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New Concepts in Chronic Urticaria

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Abstract

Chronic urticaria is a common skin disease without a clear etiology in the vast majority of cases. The similarity of symptoms and lesion pathology to allergen-induced skin reactions supports the idea that skin mast cell and blood basophil IgE receptor activation is involved, however, no exogenous allergen trigger has been identified. The presence of serum IgG autoantibodies targeting IgE or the IgE receptor in ~40 % of CIU cases supports the theory of an autoimmune basis for the disease. However, issues remain with the assays to detect autoantibodies amongst other serum factors, the relationship of autoantibodies to CIU disease activity, and the occurrence of autoantibodies in healthy subjects. Other studies have identified altered IgE receptor degranulation that reverts in disease remission and is accompanied by changes in signaling molecule expression and function in mast cells and basophils in active CIU subjects. The arrival of therapies targeting IgE and the IgE receptor pathway elements has potential use in CIU.

Introduction

Urticaria is a disorder affecting up to 25% of the United States population and can be triggered by allergic reactions or in the setting of infections. Recurrent urticaria for more than 6 weeks is called chronic urticaria, and in the vast majority of cases (>80%) no exogenous cause is determined and the condition is termed chronic idiopathic urticaria (CIU). The incidence of CIU is higher in women (2:1), but not among atopic individuals, with an estimated prevalence of up to ~1% in the US [1]. The lifespan of each skin lesion is between 4 to 36 hours and the spectrum of disease depends on the frequency, number and distribution of lesions, intensity of pruritus and associated symptoms such as angioedema, which occurs in ~40% of cases [2]. The average disease duration is 3-5 years and one-fifth of CIU cases persist beyond five years [3]. Factors associated with longer disease duration include the presence of angioedema, severe disease, and autoimmune serologic features (e.g., positive autologous serum skin test (**see below**) or anti-thyroid antibodies)[3]. Treatment for CIU targets pruritus and ranges from the intermittent use of a non-sedating H1 receptor antagonist in mild disease to combination treatment with several H1 antagonists (sedating and non-sedating), H2 receptor antagonists, leukotriene receptor antagonists, tricyclics and systemic corticosteroids in severe disease [2]. In anti-histamine-resistant or steroid-dependent cases, therapies with immunomodulators such as sulfasalazine, mycophenolate, cyclosporine, and dapsone have been tried with some success [4]. Patients with CIU report a quality of life impairment similar to patients with cardiac disease and other chronic skin diseases such as atopic dermatitis and psoriasis [5,6]. Given annual

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heathcare costs that exceed $2,000 for patients attending a university clinic and not using immunosuppressives, there is an urgent need to advance our understanding of disease mechanisms and to improve therapies [7].

Cellular Infiltrate in CIU and Disease Mechanisms

A central feature of CIU pathogenesis is mast cell degranulation of mediators such as histamine. Skin mast cells numbers are not increased in CIU [8], but they have heightened releasability of histamine in active disease as demonstrated with stimuli such as 48/80 and codeine sulfate. In remission, hyper-releasabilty to 48/80 resolves but persists to codeine sulfate [9,10]. The skin pathology seen in CIU lesions resembles that of allergen-mediated late-phase skin reactions and supports that IgE-receptor (FcεRI) activation of mast cells and basophils is involved in CIU. Lesional skin biopsies in CIU show tissue edema, vascular dilatation, mast cell degranulation and a perivascular infiltrate composed of CD3+/ CD4+/ CD8+ lymphocytes, eosinophils, neutrophils, and basophils [11,12]. A Th2 cytokine profile is present in allergen-late phase skin reactions while CIU lesions express mRNA for both TH2 (IL-4 and IL-5) and TH1 (IFNγ) cytokines [11,13]. However, the mechanisms leading to chronic mast cell activation in the generation of CIU lesions are unknown leading to a variety of approaches to classify subjects. In a subset of CIU subjects (~40%) also referred to as “autoimmune”, several groups have found circulating IgG autoantibodies to IgE or to the extracellular alpha subunit of the high affinity IgE receptor (FcεRIα) that are thought to be pathogenic [14,15]. However, the pathogenesis in the majority of CIU subjects who lack autoantibodies remains unclear [16]. In addition, issues with the detection of CIU-related autoantibodies among other serum factors, the relationship of autoantibodies to disease activity, and the existence of autoantibodies in non-CIU subjects has raised questions as to their pathogenic role [17]. More recently, changes in the expression of signaling molecules in CIU basophils, mast cells, and lymphocytes have been reported in subjects with active disease. The current review will focus on advances in our understanding of both cellular (blood basophil, mast cell and lymphocytes) and serum factors relevant to CIU pathogenesis.

