Chronic urticaria: What is new, where are we headed

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ABSTRACT

Chronic urticaria can be defined as the occurrence of widespread daily or nearly daily wheals for at least 6 weeks, which may be accompanied by angioedema. It is a disease with a considerable impact on patients' quality of life. Furthermore, these patients may undergo extensive laboratory evaluations seeking a cause only to be frustrated when none is found. There is no curative treatment for this disorder and we do not understand the mechanisms that lead to the onset of disease. However, in recent years there have been significant advances in the understanding of some of the molecular mechanisms that cause cutaneous inflammation that is manifest as urticaria and angioedema. In this review we will summarize our recent contributions to this field and try to offer insights regarding future directions for research.

Key words: Chronic urticaria. Cutaneous inflammation. Angioedema. Interleukins. Lymphocytes Th1-Th2. Mast cells. Basophils.

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INTRODUCTION

Chronic urticaria can be defined as the occurrence of widespread daily or nearly daily wheals for at least 6 weeks[1], which may be accompanied by angioedema. While the wheals are transient, the resolution of angioedema is slower and could take up to 72 hours. The natural course of chronic urticaria is self-limited, with spontaneous remissions and occasional relapses[2]. We recently calculated a 0.6 % (95 % CI: 0.4-0.8) prevalence in a population study[3].

Chronic urticaria has a considerable impact on patients' quality of life[4,5]. In a recent national survey on patients attending an Allergy Department, chronic urticaria was the disease with the greatest impact on quality of life of all the allergic diseases. Furthermore, these patients may undergo extensive laboratory evaluations seeking a cause only to be frustrated when none is found.

There is no curative treatment for this disorder and we do not understand the mechanisms that lead to the onset of disease. However, in recent years there have been significant advances in the understanding of some of the molecular mechanisms that cause cutaneous inflammation that is manifest as urticaria and angioedema. In this review we will summarize our recent contributions to this field and try to offer insights regarding future directions for research.

Malmros[6] was the first to report the ability of autologous serum to elicit a positive skin test, yet his report published in 1946 was largely forgotten. In 1982 when Leznoff et al reported a 15 % prevalence of antithyroid antibodies in patients with chronic urticaria[7] a role for autoimmunity in disease pathogenesis was again considered. Later observations reported a 5-10 % incidence of functional anti IgE antibodies again suggesting that autoimmunity might have a role[8] in the disease. Then the autologous skin

test was reexamined[9] and was found to be positive in a significant subpopulation of patients with chronic urticaria. The next development was by Greaves and co-workers[10] who demonstrated the presence of functional autoantibodies against the alpha subunit of the IgE receptor in at least one third of patients. Kaplan and coworkers[8,11] corroborated basophil activation through the alpha subunit of the IgE receptor and subsequently found the presence of these IgG antibodies in the sera of about 40 % of patients with chronic urticaria[12]. 60 % of patients' sera are negative and these remain idiopathic.

Anti IgE receptor antibodies (and anti IgE) are able to cause the release of histamine and other mediators which are responsible for urticaria and angioedema by activating blood basophils and cutaneous mast cells[12,13]. The functional activity of these autoantibodies is augmented in the presence of components of the classical complement cascade[14] with a critical role for C5a[15].

This ability to activate basophils and mast cells can be confirmed either by the autologous skin test[9] or by the ability of serum to degranulate these cells in vitro. The basophil histamine release assay appears to be the "gold standard" for detecting functional autoantibodies in the serum of patients with chronic urticaria since we found both false negative and positive results by binding assays[15,16]. Results could be optimized by preincubation of basophils with IL-3 which augments histamine release without affecting the percentage of positive sera[17].

Sabroe et al[18] compared functional and non functional sera and found that sera which were unable to activate basophils were not able to activate mast cells either. Thus their lack of activity is not caused by unresponsive basophils. The only difference found was that those patients with functional antibodies had higher severity scores and more intense inflammation on skin biopsy.

