Advanced Biomarkers: Therapeutic and Diagnostic Targets in Urticaria

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Abstract

Urticaria is a type of skin disease characterized by rapid onset of hives (superficial dermis edema, erythema, pruritus, or burning sensation). According to whether the natural course exceeds 6 weeks, urticaria can be divided into acute and chronic urticaria (CU). At present, the evaluation of CU activity mainly depends on the Urticaria Activity Score (UAS), but the evaluation indicators are relatively single, and we need more reliable experimental data for evaluation. We typically summarize advanced biomarkers and several related pathogenic pathways discovered in recent years on urticaria, including the cell adhesion/chemotaxis pathway, interleukin (IL)-6/Janus tyrosine kinase/STAT pathway, IL-17/IL-23 pathway, basophil- and mast cell-related pathway, coagulation/fibrinolysis-related pathways, single-nucleotide polymorphism, and some other pathways. This review aims to find appropriate biomarkers so that we can evaluate disease activity, discover novel therapeutic targets, and predict the patients' response more accurately to therapeutic agents.

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Introduction

Urticaria is a type of skin disease characterized by rapid onset of hives (superficial dermis edema, erythema, pruritus, or burning sensation), which can be accompanied by angioedema (edema of the deep dermis, fat tissue, and gastrointestinal tract); it is self-limiting and prone to recurrent attacks [1, 2]. Urticaria is mainly mediated by mast cell activation and degranulation, and basophils infiltrating into the skin. What is more, coagulation abnormalities and vitamin D3 deficiency have received increasing attention in the pathogenic role of urticaria [3]. According to whether the natural course exceeds 6 weeks, urticaria can be divided into acute urticaria (AU) and chronic urticaria (CU). Among CU including spontaneous urticaria and induced urticaria, chronic spontaneous urticaria (CSU) is the most common. According to the etiology, CSU can be induced by autoreactivity or other unknown causes [4, 5]. The typical clinical presentation of CSU is recurrent attacks of spontaneous wheals and/or angioedema for >6 weeks, and it occurs at least twice a week [6].

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Compared with AU, the diagnosis of CU, especially CSU, is relatively complex and requires the exclusion of recurrent angioedema or hereditary angioedema, so more accurate laboratory parameters are needed in the diagnosis of urticaria patients [7]. At present, the evaluation of CU activity mainly depends on the Urticaria Activity Score (UAS), but the evaluation indicators are relatively single and need more reliable experimental data for evaluation. Some markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are positively correlated with the disease severity and can be used for laboratory evaluation of the patients' disease activity level. Until now, only a few antihistamines, immunomodulators, and anti-IgE biologics have been approved for the treatment of patients with urticaria. However, the effects of these drugs are limited. For instance, when treating non-histamine-mediated urticaria patients with antihistamines, the response of the treatment is ineffective [8]. At the same time, although anti-IgE drugs such as omalizumab could treat these patients with less side effects, they are expensive, and also, some patients respond poorly to this treatment [9]. Therefore, it is highly desirable to find suitable biomarkers to provide promising options for individualized treatment of urticaria. It is important to find appropriate biomarkers so that we can predict the patients' response more accurately to therapeutic agents, forecast the severity of the disease, and discover novel therapeutic targets.

Biomarkers and Their Findings in Urticaria

Biomarkers are objectively measured and evaluated features and can be used as indicators of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions [10]. Recently, with the outstanding application of extensive genomic screening in modern biology, more molecular targets have been explored in the field of urticaria as biomarkers for diagnosis, treatment, and prognosis, thus increasing the number of candidate treatment strategies [11]. In this review, we have found several novel potential biomarkers, including gene and protein levels, to provide more thoughts for finding new therapeutic targets in diverse levels.

Much of the medical literature has proven that genetic factors are involved in the pathogenesis of CSU. Through Kyoto Encyclopedia of Genes and Genomes (KEGG) and other databases, Lin et al. [12] found 5 significantly up-regulated microRNAs (miRNAs) (2355-3p, 4264, 2355-

5p, 29c-5p, and 361-3p) 8 significantly downregulated genes (e.g., *CCNG2*), and 5 significantly upregulated genes (e.g., *THBS1*, selectin E [*SELE*], and *CCL2*). In addition, the polymorphisms of genes related to urticaria are of great significance in predicting the population's susceptibility to diseases and responsiveness to drugs. For example, *ORAI1* and *FCER1A* polymorphisms can predict the treatment effect of antihistamines on patients [13, 14]. An interesting study found that in patients with CSU treated with omalizumab, >75% lesional skin gene expression levels returned to normal levels. These genes include *FCER1G*, *C3AR1*, *CD93*, *S100A8*, *S100A9*, *CYR61*, *KRT6A*, and *KRT16* [15]. Giménez-Arnau et al. [16] analyzed the gene expression levels of patients who were resistant to antihistamine therapy and screened 130 abnormally expressed genes, which are involved in epidermal cell differentiation, inflammation, blood coagulation, intracellular signal transduction, and other functions.