Basophils in CIU

Several observations support a role for basophils in CIU disease pathogenesis. Blood basopenia is found in CIU and basophil numbers are inversely related to urtcaria severity [18]. Basophils are found in both lesional and non-lesional skin biopsies of CIU subjects, which suggests the possibility that basopenia is related to the active recruitment of basophils to skin tissues [11, 19]. An alternate explanation for basopenia is the destruction or sequestration of basophils by autoantibodies detected in the subset of autoimmune CIU subjects [20]. Although pathways for basophil recruitment to skin tissues in CIU are undefined, systemic corticosteroids inhibit basophil recruitment to allergen–induced skin reactions [21]. In CIU, systemic corticosteroids rapidly reduce urticarial lesions and increase blood basophil numbers, which also suggests reduced basophil movement to the skin [18]. At present, it is unknown whether blood basophils in CIU reflect the state of the tissue basophil; represent a re-circulating basophil from skin tissues, or a “bystander” of events occurring in the skin. Nonetheless, the behavior of blood basophils is a useful biomarker to uncover disease-related pathways.

Among the strongest arguments for the participation of blood basophils in CIU disease is the paradoxical suppression of FcεRI-mediated histamine degranulation observed by numerous investigators. Comparisons of blood basophils from active CIU subjects to healthy control subjects has consistently revealed a reduction in IgE receptor-induced histamine release (HR) by CIU basophils using cross-linking anti-IgE or anti-FcεRIα antibodies [22-26]. However, no significant difference in HR is seen with stimuli independent of the FcεRI pathways such as ionophore, 48/80, FMLP, bradykinin, and MCP-1, indicating a specific defect in the FcεRI

pathway of CIU basophils [22-26]. In a limited number of CIU subjects, HR response to Histamine Releasing Factor (HRF) was rarely observed as a distinct measure of hyper-releasability noted in atopic and asthmatic subjects [26]. Among the explanations for suppression of the basophil FcεRI pathway are that the basophils are desensitized *in vivo* to further FcεRI-induced activation. Recent insights into the dysregulated expression of molecules that are critical to signal propagation after IgE receptor activation (spleen tyrosine kinase, Syk) or those that are relevant to inhibition of receptor responses (Src homology 2 (SH2)-containing inositol phosphatases, SHIP-1 and SHIP-2) suggest a more complex picture.

A review of the background of basophil and mast IgE receptor activation is useful to provide a context for changes present in CIU basophils. Upon FcεRI activation, Syk tyrosine kinase is recruited to tyrosine phosphorylated FcεRIγ subunits and phosphorylates signaling molecules including Shc and PLCγ. Depletion of Syk from RBL-2H3 mast cells prevents FcεRI-mediated secretion of granular contents, and cytokines [27]. Likewise, human “non-releaser” basophils are deficient in Syk protein and release < 5% of total histamine content after FcεRI activation and occur at a frequency of 10-20% in the general population [28]. Protein levels of Syk are a major regulator of basophil HR in normal basophils and are selectively downregulated among a host of signaling elements after FcεRI triggering whereas levels of SHIP-1 and SHIP-2 are stable [29]. Levels of Syk and to some degree, SHIP-1, account for the variance seen in the range of basophil HR in normal subjects [30]. Phosphoinositide lipid phosphatases are well-established as negative regulators of hematopoietic cell activation, survival and proliferation [31]. In particular, SHIP-1 is known to associate with the FcεRI β subunit and is activated upon stimulation of rodent mast cells with supraoptimal concentrations of antigen or IgE [32,33]. Importantly, mast cells of SHIP-1 knockout mice more readily degranulated after IgE receptor activation or even sensitization with a highly cytokinergic IgE alone [34]. Similarly, in hyper-releasable human basophils a five-fold reduction in SHIP-1 protein levels was associated with heightened response to Histamine Releasing Factor [35]. SHIP-1 has also been shown to have a regulatory role in the kinetics of IgE-mediated signaling and mediator release in primary human basophils [36]. Moreover, a homologous protein, SHIP-2, has been found to limit mast cell degranulation as well as IL-4 and IL-13 gene expression upon FcεRI stimulation that is independent of SHIP-1 actions [37].

