

Basophil Responsiveness in Chronic Urticaria

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Chronic urticaria is a common skin disease without an etiology in the majority of cases. The similarity of symptoms and 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. Recent evidence supports a role for blood basophils in disease expression. Specifically, blood basopenia is noted in active disease with the recruitment of blood basophils to skin lesional sites. In addition, blood basophils display altered IgE receptor-mediated degranulation that reverts in disease remission. In active chronic idiopathic urticaria (CIU) subjects, changes in IgE receptor–signaling molecule expression levels accompany the altered degranulation function in blood basophils. The arrival of therapies targeting IgE has further shown that altered blood basophil degranulation behavior has potential use as a disease biomarker in CIU.

Introduction

Urticaria is a disorder affecting up to 25% of the US population and can be triggered by allergic reactions or in the setting of infections. Recurrent urticaria for more than 6 weeks is classified as *chronic urticaria*; in most cases (> 80%), no exogenous allergen or systemic disease is identified, and the condition is termed *chronic idiopathic urticaria* (CIU). The prevalence of CIU is approximately 1% in the United States and has a higher incidence in women, but not among atopic individuals [1]. The lifespan of an individual skin lesion is between 4 to 36 hours; the spectrum of disease depends on the frequency of episodes, number and distribution of lesions, and intensity of pruritus and associated symptoms such as angioedema, which occurs in approximately 40% of cases [2]. The average disease duration is 3 to 5 years, and one

fifth of CIU cases persists beyond 5 years [3]. Factors associated with longer disease duration include the presence of angioedema, severe disease, and autoimmune serologic features such as a positive autologous serum skin test or the presence of antithyroid antibodies [3]. The quality-of-life impairment in CIU patients is similar to patients with cardiac disease and other skin diseases such as atopic dermatitis and psoriasis [4,5]. Among CIU patients attending a university clinic and not using immunosuppressives, the average annual health care costs exceed \$2000, supporting the need to advance our understanding of disease mechanisms and improve treatments [6•].

Chronic Idiopathic Urticaria Pathogenesis: Proposed Disease Mechanisms

A central feature of CIU pathogenesis is skin mast cell degranulation and release of mediators such as histamine. Evidence supports that the number of skin mast cells is not increased in CIU [7]; rather, they have heightened releasability of histamine in active disease to stimuli such as 48/80 that reverts in remission [8,9]. 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 [10,11]. The skin pathology seen in CIU lesions resembles the infiltrate seen in allergen-mediated, late-phase skin reactions; however, the cytokine profile in CIU shows expression of mRNA for both T-helper type 2 (Th2) (interleukin [IL]-4 and IL-5) and Th1 (interferon γ) cytokines [10,12]. The exact mechanisms leading to chronic mast cell activation in the generation of CIU lesions are unknown; therefore, there are various approaches to classify subjects. In a subset of CIU subjects (approximately 40%), also referred to as *chronic autoimmune urticaria*, several groups have found circulating IgG autoantibodies to IgE or to the extracellular alpha subunit of the high affinity IgE receptor (Fc ϵ RI α) that are thought to be pathogenic [13,14]. However, the pathogenesis in the majority of CIU subjects who lack autoantibodies remains unclear and has been reviewed recently [15•]. Issues with the methods used to detect serum autoantibodies, the relationship of autoantibodies to disease activity, and the occurrence of autoantibodies in non-CIU subjects have raised questions

as to their pathogenic role [16]. More recently, changes in the degranulation phenotype of blood basophils in CIU have been reported in subjects with active disease. This review focuses on advances in our understanding of blood basophil behavior relevant to CIU pathogenesis.

Blood Basophils in Chronic Idiopathic Urticaria

Blood basophils represent less than 1% of circulating leukocytes and are characterized by secretory granules containing histamine and surface IgE receptors. These cells are often recruited to sites of allergen-induced inflammation such as the lung, nose, and skin. Although previously regarded as a circulating counterpart to the tissue mast cell, basophils are now being recognized as having distinct roles in allergic inflammation, as evidenced by recent mouse models using strategies to deplete basophils or reconstitute deficient mice with adoptive transfer of mouse basophils [17•,18]. In a model of chronic allergic inflammation of the skin that utilizes multivalent allergen injection in the skin of a mouse that has been passively sensitized with antigen-specific IgE, the delayed onset ear swelling and eosinophilic infiltration occurring 2 to 4 days after both early and late phase events was shown to be dependent on basophils and independent of mast cells or T cells [19].