Besides the target genes involved in the pathogenesis and treatment of CU, we also searched PubMed to find protein biomarkers related to the pathological mechanism and drug effect on CU, of which markers are usually increased in CU. We summarized and classified these markers into 3 categories: (1) as a potential target for treatment, (2) predicting the severity and activity of the disease, and (3) evaluating drug efficacy. Many markers have been studied in the past; among them, IgE has been clearly related to the severity of CU. Given that mast cells can be activated in an IgE or non-IgE-dependent manner and further release histamine, leukotrienes, etc., the drugs targeting IgE/FcεRI or histamine have been developed for clinical treatment including omalizumab, non-sedating antihistamines, and montelukast, a leukotriene antagonist [17]. Due to the role of eosinophils in CU, IL-5 has a chemotactic effect on eosinophils, so anti-IL-5 monoclonal antibodies such as mepolizumab can also be used for clinical treatment [18]. IL-4 can promote Th2 cell differentiation, so the monoclonal antibody dupilumab developed for IL-4 is currently available for patients with poor response to omalizumab [19]. In addition, we recorded several substances such as IL-18-binding protein, dimeric translation-controlled tumor protein, sialic acid immunoglobulin-like lectin, brain-derived neurotrophic factor, and spleen tyrosine kinase [20–24] as potential CU markers in Table 1, but the mechanism and clinical significance of most protein elevations are still unclear. We classify and describe several newly discovered genes and protein/small molecule markers according to pathogenic pathways. These pathogenic pathways and related substances can serve as new potential targets in CU.

Table 1. Molecules and protein used as biomarkers in urticaria

Protein or small molecule	Changes or functions in urticaria	Clinical significance	Reference
IL-18BP	Significantly higher than allergic diseases	Can be used to distinguish urticaria from allergic diseases	[20]
Dimeric TCTP	Elevate in CSU patients, and more significant in patients with severe CSU and anti-FcεRIα positive	Can be used as a potential target for the treatment of CSU, related to autoimmune diseases	[21]
Siglec-8	Specifically expressed in mast cells, eosinophils, and basophils	Can be used as a therapeutic target to inhibit mast cell degranulation	[22]
BDNF	Increased in CSU	Mediates neurogenic inflammation	[23]
Syk	Can positively regulate FcεRI signaling	Can be used as a therapeutic target	[24]
CCL17	Increased in CSU	Activating the inflammatory pathway related to Th2 cells	[36]
IL-6	Increased in CSU	Correlated with the response to antihistamine, the activity of the disease, plasma D-dimer concentration, and involved in wheals, itching, and angioedema	[39–44]
IL-17	Promote CRP, increased in CSU	Can be used to treat patients with poor effects of antihistamines and omalizumab	[57, 62, 63]
IL-23	Activate Th17 cells	Can be used as a biomarker related to the degree of disease activity in CSU patients	[68, 69]
CD203c	Upregulated when stimulated with anti-IgE antibodies and allergens; the most effective marker for basophil activation and differentiation	Can be used as a biomarker of responsiveness to omalizumab treatment in CU	[71, 74]
Vitamin D3/VDBP	VDBP can induce the VEGF production in mast cells; vitamin D has an effect on maintaining the stability of mast cells	Vitamin D can be used as a new type of drug for the treatment of CSU	[77–84]
Substance P	Activate the NK1 receptors on basophils surface and MRGPRX2 on mast cell surface to degranulation	SP, MRGPRX2 and NK1R antagonists are expected to become new therapeutic targets	[85–88]
IL-33	Binds to ST2 receptors on the mast cell surface to stimulate mast cell degranulation including histamine, VEGF, and prostaglandins, inducing Th2 inflammation	Is expected to be a pharmacological target in the future and may be related to disease severity	[90, 92, 95]
CRP	CRP levels and HDL levels are negatively correlated	Can evaluate CU patients' risk for developing atherosclerosis and are related to the patients' reaction to omalizumab	[43, 96–99]
D-dimer	Plasma D-dimer levels are often elevated in CU plasma; thrombin generation can increase vascular permeability and induce mast cell degranulation	Can serve as a potential blood biomarker to evaluate urticaria activity and response to omalizumab treatment	[102–107]
5-HT transporter protein	Increased in CU patients with anxiety	Can be regarded as a specific biomarker and a unique drug target for treating anxious patients	[129–131]
SSA	Higher SAA levels were associated with AU and more severe CU	Can be used as a biomarker of disease severity	[135]
PAF	Higher in CSU patients with poor effect on antihistamine drugs	Can be sued as a drug target	[109–113]

Table 1 (continued)

Protein or small molecule	Changes or functions in urticaria	Clinical significance	Reference
Keratin86; desmocollin 1; lectin, galactoside-binding, soluble, 7; lactotransferrin; keratin, type II cytoskeletal 4; keratin 31; keratin 80; premature ovarian failure, 1B; plakophilin 1; defensin, alpha 3, and neutrophil-specific	Only expressed in basophils of patients with omalizumab, but not in nonresponders	Can predict the therapeutic effect of omalizumab in CSU patients	[101]

IL-18BP, interleukin-18-binding protein; dimeric TCTP, dimeric translation-controlled tumor protein; Siglec-8, sialic acid immunoglobulin-like lectin; BDNF, brain-derived neurotrophic factor; Syk, spleen tyrosine kinase; VDBP, vitamin D-binding protein; MMP-9, matrix metalloproteinase-9; CRP, C-reactive protein; SSA, serum amyloid A; PAF, platelet-activating factor; CU, chronic urticaria; CSU, chronic spontaneous urticaria; IL, interleukin; VEGF, vascular endothelial growth factor; NK1R, NK1 receptor; MRGPRX2, MAS-related G protein-coupled receptor-X2; AU, acute urticaria.