Recently, a bimodal profile of CIU subjects' blood basophil anti-IgE HR response was reported [26] (**see** Table I). Fifty percent of CIU subjects have significant reductions in their basophil histamine release with optimal anti-IgE stimulation (< 10% of total histamine content) and are designated anti-IgE non-responders (CIU NR). The remaining 50% of CIU subjects have basophils that release greater than 10% of total histamine content after anti-IgE stimulation and are designated anti-IgE responders (CIU R). A comparison of anti-IgE-induced HR patterns from CIU basophils to their corresponding SHIP-1 and SHIP-2 levels reveal that SHIP-2 is increased in the basophils of CIU NR subjects, whereas SHIP-1 levels are reduced in basophils of CIU R donors. Furthermore, the changes in expression of SHIP-1 or SHIP-2 proteins in CIU basophils appear to be functional, as they should be inversely proportional to the cellular [PI 3,4,5 P_3] levels after anti-IgE stimulation of the CIU basophils. In fact, the heightened SHIP-2 expression observed in CIU NR basophils compared to normal basophils results in decreased anti-IgE-induced Akt phosphorylation, a surrogate measure of cellular [PI 3,4,5 P_3] [26]. In contrast, CIU R basophils were found to have constitutive phosphorylation of Akt consistent with their reduced expression of SHIP-1. Importantly, altered Syk protein levels in CIU basophils are not correlated with the patterns of anti-IgE stimulated HR basophils of CIU subjects, and in particular, the CIU NR subset. In fact, Syk-deficient donors with intact HR have been noted among CIU subjects [38]. Collectively, these observations suggest a shift in the paradigm of Syk-dominated regulation of HR found in normal basophils in the setting of disease such as CIU [38]. Further, no clear relationship between basophil functional phenotypes and the presence of serum autoantibodies detected by an immunoenzymetric assay

(IEMA) (either IgG anti-IgE or IgG anti-FcεRIα), or in limited studies by Western blot (IgG anti-FcεRIα) or by serum histamine releasing activity (HRA) (**see below**) were noted [26,39]. Thus, autoantibody-mediated desensitization of basophils' IgE receptor function seems unlikely.

Although the disease implications of basophil functional phenotypes are not fully apparent, some relevant associations with CIU disease activity have been established. A longitudinal study of CIU subjects has established the stability of the basophil IgE-receptor degranulation phenotypes (CIU R and CIU NR) in subjects with persistent disease [39]. In addition, clinical measures of CIU severity also segregate between CIU R and CIU NR subjects such as heightened itch scores reported by CIU R subjects [40]. In CIU subjects who enter natural disease remission, basophil anti-IgE induced HR and blood basophil numbers significantly increase [23,39]. Most notably, CIU NR basophil maximal HR and sensitivity to anti-IgE increases to levels observed in healthy subjects, whereas CIU R subjects basophils have heightened sensitivity to anti-IgE activation. Further, these shifts in basophil function during remission are independent of a subject's autoantibody status and in subjects with autoantibodies, occur without a parallel decrease in autoantibody titers [39]. Thus, there is ample evidence that basopenia and suppressed CIU basophil FcεRI-meditated degranulation occur in active CIU disease and improve in CIU remission. In disease remission, the rise in FcεRI-mediated histamine degranulation by blood basophils contrasts with the reduction in hyper-releasability by skin mast cells. Recent data support that distinct basophil degranulation phenotypes are present in active disease and are associated with an imbalance of FcεRI-regulating phophatases. However, the status of FcεRI signaling molecule expression and function during remission remains to be established.

