiple studies in ankylosing spondylitis, psoriatic arthritis, juvenile spondyloarthritis, and animal
models of spondyloarthritis reveal common microbial associations among these diseases as well as IBD [48].

Specific alterations in gut bacteria have been shown to enhance or attenuate susceptibility to experimentally induced arthritis and, in humans, increased relative abundance of various microbes in rheumatoid arthritis/CD and spondyloarthropathy/IBD patients have been detected [45,46]. Taking in account common dysbiota, the wide potential of luminal PTM of naïve peptides, the increased intestinal permeability and the multiple communications between the gut and joints by the blood vessels, one can foresee how the two compartments are interrelated [45].

Several mechanisms may be involved in the breaking of tolerance to self-antigens at the intestinal mucosa initiating rheumatologic manifestations in gastrointestinal condition or participating in rheumatologic disease [45,49]:

1. Toll-like receptors, part of intestinal innate immunity, triggered by endogenous nuclear material abnormally released during cell death, are associated with induction of autoimmunity. Anti-tTg antibodies are known to decrease apoptosis clearance and apoptosis generates citrullinated endogenous protein in CD and rheumatoid arthritis, respectively.

2. Mucosal microbial constituents can lead to inflammation by molecular mimicry, generating autoantibodies.

3. Migrating mucosal neutrophils may induce tissue citrullination, induced by local peptidylarginine dieminas (PAD).

4. Activated neutrophil extracellular traps (NETs), can generate anti protein citrullinated antibodies via release of citrullinated peptides.

5. Any local factor may lead to an altered balance between autoreactive and regulatory T cells.

6. Elevation of rheumatoid factor, even in the absence of arthritis, is associated with mucosal inflammation.

7. Emerging evidence indicates that blockade of TNF-α by biologics not only ameliorates rheumatoid inflammation, but can affect the secretion and action of gut hormones on appetite, body composition, energy expenditure, muscle catabolism and bone remodeling. A link between the gastrointestinal endocrine axis-immune system and joints may be established through the interaction of proinflammatory cytokines, including TNF-α and gut hormones. [50,51]

8. Additionally, some immunological pathways may be actively involved in the transition of autoimmunity from the intestinal mucosa to the joint: Citrullinated immune complex formation deposition, shared antigenic targets (tTg) in the joint or intestinal (PAD), gut- joint epitope spreading, and migration of activated effector T cells from the gut to the joints, mimicking mucosal vaccine's effects on remote organs. Very recently, citrullination of the epithelial neutrophil-activating peptide 78/CXCL5 chemokine, resulted in activation of the monocyte-recruiting chemokine [52]. In fact, epithelial neutrophil-activating peptide 78/CXCL5 is expressed in intestinal inflammation, citrulline is preferentially synthesized in the gut epithelium and PADS reside in the local microbiome and the intestinal mucosa. This may explain how mucosal citrullinated chemokines recruit monocytes to inflamed joint tissue. Most recently, IL-17 and IL-22 were suggested to bridge between the gut and synovial fluid in ankylosing spondylitis [53].

The relation between food additive (like: mTg) and CD induction [4] is strengthened by the observation that the production of cross reactive antibodies is strikingly increased in the gut of many rheumatoid arthritis patients. Their food related problems might reflect an adverse additive effect of multiple modest hypersensitivity reactions mediated, for instance, by food originated immune complexes promoting autoimmune reactions in the joints [54].

**Gut-bone axis**

Most recently the gut- bone cross talks were summarized in relation to CD [55]. Presently, the review will expand to other gastrointestinal diseases, bone health and common dominators between the two. Gastrointestinal diseases that affect bone are CD, IBD, particularly Crohn's diseases and cystic fibrosis, where bone loss is indisputable.

The etiologies, mechanisms and the gut-bone cross-talks are multifactorial and encompass a variety of domains [55-59]:


2. Secondary Hyperparathyroidism

3. Lower nutritional intake on gluten free diet, mainly of dairy products and lactose containing nutrients. It should be mention that calcium absorption is enhanced by lactose.