TGF- β Pathway

Thrombospondin 1

Thrombospondin 1 (*THBS1*) encodes a common glycoprotein that was originally discovered as a thrombin-sensitive protein [25]. It participates in many diseases such as antiphospholipid syndrome and diabetes [26, 27]. According to the previous reports, *THBS1* expression in the serum increased in patients with CSU and was associated with mast cell degranulation [28]. Lin et al. [12] screened out genes and miRNAs that are related to urticaria through KEGG and found that *THBS1* and TGF- β /smad pathways expressed differentially and predicted that the TGF- β /smad pathway may be involved in the pathogenesis of CSU through enhancing inflammation. Previous reports showed that TGF- β promoted Smad phosphorylation and further resulted in a decrease in IFN- γ and an increase in IL-4, which enhanced inflammation [12, 29]. Next, Qu et al. [30] further found that the miRNA-194 expression was downregulated in the skin lesions of CSU patients, while the expression of *THBS1*, TGF- β , smad3, and IL-4 increased, which predicted that miRNA-194 may directly target *THBS1* and regulate mast cell functions and vascular permeability. Luciferase activity assay also confirmed that *THBS1* is the direct target gene of miRNA-194. After miRNA-194 mimics and si-*THBS1* were transfected into mast cells, the degranulation of mast cells was reduced; the content of IL-4, tumor necrosis factor (TNF)- α , and IL-6 in the supernatant decreased; and blood vessel permeability reduced, and further testing found that the TGF- β /smad content decreased [30]. It showed that miRNA-194 weakened inflammation by targeting *THBS1* via TGF- β /smad pathway inhibition. Therefore, *THBS1* can serve as a new therapeutic target to weaken the inflammatory response in CSU.

Cell Adhesion/Chemotaxis Pathway

Selectin E

SELE encodes E-selectin which is involved in the early blood vessel adhesion of inflammatory cells and local inflammation production [31]. It is reported that *SELE* is significantly upregulated in skin lesions in urticaria and may be involved in the pathogenesis of urticaria [32]. Meng et al. [33] constructed a contact urticaria mouse model by inducing anti-dinitrophenol immunoglobulin E combined with 2,4-dinitrofluorobenzene. Next, the deletion of *SELE* by siRNA showed that E-selectin, intercellular cell adhesion molecule-1, CD62L, and eosinophil cationic protein expressions in the mouse skin significantly decreased compared with the initial levels and the adhesion of leukocytes receded, indicating that inhibiting *SELE* expression can reduce the adhesion of leukocytes and greatly weaken the inflammatory response in CSU, thus may act as a biomarker in CSU treatment [33].

CCL17/miR-125a-5p

CCL17 is a chemokine tracking Th2 cells and involved in a variety of Th2-mediated inflammatory diseases, including atopic dermatitis [34]. miRNAs are a class of endogenous noncoding RNA molecules, which are considered as potential biomarkers for some autoimmune diseases [35]. A study on CSU patients' serum via qPCR arrays showed serum miR-125a-5p and CCL17 were significantly increased. Additionally, the serum miR-125a-5p and CCL17 levels of 12 CSU patients in the remission phase were significantly lower than those in the active phase [36]. As the target gene of miR-125a-5p, STAT3 cooperates with CCL17 to participate in the chemokine signaling pathway, thereby activating the inflammatory pathway related to Th2 cells. Although CCL17 is not the direct target of miR-125a-5p, the study found that the

content of CCL17 and miR-125a is correlated, which indicated they may have a synergistic effect on the pathogenesis of urticaria [36]. Although the specific mechanism of CCL17 in urticaria remains unclear, it can be used as a potential marker for further study.

IL-6/Janus Tyrosine Kinase/STAT Pathway

Interleukin-6

IL-6 is a B-cell differentiation factor and Th2-related factor, secreted mainly by mast cells and T cells, involved in inflammation, hematopoiesis, immune regulation, and other functions. According to the reports, IL-6 participates in many diseases including autoimmune diseases, mastocytosis, and even breast cancer [37, 38]. IL-6 is increased in urticaria, which is related to the activity of the disease, and patients with elevated serum IL-6 levels are not ideal for antihistamines, which indicates that IL-6 promotes mast cell proliferation and activation. IL-6 forms a functional complex by binding to the IL-6 receptor (IL-6R) on the cell membrane surface and glycoprotein 130 to mediate traditional signaling pathways. IL-6 can also interact with the soluble IL-6 receptor (sIL-6R) to mediate trans-signaling pathways. IL-6 can activate Janus tyrosine kinase (JAK)/STAT3, Ras/MAPK, PI3K-PKB/Akt, and other signaling pathways, thereby participating in the pathogenesis of certain diseases [39]. Studies have shown that IL-6 was also elevated in the spontaneous urticaria wheals compared with unaffected skin [40]. And in CU, the serum level of IL-6 is significantly related to the UAS and the quality of life score. Stimulating mast cells with IL-6 can significantly promote COX-2 enzyme expression and enhance the PGD2 biosynthesis induced by FcεRI. Thus, IL-6 is involved in the inflammatory reaction in urticaria [41, 42]. In addition, it has been reported that serum IL-6 concentration and D-dimer concentration are positively correlated, which may indicate that the coagulation system/fibrinolytic system is activated in urticaria [43]. For CSU patients treated with omalizumab, the concentration of IL-6 decreased significantly [44]. Therefore, IL-6 can not only serve as an effective indicator to evaluate the disease activity of patients with urticaria but also can be used to evaluate the therapeutic effect of omalizumab and guide the medication course and dosage.