Other recent studies have examined the levels of blood basophil surface activation markers, CD 63 and CD 203c, that are remarkably sensitive to IgE receptor activation via allergen or by a cross-linking anti-IgE antibody. Levels of these markers on basophils of CIU subjects were modestly elevated and similar to levels observed on basophils in allergic subjects, suggesting a state of *in vivo* priming. Surprisingly, levels of these markers were not enhanced on basophils of CIU subjects with evidence of serologic autoimmune features (ASST, HRA or Western blot positivity for IgG anti-FcεRIα) [41,42]. In addition, basophils of CIU subjects are described to have enhanced release of histamine after incubation with sera from both normal and CIU subjects, but the exact nature and significance of this serum reactivity remains to be established [25].

Lymphocytes in CIU disease

An early report of signaling molecule differences in CIU subjects noted increased p21 ras expression in the PBMCs of CIU subjects, similar to a pattern seen in other autoimmune diseases such as diabetes, although no functional defect in the MAP kinase activation or proliferation was observed with PHA stimulation [43]. Studies focused on the profiles of circulating cytokines in CIU serum note increased IL-4 IL-6, IL-1β, and IL-12 p70 as compared to healthy controls [44,45]. Isolated PBMC PHA-stimulated cytokine profiles have also been examined and results have been variable. As compared to control subjects, some studies revealed no difference in IFNγ, IL-10, TNFα and reduced IL-4 expression predominantly in ASST positive hosts [45,46] whereas high levels of IL-10 and TNFα were seen with mitogen in a second study [47]. Given the prominence of lymphocytes in CIU lesions, further studies are necessary to clarify their role in the disease.

Mast cells in CIU disease

Skin mast cell degranulation and their secreted mediators such as histamine are strongly implicated in the generation of urticarial lesions but human *in vivo* studies are limited by the

difficulties in obtaining large numbers of skin tissue mast cells for studies. Recent alternatives include the use of cultured human mast cells derived from CD34+ progenitors or isolated from progenitors arising from cultured human skin samples after prolonged culture in a cytokine-rich environment [48]. A recent study of releasability utilizing mast cells cultured from the CD34+ cells from the peripheral blood of CIU R, CIU NR and normal donors has found an increase in spontaneous histamine release after IgE sensitization among CIU derived mast cells [49]. An analysis of the signaling molecules in the FcεRI pathway in these cultured mast cells revealed increased expression of Syk in the CIU R donor subset that is correlated to the degree of spontaneous HR. A study using skin-tissue derived human skin mast cells examined the impact of IgE levels on IgE receptor function. The findings supports that levels of IgE can contribute to skin mast cell sensitivity for IgE receptor degranulation and significant release of mediators occurs at low levels of receptor cross-linking. These results carry implications for therapies involving reduction of IgE levels in CIU (**see below**) [50].

Assessment of Serologic Autoimmune Assays

An autoimmune basis for CIU evolved from the observations of increased prevalence of thyroid autoantibodies [2,3] in CIU subjects and HLA-DR associations [51]. It is widely believed that a subset of CIU subjects have serum IgG autoantibodies that target the IgE receptor alpha subunit (30%) or, less commonly, surface-bound IgE (10%) [2]. It is further proposed these autoantibodies are functional *in vivo* and preferentially activate skin mast cells based on a high prevalence of complement-fixing IgG isotypes (IgG1 and IgG3) that act via the C5a receptor expressed by skin mast cells and not mucosal mast cells [2,52]. Although subjects with “autoimmune” CIU are reported to have increased disease severity [53,54], there are few differences from non-autoimmune CIU on skin lesion pathology [11,12], or the activation status of their blood basophils, a proposed cell target of autoantibodies [41,42]. Different approaches to detect serum autoantibodies have been employed leading to a variety of readouts and difficulty in establishing interassay agreement. The major issue with the “autoimmune” classification is the lack of a universal serum assay that is standardized and able to distinguish immunoglobulin-based serum reactivity from other bioactive serologic factors (e.g., chemokines, cytokines) present in a serum sample. The detection of CIU-related autoantibodies or serum factors in non-CIU subjects raises concerns that such autoantibodies are markers of underlying autoimmunity rather than participants in disease pathogenesis (e.g. ANA).