4. Systemic inflammation or any gastrointestinal inflammatory state, where pro-inflammatory mediators impact bone density. Examples of such mediators are: TNF-α, IL-1-β, IL-6, YTF, RANK, RANKL and osteoprotegerin

5. Epidemiological influences like: advanced age or menopause, female gender, familial history and reduced BMI might decrease bone density.

6 Life style parameters like: Smoking, low physical activity, increased alcohol consumption are detrimental for bone health

7. Therapeutic drugs like steroids and anti-TNF biologicals.

8. The gut peptide PYY was found to be critical for the control of bone remodeling [60].

9. Interestingly enough the autoantigen of CD, the tTg enzyme, was implicated in pro-mineralization activity on osteoblasts [61] and participates actively in bone erosion and arthritis induction [24].

While research in this field is limited, findings from preclinical studies support that gut microbes positively impact bone mineral density and strength. Moreover, administration of beneficial bacteria in preclinical models has demonstrated higher bone mineralization and greater bone strength. The preferential bacterial genus that has shown these beneficial effects in bone is Lactobacillus. However, their effectiveness is dependent on stage of development, as early life constitutes an important time for impacting bone health, perhaps via modulation of the intestinal microbiome. In addition, sex-specific difference also impacts the efficacy of the probiotics [62]. The gut-bone axis is mediated by nutrition since a gluten free diet modestly improved bone mass density with lower impact fractures, in CD patients [63].

**Gut-endocrine axis**

Considering the ability to impact function of distal organs and systems, in many aspects, the gut microbiota resembles an endocrine...
organ [64]. Although generally overlooked in the field of endocrinology, gut microbial symbionts are a key endocrine organ that converts nutritional cues from the gut lumen into hormone-like signals that impact both normal physiology and chronic disease in the human host. Several observations strengthen the endocrine impact of the microbiota. In germ free rodents a lower iodine uptake by the thyroid and hyporesponsiveness toward epinephrine, norepinephrine and vasopressin is observed. The microbiome, using its bile acid hydrolyses modulates cholesterol, glucose and lipid metabolisms. By its fermentation capabilities it induces short-chain fatty acids (SCFAs) like: butyrate, propionate and acetate production, glucagon-like peptide 1, peptide YY and ghrelin productions. By β-glucuronidases action it activates dopamine and norepinephrine. By its decarboxylation capacities, it induces Y-a-minobutyric acid (GABA), Tyramine and β phenylethylamine productions [64]. Manipulation of the microbiota composition modulates plasma concentration of tryptophan, an essential amino acid and precursor of serotonin, a key central and enteric neurotransmitter.

Moreover, recent evidence indicates that the microbiome can affect the development and regulation of the hypothalamic-pituitary-adrenal axis and behavior. In contrast, host-derived hormones increase the bacterial proliferative capacity and pathogenicity. In the gut lumen, this type of cross-talk between microorganisms and the host is presumed to be performed continually through various kinds of luminal molecules [65,66]. Dopamine, norepinephrine, nitric oxide and the inhibitory transmitter GABA are few examples of our own gut microbiota generating compound that interact with our own endocrine system and can be called the microbial endocrinology [64-66].

Special attention should be allocated to gut-microbiota-type 1 diabetes inter relationship. Dietary interventions, alterations in the intestinal microbiota and exposure to enteric pathogens, regulate the development of autoimmune diabetes in animal models. Early diet could modulate the development of beta-cell autoimmunity: weaning to hydrolyzed casein formula decreased the risk of beta-cell autoimmunity by age 10 in the infants at genetic risk. Increased gut permeability, intestinal inflammation with impaired regulatory mechanisms and deregulated oral tolerance have been observed in children with type 1 diabetes [67]. Even though data are still inconclusive, there are strong indications that gut microbiota dysbiosis plays an important role in T1D development and evidence from animal models suggests that gut microbiota manipulation might prove valuable in future prevention of T1D in genetically susceptible individuals [68].

