Interaction between prostaglandin D$_2$ and chemoattractant receptor-homologous molecule expressed on Th2 cells mediates cytokine production by Th2 lymphocytes in response to activated mast cells

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Summary

The mechanisms by which immunologically activated mast cells stimulate the production of proinflammatory cytokines by T helper type 2 (Th2) lymphocytes were investigated in a human cell culture system. Supernatants collected from cord blood-derived mast cells after treatment with immunoglobulin E (IgE)/anti-IgE contained an activity that stimulated the production of interleukin (IL)-4, IL-5 and IL-13 (both mRNA and protein) by Th2 lymphocytes. This activity was not detected in supernatants from unactivated mast cells and its production was inhibited by treatment of activated mast cells with the cyclo-oxygenase inhibitor diclofenac. The concentration of diclofenac used inhibited completely the production of prostaglandin D$_2$ (PGD$_2$) but did not inhibit the release of histamine or leukotriene C$_4$. The effect of supernatants from activated mast cells was mimicked by exogenous PGD$_2$ at concentrations similar to those detected in the cultures of activated mast cells, and addition of exogenous PGD$_2$ to supernatants from diclofenac-treated mast cells restored their ability to stimulate Th2 cytokine production. The ability of the mast cell supernatants to stimulate production of Th2 cytokines was not affected by addition of diclofenac to the Th2 cells directly, indicating that the production, but not the action, of the factor was sensitive to diclofenac treatment. Inhibition of chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) abolished the effect of the mast cell supernatants on Th2 cytokine production. These data indicate that mast cells have the ability to stimulate Th2 cells to elaborate cytokines independently of T cell receptor activation or co-stimulation and this response is mediated by PGD$_2$ acting upon CRTH2 expressed by Th2 cells.

Keywords: chemoattractant receptor-homologous molecule expressed on Th2 cells, cytokine, mast cells, prostaglandin D$_2$

Introduction

T helper type 2 (Th2) lymphocytes are found in high numbers at sites of allergic inflammation, including the lungs of asthmatic patients, and there is increasing evidence that these cells contribute to disease pathology through the elaboration of cytokines such as interleukin (IL)-4, IL-5 and IL-13 [1–5]. IL-5 has a well-recognized role in promoting blood and tissue eosinophilia [6–9], while both IL-4 and IL-13 have the ability to induce isotype-switching leading to the production of immunoglobulin E (IgE) [10,11]. IL-13 also acts directly on bronchial tissues to promote mucus production and airway hyperresponsiveness [12]. The central role played by Th2 cytokines in allergic disease is illustrated by the findings that transgenic mice that overproduce Th2 cytokines have elevated levels of IgE with associated pathologies that resemble aspects of atopic dermatitis and asthma [13], and that blockade of IL-4 and IL-13 signalling reduces the late-phase airway response to allergen in asthmatic subjects [14].

Mast cells also play a central role in the allergic response [15,16], and the interaction between mast cells and Th2 cells may provide an essential link between the early- and late-phase allergic responses. When allergic individuals are exposed to allergen, cross-linking of IgE on the surface of mast cells leads to the rapid release of preformed mediators such as histamine and newly synthesized mediators such as leukotriene C$_4$ (LTC$_4$) and prostaglandin D$_2$ (PGD$_2$), causing...
features of the classical early allergic response. In addition to causing the characteristic early-phase responses, mast cell activation may also promote the recruitment and activation of Th2 lymphocytes within allergic tissues, a process which can occur independently of antigen-specific T cell activation [17]. The importance of such interaction between mast cells and Th2 cells may underlie the classic observation that a late-phase lymphocytic allergic response can be induced in non-atopic human subjects by passive transfer of IgE [18], and is consistent with the ability of the anti-IgE antibody omalizumab to inhibit the late-phase airway response to allergen in asthmatic patients [19]. In a chronic model of allergic asthma in mice, mast cells are essential for accumulation of lymphocytes in bronchoalveolar fluid in addition to the development of a number of other features of airway inflammation [20]. Accumulation of various lymphocyte subtypes in inflamed tissues has been shown to be mediated by the release of distinct chemotactic cytokines from mast cells [21–24]. The role of mast cell-derived eicosanoids in promoting activation of T cells has been reviewed comprehensively by Kim and Luster [25]. Supernatants from immunologically activated mast cells display potent chemotactic activity for Th2 lymphocytes, an activity that is mediated by PGD2 acting on the chemotactic receptor chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [26]. In addition to mediating chemotaxis of Th2 cells in response to PGD2 [27], activation of CRTH2 also leads to the production of Th2 cytokines [28], an effect that can occur in the absence of antigen or any other form of co-stimulation [29]. However, a wide variety of inflammatory mediators are released by mast cells upon activation which may have the potential to modulate Th2 cell function, and to date there has been no study investigating whether such mediators promote proinflammatory cytokine production by Th2 cells and, among these diverse mediators, what role PGD2 and CRTH2 might play in such a response. We have therefore investigated the mechanisms by which immunologically activated mast cells stimulate the production of Th2 cytokines in a human in vitro culture system. Supernatants from mast cells activated with IgE/anti-IgE, but not unactivated mast cells, stimulated the production of cytokines by Th2 lymphocytes. Production of the stimulatory activity was inhibited by treatment of mast cells with the cyclooxygenase inhibitor diclofenac, and the effect of the supernatant was inhibited by the CRTH2 antagonists ramatroban and TM30089. These data suggest that the interaction of Th2 lymphocytes with activated mast cells leading to the production of cytokines is mediated through a CRTH2-dependent mechanism.