Suppressor of Cytokine Signaling 3

Suppressor of cytokine signaling 3 (SOCS3), belonging to the SOC protein family, participates in infection and autoimmune diseases by regulating signal transduction of hormones or cellular factors [45]. SOCS3 is induced by

the cytokines involving IL-6 and IL-10 and participates in a variety of tumors including prostate cancer and gastric cancer [46–48]. A study has found that SOCS3 expression increased in peripheral blood mononuclear cells in chronic idiopathic urticaria [49]. Experiments have shown that IL-6/sIL-6R/gp130 can activate the JAK pathway, thereby activating the transcription factor STAT3 and promoting the expression of SOCS3. SOCS3 can inhibit the expression of IL-6 and the JAK/STAT3 pathway and prevent IL-6 from overactivating mast cells [46]. But due to high levels of IL-6, decreased content of sIL-6R, and methylation of the promoter SOCS3, the self-inhibitory function of IL-6 is weakened, which makes IL-6 more biased toward traditional signaling pathways and promotes the proliferation and activation of mast cells to release inflammatory factors. As a result, mast cells exposed to high levels of IL-6 exhibit stronger proliferation ability and administration of SOCS3 methyltransferase inhibitors to restore the self-inhibition pathway of SOCS3 [50]. The impaired regulation of SOCS3 may be the mechanism of the pathogenesis of urticaria. Therefore, SOCS3 can serve as a therapeutic target to inhibit the traditional signaling pathway of IL-6.

Oncostatin M Receptor

Oncostatin M receptor (OSMR), a member of the IL-6 receptor family, mediates inflammation and metabolic processes [51]. OSM-OSMR can conduct JAK/STAT, ERK1/2, p38, JNK, and PI3K/AKT signaling pathways; previous reports stated that OSM-OSMR involved in the pathogenesis of a variety of diseases, including glioma and inflammatory bowel disease and so on [52, 53]. Recent studies have found that OSM-OSMR participates in the pathogenesis of CU through the JAK/STAT pathway [54, 55]. OSM is released under inflammatory conditions and binds to the heterodimer receptor. After the heterodimer binds to OSMR and gp130, it initiates the JAK/STAT pathway, which in turn promotes the release of IL-1, IL-6, and IgE and inflammation reaction [56]. Luo et al. [54] found increased expression of OSMR and JAK/STAT-related genes in CU mice skin tissues, and then, they constructed OSMR-silenced CU mouse model and found that the OSMR-silenced mice had lower levels of IL-1, IL-6, IgE, and IFN-γ; a reduced number of eosinophils in skin; and weakened pathological response compared with the control group. And the decreased expression of JAK/STAT-related genes confirmed that silencing OSMR further inhibits the JAK/STAT-related signal pathway [54]. In addition, OSMR can also mediate the activation of IL-31 on basophils to promote the progres-

sion of CU. In CU patients, the serum IL-31 level and basophil numbers are higher than those in the normal. IL-31 binds to the heterodimer composed of IL-31 receptors and OSMR to induce basophils to release inflammatory factors including IL-31 and IL-4 [57, 58]. IL-4 can promote the differentiation and maturation of Th2 cells, and IL-31 participates in inflammation and pruritic diseases [55]. In addition, an antihistamine does not effectively relieve itching for some people, indicating that histamine is not the only source of itching. The anti-IL-31 antibody nemolizumab has achieved great success in the treatment of pruritus in atopic dermatitis [59]. Therefore, for urticaria patients with severe itching, anti-IL-31 monoclonal antibody may serve as an auxiliary drug to relieve itching and improve the quality of life. Given that OSMR has a pro-inflammatory effect through multiple signal pathways in CU, it is expected to become a clinically targeted therapy marker for CU.

IL-17/IL-23 Pathway

Interleukin-17

IL-17, a Th17 cell-related cytokine, is involved in a variety of autoimmune-related diseases, including asthma and rheumatoid arthritis [60, 61]. It has recently been found that the plasma level of IL-17 in CU patients is significantly higher than that of the healthy group, and the serum level of IL-17 in severe CU patients is significantly higher than that of mild to moderate CU [57]. IL-17 can promote the CRP release in the acute phase, thereby aggravating the inflammatory response [57]. It has been reported that the plasma IL-17 level of autologous serum test (ASST)-positive patients is significantly higher than that of ASST-negative patients, indicating that IL-17 may have an effect on chronic autoimmune urticaria [62]. In another experiment, Sabag et al. [63] found that skin IL-17A expression increased in CSU patients, and then, they applied anti-IL-17A antibodies to treat 8 severe patients with poor effects of antihistamines and omalizumab. The results showed that the symptoms of 8 patients improved significantly according to the UAS. Therefore, IL-17 is expected to become a novel drug to treat CSU patients with poor response to antihistamines and omalizumab.

Interleukin-23

IL-23 is a pro-inflammatory heterodimeric cytokine expressed by T cells and natural killer cells, a key cytokine generated by peripheral effector Th17 cells [64]. IL-23 can activate Th17 cells through TLR 4, p38/MAPK, NF- κ B, and JAK signal transducer and activator of transcription pathways, further inducing chronic inflammation [64–

67]. Atwa et al. [68] found that serum IL-23 concentrations were significantly higher in CSU patients than that in healthy controls, and that IL-23 levels were directly proportional to the severity of the disease according to the UAS. Later, Chen et al. [69] also found that Th1/Th2- and Th17-related cytokines were significantly increased in CSU patients, and the plasma cytokine level was directly proportional to the severity of the disease, demonstrating that the plasma IL-23 level can be used as a biomarker related to the degree of disease activity in CSU patients.