The presence and probable role of IgG autoantibodies directed against epitopes expressed on the alpha-chain of the IgE receptor and to lesser extent to IgE in a subset of patients is generally acknowledged. Recently evidence that supports this conclusion[19] includes demonstration that sera of chronic urticaria patients induce basophil expression of CD203c[20], CD63[21], as assessed by Flow cytometry, and this expression does correlate with histamine release[22].

It has also been reported that some patients with chronic urticaria have IgG antibodies against the eosinophil low affinity IgE receptor (CD23) which activates eosinophils and then causes histamine release[23] by ECP, MBP or other eosinophil cationic proteins. However this has not yet been confirmed.

Autoimmunity is also supported by observations such as a higher frequency of HLA class DR4 and DQ8 alleles seen in patients with chronic urticaria consistent with a predisposition to this disease[24] dependent on immune response genes.

MEDIATOR PRODUCTION FROM MAST CELLS AND BASOPHILS UPON SERA STIMULATION

We first stimulated human skin mast cells and basophils with chronic urticaria sera in order to assess IL4 production, and related the results to plasma IL4 levels[25].

When we stimulated basophils from a normal donor with sera from chronic urticaria patients, we observed that those patients whose sera were able to activate basophils and induce histamine release, were also able to induce IL4 production. In contrast, when we incubated sera from patients lacking the ability to stimulate histamine release, we could not detect IL4 in the supernatant after incubating with the same basophils.

Leukotriene production by cutaneous mast cells and Leukotriene production by basophils were closely correlated when each cell type was incubated with the same chronic urticaria sera. Thus sera that activate basophils, also activate mast cells, which is consistent with earlier data regarding histamine release[14]. We observed higher serum leukotriene concentrations in those patients whose urticaria is associated with angioedema compared to sera from patients with only urticaria, however the difference did not reach statistical significance. There were no significant differences between these latter groups with regard to histamine release. There was also no difference in their ability to induce either histamine release or Leukotriene production upon incubation of patients' sera with basophils, rather than mast cells.

Our data lend further support to the presence of basophil and cutaneous mast cell activators, predominantly anti FcεRI[16], in the sera of patients with chronic urticaria and that such sera can lead to the production of leukotrienes and IL4 as well as histamine. Antibody to the IgE receptor is clearly correlated with the ability to induce IL4 release since the same sera that activate basophils and induce histamine release also induce IL4 production.

Our results also provide clues to explain the presence of a perivascular cellular infiltrate that differentiates chronic urticaria from other types of urticaria such as dermographism[26,27]. The serum factor is responsible not only for histamine release, but also C5a, cytokines, and presumably chemokines all of which contribute to the recruitment of cells[28,29].

TH 1 OR TH2 PHENOTYPE

We next questioned whether the sera of patients with chronic urticaria reflect predominance of a Th1 or Th2 phenotype. We initially approached this objective by determining the cytokine profile in the sera of patients with chronic urticaria. We measured INFgamma as a representative of a Th1 profile, and we measured IL4 and IL5 as representative of a Th2 subtype. We found that IL4 was higher in the sera of patients with chronic urticaria (as well as atopic subjects) compared to controls while IL5 and IFNγ levels were normal.

We then studied cytokine expression at the single-cell level[30] and identified the T cell subpopulations involved in cytokine production employing anti-cytokine monoclonal antibody (MoAbs) and flow cytometry. Thus we could assess the simultaneous production of different cytokines in the same cell.

We found significant differences in the ability of CD4+ lymphocytes to produce IL4 and INF gamma upon PMA-Ionomycin stimulus when healthy controls are compared to chronic urticaria patients. There was no difference in IL4 or INFgamma production by CD8+ lymphocytes of patients vs. controls. We did not find significant differences when comparing the ratio of INF-gamma/IL4 production by CD4+ or CD8+ lymphocytes of controls and urticaria patients. The cytokine profile found in our study does not reflect either a Th1 or Th2 predominance.