The connectivity of the gut-endocrine autoimmune axis is further enforced by the most recent observation that among patients with T1D, CD is a risk factor for the later development of autoimmune thyroid disease [69].

At the end of the day, the gut, brain, endocrine and immune systems cross talk and constitute an interconnected net of the gut-brain-hypothalamic-pituitary-adrenal-immune axis [66,70].

**Gut-liver axis**

Alterations in the microbiome population and/or changes in gut permeability promote microbial translocation into the portal circulation. Danger signals derived from the microbiome trigger the inflammatory cascade and activate immune cells. Liver and spleen, flooded by portal blood, are the organs that help in removing bacterial toxins and their lipopolysaccharides [LPS] from the blood. It was found that gut derived LPS played a significant role in several liver diseases. Lu et al. observed an increase in inflammatory responses as there was attrition of the protective ability of the liver to detoxify LPS derived from the gut [70,71]. A positive correlation between liver dysfunction and bacterial translocation has been reported, and in the gap between the gut ecosystem and the liver, the gut microbiota is altered (bacterial overgrowth) and the intestinal tight junction integrity is compromised, in chronic liver diseases [72]. The increasing energy extraction in some dysbiotic conditions or small intestinal bacterial overgrowth, specific gut microbiota and/or a "low bacterial richness" play a role in obesity, metabolic syndrome, and fatty liver. In non-alcoholic fatty liver disease, in face of a damaged intestinal barrier, the gut-liver axis may enhance the natural interactions between intestinal bacteria/bacterial products and hepatic receptors (e.g., toll-like receptors), thus promoting the following cascade of events: oxidative stress, insulin-resistance, hepatic inflammation, and fibrosis [73]. In the case of established liver cirrhosis, plasma endotoxin levels have been admitted as a surrogate marker of bacterial translocation and close relations of endotoxemia to hyperdynamic circulation and portal hypertension, multiple organs disturbances have been reported. Bacterial overgrowth, increased intestinal permeability, failure to inactivate endotoxin, activated innate immunity are all likely to play a role in the pathological states of bacterial translocation and enhanced inflammation, resulting in a cirrhotic state [74]. Very recently, a protective effect of salvianolic acid B on a non-alcoholic fatty liver diseased rat liver through restoring intestinal mucosal barrier function, was described [75]. Understanding the pathophysiology might enlighten new therapeutical avenues to combat those devastating conditions.

**Gut-kidney axis**

The gut-kidney connection involves the altered microbial landscape in the intestine that contributes to dysmetabolism and inflammation in chronic kidney diseases. Endotoxin derived from gut bacteria incites a powerful inflammatory response in the host organism. Furthermore, protein fermentation by gut overgrown microbiota generates myriad toxic metabolites, including some uremic toxins like p-cresol and indoxyl sulfate and trimethylamine N-oxide. Disruption of gut barrier function allows translocation of endotoxin and bacterial metabolites to the systemic circulation, which contributes to uremic toxicity, inflammation, immunosuppression and progression of kidney diseases, and associated cardiovascular disease [76,77]. Furthermore, inorganic phosphate is highly controlled by a network of players including vitamin D, PTH, kidney, and the intestine, thus establishes a renal-skeletal-gut axis [78]. Understanding the part of the microbiota and the tight junction performance in this axis will enable novel dietary protein, fiber, prebiotic, probiotic and symbiotic strategies to attenuate the renal deterioration [79].

**Gut-heart axis**

"The way to a man’s heart is through his gut microbiota' [80]. This sentence partially summarizes the gut-heart axis. The human gut microbiota has been identified as a possible novel cardiovascular disease risk factor and dysbiotic profiles have been associated with obesity, type 1 and type 2 diabetes and non-alcoholic fatty liver disease. Flux of metabolites derived from gut microbial metabolism of choline, phosphatidylcholine and l-carnitine has been shown to contribute directly to cardiovascular pathology, providing one explanation for
increased disease risk of eating too much red meat. More so, ingestion of viable microorganisms with the ability to hydrolyze bile salts can lower blood cholesterol, a recognized risk factor. On the other spectrum, plant-based dietary intake promotes a more favorable gut microbial profile. Such diets are high in dietary fiber and fermentable substrate [i.e., non-digestible or undigested carbohydrates], which are sources of metabolic fuel for gut microbial fermentation and, in turn, result in end products including SCFAs [acetic, butyric and propionic acids], gases [CO₂, CH₄, and H₂], heat, and bacterial cell mass [81]. Some SCFAs have been associated with reduced risk of developing gastrointestinal disorders, cancer, and cardiovascular diseases.

