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.

**Chronic 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 (FcεRIα) 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 nonlesional 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,