Gut Microbiome Composition in Patients with Chronic Urticaria

Subjects: Allergy

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gut microbiome | intestinal microbiome composition | chronic spontaneous urticaria | dysbiosis | metabolome

1. Introduction

Chronic urticaria (CU), whether spontaneous or inducible, is characterized by recurrent episodes of pruritic wheals, with or without associated angioedema persisting longer than 6 weeks [1][2]. Globally, up to 1% of the general population suffers from CU at some point in life, and a trend of increasing prevalence has been observed in recent years [3]. Chronic spontaneous urticaria (CSU), especially concomitant angioedema, greatly impacts patients' work, studies, quality of life and mental health, and it also imposes a huge economic and social burden on families and society [1][2][3][4].

Although the course of CSU can be self-limiting, in 10–25% of patients it lasts longer than 5 years [5]. Treatment is often focused on "symptom control". Patients with a prolonged disease duration, or therapy-refractory symptoms, experience additional quality of life burdens. The current treatment of CU is largely dependent on symptomatic treatment with second-generation non-sedating H1-antihistamines (nsAHs) [1][2]; however, 40–55% of patients are unresponsive to conventional doses of antihistamines [6][7]. Clinically, resistant CSU (rCSU) is defined by unresponsiveness to nsAHs after 2 to 4 weeks of treatment at approved dosages [8]. According to current guidelines, therapeutic options for rCSU include increasing doses (up to four-fold of the approved dose) of nsAHs, and add-on medications: glucocorticoids, cyclosporine and biological agents (omalizumab) [9], often with limitations due to the possibility of serious side effects, unresponsiveness, and the high cost to the healthcare system [1][2]. Thus, there is an urgent need to find novel diagnostic tools and alternative therapies [1][2][10]. Unravelling the pathogenesis of CSU will represent a step forward in the management of CSU patients.

Recent studies have reported an altered gut microbiota composition in patients with CSU [11][12][13]. It has been hypothesized that pro-inflammatory responses caused by alterations in the gut microbiome, mediated by the imbalance of Th1/Th2/Th17 cytokines, might contribute to the pathogenesis of CSU [14]. Additionally, recent

evidence from human metabolomics has shown enteric dysbacteriosis in CSU subjects compared to healthy subjects. Thus, uncovering potential causes of inflammation might provide new strategies for improving symptom control and minimizing the disease's burden on CSU patients [15][16][17].

2. Immunopathogenesis of Chronic Urticarial and Immune Changes in the Peripheral Blood and Skin of Patients

The pathogenesis of CU is poorly understood, especially CSU, but current evidence suggests that most CSU cases have an autoimmune etiology [18]. Understanding these principles is complex, and according to current knowledge, aside from humoral (autoantibodies), it also involves cellular responses (auto-reactive T cells) and the dysfunction of adaptive cellular immunity [19][20]. According to current literature data, crucial pathogenetic factors/events for CSU are the activation of mast cells, basophils, T cells, and eosinophils, as well as increased vascular permeability and vasodilation, activation of coagulation pathways and autoimmunity processes, and finally, the release of mast cell mediators [21]. Thus, CSU involves the participation of both innate immunity (mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, natural killer [NK] cells, innate lymphocytes [ILC], complement factors) and adaptive immunity (Th1 and, Th2 cells, Th9 cells, Th17 cells, regulatory T cells [Treg cells], B cells, antibodies), wherein mast cells link innate and adaptive immunity. Mast cells have various roles: they induce/modulate T-cell activation and polarization; stimulate B cells to produce IgE (through IL-4 and IL-13); produce mediators (e.g., TNFα), which act on vascular endothelial cells' up-regulation and adhesion molecules' expressions, which promote the recruitment of T cells; allergen-specific Th2 cells stimulate B cell production of IgE, which stimulates/activates mast cells and basophils [21]. In the skin tissue of urticarial CSU lesions, mast cells predominate, and there are increased numbers of basophils, eosinophils, macrophages, neutrophils and T cells, while there are decreased numbers of Th17 cells. In the serum of CSU patients, decreased numbers of Treg cells (among PBMC) are found, while increased IL-17 serum levels are seen (produced by Th17) [21]. Mast cells and T cells interact through various contacts, including through their inflammatory mediators and their receptors. It is also important that T cells express histamine receptor H4R (known for its role in inflammation and allergies), which activates Th2 and Th17 cells. Thus, histamine mediates the enhancement of Th2 cytokine secretion while inhibiting Th1 cytokine production, maintaining Th1/Th2 cell balance and supporting the dominance of Th2 cells. In addition, mast cells produce cytokines that promote Th2 cell activation, survival and migration (PGD2 and leukotriene E4) [21].