Basophil- and Mast Cell-Related Pathway

CD203c

CD203c (ectonucleotide pyrophosphatase) is a surface marker on basophils and mast cells, and its expression is upregulated when stimulated with anti-IgE antibodies and allergens [70]. Ye et al. [71] found that the mean expression of CD203c in basophils in the CU group was 57.5%, which was significantly >11.6% in the healthy control group, and the expression of CD203c in basophils in patients with severe CU was significantly higher than that in patients with nonsevere CU, and $\geq 72\%$ basophil CD203c expression and UAS ≥ 13 were both significant predictors of severe CU by analysis. CD203c is now considered as the most effective marker for basophil activation and differentiation [72, 73]. If peripheral basophils from CU patients are sensitized by autoantibodies or other exogenous stimulants during active urticaria, several surface markers including CD203c will be upregulated. In addition, Palacios et al. [74] retrospectively analyzed 41 adult patients with antihistamine-refractory CU; they found that 71% of 18 subjects with upregulated CD203c activity responded well to treatment and 87% of 23 patients without upregulated CD203c activity had a clinical response to omalizumab. So CD203c could be used as a biomarker of efficacy to omalizumab treatment in CU.

Vitamin D3/Vitamin D-Binding Protein

Vitamin D is an essential molecule to maintain the homeostasis of bones and minerals, and it also has immune regulation functions in the human body. Many studies have shown that vitamin D deficiency is associated with various autoimmune and allergic diseases, such as multiple sclerosis and CU [75, 76]. The availability of vitamin D supplements in the treatment of CSU has been confirmed by some small-scale clinical trials [77, 78], but the mechanism is still unclear, which may contribute to the pathogenic pathway inhibition of vitamin D-binding protein. Studies have shown that vascular endothelial growth factor (VEGF) plays a role in allergic diseases in-

cluding CSU and is a potential blood biomarker for CSU diagnosis [79]. In the study of Zhao and others [80], vitamin D-binding protein can induce VEGF production in mast cells in an IgE-dependent manner through the PI3K/Akt/p38 MAPK/HIF-1 α axis. 25-(OH)-D₃, as a metabolic intermediate of vitamin D, inhibits this signaling pathway and reduces the expression of VEGF [80]. In addition, vitamin D has an effect on maintaining the stability of mast cells. Mast cells are automatically activated in a vitamin D-deficient environment, and exposure to calcitriol will increase the expression of VDR in mast cells. The combination of VDR and TNF- α promoter can reduce the acetylation level of histone H3/H4, thereby inhibiting the TNF- α release from mast cells [81]. Recent experiments have shown that vitamin D is significantly negatively correlated with urticarial activity and vitamin D supplementation can significantly improve the quality of life of CSU patients and reduce the severity of the disease. Therefore, vitamin D can be used as a new type of drug for the treatment of CSU [82–84].

Substance P and Its Receptors

Substance P, belonging to the neuropeptide family, is involved in neurogenic inflammation by combining the NK1 receptor (NK1R) or MAS-related G protein-coupled receptor-X2 (MRGPRX2) in the skin and can be released under physical or chemical stimulation. Recent studies have found that serum SP levels in CU patients increase, and the change is more significant in women, the elderly, and patients with positive in ASSTs [85, 86]. SP can activate the NK1R on the surface of basophils to degranulation, and basophils expressing NK1 receptor were elevated in the peripheral blood of CU patients [87]. MRGPRX2 expresses increasingly on the surface of mast cells in CU patients and can be activated by SP, followed by degranulation. Fujisawa et al. [88] applied MRGPRX2 inhibitors to significantly inhibit mast cell Ca²⁺ influx and degranulation, further attenuating the subsequent secretion of cytokines and chemokines. Therefore, SP and MRGPRX2, NK1R antagonists, are expected to become new therapeutic targets.

Interleukin-33

IL-33, an inflammatory cytokine secreted by a variety of cells, belongs to the IL-1 family [89]. Lin et al. [90] found that IL-33 in the plasma of CSU patients was significantly higher than that in healthy controls, and in severe CSU patients, IL-33 was significantly higher than that in mild CSU patients, suggesting that IL-33 may be related to disease severity. Kay et al. [91] showed that IL-

4⁺ and IL-5⁺ cells were increased in the diseased skin, and the level of IL-33 in skin lesion was significantly increased. Previous reports have found that IL-33 can be released from endothelial cells under inflammatory conditions or when epithelial cells are damaged. IL-33 binds to ST2 receptors on the mast cell surface to stimulate mast cell degranulation including histamine, VEGF, and prostaglandins, inducing Th2 inflammation [89, 92, 93]. In addition, studies have shown that the responsiveness of human umbilical vein endothelial cells to histamine and VEGF is enhanced when treating with IL-33, thus human umbilical vein endothelial cells express more tissue factor, initiate the exogenous blood coagulation pathway, and participate in plasma extravasation [94]. Recently, it is shown that Th-2 cells play a crucial role in the pathogenesis of pruritus [95]. So, we can conclude that IL-33 is involved in the pathogenesis of CSU and is expected to be a pharmacological target in the future.