The original “autoimmune” assay, termed the **autologous serum skin test (ASST)**, involves the intradermal injection of autologous serum into a subject's skin to look for wheal formation, implicating a serum factor that triggers skin mast cells. Concerns about the ASST include the persistence in CIU remission [55], the false positive rate (30-47%) in allergic rhinitis patients and healthy controls [56,57], and persistence of a positive ASST upon IgG-depletion of serum samples, raising concerns about the nature of the active factor [58]. In fact, active ASST serum fractions of <30 KD have been recognized [59]. A recent adaptation of the ASST involving the use of plasma, or APST, and has a higher frequency of positivity among CIU subjects and suggests the involvement of an activated coagulation cascade in CIU [60]. The relationship of a positive APST to the presence of autoantibodies is not yet established.

A second assay for “autoimmunity” in CIU measures **serum histamine releasing activity** (**HRA**) by exposing CIU serum *in vitro* to a normal donor's basophils [14,15]. Using purified serum IgG fractions and inhibition studies with soluble alpha chain, HRA activity has been shown to indicate functional autoantibodies (mostly IgG_1 and IgG_3 isotypes) that trigger HRA in a C5a-complement-dependent fashion [61,62]. However, complement deposition is absent in CIU skin lesion biopsies, and serum complement depletion is not a feature of autoimmune CIU [3]. Although serum HRA is claimed to indicate autoantibody presence, a study of ~250 CIU patients found poor agreement between serum HRA results and serum Western blots using

FcεRIα [63]. Likewise, there is variable agreement between HRA and ASST outcomes [60]. HRA is often cited as the "gold-standard" assay to measure functional CIU autoantibodies. However, the dependance of the assay on the behavior of the normal donor's basophils for a readout has hampered the standardization of this method (eg, variable basophil priming *in vivo* by IL-3). Further, the presence of HRA in the serum of non-atopic, non-CIU subjects remains unexplained and the topic of controversy [42]. The lack of standards, the use of a normal basophil donor, and sensitivity to other serum factors such as IL-3 also impacts a newer assay testing CIU serum-induced basophil CD203c activation [2,64] and adds to the confusion about defining the autoimmune CIU subset.

An ELISA assay for IgG anti-FcεRIα autoantibodies showed that these autoantibodies occurred in subjects with other autoimmune skin diseases such as pemphigus vulgaris and dermatomyositis and have a similar frequency of autoantibodies to CIU subjects. However, different different IgG subclass (IgG_2, IgG_4) are predominant in non-CIU subjects, suggesting functional differences [65]. A sensitive IEMA has found similar titers and frequency of IgG anti-FcεRIα and IgG anti-IgE in CIU and healthy controls [39] while others have shown such autoantibodies be part of the natural repertoire of the immune system [66].

CIU therapies and insights into pathogenesis

An examination of current therapies and insight into possible pathogenic mechanisms operating in active CIU disease and has been reviewed recently [67]. The effectiveness of H1 and H2 antagonists as well as leukotriene receptor antagonists in treating CIU supports a pathogenic role for tissue-resident basophils and mast cells. The effectiveness of corticosteroids are difficult to localize given their broad anti-inflammatory properties and none of the present CIU therapies are curative.