Materials and methods

Reagents

The PGD2 was purchased from Biomol (Plymouth Meeting, PA, USA); ramatroban (BAY u3405), SQ29548, PGD2–MOX enzyme immunoassay kits and LTC4 enzyme immunoassay kits were purchased from Cayman Chemical (Ann Arbor, MI, USA); TM30089 was supplied by ChemieTek (Indianapolis, IN, USA); human CD4+ T cell isolation kit II, anti-human CRTH2 MicroBead Kit and T cell activation/expansion kits were from Miltenyi Biotec Ltd (Bergisch Gladbach, Germany); human recombinant stem cell factor, human recombinant IL-6 and human IL-4/5/13 immunoassay kits were purchased from R&D Systems (Minneapolis, MN, USA); Iscove’s modified Dulbecco’s medium and X-VIVO 15 medium were purchased from Lonza (Walkersville, MD, USA); human myeloma IgE, antibodies against human tryptase and chymase were purchased from Chemicon International (Chandlers Ford, UK); Ficoll–Hypaque was purchased from Amersham Biosciences (Little Chalfont, UK); histamine enzyme immunoassay kit was from SPI-BIO (Montigny le Bretonneux, France); RNeasy Mini kit and Omniscript reverse transcription (RT) kit were supplied from Qiagen (West Sussex, UK); and human recombinant IL-2, human recombinant IL-4, goat anti-human IgE, diclofenac and other chemicals were from Sigma-Aldrich (Dorset, UK).

Human mast cell culture and activation

Human mast cells were cultured from CD34+ progenitor cells, as described in our previous report [26]. Briefly, CD34+ progenitor cells from human cord blood (Lonza) were cultured at a density of 1 x 10⁵ cells/ml with Iscove’s modified Dulbecco’s medium containing 10% human serum, 0-55 µM 2-mercaptoethanol, penicillin/streptomycin, human recombinant stem cell factor (100 ng/ml) and human recombinant IL-6 (50 ng/ml) in 5% CO₂ at 37°C for 8–10 weeks. Half the culture medium was replaced twice weekly with fresh medium containing the same concentration of cytokines. The expression of tryptase and chymase of the cells was tested by immunostaining using the method described by Craig and Schwartz [30]. The cytospin smears were first air-dried for 2 h at room temperature and then fixed with Carnoy’s solution (ethanol : chloroform : glacial acetic acid, 6:3:1) for 1 min. The fixed smears were stained using monoclonal antibodies against human mast cell tryptase and human mast cell chymase. The mast cells used in this study were tryptase-positive (>80%) and chymase-negative (<1%). The cells were pretreated with 5 µg/ml purified human myeloma IgE and human recombinant IL-4 (10 ng/ml) for 4 days, washed and then sensitized passively with fresh IgE (5 µg/ml) for 2 h. The cells were washed with medium for 20 min and then continued to be incubated with medium or challenged with goat anti-human IgE (1 µg/ml) in the presence or absence of diclofenac (10 µM). The supernatants of the cells were collected 1 h after challenge. The supernatants were assayed for PGD2 using a PGD2–MOX enzyme immunoassay kit and histamine using an enzyme immunoassay kit according to the manufacturer’s instructions.
Human CRTH2+CD4+ Th2 cell culture