C-Reactive Protein

CRP is a marker of acute inflammation, and TNF- α and IL-6 can stimulate liver cells to secrete CRP. In CU, serum IL-6 and CRP are positively correlated with disease severity and itching [96]. In addition, studies have found that CRP, D-dimer, and MMP-9 are related, indicating that inflammation and the coagulation system are relevant [43]. The latest research focuses on the role of CRP in urticaria and metabolic syndrome. Yaldiz and Asil [97] found that CRP levels and HDL levels are negatively correlated, so CU may increase the risk of atherosclerosis [97]. For CSU patients with poor effect of antihistamines, their plasma CRP levels are significantly increased [98], for patients treated with omalizumab, and CRP levels significantly decreased after 12 weeks of treatment and are closely associated to UASs [99]. Therefore, CRP can serve as a marker for individualized treatment of patients: omalizumab can be chosen, instead of antihistamines, and also can be used evaluate CU patients' risk of developing atherosclerosis.

Basophil Proteome

Studies found that omalizumab treatment of CSU patients can restore the normal number of blood basophils and reduce the Fc ϵ RI density on the surface of basophils [100, 101]. However, only a part of them respond to omalizumab and obtained improved clinical symptoms. Researchers then analyzed the basophil protein proteome expression in both responders and nonresponders, and further found several proteins that expressed only in responders, such as keratin 86, desmocollin 1, lectin, ga-

Table 2. Genes that can potentially be used as biomarkers in CU

Potential biomarkers	Target in urticaria	Clinical significance	Reference
CRACM1/ORAI1	<i>rs12320939, rs3741596 rs3741595</i>	Susceptible to CU Insensitive to nonsedative H1 receptor antagonists H1	[13, 116]
FCER1A	<i>rs2298805 –344C>T</i>	Not sensitive to antihistamines but related to the total serum IgE concentration, which can be used as a therapeutic targets associated with AICU	[14, 117]
HNMT	<i>rs1050891</i>	Susceptible to CU	[118, 121]
IL-10	<i>rs1544224, rs1800871</i>		[121]
TNF- α	<i>rs1799724, rs1800629, rs361525, rs1800630, rs1799964</i>	Susceptible to CIU	[121, 122]
LTC4S	<i>rs730012, –444A>G</i>	Susceptible to AICU	[121, 123]
ALOX5	<i>rs2228064, rs4986832, rs2229136</i>	Susceptible to AICU	[121, 123, 124]
HLA-Cw4,Cw7 HLA-B44 HLA-Bw4 HLA-A24		Not susceptible to AICU Susceptible to AICU Susceptible to COU Not susceptible to COU	[123]
CRH2H2	<i>–466T>C</i>	Increase the amount of antihistamines required for CU patients	[127]
C5AR1	<i>rs11673309 –1,330T/G</i>	Can be used as a therapeutic target to predict the effect of antihistamines in CSU patients	[120]
ADORA3	<i>–1,050G/T rs10776727</i>	Susceptible to AIU	[121, 128]
CRP	<i>rs3093059TT</i>	Response well to antihistamines	[119]
SOCS3		Inhibit degranulation of mast cells	[46, 49, 50]
THBS1		Promote inflammation through the TGF- β /smad pathway	[12, 28, 29, 30]
SELE		Promote leukocyte adhesion	[32, 33]
ICAM-1		Promote leukocyte adhesion	[142, 144]
Gremlin1		Promote the effect of IL-31 on basophils and activate the JAK pathway to promote the release of IL-6 and IL-1	[139]
miR-125a-5p		Correlated with the chemokine signaling pathway	[36]
OSMR		Mediate the activation of IL-31 on basophils; promote IL-6 and IL-1, and release through the JAK/STAT pathway	[54, 56, 57, 58]

CU, chronic urticaria; CSU, chronic spontaneous urticaria; CIU, chronic idiopathic urticaria; AIU, aspirin-induced urticaria; AICU, aspirin-induced CU; COU, chronic ordinary urticaria; CRP, C-reactive protein; IL, interleukin; SELE, selectin E; JAK, Janus tyrosine kinase; SOCS3, suppressor of cytokine signaling 3; OSMR, oncostatin M receptor; CRACM1, calcium release-activated calcium channel 1; TNF, tumor necrosis factor.

lactoside-binding, soluble 7, and lactotransferrin. These proteins are expected to be markers for identifying patients who are responsive to omalizumab [101].

Coagulation/Fibrinolysis-Related Pathways

D-Dimer

D-dimer is a fibrin degradation product, which reflects the activation of the coagulation cascade and the generation of thrombin. Many studies have shown that the se-

verity of urticaria correlates with D-dimer levels and may be more diagnostic for AU [102–105]. Asero et al. [106, 107] showed that the extrinsic pathway of the coagulation cascade is activated in CU, plasma D-dimer levels are often elevated in CU plasma, and thrombin generation can increase vascular permeability and induce mast cell degranulation, demonstrating that coagulation cascade may be associated with the disease activity. High levels of circulating IgE can activate the extrinsic coagulation path-

way, and anti-IgE therapy can inhibit the activation of the extrinsic pathway by blocking free IgE and reducing D-dimer levels [103, 108]. Therefore, D-dimer can be used as a potential blood biomarker to evaluate urticaria activity and response to omalizumab treatment.