Newer drugs directly targeting the IgE receptor pathways of mast cells and basophils in allergic disease, such as Syk inhibitors and omalizumab, a monoclonal antibody targeting free IgE at it's binding site to the high affinity receptor [68,69], have potential in CIU. Studies with omalizumab have established that reducing free IgE levels reduces basophil and skin mast cell FcεRI expression and function in allergen mediated skin reactions [70]. Recently, mouse studies have noted unique IgE species, termed highly cyokinergic IgE (HC IgE), that have the ability to prevent mast cell apoptosis, activate FcεRI signaling and induce mediator release by sensitization alone [71]. There is debate as to the exact mechanim by which these IgE species activate cells, such as reactivity to multiple epitopes specificities or the ability to assume multiple conformational states. As such, the possibility of such altered IgE species in human disease has been raised although a consistent finding is the need to culture the cells prior to observing HC IgE activation of the cells [72]. A series of case reports [73] and two small clinical trials using omalizumab therapy in severe CIU subjects (ASST-positive or unselected for autoimmune features) showed remarkable and rapid symptom improvement in subjects unresponsive to current antihistamine therapies. Most importantly, these trials offer a insight into a disease mechanism related to free IgE capture or IgE receptor reduction on mast cells or basophils as a mechanism of CIU disease [74,75]. Of note, both basopenia and suppressed basophil FcεRI function improve under the conditions of IgE removal by omalizumab and are reminiscent of changes seen in natural disease recovery [74].

In contrast, the elucidation of changes in the expression of key regulatory elements in the FcεRI pathway of CIU subjects provides an opportunity for treatment with newer, more specific immunomodulators developed originally for the treatment of other immune-mediated diseases. Specifically, the stratification of CIU patients into subgroups such as CIU R and CIU NR in conjunction with the profiling of even a limited number of signaling proteins in basophils and cultured mast cells may prove beneficial. The increased expression of Syk kinase coupled with

increased histamine release upon IgE sensitization in CIU R mast cells suggests treatment with a Syk inhibitor such as R112, proven effective in treatment of allergic rhinitis, may be useful in CIU [69]. A recently recognized Syk inhibitor effective at preventing anaphylaxis in an animal model also offers a potential therapeutic [76]. Small molecule SHIP-1 agonists, effective in rodent mast cells, may prove useful for the treatment of CIU R, if the suppression of FcεRI-induced histamine release is protective in these subjects, he drug may exacerbate rather than help these subjects [77]. In vitro testing of the CIU subjects' basophils or mast cells with the candidate immunomodulator should shed light on the potential in vivo effects. If successful in normalizing histamine release then the drugs could be screened by skin chamber testing prior to systemic administration. The application of sensitive (< 10,000 cells), specific methods such as reverse-phase protein microarrays for profiling of signaling protein expression in CIU lesions should suggest additional treatment modalities [78].

Conclusion

Given the prevalence of the disease and lack of effective treatment, there is an urgent need to advance our understanding of disease mechanisms and to develop improved therapies for CIU. In CIU, skin lesions contain degranulated mast cells, TH1+TH2+ lymphocytes, eosinophils, neutrophils and basophils, accompanied by a paucity of circulating basophils with suppressed anti-IgE HR. Investigations have focused on mast cell releasability, basophil functional phenotypes and the role of serum factors. A recent clinical trial showed that targeting IgE with omalizumab led to rapid symptom reduction, increased blood basophil numbers and enhanced basophil FcεRI-mediated HR. These findings strongly support a role for IgE and the FcεRI signaling pathway in CIU disease pathogenesis. Furthermore, the elucidation of changes in the expression of key regulatory elements in the FcεRI pathway of CIU subjects provides an opportunity for treatment with newer, more specific immunomodulators developed originally for the treatment of other immune-mediated diseases. Specifically, the stratification of CIU patients into subgroups such as CIU R and CIU NR in conjunction with the profiling of even a limited number of signaling proteins in basophils and cultured mast cells may prove beneficial.

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Table I

Features of Basophil Phenotypes, CIU R and CIU NR, in CIU

Feature of HR	CIU Responder	CIU Non-responder
Release to optimal dose of cross-linking anti-IgE	> 10% of cellular histamine content	≤ 10% of cellular histamine content
Dose response to anti-IgE in active disease	Similar to normals subjects	10-fold higher dose for maximal release
Phosphatase levels relative to normals	Reduced SHIP-1 levels	Increased SHIP-2 levels
Kinase levels	Syk similar to normal	< or equal to normal
Sensitivity to anti-IgE in remission	Increased sensitivity at low end of dose response	Increased sensitivity and maximal release