Human CRTH2+CD4+ Th2 cells were prepared using a modified method described previously [29]. Briefly, peripheral blood mononuclear cells were isolated from buffy coats (National Blood Service, Bristol, UK) by Ficoll Hypaque density gradient centrifugation, followed by CD4+ cell purification using a magnetic affinity cell sorting (MACS) CD4+ T cell isolation kit II. After 7 days’ culture in X-VIVO 15 medium containing 10% human serum, 50 U/ml IL-2 and 100 ng/ml IL-4, CRTH2-positive cells were isolated from the CD4+ cultures by positive selection using an anti-human CRTH2 MicroBead Kit. The harvested CD4+ CRTH2+ cells were treated as Th2 cells and were amplified further by stimulation with the T cell activation/expansion kit and grown in X-VIVO 15 medium containing 10% human serum and 50 U/ml IL-2 before use.

Cytokine release assays

The Th2 cells were treated with X-VIVO 15 culture medium or various mast cell supernatants in the presence or absence of PGD2 or other compounds, as indicated in the results at 37°C and 5% CO2 for 5 h. The supernatants of the treatments were collected. The concentrations of IL-4, IL-5 and IL-13 in the supernatants were assayed using enzyme-linked immunoassay kits, according to the manufacturer’s instructions. The results were measured in a Victor2 V-1420 multi-label HTS Counter (PerkinElmer Life Sciences Wellesley, MA, USA).

Reverse transcription–polymerase chain reaction

Reverse transcription-polymerase chain reaction (RT–PCR) was conducted as described previously [29]. Total RNA of Th2 cells after different treatments for 3 h were extracted using an RNeasy Mini kit and quantitated using a Qiacube (Qiagen, Hilden, Germany). cDNA of the samples was prepared from the same starting amount of total RNA using a Omniscript RT kit. PCR products were separated on an agarose gel and detected with a Fluor-S MAX2 Multimager (Bio-Rad, Hercules, CA, USA). The intensity of ethidium bromide-stained bands was quantified using Quantity One software (Bio-Rad). mRNA level of cytokines was normalized with the level of glyceraldehyde-3-phosphate-dehydrogenase (GAPDH). Primers used were as follows – IL-4: 5’-GCTGGCTCTCAAGAACACAC-3’ and 5’-CTCTGGTGTTGCTCTTCTAC-3’ generating a 221-base pairs (bp) fragment; IL-5: 5’-CTGCCCTACTATGGCCATC-3’ and 5’-CTTCCACAGTACCCTTG-3’ generating a 217-bp fragment; IL-13: 5’-CTTCACTCCTCCTCTGTTGG-3’ and 5’-GTCAGGTGTAGCTCCATACC-3’ generating a 206-bp fragment; and GAPDH: 5’-GCAACCTGAGACTTGATGGC-3’ and 5’-GGAATGCACGCCCCAGCTAAAAG-3’ generating a 350-bp fragment.

Statistics

Data were analysed using one-way analysis of variance followed by the Newman–Keuls test. Values of P<0.05 were considered statistically significant.

Results

Supernatants from activated mast cells promote cytokine production by Th2 cells

Supernatants collected from human mast cells 1 h after activation with IgE/anti-IgE contained low levels of IL-4, IL-5 and IL-13 (Table 1). Addition of these supernatants (diluted 1:2) to human Th2 cells (~5 × 105 cells/ml) for 5 h led to the production of high levels of IL-4, IL-5 and IL-13 (Table 1; Fig. 1). The levels of the cytokines released by these Th2 cells were very similar to those produced by Th2 cells treated with 100 nM PGD2. In contrast, cytokine levels in cultures of Th2 cells treated with supernatants from unactivated mast cells were not increased significantly compared with those treated with media alone.

Inhibition of PGD2 production abolishes the release of Th2 cytokine stimulatory activity from mast cells

Co-treatment of IgE/anti-IgE-activated mast cells with diclofenac (10 μM) during the period of anti-IgE stimulation abolished completely production of both Th2 cytokine

Table 1. Cytokine levels in the supernatants from mast cells or T helper type 2 (Th2) cells after various treatments.