The prebiotic consumption has been focused on non-digestible oligosaccharides, specifically inulin-type fructans (i.e., inulin and oligofructose) and galactans (e.g., galacto-oligosaccharides, trans galactic-oligosaccharides), which have been consistently shown to selectively stimulate the growth of bifid bacteria and lactobacilli, resulting in a significant change in the gut micro biota composition and, in turn, beneficial metabolic effects in the host [81]. In fact, it has been suggested that a prebiotic intake of ~5-20 g/d is sufficient to induce a significant increase in colonic micro biota.

Collectively, through both nutrient metabolism-dependent and metabolism-independent mechanisms, the gut microbiome forms a largely overlooked plastic yet resilient endocrine organ that integrates input cues from the diet and interfaces with host to play a role in the pathogenesis of cardiovascular diseases and metabolic disorders [82]. By secreting SCFAs and converting primary bile acids to secondary ones, the micro biota can increase energy expenditure and insulin sensitivity and suppress inflammation. On the contrary, by assisting trim ethylamine-n-oxide liver production, they can enhance atherosclerotic changes, thus inducing myocardial infarction, stroke and death [82]. It seems that the nutrients-microbiota-endocrine-cardiovascular axis is a major pathway that determine human heart morbidity and mortality. Its exploration might bring new nutritional, microbial, metabolic strategies to combat those diseases.

Gut-lung axis

Intestinal symbiosis has been described for a variety of chronic respiratory diseases, such as cystic fibrosis and asthma. In particular, reduction of several so-called probiotic species including Lactobacilli and Bifid bacteria that are generally considered to be beneficial, as well as an outgrowth of potentially pathogenic bacteria is often reported [83]. There is a vital cross-talk between the intestinal and the respiratory mucosal tissues of our body, as exemplified by intestinal complications during respiratory disease and vice versa. Although, mechanistically, this phenomenon remains poorly defined, the existence of the gut-lung axis and its implications in both health and disease could be profoundly important for both disease etiology and treatment [84]. At least in two mouse models the severity of experimental idiopathic pneumonia syndrome was reduced by protecting the integrity of the gut mucosa [85] and dietary fermentable fiber and SCFAs shaped the immunological environment in the lung resulting in decreased severity of allergic inflammation [86].

Several mechanisms are proposed for the regulatory influence of the gastrointestinal microbiota on the immunology of the lung, by Samuelson et al. [86,87]. Microbes in the intestine are sampled by DCs either directly from the lumen or following translocation through M cells to the gut associated lymphoid tissue. A combination of signals from the microbes results in phenotypic changes in the DCs and migration to the draining lymph node. DCs promote the activation of various T cell subsets within the mesenteric lymph nodes and the production of various regulatory cytokines such as IL-10, TGF-β. If, and IL-6. T cell subsets then acquire immune homing molecules (i.e., CCR9, CCR4, and CCR9). Following immune challenge in the airway, cells activated in the gut traffic to the respiratory mucosa via CCR4 or CCR6 where they promote protective and anti-inflammatory responses. In addition, bacterial derived products such as LPS can bind to TLR present on both intestinal epithelial cells and macrophages, leading to the production of various cytokines and chemokine's. TLR activation also includes the expression of NF-kB in macrophages. Production of various bacterial metabolites (e.g., SCFAs) also affect the gut-lung axis, as these products are transported to the lung, where they can alter the levels of inflammation. A twist to the scenario of the intestinal microbiota is the recent discovery of the respiratory microbiota [83]. Understanding how intestinal dysbiosis affects lung health and the cross-talks between the two microbial compartmental ecosystems, represent a big scientific challenge that might impact multiple chronic and acute lung diseases.