Several collective observations in human studies support a role for basophils in CIU disease pathogenesis. Blood basopenia is found in CIU, and basophil numbers are inversely related to urticaria severity measures [20]. The presence of blood basophils in both lesional and non-lesional skin biopsies of CIU subjects suggests that blood basopenia is due to the recruitment of basophils to skin tissues [10,21]. This model is strengthened by the observation that in CIU, systemic corticosteroids rapidly reduce urticarial lesions and increase blood basophil numbers, suggesting reduced basophil movement to the skin [20]. It is known that systemic corticosteroids inhibit basophil recruitment to allergen-induced skin reactions and also suppress basophil-mediator release [22,23]. Evidence also suggests that basopenia is related to the presence of autoantibodies found in a subset of CIU subjects [24]. At present, it is unclear whether blood basophils reflect the state of the tissue basophils in CIU, represent a recirculating basophil from skin tissues, or only serve as a “bystander” of events occurring in the skin. Nonetheless, the enumeration of blood basophils has proven to be a useful biomarker of disease activity in CIU.

Numerous investigators also have noted the paradoxical suppression of blood basophil FcεRI-mediated histamine degranulation in CIU. Comparisons of blood basophils from active CIU subjects to healthy control subjects have consistently revealed a reduction in IgE receptor-induced histamine release (HR) by CIU basophils using cross-linking anti-IgE or anti-FcεRI antibodies [25–28,29••]. In contrast, no significant difference in HR was seen with stimuli inde-

pendent of the FcεRI pathway such as ionophore, 48/80, N-formyl-methionyl-leucyl-phenylalanine (FMLP), bradykinin, and monocyte chemoattractant protein (MCP-1) [25–28,29••]. Therefore, a specific defect in the FcεRI signaling pathway of CIU basophils is likely. Further, basophil HR response to histamine-releasing factor (HRF) was rare among CIU subjects, a distinct measure of hyper-releasability, as previously noted in the basophils of atopic and asthmatic subjects [29••].

Among the proposed explanations for suppression of the basophil FcεRI degranulation pathway are that the basophils are desensitized *in vivo* to further FcεRI-induced activation. However, the evidence for *in vivo* activation of basophils via their IgE receptor is mixed. For example, the average per cell histamine content of CIU blood basophils is not reduced compared with that of normal subjects [27,29••]. Other recent studies have examined the levels of blood basophil surface activation markers, CD63 and CD203c, which are remarkably sensitive to IgE receptor activation via allergen or by a cross-linking anti-IgE antibody [30]. Levels of these markers on basophils of CIU subjects were modestly elevated and similar to levels observed on basophils from allergic subjects, suggesting a state of *in vivo* priming. Furthermore, levels of these markers were not enhanced on basophils of CIU subjects with evidence of serologic autoimmune features (autologous serum skin test, histamine releasing activity, or Western blot positivity for IgG anti-FcεRIα) [30,31]. 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 remain to be established [28].

Recent insights into the dysregulated expression of molecules that are critical to signal propagation after IgE receptor activation (spleen tyrosine kinase [Syk]) or those relevant to inhibition of receptor responses (Src homology 2 (SH2)-containing inositol phosphatases [SHIP-1] and SHIP-2) suggest a more complex picture. A brief background of basophil IgE receptor activation is useful to provide a context for changes present in CIU basophils. Upon FcεRI activation, Syk is recruited to tyrosine phosphorylated FcεRIγ subunits and phosphorylates signaling molecules, including Shc (Src homology and collagen-containing protein) and PLCγ (phospholipase C-γ). It is known that human “nonreleaser” basophils are deficient in Syk protein, release less than 5% of total histamine content after FcεRI activation, and occur at a frequency of 10% to 20% in the general population [32]. 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 [33]. Levels of Syk, and to some degree, SHIP-1, account for the variance seen in the range of basophil HR in normal subjects [34•]. Phosphoinositide lipid phosphatases are well established as negative regulators of hematopoietic cell activation,