Platelet-Activating Factor

Platelet-activating factor (PAF) is released by mast cells, eosinophils, endothelial cells, and platelets in an inflammatory environment and participates in inflammatory reactions by increasing vascular permeability and promoting the white blood cell adhesion. It is important in allergic diseases such as asthma and urticaria [109]. The concentration of PAF in severe allergic reactions is much higher than that in healthy people, and its serum level is directly proportional to the severity of systemic allergic reactions [110]. In an observational study, the researchers found that the serum PAF level of CSU patients was much higher than that of the control group, and the serum PAF level of patients who responded poorly to the H1 receptor was higher [111]. Rupatadine is a second-generation anti-H1-antihistamine and PAF receptor drug, which has a definite effect on the treatment of CSU patients [112, 113].

Single-Nucleotide Polymorphism

Single-nucleotide polymorphism refers to a DNA sequence polymorphism caused by a single nucleotide variation at the genomic level, which is related to the susceptibility or prognosis of diseases, so SNP can be used as biomarkers of disease such as cancer and skin diseases [114, 115]. Studies have found that the polymorphisms of many urticaria-related genes are closely associated with the disease so can be used as markers to predict the severity of disease or the drug treatment effect.

The calcium release-activated calcium channel 1 (or *ORAI1*) gene, encoding calcium ion release-activated calcium channel protein, is related to the calcium influx during mast cell degranulation. Studies have shown that the SNP of the *ORAI1* is closely related to the susceptibility of CU patients and response to antihistamines. Among them, rs12320939 and rs3741596 can predict the high susceptibility of patients to CSU, and rs3741595 is associated with the therapeutic effect of non-sedative H1 receptor antagonists, so the *ORAI1* gene polymorphism can provide a basis for personalized treatment plans [13, 116]. The *FCER1A* encodes the FcεR1a chain; its genetic polymorphisms and non-sedating H1 receptor antagonists are correlated. For patients with effective and ineffective non-sedating H1 receptor antagonists, the allele

frequency of rs2298805A is significantly different and also related to the total serum IgE level [14]. The *FCER1A* promoter -344C>T polymorphism is also associated with aspirin-intolerant CU (AICU), so the *FCER1A* polymorphism can be used to predict AICU and evaluate the severity of the disease [117]. *HNMT* encodes histamine N-methyltransferase, and it has been found that the 939A>G polymorphism leads to the instability of *HNMT* mRNA, which increases *HNMT* expression and histamine release. This polymorphism is also significantly related to the AICU phenotype. It can predict the occurrence of AICU and prevent it [118]. *CRP* encodes CRP, and a recent study found that CRP rs3093059C predicts a poor mizolastine effect [119]. A research reported that *C5AR1* -1,330T/G polymorphism predicts a poor desloratadine effect [120]. Several other genes including *IL-10*, *TNF-α*, *LTC4S*, *ALOX5*, *CysLTR1*, *CysLTR2*, *ADORA3*, *HLA-Bw4*, *-Cw4*, *-Cw7*, *-B44*, *-A24* polymorphisms [120–128], and their meanings are presented in Table 2.

Other Pathways

5-HT Transporter Protein

5-HT transporter protein, a transmembrane protein with high affinity for 5-HT, is involved in the formation of human anxiety and depression, irritable bowel syndrome, depression, obsessive-compulsive disorder, and certain skin diseases such as urticaria and psoriasis [129, 130]. Zabolinejad et al. [131] found the 5-HT transporter content in the skin of CU patients with anxiety was significantly increased compared with healthy controls, and the level correlated with the degree of anxiety, indicating that in people with anxiety disorders, 5-HT transporter can be regarded as a specific biomarker and a unique drug target for treating such patients.

Serum Amyloid A

Serum amyloid A (SAA) is an acute-phase protein that is mainly synthesized in the liver by activated monocytes and macrophages and secreted from certain extrahepatic sites where chronic inflammation occurs, which has an important immune function in inflammation [132]. Previous studies have shown that SAA is associated with various immune diseases such as ankylosing spondylitis and rheumatoid arthritis [133, 134]. Lu et al. [135] found that SAA in the plasma of AU and CU patients was significantly higher than that in healthy controls, verifying that there was an association between SAA levels and urticaria and that higher SAA levels were associated with AU and more severe CU. However, the mechanism is still un-

clear, which may be caused by the liver through certain pro-inflammatory factors, such as IL-1, IL-2, and TNF- α , in response to inflammation [136].

Potential Biomarkers in CU

Gremlin1

Gremlin1, encoding a bone morphogenetic protein antagonist, participates in physiological functions such as organ production and tissue differentiation. Previous studies have reported that *Gremlin1* overexpresses in breast cancer and serves as a predictor of poor prognosis [137, 138]. Recent studies have shown that *Gremlin1* promotes inflammation in CSU. Qu et al. [139] found that *Gremlin1* upregulates serum pro-inflammatory factors like trypsin, β -hexosaminidase, and histamine content by regulating the TGF- β pathway. After constructing a CSU mouse model, transferring *Gremlin1* siRNA into the mouse, results found that serum pro-inflammatory factors like CRP, IL-4, and C5a levels decreased, and the application of TGF- β activator can reverse this consequence [139]. Therefore, *Gremlin1* can be serving as a potential personalized treatment target in CSU.

Intercellular Cell Adhesion Molecule-1

The intercellular cell adhesion molecule-1 (*ICAM-1*), encoding intercellular adhesion molecule-1, mediates cell adhesion. The genetic polymorphism of *ICAM-1* is involved in the pathogenesis of diabetic nephropathy and lung cancer [140, 141]. *ICAM-1*, secreted by mast cells, can mediate the leukocytes adhesion accompanied with P-selectin and VCAM-1D [142]. Recent experiments have shown that silencing *ICAM-1* with siRNA can reduce the adhesion of white blood cells in urticaria mice, thereby improving ICU-related symptoms [143, 144]. Therefore, *ICAM-1* may be a potential target for clinically individualized treatment of urticaria.