These data again strengthen an immune basis for chronic urticaria, since we demonstrate that CD4+ lymphocytes of patients with this disease are activated and they release greater amounts of cytokine with a non-specific stimulus. On the other hand, this finding is similar to a study in which the cellular infiltrate associated with chronic urticaria had a Th0 profile[31]. The authors analyzed skin biopsies of chronic urticaria patients by in situ hybridization. IL4, IL5 and INF-gamma revealed higher cytokine m-RNA expression in chronic urticaria patients than in healthy controls, without a predominance of either a Th1 or Th2 representative cytokine.

STUDY ON RELEASABILITY OF CHRONIC URTICARIA BASOPHILS

Most studies have focused on the properties of chronic urticaria sera, but few studies have compared basophils (or mast cells) derived from chronic urticaria patients to basophils derived from normal donors. Prior reports demonstrated that basophils of patients have a diminished response to anti-IgE[32-34] but no differences in releasability was found with stimuli such as fMLP, A23187 and PAF[35].

We examined the response of basophils of healthy donors, atopic donors and patients with chronic urticaria to a variety of stimuli including anti-IgE, bradykinin[36], MCP-1[37], C5a[14,15,38], and serum.

When we stimulated basophils of chronic urticaria patients (CU basophils) with anti-IgE and compared the results with histamine release upon stimulation of basophils from healthy controls with anti-IgE, we observed a significantly decreased histamine release in CU basophils and to a lesser degree with C5a. No differences were observed when basophils from patients were incubated with bradykinin or MCP-1[39].

Furthermore, we divided chronic urticaria sera in two groups, one whose serum was able to activate normal basophils and therefore believed to be autoimmune, and the group lacking this ability, designated chronic idiopathic urticaria. We compared histamine releasability when these sera are incubated with basophils derived from patients with chronic urticaria.

Surprisingly, we observed a much greater histamine release when basophils of CU patients were stimulated with other chronic urticaria patients' sera compared to healthy basophils stimulated with CU sera. Moreover, even those sera that were not able to activate healthy basophils were highly active on CU basophils. Control sera were also able to activate CU basophils but not healthy basophils.

Hence, chronic urticaria basophils, in spite of being less responsive to some stimuli, are clearly highly responsive when incubated with sera; even normal sera. Chronic urticaria basophils have several specific features that distinguish them from basophils of healthy donors or atopic controls. They are less respondent to anti-IgE and C5a with no difference when stimulated with bradykinin and MCP-1 and have much higher release when incubated with serum. The factor in serum that stimulates these cells has not been identified nor is the abnormal responsiveness of the cells understood.

CONCLUSION

There is increasing evidence in favour of an autoimmune mechanism as a cause of chronic urticaria in 40-45 % of patients. Autoimmunity is dependent on the presence of IgG antibody to the alpha subunit of the IgE receptor, and to a lesser degree anti-IgE. Such sera release histamine, leukotrienes, IL4 and induce CD203C and CD63 expression on donor basophils.

There remains a substantial group of patients in whom it is not possible to demonstrate this autoim-

mune mechanism. Yet we demonstrate similar abnormalities in both groups. They share abnormal responsiveness with basophils of patients with chronic autoimmune urticaria, just as the histology of the two groups is strikingly similar[31,40].

On the other hand, stimulation of T lymphocytes releases both IL4 and INF-γ and the histology of biopsy specimens does not have a predominance of Th1 or Th2 subtypes although most cells are CD4 positive rather than CD8 positive.

Finally we can conclude that chronic urticaria basophils have several specific features that distinguish them from basophils of healthy donors or atopic controls. They are less responsive to anti-IgE and C5a with no difference when stimulated with bradykinin and MCP-1 and have much higher release when incubated with serum. The factor in serum that stimulates these cells has not been identified nor is the abnormal responsiveness of the cells understood. One study has, however, suggested a signal abnormally involving Ras in chronic urticaria basophils[41].

These findings do not yet lead to a particular therapy although use of cyclosporine, particularly in the autoimmune subgroup may have a rationale related to the above observations[42,43]. However, they offer better understanding of the physiopathology of this disease, that help to avoid unnecessary laboratory tests and provide both to the patient and to the physician new perspective and research possibilities.

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