<table>
<thead>
<tr>
<th>Cytokine levels (pg/ml)</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unactivated mast cell supernatant alone</td>
<td>4 ± 1 (n = 2)</td>
<td>35 ± 15 (n = 2)</td>
<td>18 ± 7 (n = 2)</td>
</tr>
<tr>
<td>Activated mast cell supernatant alone</td>
<td>4 ± 2 (n = 2)</td>
<td>44 ± 21 (n = 2)</td>
<td>69 ± 24 (n = 2)</td>
</tr>
<tr>
<td>Th2 cells (~5 × 105) + medium</td>
<td>4 ± 2 (n = 8)</td>
<td>228 ± 40 (n = 8)</td>
<td>608 ± 95 (n = 8)</td>
</tr>
<tr>
<td>Th2 cells (~5 × 105) + unactivated mast cell supernatant</td>
<td>5 ± 1 (n = 4)</td>
<td>257 ± 45 (n = 5)</td>
<td>636 ± 90 (n = 8)</td>
</tr>
<tr>
<td>Th2 cells (~5 × 105) + activated mast cell supernatant</td>
<td>20 ± 7 (n = 4)</td>
<td>780 ± 81 (n = 5)</td>
<td>2215 ± 423 (n = 8)</td>
</tr>
<tr>
<td>Th2 cells (~5 × 105) + 100 nM PGD2</td>
<td>24 ± 9 (n = 8)</td>
<td>695 ± 40 (n = 8)</td>
<td>2360 ± 379 (n = 8)</td>
</tr>
</tbody>
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IL, interleukin; PGD2, prostaglandin D2.
stimulatory activity (Fig. 1) and PGD2 (Fig. 2a). While unactivated mast cells produced only low levels of PGD2 (< 1 ng/10^6 cells/ml), high levels of PGD2 (48 ± 8 ng/10^6 cells/ml) were detected in the supernatants from activated mast cells after 1-h challenge, which was reduced to < 1 ng/10^6 cells/ml by co-treatment with diclofenac (10 μM). In contrast, diclofenac did not inhibit the release of histamine (Fig. 2b) and enhanced release of LTC4 (Fig. 2c) from mast cells in response to treatment with IgE/anti-IgE. Because the mast cell supernatants were diluted 1 : 2 prior to the treatment of Th2 cells, the Th2 cells were exposed to concentrations of PGD2 in the range of 20–30 ng/ml. Addition of 100 nM PGD2 (equivalent to ~35 ng/ml) to supernatants from activated mast cells co-treated with diclofenac restored their ability to promote the production of cytokines by Th2 cells (Fig. 1).

The Th2 cytokine production in response to activated mast cell supernatants is mediated by CRTH2

The IL-4, IL-5 and IL-13 production induced by activated mast cell supernatants was inhibited completely by the dual CRTH2/thromboxane A2 receptor (TP) antagonist ramatroban (1 μM) and selective CRTH2 antagonist TM30089 (1 μM), while the selective TP antagonist SQ29548 (1 μM) was without effect (Fig. 3).

To rule out the possibility of a direct effect of diclofenac on Th2 cytokine production, we also stimulated Th2 cells with activated mast cell supernatants in the presence of

![Fig. 1. Effect of mast cell supernatants on T helper type 2 (Th2) cytokine production. Th2 cells were incubated with mast cell supernatants (1:2 dilution) (open bars) from unactivated mast cells (UMS), mast cells activated with immunoglobulin E (IgE)/anti-IgE (AMS) or diclofenac-treated mast cells activated with IgE/anti-IgE (DAMS) in the presence or absence of prostaglandin D2 (PGD2) as indicated for 5 h. Responses of Th2 cells to X-VIVO 15 medium or PGD2 alone are also shown as controls (black bars). The concentrations of interleukin (IL)-4, IL-5 and IL-13 in the incubation media were measured by enzyme immunoassay. Results are presented mean ± standard error of the mean (n = 4–6). P < 0.0001 by analysis of variance. P > 0.05 by Newman–Keuls test for (IL-4, IL-5 and IL-13) no additive versus UMS/DAMS, UMS versus DAMS, 100 nM PGD2 versus AMS; (IL-5 and IL-13) 100 nM PGD2/AMS versus DAMS + 100 nM PGD2; n = 4–6.