Gut-skin axis

More than 70 years ago a gastrointestinal mechanism for the overlap between depression, anxiety and skin conditions was forwarded. The hypothesis was that emotional states might alter the normal intestinal microflora, increase intestinal permeability and contribute to systemic inflammation, and Lactobacillus acidophilus was suggested as a remedy [88]. Many aspects of this gut-brain-skin unifying theory have recently been validated.

A study on 13,000 adolescents showed that those with acne were more likely to experience gastrointestinal symptoms such as constipation, halitosis, and gastric reflux and abdominal bloating [89]. Hypochloredia, intestinal bacterial over growth, increased intestinal permeability, increased intestinal transit time, expansion of intestinal Bacteroides spp and beneficial probiotic therapy, amelioration on omega-3 fatty acids intake, were described in acne [88,90].

Additionally, patients with psoriatic arthritis or with skin psoriasis had a lower relative abundance of multiple intestinal bacteria, mainly of Coprococcus spp. Analysis of their fatty acids revealed low fecal quantities of hexanoate and heptanoate, attesting for a persistent microflora, increase intestinal permeability and contribute to systemic inflammation, and Lactobacillus acidophilus was suggested as a remedy [88]. Many aspects of this gut-brain-skin unifying theory have recently been validated.

Adding to the scenario of the intestinal microbiota, the role of the gut microbiome in the continuum of psoriatic skin and joint's pathogenesis and the associated immune response merits further studies.

Conclusions

Human beings assemble and maintain a diverse but host-specific gut microbial community along the longitudinal axis of the intestines. Discrete bacterial communities form in microhabitats, such as the gut lumen, colonic mucus layers and colonic crypts [93]. Helped by a functional tight junction, the default response to commensal microbes is tolerance, whereas the default response to pathogens is an intricately orchestrated immune response, resulting in pathogen clearance.
However, due to genetic background and changing environment, the physiological microbiota can turn to dysbiota inducing major alterations in gut ecosystem. Presently, despite not dealing with the genetic susceptibilities for ADs, the genetic background is a major factor in their induction and progression. However, it is obvious that the rapidly changing environment impact ADs susceptibility much more, in the last decades [1,2]. The nutrients intake and the ability of the gut microbiota and oral probiotics to influence systemic inflammation and even mood itself, constitute the basis for the present multiple gut-autoimmune axes update. Figure 1 present schematically, the multiple gut-brain, joint, bone, endocrine, liver, kidney, heart, lung and skin axes. Centered by the intestinal ecosystem with nutrients, microbiota/dysbiota and their PTMPs capacity and the leaky gut, multiple arrows are directed to the corresponding organs, detailing some examples of corresponding ADs.

The scientist and philosopher Goethe is quoted as saying "everything has been thought of before, but the difficulty is to think of it again". Based on the present review compared to the original hypotheses of Metchnikoff, it seems that much of the recent scientific endeavors in the area of the gut-remote organs' axes, in the broad sense, have been thought of before. The difference, of course, is the degree of scientific sophistication with which we can now see an undeniable link between these major organ compartments. The lines of interrelationship, influenced by the nutritional composition, transformation of the macrobiota to dysbiota and the breached tight junction integrity, ultimately influencing the phenotype and the activity of multiple ADs, by a systemic effect on inflammation, oxidative stress, glycemic control, tissue lipid levels, pathogenic bacteria, as well as levels of neuropeptides and mood-regulating neurotransmitters. Presently, it was not our contention that ADs are diseases of the gastrointestinal tract. Yet, there appears to be more than...
enough supportive evidence to suggest that unbalanced or industrial processed nutrition- dysbiosis-increased intestinal permeability, and dis/malfunctioned gut compartments, are contributing factors in autoimmunogenesis. For now, many of the observations are mainly circumstantial, hopefully, causality will be investigated more profoundly in the future.

References