Discussion

Urticaria can be divided into AU and CU according to the course of the disease [4]. The cause of AU is relatively clear including drugs and food, and treatment is relatively easy. However, the pathogenesis of CU is more complicated, and most patients are accompanied by autoimmunity, which may be attributed to genetic mechanisms. Long-term itching seriously affects the patients' quality of life [145], and the treatment of CU is difficult. Many patients respond poorly to clinically used drugs such as non-sedating antihistamines and omalizumab. Therefore, it is

necessary to find new therapeutic targets [146]. Due to individual differences, patients' sensitivity and response to drugs differ. The experimental indicator changes may represent the responsiveness of various populations to a certain drug; such markers can guide different populations to use drugs correctly, including the drug type and dosage cycle.

We searched PubMed to find genes, proteins, and small molecules that could be potential markers. At the genetic level, we summarized the SNP of several genes. Two significances of such biomarkers are (1) predicting the susceptibility of patients to urticaria (e.g., rs12320939 or rs3741596 of *ORAI1* can predict patients' susceptibility to AICU) [13, 14] (2) and predicting the patients' response to therapeutic drugs (e.g., rs3741595 of *ORAI1* is closely related to the therapeutic effect of non-sedating H1 receptor antagonists) [13]. For such patients, we can prevent or choose the correct medication. Although *ICAM* and *SELE* play important roles in CSU, it is not easy to intervene clinically for lack of low specificity, which may limit their therapeutic role. At protein and small molecule levels, there are numerous types of proteins elevated in the plasma of CU patients, but most of them lack clearer experimental evidence and mechanisms. We have listed them in Table 2. We selected several newly discovered proteins with relatively clear clinical significance and mechanisms and described them. The significances of these markers have the following 3 categories: (1) as a potential target of treatment, (2) predicting the severity and activity of the disease, and (3) evaluating the drug efficacy. IL-6 and CRP are elevated in a variety of diseases, and the specificity is not high. However, combining plasma levels of IL-6 and CRP and the genetic polymorphism of CRP to predict the disease severity and guide the drug selection may increase their clinical application value. Regarding IL-6, there have been many reports on its important position in CSU, but its specific mechanism is not completely clear. In this review, we summarize the newly discovered signaling pathways related to IL-6 and the genes involved, including the JAK/STAT3 pathway, OSMR gene, and SOCS3 gene and hope to be able to treat more accurately by intervening the upstream signaling pathway. TH17 cell and related cytokines IL-17 and IL-23 are recent research hot spots in allergic diseases, and there may be more specificity than TH2 cell-related pathways. IL-17 can promote the production of CRP, which shows that CRP may only function as a downstream product in the multiple pathogenic pathways of CSU [147], and it can roughly evaluate the disease, but only by blocking the upstream pathways can the therapeutic goal be achieved.

Recently, many studies have proposed that the coagulation/fibrinolysis system and inflammation promote each other in CSU. The coagulation marker prothrombin fragment F1 + 2 and the fibrinolysis marker D-dimer have been found to be related to the severity of CSU. Tissue factor can be expressed by eosinophils in CSU and activate the exogenous coagulation pathway. The generated thrombin and C5a can increase vascular permeability, cause plasma extravasation, and further activate mast cells. At the same time, C5AR1 gene polymorphism is related to the treatment of CSU. The high level of D-dimer in the serum of CSU patients is related to the level of CRP, further indicating the close connection between the coagulation system and inflammation [148, 149]. However, the specificity and sensitivity of D-dimer are not high, and it is mainly used clinically to exclude some thrombotic diseases. Preliminary clinical trial data show that the use of heparin, anticoagulants, and antifibrinolytic drugs can greatly improve some patients who are ineffective against the use of antihistamines [150]. However, due to the small number of clinical samples, this treatment still needs deeper research, and the use of anticoagulant drugs require to rule out patients with bleeding disorders, and the clinical use is limited. In CSU, we can regard mast cells as a link that most pathogenic pathways ultimately lead to, because the substances released by mast cells can cause itching and plasma exudation, in addition to the traditional IgE-mediated mast cell degranulation, recently, many other substances that cause mast cell degranulation have also been discovered, and their levels in CSU are elevated. For example, neuropeptide P and IL-33 can mediate the activation of mast cells through their respective receptors. Thus intervening with these substances and relevant receptors can also be used as a new direction to inhibit mast cell function. Previous review also described the biomarkers in CSU and the current treatment, but the

mechanism of the substances such as IL-6 and vitamin D were not clearly described [151]. In this review, we further describe IL-6, vitamin D, CRP and relevant pathways, hoping to provide more reliable basis for treatment and prediction of disease activity. Therefore, we summarized several new substances that are expected to be potential biomarkers at the genetic and protein/small molecule levels according to different pathogenic pathways, and enumerated other substances that lack of clear clinical evidence mentioned in literatures, providing novel ideas for future research.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yue Zhang: manuscript writing, literature search, and revising. Hanyi Zhang: manuscript writing and literature search. Shengyi Du: manuscript writing and literature search. Siyu Yan: revising and structural design. Jinrong Zeng: revising and structural design.

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