![Fig. 2. Production of prostaglandin D2 (PGD2), histamine and leukotriene C4 (LTC4) by mast cells. Mast cells were preincubated with immunoglobulin E (IgE) followed by treatment with culture medium or anti-IgE antibody in the presence or absence of diclofenac, as described in Materials and methods. One h after the treatments the supernatants were collected and assayed for PGD2 (a), histamine (b) and LTC4 (c) by enzyme immunoassay. Results are expressed as the mean ± standard error of the mean (n = 3–4). P < 0.0001 for (a) or P < 0.05 for (b,c) by analysis of variance. P > 0.05 by Newman–Keuls test for (a) no additive versus anti-IgE + 10 μM diclofenac, n = 4; (b) anti-IgE versus anti-IgE + 10 μM diclofenac, n = 3; (c) no additive versus anti-IgE, n = 3.© 2009 British Society for Immunology, Clinical and Experimental Immunology, 156: 126–133
Regulation of Th2 cytokine production by activated mast cell supernatant is at gene transcriptional level

To elucidate further the mechanism of Th2 cytokine production in response to the mast cell supernatants, the levels of mRNA encoding IL-4, IL-5 and IL-13 in Th2 cells were measured after different treatments for 3 h (Fig. 4). Addition of activated mast cell supernatants to Th2 cells up-regulated mRNA for the cytokines to levels similar to those observed after treatment with 100 nM PGD2. The supernatants from unactivated mast cells or from diclofenac-treated activated mast cells did not increase the levels of cytokine mRNA significantly. The elevation of Th2 cytokine mRNA levels induced by activated mast cell supernatants was inhibited almost completely by ramatroban but not by SQ29548.

Discussion

The IgE-dependent interaction of mast cells and Th2 cells leading to the elaboration of cytokines such as IL-4, IL-5 and IL-13 is postulated to play a central role in asthma and related allergic disorders. Treatment with anti-IgE antibody omalizumab reduces both the early- and late-phase airway response to bronchial challenge with allergen in allergic

diclofenac (Fig. 3). In this situation, diclofenac did not affect significantly the response of Th2 cells to the supernatants.
subjects [19] and reduces airway inflammation (including Th2 cell accumulation) in chronic asthma [31]. While the effects of anti-IgE may, in part, be mediated by inhibition of IgE-facilitated antigen presentation [32], there is increasing evidence that activated mast cells may also contribute to Th2 cell recruitment and activation within allergic tissues [17,33]. Supernatants collected from activated mast cells promoted the migration of Th2 cells in vitro and the factor(s) responsible for this activity is most likely to be PGD$_2$ or a closely related arachidonic acid metabolite that activates Th2 cells through high-affinity interaction with CRTH2 [26], which is expressed abundantly on the surface of Th2 cells [27,34]. In addition to promoting migration of Th2 cells, PGD$_2$ is also known to stimulate production of IL-4, IL-5 and IL-13 by these cells [29]. However, the capacity of supernatants from activated mast cells to induce Th2 cytokine production has not been tested directly. As mast cells produce high levels of PGD$_2$ in vitro [35] and in vivo upon challenge with allergen [36–38], it is of interest to determine the contribution of mast cell-derived PGD$_2$ to the production of cytokines by Th2 cells. Supernatants collected from human mast cells after activation with IgE/anti-IgE contained high levels of histamine and PGD$_2$, but LTC$_4$, IL-4, IL-5 and IL-13 were detected only at low levels. This was expected, as although activated mast cells can be a rich source of both IL-4 [39] and IL-13 [40], release of these cytokines is delayed compared with performed mediators and rapidly synthesized eicosanoids [41,42], and are therefore not likely to be present in significant quantities by 1 h after stimulation in absence of priming with stem cell factor [43]. However, addition of these supernatants to Th2 cells stimulated increased production of IL-4, IL-5 and IL-13, while supernatants from unactivated mast cells were without effect. It is generally thought that the T cell receptor or co-stimulation, as occurs during antigen presentation, is required to activate T cells [44]. However, these data indicate that a soluble factor produced from activated mast cells is sufficient to drive production of cytokines by Th2 cells. Production of this activity was inhibited by diclofenac, suggesting that a cyclo-oxygenase product of arachidonic metabolism was responsible for this activity. This cyclo-oxygenase product is likely to be PGD$_2$, based on the following observations:

- The effect of the mast cell supernatants was mimicked by PGD$_2$.
- PGD$_2$ was detected in the mast cell supernatants at concentrations sufficient to stimulate cytokine production by Th2 cells.
- Diclofenac abolished both the production of Th2 cytokine stimulatory activity and PGD$_2$ without affecting the release of histamine.
- Addition of exogenous PGD$_2$ to supernatants from diclofenac-treated mast cells restored their ability to stimulate Th2 cytokine production.