Research in this field has illuminated the previously unrecognized role of pro-inflammatory Th17 cells and the immune imbalance between them and Treg cells. It is therefore important here to mention genetic factors and expressions of genes. In a study on CSU patients by Prosty et al., several upregulated Th17-related pathways were identified, including IL-17 signaling, Th17 cell differentiation, IL-6 and IL-23 mediated signaling events in lesional samples versus samples from both non-lesional and healthy persons [22]. Key Th17-related genes (e.g., IL-6) were also upregulated in lesional CSU samples compared to samples from non-lesional and healthy persons [22]. Aside from this, a study by Atwa [3]. has shown high serum levels of IL-17, IL-23 and TNF-α in CSU patients compared to controls, positively correlating with disease activity (UAS7 scores) [23]. Additionally, a recent open

label trial documented that secukinumab, an IL-17α inhibitor, significantly improved symptoms of refractory CSU, which underscores the therapeutic relevance of the Th17 pathway in CSU [24]. Concerning the skin, another interesting study by Sabag et al. revealed increased cutaneous CD4+ T cells and mast cells infiltration in CSU patients (in both lesional and non-lesional skin) compared to healthy controls [24]. These findings in the skin of CSU patients versus healthy controls were supported by a study from Toubi et al. that showed autoimmunity in CSU involving both humoral and cellular responses [25]. Notably, mast cell degranulation is mainly thought to be the result of activated mast cells coming into proximity with autoreactive T cells. When IgE antibodies to thyroid antigens or anti-FcεR1 on mast cells are seen, it might be possible that the autoreactive T cells could have responded to those antigens.

On the other hand, several reports have documented decreased Treg cells in CSU blood versus the blood of healthy controls, which may imply these cells play a role in the CSU autoimmunity [26][27]. Additionally, Treg cells participate in suppression of mast cell degranulation via the signaling of OX40-OX40L. The absence of suppression of mast cell degranulation may contribute to allergic responses and their severity [28]. The study by Prosty et al. also observed increase of Treg cells and resting mast cells in non-lesional versus lesional skin, which suggests that Tregs might inhibit wheal formation by suppressing mast cells into a resting state [22]. However, Treg suppression can be reversed in the presence of activated mast cells, an abundance of IL-6 and scarcity of Th1/Th2 cytokines, inducing a Th17 response [29].

3. Characteristics of the Gut Microbiome of Healthy Individuals and Patients with Chronic Urticaria

The human microbiota encompasses numerous bacteria and other microorganisms (archaea, fungi, viruses and protozoa) residing in/on the body, including the genomic content of organisms inhabiting a particular site in the human body [30][31]. An adult human's gut microbiota is mainly inhabited by bacteria from three major phyla: *Firmicutes, Bacteroidetes* and *Actinobacteria*, which together make up more than 90% of total gut bacteria. The human gut microbiome consists of a core microbiome (common to all or the great majority of individuals), and a variable microbiome (unique to sub-groups of individuals depending on lifestyle and physiological differences). An imbalance in the composition, or loss of function, of human microbiota is called dysbiosis [32].

Various factors can be involved in bacterial imbalances, e.g., psychosocial stress, health behaviours, nutrition, social relationships, environmental factors, tobacco and alcohol intake, and prescription drug use (e.g., antibiotics or probiotics) [32][33][34]. An alteration of microbiota components is linked to the pathogenesis of psychiatric diseases, inflammatory bowel diseases, cardiovascular and neurological conditions, allergic diseases, cancers, diabetes mellitus, rheumatoid arthritis, metabolic syndrome, liver diseases, obesity, and kwashiorkor [12][32][35].

The human microbiota has a significant impact on the immune system and is necessary for the evolution and regulation of certain elements of the immune system [36]. Bacterial colonization is essential for the establishment of immunity. Specifically, the homeostasis of microbes and the immune system protects and benefits both the microbes and the host [33]. Dysbiosis, on the other hand can contribute to the development and persistence of

different diseases. Any quantitative or qualitative changes to the intestinal microbiome may trigger an inflammatory response followed by tissue damage [33][36].

According to the literature data, when gut bacteria interact with dendritic cells and intestinal epithelium, the signalling pathways of immune effector cells, including macrophages, B cells, NK cells, and T cells are activated [37]. Gut lamina propria at a steady state contains large numbers of two populations of CD4+ T cells, helper Th17 cells and regulatory T (Treg) cells [38]. Therefore, in response to specific components of the commensal microbiota, Th17 cells are induced in the intestinal lamina propria. Treg cells, also important, maintain immune homeostasis and promote immune tolerance to allergens [38]. According to several studies, CU patients have a reduced number and function of Treg cells, and some researchers have speculated that the reduction of some bacteria may affect Treg cells' role in immunity by inducing Toll-like receptors, leading to CSU (occurrence and persistence) [12][13].

Recent studies have linked gut microorganism composition and CU; however, the underlying mechanisms responsible for this connection are unknown. Since the human immune system is in homeostasis with microbiota, and the composition of the microbiome regulates the development and function of the immune system, it is likely that an alteration of microbiota components (a dysbiosis) could influence the course of CSU, including disease severity, patient quality of life and treatment outcome. To date, several studies have identified changes in the gut microbiota composition of patients with CSU, though only a few have exhibited metabolic abnormalities associated with gut dysbiosis. The studies on CSU patients predominantly showed that the relative abundance of beneficial bacteria was decreased (Firmicutes and Bacteroides), while that of opportunistic bacteria was increased (Enterobacteria and Proteobacteria). In addition, serum metabolome analysis revealed that gut microbiota-associated alterations in unsaturated fatty acids and the butanoate metabolism pathway may play a role in CSU. These findings are potentially associated with inflammation mediated by the imbalance of Th1/Th2/Th17 cytokines, which might contribute to CSU pathogenesis. Further research in this field could improve clinical, diagnostic, and therapeutic approaches to patients with CSU. By applying new knowledge on gut microbial communities and metabolomics, future CSU therapies could modify the microbiota composition using agents such as probiotics or other similar agents, which, in combination with current standard therapies, could hopefully lead to a reduction in symptoms and an improved quality of life for CSU patients.

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