Table 1. Features of basophil functional phenotypes observed in CIU subjects

Feature of HR	CIU responder	CIU nonresponder
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 normal 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	Less than or equal to normal
Sensitivity to anti-IgE in remission	Increased sensitivity at low end of dose response	Increased sensitivity and maximal release

CIU—chronic idiopathic urticaria; HR—histamine release; SHIP—Src homology 2 (SH2)-containing inositol phosphatases; Syk—spleen tyrosine kinase.

survival, and proliferation [35]. In particular, SHIP-1 is known to associate with the FcεRIβ subunit and is activated upon stimulation of rodent mast cells with supraoptimal concentrations of antigen or IgE [36,37]. Importantly, mast cells of SHIP-1 knockout mice are more readily degranulated after IgE receptor activation or even sensitization with a highly cytokinergic IgE alone [38]. In hyper-releasable human basophils, a fivefold reduction in SHIP-1 protein levels was associated with heightened response to HRF [39]. SHIP-1 also has been shown to have a regulatory role in the kinetics of IgE-mediated signaling and mediator release in primary human basophils [40]. 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 [41].

Recently, a bimodal distribution of the blood basophil anti-IgE HR response of CIU subjects was reported [29••] (Table 1). Approximately 50% 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 nonresponders (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 protein expression of SHIP-1 or SHIP-2 proteins in CIU basophils appear to be functional, as they should be inversely proportional to the cellular phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P₃] levels after anti-IgE stimulation of the CIU

basophils. In fact, the heightened SHIP-2 expression observed in CIU-NR basophils results in decreased anti-IgE-induced Akt phosphorylation, a surrogate measure of cellular PI(3,4,5)P₃ [29••]. 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 [42]. Collectively, these observations suggest that Syk-dominated regulation of HR found in normal basophils may not be active in the setting of disease such as CIU [42]. Further, no clear relationship between basophil functional phenotypes and the presence of serum autoantibodies detected by an immunoenzymetric assay (either IgG anti-IgE or IgG anti-FcεRIα), or in limited studies by Western blot (IgG anti-FcεRIα) or by serum histamine-releasing activity were noted [29•,43••]. Thus, autoantibody-mediated desensitization of the IgE receptor function of basophils also seems unlikely.

Although the clinical disease implications of basophil histamine degranulation phenotypes are not fully apparent, some associations with CIU disease activity have been noted. A longitudinal study of CIU subjects with repeated basophil sampling has established the stability of the basophil IgE-receptor degranulation phenotypes (CIU-R and CIU-NR) in subjects with active disease [43••]. Among clinical measures of CIU disease severity, it is noted that CIU-R subjects report heightened itch scores despite similar levels of disease activity to CIU-NR [44]. In CIU subjects who enter natural disease remission, basophil anti-IgE-induced HR and blood basophil numbers are noted to significantly increase [26,43••]. Most notably, CIU-NR basophil maximal HR and sensitivity to anti-IgE increases to levels observed in healthy subjects, whereas basophils of CIU-R subjects 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 [43••]. Thus, there is ample evidence that basopenia and suppressed CIU basophil FcεRI-mediated 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. However, the status of basophil FcεRI-signaling molecule expression and function during remission remains to be established.

Chronic Idiopathic Urticaria Treatment and Blood Basophils

Treatment for CIU targets pruritus and ranges from the intermittent use of a nonsedating H1 receptor antagonist in mild disease to combination treatment with several

H1 antagonists (sedating and nonsedating), 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 [45]. Patterns of blood basophil degranulation have been noted to shift in a clinical trial using a monoclonal antibody targeting IgE, omalizumab [46•]. In CIU subjects receiving omalizumab, improvement in clinical symptoms was mirrored by the behavior of blood basophils and recapitulated the basophil's behavior in natural CIU disease remission. The utility of monitoring blood basophil degranulation phenotype and basopenia has yet to be fully integrated in clinical trials.

Conclusions

In CIU basophils, the observed changes in FcεRI-signaling pathway molecule expression may underlie changes in basophil releasability seen in active disease. Patients with CIU can be segregated on the basis of basophil functional phenotype (CIU-R or CIU-NR), which remains stable during active disease and shifts in natural disease remission. The response to clinical therapies for CIU may also be reflected in the degranulation behavior of basophils and improvements in basopenia.

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Disclosure

Dr. Saini is a consultant for Genentech and Novartis.

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