Although PGD$_2$ was detected in the mast cell supernatants at sufficient concentrations to stimulate Th2 cytokine production, it is possible that biologically active metabolites of PGD$_2$ may also make a contribution in vivo. In particular, both $\Delta^9$PGD$_2$ and $\Delta^9$PGJ$_2$ are formed rapidly in biological fluids such as plasma [45] and are potent CRTH2 agonists [46,47].

The IgE-mediated activation of mast cells orchestrates an inflammatory cascade through secretion of variety of biologically active mediators. These mediators may be categorized into three groups: preformed secretory granule-associated mediators, lipid-derived mediators and cytokines. The well-known mediators in the first group include histamine, which we measured and showed was not inhibited by diclofenac, so although it has been reported that histamine is able to enhance the production of Th2 cytokines [48,49], this mediator is unlikely to play a major role in this response. The most important second-group mediators are the cyclo-oxygenase and lipooxygenase metabolites of arachidonic acid. We also measured the levels of LTC$_4$, a downstream product of lipooxygenase, in the mast cell supernatants. Treatment of mast cells with diclofenac did not suppress but rather enhanced LTC$_4$ secretion from activated mast cells. This result suggested that blockade of the cyclo-oxygenase pathway diverts arachidonic acid to lipooxygenase products. Because these diclofenac-treated mast cells lack Th2 cytokine stimulatory activity, this effectively rules out leukotrienes as stimulators of cytokine production by Th2 cells. Therefore, the high correlation between inhibition of PGD$_2$ secretion from mast cells and cytokine production from Th2 cells by diclofenac suggested strongly that PGD$_2$ is the dominant mast cell mediator driving cytokine production by Th2 cells.

The effect of the activated mast cell supernatant on the production of Th2 cytokines was inhibited by ramatroban, a dual CRTH2/TP antagonist. The selective TP antagonist SQ29548 was without effect, implicating CRTH2 in mediating Th2 cytokine production in response to mast cell supernatants. This conclusion is supported by findings that the selective CRTH2 antagonist TM300089 also inhibited Th2 cytokine in response to mast cell supernatants. These data extend our earlier observation that mast cell supernatants promote chemotaxis of Th2 cells through a CRTH2-dependent mechanism, and suggest that CRTH2 may play a central role in both the recruitment of Th2 cells and their subsequent activation to elaborate proinflammatory cytokines. This mechanism may underlie the observed ability of selective CRTH2 antagonists to inhibit allergen-induced airway inflammation in the mouse [50] and the guinea pig [51]. Furthermore, these effects are relevant to the effects observed in mice genetically deficient in CRTH2. In a mouse model of skin inflammation, genetic ablation of CRTH2 was associated with diminished dermal infiltration of various leucocyte populations, including lymphocytes and eosinophils, reduced tissue swelling and a reduction in the levels of serum IgE [52]. It is plausible that the reduction
in IgE observed in CRTH2−/− mice is related to the effects on Th2 cytokine production. Production of IgE was also reduced in CRTH2-deficient mice exposed to Japanese cedar pollen intranasally, an effect associated with reduced inflammation of the nasal mucosa and signs of rhinitis [53]. In Japanese cedar pollen-induced dermatitis, skin inflammation is dependent upon both mast cell activation and the presence of CRTH2 [54]. Taken together, these studies support the view that mast cell-derived PGD2 plays a critical role in the development of allergic responses via activation of CRTH2.

In conclusion, activated mast cells promote the production of cytokines by Th2 cells. This effect is mediated by the production of PGD2 from mast cells which stimulates Th2 cells by an action on the cell surface receptor CRTH2. These findings, combined with previous studies, suggest that PGD2 is the dominant mast cell mediator that activates Th2 cells. In addition to promoting the recruitment of Th2 cells during the initiation of an allergic response, activation of CRTH2 may contribute to Th2 cytokine production at sites of allergic inflammation.

References

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